Cost-Effectiveness of Transfusion of Platelet Components Prepared with Pathogen Inactivation Treatment in the United States

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ABSTRACT

Background: The Intercept Blood System (IBS) for platelets has been developed to reduce pathogen transmission risks during transfusions.

Objective: This study was a comprehensive economic analysis of the cost-effectiveness of using the IBS for single-donor apheresis platelets (AP) and random-donor pooled platelet concentrates (PC) versus AP and PC without the IBS in the United States in patient populations in which platelets are commonly transfused.

Methods: All data used in this analysis were summarized from existing published sources (primarily indexed in MEDLINE) and data on file at Baxter Healthcare Corporation (Chicago, Illinois) and Cerus Corporation (Concord, California). A literature-based decision-analytic model was developed to assess the economic costs and clinical outcomes associated with the use of AP and PC treated with the IBS for several conditions and procedures that account for a considerable proportion of the platelet usage in the United States: acute lymphocytic leukemia, non-Hodgkin's lymphoma, coronary artery bypass graft, and hip arthroplasty. Risks of infection with HIV, hepatitis C virus (HCV), hepatitis B virus, human T-cell lymphotropic virus type 1, or bacterial agents were incorporated into the model. Possible benefits of reduction of the risk of emerging HCV-like pathogens and elimination of the need for gamma irradiation were explored in sensitivity analyses.

Results: The incremental cost per quality-adjusted life-year gained by using AP + IBS versus untreated AP ranged from $1,308,833 to $4,451,650 (without bacte-

rial testing) and $4,759,401 to $22,968,066 (with bacterial testing). Corresponding figures for PC + IBS versus untreated PC ranged from $457,586 to $1,816,060. Inclusion of emerging HCV-like virus and the elimination of the need for gamma irradiation improved the cost-effectiveness to a range of $177,695 to $1,058,127 for AP without bacterial testing, $176,572 to $1,330,703 for AP with bacterial testing, and $22,888 to $153,564 for PC. The model was most likely to be affected by mortality from bacterial contamination, IBS effect on platelet utilization, and the inclusion of potential benefits (ie, gamma irradiation and/or emergent HCV-like virus). The model was relatively insensitive to changes in the IBS price and viral transmission risks.

Conclusions: The cost-effectiveness of pathogen inactivation via the IBS for platelets is comparable to that of other accepted blood safety interventions (eg, nucleic acid amplification technology). The IBS for platelets may be considered a desirable strategy to increase the safety of platelet transfusions and a potential insurance against the threat of emerging pathogens. (*Clin Ther.* 2003;25:2464–2486) Copyright © 2003 Excerpta Medica, Inc.

Key words: pathogen inactivation, transfusion risks, cost-effectiveness, platelet.

INTRODUCTION

The safety of blood transfusions has been a major concern of health care policy makers, especially when faced with the risk of transmission of infectious blood-borne pathogens such as HIV, hepatitis C virus (HCV), hepatitis B virus (HBV), human T-cell lymphotropic virus type 1 (HTLV-1), and bacteria.[1] Measures to reduce transfusion-transmission risks include donor screening/education strategies, laboratory testing (eg, nucleic acid amplification technology [NAT], HIV p24 antigen test), preoperative autologous donation, limitation of donor exposure by use of single-donor apheresis platelets (AP), and leukocyte reduction.

The benefits of these measures have been realized in the form of a reduction in the risk of transmission of infectious pathogens.[1] However, these measures have limitations, and there remains a residual risk attributable to window-period donations.[2–4] For instance, the residual risk of transmission has been estimated at 1 per 734,000 to 2,135,000 units for HIV and 1 per 138,000 to 1,935,000 units for HCV, depending on donor status.[3]

Perhaps of greater concern is the challenge of protection of blood components, particularly platelets, from bacterial contamination.[5] Platelets, which are stored at room temperature, offer a nutrient-rich environment in which bacteria can multiply. Although laboratory tests to detect bacterial contamination of platelets exist, they are not routinely performed. The overall incidence of transfusion-related sepsis (TRS) due to bacterial contamination of platelets is relatively high: in 3

recent surveillance studies, the death rates due to bacterial contamination of platelets were reported to range from 2 to 15 per million units with AP and 2 to 62 per million units with random-donor pooled platelet concentrates (PC).[6–8]

Pathogen inactivation treatment with the Intercept Blood System* (IBS) for platelets is a new technology aimed at enhancing the safety of platelet transfusions. The IBS inactivates a broad spectrum of viruses, bacteria, and parasites present in platelet components by targeting the DNA and RNA in the pathogen and forming irreversible crosslinks, thus preventing pathogen replication.[9–11] The process is effective against pathogens but does not affect in vitro and in vivo platelets that do not require genetic material to function. Use of treated platelets may substantially reduce both the risk of pathogen transmission and the risk of TRS due to bacterial contamination. Furthermore, use of platelets processed with a pathogen inactivation treatment may protect future platelet recipients from emerging pathogens for which donor screening may be ineffective or for which there are no tests. Because of concomitant use of other blood products, such as red blood cells and plasma (which are often administered with platelets), transfusion risks are not entirely eliminated. However, ongoing advanced clinical trials[12,13] are investigating pathogen inactivation treatment of red blood cells[11] and plasma.[12]

When faced with the decision of whether to adopt new treatment strategies such as the IBS, health care policy makers must balance the competing interests of public safety and efficient use of health care resources. Although an improvement in the overall safety of platelet transfusions may result from the use of the IBS for platelets, the benefits of such a system presumably would be achieved at an extra cost. Cost-effectiveness analysis—assessing the net changes in costs and outcomes of medical interventions—has become an accepted method for the comparison of medical interventions and the guidance of decisions on the most efficient use of health care resources.[14] Therefore, we conducted a comprehensive economic analysis of the cost-effectiveness of using the IBS for platelets for AP and PC versus untreated AP and PC in the United States in patient populations in which platelets are commonly transfused.

MATERIALS AND METHODS
Model Overview
All data used in this analysis were summarized from existing published sources (primarily indexed in MEDLINE) and data on file at Baxter Healthcare Corporation (Chicago, Illinois) and Cerus Corporation (Concord, California). A literature-based decision-analytic model was developed to assess the economic costs and clinical outcomes associated with the use of AP and PC treated with the IBS for platelets (AP + IBS and PC + IBS). The current analysis expanded on the previ-

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*Trademark of Baxter Healthcare Corporation (Chicago, Illinois) and Cerus Corporation (Concord, California).

ously published decision-analytic model developed by Lopez-Plaza et al[15] in which the incremental cost (dollars/quality-adjusted life-year [QALY]) associated with the use of AP versus PC was evaluated. Similarly, this study simulated the possible transfusion-related events and outcomes in the patient populations that account for most platelet use in the United States. Specifically, the 2000 Health-care Cost and Utilization Project (HCUP) data[16] and other sources[17] suggest that hematology/oncology, cardiovascular, and orthopedic treatment procedures or surgeries account for ~76% of the total platelet use in the United States. There-fore, patients undergoing hematopoietic progenitor cell transplant (HPCT) for acute lymphocytic leukemia (ALL) and non-Hodgkin's lymphoma (NHL), patients undergoing coronary artery bypass graft (CABG), and patients undergoing a hip arthroplasty were chosen as representative of patients who commonly receive platelet transfusions.[17,18] Correspondingly, 4 reference patients were selected to represent the populations of all patients undergoing each procedure in the United States as reported in the 2000 HCUP[16]: (1) a 10-year-old boy undergoing HPCT for ALL (similar to the patient population included in the HCUP [60% male; mean age, 9 years]); (2) a 50-year-old man undergoing HPCT for NHL (similar to the patient population included in the HCUP [63% male; mean age, 45 years]); (3) a 60-year-old man undergoing CABG (similar to the patient population in-cluded in the HCUP [71% male; mean age, 64 years]); and (4) a 70-year-old woman undergoing a hip arthroplasty (similar to the patient population included in the HCUP [64% female; mean age, 65 years]) (Table I).[15,19–23]

A decision tree (Figure 1) was constructed for patients receiving AP + IBS versus AP without IBS. An identical decision tree was constructed for analysis of PC + IBS versus PC without IBS. The baseline model included the current risks of infection with HIV, HCV, HBV, HTLV-1, or bacterial agents for each platelet-donor exposure. The model simulated subsequent transfusion-related events and

Table I. Excess annual mortality rates and quality-adjusted life-year (QALY) weights of underlying indications in the United States.[15,19–23]

Indication	Year 1*		Subsequent Years	
	Mortality	QALY Weight	Mortality	QALY Weight
Pediatric ALL	0.06	0.75	0.00	0.95
NHL	0.53	0.75	0.05	0.95
CABG	0.03	0.90	0.03	0.95
Hip arthroplasty	0.00	0.95	0.00	0.95

ALL = acute lymphocytic leukemia; NHL = non-Hodgkin's lymphoma; CABG = coronary artery bypass graft.
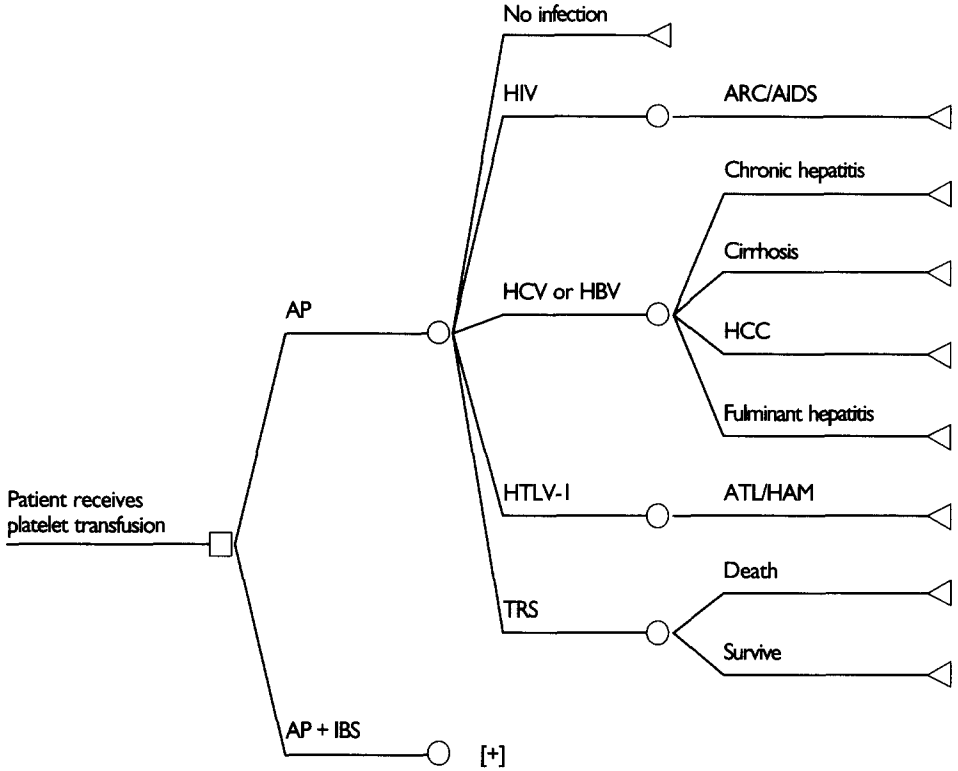*For pediatric ALL, years 1 to 3.

Figure 1. Simplified illustration of decision tree for pathogen inactivation in patients undergoing platelet transfusion. ARC = AIDS-related complex; AP = single-donor apheresis platelets; HCV = hepatitis C virus; HBV = hepatitis B virus; HCC = hepatocellular carcinoma; HTLV-I = human T-cell lymphotropic virus type I; ATL = adult T-cell lymphoma; HAM = HTLV-I–associated myelopathy; TRS = transfusion-related sepsis; AP + IBS = pathogen-inactivated AP via the Intercept Blood System (trademark of Baxter Healthcare Corporation, Chicago, Illinois, and Cerus Corporation, Concord, California); [+] = repetition of subtree (as shown for AP).

outcomes, as well as events that would occur naturally; patients may experience morbidity and mortality due to several causes (eg, their underlying disease, transfusion-related complications, general mortality of populations of same age and sex).

Clinical outcomes resulting from underlying disease and transfusion-related complications were assigned a treatment cost and utility. Life expectancy estimates were calculated using the declining exponential approximation of life expectancy method[24,25] and took into consideration competing mortality from

disease-specific and naturally occurring causes. The excess annual mortality rates and QALY weights (utility) for the study populations are presented in Table I.

The direct medical costs attributable to the use of AP + IBS and PC + IBS (as well as the present value of future costs attributable to treating transfusion-related complications) were incorporated in the baseline model. No indirect costs (eg, work productivity losses) were considered. Projected economic costs and health benefits in future years were discounted at 3% per annum, consistent with current practice.

The model then estimated the incremental cost and health benefit (ie, QALY) of using AP + IBS and PC + IBS versus untreated AP and PC, respectively. The incremental cost-effectiveness ratio (ICER) was then calculated as $(cost^{AP+IBS} - cost^{AP})/(QALY^{AP+IBS} - QALY^{AP})$, representing (in this case) the incremental cost per QALY gained of using AP + IBS versus untreated AP.

Table II. Risks for acquiring transfusion-transmitted pathogens and associated outcomes in the United States.

Variable	Baseline Value	Range
Virus transmission risk per unit* (1/X)		
HIV[3]	1,738,599	869,299–2,607,898[†]
HCV[3]	1,575,733	787,866–2,363,599[†]
HBV[3]	166,938	83,469–250,407[†]
HTLV-I[3]	2,437,296	1,218,648–3,655,944[†]
Deaths per million due to bacterial contamination (X/1,000,000)		
AP		
Without bacterial testing[6–8]	10	2–15
With bacterial testing[26,27]	1	0.1–2
PC[6–8]	17	2–62
Probability of disease outcome given transfusion event		
ARC/AIDS[15]	1.00	NA
HCV/HBV		
Chronic HCV[28,29]	0.850	0.690–0.880
Chronic HBV[30,31]	0.100	0.020–0.200
Cirrhosis[32–34]	0.200	0.050–0.350
HCC[29,35,36]	0.050	0.010–0.200
Fulminant infection[37,38]	0.010	0.001–0.010
HTLV-I, ATL/HAM[15,39,40]	0.040	0.020–0.060[†]

HCV = hepatitis C virus; HBV = hepatitis B virus; HTLV-I = human T-cell lymphotropic virus type I; AP = single-donor apheresis platelets; PC = random-donor pooled platelet concentrates; ARC = AIDS–related complex; HCC = hepatocellular carcinoma; ATL = adult T-cell lymphoma; HAM = HTLV-I–associated myelopathy.
*Weighed by 0.228 for repeat donors and 0.772 for first-time donors.
[†]±50% of baseline value.

Pathogen-Transmission Risk and Subsequent Outcomes

The risks for acquiring transfusion-transmitted pathogens were derived from published data (Table II).[3,6–8,15,26–40] For baseline values, the weighted mean risks for first-time donors and repeat donors were used. A recent study[3] stated that the viral transmission risks from first-time donors were ~2 times greater than those from repeat donors. In addition, it was estimated that 22.8% of donations were from first-time donors.[3] Therefore, the risks reported in that study were weighted by 0.228 and 0.772, respectively (Table II).

The subsequent outcome of transfusion-acquired HIV infection was AIDS-related complex, with a time to symptom onset of 5 years. Transfusion-acquired HCV or HBV outcomes were categorized into 4 groups: chronic hepatitis, cirrhosis, hepatocellular carcinoma (HCC), and fulminant hepatitis. Chronic hepatitis and fulminant hepatitis were assumed to occur in the year that transfusion was received. Cirrhosis and HCC onset were assumed to occur 15 years after transfusion. Adult T-cell leukemia/lymphoma or HTLV-1–associated myelopathy was the subsequent outcome of transfusion-acquired HTLV-1, with a time to symptom onset of 3 years. Probabilities of developing the above disease outcomes were estimated from the literature (Table II),[3,6–8,15,26–40] as were the quality-of-life impact and mortality estimates attributable to the subsequent outcomes of transfusion-acquired sequelae (Table III).[15,29,31,34,38,41–47]

The cumulative death rate was used to reflect the impact of bacterial contamination. Several studies have reported the death rates per million due to bacteria-contaminated blood transfusion.[6–8] The death rates per million for bacterial contamination were calculated as a weighted mean by sample size,[7,8] which were 10 per million for AP and 17 per million for PC (Table II). The BaCon study[6] was excluded from these calculations because its risk underestimation was well recognized and its large sample size would bias the weighted mean. However, its data were used as the low bound in the sensitivity analysis to generate the most conservative estimate (2 deaths per million for both AP and PC). The data from a study from Johns Hopkins[7] served as the high bound in the sensitivity analysis (15 and 62 deaths per million for AP and PC, respectively).

We expect the planned introduction of bacterial screening for AP in the United States in the near future to reduce the risk of bacterial contamination and TRS mortality. An alternative baseline scenario was developed that assumed that bacterial screening was widely used for AP and replaced by the IBS. Bacterial testing was assumed to cost $30 per dose of platelets and reduced mortality from bacterial contamination by 90% (ie, 1 death per million remained) with a range of 80% to 99% (ie, 0.1–2 deaths per million remained) for AP.[26,27]

Table III. Excess annual mortality rates and quality-adjusted life-year (QALY) weights attributable to the subsequent outcomes of transfusion-related sequelae in the United States.

Variable	Baseline Value	Range
Annual mortality		
ARC/AIDS[15]	0.10	0.05–0.15*
HCV/HBV		
Chronic infection[29,41]	0.02†	0.00–0.04*
Cirrhosis[31]	0.20†	0.15–0.25
HCC[42–44]	0.80	0.33–1.00
Fulminant infection[38]	1.00	N/A
HTLV-1, ATL/HAM[15]	0.10	0.05–0.15*
QALY weights		
HIV/AIDS[45]	0.76	0.60–1.00
HCV/HBV		
Chronic infection[42–44,46]	0.88	0.60–1.00
Cirrhosis[34,42]	0.80	0.30–0.90
HCC[34,42–44]	0.25	0.02–0.50
Fulminant infection[15]	0.00	N/A
HTLV-1, ATL/HAM[15,47]	0.75	0.75–0.98

ARC = AIDS–related complex; HCV = hepatitis C virus; HBV = hepatitis B virus; HCC = hepatocellular carcinoma; HTLV-1 = human T-cell lymphotropic virus type 1; ATL = adult T-cell lymphoma; HAM = HTLV-1–associated myelopathy.
*±50% of baseline value.
†Midpoint of range.

Cost Parameters

Cost parameters were valued in year-2001 US dollars (Table IV).[15,30,34,42–44,48–52] The health care component of the US Consumer Price Index was used to update costs calculated in previous years. Health care resource utilization cost components included the costs of AP and PC, pathogen inactivation treatment using the IBS for platelets, and the annual cost of treatment for transfusion-related sequelae. PC use assumed a pool of 6 random-donor units (based on a reported range of 4–10 units).[53,54]

Sensitivity Analyses

Univariate scenario and multivariate sensitivity analyses were conducted to determine the robustness of the model results, to identify the variables that contributed the most to the model results, and to identify important model uncertainties. Univariate analysis, in which model variables were varied one by one, was conducted for the transfusion-transmission risk, the cost of treatment

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Table IV. Cost parameter values (in year-2001 US $) for single-donor apheresis platelets (AP), random-donor pooled platelet concentrate (PC), pathogen inactivation, and treatment of transfusion-related sequelae in the United States.

Parameter	Cost	Range
Platelet cost		
PC (6-unit PC)[48,49]	294	294–852
AP[48,49]	469	469–595
Pathogen inactivation cost per unit*	100[†]	75–125[‡]
Annual cost of treating transfusion-related sequelae		
ARC/AIDS[30,50,51]	45,776	24,142–77,555
HCV or HBV		
Chronic infection[30,43]	1,228	359–2,327
Cirrhosis[34,42]	11,627	293–34,882
HCC[34,42,44]	16,245	5,814–33,757
Fulminant infection[15]	17,412	8,706–26,118[§]
HTLV-1, ATL/HAM[30]	12,926	6,463–25,852
Hospitalization for TRS[52]	6,408	3,204–9,611[§]

ARC = AIDS–related complex; HCV = hepatitis C virus; HBV = hepatitis B virus; HCC = hepatocellular carcinoma; HTLV-1 = human T-cell lymphotropic virus type 1; ATL = adult T-cell lymphoma; HAM = HTLV-1–associated myelopathy; TRS = transfusion-related sepsis.
*Estimated cost based on data from Baxter Healthcare Corporation (Chicago, Illinois).
[†]For bacterially screened AP, the incremental cost was $70 ± 25%.
[‡]±25% of baseline value.
[§]±50% of baseline.

for transfusion-related sequelae, the cost of IBS, and the probability of disease outcomes.

In addition, the impact of eliminating the need for gamma irradiation was assessed. Gamma irradiation, a lymphocyte inactivation method for red blood cells and platelets, is commonly used to reduce the risk of graft-versus-host disease (GVHD).[55] GVHD occurs when viable lymphocytes in transfused blood or blood components engraft, multiply, and react against the tissues of the recipient. Because the IBS for platelets targets DNA and RNA, it inactivates lymphocytes, potentially eliminating the need for gamma irradiation.[10,56] To assess this impact, a scenario in which gamma irradiation (process cost, $38 to the hospital[57]) was no longer required when using AP + IBS and PC + IBS was included in a sensitivity analysis.

Another potential benefit of pathogen inactivation via the IBS for platelets is the ability to reduce the risk of transmission of emerging pathogens. New pathogens continue to be discovered every 2 to 5 years, with >40 new diseases/

microorganisms identified in the last 30 years, including HIV/AIDS and HCV.[58] For every new pathogen discovered, there is a time lag between pathogen discovery and the widespread availability of an effective test. Even if an effective test is developed, there exists the possibility that the pathogen may not be detected (eg, because of small pathogen-load counts). In the case of HCV, ~300,000 Americans were infected via blood transfusions (primarily before 1990) before the approval of the first HCV blood test.[59] To further assess the impact of using AP + IBS and PC + IBS, a hypothetical scenario involving HCV-like pathogens was incorporated into sensitivity analyses. The risk for acquiring these emerging pathogens was assumed to be 1 per 3300 units, similar to that of HCV when first discovered.[60] Subsequent outcomes and treatment costs were based on that of HCV in the baseline models.

An additional consideration was that the use of the IBS for platelets could increase platelet use because of losses from the pathogen inactivation process and reduction of platelet recovery.[61,62] To assess this impact, the baseline model was assessed under the scenario in which platelet use was increased by 20%, with a range of 10% to 30% tested in the sensitivity analysis.

Finally, a multivariate sensitivity analysis on all variables provided with a range in Tables II to IV was conducted via Monte Carlo simulation (probabilistic sensitivity analysis). This entailed conducting 10,000 iterations of the model using (for each iteration) a random set of model parameter values selected from the assumed parameter distributions, which were based on the range of values found in the literature (see Tables II–IV). When parameter distributions were unavailable, triangular distributions were used, where the presumed likeliest value (ie, the baseline value) fell between the minimum and maximum values, assumed to be ±50% from baseline. The 10,000 iterations of expected costs and outcomes were used to calculate ICERs, from which a cost-effectiveness acceptability curve[63] was generated to illustrate the confidence with which it may be inferred that use of AP + IBS and PC + IBS would be cost-effective over a range of thresholds of acceptability.

RESULTS
Baseline Analysis
The baseline results in year-2001 US dollars are presented in Table V (for AP) and Table VI (for PC). They show that, for all 4 patient populations, IBS treatment was more cost-effective for PC ($457,586–$1,816,060) than AP ($1,308,833–$4,451,650 in baseline scenario 1 and $4,759,401–$22,968,066 in baseline scenario 2). IBS was also more cost-effective in the pediatric patient population studied versus the other 3 adult patient populations for both AP and PC.

Table V. Incremental cost-effectiveness ratio (cost per quality-adjusted life-year) of using single-donor apheresis platelets (AP) treated with the Intercept Blood System* (IBS) versus untreated AP in the United States in year-2001 US $.

Analysis	Pediatric ALL	Hip Arthroplasty	CABG	NHL
Baseline scenario 1: IBS-treated AP versus untreated AP without bacterial testing	1,308,833	2,225,819	2,644,880	4,451,650
Baseline scenario 2: IBS-treated AP versus untreated AP with bacterial testing[†]	4,759,401	10,697,249	13,408,731	22,968,066
Sensitivity analysis 1: baseline + low fatality from bacterial contamination[‡]				
Baseline scenario 1	4,120,098	8,323,879	10,201,154	17,341,912
Baseline scenario 2	7,105,810	20,128,437	26,803,402	46,905,925
Sensitivity analysis 2: baseline + high fatality from bacterial contamination[§]				
Baseline scenario 1	917,439	1,526,577	1,807,689	3,039,215
Baseline scenario 2	3,481,838	7,034,690	8,621,330	14,656,642
Sensitivity analysis 3: baseline + 30% increased platelet utilization				
Baseline scenario 1	1,858,322	3,160,073	3,754,950	6,319,736
Baseline scenario 2	6,998,621	15,728,771	19,715,079	33,768,313
Sensitivity analysis 4: baseline + emergent HCV-like virus benefit				
Baseline scenario 1	238,901	663,511	876,334	1,527,664
Baseline scenario 2	234,807	743,993	1,024,007	1,811,930
Sensitivity analysis 5: baseline + high fatality from bacterial contamination[§] + gamma irradiation benefit (for ALL and NHL) + emergent HCV-like virus				
Baseline scenario 1	177,695	583,456	759,353	1,058,127
Baseline scenario 2	176,572	550,386	982,161	1,330,703

ALL = acute lymphocytic leukemia; CABG = coronary artery bypass graft; NHL = non-Hodgkin's lymphoma; HCV = hepatitis C virus.
*Trademark of Baxter Healthcare Corporation (Chicago, Illinois) and Cerus Corporation (Concord, California).
[†]1 death per 1 million.[26,27]
[‡]2 and 0.1 deaths per 1 million for baseline scenarios 1 and 2, respectively.[6,26,27]
[§]15 and 2 deaths per 1 million for baseline scenarios 1 and 2, respectively.[7,26,27]

Table VI. Incremental cost-effectiveness ratio (cost per quality-adjusted life-year) of using the random-donor pooled platelet concentrate (PC) treated with the Intercept Blood System* (IBS) compared with untreated PC in the United States in year-2001 US $.

Analysis	Pediatric ALL	Hip Arthroplasty	CABG	NHL
Baseline analysis	457,586	881,424	1,070,533	1,816,060
Sensitivity analysis 1: baseline + low fatality from bacterial contamination[†]	1,013,670	2,639,617	3,431,576	5,957,993
Sensitivity analysis 2: baseline + high fatality from bacterial contamination[‡]	172,743	293,597	348,918	587,798
Sensitivity analysis 3: baseline + 30% increased platelet utilization	620,693	1,195,069	1,451,270	2,461,231
Sensitivity analysis 4: baseline + emergent HCV-like virus benefit	34,845	109,412	149,861	266,593
Sensitivity analysis 5: baseline + high fatality from bacterial contamination[‡] + gamma irradiation benefit (for ALL and NHL) + emergent HCV-like virus	22,888	86,992	115,445	153,564

ALL = acute lymphocytic leukemia; CABG = coronary artery bypass graft; NHL = non-Hodgkin's lymphoma; HCV = hepatitis C virus.
*Trademark of Baxter Healthcare Corporation (Chicago, Illinois) and Cerus Corporation (Concord, California).
[†]2 deaths per 1 million.[5]
[‡]62 deaths per 1 million.[6]

Sensitivity Analyses

Univariate sensitivity analyses indicated that the model results were sensitive to individual changes in the value of several parameters. Specifically, the following parameters were most likely to affect the model results: (1) mortality due to bacterial contamination; (2) IBS effect on platelet utilization; and (3) the inclusion of potential benefits (ie, gamma irradiation and/or emergent HCV-like virus).

Corresponding ICERs from different scenarios are presented in Table V and Table VI. In contrast with these findings, changes in the IBS price and transmission risks of HIV, HBV, HCV, and HTLV-1 within the ranges tested did not significantly alter the model results.

The ICERs were highly sensitive to the death rate due to bacterial contamination. When the death rate increased from 2 deaths per million for both AP

and PC to 15 deaths and 62 deaths per million for AP and PC, respectively, the incremental cost per QALY decreased from $4,120,098 to $917,439 for AP + IBS versus AP and from $1,013,670 to $172,743 for PC + IBS versus PC among pediatric ALL patients. When the mortality rate increased from 0.1 death per million to 2 deaths per million for bacterially screened AP, the incremental cost per QALY decreased from $7,105,810 to $3,481,838 for AP + IBS versus AP among pediatric ALL patients. Similar trends were found in other patient populations.

Increased platelet use due to IBS treatment also increased the ICERs. The ICERs increased ~45% when the platelet yield reduction rate was raised from 20% to 30% for both AP and PC in all patient populations. Conversely, the ratio decreased by ~33% when the platelet yield reduction rate was decreased to 10%.

Elimination of the need for gamma irradiation reduced the ICERs by ~20% to 25% for both AP and PC in ALL and NHL patients. This scenario was not assessed in patients undergoing CABG and hip arthroplasty surgery because, in our experience, these patients do not typically require irradiated blood components.

When an emerging, highly prevalent HCV-like pathogen was introduced into the model, the costs per QALY of AP + IBS and PC + IBS decreased dramatically in all 4 patient populations. For AP + IBS, the ICERs declined to a range of $238,901 to $1,527,664 per QALY using baseline scenario 1 and a range of $234,807 to $1,811,930 per QALY using baseline scenario 2. For PC + IBS, the ICERs decreased to a range of $34,845 to $266,593 per QALY.

As expected, consideration of the combined scenarios in which the high bound of death rates from bacterial contamination was used, gamma irradiation was no longer required, and an emerging HCV-like pathogen was introduced, resulting in dramatically lower ICERs compared with the baseline scenarios. The maximum observed ICER was less than $1,331,000 per QALY for AP + IBS and less than $154,000 per QALY for PC + IBS.

The probabilistic sensitivity analysis indicated that the results were sensitive to simultaneous changes to the multiple parameters listed (with a range) in Tables II to IV. For instance, in pediatric ALL patients, results of Monte Carlo simulations indicated that the ICER of AP + IBS versus untreated AP was less than $2.0 million (without bacterial testing)/$5.7 million (with bacterial testing) in 50% of model runs, and less than $4.1 million (without bacterial testing)/$8.9 million (with bacterial testing) in 95% of model runs. For the other 3 patient populations, the ICERs of AP + IBS versus untreated AP were less than $4.4 million/$14.2 million (hip arthroplasty), less than $4.9 million/$18.5 million (CABG), and less than $8.3 million/$32.1 million (NHL) in 50% of model runs, and less than $8.5/$22.0 million (hip arthroplasty), $9.4/$28.9 million (CABG), and $15.8/$49.9 million (NHL) in 95% of model runs.

DISCUSSION

The current analysis provided a comprehensive economic assessment of APs and PCs treated with the IBS for platelets. The decision-analytic model accounts for the morbidity and mortality associated with the patient's underlying condition, as well as that of transfusion-related complications. The model used the most recently published pathogen-transmission risks, subsequent transfusion-related outcomes, and treatment costs to assess the health benefit and cost-effectiveness of the IBS for platelets in patients who commonly receive platelet transfusions.

In this model, we observed that the cost of transfusion of AP + IBS versus untreated AP ranged from $1,308,833 (pediatric ALL) to $4,451,650 (NHL) for each QALY saved. For bacterially screened AP, the reduced mortality rate from bacterial contamination makes the incremental cost per QALY of IBS treatment in excess of $4 million for all patient populations at baseline. Corresponding figures for the transfusion of PC + IBS versus untreated PCs ranged from $457,586 (pediatric ALL) to $1,816,060 (NHL). Although seemingly high compared with the threshold ratios commonly used in other fields of medicine, such as $50,000 per QALY,[64] these ICERs are comparable to previously reported cost-effectiveness findings of accepted blood safety interventions. For instance, a recent study by Jackson et al[65] showed that the ICERs of whole-blood NAT for HIV, HCV, and HBV ranged from $4.7 to $11.2 million per QALY saved. Stone et al[66] also found that blood safety interventions had a median ICER of $355,000 per QALY, with values ranging from cost-saving to $8.7 million per QALY. A graphic summary of the results of published cost-effectiveness analyses of safety interventions (Figure 2) indicated that ICERs for blood safety and injury prevention measures were dominated by ratios higher than $100,000 per QALY.[39,51,67–73] These findings suggest that the IBS is associated with ICERs comparable with those of other existing or proposed blood safety interventions that are highly valued by the public and policy makers. The risk of transfusion-transmitted infections due to currently screened pathogens is relatively small, but the continued addition of new tests such as NAT suggests that safety is still paramount in policy decision-making processes.[74,75] Thus, higher cost-effectiveness thresholds may apply in the evaluation of new blood safety technologies.

The results of the present analysis indicated that the IBS for platelets was relatively more cost-effective for pediatric ALL patients and orthopedic patients, followed by CABG and NHL patients. Overall, this finding reflected the favorable short-term prognosis of pediatric ALL and orthopedic patients, because mortality and quality of life after treatment were relatively similar to those expected for normal populations. The anticipated life expectancy of pediatric ALL patients was also greater due to their younger age at the time of transfusion. In contrast, the NHL and CABG patient populations were associated with relatively higher first-year posttreatment mortality rates, reducing the potential benefits of avoidance of transfusion-related infections.
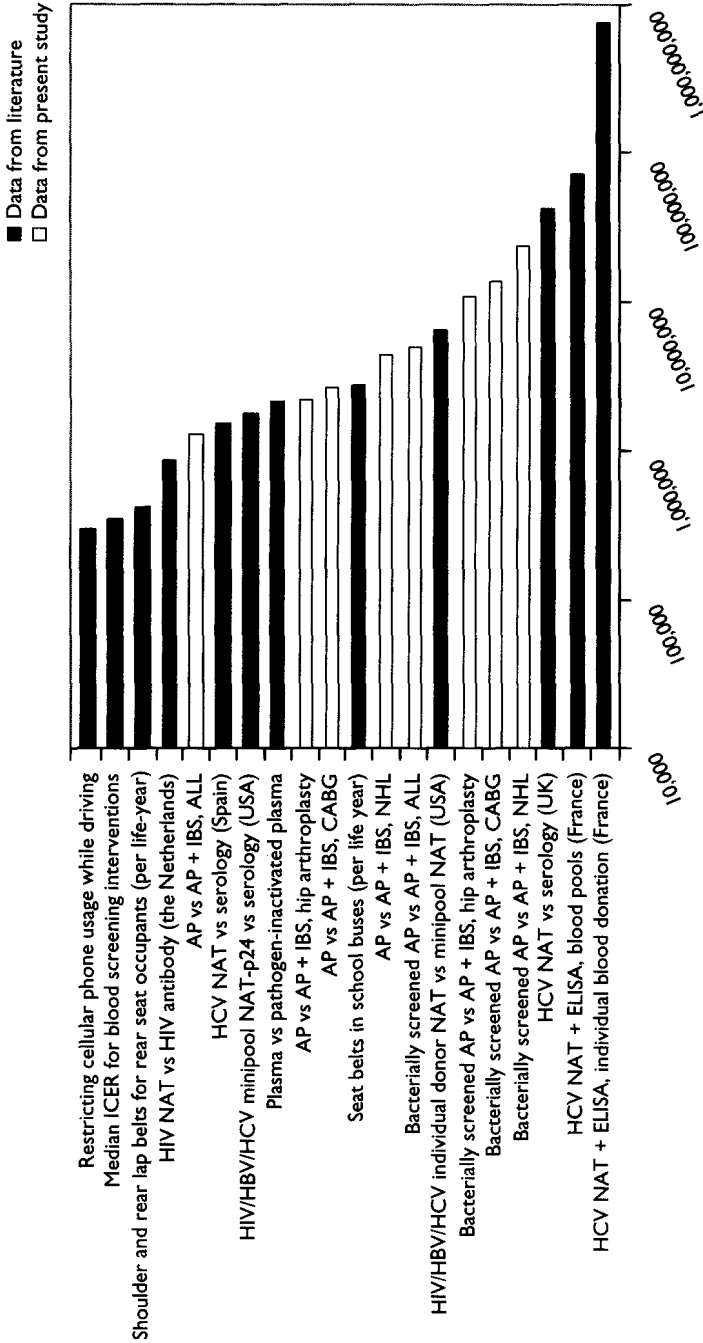
Figure 2. Illustration of incremental cost-effectiveness ratios (ICERs) for implemented blood safety interventions and other injury prevention measures,[39,51,66–72] shown as US $ per quality-adjusted life-year gained. NAT = nucleic acid amplification technology; AP = single-donor apheresis platelets; IBS = Intercept Blood System (trademark of Baxter Healthcare Corporation, Chicago, Illinois, and Cerus Corporation, Concord, California); ALL = acute lymphocytic leukemia; HCV = hepatitis C virus; HBV = hepatitis B virus; CABG = coronary artery bypass graft; NHL = non-Hodgkin's lymphoma; ELISA = enzyme-linked immunosorbent assay.

Sensitivity analysis indicated that the model results were not significantly affected by changes in viral-transmission risks for which testing is currently performed. The benefits of the IBS for platelets were driven by TRS mortality due to bacterial contamination of platelets. Currently, bacterial contamination remains the most frequent infectious complication associated with platelet transfusions.[6]

Although the adoption of bacterial testing in the United States in the near future is expected to reduce the risk of bacterial contamination and TRS mortality, residual risks will remain due to the limitations of bacterial testing systems.[26,27] In such circumstances, the benefit of the IBS would actually be substantially reduced (as shown in the baseline scenario 2). However, the concurrent use of pathogen inactivation and bacterial testing is very unlikely. A generalized use of the IBS would probably omit the need for bacterial testing.[56]

The mortality from bacterial contamination was directly modeled in the current analysis without consideration for nonfatal outcomes. The rationale for such an approach is as follows: (1) Varying clinical definitions of transfusion reactions have led to a number of differing reports of TRS incidence, such as the incidence of sepsis, mild/severe septic reactions, bacterial contamination, bacteria-related events, transfusion reactions, and so on, all of which lack a clear consensus of the true incidence—however, the cumulative mortality rate per million units has been consistently used in the literature to estimate the impact of TRS; (2) rates for nonfatal reactions are often underestimated because of underrecognition and underreporting[76]; (3) the economic impact of septic reactions (mild or severe) due to bacterial contamination is minimal and may be neglected due to the rare occurrence; and (4) focusing on the critical effect of TRS—patient mortality—may simplify, as well as clarify, the model.

The mortality rate due to bacterial contamination has been reported in several well-known studies.[6–8,77] A surveillance study in the United States found cumulative death rates of 2.2 and 1.9 per million for AP and PC, respectively, based on data for the years 1998 to 2000.[6] However, as with other surveillance studies (eg, US Food and Drug Administration surveillance for bacterial safety[77]), the fatality and incidence rates were underestimated because of limitations of surveillance study methodology.[6,77] A study conducted in France[8] with a matched case-control study design reported that the cumulative death rates with PC and AP were 0.0 (95% CI, 0.0–35.8) and 7.1 (95% CI, 0.8–25.6) per million. A study at Johns Hopkins[7] revealed that the cumulative death rates during the 12-year period (1987–1998) were 15 per million for AP and 62 per million for PC. These rates were much higher than those from surveillance data,[6,77] and may reflect the more aggressive ability of hospital-based studies to detect and report cases. Considering the limitations and strengths of each study, the death-per-million rates for bacterial contamination were conservatively calculated in our study as a weighted average by sample size[7,8]: 10 per million for AP and 17 per million for PC. The

BaCon study[6] was excluded from these calculations because its underestimation was well recognized and the large sample size would bias the weighted average.

The IBS for platelets was designed to reduce the risk of transmission of known pathogens (eg, HIV, HCV, HBV, HTLV-1, bacterial agents) for the >4 million units of platelets transfused annually in the United States, Europe, and Japan (ie, ~2.3 HIV, ~2.5 HCV, ~24.0 HBV, ~1.6 HTLV-1 infections, and ~68 deaths due to bacterial contamination could be avoided). However, the system also has the potential to reduce the risks associated with emerging pathogens for which no donor screening strategy or laboratory test currently exists. Therefore, this study conservatively adopted a hypothetical HCV-like pathogen to assess the potential benefit of the IBS in preventive reduction of the infection risk from emerging pathogens. Unlike HIV-like viruses, most HCV infections do not result in severe clinical illness and remain asymptomatic.[78] To generate conservative estimates, this virus was selected to mimic an emerging virus scenario. The results from the sensitivity analysis indicated that the IBS would be much more cost-effective in all 4 patient populations with this potential benefit included in the model. As expected, a scenario in which multiple new pathogens were encountered would further improve the cost-effectiveness of the IBS.

One of the most important trends in health care is the increasing emphasis on disease prevention. The potential of the IBS to prevent the transmission of emerging pathogens such as the causative agent of severe acute respiratory syndrome[79] and West Nile virus[56,80] may increase the safety of platelet transfusions. The IBS may also help avoid the otherwise inevitable addition of new screening tests.[56]

This study was intended to generate conservative results. For example, the study did not include the potential benefit of the IBS in extending the shelf-life of platelet concentrates, although it has been reported that, in principle, pathogen inactivation may extend the storage time of platelet concentrates to 7 days (from the current 5 days).[56] In addition, no indirect costs were considered attributable to worker productivity losses due to premature death and litigation costs stemming from pathogen transmission and sequelae. Inclusion of these potential benefits would result in more favorable results for both AP + IBS and PC + IBS.

A critical assumption of the current analysis was that the IBS for platelets was 100% effective in the prevention of transmission of the pathogen used in the model[11] and was not associated with adverse health effects. Clinical trials in the United States[61] and Europe[62] have assessed the efficacy and safety of the IBS for platelets, and no excess treatment-related adverse events have been detected in patients receiving treated platelet components. However, inherent to the assumed benefit of use of platelets treated with the pathogen inactivation process is a level of uncertainty, and any benefit gained from the use of pathogen-inactivated platelets may be offset by the incidence of an unanticipated adverse event or any other treatment-related hazard.

CONCLUSIONS

The cost-effectiveness of pathogen inactivation via the IBS for platelets is compara-ble to that of other accepted blood safety interventions (eg, NAT testing, HIV p24 antigen testing, solvent-detergent treatment). The major advantages of the IBS are the prevention of virus transmission, bacterial contamination, and emerging pathogens, and perhaps the avoidance of future screening tests as well. Blood banks, hospitals, and other institutions that administer platelet transfusions could consider the IBS for platelets a desirable strategy to increase the safety of platelet transfusions and a potential insurance against the threat of emerging pathogens.

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