Impact of allogenic packed red blood cell transfusion on nosocomial infection rates in the critically ill patient*

Robert W. Taylor, MD, FCCM; Lisa Manganaro, RN; Jacklyn O’Brien, RN; Steven J. Trottier, MD, FCCM; Nadeem Parkar, MD; Christopher Veremakis, MD

Objective: To determine whether critically ill patients who receive allogenic packed red blood cell transfusions are at increased risk of developing nosocomial infections during hospitalization.

Design: Retrospective database study utilizing Project IMPACT.

Setting: A 40-bed medical-surgical-trauma intensive care unit in an 825-bed tertiary referral teaching hospital.

Patients: One thousand seven hundred and seventeen patients admitted to the medical-surgical-trauma intensive care unit.

Measurements and Main Results: Data were collected by using the Project IMPACT database. Nosocomial infection rates were compared among three groups: the entire cohort, the transfusion group, and the nontransfusion group. We determined the nosocomial infection rates in these groups while adjusting for probability of survival by using Mortality Prediction Model (MPM-0) scores, age, gender, and number of units of packed red blood cells transfused. The average number of units transfused per patient was 4.0. The nosocomial infection rate for the entire cohort was 5.94%. The nosocomial infection rates for the transfusion group (n = 416) and the nontransfusion group (n = 1301) were 15.38% and 2.92%, respectively (p < .0001 chi-square). Transfusion of packed red blood cells was related to the occurrence of nosocomial infection, and there was a dose-response pattern (the more units of packed red blood cells transfused, the greater the chance of nosocomial infection; p < 0.0001 chi-square). The transfusion group was six times more likely to develop nosocomial infection compared with the nontransfusion group. In addition, for each unit of packed red blood cells transfused, the odds of developing nosocomial infection were increased by a factor of 1.5. A subgroup analysis of nosocomial infection rates adjusted for probability of survival by using MPM-0 scores showed nosocomial infection to occur at consistently higher rates in transfused patients vs. nontransfused patients. A second subgroup analysis adjusted for patient age showed a statistically significant increase in rates of nosocomial infection for transfused patients regardless of age.

Conclusions: Transfusion of packed red blood cells is associated with nosocomial infection. This association continues to exist when adjusted for probability of survival and age. In addition, mortality rates and length of intensive care unit and hospital stay are significantly increased in transfused patients. (Crit Care Med 2002; 30:2249–2254)

Keywords: anemia; blood transfusion; immune modulation; immune response; infection; intensive care unit; nosocomial infection; packed red blood cells; red blood cells; transfusion

A

nemia is pervasive in the intensive care unit (ICU) (1), and its causes are multifactorial. Hemorrhage, decreased red blood cell production, increased destruction, and sequestration are the fundamental mechanisms. Many patients are admitted to the ICU following hemorrhage from trauma or operation. Production of red blood cells by the bone marrow is commonly decreased in acutely ill patients consistent with the anemia of chronic disease. Premature destruction of red blood cells may occur in critically ill patients because of intra- or extravascular hemolysis or splenic sequestration. Anemia is common in patients admitted to the ICU with chronic illness. Blood loss in the ICU is very common. Occult or overt blood loss from phlebotomy, stress gastritis, or other sites also causes anemia in the ICU. Smoller and Kruskall (2) found that an average of 65 mL of blood was phlebotomized from ICU patients per day.

Packed red blood cell (PRBC) transfusions are routinely administered in the ICU (3) Hebert et al. (4) reported that 28% of 4,875 patients admitted to six tertiary ICUs in Canada received PRBC transfusion. Up to 50% of ICU patients received at least one unit of PRBC during their ICU stay in a study reported by Littenberg et al. (5). Corwin and colleagues (1) reported that 85% percent of patients with an ICU stay of >1 wk receive at least one unit of PRBC during their stay. Few would argue with PRBC transfusion in a hemodynamically unstable patient during active hemorrhage. However, precise indications for transfusion of PRBCs in other settings remain controversial in the critically ill patient. Guidelines for blood transfusion have been published by several organizations including a National Institutes of Health consensus conference on perioperative transfusion of red blood cells (6), the American College of Physicians (7), and the Canadian Medical Association (8). These guidelines recommend that blood should not be transfused prophylactically. They suggest that the threshold for transfusion should be between 7 and 8 g

*See also p. 2389.

From the Department of Critical Care Medicine, St. John’s Mercy Medical Center, St. Louis, MO.

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Address requests for reprints to: Robert W. Taylor, MD, FCCM, Department of Critical Care Medicine, Suite 4006B, St. John’s Mercy Medical Center, St. Louis, MO 63141.

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of hemoglobin per deciliter in noncritically ill patients.

Despite these published guidelines, we have observed that many ICU patients appear to be transfused prophylactically based on a seemingly arbitrary level of hemoglobin rather than on true physiologic need. Indeed, investigations looking systematically at transfusion indications have reported that up to 57% of transfusions may be inappropriate (9–11). Herbert et al. (12) studied a restrictive strategy of transfusion (trigger for transfusion hemoglobin <7 gm/dL) vs. a liberal strategy of transfusion (trigger for transfusion hemoglobin <10 gm/dL) in critically ill patients. The restrictive strategy was found to be at least as effective and perhaps superior to the liberal strategy. Patients with acute myocardial infarction and unstable angina were excluded from the study.

Significant risks are associated with PRBC transfusion. As many as 20% of patients receiving PRBC transfusion may experience some type of adverse event (13–48). Although most of these adverse events are minor, some increase patient morbidity and mortality (Table 1). Recent concern over human immunodeficiency virus and hepatitis C virus transmission during PRBC transfusion has heightened public awareness of the risks associated with blood transfusion. In fact, transmission of these viruses with modern blood banking practices is exceedingly rare. The estimated risk of transfusion-associated human immunodeficiency virus infection is 1:200,000–1:2,000,000 and the risk of transfusion-associated hepatitis C infection is 1:30,000–1:150,000 (49).

Of much greater concern to the critically ill patient is the profound effect of allogenic blood transfusion on the immune system (50–52). Both cellular and humoral immunity is adversely affected. Following PRBC transfusion, decreased production of interleukin-2 and increased production of prostaglandin-E2 have been documented. A decrease in CD4 helper cells, interleukin-2 receptor-positive helper cells, and natural killer cells is seen, while an increase in B cells and CD8 suppressor cells occurs. Some immune functions return to normal within hours following PRBC transfusion, but evidence suggests that long-term or permanent alteration in immune function may occur (53).

The precise agents contained within PRBCs responsible for the immune modulation have not been clearly identified. Leukocytes contained within the PRBC transfusion have been implicated (54). Other components of the transfused blood may also be responsible for immunosuppression. Evidence has been mounting for over a decade suggesting that the immunosuppressive effects of PRBC transfusion are associated with increased risk of infection (55–63).

The objective of this retrospective analysis was to determine whether critically ill patients who receive PRBC transfusions are at increased risk of developing nosocomial infection (NI) during hospitalization in a multidisciplinary medical-surgical-trauma ICU compared with nontransfused patients with a similar probability of survival.

### Table 1. Adverse effects of blood transfusions

<table>
<thead>
<tr>
<th>Serious adverse effects</th>
<th>Ratio</th>
<th>References</th>
</tr>
</thead>
<tbody>
<tr>
<td>Viral hepatitis (clinical and subclinical cases)</td>
<td>1 in 200</td>
<td>14–21</td>
</tr>
<tr>
<td>Circulatory overload</td>
<td>1 in 10,000</td>
<td>22, 23</td>
</tr>
<tr>
<td>Acute lung injury</td>
<td>1 in 10,000</td>
<td>24, 22, 23</td>
</tr>
<tr>
<td>Acute hemolytic transfusion reactions</td>
<td>1 in 25,000</td>
<td>25, 22, 23</td>
</tr>
<tr>
<td>Anaphylactic hypotensive reaction</td>
<td>1 in 150,000</td>
<td>26, 22, 23</td>
</tr>
<tr>
<td>Bacterial/endotoxin reaction</td>
<td>Rare</td>
<td>27, 28</td>
</tr>
<tr>
<td>Malaria and other parasitic infections</td>
<td>Rare</td>
<td>28</td>
</tr>
<tr>
<td>Graft vs. host disease</td>
<td>Rare</td>
<td>29</td>
</tr>
<tr>
<td>Acquired immune deficiency syndrome</td>
<td>Rare</td>
<td>30–35</td>
</tr>
</tbody>
</table>

### Table 2. Nosocomial infections

<table>
<thead>
<tr>
<th>Infections not related to procedures*</th>
<th>Patients With PRBC, n (%)</th>
<th>Patients Without PRBC, n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pneumonia</td>
<td>15 (2.61)</td>
<td>16 (1.23)</td>
</tr>
<tr>
<td>Cystitis</td>
<td>12 (2.88)</td>
<td>9 (0.69)</td>
</tr>
<tr>
<td>Bacteremia/fungemia</td>
<td>23 (5.53)</td>
<td>7 (0.54)</td>
</tr>
<tr>
<td>Acute sinusitis</td>
<td>0 (0)</td>
<td>1 (0.08)</td>
</tr>
<tr>
<td>Sepsis</td>
<td>14 (3.37)</td>
<td>2 (0.15)</td>
</tr>
</tbody>
</table>

Infections related to procedures

| Pneumonia                                    | 17 (4.69)                 | 10 (0.77)                    |
| Line-related infection                        | 10 (2.40)                 | 2 (0.15)                     |

*Infections that were not present at the time of intensive care unit admission and were not associated with a specific procedure. An infection was recorded if noted in the nurses’ notes or physicians’ progress notes.
of survival. The mortality prediction model (MPM-0) was used to predict probability of survival (64). Mortality was defined as death occurring before hospital discharge. The St. John’s Mercy Medical Center Investigational Review Board approved this study.

RESULTS

The NI rate for the entire cohort was 5.94%. The NI rates for the transfusion group (n = 416) and the nontransfusion group (n = 1301) were 15.38% and 2.92%, respectively (p < .005 chi-square; Fig. 1). PRBC transfusion was related to the occurrence of NI, and there was a dose-response pattern. The more units of PRBCs transfused, the greater the chance of infection (p < .0001 chi-square). The transfusion group was six times more likely to develop NI compared with the nontransfusion group. In addition, for each unit of PRBCs transfused, the odds of developing an infection were increased by a factor of 1.5. The mean number of PRBC units transfused for patients without NI was 0.613. The mean number of PRBC units transfused for patients with NI was almost four times greater at 2.402 (Satterthwaite t-test). The unequal variance t-statistic for testing equality of these means is 7.19 with 105 degrees of freedom and p < .0001. A subgroup analysis of NI rates adjusted for probability of survival by using MPM-0 scores showed NI to occur at consistently higher rates in transfused patients vs. nontransfused patients (Fig. 2). A second subgroup analysis adjusted for patient age showed a statistically significant increase in rates of NI for transfused patients regardless of age (Fig. 3). The mortality rate for the entire cohort was 13.6%. In the transfusion group, mortality was 24.3%, while mortality in the nontransfusion group was 10.2% (p < .0001 chi-square; Fig. 4). The length of ICU stay and hospital stay were significantly longer in the transfused group compared with the nontransfused group (p < .0005 chi-square; Table 3). The patients’ gender did not impact the study findings. Forty-nine ICU admitting diagnoses were identified in the entire cohort by using Acute Physiology and Chronic Health Evaluation II diagnostic categories. There were too few patients in any one diagnostic category to determine whether the ICU admitting diagnosis influenced the probability of transfusion or NI rate.

DISCUSSION

In this study, PRBC transfusion was closely associated with NI. This association exists when adjusted for probability of survival and age. Mortality rates were significantly increased (p < .0001) in transfused patients compared with nontransfused patients. The more blood transfused, the greater the likelihood of developing an NI. Length of ICU stay and hospital stay were also significantly increased in the transfused patients.

Clear evidence links PRBC transfusion with alteration in immune function (50–54). Nichols and colleagues (55) published one of the first reports that linked transfusion with an increased incidence of infection. They studied postoperative infection rates in trauma patients with intestinal perforation and documented that the number of blood transfusions positively correlated with postoperative infection rate. Edna and Bjerkeset (56) also found an association between infection and blood transfusion in trauma pa-
tients. Vamvakas and Carven (57) re-
ported that colorectal surgery patients
receiving perioperative allogenic blood
transfusion have strikingly longer hospi-
tal stays than similar patients who do not
receive transfusions. The main contribu-
tion to the increased length of stay was a
higher incidence of postoperative infec-
tion in recipients of PRBC transfusions.
In separate studies, postoperative infec-
tion rates were increased in transfused
patients undergoing colorectal surgery
secondary to trauma and cancer (58, 59).
Braga and colleagues (60) found that
transfusion of >1000 mL of blood was an
independent risk factor in development of
postoperative infection in patients under-
going operations for gastrointestinal
cancer. Ottino et al. (61) documented that
PRBC transfusion was an independent
risk factor for sternal wound infection in
2,579 consecutive open-heart procedures.
Studies show that patients with arm or
leg open fractures and burn patients have
an increased risk of infection in trans-
fused compared with nontransfused pa-
tients (62, 63). Moore et al. (65) found a
linear trend between the number of units
of PRBCs transfused and incidence of
multiple organ failure in trauma patients.

Many questions related to anemia,
blood transfusion, immunosuppression,
and NI in critically ill patients remain to
be answered. What are the precise indi-
cations for transfusion of PRBCs in the
critically ill patient? Hebert et al. (12)
suggested that a lower (7 gm/dL hemo-
globin) rather than a higher (10 gm/dL
hemoglobin) trigger for transfusion is ap-
propriate for most critically ill patients.
Although this study needs to be con-


cfirmed, we believe it is currently the best
evidence available to guide transfusion
practice in the critically ill. Because of
the pervasive nature of anemia in criti-
cally ill patients, should erythropoietin be
routinely administered to ICU patients?
In a prospective, randomized, controlled
trial, Corwin et al. (66) documented an
increase in hematocrit and a reduction in
PRBC transfusion in critically ill patients
by use of recombinant human erythro-
poietin (epoetin alfa). Further studies are
underway to better define the proper role
of epoetin alfa in this setting. Should
transfusion practices be altered such that
only leukocyte-depleted blood is used for
transfusion? Blumberg and Heal (67)
made a powerful biological and economic

Figure 3. Nosocomial infection rates by age in transfusion vs. nontransfusion groups.

Figure 4. Mortality rates.
argument that this practice would save lives and money. Regarding age of blood, there are questions about the efficacy of PRBC stored >12–15 days because of the reduced ability of transfused PRBC to improve tissue oxygenation. PRBCs stored >15 days lose adenosine triphosphate, thus causing a decrease in deformability that affects the transportation of oxygen in the microcirculation. In septic models, old red blood cells have been shown to sludge within capillaries, thereby affecting tissue oxygenation at the microcirculatory level (68).

This study differs from previously published reports because the patients were stratified by probability of survival and NI rates were compared in transfused patients and nontransfused patients with equivalent probability of survival scores. Because of the retrospective, observational design of this investigation, potential limitations in interpretation of the study findings must be acknowledged. The results of this investigation as well as others strongly suggest that PRBC transfusion is associated with altered immune function, increased NI rates, increased organ failure, increased length of ICU stay, increased length of hospital stay, and increased mortality rates. Therefore, randomized, prospective studies to further investigate these findings should be undertaken.

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