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Cost-Effectiveness of Recombinant Human Erythropoietin for Reducing Red Blood Cells Transfusions in Critically Ill Patients

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ABSTRACT

Objective: To examine the cost-effectiveness of using recombinant human erythropoietin (rHuEPO) to reduce red blood cells (RBC) transfusions in intensive care unit (ICU) patients.

Methods: Decision analysis examining costs and effectiveness of using rHuEPO versus not using rHuEPO in a simulated adult medical/surgical/trauma (mixed) ICU. Two independent cost-effectiveness models were created based on the results of two multicenter studies that investigated the use of rHuEPO. Base case assumptions and estimates of effectiveness were obtained from these two studies. Mean cumulative doses of rHuEPO were 190,900 units and 102,400 units for studies 1 and 2, respectively. The models accounted for the deferral rate for allogeneic RBC transfusions, rHuEPO efficacy (the reduction in allogeneic RBC use), and adverse effects of rHuEPO and allogeneic RBC transfusions. Model estimates were obtained from published sources. Costs were expressed in 2002 US dollar ($) and effectiveness was measured using discounted quality-adjusted life-years (QALYs). A 3% discount rate was used. Probabilistic sensitivity analysis was conducted using second-order Monte Carlo simulation.

Results: Incremental costs of using rHuEPO to reduce RBC transfusions amounted to $1918 and $1439; incremental effectiveness values were 0.0563 QALYs and 0.0305 QALYs; and the cost-effectiveness ratios were $34,088 and $47,149 per QALY for studies 1 and 2, respectively. The model was most sensitive to the attributable risk of nosocomial bacterial infections per RBC unit. rHuEPO was cost-effective in 52.0% of the Monte Carlo simulations for a willingness to pay of $50,000/QALY.

Conclusion: rHuEPO appears to be cost-effective for reducing RBC transfusions in heterogeneous ICU populations, assuming RBC transfusions increase the risk of nosocomial bacterial infections.

Keywords: anemia, cost-effectiveness, costs, critical care, erythropoietin, transfusion.

Introduction

Anemia occurs in approximately 75% to 95% of patients admitted to the intensive care unit (ICU) for at least 3 days [1–5] and is associated with lengthened ICU stay [3–5]. The most prominent factors contributing to the development of anemia in the ICU include preexisting renal failure, decreased production and survival of red blood cells (RBC), gastrointestinal blood losses, and iatrogenic blood losses from phlebotomy [2–4]. Treatment of ICU-associated anemia frequently involves the administration of allogeneic RBC transfusions but the number of transfusions is independently associated with lengthened ICU stay and mortality. Consensus guidelines for ICU transfusion practices recommend restricting RBC transfusions for the purpose of decreasing signs, symptoms, and morbidity associated with poor tissue oxygenation related to low hematocrit (Hct) or hemoglobin (Hb) but specific threshold values are rarely provided [6–11].

In clinical practice, RBC transfusions are provided for multiple indications. The most common reasons are bleeding episodes, the augmentation of oxygen delivery, surgery, and myocardial ischemia [11–13]. Nevertheless, the administration of RBC transfusions is an independent risk factor for hospital mortality [3,4]. Liberal transfusion strategies may further increase the mortality risk [14]. Mortality may be related to transfusion-induced adverse effects, increased infection risk [3,4,15–28], or the administration of RBCs that have lost their cellular deforming or oxygen carrying capacities because of

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prolonged storage [6,29,30]. The deleterious effects, the limited supply of RBC transfusions, and the costs associated with RBC transfusions have caused transfusion practices to be reevaluated [7,31], necessitating the exploration of alternative therapeutic and preventive strategies for ICU-associated anemia.

Recombinant human erythropoietin (rHuEPO) is a promising pharmacological approach for treating and preventing ICU-associated anemia and reducing the number of RBC transfusions. The proinflammatory cytokines, interleukin (IL)-1β and tumor necrosis factor (TNF)-α, directly suppress bone marrow production of reticulocytes [1,32] and have restrictive effects on reticulocytosis by inhibiting erythropoietin production at the nuclear level [33,34]. In addition, interferon (IFN)-β, IFN-γ, and TNF-α blunt erythropoietin response at the level of the receptor on RBC precursor cells [35]. Therefore, inhibited erythropoietin production and reduced erythropoietin response contribute to ICU-associated anemia. The results of prospective studies have demonstrated that early administration of rHuEPO to critically ill patients increases reticulocyte counts and reduces RBC transfusion requirements [36–41]. Some institutions are using rHuEPO in critically ill patients to reduce RBC transfusion requirements [42]. The acquisition cost of rHuEPO is very expensive, however, and it is unclear whether the concomitant reduction in RBC transfusion requirements offsets other possible significant downstream costs. A rudimentary cost analysis included in the discussion of one study suggests that using rHuEPO to prevent anemia may produce cost savings depending on the rHuEPO dosage regimen and relative reduction in RBC transfusions [38]. To date, comprehensive economic models examining the cost-effectiveness of using rHuEPO in an ICU population are nonexistent. The purpose of this study was to assess the cost-effectiveness of rHuEPO for preventing RBC transfusions in critically ill patients using the results of two previously published clinical trials [38,39].

Methods

Decision Analysis

Decision analysis was used to model the costs and effectiveness of utilizing rHuEPO for reducing and possibly preventing RBC transfusions in an adult medical/surgical/trauma (mixed) ICU from a societal perspective (Fig. 1). Two independent cost-effectiveness models were created based on the results of two multicenter clinical trials that investigated the use of rHuEPO for the prevention of RBC transfusions (one model for each study) [38,39]. These two studies were chosen because they represent the largest trials enrolling mixed ICU patients and they used methods of high quality. The search strategy to identify these two studies has been previously described [43]. Two models were created because the methodologies of the two studies differ substantially. The primary decision node of both models was whether or not to use rHuEPO. The clinical pathway within the models depicted patients receiving or not receiving allogeneic RBC transfusions and the associated adverse effects of rHuEPO and RBC transfusions. The immediate and lifetime costs for each intervention were modeled using estimates from the published literature. All costs are expressed in 2002 US dollars ($) using an annual discount rate of 3%. The analysis adhered to

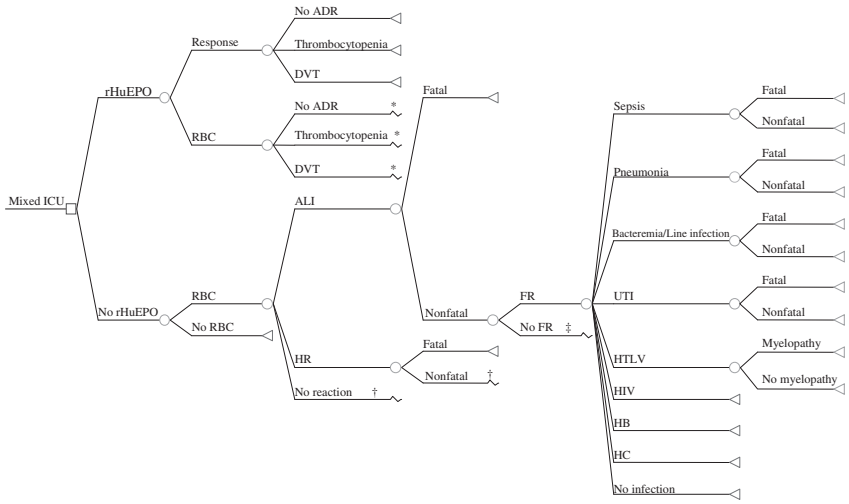

Figure 1 Decision analysis of utilizing rHuEPO for reducing RBC transfusions. ICU, intensive care unit; rHuEPO, recombinant human erythropoietin; RBC, red blood cell; ADR, adverse drug reaction; DVT, deep venous thrombosis; ALI, acute lung injury; HR; hemolytic reaction; FR, febrile reaction; UTI, urinary tract infection; HTLV, human T-cell lymphotrophic virus; HIV, human immunodeficiency virus; HB, hepatitis B; HC, hepatitis C; *Same as RBC (No rHuEPO); †Same as Nonfatal (ALI); ‡Same as FR (Nonfatal).

the recommendations of the Panel on Cost-Effectiveness in Health and Medicine [44]. The models were constructed using decision analysis software (DATA Professional, TreeAge Software, Inc, Williamston, MA, 2003) and Microsoft Excel software (Microsoft Corporation, Redmond, WA, 2000). Primary output parameters of the models were expected costs, expected effectiveness (discounted quality-adjusted life-years [QALYs]), and incremental cost-effectiveness.

Model Assumptions

For the base case analyses, the profiles of two mixed ICU patient cohorts were simulated from the two multicenter studies [38,39]. Both studies investigated patients of 18 years old or above already in the ICU for 2 or more days with an additional expected ICU stay of 3 or more days. Study 1 enrolled 54% male with an average age of 60 years and the majority of patients having primary diagnoses relating to respiratory illnesses [38] whereas study 2 enrolled 61.9% male with an average age of 51 years and the majority of patients having primary diagnoses relating to trauma or surgery [39]. The rHuEPO dosage regimens modeled were 23,000 units administered subcutaneously for 8.3 doses, daily for the first 5 days then every other day, and 40,000 units administered subcutaneously every week for 2.56 doses based on studies 1 and 2, respectively [38,39]. The doses and number of doses are weighted means extracted from the two studies. Both studies initiated rHuEPO when Hct fell below 38%. Iron was administered enterally at a daily elemental dose of 150 mg as generic liquid ferrous sulfate.

The models accounted for the following factors: the deferral rate for allogeneic RBC transfusions, rHuEPO efficacy, the reduction in allogeneic blood use, and adverse effects of rHuEPO and allogeneic RBC transfusions. The only clinically relevant benefit of using rHuEPO demonstrated in both studies was a reduction in transfusion requirements [38,39]. In study 1, 55% of patients in the no rHuEPO group required 6.93 RBC units per patient and 45% of patients in the rHuEPO group required 4.61 RBC units per patient [38]. In study 2, 60.4% of patients in the no rHuEPO group required 4.98 RBC units per patient and 50.5% of patients in the rHuEPO group required 4.85 RBC units per patient [39]. Transfusions were administered according to clinical judgment in study 1 and to maintain an Hct of 27% in study 2 [38,39].

The 2002 average wholesale price for rHuEPO was discounted 15% to reflect the average institutional contract in the United States, resulting in a cost of $0.0119 per unit [45]. Including the costs associated with administration (pharmacy and nursing time), concurrent enteral iron administration, and a baseline erythropoietin serum concentration, the total cost of rHuEPO therapy was $2561 for study 1 and $1508 for study 2 [38,39]. The cost of administering a unit of RBC included the costs associated with blood collection (including donor time) and storage, typing, screening, cross-matching, nurse administration, and follow up laboratory determination of Hct and was estimated at $297. These estimates were based on published data from different sources that were consistent between reports [46–48]. We did not assume universal leucodepletion because it is unclear whether this practice alters the outcome of critically ill patients [49,50].

The adverse effects of rHuEPO considered were deep venous thrombosis (DVT) and thrombocytopenia with attributable occurrence rates of 3% [46–48] and 7.5% [38] and associated direct costs of $4599 [51–53] and $2896 [54], respectively. Adverse effects of allogeneic RBC transfusions considered were acute lung injury (ALI); hemolytic reaction (HR); febrile reactions (FR); viral infections including human immunodeficiency virus (HIV), hepatitis B (HB), hepatitis C (HC), and human T-cell lymphotrophic virus (HTLV); and bacterial infections including sepsis, pneumonia, bacteremia, and urinary tract infections (Table 1) [3,6,15,55–62]. The nosocomial bacterial infection rates for patients not requiring RBC transfusions (baseline infection rates) were 0.15%, 1.23%, 0.54%, and 0.69% for sepsis, pneumonia, bacteremia, and urinary tract infections, respectively [15]. The attributable risk of developing a nosocomial bacterial infection from RBC transfusion was 0.5 per unit RBC, based on previous research delineating the increased risk of nosocomial infection associated with RBC transfusion in critically ill patients [15]. Therefore, the attributable risk of each specific infection per course of therapy was calculated according to the following equation: (baseline rate of specific infection) $\times$ 0.5 $\times$ (number of RBC units).

RBC Transfusion Threshold

A recent study showed that restricting transfusion administration to maintain Hct above approximately 21% was safe and may reduce mortality compared with administering transfusions to keep Hct above approximately 30% [14]. This study reduced the number of transfusions by 54% and the number of patients receiving a transfusion by 33%.

Table 1 Adverse effects of RBC transfusions

RBC transfusion outcome	Incidence [3,6,15,55–62]	Cost estimate/event [46–48, 56–62]	Quality-adjusted life-years (study 1) [38,63–65]	Quality-adjusted life-years (study 2) [39,63–65]
Acute lung injury	2×10^{-4}/RBC unit	$6,180	10.56	15.16
Fatal	0.001/event			
Acute hemolytic reaction	2.5×10^{-6}/RBC unit	$1,779	10.56	15.16
Fatal	0.268/event			
Febrile reaction	0.01/RBC unit	$169.53	10.56	15.16
Viral infections				
HIV	2.75×10^{-6}/RBC unit	$63,272	7.52	9.82
Hepatitis B	1.87×10^{-5}/RBC unit	$12,209	9.12	13.09
Hepatitis C	2.0×10^{-5}/RBC unit	$27,204	9.54	13.70
HTLV	2.25×10^{-6}/RBC unit		10.56	15.16
Myelopathy	0.04/event	$14,632	10.10	14.70
Bacterial infections				
Sepsis*	0.5/RBC unit	$16,667	6.59	9.46
Fatal	0.376/event			
Pneumonia*	0.5/RBC unit	$12,375	7.39	10.61
Fatal	0.30/event			
Bacteremia*	0.5/RBC unit	$42,143	6.91	9.91
Fatal	0.346/event			
Urinary tract*	0.5/RBC unit	$663	10.56	15.16

*Actual infection risk per course of therapy calculated according to the following equation: (baseline rate of specific infection) × 0.5 × (number of RBC units) [15].
HIV, human immunodeficiency virus; HTLV, human T-cell lymphotrophic virus; RBC, red blood cell.

The transfusion thresholds used in the current cost-effectiveness analyses were weighted mean Hcts of approximately 27.3% and 25.7% for studies 1 and 2, respectively. To determine whether using an Hct of 21% as the transfusion threshold alters the cost-effectiveness of rHuEPO, we conducted a separate sensitivity analysis, incorporating the lower transfusion Hct threshold and the transfusion-sparing results of the restrictive transfusion study.

Quality-Adjusted Life-years

QALYs were calculated independently for each study based on the mean age and sex distribution of the study population [38,39]. To derive baseline QALYs for the respective ICU cohorts, the quality-adjusted life expectancy (QALE) of the matching age and sex population in the United States was adjusted by the mortality rate and the annual utility decrement corresponding to mixed ICU populations [63–65]. For an ICU population, the cumulative fatality rate at 12 months post hospital discharge was 25% and the average EQ-5D tariff (utility) was 0.62 for subsequent years. For those who survived 12 months post hospital discharge (75%), we assumed the life expectancy of a male and female to be 80 and 83 years of age, respectively [63]. The resulting discounted QALE (reported as QALYs) were 10.56 QALYs for the cohort in study 1 [38] and 15.16 QALYs for study 2 [39] (Table 1). In the studies used to estimate utility decrement, approximately 55% of patients were male with a mean age of 54 years [64,65]. Similar to the two rHuEPO studies used in this analysis, the majority of primary diagnoses of one study related to respiratory illnesses [65] whereas the majority of primary diagnoses of the other study related to trauma or surgery [64]. The long-term utility impacts of ALI or acute hemolytic reaction were assumed to be negligible and surviving patients were assumed to have similar post ICU utilities as patients without these reactions.

Early and late morbidities were considered with all viral transmissions. Patients with HIV infection were assumed to follow a disease progression of 4 phases based on previously published research: patients in phase 1 are HIV infected, but there is no impact on utility for 9 years; patients in phase 2 have an estimated utility of 0.76 for 4 years; patients in phase 3 have an estimated utility of 0.65 for 1 years; and patients in phase 4 have an estimated utility of 0.62 for 1 years before dying of acquired immunodeficiency syndrome (AIDS) [66]. These estimates were applied to the age and sex-adjusted life expectancy of ICU patients and resulted in 7.52 QALYs for study 1 and 9.82 QALYs for study 2 for patients infected with HIV due to RBC transfusions.

QALYs for patients infected with HB, HC and HTLV-induced myelopathy were calculated using previously published evidence of the impact on utility and survival [47,67,68]. QALYs for HB, HC and HTLV-induced myelopathy for studies 1 and 2 were

Table 2 Cost-effectiveness of base cases

	No rHuEPO (study 1)	rHuEPO (study 1)	No rHuEPO (study 2)	rHuEPO (study 2)
Cost ($)	1928	3,846	1,595	3,034
Incremental cost ($)		1,918		1,439
Effectiveness (QALY)	10.4365	10.4928	15.0035	15.0340
Incremental effectiveness (QALY)		0.0563		0.0305
Incremental cost-effectiveness ratio ($/QALY)		34,088		47,149

QALY, quality-adjusted life-year.

9.12 and 13.09 QALYs; 9.54 and 13.70 QALYs; and 10.10 and 14.70 QALYs, respectively. Because of the acute nature of nosocomial bacterial infections, the utility impact was assumed to be negligible and surviving patients were assumed to have similar post ICU utilities as patients without bacterial infections. Therefore, decrements in QALYs for bacterial infections were based solely on decreased survival. QALYs for sepsis, pneumonia, and bacteremia for studies 1 and 2 were 6.59 and 9.46 QALYs; 7.39 and 10.61 QALYs; and 6.91 and 9.91 QALYs, respectively. It was assumed that survival and utility were not influenced by the development of urinary tract infections or rHuEPO-induced adverse effects (DVT and thrombocytopenia).

Sensitivity Analyses

Univariate sensitivity analyses were conducted by varying each input parameter by ±15% from the base case value to identify the individual variables with the greatest impact on the model results. Comprehensive threshold analyses were conducted for parameters identified as having the greatest impact on model results.

To more comprehensively examine the inherent uncertainty in the assumptions underpinning the model, a probabilistic sensitivity analysis using a second-order Monte Carlo simulation was conducted [69]. Incidence, cost, utility and effectiveness parameters were assigned a probability distribution incorporating the estimates from both studies and reflecting the feasible range of values that each input parameter could realize. The simulation then drew one value from each distribution simultaneously and calculated cost and effectiveness pairs. This process was repeated 10,000 times to provide a range of possible values given the specified probability distributions. Probabilities, incidence rates, and utilities were assumed to follow a beta distribution because they are normally distributed but restricted to take on values between zero and one. Estimates of mean cost were assumed to follow either a gamma distribution or, when large enough to ensure positive values, a normal distribution, although individual estimates of cost are typically not normally distributed, estimates of mean cost are normally distributed [69].

Results

Cost-Effectiveness Estimates

For the base case analysis of studies 1 and 2, the incremental costs of using rHuEPO to prevent RBC transfusions were $1918 and $1439 and incremental effectiveness values were 0.0563 QALYs and 0.0305 QALYs, respectively (Table 2). The resulting cost-effectiveness ratios were $34,088 and $47,149 per QALY for studies 1 and 2, respectively. The incremental costs per allogeneic RBC unit avoided were $827 and $11,072, respectively. Incorporating the restrictive transfusion study into the model resulted in an incremental cost of $2086 and an incremental effectiveness of 0.0143 QALYs for a cost-effectiveness ratio of $145,455 per QALY.

Sensitivity Analyses

The results of the univariate sensitivity analyses revealed that the attributable risk of developing a nosocomial bacterial infection per RBC unit (assumed baseline rate of 0.5) was the most important driver of incremental cost-effectiveness for both studies. Threshold analysis demonstrated that using rHuEPO was cost-effective for a willingness to pay of $50,000 per QALY if the attributable risk of nosocomial infection per unit of RBC is >0.36 and >0.46 in study 1 (Fig. 2) and study 2 (Fig. 3), respectively. Univariate alteration of all other parameters had little impact on the results of the model. Even if the occurrence rates of viral infections are assumed to be nonexistent, as would be the case if viral blood screening was flawless, the cost-effectiveness ratio does not exceed $47,246 per QALY. For both studies, rHuEPO is cost-effective only if RBC transfusions are associated with nosocomial bacterial infections even if the price per unit of rHuEPO is reduced by 100% (in addition to the

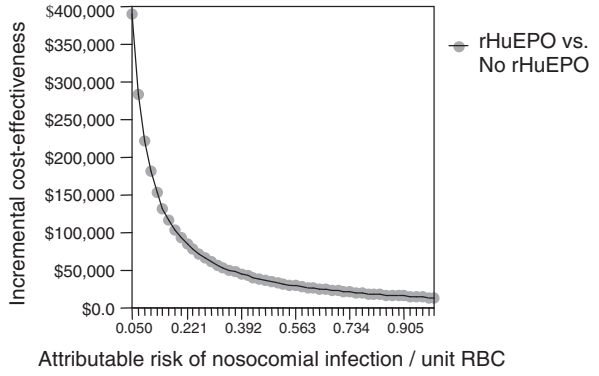

Figure 2 Threshold sensitivity analysis of model 1 (study 1): impact of varying attributable risk of nosocomial infection per RBC unit on incremental cost-effectiveness ($/QALY). Assumed baseline rate is 0.5 and the threshold analysis demonstrated rHuEPO was cost-effective for a willingness to pay of $50,000 per QALY if the attributable risk of nosocomial infection per unit of RBC is >0.36. rHuEPO, recombinant human erythropoietin; RBC, red blood cell.

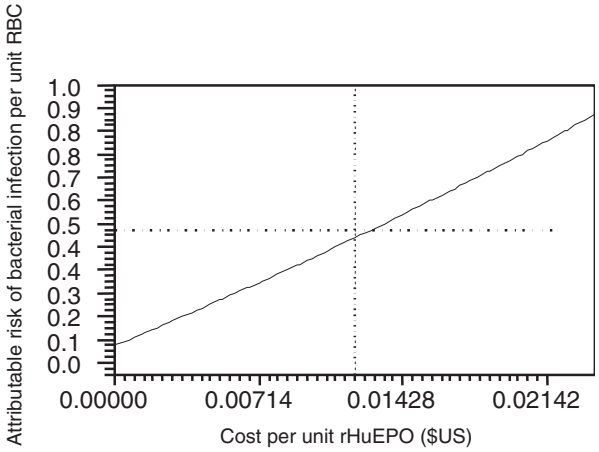

Figure 4 Bivariate sensitivity analysis varying the attributable risk of nosocomial bacterial infections per unit of RBC and the cost ($) per unit of rHuEPO by ±100%. The dashed lines represent the base case assumptions ($0.0119/rHuEPO unit and risk of infection of 0.50). Points above the diagonal line are cost-effective for a willingness to pay of $50,000 per QALY. RBC, red blood cell; rHuEPO, recombinant human erythropoietin.

price per unit, there are costs associated with administering rHuEPO—Fig. 4). This result is due primarily to the fact that, absent an increased risk of nosocomial infection due to RBC transfusion, the incremental effectiveness of rHuEPO is negligible. Varying the cost per unit of rHuEPO changes the threshold at which the attributable risk of bacterial infection is cost-effective (Fig. 4).

The 95% range of all input variables gives the credible interval of values from the 2.5th and 97.5th percentiles of the 10,000 second-order Monte Carlo simulations (Table 3). Incremental cost varied from $130 to $3594 and incremental effectiveness ranged from –0.0099 to 0.1638 QALYs. The cost-effectiveness of each of the 10,000 cost and effectiveness pairs depends on its location relative to the willingness to pay line. Overall, rHuEPO was cost-effective in 52.0% of the Monte Carlo simulations. If $100,000 per QALY is used as the willingness to pay threshold, rHuEPO is cost-effective in 72% of the simulations (Fig. 5). Given the specifications of the distributions of the input parameters in the model, these percentages may be interpreted more generally as the probability that rHuEPO is cost-effective at the respective willingness to pay thresholds [70].

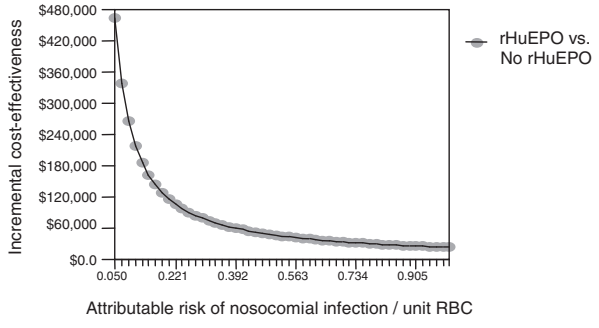

Figure 3 Threshold sensitivity analysis of model 2 (study 2): impact of varying attributable risk of nosocomial infection per RBC unit on incremental cost-effectiveness ($/QALY). Assumed baseline rate is 0.5 and the threshold analysis demonstrated rHuEPO was cost-effective for a willingness to pay of $50,000 per QALY if the attributable risk of nosocomial infection per unit of RBC is >0.46. rHuEPO, recombinant human erythropoietin; RBC, red blood cell.

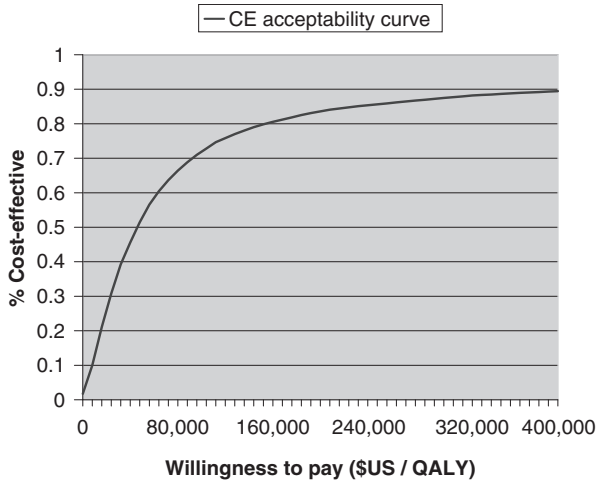

Figure 5 Cost-effectiveness (CE) acceptability curve.

Table 3 The 95% credible intervals of input variables and outcomes from Monte Carlo simulations

Input variables and outcomes	Range*
Cost parameters ($)	
rHuEPO (per unit)†	0.0057–0.0205
RBC (per unit)†	143–510
DVT (per rHuEPO course of therapy)†	2630–6555
Thrombocytopenia (per rHuEPO course of therapy)‡	1698–4074
Acute lung injury‡	4238–8106
Acute hemolytic reaction‡	1100–2451
Febrile reaction[2]	111–228
HIV‡	44,242–82,542
Hepatitis B‡	10,217–14,146
Hepatitis C‡	21,389–33,084
HTLV-induced myelopathy‡	9700–19,491
Sepsis‡	11,728–21,591
Pneumonia‡	9426–15,276
Bacteremia‡	34,429–51,993
Urinary tract infection‡	503–819
Dosage and incidence parameters	
rHuEPO (total units)†	81,634–232,178
RBC rHuEPO (total units)†	3.84–5.70
RBC no rHuEPO (total units)†	3.86–8.45
Probability of RBC rHuEPO§	0.377–0.580
Probability of RBC no rHuEPO§	0.493–0.659
DVT (per rHuEPO course of therapy)§	0.015–0.051
Thrombocytopenia (per rHuEPO course of therapy)§	0.062–0.090
Acute lung injury (per RBC unit transfused)[3]	9.71×10^{-5}–3.45×10^{-4}
Fatality rate§	5.79×10^{-4}–2.06×10^{-3}
Acute hemolytic reaction (per RBC unit transfused)§	1.21×10^{-6}–4.27×10^{-6}
Fatality rate§	0.225–0.314
Febrile reaction (per RBC unit transfused)§	4.76×10^{-3}–1.69×10^{-2}
Hepatitis B (per RBC unit transfused)§	9.04×10^{-6}–3.19×10^{-5}
Hepatitis C (per RBC unit transfused)§	9.62×10^{-6}–3.41×10^{-5}
HIV (per RBC unit transfused)§	1.32×10^{-6}–4.69×10^{-6}
HTLV (per RBC unit transfused)§	1.10×10^{-6}–3.85×10^{-6}
Myelopathy rate§	1.96×10^{-2}–6.76×10^{-2}
Attributable risk of infection (per RBC unit transfused)†	0.138–1.089
Sepsis (baseline)§	1.22×10^{-3}–1.80×10^{-3}
Fatality rate§	0.319–0.435
Pneumonia (baseline)§	1.00×10^{-2}–1.48×10^{-2}
Fatality rate§	0.252–0.349
Bacteremia (baseline)§	4.39×10^{-3}–6.52×10^{-3}
Fatality rate§	0.293–0.402
Urinary tract infection§	5.61×10^{-3}–8.30×10^{-3}
QALYs	
ICU[1] (QALE)	8.25–18.38
Hepatitis B decrement†	1.15–2.50
Hepatitis C decrement†	0.81–1.78
HIV decrement†	2.58–8.98
HTLV-induced myelopathy decrement†	0.37–0.56
Cost-effectiveness results	
Total expected cost rHuEPO ($)	2119–5349
Total expected cost no rHuEPO ($)	798–3236
Expected effectiveness rHuEPO (QALY)	8.20–18.28
Expected effectiveness no rHuEPO (QALY)	8.17–18.19

*The 95% intervals give the credible range of values from the 2.5th and 97.5th percentiles of the 10,000 second-order Monte Carlo simulations.
†Gamma distribution.
‡Normal distribution.
§Beta distribution.
DVT, deep venous thrombosis; HIV, human immunodeficiency virus; HTLV, human T-cell lymphotrophic virus; QALY, quality-adjusted life-year; RBC, red blood cell; rHuEPO, recombinant human erythropoietin.

Discussion

Recombinant human erythropoietin therapy has been shown to reduce the need for RBC transfusions in ICU patients, but studies have not examined its cost-effectiveness in this patient population. In the current study, decision analysis was used to create economic models of the patient populations involved in two previously published multicenter clinical trials that were designed to assess rHuEPO for reducing the need of RBC transfusions in adult ICU populations. The results of both models suggest that rHuEPO is cost-effective when used to reduce RBC transfusion requirements in an ICU population due largely to the reduction in the risk of developing nosocomial bacterial infections associated with RBC transfusions. Although there is no consensus about the acceptable upper limit of society's willingness to pay for a given intervention, the range of base case estimates from both models is below the typical threshold of consideration ($50,000 per QALY). Using Monte Carlo analysis, 52.0% of simulations were deemed cost-effective if $50,000 per QALY is the acceptable upper limit of willingness to pay (Fig. 5). Of note, our results differ from other analyses that have not shown rHuEPO to be cost-effective in patient populations outside the ICU [46–48]. Nevertheless, only our analyses included the risk of bacterial infections associated with RBC transfusions, an phenomenon that currently is only recognized in ICU and cancer populations [15–28].

Our estimates are generated from the results of previously published clinical trials. Although modeling two multicenter studies involving separate ICU populations provides greater generalizability, the results of the base case analyses are limited by the patient populations and clinical criteria in these studies. In general, the magnitude of effect is usually smaller in practice than in controlled studies because of poor patient selection, failure to properly administer therapy, and inappropriate provisions of other aspects of care [71]. Altering the use of rHuEPO based on different criteria and/or patient populations may alter the cost-effectiveness results. Both studies initiated rHuEPO when Hct dropped below 38%. It is difficult to predict patients at risk for developing anemia in the ICU and little information exists to distinguish specific ICU populations at greatest risk. Altering the threshold for initiating rHuEPO therapy may change the cost-effectiveness results positively or negatively depending on whether the resultant effect is drug sparing or transfusion requiring, respectively. Reducing the

transfusion thresholds from weighted mean Hct values of approximately 27.3% and 25.7% used in Studies 1 and 2, respectively, to the 21% threshold shown to be safe in the restrictive transfusion study produced a less favorable cost-effectiveness ratio of $145,455 per QALY [14]. The benefit of lowering the Hct transfusion threshold to 21% is likely overestimated because the comparative arm in the restrictive transfusion study administered transfusions to maintain Hct above approximately 30%. Of note, surveys and cohort studies conducted after the publication of the restrictive transfusion study indicate that the majority of ICU practitioners continue to transfuse RBC units to maintain Hct at approximately 24% to 27% [3,4,72,73]. Future comparative studies of rHuEPO, however, should incorporate a restrictive transfusion protocol to determine the effectiveness of rHuEPO against evidence-based practice.

We found the attributable risk of developing nosocomial bacterial infections to be the most important determinant of cost-effectiveness. Several studies have demonstrated an association between RBC transfusions and infection risk but the degree of risk is variable and related to the cumulative number of RBC units transfused [3,15–28]. We used an attributable risk of 0.5 per RBC unit based on previously published evidence, but the thresholds of risk to maintain cost-effectiveness are 0.36 and 0.46 for a willingness to pay of $50,000 per QALY or less for studies 1 and 2, respectively. These thresholds are within the range of uncertainty reported in the literature. In addition, altering the cost per unit of rHuEPO substantially impacts the threshold of bacterial infection risk that is cost-effective (Fig. 4). Immunomodulation is the most likely explanation for enhanced infection risk with RBC transfusions because they have been shown to downregulate macrophage class II antigen production, decrease B-cell stimulation and CD4 helper T-cell number, and impair natural killer cell activity [74,75]. The immunosuppressive effect is related to leukocyte exposure with subsequent sensitization [3]. Some countries have implemented universal leucodepletion of RBC transfusions but the estimated cost to do so in the United States exceeds $500 million [3]. We did not assume universal leucodepletion because it is unclear whether this practice alters outcomes of critically ill patients [49,50]. If proven effective, leucodepletion would be a competing strategy for reducing bacterial infections and would minimize the benefit associated with rHuEPO.

The results of both studies included in the analyses showed that approximately 10% fewer patients require RBC transfusions with rHuEPO therapy [38,39]. Nevertheless, the mean number of transfusions per patient varied substantially between studies. Study 1 saved 2.32 RBC units per patient requiring a transfusion, whereas study 2 saved only 0.13 RBC units. This difference between studies is likely due to dosage regimen variations because study 1 used aggressive early rHuEPO therapy for a mean cumulative dose of 190,900 units and study 2 used weekly administration for a mean cumulative dose of 102,400 units. Based on the results of the sensitivity analyses, however, both dosing strategies appear cost-effective. Whether alternative rHuEPO dosage regimens are cost-effective is unknown. We used average wholesale price discounted 15% to represent rHuEPO acquisition cost [45]. This may not accurately reflect the specific contract price of certain institutions, but is indicative of the average contract price in the United States and allows for more general application of the results.

We included the costs of thrombocytopenia and DVT associated with rHuEPO therapy. Study 1 showed a substantial, although statistically insignificant, increase in the occurrence of thrombocytopenia with rHuEPO. Study 2 did not report thrombocytopenia as an independent adverse effect. DVT is a recognized rare event associated with rHuEPO therapy. The exclusion of these side effects had no impact on the model results.

The incidences and costs of adverse effects associated with RBC transfusions were obtained from published sources examining the use of RBC transfusions in critically ill patients or rHuEPO for reducing transfusions in other populations [3,6,15,46–48,55–65]. Neither the incidence rates nor the costs associated with the adverse effects of RBC transfusion had a significant impact on the results of the model because of the fact that these events are extremely rare. Of note, we included only adverse effects that were well established and assumed similar adverse effect profiles for each unit of RBC. Other possible complications not included in the current analysis are psychrophile-induced shock, blood stasis, post-transfusion purpura, suppression of erythropoiesis, and alterations of oxygen carrying capacity with RBC storage [6]. Including these effects, however, would enhance the cost-effectiveness of rHuEPO.

Estimating the baseline QALE of an average ICU population is inherently unwieldy because of the heterogeneous nature of any ICU. QALE varies according to patient demographics, the reason for ICU admission, and associated patient utility esti-

mates. Nevertheless, the same baseline QALE estimate was applied to both groups of a study and thus any bias in the baseline QALE estimate would equally impact both groups. We made assumptions that several adverse effects associated with transfusions would not affect post ICU patient utility (e.g., ALI, acute hemolytic reactions, bacterial infections). These events most likely do impact QALYs but limited data exist describing long-term decrements. Including these effects, however, would enhance the cost-effectiveness of rHuEPO.

Beyond reducing RBC transfusions, studies have not shown other clinical benefits with rHuEPO therapy in critically ill patients [36,37,40,41]. In study 2, there was a trend toward reduced ICU readmission rate with rHuEPO therapy (9.8% vs. 13.3%, $P = 0.07$, respectively) [39]. Any additional clinical benefit would enhance the cost-effectiveness associated with rHuEPO use.

The estimates used in modeling the cost-effectiveness of rHuEPO are based on multiple sources and assumptions and are therefore subject to uncertainty. Hence, we urge some degree of caution when interpreting these results. Moreover, cost-effectiveness analyses serve as one piece of information in the decision-making process when considering the implementation of health interventions. Nevertheless, we have attempted to examine the impact of this inherent uncertainty on the results of the model through the use of comprehensive sensitivity analyses. All estimates and assumptions were simultaneously varied to include all plausible values. After incorporating these extreme values, the use of rHuEPO to reduce transfusion requirements in an ICU population was cost-effective in 52.0% of the simulations.

Conclusions

The results of these models suggest that using rHuEPO to reduce RBC transfusions in an ICU population is cost-effective, due primarily to the risk of nosocomial bacterial infection associated with RBC transfusions. Our findings were robust to a wide range of sensitivity analyses and two separate cost-effectiveness models. Future studies should focus on clinical outcomes other than RBC transfusion independence, determination of patients most at risk for developing anemia in the ICU, rHuEPO use while incorporating a restrictive transfusion protocol, and a priori cost-effectiveness analysis.

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