



# PULMONARY AND CRITICAL CARE BULLETIN

Vol. XIV, No. 3, July 2008  
 Website : <http://indiachest.org>  
 (pp. 17 to 24)

## IN THIS ISSUE

### 1. MANAGEMENT OF ANEMIA IN THE INTENSIVE CARE UNIT & TRANSFUSION RELATED ACUTE LUNG INJURY

**Dr. Alok Nath, M.D.**  
 D.M. Fellow,  
 Department of Pulmonary Medicine,  
 PGIMER, Chandigarh

## Published under the auspices of

Pulmonary C.M.E. Programme of  
 The CHEST  
 (Chest Health Care, Education & Research Trust)

## Editorial Board

Dr. D. Gupta, Chief Editor  
 Dr. S.K. Jindal  
 Dr. A.N. Aggarwal  
 Dr. Ritesh Agarwal  
 Dr. Navneet Singh  
 Department of Pulmonary Medicine,  
 Postgraduate Institute of Medical  
 Education & Research, Chandigarh

## Subscription

Annual : Rs. 100

Life Subscription : Rs. 700

Subscription should be paid through a draft drawn in favour of "The CHEST, PGI, Chandigarh: Add bank charges (Rs.50) for outstation cheques.

**Address all correspondence to the Chief Editor**

## MANAGEMENT OF ANEMIA IN THE INTENSIVE CARE UNIT & TRANSFUSION RELATED ACUTE LUNG INJURY

### INTRODUCTION

Anemia is a common occurrence in Intensive Care Units (ICUs). It is mostly managed with blood transfusions. The transfusion requirements are increasing globally and it has been estimated that in the United States nearly 15 million units are donated and 14 million units transfused annually. This has a direct bearing on the cost of health care. This increase in the cost is due to increasing requirements and rigorous screening procedures required for the processing of blood and blood products.

### EPIDEMIOLOGY

About 16 % of the medical ICUs and 27 % of the surgical ICU patients receive transfusions daily in the USA. A number of studies have documented the high rates of prevalence of anemia among critically ill patients and of transfusion requirements in ICUs (see Table 1). More than 90% of critically ill patients have subnormal hemoglobin (Hb) after three days of ICU stay.

**Table 1: Comparison of the major trials on transfusions in critically ill patients**

Study	TRICC Investigators (Canada) 1998	ABC trial (Western Europe) 2002	North Thames Blood Interest Group (UK) 2002	CRIT Study (USA) 2004
No of patients	5298	3534	1247	4852
Mean admission Hb (gm/dL)	9.9 ± 2.2	11.3 ± 2.3	--	11.0 ± 2.4
Percentage of patients transfused in ICU	25%	37%	53.4%	44.1%
Mean transfusions per patient (units)	4.6 ± 6.7	4.8 ± 5.2	5.7 ± 5.2	4.6 ± 4.9
Mean pre-transfusion Hb (gm/dL)	8.6 ± 1.3	8.4 ± 1.3	8.5 ± 1.4	8.5 ± 1.7
Mean ICU length of stay (days)	4.8 ± 12.6	4.5	--	7.4 ± 7.3
ICU mortality	22%	10.5%	21.5%	13%
Hospital mortality	--	20.2%	--	17.6%
Admission APACHE II score (mean)	18.0 ± 11.0	14.8 ± 7.9	18.1 ± 9.1	19.7 ± 8.2

In one series, the mean Hb of ICU patients was 11.3 gm/dL with 29 % having Hb levels of less than 10 gm/dL. About 85 % of patients with an ICU stay of more than 1 week received blood transfusion with a mean of 9.5 ± 0.8 units/patient. The reason for transfusion was not clear in about 29 % of the patients.

In the ABC trial (Western Europe 2002) which included 3534 patients, the mean Hb was 11.3 ± 2.3 gm/dL. Twenty nine percent of the patients had Hb less than 10

---

---

gm/dL. The overall transfusion rate was 37%. Surgical patients received more transfusions as compared to medical patients. Seventy three percent of patients who stayed in the ICU for more than 7 days received blood transfusions. The overall mean pre-transfusion Hb was  $8.4 \pm 1.3$  gm/dL.

In another large study called the CRIT study conducted in the USA, 4892 patients were enrolled from among 284 ICUs. The mean baseline Hb was  $11.0 \pm 2.4$  gm/dL and the mean decrease was to a value of  $9.8 \pm 1.4$  gm/dL. Forty four percent patients were transfused during the course of their ICU stay ( $4.6 \pm 4.9$  units/patient). An ICU stay of more than 7 days was significantly associated with more transfusions (63% vs 33.4%;  $p < 0.0001$ ). The mean pre-transfusion Hb was  $8.6 \pm 1.7$  gm/dL in this study.

A post hoc analysis of CRIT study involving 1247 patients was done by Rao et al. It was seen that the mean baseline Hb was  $11.1 \pm 2$  gm/dL. A total of 55 % patients were transfused. There was higher mortality among transfused patients. The average pre-transfusion Hb was 9 gm/dL in 75% of transfusion episodes. Seventy two percent of patients were transfused for low Hb and rest for hemorrhage.

In a study by Nguyen and colleagues ( $n = 91$ ) which was a prospective, single-institution observational study, the mean fall in Hb averaged  $0.52 \pm 0.69$  gm/dL per day. After the 3rd ICU day, the change in Hb concentrations was inversely proportional to the APACHE II and SOFA scores. Hemoglobin concentrations decreased by  $0.44 \pm 0.70$  gm/dL per day in the non septic patients and  $0.68 \pm 0.66$  gm/dL per day in the septic patients ( $p = 0.13$ ). The authors concluded that Hb concentrations typically decline by more than 0.5 gm/dL per day during the initial days of ICU stay in non-bleeding patients. Beyond the third ICU day, Hb concentrations remained relatively constant in non septic patients but continued to decrease in septic patients.

There were many similarities in the above trials (see table 1). The vast majority of patients in ICU had anemia. The transfusion trigger was usually about 8.5 gm/dL. Transfusion rates were increased in patients with long ICU stay. Patients with higher age received more transfusions and the most common reason for transfusion was anemia.

## **PATHOPHYSIOLOGY OF ANEMIA IN THE ICU**

The most common cause incriminated in the etiology of anemia in the ICU is frequent blood sampling. Clinically apparent and/or occult blood loss from the gastrointestinal tract, blood loss at the time of surgical procedures preceding admission to the ICU, blood loss due to trauma preceding admission to the ICU are other causes. It has also been demonstrated that there are inappropriately low circulating concentrations of erythropoietin (EPO) in these patients and there is diminished responsiveness of bone marrow precursor cells to EPO.

Erythropoietin is a glycoprotein that regulates RBC production by modulating the survival and proliferation of erythroid colony-forming units in the bone marrow. Diminished tissue oxygen tension is the primary stimulus for EPO release, and in humans, the kidney is the main organ responsible for EPO production. Tissue oxygen tension is thought to regulate

EPO production via an oxygen-responsive transcription factor called hypoxia-inducible factor (HIF)-1.

HIF-1 is a heterodimeric transcription factor composed of a HIF-1 $\alpha$  chain and a constitutively expressed HIF-1 $\beta$  chain. HIF-1 $\alpha$  protein is present at extremely low levels under normoxic conditions. Newly synthesized HIF-1 $\alpha$  is subjected to polyubiquitination and targeted for degradation in proteosomes. When cells become hypoxic, polyubiquitination of nascent HIF-1 $\alpha$  decreases and cytosolic levels of this protein increase. HIF-1 $\alpha$  combines with HIF-1 $\beta$  to form the fully functional transcription factor, which is capable of binding to cis - acting regulatory elements in a number of hypoxia-responsive genes, including the gene for EPO.

It has been observed that the response to endogenous EPO is blunted in critically ill patients. Rogiers and coworkers addressed this issue and showed that a significant inverse correlation was observed between hematocrit values and EPO levels in the control individuals ( $r = -0.81$ ;  $p < 0.001$ ). Ambulatory patients with iron-deficiency anemia served as the control group. No such correlation was apparent for the critically ill patients ( $r = -0.09$ ;  $p = \text{NS}$ ).

Krafte-Jacobs and coworkers estimated EPO levels in critically ill pediatric patients instead of adults. In 21 acutely anemic critically ill patients, the mean Hb concentration was  $7.8 \pm 1.5$  gm/dL and the mean EPO level was  $39 \pm 62$  mU/ml. In comparison, the mean Hb concentration in 21 chronically anemic patients was  $7.3 \pm 1.3$  gm/dL and the mean EPO level was  $861 \pm 758$  mU/ml .

Similar findings were shown by Von Ahsen and coworkers. In patients in a medical ICU, these investigators also found that EPO levels were inappropriately low for the degree of anemia in critically ill adults. In addition, they found that iron deficiency (plasma transferrin saturation less than 20%) is also common in critically ill patients. Inappropriately low EPO levels persist for the duration of critical illness.

Interestingly, critically ill patients appear to retain their responsiveness to exogenous EPO. Three randomized prospective trials documented that administration of recombinant human EPO (rHuEPO) can stimulate reticulocytosis and increase circulating Hb concentration in critically ill adults. The cumulative number of units of packed RBCs transfused was significantly less in the rHuEPO group than in the placebo group. Patients receiving rHuEPO were less likely to undergo transfusions.

Functional iron deficiency is a major cause for anemia in critically ill patients. Laboratory studies typically reveal a low serum iron concentration, low transferrin level, low transferrin saturation, and elevated serum ferritin concentration. Circulating iron concentrations are low and less free iron is available to support erythropoiesis. In patients with multi organ failure, victims of multiple trauma, and patients recovering from major surgery, similar results were observed. Low concentrations of vitamin B12 and folic acid, also might contribute to ineffective erythropoiesis in critically ill patients. Von Ahsen and coworkers observed normal vitamin B12 levels but abnormally low folic acid

concentrations in some anemic ICU patients. RBC size was not increased, and therefore the significance of folic acid deficiency as a factor contributing to ICU-acquired anemia remains uncertain. Rodriguez and colleagues reported iron deficiency in 9% of ICU patients, 2% of the patients were deficient in vitamin B12 and another 2% suffered from folic acid deficiency.

## TRENDS IN TRANSFUSION PRACTICES

There have been considerable variations in RBC transfusion practices in critical care in the past. There are several reasons for this. The optimal therapy for anemia has not been fully defined as yet. There is no universal transfusion trigger. Uncertainties still exist concerning the most appropriate Hb concentration for patients with significant cardiorespiratory disease.

A Canadian scenario-based national survey to characterize the contemporary RBC transfusion practice in the critically ill was performed. Most respondents were from internal medicine (56%). Baseline Hb transfusion thresholds averaged from  $8.3 \pm 1.0$  gm/dL in a scenario involving a young stable trauma victim to  $9.5 \pm 1.0$  gm/dL for an older patient after gastrointestinal bleeding. Transfusion thresholds differed significantly between each of the four separate scenarios namely, cardiovascular disease, respiratory failure, major surgery and trauma. Except congestive heart failure, all clinical factors (including age, APACHE II score, preoperative status, hypoxemia, shock, lactic acidosis, coronary ischemia, and chronic anemia) significantly modified the transfusion thresholds. A statistically significant difference in baseline transfusion thresholds was noted across four major regions.

Hebert and coworkers, in a study involving 6 tertiary level ICUs and 5298 patients also studied the transfusion practices. They reported that the overall number of transfusions per patient day in the ICU averaged  $0.95 \pm 1.39$  and ranged from  $0.82 \pm 1.69$  to  $1.08 \pm 1.27$  between institutions. Independent predictors of transfusion thresholds (pre transfusion Hb) included patient age, admission APACHE II score and institution. A very significant institution effect persisted even after multivariate adjustments for age and for APACHE II score, and within four diagnostic categories (cardiovascular disease, respiratory failure, major surgery and trauma). Thirty five % (202 out of 576) of pre transfusion Hb was in the range 9.5–10.5 gm/dL, and 80% of the orders were for 2 units of blood. Acute bleeding (35%) and augmentation of oxygen delivery (25%) were the commonest reasons for transfusion.

## ADVERSE EFFECTS OF TRANSFUSION

### RBC storage and physiological alterations

RBCs stored for 15 days have a decreased ability to deform and unload oxygen in the microcirculation. Complete depletion of 2, 3-diphosphoglycerate concentrations occur after 2 weeks of storage, thereby reducing the ability of transfused RBCs to offload oxygen by 50%. RBC shape changes from discoid to spherocytic, become more adhesive, lose membrane lipid, and a decrease in cellular deformability causing capillary sludging and obstruction, thereby predisposing the patient to tissue ischemia and decreased oxygen delivery.

RBC antioxidants get depleted during the storage of blood. This increases oxidative injury of the cytoskeleton proteins and membrane phospholipids, and results in the conversion of Hb to methemoglobin, which is incapable of binding oxygen. The resultant tissue ischemia predisposes critically ill patients to an increased risk of infections and organ dysfunction.

### Immunological alterations

Many studies have indicated that leukocyte contamination of erythrocyte or platelet preparations can cause a wide range of physiologic and immunologic dysfunction in recipients (Table 2).

**Table 2 : Transfusion related immunomodulation**

Immune induction	Immune tolerance
Transfusion reactions	Nosocomial infections
Transfusion associated Graft Versus Host Disease (TAGVHD)	Cancer recurrence
Transfusion related acute lung injury (TRALI)	Enhanced survival of allograft
Alloimmunization	
Autoimmune diseases	

The accumulation of various soluble bioactive substances occurs during storage, and includes histamine, lipids, cytokines, fragments of cellular membranes, soluble human leukocyte antigen (HLA) class I antigens, many of which are white blood cell (WBC)-derived and play an important role in transfusion-induced immunomodulation (TRIM). The transfusion of stored RBCs has been shown to trigger neutrophil activation, and the release of various cytokines like IL-1, IL-6 and IL-8 and secretory phospholipase A2, thereby predisposing the patient to systemic inflammatory response syndrome. Arginase release from stored RBCs has been implicated in TRIM. Arginine stimulates lymphocyte function while arginase impairs it. A relationship between the transfusion of non-leukocyte-reduced RBCs that had been stored for 14 days and the associated increased length of stay in the ICU has been described. Length of stay was significantly associated with the aging of RBCs, the total number of units transfused, and the median storage duration.

When transfused patients were analyzed separately from nontransfused patients, only RBC storage for 14 days was independently predictive of length of stay.

A positive correlation between mortality in patients with severe sepsis and the age of the non-leukocyte-reduced RBC units that were transfused has also been described. The median age of RBCs transfused to survivors was 17 days (range 5-35 days) compared with 25 days (range 9-36 days) for non survivors ( $p < 0.0001$ ). Allogenic blood transfusion leads to a multitude of immune dysregulation. Various types of interactions between T lymphocytes and antigens occur and induce the production of cytokines such as IL-2 and IL-4, which in turn activate T helper (Th) type 1 (IL-2) and Th-2 (IL-4) subsets, respectively. Th-2 subset activation leads to B-cell proliferation and antibody production. Blood transfusions may lead to development of two

different situations, alloimmunization or tolerance induction.

## Infections

A list of different types of infections related to transfusions is given in Table 3.

**Table 3 : Transfusion related infections**

Type of Infection	Infection
Transfusion-transmitted infections	CMV, EBV West Nile virus Human herpes virus-6,7,8 Parvovirus B19 Human T-cell leukemia/lymphoma virus-I and II HIV-1 & 2 Hepatitis B & C <i>Toxoplasma gondii</i> <i>Trypanosoma cruzi</i> Babesiosis
Newer agents	TTV SEN-V
Adverse effects of leukocyte contamination	Febrile non-hemolytic transfusion reactions Refractoriness to platelet transfusions TRALI TAGVHD Immune suppression and allograft tolerance Development of possible autoimmune diseases

Several studies have clearly identified the increased risk of nosocomial infections among critically ill transfused patients. The possible mechanisms are:

1. A TRIM effect mediated by immunologically active allogenic WBCs that down-regulate the immune function of recipients
2. A TRIM effect mediated by soluble biological response modifiers that are released in a time-dependent manner from WBC granules or membranes into the supernatant fluid of RBCs during storage
3. A TRIM effect mediated by soluble HLA peptides or other soluble mediators that circulate in allogenic plasma
4. A possible non-TRIM effect causing postoperative organ dysfunction that predisposes patients to infections.

It is difficult to establish a cause-and-effect relationship and to separate the effects of transfusion with the effect underlying condition per se. The results of several prospective and randomized studies have supported these findings. In these studies, the underlying hypothesis links the immunodepressant effect of transfusion to the presence of leukocytes (or leukocyte products).

With the above data, it can be hypothesized that giving patients transfusions with leukocyte-reduced blood should result in reduced morbidity and mortality compared with patients receiving transfusions with non-leukocyte-reduced blood. Meta-analyses of these substantial studies have failed to identify a statistically significant effect of leukocyte reduction. A recent study evaluating clinical outcomes after the institution of a universal leukocyte reduction program in Canada noted a reduction in hospital mortality after the introduction of this program.

## Transfusion related acute lung injury

Transfusion related acute lung injury (TRALI) is a life-threatening complication of allogenic transfusions and is the third most common cause of transfusion-associated death. The estimated prevalence of TRALI is 1 in 1120 cellular component transfusions with a mortality rate ranging from 1 to 10%. Passively transferred donor blood containing anti-leukocyte antibodies (i.e. IgG) directed against recipient leukocytes causes pulmonary sequestration, complement activation, and lung injury.

## Transfusion associated Graft Versus Host Disease

Transfusion associated Graft Versus Host Disease (TAGVHD) is a rare but lethal complication with a mortality rate of 90%, in which immunocompetent donor cells proliferate and attack host hemopoietic cells, skin, liver, and bile duct epithelial cells. It is more common in immunocompromised patients. The risk factors for the development of TAGVHD include patients receiving transfusions from HLA-homozygous donors who are haplo-identical, the use of relatives as donors, male recipients and fresh blood containing viable lymphocytes. Only a small fraction of such transfusions cause TAGVHD. Irradiated and leukodepleted cellular products avert the development of TAGVHD.

## PREVENTION OF ANEMIA IN ICU

Various strategies have been proposed to decrease the incidence of anemia in the ICU, but the practical ones are:

1. Decreasing diagnostic blood loss "Vampirism"
2. The use of a blood conservation device to minimize diagnostic phlebotomy
3. Methods to prevent intra-operative and periprocedural blood loss
4. "Point of care" testing
5. Non invasive hemodynamic monitoring

## MANAGEMENT OF ANEMIA IN ICU

### Blood Transfusion

In the acute setting, this is the commonest mode of treatment offered to the patients. As discussed above, the risks and benefits should be well balanced before embarking upon the decision to transfuse a given patient. The threshold for initiating

transfusion therapy should be high and a pre-transfusion value of 7 gm/dL [“restrictive strategy”] seems to be a reasonable value on the basis of available evidence. An exception to this rule is patients with acute myocardial infarction (MI) and unstable angina where Hb value of more than 10 gm/dL is necessary to ensure adequate oxygen delivery to the tissues. Directed transfusion should be avoided to prevent TRALI and TAGVHD and leukoreduction / filtering should be practiced.

There had been a lot of debate about the liberal and restrictive strategies of blood transfusion. In the CRIT study, which was a multicenter, prospective, randomized clinical trial, 69 normovolemic critically ill patients with Hb values less than 9 gm/dL were included. Patients were randomly assigned to one of two RBC transfusion strategies. Hemoglobin values were maintained between 10 and 12 gm/dL in the liberal group and 7 and 9 gm/dL in the restrictive group. Daily Hb values averaged 9 gm/dL in the restrictive group and 10.9 gm/dL in the liberal group ( $p < 0.001$ ). The restrictive group received 2.5 units per patient compared with 4.8 units per patient in the liberal group. No differences in 30-day mortality (24% vs. 25%; 95% confidence interval [CI] –19% to +21%), ICU mortality and 120-day mortality were observed. Survival analysis comparing time until death in both groups did not reveal any significant difference. Organ dysfunction scores were also similar. So it was concluded that a more restrictive approach to the transfusion of RBCs may be safe in critically ill patients.

In the TRICC study, 838 critically ill patients were randomized to liberal and restrictive transfusion strategy groups. Thirty day mortality rates were similar in the two groups. Hospital mortality rate was significantly lower in the restrictive strategy group (22.2% vs. 28.1%;  $p = 0.05$ ). Mortality rates were also significantly lower with the restrictive strategy among patients who were less acutely ill and young. Again it was concluded that a restrictive strategy of RBC transfusion in critically ill patients was at least as effective as, and possibly superior to, a liberal transfusion strategy with exception of patients with acute MI and unstable angina.

Similarly, in the ABC trial, a higher mortality was observed in patients who were transfused [ICU mortality 18.5% vs. 10.1%,  $p < 0.001$ ; overall mortality 29.0% vs. 14.9%,  $p < 0.001$ ; 28-day mortality 22.7% vs. 17.1% ,  $p = 0.02$ ].

In the post hoc analysis for all patients with cardiovascular disease (see table 4), overall mortality rates were similar in both groups. Changes in multiple organ dysfunction from baseline scores were significantly less in the restrictive transfusion group. Among patients with severe ischemic heart disease ( $n = 257$ ), lower but statistically non-significant absolute survival rates were seen in the restrictive transfusion group compared to the liberal group. Thus, a restrictive RBC transfusion strategy appears to be generally safe in most critically ill patients with cardiovascular disease, with the possible exception of patients with acute MI and unstable angina.

**Table 4 : Comparison of patients with cardiovascular diseases in restrictive and liberal transfusion strategy groups**

	Restrictive Strategy	Liberal Strategy	p value
No of patients	160	197	
30-day mortality	23%	23%	1.0
ICU mortality	19%	16%	0.49
Hospital mortality	27%	28%	0.81
Organ dysfunction scores, change from baseline	0.23 ± 4.2	1.28 ± 4.4	0.023
Mean hemoglobin (gm/dL)	8.5 ± 0.62	10.3 ± 0.67	<0.01
Mean blood transfusion (units)	2.4 ± 4.1	5.2 ± 5.0	<0.01

So it can be concluded that a “restrictive” transfusion strategy is superior to a “liberal” strategy and each unit of blood transfused confers an additional risk for occurrence of the various adverse effects listed above. Decisions to initiate transfusion therapy for patients who are critically ill should be carefully made.

### Iron Supplementation

‘Functional iron deficiency’, when diagnosed by cytometry, is present in 35% of patients on admission to the ICU. Disturbed iron metabolism from enhanced immune activation has also been documented in surgical ICU patients and in patients with multiple organ dysfunction syndrome. Iron supplementation in critically ill patients has not been found to improve hematological parameters. Moreover, both oral and parenteral iron supplementation in critically ill patients has been shown to be counterproductive. Increased susceptibility to infections, increased incidence of infections and iron overload are common adverse effects related to iron supplementation in critically ill patients. This effect is believed to be related to the influence of iron on the immune system. The cytokine-mediated defect in iron release from macrophages in humans is said to have evolved as a primitive mechanism of defense against microbial pathogens to limit their access to iron.

Studies of iron supplementation, although plentiful in the chronic kidney disease (CKD) population, in pregnancy and in the pediatric setting, are lacking in ICU population. Another clinical concern is the risk of its effect on the physiological redox potential. During biological stress, free radicals are formed. These radicals can have detrimental effects at different cellular levels (such as nucleic acid modification) and are involved in many biological processes that can damage lipid and protein membranes. In a few studies, it has been shown that the requirement of EPO was reduced with iron supplementation. These studies were mainly conducted in the CKD population and patients undergoing orthopedic surgery. However, the preferred route and iron formulation have not been addressed to, in these studies.

Iron deficiency is noted in a small subset of critically ill patients and iron supplementation following identification of such patients is appropriate. Mostly anemia is multifactorial, as is usually the case in a critically ill patient. Iron alone may not

be sufficient to stimulate erythropoiesis but may be useful as an adjunct with EPO. Until proven otherwise, clinicians should probably monitor iron parameters on a regular basis, if they elect to administer iron and EPO therapies concomitantly. Whenever given, parenteral iron should be given rather than oral iron. Oral iron may be poorly absorbed, associated with increased gastrointestinal distress and may not maintain iron stores in critically ill patients receiving EPO therapy. The optimal dose, route, and timing of iron administration in critically ill patients, especially when given concurrently with EPO therapy, remains an open issue that requires further study.

### Erythropoietin

A blunted EPO response resulting from inhibition of the EPO gene by inflammatory mediators is observed in the critically ill. Some inflammatory cytokines directly inhibit RBC production by the bone marrow and may produce the distinct abnormalities of iron metabolism. rHuEPO therapy at a dose of 600 units/kg in patients with multi organ dysfunction syndrome (MODS) was shown to stimulate erythropoiesis. rHuEPO therapy resulted in an almost 50% reduction in RBC transfusions as compared with placebo. In patients with hematocrit below 38% on ICU day 3, rHuEPO was given at a dose of 300 units/kg daily for 5 days, followed by every other day until ICU discharge. Despite receiving fewer RBC transfusions, patients in the rHuEPO group had a significantly greater increase in hematocrit.

In a recent randomized trial involving 1302 patients, rHuEPO was given weekly at a dose of 40,000 units. All patients received three weekly doses, and patients who remained in the ICU on study day 21 received a fourth dose. A 10% reduction in the number of patients receiving any RBC transfusion (60.4% with placebo vs. 50.5% with rHuEPO,  $p < 0.0004$ ) and a 20% reduction in the total number of RBC units transfused (1963 units with placebo vs. 1590 units with rHuEPO,  $p < 0.001$ ) was observed. Similar to the initial study, the increase in Hb from baseline was greater in the rHuEPO group.

Although similar results were seen in other small randomized trials, final clinical outcomes did not show significant improvements. However, these studies were not designed to address these issues. Further studies are needed to determine whether there are any benefits in clinical outcomes associated with a reduction in the exposure to RBC transfusion with rHuEPO administration among critically ill patients admitted to ICUs/long-term acute care facilities.

### Hemoglobin Based Oxygen Carriers

Oxygen-carrying solutions with crystalloid and colloid elements may be effective in many clinical situations. By the early to mid-1990s, it became clear that pure solutions of Hb were needed as starting materials, and technologies were being developed to synthesize such compounds. Unfortunately, these efforts proved to be prohibitively expensive.

The properties of various hemoglobin based oxygen carriers (Hb based O<sub>2</sub> carriers) are shown in table 5.

**Table 5 : Comparison of commercially available hemoglobin based oxygen carriers**

Details	Product name		
	PolyHeme®	Hemopure® (HBOC-201)	HemoLink™ (Hb-rafimer)
Company	Northfield Laboratories, (Evanston, IL, USA)	Discove Corporation (Cambridge, MA, USA)	Hemosol Inc. (Toronto, Canada)
Modification method	Pyridoxylated glutaraldehyde polymerization (polymer)	Glutaraldehyde polymerization (polymer)	Crosslinking with D-rafinesc glutaraldehyde polymerization (oligomer)
Hemoglobin source	Human hemoglobin	Bovine hemoglobin	Human hemoglobin
Hemoglobin concentration (g/dL)	10	13	10
Molecular weight	NR (< 54 kDa: < 0%)	Average molecular weight (MW) < 64 kDa: < 5%	250 kDa: 50% < 500 kDa: < 5%
pH	NR	7.6-7.9	7.5
PSt (horq)	26-32	28	52
Viscosity (cP)	NR	1.3	1.14
Shelf life	>1 year	>1 year	>1 year

All these compounds are in phase II/III trials. The addition of Hb based O<sub>2</sub> carriers to the armamentarium is welcome and may allow us to focus on the underlying issues of when to transfuse and what to use to accomplish the goal.

### TRANSFUSION RELATED ACUTE LUNG INJURY

The term transfusion related acute lung injury (TRALI) was first coined by Popovsky et al in 1983. Previously, it had been referred to by various terms like pulmonary hypersensitivity reaction, allergic pulmonary edema, noncardiogenic pulmonary edema and pulmonary leukoagglutinin reaction. It is primarily characterized by non-cardiogenic pulmonary edema temporally related to the transfusion of blood products. It is associated with all plasma-containing blood products, but most commonly involves whole blood, packed RBCs (PRBCs), fresh-frozen plasma and platelets. TRALI has also occurred after the transfusion of cryoprecipitate and intravenous immunoglobulin (IVIG).

The most common symptoms associated with TRALI are dyspnea, cough, and fever. Systemic hypotension and hypertension both have been reported. It can be sudden and fulminant. It most commonly occurs between 1 and 2 hours after the initiation of transfusion, but may develop within 30 minutes. Almost all reactions occur within 6 hours from the start of a transfusion. It remains an under-recognized and under-reported entity. The reported incidence is 0.02-0.16 %. TRALI is the third most common cause of fatal transfusion reactions next to ABO blood type incompatibility and hepatitis.

The largest series of TRALI included (Popovsky and Moore, Mayo clinic 1985) 36 cases over 2 years. All patients in that study required oxygen supplementation and 72% required mechanical ventilation. Bilateral pulmonary infiltrates were present in all patients and rapidly resolved (within 96 hours) in 81% of the patients. The mortality was only 6% with no survivors having long-term sequelae. The 5-8% mortality rate in TRALI cases distinguishes it from ALI/ARDS, which has a mortality rate of 30-50% .

---

---

## Pathophysiology

A “two-hit” hypothesis has been proposed in the pathogenesis of TRALI. The first hit is thought to be the underlying condition of the patient, with the second hit being the transfusion of injurious blood products. Conditions for producing the first insult in TRALI include surgery, sepsis, trauma, and massive transfusions themselves. There is controversy as to what constitutes the second insult in TRALI.

The antibody theory remains the most inclusive and published etiology of TRALI which has been amply cited in literature. Donor antibodies attach to specific antigens on primed neutrophils leading to the release of oxidative and nonoxidative products that damage the pulmonary endothelium and lead to an increased permeability pulmonary edema. Rarely recipient antibodies attack donor WBCs and produce TRALI. TRALI can occur with the transfusion of only 10 to 15 ml of plasma.

In approximately 10%, no leukocyte antibody can be found in either the donor or recipient. Biologically active lipids are breakdown products of cell membranes that normally accumulate in older, cellular blood components. Lysophosphatidylcholines have been identified as a component of these lipids and have been shown to prime neutrophils. The main weakness of this theory (lipid theory) is that it requires cellular blood products. Fresh-frozen plasma, a blood product often implicated in TRALI, does not possess these biologically active lipids.

Both the theories are however not mutually exclusive and may even be complimentary. Threshold effects may be present that could potentially allow both mechanisms to participate in injury.

## Risk Factors

Various risk factors identified in the causation of TRALI include :

1. Recent surgery
2. Sepsis
3. Trauma
4. Massive transfusions
5. Hematologic
6. Malignancies
7. Cardiac disease
8. Multiparity
9. Age of blood
10. Directed transfusions

Multiparity as a risk factor has gained special attention due to its high frequency of association. A mother is exposed to the paternal HLA antigens of the in-utero fetus and antibodies can develop to these antigens. With increasing parity, the percentage of women with HLA antibodies increases. HLA sensitization of women with one to two pregnancies was 15%. For women with three or more pregnancies, the sensitization rate was 26%.

Only one RCT has been published in this regard. Intensive care patients were transfused with plasma from a multiparous donor or a control donor (presumably male or nulliparous

female donors). It was a double-blind, crossover study. Only one case of TRALI occurred after the transfusion of 200 U of plasma to 100 patients. The donor in this case was multiparous and possessed a granulocyte antibody. A small but statistically significant decrease in the PaO<sub>2</sub>/FiO<sub>2</sub> ratio occurred in the multiparous plasma group.

In support of the biologically active lipid theory of TRALI, studies of the association of older blood products with TRALI and organ failure have been published. In a nested case-control study, transfusion of older whole blood or platelets was associated with a greater incidence of TRALI compared with control subjects (4.5 days vs. 4.2 days).

Mean age of transfused PRBCs in the multiorgan failure group was significantly older (31 days vs 24 days). Relationship persisted on multivariate analysis. Unfortunately, the pulmonary injury was not detailed in these studies, nor was it mentioned if the diagnosis of TRALI was pursued.

## Diagnosis

A high index of suspicion is very important for diagnosing TRALI. Diagnosis is essentially clinical. Corroborative evidence can be obtained by analysis of the edema fluid. The edema fluid/plasma protein ratio is less than 0.65 in hydrostatic pulmonary edema, and more than 0.75 with increased permeability pulmonary edema.

Leucopenia and thrombocytopenia may also be present. The only lab feature which has been closely linked to TRALI is leukopenia. Confirmatory and definitive evidence for the diagnosis of TRALI requires investigating the donor and recipient for passively transfused antibodies.

## Treatment

Treatment is mostly supportive in the form of:

1. Immediate discontinuation of transfusion
2. Fluid resuscitation, in case of hypotension
3. Inotropic support, if needed
4. Avoidance of diuretics
5. Supplemental oxygen
6. Mechanical ventilation

Most of the times, this condition is self limited and without any long term sequelae. Prevention seems to be of paramount importance and comprises of,

1. Avoiding unnecessary transfusions
2. Notification of all transfusion reactions to the transfusion medicine department
3. Notification and identification of sensitized donors
4. Avoiding transfusions from multiparous females (practically difficult)
5. Avoiding directed transfusions
6. Avoiding old blood transfusion
7. Leukoreduction or filtration

## SUMMARY

Concerns regarding the excess morbidity and mortality associated with nonrestrictive transfusion strategies, coupled with the emerging increased risk of the transmission of newer infectious agents and immunomodulation, should prompt the reevaluation of current transfusion protocols in critically ill patients. A restrictive transfusion strategy appears to improve outcomes in critically ill patients. Lowering the trigger for transfusion to a Hb concentration of approximately 7 gm/dL in patients without coronary disease and implementing other blood conservation techniques, such as minimizing phlebotomy, the reuse of discarded blood by using closed circuits of blood sampling and the use of recombinant EPO could help to lower transfusion requirements. In addition, the implementation of prestorage leukodepleted blood, along with pathogen inactivation techniques may reduce the adverse effects associated with allogenic transfusions. The benefit of fresh leukodepleted blood (i.e. less than 15 days) compared to leukodepleted old blood (i.e. more than 15 days) has yet to be determined. However, the major clinical dilemma is not between the use of fresh vs. old blood and/or leukocyte-depleted vs. non-leukocyte-depleted blood but between stored blood vs. no blood.

## SELECT REFERENCES AND SUGGESTED READING

1. Bux J, Sachs UJ. The pathogenesis of transfusion-related acute lung injury (TRALI). *Br J Haematol* 2007; 136: 788-799.
2. Corwin HL, Gettinger A, Fabian TC, et al. Efficacy and safety of epoetin alfa in critically ill patients. *N Engl J Med* 2007; 357: 965-976.
3. Corwin HL, Gettinger A, Pearl RG, et al. The CRIT Study: Anemia and blood transfusion in the critically ill—current clinical practice in the United States. *Crit Care Med* 2004; 32: 39-52.
4. Dellinger PE, Anaya DA. Infectious and immunologic consequences of blood transfusion. *Crit Care* 2004; 8(Suppl 2): S18-S23.
5. Fink MP. Pathophysiology of intensive care unit-acquired anemia. *Crit Care* 2004; 8(Suppl 2): S9-S10.
6. Gajic O, Gropper MA, Hubmayr RD. Pulmonary edema after transfusion: how to differentiate transfusion-associated circulatory overload from transfusion-related acute lung injury. *Crit Care Med* 2006; 34(5 Suppl): S109-S113.
7. Hébert PC, Tinmouth A, Corwin HL. Controversies in RBC transfusion in the critically ill. *Chest* 2007; 131: 1583-90.
8. Hébert PC, Wells G, Blajchman MA, et al. A multicenter, randomized, controlled clinical trial of transfusion requirements in critical care. Transfusion Requirements in Critical Care Investigators, Canadian Critical Care Trials Group. *N Engl J Med*. 1999; 340: 409-417.
9. Raghavan M, Marik P. Anemia, Allogenic Blood Transfusion and Immunomodulation in the Critically Ill. *Chest* 2005; 127: 295-307.
10. Rao MP, Boralessa H, Morgan C, et al; North Thames Blood Interest Group. Blood component use in critically ill patients. *Anaesthesia* 2002; 57: 530-534.
11. Sheppard CA, Lögdberg LE, Zimring JC, et al. Transfusion-related acute lung injury. *Hematol Oncol Clin North Am* 2007; 21: 163-176.
12. Silver M, Corwin MJ, Bazan A, et al. Efficacy of recombinant human erythropoietin in critically ill patients admitted to a long-term acute care facility: a randomized, double-blind, placebo-controlled trial. *Crit Care Med* 2006; 34: 2310-2316.
13. Vincent JL, Baron JF, Reinhart K, et al; ABC (Anemia and Blood Transfusion in Critical Care) Investigators. Anemia and blood transfusion in critically ill patients. *JAMA* 2002; 288: 1499-1507.
14. Vincent JL, Piagnerelli M. Transfusion in the intensive care unit. *Crit Care Med* 2006; 34(5 Suppl): S96-S101.
15. Zarychanski R, Turgeon AF, McIntyre L, et al. Erythropoietin-receptor agonists in critically ill patients: a meta-analysis of randomized controlled trials. *CMAJ* 2007; 177: 725-734.

**Dr Alok Nath, M.D.**

D.M. Fellow,

Department of Pulmonary Medicine,  
Postgraduate Institute of Medical Education and Research  
(PGIMER), Chandigarh.

## 23rd Annual Update

### Pulmonary & Critical Care Medicine

**October 12, 2008**

### Theme : Pleural Effusions

Registration : Upto 30th September Rs. 200/-  
After October 1st Rs. 300/-

(Payment should be drawn in favour of The CHEST,  
P.G.I. Chandigarh through a draft. Include  
Rs. 50 for outstation cheques)

**Organizing Secretary :** Dr. D. Gupta, Addl. Professor,  
Deptt. of Pulmonary Medicine,  
PGIMER, Chandigarh - 160 012  
E-mail : dheeraj@indiachest.org  
Fax : 0172-2745959, 2747759

**The CHEST**  
Department of Pulmonary Medicine, Postgraduate  
Institute of Medical Education & Research,  
Chandigarh

