Management Of Anemia In ICU Tranfusion Related Acute Lung Injury

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Introduction

A common occurrence in ICUs

Mostly managed with blood transfusions.

Transfusion requirements increasing

In the United States nearly 15 million units are donated and 14 million units transfused annually

Increased cost due to increasing requirements and rigorous screening procedures

Epidemiology

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 prevalence of anemia in critically ill patients and high rate of transfusion requirements in the ICU

More than 90% of critically ill patients have subnormal hemoglobin 3rd day past the stay in the ICU

Corwin et al 1997 Crit Care Med

Epidemiology

In one series the mean Hb of patients in ICU was 11.3 gm/dl with 29 % having Hb levels < 10 gm/dl

Von Ahsen N et al Crit Care Med 1999

85 % of the patients with an ICU stay of >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

Corwin et al 1995 Chest

Epidemiology

The ABC trial

3534 patients
Mean Hb 11.3 ± 2.3 gm/dl
29 % - Hb < 10gm/dl
Transfusion rate 37%
Surgical patients - more transfusion
Stay more than 7 days- 73% received transfusion
Overall mean pretransfusion Hb 8.4 ± 1.3gm/dl

Epidemiology

The CRIT study

4892 patients; 284 ICUS
Mean baseline Hb 11.0 ± 2.4 gm/dl
Mean decrease to 9.8 ± 1.4 gm/dl(p< 0.0045)
44% transfused during ICU stay(4.6 ± 4.9 units per patient)
Stay > 7 days More transfusion(63% vs 33.4%;p<0.0001)
Mean pretransfusion Hb 8.6 ± 1.7gm/dl

Epidemiology

Post hoc analysis of CRIT study patients
Mean baseline Hb 11.1 ±2.4 gm/dl
Higher transfusion rate in post op trauma patients
55.4% patients transfused(5.8 ± 5.5 units)
Mean pretransfusion Hb 8.9 ± 1.8 gm/dl

1247 patients
666(53%) received transfusions
Transfused patients - higher mortality
Average pretransfusion Hb 9gm/dl in 75% of transfusion episodes
72% patients transfused for low Hb rest for hemorrhage

Rao et al Anaesthesia 2002

Epidemiology

Study	TRICC Investigators (Canada) 1998	ABC trial((Western Europe) 2002	North Thames Blood Interest Group (UK) 2002	CRIT Study (USA) 2004
n	5298	3534	1247	4892
Mean admission Hb (g/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 pretransfusion Hb(g/dl)	8.6 ± 1.3	8.4 ± 1.3	8.5 ± 1.4	8.6 ± 1.7
Mean ICU length of stay (days)	4.8 ± 12.6	4.5		7.4 ± 7.3
ICU mortality	22%	13.5%	21.5%	13%
Hospital mortality		20.2%		17.6%
Admission APACHE II (mean)	18 ± 11	14.8 ± 7.9	18.1 ± 9.1	19.7 ± 8.2

Epidemiology

Nguyen and colleagues (n = 91)

Prospective, single-institution observational study

Fall in Hb concentrations averaged 0.52 ± 0.69 g/dl per day

After the 3rd ICU day the change in Hb concentrations was inversely proportional to APACHE II and SOFA scores

Hb concentrations decreased by 0.44 ± 0.70 g/dl per day in the non septic patients and 0.68 ± 0.66 g/dl per day in the septic patients (*P = 0.13)*

Epidemiology

The authors concluded that Hb concentrations typically decline by more than 0.5 g/dl per day during the first days of ICU stay in nonbleeding patients.

Beyond the third ICU day, Hb concentrations remained relatively constant in non septic patients but continued to decrease in septic patient

Epidemiology

Similarities in above trials

- Vast majority of patients in ICU have Anemia
- Transfusion trigger usually 8.5 gm/dl
- Transfusion rates were increased in patients with long stay
- Patients with higher age received more transfusion
- Most common reason for transfusion was Anemia

Pathophysiology

- 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
- Inappropriately low circulating concentrations of erythropoietin (EPO)
- Diminished responsiveness of bone marrow precursor cells to EPO

Pathophysiology

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

Pathophysiology

HIF-1 is a heterodimeric transcription factor composed of a HIF-1α chain and a constitutively expressed HIF-1β chain

HIF-1 α protein is present at extremely low levels under normoxic conditions newly synthesized HIF-1 α is subjected to polyubiquitination and targeted for degradation in proteosomes

When cells become hypoxic, polyubiquitinization of nascent HIF-1 α decreases, and cytosolic levels of this protein increase

HIF-1 α combines with HIF-1 α 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

Pathophysiology

Response to endogenous EPO is blunted in critically ill patients

Rogiers and coworkers (36 patients)

Eighteen ambulatory patients with iron-deficiency anemia served as a control group.

Significant inverse correlation between Hct values and EPO levels was observed in the control individuals (*r = –0.81; P < 0.001)*

No such correlation was apparent for the critically ill patients (*r = –0.09; P = NS)*

Pathophysiology

Krafte-Jacobs and coworkers

EPO levels in critically ill pediatric patients instead of adults

In 21 acutely anemic critically ill patients, the mean Hb concentration was 7.8 ± 1.5 g/dl and the mean EPO level was 39 ± 62 mU/ml

In comparison, the mean hemoglobin concentration in 21 chronically anemic patients was 7.3 ± 1.3 g/dl and the mean EPO level was 861 ± 758 mU/ml

Pathophysiology

Similar findings by Von Ahsen and coworkers

Patients in a medical ICU, those 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 saturated < 20%) is also common in critically ill patients

Inappropriately low EPO levels persist for the duration of critical illness

Pathophysiology

Critically ill patients appear to retain their responsiveness EPO

Three randomized prospective trials documented that administration of rHuEPO can stimulate reticulocytosis and increase circulating hemoglobin concentration in critically ill adults

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 transfusion

Van Iperen Crit Care Med 2000, Corwin Crit Care Med 1999, JAMA 2002

Pathophysiology

Functional iron deficiency is a major cause for anemia in critically ill patients

Laboratory studies typically reveal low serum iron concentration, low transferrin level, low transferrin saturation, and elevated serum ferritin concentration

Circulating iron concentrations are low, less free iron is available to support erythropoiesis

In patients with MOFS, victims of multiple trauma, and patients recovering from major surgery similar results were observed

Baumann H Immunol Today 1994, Weiss G Immunol Today 1995 , Gabriel A J Trauma 1998, Van Iperen CE Br J Surg 1998

Pathophysiology

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 tranfusion practices

Some Facts

Considerable variation in RBC transfusion practices in critical care

Optimal therapy for anemia have not been fully defined

There is no universal transfusion trigger

Uncertainties still exist concerning the most appropriate hemoglobin concentration for patients with significant cardiorespiratory disease

Trends in tranfusion practices

Canadian scenario-based national survey (n = 254) to characterize the contemporary RBC transfusion practice in the critically ill

Most respondents were from internal medicine (56%)

Baseline hemoglobin transfusion thresholds averaged from 8.3 ± 1.0 g/dl in a scenario involving a young stable trauma victim to 9.5 ± 1.0 g/dl for an older patient after gastrointestinal bleeding

Transfusion thresholds differed significantly ($P < 0.0001$) between each of the four separate scenarios

Trends in tranfusion practices

Except congestive heart failure ($P > 0.05$), all clinical factors (including age, APACHE II score, preoperative status, hypoxemia, shock, lactic acidosis, coronary ischemia, and chronic anemia) significantly modified the transfusion thresholds ($P < 0.0001$)

A statistically significant ($P < 0.01$) difference in baseline transfusion thresholds was noted across four major regions

Trends in tranfusion practices

Hebert and coworkers, 5298 patients, 6 tertiary level ICUs

The overall number of transfusions per patient day in the ICU averaged 0.95 ± 1.39 and ranged from 0.82 ± 1.69 to 1.08 ± 1.27 between institutions (*$P < 0.001$*)

Independent predictors of transfusion thresholds (pretransfusion Hb) included patient age, admission APACHE II score, and institution (*$P < 0.0001$*)

A very significant institution effect ($P < 0.0001$) 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; *$P < 0.0001$*)

Trends in tranfusion practices

35% (202 out of 576) of pretransfusion Hb was in the range 9.5–10.5 g/dl, and 80% of the orders were for 2 units of blood

Acute bleeding (35%) and augmentation of oxygen delivery (25%) were commonest reasons for transfusion

Hebert PC Crit Care 1999

Adverse effects of transfusion

RBC Storage and Physiologic 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

Adverse effects of transfusion

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 hemoglobin 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

Adverse effects of transfusion

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

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 WBC-derived and play an important role in transfusion-induced immunomodulation (TRIM)

Stack G Transfusion 1995 Fransen E Chest 1999

Adverse effects of transfusion

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

Mynster T Vox Sang 1998, Zallen G Shock 2000

Arginase release from stored RBCs has been implicated in TRIM Arginine stimulates lymphocyte function, arginase impairs it

Prins HA Shock 2001

Adverse effects of transfusion

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 (p 0.0001) has been described

Length of stay was significantly associated with the aging of RBCs (p 0.003), the total number of units transfused (p 0.004), and the median storage duration (p 0.02)

When transfused patients were analyzed separately from nontransfused patients, only RBC storage for 14 days was independently predictive of length of stay (p 0.0001)

Martin CM Clin Invest Med 1994

Adverse effects of transfusion

Positive correlation between mortality in patients with severe sepsis and the age of the non-leukocyte-reduced RBC units that were transfused

The median age of RBCs transfused to survivors was 17 days (range, 5- 35 days) compared with 25 days (range, 9 to 36 days) for nonsurvivors (p 0.0001)

Purdy FR, Can J Anaesth 1997

Similar results in other studies have been documented

Moore FA Arch Surg 1997 Zallen GAm J Surg 1999

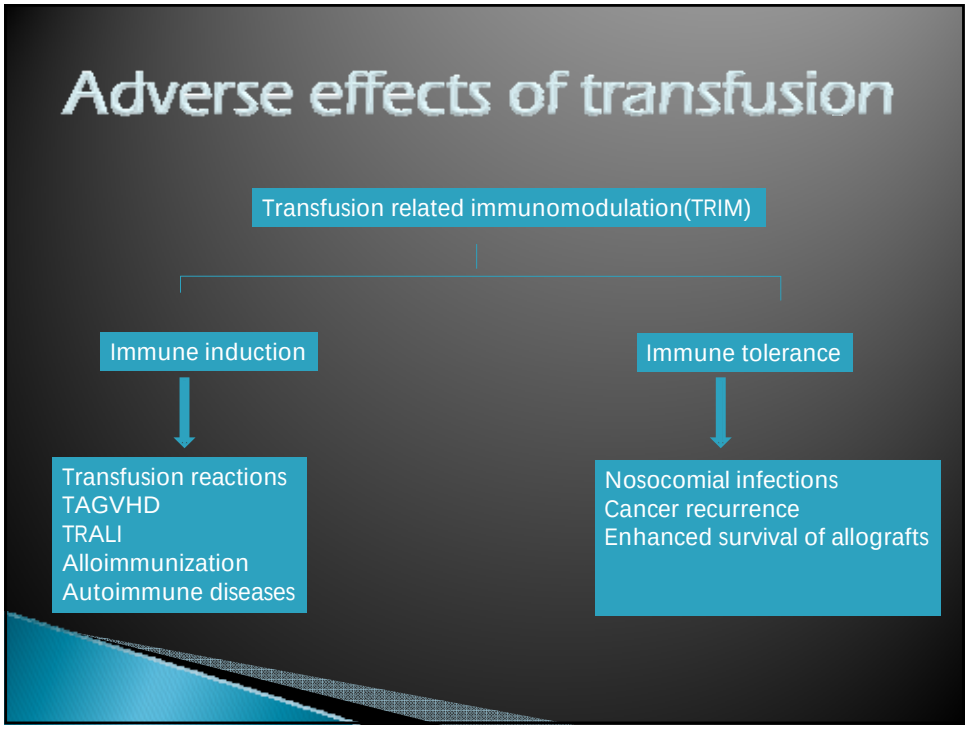
Adverse effects of transfusion

Allogenic blood transfusion lead to a multitude of immune dysregulation

Various T-cell – antigen interactions 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 in turn activates B-cell proliferation and antibody production

Blood transfusions may lead to development of two different situations alloimmunization or tolerance induction

Adverse effects of transfusion



Adverse effects of transfusion

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 and 2 Hepatitis B and C *Toxoplasma gondii* *Trypanosoma cruzi* Babesiosis
Newer agents	TTV SEN-V
Adverse effects of leukocyte contamination	Febrile nonhemolytic transfusion reactions Refractoriness to platelet transfusions TRALI TAGVHD Immune suppression and allograft tolerance Development of possible autoimmune diseases

Adverse effects of transfusion

Several studies have clearly identified the increased risk of nosocomial infections among critically ill transfused patients

Vamvakas EC Arch Pathol Lab Med 1998
Moore FA Arch Surg 1997; Nichols RLN Engl J Med 1984;
Edna TH J Trauma 1992; Braga M Eur J Surg 1992 ;
Ottino G Ann Thorac Surg 1987 ;Graves TAJ Trauma 1989;
Dellinger EP Arch Surg 1988

Adverse effects of transfusion

Four possible mechanisms

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

Adverse effects of transfusion

Difficult to establish a cause-and-effect relationship and to separate the effects of transfusion

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)

Gazmuri RJ Crit Care Med 2002, Houbiers JG Transfusion 1997, van de Watering LM Circulation 1998

Adverse effects of transfusion

With 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

Metaanalyses of these substantial studies have failed to identify a statistically significant effect of leukocyte reduction

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

Van de Watering LM Circulation 1998
Vamvakas EC Blood 2001,
Vamvakas EC Transfusion 2001,
McAlister FABr J Surg 1998

Adverse effects of transfusion

TRALI

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 1,120 cellular component transfusions with a mortality rate ranging from 1 to 10%

Passively transferred donor blood containing antileukocyte antibodies (ie, IgG) directed against recipient leukocytes causes pulmonary sequestration, complement activation, and lung injury

Adverse effects of transfusion

TAGVHD

TAGVHD is a rare but lethal complication with a mortality rate 90%, in which immunocompetent donor cells proliferate and attack host hemopoietic cells, skin, liver, and bile duct epithelial cells

More common in immunocompromised patients

The risk factors for the development of graft vs host disease (GVHD) include patients receiving transfusions from HLA-homozygous donors who are haploidentical, the use of relatives as donors, male recipients, and fresh blood containing viable lymphocytes

Only a small fraction of such transfusions cause GVHD

Irradiated and leukodepleted cellular products avert the development of GVHD

Prevention of Anemia in ICU

Decreasing diagnostic blood loss “Vampirism”

The use of a blood conservation device to minimize diagnostic phlebotomy

Methods to prevent intra-operative and periprocedural blood loss

“Point of care” testing

Non invasive hemodynamic monitoring

Management

Blood Transfusion

In acute setting – commonest mode of treatment

- High threshold
- To manage with “restrictive strategy” (Hb 7 – 9gm/dl)

Exception – Acute myocardial infarction and unstable angina (Hb > 10 gm/dl)

Avoid directed transfusion

Leukoreduction / filtering should be practiced

Liberal vs. restrictive strategy

Canadian Critical Care Trials Group,

Multicenter, prospective, randomized clinical

69 normovolemic critically ill patients hemoglobin values less than 9 g/dl

Patients were randomly assigned to one of two RBC transfusion strategies.

Hb values were maintained between 10 and 12 g/dl in the liberal group

7 and 9 g/dl in the restrictive group

Daily hemoglobin values averaged 9 g/dl in the restrictive group and 10.9 g/dl in the liberal group ($P < 0.001$)

Liberal vs. restrictive strategy

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% versus 25%; 95% confidence interval [CI] –19% to +21%), ICU mortality ($P = 0.76$) and 120-day mortality ($P > 0.99$)

Survival analysis comparing time until death in both groups did not reveal any significant difference ($P = 0.93$) between groups. Organ dysfunction scores were also similar ($P = 0.44$)

More restrictive approach to the transfusion of RBCs may be safe in critically ill patients

Liberal vs. restrictive strategy

TRICC study, 838 critically ill patients

30-day mortality rates were similar in the two groups

Hospital mortality rate was significantly lower in the restrictive strategy group (22.2% versus 28.1%; *P = 0.05*)

Mortality rates were also significantly lower with the restrictive strategy among patients who were less acutely ill and young

Restrictive strategy of RBC transfusion in critically ill patients was at least as effective as, and possibly superior to, a liberal transfusion strategy

Exception - patients with acute MI and USA

Liberal vs. restrictive strategy

ABC trial

Higher mortality in patients who were transfused (ICU mortality 18.5% versus 10.1%, $\chi^2 = 50.1$, $P < 0.001$; overall mortality 29.0% versus 14.9%, $\chi^2 = 88.1$, $P < 0.001$)

The 28-day mortality was 22.7% among patients with transfusions and 17.1% among those without (P = 0.02); the Kaplan–Meier log-rank test confirmed this difference

Liberal vs. restrictive strategy

Post hoc analysis (357 pts.) for cardiovascular patients
Overall, all mortality rates were similar in both study groups
No difference after stepwise logistic regression analysis
Changes in multiple organ dysfunction from baseline scores were significantly less in the restrictive transfusion group overall (0.2 ± 4.2 versus 1.3 ± 4.4; *P = 0.02)*

In the 257 patients with severe ischemic heart disease had lower but nonsignificant absolute survival rates compared with the patients in the liberal group
Restrictive RBC transfusion strategy generally appeared to be safe in most critically ill patients with cardiovascular disease, with the possible exception of patients with acute myocardial infarcts and unstable angina

Liberal vs. restrictive strategy

	Restrictive	Liberal	p
n	160	197	
Mortality, 30-day	23%	23%	1.0
Mortality, ICU	19%	16%	0.49
Mortality, hospital	27%	28%	0.81
MODS, change from baseline scores	0.23 ± 4.2	1.28 ± 4.4	0.023
Mean hemoglobin (g/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

Hebert and coworkers TRICC study

Liberal vs. restrictive strategy

Large Scottish teaching hospital ICU
Prospective data were collected daily for 6 months
A total of 176 patients who utilized 1237 ICU days were studied
52% received RBC transfusions
A Hb of 9 g/dl or less was measured in 55% of patients
Hb was 9 g/dl or less for 45% of all patient days
Mean RBC transfusion was 3.1 units per ICU admission
Only 18% of transfusion episodes were required for hemorrhage
For nonhemorrhage transfusion episodes, the median pretransfusion Hb was 7.8 g/dl (interquartile range 7.4–8.4 g/dl), and 64% of trans-fusion episodes were for 2 units

Management

Role of 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

Patteril MV Anaesth Intensive *Care 2001,* Viljoen M Haematologica 1994,Gabriel A J *Trauma 1998*

Management

Iron supplementation in critically ill patents have not been found to improve hematological parameters

Moreover to initiate iron supplementation also needs further study

Both oral and parenteral iron supplementation in critically ill patients have found To be counterproductive

Hoen B Am J Kidney Dis 1999 ,Jurado RL Clin Infect Dis 1997, Besarab A J Am Soc Nephrol 1999, Collins AJ Am Soc Nephrol 1997

Management

Increased susceptibility to infections
Increased incidence of infections
Iron overload

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

Hoen B Am J Kidney *Dis 1999,*Jurado RL Clin *Infect Dis 1997,* Besarab A J Am Soc Nephrol 1999, Collins A J Am Soc Nephrol 1997

Management

Studies of iron supplementation are plentiful in the CKD literature, in pregnancy, and in the pediatric setting

Besarab A Am J Kidney Dis 1999 ,Hudson JQ Clin Ther 2001, Rutherford CJAm J Med 1994

Similar studies in ICU population are lacking

Another clinical concern is risk to affect the physiological redox potential.
During biologic 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 biologic processes that can damage lipid and protein membranes

Britton RS Int J Hematol 2002 Meneghini R Free Rad Biol Med 1997 Loebstein R Diabetic Care 1998Saran MFree Rad Res 2000

Management

In few studies it has been shown that patients on the requirement of erythropoietin was decreased with iron supplementation

Studies were mainly in CKD population and orthopedic surgery patients

In these studies the preferred route and iron formulation have not been addressed to

Silverberg DS Clin Nephrol 2001 Olijhoek G Transfusion 2001

Management

Iron deficiency is noted in a small subset of critically ill patients, iron supplementation following identification of such patients is appropriate

Mostly anemia is multifactorial, as is usually the case in a critically ill patient, then iron alone may not be sufficient to stimulate erythropoiesis but may be useful as an adjunct with erythropoietin

Until proven otherwise, clinicians should probably monitor iron parameters on a regular basis if they elect to administer iron and erythropoietin therapies concomitantly

Management

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 erythropoietic therapy

The optimal dose, route, and timing of iron administration in critically ill patients, especially when given concurrently with erythropoietin therapy, remains an open issue that requires further study

Management

Role of Erythropoietin (rHuEPO)

Blunted EPO response observed in the critically ill resulting from inhibition of the EPO gene by inflammatory mediators
Same inflammatory cytokines directly inhibit RBC production by the bone marrow and may produce the distinct abnormalities of iron metabolism

rHuEPO in patients with MOFS therapy (600 units/kg) was shown to stimulate erythropoiesis

Gabriel AJ Trauma 1998

Management

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

Corwin HL Crit Care Med 1999

Management

Recent RCT - 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

10% reduction in the number of patients receiving any RBC transfusion (60.4% with placebo versus 50.5% with rHuEPO, *P < 0.0004* and a 20% reduction in the total number of RBC units transfused (1963 units with placebo versus 1590 units with rHuEPO, *P < 0.001).*

Similar to the initial study, the increase in hemoglobin from baseline to final was greater in the rHuEPO group

Corwin HL. JAMA 2002

Management

Almost similar results seen in small RCT of 86 patient

Silver M Crit Care Med 2003

Final clinical outcomes did not show significant improvements

Studies were not designed to address these issues

Further study is needed to determine whether there are clinical outcome benefits in critically ill patients admitted to either the ICU and/or long-term acute care facilities associated with a reduction in the exposure to RBC transfusion with rHuEPO administration

Management

Hemoglobin based o_2 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 latter efforts proved to be prohibitively expensive

Management

Details	Product name		
	PolyHeme®	Hemopure® (HBOC-201)	HemoLink™ (Hb-raffimer)
Company	Northfield Laboratories. (Evanston, IL, USA)	Biopure Corporation (Cambridge, MA, USA)	Hemosol Inc. (Toronto, Canada)
Modification method	Pyridoxylation glutaraldehyde polymerization (polymer)	Glutaraldehyde polymerization (polymer)	Crosslinking with o-raffinose glutaraldehyde polymerization (oligomer)
Hemoglobin source	Human hemoglobin	Bovine hemoglobin	Human hemoglobin
Hb concentration(gm/dl)	10	13	10
Molecular weight	NR (< 64 kDa; 1.0%)	Average molecular weight: <64 kDa: <5%	250 kDa 64–500 kDa: >90% >500 kDa: <3%
pH	NR	7.6–7.9	7.5
P50 (torr)	26-32	28	52
Viscosity (cP)	NR	1.3	1.14
Shelf life	>1 year	>1 year	>1 year

Management

All these compounds are in phase II/III trials

The addition of HBOCs 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 ALI

Transfusion-related acute lung injury (TRALI) was first coined by Popovsky et al in 1983

Previously been referred to as pulmonary hypersensitivity reaction allergic pulmonary edema, noncardiogenic pulmonary edema, and pulmonary leukoagglutinin reaction

Noncardiogenic pulmonary edema temporally related to the transfusion of blood products. 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 IV Ig

Transfusion related ALI

Most common symptoms associated with TRALI are dyspnea, cough, and fever

Systemic hypotension and hypertension both have been reported

Can be sudden and fulminant, and most commonly occur between 1 h and 2 h after the onset of transfusion, but may develop within 30 min of transfusion. Almost all reactions occur within 6 h from the start of a transfusion

Epidemiology

Underreported entity. Reported incidence is 0.02 to 0.16 %
TRALI is the third most common cause of fatal transfusion reactions next to ABO blood type incompatibility and hepatitis

Largest series of TRALI (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 were* rapidly resolved (96 h) in 81% of the patient
Mortality was only 6%, with no survivors having long-term sequelae.
The 5 to 8% mortality rate in TRALI cases distinguishes it from ALI/ARDS, which has a mortality rate of 30 to 50%

Pathogenesis

"Two-hit" hypothesis.
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

Pathogenesis

The antibody theory remains the most inclusive and published etiology of TRALI. Amply cited in literature

Donor antibodies attach to specific antigens on primed neutrophils leading to the release of oxidative and nonoxidative products that damages the pulmonary endothelium and leads to an increased permeability pulmonary edema.
Rarely recipient antibodies attack donor WBCs and produce TRALI

Pathogenesis

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

First reported by Silliman et al(Transfusion 1997)

Pathogenesis

The main weakness of the 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.

Not mutually exclusive theories and may even be complimentary. Threshold effects may be present that could potentially allow both mechanisms to participate in injury

Risk factors

Recent surgery
Sepsis
Trauma
Massive transfusions
Hematologic
Malignancies
Cardiac disease
Multiparity
Age of blood
Directed transfusions

Risk factors

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%

Risk factors

Only one RCT
Intensive care patients were transfused with plasma from a multiparous donor or a control donor (presumably male or nulliparous female donors)
Double- blind, crossover
Only one case of TRALI occurred after the transfusion of 200 U of plasma to 100 patients.
Donor in this case was multiparous and possessed a granulocyte antibody.
A small but statistically significant decrease in the Pao2/Fio2 ratio occurred in the multiparous plasma group

Risk factors

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)

Silliman CC Blood 2003

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

Zallen G Am J Surg 1999

Diagnosis

High index of suspicion

Essentially clinical

Corroborative evidence- edema fluid/plasma protein ratio is < 0.65 in hydrostatic pulmonary edema, and > 0.75 with increased permeability pulmonary edema

Leucopenia

Thrombocytopenia

Confirmatory and definitive evidence for the diagnosis of TRALI requires investigating the donor and recipient for passively transfused antibodies

Treatment

Immediate discontinuation of transfusion
Fluid resuscitation if hypotension
Inotropic support if needed
No diuretics
Supplemental oxygen
Mechanical ventilation

Mostly self limited without long term sequelae

Prevention

- Avoiding unnecessary transfusions
- Notification of all transfusion reactions to transfusion medicine department
- Notification and identification of sensitized donors
- Avoiding transfusions from multiparous females(practically difficult)
- Avoiding directed transfusions
- Avoiding old blood transfusion
- Leukoreduction or filtration