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INSIDE

Should Patients with Acute Coronary Syndromes Receive Blood Transfusions?

ABSTRACT & COMMENTARY

Synopsis: *Post hoc analysis of 3 large multicenter trials of patients with acute coronary syndromes demonstrates a strong association between transfusion and mortality.*

Source: Rao SV, et al. *JAMA*. 2004;292(13):1555-1562.

RAO AND ASSOCIATES AIMED TO DETERMINE THE ASSOCIATION between blood transfusion and mortality in patients with acute coronary syndromes (ACS), with attention to presence of bleeding and/or anemia. The analysis was based on data from 3 previously published large multicenter randomized controlled trials of ACS treatment. Patients with complete data on bleeding occurrence and transfusion were included. Only episodes of moderate or severe bleeding were considered in this analysis. Usual demographics, history and laboratory data were available. The primary outcome was 30-day all-cause mortality. The statistical approach was sophisticated and thorough. Five models were created: 2 stepwise logistic regression models that identified predictors of bleeding or transfusion and derived propensity scores for these outcomes; Cox proportional hazards model with transfusion as a time-dependent covariate; landmark analysis, using transfusion as a time-fixed covariate to analyze 24-hour units for the first 7 days; multivariate logistic regression model examining interaction between nadir hematocrit (Hct) and the association of death and transfusion.

Data from 24,112 hospitalized patients were analyzed: 2401 (10%) of these patients received at least 1 transfusion. There were several differences between patients who received blood and those who did not: for instance, the former were more likely to be older (median age, 69 vs 64 years), female, black and have comorbidities. There was a significantly greater risk of death at 30 days in patients receiving transfusion. This association persisted after adjusting for bleeding and transfusion propensity, baseline characteristics and nadir Hct: hazard ratio for death in patients receiving transfusion was 3.94 (95% CI, 3.26-4.75). Similarly, landmark analysis adjusting for baseline characteristics and nadir Hct supported a trend towards increased mortali-

ty in patients receiving transfusion but this was not statistically significant. Finally, there was no association between death and transfusion in patients with nadir Hct 25% or less but a significantly increased risk at nadir Hct > 25%. Analyses were repeated after excluding patients who underwent coronary artery bypass grafting (CABG) and results were unchanged.

Rao et al conclude that blood transfusion in patients with ACS is associated with increased 30-day mortality. They suggest that "a hematocrit as low as 25% may be tolerated without blood transfusion in otherwise stable patients with ischemic heart disease." They make note of conflicting observational data in the literature and the limitations of their post hoc analysis, summarizing that "our study . . . should not be considered as evidence to change practice; rather, it should be considered as evidence that caution is warranted when making transfusion decisions."

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COMMENT BY SAADIA R. AKHTAR, MD, MSC

Rao and colleagues have produced a thoughtful analysis that further challenges our usual transfusion practices. Traditional teaching has been that blood transfusion to maintain Hct at least 30% or hemoglobin (Hgb) 10g/dL or more may improve oxygen delivery and thus be beneficial for critically ill patients. More recently, risks of transfusion and safety of lower transfusion thresholds in general ICU populations have been well-documented.[1,2] It is less clear whether these lower thresholds should apply to patients with ACS. Two large studies have previously tried to address this issue.[3,4]

The first was a post-hoc subset analysis of the Transfusion Requirements in Critical Care Trial (TRICC). TRICC was the randomized controlled study demonstrating safety of restrictive (threshold Hgb, 7 g/dL) transfusion strategies.[1] The subset consisted of 357 patients with cardiovascular disease as a primary or secondary diagnosis or as a functionally limiting comorbidity. Though 70% of these patients had a history of coronary artery disease, only about 25% had a primary admitting diagnosis of ischemic heart disease or cardiac arrest. Others' diagnoses ranged from pulmonary embolism to hypertensive urgency. The study found no difference in 30-day mortality of patients with cardiovascular disease and restrictive vs liberal transfusion strategies.[3]

In contrast, the work of Wu and colleagues[4] suggested lower short-term mortality with blood transfusion in specific populations. Their retrospective Medicare database review examined the association between transfusion and mortality in patients at least 65 years age with acute myocardial infarction (AMI). 78,974 patients were identified and categorized by admission Hct. Patients with bleeding complications and those undergoing CABG were excluded. 3680 patients (4.7%) received transfusions. Lower admission Hct was associated with higher 30-day mortality. Furthermore, transfusion in patients with admission Hct 33% or less was associated with reduced 30-day mortality: adjusted odds ratio for death 0.69 (95% CI, 0.53-0.89) in patients with admission Hct 30.1 to 33%.[4]

Differences in patient populations (age and primary diagnoses), methods for patient identification (randomized trials with a different primary outcome variable vs database screening), exclusion criteria (bleeding complications) and statistical analyses (factors included in multivariate models and approach to addressing survivor bias) are some of the reasons for the dissimilar findings between the 2 prior studies and

that of Rao et al. Most of all, it is essential to remember that all 3 reports are retrospective, secondary analyses. They are quite valuable for hypothesis-generation but do not in themselves provide maximally robust evidence to guide practice. Recent medical history provides several examples (such as hormone replacement therapy for post-menopausal women) of post hoc analyses and observational studies having "led us astray" until well-designed, adequately-powered, randomized prospective trials provided more clear evidence. It is apparent that such a trial is justified to answer the question of whether and when to transfuse patients with ACS.

For now, we must implement the practice that is supported by good evidence: that of transfusion threshold as defined by TRICC (Hgb at least 7 g/dL) for general medical-surgical critically ill patients. I strongly suggest considering Rao et al's recommendation, to lower transfusion threshold (perhaps to Hct 25%) in otherwise stable patients with ACS. In reality, each of us must use the information at hand in combination with our best clinical experience and judgment to define this threshold until further data are available. ■

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Has ICU Transfusion Practice Changed in the Past Decade?

ABSTRACT & COMMENTARY

Synopsis: *This multicenter prospective observational study reveals that transfusion practice in the critically ill has not changed in the past decade. 44% of ICU patients receive transfusions, and transfusions continue to be associated with worse clinical outcomes.*

Source: Corwin HL, et al. *Crit Care Med*. 2004;32(1): 39-52.

In the past 2 decades, risks of red blood cell (RBC) transfusion in the critically ill have begun to be defined more clearly and the safety of lower transfusion thresholds in this population has been well documented.[1-3] The effect of these findings on current clinical practice in the United States has not been described previously. Corwin and colleagues aimed to quantify current RBC transfusion practice in critically ill patients. A secondary endpoint was to describe outcomes associated with anemia and transfusion in this cohort.

A multicenter prospective observational cohort study was conducted from August 2000 to April 2001 at US ICUs. Adult patients with anticipated ICU length of stay (LOS) > 48 hours were eligible. Patients admitted to pediatric, cardiac, cardiothoracic and neurology ICUs were excluded. Patients were also excluded for renal failure on dialysis or if they were prohibited from receiving transfusions. Usual demographics, admitting diagnoses, severity of illness scores, baseline, weekly and pre-transfusion hemoglobin (Hgb) levels, and number and age of RBC transfusions were recorded for all patients. Studied outcomes were mortality, ICU and hospital LOS, ventilator days and a variety of clinical complications. Patients were followed for 30 days or until death or hospital discharge (if these occurred within 30 days). Standard statistical analyses were used.

In this study, 284 ICUs at 213 (70% urban) hospitals participated. There was a fairly equal distribution of medical, surgical and combined units. A total of 4892 patients were enrolled. Baseline Hgb was 11.0 ± 2.4 g/dL and was not predictive of poorer outcomes: nadir Hgb of < 9 g/dL though was associated with increased mortality and LOS. 44% of patients received RBC transfusion in the ICU with mean 4.6 ± 4.9 units. About another 5% received transfusions in their post-ICU hospital stay. The most common reason given for transfusion was low Hgb: mean pre-transfusion Hgb was 8.6 ± 1.7 g/dL. This value did not differ for transfusions given post-ICU or across most hospital characteristics: however, the threshold for transfusion was minimally but statistically significantly lower in closed vs open ICUs, medical vs surgical or combined ICUs and small (< 12 beds) vs larger ICUs.

Transfusion was less likely to be given in patients with lower severity of illness. It was not related to patient age or to most co-morbidities (except anemia, hematologic disease and gastrointestinal bleeding) but was associated with increased ICU and hospital LOS. Transfusion reactions occurred 4% of the time. Age of RBC transfused was not associated with any clinical outcome. Finally, even after multivariate regression including propensity scores for transfusion, RBC transfusion was associated with increased risk of death.

COMMENT BY SAADIA R. AKHTAR, MD, MSC

Corwin et al have produced a thought-provoking, well-conducted observational study that focuses the

critical care community's attention once again on the topic of RBC transfusion. Their finding that transfusions are associated with worse clinical outcomes is consistent with prior data. The observation that a specific nadir Hgb has the same association is intriguing and deserves further study. But, to me, the most interesting and important result here is that transfusion practice has not changed despite developing data about risks of transfusion and quite robust data demonstrating the safety of lower transfusion thresholds.[1-3]

Is this a false or biased finding from a flawed study? I do not believe so. The study is well designed. It was conducted at multiple centers of varying characteristics all across the United States and carried out over several months: the results should be generalizeable. There is reasonably good evidence that we should have higher transfusion thresholds for patients with cardiac ischemia. For this reason, patients admitted to cardiac or cardiothoracic units were excluded from this study. Twelve percent (12%) of study patients did have an admitting diagnosis that was categorized as cardiovascular and some had co-morbid cardiac disease. Thus there is a possibility that this may have had an effect on the results, but it would be small. The majority of ICUs in the study (71%) were open units. Perhaps transfusion practice in closed units, by physicians specifically trained in critical care, is more conservative. Corwin et al found no difference between closed and open units in their study. The number of closed units sampled may have been too low to detect a small difference but it is at least clear that a large difference does not exist.

I suspect that the reasons transfusion rates have not changed over time are the same reasons it has been difficult to incorporate many new data and standards of care into practice. For instance, since Semmelweis's observations that the incidence of puerperal fever was reduced by hand washing, we have known that hand hygiene is a simple and effective way to prevent transmission of contagious diseases. Yet adherence with hand washing remains at best 50-60%.[4] Aspirin prescription post-myocardial infarction is at similarly low rates despite its well-established mortality benefit.[5] In critical care, use of recommended interventions such as elevation of head of bed for ventilator-associated pneumonia prevention or low tidal volume ventilation for acute lung injury is also suboptimal.[6,7] Despite the growth of clinical research and enthusiasm about evidence-based medicine, it is clear that actually translating evidence into practice change is quite challenging.

Many investigators are now studying this very issue by trying to identify the barriers to implementation of new standards and guidelines and developing approaches to overcoming them. One potential barrier is not believing the data. It is possible that the critical care community is not convinced that a lower transfusion threshold (< 7 g/dL) is safe or that transfusion has considerable risks (of increased infection and risk of death) aside from immediate reactions. More and more supportive evidence is accumulating and may convince practitioners over time. The greater barriers may be not being aware of the data or not understanding how to begin to implement it. Increased efforts to disseminate information and educate care providers are necessary: employing the help of recognized local leaders and teachers in these efforts has been shown to be quite effective. For instance, a practice taught, endorsed and carried out by the director of the ICU may lead to change. Extending this further to develop and disseminate specific local guidelines/protocols is helpful in changing practice. This must, however, be combined with continuous updating and follow-up to achieve consistent compliance. Interestingly, only 19% of hospitals in this study had a transfusion protocol in place. Although the authors did not find a significant difference in practice associated with having a protocol, they did not obtain information about what the protocols recommended. Thus it is difficult to make conclusions about the effectiveness of protocols. Finally, concerns about potential risks or costs of a new practice may be another potential barrier. Education as well as formal audits and cost analyses can help to allay such concerns.[8]

I expect that Corwin et al's report will encourage us to strive to further understand the impact of RBC transfusions and its underlying mechanisms. I hope that it also pushes us to focus more on incorporating new evidence into our practices. ■

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Special Feature

Brain Natriuretic Peptide in the ICU

By Francisco Baigorri, MD

Brain natriuretic peptide (BNP), also called B-type natriuretic peptide, is mainly secreted by the cardiac ventricles during increased ventricular wall stress. BNP plasma concentration provides important information on the prognosis in patients with heart failure, myocardial infarction, and acute coronary syndromes without ST-segment elevation. Moreover, used in conjunction with other clinical information, rapid measurement of BNP in the emergency department improves the evaluation and treatment of patients with acute dyspnea. Added to that, recent data suggest that BNP concentration may be increased in a variety of critically ill patients and that it appears to be associated with poor outcome of sepsis. The objective of this essay is to briefly review currently available information about the usefulness of BNP measurement in the evaluation and treatment of critically ill patients.

Pathophysiology of BNP[1,2]

BNP is a member of a family of structurally related hormones that seem to play an important role in the defense against excess salt and water retention. This natriuretic peptide family essentially consists of three peptides: atrial natriuretic peptide, BNP, and C-type natriuretic peptide. The physiologic effects of the natriuretic peptides include natriuresis and diuresis, aldosterone antagonism, vasorelaxation, and reduction of cardiac preload. Atrial natriuretic peptide and BNP seem also able to decrease the sympathetic outflow and inhibit vasopressin release.

Atrial natriuretic peptide was the first natriuretic peptide ever discovered and it is primarily produced in cardiac atria. Increased intravascular volume and increased atrial wall tension are the predominant stimulus, along with hormones and neurotransmitters such as endothelin or cathecolamines. C-type natriuretic peptide is found in endothelial and vascular smooth muscle cells and throughout the central nervous system. As for BNP, the name was given because it was first identified in extracts of porcine brain. However, this 32-amino acid peptide is mainly secreted in the ventricle during increased ventricular wall stress. It seems that gene expression and ventricular secretion of BNP occur more rapidly than those of atrial natriuretic peptide in an acute overload, indicating that the characteristics of the BNP gene expression are suitable for its possible role as an "emergency" cardiac hormone against ventricular overload.[3]

After being synthesized in the ventricle, the precursor of BNP (pro-BNP) is cleaved by a protease into BNP and N-Terminal-proBNP (the biologically inactive amino portion of pro-BNP). Three kinds of receptors have been described for natriuretic peptides: A, B, and C. The first 2 (members of the guanylyl cyclase receptor family) seem to mediate the peptides' biological actions, while the third one is a clearance receptor. Natriuretic peptide removal from the circulation is also achieved through the enzyme endopeptidase.

The exact mechanism that regulates BNP production is unknown but cardiac wall tension and dilation play important parts. Therefore, intense exercise moderately raises BNP plasma level, while this increment is more pronounced in patients with left ventricular hypertrophy or heart failure. BNP plasma concentration also rises in pulmonary hypertension and in non-cardiac disorders associated with excess of fluid volume such as renal failure, liver cirrhosis with ascites, and primary aldosteronism. It has also been observed that BNP plasma concentration can be influenced by other non-cardiac disorders, as well as by drugs that inhibit its degradation (*see Table 1*).

Considering these factors, BNP concentrations obtained from whole blood samples seem to be useful in the diagnosis of congestive heart failure (CHF) and in staging the severity of this disease. It has been shown that circulating BNP concentrations determined by a rapid fluorescence immunoassay increased with CHF severity, as determined by the NYHA classification system (*see Figure 1*), but were only statistically significant ($P < .001$) between individuals with and without CHF.[4] With the use of a decision threshold of 100 pg/mL, the assay demonstrated 82% sensitivity and 99% specificity for distinguishing control patients and patients with CHF. This threshold has been used to improve evaluation and treatment of patients with acute dyspnea in the emergency department,[5] reducing the time to discharge and the total cost of treatment.[6]

BNP also increases after ST-elevation myocardial infarction. The time course of the plasma BNP level could be divided into two patterns: a monophasic pattern with one peak at about 16 hours after admission and a biphasic pattern with 2 peaks at about 16 hours and 5 days after admission (*see Figure 2*).[7] There were significantly more patients with anterior infarction, congestive heart failure, higher level of maximal creatine

Table 1

Non-Cardiac Disorders that Can Produce an Increment of BNP Plasma Levels[1]

- Excess of fluid volume
- Renal failure
- Liver cirrhosis with ascites
- Primary hyperaldosteronism
- Inappropriate BNP production by tumors
- hydoid disorders
- Increase of circulating glucocorticoids
- Hypoxia

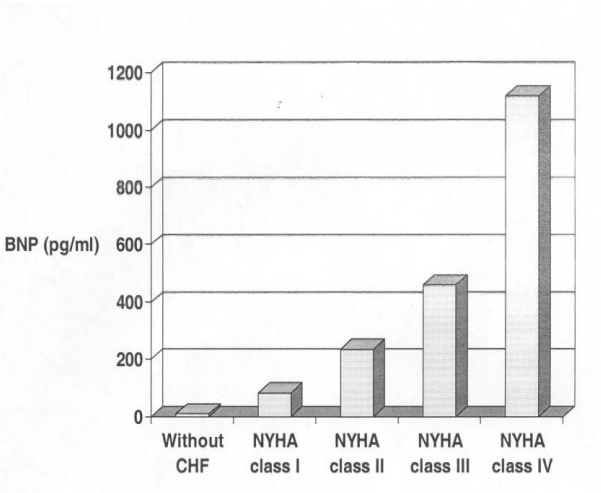
kinase-MB isoenzyme, and lower left ventricular ejection fraction in the biphasic group than in the monophasic group. This suggests that high BNP concentrations in the days following an acute myocardial infarction may predict a higher risk of depressed ventricular function. On the other hand, the initial rapid increase in BNP level suggests that the synthesis and production of BNP may be related to myocardial necrosis, local mechanical stress, or both, and not only to ventricular dysfunction.

Moreover, it has been shown that a single measurement of BNP, obtained in the first few days after the onset of ischemic symptoms, provides predictive information for use in risk stratification across the spectrum of acute coronary syndromes (myocardial infarction with ST-segment elevation, myocardial infarction without ST-segment elevation, and unstable angina).[8] Patients with a BNP level above 80 pg/mL were significantly more likely to die, have a new or recurrent myocardial infarction, or have new or progressive heart failure than those with a level of 80 pg/mL or less. After adjustment for other independent predictors of the long-term risk of death, a BNP level of more than 80 pg/mL remained significantly associated with an increased 10-month mortality rate. This association between BNP and the long-term risk of death was independent of the presence or absence of clinical evidence of heart failure, as well as renal function, the troponin I level, electrocardiographic changes, and other known predictors of the risk of death in patients with acute coronary syndromes.

Taken together, these findings suggest that myocardial ischemia augments the synthesis and release of BNP, even in the absence of myocardial necrosis or preexisting left ventricular dysfunction. Reversible ischemia may transiently increase left ventricular wall stress, which may be sufficient to cause an elevation in B-type natriuretic peptide levels.

Figure 1

Circulating BNP Concentrations According to the Severity of CHF



Source: *Wieczorek SJ, et al. Am Heart J. 2002;144:834-839.*

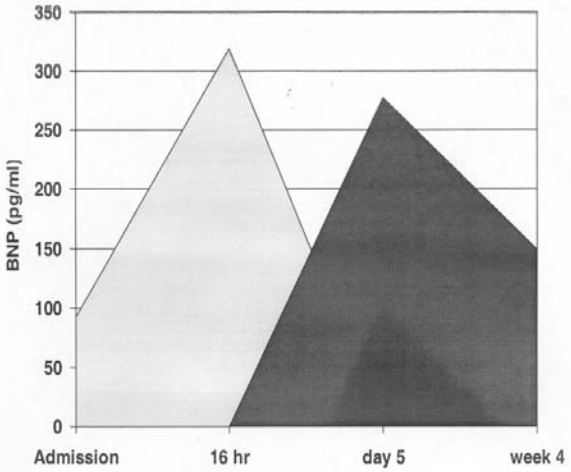
BNP in ICU Patients

There are data showing that concentrations of atrial natriuretic peptide and BNP are markedly increased in many patients on a surgical intensive care unit (ICU).[9] The largest BNP concentrations were observed in patients who underwent cardiac surgical procedures and also in patients with subarachnoid hemorrhage, a phenomenon previously described.[10] Anyway, it has been observed that, in a combined medical and surgical ICU population, patients with cardiac dysfunction had a significantly higher level of BNP when compared to the non-cardiac dysfunction group: 516 ± 385 pg/mL (n = 26) vs 67 ± 89 pg/mL (n = 58) ($P < 0.0001$).[11] A BNP cut-off value at 144 pg/mL exhibited a 92% sensitivity, 86% specificity and 96% negative predictive value. A further aspect is whether high plasma BNP levels are able to predict high pulmonary wedge pressure. A BNP cut-off value > 300 pg/mL also has high sensitivity for pulmonary capillary wedge pressure > 15 mm Hg but the specificity was lower when tested in a heterogeneous population of critically ill patients.[12]

A broad array of conditions associated with tissue inflammation and metabolic stress may be associated with reversible myocardial dysfunction.[13] It may occur in up to 40% of cases of sepsis. This brings us to the question of whether BNP could reflect left ventricular dysfunction in this kind of patients. BNP increases significantly in patients with septic shock and BNP level

Figure 2

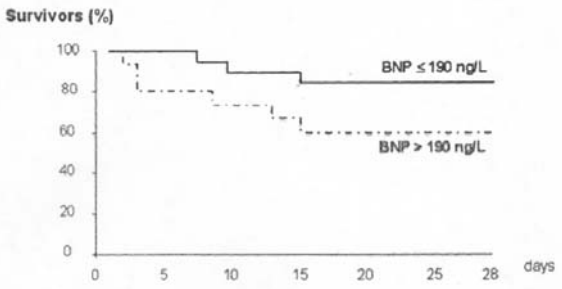
Time Course of the Plasma BNP Level in Patients with Acute Myocardial Infarction



Source: *Morita E, et al. Circulation. 1993;88:82-91.*

Figure 3

Kaplan-Meier Survival Analysis of Septic Patients with BNP Plasma Levels > 190 pg/mL and 190 pg/mL or Less During their ICU Stay



Source: Colucci W, et al. N Engl J Med. 2000;343:246-253.

seems to be inversely correlated with cardiac index.[14] It has been confirmed in a recent study performing serial measurements of BNP plasma levels in septic patients and assessing myocardial systolic performance by fractional area contraction (FAC) using echocardiography performed on days 2 and 8.[15] On day 1, plasma levels of BNP were significantly higher in the group of patients with myocardial dysfunction (FAC < 50%) (425 ± 184 vs 95.6 ± 30 pg/mL; $P < .05$).

This difference was present throughout the first 4 days after the onset of sepsis. Interestingly, plasma levels of myoglobin, creatinine kinase, and cardiac troponin I were also measured at the same time points. Plasma levels of these proteins did not differ at day 1 between patients with and without myocardial systolic dysfunction, but plasma levels of cardiac troponin I increased significantly at day 2 and day 3 in patients with myocardial dysfunction. The prognosis value of cardiac markers was also analyzed and these values were compared between non-survivors and survivors. BNP levels increased significantly at day 2 and 3 in the non-survivors group (905 ± 246 vs 181 ± 46 pg/mL; $p < .05$) whereas cardiac troponin I levels did not differ between non-survivors and survivors. A BNP plasma level cut-off value > 190 pg/mL could differentiate survivors from non-survivors with a sensitivity of 70% (CI, 55-85) and a specificity of 67% (CI, 51-83) (*see Figure 3*). According to these data, BNP plasma levels seem useful to detect myocardial dysfunction in critically ill patients, and high plasma levels appear to be associated with poor outcome.

BNP as a Drug[2]

Human recombinant form of BNP has revealed itself as a unique agent in the management of decompensated heart failure.[16] Unlike the situation with nitroglycerin, its use has not been associated with tolerance. Compared to nitroprusside, the use of human recombinant BNP is not accompanied by an increased risk of thiocyanate or cyanide toxicity in patients with renal or hepatic dysfunction, respectively. Moreover, it seems to have a more positive effect on neuro-hormonal activation decreasing plasma aldosterone levels while producing no effect on rennin levels. Added to that, the hemodynamic improvements seen with this therapy are not secondary to increases in intracellular cyclic AMP and calcium, as occurs with the use of positive inotropes such as dobutamine, and therefore the use of human recombinant BNP does not result in any increased risk of ventricular arrhythmias. However, there are no data about the use of this drug in critically ill patients with reversible myocardial dysfunction.

Conclusions

BNP is mainly produced and released from the ventricles in response to increased wall stress and tension. The measurement of BNP plasma levels seems useful to detect myocardial dysfunction in critically ill patients, and high plasma levels appear to be associated with poor outcome although these results need to be confirmed in further studies. The potential advantages of BNP as a drug to treat heart failure in ICU patients will still have to be tested. ■

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CME / CE Questions

16. In the cohort of patients with acute coronary syndromes reported by Rao et al, what percentage of patients received at least 1 transfusion?

a. 10%
b. 15%
c. 20%
d. 25%
e. 30%

17. In Rao et al's study, transfusion was associated with:

a. increased length of stay in the hospital.
b. decreased length of stay in the hospital.
c. increased mortality.
d decreased mortality.
e. Both a and c

18. Based on their results, Rao et al suggest it may be safe in patients with acute coronary syndromes to use a transfusion threshold of hematocrit:

a. 21%.
b. 25%.
c. 28%.
d. 30%.
e. 35%.

19. What percentage of patients admitted to an ICU in the United States receive at least one RBC transfusion?

a. 8.6%
b. 19%
c. 37%
d. 44%
e. 70%

20. Transfusion was less likely to be given if patients:

a. had cardiac co-morbidities
b. had low severity of illness scores
c. were receiving hemodialysis
d. were > age 65 years
e. were in an urban hospital

21. Age of RBC was directly associated with:

a. hospital LOS
b. ICU LOS
c. infection risk
d. mortality
e. none of the studied outcomes

22. Which of the following, besides congestive heart failure, can raise plasma levels of brain natriuretic peptide (BNP)?

a. Renal failure
b. Cirrhosis with ascites
c. Hypoxia
d. All of the above
e. None of the above

23. Brain natriuretic peptide (BNP) is:

a. secreted by the cardiac ventricles in response to increased wall stretch and tension.
b. produced by the adrenal cortex during critical illness.
c. present in a wide variety of tissues and secretions in both health and disease.
d. a component of brain cells that is released into the blood by severe hypoxia
e. secreted by lymphocytes in response to stimulation by inflammatory cytokines

Answers: 16 (a); 17 (c); 18 (b); 19 (d); 20 (b); 21 (e); 22 (d); 23 (a)

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:

Web-Based ARDS Management Tool

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.*

ACE Inhibitors and Receptor Blockers: Which is Inferior?

The first head-to-head comparison study of an ACE inhibitor and an angiotensin receptor blocker, to assess renoprotective effects in type 2 diabetes, has shown that the drugs are comparable in their benefit. It has been known for more than a decade that ACE inhibitors prevent progression of microalbuminuria in type 2 diabetes, out of proportion to their blood pressure lowering effects. It has also been shown that angiotensin receptor blockers are renoprotective, but it has not been shown that the drug classes are equivalent in their benefit. The Diabetics Exposed to Telmisartan and Enalapril Study Group (DETAIL study) was designed in 1996 to compare the 2 drugs in 250 patients with type 2 diabetes and early nephropathy. Patients were randomized to 80 mg of telmisartan or 20 mg enalapril daily. The primary end point was the change in Glomerular Filtration Rate (GFR) during 5 years of the study. Secondary end points included annual changes in GFR, serum creatinine level, urinary albumin excretion, and blood pressure; the rates of end stage renal disease and cardiovascular events; and all-cause mortality. After 5 years, the change in GFR was -17.9 mL/min with telmisartan and -14.9 mL/min with enalapril (the 95% CI, -7.6- 1.6 mL/min). The data suggest that telmisartan is not inferior to enalapril in providing long-term renotection in patients with type 2 diabetes (*N Engl J Med*. 2004;351:1952-1961). In the same issue of the *Journal*, researchers in Italy compared the ACE inhibitor trandolapril plus verapamil, trandolapril alone, verapamil alone, or placebo in patients with hypertension and type 2 diabetes, and normal urinary albumin excretion. The end point was the development of persistent microalbuminuria. Over 3 years of treatment, the percentage of those patients developing microalbuminuria were: trandolapril 6%, trandolapril plus verapamil 5.7%, verapamil alone 11.9%, and placebo 10%. The authors conclude that trandolapril plus verapamil and trandolapril alone decrease the incidence of microalbuminuria to similar extent, whereas the effectiveness of verapamil alone was similar to that of placebo (*N Engl J Med*. 2004; 351:1941-1951).

The Infection Risk of Acid-Suppressing Drugs

Ever since cimetadine was first marketed in 1977, physicians have been concerned about the risk of infection associated with acid-suppressing drugs. Now researchers from the Netherlands have shown that concern is warranted, by demonstrating a link between acid-suppressing drugs and community-acquired pneumonia (CAP). Utilizing the Integrated Primary Care Information database in the Netherlands between 1995 and 2002, incidence rates for pneumonia were calculated for those exposed to acid-suppressive drugs and those who were unexposed. A case control analysis was conducted, nested in a cohort of incident users of acid-suppressive drugs, with up to 10 controls matched to each case for practice, year of birth, sex, and index date.

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The main outcome was CAP. The incidence rates for pneumonia in non-acid-suppressive drug users and acid-suppressive drug users were 0.6 in 2.45 per hundred person-years, respectively. The adjusted relative risk for pneumonia among persons currently using a proton pump inhibitor (PPI), compared with those who stopped using a PPI, was 1.89 (95% CI, 1.36-2.62). The risk for current users of H2 antagonists was 1.63 (95% CI, 1.07-2.48). The authors conclude that acid-suppressive drugs, especially proton pump inhibitors (PPIs), are associated with an increased risk of pneumonia, and suggest that these drugs should be used with caution, and at the lowest possible doses in patients who are at risk for pneumonia (*JAMA.* 2004;292:1955-1960). An accompanying editorial points out the biological plausibility of the findings and suggest that, while acid-suppressive drugs are indicated for a wide variety GI conditions, long-term, chronic use of these drugs should always be balanced with patient safety (*JAMA.* 2004;292:2012-2013).

Is Rosuvastatin As Safe As Other Statins?

Rosuvastatin (Crestor), AstraZeneca's entry into the high potency statin market, has not achieved marketshare comparable to Pfizer's atorvastatin (Lipitor) or Merck's simvastatin (Zocor). This, despite the facts that the drug is very potent and AstraZeneca has priced the drug 15-20% lower than Lipitor. Some physicians remember the cerivistatin (Baycol) withdrawal from the market, and may be concerned regarding the highest doses of rosuvastatin, especially since European regulators issued a warning earlier this year about the drug. New postmarketing data suggest, however, that rosuvastatin is as safe and well-tolerated as other statins. The records of 12,400 patients who received 5-40 mg/day were reviewed, representing 12,212 continuous patient years. In fixed dose trials with comparator statins, 5-40 mg of rosuvastatin showed an adverse event profile similar to those for 10-80 mg of atorvastatin, 10-80 mg of simvastatin, and 10-40 mg of pravastatin. Clinically significant increases in liver transaminases were uncommon (≤ 0.2%) in all groups. Myopathy with creatine kinase increases > 10 times the upper limit of normal, with muscle symptoms occurring in ≤ 0.03 % of patients who took rosuvastatin at doses of 40 mg or less. Proteinuria, at the same doses, was comparable to the rate seen with other statins as well. There were no deaths and no cases of rhabdomyolysis in patients on 40 mg or less of rosuvastatin. The authors conclude that rosuvastatin was well-tolerated, and out of safety profile similar to other commonly statins (*Am J Cardiol.* 2004;94:882-888).

Which Estrogen Preparation is the Safest?

Is esterified estrogen safer than conjugated equine estrogen? At least with regard to venous thrombosis, the answer may be yes, according to a recent study. Group Health Cooperative in Washington State, a large HMO, switched their patients from conjugated equine estrogen (CEE) to esterified estrogens (EE) in 1999. Records of perimenopausal and postmenopausal women were studied between January 1995 and the end of 2001. The primary outcome was the risk of first venous thrombosis, in relation to current use of either estrogen with or without a progestin. There were 586 cases of venous thrombosis identified. Compared with women not currently using hormones, current users of EE had no increase in venous thrombotic risk (odds ratio, 0.92; 95% CI, 0.69-1.22). Women taking CEE however, had an elevated risk (OR, 1.65; 95% CI, 1.24-2.19). Comparing users of the 2 estrogens, current users of CEE had an odds ratio of 1.78 for venous thrombosis, compared to users of EE (95% CI, 1.11-2.84), and higher doses of CEE were associated with a higher risk. Among all estrogen users, concomitant use of progestin was associated with an increased risk, compared to use with estrogen alone (OR, 1.60; 95% CI, 1.13-2.26). The authors conclude that conjugated equine estrogen, but not esterified estrogen, is associated with an increased risk of venous thrombosis (*JAMA.* 2004; 292:1581-1587). While the authors acknowledge that these data need to be replicated, the study raises the interesting question of the differences between various estrogen preparations and the potential risks associated with them, especially when noting that conjugated equine estrogen was the only estrogen preparation used in the Women's Health Initiative.

FDA Actions

Serono has been given approval to market recombinant human luteinizing hormone (Luveris) for the treatment of infertility in women. The drug, which was granted orphan status, has been available in more than 60 countries for several years.

The FDA and Centocor have issued a warning to health care professionals about the increase risk of lymphoma associated with inflixamab (Remicade) in patients with rheumatoid arthritis and Crohn's disease. The warning applies to all tumor necrosis factor blocking agents. The drugs are associated with a 1 in 1400 risk of lymphoma, according to MedWatch, the FDA's safety information program.