Blood Transfusion and Adjuvant Therapies in Perioperation and ICU

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Outline

- Overview
- Benefit and risk of blood transfusion
- Determine when to transfuse
- Evidences in blood transfusion
- Adjuvant methods

Introduction

- Transfusion have been used for over 50 years, increasing burden of chronic disease in an aging population.
- Approximate 14 million units of whole blood were collected and transfused, predominately PRBC.
- Transfusion has come under increased scrutiny over last 20 years.

Prevalence of Anemia

- 95% of ICU patients below normal by ICU-day 3
- 50% of ICU patients received at least 1 PRBC unit
- 85% of ICU patients stayed for more than one week received at least 1 PRBC unit

Vincent JL et al. JAMA 2002;228:1499-507

Signs and Symptoms of Anemia

- Exertional dyspnea
- Chest pain
- Lethargy
- Pallor
- Hypotension
- Tachycardia
- Impaired consciousness

Physiologic Response to Anemia

- Increased cardiac output
  - Increased heart rate
  - Increased stroke volume
- Increased oxygen extraction
- Reallocation of blood flow
- Right shift in hemoglobin-oxygen dissociation curve

Causes of Anemia in ICU

- Pre-existing chronic anemia
- Hemodilution
- Blood loss
  - Surgery
  - GI bleeding
  - Blood sampling
  - Other procedure
- Decreased red blood cell production
  - Decreased erythropoietin synthesis
  - Resistance to erythropoietin
  - Iron deficiency
- Increased hemolysis

Hajjar LA et al, Clinics 2007;62:507-24

Risks of Anemia

- Anemia is associated with worse outcomes.
  - Preoperative anemia was associated with a significant increase in perioperative mortality.
  - Patients with cardiac disease and Hgb <9.5 g/dL had a trend toward increased mortality compared with anemic patients without cardiac disease.
  - Risk factor of outcome for COPD patients with mechanical ventilation.
- Increased duration of mechanical ventilation
  - Hemoglobin < 10g/dl increased extubation failure.

Marik PE et al, Crit Care Med 2008; 36:2667-74

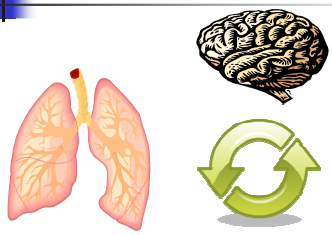
Hajjar LA et al, Clinics 2007;62:507-24

Khamiees M et al, Chest 2001;120:1262-70

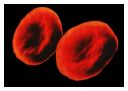
Benefits of Blood Transfusion

- Improved oxygen delivery
- Limiting tissue hypoxia and damage

Determinants of O2 Delivery to Tissues



O_2 delivery = O_2 content x C.O.



O_2 content: O_2 Sat x Hgb x $1.34+PaO_2$ x0.0031

Risk of Blood Transfusion

- Transfusion-transmissible infections
- Immunological risks
- Mistransfusion
- Transfusions related acute lung injury (TRALI)
- ARDS
- Multiple organ failure
- GVHD

Transfusion-Infectious Risk

- HIV, hepatitis B, C virus, West Nile virus, Variant Creutzfeldt-Jakob disease
- Increased infection rate
  - Bloodstream infection
  - Pneumonia
  - Post-operative infection

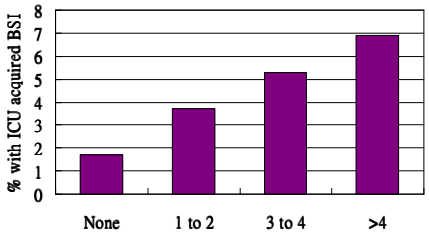
Hajjar LA et al, Clinics 2007;62:507-24

Independent Predictors of ICU-Acquired Bloodstream Infection

Variables	OR	95% CI	P Value
Baseline cephalosporin	1.84	1.26-2.68	0.002
Day 3-4 SOFA score	1.11	1.06-1.16	<0.001
Any PRBC transfusion	2.23	1.43-3.52	<0.001
Amount transfused, U*			
1-2	1.89	1.10-3.23	0.021
3-4	2.41	1.33-4.35	0.004
>4	2.63	1.52-4.53	<0.001

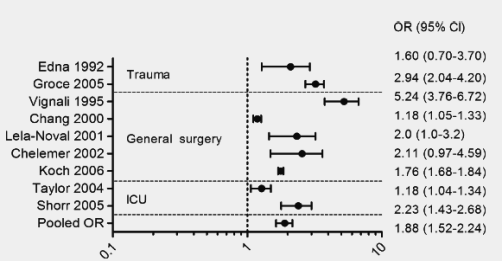
Shorr AF et al, Chest 2005; 127: 1722-1728

PRBC Transfusion is Associated with ICU-acquired BSI



Shorr AF et al, Chest 2005; 127: 1722-1728

Blood Transfusion and Risk of Infectious Complications



Marik PE, Crit Care Med 2008;36:2667-2674

Transfusion-Immunologic Risk

- Blood products contained high level of cytokines, bradykinin, serotonin, white cell
- Immunosuppressive effect
  - Less acute or chronic rejection post transplantation
  - Leukodepleted blood may have less immunomodulating properties.

Hajjar LA et al, Clinics 2007;62:507-24

Transfusion-related Acute Lung Injury (TRALI)

- Under-diagnosed and under-reported
  - Incidence: 0.02% per unit or 0.16% per patients for all blood products
- Most frequently reported cause of transfusion-related death.
- Mechanism: unclear
  - leukoagglutinin

Gajic O et al, AJRCCM 2007; 176: pp886-891

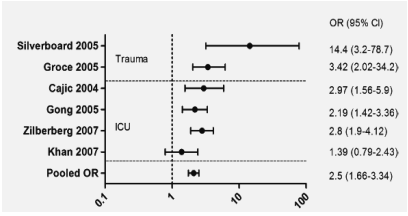
Transfusion-related Acute Lung Injury (TRALI)

- Diagnosis: based on clinical symptoms
  - Multiple hits for full expression of this syndrome
- Onset: 1-6 hours after transfusion, resolve in 48 hours
- Clinical symptoms or signs: fever, dyspnea, CXR showed lung infiltrates, hypotension
- Risk factors:
  - Massive transfusion
  - High plasma volume product (FFP)
  - Female donors

Gajic O et al, AJRCCM 2007; 176: pp886-891

Risks of Transfusion-ARDS

- Transfusion increased risk of developing ARDS.



Marik PE, Crit Care Med 2008;36:2667-2674

Age of Transfused Blood Is an Independent Risk Factor for Postinjury Multiple Organ Failure

Garret Zallen, MD, Patrick J. Offner, MD, MPH, Ernest E. Moore, MD, John Blackwell, MD, David J. Ciesla, MD, Julie Gabriel, BA, Chris Denny, BA, Christopher C. Silliman, MD, PhD,
Denver, Colorado

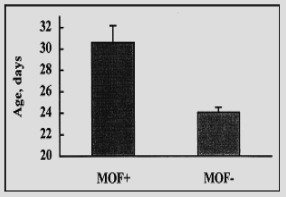


Figure 1. The age of transfused blood was analyzed in patients who developed multiple organ failure (MOF+) and was compared with patients who did not develop MOF (MOF−). The age of transfused blood was significantly older in the MOF+ group (*P* <0.05 compared with MOF−).

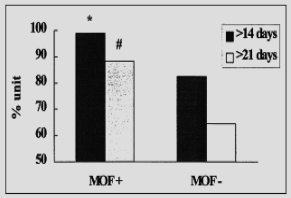


Figure 2. Subgroup analysis of the individual units of blood demonstrated that multiple organ failure patients (MOF+) received significantly more units of blood >14 days old and >21 days old. *P <0.05 compared with MOF−, >14 days. #*P* <0.05 compared with MOF−, >21 days.

Zallen G et al, Am J Surg 1999;178:570-2

Transfusion Related GVHD

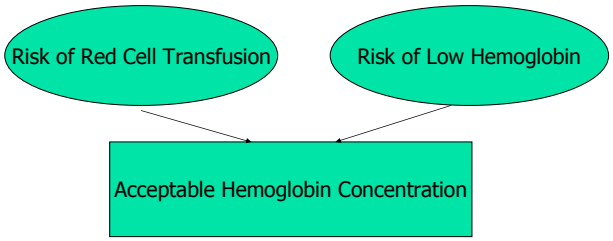
- Rash, elevated liver function tests and severe pancytopenia
- Mortality: 75-90%
- Blood from relatives must be irradiated
- No effective treatment.

Guideline form blood transfusion services of the United Kingdom

Trigger of Blood Transfusion

- Hemoglobin
  - What is critical hemoglobin ?
  - Good surrogate of tissue oxygenation? clinically variable
- Tissue oxygenation
  - Mixed venous oxygenation (SvO_2)
  - Base excess
  - Blood lactate
- Oxygen consumption

Transfusion Trigger for PRBC



Transfusion Trigger for PRBC

- Prior to 1980s, hemoglobin level and hematocrit above 10 g/dL and 30% respectively.
- O2 delivery peaks at a hematocrit of 30% and survival in animals is maximized at hematocrits of between 30% and 40%.

McFarland JG. Chest 1999;115(S):113-122

Restrictive Transfusion vs Liberal Transfusion Strategy (TRICC Study)

The New England
Journal of Medicine

VOLUME 340 FEBRUARY 11, 1999 NUMBER 6

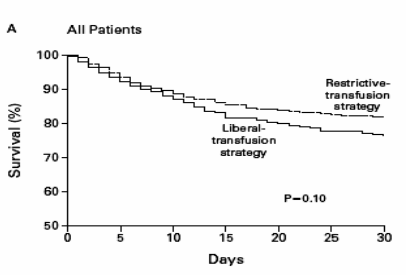
A MULTICENTER, RANDOMIZED, CONTROLLED CLINICAL TRIAL OF TRANSFUSION REQUIREMENTS IN CRITICAL CARE

PAUL C. HÉBERT, M.D., GEORGE WELLS, PH.D., MORRIS A. BLAJCHMAN, M.D., JOHN MARSHALL, M.D., CLAUDIO MARTIN, M.D., GIUSEPPE PAGLIARELLO, M.D., MARTIN TWEEDDALE, M.D., PH.D., IRWIN SCHWEITZER, M.SC., ELIZABETH YETISIR, M.SC., AND THE TRANSFUSION REQUIREMENTS IN CRITICAL CARE INVESTIGATORS FOR THE CANADIAN CRITICAL CARE TRIALS GROUP*

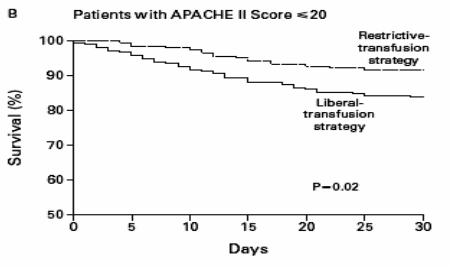
Restrictive Transfusion vs Liberal Transfusion Strategy

- Restrictive transfusion strategy:
  - Hgb maintained in the range of 7-9 mg/dl
  - 418 patients
- Liberal transfusion strategy :
  - Hgb maintained in the range of 10-12 mg/dl
  - 420 patients

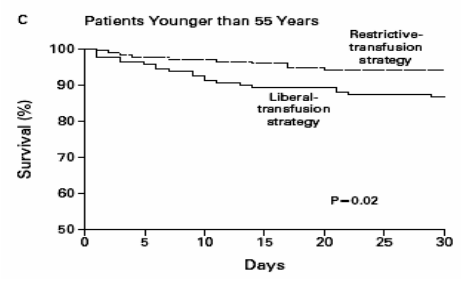
No difference of mortality in overall patients



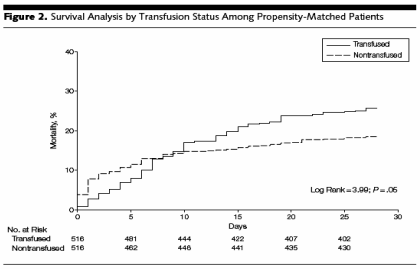
Better outcome of Restrictive Strategy in the Patients with APACHE II < 20



Better outcome of Restrictive Strategy in the Patients with Age Younger than 55

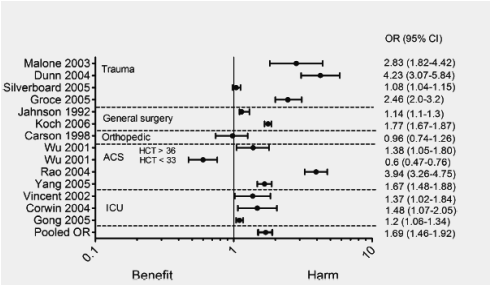


Anemia and Blood Transfusion in Critically Ill Patients (ABC study)



Vincent JL et al, JAMA 2002; 288:1499-1507

Association of Blood Transfusion and Risk of Death



Marik PE, Crit Care Med 2008;36:2667-2674

Why Blood Transfusion Can Not Improve Outcome ?

Limitations of Blood Transfusion

- Characteristic changes of stored RBC
  - Low P50
  - Dysfunction of cell flexibility
  - Bizarre cellular shapes of RBC
  - Erythorcyte clumping
- No increase in oxygen delivery to microcirculation if transfusion of 1 or 2 units of RBC.

Hajjar LA et al, Clinics 2007;62:507-24

Are Blood Transfusions Associated with Greater Mortality Rates ?

SOAP- Sepsis Occurrence in Acute Ill Patients Study

- A prospective, multi-center, observational study in 2002.
- 3247 ICU adult patients in 198 ICUs of European country.
- Patients were followed up until death, until hospital discharge or for 60 days.

Vincent JL et al. Anesthesiology 2008; 108: 31-9

Table 2. Characteristics of the Study Group

		Stratified According to Transfusion Status		
	All Patients (n = 3,147)	No Transfusion (n = 2,107)	Transfusion (n = 1,040)	*P* Value
Age,* mean ± SD, yr	61 ± 17	60 ± 16	62 ± 17	0.035
Male sex,† n (%)	1,920 (61.7)	1,293 (62.0)	627 (61.0)	0.570
Chronic diseases, n (%)				
COPD	340 (10.8)	228 (10.8)	112 (10.8)	0.965
Cancer	415 (13.2)	267 (12.7)	148 (14.2)	0.224
Heart failure	307 (9.8)	190 (9.0)	117 (11.3)	0.047
Diabetes	226 (7.2)	146 (6.9)	80 (7.7)	0.435
Liver cirrhosis	121 (3.8)	54 (2.6)	67 (6.4)	<0.001
Hematologic cancer	69 (2.2)	30 (1.4)	39 (3.8)	<0.001
HIV/AIDS	26 (0.9)	14 (0.7)	12 (1.2)	0.225
Medical admissions, n (%)	1,759 (55.9)	1,352 (64.2)	407 (39.1)	<0.001
SAPS II, mean ± SD	36.5 ± 17.1	34.7 ± 17.1	40.2 ± 16.5	<0.001
SOFA score, mean ± SD				
Initial SOFA score	5.1 ± 3.8	4.5 ± 3.6	6.5 ± 3.9	<0.001
Mean SOFA score	4.5 ± 3.5	3.9 ± 3.3	5.8 ± 3.5	<0.001
Maximum SOFA score	6.6 ± 4.4	5.5 ± 4.0	8.7 ± 4.5	<0.001
ICU stay, median [IQR]	3.0 [1.7–6.9]	2.5 [1.4–4.9]	5.9 [2.6–14.3]	<0.001
Hospital stay,‡ median [IQR]	15 [7–32]	13.0 [6.0–25.0]	23.0 [12.0–46.0]	<0.001
Infection, n (%)	1,177 (37.4)	622 (29.5)	555 (53.4)	<0.001
On admission	777 (24.7)	446 (21.2)	331 (31.8)	<0.001
ICU acquired	279 (8.9)	113 (5.4)	166 (16.0)	<0.001
Severe sepsis, n (%)	930 (29.6)	447 (21.2)	483 (46.4)	<0.001
On admission	552 (17.5)	291 (13.8)	261 (25.1)	<0.001
Septic shock, n (%)	462 (16.5)	179 (9.5)	283 (27.2)	<0.001
On admission	243 (7.7)	106 (5.0)	137 (13.2)	<0.001
ICU mortality,§ n (%)	583 (18.5)	344 (16.3)	239 (23.0)	<0.001
Hospital mortality,‡ n (%)	747 (23.7)	436 (21.0)	311 (30.2)	<0.001

Table 3. Simplified Acute Physiology Score II, ICU and Hospital Mortality According to the Number of Transfused Units during ICU Stay

Units Transfused	Frequency (%)	SAPS II	ICU Mortality (%)	Hospital Mortality (%)
1	144 (13.8)	37.4 ± 16.7	24 (16.7)	32 (22.2)
2	291 (28.0)	38.0 ± 15.9	54 (18.6)	77 (26.7)*
3	114 (11.0)	40.8 ± 15.5	21 (18.4)	32 (28.6)†
4	123 (11.8)	40.7 ± 19.1	33 (26.8)	42 (34.1)†
>4	368 (35.4)	42.8 ± 16.4	107 (29.2)‡	128 (34.8)*

Missing data: * 8 missing. † 2 missing. ‡ 1 missing.
ICU = intensive care unit; SAPS = Simplified Acute Physiology Score.

Blood Transfusions

An Index of Severity of Illness

Table 6. Patient Characteristics by Transfusion Status for the Propensity-matched Patients

	No Transfusion (n = 621)	Transfusion (n = 621)	P Value
Age, mean ± SD, yr	62.2 ± 17.1	61.8 ± 16.9	0.511
Male sex, n (%)	482 (58.7)	499 (60.6)	0.392
Chronic diseases, n (%)			
COPD	108 (13.2)	92 (11.2)	0.227
Cancer	135 (16.4)	126 (15.3)	0.544
Heart failure	92 (11.2)	93 (11.3)	0.938
Diabetes	58 (7.1)	67 (8.2)	0.402
Liver cirrhosis	44 (5.4)	42 (5.1)	0.825
Hematologic cancer	21 (2.6)	28 (3.4)	0.310
HIV/AIDS	5 (0.6)	9 (1.1)	0.386
Medical admissions, n (%)	359 (43.7)	363 (44.2)	0.842
Trauma, n (%)	70 (8.5)	75 (9.1)	0.664
SAPS II, mean ± SD	38.5 ± 16.6	39.0 ± 16.4	0.308
Admission SOFA score, mean ± SD	5.8 ± 4.0	5.9 ± 3.8	0.455
Admission SOFA scores, median [IQR]			
Respiratory	0.0 [0.0–3.0]	0.0 [0.0–3.0]	0.970
Hepatic	0.0 [0.0–1.0]	0.0 [0.0–1.0]	0.943
Coagulation	0.0 [0.0–1.0]	0.0 [0.0–1.0]	0.623
Renal	0.0 [0.0–2.0]	0.0 [0.0–2.0]	0.396
CNS	0.0 [0.0–2.0]	0.0 [0.0–2.0]	0.369
Cardiovascular	1.0 [0.0–3.0]	1.0 [0.0–3.0]	0.775
Sepsis syndromes on admission			
Sepsis	246 (30.0)	244 (29.7)	0.914
Severe sepsis	174 (21.2)	180 (21.9)	0.719
Septic shock	80 (9.7)	78 (9.5)	0.867
Procedures on admission, n (%)			
Mechanical ventilation	565 (68.8)	559 (68.1)	0.727
Hemofiltration	26 (3.2)	26 (3.2)	1.000
Hemodialysis	11 (1.3)	17 (2.1)	0.253
ICU mortality, %	186 (22.7)	181 (22.1)*	0.777
Hospital mortality, n (%)	235 (29.1)†	236 (29.0)‡	0.655

SOAP Study – Death Risk Reduction in Blood Transfusion Group

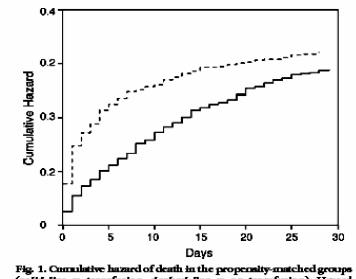


Fig. 1. Cumulative hazard of death in the propensity-matched groups (*solid line* = transfusion; *dashed line* = no transfusion). Hazard ratio = 0.75; 95% confidence interval = 0.59–0.90; $P = 0.004$.

Adjuvant Therapies

- Erythropoietin
- Blood substitute
- Options for surgery patients:
  - Predeposit autogolous donation
  - Acute normovolemic hemodilution
  - Intraoperative cell salvage

Erythropoietin

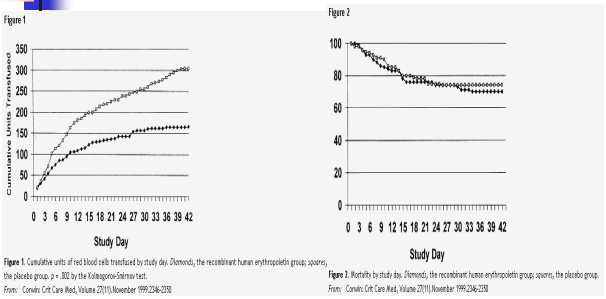
- Causes of anemia in critically ill patients.
  - Decreased red blood cell production
    - Decreased erythropoietin synthesis
    - Resistance to erythropoietin
- Avoid risks of blood transfusion.
  - Infection
  - TRALI
  - Fluid overload

EPO-1 Study

- Design: a prospective, double-blinded, multi-center RCT.
- Setting: ICU
- Patients: 160 patients
  - EPO:80 patients, subcutaneous 300 U/kg daily for 5 days
  - Placebo: 80 patients

Corwin HL, et al. Crit Care Med 1999;27:2346-2350

EPO-1 study



Cumulative blood transfusion, P<0.002

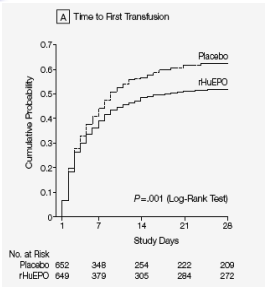
Mortality: No significant difference

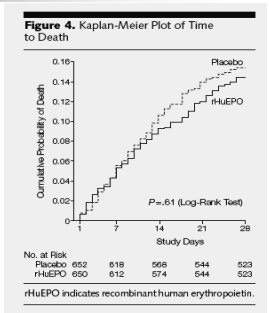
EPO-2 Study

- Design: a prospective, double-blinded, multi-center RCT.
- Setting: medical and surgical ICU patients
- Patients: 1302 patients
  - EPO: 650 patients, 40,000U epoetin alfa weekly for 4 doses.
  - Placebo: 652 patients

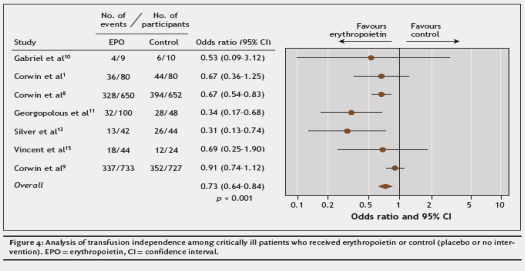
Corwin HL et al. JAMA 2002; 288: 2827-2835

EPO-2 Study





Erythropoietin- Reduced Transfusion

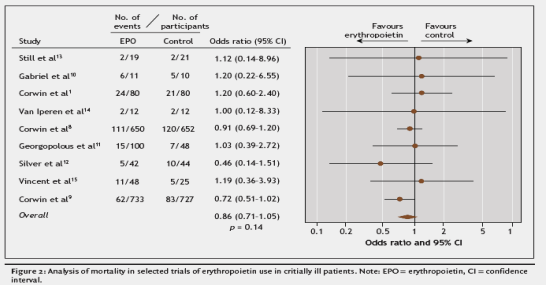


Study	No. of events / No. of participants: EPO	Control	Odds ratio (95% CI)
Gabriel et al[10]	4/9	6/10	0.53 (0.09-3.12)
Corwin et al[1]	36/80	44/80	0.67 (0.36-1.25)
Corwin et al[8]	328/650	394/652	0.67 (0.54-0.83)
Georgopolous et al[11]	32/100	28/48	0.34 (0.17-0.68)
Silver et al[13]	13/42	26/44	0.31 (0.13-0.74)
Vincent et al[15]	18/44	12/24	0.69 (0.25-1.90)
Corwin et al[9]	337/733	352/727	0.91 (0.74-1.12)
Overall			0.73 (0.64-0.84) $p < 0.001$

Figure 4: Analysis of transfusion independence among critically ill patients who received erythropoietin or control (placebo or no intervention). EPO = erythropoietin, CI = confidence interval.

Zarychanski R et al. CMAJ 2007;177;725-734

Erythropoietin- Mortality



Study	No. of events / No. of participants: EPO	Control	Odds ratio (95% CI)
Still et al[13]	2/19	2/21	1.12 (0.14-8.96)
Gabriel et al[10]	6/11	5/10	1.20 (0.22-6.55)
Corwin et al[1]	24/80	21/80	1.20 (0.60-2.40)
Van Iperen et al[14]	2/12	2/12	1.00 (0.12-8.33)
Corwin et al[8]	111/650	120/652	0.91 (0.69-1.20)
Georgopolous et al[11]	15/100	7/48	1.03 (0.39-2.72)
Silver et al[12]	5/42	10/44	0.46 (0.14-1.51)
Vincent et al[15]	11/48	5/25	1.19 (0.36-3.93)
Corwin et al[9]	62/733	83/727	0.72 (0.51-1.02)
Overall			0.86 (0.71-1.05) $p = 0.14$

Figure 2: Analysis of mortality in selected trials of erythropoietin use in critially ill patients. Note: EPO = erythropoietin, CI = confidence interval.

Zarychanski R et al. CMAJ 2007;177;725-734

Erythropoietin Administration

- Erythropoietin can reduce red cell blood transfusion, but the effect is very small.
- There is no sufficient evidence of benefits of mortality reduction.
- It can not be recommended to routinely use for critically ill patients.

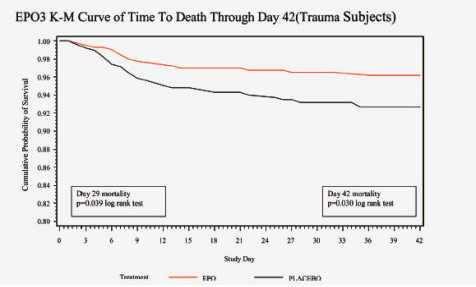
Zarychanski R et al. CMAJ 2007;177;725-734

EPO-3 Study

- Design: a prospective, double-blind, multi-center, RCT.
- Setting: trauma center
- Patients:
  - EPO:402 patients, 40,000 U epoetin alfa weekly for 3 dose.
  - Placebo:391 patients

Napolitano LM et al. J Trauma 2008;65:285-299

EPO-3 study showed improved survival of critically ill trauma patients



Blood Substitutes

- A substitute for RBCs had oxygen-carrying capacity.
  - Hemoglobin solutions
    - Limitations: vasoconstriction and renal dysfunction
  - Perfluorochemical solutions
    - Limitation: gas embolism

Predeposit Autologous Donation

- Donate blood to be stored 6 weeks in advance of the surgery.
- Prohibiting taking donation within 72 hours of planned surgery.
- Oral iron supplement is standard during phlebotomy sequence.
- Contraindication:
  - Anemia
  - Severe cardiac disease

McFarland JG Chest 1999;115:113-121

Acute Normovolemic Hemodilution

- Intraoperative hemodilution to a hematocrit of 20-25% was well tolerated.
- Autologous blood donation occurs immediately preoperatively after anesthesia and before surgery begins.
- The volume is replaced with colloid or crystalloid.
- Collected blood are reinfused at the end of procedure.
- Indications:
  - High initial hematocrit (>42%)
  - Tolerate dilutional anemia

Intraoperative Cell Salvage

- Another form of autologous blood donation.
- Shed blood at surgery is suctioned under low pressure into a reservoir=> saline washed and filtered => returned to patients during surgery.
- Contraindication: malignancy.
- Cost-benefit: at least 2 U of shed PRBC.

FFP

- There is wide variability in the manner with which physicians utilize FFP.
- FFP is associated with increased risk of infection.
- Similar immunosuppressive effect as PRBC transfusion.

Infectious Risk of FFP Transfusion

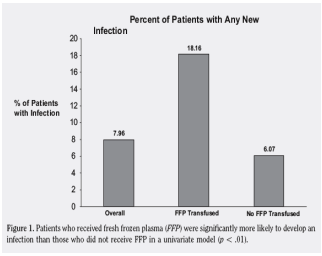


Figure 1. Patients who received fresh frozen plasma (*FFP*) were significantly more likely to develop an infection than those who did not receive FFP in a univariate model ($p < .01$).

Table 4. Multivariate regression results

	OR	95% CI	*p* Value
Age	0.994	0.982–1.005	.27
FFP	1.039	1.013–1.067	<.01
PRBCs	1.074	1.043–1.107	<.01
APACHE II	1.126	1.102–1.152	<.01

Sarani B et al, Crit Care Med 2008;36:1114-1118

FFP

- Routine use of FFP to correct laboratory clotting abnormalities is not recommended, except:
  - Bleeding
    - Increased PT
    - Increased APTT
  - Planned invasive procedures
  - Surgical procedures
- Dose: 10-15 ml/kg (Grade E)

Zimmerman et al. Crit Care Med 2004; 32: S542-547

FFP, Unjustified Use

- Hypovolemia
- Nutritional support
- Immunodeficiency states

Thrombocytopenia in ICU

- Incidence: 15-58%
- Higher mortality rate and morbidity rate
  - Bleeding incidence
  - Greater transfusion requirement
  - Longer ICU day

Platelet Transfusion

- Platelet should be administered when counts are 5000/mm^3.
- Platelet transfusion may be considered when counts are 5000-30000/mm^3
  - If there is a significant risk of bleeding
- Higher platelet counts 50000/mm^3 may be required for surgery or invasive procedures. (Grade E)

Zimmerman et al. Crit Care Med 2004; 32: S542-547

Risk of Platelet Transfusion

- Allergic reaction
- Bacterial infection
- Transfusion related acute lung injury (TRALI)

Cryoprecipitate

- 將FFP 在低溫慢速解凍，沉於下層沉澱品（剩餘plasma 即FP）
- Enriched for fibrinogen, vWF, factor VIII and factor XIII

CRYO, Transfusion Guidelines

- Active bleeding, uncontrollable by local measures, or planned invasive procedure **AND**
- Fibrinogen <100 mg/dL
- von Willebrand Disease Emergency [suitable FVIII/vWF Concentrate* not available]

Take Home Message

- Anemia is common in critically ill patients.
- Blood transfusion is not a risk-free procedure, not all patients benefit from blood transfusion.
- In hemodynamic stable patients without active bleeding, limiting blood transfusions reduce morbidity and mortality.

2008 Surviving Sepsis Campaign: Blood Product Administration

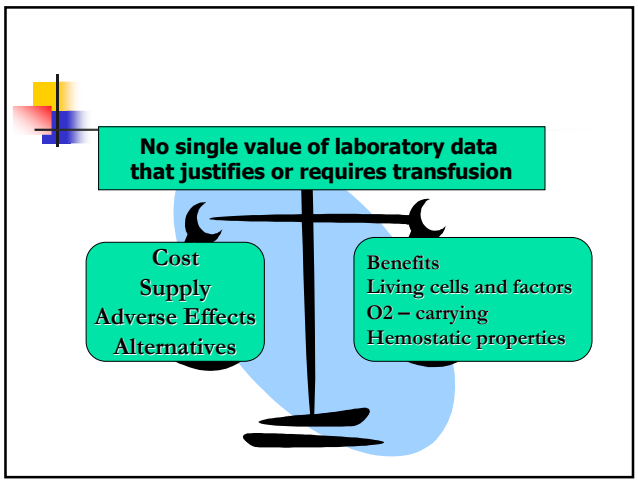
- Target a hemoglobin of 7.0-9.0 g/dL in adults, red blood cell transfusion when hemoglobin decreases to 7.0 g/dl.
  - Tissue hypoperfusion has resolved
  - In the absence of extenuating circumstances
    - such as myocardial ischemia
    - severe hypoxemia
    - acute hemorrhage
    - cyanotic heart disease
    - lactic acidosis (Grade 1B)
- Do not use erythropoietin to treat sepsis-related anemia.

2008 Surviving Sepsis Campaign: Blood Product Administration

- Do not use FFP to correct laboratory abnormalities unless there is bleeding or planned invasive procedure.
- Administer platelet transfusion when:
  - Platelet count < 5000/mm^3 regardless of bleeding
  - 5000-30000/mm^3 and there is significant bleeding risk
  - Platelet> 50000 /mm^3 are required for surgery or invasive procedure

To transfuse – or not to transfuse

- Dose transfusion improve outcome ?
- Is there a risk of under-transfusing ?



Thanks for Your Attentions !