Outcomes with the Use of Recombinant Human Erythropoietin in Critically Ill Burn Patients

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Recent data demonstrate a possible mortality benefit in traumatically injured patients when given subcutaneous recombinant human erythropoietin (rhEPO). The purpose of this report is to examine the effect of rhEPO on mortality and transfusion in burn patients. We conducted a review of burn patients (greater than 30% total body surface area, intensive care unit [ICU] days greater than 15) treated with 40,000u rhEPO over an 18-month period (January 2007 to July 2008). Matched historical controls were identified and a contemporaneous cohort of subjects not administered rhEPO was used for comparison (NrhEPO). Mortality, transfusions, ICU and hospital length of stay were assessed. A total of 105 patients were treated (25 rhEPO, 53 historical control group, 27 NrhEPO). Hospital transfusions (mean 13,704 ± mL *vs* 13,308 ± mL; $P = 0.42$) and mortality (29.6 *vs* 32.0%; $P = 0.64$) were similar. NrhEPO required more blood transfusions (13,308 ± mL *vs* 6,827 ± mL; $P = 0.004$). No difference in mortality for the rhEPO and NrhEPO (32.0 *vs* 22.2%; $P = 0.43$) was found. Thromboembolic complications were similar in all three groups. No effect was seen for rhEPO treatment on mortality or blood transfusion requirements in the severely burned.

THE TRANSFUSION OF blood in anemic, thermally injured patients is common. In a recent analysis of United States burn centers, the need for transfusion was 75 per cent for patients with burns over 20 per cent of total body surface area (TBSA).[1] The cause of anemia in this population of patients is multifactorial. Frequent burn wound excision with skin grafting, phlebotomy, and systemic factors associated with critical illness are all contributors.[2, 3] Interventions to decrease blood loss and correct anemia in critically ill burn patients include a myriad of procedure modifications and therapeutics. Early burn wound excision, topical application of epinephrine-soaked gauze and thrombin to the wound immediately after excision, and extremity burn wound excision while using a tourniquet can decrease acute blood loss anemia in the perioperative period.[4, 5] Use of pediatric vials for laboratory examination minimizes the effects of phlebotomy.[6] Stimulation of erythropoiesis in the intensive care unit has received much interest in recent years. Recombinant, human erythropoietin (rhEPO) has been approved by the U.S. Food and Drug Administration for use in anemic patients with chronic kidney disease (CKD).[7] Corwin and colleagues have carried out three prospective studies to determine the efficacy of rhEPO in anemic, adult, critically ill patients with mixed results.[8–10] EPO1 and EPO2 demonstrated a transfusion benefit in patients who received rhEPO. After a mortality improvement signal was detected in the trauma subgroup of patients in EPO2, Corwin's group conducted a third EPO trial, which prospectively identified admission categories to include trauma, surgical nontrauma, and medical.[9, 10] Although no improvement in indices of anemia or transfusion requirement was noted, the trauma subgroup of patients had a significant mortality benefit compared with placebo (6.0 *vs* 9.2%, adjusted hazards ratio 0.40 with 95% CI 0.23–0.69).[10] In addition to its potential effects on transfusion and mortality, rhEPO may improve wound healing after thermal injury. Galeano and colleagues demonstrated increased wound re-epithelialization and decreased wound closure time in an animal model of scald injury treated with rhEPO compared with placebo.[11] As a result of the

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frequency of anemia in thermally injured patients, the potential benefit in transfusion requirements in critically ill patients, a possible benefit in wound healing in thermal injury, and the recent report of a possible mortality improvement in trauma patients with the use of rhEPO, the U.S. Army Institute of Surgical Research (USAISR) began administering rhEPO to severely burned patients admitted to the burn intensive care unit (BICU). The purpose of this study is to determine if the use of rhEPO in patients with severe thermal injury reduces transfusion requirements or impacts mortality.

Methods

This study was conducted under a protocol reviewed and approved by the Brooke Army Medical Center Institutional Review Board and in accordance with good clinical practices. A retrospective chart review was carried out to identify severely burned patients who received rhEPO over a 24-month period after the publication of Corwin's most recent rhEPO study in critically ill patients (January 1, 2007 to December 31, 2008). Patients treated with rhEPO who also had any other indication for erythropoiesis before BICU to include CKD or anemia associated with malignancy were excluded. The decision to begin rhEPO was made by the intensivist and the individual burn surgeon based on anemia, severity of thermal injury, and presence of organ dysfunction. Patients who were considered for treatment with rhEPO had burns greater than 30 per cent TBSA, required multiple burn wound excisions, required a BICU stay greater than 48 hours, and were predicted to have a high probability of BICU admission-related complications (prolonged need for mechanical ventilation, sepsis, acute kidney injury). Thermally injured patients received subcutaneous rhEPO at a dose of 40,000 U weekly starting within 72 hours of BICU admission. Historical controls with similar size thermal injury were identified before the USAISR's use of rhEPO (January 1, 2005 to December 31, 2006). A contemporaneous control group was also identified that included patients admitted to the BICU during the study period but who did not receive rhEPO. Demographics compared between the three groups included: age, percent TBSA burn, percent full-thickness involvement, presence of inhalation injury, Injury Severity Score (ISS) at admission, BICU length of stay (LOS), ventilator days, the presence of concomitant thermal and traumatic injuries, the development of sepsis during BICU admission, and the need for continuous venovenous hemofiltration (CVVH) for acute kidney injury (AKI). Criteria for inclusion in this study were identified to make the three groups more homogenous and included: burn size greater than 30 per cent TBSA, ventilator time greater than 72 hours, BICU LOS greater than 15 days, and ISS on admission greater than 25. The purpose of these criteria was to ensure that all patients evaluated were severely burned and had similar risk factors for BICU-related complications and mortality. Specific subgroups were also separately evaluated to determine outcomes in the most severely ill patients. These subgroups included: ISS greater than 30, presence of inhalation injury, concomitant thermal and traumatic injuries, development of sepsis during BICU admission, need for CVVH for AKI, and burn size greater than 50 per cent TBSA. Data collected for comparison included: hemoglobin (Hb) at admission and discharge, total packed red blood cell (pRBC) transfusion requirement (mL pRBC/hospital stay), complications, and mortality. Thromboembolic complication rates to include myocardial infarction, deep venous thrombosis, and pulmonary embolism were also collected. Data were analyzed using SAS, Version 9.1 (SAS Institute, Cary, NC). Comparisons were made between the rhEPO group and historical controls and between the rhEPO group and contemporaneous controls. Data are presented as mean ± SD. Continuous variables were compared by paired Student t test. χ^2 testing was used to compare categorical variables. All testing was two-tailed with $P < 0.05$ considered significant.

Results

A total of 32 thermally injured patients received rhEPO. After elimination of less severely ill patients (ventilator time less than 72 hours, n = 5; BICU LOS less than 15 days, n = 2), 25 patients were treated with rhEPO during the study period who met all inclusion criteria. Patients received a mean of 10 total doses (range, 1–36 doses). A total of 116 patients with greater than 30 per cent TBSA burns were identified during the historical control period. After elimination of patients not meeting criteria (ventilator time less than 72 hours, n = 33; BICU LOS less than 15 days, n = 29; ISS less than 25, n = 2), a total of 52 patients in the historical control group remained. The initial patients identified in the contemporaneous control period numbered 62 with 27 meeting all inclusion criteria (ventilator time less than 72 hours, n = 28; BICU LOS less than 15 days, n = 6; ISS less than 25, n = 1). Table 1 compares demographics between the rhEPO group and the historical controls. All categories were similar with the exception of significantly more rhEPO-treated patients with inhalation injury. Table 2 is a comparison of demographics between the rhEPO-treated patients and the contemporaneous controls. As expected, the patients who received rhEPO had more severe injuries and had significantly more BICU-related complications (AKI with need for CVVH, sepsis) than the less severely ill contemporaneous controls.

Recombinant Human Erythropoietin-Treated Patients Compared with Historical Controls

Table 3 compares discharge Hb, overall transfusion requirements and mortality between these two groups. There was no significant difference between the two groups for discharge Hb, total hospital volume of transfused red blood cells, or mortality. Table 4 is a breakdown of the more severely ill subgroups discussed in the "Methods" section. Of note, patients with AKI requiring CVVH treated with rhEPO received significantly less transfused blood than similar historical controls (17,607 ± 12,130 mL *vs* 31,245 ± 17,371 mL; $P = 0.047$). When specifically evaluating survivors with AKI treated with CVVH (n = 5 in both rhEPO and historical control groups), however, there is no difference in total transfusion requirements (17,820 ± 14,894 *vs* 17,622 ± 6,998; $P = 0.98$).

Recombinant Human Erythropoietin-Treated Patients Compared with Contemporaneous Controls

Table 5 compares discharge Hb, overall transfusion requirements, and mortality between these two groups. There was no difference in Hb value at discharge. Compared with the contemporaneous controls, rhEPO-treated patients received significantly more transfused blood (13,308 ± 9,085 mL *vs* 7,227 ± 14,350 mL; $P =$

TABLE 1. *Demographics of rhEPO Group and Historical Controls*

	Historical Controls (n = 52)	rhEPO (n = 25)	*P*
Age	29.3 ± 12.3	29.7 ± 14.1	0.89
Percent TBSA	54.3 ± 15.6	56.6 ± 17.1	0.56
Percent full thickness	45.7 ± 19.9	40.6 ± 23.4	0.32
Inhalation injury	38.5% (n = 20)	72% (n = 18)	0.006*
Injury Severity Score	35.6 ± 12	34.2 ± 8	0.61
BICU length of stay	62.5 ± 67.2	73.2 ± 54.7	0.49
Ventilator days	41.7 ± 67.0	37.8 ± 31.5	0.79
Trauma and burns	54% (n = 28)	44% (n = 11)	0.16
Sepsis	75% (n = 39)	88% (n = 22)	0.18
Baseline hemoglobin	11.9 ± 4.1	12.8 ± 3.3	0.34
CVVH	25% (n = 13)	40% (n = 10)	0.18

* Statistical significance.
rhEPO, recombinant human erythropoietin; TBSA, total body surface area; BICU, burn intensive care unit; CVVH, continuous venovenous hemofiltration.

TABLE 2. *Demographics of rhEPO Group and Contemporaneous Controls*

	Contemporaneous Controls (n = 27)	rhEPO (n = 25)	*P*
Age	36.6 ± 15.5	29.7 ± 14.1	0.10
Percent TBSA	47.0 ± 14.2	56.6 ± 17.1	0.03*
Percent full thickness	25.8 ± 21.0	40.6 ± 23.4	0.02*
Inhalation injury	37% (n = 10)	72% (n = 18)	0.01*
Injury Severity Score	31.7 ± 11.6	34.2 ± 8	0.37
BICU length of stay	33.8 ± 21.6	73.2 ± 54.7	0.001*
Ventilator days	18.7 ± 18.8	37.8 ± 31.5	0.01*
Trauma and burns	22% (n = 6)	44% (n = 11)	0.09
Sepsis	63% (n = 17)	88% (n = 22)	0.04*
Baseline hemoglobin	14.0 ± 3.7	12.8 ± 3.3	0.22
CVVH	33% (n = 9)	40% (n = 10)	0.62

* Statistical significance.
rhEPO, recombinant human erythropoietin; TBSA, total body surface area; BICU, burn intensive care unit; CVVH, continuous venovenous hemofiltration.

TABLE 3. *Comparison of Transfusion Data and BICU Mortality between rhEPO and Historical Control Groups*

	Historical Controls (n = 52)	rhEPO (n = 25)	*P*
Discharge hemoglobin (g/dL)	8.3 ± 1.4	9.0 ± 1.8	0.09
Total hospital transfusion requirements (total mL)	13,704 ± 14,350	13,308 ± 9,085	0.42
BICU mortality	27% (n = 14)	32% (n = 8)	0.64

BICU, burn intensive care unit; rhEPO, recombinant human erythropoietin.

TABLE 4. *Comparison of Outcomes between More Severely Ill rhEPO and Historical Control Subgroups*

	Historical Controls (n = 52)	rhEPO (n = 25)	*P*
Trauma and burns transfusion requirement	15,042 ± 15,544	12,516 ± 7,641	0.61
Trauma and burns mortality	25% (n = 7/28)	27% (n = 3/11)	0.88
Inhalation injury transfusion requirement	17,636 ± 18,085	11,833 ± 6,516	0.21
Inhalation injury mortality	35% (n = 7/20)	28% (5/18)	0.63
ISS greater than 30 transfusion requirement	15,472 ± 15,328	11,844 ± 6,516	0.35
ISS greater than 30 mortality	27% (n = 8/30)	28% (5/18)	0.93
Sepsis transfusion requirement	16,045 ± 15,829	13,442 ± 8,918	0.48
Sepsis mortality	29% (n = 11/38)	28% (n = 6/22)	0.90
CVVH transfusion requirement	31,245 ± 17,371	17,607 ± 12,130	0.047*
CVVH mortality	62% (n = 8/13)	50% (n = 5/10)	0.58
50% or greater TBSA transfusion Requirement	19,003 ± 16,158	14,137 ± 8,724	0.27
50% or greater TBSA mortality	39% (n = 12/31)	31% (n = 5/16)	0.61

* Statistical significance.
rhEPO, recombinant human erythropoietin; ISS, Injury Severity Score; CVVH, continuous venovenous hemofiltration; TBSA, total body surface area.

TABLE 5. *Comparison of Transfusion Data and BICU Mortality between rhEPO and Contemporaneous Control Groups*

	Contemporaneous Controls (n = 27)	rhEPO (n = 25)	*P*
Discharge hemoglobin (g/dL)	8.8 ± 1.5	9.0 ± 1.8	0.68
Total hospital transfusion requirements (total mL)	7,227 ± 6,086	13,308 ± 9,085	0.004*
BICU mortality	22% (n = 6)	32% (n = 8)	0.43

* Statistical significance.
BICU, burn intensive care unit; rhEPO, recombinant human erythropoietin.

0.004). Despite requiring more total transfused blood, mortality was similar between the two groups. Table 6 is a breakdown of the more severely ill subgroups discussed in the "Methods" section. Only the sepsis subgroup of patients treated with rhEPO showed a significantly higher transfusion requirement than contemporaneous controls (13,442 ± 8,918 *vs* 7,631 ± 7,095; $P = 0.003$). When survivors with sepsis were specifically compared (n = 16 in rhEPO and n = 12 in contemporaneous control groups), this higher transfusion requirement remained significant (12,732 ± 9,227 *vs* 4,279 ± 2,534; $P = 0.005$).

Complications

Figure 1 shows the frequency of thromboembolic (TE) complications noted in the three groups evaluated in our study. A total of 4 per cent of rhEPO-treated patients had TE complications compared with 6 per cent of historical controls and 4 per cent of contemporaneous controls. There was no significant difference in the frequency of TE complications between the groups ($P = 0.74$ when rhEPO compared with TE rate in historical controls and 0.96 compared with TE rate in contemporaneous controls).

Discussion

The use of rhEPO as a therapeutic agent to stimulate erythropoiesis and decrease transfusion needs in anemic critically ill patients seems very attractive. Corwin and colleagues have evaluated rhEPO in three sequential prospective trials in adult ICUs.[8–10] EPO2 revealed a transfusion benefit based on a reduction in percentage of patients requiring a transfusion in 28-day followup (50.5 *vs* 60.4%; $P < 0.001$).[9] In addition, a mortality benefit was apparent in the *post hoc* identified subgroup of trauma patients. This led to the third trial of rhEPO in critical illness in which the subgroups of trauma, surgical nontrauma, and medical patients were prospectively identified.[10] This trial found no benefit in transfusion requirements in rhEPO, but determined that mortality in the trauma subgroup was significantly reduced in the patients receiving rhEPO. The reason for the mortality benefit appears to be exclusive of rhEPO erythropoietic properties. Preclinical data indicate that rhEPO also provides an antiapoptotic and anti-inflammatory effect that may contribute to the mortality benefit noted in trauma patients.[12] Still and colleagues evaluated the efficacy of rhEPO in thermally injured patients in a multicenter trial, which dosed patients with 300 U/kg daily for 7 days.[13] Although Still's prospective trial, which included 40 patients, did not demonstrate a benefit in total volume of transfusion required during hospitalization, his findings were reported based on a transfusion practice in burn centers at the time that included goals of preoperative Hb of 10 g/dL and postoperative values of 8 g/dL. Hebert has since demonstrated that no outcome

TABLE 6. *Comparison of Outcomes between More Severely Ill rhEPO and Contemporaneous Control Subgroups*

	Contemporaneous Controls (n = 27)	rhEPO (n = 25)	*P*
Trauma and burns transfusion requirement	6,802 ± 4,692	12,516 ± 7,641	0.12
Trauma and burns mortality	0% (0/6)	27% (n = 3/11)	0.16
Inhalation injury transfusion requirement	7,007 ± 6,783	11,833 ± 6,516	0.08
Inhalation injury mortality	20% (n = 2/10)	28% (5/18)	0.64
ISS greater than 30 transfusion requirement	7,742 ± 6,485	11,844 ± 6,516	0.12
ISS greater than 30 mortality	20% (2/10)	28% (5/18)	0.64
Sepsis transfusion requirement	7,631 ± 7,095	13,442 ± 8,918	0.03*
Sepsis mortality	29% (n = 5/17)	28% (n = 6/22)	0.90
CVVH transfusion requirement	13,287 ± 6,876	17,607 ± 12,130	0.36
CVVH mortality	44% (n = 4/9)	50% (n = 5/10)	0.81
50% or greater TBSA transfusion requirement	8,789 ± 5,872	14,137 ± 8,724	0.10
50% or greater TBSA mortality	40% (n = 4/10)	31% (n = 5/16)	0.65

* Statistical significance.

rhEPO, recombinant human erythropoietin; ISS, Injury Severity Score; CVVH, continuous venovenous hemofiltration; TBSA, total body surface.

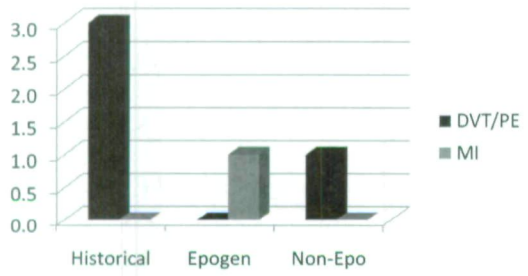

FIG. 1. Complications. DVT, deep venous thrombosis; PE, pulmonary embolisms; MI, myocardial infarction.

improvements are seen when liberal transfusion criteria are compared with a conservative transfusion strategy.[14] The USAISR began the routine use of rhEPO in severely burned adult patients in its BICU after the report of mortality improvement in critically ill trauma patients. Dosing was 40,000 U administered subcutaneously on a weekly basis beginning within 72 hours of BICU admission. The USAISR transfusion practice includes transfusion in BICU patients for Hb values below 7 mg/dL or hematocrit below 21 per cent. The exceptions to this rule are in the setting of acute blood loss anemia such as that experienced intraoperatively during burn wound excision, anemic patients with septic shock, and anemia in a patient with an acute coronary syndrome. Based on our study, it appears that the routine use of rhEPO does not reduce the requirement for total volume of transfusion during hospitalization or mortality in severely burned patients. This is seen when rhEPO-treated patients are compared with both a historical control arm and contemporaneous controls.

Why is it that burn patients do not appear to benefit from routine use of rhEPO? Burn patients are dissimilar from the patients enrolled in Dr. Corwin's studies (he excluded this population in all three EPO trials) in multiple ways. Corwin evaluated the efficacy of rhEPO in a large, diverse group of adult critically ill patients with the lowest rate of transfusion independence being 40 per cent in the placebo arm of EPO2.[9] Transfusion independence is very uncommon in patients sustaining large TBSA burns such as in our study. Palmieri and colleagues revealed that in U.S. burn centers, 75 per cent of patients with burns of 20 per cent or more TBSA are transfused at least 1 U of blood.[1] The rate of transfusion for 30 per cent or greater TBSA in our study was 99 per cent. Only one patient with 33 per cent TBSA partial-thickness-only burns did not require transfusion of blood during the hospitalization. One reason for anemia in critical illness and potentially a basis for the efficacy of rhEPO in other adult critically ill patients is that as a result of circulating inflammatory mediators, these patients do not respond to an appropriate physiological level of EPO.[2, 3] Thermally injured patients exhibit some of the highest concentrations of circulating markers of inflammation such as macrophage hyperactivity compared with any other populations of critically ill patients.[15] Evidence also exists that as burn TBSA involvement increases, the inflammatory response increases.[16] If the larger the systemic inflammatory burden present results in a decreased response to erythropoiesis, then as burn TBSA increases, response will also decrease. This is supported by the finding in Still's multicenter trial that larger severity burns seem to result in less effective erythropoiesis in response to pharmacologic doses of rhEPO.[13] This raises the question of whether or not the dosing of rhEPO used in other critically ill patient groups and in our study is enough. The mean number of units of blood transfused per patient in Palmieri's study was 13.7 ± 1.1 U during the entire hospitalization.[1] Of those units, 4.3 ± 0.3 U were given in the operating room. The Hb trigger before intraoperative transfusion was 10.2 g/dL, significantly higher than the pretransfusion Hb value of 8.9 g/dL for blood

administered outside the operating room ($P < 0.05$). This demonstrates that the need for transfusion in critically ill burn patients is not only related to anemia associated with inflammatory mediators, but also to large-volume blood loss during extensive burn wound excision and skin grafting. The use of rhEPO would have no impact on hemorrhage, hypovolemic shock, or the trigger to transfuse in this situation that is unique to critically ill burn patients. The subgroup of patients with AKI treated with CVVH may have a transfusion reduction benefit from rhEPO compared with other burned patients (see Table 5). However, when survivors are exclusively evaluated, this benefit is no longer significant. Pharmacologic dosing of rhEPO may be beneficial as a result of the fact that the initially elevated EPO levels in AKI decrease to potentially inadequate values during treatment with CVVH.[17] In addition, mechanisms that lead to benefit in anemic patients with CKD may be at play in AKI.[18] Whether there may be a mortality benefit with rhEPO use in thermal injury would be a much more difficult question to answer.

Weaknesses of this report include the fact that it is retrospective, it is limited by the evaluation of a small number of patients, and end points evaluated such as transfusion volumes are very heterogenous as evidenced by large SDs. Unlike the standardized dosing regimen in Corwin's EPO2 (four doses) and EPO3 (three doses) studies, patients in our BICU received a mean of 10 doses of rhEPO with a range of one to 36 doses.[9, 10] This study is in no way a definitive answer to the question of whether rhEPO would benefit severely burned adult patients. As discussed, as a result of the markedly elevated markers of inflammation, the appropriateness of the dosing in thermal injury should be determined.

Conclusions

Our trial comparing rhEPO-treated patients with historical controls demonstrates a significant reduction in transfusion requirements in patients who develop AKI and require CVVH. There appears to be no mortality benefit or reduction in transfusion requirements in any other subgroup or overall when rhEPO-treated patients are compared with historical and contemporaneous controls. Based on these data, we do not currently recommend the routine use of rhEPO in the treatment of severely burned patients to reduce hospital transfusion requirements or reduce mortality.

REFERENCES

1. Palmieri TL, Caruso DM, Foster KN, et al. Effect of blood transfusion on outcome after major burn injury: a multicenter study. Crit Care Med 2006;34:1602–7.

2. Corwin HL, Krantz S. Anemia in the critically ill: 'acute' anemia of chronic disease. Crit Care Med 2000;28:3098–9.

3. Rodriguez RM, Corwin HL, Gettinger A, et al. Nutritional deficiencies and blunted erythropoietin response as causes of the anemia of critical illness. J Crit Care 2001;16:36–41.

4. Desai MH, Herndon DN, Broemling L, et al. Early burn wound excision significantly reduces blood loss. Ann Surg 1990; 221:753–62.

5. Herdon DN ed. Total Burn Care, 3rd ed. Philadelphia: Saunders-Elsevier; 2007;180–1.

6. Mahdy S, Khan EI, Attia M, et al. Evaluation of a blood conservation strategy in the intensive care unit: a prospective, randomized study. Middle East J Anaesthesiol 2009;20:219–23.

7. Fishbane S, Nissenson AR. The new FDA label for erythropoietin treatment: how does it affect hemoglobin target? Kidney Int 2007;72:806–13.

8. Corwin HL, Gettinger A, Rodriguez RM, et al. Efficacy of recombinant human erythropoietin in the critically ill patient: a randomized double-blind placebo-controlled trial. Crit Care Med 1999;27:2346–50.

9. Corwin HL, Gettinger A, Pearl RG, et al. Efficacy of recombinant human erythropoietin in critically ill patients. JAMA 2002;288:2827–35.

10. Corwin HL, Gettinger A, Fabian TC, et al. Efficacy and safety of epoetin alfa in critically ill patients. N Engl J Med 2007; 357:965–76.

11. Galeano M, Altavilla D, Bitto A, et al. Recombinant human erythropoietin improves angiogenesis and wound healing in experimental burn wounds. Crit Care Med 2006;34:1139–46.

12. Napolitano LM, Fabian TC, Kelly KM, et al. Improved survival of critically ill trauma patients treated with recombinant human erythropoietin. J Trauma 2008;65:297–9.

13. Still JM, Belcher K, Law EJ, et al. A double-blinded prospective evaluation of recombinant human erythropoietin in acutely burned patients. J Trauma 1995;38:233–6.

14. Hebert PC, Wells G, Blajchman MA, et al. A multicenter, randomized, controlled clinical trial of transfusion requirements in critical care. Transfusion requirements in critical care investigators, Canadian Critical Care Trials Group. N Engl J Med 1999;340:409–17.

15. Schwacha M. Macrophages and post-burn immune dysfunction. Burns 2003;29:1–14.

16. Jeschke MG, Micak RP, Finnerty CC, et al. Burn size determines the inflammatory and hypermetabolic resonse. Crit Care 2007;11:R90.

17. Morgera S, Heering P, Szentandrasi T, et al. Erythropoietin in patients with acute renal failure and continuous veno-venous haemofiltration. Int Urol Nephrol 1997;29:245–50.

18. Liangos O, Pereira BJ, Jaber BL. Anemia in acute renal failure: a role for erythropoiesis-stimulating proteins? Artif Organs 2003;27:786–91.

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