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"Aspetti di clinica geriatrica"

La problematica trasfusionale

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“10/30 Rule” → per decenni, si è considerato che valori di Hb di 10 g/dl o di Hct del 30% rappresentassero il valore minimo accettabile per emotrasfondere un paziente

POICHÉ [illegible] inferiori di ematocrito sono compensati da un [illegible]o incremento dell’output cardiaco per [illegible]n’adeguata disponibilità di O2 tissutale

Disponibilità di O2 per i tessuti (DO2)
= flusso ematico ai tessuti (→ output cardiaco & vasoregolazione periferica)
x contenuto O2 arterioso (→ Hb & %Sat. Hb)
In caso di riduzione Hb, il flusso O2 ai tessuti aumenta al punto in cui DO2 è massimale con il minimo dispendio energetico per l’organismo. Questo si verifica per valori di Hct=30%.
L’output cardiaco aumenta e ha raggiunge il picco del 180% quando Hct =20%.

raccomandano una strategia trasfusionale più restrittiva, con valori trigger di Hb pari a 7-8 g/dl.

(Sadaka, J Disord Blood Trasfusion, 2012. Saugel, Scandinavian J Trauma, 2013. Shaw et al, Interactive Cardiovascular&Thoracic Surgery, 2013)

Sommario

- Effetti emodinamici ed eventi avversi delle trasfusioni
- Trasfusioni e cardiopatia ischemica
- Trasfusioni e pazienti critici (terapia intensiva, sepsi)
- Trasfusioni in ortopedia
- Trasfusioni ed emorragia acuta gastrointestinale
- Trasfusioni e anemia cronica
- Sintesi LG

A tolerance of anaemia varies greatly among patients.

In healthy patients, Hb levels of 6–7 g/dl and Hct of 15–20% are sufficient to maintain proper tissue oxygenation.

Only at Hb ≤5 g/dl has an appreciable increase in mortality also for cardiac patients.

Hct values ≤14% for low-risk and ≤17% for high-risk patients were shown to predict mortality.

Sistemi fisiologici di adattamento all'anemia

- In low-oxygen situations, the cells promote increased erythropoiesis, angiogenesis and anaerobic metabolism.
- The lungs also release more NO, increase the respiration rate in order to raise the

The higher rates of complications and mortality seen in trasfused patients could be in part related to the transfused blood products interfering with the body's natural mechanisms for handling anaemia.

  * right shift of the oxyhaemoglobin dissociation curve to reduce Hb oxygen affinity
  * increased tissue blood flow
  * increased capillary recruitment and density.

(Shander et al. British Journal of Anaesthesia, 2011; Shaw et al. Interactive Cardiovascular&Thoracic Surgery, 2013)

Effetti emodinamici ed eventi avversi delle trasfusioni

Table 1. Adverse Consequences of Red Blood Cell Transfusion

General
Acute complications (acute reactions, infection, lung injury, renal failure)
Long-term consequences (immunomodulating problems)
Hemodynamic
Volume overload (preload)
Increased blood viscosity (afterload)
Changes in stored red blood cells
Morphologic changes in red blood cells (impaired advance into microvascular bed)
Loss of 2,3-diphosphoglycerate (shift oxyhemoglobin dissociation curve)
Reduced nitric oxide bioactivity (impaired vasodilation, enhanced platelet aggregation)
Hemolysis (release of vasoactive and pro-inflammatory substances)

Transfusion further deteriorates microcirculatory damage in patients with acute myocardial infarction.

Complicanze acute delle Emotrasfusioni

- Transfusion-Related Acute Lung Injury (TRALI)
- Transfusion-Associated Circulatory Overload (TACO)
- Transfusion-Related Immuno Modulation (TRIM)
- Hemolytic Transfusion Reactions
  - Immediate reactions
  - Delayed raections
- Nonhemolytic Febrile Reactions
- Infections
- Allergic Reactions
- Electrolyte abnormalities
  - Hyperkalemia
  - Hypocalcemia

Complicanze acute delle Emotrasfusioni - 1

Transfusion-related acute lung injury (TRALI)

= Acute Lung Injury (ALI) that occurs within 6 h of transfusion (may happen up to 72 hours) and is not related to other risk factors for ALI or ARDS.

Is the most common cause of major morbidity and mortality after transfusion. The risk of TRALI is estimated at 1 case per 5,000 units RBC.

The estimated mortality rate for TRALI is 5-8%**.**

Pathogenesis: endothelial damage induced by pulmonary endothelial activation and Polymorphonuclear (PMN) sequestration & transfusion of biologic response modifiers (including anti-granulocyte antibodies, lipids, and CD40-ligand) that activates these adherent PMN.

Transfusion-associated circulatory overload (TACO)

= fluid overload and pulmonary edema secondary to transfusion $\Rightarrow$ patients develop hypoxemia, tachypnea, tachycardia, and develop bilateral infiltrates on RX.

This also happens during or within few hours of transfusion.

TACO is hydrostatic pulmonary edema (a pressure phenomenon), whereas TRALI is a phenomenon of increased permeability.

A marker of heart distention can be helpful in differentiating, such as B-type natriuretic peptide**.**

Risk Factors and Outcomes in *Transfusion-associated Circulatory Overload*

Murphy EL, et al. *(American Journal of Medicine, 2013)*

DEFINIZIONE TACO = segni e sintomi di edema polmonare acuto che insorgono entro 6 ore da un'emotrasfusione *(Centre of Disease Control & Prevention)*.

Differenza con *TRALI* = meccanismo dell'edema polmonare: aumento della pressione idrostatica vs alterazione della permeabilità capillare.

Incidenza TACO = 1-8% delle emotrasfusioni.

2° causa di mortalità per emotrasfusioni *(FDA)*.

FATTORI PREDISPONENTI

- infusione di eccessive quantità di sangue (ogni sacca di EC aumenta il rischio del 11%)
- infusione di sangue in poco tempo e soprattutto troppo rapidamente
- sesso femminile (OR 2.1, 95%CI 1.03-4.1)
- età <3 anni o >60 anni
- IRC (OR 27.0, 95%CI 5.2-143)
- scompenso cardiaco (OR 6.6, 95%CI 2.1-21)
- interventi chirurgici nelle precedenti 24 ore (spt. cardiovascolari e al fegato)

Complicanze acute delle Emotrasfusioni - 2

Transfusion-related immunomodulation (TRIM)

= immunosuppression secondary to allogenic blood transfusion, involving donor allogeneic leukocytes.

Hemolytic transfusion reactions

= interactions between antibodies in the recipient's plasma and surface antigens on donor RBC. There are immediate or delayed reactions.

Immediate reactions: are typically the result of ABO incompatability produces an antigen–antibody complex causing complement activation, intravascular hemolysis and thus destruction of the transfused blood.

Symptoms start very soon: headache, chest and flank pain, nausea and vomiting, fever, chills, flushing, urticaria, shortness of breath, hypotension, hemoglobinuria and disseminated intravascular coagulation.

The transfusion should be stopped immediately, and patient should be treated emergently and mainly with supportive therapy.

Delayed reactions: the donor RBC antigen–plasma antibody interactions are usually the result of incompatibility with minor blood groups such as Rh and Kidd

$\Rightarrow$ extravascular hemolysis that typically happens *3 days to 3 weeks later*.

The patient presents with reduction in Hct despite transfusion, jaundice (unconjugated hyperbilirubinaemia) and a positive direct Coomb's test.

In general, no treatment is required**.**

Complicanze acute delle Emotrasfusioni - 3

Non hemolytic febrile reactions

Fever is the hallmark of this reaction, in addition to fatigue, malaise, myalgias, chills, and rarely hypotension, vomiting and shortness of breath.

This is a *relatively benign reaction* that results from donor leukocyte antigens reacting to antibodies present in the recipient's plasma forming a leukocyte antigen–antibody complex that binds complement and results in the release of IL-1, IL-6 and TNF.

Management involves slowing the transfusion and in rare cases stopping it, as well as prescribing *antipyretics*.

Transfusion-related infections

Possible transfusion transmitted infections are HIV or hepatitis and the newly discovered Creutzfeld-Jacob disease and the Dengue virus.

Bacterial and viral contaminations are infrequent these days.

[For the first time in its 14 yr history, the 2010 report of the UK's Serious Hazards of Transfusion Haemovigilance Initiative had no confirmed case of transfusion-transmitted infection].

Complicanze acute delle Emotrasfusioni - 4

Transfusion-related allergic reactions

= pruritis, urticaria, and fever.

These reactions are usually mediated by Ig-E in response to foreign proteins in donor plasma.

The transfusion should be stopped and anti-histamines administered.

Electrolyte abnormalities = Hyperkalemia and Hypocalcemia

Plasma potassium and calcium concentrations should be monitored in patients who require transfusions, particularly with multiple units transfused, renal insufficiency or liver disease.

Loss of 1 unit of blood through bleeding results in a loss of 1.5 mEq of potassium, whereas transfusion of 1 RBC unit of RBC can provide approximately 10 mEq of potassium, leading to a net gain of 8.5 mEq.

Meccanismi delle complicanze delle Emotrasfusioni

Several changes occur to the RBCs during ***storage***.

RBCs are stored up to 42 days.

Storage lesions become apparent after about 14 days.

- Longer RBC unit storage
  - ⇒ lower levels of 2,3- Bisphosphoglycerate concentration
  - ⇒ left shift in the oxygen-hemoglobin dissociation curve
  - ⇒ less O2 delivered to the tissues
- Storing RBC can lead to increase levels of cytokines, lipids and other inflammatory mediators
- Longer RBC unit storage ⇒ progressive increase in rigidity
  - ⇒ loss of rheologic capability and deformability of the RBC
  - ⇒ RBC unability to pass freely through capillaries
  - ⇒ worsening microcirculatory dysfunction, above all in sepsis

Meccanismi delle complicanze delle Emotrasfusioni

- Exposure of RBCs to endotoxin and inflammatory cytokines increases RBC adhesion to microvascular endothelium $\Rightarrow$ compromission of tissue blood flow.
- Inappropriate blood trasfusion may lead to circulatory overload and increased thrombogenicity.
- RBC units may contain bioactive particles capable of influencing the cellular injury that leads to organ failure in susceptible patients with preexisting insults such as sepsis or mechanical ventilation.
- *In vivo* models have demonstrated that older RBC units exhibit reduced deformability, which may actually impair capillary flow and oxygen delivery in an already compromised microvascular system.

Reference for complication of trasfusion

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- Parsons EC, et al. Red Blood Cell Transfusion and Outcomes in Patients With Acute Lung Injury, Sepsis and Shock. Crit Care, 2011

Studi clinici & Emotrasfusioni

- **CADILLAC** is the first study assessing the implications of transfusions in *patients subdue to primary angioplasty*. These investigators found that transfusion was *independently* associated with major adverse events and, more importantly, with 30-days and 1-year mortality.
- **TRICC** = Randomized trial of *critically ill patients* found no benefit with the use of a liberal transfusion strategy to maintain Hb levels of 10 mg/dl as compared with a restrictive approach where transfusions were only indicated to patients with a Hb level 7 mg/dl.
- **FACTT** (Fluid and Catheter Treatment Trial) = showed that liberal volume administration (which could include RBC transfusion) was associated with poor outcomes in *hemodynamically stable ALI patients*.
- **Medicare administrative database** = in subjects with *acute myocardial infarction* aged 65 years and managed largely conservatively, transfusion was associated with a lower 30-day mortality in those with a Hct 33% at admission, whereas transfused patients with Hct 36% had a higher mortality.
- **GUSTO** = (Global Use of Strategies To open Occluded coronary arteries) in which patients with *myocardial infarction* treated with only pharmacological reperfusion, blood transfusion was associated with a more than 2-fold increase in 30 day and 1 year mortality as well as increased rates of reinfarction

Trasfusioni & Cardiopatia ischemica

- In U.S. 20% of blood trasfusion are associated with cardiovascular surgery.

- Recent systematic reviews of studies on red blood cell transfusion in patients with ischemic heart disease indicate that routine transfusion is of little clinical benefit and, in fact, may carry the potential for adverse serious consequences (2009).

- When patients under the age of 80 receive just 1–2 units of blood, risk of low-output heart failure is increased by 27%, and both short- and long-term survival are decreased.

- Even in patients undergoing cardiac surgery, who were considered low-risk preoperatively, the transfusion of blood added significant risks for cardiac events, infection and morbidity postoperatively.

(Shaw et al. Interactive Cardiovascular&Thoracic Surgery, 2013)

CADILLAC (2004)

- 2,082 patients of any age with AMI within12 hours of symptom onset undergoing primary PCI in a native coronary artery eligible for stent implantation
- Patients were stratified into 3 groups:
  1) patients administered 1 or more units of RBC due to moderate-severe bleeding
  2) patients administered RBC in the absence of overt major bleeding
  3) patients who did not receive RBC transfusion
- 3.98% received RBC transfusion:
  - 1.60% in the case of moderate-severe bleeding
  - 2.38% in the absence of moderate-severe bleeding
- Patients who received RBC transfusion were *older*, more frequently *female*, had a higher prevalence of *prior gastrointestinal bleeding*, *chronic renal insufficiency*, *multivessel disease* and *lower BMI*.
- RBC transfusion were associated with *worse clinical and angiographic features* at baseline, *larger infarct sizes*, *longer time from symptom* onset to balloon inflation, *longer procedure duration*, lower post-procedure TIMI flow grade, smaller post procedure reference vessel diameter and *worse procedural outcomes*.

CADILLAC (2004)

- Baseline anemia (Hct 39% for men and 36% for women) was frequently found (12.8%) in patients undergoing primary angioplasty and this finding was strongly associated with 30-days and 1-year mortality (3-fold risk increase).
- Baseline anemia was identified as the strongest *independent* predictor of 1-year mortality on multivariate analysis.
- Blood transfusion was strongly associated with adverse clinical outcomes at 1 year: of the 4% of patients that received transfusions, 1 in 4 died and 1 in 2 suffered adverse clinical events (death, myocardial reinfarction, target vessel revascularization, or disabling stroke).
- After multivariable adjustment for potential confounders (including baseline anemia and transfusion propensity), *RBC transfusion, but NOT anemia, was identified as an independent predictor of mortality at 30-days and 1-year*.
- Patients who received blood transfusion without associated moderate or severe bleeding tended to have higher rates of 30-days and 1-year death, target vessel revascularization and composite major adverse cardiac events.

CADILLAC (2004)

LIMITS

- Anemia and transfusion were so closely related that the resulting in
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and antiplatelet drugs on outcome measures was not investigated.

CONCLUSION

In patients with AMI, *bleeding prevention* is of paramount importance: strategies that diminish bleeding risk while maintaining efficacy in reducing ischemic complications are very important.

The role of newer anticoagulants, dose adjustments per gender, body mass index and baseline bleeding risk, meticulous puncture technique are some important attractive measures to diminish bleeding risk.

Prognostic impact of red blood cell transfusion in patients undergoing primary angioplasty for STEMI

Ergelen Mehmeta, et al. *(Coronary Artery Disease,2012)*

Objectives: We aimed to examine in-hospital and long-term outcomes of red blood cell (RBC) transfusions in patients undergoing a PCI for STEMI.

Methods: Overall, 2537 consecutive STEMI patients (mean age 56.2±11.7 years, 16.7% women) undergoing PCI were enrolled retrospectively. Patients were categorized according to whether they received RBC transfusions during hospitalization.

Results: n.88 (3.4%) received RBC transfusions.

The transfused patients:

- were older (mean age 63.6±12.1 vs 56.2±11.8, *P*<0.001)
- were prevalently female (45.4 vs 15.8%, *P*<0.001)
- had hypertension more frequently (52.3 vs. 40.7%, *P*=0.04)
- had lower baseline Hct (33±6.2 vs. 40.2±4.7%, *P*<0.001)
- had lower baseline Hb (11.1±2.3 vs. 13.7±1.6 mg/dl, *P*<0.001).

The transfused patients had higher in-hospital and long-term mortality (for in-hospital mortality: 10.2 vs. 2.7%, P<0.001; for long-term mortality: 14.1 vs. 5.1%, P=0.001).

By multivariate Cox regression analysis, in all 2537 patients, *RBC transfusion was found to be a powerful independent predictor of in-hospital cardiovascular mortality (OR 8.31, P<0.001).*

Red blood cell transfusion and mortality among patients hospitalized for acute coronary syndromes: A systematic review

Garfinkle, et al. *(International Journal of Cardiology, 2013)*

Background: Observational studies have suggested a relationship between anemia and adverse outcomes among patients presenting with acute coronary syndromes (ACS). However, the Hb level at which packed red blood cell (RBC) transfusion is beneficial remains unclear as available data are conflicting.

We therefore performed a systematic review of all relevant observational studies, with a particular focus on examining optimum Hb thresholds for transfusion among patients hospitalized for ACS.

Results: 11 studies that met inclusion criteria, involving a total of 290,847 patients.

The main indication for transfusion was major bleeding.

Overall, patients who received transfusions were at greater unadjusted risk of mortality (range OR: 1.9-11.2). When Hb-stratified analyses were examined, a graded association between RBC transfusion and mortality was seen:

- transfusion had beneficial or neutral effects on mortality if Hb < 8.0g/dL

- transfusion had harmful or neutral effects if Hb > 11.0g/dL.

Conclusions: data support a more conservative transfusion strategy.

Association of blood transfusion with increased mortality in myocardial infarction: A meta-analysis and diversity-adjusted study sequential analysis.

Chatterjee S et al. *(Arch Intern Med, December 2012)*

A meta-analysis of 10 studies (203,665 patients)
comparing blood transfusion with no blood transfusion or a liberal transfusion approach with a restrictive approach.
Only one randomized controlled trial was included; the other studies were observational.
Transfusion was associated with significantly increased risks for death from all causes:

18.2% vs 10.2%; RR 2.91, 95%CI 2.46-3.44
absolute risk increase 12% *p*<.001
estimated number needed to harm = 8, 95%CI 6-17

and for recurrent myocardial infarction: RR 2.04, 95%CI 1.06-3.93**,** *p*<.03.
The results were similar after adjustment for a variety of study characteristics (follow-up period, history of bleeding, creatinine, baseline and nadir Hb level, change in Hb during hospitalization, uso of glycoprotein IIb/IIIa, thrombolytics or antiplatelets).

The association of transfusion with mortality was nonsignificant in patients
with STEMI → RR 2.89, 95%CI 0.54-15.58
or Hct levels < 30% → RR 1.72, 95%CI 0.39-7.63

COMMENTS ON

Association of blood transfusion with increased mortality in myocardial infarction: A meta-analysis and diversity-adjusted study sequential analysis.

Chatterjee S et al. (*Arch Intern Med,* December 2012)

Frederick A. Masoudi. Published in Journal Watch Cardiology January 23, 2013:

The results of this meta-analysis are limited by the quality of the studies included. Because most of the individual studies were observational, the results may reflect confounding by unmeasured patient characteristics. Nevertheless, the study will make me think more carefully about employing blood transfusions in my patients with myocardial infarction who have anemia, and it sets the stage for a definitive trial to address this clinically important question.

Jeffrey L. Carson. Published online in Archives Internal Medicine December 24, 2012:

What might we take away from this systematic review? The authors remind us that patients with an AMI are often anemic and receive red blood cell transfusion. However, because of its many limitations, as physicians, we should not use the results of this review to justify or limit the use of red blood cells.

Given that real risks and potential benefits, we believe that high-quality research is long overdue".

Balancing the benefits and risks of blood transfusions in patients undergoing cardiac surgery: a propensity-matched analysis

Shaw RE, et al. *(Interactive CardioVascular and Thoracic Surgery, 2013)*

N.3516 consecutive patients underwent cardiac surgery (mean age 69 years)
1922 patients received blood products (54.5%).

Patients receiving blood products were found to be

- *older*
- with higher rates of diabetes, peripheral vascular disease, renal failure
- with higher rates of myocardial infarction, NYHA III–IV heart failure, more severe coronary disease, FE <35%
- more likely to be having a reoperation and more urgent presentation

(all significant at $P < 0.001$ level).

Of the 3519 patients, 1714 were matched: 857 in the transfused group (TG) and 857 in the non-transfused control group (CG).

Table 4: In-hospital and 30-day outcomes

	TG (*N* = 857)	CG (*N* = 857)	*P*-value
Reoperation for bleeding	54 (6.3%)	3 (0.4%)	0.0001
Perioperative MI	19 (2.2%)	4 (0.5%)	0.002
Deep sternal wound infection	3 (0.4%)	0 (0.0%)	0.083
Permanent stroke	17 (2.0%)	5 (0.6%)	0.010
Prolonged ventilation	103 (12.0%)	34 (4.0%)	0.0001
Postoperative renal failure	36 (4.2%)	10 (1.2%)	0.0001
Postoperative atrial fibrillation	200 (23.3%)	161 (18.8%)	0.021
30-day mortality	20 (2.3%)	3 (0.4%)	0.0001

Table 7: Logistic regression analysis

	Adjusted odds ratio	95% Confidence interval	*P*-value
History of renal failure	25.30	3.80–168.41	<0.0001
Blood transfusion	7.24	2.94–13.62	0.008
Cross-clamp time >89 min	5.54	1.11–38.11	0.035
NYHA Class III/IV	5.28	1.04–26.81	0.038
Preoperative HCT >43	2.53	1.01–21.76	0.047

TG patients with Hct <36 had significantly more postoperative complications and 30-day mortality than CG patients.

For presurgery Hct levels between 40 - 42, there were more complications in the TG group and a significantly higher rate of mortality (1.9 vs 0.0%; $P = 0.044$).

Transfusing patients with preoperative Hct >42 placed them at a 2.5-fold increase risk of mortality independent of other factors.

For Hct 36–39, operative mortality was similar between TG and CG.

(Shaw. Interactive CardioVascular and Thoracic Surgery, 2013)

- Ferraris VA, et al. **Perioperative blood transfusion and blood conservation in *cardiac surgery*: the Society of Thoracic Surgeons and The Society of Cardiovascular Anesthesiologists clinical practice guideline**. Ann Thorac Surg 2007;83:S27–86.

- Ferraris VA, et al. **2011 update to the Society of Thoracic Surgeons and the Society of Cardiovascular Anesthesiologists blood conservation clinical practice guidelines.** Ann Thorac Surg 2011;91:944–82.

These clinical practice guidelines indicate red blood cell (RBC) transfusion in patients with uncontrolled blood loss or who have lost >1500 ml or ≥ 30% of the total blood volume regardless of Hct levels.

Patients with chronic cardiovascular/pulmonary disease or Hb ≤ 7.0 g/dl (≤ 6.0 g/dl if on cardiopulmonary bypass) should also receive packed RBC.

There are no clear benefits or consequences of transfusing patients with Hb levels between 7 and 10 g/dl.

Trasfusioni & pazienti critici (terapia intensiva, sepsi)

By day two in the ICU, nearly 95% of patients are anemic.

CAUSES

Phlebotomy and bleeding

Phlebotomy accounts for up to 20% of total blood loss.

Bleeding accounts for up to 20 % of blood loss, as occult or overt bleeding (like GI bleeding, surgery, trauma, procedures, etc).

RBC destruction

From intravascular causes (Disseminated Intravascular Coagulation,Thrombotic Thrombocytopenic Purpura, endovascular devices, and prostheses) or immune mediated (hemolytic transfusion reactions and drug-induced -penicillin's, cephalosporin's, sulfas, and quinines).

Abnormal iron metabolism

Inflammatory cytokines play a major role in alterations in iron metabolism, leading to decrease serum iron levels, and increasing iron storage by the reticuloendothelial system, limiting the availability of iron for erythropoiesis.

Erythropoesis

In septic and critically ill patients, inflammatory cytokines play an inhibitory role on erythropoietin production as well as a direct inhibitory effect on erythroid progenitor cell production in the bone marrow**.**

(Sadaka, J Blood Disord Trasfusion, 2012)

By day two in the ICU, nearly 95% of patients are anemic.

MOREOVER

- Proinflammatory cytokines decrease erythrocyte survival time
- In sepsis, functional and structural changes are found in erythrocytes (decreased red blood cell deformability and antioxidant activity, decreased Hb content)
- Oxidative stress and free radicals can trigger RBC apoptosis
- Hypersplenism due to infection can increase the sequestration and phagocytosis of erythrocytes
- RBCs' decreased deformability
- Inflammation and lipopolysaccharides can also increase RBC adhesion to the vessel endothelium which could also lead to microcirculatory dysfunction

(Sadaka, J Blood Disord Trasfusion, 2012)

RBC transfusions might benefit patients with sepsis by improving oxygen delivery while patients are in a state of high metabolic demand and overall oxygen deficit.

Conflicting evidence regarding RBC transfusion and outcomes has led to significant controversy over the use of RBC transfusion in goal-directed sepsis resuscitation strategies and in critically ill septic patients in the ICU.

Practice guidelines do not address the use of RBC transfusion beyond the first 6 hours after sepsis diagnosis.

Surviving Sepsis Campaign: international guidelines for management of severe sepsis and septic shock: 2008;

Clinical practice guideline: red blood cell transfusion in adult trauma and critical care, 2009.

TRICC (1999)

- Patients of a general medical and surgical critical care population, who were euvolemic after initial treatment who had a Hb concentration < 9 g/dL within 72h were enrolled.
- In this study, a *liberal transfusion strategy* (Hb 10-12 g/dL, with a transfusion trigger of 10 g/dL) was compared to a *restrictive transfusion strategy* (Hb 7-9 g/dL, with a transfusion trigger of 7 g/dL).
- Trial documented an overall nonsignificant trend toward decreased 30-day mortality in the restrictive group.
- There was a significant decrease in mortality in the restrictive group among patients who were less acutely ill (APACHE II scores < 20) and among younger patients (< 55 years of age).
- The diversity of patients enrolled in the trial and the consistency of the results suggest that the conclusions may be generalized to most critical care patients including septic patients, with the possible exception of patients with acute coronary syndromes.

Red Blood Cell Transfusion and Outcomes in Patients With Acute Lung Injury, Sepsis and Shock

Parsons EC, et al. *(Crit Care, 2011)*

FACTT enrolled 1,000 subjects within 48 hours of a new ALI diagnosis.
All subjects were randomized to a liberal or conservative fluid management strategy.
Transfusion was not a part of the FACTT protocol and was initiated according to the physician's discretion.

N.53 (19%) of the 285 subjects with shock were transfused within 24 hours of randomization.
Transfused and nontransfused subjects were similar in terms of age, sex, ICU location, comorbidities, PaO2/FiO2 ratio.

N.23 transfused subjects (43%) died by day 28 compared with 70 nontransfused subjects (30%) (*P* =.06).
In multivariable regression analysis, we observed no independent association between transfusion and

- 28-day mortality (adjusted OR 1.49, 95%CI 0.77-2.90; *P* =.23)
- ventilatory-free days (adjusted mean difference −0.35, 95%CI −4.03 to 3.32, *P*=.85)
- 90-day mortality (adjusted OR 1.55, 95%CI 0.81-2.96; *P* =.19).

Red Blood Cell Transfusion and Outcomes in Patients With Acute Lung Injury, Sepsis and Shock

Parsons EC, et al. *(Crit Care; 2011)*

We identified a subgroup of subjects with shock meeting 4 physiological criteria
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=.02) and lower Hb (mean 8.2 vs 9.0 g/dL; *P* =.02).

CONCLUSIONS

We did not observe a statistically significant benefit or harm associated with RBC transfusion among patients with a recent diagnosis of ALI, sepsis and shock.

Physiological indicators may not necessarily identify those patients likely to benefit from RBC transfusion.

In multivariable regression analysis, after adjusting for our predetermined confounders, we observed no independent association between transfusion and 28-day mortality and 90-day mortality or ventilatory-free days.

Red blood cell transfusions are associated with lower mortality in patients with severe sepsis and septic shock: A propensity-matched analysis*

Park DW, et al. *(Critical Care Medicine, December 2012)*

Setting & Patients

n.22 medical and surgical intensive care units in 12 teaching hospitals in Korea.
N.1054 patients with community-acquired severe sepsis and septic shock.

Main Results

n.407 (38.6%) received a blood transfusion.
Mean pretransfusion Hb level was 7.7 ± 1.2 g/dL.
Transfused patients had

- higher 28-day mortality rates 32.7% vs 17.3%; *p* <.001
- higher in-hospital mortality rates 41.3% vs 20.3%; *p* <.001
- longer duration of hospital stay 21 vs 13 days; *p* <.001

BUT were more severely ill at admission (lower systolic blood pressure, higher APACHE-II score, and SOFA score at admission).

Red blood cell transfusions are associated with lower mortality in patients with severe sepsis and septic shock: A propensity-matched analysis*

Park DW, et al. *(Critical Care Medicine, December 2012)*

In 152 pairs matched according to the propensity score depending on patient transfusion status,
transfused patients had a lower risk of 7-day (9.2% vs 27.0%; *p* <.001), 28-day (24.3% vs 38.8%; *p* =.007), and in-hospital mortality rates (31.6% vs 42.8%; *p* =.044).

After adjusting for blood transfusion as a time-dependent variable in multivariable analysis, blood transfusion was independently associated with

- lower risk of 7-day mortality — HR 0.42, 95%CI 0.19–0.50, *p* =.026
- lower 28-day mortality — HR 0.43, 95%CI 0.29–0.62, *p* <.001
- lower in-hospital mortality — HR 0.51, 95%CI 0.39–0.69, *p* <.001.

Conclusions: In this observational study of patients with community-acquired severe sepsis and septic shock, red blood cell transfusions were associated with lower risk of mortality.

Recent guidelines were put together by the American College of Critical Care Medicine of the Society of Critical Care Medicine & the Eastern Association for the Surgery of Trauma Practice Management Workgroup - 2009

Within 6 Hours of Severe Sepsis

Transfuse RBC when Hb < 10 g/dL to achieve ScvO2 =70% (only after CVP of 8 -12 mmHg and MAP >65mmHg are achieved).

Sepsis Beyond The Initial 6 Hours

- RBC transfusion is indicated for patients with evidence of hemorrhagic shock
- A “restrictive” strategy of RBC transfusion (transfuse when Hb < 7 g/dL) in patients with hemodynamically stable anemia
- In the absence of acute hemorrhage RBC transfusion should be given as single units
- There is no benefit of a “liberal” transfusion strategy (when Hb < 10 g/dL) in patients with stable cardiac disease
- Consider transfusion if Hb < 7 g/dL in patients with stable cardiac disease
- RBC transfusion may be beneficial in patients with acute myocardial ischemia who are anemic (Hb<8g/dL)

New Surviving Sepsis Campaign Guidelines Released

Dellinger RP et al. **Surviving Sepsis Campaign: International guidelines for management of severe sepsis and septic shock, 2012.**

Crit Care Med 2013 Feb; 41:580.

Blood Products

After tissue hypoperfusion is corrected, red blood cell transfusion *only when* Hb concentration decreases to <7.0 g/dL,

to a target Hb concentration of 7.0–9.0 g/dL in adults. *(grade 1B)*

Trasfusioni in Ortopedia

Anemia and Patient Blood Management in Hip and Knee Surgery. *A Systematic Review of the Literature*

Spahn DR. *(Anesthesiology, 2010)*

A systematic review of 49 publications on elective total hip or knee arthroplasty or hip fracture surgery.

	Elective total hip or knee arthroplasty	Hip fracture surgery
Hb pre-operative (g/dl)	13.6 ± 0.4	12.5 ±0.2
Hb post-operative (g/dl)	10.6 ± 0.8	8.2 ± 2.1
Pre-operative anemia	24%	44%
Post-operative anemia	51%	87%
Allogenic blood transfusion	45% (range 10–69%)	44% (range 34-69%)

Anemia and Patient Blood Management in Hip and Knee Surgery.

A Systematic Review of the Literature

Spahn DR. *(Anesthesiology, 2010)*

OUTCOMES

Physical Function

✓ Early post-operative anemia (first 3 days post-surgery Hb<10 g/dl)

⇒ impaired functional mobility in the early post-operative phase

✓ Lower post-operative Hb level

⇒ shorter walking distance at time of hospital discharge

✓ 3 studies reported the *absence of an association* between anemia and poorer physical functioning

✓ The difference in recovery of ambulatory activity and of BADL and IADL at 3, 6, or 12 months after surgical intervention *did not* reach statistical significance between anemic and not-anemic patients

Infection

✓ Pre-operative anemia compared with no anemia was associated with an increased incidence of post-operative urinary tract infections (28 *vs* 14%, *P*=.039) and numerically more frequent respiratory tract infections.

Anemia and Patient Blood Management in Hip and Knee Surgery.

A Systematic Review of the Literature

Spahn DR. *(Anesthesiology, 2010)*

OUTCOMES

Length of Hospital Stay

✓ Anemia on admission and post-operative anemia ⇒ significantly increased LOS

Mortality

✓ Pre-operative and post-operative anemia ⇒ significantly increased mortality

Quality of Life

✓ None of the selected studies reported the effects of anemia on QoL in patients undergoing hip or knee surgery

FOCUS (2006)

- 2,016 patients > 50 years (mean age 81.6, range 51-103) undergoing primary surgical repair of a hip fracture and who had clinical evidence of or risk factors for cardiovascular disease + they had a Hb < 10g/dl within 3 days after surgery
- Randomization:

  Liberal-strategy group (n.1007) → Hb threshold for blood transfusion = 10g/dl

  Restrictive-strategy group (n.1009) → Hb threshold for blood transfusion = 8g/dl or symptoms (cardiac chest pain, congestive hearth failure, tachycardia, hypotension unresponsive to fluid replacement)
- PRIMARY OUTCOMES = death

  = inability to walk 10 ft or cross a room without human assistence at the 60-day follow-up
- SECONDARY OUTCOMES = current residence, survival, functional measures (lower extremity physical and IADL), fatigue at 30- and 60-day follow-up
- TERTIARY OUTCOME = in-hospital morbidity up to 30 days

(Carson JL, NEJM 2011)

FOCUS (2006)

(Carson JL, NEJM 2011)

	Liberal-strategy group	*Restrictive-strategy group*
Median N. units transfused	2	0
Death 30- & 60-day period	5.2% & 7.6%	4.3% & 6.6%
Inability to walk 30- & 60-day period	40.9% & 27.6%	43.8% & 28.1%
In-hospital acute myocardial infarction, angina or death	4.3%	5.2%
Residence in home 30- & 60-day period	46% & 61.9%	42.5% & 60.2%
IADL lost 30-day period	3.9 $\pm$ 0.5	3.9 $\pm$ 0.4
IADL lost 60-day period	3.7 $\pm$ 0.8	3.7 $\pm$ 0.9
Lower extremity physical activities 30-day period	7.3 $\pm$ 4.0	7.4 $\pm$ 3.9
Lower extremity physical activities 60-day period	5.1 $\pm$ 4.3	5.1 $\pm$ 4.3

Outcome in hip fracture patients related to anemia at admission and allogeneic blood transfusion: an analysis of 1262 surgically treated patients

Anne Vochteloo, et al. *(BMC Musculoskeletal Disorders 2011)*

In the Netherlands, the national guideline advises allogenic blood transfusion (ABT) for subjects aged > 60 years when Hb level drops below 8.0 g/dL in the general population or 9.7 g/dL if the patient has a serious cardiac condition or when anemia becomes symptomatic.
Observational cohort study of 1222 patients subdue to a surgical treatment of a hip fracture (73.9% female, mean age 83.6 +7.1), observed during 3.5 years follow-up.

RISULTATI

- Receiving an ABT, an ASA classification III/IV and higher age were risk factors for post-operative mortality.
- Anemia was not a significant risk factor for mortality in Cox regression analysis.
- Receiving an ABT was a risk factor for mortality at all follow-up moments, but not for the 3 to 12 months interval. Th main effect was in the first 3 months.
- The RR for 3-month mortality in patients receiving an ABT was comparable between anemic and non-anemic patients; both groups are negatively affected by an ABT.
- Anemia at admission was a significant risk factor for discharge to a nursing home and readmission within 90 days.
- Receiving an ABT was correlated with a longer LOS and a higher delirium incidence.
- Anemia did not have a negative effect on delirium incidence.

Alternative alle emotrasfusioni nei pazienti sottoposti a interventi ortopedici

- In pazienti sottoposti a chirurgia ortopedica in elezione, i valori di Hb e l'assetto marziale andrebbero valutati 28 giorni prima dell'intervento, al fine di distinguere le forme di anemia sideropenica da quelle da disordine cronico
- *Terapia con ferro orale* in pazienti in lista d'attesa per interventi di protesizzazione del ginocchio e dell'anca. Ancora più efficace *l'infusione endovenosa di ferro* (soprattutto per le forme di anemia sideropenica). La differenza tra somministrazione ev rispetto a os è la velocità ed entità del ripristino del ferro (7-14 giorni vs 30-40 giorni), oltre all'assenza di effetti avversi gastrointestinali
- Risultati controversi per uso di *Eritropoietina* in pazienti in lista d'attesa per interventi di protesizzazione del ginocchio e dell'anca (riduce n° emotrasfusioni, ma non migliora outcome)
- Risultati controversi per *salvataggio di sangue* durante l'intervento
- Risultati controversi per la *donazione pre-operatoria di sangue autologo*

(Anesthesiology, 2010; *Anemia, 2013)*

The impact of an algorithm-guided management of preoperative anemia in perioperative Hb level in transfusion of major orthopedic surgery patients. *Enko D, et al.* *(Anemia, 2013)*

N.335 pazienti (età media 68 anni), sottoposti a *intervento in elezione di protesi* d'anca o ginocchio: GRUPPO I (n.101) sottoposti a procedure pre-operatorie convenzionali, GRUPPO II (n.234) sottoposti a gestione pre-operatoria dell'anemia secondo il seguente algoritmo:

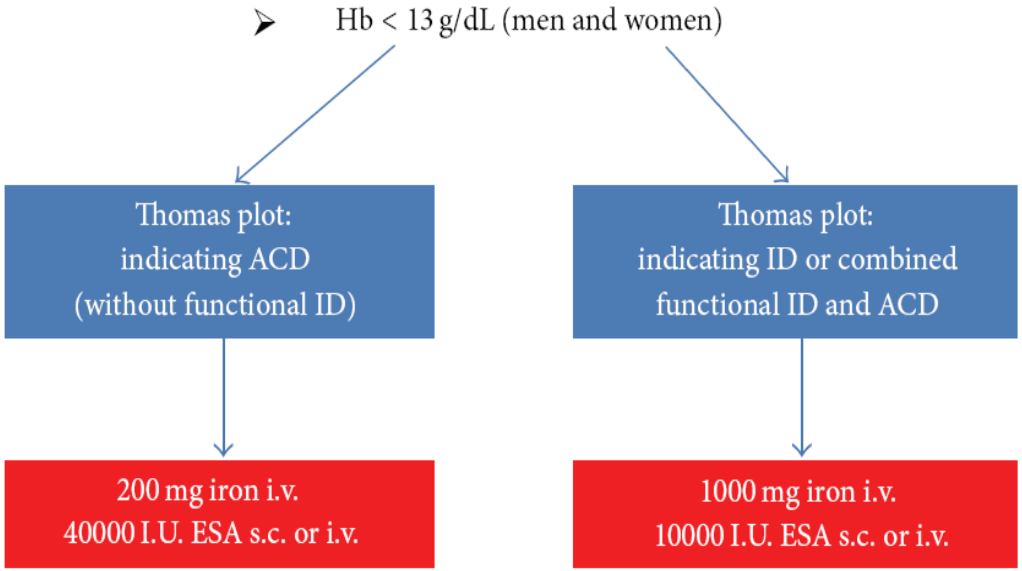

FIGURE 1: Preoperative diagnostic and therapeutic algorithm applied in Group II. Hb: hemoglobin; ID: iron deficiency; ACD: anemia of chronic disease; ESA: erythropoiesis stimulating agent; I.U.: international unit; s.c.: subcutaneous; i.v.: intravenous.

Thomas-plot = permette di distinguere tra diversi gradi di deficit di ferro e anemia da disordine cronico. Viene calcolato sulla base del Contenuto Reticolocitario di Hb e del rapporto tra il Recettore solubile della Transferrina e il logaritmo della Ferritina, quest'ultimo a sua volta "pesato" con i valori di Proteina C Reattiva.

The impact of an algorithm-guided management of preoperative anemia in perioperative Hb level in transfusion of major orthopedic surgery patients. *Enko D, et al.* *(Anemia, 2013)*

N.335 pazienti (età media 68 anni), sottoposti a *intervento in elezione di protesi* d'anca o ginocchio: GRUPPO I (n.101) sottoposti a procedure pre-operatorie convenzionali, GRUPPO II (n.234) sottoposti a gestione pre-operatoria dell'anemia secondo il seguente algoritmo:

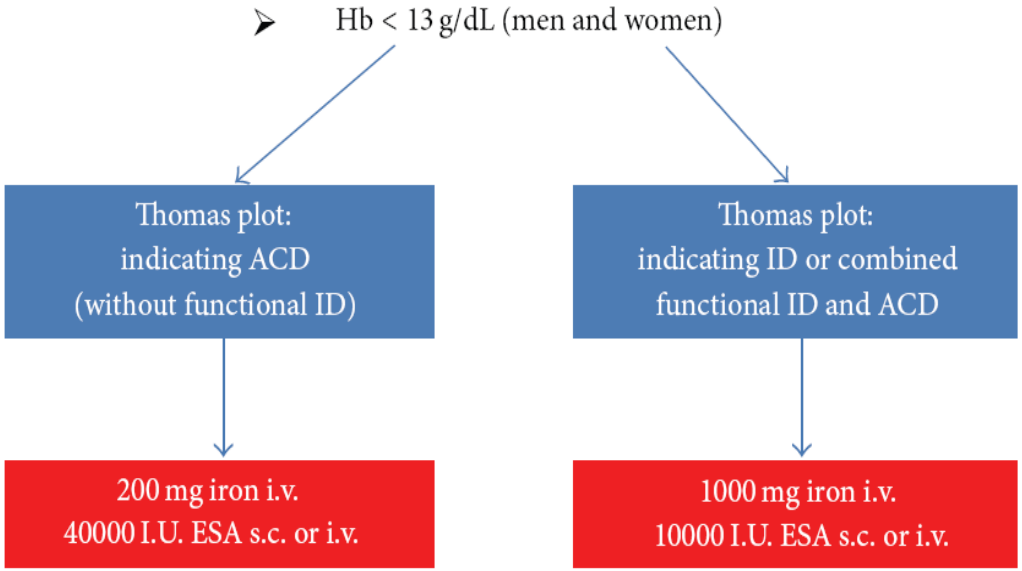

FIGURE 1: Preoperative diagnostic and therapeutic algorithm applied in Group II. Hb: hemoglobin; ID: iron deficiency; ACD: anemia of chronic disease; ESA: erythropoiesis stimulating agent; I.U.: international unit; s.c.: subcutaneous; i.v.: intravenous.

Network for Advancement of Transfusion Alternatives (NATA) Guidelines =

- Ferritina < 30ng/ml e/o Sat.Transferrina < 20% ⇒ anemia da carenza di Ferro
- Ferritina > 100ng/ml e/o Sat.Transferrina > 20% ⇒ anemia da disordine cronico
- Ferritina = 30-100ng/ml e/o Sat.Transferrina < 20% ⇒ anemia a eziologia mista

The impact of an algorithm-guided management of preoperative anemia in perioperative Hb level in transfusion of major orthopedic surgery patients.

Enko D, et al. *(Anemia, 2013)*

CONCLUSIONI

- Nel GRUPPO II il numero totale di emotrasfusioni è stato ridotto del 44%
- Anche nei soggetti anemici del GRUPPO II il numero di emotrasfusioni si è ridotto del 60%
- Il Thomas plot è risultato più efficace delle LG NATA nell'identificare la causa di anemia (nel secondo caso rimane un 50% di anemia a eziologia non chiara)
- Pazienti con Hb tra 10-13g/dl dovrebbero essere considerati per un trattamento pre-operatorio con ferro/Epo
- In particolare, in donne con Hb pre-operatoria tra 12-13g/dl beneficiano del trattamento secondo algoritmo, riducendo il rischio di anemizzazione post-operatoria (<9g/dl) dal 44 al 22%
- L'effetto massimo terapeutico secondo algoritmo si ottiene nell'arco dei 20 giorni prima dell'intervento
- In questo studio l'anemia pre-operatoria era determinata da deficit di vitamina B12 e Folati in una bassa percentuale dei casi (3% e 2.8% rispettivamente)

The risks of red cell transfusion for hip fracture surgery in the elderly

Shokoohi A, et al. *(Vox Sanguinis, 2012)*

N.919 U.K. patients undergoing surgery for hip fracture: 76.5% females, mean age of 83.2 years (range 65–106). 32.6% were transfused.

29.5% patients suffered from at least one infectious episode during their stay in hospital: 17.3% urinary tract infection, 13.9% chest infection, 1.2% deep tissue infections, and 0.7% superficial wound infections.

When adjusted for age (*P*<.001), delayed operation time (*P*=.001), COPD (*P* =.006), pressure sore buttock (*P*=.030), pressure sore heel (*P*=.025) and fracture type (*P*=.042),

there was a significant difference between transfused and nontransfused patients in terms of risk of developing infection

⇒ Composite infection RR 1.99 (95%CI 1.44-2.74, p<.001)

The mechanism underlying any association between transfusion and increased infections is unclear and may reflect immunomodulatory changes by transfusing a biological component or the storage lesion in red cells.

Emotrasfusioni & Interventi ortopedici

CONCLUSIONI

The incidence of preoperative anemia in patients undergoing elective orthopaedic surgery reportedly ranges from 21% to 35%.

In England, major orthopedic hip and knee surgery (total hip arthroplasty, total knee arthroplasty, and surgical hip fracture repair) consumed 8% of all transfused units and was the leading indication for blood transfusions in surgical patients.

Preoperative anemia correction with supplemental intravenous or oral iron or recombinant human erythropoietin therapy and autologous transfusion techniques, such as preoperative autologous blood donation and intra- or postoperative cell salvage, have been proposed to reduce the need for allogenic blood transfusions.

(Pape A; Best Pract Res Clin Anaesthesiol 2007)

Regarding transfusion strategies to manage anemia, there is little evidence that liberal transfusion to maintain a Hb level > 10 g/dL has additional benefit beyond a more restrictive strategy of maintaining a Hb level > 8 g/dL in the absence of symptoms of anemia (class 1B).

(Carson JL, NEnglJMed 2011.
Hung WW, JAMA 2012: Hip Fracture Management. Tailoring Care for the Older Patient)

NHS
National Institute for
Health and Clinical Excellence

Hip fracture overview

A NICE pathway brings together all NICE guidance, quality standards and materials to support implementation on a specific topic area. The pathways are interactive and designed to be used online. This pdf version gives you a single pathway diagram and uses numbering to link the boxes in the diagram to the associated recommendations.

To view the online version of this pathway visit:

http://pathways.nice.org.uk/pathways/hip-fracture

Pathway last updated: October 2012

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Non dice nulla in merito ad anemia.

Trasfusioni & Emorragia acuta gastrointestinale

Circa 14% delle trasfusioni di emazie avviene per sanguinamenti acuti del tratto gastrointestinale superiore.

Incidenza = 1:1000 adulti / anno.

Mortalità = 10-30% dei casi.

Conseguenze:

- perdita del volume circolante
- ipotensione
- ridotta perfusione tissutale.

Primo obiettivo terapeutico → ripristinare il volume circolante per ottenere una PA sistolica > 100mmHg e FC < 100bpm.

British Society of Gastroenterology (2002) & American Society of Gastrointestinal Endoscopy (2004) indicano emotrasfusioni *SOLO* in caso di

- perdita ematica estrema (continua e attiva ematemesi con shock)
- Hb <10g/dl
- concomitante ischemia miocardica

Transfusion Strategies for Acute Upper Gastrointestinal Bleeding

Villanueva C, et al. *(NEJM, 2013)*

N. 921 patients with severe acute upper gastrointestinal bleeding (peptic ulcer 49%, esophageal varices 21%, cirrhosis 31%), randomly assigned to:

- *restrictive strategy* (n.444)
  = Hb threshold was 7 g/dl,
  with a target range for the post-transfusion Hb level of 7-9 g/dl

- *liberal strategy* (n.445)
  = Hb threshold was 9 g/dl,
  with a target range for the post-transfusion Hb level of 9-11 g/dl

Transfusion Strategies for Acute Upper Gastrointestinal Bleeding

Villanueva C, et al. *(NEJM, 2013)*

Table 3. Study Outcomes.*

Outcome	Restrictive Strategy (N = 444)	Liberal Strategy (N = 445)	Hazard Ratio with Restrictive Strategy (95% CI)	P Value
Death from any cause within 45 days — no. (%)	23 (5)	41 (9)	0.55 (0.33–0.92)	0.02
Further bleeding — no. of patients/total no. (%)				
Overall	45/444 (10)	71/445 (16)	0.62 (0.43–0.91)	0.01
Patients with cirrhosis	16/139 (12)	31/138 (22)	0.49 (0.27–0.90)	0.02
Child–Pugh class A or B	12/113 (11)	23/109 (21)	0.53 (0.27–0.94)	0.04
Child–Pugh class C	4/26 (15)	8/29 (28)	0.58 (0.15–1.95)	0.33
Bleeding from esophageal varices	10/93 (11)	21/97 (22)	0.50 (0.23–0.99)	0.05
Rescue therapies				
Balloon tamponade	3/139 (2)	11/138 (8)		0.03
TIPS	6/139 (4)	15/138 (11)		0.04
Patients with bleeding from peptic ulcer	23/228 (10)	33/209 (16)	0.63 (0.37–1.07)	0.09
Rescue therapies				
Second endoscopic therapy	20/228 (9)	26/209 (12)		0.21
Emergency surgery	4/228 (2)	12/209 (6)		0.04
No. of days in hospital	9.6±8.7	11.5±12.8		0.01
Adverse events — no. (%)†				
Any‡	179 (40)	214 (48)	0.73 (0.56–0.95)	0.02
Transfusion reactions	14 (3)	38 (9)	0.35 (0.19–0.65)	0.001
Fever	12 (3)	16 (4)	0.74 (0.35–1.59)	0.56
Transfusion-associated circulatory overload	2 (<1)	16 (4)	0.06 (0.01–0.45)	0.001
Allergic reactions	1 (<1)	6 (1)	0.16 (0.02–1.37)	0.12
Cardiac complications§	49 (11)	70 (16)	0.64 (0.43–0.97)	0.04
Acute coronary syndrome¶	8 (2)	13 (3)	0.61 (0.25–0.49)	0.27
Pulmonary edema	12 (3)	21 (5)	0.56 (0.27–1.12)	0.07
Pulmonary complications	48 (11)	53 (12)	0.89 (0.59–1.36)	0.67
Acute kidney injury	78 (18)	97 (22)	0.78 (0.56–1.08)	0.13
Stroke or transient ischemic attack	3 (1)	6 (1)	0.49 (0.12–2.01)	0.33
Bacterial infections	119 (27)	135 (30)	0.87 (0.63–1.21)	0.41

The harmful effects of transfusion may be related to an impairment of hemostasis.

Transfusion may counteract the splanchnic vasoconstrictive response caused by hypovolemia, inducing an increase in splanchnic blood flow and pressure that may impair the formation of clots.

Transfusion may also induce abnormalities in coagulation properties.

Restitution of blood volume can induce rebound increases in portal pressure that may precipitate portal hypertensive related bleeding.

Clinical studies have shown that transfusion increases portal pressure during acute variceal bleeding, an increase that may be prevented with somatostatin.

Transfusion-related immunomodulation may increase the risk of complications or death.

(Villanueva. NEJM, 2013)

Red Cell Transfusion for the Management of Upper Gastrointestinal Haemorrahage

Cochrane Review - 2010

Su 1174 referenze solo 3 RCT sono risultati con dati appropriati per essere inclusi nella review.

RISULTATI

- No beneficio su sopravvivenza
- Nessun effetto su durata della degenza
- Aumentato rischio di incrementare un circolo ematico iperdinamico ⇒ aumento pressione portale ⇒ aumentato rischio di risanguinamento
- Aumento tempo di coagulazione
- Nessuna evidenza che una rianimazione aggressiva con trasfusione di emazie concentrate apporti beneficio rispetto alla rianimazione con soluzioni colloidi e cristalloidi

Le LG delle società di epatologia consigliano di mantenere Hb = 8g/dl e non superiori in pazienti con sanguinamento da varici esofagee
(Hepatology 2008)

THE COCHRANE COLLABORATION®

Transfusion policy for acute anaemia. Blood transfusion guideline. The Netherlands: Dutch Institute for Healthcare Improvement - 2011

Massive Blood Loss: The Decompensated/Hypovolemic Shock Situation

- Start resuscitation quickly according. Accept so-called 'permissive hypotension'. Ensure good intravenous access.
- Take measures to stop blood loss as soon as possible.
- In the case of severe continuing blood loss, consider rapid 'damage control' surgery and/or a radiological intervention
- Aim for normothermia, adequate oxygenation and avoid acidosis.
- Correct haemostasis with multi-component transfusions. Fibrinogen preparations are indicated early on in the treatment of extreme blood loss and in case of coagulopathy.
- Administer *multi-component transfusions*, for example in a *3:3:1 ratio between erythrocytes/plasma/platelets*.
- Preheat blood components and infusion solutions in order to prevent hypothermia.
- Consider tranexamic acid in the case of massive blood loss following severe trauma.

Transfusion policy for acute anaemia. Blood transfusion guideline. The Netherlands: Dutch Institute for Healthcare Improvement - 2011

Massive Blood Loss in the Compensated Situation

- Take measures to stop bleeding as soon as possible.
- Normalise the circulating blood volume with fluid therapy.
- Aim for normothermia (preheat blood components and infusion solutions if possible).
- Correct the calcium level with Ca-gluconate when administering large quantities of transfusion components that contain citrate.
- The erythrocyte transfusion policy can then be based on *the 4-5-6 rule for Acute Normovolemic Anaemia*.
- Additional single component transfusions can be used to achieve an aPTT and PT <1.5 times prolonged, platelets > 50.000/m3 and fibrinogen >1.0–1.5 g/L.
- If the first fibrinogen measurement is <1.5 g/L and severe bleeding is still continuing, increase the fibrinogen level by using plasma or a fibrinogen preparation.

The 4-5-6 Rule for Erythrocyte Transfusion for Acute Normovolemic Anaemia

Consider a transfusion if the following occurs at a **Hb <4 g/dl**:

- Acute blood loss in a healthy individual (ASA I) <60 years, normovolemic, blood loss at 1 location

Consider a transfusion if 1 of the following situations occurs at a **Hb <5 g/dl**:

- Acute blood loss in a healthy individual (ASA I) of >60 years and normovolemic, blood loss from 1 location
- Acute blood loss in healthy individuals <60 years, normovolemic, bleeding from several locations (polytrauma patients)
- Patient <60 years, pre-operative, with an expected blood loss >500 mL
- Fever
- Post-operative phase following open heart surgery, uncomplicated
- ASA II and ASA III

Consider a transfusion if one of the following situations occurs at a **Hb <6 g/dl**:

- ASA-IV
- Patient who is unable to increase the heart minute volume to compensate for haemodilution
- Septic and toxic patient
- Patient with severe lung disease
- Patient with symptomatic cerebrovascular disease

Acute upper gastrointestinal bleeding: management. NICE - 2012

Resuscitation and Initial Management

- Base decisions on blood transfusion on the full clinical picture, recognising that over-transfusion may be as damaging as under-transfusion.
- Do not offer *platelet transfusion* to patients who are not actively bleeding and are haemodynamically stable.
- Offer *platelet transfusion* to patients who are actively bleeding and have a platelet count of less than 50.000/m3.
- Offer *fresh frozen plasma* to patients who have either: Fibrinogen level <1 g/litre, or PT/INR or aPTT > 1.5 times normal.
- Offer *prothrombin complex concentrate* to patients who are taking warfarin and actively bleeding.
- Treat patients who are taking warfarin and whose upper gastrointestinal bleeding has stopped in line with local warfarin protocols.
- Do not use recombinant factor Vlla except when all other methods have failed.

Trasfusioni & Anemia cronica

- It is not possible to give a single Hb value as a trigger for red cell transfusion, since the requirement for a transfusion *is based on the patient's underlying condition and symptoms*.

- Red cell transfusions *are not routinely recommended for the correction of anaemia in patients with malignant or serious chronic diseases*, unless the correction of Hb concentration is expected to significantly improve the patient's condition and independence.

- Most patients will suffer uncomfortable symptoms of anaemia if the concentration of *Hb falls below 7 g/dl*. *Even a less significant fall in the Hb concentration may cause symptoms in patients with heart or lung diseases*.

(Finnish Medical Society EBM Guidelines.
Blood transfusion: indications, administration and adverse reactions; 2011)

General Guidelines for Giving Erythrocyte Transfusions for Chronic Anaemia

- The only indication for a therapeutic erythrocyte transfusion in chronic anaemia is a *symptomatic anaemia* (= tachycardia, dyspnoea, palpitations, angina pectoris, dizziness, syncope, de novo ST depression or elevation on the ECG and new arrhythmia).
- A *Hb <3 g/dl is an absolute indication* for an erythrocyte transfusion.
- Prophylactic erythrocyte transfusions can be indicated *in the case of limited cardio-pulmonary compensation abilities or risk factors* in accordance with

'The 4-5-6 rule for erythrocyte transfusion for normovolemic anaemia'

- If there are *no obvious limited cardio-pulmonary compensation abilities or risk factors*, the following Hb triggers can be maintained for prophylactic erythrocyte transfusions for chronic anaemia:

Age (years)	*Hb Trigger (g/dl)*
<25	3.5 – 4.5
35 – 50	4.0 – 5.0
50 – 70	5.5
> 70	6.0

(Chronic anaemia. In: Blood transfusion guideline. Dutch Institute for Healthcare Improvement; 2011)

General Guidelines for Giving Erythrocyte Transfusions for Chronic Anaemia

Essential Nutrient Deficiencies (Iron, Folic Acid, Vitamin B12)

- Anaemia caused by iron deficiency does *not form an indication for transfusion, unless Hb <3 g/dl* (absolute indication) *or if hypoxic symptoms occur at rest*.
- In patients undergoing elective, major surgical procedures *it is recommended to treat any iron-deficiency anaemia for a minimum of 4 weeks prior to surgery*.

Anaemia with Chronic Illness, Excluding Renal Failure/Malignancy

- Anaemia with chronic illness rarely results in a transfusion indication at an Hb >5.0 g/dl.

(Chronic anaemia. In: Blood transfusion guideline. Dutch Institute for Healthcare Improvement; 2011)

Emotrasfusioni.
Cosa dicono ultime LG

Transfusion thresholds and other strategies for guiding allogeneic red blood cell transfusion (Review) - 2012

Objectives: To examine the evidence for the effect of transfusion thresholds on the use of allogeneic and/or autologous red cell transfusion, and the evidence for any effect on clinical outcomes.

Main results: N.19 trials, 6264 patients.

Restrictive transfusion strategies reduced the risk of receiving a RBC transfusion by 39% (RR 0.61, 95%CI 0.52-0.72) ⇒ absolute risk reduction of 34%(95%CI 24-45%) ⇒ the volume of RBC transfused was reduced by 1.19 units (95%CI 0.53-1.85 units).

However, heterogeneity between trials was statistically significant (*P*<0.00001) for these outcomes.

Restrictive transfusion strategies did not appear to impact the rate of adverse events compared to liberal transfusion strategies (mortality, cardiac events, myocardial infarction, stroke, pneumonia and thromboembolism).

Restrictive transfusion strategies were associated with a statistically significant reduction in hospital mortality (RR 0.77, 95%CI 0.62-0.95) but not 30-day mortality (RR 0.85, 95%CI 0.70-1.03).

Restrictive transfusion strategies did not reduce functional recovery, hospital or intensive care length of stay.

THE COCHRANE COLLABORATION®

Transfusion thresholds and other strategies for guiding allogeneic red blood cell transfusion (Review) - 2012

Authors' conclusions: The existing evidence supports the use of restrictive transfusion triggers in most patients, including those with pre-existing cardiovascular disease.

As there are no trials, the effects of restrictive transfusion triggers in high-risk groups, such as acute coronary syndrome, need to be tested in further large clinical trials.

Because of the risks of blood transfusions, doctors try to avoid giving blood unless it is really necessary. One approach is to give the transfusion only if the amount of Hb in the patient's blood has dropped below a certain 'threshold' level.

We conclude that, for most patients, giving less blood is safe and blood transfusion is probably not essential until Hb levels drop below 7.0 to 8.0 g/dl.

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Clinical Practice Guideline From the American Association of Blood Banks - 2012

Recommendations

The AABB suggests that in hospitalized, hemodynamically stable patients transfusion decisions be influenced by symptoms as well as Hb concentration.

(Grade: weak recommendation; low-quality evidence)

Question 1

In hospitalized, hemodynamically stable patients, at what Hb concentration should a decision to transfuse RBC be considered?

Recommendations

The AABB recommends adhering to a restrictive transfusion strategy.

In adult and pediatric intensive care unit patients, transfusion should be considered at Hb concentrations of 7 g/dL or less.

In postoperative surgical patients, transfusion should be considered at a Hb concentration of 8 g/dL or less or for symptoms (chest pain, orthostatic hypotension or tachycardia unresponsive to fluid resuscitation, or congestive heart failure).

(Grade: strong recommendation; high-quality evidence)

Clinical Practice Guideline From the American Association of Blood Banks - 2012

Question 2

In hospitalized, hemodynamically stable patients with preexisting cardiovascular disease, at what Hb concentration should a decision to transfuse RBCs be considered?

Recommendations

The AABB suggests adhering to a restrictive transfusion strategy.

Transfusion should be considered at a Hb concentration of 8 g/dL or less or for symptoms (chest pain, orthostatic hypotension or tachycardia unresponsive to fluid resuscitation, or congestive heart failure).

(Grade: weak recommendation; moderate-quality evidence)

Question 3

In hospitalized, hemodynamically stable patients with the acute coronary syndrome, at what Hb concentration should an RBC transfusion be considered?

Recommendations

The AABB cannot recommend for or against a liberal or restrictive RBC transfusion threshold. Further research is needed to determine the optimal threshold.

(Grade: uncertain recommendation; very low-quality evidence)

Until better evidence is available,
a “restrictive” strategy of RBC transfusion
(transfuse when Hb < 7 g/dL)
is recommended

except in acute hemorrhage,
or in acute myocardial ischemia,
when a hemoglobin trigger of 8 g/dl is
reasonable.