

Anaemia in Surgical Sepsis and Stress: The Roles of Erythropoietin, Iron and Steroids

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Abstract Background: Inflammation in surgical sepsis and stress frequently causes anaemia, leading to increased rates of blood transfusions. Recent evidence shows that blood transfusions carry a greater risk for short- and long-term complications than previously thought. **Objective:** To review the role of erythropoietin (EPO), iron and/or steroids as an alternative treatment to blood transfusions in critically ill patients. **Methodology:** A systematic review was prepared from recent literature on inflammation-induced anaemia, anaemia in the critically ill and/or septic patient and the roles of EPO, iron and corticosteroids in these patients. A meta-analysis was completed for EPO. **Results:** Inflammatory cytokines alter haematopoietic and biochemical pathways, leading to anaemia. Inflammation decreases circulating EPO and upregulates hepcidin, resulting in decreased free iron. Twelve randomised-controlled trials demonstrate that EPO administration in critically ill patients reduces the need for blood transfusions by 31% ($p=0.005$) however does not significantly decrease mortality ($p=0.15$). Intravenous iron also reduces the need for blood transfusions but has not been utilised in sepsis-associated anaemia. No trials focusing on the effects of steroids on sepsis-associated anaemia were identified. **Conclusion:** Due to the lack of data specific to sepsis-associated anaemia in post-operative patients, the roles of EPO, iron and steroids remain under investigation. More research specific to surgical patients is needed.

Keywords: anaemia, sepsis, erythropoietin, iron, steroids

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1. Introduction

Post-operative complications are a common concern, of which sepsis has the highest incidence and attracts an overall mortality of 5.4% [1]. Patients who develop sepsis often develop significant anaemia, which leads to an increased rate of blood transfusions [2]. Blood transfusions are not without risk and are associated with morbidity and mortality. The leading cause of mortality following allogeneic blood transfusion includes transfusion-related acute lung injury, febrile reactions, ABO and non-ABO haemolytic transfusion reactions and transfusion associated sepsis [3]. The rate of febrile non-haemolytic reactions is 1% while severe acute haemolytic reactions occur at a rate of 1:76,000. The rate of ABO incompatibility is 1:40,000 [4,5]. Intraoperative transfusions occurred in 3.8% of general surgical patients and were associated with increased risk of 30-day mortality, pneumonia and sepsis [6]. In other surgical patients, blood transfusions have been associated with delayed wound healing, increased long-term mortality risk and increased hospital stay [7,8]. The negative transfusion

related immunomodulatory (TRIM) effects have also been associated with increased risk of nosocomial infections and the development of autoimmune disease later in life [9,10,11]. Unfortunately, RBC transfusions have also been found to promote tumour recurrence in colorectal, hepatocellular and possibly other cancers [12,13,14].

In light of this growing body of concerning research, there has been a move to implement strategies to decrease transfusion rates. Recent studies have showed that simply lowering the haemoglobin (Hb) threshold for transfusion is an effective way of reducing transfusion rates in critically ill patients without significantly affecting mortality [15]. The Transfusion Requirements in Septic Shock (TRISS) trial included 998 septic patients who were randomized to have a transfusion threshold of 70 g/L or 90 g/L [15]. The data showed that the lower threshold group received a median of 1 transfusion, while the higher received 4 transfusions [15]. Importantly there was no significant difference in 90-day mortality ($p=0.44$, 95% CI 0.78-1.09) [15]. As the target is to continue to decrease transfusion rates in critically ill patients, it is important to understand the underlying physiology and explore further strategies to reduce exposure to blood products.

This review will discuss the pathophysiology that underpins sepsis-associated anaemia and the possible alternative treatment options.

2. Methods

A literature search was conducted using CINAHL, MEDLINE, EMBASE and the Cochrane Library databases from the years 1950-2014. Additional articles were identified through manually reviewing references from articles that were retrieved. For pathophysiology of anaemia in septic patients the Mesh search terms and keywords used in this study included: “sepsis”, “systemic inflammatory response syndrome”, “anemia”, “immune response”, “cytokines”, “inflammatory mediators”. For intravenous iron and steroids in post-operative septic patients the search strategy used medical subject heading terms and text words, including: “sepsis”, “sepsis syndrome”, “septicemia”, “systemic inflammatory response syndrome”, “SIRS” AND “postoperative”, “perioperative” AND “intravenous iron”, “ferric compounds”, “ferrous compounds”, “perioperative” AND “steroids”, “corticosteroids”, “adrenal cortex hormones”, and “glucocorticoids”. The search was limited to articles published in English.

2.1. Systematic Review and Meta-analysis on Use of EPO in Critically Ill Patients

2.1.1. Search Strategy

A systematic search was carried out to include studies between 1950 and April 2014, using CINAHL, MEDLINE, EMBASE and the Cochrane Library databases. The medical subject heading terms and text words included: “sepsis”, “sepsis syndrome”, “septicemia”, “systemic inflammatory response syndrome”, “SIRS” AND “postoperative”, “perioperative” AND “erythropoietin”. The complete search strategy is presented in Appendix 1. Additional papers were discovered by manually searching through the reference lists of relevant publications.

2.1.2. Study Selection and Search Results

The following protocol was used to identify studies for inclusion in the systematic review:

1. Patients admitted to the intensive care unit
2. Patients > 1 year of age
3. Patients receiving scheduled doses of an erythropoietin receptor agonist
4. Randomised clinical trial
5. Any comparator: none, placebo or other medications

The following protocol was used to identify studies for exclusion in the systematic review:

1. Neonates and infants
2. Uncontrolled trials

Of the 174 records identified, 162 were excluded using the above inclusion and exclusion criteria. This resulted in 12 remaining studies which were included for meta-analysis.

2.1.3. Data Extraction

Data were extracted by two reviewers and cross-checked to reach consensus. Disagreements were settled by discussion and consensus. Study characteristics, baseline

characteristics of the study and control groups and the characteristics of intervention were extracted. Outcome measures included: mortality, ICU and hospital length of stay, incidence of bloodstream infection, rate and total amount of red cell transfusion. Complications extracted included thrombosis, hypertension, stroke and myocardial infarction.

2.1.4. Data Synthesis

Discrete and continuous data were analysed using the Cochrane Review Manager (version 5.3.3). The Mantel-Haenszel test was applied to our fixed-effects model to develop summary measures of effect. Intention-to-treat analysis was performed. For dichotomous data, we expressed summary measures of effect across studies as odds ratios with 95% confidence intervals. For continuous data such as units of red blood cells received, measure of effect was expressed as weighted mean differences with 95% confidence intervals. Statistical heterogeneity was assessed using the I^2 statistic.

3. Results

3.1. Pathophysiology of Anaemia in Surgical Stress and Sepsis

Critically ill patients, including those with sepsis, develop anaemia in up to 70% of cases, of which 44-50% will require a blood transfusion [16,17,18]. In septic patients, blood transfusion are required in up to 50% of cases due to a normocytic, normochromic anaemia with low iron, low transferrin but high ferritin, which usually develops through altered iron metabolism and erythropoiesis [17-22]. This is due to the inflammatory response stimulated by surgical sepsis and stress leading to elevated inflammatory markers, which inversely correlates with Hb levels [21,23,24].

3.1.1. Altered Erythropoiesis

Rogiers et al. showed that non-septic critically ill patients had a normal correlation between haematocrit and EPO levels, while septic patients developed more severe anaemia and had lower circulating EPO levels [20]. The inflammatory cytokines IFN-gamma, IL-1 and TNF-alpha have been implicated in the alteration of EPO production [19,25,26]. These inflammatory markers inhibit hypoxia-induced EPO production [25]. High TNF- α levels inhibit erythropoiesis by suppressing haematopoietic stem cells [27]. Conversely, IL-6 showed a stimulatory effect on EPO production and was able to reverse the inhibitory effects of other inflammatory cytokines [25]. These inflammatory cytokines, as well as oxidative stress pathways, have also been implicated in impaired red cell longevity in septic patients [28].

3.1.2. Altered Iron Metabolism

In septic patients a functional iron deficiency can lead to ineffective erythropoiesis [2,18]. This phenomenon may be partly explained by the hormone, hepcidin [29]. After iron is absorbed by enterocytes, the haem is catabolised and pumped through a basal transporter (ferroportin-1),

which is inhibited by hepcidin [30,31]. Therefore, hepcidin causes ferritin to accumulate within these cells [30].

There is a significant increase of IL-6 in hypoxic conditions, which induces EPO and hepcidin [25,32]. IL-6 has also been implicated as the main inducer of hepcidin in septic patients, causing a subsequent drop in serum iron levels and therefore impairing Hb production [33,34]. Furthermore, patients who needed transfusions had significantly higher hepcidin levels than patients who did not require transfusions [34].

3.1.3. Induction of Stress Erythropoiesis

In response to the physiological stress in hypoxia and sepsis, the rate of erythropoiesis can increase by up to 10-fold. This process is known as stress erythropoiesis and the regulators include erythropoietin and glucocorticoids [35]. It has been demonstrated in vitro that glucocorticoid availability, as well as effective binding of glucocorticoids to the glucocorticoid receptor, is required for stress erythropoiesis [36].

Glucocorticoid levels are often suppressed in patients with sepsis due to adrenal insufficiency that occurs in 30-70% of septic patients [37]. This likely occurs due to poor venous drainage and increased arterial blood flow in the glands, decreased cortisol-binding globulin and glucocorticoid receptors [37,38,39].

3.2. Alternative Treatments

3.2.1. Erythropoietin

As EPO deficiency has been detected in critically ill patients, it has been hypothesised that administering EPO may improve Hb levels. Although there have been no studies specific to post-operative patients, an array of randomised controlled trials have been performed to

assess the clinical benefits and possible harms associated with EPO in burn, critically-ill, trauma and cardiothoracic patients (Table 1). These 12 RCTs, containing 3,716 patients in total, have been systematically reviewed and a meta-analysis completed for both transfusion independence and mortality (Figure 1 and Figure 2). Blood transfusion independence is defined as the ability of EPO to prevent the need for at least 1 red blood cell transfusion. This was assessed by comparing the percentage of patients who received any RBC transfusion within the study period. The study periods used to determine mortality and transfusion differences were between 21 – 42 days, except for Luchette et al who collected data at 12 weeks.

Two studies showed that EPO was able to significantly increase reticulocyte counts, while three reported significantly increased Hb levels [40,41,42,43,44]. Corwin et al. showed a significant reduction in total units transfused ($p < 0.002$) [45]. However, the total number of patients that received blood transfusions was not significantly different between the two groups [45]. Their second study also showed significant reduction in the total number of units transfused and total number of patients requiring transfusion (50.5% vs. 60.4%; $p < 0.001$) [46]. Georgopoulos and colleagues showed that both EPO treatment groups had lower transfusion rates (37% and 27% vs. 58%) [42]. Silver et al. also showed a significant reduction in the percentage of patients requiring a transfusion in a long-term acute care setting [43]. Corwin et al. demonstrated a significantly lower 29-day mortality (8.5% vs. 11.4%, $p = 0.04$) [44]. Five of the 12 studies, including the two RCTs which only utilized one dose of EPO, showed no benefits across all parameters [47-51]. Thromboembolic disease was the most commonly recorded adverse event and was only significantly increased in one study (8.7% vs. 5.8%, $p = 0.04$) [44].

Table 1. Descriptions of 12 studies included in EPO meta-analysis

Study	n	EPO/control	Population	EPO protocol†	Control	Transfusion Protocol	Study Duration (max days)
Still et al [39]	40	19/21	Burn unit	300 U/kg/d for 7 d then 150 U/kg every 2 d for 23 d	Placebo	Hct > 30%	30
Gabriel et al [47]	19	11/10	Mixed ICU	3 x 600 U/kg/wk IV plus iron, folic acid and B12	Placebo plus iron, folic acid and B12	Hct > 30%	21
Corwin et al [44]	160	80/80	Mixed ICU	300 U/kg/d for 5 d then every 2 d plus iron	Placebo plus iron	NR	42
Van Iperen et al [40]	36	12/24	Mixed ICU	300 U/kg every 2 d plus iron and folic acid	folic acid or folic acid plus iron	Hb > 89 g/L or 97 g/L if cardiac history	21
Corwin et al [45]	1302	652/650	Mixed ICU	40 000 U/wk plus iron	Placebo plus iron	Suggested Hb > 90 g/L	21
Georgopoulos et al [41]	148	100/48	Mixed ICU	40 000 U/wk plus iron or 3 x 40 000 U/wk plus iron	Iron	Hb > 70 g/L	21
Silver et al [42]	86	42/44	Long-term acute care	40 000 U/wk plus iron	Placebo plus iron	Suggested Hct > 24%	42
Vincent et al [51]	73	48/25	Mixed ICU	40 000 U/wk plus iron	Placebo plus iron	NR	28
Corwin et al [43]	1460	733/727	Mixed ICU	40 000 U/wk plus iron	Placebo plus iron	Suggested Hb > 90 g/L	28
Luchette et al [48]	192	96/92	Trauma	10 000 - 40 000 U/wk depending on Hb levels plus iron	Placebo plus iron	NR	84
Madi-Jebara et al [49]	120	40/80	Cardio-thoracic	300 U/kg once	Placebo plus iron or placebo	Hb > 70 g/L	30
Seigneux et al [50]	80	40/40	Cardio-thoracic	20 000 or 40 000 U once	Placebo	NR	28

Note: EPO = erythropoietin, Mixed ICU = medical and surgical intensive care unit, Hb = haemoglobin, Hct = Haematocrit, IV = intravenous, NR = not reported.

†EPO delivered subcutaneously unless otherwise specified.

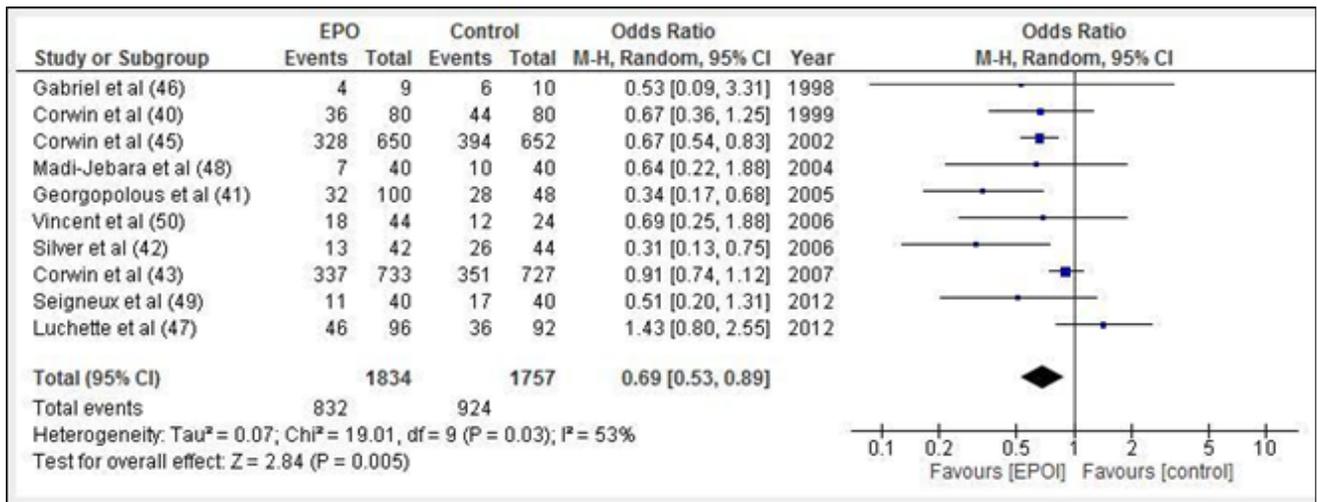


Figure 1. Analysis of transfusion independence among critically ill patients who received erythropoietin or placebo

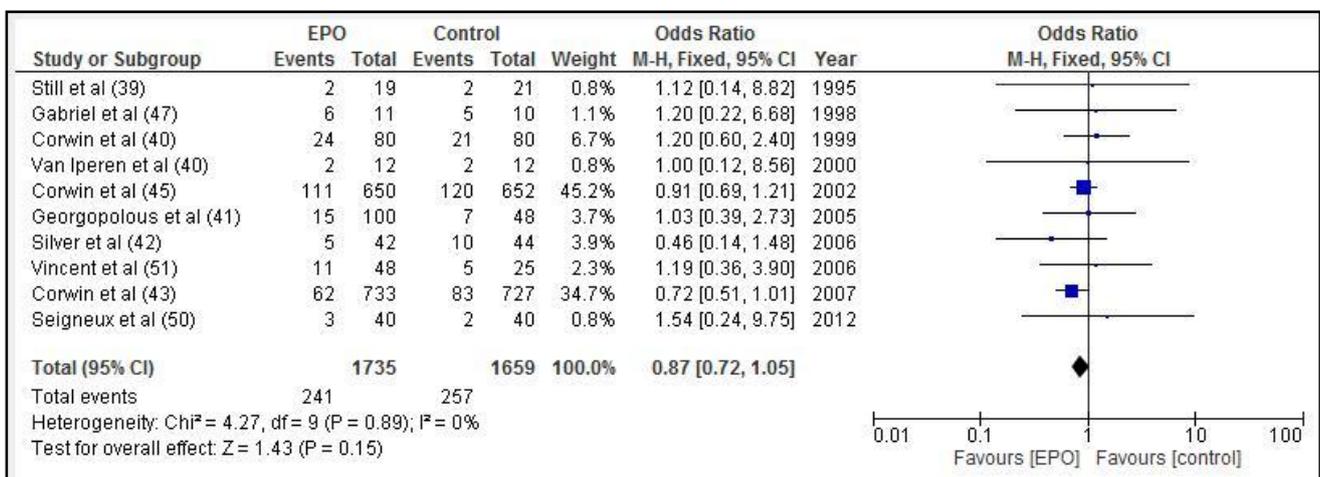


Figure 2. Analysis of mortality among critically ill patients who received erythropoietin or placebo

The data in Figure 2 shows no significant difference in mortality between the groups ($p=0.15$). In the trials reviewed, the EPO group showed an overall reduction in mortality of 13%, however, the confidence interval could not exclude and increase in mortality up to 5% (95% CI 0.72-1.05) (Figure 2). Interestingly, Figure 1 illustrates that the EPO group showed a 31% increase in transfusion independence ($p=0.005$, 95% CI 0.53-0.89). However, due to the lack of studies specific to surgical sepsis and stress, variability in EPO dosing and study endpoints the heterogeneity of these studies must be noted.

3.2.2. Iron

A recent systematic review of 72 studies, involving 10,605 participants, demonstrated IV iron was associated with a significant increase in mean Hb concentrations compared with oral iron or no iron supplementation [52]. Furthermore, they showed that IV iron therapy was associated with a significant reduction in transfusion requirements, particularly when combined with EPO ($p=0.04$) [52]. Unfortunately, IV iron was associated with a significant increase in the risk of infection (1.33, 95% CI [52]).

There is limited clinical data available on the use of iron therapy in post-operative septic patients and critically-ill patients. This likely stems from the concept of

iron having potentially toxic effects through the formation of reactive oxygen species and increasing iron availability, which may facilitate infection [53].

It has also been suggested that IV iron administration can increase hepcidin levels, therefore exacerbating the anaemia [54]. Recently, there has been a wave of research into novel therapies that target the hepcidin-ferroportin axis [30]. Although the majority are still within Phase 1 and 2 clinical trials, there has been some success in animal models with direct hepcidin antagonists, hepcidin production inhibitors and ferroportin stabilizers [55].

3.2.3. Steroids

The use of steroids as an adjunctive therapy for patients with severe sepsis and septic shock has fluctuated over the last few decades. However, a recent systematic review by Annane et al. demonstrated a reduction in patient mortality ($p<0.02$) and increase in shock reversal ($p<0.02$), following low-dose corticosteroid treatment [56].

Unfortunately there is limited data available on the effect of steroid intervention on septic patients' Hb levels, although the RCT by Annane et al. demonstrated no significant improvement in patients receiving steroids (100g/L vs. 102g/L) [57]. Glucocorticoid dependent stress erythropoiesis is a major physiological factor in maintaining haemoglobin levels in septic patients [35,36].

When up to 70% of these patients may in fact be deficient in glucocorticoids due to adrenal insufficiency, it will be important to assess whether steroid replacement therapy could benefit through maintenance of stress erythropoiesis [37].

4. Discussion

Negative transfusion outcomes may be related to TRIM effects which have been linked to higher risks of nosocomial infections, development of autoimmune disease and recurrence and progression of solid malignancies. The cellular mechanisms involved seem to provide an overall immune inhibitory effect which potentiates these damaging pathological processes. Unfortunately, these detrimental effects are imposed on critically ill patients if their Hb falls to a transfusable level.

The anaemia of critical illness is a complex process that has three main contributing pathways. Firstly, expression of inflammatory cytokines cause decreases in EPO transcription, mRNA and haematopoietic stem cell potential as well as blunting erythroid maturation. Secondly, inflammatory cytokine IL-6 has been demonstrated to be a strong inducer of hepcidin, which subsequently promotes the development of a functional iron deficiency. Finally, specifically in septic patients, adrenal insufficiency can lead to the lack of endogenous glucocorticoids and consequently hinder the process of stress erythropoiesis. In light of these mechanisms, EPO, iron and steroids could be considered as alternative treatments.

EPO has been validated as effective treatment for anaemia associated with multiple illnesses, however, its efficacy in critically ill patients has been a topic for debate. This review shows a benefit for the use of EPO to reduce transfusion requirements and therefore reduce the need for harmful PRBC transfusion. Importantly, there was no significant increase in mortality in the EPO group. However, lack of efficacious sepsis-specific data has also led to the marked heterogeneity of studies illustrated in this review. Currently, guidelines are not recommending the use of erythropoietin in sepsis-associated anaemia due to this lack of specific data [58,59]. It may also be hypothesised that exogenous EPO is of even lesser value in septic patients due to inflammatory cytokine suppression of other steps of the erythropoietic pathway [20].

IV iron is effective in raising Hb levels in many clinical settings, however, the trials are lacking in septic patients. This is likely due to the assumption that increasing levels of iron could potentiate ROS (reactive oxygen species) formation and bacterial infections [53]. However, this risk has been thoroughly investigated in animal models and more recently in haemodialysis patients to show no significant correlation with bacteraemia [60,61]. Unfortunately, it has been demonstrated that IV iron administration may increase hepcidin levels and therefore exacerbate the iron withholding mechanisms which are activated during anaemia of inflammation [54]. Hepcidin targeting therapies are currently under evaluation and may provide an exciting and effective treatment that targets one of the root causes of inflammation-associated anaemia.

The role of steroids in the treatment of anaemia in surgical sepsis and stress has not been explored. Recently

the use of low-dose hydrocortisone has become recommended in severe sepsis and septic shock, which may provide excellent opportunities to investigate whether steroids have an effect on Hb levels and transfusion rates.

5. Conclusion

This meta-analysis shows that the use of EPO in critically ill patients can significantly decrease transfusion requirements. However, further studies are needed to understand the pathophysiological mechanisms underlying the development of inflammation induced anaemia in the surgical patient. To date there have been limited clinical trials in these patients, therefore, further clinical trials are required to assess the effectiveness and safety of EPO, IV iron and steroids.

References

- [1] Moore LJ, Moore FA, Todd SR, Jones SL, Turner KL, Bass BL. Sepsis in General Surgery. Arch Surg [Internet]. American Medical Association; 2010 Jul 1; 145(7): 695-700.
- [2] Piagnerelli M, Boudjeltia K, BOUDJELTIA KZ, GULBIS B, Gulbis B, et al. Anemia in sepsis: the importance of red blood cell membrane changes. Transfus Alternat Transfus Med [Internet]. 2007 Sep; 9(3): 143-9.
- [3] Vamvakas EC, Blajchman MA. Transfusion-related mortality: the ongoing risks of allogeneic blood transfusion and the available strategies for their prevention. Blood [Internet]. American Society of Hematology; 2009 Apr 9; 113(15): 3406-17.
- [4] Roback JD. Non-Infectious complications of blood transfusion. 17 ed. Bethesda: AABB; 2011.
- [5] Karim F, Moiz B, Shamsuddin N, Naz S, Khurshid M. Root cause analysis of non-infectious transfusion complications and the lessons learnt. Transfusion and Apheresis Science [Internet]. Elsevier; 2014 Feb; 50(1): 111-7.
- [6] Bernard AC, Davenport DL, Chang PK, Vaughan TB, Zwischenberger JB. Intraoperative Transfusion of 1 U to 2 U Packed Red Blood Cells Is Associated with Increased 30-Day Mortality, Surgical-Site Infection, Pneumonia, and Sepsis in General Surgery Patients. Journal of the American College of Surgeons [Internet]. Elsevier; 2009 May; 208(5): 931-2.
- [7] Weber EWG, Slappendel R, Prins MH, van der Schaaf DB, Durieux ME, Str mper D, et al. Perioperative Blood Transfusions and Delayed Wound Healing After Hip Replacement Surgery: Effects on Duration of Hospitalization. Anesthesia & Analgesia [Internet]. 2005 May; 100(5): 1416-21.
- [8] Surgenor SD, Kramer RS, Olmstead EM, Ross CS, Sellke FW, Likosky DS, et al. The Association of Perioperative Red Blood Cell Transfusions and Decreased Long-Term Survival After Cardiac Surgery. Anesthesia & Analgesia [Internet]. 2009 Jun; 108(6): 1741-6.
- [9] Taylor RW, Manganaro L, O'Brien J, Trotter SJ, Parkar N, Veremakis C. Impact of allogenic packed red blood cell transfusion on nosocomial infection rates in the critically ill patient. Critical Care Medicine [Internet]. 2002 Oct; 30(10): 2249-54.
- [10] Raghavan M, Marik PE. Anemia, Allogenic Blood Transfusion, and Immunomodulation in the Critically Ill. Chest [Internet]. American College of Chest Physicians; 2005 Jan; 127(1): 295-307.
- [11] Toy P, Popovsky MA, Abraham E, Ambruso DR, Holness LG, Kopko PM, et al. Transfusion-related acute lung injury: definition and review. Critical Care Medicine [Internet]. 2005 Apr; 33(4): 721-6.
- [12] Heiss MM, Mempel W, Delanoff C, Jauch KW, Gabka C, Mempel M, et al. Blood transfusion-modulated tumor recurrence: first results of a randomized study of autologous versus allogeneic blood transfusion in colorectal cancer surgery. Journal of clinical oncology: official journal of the American Society of Clinical Oncology [Internet]. 1994 Sep; 12(9): 1859-67.

- [13] Shiba H, Ishida Y, Wakiyama S, Iida T, Matsumoto M, Sakamoto T, et al. Negative Impact of Blood Transfusion on Recurrence and Prognosis of Hepatocellular Carcinoma After Hepatic Resection. *J Gastrointest Surg* [Internet]. Springer-Verlag; 2009 Jul 7; 13(9): 1636-42.
- [14] Cata JP, Wang H, Gottumukkala V, Reuben J, Sessler DI. Inflammatory response, immunosuppression, and cancer recurrence after perioperative blood transfusions. *British Journal of Anaesthesia* [Internet]. 2013 Apr 18; 110(5): 690-701.
- [15] Holst LB, Haase N, Wetterslev J, Wernerman J, Guttormsen AB, Karlsson S, et al. Lower versus Higher Hemoglobin Threshold for Transfusion in Septic Shock. *N Engl J Med* [Internet]. 2014 Oct 9; 371(15): 1381-91.
- [16] Corwin HL, Gettinger A, Pearl RG, Fink MP, Levy MM, Abraham E, et al. The CRIT Study: Anemia and blood transfusion in the critically ill—Current clinical practice in the United States*. *Critical Care Medicine* [Internet]. 2004 Jan; 32(1):39-52.
- [17] Juffermans NP, Prins DJ, Vlaar APJ, Nieuwland R, Binnekade JM. Transfusion-Related Risk of Secondary Bacterial Infections in Sepsis Patients. *Shock* [Internet]. 2011 Apr; 35(4): 355-9.
- [18] Vincent J, Baron J-F, Reinhart K, Gattinoni L, Thijs L, Webb A, et al. Anemia and blood transfusion in critically ill patients. *JAMA: the journal of the American Medical Association* [Internet]. 2002 Sep 25; 288(12): 1499-507.
- [19] Hayden SJ, Albert TJ, Watkins TR, Swenson ER. Anemia in Critical Illness. *Am J Respir Crit Care Med* [Internet]. 2012 May 15; 185(10): 1049-57.
- [20] Rogiers P, Zhang H, Leeman M, Nagler J, Neels H, Mélot C, et al. Erythropoietin response is blunted in critically ill patients. *Intensive Care Med* [Internet]. 1997 Feb; 23(2): 159-62.
- [21] Piagnerelli M, Cotton F, Herpain A, Rapotec A, Chatti R, Gulbis B, et al. Time course of iron metabolism in critically ill patients. *Acta clinica Belgica* [Internet]. 2013 Jan; 68(1): 22-7.
- [22] Walsh TS, Wyncoll DL, Stanworth SJ. Managing anaemia in critically ill adults. *BMJ* [Internet]. 2010 Sep 3; 341 (sep03 1): c4408-8.
- [23] Jacober MLV, Mamoni RL, Lima CSP, Anjos Dos BL, Grotto HZW. Anaemia in patients with cancer: role of inflammatory activity on iron metabolism and severity of anaemia. *Medical oncology (Northwood, London, England)* [Internet]. 2007; 24(3): 323-9.
- [24] Shinoda N, Sullivan KM, Tripp K, Erhardt JG, Haynes BM, Temple VJ, et al. Relationship between markers of inflammation and anaemia in children of Papua New Guinea. *Public Health Nutr* [Internet]. 2012 May 21; 16(02): 289-95.
- [25] Faquin WC, Schneider TJ, Goldberg MA. Effect of inflammatory cytokines on hypoxia-induced erythropoietin production. *Blood* [Internet]. 1992 Apr 15; 79(8): 1987-94.
- [26] Jelkmann W. Proinflammatory Cytokines Lowering Erythropoietin Production. *Journal of Interferon & Cytokine Research* [Internet]. 1998 Aug; 18(8): 555-9.
- [27] Okonko DO, Marley SB, Anker SD, Poole-Wilson PA, Gordon MY. Suppression of erythropoiesis in patients with chronic heart failure and anaemia of unknown origin: evidence of an immune basis. *International Journal of Cardiology* [Internet]. Elsevier Ireland Ltd; 2013 Jul; 166(3): 664-71.
- [28] Lang KS, Duranton C, Poehlmann H, Myssina S, Bauer C, Lang F, et al. Cation channels trigger apoptotic death of erythrocytes. *Cell Death Differ* [Internet]. 2003 Feb; 10(2): 249-56.
- [29] Fleming RE, Sly WS. Hepcidin: A putative iron-regulatory hormone relevant to hereditary hemochromatosis and the anemia of chronic disease. *Proceedings of the National Academy of Sciences* [Internet]. National Acad Sciences; 2001 Jul 17; 98(15): 8160-2.
- [30] Nemeth E, Tuttle MS, Powelson J, Vaughn MB, Donovan A, et al. Hepcidin Regulates Cellular Iron Efflux by Binding to Ferroportin and Inducing Its Internalization. *Science* [Internet]. 2004 Dec 17; 306(5704): 2090-3.
- [31] McKie AT, Marciani P, Rolfs A, Brennan K, Wehr K, Barrow D, et al. A novel duodenal iron-regulated transporter, IREG1, implicated in the basolateral transfer of iron to the circulation. *Molecular cell* [Internet]. 2000 Feb; 5(2): 299-309.
- [32] Sonnweber T, Nachbaur D, Schroll A, Nairz M, Seifert M, Demetz E, et al. Hypoxia induced downregulation of hepcidin is mediated by platelet derived growth factor BB. *Gut* [Internet]. BMJ Publishing Group Ltd and British Society of Gastroenterology; 2014 Oct 31; 63(12): 1951-9.
- [33] Kemna E, Kemna E, Pickkers P, Nemeth E, van der Hoeven H, Swinkels D. Time-course analysis of hepcidin, serum iron, and plasma cytokine levels in humans injected with LPS. *Blood* [Internet]. 2005 Sep 1; 106(5): 1864-6.
- [34] van Eijk LT, Kroot JJ, Kroot JJC, Tromp M, van der Hoeven JG, Swinkels DW, et al. Inflammation-induced hepcidin-25 is associated with the development of anemia in septic patients: an observational study. *Crit Care* [Internet]. BioMed Central Ltd; 2011; 15(1): R9.
- [35] Broudy VC, Lin NL, Priestley GV, Nocka K, Wolf NS. Interaction of stem cell factor and its receptor c-kit mediates lodgment and acute expansion of hematopoietic cells in the murine spleen. *Blood* [Internet]. 1996 Jul 1; 88(1): 75-81.
- [36] Bauer A, Tronche F, Wessely O, Kellendonk C, Reichardt HM, Steinlein P, et al. The glucocorticoid receptor is required for stress erythropoiesis. *Genes & development* [Internet]. 1999 Nov 15; 13(22): 2996-3002.
- [37] Maxime V, Lesur O, Annane D. Adrenal Insufficiency in Septic Shock. *Clinics in Chest Medicine* [Internet]. 2009 Mar; 30(1): 17-27.
- [38] Beishuizen A, Thijs LG, Vermes I. Patterns of corticosteroid-binding globulin and the free cortisol index during septic shock and multitrauma. *Intensive Care Med* [Internet]. 2014 Apr 21; 27(10): 1584-91.
- [39] Huang ZH, Gao H, Xu RB. Study on glucocorticoid receptors during intestinal ischemia shock and septic shock. *Circulatory shock* [Internet]. 1987; 23(1): 27-36.
- [40] Still JM, Belcher K, Law EJ, Thompson W, Jordan M, Lewis M, et al. A double-blinded prospective evaluation of recombinant human erythropoietin in acutely burned patients. *J Trauma* [Internet]. 1995 Feb; 38(2): 233-6.
- [41] van Iperen CE, Gaillard CA, Kraaijenhagen RJ, Braam BG, Marx JJ, van de Wiel A. Response of erythropoiesis and iron metabolism to recombinant human erythropoietin in intensive care unit patients. *Critical Care Medicine* [Internet]. 2000 Aug; 28(8): 2773-8.
- [42] Georgopoulos D, Matamis D, Routsis C, Michalopoulos A, Maggina N, Dimopoulos G, et al. Recombinant human erythropoietin therapy in critically ill patients: a dose-response study [ISRCTN48523317]. *Crit Care* [Internet]. BioMed Central Ltd; 2005; 9(5): R508-15.
- [43] Silver M, Corwin MJ, Bazan A, Gettinger A, Enny C, Corwin HL. Efficacy of recombinant human erythropoietin in critically ill patients admitted to a long-term acute care facility: A randomized, double-blind, placebo-controlled trial*. *Critical Care Medicine* [Internet]. 2006 Sep; 34(9): 2310-6.
- [44] Corwin HL, Gettinger A, Fabian TC, May A, Pearl RG, Heard S, et al. Efficacy and Safety of Epoetin Alfa in Critically Ill Patients. *N Engl J Med* [Internet]. 2007 Sep 6; 357(10): 965-76.
- [45] Corwin HL, Gettinger A, Rodriguez RM, Pearl RG, Gubler KD, Enny C, et al. Efficacy of recombinant human erythropoietin in the critically ill patient: a randomized, double-blind, placebo-controlled trial. *Critical Care Medicine* [Internet]. 1999 Nov; 27(11): 2346-50.
- [46] Corwin HL, Gettinger A, Pearl RG, Fink MP, Levy MM, Shapiro MJ, et al. Efficacy of recombinant human erythropoietin in critically ill patients: a randomized controlled trial. *JAMA: the journal of the American Medical Association* [Internet]. 2002 Dec 11; 288(22): 2827-35.
- [47] Gabriel A, Kozek S, Chiari A, Fitzgerald R, Grabner C, Geissler K, et al. High-dose recombinant human erythropoietin stimulates reticulocyte production in patients with multiple organ dysfunction syndrome. *J Trauma* [Internet]. 1998 Feb; 44(2): 361-7.
- [48] Luchette FA, Pasquale MD, Fabian TC, Langhoff WK, Wolfson M. A randomized, double-blind, placebo-controlled study to assess the effect of recombinant human erythropoietin on functional outcomes in anemic, critically ill, trauma subjects: the Long Term Trauma Outcomes Study. *The American Journal of Surgery* [Internet]. Elsevier; 2012 Apr; 203(4): 508-16.
- [49] Madi-Jebara SN, Sleilaty GS, Achouh PE, Yazigi AG, Haddad FA, Hayek GM, et al. Postoperative intravenous iron used alone or in combination with low-dose erythropoietin is not effective for correction of anemia after cardiac surgery. *Journal of Cardiothoracic and Vascular Anesthesia* [Internet]. 2004 Feb; 18(1): 59-63.
- [50] de Seigneux S, Ponte B, Weiss L, Pugin J, Romand JA, Martin P-Y, et al. Epoetin administered after cardiac surgery: effects on

- renal function and inflammation in a randomized controlled study. *BMC Nephrol* [Internet]. BioMed Central Ltd; 2012 Oct 3; 13(1): 14.
- [51] VINCENT J-L, Vincent J, Spapen HDMH, Creteur J, Piagnerelli M, PIAGNERELLI M, et al. Pharmacokinetics and pharmacodynamics of once-weekly subcutaneous epoetin alfa in critically ill patients: Results of a randomized, double-blind, placebo-controlled trial*. *Critical Care Medicine* [Internet]. 2006 Jun; 34(6): 1661-7.
- [52] Litton E, Xiao J, Ho KM. Safety and efficacy of intravenous iron therapy in reducing requirement for allogeneic blood transfusion: systematic review and meta-analysis of randomised clinical trials. *BMJ* [Internet]. 2013; 347: f4822.
- [53] Pieracci FM, Barie PS. Iron and the Risk of Infection. *Surgical Infections* [Internet]. 2005 Jun;6(s1): s41-6.
- [54] Ashby DR, Gale DP, Busbridge M, Murphy KG, Duncan ND, Cairns TD, et al. Plasma hepcidin levels are elevated but responsive to erythropoietin therapy in renal disease. *Kidney International* [Internet]. 2009 May; 75(9): 976-81.
- [55] Cooke KS, Cooke KS, Hinkle B, Hinkle B, Salimi-Moosavi H, Salimi-Moosavi H, et al. A fully human anti-hepcidin antibody modulates iron metabolism in both mice and nonhuman primates. *Blood* [Internet]. 2013 Oct 24; 122(17): 3054-61.
- [56] Annane D, Bellissant E, Bollaert P-E, Briegel J, Confalonieri M, De Gaudio R, et al. Corticosteroids in the Treatment of Severe Sepsis and Septic Shock in Adults. *JAMA* [Internet]. 2009 Jun 10; 301(22): 2362-75.
- [57] Annane D, Sébille V, Charpentier C, Bollaert P-E, François B, Korach J-M, et al. Effect of treatment with low doses of hydrocortisone and fludrocortisone on mortality in patients with septic shock. *JAMA: the journal of the American Medical Association* [Internet]. 2002 Aug 21; 288(7): 862-71.
- [58] The Surviving Sepsis Campaign Guidelines Committee including The Pediatric Subgroup*, Dellinger RP, Levy MM, Rhodes A, Gerlach H, Annane D, et al. Surviving Sepsis Campaign: International Guidelines for Management of Severe Sepsis and Septic Shock, 2012. *Intensive Care Med* [Internet]. Springer-Verlag; 2013 Jan 30; 39(2): 165-228.
- [59] Retter A, Wyncoll D, Pearse R, Carson D, McKechnie S, Stanworth S, et al. Guidelines on the management of anaemia and red cell transfusion in adult critically ill patients. *Br J Haematol* [Internet]. 2012 Dec 27; 160(4): 445-64.
- [60] Hoen B, Paul-Dauphin A, Kessler M. Intravenous iron administration does not significantly increase the risk of bacteremia in chronic hemodialysis patients. *Clinical nephrology* [Internet]. 2002 Jun; 57(6): 457-61.
- [61] Heming N, Lettéron P, Driss F, Millot S, Benna El J, Tourret J, et al. Efficacy and toxicity of intravenous iron in a mouse model of critical care anemia*. *Critical Care Medicine* [Internet]. 2012 Jul; 40(7): 2141-8.



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