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Noninvasive Ventilation Improves Outcomes in Immunosuppressed Patients with Respiratory Failure

ABSTRACT & COMMENTARY

This is a study from bordeaux, france, of immunosuppressed patients who were transferred from general medical wards to the ICU with acute hypoxic respiratory failure (AHRF). All patients had severely impaired arterial oxygenation (PaO_2/FIO_2 < 200 mm Hg on mask oxygen), a respiratory rate > 30/min, fever, and persistent pulmonary infiltrates on chest x-ray. Patients who were hypercapnic or hemodynamically unstable, or who had Glasgow Coma Scale scores < 8, congestive heart failure, more than 2 failing organ systems, or uncorrected bleeding diathesis were excluded, as were those who required urgent intubation on transfer.

The patients were stratified as to type of immunosuppression and were randomized to receive either standard therapy alone or that plus noninvasive positive-pressure ventilation (NPPV). The latter was delivered in the form of pressure support plus positive end-expiratory pressure via full-face mask so as to give an exhaled tidal volume of 7-10 mL/kg and respiratory rate < 25/min. NPPV was applied intermittently, but for at least 45 minutes at a time, with breaks every 3 hours. Standard criteria for intubation were used in all patients: a PaO_2/FIO_2 < 85 mm Hg, hypercapnia with pH < 7.30, agitation requiring sedation, seizure or other need for airway protection, hemodynamic instability, or inability to tolerate the face mask for effective delivery of NPPV.

Of 69 eligible immunosuppressed patients with AHRF, 52 (30 with hematologic malignancies and polymorphonuclear leukocytes < 100/mL; 18 were drug-induced; 4 with AIDS) were included in the study. In the NPPV group, a mean pressure support level of 15 ± 2 cm H_2O was used, with PEEP 6 ± 1 cm H_2O. NPPV was used 9 ± 3 h in the first 24 hours, 7 ± 3 h/d after day 1, for 1-9 days (mean, 4 ± 2 days).

The PaO_2/FIO_2 ratio improved from 141 to 180 mm Hg in the NPPV group as compared to a fall from 136 to 115 mm Hg in the standard care group, and this improvement was both initial and sustained (P < 0.005). Intubation was required in 12/26 (46%) of the

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NPPV patients as compared to 20/26 (77%) of the control patients (P = 0.03). Intubation was avoided in 47% of the patients with hematologic cancers and neutropenia who received NPPV as compared to 7% in the controls (P = 0.02). The interval to intubation and reasons for intubation were not different in the 2 patient groups. ICU mortality was 38% and 69% in the NPPV and control groups, respectively (P = 0.03).

Ventilator-associated pneumonia occurred in 2 (8%) of the NPPV patients and in 6 (23%) of the controls, although this difference was not statistically significant (P = 0.12). However, when all serious ICU-acquired complications were taken together, the difference was significant: 13 (50%) of patients vs. 21 (81%) in the 2 groups (P = 0.02). Ten NPPV patients (38%) had complications causing death in the ICU, as compared with 18 (69%) in the control patients (P = 0.03). (Hilbert G, et al. Noninvasive ventilation in immunosuppressed patients with pulmonary infiltrates, fever, and acute respiratory failure. *N Engl J Med.* 2001;344:481-487).

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COMMENT BY DAVID J. PIERSON, MD

This is an important study for clinicians who help to care for severely immunocompromised patients in the ICU. Its results indicate that NPPV, applied relatively early in hemodynamically stable patients with intact mental status, may prevent the need for intubation and invasive mechanical ventilation when such patients develop AHRF. Further, it suggests that by avoiding intubation and all its attendant complications, more of these patients can be brought through their episode of AHRF successfully, at least to the point of ICU discharge. Hilbert and colleagues suggest that avoidance of ventilator-associated pneumonia, an NPPV outcome that has has been suggested in studies of other patient populations, may be the fundamental reason for the mortality improvement.

Another study of NPPV in immunocompromised patients with AHRF—this one in individuals with solid organ transplants rather than with hematologic cancer—was published a few months before the Hilbert study and showed similar results. Antonelli and colleagues in Rome reported a randomized, controlled trial of 40 patients who had undergone liver (22 patients), lung (6), or kidney (12) transplants.[1] Clinical presentations and criteria for NPPV management and intubation were similar to those used by Hilbert et al. Again, more patients in the NPPV group had improvement in PaO_2/FIO_2, and fewer of them required intubation—4 of 20 (20%) vs. 14 of 20 (70%); P = 0.002. Both the incidence of fatal complications (4 vs 10; P = 0.05) and of ICU mortality (4 vs 10; P = 0.05) were lower in the patients managed with NPPV.

Taken together, these studies suggest that patients with severe underlying immunocompromise who develop a syndrome of tachypnea, fever, persistent pulmonary infiltrates, and severe reductions in PaO_2/FIO_2, who have preserved mental status and who are hemodynamically stable, may benefit from a trial of NPPV. This is a patient population and clinical setting in which an extremely poor outcome is usual.[2] If intubation can be avoided and the infectious or other precipitating process brought under control without the development of ventilator-associated pneumonia or other ICU complications, it may be possible to achieve a considerably better outcome in these patients. ❖

References

1. Antonelli M, et al. *JAMA*. 2000;283:235-241.
2. Rubenfeld GD, Crawford SW. *Ann Intern Med*. 1996;125:625-633.

Effects of Hydroxyethylstarch on Renal Function in Severe Sepsis

ABSTRACT & COMMENTARY

Synopsis: The use of hydroxyethylstarch as a plasma-volume expander may increase the risk of acute renal failure in patients with severe sepsis or septic shock.

Source: Schortgen F, et al. Effects of hydroxyethylstarch and gelatin on renal function in severe sepsis: A multicentre randomised study. *Lancet.* 2001;357: 911-916.

Volume expansion is the mainstay of hemodynamic resuscitation. Primary choices for volume expanders are crystalloids or colloids. Whether crystalloids or colloids are preferable and whether one colloid is better than the others have been debated for a long time. Most studies have examined intermediate outcomes (such as hemodynamic responses) but no clinically relevant end points (such as mortality or tissue injury). A common practice is to use crystalloids for maintenance fluid therapy and colloids when fluid boluses are required to acutely increase the vascular volume. However, colloids have significant toxicities that must be considered when using them.

The study of Schortgen and colleagues raises the question of whether hydroxyethylstarches (HES) can impair renal function in critically ill patients, based on previous data showing that the use of HES in a selected population of brain-dead kidney donors was associated with immediate impairment of renal function in the transplant recipients.[1]

Schortgen et al carried out a multicenter, randomized study assessing the frequency of acute renal failure (ARF) in patients with sepsis or septic shock treated with HES or gelatin. The study took place between April 1998, and September 1999, in the ICUs of 3 French hospitals. Adults were eligible if they had severe sepsis or septic shock at admission or at any time during the stay in the ICU and were deemed by the physician to require fluid loading. Reasons for exclusion were: pregnancy, history of allergy to HES or gelatin; severe acute or chronic renal dysfunction; and previous administration of HES or mannitol. Eligible patients were randomized as soon as they met the study criteria for severe sepsis or septic shock requiring fluid loading. Patients assigned HES treatment received a 6% solution of HES of molecular weight 200 kDa and degree of substitution between 0.60 and 0.66 (33 mL/kg during the first day and 20 mL/kg daily thereafter). Patients assigned gelatin received 3% fluid-modified gelatin of molecular weight 35 kDa (with no dose limitation). The primary end point was ARF (defined as a 2-fold increase in serum creatinine from baseline or need for renal replacement therapy) during the ICU stay.

Of 328 patients screened, 129 were eligible and consented to take part in the study (HES 65, gelatin 64). The study groups were similar at admission to the ICU and at study inclusion. ARF developed after admission in 27 (42%) out of 65 in the HES group and 15 (23%) of 64 in the gelatin group ($P = 0.028$). Serum creatinine was 225 µmol/L vs. 169 µmol/L ($P = 0.04$). The frequency of oliguria was also higher in the HES group. However, similar numbers of patients required renal-replacement therapy in the 2 groups. Mortality and length of stay in the ICU were also similar in the 2 study groups. In a multivariate analysis, risk factors for ARF were mechanical ventilation and use of HES.

COMMENT BY FRANCISCO BAIGORRI, MD

A postal survey in Germany suggested that no "standard" exists for volume replacement in the critically ill.[2] The kind of volume therapy used differs widely among the different ICUs. There are no clinical trials demonstrating the superiority of either form of fluid. Two recently published systematic reviews of randomized trials showed that resuscitation with colloids was associated with similar or even increased mortality.[3,4] The benefits of colloids are that similar hemodynamic responses can be achieved with smaller volumes and the effects last longer, but colloids have significant toxicities (such as hypersensitivity reactions and coagulopathies). These adverse effects seemed to be less common with HES, such as hetastarch and pentastarch. Moreover, some studies suggested that these colloids might reduce abnormally increased microvascular permeability.[5] However, the study of Schortgen et al prompts the thought that the use of HES should be avoided in patients at risk of ARF.

A combination of extreme ischemia and osmotic-nephrosis-like lesions has been pointed out as an explanation for the impairment of the renal function associated with the use of HES. The clinical relevance of the findings in the study of Schortgen et al, without an increased requirement of renal-replacement therapy, ICU mortality, or length of stay may be questionable, but we must consider carefully the potential implica-

tions. Most critically ill patients requiring fluid loading are at risk of multiple organ failure. Of course, further studies are needed to determine the exact problem. Meanwhile, fluid administration will continue to be individualized to each patient.[4] ❖

References

1. Cittanova ML, et al. *Lancet*. 1996;348:1620-1622.
2. Boldt J, et al. *Intensive Care Med*. 1998;24:147-151.
3. Schierthout G, Roberts I. *BMJ*. 1998;316:961-964.
4. Choi P, et al. *Crit Care Med*. 1999;27:200-210.
5. Zikria BA, et al. *Crit Care Med*. 1989;17:1306-1309.

Hospital Volume Influences Survival After Resection for Lung Cancer

ABSTRACT & COMMENTARY

Synopsis: Patients who undergo resection for lung cancer at high-volume hospitals are likely to have fewer complications and survive longer than those who have surgery at low-volume hospitals.

Source: Bach P, et al. The influence of hospital volume on survival after resection for lung cancer. *N Engl J Med*. 2001;345:181-188.

The study included patients who met the following requirements: 1) 65 years of age or older; 2) insured by Medicare; 3) diagnosis of primary cancer of the lung; 4) non-small-cell histology; 5) Stage I, II, or IIIA disease; 6) lung resection < 4 months after diagnosis; and 7) resident of an area covered by the Surveillance, Epidemiology, and End Results Program (SEER) and the Nationwide Inpatient Sample (NIS) databases. The NIS is a stratified random sample of 1012 hospitals in 22 states. Five of these states overlap with the SEER database, which includes 7 metropolitan areas (San Francisco, Oakland, San Jose, Detroit, Atlanta, Seattle, and Los Angeles County) and 5 states (Connecticut, Utah, New Mexico, Iowa, and Hawaii). Data were analyzed for 1 year (1997). The final sample included 2118 patients and 76 hospitals.

There was considerable variation in the volume of lung cancer resections performed at the 76 institutions. Thirty-four (45%) of the hospitals performed fewer than 9 procedures per institution. In contrast, 16 (21%) performed 20-66 procedures and 2 (3%) performed 67-100 procedures per institution. The volume of procedures performed at the hospital was positively associated with the survival of patients ($P < 0.0001$). Five years after surgery, 44% of patients who underwent operations at either of the 2 hospitals with the highest volume of procedures were alive, compared with 33% of those who underwent operation at the hospitals with fewer than 9 procedures performed. At the highest volume hospitals, patients also had a lower rate of postoperative complications (20% vs 44%) and lower 30-day mortality (3% vs 6%). In addition, the rate of 5-year survival among patients who underwent surgery at a teaching hospital was higher (42%) than for a nonteaching hospital (34%) ($P < 0.001$). Survival was improved at teaching vs. nonteaching hospitals regardless of volume.

COMMENT BY LESLIE A. HOFFMAN, RN, PhD

The major findings of this study were that: 1) rate of survival at 5 years was higher by 11 percentage points (44% vs 33%) among patients who underwent resections for lung cancer at hospitals with the highest volumes of such procedures than among those at the hospitals with the lowest volumes; 2) serious postoperative complications occurred at hospitals with the lowest volume twice as often as at those with the highest volume (44% vs 20%); and 3) survival was significantly better among patients who underwent surgery at teaching vs. nonteaching institutions, regardless of the number of procedures performed.

The association between volume (number of patients with a particular disease or procedure managed in a given hospital) and morbidity and mortality is not new. Prior studies have shown similar findings for patients diagnosed with other types of cancer (eg, breast, colon, and prostate cancer). In addition, a prior study has shown an association between increased volume and improved outcomes for elderly patients diagnosed with acute myocardial infarction.[1] Thus, the volume of patients managed appears to have a major influence on morbidity and mortality, regardless of whether the underlying condition is medical or surgical. This finding is not surprising, given the learning curve associated with gaining the highest level of expertise. In essence, "practice makes perfect."

One response to these findings would be to recommend that patients be channeled to *centers of excellence*. This change would likely be impossible to implement and could have untoward consequences (eg, increasing surgical volume beyond capacity). A more productive approach might be to refer patients from

very low-volume centers (eg, < 9 procedures per year), to a regional higher volume center. If that were accomplished, findings of this study suggest that the consequence could be a decrease in morbidity, mortality, and health care costs.

There are a number of limitations to this study. Only data included in the SEER, NIS, and Medicare databases could be used for analysis and the analysis was limited to 1 year. Hospitals were coded as either a teaching or a nonteaching institution. Given the complex organizational frameworks that exist today, this distinction was likely imperfect. Finally, the database did not provide complete information regarding adjuvant treatment, a factor that may have influenced survival. ❖

Reference

1. *N Engl J Med*. 1999;340:1640-1648.

Respiratory Failure in Patients with Pulmonary Fibrosis

ABSTRACT & COMMENTARY

Synopsis: In 2 retrospective series of patients with idiopathic pulmonary fibrosis who developed progressive respiratory failure and were intubated and ventilated in the ICU, only 3 (< 10%) survived, raising the question of whether such management is justified in this condition.

Source: Blivet S, et al. Outcome of patients with idiopathic pulmonary fibrosis admitted to the ICU for respiratory failure. *Chest.* 2001;120:209-212.

In this paper from lyon, france, blivet and associates report the results of a retrospective review of all patients with advanced idiopathic pulmonary fibrosis (IPF) who were admitted to their ICU because of an episode of acute hypoxemic respiratory failure (AHRF) during a 9.5-year period. Fifteen patients (age 64 ± 10 years; 11 men) met entry criteria. The diagnosis of IPF had been established histologically in 7 patients and on the basis of typical clinical, functional, and radiographic features in the remaining 8. Mean duration from diagnosis to ICU admission was 26 ± 28 months, range 1.3-81 months. All 15 patients had previously been treated with corticosteroids, and 11 had been on long-term oxygen therapy prior to the episode of AHRF. At ICU admission, the patients had mean arterial blood gas values of pH 7.32, PCO_2 55 mm Hg, and PaO_2/FIO_2 113 mm Hg.

All 15 patients received ventilatory assistance. Of 5 treated initially with noninvasive positive-pressure ventilation (NPPV), 2 improved and were discharged from the ICU, 1 died during NPPV, and 2 were converted to invasive mechanical ventilation. In all, 12 patients were intubated for ventilatory support, and 2 of them survived to leave the unit. Of the 4 patients who were transferred out of the ICU, 2 died shortly thereafter, 1 was still alive 6 months after discharge, and 1 was lost to follow-up. Causes of death in the ICU were progressive hypoxemia in 8 patients and septic shock in 3. Length of ICU stay in this 15-patient cohort was 13.9 ± 11.2 days.

A similar patient series was reported in the same issue of *Chest* by Stern and colleagues.[1] These investigators performed a 10-year review of all patients with IPF who were intubated and ventilated for acute respiratory failure in their respiratory ICU in Clichy, France. Their review included 23 patients (mean age, 53 years; 19 men) whose diagnoses of IPF had been made mainly on clinical grounds and radiographic imaging studies. These patients had severe disease, with mean total lung capacity of 48% of predicted and diffusing capacity of the lung for CO, 30% of predicted. Twenty-one patients (91%) had received immunosuppressive therapy for IPF, and most were on home oxygen therapy. The patients were severely hypoxemic at the time of admission, with PaO_2 59 ± 5 mm Hg on high-concentration mask oxygen, and only 4 had PaO_2/FIO_2 ratios > 100 mm Hg. With the exception of 1 patient who received a single-lung transplant 6 hours after intubation, the remaining 22 patients all died after 1 hour to 60 days (median, 3 days) of mechanical ventilation.

COMMENT BY DAVID J. PIERSON, MD

IPF, called cryptogenic fibrosing alveolitis in the United Kingdom, is a progressive interstitial lung disease of unknown cause with an almost invariably poor prognosis. Most patients die within 3-5 years following diagnosis. The disease is progressive and generally unresponsive to treatment, with the majority of patients succumbing to acute hypoxemic respiratory failure. These 2 case series support the widely held clinical impression that the development of AHRF is nearly always fatal in these patients.

Although Blivet et al and Stern et al saw only a few patients who had respiratory failure precipitated by such potentially reversible circumstances as a pneumothorax or general anesthesia, in most cases no specific etiology

for the deterioration could be found. A sepsis-like picture was present in a number of the patients, but causative organisms were seldom identified. One could therefore conclude, as do Blivet et al and Stern et al, that acute respiratory failure in patients with advanced IPF is very unlikely to be a reversible process. In fact, Stern et al recommend that mechanical ventilation be offered only to IPF patients with acute respiratory failure who are awaiting lung transplantation, in whom this can be performed within a few days. ❖

Reference

1. Stern JB, et al. *Chest*. 2001;120:213-219.

Special Feature

Should the Definition of ARDS be Changed?

By Jun Takezawa, MD

Although a tremendous amount of resource has been allocated to develop a novel treatment for the acute respiratory distress syndrome (ARDS), all the clinical trials to date—such as those using anticytokine therapies, NO inhalation, surfactant, and prone positioning—have failed, except for the low tidal volume strategy trial organized by the ARDS network of the National Institutes of Health (NIH).[1] Several factors are speculated to be responsible for these disappointing results, and most of them are addressed to the definition or diagnostic criteria of ARDS. In this article, background of this argument and its rationale are reviewed and the future direction of clinical trials on ARDS is addressed.

Background: Why Change of ARDS Definition is Recommended

One of the biggest arguments in the definition of ARDS is related to diagnostic criteria. Regarding the interpretation of chest x-ray film, massive atelectasis in the dependent regions of both lungs and the bilateral presence of small amounts of pleural effusion are easily misdiagnosed as bilateral infiltrates. Considerable interobserver variation in chest radiograph interpretation has been documented.[2,3] Interobserver variation of chest radiograph interpretation for ARDS by intensivists was also evaluated by Canadian hospitals, and it was found that agreement of the interpretation between intensivist and radiologist was 60-80%. Meade and colleagues recommended the provision of chest x-ray reading consensus training before starting a clinical trial;[4] otherwise, the findings of the study may be misled, and/or a very large sample size is required to reach the final conclusion.

The second argument is related to severity of lung injury. According to the definition of ARDS by the American-European Consensus Conference on ARDS,[5] the deterioration of pulmonary gas exchange is assessed by the P/F ratio (arterial PO_2 divided by inspired oxygen fraction), independently of the level of positive end-expiratory pressure (PEEP). However, it is well known that the PEEP level can easily affect the P/F ratio, and this can become the source of bias for patient entry in the clinical trial. Additionally, whether the magnitude of deterioration in pulmonary gas exchange at the initial stage of ARDS affects outcome is still unknown. On the other hand, although the peak airway pressure (PIP) level is well known to affect the outcome of ARDS patients, lung compliance—that is, the reflection of PIP during volume-targeted ventilation—was not taken into account in determining the severity of lung injury. As a result, severity of lung injury in terms of both pulmonary gas exchange and lung mechanics is not included as a risk factor in the outcome of ARDS.

The third argument is related to diverse etiologies and a variety of clinical manifestations of ARDS. Although several etiologic factors such as the effects of neutrophils and cytokines have been nominated as candidates, the precise mechanism for developing ARDS is still unclear. Thus, it is likely that treatment modalities may attempt to target diseases of different etiologies, which are encompassed in disease categories termed as a syndrome. This would not only require a large sample size but also inherit a risk of unknown confounders being unequally distributed in both arms of the randomized clinical trials (RCTs).

Bilateral infiltrates developed during bacterial and interstitial pneumonia can fulfill the diagnostic criteria of ARDS. However, treatment should be focused on the original disease rather than ARDS itself to improve outcome. Therefore, unequal distribution of these types of pneumonia in the treatment and control arms interferes with the quality of any RCT. Evaluation of a risk factor and its outcome also supports this context where mortality of ARDS associated with sepsis is much higher than that associated with trauma, extracorporeal circulation, and massive transfusion.

The fourth argument is similar to that being referred to during the clinical trial for sepsis such that the initiation of intervention as a trial was too late to affect the outcome of septic patients. This concern encouraged the development

of the new concept of the systemic inflammatory response syndrome (SIRS). However, this expansion of inclusion criteria requires a large number of enrolled patients, and the improvement of mortality becomes extremely small even though it reaches a significant difference (thus making the interpretation of its clinical merit difficult).

The fifth argument is that ARDS can be regarded as a complication, such as with nosocomial infections. Therefore, patient outcome is affected by both severity of illness (usually assessed by the APACHE scoring system) and severity of complication (ARDS) itself. However, the overlapped effect of this complication on outcome has not been well stratified.[6] Table 1 shows a comparison of outcomes between ARDS and overall patients who were admitted to ICUs and required mechanical ventilation in 31 Japanese ICUs. Both predicted and actual mortality of ARDS patients were higher than that of patients who required mechanical ventilatory support. However, the standardized mortality rate (SMR) of ARDS patients was much higher than that of overall ventilated patients (1.25 vs 0.76). In other words, the APACHE score could not accurately predict mortality of ARDS patients.

Comparison of actual and predicted mortality of the ARDS patients (289 patients) in Japanese ICUs indicates that the actual mortality of the ARDS patients was higher than predicted mortality in the full range of APACHE score (*see Figure*). Especially in the 5-10 and 10-15 ranges of APACHE score, actual mortality was more than twice of that predicted, indicating again that the APACHE scoring system did not stratify the ARDS patients.

The Future Direction of Clinical Trials for ARDS

In order to organize a clinical trial either from the standpoint of a professional society, government, or pharmaceutical company, the effect of ARDS on the overall health care system such as volume, mortality, cost, and burden should be assessed. Each country has a different priority for ARDS as a health care challenge. Unfortunately, most countries, including Japan, have no such database, making it difficult to determine the priority of ARDS as an issue of health care policy.

In addition to the inaccuracy of diagnosis, the biggest problem associated with clinical trials of ARDS is that severity of lung injury is not taken into account as a risk factor for the outcome. If severity of lung injury does not affect the outcome of ARDS, ARDS should not be a target of treatment. It should be the first step to make a (inter) national database for disease registration for the stratification of severity of ARDS in terms of outcome. A new prognosis predicting scoring (PPS) system may be required with the combination of both APACHE score and severity of lung injury, because APACHE system alone does not stratify ARDS patients. This PPS system may be made based on primary diseases. If this attempt is to be made, international collaboration is required because a large number of patients should be registered to establish a primary disease-based PPS system of ARDS for epidemiological evaluation. ❖

Table

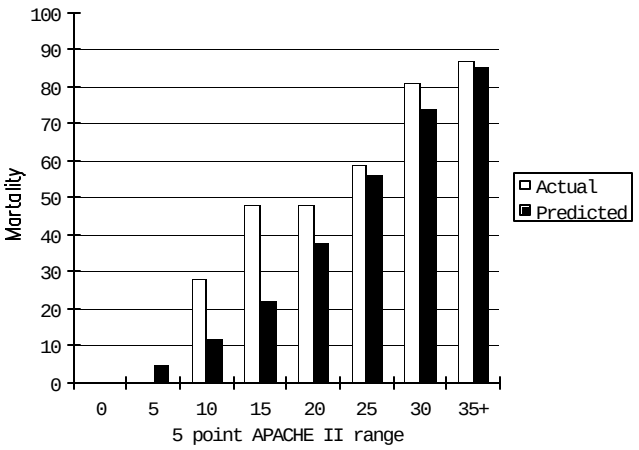
Outcome Comparison Between ARDS and All Ventilated Patients in ICUs

	ARDS	Ventilated Cases
No. of Patients	289	5738
Predicted Mortality (%)	49.5	27.5
Actual Mortality (%)	61.9	20.9
SMR	1.25	0.76
ICU Mortality (%)	48.4	13.3
LOS in ICU (days)	12.9	5.9
LOS in Hospital (days)	67.4	55.7
Ventilation Day (days)	10.9	3.1

LOS: Length of stay

Figure

Comparison of Predicted/Actual Mortality of the Patients with ARDS



References

1. The Acute Respiratroy Distress Syndrome Network. *N Engl J Med*. 2000;342:1301-1308.
2. Tudor GR, et al. *Clin Radiol*. 1997;52:235-238.
3. *Acad Radiol*. 1969;41:10-14.
4. Meade MO. *Am J Respir Crit Care Med*. 2000;161: 85-90.
5. Bernard GR. *Am J Respir Crit Care Med*. 1994; 149:818-824.
6. Knaus WA, et al. *Am J Respir Crit Care Med*. 1994; 150:311-317.

CME/CE Questions

4. **Which of the following statements is true about the use of non-invasive ventilation in immunosuppressed patients with acute hypoxemic respiratory failure?**
   a. It improves oxygenation but has no effect on intubation rate, complications, or ICU mortality
   b. It improves oxygenation and decreases the need for intubation but has no effect on complications or ICU mortality.
   c. It improves oxygenation and decreases both intubations and complications but has no effect on ICU mortality.
   d. It improves oxygenation and decreases intubations, complications, and ICU mortality.

5. **In patients with sepsis or septic shock, the use of hydroxyethyl-starch seems to be associated with:**
   a. a higher mortality.
   b. an improvement of coagulopathy.
   c. a shorter ICU length of stay.
   d. an increased need for renal-replacement therapy.
   e. an impairment of renal function

6. **Which of the following may be misinterpreted as diffuse parenchymal pulmonary infiltrates in diagnosing ARDS?**
   a. Pleural effusions
   b. Extensive bilateral basilar atelectasis
   c. All of the above
   d. None of the above

7. **When hospitals with a high volume of lung-cancer resections were compared to those with a lower volume, survival was significantly better in:**
   a. nonteaching institutions, regardless of volume.
   b. hospitals performing 67-100 procedures per year.
   c. community facilities with no resident staff.
   d. not-for-profit hospitals.
   e. hospitals located in more affluent areas.

8. **Survival among patients with severe idiopathic pulmonary fibrosis who develop acute hypoxemic respiratory failure and are treated with invasive mechanical ventilation in the ICU is:**
   a. 50%.
   b. 40%.
   c. 30%.
   d. 20%.
   e. Less than 10%.

CME/CE Objectives

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

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

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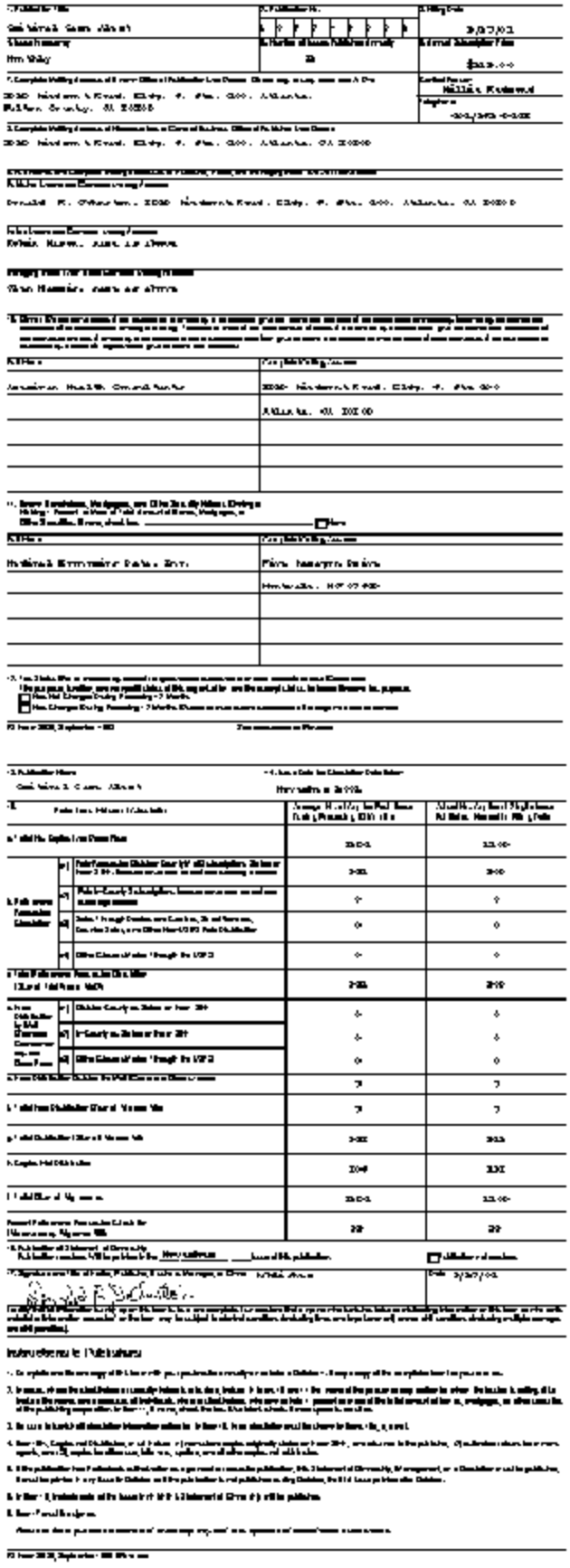

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Transfusions in the ICU Call for Rethinking Old Practices

By Julie Crawshaw, CRC Plus Editor

New studies, products expected to create major overhauls

Concerns about a dwindling blood supply are driving many icu physicians and researchers to simultaneously rethink their transfusion practices and consider new technologies.

The physician population needs to begin making the situation better by better understanding transfusion medicine and guidelines, says A. Gerson Greenburg, MD, PhD, surgeon in chief at Miriam Hospital in Providence, RI, who also is a professor of surgery at Brown University. "A lot of blood is given inappropriately, without an indication to use the product," Greenburg says. "There's a lot of knee-jerk reaction that goes back to an out-of-context statement made in the 1940s about what constitutes a transfusion trigger."

Greenburg's department participated in a transfusion trigger study that evaluated whether patients kept above 10 g/dL fared better than those kept at 8 g. "We found no differences in outcomes when we used 8 g as a trigger point," he says. "And we managed to save over 2 units of blood per patient, which is tremendous. Viewing a hemoglobin of 10 as a transfusion trigger no longer applies."

In the past, says David J. Pierson, MD, FACP, FCCP, many intensivists have used a hematocrit (Hct) threshold of about 30 for transfusion. Pierson, who is professor of medicine at the University of Washington and medical director of respiratory care at the Harborview Medical Center in Seattle, says recent studies found that patients who were allowed to be more anemic before transfusion actually did better.

"Everyone would agree that a patient with cardiac ischemia should be transfused at a higher Hct threshold than others, all things otherwise being equal," Pierson says. "It appears safe to say that we have used more red blood cell [RBC] transfusion in the past than we absolutely needed."

Harvey G. Klein, MD, says the correct hematocrit level is controversial now following a study of patients in Canada that showed a lower hematocrit appears to be better than a higher hematocrit,[1] contrary to conventional wisdom. Canadian researchers studied 838 critically ill patients with euvolemia after initial treatment with hemoglobin concentrations of less than 9 g/dL within 72 hours after admission to the intensive care unit.

RBCs were transfused for 418 randomly assigned patients if the hemoglobin concentration dropped below 7 g/dL and hemoglobin concentrations were maintained at 7-9 g/dL. The remaining 420 patients received transfusions when the hemoglobin concentration fell below 10 g/dL and hemoglobin concentrations were maintained at 10-12 g/dL.

The research team found the 30-day mortality was similar between the 2 groups (18.7% vs 23.3%; $P = 0.11$). However, the rates were significantly lower with the restrictive transfusion strategy among patients who were less acutely ill.[2]

Klein, who heads the department of transfusion medicine at the Warren G. Magnuson Clinical Center of the National Institutes of Health (NIH) in Bethesda, Md, is also president of the American Association of Blood Banks. He says the study is also in line with common sense because the hematocrit wasn't extremely low.

"The current belief is that the hematocrit should range between 8-10 but doesn't necessarily have to be brought back up to normal," Klein says. "Raising the Hct to levels we might consider normal may in fact have a deleterious

effect, though that probably needs to be confirmed."

Pierson agrees, observing that a physician who previously transfused patients without severe cardiac disease, acute brain disease, or uncorrectable hypoxemia whenever the Hct dipped below 30%, could probably lower that threshold to the mid-20s without causing worse patient outcomes. "I see lower transfusion thresholds being used in the ICUs in which I work than was the case 2-3 years ago," he says.

Use the Options at Hand and Watch the Horizon

Reassessing the Hct levels at which patients need to be transfused goes hand-in-glove with carefully husbanding a decreasing blood supply and more effectively using the options already available, Greenburg observes. "We can't easily salvage ICU patients' blood, but we can increase blood reserves through the operating room by using products that allow autologus transfusion," he says. "And if we practice surgery as if every patient is a Jehovah's Witness, we don't need to use a lot of blood, and Jehovah's Witnesses don't have a higher surgical death rate."

However, Greenburg is quick to say that while minimizing blood loss can preserve the blood supply, the tradeoff is longer operations and different techniques. "The kind of bleeding that creates a need for transfusion has to be operated on, clamped, or sewn. The micro bleeding associated with much of surgery isn't really a problem," he says.

New products are on the horizon that may redirect some of the more than $15 billion spent annually worldwide to acquire RBC units. One such option is Hemolink, a human hemoglobin-based oxygen carrier that Greenburg says will be very useful if approved by the Food and Drug Administration (FDA).

The product would temporarily replace the patient's own withdrawn blood, which would later be transfused back. Hemolink has completed phase III clinical trials in Canada and Europe and is currently involved in US phase III clinical trials for patients undergoing coronary artery bypass graft surgery.

Third-phase clinical trials for RBC substitutes show a statistically significant decrease in banked blood use for orthopedic and cardiac surgery, which would increase the overall banked blood supply.

Recombinant erythropoietin, which causes the body to make more RBCs, may well have a similar effect on RBC demand. Miriam Hospital is part of a major collaborative blind study to test the theory that giving erythropoietin in the ICU may reduce the need for blood transfusions, Greenburg says.

"The companies manufacturing the erythropoietin preparations would have us giving it to everyone, but these agents are expensive," Pierson says. "It takes many days for them to act, their proper role has not been defined, and the data aren't in as to who should receive them."

Erythropoeitin has its place, Klein adds, especially for patients with renal disease. "But it really has limited use in the ICU," he says.

Safety and Availability Hot Issues

Klein says one positive technological is the degree to which labeling both the unit of blood and the patient has improved. "Before current technology, labeling was done manually, but the risk of giving an inappropriate unit of blood ranged from one in 19,000 to one in 12,000 units transfused," he says. "Compare that with the HIV risk of one in every million-and-a-half units transfused and you can see that labeling and identification technology, now generally computerized, has dramatically decreased the risk of giving the wrong blood."

Klein observes that most errors, whether in the ICU or operating room, occur during sudden emergencies when failsafe systems are bypassed.

"Call that a human factor, standard operating procedure, error control, whatever," he says. "It's extremely important, whether it's high tech, medium tech, low tech, or no tech."

Jerry Squires, MD, vice president and chief scientific officer for the Red Cross, says that his organization has invested $335 million in blood safety initiatives. "I think by and large, blood centers are making every effort to make the blood supply as safe as it can be," Squires says.

Squires says that current media attention to the variant of Creutzfeldt-Jakob disease (vCJD) popularly referred to as "mad cow disease" highlights mounting public fears about blood supply safety. The Red Cross is now indefinitely deferring donations from people who have spent 3 months in the United Kingdom or in Western Europe for 6 months or if they have received a blood transfusion in the United Kingdom. Current FDA deferral is 6 months for UK visitors, with suggested guidance of 5 years deferral for people who have lived in Western Europe.

According to Squires, the Red Cross tightened donation deferral because of documented vCJD cases in animals in other European countries. "There is no documented case of vCJD transmission to a patient through transfusion, but the disease can have a latency period as long as 20 years," he says.

Greenburg believes public concern about blood safety is also driving the medical community to find alternatives. "I have lots of patients who look at the informed consent and scratch off the blood transfusion piece," he says. "There is a perception (with data on both sides) that blood transfusions cause immune suppression."

Squires says his organization led a nationwide effort to implement nucleic acid testing, which has the potential to lessen the already-low risk of receiving HIV or hepatitis C through a blood transfusion. "It used to be that the window period between infection and when a donor actually tested positive was up to 90 days," Squires says. "With nucleic acid testing, that's reduced to 30 days." Klein adds that most institutions will go 10-20 years without seeing a transfusion-transmitted HIV infection. "It will never be perfect, but the US blood supply is extremely safe," he says.

Using leukocyte-free RBCs has decreased the incidence of minor transfusion reactions and incidence of infection with cytomegalovirus (CMV). "Those of us with normal immune systems don't have much trouble with CMV," Squires says. "I'm CMV-positive and I don't even know when I was infected. However, premature neonates and immunocompromised patients are very seriously affected by CMV."

Squires points out that this year, the Red Cross has increased blood collections by 1.9%. At the same time, blood distributions to hospitals have increased 4.1%. To increase blood donations, the Red Cross is mounting an ad campaign on radio and TV and sending out millions of request letters to donors of record.

Greenburg says the press and TV news inadvertently contribute to the donor apathy responsible for current low blood reserves. "The evening news reports that a product has been approved for transfusion in another part of the world," Greenburg says. "There is a public perception that other things are available but that's not really true."

Tracking TRALI in the ICU

According to Klein, the noninfectious serious hazards of transfusion are greatly underappreciated. ICU physicians may confuse transfusion related acute lung injury (TRALI) with fluid overload or with various acute respirator syndromes. "TRALI is a very specific disorder related to blood transfusions or to transfusion of antibody-containing plasma," Klein says. "It causes an acute lung syndrome that looks like pulmonary edema. It's an immune side effect that usually occurs during transfusion but can occur up to a couple of hours afterward." He advises ICU physicians to use oxygenation, careful monitoring, and stopping the plasma flow from that donor—not volume restriction—to treat TRALI.

"ICU physicians need to be aware that this is different from fluid overload," Klein says. "Once you appreciate that this acute lung syndrome is transfusion-related, the blood bank can help you."

Klein also observes physicians aren't usually concerned about blood availability in the ICU. "When someone is dying, we don't say 'We don't have blood for you.' We find it," he says.

But ICU physicians, says Klein, need to be cognizant of the fact that blood is short in the United States, and for a lot of reasons is likely to become less available than it is now.

"Family members and friends of intensive care patients frequently ask what they can do to help," he says. "Tell them they can give blood." ❖

References

1. Hébert P, et al. *N Engl J Med.* 1999;340:409-417; 438-447.
2. Ibid.

Effort Seeks to Boost Pediatric Palliative Care

Children don't receive same level of care as adults

Seriously ill children frequently don't get appropriate pain management and supportive services at the end of life because their conditions and treatments don't fit existing care models designed for adults. But federally funded demonstration projects in 5 states are designing new ways of providing services to kids—ones that don't require parents and physicians to abandon treatments aimed at a cure in order to examine other options.

"The bottom line is, from the patient and family standpoint, we want to allow them to choose hospice-type care, which is really comprehensive compassionate care that is known as hospice, from the time of the diagnosis of a life-threatening condition, even when there is hope for a cure, through bereavement follow-up if a cure is not obtained," says Anne Armstrong-Dailey. She is the director of the Alexandria, Va. based Children's Hospice International (CHI), the organization in charge

of administering the projects and distributing the funds.

Last year, CHI received congressional funding for the first 5 demonstration projects of its Program for All-inclusive Care for Children (PACC). The PACC programs develop and coordinate comprehensive systems of care that allow seriously ill children and their families to have access to palliative pain management, supportive counseling, and, in some cases, home health and hospice services even while curative treatment is pursued, says Daily. This year, the program received an additional $885,000 from Congress, which will allow CHI to continue funding the existing 5 projects and start a sixth demonstration project in another state.

Studies have shown that more integrated models of providing palliative care and hospice support work best for children, as opposed to traditional "adult" models that have focused on providing palliative treatments to patients when there is little or no hope of recovery.[1-3]

Although advocates urge providers to see palliative care as part of the overall care plan for all patients, including adults, this inclusive approach is especially important for children, says Cynda Rushton, DNSc, RN, FAAN, clinical nurse specialist in ethics at Johns Hopkins Children's Center in Baltimore. "Part of the problem with children is that sometimes their disease trajectories have been unpredictable," she explains. "Children who we think are not going to survive—they do. Then, you are sort of on this roller coaster of trying to figure out what the outcome will be."

In 1982, changes in the Medicare and Medicaid hospice eligibility standards required patients to have a physician's diagnosis that they were in their last 6 months of life. Additionally, all curative treatments must have stopped in order for hospice services to be reimbursed through Medicare and Medicaid. Many private health plans followed suit. The result is that children are referred to hospice very late in their course of illness, if at all, says Armstrong-Dailey.

"Seldom is a physician able to say—until it's at the very last moment—that the child is at death's door," she explains. "Most often, pediatric patients are in and out of the terminal stage for a number of years. And, how many parents do you know, or how many pediatricians do you know, who would be willing to stop curative treatments on a child, even if his or her chance for survival were one in 10 million?"

Lack of Appropriate Services a Problem

Even if hospice referrals could be made in a timely manner, however, many communities don't have the resources to provide appropriate end-of-life care to children outside the acute-care setting, says Rushton. "We don't have a lot of providers skilled enough to provide the care," she continues. "Some of it is lack of education and some of it is lack of specialized resources. Children, even in the end stages of their lives, still are usually receiving quite a bit of [medical] technology. We need people to be able to provide the emotional, psychosocial, and spiritual support as well as some of that high-tech nursing care in the home."

Because seriously ill children typically need a high level of medical interventions for a longer period of time, it is very difficult to get them plugged into existing services, she says.

And, one of the main goals of PACC is to secure benefits of hospice services for chronically ill children who may not necessarily be near the end of life, says Armstrong-Dailey. Families dealing with the serious, life-threatening illness of a child desperately need the supportive counseling and health care services that hospice provides for dying patients and that a comprehensive program should provide for all patients, she believes. "I have personally talked with tens of thousands of parents over the past 20 years and, without exception, the parents will tell me that the time of crisis is the time of diagnosis, even when there is still hope for a cure," she says. "Most parents will tell you that the time of the child's death is anticlimactic, by comparison."

Parents of seriously ill children feel tremendous pain and guilt at the time of diagnosis, particularly if the disease is genetically linked, she notes. Families need help dealing with these issues early on in order to avoid preserve the strength of the family unit and appropriately make decisions about the care of the child. "By dealing with these emotions, we can help families look at the situation in a realistic way, and to realistically examine what the options might be," says Armstrong-Daily. "It can help prevent the dysfunctional, destructive behavior that can shatter families. Without support, you often see an enormous increase in alcohol and drug abuse within families and destructive behavior by surviving siblings." ❖

References

1. Kane JR, Primomo M. *Am J Hosp Palliat Care.* 2000; 18:161-169.
2. American Academy of Pediatrics' Committee on Bioethics and Committee on Hospital Care. *Pediatrics.* 2000;106:351-357.
3. Masri C, et al. *J Palliat Care.* 2000;16(Suppl):S45-S52.