CRITICAL CARE ALERT®

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

Thomson American Health Consultants Home Page— www.ahcpub.com

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

THOMSON AMERICAN HEALTH CONSULTANTS

INSIDE

The Effect of Prompt Physician Visits on ICU Mortality and Cost

ABSTRACT & COMMENTARY

Synopsis: *A retrospective study comparing patients seen within the first 6 hours of ICU admission to those seen later showed that patients seen earlier had a decreased risk of death, shorter hospital stays, and similar direct variable costs.*

Source: Engoren M. *Crit Care Med*. 2005;33:727-732.

This observational study from a university-affiliated, urban, tertiary hospital in Toledo, OH, retrospectively reviewed the records of 840 patients admitted to various ICUs to determine if the time to first visit by a physician had an effect on a number of clinically relevant outcomes. The hospital operates with an open ICU structure, with some patients covered by housestaff and others cared for directly by attending physicians. Data collected included $APACHE_0$ (scores calculated from data available at the time of admission), APACHE II scores, many physiologic variables, location prior to ICU admission, ICU and hospital length of stay, and hospital outcome. Direct variable costs were also calculated. Patients were divided into 2 groups: the "Prompt" group, defined as patients seen by a physician within 6 hours of ICU admission, and the "Delayed" group, seen more than 6 hours after admission.

To help separate out the effects of severity of illness and other factors that might affect a physician's decision to see the patient promptly, a propensity score was calculated to predict the likelihood of belonging to either the Prompt or Delayed group. This score was then used in multivariate modeling of mortality and used to find patients with similar propensity scores in the 2 treatment groups for purposes of comparison.

Median time to first physician visit was 6 hours. Patients in the prompt group differed from those seen later in several ways. They were seen in different ICUs. Patients in the prompt group were more likely to be seen by housestaff and more likely to be admitted during the day; they had higher APACHE II and $APACHE_0$ scores, and higher direct variable costs. Despite these differences, these patients had a lower mortality ratio (55% vs 88%) as predicted by APACHE

VOLUME 12 • NUMBER 3 • JUNE 2005 • PAGES 17-24

II. In the subgroup matched by propensity scores, the prompt group had shorter hospital stays (11 d vs 13 d), similar direct variable costs and similar mortality rates. By binary logistic regression, higher $APACHE_0$, score, older age, mechanical ventilation on arrival, and longer time to being seen by a physician were predictors of hospital mortality. Each 1-hour physician delay in initially seeing the patient was associated with a 1.6% increased risk of hospital death.

COMMENT BY JAMES E. McFEELY, MD

This article contributes to a body of work published in the last few years studying the effect of staffing models and speed of intervention on ICU outcomes. Most of that work has focused on the organization of the ICU (closed vs open models) or on treatments for specific diseases such as early goal-directed therapy for sepsis, thrombolytics for acute myocardial infarction, and treatment for stroke. The overriding theme of that work is that faster is better. This paper answers the question more generally, by confirming that patients seen by a physician within 6 hours of ICU admission do better than those seen less promptly. The study was performed in a hospital with an open ICU structure, and included a wide variety of admitting diagnoses. Even after controlling for initial severity of illness and other factors using sophisticated statistical methods, researchers still found that time to initial physician visit was a significant predictor of hospital mortality.

As with all good research, this paper raises as many questions as it answers. Can outcomes be improved by seeing the patient within the first hour as with other specific diseases? Does it matter if the initial visit is by an attending physician or by a member of the housestaff? Would outcomes be different comparing an intensivist to a generalist making the first visit? Although this study found no difference based on the type of physician that made the initial visit (good news for those of you with housestaff), the question is difficult to answer in a randomized fashion, and further observational studies from a greater variety of institutions are required to gain better insight into these and similar issues.

Despite the need for further research, however, this paper should cause ICU medical directors to reconsider the practice of allowing ER staff to *tuck in* patients, and probably should prompt a change in policy to require onsite physician evaluation within a few hours of admission to the ICU. ■

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

VICE PRESIDENT/GROUP PUBLISHER: Brenda Mooney.

EDITORIAL GROUP HEAD: Lee Landenberger.

MANAGING EDITOR: Robert Kimball.

ASSOCIATE MANAGING EDITOR: Leslie Hamlin.

MARKETING PRODUCT MANAGER: Gerard Gernazian.

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.

This is an educational publication designed to present scientific information and opinion to health professionals, to stimulate thought, and further investigation. It does not provide advice regarding medical diagnosis or treatment for any individual case. It is not intended for use by the layman.

Subscriber Information

Customer Service: 1-800-688-2421

Customer Service E-Mail Address: customerservice@ahcpub.com

Editorial E-Mail Address: robert.kimball@thomson.com

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

Subscription Prices

United States

1 year *with* free AMA Category 1 credits: $269

(Student/Resident rate: $120)

Multiple Copies

Documents are available for multiple subscriptions. For pricing information, please call Steve Vance at (404) 262-5511.

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 publication.

THOMSON AMERICAN HEALTH CONSULTANTS™

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.

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 2004 financial disclosure form. Thomson American Health Consultants accepts pharmaceutical sponsorship of some programs but only in the form of unrestricted educational grants that must meet all ACCME and ANCC requirements.

Subglottic Secretion Drainage for Preventing Ventilator-Associated Pneumonia

ABSTRACT & COMMENTRAY

Synopsis: *Subglottic secretion drainage appears effective in preventing early onset ventilator-associated pneumonia among patients expected to require > 72 hours of mechanical ventilation.*

Source: Dezfulian C, et al. *Am J Med*. 2005;118:11-18.

THE PURPOSE OF THIS META-ANALYSIS WAS TO ASSESS the efficacy of subglottic secretion drainage in preventing ventilator-associated pneumonia (VAP). Dezfulian and colleagues performed a comprehensive analysis of randomized trials that have compared sub-

glottic secretion drainage with a standard endotracheal tube care in mechanically ventilated patients. Studies were identified by searching computerized databases (MEDLINE, CINAHL, EMBASE, Cochrane Library, Current Contents, and Biological Abstracts), reviewing bibliographies, and expert consultation. Summary risk ratios and weighted mean differences with 95% confidence intervals were calculated for each outcome using a fixed-effects model.

Of 110 studies retrieved, 5 met the inclusion criteria of mechanically ventilated patients prospectively assigned randomly to some form of subglottic secretion drainage vs no drainage (control), and also that the incidence of pneumonia was reported in both groups. The 5 studies enrolled 896 patients. Subglottic secretion drainage reduced the incidence of VAP by nearly half (risk ratio = 0.51; 95% confidence interval [CI], 0.37-0.71), primarily by reducing early onset pneumonia (pneumonia occurring within 5 to 7 days after intubation). Although significant heterogeneity was found for several end points, this was largely resolved by excluding a single outlying study. The outlier study recruited cardiac surgery patients whose duration of mechanical ventilation (mean, 1.5 days) was shorter than the other studies.

The method of subglottic secretion drainage was intermittent suction in 2 studies, continuous 2 studies, and hourly aspiration with a syringe in the remaining study. In the 4 studies other than the outlier, subglottic secretion drainage shortened the duration of mechanical ventilation by 2 days (95% CI, 1.7-2.3 days) and the length of stay in the ICU by 3 days (95% CI, 2.1-3.9 days), and delayed the onset of pneumonia by 6.8 days (95% CI, 5.5-8.1 days). Dezfulian et al concluded that subglottic secretion drainage appears to be effective in preventing early onset VAP among patients expected to require > 72 hours of mechanical ventilation.

COMMENT BY DEAN R. HESS, PhD, RRT

VAP is an important clinical problem. It has been reported to occur in about 10% of mechanically ventilated patients.[1] Although its impact on mortality is debated, there is no question that it increases morbidity by increasing the requirement for antibiotic therapy, and also by increasing the time on mechanical ventilation and days in the ICU. The term ventilator-associated pneumonia is misleading, as it is well accepted that VAP arises most commonly due to micro-aspiration of pharyngeal secretions around the cuff of the endotracheal tube rather what is breathed through the endotracheal tube from the ventilator. Accordingly, a method to prevent micro-aspiration might be expected to reduce the incidence of VAP.

Many practices have been identified to prevent VAP.[2] One such practice is subglottic secretion drainage. Subglottic secretion drainage is accomplished through use of a specially designed endotracheal tube with a separate dorsal lumen that opens directly above the endotracheal tube cuff. Although originally designed for use with an endotracheal tube, it is also now available in the design of some tracheostomy tubes.

The results of this meta-analysis suggest a strong benefit for the use of subglottic secretion drainage to prevent early onset VAP. However, there are several issues that remain to be resolved before this practice can be widely adopted. The benefit of subglottic secretion clearance is in patients who require > 72 hrs of mechanical ventilation. Unfortunately, it is difficult to predict which patients will require > 72 hrs of mechanical ventilation at the time of intubation. Because tubes capable of providing subglottic secretion clearance cost about 10 times more than standard endotracheal tubes, it is likely not cost-effective to use these tubes in all patients who are intubated. Moreover, patients should generally not be reintubated with this tube if they require > 72 hrs of ventilation, as reintubation itself is a risk factor for VAP.

The safety of these tubes is yet to be determined. In an animal study, tracheal wall injury due to subglottic suction was reported.[3] However, whether similar injury occurs in humans is unknown; this complication was not reported in any of the studies included in the meta-analysis reported here. The higher rigidity of the endotracheal tube incorporating subglottic suction may contribute to tracheo-innominate artery fistula[4] and upper airway edema.

Finally, the cost-effectiveness of these tubes remains to be determined. Their use does not appear to affect mortality, but this meta-analysis suggests that ventilator days and ICU days may be reduced. A formal economic assessment of these devices would help to answer the question of cost-effectiveness. To my knowledge, such an analysis is not yet available, although it has been suggested that the use of subglottic suction can be supported on the basis of the cost of VAP.[5]

There is no doubt that aspiration of subglottic secretions decreases the risk of early-onset VAP. Appropriate patient selection for this procedure, however, remains elusive. Until the cost-effectiveness of endotracheal tubes with a subglottic suction port is established, their use will likely not become standard practice. The finding of lower rates of VAP with the use of this procedure does support the fact that VAP often arises from micro-aspiration of secretions around the cuff of the airway.

References
1. Rello J, et al. *Chest*. 2002;122:2115-2121.
2. Kollef MH. *Crit Care Med*. 2004;32:1396-1405.
3. Berra L, et al. *Crit Care Med*. 2004;32:2071-2078.
4. Siobal M, et al. *Respir Care*. 2001;46:1012-1018.
5. Shorr AF, O' Malley PG. *Chest*. 2001;119:228-235.

Closing the Books on Low-Dose Dopamine in the ICU

ABSTRACT & COMMENTARY

Synopsis: *This extensive meta-analysis of available randomized, controlled trials shows that low-dose dopamine offers transient improvements in renal physiology but no good evidence that it offers important clinical benefits to patients with or at risk for renal failure.*

Source: Friedrich JO, et al. *Ann Intern Med*. 2005;142: 510-524.

In the absence of definitive systematic reviews, and in the presence of evidence for continued widespread administration of low-dose dopamine infusions to critically ill patients for the purpose of preventing renal failure, Friedrich and colleagues performed an exhaustive review of the literature on this subject. They searched MEDLINE, EMBASE, CINAHL, the Cochrane Library, and other sources, in an attempt to identify acceptable clinical trials to use in a meta-analysis. Included were parallel-group randomized and quasi-randomized controlled trials of low-dose dopamine versus control. Friedrich et al examined each trial's methodology, outcomes, and adverse events.

After a comprehensive search, 61 trials, comprising data from 3359 randomized patients, were identified. Methodologic quality varied, but follow-up was largely complete. Meta-analyses using random-effects models showed that low-dose dopamine had a positive effect on urine output, increasing it by 24% (95% confidence interval [CI], 14%-35%) on the first day of infusion. Improvements in serum creatinine level (4% fall; with 95% CI, 1%-7%) and measured creatinine clearance (6% relative increase; 95% CI, 1%-11%) on day 1 were clinically insignificant. No significant effects on these variables could be detected on days 2 or 3 of therapy. Low-dose dopamine had no effect on mortality (relative risk, 0.96; 95% CI, 0.78%-1.19%), or on the need for dialysis or other renal replacement therapy (relative risk, 0.93; 95% CI, 0.76%-1.15%). There was also no evidence for an effect on adverse events (relative risk, 1.13; 95% CI, 0.90%-1.41%). Several statistical tests for heterogeneity, which would weaken the strength of the conclusion that the therapies were not different, failed to demonstrate it.

COMMENT BY DAVID J. PIERSON, MD

For more than 40 years, the concept that low-dose (or renal-dose) intravenous dopamine infusions increase urine flow and protect the kidney from damage during acute illness has exerted a pervasive influence on clinical medicine, including patient management in the ICU. Recent surveys in several countries demonstrate that low-dose dopamine is still very widely used in critical care. No doubt this use is abetted by the bedside observation, corroborated by the present meta-analysis, that initiating low-dose dopamine therapy improves urine output, at least in many patients. However, Friedrich et al found that the improvements in urine output were short lived, and any salutary effects on serum creatinine levels or creatinine clearance were small and only temporary. And most importantly, this rigorous meta-analysis—the most extensive examination of this topic to date—failed to find any evidence for a detectable effect of low-dose dopamine on patient-relevant outcomes.

A widely used therapy has a solid theoretical rationale and produces short-term improvements in physiologic end points, but evidence that it helps patients in any meaningful way is lacking. Does that sound familiar? It reminds me of the current state of our knowledge about prone positioning in acute lung injury and the acute respiratory distress syndrome (ARDS).[1] The same could be said for the administration of inhaled nitric oxide and its current spinoff, aerosolized prostacyclin. These interventions improve arterial PO_2 in many if not most patients with severe ARDS. The clinical trials have consistently demonstrated this physiologic improvement, and yet those same trials have been unable to demonstrate improvements in survival or other outcomes that the patient would care about.

This rigorously performed meta-analysis should close the books, finally, on low-dose dopamine to prevent or ameliorate renal failure in critically ill patients. It does not seem to hurt-except for its cost in material and human resources-but it does not help. We should stop using it. ■

Reference
1. Guerin C, et al. *JAMA*. 2004;292:2379-2387.

Special Feature

The Critically Ill Pregnant Patient: Chapter I

By Saadia R. Akhtar, MD, MSc

Care of the critically ill pregnant patient poses unique challenges. The normal physiology of a pregnant patient differs considerably from that of a non-pregnant patient and these differences may affect many aspects of routine care: resuscitation, mechanical ventilation, choice of drugs and use of diagnostic studies are some examples. Pregnancy may increase the risk of some life-threatening disorders (such as venous thromboembolic disease). In addition, there are some potentially serious diseases (such as eclampsia) that occur only during pregnancy. Although obstetric patients make up < 1% of ICU admissions, and ICU admissions are necessary for only about 0.5% of all pregnant women, the mortality for these patients can be as high as 20%.[1-4] Finally, the condition and care of the mother directly impact the survival and health of the fetus. For these reasons, it is essential that all personnel working in an ICU familiarize themselves with the critical care issues of pregnancy. A multidisciplinary approach to care of these patients, involving an obstetrician and a neonatologist, is imperative.

This essay will begin the discussion on management of the critically ill pregnant patient, which will be continued in a later issue of this newsletter. It will review the cardiovascular and pulmonary physiology of normal pregnancy and ways in which this may impact ICU management. It will address maternal resuscitation in the event of cardiorespiratory arrest and comment on some routine ICU issues such as choice of vasopressors, sedatives and antibiotics, and the safety of diagnostic studies during pregnancy.

Cardiovascular Physiology of Normal Pregnancy[5-6]

A variety of physiological changes are necessary in order to ensure adequate perfusion and oxygenation of the growing fetus as well as to continue to meet the needs of the mother. Blood flow to the uterus must increase 10-fold (up to 500-700 mL/min) during pregnancy. This is accomplished by an increase in blood volume as well as a rise in cardiac output. Blood volume expands by about 40-50% (or 2 L): the increase in plasma volume is proportionally higher than the change in red cell mass, resulting in the relative anemia of pregnancy. Total body water also increases and plasma oncotic pressure decreases: the latter is one of the factors that predisposes pregnant women to edema formation. Simultaneously, the cardiac output rises by up to 30-50% (even further increases occur during labor). Initially, this rise is due primarily to an increase in stroke volume; as pregnancy proceeds, the heart rate also goes up by about 10-15 beats per minute on average. Echocardiography demonstrates a definite increase in left ventricular mass.

Peripheral vasodilation begins early in pregnancy and results in a 20-30% reduction in systemic vascular resistance. This may be the stimulus for the rise in cardiac output. It is also one of the factors contributing to venous stasis and increased risk for venous thrombosis during pregnancy. Other typical hemodynamic changes include a 20-30% reduction in pulmonary vascular resistance, a 10-20% drop in diastolic blood pressure and a smaller decrease in systolic blood pressure.

These cardiovascular changes peak at about the end of the second trimester and though the return to normal is fairly rapid (hemodynamic changes begin to resolve within days to 2 weeks post-partum and return to pre-pregnancy levels by 6 months), it is not immediate. Following delivery then, there is a large increase in maternal blood volume and preload: for women with any significant cardiac disease or pulmonary hypertension, this may lead to acute decompensation.

Finally, unique to pregnancy is the phenomenon of aortocaval compression by the enlarging uterus when the patient is in the supine position. This begins to occur by about 20 weeks of gestation and can result in a 25% reduction in cardiac output. Additionally, up to 30% of women (usually in the second half of pregnancy) will exhibit the more severe symptoms of the supine hypotension syndrome with marked hypotension, bradycardia, and syncope while supine.[7] Thus it is important to place bed-bound pregnant patients in a left lateral tilt position. Note that caval compression also leads to increased venous stasis and is one of the factors predisposing pregnant women to thromboembolic disease.

In addition to usual ICU cardiopulmonary monitoring of the mother, continuous electronic fetal heart rate monitoring is essential in all circumstances. Non-reassuring readings (such as bradycardia, abnormal fetal heart rate variability, late decelerations or absence of appropriate spontaneous accelerations) should prompt further evaluation.

Pulmonary Physiology of Normal Pregnancy[5-6]

Pulmonary mechanics and gas exchange are altered

during normal pregnancy. The enlarging uterus pushes upward on the diaphragm and leads to a reduction in functional residual capacity (FRC) of up to 25%. Total lung capacity changes only slightly, by 0 to -4%. Other lung volumes are unaltered. Airway mucosal edema and hyperemia are observed but do not impact airflow rates. These airway mucosal changes do however lead to symptomatic rhinitis in 30% of pregnant women. They may also be an important reason for the relatively high failed intubation rates reported in obstetric patients. It is essential to keep this in mind and downsize endotracheal and naso- or oro-gastric tubes.

In order to accommodate the 15-20% rise in oxygen consumption and carbon dioxide production during pregnancy, maternal minute ventilation must increase considerably. A change of up to 40-50% above baseline is seen and leads to the familiar complaint of dyspnea during the latter half of pregnancy. This increase in minute ventilation is accomplished primarily by an increase in tidal volume which may be caused by progesterone's central respiratory stimulant effect. (Tachypnea is uncommon and, when present, is likely a sign of disease.) Interestingly, the resulting minute ventilation is beyond what is necessary to maintain neutrality. That is, a mild respiratory alkalosis and associated mild compensatory metabolic acidosis are found throughout pregnancy. Normal arterial blood gas values during pregnancy are: pH 7.40-7.47, pCO_2 28-32 mm Hg, pO_2 > 100 mm Hg, HCO_3 18-21 mEq/L. Due to the reduced FRC, mild hypoxemia and elevated alveolar-to-arterial PO_2 gradient [$P(A\text{-}a)O_2$] may develop in the supine position.[8] In addition, the low FRC in conjunction with baseline high maternal oxygen consumption leads to poor maternal oxygen reserve and makes pregnant patients prone to hypoxia with even short periods of apnea. Pre-oxygenation before sedation and intubation is thus particularly important for these patients.

When pregnant patients require mechanical ventilatory support, it is essential to adjust ventilator settings to target the *usual* arterial blood gas values described above.[9] Further hyperventilation leads to uterine vasoconstriction, reduced placental and fetal perfusion and fetal distress. Similarly, although an arterial PCO_2 up to 55-60 mm Hg appears to be tolerated well, more severe hypoventilation and hypercapnia clearly result in fetal acidemia and distress. The role of bicarbonate infusions for acidemia in pregnant patients is undefined. Animal studies suggest that bicarbonate does not cross the placenta but carbon dioxide does, thus implying that bicarbonate infusion may worsen fetal acidosis; it is unclear whether this finding holds for humans.[10] In regard to airway pressures, while maternal plateau pressures may be 'falsely' elevated due to increased abdominal pressure and decreased chest compliance during normal pregnancy, there is no evidence to support targeting or accepting higher plateau pressures than for non-pregnant patients. Thus, although there are no specific studies of low-tidal-volume ventilation or management of acute lung injury in pregnant patients, experts suggest applying this strategy for usual indications but limiting permissive hypercapnia to PCO_2 no higher than 55-60 mm Hg.[9]

Maternal Resuscitation[9,11]

Fetal oxygenation is related to maternal oxygen delivery, placental function, and fetal extraction. Maternal oxygen delivery is determined by blood flow to the uterus and by the oxygen content of that blood: maternal anemia, hypoxemia, hypotension or uterine vasoconstriction will all impair fetal oxygenation. If necessary, blood flow to critical maternal organs will be maintained at the expense of the fetus. Thus, for a critically ill pregnant patient, rapid support and correction of maternal blood pressures and gas exchange are essential for fetal viability.[6]

Usual Advanced Cardiac Life Support (ACLS) guidelines apply for pregnant patients who experience cardiorespiratory arrest. As fetal oxygenation depends on maternal oxygenation and the latter has poor reserve, establishing an airway quickly is essential. As noted above, airway edema and hyperemia should prompt use of smaller-than-usual artificial airways. Manual lateral displacement of the uterus or positioning of the patient in a left lateral tilt position are essential to minimize aortocaval compression. Fetal monitoring is reasonable during resuscitation, although the findings generally correlate closely with maternal condition. It is essential, if fetal monitors are in place, to remove or disconnect them prior to defibrillation or cardioversion.

If initial efforts appear to be failing after 4 to 5 minutes of resuscitation and the patient is at or beyond about 24 weeks of gestation, emergent Cesarean section is recommended. ACLS interventions should be continued during delivery. Delivery may ease resuscitation of the mother by increasing preload and cardiac output and facilitating maternal ventilation. Good fetal neurological outcome is most likely if delivery occurs within 4 to 5 minutes of arrest but has been reported after as much as 45 minutes after maternal arrest (with continued aggressive cardiopulmonary resuscitation).[12]

Choice of Medications During Pregnancy[6,13-16]

The distribution and clearance of many drugs are

greatly altered by the normal physiological changes of pregnancy. (These include the increases in total body water and plasma volume as discussed above. They also include a decrease in plasma protein concentration, slowing of gastric emptying and changes in renal perfusion and hepatic perfusion and metabolism.) These changes in pharmacokinetics may place the mother at increased risk of drug toxicity or 'under-dosing.' Furthermore, almost all medications cross the placenta to some degree and may adversely affect the fetus. Thus, it is essential to be vigilant in the choice, dosing, and monitoring of medications during pregnancy.

The Federal Food and Drug Administration (FDA) classifies medications for use during pregnancy into 5 categories: A (controlled human studies demonstrate safety of the drug during pregnancy); B (presumed safe based on animal studies), C (*see below*), D (clear evidence of some risk to the fetus); or X (absolutely contraindicated in pregnancy). The majority of drugs (66% of those in the *Physicians' Desk Reference*) are classified as category C (risk cannot be ruled out: human studies are lacking, and animal studies are either positive for fetal risk or lacking).[17] Most vasopressors and sedatives used in the ICU fall into risk category C.

Untreated maternal hypotension is obviously detrimental to the mother and the fetus. However, vasopressors have the potential to constrict uterine vessels and reduce blood flow to the placenta and fetus despite improving maternal blood pressures. There is little literature on choice of vasopressors for pregnant patients with persistent shock. Most available studies address transient use of vasopressors for hypotension associated with spinal anesthesia or in the operative setting. These along with animal and in vitro studies suggest that ephedrine is least likely to cause uterine vasoconstriction and this remains the recommended first line agent for pregnant patients (again, particularly during obstetric anesthesia). Phenylephrine and metaraminol are also favored for short-term use. Norephinephrine is suggested for persistent shock in pregnant patients in the ICU setting but there are no specific data for or against this.

With respect to sedatives and paralytics, the only agents clearly shown to be teratogenic are benzodiazepines. When administered in the first trimester, benzodiazepines increase the risk of cleft deformities. There is weak evidence that they may also be associated with developmental delays. The primary risk of other sedatives (narcotics, propofol) or the paralytics is that of fetal and neonatal depression. When these agents are used, it is important to remember that the newborn infant may need cardiorespiratory support for a period of time following delivery.

Finally, antimicrobial choice should be guided first and foremost by what is appropriate treatment for the suspected source of infection or sepsis. When possible, drugs from the penicillin, cephalosporin or macrolide classes should be chosen because extensive experience has demonstrated their safety during pregnancy. One exception in the macrolide class is clarithromycin, which has adversely affected fetal development in animal studies. Quinolones are also FDA pregnancy class C due to arthropathy noted in animal studies of ciprofloxacin. Aminoglycosides may cause fetal ototoxicity but are otherwise safe. Sulfonamides alone are acceptable but trimethoprim does increase the risk of congenital malformations with first trimester exposure. The antifungal of choice during pregnancy is amphotericin B. Lastly, although the anti-herpetic agents are safe to use, those antivirals targeting influenza are not tested or approved in pregnancy.

Diagnostic Studies and Fetal Radiation Exposure[6, 18-19]

Diagnostic studies crucial for care of the critically ill pregnant patient should never be delayed or deferred: maternal survival and good health are essential for good fetal outcomes. With that in mind, it is reassuring that estimated fetal radiation exposure for most diagnostic studies is low and acceptable. With the appropriate use of an abdominal lead shield, the fetal radiation exposure (in rads) for common studies is: PA and lateral chest X-ray $\leq$ 0.001-0.008, ventilation-perfusion scan $<$ 0.031, chest CT scan with pulmonary embolism protocol $<$ 0.0131 and pulmonary angiogram 0.221-0.405. Not surprisingly, abdominal and pelvic CT scans are associated with the highest fetal radiation exposures, of up to 5 rads. Teratogenicity does not appear to occur until the total fetal radiation exposure over the course of gestation exceeds 10 rads. Cumulative exposure to $<$ 5 rads increases the risk of childhood leukemia from 1/2800 to 2/2800 but is not teratogenic. (To put this into perspective, these cancer rates are less than the rates of spontaneous congenital malformations.) Thus, in general, it is quite safe to proceed with selected and clinically indicated radiological studies in pregnant patients.

Summary

'Routine' ICU care must be tailored to support the unique physiology and meet the special needs of the pregnant patient. An understanding of the normal cardiopulmonary physiology of pregnancy provides the foundation on which to develop further expertise and comfort in the management of this patient population.

This essay has reviewed these normal changes and discussed mechanical ventilation, resuscitation, usual ICU medications and diagnostic studies during pregnancy. Other aspects of the critical care of pregnancy will be addressed in future reports. ■

References

1. Kilpatrick SJ, Matthay MA. *Chest*. 1992;101: 1407-1412.
2. Lapinsky SE, et al. *Can J Anaesth*. 1997;44:325-329.
3. Mahutte NG, et al. *Obstet Gynecol*. 1999;94:263-266.
4. Hazelgrove JF, et al. *Crit Care Med*. 2001;29:770-775.
5. Chesnutt AN. *Crit Care Clin*. 2004;20:609-615.
6. Lapinsky SE, et al. *Am J Respir Crit Care Med.* 1995; 152:427-455.
7. Kinsella SM, Lohmann G. *Obstet Gynecol*. 1994;83: 774-788.
8. Garcia-Rio F, et al. *Eur Respir J*. 1997;10:2371-2375.
9. Campbell LA, Klocke RA. *Am J Respir Crit Care Med*. 2001;163:1051-1054.
10. Ron-El R, et al. *Acta Obstet Gynecol Scand*. 1980;59: 225-230.
11. The American Heart Association in collaboration with the International Liaison Committee on Resuscitation. Guidelines 2000 for Cardiopulmonary Resuscitation and Emergency Cardiovascular Care. *Circulation*. 2000;102 (8 Suppl):I229-I252.
12. Yildirim C, et al. *Yonsei Med J*. 2004;45:561-563.
13. Webster WS, Freeman JA. *Expert Opin Pharmacother*. 2003;4:949-961.
14. Niebyl JR. *Am J Perinatol*. 2003;20:405-414.
15. Lee A, et al. *Anesth Analg*. 2002;94:920-926.
16. Chestnut DH, et al. *Anesthesiology*. 1988;68:363-366.
17. Doering PL, et al. *Am J Obstet Gynecol*. 2002;187: 333-339.
18. Toppenberg KS, et al. *Am Fam Physician*. 1999;59: 1813-1818.
19. Winer-Muram HT, et al. *Radiology*. 2002;224:487-492.

CME Questions

9. Which of the following were associated with increased mortality in the study relating first physician visits to ICU outcomes?
a. Higher $APACHE_0$, score
b. Older age
c. Mechanical ventilation on arrival
d. Longer time until seen by a physician
e. All of the above

10. Each 1-hour delay in initially seeing the patient after ICU admission was associated with what percentage increase in mortality?
a. 1.6
b. 4.4
c. 6.9
d. 12.0
e. 27.4

11. Which of the following is *not* decreased with the use of an endotracheal tube that provides subglottic aspiration of secretions?
a. Incidence of ventilator-associated pneumonia
b. Micro-aspiration around the cuff
c. Ventilator days
d. ICU days
e. Cost of the endotracheal tube

12. Which of the following is the most important mechanism in the development of pneumonia in patients who require ventilatory support?
a. Hematogenous dissemination from the gut
b. Use of sterile technique at the time of intubation
c. Aerosolization of bacteria contaminating the ventilator circuit
d. Micro-aspiration of subglottic secretions around the cuff
e. None of the above

13. The standardized mortality ratio is determined by dividing observed mortality by which of the following?
a. Mortality in the population of the same age group
b. Mortality in all ICUs for that age group
c. Predicted mortality based on disease severity scoring system prediction models
d. Predicted mortality for the same age group
e. None of the above

Answers: 9 (e); 10 (a); 11 (e); 12 (d); 13 (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: **The Critically Ill Pregnant Patient, Part II**

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.

Is Nesiritide Associated with a Higher Death Rate?

Nesiritide, Scios' intravenous recombinant form of human B-type naturetic peptide, has been widely used for the treatment of congestive heart failure in hospitalized patients. On Scios' website, nesiritide is touted as the "best-selling IV cardiovascular drug ever brought to market." All that may change with the publication of a new study that suggests that patients with acutely decompensated heart failure (ADHF) treated with nesiritide have a higher death rate at 30 days compared with patients who are not treated with the drug. The study was a pooled analysis of 12 randomized, controlled trials, of which 3 met all inclusion criteria. In those 3 trials, 485 patients with ADHF were randomized to nesiritide and 377 to control therapy which was noninotrope-based treatment. Thirty-day death rate was higher among the nesiritide group (7.2% vs 4.0% for placebo, 1.74 risk ratio; 95% CI [0.97-3.12]; *P* = .059). The authors conclude that therapy with nesiritide may be associated with increased risk of death after treatment for acutely decompensated heart failure, and suggest that an adequately powered, controlled trial should be undertaken (*JAMA*. 2005;293:1900-1905). This follows an earlier study that suggested nesiritide may worsen in renal function in patients with ADHF. In that study, which was also a pool analysis from 5 randomized studies, 1269 patients with ADHF were reviewed. Nesiritide was associated with a significantly increased risk of worsening renal function, compared with noninotrope control therapy (RR, 1.52; 95% CI, 1.16-2.0; *P* = .003) or any control therapy, including noninotrope and inotrope based therapies (RR, 1.54; 95% CI, 1.19-1.98 ; *P* = .001). Even low-dose nesiritide was found to worsen renal function. The authors conclude that nesiritide significantly increases the risk of worsening renal function in patients with ADHF, but suggests further investigation to determine the prognostic importance of this finding (*Circulation*. 2005;111:1487-1491).

Stopping Aspirin Before Surgery

A new study suggests that stopping aspirin 5 days prior to surgery is optimal. Researchers from Ireland recruited 51 volunteers who were randomly assigned to 3 groups: placebo, aspirin 75 mg per day, or aspirin 300 mg per day. Utilizing template bleeding times and specific platelet function testing, all bleeding times normalized within 96 hours and all platelet function test normalized within 144 hours after discontinuing aspirin. By day 6, there was no demonstrable hemostatic defect in any of the volunteers. There was also no difference between the 75 mg or 300 mg dose of aspirin. The authors conclude the data sup-

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. 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. Questions and comments, call: (404) 262-5416. E-mail: leslie.hamlin@thomson.com.

ports withholding aspirin for 5 days with elective surgery been performed on the sixth day (*J Am Coll Surg*. 2005;200:564-573). This study is important because of recent data that cardiovascular events are much more likely to occur in patients who had recently withdrawn from aspirin—with the peak of events occurring at 10 days (*Pharmacology Watch*. March, 2005). Safely stopping aspirin for 5 days prior surgery, with reinstitution as soon as possible after surgery, makes good clinical sense.

The Sponge Returns

The Today Sponge contraceptive device is returning to the US market this summer. Last marketed more than 10 years ago, the sponge was removed from the market because of manufacturing problems. It is being brought back by Allendale pharmaceuticals, whose manufacturing facility met FDA standards. The sponge, which was made infamous by a memorable *Seinfeld* episode, is an over-the-counter, round, disposable, soft sponge that is impregnated with spermicide. It is inserted vaginally, and can be kept in place for 24 hours and for multiple sexual encounters. When it was taken off the market in 1994, the sponge was the most popular over-the-counter female contraceptive available, with 250 million of them sold in the 11 years it was available.

Preventing Metabolic Syndrome

Metformin and intensive lifestyle intervention both help prevent metabolic syndrome in patients who have impaired glucose intolerance. In a study derived from the Diabetes Prevention Program, 1711 patients with impaired glucose tolerance (defined by World Health Organization criteria plus fasting glucose level < 95) were evaluated. More than half the participants (53%) had metabolic syndrome at the baseline. In patients who did not have metabolic syndrome, metformin 850 mg twice daily or intensive lifestyle intervention designed to achieve and maintain 7% weight loss and 150 minutes of exercise per week were both effective in preventing metabolic syndrome. Lifestyle intervention was the more effective intervention with a 41% reduction in the incidence of metabolic syndrome ($P < .001$) while metformin reduced the incidence by 17% ($P = .03$) compared to placebo. Three-year cumulative incidences of metabolic syndrome were 51%, 45%, and 34% in the placebo, metformin, and lifestyle groups, respectively. The authors conclude that both lifestyle intervention and metformin are effective in reducing the development of metabolic syndrome in patients with glucose intolerance, although the impact of lifestyle intervention was more marked than that of metformin (*Ann Intern Med*. 2005;142:611-619).

FDA Actions

The FDA has approved exenatide for the treatment of type 2 diabetes in patients who have not responded to other treatments. The drug was derived from lizard saliva, and represents a new class of antidiabetic agents known as incretin mimetics—which mimic the effect of GLP-1, a naturally occurring incretin hormone found in human gut. Exanatide normalizes postprandial physiology by stimulating beta cells to secrete insulin in glucose dependent fashion. In alpha cells, the drug normalizes the pathologic hypersecretion of glucagon in a glucose dependent fashion. It also slows gastric emptying and improves satiety, all which serve to reduce postprandial hyperglycemia. There is some evidence that the drug may also attenuates weight gain seen with other hypoglycemic agents and may even be associated with weight loss. The drug will be marketed by Eli Lilly and Amylin Pharmaceuticals under the trade name Byetta.

Ropinirole (Requip) has been approved for the treatment of moderate-to-severe restless leg syndrome (RLS), the first US medication to be approved for this indication. The drug has been available for the treatment of Parkinson's disease since 1997. The approval was based on 3 randomized, double-blind, placebo-controlled trials in adults diagnosed with moderate to severe RLS. All 3 studies demonstrated a statistically significant improvement in the treatment group receiving ropinirole. Side effects include nausea, extreme drowsiness, and dizziness, and the drug will be labeled to warning about the possibility of falling asleep while engaged in activities of daily living including driving. GlaxoSmithKline is enthusiastic about the prospect of treating the estimated 1 out of 10 adults in this country with restless leg syndrome, the most common cause of insomnia. ■