

Number needed to treat and cost of recombinant human erythropoietin to avoid one transfusion-related adverse event in critically ill patients*

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LEARNING OBJECTIVES

On completion of this article, the reader should be able to:

1. Describe the benefits of using erythropoietin.
2. Explain the potential adverse events related to red cell transfusions.
3. Explain the cost of erythropoietin required to avoid one transfusion adverse event.

The authors have disclosed that they have no financial relationships or interests in any commercial companies pertaining to this educational activity. The authors have also disclosed that they will be discussing unlabeled/investigational uses of erythropoietin, a commercial product, and will disclose this to the audience.

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Objective: To calculate the absolute risk reduction of transfusion-related adverse events, the number of patients needed to treat, and cost to avoid one transfusion-related adverse event by using erythropoietin in critically ill patients

Design: Number needed to treat with sensitivity analysis.

Setting: Teaching hospital.

Patients: Hypothetical cohort of critically ill patients who were candidates to receive erythropoietin.

Interventions: Using vs. not using erythropoietin to reduce the need for packed red blood cell transfusions.

Measurements and Main Results: We used published estimates of known transfusion risks: transfusion-related acute lung injury, transfusion-related errors, hepatitis B and C, human immunodeficiency virus, human T-cell lymphotropic virus, and bacterial contamination, stratified by severity. Based on the estimated risk and frequency of transfusions with and without erythropoietin, we calculated the absolute risk reduction of transfusion-related adverse events, the number needed to treat, and cost to avoid one transfusion-related adverse event by using erythropoietin. The estimated incidence of transfusion-related adverse event was 318 permillion

units transfused for all transfusion-related adverse events, 58 per million for serious transfusion-related adverse events, and 21 per million for likely fatal transfusion-related adverse events. The routine use of erythropoietin resulted in an absolute risk reduction of 191 per million for all transfusion-related adverse events, 35 per million for serious transfusion-related adverse events, and 12 per million for likely fatal transfusion-related adverse events. The number needed to treat was 5,246 to avoid one transfusion-related adverse event, 28,785 to avoid a serious transfusion-related adverse event, and 81,000 for a likely fatal transfusion-related adverse event. The total cost was \$4,700,000 to avoid one transfusion-related adverse event, \$25,600,000 to avoid one serious transfusion-related adverse event, and \$71,800,000 to avoid a likely fatal transfusion-related adverse event. The magnitude of these results withstood extensive sensitivity analysis.

Conclusions: From the perspective of avoidance of adverse events, erythropoietin does not appear to be an efficient use of limited resources for routine use in critically ill patients. (*Crit Care Med* 2005; 33:497–503)

KEY WORDS: blood transfusion; anemia; costs and cost analysis; pharmacoepidemiology; risk assessment; health resources

A recent study suggests that the use of 40,000 units weekly of recombinant human erythropoietin (EPO) in critically ill patients reduces the need for allogeneic

blood transfusions (1). Patients who were randomized to receive EPO were less likely to undergo a transfusion than those who received placebo (50.5% vs. 60.4%, respectively). Patients in the EPO group also ex-

perienced a 19% decrease in the total units of red blood cells transfused: an average of three transfusions in the placebo group compared with 2.4 in the EPO group. No difference was detected between the groups

*See also p. 672.

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in morbidity and mortality measures (although the study was not powered to detect such differences). Despite the lack of clinical findings, the authors emphasized the direct benefit of reducing the number of transfusions, in terms of a decrease in transfusion-associated adverse events. However, with the advent of better screening techniques, the incidence of transfusion-related infections has been greatly reduced in the past decade (2–4).

The primary reasons to restrict blood transfusions are to protect blood as a scarce resource and to avoid known and unknown transfusion-related adverse events. However, the costs associated with reducing transfusions by substituting treatment with EPO are unknown. To answer this question, a formal analysis of the costs and risks associated with using EPO to reduce transfusions is required (1). The purpose of this study was to assess the number needed to treat (NNT) and the incremental cost required to avoid one transfusion-related adverse event or death by using EPO.

MATERIALS AND METHODS

There were no human subjects associated with our study and, therefore, it is not subject to federal regulations regarding protection of human subjects. We conducted a series of NNT analyses based solely on data collected from previously published sources.

For the primary analysis, we estimated transfusion-related adverse event rates for which there is general consensus regarding the causal nature and for which there are incidence rate data in the peer-reviewed literature. The risks associated with a blood transfusion were quantified using the most recently available published evidence. A PubMed search with MESH headings was conducted to obtain literature regarding various risks of transfusion. This search used the following terms: blood transfusion, hepatitis B, hepatitis C, human immunodeficiency virus, human T-cell lymphotropic virus,

errors, hemolytic reactions, contamination, immunodeficiency, wound infection, acute lung injury, and febrile reactions.

Our base analysis was repeated for each of three categories of adverse events: all known transfusion-related adverse events, serious transfusion-related adverse events, and transfusion-related adverse events that are likely fatal. These are not mutually exclusive categories; however, they represent distinct clinical groupings that deserve separate analysis. An adverse event was considered serious if it was associated with symptomatic acute hemolytic reaction, prolonged intubation lasting >7 days associated with transfusion-related acute lung injury (TRALI), development of a chronic viral disease, receipt of a bacterially contaminated unit of blood, or mortality. All viral and bacterial infections were considered likely fatal. Additionally, fatality rates for cases of TRALI and acute hemolytic reaction were assigned based on recent surveillance data (4–6).

Using estimates from a recent randomized controlled trial, we calculated the absolute risk of an adverse event per course of therapy by multiplying the risk per transfusion by the mean number of transfusions in patients receiving EPO (2.4) and not receiving EPO (3.0), respectively (1). The absolute risk reduction associated with EPO was calculated by taking the difference between the absolute risk per course of therapy with EPO and the absolute risk without EPO. The NNT with EPO to avoid one serious transfusion-related adverse event was calculated by taking the inverse of the absolute risk reduction when using EPO.

Cost calculations were conducted using the following assumptions: the mean number of doses for patients receiving EPO is 2.56; the cost of a 40,000 unit dose of EPO, in 2004 U.S. dollars, is \$420; and the cost of a one unit blood transfusion is \$315 (1). The cost of EPO to avoid one transfusion-related adverse event was calculated by multiplying the NNT by the mean number of EPO doses and by the cost per EPO dose (Table 1). The cost savings generated by EPO via a reduction in blood transfusions was accounted for in the total cost to avoid a transfusion-related adverse event cal-

culated. Total cost to avoid a transfusion-related adverse event was calculated by summing the cost of EPO and the cost of transfusions for all patients. The incremental total cost of using EPO to avoid an adverse event was calculated as the difference between the EPO and non-EPO groups in the total cost (7, 8). The total cost to avoid one transfusion-related adverse event was calculated by multiplying the incremental total cost per patient of using EPO by the NNT to avoid one transfusion-related adverse event. All cost estimates are expressed in 2004 U.S. dollars.

Sensitivity Analyses. To assess the robustness of our calculations to variation in model estimates, we performed a series of sensitivity analyses. First, to assess the impact of variation in known and quantified risks of transfusion, we used the upper and lower bounds of the 95% confidence intervals of the risk of these events as initial variables for sensitivity analysis. The upper and lower sensitivity values for risk were established by simultaneously setting all risk estimates to the upper and lower bounds of their 95% confidence interval, respectively.

The impact of potential adverse events, or events that do not have a strong causal link established and/or no reasonable estimation of incidence can be made (e.g., bacterial infection, immunosuppression, and late-onset malignancies), were assessed in separate sensitivity analyses. For these analyses, the upper bounds of the 95% confidence interval for known risks were first doubled and then quadrupled.

To assess the impact of a potential dose-response relationship between EPO and the requirement for blood transfusions, data from a previous randomized trial in which there was greater EPO use and greater reduction in transfusions were used (9). In this study, patients received on average 190,000 units of EPO (1.9 times the amount in our base case assessment) and experienced a 45.6% reduction in units of blood transfused.

RESULTS

Risk Estimates. The prevalence of TRALI has been estimated to be 0.02%

Table 1. Description of key cost calculations

Cost Category	Derivation
Cost of EPO to prevent one transfusion-related adverse event (drug cost only)	$(\text{NNT}) \times (\text{mean no. of EPO doses per patient}) \times (\text{cost of one 40,000-unit EPO dose})$ $(\text{NNT}) \times (2.56) \times (\$421)$
Total cost to prevent one transfusion-related adverse event (drug + blood cost)	$\text{Drug cost only} + [(\text{NNT}) \times (\text{mean no. of transfusions per EPO patient}) \times (\text{cost of one transfusion})]$ $\text{Drug cost only} + [(\text{NNT}) \times 2.4 \times \$315]$
Incremental cost to avoid one transfusion-related adverse event (drug + blood cost) – (blood cost)	$(\text{Drug} + \text{blood cost}) - [(\text{NNT}) \times (\text{mean no. of transfusions per placebo patient}) \times (\text{cost of one transfusion})]$ $(\text{Drug} + \text{blood cost}) - [(\text{NNT}) \times (3.0) \times (\$315)]$

EPO, erythropoietin; NNT, number needed to treat.

per unit transfused (5, 6, 10). Of these TRALI cases, approximately 20% (40 per million transfusions) result in a serious adverse event, including hypoxemia and pulmonary infiltrates that persist for ≥ 7 days (5, 6). Mortality estimates due to TRALI range from approximately one per 3 million to ten per 1 million transfusions (4, 6). The more conservative one per 3 million mortality rate was used for mortality calculations in this study.

Transfusion-related errors that result in ABO-incompatible blood administration can cause an acute hemolytic reaction, a potentially fatal reaction (10–12). A recent study of transfusion errors in New York State estimated the frequency of all errors to be one in 14,000 units transfused (11). Many of these errors did not result in adverse events, for example, errors resulting from ABO-compatible units. The rate of symptomatic acute hemolytic reaction, the rate used for serious event calculations, was 101 per 9,000,000 units transfused (13 per million). The most recent evidence regarding mortality associated with receipt of ABO-incompatible blood suggests a rate of 1 per 1,700,000 units (4). Delayed hemolytic reactions probably occur more frequently but have less severe clinical sequelae (13).

The risk of viral transmission was estimated based on a recent incidence and prevalence study of Red Cross blood donors (2). This study also used Schrieber and colleagues' (14) method to define residual infection risk attributable to window period infections, allowing calculation of 95% confidence intervals around infection rates. The estimated risk of human immunodeficiency virus (HIV) infection was calculated as 0.7 per million units. The incidences of hepatitis B virus and hepatitis C virus were estimated to be 4.9 and 3.6 per million units, respec-

tively. The risk of human T-cell lymphotropic virus was estimated to be 0.3 per million red blood cell units. All viral infections were considered serious and potentially fatal.

The incidence of transfusion-transmitted bacterial infections was estimated from a recent study based on a prospective reporting system created by the American Red Cross, the Centers for Disease Control, and the Department of Defense (15). From 1998 through 2000, five confirmed cases of transfusion-transmitted bacterial infection occurred from a total of 23,711,169 units transfused (0.2 cases per million units).

To calculate the risk of all, serious, and likely fatal adverse events, we summed these incidence estimates (Table 2). The estimated combined risk of transfusion-related adverse events for the three risk strata in our study were as follows: 318 transfusion-related adverse events per million transfusions, 58 serious events per million transfusions, and 21 likely fatal events per million transfusions.

Absolute Risk Reduction, NNT, and Cost. Assuming transfusion rates of 2.4 for patients treated with EPO and three per patient with no EPO treatment (1), two patients need to be treated with EPO to avoid one blood transfusion at a cost of \$2,154.

The absolute risk of any transfusion-related adverse event per course of therapy for patients receiving EPO was estimated to be 762 per million, compared with 953 per million courses of therapy for those not receiving EPO (Table 3). Therefore, the absolute risk reduction for all adverse events associated with EPO therapy was estimated to be 191 per million courses of therapy. The NNT to avoid one transfusion-related adverse event was 5,246. The cost of EPO to avoid one

transfusion-related adverse event was \$5,649,942. When considering the reduced need for transfusions in patients treated with EPO, the total cost to avoid one transfusion-related adverse event was \$4,656,773.

The risk of a serious transfusion-related adverse event per course of therapy was estimated to be 139 per million for EPO-treated patients and 174 per million for those without EPO treatment (Table 3). Consequently, the absolute risk reduction of serious transfusion-related adverse events was 35 per million courses of therapy, and the NNT to avoid one such event was 28,785 patients. The cost of EPO to avoid one serious event was \$31,001,497. When we factored in the reduced need for transfusions, the total cost to avoid one adverse event in patients treated with EPO was \$25,551,929.

For likely fatal transfusion-related adverse events, the estimated risk per course of therapy for EPO-treated patients was 49 per million and for patients who do not receive EPO 62 per million (Table 3). The absolute risk reduction of using EPO for likely fatal events is 12 per million courses of therapy, resulting in an NNT of approximately 81,000. The cost of EPO to avoid a likely fatal event was \$87,135,275; and the net cost accounting for reduced transfusions was \$71,818,285.

Sensitivity Analyses. Complete results from all sensitivity analyses can be found in Table 4. When we used the lower and upper bounds of the 95% confidence intervals for risk estimates, the NNT and cost to avoid a serious adverse event ranged from approximately 16,762 to 67,833 and \$14.9 million to \$60.2 million, respectively. The NNT and cost to avoid a likely fatal event ranged from 34,875 to 1,089,325 and \$31 million to \$968 million, respectively.

When we accounted for unknown or

Table 2. Estimated risks associated with allogeneic blood transfusion

Risk Factor	Incidence of All Events Per Million (95% CI)	Incidence of Serious Events Per Million (95% CI)	Incidence of Potentially Fatal Events Per Million (95% CI)	References
Transfusion-related acute lung injury	184.9 (125, 245)	37 (10, 64)	0.3 (0, 0.7)	4–6
Delayed hemolytic reactions	110 (22, 198)	0 n/a	0 n/a	4, 13
Acute hemolytic reactions	13.1 (11, 16)	11.2 (9, 13)	0.6 (0, 1.3)	4, 11
Hepatitis B virus	4.9 (2.7, 7.9)	4.9 (2.7, 7.9)	4.9 (2.7, 7.9)	2, 4
Hepatitis C virus	3.6 (2.4, 11.2)	3.6 (2.4, 11.2)	3.6 (2.4, 11.2)	2, 4
Human immunodeficiency virus	0.7 (0.2, 1.9)	0.7 (0.2, 1.9)	0.7 (0.2, 1.9)	2, 4
Human T-cell lymphotropic virus	0.3 (0.2, 0.6)	0.3 (0.2, 0.6)	0.3 (0.2, 0.6)	2, 4
Bacterial infection	0.2 (0, 0.4)	0.2 (0, 0.4)	0.2 (0, 0.4)	4, 15, 45
Total	317.7 (163, 481)	57.9 (25, 99)	20.6 (1, 48)	

CI, confidence interval.

unquantified risks by quadrupling the upper bound of the risk estimate, the NNT was $\geq 4,188$ for serious adverse events and 8,726 for likely fatal events. Costs associated with these estimates were \$3.7 million for serious events and \$7.7 million for likely fatal events. The relationship between absolute risk reduction by using EPO, which is dependent on the risk of a transfusion, and NNT and total cost is summarized in Figure 1.

Using EPO dosing and response from a previous randomized trial (9), approximately 10,000 patients would need to be treated with EPO at a cost of \$14.5 million to avoid a serious adverse event. Approximately 28,000 would need to be treated at a cost of \$40.8 million to avoid a likely fatal adverse event.

DISCUSSION

The main finding of our analysis was that 5,246 patients need to be treated at our institution at a cost approaching \$5,000,000 to avoid one transfusion-related adverse event as a result of EPO therapy. These findings were magnified greatly when the outcome of interest was avoiding a serious or likely fatal transfusion-related adverse event; >25,000 patients need to be treated at costs exceeding \$25,000,000. Although the direction of the findings was expected, their magnitude was surprisingly large.

The growing cost of pharmaceuticals puts financial pressure on institutions and, therefore, increases the need for rational resource utilization. In an environment of unlimited resources, any inter-

vention that provides a net benefit should be performed regardless of the cost. However, resources are constrained in reality, and therefore the efficiency whereby they are expended must be explicitly considered to optimally deploy the resources. Expenditures become more efficient as greater benefit is derived from them. Although the study conducted by Corwin and colleagues (1) showed a reduction in number of transfusions when using EPO, there was no significant difference in morbidity or mortality outcomes between treatment groups. Our analysis provides a gauge of efficiency by explicitly calculating costs and, in terms of transfusion-related adverse events avoided, of using EPO in the critically ill.

The formal quantification of the costs associated with reducing the risk of blood transfusions in our analysis gives important context to the expectation of "zero-risk" transfusions. This expectation of zero-risk has driven the search for better, yet more costly, interventions (16, 17). However, some have questioned the efficiency of paying for further gains in the safety of the blood supply, given the current low level of risk (16–20). When the cost-effectiveness of interventions to improve blood safety has been formally assessed, they have not been found cost-effective compared with other commonly used medical interventions (3, 21–23). One author has even questioned the appropriateness of using a prevented transfusion as an outcome measure, while suggesting that improved morbidity and mortality are more appropriate measures (17). This situation is not unlike the famed sixth stool guaiac example, which demonstrated that the law of diminishing returns has a surprisingly large economic impact for medical interventions (24). In

Table 3. Summary of overall transfusion-related adverse event calculations

Variable	No EPO	EPO
All adverse events		
Risk of event per million transfusions	318	318
Mean no. of transfusions per course of therapy	3.0	2.4
Risk of reaction per million courses of therapy	953	762
Absolute risk reduction per million courses of therapy	NA	191
No. needed to treat to avoid one transfusion-related adverse event	NA	5,246
Serious adverse events		
Risk of serious event per million transfusions	58	58
Mean no. of transfusions per course of therapy	3.0	2.4
Risk of serious event per million courses of therapy	174	139
Absolute risk reduction per million courses of therapy	NA	35
No. needed to treat to avoid one serious transfusion-related adverse event	NA	28,785
Likely fatal adverse events		
Risk of likely fatal event per million transfusions	21	21
Mean no. of transfusions per course of therapy	3.0	2.4
Risk of likely fatal event per million courses of therapy	62	49
Absolute risk reduction per million courses of therapy	NA	12
No. needed to treat to avoid one likely fatal transfusion-related adverse event	NA	80,906

EPO, erythropoietin; NA, not applicable.

Table 4. No. needed to treat (NNT) and total cost to avoid one transfusion-related adverse event: Results from sensitivity analyses

Analysis	Any Adverse Event		Serious Adverse Events		Likely Fatal Adverse Events	
	NNT	Total Cost (Millions)	NNT	Total Cost (Millions)	NNT	Total Cost (Millions)
Base case analysis	5,246	\$4.7	28,785	\$25.6	80,906	\$71.8
Upper bound of risk estimates	3,467	\$3.1	16,762	\$14.9	34,875	\$31
Lower bound of risk estimates	10,238	\$9.1	67,833	\$60.2	1,089,325	\$968
Double upper bound of risk	1,733	\$1.5	8,381	\$7.4	17,437	\$15.4
Quadruple upper bound of risk	867	\$0.8	4,188	\$3.7	8,726	\$7.7
Dose EPO 300 units/kg \times 5 days, 46% reduction in transfusions	1,812	\$2.6	9,937	\$14.5	27,966	\$40.8
50% reduction in mean number of transfusions (EPO dose 40,000 units per week)	2,098	\$1.3	11,514	\$6.9	32,362	\$19.5

EPO, erythropoietin.

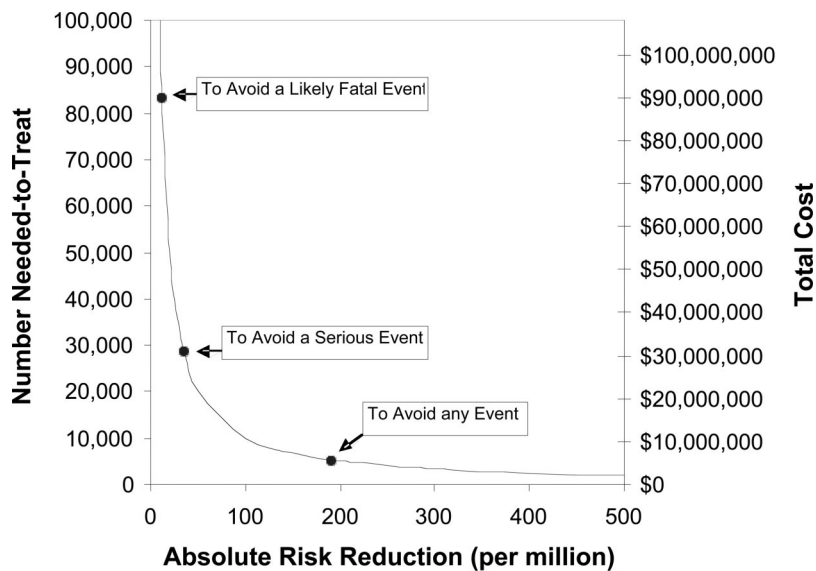


Figure 1. Relationship between absolute risk reduction and the number needed to treat and total cost to avoid one transfusion-related adverse event.

this example, the cost of identifying an additional case of cancer became exponentially more expensive when, according to American Cancer Society guidelines, up to six sequential guaiac stool tests were conducted. To find one case of cancer in patients who had five negative tests cost >\$132,000,000 (2004 U.S. dollars). The American Cancer Society changed their recommendation after this article was published. Likewise, we believe that although zero-risk transfusions is optimal in principle, the economic inefficiency of reaching this goal cannot be ignored. In the absence of morbidity or mortality benefit of EPO in this population, greater overall patient benefit could be realized by redeploying resources elsewhere.

Future efforts should attempt to identify populations that may derive maximal benefit from EPO therapy. A recent abstract suggested that long-term critically ill patients experience a 50% reduction in the total number of units transfused when treated with 40,000 units EPO weekly compared with placebo (40 vs. 85) (25). Additionally, there was a nonstatistically significant improvement in mortality in patients treated with EPO. This preliminary evidence suggests that EPO may have a greater benefit in the long-term critically ill. If the increased effect maintains durability in larger studies, the challenge will shift to identifying critically ill patients who will require a long-term stay. Although it has been shown that clinicians can predict who will stay 3

days quite routinely, this is difficult to predict on admission for longer term patients who may stay in the ICU for months (26). Other populations that are reasonable candidates for EPO therapy include patients with either acute or chronic renal failure on renal replacement therapy, for whom EPO has become the standard of care. Patients who are Jehovah's Witnesses may also benefit by using EPO to help maintain higher hemoglobin levels that would obviate the need for transfusion. We also encourage a multiple-prong approach to the reduction of risk from transfusion that includes adhering to a transfusion threshold such as suggested by Hebert et al. (27) and reduction in blood waste and lab draws.

Our analysis has several limitations. Although accounting for all potential adverse events would be ideal, sufficient data regarding the incidence of potential adverse events, such as transfusion-related immunomodulation, infection, and cancer recurrence, are not available. Therefore, our base analysis does not consider the impact of these potential events. To best account for these potential effects, we conducted sensitivity analyses that increased the incidence of transfusion-related adverse events up to four times the upper limit of the 95% confidence interval of known adverse events. As new data become available regarding these potential adverse events, this analysis should be repeated. Nevertheless, our study is based on the best available evi-

From the perspective of avoidance of adverse events, erythropoietin does not appear to be an efficient use of limited resources for routine use in critically ill patients.

dence, which is indeterminate regarding the presence and incidence of these potential adverse events (28–41).

Our analysis did not compare EPO to other blood safety interventions, such as universal leukoreduction and improved HIV and hepatitis C virus testing. The cost and effect of these interventions relative to EPO have not been formally assessed. However, such comparisons assess the value of these interventions relative to each other and not the more basic question of their worth compared with doing nothing. For example, if intervention A is cost-effective compared with intervention B, it could still be the case that neither is an efficient use of resources. In any case, such comparisons of relative value are beyond the scope of this article and do not affect the results contained herein.

Our study did not account for the fact that blood is a limited resource and as such conservation is a worthwhile goal. Although this is indisputable, the economic value of this precious resource above and beyond acquisition cost is difficult to quantify. We also recognize that our analysis does not include other interventions that may reduce the risk of transfusions, such as leukoreduction and advanced blood screening procedures. The results of the current analysis may be put in a new context as data become available regarding the costs and effectiveness of these interventions and how they interact with EPO treatment to further reduce risk. Evidence has emerged recently that new pathogens such as the West Nile virus may be transmitted via blood products (42–44). The transmission of West Nile virus is highly variable based on geography and time of year. Therefore, we were unable to quantify a useful risk estimate for West Nile virus transmission. However, the sensitivity

analyses cover the range of transmission, morbidity, and mortality reported in the literature. Our analysis did not account for the societal cost of transfusion-related adverse events. Nevertheless, it is unlikely that any adverse event, including death, would be valued as high as the cost to avoid one adverse event in our analysis. For example, a recent study of HIV infection estimated the total lifetime cost for a newly infected patient to be approximately \$270,000 (2004 U.S. dollars, adjusted using medical care services component of the Consumer Price Index) (14). As data regarding societal costs and effectiveness become available, a formal assessment of the cost-effectiveness of using EPO should be conducted. Finally, our study is highly reliant on data from one randomized trial.

CONCLUSIONS

From the perspective of avoidance of transfusion-related adverse events, the use of EPO to reduce the need for blood transfusion in critically ill patients is associated with a high NNT and cost to avoid one transfusion-related adverse event and, as such, its routine use for this purpose is not recommended.(45)

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REFERENCES

- Corwin HL, Gettinger A, Pearl RG, et al: Efficacy of recombinant human erythropoietin in critically ill patients. *JAMA* 2002; 288: 2827-2835
- Dodd RY, Notari EP, Stramer SL: Current prevalence and incidence of infectious disease markers and estimated window-period risk in the American Red Cross blood donor population. *Transfusion* 2002; 42:975-979
- Jackson BR, Busch MP, Stramer SL, et al: The cost-effectiveness of NAT for HIV, HCV, and HBV in whole-blood donations. *Transfusion* 2003; 43:721-729
- Linden JV, Tourault MA, Scribner CL: Decrease in frequency of transfusion fatalities. *Transfusion* 1997; 37:243-244
- Popovsky MA, Chaplin HC, Moore SB: Transfusion-related acute lung injury: A neglected, serious complication of hemotherapy. *Transfusion* 1992; 32:589-592
- Popovsky MA, Moore SB: Diagnostic and pathogenetic considerations in transfusion-related acute lung injury. *Transfusion* 1985; 25:573-577
- Gold MR, Siegel JE, Russell LB, et al: Cost-Effectiveness in Health and Medicine. New York, Oxford University Press, 1996
- Drummond MF, O'Brien B, Stoddart GL, et al: Methods for the Economic Evaluation of Health Care Programmes. Second Edition. Oxford, UK, Oxford Medical Publications, 1997
- 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; 27:2346-2350
- Goodnough LT: Risks of blood transfusion. *Crit Care Med* 2003; 32(12 suppl):S678-S686
- Linden JV, Wagner K, Voytovich AE, et al: Transfusion errors in New York State: An analysis of 10 years' experience. *Transfusion* 2000; 40:1207-1213
- Myhre BA, McRuer D: Human error—A significant cause of transfusion mortality. *Transfusion* 2000; 40:879-885
- Ness PM, Shirey RS, Thoman SK, et al: The differentiation of delayed serologic and delayed hemolytic transfusion reactions: Incidence, long-term serologic findings, and clinical significance. *Transfusion* 1990; 30: 688-693
- Schreiber GB, Busch MP, Kleinman SH, et al: The risk of transfusion-transmitted viral infections. *N Engl J Med* 1996; 334: 1685-1690
- Kuehnert MJ, Roth VR, Haley NR, et al: Transfusion-transmitted bacterial infection in the United States, 1998 through 2000. *Transfusion* 2001; 41:1493-1499
- Klein HG: Will blood transfusion ever be safe enough? *JAMA* 2000; 284:238-240
- Carson JL: Should patients in intensive care units receive erythropoietin? *JAMA* 2002; 288:2884-2886
- AuBuchon JP, Birkmeyer JD, Busch MP: Safety of the blood supply in the United States: Opportunities and controversies. *Ann Intern Med* 1997; 127:904-909
- Dzik S, Aubuchon J, Jeffries L, et al: Leukocyte reduction of blood components: Public policy and new technology. *Transfus Med Rev* 2000; 14:34-52
- Berman KE: Expensive blood safety technologies: Understanding and managing cost and access-to-care issues. *Transfus Med Rev* 2004; 18:1-10
- AuBuchon JP, Birkmeyer JD, Busch MP: Cost-effectiveness of expanded human immunodeficiency virus-testing protocols for donated blood. *Transfusion* 1997; 37:45-51
- Sonnenberg FA, Gregory P, Yomtovian R, et al: The cost-effectiveness of autologous transfusion revisited: Implications of an increased risk of bacterial infection with allogeneic transfusion. *Transfusion* 1999; 39: 808-817
- Cohen BJ, Field AM, Gudnadottir S, et al: Blood donor screening for parvovirus B19. *J Virol Methods* 1990; 30:233-238
- Neuhauser D, Lweicki AM: What do we gain from the sixth stool guaiac? *N Engl J Med* 1975; 293:226-228
- Silver M, Bazan A, Corwin H, et al: Randomized double blind placebo controlled trial of recombinant human erythropoietin in long term acute care patients. *Crit Care Med* 2002; 30(12 suppl):A153
- Pelz RK, Hendrix CW, Swoboda SM, et al: Double-blind placebo-controlled trial of fluconazole to prevent candidal infections in critically ill surgical patients. *Ann Surg* 2001; 233:542-548
- 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: 409-417
- Taylor RW, Manganaro L, O'Brien J, et al: Impact of allogeneic packed red blood cell transfusion on nosocomial infection rates in the critically ill patient. *Crit Care Med* 2002; 30:2249-2254
- Shorr AF, Duh MS, Kelly KM, et al: Red blood cell transfusion and ventilator-associated pneumonia: A potential link? *Crit Care Med* 2004; 32:666-674
- Houbiers JG, Brand A, van de Watering LM, et al: Randomised controlled trial comparing transfusion of leucocyte-depleted or buffy-coat-depleted blood in surgery for colorectal cancer. *Lancet* 1994; 344:573-578
- Jensen LS, Hokland M, Nielsen HJ: A randomized controlled study of the effect of bedside leucocyte depletion on the immunosuppressive effect of whole blood transfusion in patients undergoing elective colorectal surgery. *Br J Surg* 1996; 83:973-977
- Jensen LS, Kissmeyer-Nielsen P, Wolff B, et al: Randomised comparison of leucocyte-depleted versus buffy-coat-poor blood transfusion and complications after colorectal surgery. *Lancet* 1996; 348:841-845
- Houbiers JG, van de Velde CJ, van de Watering LM, et al: Transfusion of red cells is associated with increased incidence of bacterial infection after colorectal surgery: A prospective study. *Transfusion* 1997; 37: 126-134
- Thomas D, Wareham K, Cohen D, et al: Autologous blood transfusion in total knee replacement surgery. *Br J Anaesth* 2001; 86: 669-673
- Jensen LS, Andersen AJ, Christiansen PM, et al: Postoperative infection and natural killer cell function following blood transfusion in patients undergoing elective colorectal surgery. *Br J Surg* 1992; 79:513-516
- Heiss MM, Mempel W, Jauch KW, et al: Beneficial effect of autologous blood transfusion on infectious complications after colorectal cancer surgery. *Lancet* 1993; 342:1328-1333
- Vamvakas EC, Blajchman MA: Deleterious clinical effects of transfusion-associated im-

- munomodulation: Fact or fiction? *Blood* 2001; 97:1180–1195
38. Busch OR, Hop WC, Hoyneck van Papendrecht MA, et al: Blood transfusions and prognosis in colorectal cancer. *N Engl J Med* 1993; 328:1372–1376
 39. Farrer A, Spark JI, Scott DJ: Autologous blood transfusion: The benefits to the patient undergoing abdominal aortic aneurysm repair. *J Vasc Nurs* 1997; 15:111–115
 40. van de Watering LM, Hermans J, Houbiers JG, et al: Beneficial effects of leukocyte depletion of transfused blood on postoperative complications in patients undergoing cardiac surgery: A randomized clinical trial. *Circulation* 1998; 97:562–568
 41. Talbot TR, D'Agata MC, Brinsko V, et al: Perioperative blood transfusion is predictive of poststernotomy surgical site infection: marker for morbidity or true immunosuppressant? *Clin Infect Dis* 2004; 38:1378–1382
 42. Biggerstaff BJ, Petersen LR: Estimated risk of transmission of the West Nile virus through blood transfusion in the US, 2002. *Transfusion* 2003; 43:1007–1017
 43. Pealer LN, Marfin AA, Petersen LR, et al: Transmission of West Nile virus through blood transfusion in the United States in 2002. *N Engl J Med* 2003; 349:1236–1245
 44. Petersen LR, Marfin AA: West Nile virus: A primer for the clinician. *Ann Intern Med* 2002; 137:173–179
 45. Red blood cell transfusions contaminated with *Yersinia enterocolitica*—United States, 1991–1996, and initiation of a national study to detect bacteria-associated transfusion reactions. *MMWR Morb Mortal Wkly Rep* 1997; 46:553–555

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The Guidelines and Practice Parameters developed by the American College of Critical Care Medicine are now available online at http://www.sccm.org/professional_resources/guidelines/index.asp. The printed version of the Guidelines, provided in a binder, is also available through the SCCM Bookstore, located at <http://www.sccm.org/pubs/sccmbookstore.html>. Please watch the Website to stay updated on the ACCM Guidelines and Practice Parameters.