市販後調査及び観察研究の報告①

A prospective observational cohort safety study of 5106 platelet transfusions with components prepared with photochemical pathogen inactivation treatment

Jean C. Osselaer, Nathalie Messe, Tor Hervig, Jose Bueno, Emma Castro, Aurora Espinosa, Patrizia Accorsi, Klaus Junge, Michele Jacquet, Jocelyne Flament, and Laurence Corash

BACKGROUND: Inactivation of pathogens and white blood cells in platelet (PLT) components with amotosalen and UVA light (INTERCEPT, Cerus Europe BV) has entered clinical practice in European blood centers. A prospective cohort study was implemented to characterize the safety profile of this new PLT component in a broad patient population.

STUDY DESIGN AND METHODS: Apheresis or buffy-coat PLT components were leukoreduced, suspended in approximately 35 percent plasma and 65 percent PLT additive solution, and treated with the INTERCEPT process. Blood centers were requested to complete a safety data form after each transfusion.

RESULTS: Data for 5106 INTERCEPT components administered to 651 patients were monitored. A total of 5051 (98.9%) transfusions and 609 (93.5%) patients had no reported reactions. Fifty-five (1.1%) transfusions were associated with adverse events, and 42 (0.8%) were possibly, probably, or related to the PLT transfusion. Adverse events occurred in 42 (6.4%) patients, but in only 32 (4.9%) patients was a causal relationship to PLT transfusion established. One reaction was serious, and no deaths were related to PLT transfusion. Among the transfusions reactions, the most frequent clinical events in descending frequency were chills, fever, dermatologic reactions, dyspnea, nausea or vomiting, and hypotension. No episodes of transfusion-related acute lung injury were reported.

CONCLUSIONS: In this cohort study, 99.2 percent of transfusions were without reactions attributed to PLTs. INTERCEPT PLTs exhibited a safety profile similar to that previously reported for conventional PLT components.

In late 2002 a photochemical treatment (PCT) process (INTERCEPT Blood Systems, Cerus Europe BV, Leusden, Netherlands) for inactivation of pathogens and white blood cells that may contaminate platelet (PLT) components received CE Mark registration and became available for routine use within certain European countries. During the clinical development of this technology, randomized controlled trials were conducted in selected patient populations frequently supported with PLT transfusions during periods of thrombocytopenia.[1,2] By necessity for conduct of the clinical trials, these studies primarily enrolled patients with hematology–oncology disorders. The trials focused on posttransfusion PLT count increments[1] and on assessments of hemostatic efficacy in patients with relatively stable thrombocytopenia requiring repeated PLT transfusions.[2] Based on the design of these clinical trials, the number of patients studied was determined by the statistical power required to assess the primary endpoints. In the European trial of whole blood–derived buffy-coat PLT components, 52 patients received 311 PCT PLT component transfusions. To assess hemostatic efficacy, a larger study was conducted in the United States in which 318 patients received 2678 PCT PLT component transfusions. In both studies patients were assessed specifically for acute transfusion reactions for 6 hours after study transfusions and for other adverse events for either 7[2] or 28 days[1] after the last study PLT transfusion. In both studies the incidence of acute transfusion reactions after receipt of photochemically treated PLTs was low, and the safety profile was similar to that of conventional PLTs.[3]

In general, prospective studies regarding the safety of PLT transfusion have been limited. The largest prospective PLT transfusion study before the SPRINT study[2,3] was the TRAP study of PLT alloimmunization, which enrolled 533 patients treated with 6379 transfusions, but this study did not specifically examine safety.[4] After CE Mark registration of the INTERCEPT system, an observational cohort safety study was implemented to prospectively collect information on at least 5000 PLT transfusions to extend the safety profile of PLT components prepared with PCT administered to a broad patient population.

ABBREVIATIONS: DSMB = data and safety monitoring board; HPC(s) = hemovigilance plan coordinator(s); PCT = photochemical treatment.

From the Blood Transfusion Center, Cliniques Universitaires de Mont Godinne, Université Catholique de Louvain, Yvoir, Belgium; Haukeland University Hospital, Bergen, Norway; Centro de Transfusión, Cruz Roja Española, Madrid, Spain; St Olav Hospital, Trondheim, Norway; Centro Trasfusionale, Ospedale di Pescara, Pescara, Italy; Omega Mediation, Offenbach, Germany; Transfusion Therapies, Baxter Healthcare, Nivelles, Belgium; and Medical Affairs, Cerus Corp., Concord, California.

Address reprint requests to: Laurence Corash, MD, Medical Affairs, Cerus Corp., 2411 Stanwell Drive, Concord, CA 94520; e-mail: larry_corash@cerus.com.

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MATERIALS AND METHODS

General study design

Blood transfusion centers with the INTERCEPT Blood System for PLTs for routine production of PLT components were invited to participate in this study. Patients in clinical care institutions who received PLTs prepared with PCT were specifically monitored for adverse health effects for 24 hours after each transfusion; however, there was no time limitation on reporting adverse events after transfusion. The sole inclusion criterion for enrollment was receipt of at least one PLT component prepared with PCT. Patients who received PLT transfusions administered in an outpatient clinic were observed for approximately 6 hours after transfusion and assessed before discharge. Study personnel contacted outpatient transfusion recipients the following day to complete the assessment with the standard data record form. There were no other inclusion or exclusion criteria. Patients in this study received only PLT components prepared with pathogen inactivation treatment.

The study was designed as a prospective, single cohort observational study to be consistent with European Hemovigilance Network recommendations for surveillance of adverse reactions to transfusion of labile blood components and with those of national transfusion services.[5,6] Study centers transfusing PLT components prepared with PCT for pathogen inactivation (INTERCEPT Blood System for Platelets) in routine clinical practice were requested to complete a report for each PLT transfusion regardless of whether or not an adverse event occurred following transfusion. Transfusions associated with serious adverse events were reported in greater detail. Patients were assigned a center specific study number to preserve anonymity.

Conduct of the study

In each study center blood transfusion service, hemovigilance plan coordinators (HPCs) were designated as responsible persons for the conduct of the hemovigilance plan and coordinated all the related activities on site. These HPCs, with expertise in transfusion medicine, were responsible for oversight of data collection, ensuring data completion, reviewing assessments for relation to PLT transfusion, and completion of reporting information on any adverse event after PLT transfusion regardless of potential relation to the transfusion.

Before initiation of the study, clinical care personnel were trained to the study protocol and the specific form for data collection. For each study PLT component issued for transfusion, a specific transfusion report form was issued with the PLT component (Fig. 1). This form was completed by the primary care physician and returned to the HPC in the blood center. The primary care attending physician was responsible for assessing the relation of adverse events to the PLT transfusion. The HPC reviewed the completed forms and contacted the primary care physician if data were incomplete or assessments of relation did not match the reported clinical data. The HPC had access to patient medical care records to query transfusion reports. The ultimate decision for assessment of the relation of adverse events to the PLT transfusion was the responsibility of the primary treating physician. HPCs were charged with populating the database, by completing electronic data entry. In centers where electronic data entry was not possible, paper forms were submitted and a sponsor representative populated the database. The active HPCs were Dr P. Accorsi, Pescara Italy (Site 02); Dr J.L. Bueno, Madrid Red Cross, Spain (Site 04); Dr A. Espinosa, Trondheim, Norway (Site 03); Dr T. Hervig, Bergen, Norway (Site 08); and Dr J.C. Osselaer, Mont Godinne, Belgium (Site 01).

A data and safety monitoring board (DSMB) was constituted to review the study protocol and provide oversight of the study. The DSMB reviewed an interim analysis of the data after 2500 transfusions and the final report after 5106 transfusions.

Study report forms

The report form used for this study was developed on the basis of hemovigilance report forms already in use and

PLATELET TRANSFUSION REPORT

Patient

Age : Sex : F ☐ M ☐

Hospital name and city :

Location: Surgical ☐ Medical ☐ ICU ☐ Outpatient ☐ Other

Reporting

Reporting date :

Reporter name: _____

Signature: _____

INTERCEPT Platelet Characteristics and Transfusion

Type:

Apheresis platelets ☐

Random-donor platelets ☐

Characteristics:

Leucodepleted ☐ Irradiated ☐

Plasma depleted ☐ Other, specify ☐

Antigen matched ☐ _____

Product id #: _____ Blood Bank id #: _____

Date and time of transfusion :

Did the patient experience any acute adverse transfusion reaction within 24 hours after transfusion ?

Yes ☐ No ☐ *If no, stop here*

If yes : Start date and time of adverse reaction:

Causal relation	Grade	
☐ Unrelated	0 ☐	Isolated dysfunction without clinical or biological manifestation
☐ Probably Unrelated	1 ☐	Absence of immediate or long-term life-threatening
☐ Possibly Related	2 ☐	Long-term life-threatening
☐ Probably Related	3 ☐	Immediate life-threatening
☐ Related	4 ☐	Death

Symptoms / Signs

Fever ☐	Urticaria ☐	Dyspnea ☐	Shock ☐
Chills ☐	Skin rash ☐	Nausea/vomiting ☐	Platelet refractoriness ☐
Cardiac arrhythmia ☐	Jaundice ☐	Lower back pain ☐	TRALI ☐
Hypotension ☐	Pulmonary oedema ☐	Chest / abdominal pain ☐	Other ☐
Itching ☐	Bronchospasm ☐		Specify: _____

Clinical signs

Parameters	Before transfusion	After transfusion
Temperature	. °C ☐ ND	. °C ☐ ND
Blood pressure (Systolic/Diastolic)	- mmHg ☐ ND	- mmHg ☐ ND
Pulse	per min ☐ ND	per min ☐ ND

Transfusion-related laboratory abnormalities

Parameters (specify)	Date	Value	Unit

Bacteriological assessments

Blood culture ☐	Date	☐ Negative or ☐ Positive If positive, strain: _____
Platelet culture ☐	Date	☐ Negative or ☐ Positive If positive, strain: _____

Conclusion/Diagnosis/Additional examinations (e.g. X-Ray, ...)

Please keep a copy of this report in the patient file and do not forget to complete a "Delayed Transfusion Reaction Report" if any delayed transfusion reaction occurs (e.g. GVHD, ...)

Fig. 1. Case report form for reporting responses to PLT transfusions and classification of adverse events after transfusion.

DELAYED TRANSFUSION REACTION REPORT

Patient

Age : Sex : F ☐ M ☐

Hospital name and city :

Location: Surgical ☐ Medical ☐ ICU ☐ Outpatient ☐ Other _____

Reporting

Reporting date :

Reporter name: _____

Signature: _____

Start date of the delayed transfusion reaction:

Suspected or confirmed diagnosis

Products transfused that can be related to this event (by decreasing imputability order)

Type of product (RBC/SDP platelets/random donor platelets/plasma/other)	Product number	Date of transfusion	Blood bank ID

Comments

Please keep a copy of this report in the patient file

Fig. 1. *Continued.*

was reviewed by the DSMB before utilization (Fig. 1). Information was collected in several specific categories: patient demographics, PLT component characteristics, transfusion time, transfusion-related events, documentation of adverse events, causal relation, severity, symptoms, clinical findings, and laboratory data. For each transfusion the following signs, symptoms, and specific clinical syndromes were evaluated with a checklist format: fever, chills, cardiac arrhythmia, hypotension and/or hypertension, itching, urticaria, skin rash, jaundice, pulmonary edema, bronchospasm, dyspnea, respiratory distress, nausea, vomiting, lower back pain, chest pain, abdominal pain, clinical shock, refractoriness to PLT transfusion, and transfusion-related acute lung injury (TRALI). Criteria were provided for the diagnosis of TRALI.[7] Any other findings classified as adverse events were entered as free text. The following clinical signs were recorded before and after each transfusion: temperature, blood pressure, and heart rate. After study transfusions, abnormal clinical laboratory values, results of diagnostic procedures, chest radiographs, and bacterial cultures from patient and blood component sources were recorded from the medical record as required to verify the adverse event and relation to transfusion. A supplemental form was provided, on which adverse events occurring more than 24 hours after the transfusion, considered as potential delayed transfusion reactions, were reported with free text to define the event and the relationship to the imputed PLT component.

The relation of the adverse event to the PLT transfusion was classified within the following categories: unrelated, probably unrelated, possibly related, probably related, and related. Adverse events classified as possibly, probably, or related to transfusion were defined as transfusion reactions. Adverse events and transfusion reactions were graded for clinical severity by the HPC within the following categories: Grade 0 = isolated dysfunction without clinical or biologic manifestation; Grade 1 = absence of immediate or long-term life-threatening effects; Grade 2 = long-term life-threatening effects; Grade 3 = immediate life-threatening effects; and Grade 4 = death.

Preparation of PLT components

PLT components were collected by apheresis or by whole blood–derived buffy-coat procedures from volunteer donors according to standard operating procedures at each center. Donors were screened and tested for transfusion-transmitted pathogens according to each center's standard operating procedures in compliance with respective national regulations. All components were leukoreduced, either by filtration or by process leukodepletion. PLT components (containing 2.5×10^{11}-6.0×10^{11} PLTs) were suspended in approximately 35 percent plasma and 65 percent PLT additive solution (AS; Intersol, Baxter Transfusion Therapies, La Chatre, France) and prepared with amotosalen-HCl (nominal final concentration 150 µmol/L) and a 3 J per cm^2 UVA light treatment (320-400 nm) according to the manufacturer's instructions (Cerus Europe BV).[8] Treated PLT components were stored for up to 5 days with temperature control (22-24°C) according to standard operating procedures for each center in compliance with national regulations. Photochemical pathogen inactivation treatment was used in place of bacterial detection to prevent bacterial contamination and in place of gamma irradiation for prevention of transfusion associated graft-versus-host disease (GVHD) at all centers except Trondheim, Norway.

PLT transfusion

Primary care physicians ordered PLT components for transfusion according to standard indications within each institution. Primary care physicians prescribed pretransfusion medication per standard of care. Participating primary care physicians were requested to report all adverse health effects for a period of 24 hours after each transfusion with the standard report form and could report any adverse health effects after a study transfusion without time limitation.

Statistical analyses

A detailed statistical analysis plan for the study was prepared and approved before analysis. All statistical analyses, summary tables, and data listings were generated with computer software (SAS Version 8.2, SAS Institute, Cary, NC). The primary assessment was the incidence of transfusion reactions. The number and proportion (%) of transfusions and of patients with one or more transfusion reactions were summarized overall, by seriousness and by relationship to PLT transfusion. Corresponding 95 percent confidence intervals (CIs) were calculated for the overall summaries on a per-transfusion basis. In addition, the patient population profile, the characteristics of the PLT transfusions, and the characteristics of the adverse events after PLT transfusion were analyzed. Analyses to identify risk factors potentially associated with transfusion reactions were conducted with multivariate logistic regression analysis and by assessing association at a 10 percent significance level.

Data were analyzed on a per-transfusion or a per-patient basis as appropriate. All INTERCEPT PLT transfusions administered to patients were part of the full analysis population and were analyzed, whether or not an adverse event was observed. All analyses were conducted with this full analysis population.

RESULTS

A total of 5106 transfusions with PLT components prepared with PCT were documented during the study from October 1, 2003, to December 16, 2005, and constitute the full analysis population of this study. Overall, 4494 transfusion reports (88.0%) were issued from Mont Godinne, Belgium; 282 transfusion reports (5.5%) from Bergen, Norway; 189 transfusion reports (3.7%) from Madrid, Spain; 139 transfusion reports (2.7%) from Trondheim, Norway; and 2 reports from Pescara, Italy.

Study patient demographics

A total of 651 patients received transfusions during the conduct of this hemovigilance plan (Table 1). Slightly more patients were male. The median age for all patients was 65 years (range, <1-93 years). The majority of patients received PLT transfusions in nonintensive care hospital locations, although a substantial number of study PLT components were transfused in intensive care units and a small proportion in outpatient clinics (Table 1). Hematooncology diseases with or without chemotherapy and/or stem cell transplant constituted 58.1 percent of the primary diagnoses among the transfused patient population (Table 1). A significant number of patients receiving PLT transfusion (26.9%) underwent cardiovascular surgery. Other diagnoses included surgical interventions (such as orthopedic, neurologic, obstetric, organ transplant, and multiple trauma). Additional primary indications for PLT transfusions were systemic sepsis due to unspecified sources, gastrointestinal bleeding, and sepsis secondary to localized infections.

TABLE 1. Patient demographics at first study transfusion

Patient characteristics (n = 651)	
Sex n (%)*†	
Male	385 (59.1)
Female	262 (40.2)
Age (years)	
Mean ± SD	61.2 ± 17.0
Median (range)	65 (<1-93)
Patient location†	
Intensive care unit	214 (32.9)
Outpatient care unit	46 (7.1)
Nonintensive care unit	391 (60.1)
Hematology-oncology patients	378 (58.1)
Conventional chemotherapy	315 (48.4)
Stem cell transplant (SCT)	47 (7.2)
No chemotherapy or SCT	16 (2.5)
Surgery patients	221 (33.9)
Cardiovascular	175 (26.9)
Organ transplant	8 (1.2)
Other surgical procedures	38 (5.8)
Other diagnoses	52 (8.0)

* Four patients had missing data for sex.
† Data are reported as number (%).

Overall, 223 patients (34.3%) had no previous transfusion history at time of the first study PLT transfusion, and 362 patients (55.6%) had already received another blood product before the first study transfusion. Information about transfusion history was missing for 66 patients (10.1%). Among the 362 patients with a transfusion history, 22 patients (3.4%) reported experiencing a transfusion reaction of some type in association with prior transfusions. The majority of the PLT components (3525/69.0%) were administered to patients who had already received another blood component before the first study PLT transfusion. Among these transfusions, 634 (12.4%) PLT products were transfused to patients reported to have experienced at least one transfusion reaction in the past.

PLT component demographics

A large proportion of the PLT components were transfused on nonintensive hospital care units. Most of the PLT components (90.3%) were administered to hematooncology patients. While a significant number of patients receiving study PLT components (26.9%) were undergoing cardiovascular surgery, they used only 5.5 percent of the total PLT components, because most of these patients required only one PLT transfusion episode.

Most of the study components were manufactured from apheresis collections (92.0% vs. 8.0% for buffy-coat products). All centers, except Trondheim, elected to use PCT PLTs without gamma irradiation (97.3%) for patients at risk of transfusion-associated GVHD based on reported data[9] showing that the photochemical process effectively inactivates T cells. Among the 5106 study products transfused, 158 PLT units (3.1%) were human leukocyte antigen (HLA) matched.

Extent of exposure

During the observational period, the range of study transfusions per patient was 1 to 156, with a mean of 7.8 ± 16.2 transfusions per patient. The median value was 2 transfusions per patient. A substantial proportion of patients (58.4%) received between 2 and 10 PLT components (Table 2).

Adverse events and transfusion reactions after PLT transfusions

On a per-transfusion basis, 55 of 5106 transfusions (1.1%; 95% CI, 0.81-1.40) were reported with adverse events after PLT transfusion and 3 of these (0.1%) were reported with serious adverse events. Forty-two transfusions (0.8%; 95% CI, 0.59-1.11) were reported with adverse events (Table 3) causally related to the proximate PLT transfusion; thus these transfusions were associated with a transfusion reaction. These adverse events were within the spectrum

of adverse events associated with transfusion reactions (Table 3). One of 42 transfusions was reported with a serious adverse event, Grade 3, causally related to PLT transfusion. All of the other transfusion-related adverse events were Grade 1. Thirteen transfusions had adverse events reported that were excluded as related to the transfusion (Table 4), and 2 of these transfusions had serious adverse events reported that were excluded as related to the transfusion.

On a per-patient basis, 42 patients (6.5%) experienced adverse events after study transfusions. Eight patients (1.2%) experienced adverse events after two different study transfusions, and 1 patient (0.15%) had adverse events after six different study transfusions. Among the patients experiencing adverse events after transfusion, 32 patients (4.9%) experienced adverse events attributed to the study PLT transfusion (possibly related, probably related, or related) and were classified as patients with a transfusion reaction. Three of the 42 patients had serious adverse events after PLT transfusion, but for only 1 patient was the serious adverse event attributed to the PLT transfusion. Of the 42 transfusion reactions in 32 patients, 33 transfusions were associated with a single symptom and/or sign, 8 with two, and 1 with six. Among these 42 transfusions classified as resulting in transfusion reactions, the time to the first reaction was variable (Table 5). Only 4 transfusions were preceded by medication to reduce potential transfusion reactions (antihistamines and corticosteroids for 3 and corticosteroids alone for 1 transfusion).

TABLE 2. Patient exposure to study PLT components

Number of study transfusions	Number of patients and proportion (%)
Received at least one study transfusion	651 (100)
Received only 1 transfusion	271 (41.6)
Received more than 1 transfusion	
From 2 to 10 transfusions	271 (41.6)
From 11 to 20 transfusions	47 (7.2)
From 21 to 40 transfusions	33 (5.1)
From 41 to 60 transfusions	11 (1.7)
From 61 to 80 transfusions	8 (1.2)
From 81 to 100 transfusions	7 (1.1)
More than 100 transfusions	3 (0.5)
Number of transfusions per patient	
Mean ± SD	7.8 ± 16.2
Range	1-156
Median	2

TABLE 3. Adverse events related to PLT transfusions classified as transfusion reactions*

Adverse event (clinical observation)	Number of events (%)
Chills	27 (36.0)
Fever	14 (18.6)
Urticaria	14 (18.6)
Dyspnea	4 (5.3)
Skin rash (not otherwise specified)	4 (5.3)
Nausea/vomiting	3 (4.0)
Itching	3 (4.0)
Other: flushing	3 (4.0)
Hypotension	3 (4.0)

* Adverse events (n = 75) reported after PLT transfusions attributed to the transfusion and classified as part of a transfusion reaction involving 42 of 5106 transfusions.

Transfusions associated with suspected bacterial sepsis

Five transfusions were associated with chills and fever or hypotension that met institutional criteria for suspicion of transfusion-associated sepsis, resulting in bacterial cultures of PLT components and patients (Table 6). Twenty-one other PLT components were cultured based on blood center surveillance practice, but were not associated with suspected sepsis, and all of these were sterile.

TABLE 4. Adverse events classified as unrelated to PLT transfusions

Patient	Adverse events*	Causality†	Grade‡	Basis for causality assessment
01-010	Fever, chills, nausea, vomiting	Probably unrelated	1	Prior infection under treatment
01-008	Cardiac arrhythmia	Probably unrelated	1	Condition before transfusion
01-096	Hypotension	Probably unrelated	3	Hypotension before transfusion
01-099	Chills	Probably unrelated	1	Anxiety crisis, not verified as chills, no fever
01-168	Chills, headache	Probably unrelated	1	Fever before transfusion with prior infection
01-098	Fever, chills, hypotension, flushing	Unrelated	3	Prior sepsis due to dental abscesses
01-106	Dyspnea, nausea, vomiting	Probably unrelated	1	Indwelling catheter infection documented
01-178	Fever, chills	Probably unrelated	1	Febrile neutropenia before transfusion
01-230	Chills	Probably unrelated	1	Event after RBC transfusion
01-389	Chills, nausea, vomiting	Probably unrelated	1	Coincident with other medications
01-421	Fever, dyspnea, chest-abdominal pain	Probably unrelated	1	Onset 2 hr after transfusion, blood cultures negative
01-427	Chills	Probably unrelated	1	Onset 76 min after transfusion, blood cultures negative
01-395	Chills	Unrelated	1	No fever increase, PLT unit culture negative

* Adverse events reported after PLT transfusion.
† Causal relation to transfusion as assessed by primary care physician.
‡ Adverse event severity grade where: Grade 0 = isolated dysfunction without clinical or biological manifestation; Grade 1 = absence of immediate or long-term life-threatening consequence; Grade 2 = long-term life-threatening consequence; Grade 3 = immediate life-threatening consequence; Grade 4 = death.

TABLE 5. Number of study transfusions before the first transfusion reaction

Transfusions before first reaction	Transfusions with reactions (n = 42)
1	8
2	6
3	5
4	5
5	2
6-11	7
11-20	3
>20	6

TABLE 6. Transfusions associated with suspected bacterial sepsis

Patient ID	Vital signs	Culture result
01-007	36.8/38.6°C BP* 150/80	Patient blood culture negative
01-039	36.1/36.1°C BP 140/80	Patient blood culture negative
01-464	Afebrile, severe hypotension	PC culture negative
01-178	39°C 12 hr after BP 120/80	PC culture negative
01-098	37.3/39.9°C BP 60/40	PC negative, dental abscess positive

* BP = blood pressure; PC = platelet component.

Patient 01-007 had chills, fever, and urticaria after a transfusion. Culture of a tubing segment was positive for micrococcus, but blood culture from the patient was negative. The urticaria was attributed to antibiotic medication. The tubing segment culture result was considered a laboratory contaminant. Patient 01-039 experienced chills without fever, but with dyspnea after a transfusion. No other symptoms or signs were reported. Culture of the administration tubing set was positive for coagulase-negative staphylococcus, but blood cultures from the patient were negative. Patient 01-464 experienced posttransfusion hypotension. Culture of a detached tubing segment was positive for *Staphylococcus warneri*, but culture of the PLT component and blood cultures were negative. Patient 01-178 developed fever and chills after a PLT transfusion with a positive blood culture for *Escherichia coli*. Culture of the PLT component, however, was negative. Patient 01-098 developed fever (39.9°C) with chills and hypotension 12 hours after a PLT transfusion. Blood culture was positive for the presence of *Actinomyces*, but culture of the associated PLT component was negative. Subsequently, the source of sepsis was identified as a dental abscess. In summary, no posttransfusion adverse events suspicious for transfusion-associated sepsis were confirmed with concomitant-positive PLT component and patient blood cultures.

Serious adverse events after PLT transfusion

Three serious adverse events were reported after PLT transfusion. Patient 01-096 had severe hemodynamic instability after liver biopsy associated with bleeding and was transferred to intensive care. After the onset of hemorrhage, she received a study PLT transfusion followed by severe hypotension (blood pressure, 42/22; heart rate, 92 beats/min). She was treated with fresh-frozen plasma (FFP), vasopressors, and fibrinogen and recovered. The primary care physician assessed the event as probably unrelated to the PLT transfusion and attributed the hypotension secondary to hepatic hemorrhage with hemodynamic instability.

Patient 01-098, receiving chemotherapy for acute leukemia, experienced fever, chills, and hypotension 12 hours after his 31st PLT transfusion. Subsequent blood cultures were positive for the presence of *Actinomyces*, but the PLT component culture was negative. The source of sepsis was attributed to a dental abscess and was classified as unrelated to the PLT transfusion.

Patient 01-464 developed hemorrhage during mitral valve surgery and was treated with PLT transfusions and methylene blue FFP. He experienced hypotension after the second study transfusion. Cultures of the PLT component and blood cultures were negative. One day later the patient experienced a second hypotension episode after transfusion of red blood cells (RBCs). The investigator attributed the event as an allergic adverse event related to the PLT transfusion. The patient had no other allergic symptoms. The patient recovered and was discharged in good condition.

Risk factors associated with transfusion reactions

Both patient and PLT component characteristics were analyzed for association with transfusion reactions. The analyses showed that 6.0 percent of male patients experienced at least one transfusion reaction and 7.3 percent of the female patients experienced at least one transfusion reaction ($p = 0.59$; odds ratio [OR], 1.19). Stratification by age showed that 4.6 percent of the patients older than 64 years of age presented with at least one transfusion reaction compared to 8.3 percent of patients below 64 years of age ($p = 0.06$; OR, 0.54). Finally, 8.8 percent of patients with a prior history of transfusion experienced at least one reaction while only 4.5 percent of patients with no prior transfusion history experienced at least one reaction ($p = 0.07$; OR, 1.99). These factors may be confounded with the diagnostic category of the patients; however, there were no significant associations between diagnostic category and transfusion reactions. Most of the transfusions with attributed reactions were associated with apheresis preparations. Only one random-donor PLT component was reported with a transfusion reaction, but this low incidence of reactions was most likely due to the

disproportionate use of apheresis components in this study and not a true effect of preparation method.

Extent of exposure before the first transfusion reaction

Among the 42 transfusions associated with a transfusion reaction, reactions occurred after single and multiple transfusions (Table 5). These data suggest that repeated exposure to INTERCEPT PLTs did not increase the likelihood of a transfusion reaction. Among the 10 patients without a previous transfusion history who experienced a transfusion reaction, 3 patients had an event at the first PLT transfusion, 1 after the 4th, and 6 patients after more than 5 transfusions. Patient 01-113 experienced the first reaction (urticaria and flushing) after the 139th INTERCEPT transfusion. Thus, for this patient population without prior blood product exposure, the risk of a transfusion reaction after INTERCEPT PLTs did not appear to increase with increased exposure.

DISCUSSION

Generally when a new type of labile blood component is introduced into routine clinical practice, initial information characterizing the safety profile is derived from a limited number of observations during the clinical development phase.[3] The introduction of PCT PLTs into routine clinical practice provided an opportunity to collect more information on the tolerability and safety of PCT PLTs in a broader patient population and under routine clinical conditions in contrast to a clinical trial environment. This approach is consistent with the recent recommendation from a consensus conference that new blood safety technologies should be evaluated with postmarketing hemovigilance studies.[10]

A prospective observational study with obligatory reporting for all transfusions regardless of outcome was designed to assess the safety profile of PCT PLTs in routine clinical practice. The data from the present study represent the largest prospective experience to date for recording potential adverse events associated with PLT transfusions compared to prior studies of retrospective design and limited size.[11-14] This study was planned to be consistent with European hemovigilance practices in which reporting of all grades of transfusion-associated reactions has been emphasized.[5,6] In contrast to passive hemovigilance studies, in this study obligatory reporting for all PLT transfusions was required irrespective of outcome. This study focused on adverse events that could be linked to PLT transfusions, specifically in the first 24 hours after transfusion, but there were no specific limitations on when adverse events could be reported after transfusion. This study captured information on repeated transfusions within patients to determine potential effects of repeated exposure to this new type of PLT component.

A potential limitation of this study was the absence of a concurrent control group receiving conventional PLT components with which to determine a comparative incidence of acute transfusion reactions. Another limitation was the potential for overreporting due to the absence of a blinded design and the increased awareness among observers that a new type of PLT component was under evaluation.

These potential limitations were addressed in several ways. A large portion of the transfusions were administered at the Mont Godinne Blood Transfusion Center, which had prospectively collected data for both PLT and RBC transfusions during an 18-month period before routine implementation of PLT components treated with pathogen inactivation. After the universal introduction of treated PLT components into clinical use at this center, the methods for RBCs did not change. During both periods of observation, PLT ASs were used to reduce exposure to allogeneic plasma.[15] Thus, in this center, we were able to compare the prevalence of transfusion associated adverse events with the same group of observers for one component with a new intervention (PCT PLTs) and another component that was unchanged (RBCs). Based on a comparison of the two observation periods, Osselaer and coworkers[15] reported a significant reduction in reactions to treated PLT components, from 1.3 to 0.9 percent ($p = 0.02$), while the incidence of reactions to RBCs was equal in both periods (0.4%). The experience from this two-period, two-component analysis suggested that observer sensitivity for overreporting did not occur. In addition, these data provided a background rate for acute transfusion reactions for leukoreduced PLT components with PLT AS (1.3% of transfusions).

Other estimates on the background prevalence of transfusion reactions can be obtained from the literature. On a per-transfusion basis, the prevalence has been reported to range from 18 to 31 percent; however, these studies were conducted some years ago with variable methods of PLT preparation.[11,16-18] More recently, the incidence of moderate and severe transfusion reactions has been reported from the TRAP study, which examined 8769 PLT transfusions in 598 patients during induction therapy for acute leukemia.[19] The overall incidence of reactions was 2.2 percent of transfusions, and 22 percent of patients experienced at least one transfusion reaction. In comparison to the TRAP trial, in this study in which all grades of reactions were reported, both the proportion of transfusions associated with a reaction (0.8%) and the proportion of patients (4.9%) experiencing at least one transfusion reaction causally attributed to a PLT component were lower.

Another comparison can be made with data from the hemovigilance network in France.[5] In that study, which

reported data for transfusion reactions during 2 years in which the reporting system was first implemented, an incidence of four events per 1000 PLT components (0.4%) was reported. This may be an underestimate, however, since each whole-blood PLT concentrate in a pool was tabulated as an individual component. More recently, Kerkhoffs and colleagues[14] compared the incidence of transfusion reactions for leukoreduced pooled PLT components in plasma and plasma with AS in a study of 168 patients and 765 transfusions. They observed an incidence of 5.5 percent of transfusions with reactions for PLTs in plasma versus 2.4 percent of transfusions for PLTs in a mixture of plasma and AS. On a per-patient basis, 9.5 percent of patients transfused with PLTs in plasma-ASs had reactions compared to 15.5 percent of patients supported with PLTs suspended in plasma.

In this study, which is the largest prospective PLT transfusion study to date specifically designed to capture all grades of transfusion reactions, the prevalence of reactions per transfusion and per patient was at the lower range of those reported in studies with conventional components. Younger patient age and prior exposure to blood transfusions were risk factors trending to a higher incidence of transfusion reactions. Recently, a higher rate of transfusion reactions also was reported in a hemovigilance survey of pediatric hematology patients.[20]

Prior exposure to INTERCEPT PLT transfusions did not increase the likelihood of a transfusion reaction. In comparison to other studies of PLT components in plasma-AS mixtures, the incidence of transfusion reactions on a per-patient basis for components prepared with PCT was reduced further. Importantly, this study enrolled a substantial number of patients with hematology–oncology disorders treated with complex therapies and supported with repeated PLT transfusions as well as surgical patients requiring PLT support. No incidents of TRALI, transfusion-transmitted bacterial sepsis, or death associated with acute transfusion reactions were observed in this study. Based on this experience in a broad patient population, PLT components prepared with PCT were well tolerated in routine clinical practice. The types and severity of acute reactions to PLT components prepared with pathogen inactivation treatment were consistent with previous reports of adverse events to conventional PLT components, and the data from this study provide additional data on the safety of PLT components treated with amotosalen and UVA light.

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市販後調査及び観察研究の報告②

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An active haemovigilance programme characterizing the safety profile of 7437 platelet transfusions prepared with amotosalen photochemical treatment

J. C. Osselaer,[1] J. P. Cazenave,[2] M. Lambermont,[3] O. Garraud,[4] M. Hidajat,[5] L. Barbolla,[6] R. Tardivel,[7] L. Defoin,[1] C. Waller,[2] I. Mendel,[2] J. P. Raidot,[2] G. Kandel,[2] R. De Meuter,[3] P. Fabrigli,[4] D. Dehenau,[5] J. L. Arroyo,[6] F. Padrón,[6] H. Gouezec,[7] M. Corral,[8] M. Jacquet,[9] D. Sundin,[9] L. Lin[9] & L. Corash[9]

[1]Blood Transfusion Center, Cliniques Universitaires de Mont Godinne, Universite Catholique de Louvain, Yvoir, Belgium
[2]EFS Alsace, Strasbourg, France
[3]Service du Sang, Belgian Red Cross, Erasme University Hospital, Brussels, Belgium
[4]EFS Auvergne Loire, St. Etienne, France
[5]Blood Transfusion, AZ St Jan AV, Brugge, Belgium
[6]Centro de Hematerapia y Hemodonacion de Castilla y Leon, Valladolid, Spain
[7]EFS Bretagne, Rennes, France
[8]Hospital Universitario de Salamanca, Salamanca, Spain
[9]Cerus Corporation, Concord, CA, USA

Vox Sanguinis

Background An active haemovigilance programme was implemented to survey adverse events (AE) associated with transfusion of platelets photochemically treated with amotosalen and ultraviolet A (PCT-PLT). The results of 5106 transfusions have already been reported. Here we report the results of an additional 7437 PCT-PLT transfusions.

Methods The focus of this ongoing haemovigilance programme is to document all AEs associated with PCT-PLT transfusion. Data collected for AEs include: time of event after starting transfusion, clinical descriptions, vital signs, results from radiographs and bacterial cultures, event severity (Grade 0–4) and causal relationship to PCT-PLT transfusion.

Results One thousand four hundred patients (mean 60 years, range 1–96) received PCT-PLT transfusions. The majority of the patients (53·4%) had haematology–oncology diseases and required conventional chemotherapy (44·8%) or stem cell transplantation (8·6%). Sixty-eight PCT-PLT transfusions were associated with AE. Acute transfusion reactions (ATR), classified as an AE possibly related, probably related, or related to PCT-PLT transfusions were infrequent ($n = 55$, 55/7437 = 0·7%) and most were of Grade 1 severity. Thirty-nine patients (39/1400 = 2·8%) experienced one or more ATRs. The most frequently reported signs/symptoms were chills, fever, urticaria, dyspnoea, nausea and vomiting. Five AEs were considered severe (≥ Grade 2); however, no causal relationship to PCT-PLT transfusion was found. Repeated exposure to PCT-PLT did not increase the likelihood of an ATR. No cases of transfusion-related acute lung injury and no deaths due to PCT-PLT transfusions were reported.

Conclusions Routine transfusion of PCT-PLT is well-tolerated in a wide range of patients. ATRs related to PCT-PLT transfusion were infrequent and most were of mild severity.

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Correspondence: Lily Lin, Cerus Corporation, 2411 Stanwell Drive, Concord, CA 94520, USA
E-mail: llin@cerus.com

Introduction

INTERCEPT Blood System™ uses a photochemical treatment methodology [PCT: amotosalen plus ultraviolet A (UVA) light] to inactivate viruses, bacteria, protozoa, and leucocytes in platelet (PLT) and plasma components. The PLT system received CE Mark registration in Europe in 2002. Several centres in Belgium, Spain, Norway and Italy began routine production of PCT-PLT in 2003. An active haemovigilance programme was immediately implemented to prospectively collect information on PCT-PLT transfusions administered to patients in routine clinical settings. Prior to CE Mark registration, the safety data of PCT-PLT were primarily obtained from controlled clinical trials with a limited number of patients and predetermined clinical and safety end-points [1–3]. The postmarketing haemovigilance programme provided a means to extend the characterization of the safety profile of PCT-PLT in routine use and in a broad patient population. The results of the first 5106 PCT-PLT transfusions have already been reported [4]. With additional centres in Belgium, Spain and France starting with the routine production of PCT-PLT, the database of this haemovigilance programme has been expanded [5].

In March 2007, the Canadian Blood Services and Héma-Québec organized a consensus conference to provide recommendations and guide decision-making about new pathogen inactivation technologies [6]. The panel, consists of nine healthcare professionals and members of the public, stressed the importance of postmarketing surveillance studies in the introduction of new technologies for blood safety. The panel recommended that specific studies should be mandated by the regulatory authorities and supported by the manufacturers and/or the blood suppliers. Postmarketing surveillance for adverse reactions to pathogen inactivation products should be linked to the national haemovigilance systems if possible. Depending on the new pathogen inactivation technologies implemented, specific additional surveillance outcomes may be identified. The panel also suggested that chronically transfused patients might serve as an ideal surveillance population to identify long-term toxicities of pathogen-inactivated products.

The active haemovigilance programme described in this study is in concordance with these recommendations. Although this programme is not directly linked to a specific country haemovigilance system nor designed to replace any existing haemovigilance system, the format of data collection is modelled after the data collection format of the French haemovigilance system for documentation of transfusion incidents [7]. The focus of the current programme is on all adverse events (AE), serious or non-serious, occurring after the start of PCT-PLT transfusion. Following the recent report of 5106 PCT-PLT transfusions [4], here we report the results of an additional 7437 transfusions of PCT-PLT.

Materials and methods

General study design

This was a prospective observational active haemovigilance study. The objective of this study was to document the transfusion safety profile for approximately 7500 PCT-PLT components prepared with the INTERCEPT Blood System™ for platelets (Cerus Europe BV, Leusden, the Netherlands). These components were prepared in three centres in Belgium (CTS UCL Mont Godinne, CTS Brabant-Hainaut and AZ Sint Jan AV), three centres in France (EFS-Alsace, EFS-Auvergne-Loire and EFS-Bretagne), and one centre in Spain (CHEMCYL Valladolid) and administered to thrombocytopenic patients under standard clinical practice in hospitals. There were no randomization requirements, no inclusion criteria and no exclusion criteria of patients other than the need to receive a platelet transfusion. Baseline demographical information was collected on all study participants. Patients were assigned a centre-specific study number to preserve anonymity.

Patients who received transfusions of PCT-PLT were monitored for any AEs after the start of each platelet transfusion, which is consistent with European Haemovigilance Network recommendations for surveillance of AE to transfusion of labile blood components, and with those of national transfusion services [7,8]. However, in this study, reporting was obligatory for all PCT-PLT transfusions in each participating clinical site. A transfusion report was required for each PLT transfusion regardless of whether or not an AE occurred. In case of occurrence of an AE, additional clinical and biological information was collected to allow diagnosis and assessment of causality and severity. The data in the final database were anonymous and were reported on a per-transfusion basis as well as on a per-patient basis. Transfusions associated with serious AEs were reported in greater detail.

Study report forms

The report form used for this haemovigilance programme was developed on the basis of haemovigilance report forms already in use. Information was collected in several broad categories: patient demographic/diagnosis data, platelet component characteristics, transfusion events and documentation of all AEs following transfusion. An acute transfusion reaction (ATR) was defined as an AE possibly related, probably related, or related to a PCT-PLT transfusion.

AEs were graded for clinical severity within the following categories: Grade 0, isolated dysfunction without clinical or biological manifestation; Grade 1, absence of immediate or long-term life-threatening effects; Grade 2, long-term life-threatening effects; Grade 3, immediate life-threatening effects; and Grade 4, death. For each transfusion, the following

signs, symptoms and specific clinical syndromes were evaluated: fever, chills, cardiac arrhythmia, hypotension, itching, urticaria, skin rash, jaundice, pulmonary oedema, bronchospasm, dyspnoea, respiratory distress, nausea, vomiting, lower back pain, chest pain, abdominal pain, and shock. Any other findings could be entered as free text including refractoriness to platelet transfusion and transfusion-related acute lung injury. The following available clinical signs were recorded before and after each transfusion: temperature, blood pressure and heart rate. Abnormal clinical laboratory values, results of diagnostic procedures (chest X-ray) and bacterial cultures from patient and blood component sources were recorded when associated with an AE following a PCT-PLT transfusion.

Preparation of platelet components

Platelet components were collected by apheresis or from whole blood-derived buffy-coat procedures according to each centre's standard operating procedures. Volunteer donors were screened and tested for transfusion-transmitted pathogens according to each centre's standard operating procedures in compliance with respective national regulations. All components were leucocyte reduced, either by filtration (Sepacell PLS-5A, Asahi Biomedical, Tokyo, Japan) or process leucodepletion (Amicus Cell Separator, Fenwal, La Chatre, France; Haemonetics MCS+, Haemonetics, Braintree, MA, USA). Platelet components containing 2·5 to 6·0 × 10^{11} platelets were suspended in approximately 35% plasma and 65% InterSol™ (Fenwal) and prepared with amotosalen (nominal final concentration 150 μM) and a 3 J/cm² UVA light treatment (320–400 nm) according to the manufacturer's instructions for use (Cerus Europe BV). After treatment, PCT-PLTs were stored up to either 5 or 7 days under temperature-controlled conditions (22 ± 2 °C) before release for transfusion depending on country-specific regulations. PCT-PLTs were transfused before the expiration period of 5 days in France and Spain or 7 days in Belgium. PCT-PLTs were not cultured for bacterial contamination prior to release, and PCT was used in place of γ-irradiation for prevention of transfusion-associated graft-versus-host disease in all sites except EFS-Bretagne and EFS-Auvergne-Loire.

Platelet transfusion

PCT-PLT components for transfusion were ordered according to standard indications within each institution. The investigator was requested to report all AEs occurring after starting transfusion without time limitation. The severity of each AE (Grade 0 to 4) and the relationship of each AEs to the preceding platelet transfusion were assessed by the investigator. Serious adverse events were reported in greater detail with a narrative for each event.

Statistical analyses

All statistical analyses, summary tables and data listings were generated using SAS® version 8·2. The primary assessment of safety was the proportion of ATR for the transfusions reported. The safety profile of PCT-PLT transfusions included information on: the number of PCT-PLT transfusions by patient; the patient population profile; the characteristics of the PCT-PLT transfused, and the characteristics of the AE following platelet transfusion.

Data were analysed on a per-transfusion basis as well as on a per-patient basis. All PCT-PLT transfusions administered to a patient were included in the full analysis population, whether or not an AE was observed. Data were summarized for each parameter using descriptive statistics (mean, standard deviation, median, and range).

Statistical tests were performed for the exploration of risk factors only (multivariate logistic regression at 10% significant level). The variables included in the analysis are patient gender, age, previous transfusion history, type of platelet concentrate, γ-irradiation, antigen-matching and primary diagnosis. Variables with descriptive statistics were tested for *P* values and odds ratio. The number and proportion (%) of transfusions with one or more AEs were summarized overall, by seriousness and by relationship to platelet transfusion. Corresponding 95% confidence intervals (CIs) were calculated.

The non-survival analysis method is a univariate analysis of the number of transfusions received before the first occurrence of an AE. Only patients with at least one AE were considered in this analysis.

Results

Distribution of transfusions

A total of 7437 PCT-PLT transfusions were documented between May 2005 and January 2007 and constitute the full analysis population. The distribution of transfusion reports were: 3057 (41·1%) from CTS UCL Mont Godinne, 2048 (27·5%) from EFS-Alsace, 899 (12·1%) from CTS Brabant-Hainaut, 572 (7·7%) from EFS-Auvergne-Loire, 440 (5·9%) from AZ Sint Jan AV, 381 (5·1%) from CHEMCYL, and 40 (0·5%) from EFS-Bretagne.

Patient demographics

A total of 1400 patients underwent transfusion (Table 1). The majority of the patients were male (61·3%) and the mean age was 60 years (range < 1–96 years). Haematology–oncology diseases treated by chemotherapy (44·8%) and stem cell transplantation (8·6%) constituted 53·4% of the primary diagnoses and therapies among the transfused population. A significant number of patients receiving platelet transfusion (17·2%) were undergoing cardiovascular surgery or solid organ transplantation. Other diagnoses included haematology–oncology diseases not treated by chemotherapy and/or stem cell transplantation and surgery other than cardiovascular surgery and solid organ transplantation.

Table 1 *Patient and transfusion demographics*

	Patient characteristics (*n* = 1400)	Transfusion characteristics (*n* = 7437)
Gender (*n*, %)		
Male	858 (61·3%)	4354 (58·5%)
Female	542 (38·7%)	3082 (41·4%)
Unknown		1 (< 0·1%)
Age (years)		
Mean ± SD	60·0 ± 17·8	
Median	63	
(minimum–maximum)	(<1–96)	
Location of transfusion		
Intensive care unit		1145 (15·4%)
Outpatient		382 (5·1%)
Regular ward		5908 (79·4%)
Unknown		2 (< 0·1%)
Haematology–oncology patients	748 (53·4%)	5463 (73·5%)
Conventional chemotherapy	627 (44·8%)	4481 (60·3%)
Stem cell transplant	121 (8·6%)	982 (13·2%)
Surgery patients	241 (17·2%)	480 (6·5%)
Cardiovascular surgery	209 (14·9%)	349 (4·7%)
Solid organ transplantation	32 (2·3%)	131 (1·8%)
Other diagnoses	397 (28·4%)	859 (11·6%)
Missing diagnosis	14 (1·0%)	635 (8·5%)
History of a previous transfusion		
Yes	837 (59·8%)	5029 (67·6%)
No	398 (28·4%)	1927 (25·9%)
Unknown	165 (11·8%)	481 (6·5%)
If 'Yes' – did they experience a transfusion-related adverse event?[a]		
Yes	53 (6·3%)	382 (7·6%)
No	779 (93·0%)	4639 (92·2%)
Unknown	5 (0·6%)	8 (0·2%)

[a]For per-patient basis, the denominator is 837; for per-transfusion basis, the denominator is 5029.

Of all patients, 837 patients (59·8%) had already received another blood product before the first PCT-PLT transfusion (Table 1). Among these patients, 53 patients (6·3% of 837) had a history of a transfusion reaction of some type in the past.

Platelet component demographics

Most of the PCT-PLT units were manufactured from apheresis platforms (4822, 64·8% vs. 2615, 35·2% for buffy-coat products). The majority of the PCT-PLTs (7357, 98·9%) were not treated with γ-irradiation [9]. Among the 7437 PCT-PLTs transfused, only 2·5% (189 units) of platelet units were human leucocyte antigen-matched products.

A large proportion of the PCT-PLT components (5908, 79·4%) were transfused in non-intensive care hospital wards (Table 1). Intensive care units and day-hospital units were the location for 15·4 and 5·1% of the PCT-PLT transfusions (1145 and 382 units, respectively). While most of the PCT-PLT components (5463, 73·5%) were administered to haematology–oncology patients, only 480 PCT-PLT components (6·5%) were administered to surgery patients.

The majority of the PCT-PLT components (5029, 67·6%) were administered to patients who had already received another blood component before the first PCT-PLT transfusion (Table 1). Among these transfusions, 382 (7·6% of 5029) PCT-PLT components were transfused to patients reported to have experienced at least one transfusion reaction in the past.

Number of transfusions per patient

The range of PCT-PLT transfusions per patient was 1 to 129, with an average of 5·3 ± 10·8 (median: 2) transfusions per patient. Of the 1400 patients who received PCT-PLT transfusions, 529 patients (37·8%) received only one PCT-PLT transfusion during this study period, 418 patients (29·9%) received two to three transfusions, and 453 patients (32·4%) received more than four PCT-PLT transfusions during the study. The majority of patients who received multiple transfusions had a primary diagnosis of haematology–oncology diseases treated by chemotherapy and/or stem cell transplantation.

Two patients from CTS UCL Mont Godinne received more than 100 transfusions analysed in this haemovigilance plan. One 56-year-old man (J01-636) who was treated by conventional chemotherapy for haematology–oncology disease received 129 PCT-PLT components within an 8-month period (from April 2006 to November 2006). One 72-year-old woman (J01-071) who was also treated by conventional chemotherapy for haematology–oncology disease received 107 PCT-PLT components within a 10-month period (from August 2005 to November 2006).

Adverse events following PCT-PLT transfusion

On a per-transfusion basis, 68 (0·9% of 7437 transfusions, 95% CI: 0·7–1·2%) transfusions were associated with an AE (Table 2). Of which, 55 (0·7% of 7437 transfusions, 95% CI: 0·6–1·0%) were classified as ATR possibly related, probably related, or related to PCT-PLT transfusion. Only five events were classified as serious AEs (0·07%, 95% CI: 0·0–0·2%), and were judged as probably unrelated to the PCT-PLT transfusion based on the observation of alternative causes for symptoms and no evidence of causal relationship to the platelet transfusion. No cases of transfusion-related acute lung injury and no deaths due to PCT-PLT transfusions were reported.

Table 2 Clinical characteristics of adverse events (AE)

	On a per-transfusion basis n (% = n × 100/7437)				On a per-patient basis n (% = n × 100/1400)			
	Any AEs	AE attributed to platelets (ATR)[b]	SAE[a]	SAE attributed to platelets[a,b]	Any AEs	AE attributed to platelets (ATR)[b]	SAEs[a]	SAE attributed to platelets[a,b]
Number with at least one event	68 (0·9%)	55 (0·7%)	5 (< 0·1%)	0 (0·0%)	45 (3·2%)	39 (2·8%)	4 (0·3%)	0 (0·0%)
Signs/Symptoms[c]								
Fever	8 (0·1%)	6 (< 0·1%)	0 (0%)	–	7 (0·5%)	5 (0·4%)	0 (0%)	–
Chills	45 (0·6%)	40 (0·5%)	2 (< 0·1%)	–	31 (2·2%)	28 (2·0%)	1 (< 0·1%)	–
Itching	2 (< 0·1%)	2 (< 0·1%)	0 (0%)	–	1 (< 0·1%)	1 (< 0·1%)	0 (0%)	–
Hypotension	1 (< 0·1%)	0 (0%)	1 (< 0·1%)	–	1 (< 0·1%)	0 (0%)	1 (< 0·1%)	–
Urticaria	14 (0·2%)	14 (0·2%)	0 (0%)	–	13 (0·9%)	13 (0·9%)	0 (0%)	–
Skin rash	5 (< 0·1%)	5 (< 0·1%)	0 (0%)	–	4 (0·3%)	4 (0·3%)	0 (0%)	–
Dyspnoea	8 (0·1%)	6 (< 0·1%)	1 (< 0·1%)	–	8 (0·6%)	6 (0·4%)	1 (< 0·1%)	–
Respiratory distress	1 (< 0·1%)	0 (0%)	1 (< 0·1%)	–	1 (< 0·1%)	0 (0%)	1 (< 0·1%)	–
Nausea/vomiting	8 (0·1%)	5 (< 0·1%)	3 (< 0·1%)	–	5 (0·4%)	3 (0·2%)	2 (0·1%)	–
Lower back pain	6 (< 0·1%)	1 (< 0·1%)	0 (0%)	–	2 (0·1%)	1 (< 0·1%)	0 (0%)	–
Chest/abdominal pain	1 (< 0·1%)	1 (< 0·1%)	0 (0%)	–	1 (< 0·1%)	1 (< 0·1%)	0 (0%)	–
Shock	4 (< 0·1%)	0 (0%)	4 (< 0·1%)	–	3 (0·2%)	0 (0%)	3 (0·2%)	–
Tachycardia	4 (< 0·1%)	3 (< 0·1%)	1 (< 0·1%)	–	3 (0·2%)	2 (0·1%)	1 (< 0·1%)	–
Other	14 (0·2%)	11 (0·1%)	3 (< 0·1%)	–	12 (0·9%)	10 (0·7%)	3 (0·2%)	–

[a]Serious adverse event (SAE): long-term life threatening, immediate life threatening or death.
[b]Causal relationship that was possibly related, probably related, or related to PCT-PLT transfusion.
[c]Number of signs/symptoms can exceed number of AE due to multiple observed signs/symptoms per AE.

On a per-patient basis, 45 patients (3·2% of 1400 patients) who received at least one transfusion of PCT-PLT experienced the 68 AEs following PCT-PLT transfusions (Table 2). Only 39 patients (2·8% of 1400 patients) experienced the 55 ATRs attributed to the PCT-PLT transfusion. Four patients experienced serious AEs following transfusion; however, no causal relationship to PCT-PLT transfusion could be established.

All AEs regardless of the relationship with the PCT-PLT transfusion occurred within 4 h after the start of the platelet transfusion (mean time: 0·3 ± 0·51 h, 0–3·3 h). The majority of AEs (64, or 94·1% of 68 AEs) occurred in patients who were not premedicated. The other four AEs occurred in patients who were premedicated with antipyretic or antihistaminic drugs, or corticosteroids.

Characteristics of clinical signs and symptoms associated with adverse event

On a per-transfusion basis, the most frequently observed symptoms/signs (≥ 0·1% of the total 7437 transfusions) were fever, chills, urticaria, dyspnoea, nausea and/or vomiting (Table 2). The individual incidence of each of the following signs/symptoms was < 0·1%: itching, hypotension, skin rash, respiratory distress, lower back pain, chest or abdominal pain, shock and tachycardia. All additional symptoms included in the category of other, such as refractoriness to platelet transfusion, hypertension, cephalea, pain in the leg, flush, malaise, cyanosis, oxygen desaturation and volume overload were also reported but with an individual incidence of less than 0·1%. Most of ATRs were described principally as Grade 1 chills and urticaria (Table 2).

On a per-patient basis, the most frequently observed symptoms/signs (≥ 0·5% of the total 1400 patients) were fever, chills, urticaria and dyspnoea (Table 2). Approximately 0·1–0·4% of the population (from 2 to 5/1400) experienced the following signs/symptoms: skin rash, nausea/vomiting, shock, lower back pain and tachycardia. Clinical refractoriness to transfusion, hypertension, headache and flushing were additional symptoms reported in the category of 'other'. Less than 0·1% of the study population (only 1/1400) experienced the following signs/symptoms such as hypotension, itching, respiratory distress and chest/abdominal pain. Symptoms such as pulse increase, leg pain, cyanosis, oxygen desaturation, malaise and/or volume overload were also reported in the category of 'other'. Most of the ATRs consisted of various combinations of fever (0·4%), chills (2·0%), urticaria (0·9%), skin rash (0·3%), dyspnoea (0·4%), nausea/vomiting (0·2%), tachycardia (0·1%) and others symptoms (0·7%) (Table 2).

Serious adverse events following platelet transfusion

During the course of this surveillance, five serious AEs were reported following transfusion of PCT-PLT (0·07%, 95% CI: 0·0–0·2). These serious AEs were assessed by the investigators as being 'unrelated or probably unrelated' to the PCT-PLT transfusions and were attributed to progression of underlying illness.

Patient B01-201 was admitted to hospital for a presumed pulmonary infection postchemotherapy. Additional co-morbidities at the time of admission were septic shock, acute renal insufficiency, neutropenia and thrombocytopenia. Intravenous (i.v.) antibiotic therapy was initiated and multiple transfusions of blood products (including PCT-PLT) were administered. One hour after administration of the second platelet unit, the patient complained of dyspnoea, respiratory distress was found to be hypotensive and tachycardic. Severe volume overload was determined to be the aetiology and treatment with oxygen, diuretics, and dialysis was initiated. The event was assessed by the investigator to be unrelated to the PCT-PLT transfusion.

Patient J01-382 experienced chills, nausea and sudden hypotension during transfusion with PCT-PLT. Prior to this, the patient had received at least four PCT-PLT transfusions with no AE. The transfusion was stopped and the patient was treated with i.v. fluids and recovered. Four days later, the patient experienced a second hypotensive episode after transfusion, which was spontaneously resolved. Subsequent to this, the patient received 19 additional PCT-PLT transfusions without any clinical sequelae. This patient did not receive any angiotensin-converting enzyme (ACE) inhibitors. Based on the patient's history and the lack of transfusion reaction with the subsequent transfusions, the investigator assessed both of these events as probably unrelated to PCT-PLT transfusion.

Patient J01-516 was admitted for ischaemic cardiomyopathy and underwent double vessel coronary artery bypass graft (CABG). The patient's postoperative recovery was complicated by a significant decrease in blood pressure, which occurred 10 min after start of transfusion of PCT-PLT. Despite vasopressor support and a 6-min period of circulatory arrest, the patient's condition continued to deteriorate and he died. Cause of death was attributed to an aortic dissection with major disseminated intravascular coagulopathy and mesenteric infarct and was assessed by the investigator as unrelated to the PCT-PLT transfusion.

Patient J01-780 experienced a hypotensive episode, cyanosis, oxygen desaturation and nausea approximately 30 min after receipt of PCT-PLT. The patient received oxygen therapy to treat the event and recovered. The patient had received two units of PCT-PLT before and one unit after this event with no adverse reactions. The patient had a history of hypotensive episodes, which occurred in the absence of transfusions. Based on the patient's history, the event was assessed by the investigator as probably unrelated to the PCT-PLT transfusion.

Risk factors associated with adverse event

The risk for AE was not correlated with the patient gender, age, or antigen-matching. The risk for AE for patients who already had been transfused before the first PCT-PLT transfusion appeared trending higher compared to patients who did not have any transfusion history; however, the difference did not reach statistical significance (P = 0·0675; odds ratio: 1·875; 95% CI: 0·956–3·648). Buffy-coat-derived platelets were associated with a lower risk for AE compared to apheresis products (P = 0·0305; odds ratio: 0·473; 95% CI: 0·240–0·932). Irradiated PCT-PLTs were of similar risk for AE compared to non-irradiated PCT-PLTs (P = 0·0848; odds ratio: 6·344; 95% CI: 0·776–51·862). No trending can be concluded because, of the total 7437 platelet transfusions, only 80 PCT-PLT components were γ-irradiated in EFS-Bretagne and EFS-Auvergne-Loire. Haematology–oncology patients treated with conventional chemotherapy were at a higher risk for AE compared to the other patients ($P \leq$ 0·0001; odds ratio: 7·660; 95% CI: 3·014–19·467).

Number of transfusions prior to the first adverse event

Among the 45 patients who experienced at least one AE, repeated exposure to PCT-PLT did not appear to increase the likelihood of a transfusion reaction (Table 3). By using the non-survival analysis method (a subset analysis for patients with any AE only), the mean number of transfusions before first AE occurrence was 8·8 ± 10·1 (median = 4, minimum = 0 and maximum = 37).

Discussion

In accordance with the recommendations made by the panel of the Canadian Consensus Conference, an active haemovigilance programme has been implemented in Europe to document the occurrence of AE following transfusion of PCT-PLT [6]. To date, two reports have been prepared. The first report was on the transfusion of 5106 PCT-PLT components administered to patients in five European centres from October 2003 to December 2005 [4]. The second report as described here was on additional 7437 transfusions of PCT-PLT administered to patients in seven European centres between May 2005 and January 2007. This represents a total of 12 543 independent transfusions documented to date. There are no overlaps of PCT-PLT transfusions reported in this haemovigilance programme.

Overall, the incidence of ATR attributed to transfusion of PCT-PLT in both of the haemovigilance reporting periods was infrequent either on a per-transfusion basis (0·8% first period

Table 3 Number of PCT-PLT transfusions per patient prior to the first adverse event (AE)

Number of PCT-PLT transfusions per patient until first occurrence of AE	Full analysis population (n = 1400)
1	11 (0·79%)
2	6 (0·43%)
3	3 (0·21%)
4	3 (0·21%)
5	1 (0·07%)
6–10	9 (0·64%)
11–19	6 (0·43%)
≥ 20	6 (0·43%)
N (non survival analysis method)	45
Mean ± SD	8·8 ± 10·1
Median	4
Minimum–maximum	0–37

vs. 0·7% second period) or on a per-patient basis (4·9% first period vs. 2·8% second period). The slightly higher occurrence of ATR per patient in the first reporting period was not surprising, because the mean number of transfusions per patient (7·8 ± 16·2) [4] was greater than those observed in the second period (5·3 ± 10·8). All ATRs were mild in severity and of Grade 1 or lower. No serious AE from both study periods were attributed specifically to transfusion of PCT-PLT.

On a per-transfusion basis, the prevalence of ATR has been reported in the literature to range from 18 to 31%; however, these studies were conducted some years ago with variable methods of platelet preparation [10–13]. More recently, the incidence of moderate and severe ATR has been reported from the trial to reduce alloimmunization to platelets (TRAP) study, which examined 8769 platelet transfusions in 598 patients during induction therapy for acute leukaemia [14]. In the TRAP study, platelet components were prepared by four methods: unfiltered pooled whole blood-derived platelets in plasma; filtered pooled whole blood-derived platelets in plasma; unfiltered pooled whole blood-derived platelets in plasma treated with ultraviolet B illumination to reduce human leucocyte antigen sensitization; and filtered apheresis platelets in plasma. None of these components were prepared with additive solutions. The overall incidence of ATR was 2·2% of transfusions, and 22% of patients experienced at least one ATR. In comparison to the TRAP trial, the current study in which all grades of reactions were reported, both the proportion of transfusions associated with a reaction was lower (0·7%) as well as the proportion of patients (2·8%) experiencing at least one ATR. The use of 65% InterSol, a platelet additive solution, in the preparation of PCT-PLT may partially contribute to the reduction in the observed incidence of ATR [15].

The incidence of ATR in this study can be compared to data from the haemovigilance network in France [7]. In France, data were reported for transfusion reactions, with an incidence of four events per 1000 platelet components (0·4%), during 2 years in which the reporting system was first implemented. However, this may be an underestimate since each whole blood platelet concentrate in a pool was tabulated as an individual component transfusion. More recently, Kerkhoffs *et al.* [16] compared the incidence of transfusion reactions for leucoreduced pooled platelet components in plasma and plasma with additive solution in a study of 168 patients and 765 transfusions. They observed an incidence of 5·5% of transfusions with reactions for platelets in plasma vs. 2·4% of transfusions for platelets in a mixture of plasma and additive solution. On a per-patient basis, 9·5% of patients transfused with platelets in plasma plus additive solutions had reactions compared to 15·5% of patients supported with platelets suspended in plasma. These results further support the role of the platelet additive solution, InterSol, in the reduction of ATR observed in this study.

During the conduct of this study, an interim analysis of 2497 PCT-PLT transfusions administered to 606 patients in the three regions of France (EFS-Alsace, EFS-Auvergne-Loire and EFS-Bretagne) was performed [5]. Of the 606 patients, the predominant recipients of PCT-PLT were haematology-oncology patients (46·2%); 39·9% treated with chemotherapy and 6·3% treated with stem cell transplantation. These proportions were only slightly lower than those in the overall study population of 1400 patients, yet only four of the 606 patients (0·7%) reported an AE, including one serious AE of volume overload classified as unrelated to PCT-PLT transfusion. This low rate of AE observed in the French regions could contribute to the overall low incidence of ATR per patient in this study.

Premedication in patients did not play a role in the overall low incidence of ATR reported in this study. Information on premedication was only requested in case of AE occurrence. Of the 68 transfusions with occurrence of at least one AE, only two antipyretic, two antihistaminic and one corticosteroid were prescribed to patients. For the majority (64/68, or 94·1%) of these transfusions, patients were not premedicated.

The active haemovigilance programme described here is a prospective observational study, which was designed to assess the safety profile of PCT-PLT in routine clinical practice. The data from this programme represent the largest prospective experience to date for recording potential AE associated with platelet transfusions compared to prior studies of retrospective design and limited in size [10,16–18]. The present study was designed to be consistent with European haemovigilance practices in which reporting of all grades of transfusion-associated reactions has been emphasized [7,8]. In contrast to other haemovigilance studies, obligatory reporting for all platelet transfusions was required irrespective of whether or not an AE was observed. The current study focused on AE that could be linked to PCT-PLT transfusions after starting transfusion, but there were no specific limitations

on when adverse events could be reported following transfusion. Based on the patient population supported with platelet transfusion, the study was designed to capture repeated transfusions of PCT-PLT within patients to determine potential effects of repeated exposure to this new type of platelet component.

A limitation of the present study is the absence of a concurrent control group receiving conventional platelet components with which to determine a comparative baseline incidence of ATR. However, because reporting is obligatory, the expected outcomes of this active haemovigilance study are the increase in clinical experience with transfusion of PCT-PLT, the detection of unexpected AE following PCT-PLT transfusions in patient populations and for indications that were not studied previously in a formal clinical trial environment, and the establishment of a safety database for future reference.

In the current study, which was specifically designed to capture all grades of transfusion reactions, the prevalence of ATR per transfusion, was at the lower range of those reported in studies with conventional components. Prior exposure to PCT-PLT transfusions did not increase the likelihood of an ATR. The overall incidence of ATR was lower than that previously reported either on a per-transfusion or on a per-patient basis. Based on experience in a broad patient population, platelet components prepared with amotosalen photochemical treatment were well-tolerated in routine clinical practice.

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市販後調査及び観察研究の報告③

Transfusion of platelet components prepared with photochemical pathogen inactivation treatment during a Chikungunya virus epidemic in Ile de La Réunion

Patrice Rasonglès, Marie France Angelini-Tibert, Philip Simon, Caroline Currie, Herve Isola, Daniel Kientz, Marc Slaedts, Michele Jacquet, David Sundin, Lily Lin, Laurence Corash, and Jean Pierre Cazenave

BACKGROUND: During the Chikungunya virus (CHIKV) epidemic on Ile de La Réunion, France, more than 30% of 750,000 inhabitants were infected. Local blood donation was suspended to prevent transfusion-transmitted infection (TT-CHIKV). To sustain the availability of platelet (PLT) components, the Établissement Français du Sang implemented universal pathogen inactivation (INTERCEPT, Cerus Europe BV) of PLT components (CPAs). The study assessed the safety of PLT components treated with pathogen inactivation transfused in routine clinical practice.

STUDY DESIGN AND METHODS: This was a retrospective observational study using patient medical records and the AFSSAPS hemovigilance database (eFIT) to identify TT-CHIKV and adverse events (AEs) classified as acute transfusion reactions (ATRs) to PLT components prepared with pathogen inactivation.

RESULTS: During 1 year, 1950 INTERCEPT-CPAs were transfused to 335 adult, 51 pediatric, and 41 infant patients. Nineteen AEs were observed in 15 patients and 10 were classified as ATRs. Eight ATRs occurred in 6 pediatric hematology-oncology patients. No ATRs were observed in infants. The most frequently reported signs and symptoms were Grade 1 urticaria, itching, chills, fever, and anxiety. No cases of transfusion-related acute lung injury, TT-sepsis, or TT-CHIKV were detected.

CONCLUSIONS: INTERCEPT-CPAs were well tolerated in a broad range of patients, including infants. ATR incidence was low and when present ATRs were of mild severity.

Starting in 2005, an epidemic of Chikungunya virus (CHIKV) in the overseas French department of Ile de La Réunion, an island in the South Indian Ocean, resulted in the infection of more than one-third of the 750,000 inhabitants by early 2006.[1] CHIKV is an enveloped single-stranded alpha virus from the Togaviridae family transmitted by *Aedes* mosquitoes. It generally causes a mild febrile illness characterized by arthralgias lasting up to 10 days, but the recent epidemic was associated with myalgias, dermatitis, hemorrhage, meningoencephalitis, respiratory failure, cardiovascular decompensation, and fulminant hepatitis with persistent arthralgias in some patients.[2] Subsequently, more than 700 cases of CHIKV infection were reported in metropolitan France among returning travelers, and 1 infection after needle stick of a health care worker.[3,4] Owing to the high prevalence of CHIKV infection and the potential for transfusion-transmitted (TT) infection, the Établissement Français du Sang (EFS [French National Transfusion Service]) suspended blood donation on Ile de La Réunion to prevent TT-CHIKV.[1] To meet the requirements for safe blood components on Ile de La Réunion, red blood cells and plasma components (fresh-frozen plasma) were supplied by EFS from metropolitan France. Because of the limited shelf life (5 days) of platelet (PLT) components, EFS-La Réunion implemented pathogen inactivation preparation of apheresis PLT components (CPAs) to maintain local PLT component supplies.[5]

Prior research studies had demonstrated that CHIKV was inactivated by photochemical treatment with amotosalen HCl and UVA light (INTERCEPT Blood System for platelets, Cerus Europe BV, Amersfoort, The Netherlands).[6] In addition, this system had been shown to inactivate high levels of a broad spectrum of viruses, bacteria, protozoa, and white blood cells (WBC) in PLT components.[7-9] The INTERCEPT system received CE Mark registration as a Class III drug device and as of 2005 received approval from the Agence Française de Sécurité Sanitaire des Produits de Santé (AFSSAPS, French Agency of Medical Safety of Health Products) for use with both apheresis- and whole blood–derived PLT components in France.

The INTERCEPT Blood System was implemented in routine practice as of March 13, 2006, by EFS-Ile de La Réunion. To date, approximately 4000 INTERCEPT-CPAs have been administered to a broad range of patients on Ile de La Réunion. After the first year of routine use of pathogen inactivation to prepare PLT components, we conducted a retrospective analysis of the response to transfusion of 1950 components to determine the incidence of acute transfusion reactions (ATRs) and serious adverse events (SAEs) attributed to use of this novel component. In addition, we determined the incidence of TT-CHIKV infection for the first year after implementation of pathogen inactivation treatment during the CHIKV epidemic.

ABBREVIATIONS: AE(s) = adverse event(s); ATR(s) = acute transfusion reaction(s); CHIKV = Chikungunya virus; CPA(s) = apheresis platelet component(s); CRF(s) = case report form(s); EFS = Établissement Français du Sang; SAE(s) = severe adverse event(s); TT = transfusion transmitted.

From the EFS Ile de La Réunion and CHR Centre Hospitalier Départemental Felix Guyon, St Denis, Ile de La Réunion, France; CHR Groupe Hospitalier Sud Réunion de St Pierre, Ile de La Réunion, France; Cerus Corporation, Concord, California; EFS Alsace, Strasbourg, France; Cerus Europe BV, Amersfoort, The Netherlands; the University of California School of Medicine, San Francisco, California; INSERM U.311 and Université Louis Pasteur, Strasbourg, France.

Address reprint requests to: Laurence Corash, MD, Cerus Corporation, 2411 Stanwell Drive, Concord, CA 94520; e-mail: lcorash@cerus.com.

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MATERIALS AND METHODS

Collection of PLT components

Before introduction of the INTERCEPT system, CPAs were the sole type of PLT component provided by EFS-La Réunion. All CPAs were collected in donor plasma with integral filtration leukoreduction (Haemonetics, Braintree, MA). After introduction of INTERCEPT, PLTs were collected in approximately 40% donor plasma and 60% PLT additive solution (InterSol, Fenwal, La Chatre, France) from donors with PLT counts of 250×10^9/L or more using a blood component collection system (Haemonetics MCS+ system with the CSDP software) to allow automatic addition of InterSol. The targeted PLT dose per collection was 4.0×10^{11} or greater. WBC contamination was reduced by filtration with an integral WBC filter (Haemonetics). In addition to standard viral screening tests, donors were tested for CHIKV infection by an investigational reverse-transcriptase polymerase chain reaction assay (RT-PCR).[3,10]

Pathogen inactivation treatment of PLT components

CPAs containing 2.5×10^{11} to 6.0×10^{11} PLTs in 300 to 390 mL of approximately 40% plasma and 60% InterSol were prepared with pathogen inactivation using the INTERCEPT processing system (INT2202, Cerus Europe BV) according to manufacturer's instructions for use. Briefly, a unit of CPA was mixed with amotosalen (nominal final concentration of 150 µmol/L) and illuminated with long-wavelength ultraviolet UVA (320-400 nm) light for a 3 J/cm² treatment. The illuminated PLT mixture was incubated in a compound adsorption device in a temperature controlled PLT shaker/incubator (22 ± 2°C) for 6 to 16 hours before transferring to the final storage container. Treated CPAs were stored for up to 5 days under standard blood bank conditions before issue for transfusion.

Hemovigilance surveillance

General study design

This was a retrospective analysis of data recorded prospectively in primary care medical records and as part of the AFSSAPS active hemovigilance surveillance program.[11] There were no patient inclusion or exclusion criteria other than the requirement for PLT transfusion. All patients who received PLT transfusion support during the defined study period were included in the analysis. Case report forms (CRFs) were used to collect patient data[12] on each transfusion of INTERCEPT-CPAs between March 13, 2006, and March 13, 2007, regardless of whether an adverse event (AE) was reported.

The primary endpoint of the study was the proportion of transfusions with ATR after administration of PLT components. ATRs were defined as AEs possibly related, probably related, or related to a PLT transfusion. SAEs were defined as AEs that were fatal, life-threatening, or disabling; resulted in or prolonged hospitalization or morbidity; or were incapacitating. Secondary endpoints included evidence of acute TT-CHIKV infection (based on nucleic acid amplification of viral sequences). All transfused patients were monitored for 7 days after each transfusion for potential TT-CHIKV infection using standard EFS operating procedures.[10] Data also were collected on use of INTERCEPT-CPAs by patient primary diagnosis category and clinical indication for transfusion.

Data collection methods

All patients transfused with PLTs prepared by EFS-La Réunion from March 13, 2006, through March 13, 2007, were identified from the EFS-La Réunion electronic database for the collection, production, and issuance of blood components. Each patient was identified with a unique study number to preserve anonymity. The following data were collected: PLT product code; patient unique identification number associated with the component, patient demographics (age, sex), and primary diagnosis based on clinical care area; primary therapy (chemotherapy, hematopoietic stem cell transplant); surgery (cardiovascular or organ transplant); or other (general medical or multisystem organ failure).

Primary care medical records of each patient were reviewed for the 24 hour period before each transfusion to establish a baseline profile of the patient's clinical condition, for 7 days after each PLT transfusion to identify new AEs arising after transfusion, and to record the relationship of AEs to PLT transfusion in the primary medical record as assessed by primary care physicians. This review was conducted by an observer without knowledge of AEs reported in the AFSSAPS hemovigilance system (eFIT).[11] For the 24 hours before and for the 7 days after each PLT transfusion, medical records were specifically reviewed for evidence of clinical conditions that could be attributed to transfusion-related reactions, including fever (increase in temperature of 2 or 1°C with chills), chills, nausea, skin rash, urticaria, dyspnea, bronchospasm, tachycardia or bradycardia (change in heart rate by >25 bpm), hypotension or hypertension (decrease or increase in systolic or diastolic blood pressure >30 mm Hg, respectively), hemoglobinuria, hemolysis, and change in general well-being. Specific criteria were provided for the diagnosis of transfusion-associated acute lung injury (TRALI).[13] Clinical microbiology laboratory records were reviewed for documentation of transfusion-associated sepsis. The diagnosis of transfusion-associated sepsis required the isolation of the same bacteria species from the patient and the implicated PLT component.

Transfusion CRFs were completed for each PLT transfusion regardless of whether or not an AE was noted in the medical record. In case of the occurrence of an AE, additional clinical and biologic information as well as test results for CHIKV infection (nucleic acid testing (NAT) by RT-PCR) were collected. These data were used by the medical record reviewer for assessment of causality and severity based on the medical record. Clinical severity of AEs was classified according to the following scale: Grade 0 = isolated dysfunction without clinical or biologic manifestation; Grade 1 = absence of immediate or long-term life-threatening effects; Grade 2 = long-term life-threatening effects; Grade 3 = immediate life-threatening effects; and Grade 4 = death. The relationship of AEs to the most proximate PLT transfusion was classified using the same criteria as used by the AFSSAPS hemovigilance system.[11]

The standardized CRFs had been validated in a prior hemovigilance study.[14] Data from the CRF were entered into an independent electronic database used for postmarketing hemovigilance programs[12,14] and reviewed by the principal investigator for incomplete data. At the conclusion of the study, AEs classified as transfusion reactions based on review of the primary care medical records were compared against AEs previously reported under the AFSSAPS hemovigilance program recorded in the eFIT database[11] to determine the total incidence of AEs attributed to PLT transfusion. These data were then analyzed to determine the incidence of ATRs.

Statistical analyses

A statistical analysis plan for the study was prepared and approved before analysis. All statistical analyses, summary tables, and data listings were generated using computer software (SAS, Version 8.2, SAS Institute, Cary, NC). The primary assessment was the incidence of transfusion reactions. The number and proportion (%) of transfusions and the proportion of patients with one or more transfusion reactions were summarized overall, by seriousness and by relationship to PLT transfusion. Corresponding 95% confidence intervals (CIs) for the binomial proportion were calculated using the F distribution method. The 95% CI were based on number of patients with any AE/ATR and the number of transfusions associated with any AE/ATR. In addition, the patient population profile, the characteristics of the PLT components, and the characteristics of the AEs after PLT transfusion were analyzed. Analyses to identify risk factors potentially associated with transfusion reactions were conducted using multivariate logistic regression analysis and by assessing association at a 10% significance level. Data were analyzed on a per-transfusion and a per-patient basis. All INTERCEPT PLT components administered to patients were part of the full analysis population and were analyzed, whether or not an AE was observed. All analyses were conducted using this full analysis population.

RESULTS

PLT component characteristics

Each CPA was treated with pathogen inactivation using the INTERCEPT Blood System on either Day 0 or Day 1 after PLT collection and stored for up to 5 days before release for transfusion. PLT components were released after completion of serologic and NAT. Pathogen inactivation treatment was used without bacteria detection other than routine quality control (QC) assays. Pathogen inactivation treatment replaced cytomegalovirus (CMV) serology for patients who required CMV-safe PLTs and replaced gamma irradiation for prevention of transfusion-associated graft versus host disease.

The INTERCEPT process resulted in a mean PLT loss of 7.8% due to volume loss during container transfers. The mean PLT yield of INTERCEPT-CPAs was $4.2 \times 10^{11} \pm 0.7 \times 10^{11}$ PLTs per component. The residual WBC count met the national QC requirement ($<0.5 \times 10^{6}$/unit). Approximately 15% of PLT components were divided into 2 units before transfusion to fulfill clinical demand. The proportion of split PLT components was similar to that in the period before implementation of pathogen inactivation.

Patient demographics

Between March 13, 2006, and March 13, 2007, a total of 1950 INTERCEPT-CPAs were transfused to 427 patients (Table 1). Each patient received at least one INTERCEPT-CPA. The patient population consisted of 335 adult patients (>18 years), 51 pediatric patients (≥1 to <18 years), and 41 infants (<1 year). There were more male patients in each age group (Table 1).

Hematology-oncology disorders treated with chemotherapy and stem cell transplantation constituted 29.0% of the primary diagnoses among the transfused patient population and these patients received 61% of the PLT components (Tables 1 and 2). The largest patient group supported with PLT components was the general medical population (58.5%), but they received only 30% of the PLT components. A number of patients receiving PLT transfusions (12.2%) underwent major surgical procedures including cardiovascular surgery or solid organ transplantation. Among the pediatric patient group, the proportion of hematology-oncology patients (66.7%) was significantly higher ($p = 0.001$) than among the adult patient group (26.3%).

Approximately half of the patient population (51.5%) received transfusions in intensive care units and the other half (48.5%) were transfused on non–intensive care hospital services (Table 1). There were no outpatient transfusions in the current surveillance program. Subgroup analysis showed that, while most of the pediatric patients (78.4%) were transfused in non–intensive care hospital wards, the majority of infants (90.2%) were transfused on intensive care units.

PLT transfusion exposure

Approximately 53% of patients had a prior history of transfusion exposure to some blood component. The median number of PLT transfusions per patient was 2.0 (range, 1-66; Table 2). Of 1950 PLT transfusions, 1372 transfusions were administered to adult patients while 487 and 91 transfusions were administered to pediatric patients and infants, respectively. Based on the respective patient population, 36 to 47% of patients received two or more PLT transfusions. The number of transfusions per pediatric patient (9.5 ± 14.7) was significantly higher ($p < 0.001$) compared to those in the adult population (4.1 ± 6.2) while the opposite was true for infants (2.2 ± 2.4, $p < 0.002$). Based on primary diagnosis category, hematology-oncology patients in all age groups received a higher proportion of PLT transfusions per patient than those in other diagnosis groups (Table 2).

TABLE 1. Demographics of patients transfused with INTERCEPT-CPAs*

Demographic	Patients (n = 427)	Adult (n = 335)	Pediatric (n = 51)	Infants (n = 41)
Gender				
Male	262 (61.4)	202 (60.3)	35 (68.6)	25 (61.0)
Female	165 (38.6)	133 (39.7)	16 (31.4)	16 (39.0)
Age (years)				
Mean ± SD	42.4 ± 24.8	52.6 ± 17.1	9.4 ± 5.3	NA†
Median	46.0	53.0	10.0	NA†
Range	<1 to 87	>18 to 87	1 to 18	<1
Care location				
Intensive	220 (51.5)	172 (51.3)	11 (21.6)	37 (90.2)
Nonintensive	207 (48.5)	163 (48.7)	40 (78.4)	4 (9.8)
Hematology-oncology primary therapy	124‡ (29.0)	87 (26.3)	34 (66.7)	3 (7.3)
Conventional chemotherapy	102 (82.2)	69 (79.3)	30 (88.2)	3 (100)
Stem cell transplant	14 (11.3)	10 (11.5)	4 (11.8)	0 (0)
Surgery	52 (12.2)	48 (14.3)	3 (5.9)	1 (2.4)
Cardiovascular	49 (94.2)	45 (93.8)	3 (100)	1 (100)
Solid organ transplant	3 (5.8)	3 (6.2)	0 (0)	0 (0)
General medical	250 (58.5)	199 (59.4)	14 (27.4)	37 (90.3)
Missing diagnosis	1 (0.2)	1 (0.3)	0 (0)	0 (0)

* The number of patients (n) and the proportion (%) within each category are presented.
† Age for infants was only recorded as <1 year. NA = not applicable.
‡ Eight adult patients had no active therapy specified at time of transfusion.

TABLE 2. Transfusion exposure among patient populations

Population	All patients (n = 427)	Adult patients (n = 335)	Pediatric patients (n = 51)	Infant patients (n = 41)
All patients				
Transfusions (n)	1950	1372	487	91
Mean ± SD	4.6 ± 7.7	4.1 ± 6.2	9.5 ± 14.7	2.2 ± 2.4
Median	2.0	2.0	4.0	1.0
Range	1-66	1-46	1-66	1-11
Hematology-oncology				
Transfusions (n)	1192	738	446	8
Mean ± SD	9.6 ± 11.7	8.5 ± 8.9	13.1 ± 16.8	2.7 ± 2.9
Median	6.0	6.0	6.5	1.0
Range	1-66	1-46	1-66	1-6
Surgical				
Transfusions (n)	149	135	8	6
Mean ± SD	2.9 ± 3.6	2.8 ± 3.7	2.7 ± 1.5	6.0 ± 0.0
Median	2.0	2.0	3.0	6.0
Range	1-24	1-24	1-4	6.0
General medical				
Transfusions (n)	596	486	33	77
Mean ± SD	2.4 ± 3.6	2.4 ± 3.8	2.4 ± 2.8	2.1 ± 2.3
Median	1.0	1.0	1.0	1.0
Range	1-37	1-37	1-11	1-11
Missing diagnoses				
Transfusions (n)	13	13	0	0
Mean ± SD	13.0 ± 0.0	13.0 ± 0.0		
Median	13.0	13.0		
Range	13	13		

TABLE 3. Clinical characteristics of AEs and ATRs among patient populations*

Characteristic	All patients (n = 427) Transfusions (n = 1950) Any AE	ATRs	Adult patients (n = 335) Transfusions (n = 1372) Any AE	ATRs	Pediatric patients (n = 51) Transfusions (n = 487) Any AE	ATRs
Patients with 1 or >AE	15 (3.5)	8 (1.9)	6 (1.8)	2 (0.6)	9 (17.6)	6 (11.8)
Transfusions with 1 or >AE	19 (1.0)	10 (0.5)	6 (0.4)	2 (0.1)	13 (2.7)	8 (1.6)
Signs/symptoms per transfusion†						
Fever	5 (0.3)	1 (<0.1)	2 (0.1)	1 (<0.1)	3 (0.6)	0
Chills	7 (0.4)	2 (0.1)	4 (0.3)	2 (0.1)	3 (0.6)	0
Itching	5 (0.3)	4 (0.2)	1 (<0.1)	0	4 (0.8)	4 (0.8)
Urticaria	7 (0.4)	6 (0.3)	1 (<0.1)	0	6 (1.2)	6 (1.2)
Dyspnea	1 (<0.1)	0	1 (<0.1)	0	0	0
Anxiety	4 (0.2)	0	2 (0.1)	0	2 (0.4)	0
Other	6 (0.3)	2 (0.1)	1 (<0.1)	0	5 (1.0)	2 (0.4)
Signs/symptoms per patient†						
Fever	4 (0.9)	1 (0.2)	2 (0.6)	1 (0.3)	2 (3.9)	0
Chills	5 (1.2)	2 (0.5)	4 (1.2)	2 (0.6)	1 (2.0)	0
Itching	5 (1.2)	4 (0.9)	1 (0.3)	0	4 (7.8)	4 (7.8)
Urticaria	5 (1.2)	4 (0.9)	1 (0.3)	0	4 (7.8)	4 (7.8)
Dyspnea	1 (0.2)	0	1 (0.3)	0	0	0
Anxiety	4 (0.9)	0	2 (0.6)	0	2 (3.9)	0
Other	6 (1.4)	2 (0.5)	1 (0.3)	0	5 (9.8)	2 (3.9)

* Data are reported as number (%). No AEs were reported for infant patients; thus, these patients and transfusions are not included in this table.
† Number of signs/symptoms can exceed number of AEs due to multiple observed signs/symptoms per AE.
ATR = causal relationship that an AE was possibly related, probably related, or related to INTERCEPT-CPA transfusion.

AEs and ATRs after PLT transfusion

The incidences of AEs and ATRs were evaluated on a per-transfusion as well as per-patient basis (Table 3). On a per-transfusion basis, 19 transfusions (95% CI, 1.0%-1.5%) were associated with an AE. Of these AEs, 10 (95% CI, 0.5%-0.9%) were classified as ATRs possibly, probably, or related to INTERCEPT-CPA transfusion. No SAEs, no cases of TT-sepsis, no cases of TRALI, and no deaths due to INTERCEPT-CPA transfusions were reported. On a per-patient basis, 15 patients (95% CI, 3.5%-5.7%) who received at least one transfusion of INTERCEPT-CPAs experienced an AE after PLT transfusions (Table 3). Only 8 patients (95% CI, 1.9%-3.6%) experienced an ATR attributed to INTERCEPT-CPA transfusion (Table 3).

Overall patient population: characteristics of clinical signs and symptoms associated with PLT transfusion

Of all AEs, on a per-transfusion basis, the most frequently observed symptoms/signs (0.3%-0.4% of 1950 transfusions) were fever, chills, itching, and urticaria (Table 3). Anxiety (0.2%) was the second most frequently reported symptom/sign. Only one incident of dyspnea was reported. Additional symptoms in the category of "other" included tachycardia, facial flushing, body pain, and cough, but with an individual incidence of 0.1% or less of transfusions. Most of the ATRs were described principally as Grade 1 urticaria (0.3%) and itching (0.2%) with all other symptoms/signs observed at a rate of 0.1% or less of transfusions.

On a per-patient basis, the most frequently observed symptoms/signs (1.2% of 427 patients) were chills, itching, and urticaria (Table 3). Fever and anxiety (0.9%) were the second most frequently observed symptoms/signs. One patient (0.2%) experienced a single episode of dyspnea. Additional symptoms in the category of "other" included tachycardia, facial flushing, body pain, and cough, each with an individual incidence of 0.5% or less on a per-patient basis. Most of ATRs were described as Grade 1 itching (0.9%), urticaria (0.9%), and chills (0.5%) with all others observed at a rate of 0.2% or less per patient.

Characteristics of AEs and ATRs in pediatric patients

Pediatric patients experienced a higher incidence of AEs than adult patients (Table 3). On a per-transfusion basis, 13 AEs (2.7%) and 8 ATRs (1.6%) occurred in pediatric patients compared to 6 AEs (0.4%) and 2 ATRs (0.1%) in adult patients. On a per-patient basis, 9 pediatric patients (17.6%) experienced at least 1 AE compared to 6 adult patients (1.8%). Similarly, 6 pediatric patients (11.8%) experienced at least 1 ATR compared to 2 adult patients (0.6%).

For all AEs reported in pediatric patients, the symptoms/signs were predominantly Grade 1 in severity consisting of fever, chills, itching, urticaria, anxiety, tachycardia, and facial flushing (Table 3). For pediatric patients experiencing ATRs, the symptoms/signs included itching, urticaria, tachycardia, and facial flushing, none of which were reported in adult patients. No AEs were associated with the 91 INTERCEPT-CPA transfusions administered to 41 infants who required PLT support.

Characteristics of AEs and ATRs associated with transfusion of split components

Of the 1950 transfusions, 540 INTERCEPT-CPAs were obtained from a split PLT component. The rates of AEs and ATRs on a per-transfusion basis for split components were 0.4 and 0%, respectively, compared to 1.2 and 0.7% for whole components. Of the 19 AEs reported, only 2 AEs (one in a 77-year-old male patient and one in a 16-year-old male patient) were associated with transfusion of a split INTERCEPT-CPAs (Table 4).

TABLE 4. Effect of split components on the frequency of AEs and ATRs*

Component	Transfusions	AEs	ATRs
Split INTERCEPT-CPAs	540	2 (0.4)	0 (0)
Whole INTERCEPT-CPAs	1410	17 (1.2)	10 (0.7)
Total	1950	19 (1.0)	10 (0.5)

* Data are reported as number (%).

Incidence of TT-CHIKV

A substantial proportion of transfusions were administered to hematology-oncology patients treated with potentially immune-suppressive therapy. There were no cases of TT-CHIKV reported in this survey based on the test results using an investigational assay for viral nucleic acid or posttransfusion clinical observation for signs and symptoms of CHIKV infection.

DISCUSSION

CHIKV resulted in an epidemic on La Réunion Island in which approximately 41% of the population was infected. Serologic and epidemiologic surveillance studies estimated the prevalence of asymptomatic infection at 15% of total CHIKV infections.[1] Efforts to identify infected blood donors with either serologic assays or CHIKV specific nucleic acid amplification assays have shown considerable variability and suboptimal sensitivity.[15] The mean risk of contamination of a blood donation throughout the epidemic was estimated at 132 per 100,000 donations, and at the peak of the epidemic, the risk was estimated at 1,500 per 100,000 donations.[1] At the time of the current study, optimal methods to detect infected donors with low viral titers were not available, and a NAT with sensitivities of 40 to 350 copies/mL was only developed later.[16] In the period of this study, collection of CHIKV-contaminated PLTs from asymptomatic donors was plausible. During the epidemic before use of pathogen inactivation, two cases of TT-CHIKV were suspected, but neither case could be conclusively proven.[10] At least one blood-borne transmission due to a needle-stick has been documented.[4]

This study accomplished multiple objectives. Foremost, it provided hemovigilance data to evaluate the effectiveness of the INTERCEPT Blood System to prevent PLT TT-CHIKV during an epidemic. These data are especially relevant given the specific association of CHIKV with

PLTs,[17,18] which could lead to low detection sensitivity for serum-based tests. In addition to evaluating the efficacy to prevent TT-CHIKV, this study provided an opportunity to extend the safety profile of INTERCEPT PLTs transfused to a broad patient population. Finally, this study permitted an evaluation of the operational logistics of the INTERCEPT PLT system implemented under emergency conditions.

Data provided by EFS-La Réunion for the years 2004 and 2005 with conventional PLT components suspended in 100% plasma indicated an ATR incidence of 2.2 and 5.4% of PLT transfusions among heavily transfused pediatric oncology-hematology patients, respectively.[19] In comparison, this study demonstrated a lower incidence (1.6%) of ATRs per PLT transfusion. These results are consistent with reported ATR frequencies reported for INTERCEPT PLT components in routine use from multiple European centers,[12,14] but lower than the frequencies reported for treated PLT components in the EuroSprite (6%) and the SPRINT clinical trials (3%).[20,21] The higher incidence of ATRs observed in the clinical trials may have been due to differences in patient populations, which in the clinical trials consisted largely of heavily transfused hematology-oncology patients undergoing hematopoietic stem cell transplantation. Similar to previous studies, all of the ATRs observed in the current survey were of mild severity, and none were indicative of clinical CHIKV. It is relevant to note that the size of this study was insufficient to characterize the incidence of septic transfusion reactions, although none were reported.

The clinical symptoms of CHIKV infection include fever, severe polyarthralgia, myalgia, dermatitis, hemorrhage, meningoencephalitis, respiratory failure, cardiovascular decompensation, and fulminant hepatitis with a mortality rate of one in 1000 during the La Réunion epidemic.[22] Thus, review of primary medical records should have been sufficiently sensitive to detect TT-CHIKV. No TT-CHIKV cases were detected in the patient population monitored in this study after implementation of the INTERCEPT Blood System for PLTs.

The retrospective surveillance described in this report provided an opportunity to evaluate the sensitivity of the AFSSAPS active hemovigilance system[11] to detect transfusion-related AEs. We did not detect any additional transfusion-related AEs in our independent review of primary medical records compared to the AFSSAPS/eFIT database for transfusion-related incidents. This limited experience is consistent with the sensitivity of the AFSSAPS hemovigilance system in detecting transfusion-related AEs.

This study included a substantial number of pediatric patients, some of whom were infants. None of the prior studies with INTERCEPT PLT components included a substantial infant patient population. Interestingly, pediatric patients had the highest rate of AEs and ATRs after transfusion of INTERCEPT-CPAs. This finding may not be surprising because the proportion of hematology-oncology patients and the levels of PLT component exposure were higher among pediatric patients. On the other hand, no AEs or ATRs were observed in infants who received INTERCEPT-CPA transfusions largely for nonmalignant medical disorders, but this population was of limited size and less intensively transfused.

The study also provided experience with the implementation and operational logistics of the INTERCEPT system in a remote, small regional blood center. EFS-Ile de La Réunion performs approximately 100 to 150 apheresis PLT collections per month.[23] Complete conversion to pathogen inactivation of PLT components was achieved in 2 weeks. In routine operation, no additional personnel were required after implementation of the INTERCEPT system.

This is the first study to demonstrate the utility of pathogen inactivation as a proactive approach to prevent a potentially TT infection during an epidemic. The technology facilitated the availability of PLT components that otherwise were in limited supply. This experience is relevant given the observation of imported cases of CHIKV infection in metropolitan France, Germany, the United Kingdom, Belgium, Norway, the Czech Republic, Canada, and the United States[3,24,25] and the autochthonous outbreak of CHIK infection in the Emilia-Romagna region of Italy.[26] The success of EFS-La Réunion in implementing the INTERCEPT Blood System demonstrates the utility of pathogen inactivation to support the availability of labile blood components during an epidemic.

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CONFLICT OF INTEREST

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市販後調査及び観察研究の報告④

Universal adoption of pathogen inactivation of platelet components: impact on platelet and red blood cell component use

Jean Claude Osselaer, Chantal Doyen, Laurence Defoin, Cecile Debry, Maité Goffaux, Nathalie Messe, Maryse Van Hooydonk, Andre Bosly, Jin Sying Lin, Lily Lin, and Laurence Corash

BACKGROUND: Pathogen inactivation of platelet (PLT) components (INTERCEPT Blood System, Cerus Europe) was implemented into routine practice at a blood center supporting a tertiary care hospital. Utilization of platelet components (PCs) and red blood cell (RBC) components was analyzed for 3 years before and 3 years after introduction of pathogen inactivation to assess the impact of pathogen inactivation on component use.

STUDY DESIGN AND METHODS: This was a retrospective analysis of prospectively collected data. An electronic database used in routine blood bank hemovigilance to monitor production and use of blood components was analyzed to assess clinical outcomes.

RESULTS: Transfusion records were analyzed for 688 patients supported with conventional PCs and 795 patients supported with pathogen inactivation PCs. Additional analyses were conducted for intensively transfused hematology patients. Patient demographics (age category, sex, and diagnostic category) were not different in the two observation periods. For all patients, mean numbers of PC per patient were not different for conventional PCs and pathogen inactivation PCs (9.9 ± 19.5 vs. 10.1 ± 20.9, $p = 0.88$). Data for hematology patients (272 conventional PCs and 276 pathogen inactivation PCs) confirmed that days of PLT support were not different (31.6 ± 42.6 vs. 33.1 ± 47.9, $p = 0.70$) nor was total PLT dose (10^{11}) per patient (87.3 ± 115.4 vs. 88.1 ± 111.6, $p = 0.93$). RBC use, for all patients and hematology patients, was not different in the two observation periods, either during periods of PLT support or outside periods of PLT transfusion support.

CONCLUSION: Pathogen inactivation of PCs had no adverse impact on component use during a 3-year observation period of routine practice.

During the past four decades multiple new procedures and practices have been introduced to improve the safety and efficacy of platelet (PLT) transfusion therapy. Technology innovations for collection and preparation have included plateletpheresis, preparation of whole blood–derived buffy coat PLTs, additive solutions (ASs), process and filtration leukoreduction, initial blood draw diversion, and gamma irradiation.[1] Additional innovations to detect bacterial contamination,[2] change the PLT transfusion threshold,[3] reduce the incidence of alloimmunization,[4] and change the PLT transfusion dose[5] have been evaluated in clinical trials of varying size and scope, and many of these innovations have been introduced into routine clinical practice.[6,7] In 2003 pathogen inactivation preparation of PLT components was introduced into clinical practice in Europe.[8,9]

These innovative technologies have been evaluated in clinical trials; however, additional information regarding the impact of new technology on blood center operations and patient outcomes can be obtained from the experience in routine use. A recent international consensus conference on pathogen inactivation technology recommended that data be collected during routine use to monitor impact as these novel technologies were adopted.[10] In 2003 the Blood Transfusion Center (BTC), Cliniques Universitaires Mont Godinne (CUMG), initiated universal routine use of PLT components prepared with photochemical pathogen inactivation treatment (INTERCEPT Platelet System, Cerus Europe BV, Amersfoort, The Netherlands) for transfusion support of patients with thrombocytopenia. Three randomized controlled clinical trials were conducted with this pathogen inactivation technology in support of CE Mark registration,[11-13] but data on component utilization were collected only for conduct of clinical trials in which the experimental components were produced in limited quantities rather than in routine production.

The BTC Mont Godinne is the sole source of PLT components and the principal source of red blood cell (RBC) concentrates for a tertiary care medical center. The blood center collects data on the use of blood components under the auspices of a hemovigilance program. We conducted an analysis of the utilization of PLT and RBC components for 3 years before the adoption of pathogen inactivation technology for PLTs and for 3 years after the adoption of this technology to evaluate the impact of this new technology on component utilization under routine clinical practice conditions.

ABBREVIATIONS: BTC = Blood Transfusion Center; CUMG = Cliniques Universitaires Mont Godinne; PC(s) = platelet component(s).

From the Transfusion Center and the Hematology Service, Cliniques Universitaires de Mont Godinne, Université Catholique de Louvain, Yvoir, Belgium; and Cerus Corporation, Concord, California.

Address reprints requests to: Laurence Corash, MD, Cerus Corporation, 2411 Stanwell Drive, Concord, CA 94520; e-mail: lcorash@cerus.com.

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MATERIALS AND METHODS

Overall study design

The BTC Mont Godinne collects and supplies all blood components for a 400-bed teaching hospital of the Université Catholique de Louvain (Mont Godinne, Yvoir, Belgium). The BTC performs approximately 2000 plateletpheresis and 7000 whole-blood collections per year to support a diverse patient population with major subpopulations cared for by hematology-oncology and cardiovascular surgery specialists. The BTC issues all labile blood components for transfusion and maintains an electronic database to record the transfusion or destruction of all issued blood components. Longitudinal transfusion records are maintained for all recipients of these components either in hospital or in outpatient treatment clinics. Data for this study on utilization of blood components were obtained from electronic blood bank records and clinical laboratory records. The period from October 1, 2000, to September 30, 2003, constituted the control period when all PLT components were prepared without pathogen inactivation treatment, and the period from November 1, 2003, through October 30, 2006, constituted the test period when all PLT components were prepared with pathogen inactivation. One of the authors (JCO) has been the medical director of the BTC during the entire period covered by this study and supervised the hemovigilance program. Individual patient informed consent was not required to obtain the data collected as this study was conducted under the existing hemovigilance program for the BTC in compliance with Belgian Law to monitor the impact of new technologies on blood transfusion practice.[14] Patient privacy was protected under the hemovigilance program.

Collection and preparation of PLT components

Control period

During this 3-year period 85% of PLT components were collected on a cell separator (Amicus, Fenwal, Inc., Round Lake, IL) and 15% on another cell separator (Spectra, Gambro BCT, Boulder, CO) with process leukoreduction. For components collected on the Amicus device, T-Sol PLT AS (Fenwal, Inc., La Châtre, France) was used in a ratio of approximately 35% plasma and 65% T-sol. For components collected on the Spectra device, PLTs were suspended in 100% plasma. For both platforms, components were prepared as conventional PLT components in compliance with national regulatory requirements. After component preparation the PLT concentrations (10^9/L) and the volumes (mL), based on weight, of each component were measured and the total PLT dose per component was calculated (10^{11} PLTs). PLT components were treated with gamma irradiation as required for patient specific indications, and tested for cytomegalovirus (CMV) antibodies as required for patient specific indications. During this period, PLT components were stored for up to 5 days.

Test period

During this 3-year period all PLT components were collected on the Amicus cell separator (Fenwal, Inc.) with process leukoreduction and with the InterSol PLT AS (Cerus Europe BV) in a ratio of approximately 35% plasma and 65% Intersol. After collection, the PLT concentrations (10^9/L) and volumes (mL), based on weight, of each component were measured and the total PLT dose was calculated (10^{11} PLTs). These components were prepared with pathogen inactivation under the CE Mark registration and in accordance with national regulatory requirements. Within the first 24 hours after collection, all PLT components were treated with pathogen inactivation (150 µmol/L amotosalen HCl and 3 J/cm² UVA light, 320-400 nm) according to the manufacturer's directions for use (INTERCEPT, Cerus Europe BV). For quality control (QC), the final volume of treated PLT components was measured on approximately 30% of components and used to estimate the final PLT content of each component based on volume loss. Pathogen inactivation treatment was used in place of gamma irradiation and CMV serology testing to meet specific patient indication requirements, and it was used instead of bacteria detection to meet national regulatory requirements. With pathogen inactivation treatment, PLT components were stored for either 5 or 7 days in accordance with national regulatory requirements.

During both study periods, blood center operational logistics permitted issuance of PLT components within the

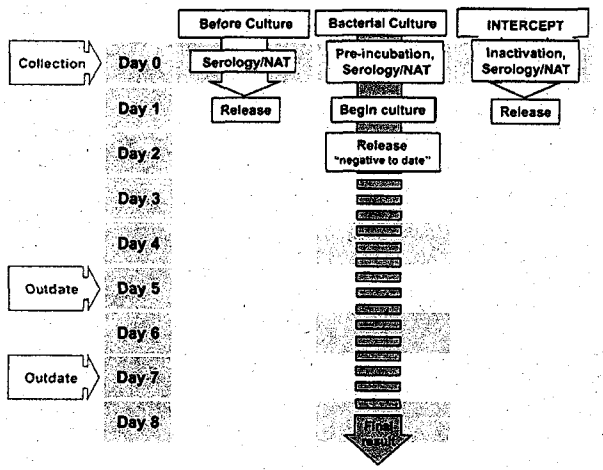

Fig. 1. Operational logistics for production and release of PLT components using three methods. Before culture = conventional testing without bacterial culture; bacterial culture = conventional testing with bacterial culture; and INTERCEPT pathogen inactivation with conventional testing.

same time frame after collection, testing, and pathogen inactivation treatment (Fig. 1). The preparation of RBC concentrates did not change in any substantial manner during the 6-year study observation period, and all RBC concentrates were leukoreduced by filtration during both periods. RBC concentrates were treated with gamma irradiation and tested for CMV antibody per specific patient requirements using the same methods in both study periods.

Transfusion of PLT and RBC components and data collection

During both study periods, primary care physicians ordered all blood components per standard of care. A proportion of patients had multiple PLT transfusions and multiple periods of PLT support during the 6-year observation period. A period of PLT support was defined as the interval between the first PLT transfusion and all subsequent PLT transfusions with less than 5 days between PLT transfusions. If an interval of more than 5 days occurred between PLT transfusions, then a new period of PLT support was considered initiated. The total duration of PLT support for each patient was defined as the number of days between the first and the last PLT transfusion within the same period of PLT support. The days of PLT support for multiple periods were summed to obtain a total duration of support for each patient during each observation period. These definitions were based on the assumption that if no PLT transfusions were required after a 5-day interval then transfusion-dependent thrombocytopenia was no longer present. These definitions have previously been used in randomized clinical trials to evaluate PLT transfusion therapeutic efficacy.[11-13]

The BTC Mont Godinne entered all blood components into an electronic database at time of collection and labeling (Blood Bank Management System, 4S Information Systems, Minthorne, UK; or CTS Serveur, INLOG, Limonest, France). When components were issued for transfusion a standard form accompanied each component and was returned to the blood center after transfusion or with unused components. No patients were excluded from this analysis. The BTC maintained a longitudinal transfusion record for each patient supported with blood components including unique patient identification data, clinical service location for transfusion, unique blood component identification number, date of transfusion, dose of PLT component transfused, and age of PLT component transfused. The BTC obtained patient clinical laboratory data from electronic laboratory records linked to unique patient identification records with protection of patient confidentiality under the hemovigilance program. Using these electronic data capture systems, greater than 99% of issued blood components were traceable within the system.

Data analysis and statistical methods

Data from the BTC were extracted into a computer database (SAS, SAS, Inc., Cary, NC). Values for all continuous variables were summarized as mean and standard deviation (SD), median, and range. Differences in mean values between the two observation periods were compared by two-sample t-test for continuous data and Fisher's exact test for categorical data. Differences in median values between the two observation periods were compared by the two-sample Wilcoxon test. All p values reported were two-sided, and statistical significance was declared at a p value of less than 0.05.

RESULTS

PLT collections, yields, and processing losses

During the control period, 5576 collections were performed with a mean yield of 6.28×10^{11} PLTs. The 95% central interval for the distribution of transfused doses in the control period ranged from 2.1×10^{11} to 6.3×10^{11} PLTs. During the test period, 5997 collections were performed with a mean yield of 6.82×10^{11} PLTs. After routine implementation of the INTERCEPT technology, 12,002 products were treated with pathogen inactivation. Approximately 50% of collections were targeted as double-dose collections and were divided into two therapeutic PLT doses. The 95% central interval for the distribution of transfused doses ranged from 1.9 to 5.3×10^{11} PLTs during the test period. Eight pathogen inactivation procedures had technical failures (0.06%), of which 5 were due to operator error and 3 were due to disposable failures associated with incorrect placement of a clamp during storage leading to pinhole leaks. As part of the QC process, 4066 components during the test period were assayed for volume loss during pathogen inactivation processing. Mean volume loss without accounting for addition of amotosalen (15 mL) was 8.2 ± 2.2% and the distribution of volume losses exhibited a 25th percentile of 7.0% and a 75th percentile of 9.4%. Volume loss correlated with PLT loss. With consideration of the dilution due to addition of amotosalen (4.4%), the mean processing loss was 12.6%.

Patient populations and demographics

During the control period, 688 patients received one or more PLT components compared to 795 patients during the test period (Table 1). The increased number of patients in the test period reflected increased clinical activity as new clinical programs were implemented at the CUMG. Patient demographics with respect to age distribution, sex, and primary diagnostic category did not differ significantly in the two treatment periods (Table 1). During the two study periods approximately 90% of the population receiving PLT support also required one or more RBC concentrates, and the demographics for these patients did not change significantly during the two periods (Table 2).

TABLE 1. Demographics of all patients receiving PLT components in the two observation periods

Study period	Control	Test	p Value
Patients (n)	688	795	
Mean age, years	60.8	62.9	0.01
≤16 (%)	0.9	1.0	
17-64 (%)	49.7	45.3	
≥65 (%)	49.4	53.7	0.23*
Male (%)	62.8	62.3	0.87
Primary diagnosis (%)†			
Hematology	39.5	34.7	
Oncology	6.5	8.8	
CV surgery	31.7	34.7	
Other‡	22.2	21.8	0.12*

* Represents p value for the distribution.
† Patients were classified by primary diagnosis based on the clinical service providing medical care and ordering blood components.
‡ The designation of other refers to patients on general medical services and surgical services other than cardiovascular (CV) surgery.

Utilization of PLT and RBC components

For the complete patient population receiving one or more PLT components in either period, the mean number of PLT transfusion support periods and the distribution of support periods were not statistically different (Fig. 2, Table 3). The mean duration of PLT support, the mean number of PLT transfusions, the total PLT dose, and the

TABLE 2. Demographics of all patients receiving both PLT and RBC components in the two observation periods

Study period	Control	Test	p Value
Patients (n)	629	721	
Mean age, years (%)	61.3	62.9	0.06
≤16 (%)	0.8	0.8	
17-64 (%)	48.8	45.5	
≥65 (%)	50.4	53.7	0.48*
Male (%)	61.7	61.0	0.82
Primary diagnosis (%)†			
Hematology	40.9	36.9	
Oncology	6.0	7.9	
CV surgery	32.3	35.9	
Other‡	20.8	19.3	0.19*

* Represents p value for the distribution.
† Patients were classified by primary diagnosis based on the clinical service providing medical care and ordering blood components.
‡ The designation of other refers to patients on general medical services and surgical services other than cardiovascular (CV) surgery.

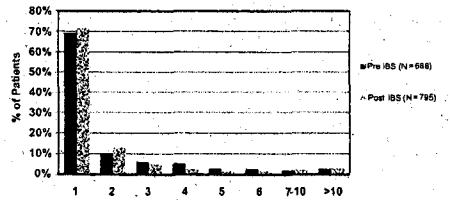

Fig. 2. The distribution of the periods of PLT transfusion support for all patients receiving PLT components. The frequency distribution of the periods of PLT support for patients during the period before INTERCEPT (pre-IBS, ■; n = 688) and the period after INTERCEPT (post-IBS, ▪; n = 795) was determined. The proportion of patients is expressed on the ordinate and the number of periods of PLT transfusion support on the abscissa. There was no statistical difference in the distribution of support cycles between observation periods.

mean dose of PLTs per day of transfusion support were not different between the two treatment periods (Table 3). For patients receiving both PLT and RBC components (control, 629; test, 721), the mean numbers of RBC concentrates transfused per patient (Table 4) were not different in the two observation periods (control 16.5 ± 20.9 vs. test 16.5 ± 21.5, p = 0.98).

Because RBC concentrates may be transfused to correct anemia due to blood loss or marrow hypoproduction arising from many different causes, we also examined the use of RBC concentrates during periods of PLT transfusion support and outside periods of PLT transfusion support to determine if there were differences during transfusion-dependent thrombocytopenia and out side periods of transfusion-dependent thrombocytopenia. No significant differences were observed between study periods in the use of RBC components during support of thrombocytopenia and outside periods of PLT component transfusion support (Table 4).

The broad patient population supported with PLT and RBC components was heterogeneous with respect to primary diagnoses and the level of PLT support required. To more specifically define the impact of pathogen inactivation on PLT component therapy, the subset of hematology patients was analyzed separately. This population required more intensive transfusion support with less acute blood loss due to surgical intervention and, thus, was a more homogeneous population in which to evaluate both PC and RBC use. The majority (more than 60%) of hematology patients had more than one period of PLT transfusion support (Fig. 3). The distributions of the periods of support were not statistically different between the two observation periods (Fig. 3).

Hematology patients were more intensively transfused with PLT components, had more periods of PLT support, and had more days of PLT support than the general patient population (Table 5). Comparison of the two observation periods demonstrated no significant differences in the mean number of PLT transfusion support periods, mean number of days of transfusion support, number of PLT transfusions, the dose of PLTs, nor the PLT dose per day of PLT support (Table 5). We examined the use of RBC components for hematology patients during the entire transfusion period as well as during and outside periods of PLT support (Table 6). In this analysis we included patients who received PLTs without RBC transfusion during PLT support and patients who received both PLT and RBC support. We observed no significant differences in use of RBC components by hematology patients during the entire observation period during periods of PLT support and outside periods of PLT support (Table 6).

Similarly, data were analyzed for a population of oncology patients followed during the 6-year observation period. These patients were less intensively transfused with PLT components than the hematology patients, but did have multiple periods of PLT support; however, the distribution of periods of support was not different (Fig. 4, Table 7). Significant differences in favor of INTERCEPT PC were detected in transfusions per patient, total PLT dose, and the dose per day of support. There were no significant differences in RBC concentrate use during the entire observation period for patients receiving PLT transfusions and for patients receiving PLT and RBC components (Table 8).

To examine the impact of transfusion practice and clinical responses to PLT and RBC transfusions, the mean

TABLE 3. PLT transfusion support for all patients before and after adoption of pathogen inactivation treatment of PLT components

Parameter	Control*	Test*	p Value
Number of patients (n)	688	795	0.01
Periods of PLT support (n)	2.2 (3.2)	2.2 (4.4)	0.86
Days of PLT support (days)	14.2 (30.5)	13.1 (32.0)	0.49
Transfusions/patient (n)	9.9 (19.5)	10.1 (20.9)	0.88
Transfusions/day of support (n)	1.0 (0.5)	1.1 (0.6)	<0.01
Total dose/patient (10^{11})	41.5 (82.8)	36.7 (76.5)	0.24
Dose per day of support (10^{11})	4.2 (2.1)	4.0 (2.3)	0.20

* Data presented as mean (SD).

TABLE 4. RBC use by all patients during the observation periods, during periods of PLT support, and outside periods of PLT support before and after adoption of pathogen inactivation treatment of PLT components

Parameter	Control*	Test*	p Value
RBC use during the entire observation period			
Patients (n)†	688	795	
RBC units/patient (n)	15.1 (20.5)	15.0 (21.0)	0.90
RBC use during the entire observation period			
Patients (n)‡	629	721	
RBC units/patient (n)	16.5 (20.9)	16.5 (21.5)	0.90
RBC use during periods of PLT support			
Patients (n)§	545	634	
RBC units/patient (n)	10.4 (14.4)	10.7 (16.2)	0.71
RBC use outside periods of PLT support			
Patients (n)‖	504	581	
RBC units/patient (n)	9.4 (14.5)	8.8 (13.6)	0.47

* All values expressed as mean (SD).
† Patients transfused with PLT components during the observation period.
‡ Patients transfused with RBC components and PLT components during the entire observation period.
§ Patients transfused with RBC components during periods of PLT transfusion support.
‖ Patients transfused with RBC components outside periods of PLT transfusion support.

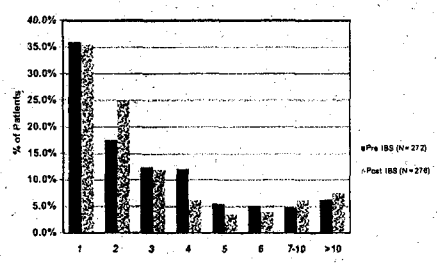

Fig. 3. The distribution of the periods of PLT transfusion support for hematology patients receiving PLT components. *The frequency distribution of the periods of PLT support for* patients for the period before INTERCEPT (pre-IBS, ■; n = 272) and the period after INTERCEPT (post-IBS, □; n = 276) was determined. The proportion of patients is expressed on the ordinate and the number of periods of PLT transfusion support on the abscissa. There was no statistical difference in the distribution of support cycles between observation periods.

TABLE 5. PLT transfusion support for hematology patients before and after adoption of pathogen inactivation treatment of PLT components

Parameter	Control*	Test*	p Value
Number of patients (n)	272	276	
Periods of PLT support (n)	3.7 (4.6)	4.1 (6.9)	0.40
Duration of support (days)	31.6 (42.6)	33.1 (47.9)	0.70
Transfusions/patient (n)	20.8 (27.1)	24.2 (30.5)	0.17
Transfusions/day of support (n)	0.8 (0.4)	0.8 (0.3)	0.13
Total dose/patient (10^{11})	87.3 (115.4)	88.1 (111.6)	0.93
Dose per day of support (10^{11})	3.2 (1.4)	3.0 (1.3)	0.12

* Data presented as mean (SD).

TABLE 6. RBC use by hematology patients during the observation periods, during periods of PLT support, and outside periods of PLT support before and after adoption of pathogen inactivation treatment of PLT components

Parameter	Control*	Test*	p Value
RBC use during the entire observation period			
Patients (n)†	272	276	
RBC units/patient (n)	24.5 (27.1)	26.4 (30.4)	0.43
RBC use during the entire observation period			
Patients (n)‡	257	266	
RBC units/patient (n)	25.9 (27.2)	27.4 (30.5)	0.55
RBC use during periods of PLT support			
Patients (n)§	222	244	
RBC units/patient (n)	16.4 (19.1)	17.6 (23.3)	0.54
RBC use outside periods of PLT support			
Patients (n)‖	237	235	
RBC units/patient (n)	12.7 (18.8)	12.7 (19.2)	1.00

* All values expressed as mean (SD).
† Patients transfused with PLT components during the observation period.
‡ Patients transfused with RBC components and PLT components during the entire observation period.
§ Patients transfused with RBC components during periods of PLT transfusion support.
‖ Patients transfused with RBC components outside periods of PLT transfusion support.

and median lowest daily PLT counts were determined on a per-transfusion basis for the various patient populations during both observation periods (Table 9). We did not analyze data for the oncology patients due to the small number of transfusions; however, we did analyze data separately for cardiovascular surgery patients since they received PLT transfusions at higher PLT count levels. There was a very broad and asymmetric distribution of the daily lowest PLT count for all patient groups, and the median values were considerably different from the mean values. The proportion of PLT transfusions with recorded PLT counts in the medical record on the day of transfusion was similar in each period for each patient group (Table 9). While the mean values for the daily lowest PLT count were significantly higher (p < 0.001) in the test period for all patient groups, the median values were not statistically different (p = 0.23). Exploratory analyses using analysis of covariance (ANCOVA) models were performed on the transfused PLT dose with the nadir of PLT count included as a covariate in the models. Treatment group (test vs. control) and patient's primary diagnosis (hematology, oncology, cardiovascular surgery, and other) were also included in the models. Results from these exploratory analyses showed that, within each treatment group, the adjusted means (after the adjustment for the nadir of PLT count and/or the primary diagnosis) were nearly the same as the unadjusted sample means, and the observation of significant differences for the means and the nonsignificant difference for the median remain unchanged with and without the adjustment for the nadir of PLT count and/or the primary diagnosis.

To further examine the impact of the adoption of pathogen inactivation treatment of PLT components on RBC use as a surrogate measure for bleeding, we determined the mean daily lowest hemoglobin (Hb) level per patient for those patients receiving both PLT and RBC concentrates (Table 10). No differences in the mean lowest daily Hb level were detected in any patient groups before and after implementation of pathogen inactivation for PLT components.

DISCUSSION

This study provides an assessment of the impact of pathogen inactivation on the utilization of PLT and RBC components in both broad and

TABLE 7. PLT transfusion support for oncology patients before and after adoption of pathogen inactivation treatment of PLT components

Parameter	Control*	Test*	p Value
Number of patients (n)	45	70	
Periods of PLT support (n)	2.0 (1.5)	1.8 (2.6)	0.72
Duration of support (days)	7.9 (11.2)	5.0 (11.0)	0.17
Transfusions/patient (n)	6.8 (9.1)	3.9 (6.1)	0.05
Transfusions/day of support (n)	1.0 (0.4)	1.0 (0.4)	0.91
Total dose/patient (10^{11})	27.5 (37.7)	14.5 (22.5)	0.02
Dose per day of support (10^{11})	4.3 (1.7)	3.7 (1.4)	0.04

* Data presented as mean (SD).

TABLE 8. RBC use by oncology patients during the two observation periods, before and after adoption of pathogen inactivation treatment of PLT components

Parameter	Control*	Test*	p Value
RBC use during the entire observation period			
Patients (n)†	45	70	
RBC units/patient (n)	8.6 (9.0)	8.0 (7.7)	0.73
RBC use during the entire observation period			
Patients (n)‡	38	57	
RBC units/patient (n)	10.2 (9.0)	9.9 (7.4)	0.86

* All values expressed as mean (SD).
† Patients transfused with PLT components during the observation period.
‡ Patients transfused with RBC components and PLT components during the entire observation period.

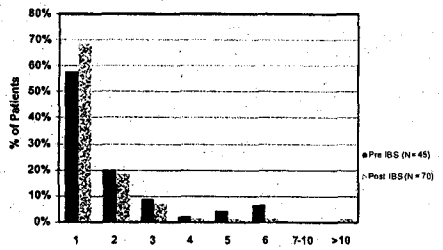

Fig. 4. The distribution of the periods of PLT transfusion support for oncology patients receiving PLT components. The frequency distribution of the periods of PLT support for patients before adoption of INTERCEPT (pre-IBS, ■; n = 45) and the period after INTERCEPT (post-IBS, ▨; n = 70) was determined. The proportion of patients is expressed on the ordinate and the number of periods of PLT transfusion support on the abscissa. There was no statistical difference in the distribution of support cycles between observation periods.

specialized patient populations. This study is unusual in its scope, in that it covers a relatively long period during which the new technology was used in routine practice, and it provides data from a comparative period before adoption of the new process. In addition to providing information on the impact of the innovation, the study provides information on the utilization of PLT and RBC components in a broad patient population and in specific patient populations with more intense transfusion requirements. To our knowledge, this is the first study to examine the impact of a new PLT preparation technology on the routine production and utilization of PLT components for an observation period as long as 6 years.

In Phase 1 and 2 clinical trials with autologous radiolabeled 5-day-old PLT components transfused to healthy subjects, we detected a 15% to 20% reduction in PLT viability.[15] Subsequently, a large Phase 3 clinical trial demonstrated increased utilization of PLT components treated with pathogen inactivation compared to conventional PCs.[12] This observation was due in part to difficulties with production of consistent PLT doses during the clinical trial and the stringent requirement to avoid off-protocol transfusions.[12] Analysis of patients in both treatment groups supported with components consistently containing more than 3.0×10^{11} PLTs, showed no difference in utilization of PLT components.[16] In light of these observations, we sought to evaluate PLT component utilization in the context of routine practice with production of PLT components over long periods.

In this study, the patient populations in the two observation periods were comparable with the exception of a 15% increase in the number of patients receiving PLT transfusions due to increased clinical activity at the study center. In both periods, approximately 90% of patients were transfused with PLT and RBC components providing the opportunity to examine the impact of the new PLT technology on use of RBCs. There was considerable variation in the duration of PLT support due to heterogeneity of the patient population, even among specific diagnostic groups, such as hematology patients. This heterogeneity reflected the diverse population of patients who received PLT support in clinical practice and provided a realistic measure of the impact of a new technology. In addition, the long time of observation in which patients experienced multiple periods of PLT support during multiple chemotherapy cycles contributed to the heterogeneity, but provided a comprehensive assessment of the impact of the new technology on component use.

A substantial number of more intensively transfused hematology patients were available in both periods to allow assessment of the impact of pathogen inactivation on PLT and RBC utilization among repeatedly transfused patients. During both observation periods, hematology patients received the majority of PLT components due to longer periods of transfusion-dependent thrombocytopenia. While it is possible that changes in chemotherapy regimens over the 6-year observation period resulted in less intensive marrow suppression minimizing the impact of a change in PLT component use, several factors argue against this effect. First, the mean duration of PLT transfusion support and the number of periods of transfusion support were similar in the two observation periods, indicating that changes in primary disease treatment had minimal impact on the marrow suppression and the extent of transfusion-dependent thrombocytopenia. In addition, the similar use of RBC components during and outside periods of PLT support in both observation periods is consistent with a lack of change in hematopoietic function secondary to primary disease therapy.

Implementation of pathogen inactivation did result in mean PLT losses of 12.6%. This was partially compensated for by collection of larger PLT doses during the period after implementation of pathogen inactivation. This required an additional 10 minutes of donor collection time, but was well tolerated without impact on donor recruitment or retention. For the broad patient population, adoption of pathogen inactivation for PLT components had no significant impact on utilization of PLT components as measured by multiple indices including mean number of transfusions per patient, mean total dose of PLTs per patient, or mean PLT dose per day of support. The only significant difference detected was an increase in the mean number of PLT transfusions per day of support from 1.0 to 1.1 ($p < 0.01$) among the broad patient population. This difference may have arisen due to a small decrease in the mean duration of PLT support from 14.2 to 13.1 days ($p = 0.49$) after implementation of pathogen inactivation. The reason for the slight decrease in the mean duration of PLT support is unclear. Because the decrease in duration of PLT support was not significant, we concluded that the increase in mean number of PLT transfusions per day was likely not clinically relevant. This difference was not detected among hematology or oncology patients.

Because PLT transfusions are used to support patients with either quantitative or qualitative PLT deficits with potential for bleeding, we examined the use of RBC concentrates as an indirect measure of hemostasis. While RBC transfusions may be administered to correct anemia due to hypoproduction as well as bleeding, data on use of RBC support provide a partial measure of the impact of PLT transfusion on prevention of bleeding. For all patients supported with PLT components in either period, there was no impact on the requirement for RBC transfusion after introduction of pathogen inactivation of PLT components. This trend was consistent for patients supported with PLT and RBC components during periods of PLT support, when patients would be at greatest risk for bleeding, and outside periods of PLT support when RBC use would be most reflective of transfusion to support hypoproductive anemia.

The broad patient population included a substantial proportion of cardiovascular surgery patients (approx. one-third of the population in both periods) with short-term PLT support and obligatory intraoperative blood loss. To examine the impact of pathogen inactivation in a

TABLE 9. Daily lowest PLT count for patients transfused before and after adoption of pathogen inactivation treatment of PLT components

Parameter	Control	Test	p Value
All patients			
PLT transfusions (n)*	6812	7994	
PLT dose/transfusion†	4.2 (1.0)	3.6 (0.9)	<0.001
PLT count (10^9/L)‡	47.1 (71.4)	63.5 (95.3)	<0.001
Median PLT count (10^9/L)	23.0	22.0	0.39§
Cardiovascular surgery patients			
PLT transfusions (n)*	415	534	
PLT dose/transfusion†	4.3 (1.0)	3.8 (0.8)	<0.001
PLT count (10^9/L)‖	71.2 (51.4)	77.4 (45.1)	0.09
Median PLT count (10^9/L)	59.0	68.0	0.005§
All hematology patients			
PLT transfusions (n)*	5658	6686	
PLT dose/transfusion†	4.2 (1.0)	3.6 (0.9)	<0.001
PLT count (10^9/L)¶	44.1 (72.3)	60.6 (97.8)	<0.001
Median PLT count (10^9/L)	21.0	20.0	0.23§
*Intensively transfused hematology patients***			
PLT transfusions (n)*	5630	6663	
PLT dose/transfusion†	4.2 (1.0)	3.6 (0.9)	<0.001
PLT count (10^9/L)††	44.0 (72.0)	60.5 (97.7)	<0.001
Median PLT count (10^9/L)	21.0	20.0	0.25§

* The total number of PLT transfusions administered during each period with at least one PLT count on the day of transfusion.
† The mean (SD) for the PLT dose (10^{11}).
‡ The mean daily lowest PLT count (SD) for transfusions with a PLT count available in the medical record on day of transfusion. During the control and test periods there were 4690 (68.8%) and 5797 (72.5%) transfusions, respectively, with recorded PLT counts.
§ Based on two-sample Wilcoxon test.
‖ The mean daily lowest PLT count (SD) for transfusions with a PLT count available in the medical record on day of transfusion. During the control and test periods there were 320 (77.1%) and 370 (69.3%) transfusions, respectively, with recorded PLT counts.
¶ The mean daily lowest PLT count (SD) for transfusions with a PLT count available in the medical record on day of transfusion. During the control and test periods there were 4144 (73.2%) and 4914 (73.4%) transfusions, respectively, with recorded PLT counts.
** Intensively transfused hematology patients were defined as those patients who received two or more PLT transfusions in a treatment period.
†† The mean daily lowest PLT count (SD) for transfusions with a PLT count available in the medical record on day of transfusion. During the control and test periods there were 4120 (73.1%) and 4893 (73.4%) transfusions, respectively, with recorded PLT counts.

TABLE 10. Daily lowest Hb level for patients transfused before and after adoption of pathogen inactivation treatment of PLT components

Parameter	Control	Test	p Value
All patients			
Patients (n)[1]	626	713	
Hb (g/dL)[2]	8.5 (1.1)	8.5 (1.0)	0.82
Median Hb (g/dL)	8.6	8.5	
Cardiovascular surgery patients			
Patients (n)*	201	257	
Hb (g/dL)†	8.3 (1.0)	8.2 (1.0)	0.11
Median Hb (g/dL)	8.2	8.1	
All hematology patients			
Patients (n)*	257	266	
Hb (g/dL)†	9.0 (0.7)	8.9 (0.7)	0.12
Median Hb (g/dL)	9.0	8.9	
Intensively transfused hematology patients‡			
Patients (n)*	235	249	
Hb (g/dL)†	8.9 (0.6)	8.9 (0.6)	0.42
Median Hb (g/dL)	9.0	8.9	

* The number of patients transfused with both PLT and RBC concentrates and a Hb level recorded in the medical record on the day of PLT transfusion.
† The mean (SD) daily lowest Hb level (g/dL) per patient for each patient group.
‡ Intensively transfused hematology patients were defined as those patients who received two or more PLT transfusions in a treatment period.

more stable and intensively transfused population, we specifically analyzed data for hematology patients. This subpopulation comprised slightly more than one-third of the broad patient population in both observation periods, and the hematology patients had more periods of PLT support and a longer cumulative duration of PLT support (mean, 32-33 days) compared to that of the general population (mean, 13-14 days). The multiple periods of PLT support (approx. four as the average) included many patients repeatedly transfused during each 3-year observation period. Multiple indices of PLT component utilization including mean transfusions per patient, mean transfusions per day of PLT support, mean total PLT dose per patient, and mean dose per day of support were not statistically different between the observation periods. Among hematology patients, we observed a significantly lower PLT dose per day of PLT support (3.0×10^{11} vs. 3.2×10^{11} PLTs per day, $p = 0.05$) after introduction of pathogen inactivation. However, the data for this intensively transfused population supported during multiple periods of PLT transfusion over a 3-year observation period did not indicate any impact on PLT utilization after introduction of pathogen inactivation for PLT components (Table 5).

The hematology patient subpopulation provided a patient population in which to evaluate the impact of a change in PLT component preparation on the use of RBCs both during and outside periods of PLT support. This population was not substantially impacted by major surgical interventions, thus providing a more reliable estimate of the impact of a change in PLT component on both hemostasis, as measured by RBC transfusion requirements during periods of PLT support, and the impact on RBC production, as measured by RBC transfusion outside periods of PLT support. No significant differences in RBC use were detected after introduction of pathogen inactivation for PLT components. We interpret these observations to indicate that hemostasis and RBC production were not affected by a change in PLT component preparation.

We also examined the impact of pathogen inactivation on PLT use by oncology patients. However, this was a small patient population; and the data were limited. Consistent with the observations for hematology patients, we did not detect any highly significant impact on PC or RBC use due to the change in PLT component; however, these observations require confirmation in a larger population.

As an added means to examine the impact of a change in PLT component on transfusion practice and clinical outcome, we examined data on the daily lowest PLT count and daily lowest Hb level on days of PLT and RBC transfusions. We hypothesized that the lowest PLT count and the lowest Hb within 1 day on days of PLT and RBC transfusion, respectively, would provide a comparative indicator of the level of thrombocytopenia and anemia on the day of transfusion in the two observation periods. These data were analyzed on a per-transfusion basis as the laboratory indices were related to specific transfusion events. We analyzed these data for all patients as well as for specific subsets including cardiovascular surgery patients, hematology patients, and intensively transfused hematology patients (those with two or more periods of PLT transfusion support). During the 6-year period of this study at CUMG, the broadly accepted clinical threshold for PLT transfusion was a PLT count of 10×10^9 to 20×10^9/L and for RBC transfusion a Hb level of 9 to 10 g/dL. The BTC Mont Godinne does not require a specific pretransfusion PLT count or Hb level to issue a blood component. Primary care physicians ordered blood components based on individual patient assessments and their independent clinical judgment.

We used the PLT count data in two ways. First, the daily lowest PLT count served as a comparison of potential changes in degree of thrombocytopenia between the two observation periods. For all the patient groups analyzed, the mean lowest daily PLT count was associated with a large SD, and the difference in the mean and median values was a result of the heterogeneous distribution of PLT levels in the large patient population. Except for cardiovascular surgery patients, the median values were not significantly different between the groups and were 21×10^9 to 23×10^9/L, reasonably close to expected transfusion threshold values for patients with hypoproliferative thrombocytopenia. This trend was similar for more intensively transfused hematology and oncology patients as well. Cumulatively, these data suggest that after implementation of pathogen inactivation, patients did not experience a lower PLT count nadir during PLT support.

We postulated that the mean lowest daily Hb level could serve as a surrogate measure for hemostasis provided that there was no indication for differential suppression of erythropoiesis by the new PLT component. We concluded that the similar use of RBC components outside periods of PLT support, especially for hematology patients, supported this hypothesis. The lack of difference in the lowest daily mean Hb levels on days of PLT transfusion is consistent with the conclusion that the new PLT components provided adequate hemostasis.

Recently, two multicenter hemovigilance studies monitoring the safety of 12,543 PLT components transfused to 2051 patients have shown that PLT components prepared with pathogen inactivation were well tolerated when used in routine practice.[17,18] In conjunction with these observations, the current study utilizing longitudinal data collected as part of a hemovigilance program demonstrates that PLT components prepared with pathogen inactivation can be implemented into routine practice without substantially impacting PLT or RBC component utilization over a substantial period of transfusion support.

CONFLICT OF INTEREST

J.C. Osselaer received research support for conduct of this study and serves on a speaker board for Cerus Corporation. J.S. Lin is a consultant to Cerus Corporation. L. Lin and L. Corash are employees of Cerus Corporation.

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市販後調査及び観察研究の報告⑤

ORIGINAL ARTICLE

Use of additive solutions and pathogen inactivation treatment of platelet components in a regional blood center: impact on patient outcomes and component utilization during a 3-year period

Jean-Pierre Cazenave, Hervé Isola, Chantal Waller, Isabelle Mendel, Daniel Kientz, Michel Laforêt, Jean-Pierre Raidot, Gérard Kandel, Marie-Louise Wiesel, and Laurence Corash

BACKGROUND: The Etablissement Français du Sang Alsace (EFS Alsace) successively implemented universal use of platelet additive solutions (PASs) and pathogen inactivation (PI) for platelet components (PCs). To assess the impact of these changes, EFS Alsace evaluated PC use, red blood cell (RBC) component use, and transfusion-related adverse events after implementation of these new technologies.

STUDY DESIGN AND METHODS: EFS Alsace prospectively collects data on production, distribution, and response to transfusion of all blood components with greater than 99.5% data acquisition. Adverse events attributed to platelet (PLT) transfusions were collected through a mandatory, active hemovigilance program. A retrospective review of prospectively collected data was conducted covering three periods: 1) apheresis and whole blood–derived PCs in plasma, 2) apheresis and whole blood–derived PCs with PAS, and 3) PCs prepared with PI and PAS. Data on component utilization were analyzed for all patients receiving PCs in each period and for the subset of hematology-oncology patients to evaluate PC use in an intensely transfused population. Values for all continuous variables were summarized as mean and standard deviation, median, and range.

RESULTS: Approximately 2000 patients received PCs in each period. PLT and RBC use per patient was not increased after PI (analysis of variance, $F = 1.9$ and 2.9, respectively) and the incidence of acute transfusion reactions was significantly reduced ($p < 0.001$).

CONCLUSIONS: Universal use of PI was implemented without impacting component use, as indicated by total dose of PLTs per patient, and outcomes to transfusion were improved.

The Etablissement Français du Sang Alsace (EFS Alsace) is the sole provider of blood components for approximately 2 million inhabitants of the Alsace region of France and issues approximately 17,000 platelet components (PCs) per year. In 2005, the EFS Alsace implemented routine use of platelet additive solution (PAS) for production of PCs to reduce recipient exposure to allogeneic donor plasma and to increase salvage of plasma for production of therapeutic and fractionated plasma. The following year, 2006, the EFS Alsace implemented routine use of photochemical pathogen inactivation (PCT) to reduce the risk of transfusion-transmitted infection and adverse immune reactions associated with transfusion of PCs.

Each of these interventions has the potential to impact the therapeutic efficacy of PCs as well as impact utilization of other blood components and patient outcomes in response to transfusion therapy.[1,2] Component utilization and transfusion-related adverse events were selected as outcome variables because of clinical relevance to patient management. A decrease in therapeutic efficacy due to changes in PC treatment could result in the need for more transfusion support. A change in the incidence of adverse events associated with novel PCs would be highly relevant to both patients and treating physicians. To assess the impact of use of PASs and pathogen inactivation (PI) treatment, EFS Alsace conducted a retrospective review of PC use, red blood cell (RBC) component use, and transfusion-related adverse events during three different periods to evaluate the effect of each change in platelet (PLT) preparation. This review provided useful information regarding the progressive effects of each change for all patients supported with PCs during each observation period, and for specific patient populations, such as pediatric and hematology-oncology patients, which might be differentially affected by changes in the manufacture of PCs.

ABBREVIATIONS: CSDP = concentrated single-donor platelet (program); EFS Alsace = Etablissement Français du Sang Alsace; PAS(s) = platelet additive solution(s); PC(s) = platelet component(s); PCT = photochemical pathogen inactivation; PI = pathogen inactivation; TA-GVHD = transfusion-associated graft-versus-host disease.

From the Etablissement Français du Sang (EFS)–Alsace, INSERM UMR-S949, and the Université de Strasbourg, Strasbourg, France; and Cerus Corp., Concord, California.

Address reprint requests to: Jean-Pierre Cazenave, Etablissement Français du Sang-Alsace, 10 rue Spielmann, BP 36, 67065 Strasbourg Cedex, France; e-mail: jeanpierre.cazenave@efs-alsace.fr.

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TRANSFUSION **;**:**-**.

MATERIALS AND METHODS

Overall study design

The study covered three observation periods, each lasting from 9 to 13 months in duration. The variable length of each period was in part determined by the time required for switching between types of PCs and data for each period were utilized only once production consisted entirely of the new type of PC product. Period 2 was arbitrarily shorter due to the decision to implement PI as soon as possible. During the 13-month period from January 2003 to February 2004 (Period 1) all PCs derived either from whole blood collections or by apheresis collections were prepared in 100% allogeneic donor plasma. During the 9-month period from September 2005 to June 2006 (Period 2) all PCs were prepared in PAS (53%-68%) and residual donor plasma (32%-47%). During the 11-month period from September 2006 to August 2007 (Period 3) all PCs were prepared in PAS (53%-68%) and residual plasma (32%-47%) with PCT for PI. During each of these three periods, data were collected on the production, transfusion, and transfusion-related adverse events for all patients supported by the EFS Alsace.

Data were collected in compliance with a national hemovigilance program with protection of patient confidentiality, and individual patient informed consent was not required.[3] Data on PC and RBC component use were analyzed for all patients receiving PCs during each observation period and for the subset of hematology-oncology patients. Hematology-oncology patients were selected for separate analysis with respect to blood component utilization because they are intensively transfused for prophylaxis of bleeding and provide a more stringent population in which to assess component utilization.

Production of PCs

The variables for preparation of PCs during each of the three periods are summarized in Table 1. Whole blood was collected into CPDA-1 anticoagulant from volunteer blood donors who met the EFS requirements for blood donation. Whole blood–derived buffy coat PCs were prepared as previously described.[4] Single-donor apheresis PCs were collected from qualified donors using an apheresis system (MCS+, Haemonetics, Braintree, MA). During the three periods, all PCs were leukoreduced by filtration ($<1 \times 10^6$ white blood cells [WBCs]/PC) to produce a therapeutic PC that was stored for up to 5 days with reciprocal agitation under temperature control (22-24°C) before transfusion.

Period 1

Whole blood donation had a mean volume of 462 ± 14 mL. Six whole blood–derived buffy coat concentrates were pooled and suspended in 100% donor plasma. Single-donor apheresis PCs were suspended in 100% donor plasma. During this period, two target doses for apheresis components were used, 3.5×10^{11} or 5.5×10^{11} PLTs per collection. Both whole blood–derived pooled buffy coat and apheresis PCs were irradiated with 2500 cGy, using a cesium source, according to established indications for prevention of transfusion-associated graft-versus-host disease (TA-GVHD).

Period 2

Whole blood donation had a mean volume of 460 ± 11 mL. Six buffy coat concentrates were pooled and suspended in approximately 35% donor plasma and 65% PAS (T-Sol, Fenwal, Inc., La Châtre, France). Single-donor apheresis PCs were collected from qualified donors using the MCS+ platform with the concentrated single-donor PLT (CSDP) program (Haemonetics) and suspended in approximately 45% donor plasma with 55%

TABLE 1. Variables for preparation of PCs

Variable	Period 1 (Plasma)	Period 2 (PAS)	Period 3 (PI)
Buffy coat PCs			
Whole blood (mL)	462 ± 14	460 ± 11	461 ± 11
Anticoagulant	CPDA-1	CPDA-1	CPDA-1
Pool size	6	6	6
Plasma target (%)	100	35	35
PAS (%)	0	65	65
Apheresis PCs			
Platform	MCS+	MCS+/CSDP	MCS+/CSDP
Target dose ($\times 10^{11}$)	3.5 or 5.5	4.5	4.5
Plasma target (%)	100	45	45
PAS (%)	0	55	55

95

T-Sol. During this second period, the collection target for apheresis products was set at 4.5×10^{11} PLTs per collection. Both whole blood–derived pooled buffy coat and apheresis PCs were irradiated with 2500 cGy according to established indications for prevention of TA-GVHD.

Period 3

Whole blood donation had a mean volume of 461 ± 11 mL. Six buffy coat concentrates were pooled and suspended in approximately 35% donor plasma and 65% PAS (Intersol, Fenwal, Inc.). Single-donor apheresis PCs were collected from qualified donors using the MCS+ platform and CSDP software (Haemonetics) and suspended in approximately 45% donor plasma with 55% Intersol. During the third period, the collection target for apheresis products was set at 4.5×10^{11} PLTs per collection. Both pooled whole blood–derived and apheresis PCs were processed (Fig. 1) within 24 hours of collection using amotosalen-HCl and UVA light photochemical PI treatment (INTERCEPT Blood System for Platelets, Cerus Europe BV, Amersfoort, the Netherlands) according to the manufacturer's directions for use.[5] In both cases, residual amotosalen and photoproducts were removed after 4 to 8 hours of incubation using a compound adsorption device. Apheresis PCs were released on Day 1 and pooled whole blood–derived PCs on Day 2 (Fig. 1). PI treatment was used in place of gamma irradiation for prevention of TA-GVHD. Residual amotosalen levels were measured in 1% of treated PCs for quality control.

Transfusion of PCs and hemovigilance monitoring

In all three study periods the PLT count and total PLT content were determined for each apheresis PC. In the first two periods, the PLT count and PLT content of pooled leukoreduced whole blood–derived buffy coat components were determined in a subset (3% for Period 1 and 17% for Period 2) of components for process control. In Period 3 PLT count and total PLT content was determined for each pooled leukoreduced whole blood–derived buffy coat component. PLT counts were measured by electrical impedance with calibration using an optical PLT counter (Sysmex XE 2100D, Roche Diagnostics, Meylan, France). Total PLT content of transfused components was determined based on PLT concentration and component volume expressed as total PLTs × 10^{11}.

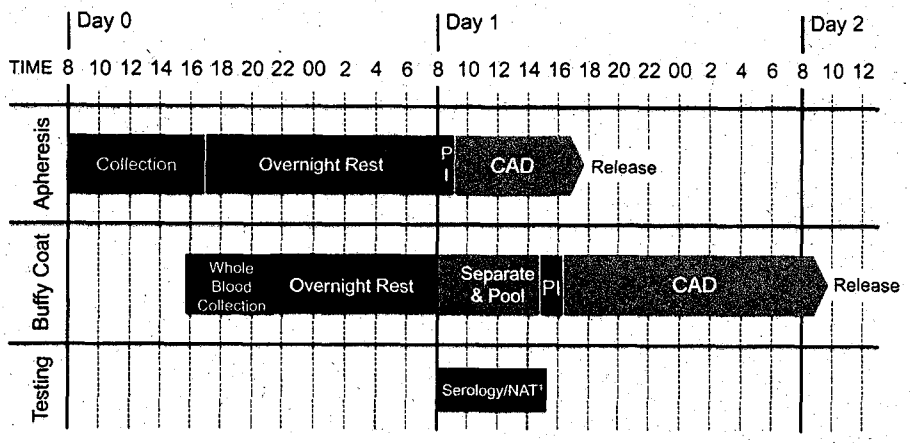

Fig. 1. PC processing workflow. The time in hours starting with the day of collection (Day 0) is indicated. Apheresis components are stored overnight on temperature-controlled shakers (22-24°C) followed by PI treatment and incubation in a compound absorption device (CAD) container from a minimum of 6 hours to a maximum of 16 hours before release for transfusion. Whole blood collections are stored overnight after collection. On Day 1 buffy coat concentrates are isolated, pooled, and treated with PI followed by CAD incubation and release on the beginning of Day 2. [1]Serology/NAT 8 a.m.–3 p.m. daily. PI and CAD = pathogen inactivation using the INTERCEPT Blood System; NAT = nucleic acid testing.

The EFS Alsace blood center maintains a database to monitor the production, issuance, transfusion, and utilization of all blood components. The blood center database contains information on patient demographics and clinical service location of transfusion. In each period, primary care physicians ordered PCs for transfusion according to French national guidelines published by the French Agency of Medical Safety of Health Products in 2003 and based on a recommended dose of 0.5×10^{11} to 0.7×10^{11} PLTs per 7 kg in adults and 0.5×10^{11} PLTs per 5 or 7 kg in pediatric patients for support of thrombocytopenia. The response to transfusion of blood components was monitored through the national active hemovigilance program under the direction of French Agency of Medical Safety of Health Products.[3] Under this program, all blood transfusions are monitored and potential transfusion adverse incidents are evaluated for severity and relationship to the transfused component in a transfusion incident report. Declaration is mandatory for each transfusion, whether or not a transfusion incident report has occurred. The severity of incidents is classified based on WHO criteria: Grade 1—absence of immediate or long-term vital threat, Grade 2—potential long-term morbidity, Grade 3—immediate vital threat, and Grade 4—death of the patient. The relation of the transfusion to the adverse effect is evaluated using a five-point scale basis: 0—excludes any causal relationship, 1—is doubtful, 2—is possible, 3—is likely, and 4—is unquestionable. The transfusion incident reports are submitted to regional hemovigilance network coordinators and entered into an electronic database.

Statistical analysis

Descriptive analyses were conducted for the demographic and clinical variables. Values for all continuous variables were summarized as mean and standard deviation (SD), median, and range. A one-way analysis of variance (ANOVA; single factor) was used to test the equality of PLT content per product, of the number of PCs transfused per patient, and of total dose of PLTs received by the patient between the three periods studied (Table 2). When the difference of ANOVA during the three periods was significant, a t test was used a priori to compare between Period 1 and 2, Period 1 and 3, and Period 2 and 3. All p values reported were two-sided, and significance was declared at a p value of less than 0.05 ($p < 0.05$). All statistical calculations were done with computer software (Excel, 2007 SP2 MSO, Microsoft Corp., Redmond, WA).

RESULTS

Demographics of patients transfused with PCs

In each of the three periods, 1678 to 2069 consecutive patients received one or more PCs (Table 3). Within each period, the largest proportion of PLT transfusions were administered on hematology-oncology care services (Table 3). Patients ranged in age from less than 1 to 106 years of age (Table 3).

TABLE 2. Production and utilization of PCs

Variable	Period 1*	Period 2†	Period 3‡
Number of components	10,629	9,151	13,241
PLT content of transfused components§			
Mean dose/unit (×10^{11})	5.2	4.4	4.2
Median (×10^{11})	5.4	4.7	4.4
Range (×10^{11})	0.6-9.2	0.8-7.8	0.5-7.3
PC use/patient (n)‖			
Patients	2,050	1,678	2,069
Mean	5.2[b]	5.5[c]	6.4[b,c]
Median	2.0	2.0	2.0
Range	1-104	1-114	1-289
Total PLT dose/patient (×10^{11})¶			
Mean	27.1	24.1	26.9
Median	10.9	9.4	9.1
Range	0.2-543	0.2-503	0.5-1,302

* PCs were prepared in plasma. During Period 1, PLT content of whole blood–derived PC was determined in 3% of components.
† PCs were prepared in plasma with PAS. During Period 2, PLT content of whole blood–derived PC was determined in 17% of components.
‡ PCs were prepared in plasma with PAS and PI treatment.
§ ANOVA, difference if $F \geq 3.0$. The difference is significant for the three periods ($F = 4396.9$). t test for two samples assuming equal variances: [a]P1 – P2, [b]P1 – P3, [c]P2 – P3, $p < 0.05$.
‖ ANOVA, difference if $F \geq 3.0$. The difference is significant for the three periods ($F = 6.8$). t test for two samples assuming equal variances: [a]P1 – P2, $p = 0.37$; [b]P1 – P3, $p = 0.0006$; [c]P2 – P3, $p = 0.01$.
¶ ANOVA. The difference is not significant for any comparisons: $F = 1.9$.

TABLE 3. Demographics of patients transfused with PCs

Demographic	Period 1*	Period 2†	Period 3‡
Number of patients	2050	1678	2069
Median age (years)	64	63	63
Age range (years)	3-97	<1-99	<1-106
Male (%)	59	60	62
Proportions (%) of patients transfused by clinical service			
Hematology-oncology	56.1	50.5	58.1
General medical	36.6	43.6	36.3
Cardiovascular surgery	7.3	5.9	5.7

* PCs were prepared in plasma.
† PCs were prepared in plasma and PAS.
‡ PCs were prepared in plasma and PAS with PI treatment.

Characteristics of PCs

During the three periods the PLT content per component changed as the methods of production changed (Table 2). With the introduction of PASs, production methods were adjusted to equalize the PLT content of apheresis and whole blood–derived PCs that were ordered interchangeably by primary care physicians. All PCs transfused demonstrated retention of swirling when issued by the blood center. PLT content per PC unit was significantly less in Period 2 compared to Period 1 ($p < 0.05$) and in Period 3 compared to Period 2 ($p < 0.05$) (Table 2). During Period 3, all the 13,241 components were tested for PLT content; the mean ± SD PLT content was $4.2 \times 10^{11} \pm 0.4 \times 10^{11}$ and the mean ± SD loss due to PI was 24 ± 4 mL containing $0.3 \times 10^{11} \pm 0.07 \times 10^{11}$ PLTs. For PCs treated with PI, residual amotosalen levels were measured in 1% of products (n = 201). The mean residual amotosalen concentration for whole blood and apheresis components was 0.24 ± 0.09 µmol/L (median, 0.22 µmol/L; maximum, 1.25 µmol/L).

Utilization of PCs

The utilization of PCs was determined per patient based on the number of components transfused and the total number of PLTs transfused per patient. The latter was of specific importance as the PLT content per component changed according to changes in the methods of production during the three periods (Table 2). For each period, the relative proportion of whole blood–derived and apheresis PCs remained constant, approximately 65%:35%, respectively. The mean number of PCs transfused per patient increased in Periods 2 and 3 compared to Period 1 (Table 2); however, the number of transfusion episodes and the total dose of PLTs transfused per patient were not different between the two periods (Table 2).

Utilization of RBC components

Utilization of RBCs was determined for patients who received one or more PCs during each observation period (Table 4). In each observation period, approximately 85% of patients transfused with PCs received at least one RBC unit. No significant difference in utilization of RBCs was detected between the three observation periods.

Acute transfusion reactions

Adverse events after transfusion of PCs were evaluated for relationship to transfusion and all events classified as doubtful, possible, likely, or unquestionable were defined as acute transfusion reactions. These events also included the observation of newly detected alloantibodies to RBC antigens with or without evidence of hemolytic transfusion reactions (Table 5). Cumulatively, for all three periods, 145 adverse events were reported, of which 46 were newly detected RBC alloantibodies without hemolysis secondary to concomitant transfusion of RBCs in 85% of the patients receiving PCs (Table 5). In Period 1, one death due to volume overload was reported. All other reactions were Grades 1 (61%) and 2 (33%) in severity. During Period 3 among the 18 reported reactions not due to RBC alloantibodies, eight were characterized by febrile reactions, three were characterized as allergic reactions, and one episode of transfusion-related acute lung injury (TRALI) associated with high-titer HLA antibodies from a multiparous donor was reported during Period 3 in association with transfusion of PI-treated apheresis PCs without exposure to any other blood components. Six transfusion reactions were not characterized further. No cases of transfusion-related sepsis were reported in any period. The incidence of transfusion-related adverse events per 1000 PCs transfused was significantly reduced with the implementation of PAS ($p = 0.005$) and further reduced with the implementation of PI ($p = 0.021$). Analysis of the incidence of transfusion-related adverse events per patient demonstrated significant reduction after implementation of PAS ($p = 0.009$) and further reduction with the implementation of PI ($p = 0.0779$).

TABLE 4. Utilization of RBC components

Variable	Period 1*	Period 2†	Period 3‡
Number of patients transfused with PCs	2,050	1,678	2,069
Number (%) of patients transfused with PCs and RBCs	1,715 (83.7)	1,355 (80.8)	1,749 (84.5)
Number of RBC units§	24,693	17,732	23,824
Mean number RBC units/patient	14.4	13.1	13.6

* PCs were prepared in plasma.
† PCs were prepared in plasma and PAS.
‡ PCs were prepared in plasma and PAS with PI treatment.
§ ANOVA. The difference between the three periods is not significant: $F = 2.9$.

TABLE 5. Adverse reactions after transfusion of PCs

Variable	Period 1*	Period 2†	Period 3‡
Number of patients transfused	2,050	1,678	2,069
Number of components transfused	10,629	9,151	13,241
Number of patients with adverse reactions	59	33	36
Number of adverse events§	67	41	37
Number of RBC alloantibodies detected	11	16	19
Number of RBC alloantibodies/1000 PCs	1.03	1.75	1.43
Number of transfusion reactions	56	25	18
Number of total reactions/1000 PCs	6.3	4.5	2.8
Number of PC-related reactions/1000 PCsII	$5.3^{a,c}$	$2.7^{a,b}$	$1.4^{b,c}$
Patients with PC reactions (%)¶	$2.9^{a,c}$	2.0^{a}	1.7^{c}

* PCs were prepared in plasma.
† PCs were prepared in plasma and PAS.
‡ PCs were prepared in plasma and PAS with PI treatment.
§ Total transfusion reactions including alloantibodies detected to RBC antigens.
II Transfusion reactions excluding RBC alloantibodies not associated with symptomatic reactions. Chi-square test with $\alpha = 0.05$, difference if $p < 0.05$: $^{a}P1 - P2$, $p = 0.0053$; $^{b}P2 - P3$, $p = 0.0214$; $^{c}P1 - P3$, $p = 7 \times 10^{-4}$.
¶ Symptomatic reactions to PCs, excluding RBC alloantibodies. Chi-square test with $\alpha = 0.05$, difference if $p < 0.05$: $^{a}P1 - P2$, $p = 0.0094$; $^{b}P2 - P3$, $p = 0.0779$; $^{c}P1 - P3$, $p = 6.7 \times 10^{-4}$.

Utilization of PCs by intensively transfused patients

To further characterize the impact of changes in PC production, the utilization of PCs and RBCs by intensively transfused patients with hematology-oncology disorders was examined. Evaluation was restricted to Periods 1 and 3 since use of PAS without PI was only an intermediate phase in the evolution of the PLT production process at EFS Alsace. During both Period 1 and Period 3 all PCs were leukoreduced ($<1 \times 10^{6}$ WBCs/PC), and the proportion of whole blood–derived buffy coat and apheresis PCs remained constant (62:38), respectively. Mean PLT content per PC was lower during Period 3 (4.2×10^{11}) compared to Period 1 (5.2×10^{11}) due to a decision to harmonize the PLT content of both types of products.

Approximately similar numbers of hematology-oncology patients were transfused during Periods 1 and 3 (Table 6). Although the number of PCs transfused per patient was increased during Period 3 compared to Period 1, the total dose of PLTs per patient was not increased (Table 7). The increase in the number of PCs was due to decreased PLT content per unit in Period 3 compared to Period 1.

DISCUSSION

In 2005, the EFS Alsace regional blood center initiated changes in the routine preparation of PCs with the introduction of PAS, which was followed by implementation of PI treatment in 2006. Each of these changes had the potential to impact the PLT content of components, the utilization of components, and patient outcomes. To assess these potential impacts, EFS Alsace conducted a retrospective analysis of three different periods, each of approximately 1 year duration. The comparison of each of these innovations with conventional PCs in 100% plasma provided a means to assess the impact in a controlled manner since the same blood center and processing staff prepared PCs in each of the observation periods. Although primary care physicians were aware of the changes in methods of PLT production, they continued to prescribe PCs based on similar standard of care guidelines in each of the observation periods. This provided approximately similar clinical conditions to monitor patient responses in each of the periods.

This analysis was based on a comprehensive longitudinal database that tracked greater than 99% of PCs with respect to patient demographics and utilization by patients. In addition, the response to transfusion with respect to adverse outcomes was evaluated using an active hemovigilance program[3] for which data for greater than 99% of transfusions were reported in the EFS Alsace region. This study offered a unique opportunity to examine the impact of these changes in PLT production when implemented in routine use for support of a broad spectrum of patients. In addition, this study included a substantial population of intensively transfused hematology-oncology patients who may have been more sensitive to changes in the methods of PC production.

TABLE 6. Age demographics of hematology-oncology patients transfused with PCs

Demographics	Period 1*	Period 3†
Number of patients	671	699
Number (%) of infants-toddlers‡	10 (1.5)	5 (0.7)
Number (%) of children§	49 (7.3)	49 (7.0)
Number (%) of adultsII	612 (91.2)	645 (92.3)

* PCs were prepared in plasma.
† PCs were prepared in plasma and PAS with PI treatment.
‡ Infants and toddlers were 1 month to less than 3 years of age.
§ Children were 3 to 17 years of age.
II Adults were greater than 17 years of age.

TABLE 7. Utilization of PLT and RBC components by hematology-oncology patients

Variable	Period 1*	Period 3†	p value
Number of patients	671	699	
Number of PCs transfused			
Mean ± SD‡	8.7 ± 12	11 ± 20	0.01
MedianII	4.0	4.0	
RangeII	1-103	1-264	
Total PLT dose			
Mean ± SD‡	45.3 ± 62.8	46.1 ± 86.1	0.85
Median	21.6	18.4	
RangeII	0.8-536	1.5-1189	
Number of RBC units transfused			
Mean§	15.2 ± 16.5	13.6 ± 18.4	0.10
MedianII	9.0	8.0	
RangeII	0-93	0-272	

* PCs were prepared in plasma.
† PCs were prepared in plasma with PAS and PI treatment.
‡ Mean number of PCs transfused per patient.
‡ Mean total dose of PLTs (10^{11}) per patient.
§ Mean number of RBC units per patient.
II Data expressed per patient.

Patient demographics, in terms of age, sex, and primary care service for PC transfusion, were comparable between the three periods. Each of the observation periods included between 1678 and 2069 patients with transfusion of between 9151 and 13,241 PCs and 17,732 to 24,693 RBC units. Thus, this observational study encompasses a large experience, indeed much larger than that of most clinical trials in transfusion medicine that have been used to support implementation of major changes in transfusion practice, such as leukoreduction and adjustment of the transfusion threshold.[6,7] When adjustments were made for differences in PLT content of individual components, there were no significant differences in the total PLT dose required per patient, either for all patients or for intensively transfused hematology-oncology patients. Changes in the methods of PC production did not impact utilization of RBCs, indicative of preservation of effective hemostasis during periods of PLT transfusion support. This observation is of particular interest with respect to cardiovascular surgery patients and general medical patients who have not been studied in the randomized clinical trials of PCs treated with PI.[5,8,9] While the utilization of PCs and RBCs did not change in response to modifications in PLT processing, the incidence of adverse events imputed to transfusions of PCs decreased on both a per-transfusion and a per-patient basis. This observation is consistent with the significant reduction in acute transfusion reactions noted in a prior large randomized clinical trial.[9] Only a single case of TRALI was reported during each of these observation periods; this case was attributable to high-titer HLA antibodies in a multiparous apheresis PLT donor. No cases of transfusion-related sepsis were reported in any period.

The conclusions regarding efficacy and safety that may be drawn from this study are potentially limited due to the lack of a blinded, randomized trial design. However, the study has the advantage of comparative observation periods in a single region in which the staff preparing the PCs and the primary care physicians prescribing PCs and monitoring patient outcomes remained relatively stable. Moreover, the study was conducted in observation periods when each of the PC methods reflected routine production practices. Thus, the study involved assessment of the changes in PC production under realistic conditions. In addition, monitoring of patient clinical outcomes utilized objective measures, such as utilization of PCs and RBCs, and an active hemovigilance program with oversight by clinical monitors who were not associated with the blood center producing the blood components. On the basis of these factors, we believe that the data reported from this study indicate that PASs and PI treatment can be implemented into routine practice without impacting either PC or RBC utilization and with a reduction in acute transfusion reactions. The experience with respect to the safety profile and tolerability of PCs treated with PI in this study is consistent with that reported for several other large postmarketing hemovigilance studies.[10-12] It is also similar to the Belgian experience of universal routine use of Intercept-inactivated PCs for 3 years, that enables learning of how well the products function in broad populations.[13] In addition, the PI process was used in place of gamma irradiation for prevention of TA-GVHD and in place of cytomegalovirus serology resulting in the use of a single PLT inventory with elimination of these additional tests and procedures.

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CONFLICT OF INTEREST

JPC is a member of the European Scientific Advisory Board of Cerus Corporation. LC is an employee of Cerus Corporation. HI, CW, IM, DK, ML, JPR, GK, and MLW have no conflicts of interest.

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市販後調査及び観察研究の報告⑥

Therapeutic efficacy of platelet transfusion in patients with acute leukemia: an evaluation of methods

Torunn O. Apelseth, Øystein Bruserud, Tore Wentzel-Larsen, and Tor Hervig

BACKGROUND: Clinical effect of platelet (PLT) transfusion is monitored by measures of PLT viability (PLT recovery and survival) and functionality. In this study we evaluate and compare transfusion effect measures in patients with chemotherapy-induced thrombocytopenia due to treatment of acute leukemia.

STUDY DESIGN AND METHODS: Forty transfusions (28 conventional gamma-irradiated and 12 pathogen-inactivated photochemical-treated PLT concentrates [PCs]) were investigated. PC quality was analyzed immediately before transfusion. Samples were collected from thrombocytopenic patients at 1 and 24 hours for PLT increments and thromboelastography (TEG) with assessments of bleeding score and intertransfusion interval (ITI). Data were analyzed by Spearman's correlation. Patient and PC variables influencing the effect of transfusion were analyzed by use of a mixed-effects model.

RESULTS: PLT dose, storage time, and pathogen inactivation correlated with PLT recovery but not with PLT survival (including ITI), TEG, or clinical bleeding. Fever was negatively correlated with PLT survival but did not affect PLT recovery. After 1 and 24 hours, strong correlations were observed within measures of PLT viability and between PLT increment and the TEG value maximal amplitude (MA). Negative correlation was observed between late MA increment and clinical bleeding status after transfusion ($r = -0.494$, $p = 0.008$). PLT count increments did not correlate to clinical bleeding status.

CONCLUSIONS: PLT dose and quality of PCs are important for optimal immediate transfusion response, whereas duration of transfusion effect is influenced mainly by patient variables. The TEG value MA correlates with PLT count increments and bleeding, thus reflecting both PLT viability and functionality.

Allogeneic platelet (PLT) transfusions are used to prevent (prophylactic transfusions) and control (therapeutic transfusions) bleeding in patients receiving intensive chemotherapy.[1-5] But even though the risks of severe transfusion reactions and transmission of pathogens are minimized due to technologic progress and pathogen reduction methods, PLT transfusions are not free of complications.[6-8] It is therefore important to continue the search for an optimal transfusion policy in patients receiving PLT transfusions. Large randomized clinical trials are now performed aiming to define the optimal use of PLT transfusions, both by evaluation of transfusion strategies and by investigations of the influence of variables like PLT dose and transfusion triggers on the results of treatment.[3,5]

The tests used to assess the clinical efficacy of PLT transfusion reflect different approaches to minimize bleeding in patients. They influence routine transfusion practice as well as the results of clinical PLT transfusion studies. The clinical effect of PLT transfusion is monitored by measures of PLT viability and functionality. In studies of thrombocytopenic patients, PLT viability is usually investigated by immediate PLT count increments, reflecting the PLT recovery together with late PLT count increment and intertransfusion interval (ITI) which reflects the PLT survival.[4,5,9-12] PLT functionality may be monitored by bleeding assessments[12,13] and point-of-care tests of hemostasis and PLT function like the thromboelastography (TEG) analysis.[14] While PLT count increments are fundamental in the prophylactic PLT transfusion strategy, the therapeutic transfusion strategy is based on bleeding assessments.

In our study we aim to evaluate and compare methods for measurement of clinical efficacy in acute leukemia patients receiving regular PLT transfusions due to severe chemotherapy-induced thrombocytopenia.

ABBREVIATIONS: API = absolute platelet increment; ITI = intertransfusion interval; MA = maximal amplitude; PC(s) = platelet concentrate(s); PCT = photochemical treated; TEG = thromboelastography.

From the Blood Bank, the Section for Hematology, Department of Medicine, and the Centre for Clinical Research, Haukeland University Hospital, Bergen; and the Gades Institute and the Institute of Medicine, University of Bergen, Bergen, Norway.

Address reprint request to: Torunn Oveland Apelseth, MD, Blood Bank, Haukeland University Hospital, N-5021 Bergen, Norway; e-mail: torunn.oveland.apelseth@helse-bergen.no.

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MATERIALS AND METHODS

Study design

This prospective observational study was approved by the local research ethics committee (Region III, University of Bergen, Bergen, Norway), and patients were recruited from the Section for Hematology, Department of Medicine, at Haukeland University Hospital from December 2006 until April 2007. During the study period, all patients diagnosed with acute leukemia expected to be in need of PLT transfusions due to severe chemotherapy-induced cytopenia were invited to participate in the study. With one exception, all patients accepted. After informed written consent was obtained, 10 patients with acute leukemia were included in the study, giving a total of 188 patient-days with chemotherapy-induced cytopenia. Of a total of 109 PLT transfusions, 40 PLT transfusions were selected to be characterized in detail based on the following criteria: daytime transfusions and data collection performed according to procedures. The study unit was defined as the PLT transfusion.

Preparation of PLT concentrates for transfusion

All PLT concentrates (PCs) fulfilled the European requirements.[15] Single-donor PCs (n = 17) were collected by single-needle apheresis procedure employing the elutriation principle to provide leukoreduced PLTs (Fenwal Amicus cell separator, Baxter Healthcare Corp., Deerfield, IL). Prestorage leukofiltered buffy coat PCs (n = 23) were produced by use of automated procedures (OrbiSac, CaridianBCT, Inc., Lakewood, CO). Twelve of the 40 single-donor and buffy-coat PCs were pathogen inactivated by photochemical treatment using amotosalen and UVA light (Intercept Blood System for Platelets, Cerus Corp., Concord, CA). Photochemical-treated (PCT) PCs were suspended in PASIII (Intersol, Fenwal, Inc., Lake Zurich, IL) and conventional PCs in PAS II (T-sol, Fenwal, Inc.) with 35% to 37% autologous plasma. Conventional PCs (n = 28) were gamma-irradiated immediately before transfusion (25 Gy; Gammacell 3000 Elan, Nordion International, Inc., Ottawa, Ontario, Canada). PCs were stored up to 168 hours at 22 ± 2°C under constant agitation in a flatbed PLT incubator (Helmer, Noblesville, IN). Bacterial testing was performed on all conventional PCs (BacT/ALERT, bioMerieux, Inc., Marcy l'Etoile, France). The preparation method of PCs transfused was not influenced by the investigators.

Patients

All patients were treated according to the same institutional guidelines with conventional intravenous cytarabine-based chemotherapy, and all developed severe chemotherapy-induced leukopenia with neutrophil counts below 0.5×10^9/L. PLT transfusions were requested by the patient's physician in accordance with international guidelines.[3,4,9] Prophylactic PLT transfusions were given to nonfebrile and clinically stable patients with peripheral blood PLT counts below 10×10^9/L and to febrile patients when PLT counts were below 20×10^9/L. In patients with increased risk of bleeding (e.g., before invasive procedures or recent hemorrhage) or ongoing bleeding, PLT transfusions were administered when peripheral blood PLT counts were below 20×10^9 to 50×10^9/L. Patients were examined for human leukocyte antibodies (FlowPRA Class I screening test, One Lambda, Inc., Canoga Park, CA) and human PLT antibodies.[16] Reticulated PLTs were examined regularly and used for prediction of hematopoietic reconstitution.[17]

Investigation procedure

A sample was drawn by sterile procedures from the PCs immediately before transfusion. The following analyses were performed for characterization of PC quality: 1) PLT dose, that is, number of CD61+ PLTs in PC and CD61+ PLT microparticles[18] (Cell-Dyn CD4000, Abbott Laboratories, Round Lake, IL); 2) metabolic variables, that is, pH at 22°C, pCO_2, HCO_3, pO_2, and concentrations of glucose and lactate (ABL 725, Radiometer Copenhagen, Denmark; Modular, Hitachi High-Technologies Corp., Tokyo, Japan); 3) PLT density (mean PLT component) concentration (Advia 120, Bayer HealthCare, Tarrytown, NY); and 4) lactate dehydrogenase (LDH; Modular, Hitachi High-Technologies Corp.).[18,19] Preparation method and storage time were registered for each PC.

Blood samples from the study patients were collected through a central venous catheter before (<8 hr) transfusion, 45 to 120 minutes after transfusion, and 18 to 24 hours after transfusion for examination of PLT counts (Cell-Dyn CD4000, Abbott Laboratories) and TEG (TEG hemostasis system 5000 series, Software Version 4.2, Haemoscope Corp., Niles, IL). For every study transfusion, the following

patient characteristics were evaluated: pretransfusion PLT count, bleeding, patient weight, fever at time of transfusion, infection (i.e., patient diagnosed with neutropenic fever, treatment with antibiotics, and/or serum level of C-reactive protein ≥100 mg/L the day of transfusion), and treatment with steroids or granulocyte-colony stimulating factor (G-CSF). In addition white blood cell counts, medication, ABO and HLA compatibility of transfusion, occurrence of transfusion complications, transfusion sequence number, and ITI were registered throughout study period. Event charts including transfusion patterns, reticulated PLT counts, PLT counts, and duration of neutropenia were made for all patients and treatment cycles to serve as basis for interpretation of results.

Methods for documentation of transfusion effect

Posttransfusion absolute PLT increment (API) is affected by quality and number of PLTs transfused, as well as the dilution of PLTs in the patient's blood volume. According to European recommendations, we defined that an acceptable immediate API (at 1 hr after transfusion) occurred when PLT transfusion raised the PLT count above the transfusion threshold, that is, greater than 10×10^9/L.[9] To adjust for differences in PLT dose and blood volume of the patient, the corrected count increment (CCI) was calculated by use of the formula[9,20]

$$CCI = \frac{API \times \text{body surface area } (m^2) \times 10^{11}}{\text{Number of PLTs transfused}}.$$

According to international guidelines, a successful transfusion was defined as a CCI of more than 7.5 for immediate clinical effect (PLT recovery) and a CCI of more than 4.5 for late clinical effect (PLT survival).[4,20] Body surface area was estimated by the formula of DuBois and DuBois.[21]

ITI was defined as hours from onset of study transfusion to the onset of the subsequent transfusion. When the interval between transfusions was more than 240 hours, which is longer than the expected life span of transfused PLTs,[22,23] we assumed that autologous PLT recovery had occurred, and transfusions were excluded from analysis.

Bleeding assessments consisting of physical examination and patient interview were performed each morning by trained nurses working at the hematologic ward.[12] For additional clinical information, the medical records of the patients were consulted. The bleeding assessments were reviewed independently by two adjudicators and graded in accordance with the WHO hemostatic assessments.[12] If disagreement occurred, the patient data were evaluated by a third adjudicator and consensus was achieved. WHO Grade of 2 or more was defined as primary bleeding endpoint according to recent PLT studies.[12,24-27] Accordingly therapeutic transfusions were defined as transfusions given to patients with WHO Grade 2 or more bleedings before transfusion. The proportion of days with WHO Grade 2 or more bleeding during neutropenia was calculated.[13] To evaluate WHO bleeding assessments used for daily monitoring of PLT transfusion effect, we calculated the difference in WHO bleeding status before and after each transfusion.

The blood coagulation process in patients before and after transfusion was investigated by TEG in citrated kaolin samples with heparinase cups to avoid contamination of sample by heparin from the central venous catheter. The following variables were investigated: 1) R, reaction time, the time to the beginning of clot formation, reflecting the level of coagulation factors; 2) angle (α), the buildup and cross-linking of fibrin, dependent on sufficient amounts of fibrinogen, thrombin, and PLTs; and 3) MA, the maximum amplitude, a measurement of maximum strength or stiffness of the developed clot, reflecting the amount and functional capacity of PLTs including their interaction with fibrin.[14] Reference levels were provided by the manufacturer.

Statistical analysis

Descriptive statistics were performed by use of computer software (SPSS 15.0 for Windows, SPSS, Chicago, IL) and results are presented as mean ± standard deviation (SD) if not otherwise stated. When analyzing PC characteristics not influenced by individual patient effects, two-sample t tests were performed (SPSS, Version 15.0). All patient data were analyzed, adjusted for individual patient effects. Analyses of dichotomous data were performed with generalized estimating equations (package gee, R Version 2.8.0, http://www.R-project.org, The R Foundation for Statistical Computing, Vienna, Austria). Correlation analysis, not adjusted for individual patient effect, was performed by Spearman's correlation (SPSS, Version 15.0) due to partly categorical data. Confidence intervals (CIs) were calculated as bootstrap BC_a CIs (package boot, R Version 2.8.1, The R Foundation for Statistical Computing).[28] Differences were considered significant when p values were less than 0.05.

To separate the effects of PC and patient variables on transfusion outcome measures, mixed-effects model (package nlme, R Version 2.8.0, The R Foundation for Statistical Computing) was performed.[29,30] If random parts of the mixed-effects model were unstable, generalized least squares were used. In this analysis we investigated the relationship between posttransfusion values of PLT counts, posttransfusion TEG values, and ITI and the following variables: fever, transfusion sequence number, patient weight, bleeding of WHO Grade 2 or more, PLT dose, storage time, preparation technique, and ABO identity. Analyses of PLT counts and TEG values were adjusted for time and pretransfusion values. The selection of variables investigated was based on previously published articles,[23,31-36] and the number of variables was adapted to the total number of study transfusions. Mixed-effects analysis could not be performed for bleeding status due to the categorical nature of the variable.

RESULTS

Patients and PCs

Ten patients, four males and six females, diagnosed with acute myelogenous leukemia (eight patients) or acute lymphoblastic leukemia (two patients), were included in the study. Transfusion requirements were followed by the investigators from the administration of chemotherapy (five remission induction and eight consolidation treatment cycles) to hematopoietic reconstitution (i.e., $\geq 0.5 \times 10^9$/L neutrophil granulocytes in blood samples and no need for PLT transfusion), patient withdrawal (two patients), or death of patient (one patient, due to infection). All patients (ages 21-62 years) had a history of previous pregnancies and/or previous PLT transfusions, but no patient with previous splenectomy or disseminated intravascular coagulation was included in the study. Patients with HLA antibodies were transfused with HLA Class I–matched PCs (three patients) according to international guidelines.[9] One patient was diagnosed with weak positive HPA antibody at the time of inclusion and transfused according to routine practice without HPA-matched PCs. No patient developed HLA or HPA antibodies during the study. All transfusions were ABO compatible, by means of recipient having no antibodies incompatible with the red blood cell type of donor. One patient was diagnosed with neutropenic septicemia. These transfusions (four) were grouped and analyzed together with the transfusions given to patients with infection. In 11 transfusions, patients received treatment with hematopoietic growth factors. Three of these transfusions were given to acute lymphoblastic leukemia patients treated according to the Hyper-CVAD regimen and eight transfusions to acute myelogenous leukemia patients due to severe bacterial infections. The mean PLT dose given was 2.79 (range, 1.46-4.42) $\times 10^{11}$ per unit, and mean storage time of the PC was 86 (range, 21-167) hours. The metabolic status of the PC was as follows (mean ± SD): pH (22°C) 7.22 ± 0.14, pCO_2 2.98 ± 0.47 kPa, pO_2 17.3 ± 2.1 kPa, glucose concentration 5.18 ± 1.55 mmol/L, and lactate concentration 7.35 ± 3.64 mmol/L. The LDH concentration was 135 (range, 21-522) U/L, and the mean level of PLT microparticles was 26 (range, 6.7-50.6) $\times 10^9$/L.

Effect of PLT transfusion

PLT viability

PLT viability was evaluated by PLT count increments and calculation of ITI. PLT transfusion increased peripheral blood PLT counts after both 1 hour (mean increase, 12.5×10^9/L; 95% CI, 10.0×10^9-14.9×10^9/L) and 18 to 24 hours (mean increase, 7.2×10^9/L; 95% CI, 4.7×10^9-9.7×10^9/L). Significant correlations were observed between pre- and posttransfusion patient PLT counts (after 1 hr, $r = 0.569$, $p < 0.001$; after 24 hr, $r = 0.457$, $p = 0.005$).

Forty-six percent of PLT transfusions raised the patients' immediate PLT counts above the transfusion threshold, that is, more than 10×10^9/L, and were thus defined as acceptable according to the European recommendations.[9] When evaluating PLT viability by use of CCIs, 46% of the study transfusions were classified as successful after 1 hour, whereas 53% of transfusions fulfilled predefined criteria after 24 hours. Eight out of 10 patients received more than one transfusion per treatment cycle, and all of them experienced both successful transfusions and transfusion failures (Fig. 1). The results of comparative analysis of patient and PC characteristics in successful transfusions and transfusion failures are reported in Table 1. When evaluated by immediate response, the successful PLT transfusions were differentiated from transfusion failures by superior PLT quality (Table 1). In contrast, successful PLT transfusions evaluated by late response showed favorable patient characteristics. Mean ITI was 41 (range, 7-121) hours, and there was no significantly higher ITI in PLT transfusions characterized as successful by CCIs after either 1 or 24 hours.

PLT functionality

Eight patients experienced minor bleedings (petechiae and minor nosebleed), giving a total of 34 days (18.0%) with WHO Grade 1 bleedings during the total study period (188 patient-days). Only four patients experienced WHO Grade 2 or 3 bleeds, giving proportions of 7.4 and 2.1% of total patient-days, respectively. The time to first bleeding (WHO Grade ≥ 2) varied between 1 and 15 days and the individual proportion of days with Grade 2 or 3 bleeds varied from 6.3% to 66.7% for the affected patients (Fig. 1). No WHO Grade 4 bleed was observed during the study period. The bleeding event chart did not indicate any association between time to the first bleed and individual number of bleeds; rather, it did illustrate the individual differences in bleeding pattern among patients with the similar diagnosis and PLT counts (Fig. 1). In spite of high frequency of PLT transfusions, bleedings still occurred, and patients with the similar morning PLT counts did not experience the same number, timing, and severity of bleeding. Significant correlations were observed between 1) WHO bleeding status before and after transfusion ($r = 0.639$, $p < 0.001$) and 2) WHO bleeding status after transfusion and ITI ($r = -0.380$, $p = 0.020$). No significant correlation was observed between pretransfusion PLT counts and bleeding assessment before and 24 hours after transfusion, neither was any correlation observed

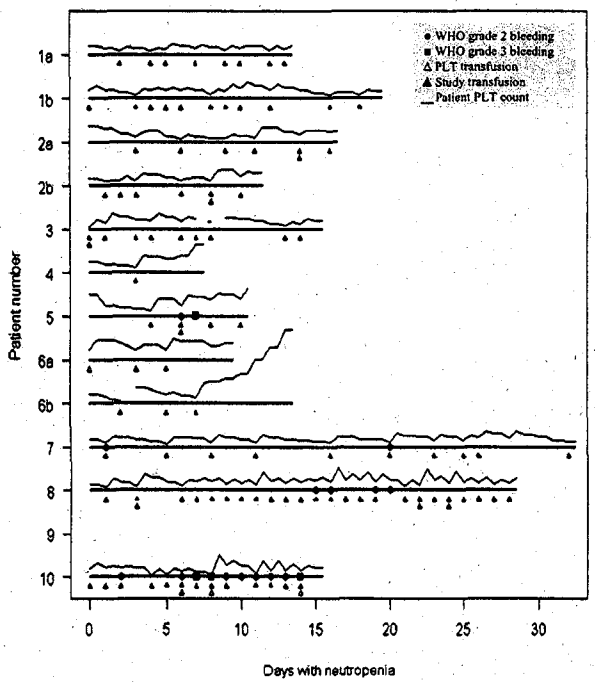

Fig. 1. The bleeding event chart displays WHO Grade 2 or higher bleedings, PLT transfusions, and morning PLT count during neutropenia for each patient and treatment cycle. During a total of 188 patient days, a total of 52 bleedings were reported: 34 minor bleeds (WHO Grade 1) and 18 clinically significant bleeds (14 WHO Grade 2 and four WHO Grade 3). The bleeding event chart illustrates the individual differences in bleeding pattern among patients with the similar diagnosis and PLT counts. During the study period two patient withdrawals (Patients 2b and 9) and one death (Patient 10) occurred.

between PLT count increments and change in clinical bleeding status after transfusion. When calculating the difference in WHO bleeding status before and after transfusion, no effect of PLT transfusion was observed either for the total of transfusions (mean ± SD, –0.03 ± 0.73) nor for the seven therapeutic transfusions when analyzed separately (mean ± SD, 0.14 ± 1.01).

The overall results of investigations by the TEG analyzer are reported in Table 2. PLT transfusion had an immediate but transient effect on initial clot formation that was reflected in the R and angle variables, whereas the effect on PLT clot strength and stability, the MA value, persisted until the next day. No effect was observed on PLT dose or the number of PLT microparticles on the shortening of R, increased angle, or MA increment after PLT transfusion when evaluated by correlation analysis.

How do the methods monitoring clinical effect of PLT transfusion intercorrelate?

Correlation analyses of the investigated methods for documentation of PLT transfusion were performed, and the results are presented in Table 3. Strong correlations were observed between the methods based on PLT counts (API, CCI, ITI, and MA) when used for evaluation of transfusion effects after both 1 hour and 24 hours. A negative correlation was observed between the increase in MA after 24 hours and the calculated difference in bleeding status after transfusion. Correspondingly, a negative correlation was observed between MA increment after 24 hours and clinical bleeding status after transfusion ($r = -0.494$, $p = 0.008$). No correlation was observed between PLT count increments and calculated difference in bleeding status or clinical bleeding status before or after transfusion.

Variables influencing effect of PLT transfusion

The effect of PLT transfusion varies between individual transfusions within patient and treatment cycle, but also between patients. The analysis of variables influencing outcome of PLT transfusion was therefore adjusted for individual patient effect. We found that the selected patient variables (transfusion sequence number, bleeding ≥ WHO Grade 2, fever, and patient weight) and PC variables (storage time, PLT dose, preparation technique, and ABO identity) influenced the different methods for documentations of transfusion effect differently (Table 4).

Elevation of PLT dose by 1×10^{11} per unit led to a mean increase in posttransfusion PLT count by 3.2×10^9/L, whereas prolonged storage time (by 1 hr) or pathogen inactivation by photochemical treatment reduced the posttransfusion PLT count by 0.04×10^9 and 3.9×10^9/L, respectively. Correspondingly prolonged storage time or pathogen inactivation reduced CCI by $0.02 \times m^2$/L and 1.7 PLTs $\times m^2$/L, respectively. Additional investigations showed reduced PLT dose and quality in pathogen inactivated PCs (Table 5). Patients being febrile

TABLE 1. Characteristics of successful transfusions versus transfusion failures*

Variable	CCI after 1 hr		CCI after 24 hr	
	CCI > 7.5, n = 17 (46%)	CCI ≤ 7.5, n = 20	CCI > 4.5, n = 19 (53%)	CCI ≤ 4.5, n = 17
Patient variables				
Fever	7 (41)	3 (15)	3 (16)	8 (47)†
Infection	12 (71)	11 (55)	8 (42)	14 (82)†
G-CSF	4 (24)	9 (45)	5 (26)	10 (59)†
PLT variables				
ABO-identical transfusion	12 (71)	13 (65)	12 (63)	12 (71)
Storage time (hr)	60 ± 30	106 ± 45‡	78 ± 39	90 ± 46
PLT dose ($\times 10^{11}$ per unit)	2.78 ± 0.63	2.81 ± 0.65	2.65 ± 0.57	3.07 ± 0.62‡
PLT concentration ($\times 10^9$/L)	929 ± 220	884 ± 147	888 ± 157	970 ± 203
Volume (mL)	301 ± 33	307 ± 42	298 ± 37	318 ± 33
pH at 22°C (mmHg)	7.30 ± 0.12	7.17 ± 0.12‡	7.23 ± 0.15	7.22 ± 0.14
pCO_2 (kPa)	3.21 ± 0.43	2.81 ± 0.37‡	3.08 ± 0.38	2.97 ± 0.48
HCO_3 (mmol/L)	7.3 ± 0.9	5.0 ± 1.5‡	6.4 ± 1.6	5.7 ± 1.6
pO_2 (kPa)	17.0 ± 2.1	17.5 ± 1.9	17.1 ± 2.0	17.3 ± 2.2
Glucose (mmol/L)	6.1 ± 0.9	4.5 ± 1.5‡	5.2 ± 1.7	5.4 ± 1.4
Lactate (mmol/L)	5.2 ± 3.0	8.9 ± 3.5‡	6.5 ± 3.4	8.4 ± 3.9
PLT density (mean PLT component) (g/dL)	19.8 ± 0.9	19.2 ± 0.8‡	19.6 ± 0.8	19.4 ± 1.0
PLT microparticles ($\times 10^9$/L)	22 ± 12	30 ± 10‡	25 ± 12	25 ± 10
LDH (U/L)	85 ± 66	162 ± 109‡	103 ± 64	159 ± 149

* Results are presented as number (%) or mean ± SD.
† $p < 0.05$ for difference between successful and nonsuccessful transfusions (test for dichotomous data adjusted for individual patient effect [gee, R]).
‡ $p < 0.05$ for difference between successful and nonsuccessful transfusions (t test for independent samples, SPSS 15.0).

TABLE 2. Investigations by TEG analyzer*

Time	R (min)	Angle (degree)	MA (mm)
Before transfusion	8.2 ± 1.7	47 ± 11	43 ± 11
1 hr after transfusion	6.8 ± 1.6†	58 ± 8†	52 ± 9†
24 hr after transfusion	8.7 ± 1.8	50 ± 8	49 ± 10†

* Test for continuous data adjusted for patient effect (package nlme, R). Results are presented as mean ± SD, n = 33.
† $p < 0.05$ for difference between posttransfusion and pretransfusion value.

at time of transfusion experienced a mean reduction of the ITI by 39% compared to nonfebrile patients (Table 4). The mean ITI was 27 ± 8 hours in febrile transfusions and 46 ± 30 hours in nonfebrile transfusions.

Whereas the selected patient or PC variables showed significant influence on the measurements of PLT viability (PLT count increments and ITI), no significant influence was observed on PLT functionality measured by TEG. Mixed-effects analysis could not be performed for bleeding status.

Correlation analysis of variables influencing effect of PLT transfusion

Spearman's correlation analysis was performed to separate between variables influencing immediate and late clinical outcome of PLT transfusion. The analysis included bleeding outcomes and was not adjusted for individual patient effect.

The immediate clinical effect of PLT transfusion evaluated by measurements of PLT viability (PLT count increments) showed strong correlations to PLT dose, storage time, and pathogen inactivation by PCT (Table 6). When evaluated after 24 hours, correlations were observed between PLT count increments and fever, transfusion sequence number, and pathogen inactivation. No significant correlation was observed between ITIs and the patient or PC variables investigated. Similarly, no significant correlation was observed between the PLT functionality measure bleeding outcome and the investigated patient and PC variables. No correlation was observed for the TEG values R and angle, while a negative correlation was observed between MA increment after 24 hours and patient weight (Table 6). In summary, the results of correlation analysis show that PLT-related factors mainly influence the immediate clinical effect of PLT transfusions, whereas patient-related factors influence late clinical effect.

DISCUSSION

In this study we aimed to evaluate and compare methods used for documentation of clinical efficacy of PLT transfusions in patients receiving regular PLT transfusions due to severe chemotherapy-induced thrombocytopenia. Our results illustrate the advantages and disadvantages of the different methods when used for documentation of clinical effect of regular PLT transfusions. The challenges identified are discussed below.

By statistical analysis of 40 PLT transfusions we observed that PLT viability was affected by both patient- and PC-related variables. The variables identified in our

TABLE 3. Correlation of methods for documentation of transfusion effect*

Transfusion outcome measure	CCI	Transfusion interval (hr)	24-hr posttransfusion difference in WHO bleeding status	Posttransfusion difference in TEG values		
				R (min)	Angle (degree)	MA (mm)
API						
After 1 hr	0.918†	0.308	0.251	−0.406‡	0.403‡	0.507†
After 24 hr	0.952†	0.549†	−0.037	0.109	0.155	0.460‡
CCI						
After 1 hr		0.275	0.212	−0.330	0.410‡	0.440‡
After 24 hr		0.518†	−0.064	0.052	0.173	0.427‡
Transfusion interval (hr)						
After 1 hr			0.302	−0.458‡	0.362‡	0.035
After 24 hr			0.302	0.091	0.306	0.263
24 hr posttransfusion difference in WHO bleeding grade						
After 1 hr				−0.003	0.042	0.157
After 24 hr				−0.147	0.015	−0.382‡
Posttransfusion difference in TEG values						
R (min)						
After 1 hr					−0.562†	−0.100
After 24 hr					−0.638†	0.015
Angle (degree)						
After 1 hr						0.465†
After 24 hr						0.352

* Results shown as correlation coefficient (Spearman's correlation, SPSS 15.0), n = 40.
† Correlation is significant at the 0.01 level.
‡ Correlation is significant at the 0.05 level.

TABLE 4. Patient and PC variables that significantly influence clinical effect of PLT transfusion*

Transfusion outcome measure	Mean difference	95% CI	p value
API (×10⁹/L), n = 40			
Increased API:			
PLT dose (by 1 × 10¹¹ per unit)	3.2	0.3 to 6.1	0.033
Decreased API:			
Storage time (per hr)	−0.04	−0.07 to −0.00	0.032
Pathogen inactivation by PCT (yes)	−3.9	−7.4 to −0.5	0.027
CCI (PLTs × m²/L), n = 40			
Decreased CCI			
Storage time (per hr)	−0.02	−0.05 to −0.00	0.041
Pathogen inactivation by PCT (yes)	−1.7	−2.7 to −0.6	0.003
Transfusion interval, n = 37			
% Reduction			
Fever (yes)	39	14 to 57	0.008

* Analyzed by mixed-effects model (package nlme, R).

study are in accordance with previous publications.[23,31-36] Evaluated by measures of PLT viability, PLT recovery was influenced by PC variables only, whereas PLT survival was influenced mainly by patient variables. Being a retrospective variable, the importance of calculated ITI in daily monitoring of thrombocytopenic patients is limited. It is also dependent on the individual transfusion trigger chosen for each patient, which makes comparisons between patients difficult.

PLT dose may influence both API and the calculated CCIs. As shown in our study, higher PLT dose may be observed in transfusions with lower CCIs. As discussed in a previous publication, this observation may be explained by the formula for calculation of CCI, which favors PLT transfusions with lower PLT dose.[33] A higher number of bleeds defined as WHO Grade 2 or higher and higher number of transfusions has previously been described in patients being transfused with low-dose PCs.[12] The majority of our study transfusions (28 of 40) would have been defined as low-dose transfusions according to this publication, and a low range of PLT dose may therefore explain why no correlation was observed between PLT dose and bleeding in our study.

Outcome measures based on bleeding are complex because the clinical impact of bleedings depend both on severity and on location. A calculation of difference in WHO bleeding status before and after each transfusion implies treating bleeding as a continuous variable, which it is not. The use of bleeding assessments in the evaluation of clinical effect of PLT transfusion therefore requires a different approach. Webert and colleagues[27] have shown that minor bleedings (WHO Grade 1) predict clinical significant bleedings (WHO Grade 2, 3, or 4) and that cumulative incidence functions for bleeding (Grade 1, 2, 3, or 4) increases with time. Correspondingly, we observed that the WHO bleeding status before and after transfusion was correlated. Webert and colleagues, however, found that the risk factors for mild bleeding included decreased PLT count, an association that was not confirmed by our observations. In our 40 transfusions, we

TABLE 5. PLT viability and transfusion characteristics presented according to preparation techniques

Transfusion outcome measure and variables	Conventional gamma-irradiated PCs, n = 28	Pathogen inactivated (PCT) PCs, n = 12	p value
PLT viability*			
CI after 1 hr	15 ± 8	7 ± 4	0.003
CCI after 1 hr	9.2 ± 4.1	5.3 ± 2.7	0.005
CI after 24 hr	9 ± 8	2 ± 6	0.196
CCI after 24 hr	5.8 ± 4.6	1.8 ± 4.4	0.890
Transfusion interval (hr)	43 ± 29	36 ± 24	0.360
PLT variables†			
Storage time (hr)	86 ± 46	86 ± 40	0.978
PLT dose (×10⁹ per unit)	2.96 ± 0.63	2.41 ± 0.46	0.009
pH at 22°C (mmHg)	7.26 ± 0.13	7.13 ± 0.10	0.004
pCO_2 (kPa)	3.11 ± 0.39	2.66 ± 0.50	0.004
HCO_3 (mmol/L)	6.6 ± 1.3	4.3 ± 1.2	<0.001
pO_2 (kPa)	16.6 ± 1.8	19.0 ± 1.7	<0.001
LDH (U/L)	96 ± 67	224 ± 148	0.014

* Test for continuous data adjusted for patient effect (package nlme, R).
† t test for two independent samples (SPSS).

TABLE 6. Patient and PC variables that significantly correlated to clinical effect of transfusion*

Transfusion outcome measure	Correlation coefficient	95% CI	p value
API after 1 hr (×10⁹/L)			
PLT dose	0.477	0.194 to 0.678	0.003
Storage time	−0.329	−0.609 to −0.001	0.047
Pathogen inactivation	−0.519	−0.712 to 0.251	0.001
CCI after 1 hr (PLTs × m²/L)			
Storage time	−0.420	−0.651 to −0.110	0.010
Pathogen inactivation	−0.438	−0.661 to −0.154	0.007
API after 24 hr (×10⁹/L)			
Fever	−0.386	−0.631 to 0.074	0.020
Transfusion sequence number	−0.392	−0.654 to −0.048	0.018
Pathogen inactivation	−0.406	−0.652 to −0.050	0.014
CCI after 24 hr (PLTs × m²/L)			
Fever	−0.444	−0.664 to −0.154	0.007
Transfusion sequence number	−0.422	−0.682 to −0.084	0.010
Pathogen inactivation	−0.364	−0.638 to 0.009	0.029
MA increment after 24 hr (mm)			
Patient weight	−0.439	−0.709 to 0.019	0.019

* Analyzed by Spearman's correlation (SPSS 15.0) and bootstrap BC$_a$ CI calculation (R).

observed no significant correlation between pretransfusion PLT counts and bleeding assessment before and 24 hours after transfusion, neither was any correlation observed between PLT count increments and change in clinical bleeding status after transfusion. This observation corresponds to the results of Friedmann and coworkers[36] who found no relationship between the lowest PLT count of the day and the risk of hemorrhage when investigating 2942 patients over a period of 10 years. These differences in conclusions may be explained by inconsistent reporting of bleeds (i.e., problems with separation of new and ongoing bleeds) or individual differences in grading and interpretation of bleeds by adjudicators, yet the discrepancy strongly indicates that the present bleeding assessment scheme does not provide the information needed to serve as documentation of clinical effect of PLT transfusion. In accordance with Heddle and colleagues[12] we therefore recommend a reevaluation of the present bleeding assessment scheme.

As individual patient and PC variables influence the methods for documentation and clinical evaluation of transfusion differently, a direct comparison between transfusion outcome measures was difficult to perform. By correlation analyses, however, we found no consistent correlation between measures of PLT viability and functionality. The strongest correlations were observed within measurements of PLT viability and between PLT count increments and MA, which reflects PLT number as well as functionality of PLTs. A negative correlation was, however, observed between clinical bleeding status and late MA increment, indicating that a high MA increment may be associated with less clinical bleeding. A previous publication reports that nonactivated thromboelastography was sufficiently sensitive to monitor changes after PLT transfusion in patients with severe to mild thrombocytopenia.[37] Our observations confirm that the effect of PLT transfusion can be visualized by TEG analysis, but by showing an association to clinical bleeding status they also indicate

that TEG may be a potentially useful surrogate measure of PLT functionality.

Based on our observations we conclude that further investigations and standardization of methods are needed for better documentation of PLT transfusion outcome and identification of patients at risk of bleeding. Our observations also indicate that both PLT dose and high quality of PC are important for achieving an optimal immediate response to PLT transfusions whereas duration of transfusion effect is influenced mainly by patient variables.

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CONFLICT OF INTEREST

The authors declare that they have no conflicts of interest relevant to the manuscript submitted to **TRANSFUSION**.

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資料６－４

Current FDA Considerations on Pathogen Reduction

Jaro Vostal, MD, PhD
Jay Epstein, MD
Center for Biologics Evaluation and Research
U.S. Food and Drug Administration (FDA)

September 2010

Merits of the Current Approach of Donor Screening and Testing

Advantages
- No toxicity issues for recipients of products
- Detection is specific for particular agents
- New methods can be developed for novel and emerging pathogens

Disadvantages
- For certain pathogens detection is not 100% successful
  - Bacteria
  - Protozoa
  - Viral (window period)
- Development of detection methods for novel and emerging pathogens would be delayed due to lack of knowledge about the pathogen
- Additional tests for emerging pathogens increase cost

Merits of Pathogen Reduction Technology as an Alternative to Donor Screening and Testing

Advantages
- Shown effective against many organisms including some emerging pathogens
- May prevent GVHD and other wbc related adverse events

Disadvantages
- May not be effective against all organisms
- May not be 100% effective even against sensitive pathogens
- Current technologies are not applicable to all types of transfusion products
- May have toxicity due to residual compounds
- May damage the transfusion product
- May lead to alloimmunization by neoantigens
- May cause unexpected adverse events

Recommendation of the HHS Advisory Committee on Blood Safety and Availability (ACBSA) Regarding Pathogen Reduction

- At a meeting in January 2008 the ACBSA recommended that the Department should:

  "Adopt as a high priority the urgent development of safe and effective pathogen reduction technologies for all blood transfusion products and implementation as they become available"
- FDA fully supports the ACBSA recommendation through its evaluation of Pathogen Reduction Technologies

Benefits of Pathogen Reduced Products Should Outweigh the Risks

Benefit =
Reduction of Current risks:

- HTLV 1/ 2,993,000
- HIV 1/ 2,135,000
- HCV 1/ 1,930,000
- WNV 1/ 350,000
- HBV 1/ 277,000
- Sepsis 1/ 86,000[1]

Reduction of future risks:

- Emerging pathogens 1/?????

Tolerable Risk
Toxicity, adverse events should be much less than the expected benefits
<< 1/86,000

1) Eder, A. F. et al. Transfusion 2009, 49:1554-1563

Phase III Clinical Trials of Pathogen Reduced Red Cell Products

Cerus S303 and Vitex pen 110

- Patients developed antibodies to treated red cells
- Both sponsors voluntarily halted their trials

Benjamin, R.J., ISBT Science Series (2006) 1, 222-226

Determination of the Risks Associated with Pathogen Reduced Components

- Pre-clinical evaluation
- Clinical trials in healthy volunteers
- Pivotal evaluation of efficacy and safety through clinical trials in transfused patients
  - Prospective, randomized, blinded clinical trials of PR treated vs. conventional transfusion products
    - Platelets
    - Red cells
    - Plasma

Clinical Endpoints that Reflect Efficacy and Safety of a Platelet Transfusion Product

- Efficacy
  - Transfusion response (corrected count increment, (CCI)
  - Transfusion frequency
  - Bleeding Frequency (Grades 2-4)
- Safety
  - Adverse events
  - Alloimmunization

配布につき、FDAの了解済み。

Clinical Trials of PR Platelets in Thrombocytopenic Patients

- Prospective studies
  - Sprint and Eurosprite trials (Cerus)
  - Hovon 86 (Dutch Blood Service)
  - Mirasol trial (Caridian)
- Surveillance studies on routine use of PR platelets
  - France and Belgium

配布につき、FDAの了解済み。

Pathogen Reduced Platelets Have Lower Corrected Count Increments (CCI)

Clinical Trial	Patients in study	% of plasma stored platelets CCI at 1 hr	P value
SPRINT [1, a]	645	-31%	< 0.001
HOVON [1, b]	184	-31%	<0.0001
MIRASOL [2, c]	118	-31%	<0.0001

1 = UVA/psoralen 2 = UVB/riboflavin

a = McCullough, J et al Blood. 2004 Sep 1;104(5):1534-41.
b = Kerkhoffs JL et al. Br J Haematol. 2010 Jul;150(2):209-17
c = Goodrich et al. Transfusion, May 2010

配布につき、FDAの了解済み。

Hemostatic Efficacy for UV A/psoralen (Intercept) Treated Platelets

SPRINT study	Control platelets	Pathogen reduced platelets	p
Proportion of pts with Grade 2 bleeding	58.5%	57.5%	NS for inferiority
Days of Grade 2 bleeding	2.5	3.2	0.023
% patients with Grade 2-4 bleeding	34	43	0.02

HOVON study	Control platelets	Pathogen reduced platelets	p
% of patients with Grade 1-3 bleeding	19	32	0.034

配布につき、FDAの了解済み。

Hemostatic Efficacy for UVB/riboflavin (Mirasol) Treated Platelets

MIRASOL study	Control platelets	Pathogen reduced platelets	p
% of patients with Grade 2-4 bleeding	15	30	NS

Adverse Events Reported in the SPRINT Study

- 898 adverse event types were reported by blinded observers
- 11 adverse event types were different with statistical significance....all went against the treatment arm
- 4 of the 11 were clinically significant Grade 3 and 4 events:
  - Hypocalcemia, Syncope, Pneumonitis, Acute Respiratory Distress Syndrome (ARDS)

Snyder E et al. Transfusion. 2005 Dec;45(12):1864-75

Can adverse event signals captured in a prospective, randomized, controlled and blinded study be evaluated through a passive adverse reporting study?

- France and Belgium have been using pathogen reduced platelets for several years
- Adverse events on transfused patients are reported through a passive hemovigilance reporting system
- Frequency of reporting of adverse events is much lower than what was reported in SPRINT trial
- There is no active control group to identify events specifically related to PR platelets

ARDS Rates in the Treatment vs. Control Arms of the SPRINT Study

Snyder E et al. Transfusion. 2005 Dec;45(12):1864-75

Prospective and blinded evaluations during the clinical trial

	Intersol (PR) platelets	Control platelets	p value
Patients (N)	318	327	
ARDS	**5**	**0**	**0.03**

Retrospective review of medical charts by a blinded expert panel

	Intersol (PR) platelets	Control Platelets	p value
Patients (N)	78	70	
Total Acute Lung Injury (ALI)	19 (6.0%)	16 (4.9 %)	0.60
ARDS	**12 (3.8%)**	**5 (1.5%)**	**0.09**
ALI, non-ARDS	7 (2.2%)	11 (3.4%)	0.48

Comparison of Adverse Event Reporting in the SPRINT Trial vs. European Hemovigilance Studies

	SPRINT Phase 3 US study		Osselar et al. Transfusion 2008 Cerus plts 2005-2007 Hemovigilance		Osselar et al. Vox Sang 2008 Cerus plts 2003-2005 Hemovigilance	
	Per transfusion	Per patient	Per transfusion	Per patient	Per transfusion	Per patient
N	**2678**	**318**	**5106**	**651**	**7437**	**1400**
% stem cell transplant patients		**78**		**7.2**		**8.6**
% of pts with any reaction		**99.7**	**1.1**	**6.4**	**0.9**	**3.2**
% of plt related reactions	**3.0**	**26.0**	**0.8**	**4.9**	**0.7**	**2.8**
% of plt with serious reactions		**27.0**	**0.1**	**0.15**	**0**	**0**

Summary and Conclusion

- Pathogen Reduction of labile blood products could improve blood product safety, especially for platelets, but should not add greater risks
  - Clinical trials with Pathogen Reduced red cells have demonstrated antibody generation
  - Clinical trials with Pathogen Reduced platelets have demonstrated decreased efficacy and associated adverse events including acute lung injury in the SPRINT trial.
  - These reports raise concern that the benefits of current pathogen reduction technologies may not outweigh the risks
- Further clinical trials of current technologies are needed to resolve FDA's concerns over decreased efficacy and increased adverse events seen with Pathogen Reduced platelets

平成22年11月24日
薬事・食品衛生審議会
血液事業部会運営委員会
提出用資料

感染性因子低減化技術導入に係る費用対効果分析の報告(概要)

資料6－3

論文タイトル	Economics of pathogen inactivation technology for platelet concentrates in Japan	Cost-effectiveness of pathogen inactivation for platelet transfusion in the Netherlands	Assessment of the economic value of the INTERCEPT blood system in Belgium	The cost-effectiveness of pathogen reduction technology as assessed using a multiple risk reduction model
	Int.J.Haemat. 2004;80:317-324	Transfusion Medicine 2005;15:379-387	Transfusion Medicine 2006;16:17-30	Transfusion 2010;50:2461-2473
目的	・日本赤十字社がアモトサレン法を導入する場合を想定し、net cost、CEを試算する。	・アモトサレン法によるプール血小板製剤の感染性因子低減化を想定し、決定木分析によりCEを評価する。	・アモトサレン法導入を想定した場合のICERを、新興感染症のリスクも含め評価する。	新規の医療経済分析ソフトにより、カナダでリボフラビン法により感染性因子低減化処理を施した場合の全血製剤(PRT-WB)及び血小板製剤(PRT-PC)の費用対効果(CE)を現在のスクリーニング法のCEと比較検討する。
方法	・アモトサレン法導入と併せて、削減可能な試験費用等を相殺する条件で、低減化血小板製剤(PRT-PC 15単位)の製造に係る費用増額を算出した。機会費用は含まない。 ・放射線照射・細菌検査(注:現状、未実施)等の中止によるPRT-PC(15単位)製造経費削減額16,908円に対し、低減化処理キット等の増額分が20,806円、差引き3,898円/bagが正味の経費増額になると仮定。	・CEは獲得生存年(LYG)当りのnet cost(net cost/LYG)で示し、直接及び間接費用と便益を含むベースライン分析及びモンテカルロシミュレーションを用いた感度分析により評価した。割引率は年4%とした。 ・低減化処理経費を116ユーロ、製造工程中のPC損失分を15%と仮定する。この損失分を製造コストに上乗せし、低減化処理費用を合算する。 ・グローニンゲン大学病院における受血者のPC輸血量の7割を占める3患者群(心臓病・血液疾患・小児がん)を薬剤経済モデルとして選択した。 ・評価モデルは、低減化処理により感染性因子が100%低減化されること、重篤な副作用がないことを前提とした。	・血小板輸血を受ける機会が高い血液疾患、BMTを受けた乳がん患者、冠動脈バイパス術を受けた患者群を評価対象とした。 ・3通りのシナリオを設定し、導入効果をICERにより評価した。 シナリオ1:検査内容等は現状通り。アモトサレン法によりHIV・HBV・HCV及び細菌感染のリスクが排除される。新興感染症は考慮しない。 シナリオ2:BacT/Alertによる細菌試験を中止、PC有効期間を7日まで延長、期限切れ率を1/2、成分採血ドナーのALT検査、成分採血PCの放射線照射を中止。 シナリオ3:シナリオ2に加え、成分採血PCについて、NAT(HCV・HIV)、梅毒検査を中止。 ・輸血による新興感染症の感染リスクも考慮する。	・全血製剤、血小板製剤を低減化処理したと想定した場合のCEを評価する。 ・分析対象として2007年を選択、同年のデータに基づき作業を行う。 ・検査方法は現状通りとし、低減化導入を想定。 ・レシピエントは、全年齢群、低年齢群(0—39歳)、高年齢群(40歳以上)の3群に分け、評価を行う。 ・全年齢群を対象とする感度分析(トルネードチャート、モンテカルロ分析)を行う。
結果	・仮定した条件により、およそ70万本のPRT-PC製造に係る費用増額は、およそ27.3億円となる。 ・アモトサレン法導入によるQALYについて各年齢、疾患別に算出した。ALLの10歳児にPRT-PCを輸血した場合の9,900万円/QALYをベースラインとし、更に新興ウイルスに感染するケース(感染確率1/10,000)を想定すると、3,500万円/QALYとなる。 ・アモトサレン法導入により費用対効果の改善が見られる。	・PRT-PCの製造コストは成人用で574ユーロ、小児用で401ユーロとなった。なお、一部のケースではγ線照射費用30ユーロの節減が可能である。 ・ベースライン分析による各群のnet cost/LYGは、心臓病-47.4万ユーロ、血液疾患-67.8万ユーロ、小児ガン-26.1万ユーロであり、3群の加重平均値は55.4万ユーロ(≒6,094万円)であった。 ・輸血用血液の安全性対策は、相対的に高額のnet cost/LYGであり、国際的にも許容されている。今回の分析結果も輸血医療においては許容範囲内と考えられる。 ・感度分析から当該モデルは、回避されたウイルス感染及び想定した間接費用の正確な金額を除外することの影響は小さく、感染症リスクとそれに伴う致死率、低減化及びLYGの割引により想定される過剰輸血の影響は大きいことが示された。	・シナリオ1(輸血による新興感染症感染リスクは無い)のCEは19.5万-346万ユーロ(≒3.8億円)。 ・感染リスクが1/10万回輸血になると、CEは16.5万—336万ユーロ、1/1000回輸血では22.3万ユーロ(≒2,450万円)に改善される。感染リスクは1/100回輸血では、全患者群においてアモトサレン導入グループのCEが優位(少額)となった。 ・ICERは新興感染症の感染リスク、適応、患者年齢にsensitiveである。 ・現在法に対し、アモトサレン法導入グループが優位となる輸血感染回数は、シナリオ1・2・3で、各々1/1074・1/1697・1/1791回輸血であった。	・現行の感染症スクリーニング検査費用は44ドル/ドナーである。 ・低減化推定処理費用は100ドル/回。 ・PRT導入により、感染リスクは、細菌では現状の1/50(1/235～250万回輸血)、HBVは1/10(1/153万回輸血)に減少すると推定された。 ・PRT-WBにおけるICERは、127.6万ドル/QALY(≒1.02億円)となった。この金額は低年齢群では平均より少なく、高年齢群では多くなった。 ・PRT-PCにおけるICERは、142.3万ドル/QALY(≒1.14億円)となった。貨調整平均獲得余命は11分/患者であった。 ・感度分析の結果、PRT-WBでは細菌感染が、PRT-PCでは輸血による年間死亡者数が最も影響が大きい要素であることが示された。
結論	・新規技術等の導入に際し、一般的に許容されうるCEは米国では10万ドル(800万円)/QALYである。これに従えば近年の輸血用血液の安全対策は何も実施できない。低減化技術の導入に際しては、同領域の施策と比較することが妥当である。これには、30万ドル(≒2,400万円)/QALYのS/D血漿、850万ドル(≒6.8億円)/QALYのHCV NAT(フランス)が相当する。 ・アモトサレン法導入は、血小板製剤の安全性の改善に寄与するとともに、既存の製造工程の簡略化や新たな検査法の導入コスト等が節減可能になる。	・今回の薬剤経済モデルから導かれたCEは、輸血医療の分野において国際的にも許容される範囲にあると考えられる。 ・別グループの報告では、アモトサレン法はノンエンベロープウイルスに対しては効果的ではないこと、また、アモトサレンの安全性が実験的には確認されたものの、アモトサレン法処理PCの安全性は不確実なレベルにあることから、予期しない副作用により期待した便益が損なわれる可能性が否定できない。	・CEの評価結果からアモトサレン法の実施は妥当である。将来の新興感染症発生時の潜在的リスクも考慮するとき、同法はより有力な戦略といえる。	・PRT-PCは、採血/製造方法によってCEが異なってくる(QALY:成分採血+buffycoatPC>成分採血+plasma richPC)。 ・本研究結果から、患者の年齢及び身体の状況がPRTのCEに対して重要な決定要因であることが示された。 ・PRTは有害事象のリスク減少という点で不確実な点は残る。 ・輸血用血液の安全性向上への取組みという点で、CE分析を通じてPRTに係る政策決定の情報を得ることができる。

【略号】CEA (Cost-Effectiveness Analysis)
費用対効果分析。異なる臨床効果の治療法を比較する場合に、発生する費用にアウトカム(QOL、余命)を加えて評価する分析法

ICER (Increment Cost Effectiveness Ratio:増分費用(対)効果比)
新規医療技術等(B)の導入に際し、現在の技術(A)からの増額分を右式により算出する。一般的に、この値が一定の値より小さければ導入は効率的と評価できる。

$$ICER = \frac{費用B-費用A(増分費用)}{効果B-効果A(増分効果)}$$

QALY (Quality Ajusted Life Years :質調整生存年)
新規医療技術の導入、医療行為、予防活動等について経済的評価を行う際、健康上の利益を数値化するために使用される方法。単に生存期間の延長を論じるのではなく、生活の質(QOL)を表す効用値としてスコア化し、これに生存年数を掛け合わせ、総合的に評価する。スコアは完全な健康を1、死亡を0とし、種々の健康状態をその間の値として計測する。
Ex) 1QALY=完全な健康状態で生存する1年

LYG (Life Years Gained:獲得生存年)
ICERの単位。Net cost /LYG とは、一年の余命を延長させるのに必要な費用をいう。

円換算レート:1ドル-80円、1ユーロ-110円とした。
また、カナダドル≒USドルとした。

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Economics of Pathogen Inactivation Technology for Platelet Concentrates in Japan

Ulf Staginnus,[a] Laurence Corash[b]

[a]Premor Associates, New York, New York; [b]Cerus Corporation, Concord, California, USA

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Abstract

Residual risk of transmitting recognized and emerging blood-borne pathogens via blood transfusion in Japan persists despite advances in blood safety screening. The INTERCEPT Blood System (IBS) for platelets was developed to inactivate a broad spectrum of pathogens to reduce the risk of transfusion-transmitted infections. In this study we assessed the economic impact of the IBS on platelet transfusion costs. An economic analysis model was used to assess both net cost and cost-effectiveness of the IBS for the patient populations accounting for most of the platelet use in Japan. Pathogen exposure included viruses currently recognized to cause transfusion-transmitted infections and emerging pathogens of potential significance for transfusion-transmitted infections. Economic assessment of the full potential of the IBS revealed that only a small increase in net cost can be expected with implementation. The cost-effectiveness of the IBS for platelets is comparable with and potentially better than that of other blood safety interventions (eg, nucleic acid testing) and, in general, other recently implemented safety interventions (eg, chemical regulations and traffic safety measures) accepted as valuable in Japan. Thus a preventive approach using pathogen inactivation with the IBS may be considered a desirable strategy for improving the current safety of platelet transfusions in Japan.

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Key words: Pathogen inactivation; Japan; Economics; Cost; Cost-effectiveness

1. Introduction

The safety of the blood supply in Japan has achieved a high level since the widespread introduction of sensitive screening tests [1]. However, residual risks of transfusion-transmitted infections remain [2]. Despite the use of highly sensitive minipool nucleic acid tests (NAT) implemented in the late 1990s, the Japan Red Cross recently reported the detection of 210 contaminated blood units and 6 patients with hepatitis C virus (HCV) or human immunodeficiency virus (HIV) infection from blood transfusions [3]. Furthermore, other reports have emphasized the challenge of detecting low levels of viruses, owing to the presence of occult hepatitis B virus (HBV) infection, among healthy blood donors [4]. These events have brought blood safety back into the forefront of the health policy agenda for Japan.

In addition to the currently recognized blood-borne pathogens (HIV, HCV, HBV, and human T-lymphotropic virus [HTLV]), newly emerging viruses [5], such as West Nile and severe acute respiratory syndrome, as well as migrating agents such as plasmodia [6], may pose a threat to the blood supply. These new threats necessitate consideration of added safety measures, previously mainly in the form of additional screening tests. However, increasing the available battery of tests makes blood banking procedures highly complex and more expensive. For example, introduction of NAT for HBV resulted in only a modest additional yield of contaminated donations, indicating that this intervention was less cost-effective [7]. In addition, the scientific data on which test to implement are not always clear [8]. On a regional geographic basis, health policy decision makers and payers must balance benefits, risks, and costs when introducing new blood safety technologies [9].

Pathogen inactivation technologies, such as the INTERCEPT Blood System (IBS) for platelets, now registered with the European Conformité Européne (CE) mark, are expected to further increase the cost of blood and blood components. Therefore the cost-effectiveness for this type of intervention is of concern to health policy makers [10]. At the same time, pathogen inactivation technology is expected to comprehensively improve blood

Correspondence and reprint requests: Ulf Staginnus, Premor Associates, 1755 York Ave #22H, New York, NY 10128, USA; 1-917-513-7047 (e-mail: ulf_staginnus@premor-assoc.com).

Table 1.
Estimated Residual Risk of Viral and Bacterial Contamination of Blood Components on a Per Donation Basis in Japan

Pathogen	Risk Per Donation*
Human immunodeficiency virus	1/2,668,696 [1,12]
Hepatitis B virus	1/51,988 [1,12]
Hepatitis C virus	1/348,091 [1,12]
Bacteria	1/50,000-500,000 (1/225,000)† [13]

*After the introduction of nucleic acid testing.
†Midpoint of range estimate for fatality due to bacterial sepsis based on data from Wagner [13].

safety and may ultimately allow a paradigm shift from testing to proactively preventing transfusion-transmitted disease [11].

Clinical benefits as well as potential blood banking economics must be evaluated in an overall and comprehensive manner in which all costs and benefits of this technology are considered before conclusions about broader economic impact can be drawn. To address these considerations, we analyzed from both a cost-consequence and a cost-effectiveness point of view the economics of pathogen inactivation with the IBS for platelets in Japan. The objectives of this study were aimed at providing information on the net cost and cost-effectiveness of the introduction of the IBS in Japan and thereby facilitating the decision-making process for implementing a novel blood safety technology.

2. Materials and Methods

A comprehensive literature analysis search of Medline and PubMed was conducted to retrieve information on current data about viral transmission due to blood transfusion as well as the associated costs of the clinical consequences. In addition, a questionnaire was designed to capture the current Japan Red Cross blood banking procedures and their associated unit costs to evaluate the impact of IBS platelets on the blood banking "value chain" to calculate the cost consequences (net cost) and cost-effectiveness of the IBS.

2.1. Estimation of Current Residual Risks for Viral and Bacterial Contamination of Blood Components in Japan

In Japan blood is generally safe. Residual viral contamination rates for HIV, HBV, and HCV are of the same order of magnitude as in European countries and the United States (Table 1) [1,12]. No data on bacterial contamination of platelet components and associated mortality from platelet transfusion were found in the literature. Therefore for the purpose of this analysis we used available data from international and US studies [13].

2.2. Potential Costs and Efficiencies of Blood Banking Operations with the IBS

The Japan Red Cross collects all platelet components in Japan, the great majority being prepared as single-donor apheresis platelets (AP) [14]. Introduction of pathogen inactivation with the IBS offers the opportunity for various blood banking process efficiencies based on experience in Europe [15].

The cost of the IBS for a therapeutic platelet dose in Japan was assumed to be approximately ¥9495. This estimate included the cost of the system (hardware and disposables) as well as the costs for material and personnel to perform the procedure. Experience had shown that use of the IBS may result in a small loss of platelets during the process, so additional platelets may have to be collected to compensate for this loss. This rate was conservatively estimated at 10% [16]. However, recent experience in European blood centers with the commercial system demonstrated minimal impact on platelet doses prepared with the IBS, and additional platelets have not been required [15]. Use of the IBS offers several potential cost efficiencies, including replacement of donor plasma with platelet additive solution, replacement of gamma irradiation for prevention of transfusion-associated graft-versus-host disease, replacement of bacterial detection assays, and replacement of future screening tests (Table 2). Estimates for these costs were obtained from information supplied by the Japan Red Cross.

Table 2.
Potential Blood Banking Efficiencies with Adoption of the Intercept Blood System (IBS) in Japan

Test or Procedure	Reasoning and Assumption	Potential Cost Savings, ¥
Gamma irradiation	Almost all platelets are treated with gamma irradiation for the prevention of graft-versus-host [18]. The IBS is as effective as gamma irradiation for inactivation of T-cells [39]. Implementation of the IBS would replace gamma irradiation.	900*
Use of platelet additive solution	Platelets treated with the IBS would be collected and stored in additive solution that would allow saving up to 200 mL of plasma per platelet dose. The saved plasma can be processed as fresh frozen plasma.	11,014*†
Bacterial testing	The IBS effectively inactivates bacteria in platelet concentrates [40-42]. Bacterial testing would not be required.	3363‡
Future screening tests	The IBS has been shown to inactivate a broad spectrum of emerging viruses, such as West Nile. For example, the IBS could replace introduction of a test for West Nile virus.	1631

*M. Satake, MD, written personal communication, July 2004.
†Based on the price of 160 mL of fresh frozen plasma.
‡Estimate based on European data.

Table 3.
Cost Consequences and Estimation of the Net Cost for the Intercept Blood System (IBS) in Japan

Cost Parameter	Cost, ¥	
Potential savings		
Avoidance of gamma irradiation	(900)	
Plasma savings due to use of additive solution	(11,014)	
Avoidance of bacterial testing	(3363)	
Avoidance of future screening tests	(1631)	
Additional cost		
Pathogen inactivation costs (IBS unit price)		9495
Potential additional platelet collections (10%)*		11,311
Subtotal	(16,908)	20,806
Net-cost when treating apheresis platelets with IBS	3898	

*Ten percent as additional cost of the base price of ¥113,190 per 3×10^{11} platelets.

2.3. Cost-Consequence and Net-Cost Analysis Methods

The economic impact of introducing a new technology can be expressed in a so-called cost-consequence analysis. This analysis includes the initial cost of implementing the technology as well as potential downstream savings associated with use if adopted. By presenting the relevant parameters and their cost, decision makers and payers can estimate the net impact of an intervention, thereby facilitating assessment of a health technology intervention without necessarily combining all cost and outcome categories into a single ratio of cost-effectiveness, such as cost per life-year (LY) gained or cost per quality-adjusted life-year (QALY) gained as used in traditional cost-effectiveness analysis. In a cost-consequence analysis, the relevant parameters must be identified and cost values assigned. The cost consequences of implementing the IBS in a systematic fashion in Japan were estimated on the basis of available information from published and personal communication sources (Table 3).

2.4. Cost-effectiveness Analysis Methods

Health care product economic value is important and of increasing concern as health care systems struggle to deliver the highest quality health care within increasing budget constraints. To understand the economic value of new products, governmental authorities and private decision-making committees for new interventions, such as improvements in transfusion safety, frequently require formal cost-effectiveness analyses. This relationship of cost to benefit is typically measured with a cost-effectiveness ratio, such as QALY saved per cost incurred. The lower the cost-effectiveness ratio (eg, the lower the cost per unit of health gained), the better is the value of the intervention. Cost-effectiveness analysis is used to allow comprehensive comparisons between alternative medical technologies (eg, NAT versus pathogen inactivation), combining clinical effectiveness and cost, and will therefore add additional information that cannot be captured in cost-consequence analysis.

2.4.1. Model Overview

A literature-based decision-analytic model was developed to assess the economic costs and clinical outcomes associated with the use of single-donor AP treated with the IBS for platelets (AP+IBS). The analysis was based on the decision-analytic model developed by Bell et al [17] in which the incremental cost (dollars/QALY) associated with the use of AP was evaluated. Similarly, this study simulated the possible transfusion-related events and outcomes in the patient populations that account for most platelet use in Japan [18]. Patients undergoing hematopoietic progenitor cell transplantation (HPCT) for acute lymphocytic leukemia (ALL) and non-Hodgkin's lymphoma (NHL), patients undergoing coronary artery bypass grafting (CABG), and patients undergoing hip arthroplasty were chosen to be representative of patients who commonly receive platelet transfusions. Correspondingly, 4 reference patients were selected to represent the populations of all patients undergoing each procedure: (1) a 10-year-old boy undergoing HPCT for ALL, (2) a 50-year-old woman undergoing HPCT for NHL; (3) a 60-year-old man undergoing CABG; and (4) a 70-year-old woman undergoing hip arthroplasty.

A decision tree (Figure 1) was constructed for patients receiving AP+IBS versus conventional AP. The baseline model included the current risks of infection with HIV, HCV, HBV, and an emerging virus as well as bacterial agents for each platelet donor exposure. The model simulated the subsequent transfusion-related events and outcomes, as well as events that would occur naturally (ie, patients may experience morbidity and mortality due to several causes, such as underlying disease, transfusion-related complications, or general mortality for populations of the same age and sex). Clinical outcomes as a result of the underlying disease and transfusion-related complications were assigned a treatment cost and utility. Life expectancy estimates were calculated according to the declining exponential approximation of life expectancy method with consideration of competing mortality from disease-specific and naturally occurring causes [17]. The direct medical costs attributable to the use of AP+IBS and the present value of future costs attributable to treating transfusion-related complications were incorporated in the baseline model. No indirect costs such as work productivity losses were considered. Economic costs and health benefits incurred in future years were discounted at 3% per annum, consistent with current practice.

The model was used to estimate the incremental cost and health benefit (QALY) of using AP+IBS as opposed to untreated AP. The incremental cost-effectiveness ratio was then calculated as $(\text{cost}^{\text{AP+IBS}} - \text{cost}^{\text{AP}})/(\text{QALY}^{\text{AP+IBS}} - \text{QALY}^{\text{AP}})$, representing, in this case, the incremental cost per QALY gained by using AP+IBS as opposed to untreated AP.

2.4.2. Data Sources

Costs related to platelet transfusions and treatment costs were obtained from official sources (Japan Red Cross) and published literature. The net costs associated with the IBS for platelets were obtained from the preceding cost-consequence analysis. Japanese life tables from official pop-

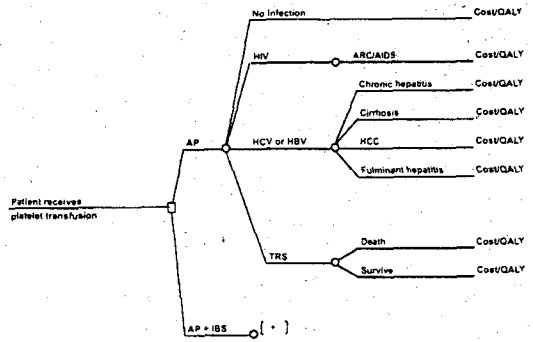

Figure 1. Decision-analytic model. AP indicates apheresis platelets; HIV, human immunodeficiency virus; ARC/AIDS, AIDS-related complex/acquired immunodeficiency syndrome; QALY, quality-adjusted life-year; HCV, hepatitis C virus; HBV, hepatitis B virus; HCC, hepatocellular carcinoma; TRS, transfusion-related sepsis; [•], repetition of subtree as shown for AP.

ulation statistics were applied to calculate life-years gained [19]. Data on mortality due to underlying disease as well as excess mortality caused by viral or bacterial infection and number of platelet units transfused were derived from the previously described US model [17]. Because blood transfusion safety practices are commonly shared among developed countries, only small differences in these data can be expected between countries, and therefore we applied these data to this model analysis. Furthermore, the general outcomes of the model are not overly sensitive to small variations in these parameters. Data on risk of transfusion-transmitted disease were derived from Japanese medical literature sources and international studies (Table 1). Cost data for treatment of viral disease were mainly derived from the Japanese literature and augmented with US data when no Japan-specific data could be obtained. The cost of platelet concentrates was obtained from the Japan Red Cross. Cost input data were summarized on the basis of previous sources (Table 4).

2.4.3. Sensitivity Analysis

Sensitivity analysis was used to determine the robustness of the cost-effectiveness analysis by testing plausible ranges of estimates for key independent variables (eg, costs, outcomes, probabilities of events) to determine whether such variations would make meaningful changes in the results of the analysis. As reported in our US publication about the model [17], the cost-effectiveness of use of the IBS was expected to be most sensitive to the rate of bacterial contamination and to the risk of emerging pathogens. To explore the effect of these variables on the results, we analyzed the effect of such variables in various scenarios.

2.5. Emerging Virus

It must be kept in mind that current safety measures have an impact on safety only with regard to the blood-borne pathogens for which tests are in use. They do not protect the transfusion recipient against untested or unknown infectious agents. Therefore the blood supply remains vulnerable to newly identified or emerging infectious agents. A primary example is the West Nile virus epidemic in the United States from 1999 to 2002 [20]. Although a number of recently examined new agents (hepatitis G and TT viruses) with a potential impact on blood safety appear to be nonpathogenic, or not to be transmitted through transfusion (human herpes virus type 8), every discovery of an agent necessitates investigation for the potential of transfusion-associated transmission [21,22]. Transfusion-related pathogenicity requires an asymptomatic viremic phase during which the infected donor can donate undetected by current screening methods, and that the virus can survive in blood components during preparation and storage [23].

Historical as well as contemporary data confirm that this risk of emerging infection is not hypothetical. With the model, we examined the health economic consequences of implementation of the IBS for different potential situations with regard to the transfusion-related infection risk of a new emerging virus. The risk was programmed at different levels, which were based on historical HCV infection rates [24]. The following transfusion-associated residual risk levels were evaluated: 1 per 100,000 and 1 per 10,000 donations.

Table 4.
Cost Data for the Cost-effectiveness Model with Intercept Blood System (IBS) Implementation in Japan*

Parameter	Cost, ¥	Reference
Apheresis platelet cost	113,119	M. Satake, MD, personal written communication, July 2004
Net cost of IBS	3898	Net-cost calculation from Table 3
ARC/AIDS care costs per case	7,200,000	[43]
HCV or HBV care costs per case		
Chronic infection	2,228,000	[44]
Cirrhosis	267,000	[44]
HCC	1,326,000	[44]
Fulminant infection	1,557,000	[44]
TRS		
Hospitalization	700,000	[17]

*ARC/AIDS indicates AIDS-related complex/acquired immunodeficiency syndrome; HCV, hepatitis C virus; HBV, hepatitis B virus; HCC, hepatocellular carcinoma; TRS, transfusion-related sepsis.

2.6. Bacterial Contamination

Bacterial contamination is currently the most prevalent residual risk associated with platelet transfusion [13]. Several surveillance systems exist (United Kingdom Serious Hazards of Transfusion report, US Food and Drug Administration) in various countries; however, inherent with all of the systems is a certain degree of underreporting [25]. Several recent European reports of data on systematic bacterial cultures at time of preparation for more than 130,000 platelet components indicated the contamination rates is approximately 0.7% (7 cases per 1000 components) [26,27]. To analyze the effects of bacterial contamination, we used sensitivity analyses to explore mortality data from the literature applicable to bacterial contamination. Of note, this analysis dealt only with mortality and not with less severe infections that arise owing to transfusion of contaminated platelet components with attendant health- and care-related consequences [28].

3. Results

3.1. Net-Cost Impact of IBS Adoption

The IBS, as most innovative technologies, will require a net cost to the Japanese health care system. At the same time, potential savings in current tests and procedures will offset this investment so that the additional net cost for the IBS amounts to only ¥3898 per platelet therapeutic dose. This calculation includes an assumed cost that 10% more platelet doses have to be collected to compensate for processing losses. This imputed added cost due to collection of additional platelets is a conservative assumption based on recent data from a clinical trial and postmarketing experience in Europe that indicated the IBS may not require collection and transfusion of additional platelet doses [29,30].

With approximately 700,000 platelet units transfused annually in Japan, use of the IBS at a net cost of ¥3898 per platelet transfusion would result in an increase of only 0.02% (¥2.7 billion) of the total hospital budget (¥11,342 billion) [31] and only an additional 0.89% increase in the cost for labile blood components in Japan. Moreover, this conservative calculation does not include potential benefit from extension of platelet storage from 3 to 5 days, benefit from avoidance of disease due to platelet transfusion and the long-term consequences associated with adverse events, benefits from avoidance of legal claims (in Japan ¥56,100,000 was awarded per hemophiliac patient with HIV infection due to exposure to contaminated clotting factors) [32] and associated judicial costs, and benefit from avoidance of indirect costs due to work loss and premature death. Furthermore, in phase 3 clinical trials, transfusion of IBS platelets resulted in a significantly reduced rate of acute transfusion reactions [33], thus the costs of care associated with transfusion reactions may be reduced. Similarly, suspension of the IBS in a reduced concentration of allogeneic plasma may reduce the incidence of transfusion-associated acute lung injury with additional savings in transfusion-related care costs [34].

3.2. Cost-effectiveness Analysis for IBS Adoption: Analysis Using Baseline Assumptions

When analyzing our previously developed cost-effectiveness model with Japanese risk factors and cost data, adding the net cost of the IBS to the current AP price, we found the cost-effectiveness of the IBS ranged from ¥99,000,000 for the pediatric ALL patient to ¥1,076,000,000 for the hip surgery patient (Table 5). The wide range of cost-effectiveness ratios can be explained by the better survival prognosis for pediatric and heart surgery patients and their age. The better prognosis allows more life-years gained by prevention of transfusion-transmitted disease compared with the situation for patients with end-stage cancer and relatively older orthopedic surgery patients.

3.3. Sensitivity Analysis

Increasing the number of deaths due to bacterial contamination of platelet components from 1 in 225,000 to 1 in 112,500 improved the range of cost-effectiveness by 30% to 40%. The same held true for the impact of emerging viruses. Cost-effectiveness improved markedly with increasing risk of viral transmission (Table 5). Given that we mimicked an HCV-like emerging virus scenario, the impact was greatest in pediatric patients receiving platelet transfusion owing to the natural history of posttransfusion hepatitis. Most cases of hepatitis C (70%-80%) are asymptomatic and do not lead to significant medical problems. In contrast, prevention of transfusion-transmission of an HIV or West Nile virus type of emerging pathogen would yield great benefits in terms of life-years gained and associated cost avoided and would lead to a highly favorable cost-effectiveness ratio.

Table 5.
Cost-effectiveness of Intercept Blood System in Japan: Cost in Yen per Quality-Adjusted Life-Year Gained*

Analysis	ALL, 10-Year-Old Boy	NHL, 50-Year-Old Woman	CABG, 60-Year-Old Man	Hip Arthroplasty, 70-Year-Old Woman
Baseline	99,000	433,000	263,000	1,076,000
Baseline plus higher risk of bacterial fatality rate: 1/112,500	69,000	267,000	163,000	605,000
Baseline plus emerging virus scenario: 1/100,000	84,000	238,000	237,000	1,022,000
Baseline plus emerging-virus scenario: 1/10,000	35,000	127,000	127,000	702,000

*In thousands of yen, rounded. ALL indicates acute lymphocytic leukemia; NHL, non-Hodgkin's lymphoma; CABG, coronary artery bypass grafting.

3.4. Interpretation of Cost-effectiveness Ratios

Cost-effectiveness ratios can be interpreted in 2 ways. First, if national health policy makers have established a certain threshold of cost-effectiveness, new technologies could be evaluated against that cutoff point. Several countries have determined official criteria for cost-effectiveness. For example, in the United States interventions that yield a cost-effectiveness ratio of more than US$100,000 per QALY gained are considered unfavorable and should ideally not be implemented. The United Kingdom National Institute of Clinical Excellence uses a similar "threshold" of approximately £30,000 per QALY gained. According to these "decision rules," none of the recently used blood safety measures should have been implemented because their cost-effectiveness ratios are much higher than the designated thresholds [35,36]. Cost-effectiveness is a relative concept and should be applied to in-group comparisons. In other words, new blood safety technologies should be evaluated against technologies in the same area (eg, NAT screening, plasma pathogen inactivation treatment). Transfusion medicine is in a situation in which additional benefits gained for protection against selected pathogens are marginal and come at a cost leading to higher cost-effectiveness ratios ranging from $300,000 (solvent detergent plasma) to $85,000,000 per QALY (HCV NAT in France) [37,38]. However, society has decided to pay for these interventions given the paramount interest in blood safety, especially in Japan, where patients expect 100% safety [14]. Comparing the cost-effectiveness of the IBS to current safety measures in Japan and elsewhere, we found the IBS is an equal and even more cost-effective intervention in preventing transfusion-transmitted disease and injury (Figure 2).

4. Discussion

In our analysis we examined the economic impact of use of the IBS in Japan. We examined both the net cost to a blood center for use of the technology and the broader health-care implications of use of the IBS by use of cost-effectiveness analysis. The net-cost analysis provided valuable information about the ultimate potential of the IBS for

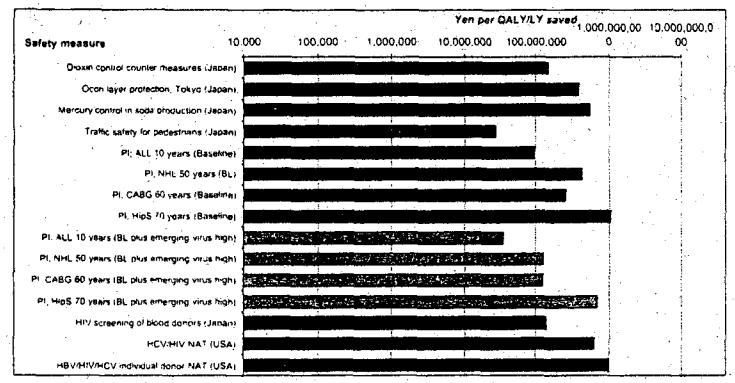

Figure 2. Cost-effectiveness of the Intercept Blood System (IBS) compared with other blood, environmental, and transport safety measures. QALY indicates quality-adjusted life-year; PI, pathogen inactivation; ALL, acute lymphocytic leukemia; NHL, non-Hodgkin's lymphoma; CABG, coronary artery bypass grafting; HipS, hip arthroplasty; BL, baseline; HIV, human immunodeficiency virus; HCV, hepatitis C virus; NAT, nucleic acid test; HBV, hepatitis B virus.

reducing the cost of platelet transfusion for the blood center by replacing several current practices (Table 3). Moreover, if additional platelets were not required for use of the IBS, consistent with the European experience to date, then introduction of the IBS could actually reduce the cost of platelet transfusion by ¥7413 per therapeutic dose (Table 3). In addition, other savings, not factored into this analysis, are possible through avoidance of additional tests such as cytomegalovirus (CMV) serologic tests and tests for other emerging pathogens, such as dengue virus.

Cost-effectiveness analysis provides another perspective from which to examine the economic impact of use of the IBS. Whereas the risk of transfusion-transmitted infections has been greatly reduced by existing safety measures, zero risk has not yet been attained. New safety interventions that can reduce bacterial and viral transfusion risks still are needed to improve blood safety. As evidenced by the cost-effectiveness ratios of reviewed studies [38], society places a high value on reducing the number of unintentional deaths and injuries. New transfusion safety measures should be evaluated by use of higher cost-effectiveness thresholds that accurately reflect the value to society of reducing unintentional deaths and injuries from a therapeutic modality presumed to be free from infectious agents, as are other parenteral medications.

In addition, we must bear in mind that cost-effectiveness analysis is limited in its ability to capture all the benefits that improved blood safety has to offer. Results of cost-effectiveness analysis actually may be misleading, underestimating the true cost-effectiveness of an intervention. Many cost-effectiveness analysis models do not account for the economic benefit of eliminating potentially redundant blood safety measures (eg, gamma radiation, CMV testing, p24 testing, HTLV testing, or testing for bacterial contamination). Furthermore, new safety measures may offer other benefits, such as increased shelf life of blood, avoidance of having to compensate infected patients, and lost productivity due to premature death following infection with lethal viruses (such as HIV). These aspects, and the peace of mind that increased safety offers to all transfusion recipients, should not be overlooked in evaluation of new blood safety interventions.

Implementation of the IBS in Japan came at a net cost to society. According to our analysis, however, realizing the full potential of the technology has reduced the additional cost to a relatively small cost considering the wide array of benefits that allow cost offsets elsewhere in the blood banking operating scheme. If the initial European experience that use of the IBS did not necessitate collection of more platelet doses is confirmed with broader experience, then the net cost of the IBS is very reasonable. Use of the IBS may initiate a paradigm shift from testing to prevention, thereby harnessing additional long-term cost savings far beyond the immediate benefits of disease prevention. Use of the system may avoid implementation of multiple new screening tests, extend the shelf life of platelet components, and broaden the donor base by avoiding travel-related donor exclusions. The greatest benefit of the IBS, however, is the potential to protect against emerging and migrating pathogens. The system therefore should be a valuable technology for enhancing blood safety in Japan.

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ORIGINAL ARTICLE

Cost-effectiveness of pathogen inactivation for platelet transfusions in the Netherlands

M. J. Postma,* M. van Hulst,*† J. T. M. De Wolf,‡ M. Botteman§ and U. Staginnus¶ *Groningen University Institute for Drug Exploration/University of Groningen Research Institute of Pharmacy (GUIDE/GRIP), †Martini Hospital, ‡University Medical Centre Groningen, Groningen, the Netherlands, §HERQuLES, Abt Associates Inc., Bethesda, MD, USA, and ¶Baxter, Madrid, Spain

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SUMMARY. The objective of this study is to estimate cost-effectiveness of pathogen inactivation for platelet transfusions in the Netherlands. We used decision tree analysis to evaluate the cost-effectiveness of the addition of pathogen inactivation of pooled platelets to standard procedures for platelet transfusion safety (such as, donor recruitment and screening). Data on transfusions were derived from the University Medical Centre Groningen (the Netherlands) for 1997. Characteristics of platelet recipients (patient group, age, gender and survival) and data/assumptions on viral and bacterial risks were linked to direct and indirect costs/benefits of pathogen inactivation. Post-transfusion survival was simulated with a Markov model. Standard methods for cost-effectiveness were used. Cost-effectiveness was expressed in net costs per life-year gained (LYG) and estimated in baseline- and sensitivity analysis. Sensitivity was analysed with respect to various assumptions including sepsis risk, reduction of the discard rate and discounting. Stochastic analysis to derive 90% simulation intervals (SIs) was performed on sepsis risk. Net costs per LYG for pathogen inactivation were estimated €554 000 in the baseline-weighted average over the three patient groups (90% SI: €354 000–1092 500). Sensitivity analysis revealed that cost-effectiveness was insensitive to viral risks and indirect costing, but highly sensitive to the assumed excess transfusions required and discounting of LYG. Given relatively high net costs per LYG that are internationally accepted for blood transfusion safety interventions, our estimated cost-effectiveness figures for pathogen inactivation may reflect acceptable cost-effectiveness in this specific area. Two main assumptions of our model were that the pathogen inactivation was 100% effective in preventing transmission of the pathogens considered and was not associated with major and/or costly adverse reactions. Validation of several crucial parameters is required, in particular the Dutch risk for acquiring and dying of transfusion-related sepsis.

Key words: cost-effectiveness, pathogen inactivation, pharmacoeconomics, platelets.

In the Netherlands, safety of transfusion of blood and blood products is largely determined by supply of available technology. The major goal of public health authorities in this field has been to achieve maximum transfusion safety. For example, newer and better tests for blood-borne infectious diseases are rapidly introduced in screening procedures for blood donors, such as nucleic acid amplification testing (NAT) for the human immunodeficiency virus (HIV). Next to the 'maximum-safety' criterion, cost-effectiveness is becoming an important issue in judging new technologies, also in blood transfusion. Relatively high cost-effectiveness ratios are seemingly accepted in the blood transfusion area (Van Hulst *et al.*, 2002; Yeh *et al.*, 2002). For example, at estimated current Dutch levels of risk for HIV transmission through transfusion, HIV NAT costs several millions per life-year gained (LYG) (Postma *et al.*, 2001). This finding is in line with

Correspondence: Dr Maarten J. Postma, Associate Professor in Pharmacoeconomics, Groningen University Institute for Drug Exploration/University of Groningen Research Institute of Pharmacy, Antonius Deusinglaan 1, Groningen 9713 AV, the Netherlands.
Tel.: +31 50 363 2607; fax: +31 50 363 2772;
e-mail: m.j.postma@rug.nl

estimates of NAT for HIV and hepatitis C virus (HCV) in other countries (Pereira & Sanz, 2000; Loubière *et al.*, 2001; AuBuchon *et al.*, 2002).

Despite high levels of safety achieved in Dutch blood transfusion, risks still remain. Relatively small residual risks have been estimated for HIV, HCV and hepatitis B virus (HBV) (Müller-Breitkreutz, 2000). Particularly, for platelets relevant risks of bacterial infection and subsequent sepsis are estimated, with significant mortality rates being reported (Sazama, 1994; Ness *et al.*, 2001). Estimated sepsis risk after transfusion is highest for pooled platelets, with risks being suggested up to one per 2000 units transfused (Sazama, 1994; Lopez-Plaza *et al.*, 1999). In the Netherlands, pooled platelets reflect almost all utilization of platelet transfusions (Sanquin, 2000).

A new pathogen inactivation technology-the INTERCEPT® Platelet Systems-achieves reductions in pathogen loads in platelets below detection limits for all relevant enveloped viruses – such as HIV-1, HIV-2, HBV and HCV – and many bacteria – such as *Staphylococci* and *Escherichia coli* (Corash, 2000). The INTERCEPT® Platelet Systems (further: pathogen inactivation) is based on psoralen treatment. Application of pathogen inactivation for platelets may achieve benefits accruing at various levels:

- Elimination of risk for parasites and viral infections, such as HIV, HCV and HBV.
- Elimination of risk for sepsis due to bacterial infection.
- Blood bank processing benefits, such as improved discard rate of platelets due to prolonged shelf-life and potential elimination of gamma irradiation.
- Elimination of risks for yet unknown emerging pathogens.
- Potential reductions in judicial claims following fatal transfusion-transmitted infections.

In the present study, we assess the cost-effectiveness of pathogen inactivation in platelets. The scope of this article is limited to elimination of risks for known bacterial and viral infections and improvements in blood bank processing with regard to elimination of gamma irradiation. Benefits with respect to reduced discard rates may have already been achieved in the Netherlands with the implementation of bacterial screening in 2002. Benefits of averted spread of yet unknown emerging viruses in platelets and inclusion of judicial claims are left for discussion and further work. Future applications of the INTERCEPT® Systems, comprising the whole spectra of pathogens (including nonenveloped viruses) and products (including red cells and plasma), enhance formal consideration of such further benefits, inclusive of potential omission of any of the usual tests on donor blood for viruses and bacteria on the long-term.

MATERIALS AND METHODS

General design

We developed a pharmacoeconomic model that links characteristics of the population of platelet recipients (age, gender and outcome in terms of survival) with economic aspects of pathogen inactivation. The pharmacoeconomic model estimates cost-effectiveness in terms of net costs per discounted LYG, with inclusion of direct and indirect costs and benefits. Direct medical costs relate to the costs of pathogen inactivation. Direct benefits are related to costs of treatment and care for transfusion-related viral and bacterial infections and elimination of gamma irradiation. Indirect benefits are related to averted production losses related to averted deaths due to infections.

Patient population

The pharmacoeconomic model was developed for three separate typical patient groups, as cost-effectiveness for blood transfusion safety interventions may strongly vary between such groups (Van Hulst *et al.*, 2002). For example, application of viral inactivated plasma was estimated to cost US$59 000 per quality-adjusted LYG in trauma patients and US$122 000 in cardiac surgery patients (AuBuchon & Birkmeyer, 1994). Application of single-donor platelets instead of pooled platelets was estimated to cost US$200 000 per quality-adjusted LYG in cardiac surgery and US$470 000 in haematology (Lopez-Plaza *et al.*, 1999). In this study, we elaborate cost-effectiveness for three patient groups giving rise to the major share of platelet transfusions in the Netherlands: cardiology, haematology and paediatric oncology.

Transfusion data of patients were gathered in the University Medical Centre Groningen (UMCG, the Netherlands) in 1997. Figure 1 shows the distributions in terms of patients (Fig. 1a) and transfusions (Fig. 1b). As shown, cardiac surgery patients – primarily undergoing coronary artery bypass grafting – represented almost 41% of the patient population receiving platelets, whereas in terms of platelet transfusions their proportion is lower (23%). In terms of the number of transfusions, haematology accounts for the major share. Table 1 lists the distributions of platelet transfusions over age

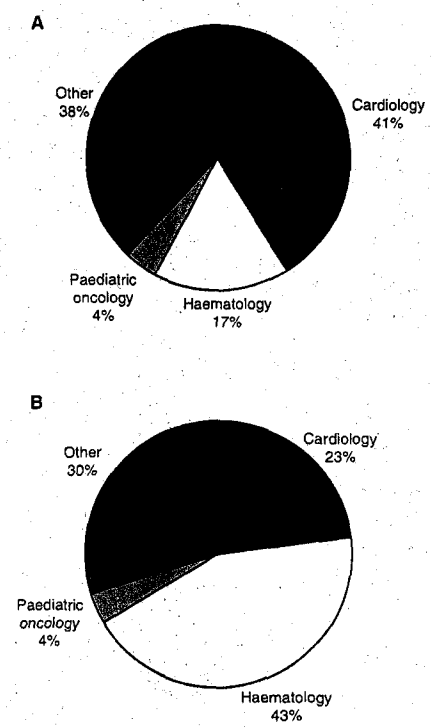

Fig. 1. Distribution of patients (upper) and transfusions (lower) over patient groups in the University Medical Centre Groningen (data for 1997).

groups and gender. This distribution is the basis for our pharmacoeconomic model below.

Risks of pathogen transmission

Given the existence of thorough donor selection and routine donation screening for HIV, HCV and HBV, virally infected donations are very rare in the Netherlands. European estimates for the risk of window period donations in 1997 were one in 2·3 million for HIV, one in 620 000 for HCV and one in 400 000 for HBV (Müller-Breitkreutz, 2000). In the model, we applied recent estimates that are considered specific to the Dutch situation at one per 200 000 for HBV and one per million for HIV and HCV (Health Council, 2003).

Transfusion-related sepsis is most often related to platelet transfusions. Approximately 80% of cases in the UK were estimated to be related to platelets (Serious Hazards of Transfusion (SHOT), 2001). An internationally published (Yomtovian *et al.*, 1993; Ness *et al.*, 2001) risk of 0·04% per platelet transfusion was deployed in the model as upper bound and investigated in sensitivity analysis (see below). Corresponding case fatality for sepsis was assumed at 15% (Ness *et al.*, 2001). For the lower bound (also investigated in sensitivity analysis), 0·025% was taken for platelet transfusion-related sepsis with a related case fatality of 17% (Morrow *et al.*, 1991; Sazama, 1994). For the baseline, the intermediate risk at 0·0325% and intermediate case fatality at 16% were assumed. On top of these estimates, we assumed that the recently implemented bacterial screening only slightly reduces the sepsis risk by approximately 5% (almost 40% of positive units are

Table 1. Percentage distribution of platelet transfusions for three patient groups in the University Medical centre Groningen in 1997 by age and gender (n = 603 for cardiology, n = 120 for haematology and n = 30 for paediatric oncology)

	Cardiology		Haematology		Paediatric oncology	
Age group (years)	Male (%)	Female (%)	Male (%)	Female (%)	Male (%)	Female (%)
<10	2·5	1·3	0·0	0·0	46·7	23·3
10–20	0·0	0·5	1·7	0·0	20·0	10·0
20–30	0·5	0·8	5·8	3·3	–	–
30–40	1·2	0·5	0·8	9·2	–	–
40–50	9·6	0·2	13·3	7·5	–	–
50–60	13·8	1·3	15·8	18·3	–	–
60–70	19·4	9·6	10·0	7·5	–	–
70–80	23·2	12·3	1·7	4·2	–	–
>80	1·0	2·3	0·0	0·8	–	–
Total	71·1	28·9	49·2	50·8	66·7	33·3

not recalled, and over 90% of recalled platelet units are already transfused) (Beckers *et al.*, 2005).

Excess mortalities for HIV and HCV were set at 6 and 1% per annum, respectively (Loubière *et al.*, 2001; Postma, Wiessing *et al.*, 2001). Mortality due to HBV infection was neglected.

Costing aspects

All costs in our analysis were estimated at price levels of 2003. If required, annual deflators of 1·8% for direct and 2% for indirect costs were used (Oostenbrink *et al.*, 2000). According to the Dutch guidelines for pharmacoeconomic research, future costs (and LYG) were discounted at 4% per annum (Riteco *et al.*, 1999).

Lifetime, discounted direct costs for transfusion-related viral infections were available from the published literature (Struijs *et al.*, 2000; Postma, Wiessing *et al.*, 2001; Postma *et al.*, 2005). Direct costs for transfusion-related sepsis were based on a recent Dutch study (Van Gestel *et al.*, 2002). Table 2 lists the cost estimates as used in the model.

To enable estimation of cost-effectiveness from the societal perspective, indirect costs were included for death due to any transfusion-related infection, i.e. HIV death, HCV death and sepsis death. The societal perspective is preferred in many international guidelines for pharmacoeconomic research, including the Dutch ones (Riteco *et al.*, 1999; Hjelmgren *et al.*, 2001). Indirect costs were estimated using the friction costing approach, as requested by the Dutch guidelines for pharmacoeconomic research (Riteco *et al.*, 1999; Oostenbrink *et al.*, 2000). As opposed to the human capital approach, the friction costing approach only counts indirect costs of production losses during a period of a limited number of months required to fill in the vacancy. The human capital approach calculates production losses during all future life-years that are lost due to premature death.

Table 2. Direct costs for viral infections and bacterial sepsis in € (price level 2003) used in the model (costs for human immunodeficiency virus (HIV), hepatitis C virus (HCV) and hepatitis B virus (HBV) are lifetime discounted costs) (Struijs *et al.*, 2000; Postma, Wiessing *et al.*, 2001; Van Gestel *et al.*, 2002; Postma *et al.*, 2005)

HIV	83 200
HCV	19 500
HBV	1100
Sepsis	20 600

The costs for pathogen inactivation were assumed at €116, the currently envisaged price for hospitals (including margins for required production process changes in the blood banks; personal communication with the manufacturer). Additional costs are posed by pathogen inactivation that may potentially involve yield losses. We assumed a 10% increase in the costs per platelet transfusion unit to account for this factor (McCullough *et al.*, 2001; Van Rhenen *et al.*, 2003). Additionally, in the trials performed for INTERCEPT®, excess transfusions were required to achieve adequate count increments. In the US SPRINT trial, such excess transfusions were more than 30%; in the European euroSPRITE trial, no significant difference was found (McCullough *et al.*, 2001; Van Rhenen *et al.*, 2003). In our analysis, we assumed 15% excess transfusions with pathogen inactivation (0 and 30% in sensitivity analysis). Excess transfusions were monetarily valuated at the estimated cost price per platelet transfusion unit of €458 for adult and €285 for paediatric application (Sanquin Blood Supply: price list as of 1 March 2003) plus €116 for bacterial inactivation.

Finally, benefits of elimination of gamma irradiation were inserted in the model, assuming this elimination in 10% of transfusions in haematology and paediatric oncology at €30 per irradiation.

Pharmacoeconomic model

The distribution of platelet transfusions in the UMCG was the basis for our pharmacoeconomic model. This distribution was conceived to reflect the probabilities that an individual unit is transfused to a patient of specific gender, age and patient group. For each patient group, an age- and gender-specific Markov model was developed for post-transfusion survival. Survival results from death risks due to viral/bacterial infection through transfusion, post-cardiac surgery death risks and those due to other causes (natural mortality). Details on transfusion-related infections are listed below; mortality for cardiac surgery, haematology and paediatric oncology patients was estimated at 17, 38 and 37%, respectively, in the first year (data from the UMCG for 1997) and 1, 5 and 0·5%, respectively, in subsequent years (The Bypass Angioplasty Revascularization Investigation (BARI) Investigators, 1996; Lopez-Plaza *et al.*, 1999; Coebergh *et al.*, 2001). Natural mortality was taken from the national statistics (source: Dutch Central Bureau of Statistics, Voorburg, the Netherlands).

For the three patient groups considered, a weighted average for cost-effectiveness was also calculated (proportions of transfusions as weights;

Fig. 1). As shown in Fig. 1, the patient groups in our model are estimated to consume 70% of Dutch platelet transfusions.

Figure 2 shows above in the concept of a decision tree.

Cost-effectiveness was expressed in net costs per LYG. Net costs reflect the costs of pathogen inactivation minus its monetary benefits. Monetary benefits were related to either the elimination of risks for viral and bacterial infection or gamma irradiation. Monetary benefits and LYG were estimated by comparing two options in the model. In a first step, the financial costs and life-years lost were estimated in the absence of pathogen inactivation with risks for transfusion-related viral and bacterial infections as specified above. In the next step, pathogen inactivation was simulated, corresponding with zero risks for infections of pathogens considered in this analysis. In addition, elimination of gamma irradiation was assumed. Differences in costs and life-years in both options were compared subsequently.

Cost-effectiveness was estimated in the baseline and sensitivity analysis. Deterministic sensitivity analysis was performed with respect to viral risks, bacterial risk, reduction in discard rate and discounting of LYG. For stochastic sensitivity analysis, Monte-Carlo simulation was performed with respect to the annual number of transfusion-related sepsis cases (Poisson distribution) allowing calculation of 90% simulation intervals (SIs) for cost-effectiveness. Microsoft Excel 97, @RISK 3·5 for Excel (Palisade, London, UK) and DATA 3·5 for Health Care (TreeAge Software, Williamstown, MA, USA) were used for computer implementation and presentation.

RESULTS

As an example, estimated annual monetary benefits of pathogen inactivation in the baseline accrued to €69 300 per 10 000 transfusions in cardiac surgery (10 000 also approximately reflects the annual number of Dutch platelet transfusions in cardiac surgery). Of these benefits, 96% referred to averted cases of sepsis (also for the other patient groups, sepsis accounts for the major share of benefits; however, additional benefits come in for elimination of gamma irradiation at approximately 30% of total benefits). Furthermore, per 10 000 transfusions in cardiac surgery, approximately 4·4 discounted life-years were gained and costs of €2169 200 were made, rendering net costs of €2099 900 and net costs per LYG at €474 000 in the baseline (90% SI: €302 500–€940 300). Baseline estimates for the other patient groups – haematology and paediatric oncology – were €678 600 (90% SI: €434 000–€1338 300) and €260 700 (90% SI: €166 800–€511 200), respectively. The weighted average over the three patient groups was estimated at €554 000 (90% SI: €354 000–€1092 500) As mentioned, SIs formally represent potential annual fluctuations in cost-effectiveness.

Sensitivity analysis revealed that our results are insensitive to the exclusion of averted viral infections and exact levels of assumed indirect costs (not shown). Model results were sensitive to sepsis risk and related case fatality, the assumed excess transfusions through inactivation and discounting of LYG (Table 3 lists results for weighted average over patient groups). In percentage changes, results were most sensitive to higher excess transfusions assumed (+74% of baseline) and nondiscounting of LYG (−38% of baseline).

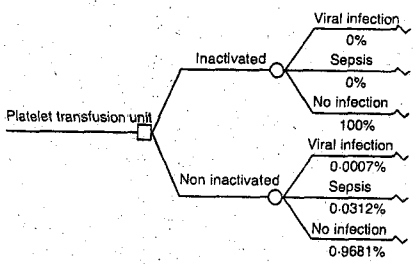

Fig. 2. Decision tree for the cost-effectiveness analysis of pathogen inactivation.

DISCUSSION AND CONCLUSIONS

Cost-effectiveness of pathogen inactivation of platelet transfusions was estimated at €554 000 per LYG in the baseline as an average over three major patient

Table 3. Sensitivity analysis for the cost-effectiveness ratio in net costs per life-year gained (LYG) (in €; price level 2003) on sepsis risk (and related case fatality), excess transfusions and discount rate for the weighted average over the three patient groups considered (cardiology, haematology and paediatric oncology)

Baseline (sepsis risk 0·0325%; case fatality 16%; 15% excess transfusions; discounting of LYG)	554 000
Sepsis risk 0·04%; case fatality 15%	476 900
Sepsis risk 0·025%; case fatality 17%	682 700
No excess transfusions required	393 500
Excess transfusions required at 30%	961 500
Nondiscounting of LYG	341 200

groups, accounting for 70% of Dutch platelet transfusions. Averted cases of sepsis were identified as major drivers of benefits of pathogen inactivation. In sensitivity analysis, a range around €554 000 from €341 200 to €961 500 was indicated, by assuming nondiscounting LYG and 30% excess transfusions due to inactivation, respectively.

In the frameworks of statin treatment for high cholesterol and several vaccination studies, a Dutch threshold for acceptable net costs per discounted LYG of approximately €20 000 has been suggested (Postma, Heijnen *et al.*, 2001). Such thresholds differ between societies and between interventions (Owens, 1998). For example, for transplantation services, relatively high thresholds for cost-effectiveness are implicitly applied with transplantations of the liver and the lung costing approximately €100 000 per discounted LYG (Michel *et al.*, 1994; Al *et al.*, 1998). Also for transfusion safety, relatively high net costs per discounted LYG – up to one million €'s – seem to be accepted in the Netherlands and other countries (Postma, Staginnus *et al.*, 2001; Van Hulst *et al.*, 2002; Yeh *et al.*, 2002). For example, we recently estimated cost-effectiveness of NAT of Dutch donors for HIV at €200 000 to over one million €'s (Postma *et al.*, 2002). From this perspective, our estimated cost-effectiveness figures for pathogen inactivation may reflect acceptable net costs per LYG.

Our analysis primarily focused on results using discounted life-years (gained). Nondiscounting of LYG reduces net costs per LYG up to almost two-thirds in our analysis. For preventive services such as the one investigated here, discounting of LYG is subject to debate among pharmacoeconomists (Gold *et al.*, 1996), and one may argue to focus on net costs per nondiscounted LYG for pathogen inactivation, i.e. €341 200 (Bos *et al.*, 2002).

We analysed the risk for transfusion-related sepsis over a plausible range from 0·025 to 0·04% per pooled platelet unit transfused. Lower risks have been reported, for example in the BACTHEM and BaCon studies (Kuehnert *et al.*, 2001; Perez *et al.*, 2001). The authors of the former study commented on their findings on incidence rates of life-threatening bacterial contaminations that these probably are underestimated due to underreporting and overestimation of the denominator in the calculus (issued numbers instead of transfused units) (Perez *et al.*, 2001). The latter study has been argued to have identified merely the top of the iceberg (Yomtovian, 2002). Another study estimated approximately one adverse reaction per 2000 platelet transfusions, higher than our baseline assumption (Robillard & Karl Itaj, 2001). Finally, we note that our assumptions on risks for bacterial infections are in line with a consensus of opinion that was expressed in an open letter to the Blood Collection Community (Brecher *et al.*, 2002).

During the conduction of our research, bacterial testing was implemented in the Netherlands and was used in Dutch blood banks during 2002 (BacTAlert®, Oreganon Teknika BV, Boxtel, The Netherlands). Bacterial testing has reduced the risk for transfusion-related bacterial infection in the Netherlands. Recent research, however, indicates that this reduction may be only limited, as mentioned in the section entitled 'Materials and Methods'. Also, for serious infection (ICD code 999·8: 'septic shock due to transfusion or transfusion reaction NOS'), no reduction in the annual number of cases was, seen in the national hospital registration data (Primant Utrecht). During 1998–2001, approximately 20 cases were registered annually (case fatality: 16%), whereas 2002 had 24 cases (case fatality: 21%) (Primant Health Care, 2002). We believe that these data do currently not support the formal inclusion of a more prominent risk reduction due to bacterial screening than the current 4% on our baseline sepsis risk of 0·0325%.

Further benefits of pathogen inactivation may be related to the occurrence of a new emerging virus of which the spread through platelet transfusion may be averted. The historic example of transfusion-related HIV in the Netherlands may serve as an illustration. Primarily, during the first 5 years of the Dutch HIV epidemic, approximately five HIV infections may have been directly caused by platelet transfusions annually (Op de Coul, 2001). Aversion of such an epidemic would translate into direct benefits of averted lifetime HIV treatments, indirect benefits and LYG for both index cases and spouses.

Our current analysis is limited to the Netherlands. Differences in health care systems, treatment patterns for viral and bacterial infections, cost prices and costing guidelines complicate country-to-country transition of pharmacoeconomic models (Welte & Leidl, 1999; Schmid *et al.*, 2001). Also, national blood banking policies and infection risks differ between European Union (EU) countries. For example, we note that the transfusion-related HIV epidemic in the Netherlands has been limited compared to that in other EU countries (Postma, 1998) and the US. A preliminary evaluation of the pathogen inactivation process for the US indicates that inclusion into the analysis of averting of an HIV-like emerging virus, to be transmitted through platelet transfusion, may result in overall life- and cost savings (Bell *et al.*, 2002).

Obviously, we cannot test definitively the validity of the assumption that spread through platelet transfusions of the next virus that comes along is averted. Its plausibility is based on the observation that this pathogen inactivation technology has been effective against all the enveloped viruses tested (Lin *et al.*, 1997). Furthermore, we know from studies on the HIV viruses using inhibition of molecular amplification that these viruses are highly modified after psoralen treatment and that the titre of virus that can be inactivated is far greater than the 6-log inhibition of infectivity (Lin *et al.*, 1992).

Two of the main assumptions of this cost-effectiveness analysis were that the pathogen inactivation for platelets was 100% effective in preventing transmission of the pathogens used in the model and was not associated with any adverse reactions. We note that the INTERCEPT® Blood System for platelets was not effective although for nonenveloped viruses that are not in our current analysis. Clinical studies conducted in the US and Europe have evaluated the efficacy and safety of the INTERCEPT® Blood System for platelets, and no excess treatment-related adverse reactions were detected in patients receiving platelet components treated with pathogen inactivation technology (McCullough *et al.*, 2001; Van Rhenen *et al.*, 2003). Also, we note that a carcinogenicity study using a sensitive and validated heterozygous p53 mouse model has been completed, and treated platelets were not carcinogenic at 1000-fold the clinical exposure (Ciaravino, 2001). This study was reviewed by federal drug administration (FDA) and EU regulatory authorities who concurred with the observation of no carcinogenicity. However, inherent to the assumed benefit of platelets treated with the pathogen inactivation process is a level of uncertainty, as with any new medical intervention, and any benefit gained from the use of pathogen-inactivated platelets may be offset by the incidence of an unanticipated adverse reaction or any other treatment-related hazard.

Finally, we note that our cost-effectiveness analysis could be based on three patient groups only, leaving 30% of platelet transfusions uncovered by our model. These transfusions may involve multitrauma with poor short-term prognosis, i.e. patient groups whose inclusion in the model may worsen cost-effectiveness.

Cost-effectiveness of pathogen inactivation of platelet transfusions was estimated at €554 000 per LYG in a weighted average for three patient groups, accounting for 70% of Dutch platelet transfusions. Given relatively high net costs that are internationally accepted for an LYG in blood transfusion safety interventions, our estimated cost-effectiveness figures for pathogen inactivation may reflect acceptable cost-effectiveness in this specific area.

Averted cases of sepsis were identified as the major driver of health gains of pathogen inactivation. Validation of several crucial parameters is required, in particular the Dutch risk of acquiring transfusion-related sepsis and subsequent case fatality. Further work should extend the model to other countries as well as including further potential benefits of pathogen inactivation. The relevance of this inclusion is enhanced if pathogen inactivation is to cover the whole spectra of pathogens and blood products.

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ORIGINAL ARTICLE

Assessment of the economic value of the INTERCEPT blood system in Belgium

K. Moeremans,* H. Warie* and L. Annemans*† *HEDM, Health economics and Disease Management, Brussels, and †Ghent University, Ghent, Belgium

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SUMMARY. Emerging pathogens continue to threaten blood safety, requiring novel safety approaches. INTERCEPT Blood System for platelets (IBSP) inactivates pathogens, aiming at eliminating the risk of transmitting current and emerging pathogens. The objective was to evaluate the incremental cost-effectiveness ratio (ICER) for IBSP in Belgium.

A decision model comparing a 'world with IBSP' to a 'world without IBSP' calculates lifetime costs and 'quality adjusted life years' (QALYs) following platelet transfusion in different indications. Disease-specific life expectancy and consequences of transfusion-transmitted infections were obtained from literature. Transfusion safety and costs were obtained from official sources. Hepatitis C virus-like emerging pathogen was simulated.

A wide range of ICERs was observed, highly sensitive to the risk of emerging pathogen transmission, underlying disease and age. In the most conservative approach, ICER ranged from 3,459,201€/QALY in absence of emerging pathogen to 195,364€/QALY. The mean threshold of emerging infection risk for IBSP dominance (saving money and producing health gains) ranged from 1/1,079 to 1/2,858 transfusions.

Considering the high value authorities appear to place on preventing accidental injury, and ICER of recent implementations in transfusion medicine (NAT: up to €2·3 million per lifeyear), IBSP can be considered cost-effective, taking into account the potential risk of emerging pathogens.

Key words: emerging, INTERCEPT, pathogen inactivation, platelets, safety, transfusion

The risk of transfusion-associated viral infections has been significantly reduced by the introduction of donor-screening and blood-screening tests in routine practice. However, some residual risk of transfusion-related infections remains. This is because of the window period between infection and positive test results on the one hand and to some pathogens which could potentially be transmitted via transfusion, but for which screening tests are not performed today on the other hand (e.g. Cytomegalovirus [CMV], Human T-lymphotropic virus [HTLV]...). In addition, viral screening tests may produce false-negative results (Laperche *et al.*, 2003; Busch, 2003). Recently, safety measures have been increased by including NAT tests for hepatitis C virus (HCV) and HIV detection in routine screening programs. However, current safety initiatives consisting of serological or viral antigen tests address only one or few selected pathogens at a time. Any new pathogen requires new safety measures in addition to the already established system.

Historical as well as contemporary data confirm that the risk of newly emerging infections is not hypothetical (WHO, 1998 (www.who.int); Leiby, European Parliament hearing June, 2003; Biggerstaff & Petersen, 2003). Depending on their clinical characteristics and modes of transmission, these emerging infections may present an enormous threat to transfusion safety. Scientific information is often limited at the time of emergence, and the development of diagnostic screening tests takes time. Therefore, these emerging agents require novel approaches to prevent transmission (Leiby, European Parliament hearing June, 2003).

As they are stored at room temperature, platelets are particularly vulnerable for bacterial contamination. Therefore, bacterial screening is routinely performed on platelet samples in Belgium; however, a potential risk of false-negative results remains.

Correspondence: Dr Karen Moeremans, HEDM, Crayerstraat 6, 1000 Brussel, Belgium.
Tel.: +32 3 899 61 19; fax: +32 3 899 61 09;
e-mail: kmoeremans@be.imshealth.com

The INTERCEPT Blood System for platelets (IBSP) is a new technology which inactivates different types of pathogens through irreversible binding to RNA/DNA in the blood (*BioDrugs*, 2003).

When new safety measures are introduced, there is clearly a need to accurately define the value of these new initiatives, and decisions regarding blood-screening policies must be based on accurate estimates of the incremental safety balanced against cost and taking into account the potential loss of donors (Busch *et al.*, 2003).

The objective of our study was to analyse the health and economic consequences of pathogen inactivation using the IBSP in Belgium, taking a perspective directed to the future, including the risk of emergence of a new transfusion transmittable virus.

SUBJECTS STUDIED

The target population included patients with haematological malignancies undergoing bone marrow or peripheral stem cell transplantation [acute lymphoid leukaemia (ALL), acute myeloid leukaemia (AML), chronic myeloid leukaemia (CML) and non-Hodgkin's lymphoma (NHL)], breast cancer patients undergoing stem cell transplantation and patients undergoing cardiac surgery, whereby coronary artery bypass graft (CABG) was selected as case. These populations are considered to receive most commonly platelet transfusions (Bell *et al.*, 2003).

MATERIALS AND METHODS

We performed a cost-effectiveness analysis in Belgium from a societal perspective, including both direct medical costs and productivity related costs (expressed in euro), as well as legal and liability costs.

A decision analytical model was developed simulating the clinical outcomes of patients requiring platelet transfusion, in a world with and in a world without the INTERCEPT blood system.

Model

The model was developed using TREEAGE DATA™ software. The model starts at the time of platelet transfusion and simulates the evolution of a cohort of patients receiving transfusions of platelets inactivated with the INTERCEPT blood system compared with the same cohort receiving untreated platelets, taking into account the risk of bacterial infection, HCV, hepatitis B virus (HBV) and HIV infection. These infections are currently tested for in Belgium and their residual transfusion-related infection risk has been assessed.

In addition, the risk of a possible newly emerging viral infection is included in the framework.

The overall risk of infection per patient is calculated in the model as the residual risk per transfusion multiplied with the average number of transfusions per patient.

If no transfusion-related infection occurs, the average life expectancy is the one of the underlying diseases. If transfusion-related infection occurs, the life expectancy is reduced because of the mortality associated with the infection. The main decision analytical model structure is outlined in Fig. 1.

Life expectancy in the absence of transfusion-related infection

The average life expectancy associated with the considered underlying diseases was calculated based on published mortality rates. By applying yearly mortality rates, average life expectancy can be calculated as the surface below the survival curve.

For both ALL and AML, 1 year mortality was 44% (Dini *et al.*, 2001). During subsequent years, the relative mortality rates as reported by Socié *et al.* (1999) were applied to age-matched general mortality rates in Belgium (1997).

In patients with NHL undergoing early stem cell transplantation, a 5-year overall survival rate of approximately 65% is reported (Dresse *et al.*, 1999; Martelli *et al.*, 2003). Patients surviving more than 5 years were assumed to have normal life expectancy.

In CML patients, based on review of recent literature (Carreras *et al.*, 2000; Davies *et al.*, 2001; Elmaagacli *et al.*, 2002; Gaziev *et al.*, 2002; Pigneux *et al.*, 2002; Radich *et al.*, 2003), an average cumulative mortality rate of 50% by year five was estimated. For the remainder 50%, long-term relative mortality rates were applied to the age-matched general population (Socié *et al.*, 1999).

For CABG patients, a weighed average life expectancy was calculated from data published by Weintraub *et al.* (2003), including mortality rates up to 20 years post-intervention. Although these patients were operated many years ago, the short-term mortality was not higher than reported in more recent studies (Calafiore *et al.*, 2000; Taggart *et al.*, 2001).

For breast cancer patients undergoing Peripheral Stem Cell Transplantation (PSCT), life expectancy was estimated equal to the weighed (for study size) average median survival reported in PSCT patients (Farquhar *et al.*, 2003).

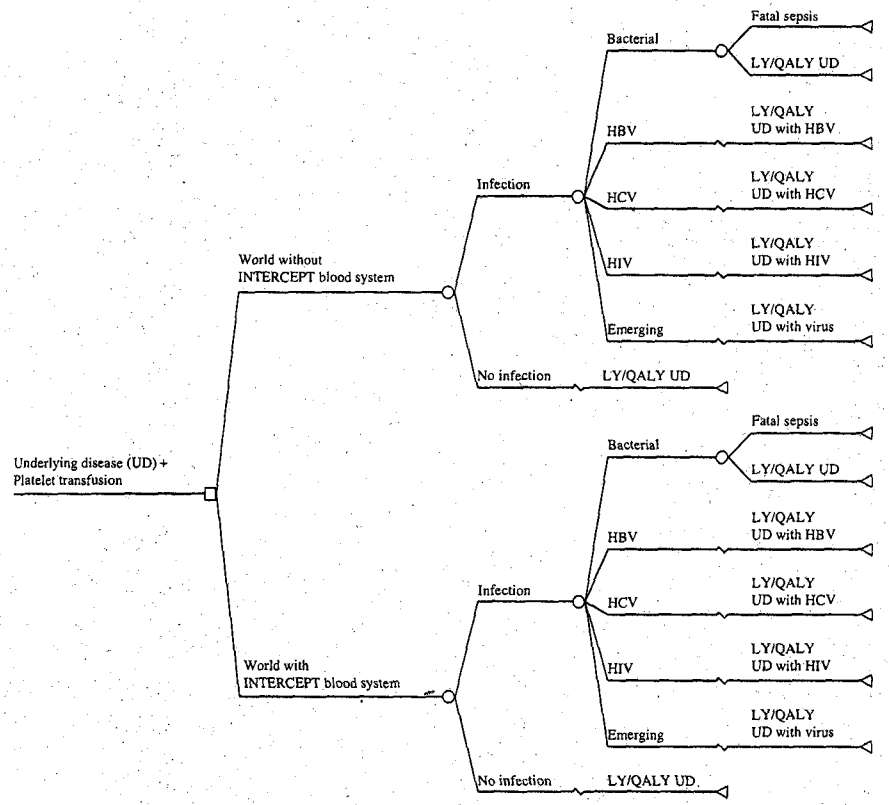

Fig. 1. Basic structure of decision tree. QALY, quality adjusted life years.

Table 1 summarizes the obtained average life expectancy per underlying disease.

Risk of known infections with untreated platelet components

Table 2 provides an overview of viral safety tests performed on blood components in Belgium today, the frequency of positive tests and the respective residual risks of viral transmission per transfusion (Belgian Red Cross 2003, see Acknowledgements). As they are stored at room temperature, platelets are particularly vulnerable for bacterial contamination. Therefore, in Belgium, a sample of the platelet component is monitored for bacterial contamination throughout storage time using the 'BactAlert system'. Because of the absence of mandatory reporting of any transfusion-related events, there is limited information on the actual risk of transfusion-associated bacterial infections in Belgium. For the current analysis, Red Cross and clinical expert estimates were collected. The most conservative estimate, reported by the Red Cross, was a rate of transfusion-associated bacterial infections of one in 5000 transfusions.

Risk of emerging pathogens

To assess the potential health economic consequences of the INTERCEPT blood system, the risk of future

Table 1. Average life expectancy in the absence of transfusion related infection

Type	Average life expectancy (years)
AML adults	1·7
AML childhood	31·9
ALL adults	3·1
ALL childhood	15·6
NHL adults	5·9
NHL childhood	26·3
CML	9·6
CABG	16·1
Breast cancer	2·7

ALL, acute lymphoid leukaemia; AML, acute myeloid leukaemia; CABG, coronary artery bypass graft; CML, chronic myeloid leukaemia; NHL, non-Hodgkin's lymphoma.

known or unknown emerging infections were taken into account. Because the characteristics of a new emerging virus are unknown, it was decided to simulate an economic, morbidity and mortality impact comparable with HCV. The simulation of infection risk for this new emerging virus can be based on the historical evolution of HCV virus transmission through transfusion, although it could be argued that, compared with the 1990s, a new virus today would be identified sooner after its emergence because of scientific progress, and hence, that transmission rates will probably not reach the level observed for HCV at the time. But, on the other hand, a lot depends on the disease characteristics. A long asymptomatic period following initial infection may significantly increase the time to identification and the time to linking the infection with blood transfusion. The American Medical Association (2000, see Chamberland, 2002) described the historical evolution of transfusion-related transmission of HCV in the United States. In the 1970s, the risk of HCV infection was very high (>1/100). The improvements in donor screening and testing have combined to result in substantial decreases in transfusion-transmitted infections during the 1980s and 1990s. On the other hand, other factors also contribute to the incidence rates of transfusion-related infections that may be reached such as the window period for the emerging pathogen, its incidence and prevelance in the donor population... (Chamberland, 2002). Our economic evaluation was performed for different levels of emerging viral infection risk between 1/100 and 1/100,000 transfusions.

Efficacy and safety of IBSP

The following pathogens are inactivated by the system (approved indications): HIV 1, HIV 2, HBV, HCV, CMV, MCMV and aerobic bacteria.

The following inactivation claims have been recently approved by the Irish Medicines board: HTLV I, HTLV II, *Treponema pallidum* (Syphilis), protozoa (*Trypanosoma cruzi*, Chagas disease, *Plasmodium falciparum*, malaria) and anaerobic bacteria.

Other inactivation studies on alternative pathogens are ongoing (Leishmaniasis, Babesiosis, *Candida albicans*, *Borrelia bugdorferi*, West Nile virus, Parvovirus B19 – last update July 2004).

The results of an extensive series of *in vitro* and *in vivo* studies have not demonstrated any toxicologically relevant effects on platelet concentrates prepared by the INTERCEPT Blood System (Ciaravino *et al.*, 2001).

In the model, the inactivation system is programmed to eliminate the risk of the considered known transfusion transmittable infections as well as to eliminate transmission of the simulated emerging virus. Two main assumptions underlying the model were that pathogen inactivation is 100% effective and is not associated with major or costly adverse events.

Table 2. Viral safety measures and residual risk of platelet transfusions (Belgium)

Virus	Screening test	Donations (Wallonia, 2002, see Acknowledgements) Tested +	True +	Donations (Flanders, 2000, see Acknowledgements) Tested +	True +	Residual risk*
HBV	HbsAg	54/100,000	17/100,000	121/100,000	10/100,000	<1/200,000
HCV	Anti-HCV	93/100,000	17/100,000	119/100,000	6/100,000	<1/200,000
	NAT					1/703,571
HIV	Anti-HIV1 and 2	111/100,000	0/100,000	103/100,000	0·3/100,000	<1/2–3 mio
	NAT HIV1					<1/4–6 mio

HBV, hepatitis B virus; HCV, hepatitis C virus.
Source: Belgian Red Cross.
*Risk of transmission per 'transfusion'.

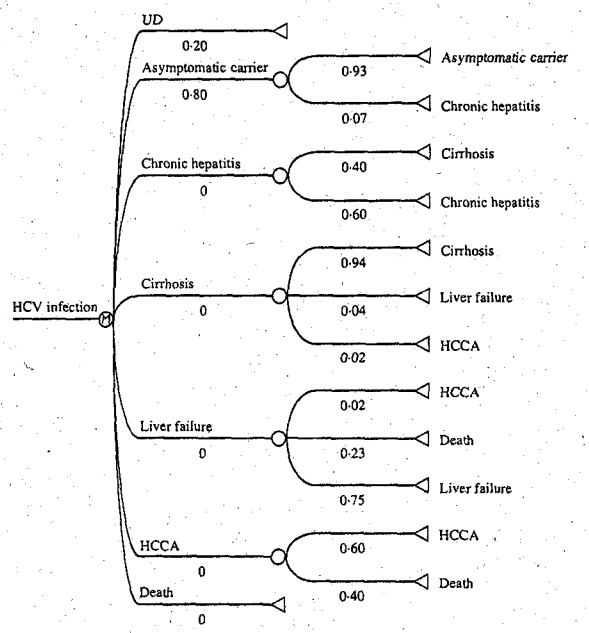

Fig. 2. Structure of subtree related to transfusion-transmitted infection with hepatitis B or C. Under each branch, the probability of transition from the left to the right health state are shown. The probabilities under the left hand side branches represent possible pathways at model start, at the time of infection. At this time, patients can either have only acute infection without becoming a carrier (20%) or become carrier (80%). Subsequently, carriers may develop chronic complications, possibly evolving over chronic hepatitis to cirrhosis, liver failure or carcinoma. The probabilities shown under the right hand side branches represent the likelihood of possible transitions from one state to another. The probabilities were obtained from published literature (Pereira, 2000; Sevinir, 2003; Gordon, 1998; Hu, 1999; Tong, 1995). Only the probability of developing chronic hepatitis is different for HCV versus HBV: 0·212 (Sevinir, 2003; Pereira, 2000) and 0·224 (Sevinir, 2003; Gordon, 1998) respectively. Other disease progression rates were programmed equally for HCV and HBV. HCCA, hepatocellular carcinoma.

Additional benefits of the IBSP

The INTERCEPT blood system is anticipated to have an additional number of future benefits, supported by a recent international forum of experts (Engelfriet *et al.*, 2003).

First, it is estimated that, in the future, some of the currently applied screening tests, leading to platelet waste, may be eliminated. These may include BactAlert testing, NAT testing (given the high burden and low yield) and Alkaline Phosphatasis (ALT) testing. It must be noted that, at present, the elimination of NAT testing is only possible for single donor platelets, because for random donor platelets, the tests are needed to ensure safety of the obtained red cells and plasma. However, pathogen inactivation for red cells may become available in the future. Nevertheless, given the uncertainty of its timing, in a secondary analysis (not in the basecase), we considered this potential benefit only for Single Donor Platelets (SDP) platelets. Secondly, studies have demonstrated that the INTERCEPT blood system is at least as effective as γ-irradiation for the inactivation of T-cells (Lin *et al.*, 1997; Grass *et al.*, 1998). Hence, the second potential benefit may be to make γ-irradiation, which is performed on the majority of platelet components in Belgium today, obsolete. The third benefit consists of a reduction of platelet waste. Today, in Belgium, of the 45,808 platelet transfusion bags donated annually, approximately 8% are wasted because of storage time overdue and 1·9% because of contamination or positive viral screening tests (Red Cross Belgium). In the past, the platelet storage time initially set at 7 days was reduced to 5 days mainly for increasing risk of bacterial contamination. With the INTERCEPT blood system, the previously applied limit of 7 days could potentially be re-introduced. In addition to the above-mentioned current potential benefits, pathogen inactivation may avoid a proportion of supplementary tests in the future for potential emerging pathogens, which will not be required for SDP. Conservatively, the latter benefit is not considered in the economic evaluation.

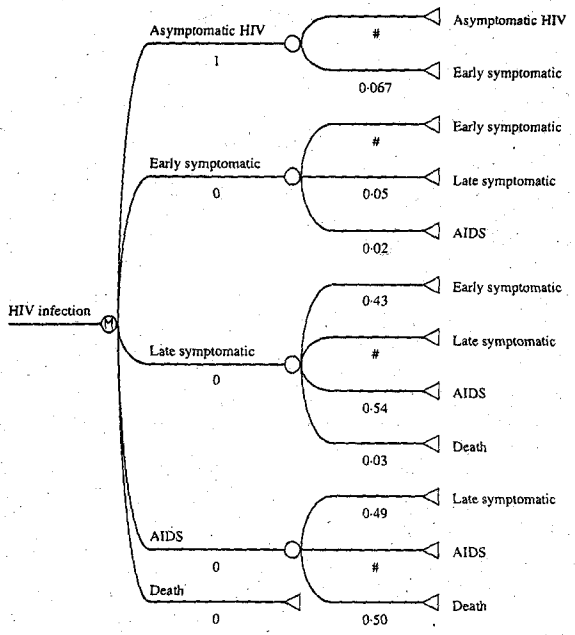

Fig. 3. Structure of subtree related to transfusion-transmitted infection with HIV. Under each branch, the probability of transition from the left to the right health state is shown. The probabilities were obtained from published literature. (Miners, 2001).

Impact of transfusion-transmitted infections

The impact of transfusion-transmitted viral infections was calculated by simulating the clinical progression rates over different disease states (Figures 2 and 3) obtained from literature and assigning costs (Table 4) and utilities to each state. Utilities are values representing the quality of life in a certain health status. Utility values can range between 0 and 1, with 0 representing death and 1 representing a state of perfect health. The time spent in a certain health state is multiplied by the corresponding utility weight to account for the quality of life in that particular state. The utility values applied in the model were obtained from previous published research (Table 3).

Regarding bacterial infections, 9·7% have been reported fatal and 26·5% life threatening (France, Andreu *et al.*, 2002). For the current analysis, non-fatal infections were not attributed any reduction in quality of life given their limited duration. Fatal or life-threatening bacterial infections were attributed a management cost derived from previous research related to severe sepsis, showing a total cost per sepsis episode of €17,988 (SE = 1145) (Laterre *et al.*, 2002).

Table 3. Utility weights applied for disease stages related to viral infection

	Utility (95% CI)
HIV	
Asymptomatic (CD4 >500 cells mm^{-3}) (Tengs 02)	0·94
CD4 200–500 cells mm^{-3}	0·82
CD4 <200	0·79
Aids	0·77
Hepatitis	
Viral negative	1
Chronic Hepatitis	0·82 (0·6–0·9)
Compensated Cirrhosis	0·78 (0·5–0·9)
Decompensated Cirrhosis	0·65 (0·3–0·88)
Hepatocellular Carcinoma	0·25 (0·1–0·5)
Liver transplantation, 1st year	0·5 (0·11–0·7)
Liver transplantation, subsequent years	0·7 (0·24–0·87)

The same utility values were applied for hepatitis C virus as for hepatitis B virus related health states (Dusheiko *et al.*, 1995)

Table 4. Cost data for disease stages related to viral infection

	Annual cost (€) (SD)
HIV*	
Stage A: Asymptomatic	2231 (1955)
Stage B: Symptomatic	7899 (7070)
Stage C: Aids	25,736 (20,766)
Hepatitis	
Viral negative	
Acute hepatitis C†	2300
Chronic hepatitis ‡	125
Compensated cirrhosis‡	250
Decompensated cirrhosis‡	8060
Hepatocellular carcinoma‡	10,000
Liver transplantation, 1st year‡	50,000
Liver transplantation, subsequent years‡	8700

*Decock *et al.* (2001).
†Occurring in approximately 25% of HCV transmissions (Harbarth *et al.*, 2000).
‡Wong & Nevens (2002).

Finally, the calculation of indirect costs incurred from transfusion-associated infections is summarized in Table 5.

Cost data

The costs per transfusion of €371·84 for SDP and €274 for average Random Donor Platelets (RDP) were obtained from official sources (RIZIV/INAMI, Red Cross Belgium). These costs include γ-irradiation and donor screening tests except NAT.

The cost of inactivation using the INTERCEPT blood system is estimated as €125 per inactivation session, hence per platelet transfusion. This cost includes the cost for the system itself (€ 90, including VAT) as well as the costs for material and personnel to perform the procedure (potential savings at the level of platelet processing not taken into account). In the model, the average transfusion cost per patient is calculated considering the basic transfusion cost, the cost of the INTERCEPT blood system and the average number of transfusions per patient.

With regard to legal costs, we assumed an average cost of €100,000 per transfusion-associated infection with HIV or with emerging virus, based on law suits or governmental action reports from different countries, including Belgium (Press conference Minister of Public Health Belgium, 19 September 2001, Hof van beroep, Gent, 1e kamer, 24 April 1998). Although for other infection types, there have been legal procedures started in Belgium, we have not included these costs in the model, because none of the law suits have been finalized (some are ongoing for up to 10 years).

Scenarios evaluated

In the basecase scenario, the implementation of the INTERCEPT blood system is assumed to eliminate the risk for HIV, HCV, HBV and bacterial infection.

Table 5. Methods for indirect cost calculations (adults)

Productivity loss calculations	Haematological cancer	Breast cancer	CABG
Employed prior to underlying diagnosis*	48%	39%	25%
Average *n* days per year active*	218	167	218
Percent resume activity post treatment†	67	67	100
Annual *n* days lost if infected‡	70	44	55
Duration of productivity loss	From month 6 to end stage§	From month 6 to end stage§	5 years¶
Unit costs			
Unit cost per hour (€)	23**		

CABG, coronary artery bypass graft.
*Age and sex matched national data (National Institute for Statistics, 2001, available at www.statbel.fgov.be).
†Bradley & Bednarek (2002).
‡The annual number of days lost if infected = % active previously × *n* working days/year × % who would resume activity despite underlying disease in the absence of infection (e.g. 48% × 218 × 67% = 70).
§Because the employment rate applied is based on calculations for the entire adult population up to all ages, the age at diagnosis does not need to be taken into account for programming duration of activity. However, during the end stage of the underlying disease, no productivity is assumed in the absence of infection; hence, no productivity loss can be attributed.
¶70% of patients are under 60 years of age at the time of intervention. 25% of these are active for an estimated further duration of 5 years. Beyond this duration, no productivity is assumed in the absence of infection; hence, no productivity loss can be attributed.
**Includes direct wages + employers charges (National Institute for Statistics, 1996, available at www.statbel.fgov.be)

Additional processing benefits (see further scenarios) are not considered in this scenario. Given the evidence, it is clear that a risk of emerging viruses in the future is existent; however, the timing and level of risk is unknown. Therefore, the assumption of neither the presence of viral risk nor the absence of viral risk can be supported as a reflection of reality. Therefore, it was decided to present the basecase scenario as a double scenario, taking into account a similar probability of absence and presence of an emerging virus. To the emerging virus, different levels of risk were attributed between 1 in 100,000 and 1 in 1000. The highest and lowest risks are shown in the first scenario in Tables 1 and 2.

In the second and third scenarios, the implementation of the INTERCEPT blood system is assumed to eliminate the risk for HIV, HCV, HBV, bacterial and emerging HCV like virus, and in addition, a set of processing benefits are considered. In scenario 2, the elimination of BactAlert testing (corresponding cost and platelet waste reduction), the storage time prolongation to 7 days, leading to 50% decrease in overdue platelets waste, the elimination of SDP ALT testing on SDP platelets and the elimination of γ-irradiation were assumed to be associated with the INTERCEPT blood system. In a third scenario, the following benefits were assumed in addition to the benefits in scenario 2: the elimination of NAT tests and syphilis tests (VDRL) on SDP units leading to reduced costs (NAT costs eliminated). Scenarios 2 and 3 imply a reduction in the cost for platelet processing and testing.

RESULTS

The cost-effectiveness ratio is highly sensitive to the risk of infection with the emerging pathogen and to the indication and age group considered.

Scenario 1: In the absence of emerging virus, the cost-effectiveness ranges between 3,459,201€ per quality adjusted life year (QALY) to 195,364€/QALY. At the lowest simulated risk of the emerging pathogen contamination (1/100,000), the cost-effectiveness ratios range between 3,355,308€/QALY and 165,051€/QALY, depending on the underlying disease (Table 6). With increasing risk of emerging pathogen transmission, the cost-effectiveness ratios steadily decrease (improve), with a maximum of 2,594,120€/QALY at 1/10,000 and of 223,255 at 1/1000 (Table 7) and INTERCEPT being dominant in the majority of cases, meaning cost saving and producing extra QALYs. At 1/100, the INTERCEPT blood system strategy becomes dominant in all cases.

Including processing benefits of INTERCEPT, resulting in a reduced cost for platelet processing and testing, leads to lower cost-effectiveness ratios (Table 8) and dominance of INTERCEPT already at an emerging infection risk of 1/1000.

The following thresholds of emerging infection risk for the INTERCEPT system to become dominant in all indications are observed. Dominance is present as from an emerging risk of 1/1074 transfusions in scenario 1, 1/1697 transfusions in scenario 2 and 1/1791 in scenario 3 (Table 9).

DISCUSSION

The objective of this study was to assess the cost-effectiveness of the INTERCEPT blood system. For this purpose, a health economic model was developed, comparing the overall outcome in a world with INTERCEPT, where infections because of blood transfusions are prevented, to a world without INTERCEPT where infections may occur.

Three scenarios were developed including different levels of INTERCEPT benefits from the prevention of infections up to multiple processing benefits: redundancy of bacterial testing, viral screening and γ-irradiation and reduction of platelet waste. Two main assumptions underlying the model were that pathogen inactivation is 100% effective and is not associated with major or costly adverse events. The INTERCEPT blood system has not only been shown to effectively inactivate current pathogens, but the main benefit of an inactivation system versus safety measures based on screening for infections is that it prevents the transmission of new pathogens before they have been identified. In the absence of the INTERCEPT blood system, the identification of the pathogen, the development and implementation of diagnostic screening tests would take time, during which the pathogen can emerge and might cause numerous transmissions.

Historical data on the rise of transfusion-associated infections with HCV, HBV and HIV have shown that the risk can reach very high levels before screening measures have been developed for implementation in donor-screening schedules. Also recently, there has been an epidemic of West Nile virus in the United States, a virus which was shown to be transmittable via blood transfusion. The risk of transmission through transfusion at the epicentre of the epidemic (1999) has been estimated as high as one in 3700 to one in 5555 transfusions in high-risk areas (Harrington *et al.*, 2003). Estimated mean risks in 2002 ranged from one in 6667 to one in 811 donations for several high incidence geographical areas (Biggerstaff & Petersen 2003). This has lead to the prompt introduction of expensive screening tests in the US transfusion safety programme (NAT tests). However, considering the time of first detection of West Nile virus in the US (1999) and the time of implementation of NAT tests in routine blood screening (2002), the lag time between emergence and blood safety measures was 3 years (Allain *et al.*, 2005). In our study, the rate of infection with an emerging virus was set at different levels representing different stages of emergence.

In the absence or at very low-risk levels of emerging virus, of <1 in 100,000 transfusions, the cost-effectiveness ratios were high in some populations, depending on the underlying disease and age

Table 6. Cost effectiveness (cost/QALY) scenario 1 – no emerging virus or emerging virus 1/100,000

Type	Emerging virus	Strategy	Cost*	Marginal cost*	Efficacy†	Marginal efficacy†	Incr C/E (ICER)‡
AML-A	Absent	Without INTERCEPT	4279		1·99953		
		With INTERCEPT	5915	1636	2·00000	0·00047	3,459,201
	Present	Without INTERCEPT	4292		1·99952		
		With INTERCEPT	5915	1623	2·00000	0·00048	3,355,308
AML-C	Absent	Without INTERCEPT	4277		31·99162		
		With INTERCEPT	5915	1638	32·00000	0·00838	195,364
	Present	Without INTERCEPT	4295		31·99019		
		With INTERCEPT	5915	1620	32·00000	0·00981	165,051
ALL-A	Absent	Without INTERCEPT	4290		2·99929		
		With INTERCEPT	5915	1625	3·00000	0·00071	2,280,181
	Present	Without INTERCEPT	4304		2·99927		
		With INTERCEPT	5915	1611	3·00000	0·00073	2,196,998
ALL-C	Absent	Without INTERCEPT	4275		15·99602		
		With INTERCEPT	5915	1640	16·00000	0·00398	411,522
	Present	Without INTERCEPT	4290		15·99562		
		With INTERCEPT	5915	1624	16·00000	0·00438	370,981
NHL-A	Absent	Without INTERCEPT	4502		5·99850		
		With INTERCEPT	6161	1659	6·00000	0·00150	1,105,343
	Present	Without INTERCEPT	4522		5·99843		
		With INTERCEPT	6161	1639	6·00000	0·00157	1,045,085
NHL-C	Absent	Without INTERCEPT	4455		25·99302		
		With INTERCEPT	6161	1706	26·00000	0·00698	244,591
	Present	Without INTERCEPT	4473		25·99200		
		With INTERCEPT	6161	1688	26·00000	0·00800	210,949
CML	Absent	Without INTERCEPT	3638		9·99797		
		With INTERCEPT	4929	1291	10·00000	0·00203	636,067
	Present	Without INTERCEPT	3659		9·99784		
		With INTERCEPT	4929	1270	10·00000	0·00216	586,459
CABG	Absent	Without INTERCEPT	360		15·99968		
		With INTERCEPT	493	133	16·00000	0·00032	422,784
	Present	Without INTERCEPT	361·3		15·99967		
		With INTERCEPT	492·9	132	16·00000	0·00033	395,535
BRCA	Absent	Without INTERCEPT	1000		2·99984		
		With INTERCEPT	1380	381	3·00000	0·00016	2,328,169
	Present	Without INTERCEPT	1003		2·99983		
		With INTERCEPT	1380	377	3·00000	0·00017	2,285,263

A, adults; ALL, acute lymphoid leukaemia; AML, acute myeloid leukaemia; C, childhood; CABG, coronary artery bypass graft; CML, chronic myeloid leukaemia; ICER, incremental cost-effectiveness ratio; NHL, non-Hodgkin's lymphoma; QALY, quality adjusted life year.
*Cost and marginal cost in €.
†Efficacy and marginal efficacy in number of QALYs.
‡Marginal cost-effectiveness in €/QALY gained.

Table 7. Cost effectiveness (cost/QALY) scenario 1 – no emerging virus or emerging virus 1/1000

Type	Emerging virus	Strategy	Cost*	Marginal cost*	Efficacy†	Marginal efficacy†§	Incr C/E (ICER)‡
AML-A	Absent	Without INTERCEPT	4279		1·9995		
		With INTERCEPT	5915	1636	2·0000	0·0005	3,459,201
	Present	Without INTERCEPT	5568		1·9985		
		With INTERCEPT	5915	347	2·0000	0·0016	223,255
AML-C	Absent	Without INTERCEPT	4277		31·9916		
		With INTERCEPT	5915	1638	32·0000	0·0084	195,364
	Present	Without INTERCEPT	6079		31·8486		
		With INTERCEPT	5915	−164	32·0000	0·1514	−1084
ALL-A	Absent	Without INTERCEPT	4290		2·9993		
		With INTERCEPT	5915	1625	3·0000	0·0007	2,280,181
	Present	Without INTERCEPT	5736		2·9973		
		With INTERCEPT	5915	179	3·0000	0·0028	64,960
ALL-C	Absent	Without INTERCEPT	4275		15·9960		
		With INTERCEPT	5915	1640	16·0000	0·0040	411,522
	Present	Without INTERCEPT	5781		15·9565		
		With INTERCEPT	5915	134	16·0000	0·0435	3086
NHL-A	Absent	Without INTERCEPT	4502		5·9985		
		With INTERCEPT	6161	1659	6·0000	0·0015	1,105,343
	Present	Without INTERCEPT	6492		5·9918		
		With INTERCEPT	6161	−331	6·0000	0·0083	−40,109
NHL-C	Absent	Without INTERCEPT	4455		25·9930		
		With INTERCEPT	6161	1706	26·0000	0·0070	244,591
	Present	Without INTERCEPT	6251		25·8903		
		With INTERCEPT	6161	−90	26·0000	0·1097	−817
CML	Absent	Without INTERCEPT	3638		9·9980		
		With INTERCEPT	4929	1291	10·0000	0·0020	636,067
	Present	Without INTERCEPT	5791		9·9845		
		With INTERCEPT	4929	−862	10·0000	0·0155	−55,479
CABG	Absent	Without INTERCEPT	360		15·9997		
		With INTERCEPT	493	133	16·0000	0·0003	422,784
	Present	Without INTERCEPT	522		15·9979		
		With INTERCEPT	493	−29	16·0000	0·0021	−14,039
BRCA	Absent	Without INTERCEPT	1000		2·9998		
		With INTERCEPT	1380	381	3·0000	0·0002	2,328,169
	Present	Without INTERCEPT	1317		2·9997		
		With INTERCEPT	1380	63	3·0000	0·0003	190,448

A, adults; ALL, acute lymphoid leukaemia; AML, acute myeloid leukaemia; C, childhood; CABG, coronary artery bypass graft; ICER, incremental cost-effectiveness ratio; NHL, non-Hodgkin's lymphoma; QALY, quality adjusted life year.
*Cost and marginal cost in €.
†Efficacy and marginal efficacy in number of QALYs.
‡Marginal cost-effectiveness in €/QALY gained.

group. In children, the results were much more favourable.

Considering the cost-effectiveness of other, recently established interventions in transfusion medicine, the INTERCEPT blood system compares well with these interventions, especially taken into account that only the economic implications of currently tested pathogens were included, whereas currently not tested pathogens may also induce costs. This result is confirmed by the results of a previous health economic evaluation of the INTERCEPT system for platelets within the US health care system (Bell *et al.*, 2003), as well as in a European setting (Postma *et al.*, 2005). For example, NAT tests, recently

Table 8. Cost effectiveness (cost/QALY) scenarios 2 and 3 – emerging virus 1/100,000

Type	Scenario	Strategy	Cost*	Marginal cost*	Efficacy†	Marginal efficacy†	Marginal C/E (ICER)‡
AML A	2	Without INTERCEPT	4292		1·9995		
		With INTERCEPT	5329	1037	2·0000	0·0005	2,143,435
	3	Without INTERCEPT	4292		1·9995		
		With INTERCEPT	5276	984	2·0000	0·0005	2,032,636
AML C	2	Without INTERCEPT	4295		31·9902		
		With INTERCEPT	5329	1034	32·0000	0·0098	105,389
	3	Without INTERCEPT	4295		31·9902		
		With INTERCEPT	5276	981	32·0000	0·0098	99,924
ALL A	2	Without INTERCEPT	4304		2·9993		
		With INTERCEPT	5329	1025	3·0000	0·0007	1,398,458
	3	Without INTERCEPT	4304		2·9993		
		With INTERCEPT	5276	971	3·0000	0·0007	1,325,297
ALL C	2	Without INTERCEPT	4290		15·9956		
		With INTERCEPT	5329	1039	16·0000	0·0044	237,275
		Without INTERCEPT	4290		15·9956		
		With INTERCEPT	5276	985	16·0000	0·0044	225,028
NHL A	2	Without INTERCEPT	4522		5·9984		
		With INTERCEPT	5552	1029	6·0000	0·0016	656,438
	3	Without INTERCEPT	4522		5·9984		
		With INTERCEPT	5496	973	6·0000	0·0016	620,812
NHL C	2	Without INTERCEPT	4473		25·9920		
		With INTERCEPT	5552	1079	26·0000	0·0080	134,763
	3	Without INTERCEPT	4473		25·9920		
		With INTERCEPT	5496	1023	26·0000	0·0080	127,783
CML	2	Without INTERCEPT	3659		9·9978		
		With INTERCEPT	4441	782	10·0000	0·0022	361,091
	3	Without INTERCEPT	3659		9·9978		
		With INTERCEPT	4397	737	10·0000	0·0022	340,449
CABG	2	Without INTERCEPT	361		15·9997		
		With INTERCEPT	444	83	16·0000	0·0003	248,647
	3	Without INTERCEPT	361		15·9997		
		With INTERCEPT	440	78	16·0000	0·0003	235,227
BRCA	2	Without INTERCEPT	1003		2·9998		
		With INTERCEPT	1244	241	3·0000	0·0002	1,459,408
	3	Without INTERCEPT	1003		2·9998		
		With INTERCEPT	1231	228	3·0000	0·0002	1,383,572

A, adults; ALL, acute lymphoid leukaemia; AML, acute myeloid leukaemia; C, childhood; CABG, coronary artery bypass graft; CML, chronic myeloid leukaemia; NHL, non-Hodgkin's lymphoma; QALY, quality adjusted life year.
*Cost and marginal cost in €.
†Efficacy and marginal efficacy in number of QALYs.
‡Marginal cost-effectiveness in €/QALY gained.

implemented in routine donor-screening programmes in many countries, including Belgium, showed cost-effectiveness ratios ranging from €25,000 to €2·3 million per life year gained (Yeh *et al.*, 2002). NAT tests for HIV have consistently been associated with cost-effectiveness ratios over €1 million per QALY (Jackson *et al.*, 2003; Marshall *et al.*, 2004).

Hence, these very high cost-effectiveness ratios have not prevented these blood safety measures to be introduced in many countries. When considering also the cost-effectiveness ratios for other interventions to prevent accidental injuries or death such as traffic safety measures, it seems that society or at least authorities tend to place a very high value on

Table 9. Threshold values emerging virus risk for INTERCEPT dominance

Type	Threshold emerging infection risk		
	Scenario 1	Scenario 2	Scenario 3
AML A	1/789	1/1230	1/1297
AML C	1/1107	1/1722	1/1816
ALL A	1/895	1/1400	1/1476
ALL C	1/925	1/1439	1/1510
NHL A	1/1205	1/1905	1/2004
NHL C	1/1057	1/1644	1/1738
CML	1/1675	1/2692	1/2858
CABG	1/1222	1/1932	1/2037
BRCA	1/838	1/1306	1/1380
Mean	1/1079	1/1697	1/1791

A, adults; ALL, acute lymphoid leukaemia; AML, acute myeloid leukaemia; C, childhood; CABG, coronary artery bypass graft; CML, chronic myeloid leukaemia; ICER, incremental cost-effectiveness ratio; NHL, non-Hodgkin's lymphoma.

measures to reduce unintentional deaths and injuries (Yeh *et al.*, 2002). Therefore, it was suggested by Yeh *et al.*, (2002) that transfusion safety measures should be evaluated using cost-effectiveness thresholds that are higher than those typically used by healthcare decision makers, reflecting the higher value placed on such types of interventions, where it is considered 'unfair' if patients have no access to the best possible protection (Yeh *et al.*, 2002).

Also the cost-effectiveness analyses should take into account all potential benefits of a new intervention such as processing benefits, indirect costs from productivity loss (Yeh *et al.*, 2002).

When a more pro-active viewpoint is taken, from a public health perspective, the apparent risk for emerging viruses should be taken into account. At emerging viral risks beyond 1/1000 to 1/2300 transfusions, the INTERCEPT strategy becomes dominant, that is saving money and producing health gains.

In conclusion, considering the apparently applied thresholds for cost-effectiveness in the field of blood transfusions, the implementation of the INTERCEPT blood system can be considered cost-effective and even a dominant strategy taking into account the potential risk of emergence of a new pathogen in the future.

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The cost-effectiveness of pathogen reduction technology as assessed using a multiple risk reduction model

Brian Custer, Maria Agapova, and Rebecca Havlir Martinez

BACKGROUND: Pathogen reduction technology (PRT) for labile blood components has the potential to reduce the risk of many adverse events associated with transfusion. Because of the potential broad-spectrum risk reduction capability of PRT, the health economics of PRT could be an important consideration in decision making for this technology.

STUDY DESIGN AND METHODS: Decision analytic models comparing current blood safety screens and interventions to riboflavin-based whole blood PRT (currently in development) and separately to platelets (PLTs)-and-plasma PRT from the health care system perspective in Canada were used to assess the cost-utility of PRT in reducing the following adverse events: human immunodeficiency virus, hepatitis B virus, hepatitis C virus, human T-lymphotropic virus, syphilis, West Nile virus, bacteria, Chikungunya virus, cytomegalovirus, *Trypanosoma cruzi*, graft-versus-host disease, febrile nonhemolytic transfusion reactions, and transfusion-related immunomodulation. PRT was modeled as an addition to rather than a replacement for current interventions. The potential of PRT to reduce the risk of an unknown pathogen was not assessed.

RESULTS: Whole blood PRT was estimated to have a cost-effectiveness of $1,276,000/quality-adjusted life-year (QALY; 95% confidence interval [CI] approximation, 600,000-3,313,000) compared to current screens and interventions. PLTs-and-plasma PRT was estimated to have a cost-effectiveness of $1,423,000/QALY (95% CI approximation, 834,000-2,818,000) on an all-transfusions basis.

CONCLUSIONS: Because of the complexity of transfusion risks and practices, the cost-effectiveness of whole blood or PLTs-and-plasma PRT can be modeled provided that assumptions and simplifications are made. Uncertainty remains with respect to the risk reduction that can be achieved for some adverse events. Nevertheless, the results of this cost-effectiveness analysis can be used to inform policy decisions regarding PRT technology in the context of other initiatives designed to improve transfusion safety.

Two methods for pathogen reduction technology (PRT), also known as pathogen inactivation, use a photoactive compound (riboflavin or amotosalen) and ultraviolet (UV) light treatment to prevent DNA or RNA replication. These methods are being adopted for the treatment of platelets (PLTs) or plasma in some European countries. Consensus statements from the panel of the Canadian Consensus Conference on Pathogen Inactivation in 2007 and summary statements, such as from one of the 2008 US Advisory Committee on Blood Safety and Availability meetings, indicate that economic evaluations of PRT should be conducted and included as part of the information used for making implementation decisions.[1,2] Previous economic analyses of photoactive compound/UV light PRT focused on human immunodeficiency virus (HIV), hepatitis B virus (HBV), hepatitis C virus (HCV), human T-lymphotropic virus (HTLV), and bacteria.[3-6] These analyses assumed that the treatment process is 100% effective (residual risk of these pathogens is eliminated in PRT-treated PLTs) and reported results for specific patient populations likely to receive such transfusions. The likelihood that these same patients would receive untreated red blood cells (RBCs) and/or plasma transfusions was not addressed. Moreover, while analyses restricted to specific patient populations

ABBREVIATIONS: FNHTR(s) = febrile nonhemolytic transfusion reaction(s); PRT = pathogen reduction technology; QALY = quality-adjusted life-year; TRIM = transfusion-related immunomodulation; WNV = West Nile virus.

From Blood Systems Research Institute, San Francisco, California; the Pharmaceutical Outcomes Research and Policy Program, University of Washington, Seattle, Washington; and Harvard University, Cambridge, Massachusetts.

Address reprint requests to: Brian Custer, Blood Systems Research Institute, 270 Masonic Avenue, San Francisco, CA 94118; e-mail: bcuster@bloodsystems.org.

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based on transfusion indication are informative for assessing *who is most likely to benefit*,[7] they do not help blood safety decision makers faced with selecting interventions to enhance the safety of components intended for all transfusion recipients.

We developed a new health economics model to assess the cost-effectiveness of riboflavin-based PRT (Mirasol PRT system, CaridianBCT, Lakewood, CO) in mitigating the risk of transfusion-associated infectious and some noninfectious threats. The first model examines the cost-effectiveness of a technology in development, whole blood PRT.[8] To model the technology that is currently available in some settings, PLTs-and-plasma PRT, we modified the whole blood PRT model, incorporating data on PLT preparation procedures and transfused components to adjust the risk reduction achieved.

MATERIALS AND METHODS

Overview

The models simulate the costs and consequences of the following infectious and noninfectious adverse events: HIV, HBV, HCV, HTLV, syphilis, West Nile virus (WNV), bacteria Chikungunya virus, cytomegalovirus (CMV), *Trypanosoma cruzi*, graft-versus-host disease (GVHD), febrile nonhemolytic transfusion reactions (FNHTR), and transfusion-related immunomodulation (TRIM). Both the set of and the prevalence of adverse events included in each version of the model can be adjusted to reflect setting-specific epidemiology or disease. In this analysis we neither included an unknown, emerging pathogen nor retrospectively included a scenario for HIV or HCV when either virus had the highest prevalence in blood donors. Our reason for not including these pathogens or scenarios is that it is relatively easy to construct a set of outcomes with a disease burden profile that is favorable to PRT. However, such a scenario in the context of trying to address or mitigate current risks could cloud the assessment of the efficiency of PRT.

We analyzed the cost-utility of PRT for Canada. Canada represents an appropriate country for such an analysis because there are 1) nationally representative health care data, 2) active hemovigilance and transfusion surveillance systems in some Provinces, and 3) interest in implementation of PRT. Similar to other economic analyses in blood safety, this analysis is from the health care system perspective and costs are limited to the costs of the safety interventions and the direct medical costs associated with infections or other adverse events.[9] The results reported here do not include the cost of lost productivity or related indirect costs incurred because of transfusion-associated adverse events. We used 2007 as the analysis year, so all monetary values are adjusted to 2007 Canadian dollars using the health and personal care component of the Canada consumer price index.[10] Data sources for disease occurrence, outcomes, and costs come from published literature specific to Canada. When data were not available for a specific disease or condition, we used data from other countries with preference for US data when available. In accord with the recommendations of the US Panel on Cost-effectiveness in Health and Medicine, future costs and effects are discounted at 3% per year[11,12] and were allowed to vary independently between 1 and 5% in sensitivity analysis. We constructed the model and performed analyses using computer software (TreeAge Pro 2009, TreeAge Software, Inc., Williamstown, MA). Aspects of the model not covered in detail under Materials and Methods, such as annual mortality probabilities and disease-specific models and variable values, are provided as an electronic Technical Appendix (available as supporting information in the online version of this paper).

Structure of the model

The model has a decision analytic format and is a cohort simulation with separate disease-specific Markov submodels to track the progression of each adverse event. Each version of the model consists of four sections. The first section is a two-armed decision tree: current screens and interventions compared with PRT added to current screens. The second section is focused on two characteristics of blood recipients that influence the likelihood of survival: age at transfusion and immunocompetence. The model can be run using survival data for three age groups: 1) an overall group that reflects the age distribution of the entire transfused population, 2) persons 0 to 39 years of age, and 3) persons 40 years or older. These categories were defined based on available posttransfusion data that indicate that the probability of survival is similar within these latter two broad age categories.[13-15] The population of blood recipients is also separated into those with and without underlying immunocompromise, because a subset of the population requiring transfusion may be immunocompromised due to a medical condition, such as cancer, organ transplantation, or specific infections like HIV. These patients may be at increased risk for more severe adverse outcomes from transfusion.[16] Estimates of the size of the immunocompromised subpopulation are not available for Canada. Data from the National Blood Service in the United Kingdom suggest that as many as 50% of blood recipients are immunocompromised to some degree, with 25% having moderate or severe immunocompromise.[17] We included immunocompromise in our analysis by assuming that 25% of the transfused population has underlying immunocompromise. In the model this patient group is at increased risk of mortality and faster disease progression, which we included as 50% increased posttransfusion mortality in the first year after transfusion, and increased risk of morbidity from each adverse event.

TABLE 1. Percentage of patients receiving transfusions by component combination from British Columbia and Yukon transfusion registry data and assumed risk reduction achieved in the PLTs-and-plasma PRT model

Transfused labile component combinations for 2007 (n = 184,842 components)	*Percentage receiving* each type of a component	Assumed PRT risk reduction adjustment factor (PRT AF)
RBCs only	75.7	None
Plasma-containing transfusions	9.9	Mixed
Plasma only	6.0 (61)	100% of PRT AF
RBCs with plasma (no PLTs)	3.9 (39)	50% of PRT AF
PLT-containing transfusions	14.4	Mixed
PLTs only	8.2 (57)	100% of PRT AF
PLTs and plasma (no RBCs)	0.6 (4)	100% of PRT AF
RBCs with PLTs and plasma	2.1 (15)	50% of PRT AF
RBCs with PLTs (no plasma)	3.5 (24)	50% of PRT AF

TABLE 2. Blood safety interventions and assumed costs

Cost	Cost element	Per donation cost	Range for sensitivity analysis
Current screens	HIV antibody		
	HIV NAT		
	HCV antibody		
	HCV NAT		
	HBV surface antigen		
	HBV core antibody		
	WNV NAT		
	HTLV(I/II) antibody		
	Serologic test for syphilis		
	Total	44.00	33.00-55.00
Bacterial culture after diversion	Bacterial culture[a]	25.00	18.75-31.25
CMV antibody		10.30	7.72-12.88
Gamma irradiation		5.00	3.75-6.25
PRT		100.00	75.00-125.00

The third section of the model differentiates recipients into three groups based on the type of blood components received. Published data consistently show that recipients of PLTs or plasma alone or in combination with RBCs have reduced long-term survival compared to RBC-only recipients.[18,19] Data on the percentage of transfusion episodes that include each blood component type were provided by the British Columbia Provincial Blood Coordinating Office for the year 2007 (Table 1). We assumed that the component combinations transfused in British Columbia and Yukon are representative of those for the entire country. We adjusted the mortality probabilities for PLT recipients and separately for plasma recipients using data published by Wallis and colleagues.[19]

The fourth section of the model addresses transfusion outcomes through detailed accounting of disease and adverse event progression and costs. Details of how each adverse event is modeled are provided in the Technical Appendix.

In the model each transfusion recipient is assumed to experience a single transfusion episode consisting of 1 unit of whole blood or the equivalent as RBCs, PLTs, and plasma. Components are not assumed to come from the same blood donor and so carry the independent risk of each adverse event, but the adverse risks for each component would be mitigated in a single inactivation if whole blood PRT becomes available. The number of transfusions received in an episode has not been modeled. Although the risk of specific infectious agents and of noninfectious hazards varies according to the type of blood component transfused, component-specific residual risks are mostly unreported and are not included in the whole blood PRT analysis.

Effectiveness of PRT

Current blood safety interventions used in Canada are listed (Table 2). In this analysis, we assumed that all of these interventions would continue and that universal leukoreduction would continue. The effectiveness of PRT at reducing the risk of each transfusion-associated adverse event is dependent on the interventions already in place, the likelihood of adverse event occurrence, and the pathogen-specific performance of riboflavin-based PRT. Actual estimates of the effectiveness of PRT under conditions of normal use will only be available after sufficient post-marketing surveillance data have accumulated. To project the effectiveness of PRT we assumed pathogen-specific risk reduction factors (Table 3). Risk without PRT is based on the observed frequency of the event, the yield of screening, or estimated residual risk given current safety measures. For example, the current estimated residual risk of HBV infection is 1 per 153,000 transfusions.[20] Good animal models to demonstrate a specific level of pathogen inactivation for HBV are not available. Studies of riboflavin-based PRT have shown that it can successfully prevent polymerase chain reaction amplification of HBV at concentrations up to 29,400 geq/mL.[21] We assumed that the risk reduction achieved by PRT would be 10-fold greater than current testing (hepatitis B surface antigen and anti-hepatitis B core antigen) giving an estimated residual risk after use of PRT of 1 per 1,530,000.

Costs

The cost of current screens and interventions applied to every donation in total sum to $44.00 per donation (Table 2). No serologic intervention for *T. cruzi* was used in

TABLE 3. Current transfusion risks in Canada and assumed residual risks using PRT

Pathogen or condition	Prevalence or yield of testing if known	Current residual or assumed risk	Source for prevalence or residual risk estimates	PRT risk reduction factor (triangular distribution values for probabilistic sensitivity analysis)	Estimated risk after PRT	Source for PRT performance
Bacteria (PLTs)	1/10,000	1/47,000	Ramirez-Arcos et al.[39] Laupland et al.[40]	50 (10-90)	1/2,350,000	Goodrich et al.[28]
Bacteria (other components)	*	1/50,000	International Forum: Haemovigilance[22]	50 (10-90)	1/2,500,000	Goodrich et al.[28]
CHIKV	*	1/10,000,000	Assumption	1.5 (1.01-1.99)	1/15,000,000	Assumption
CMV	1/40,000	1/80,000	Blajchman et al.[41]	2 (1.25-2.75)	1/160,000	Assumption
FNHTR	1/375	1/750	International Forum: Haemovigilance[22]	2 (1.01-2.99)	1/1500	Assumption
GVHD	*	1/2,400,000	Serious Hazards of Transfusion—Annual Report Summary 2007[42]	2 (1.25-2.75)	1/4,800,000	Assumption
HBV	8.09/100,000†	1/153,000	O'Brien et al.[26,43]	10 (5-15)	1/1,530,000	Assumption
HCV	8.49/100,000†	1/2,300,000	O'Brien et al.[26,44]	10 (5-15)	1/23,000,000	Assumption
HIV	0.41/100,000†	1/7,800,000	O'Brien et al.[26]	10 (5-15)	1/78,000,000	Ruane et al.[27]
HTLV	0.93/100,000†	1/4,300,000	O'Brien et al.[26]	10 (5-15)	1/43,000,000	Assumption
Syphilis	2.8/100,000†	1/2,000,000	Assumption	10 (5-15)	1/20,000,000	Assumption
T. cruzi	*	1/200,000	Based on Bern et al.[45]	20 (10-30)	1/4,000,000	Cardo et al.[29]
TRIM	*	1/150,000	Assumption	1.5 (1.01-1.99)	1/225,000	Assumption
WNV		1/1,000,000	Assumption	10 (5-15)	1/10,000,000	Ruane et al.[27]

* Not known or not applicable.
† S. O'Brien, personal communication, Canadian Blood Services, 2009.
CHIKV = Chikungunya virus.

Canada in 2007, and so no screening costs are included for this agent. CMV antibody and gamma irradiation costs are assumed to be incurred only for the units intended to be transfused to patients with underlying immunocompromise. The estimated cost of PRT ($100 on a per donation or component treated basis) covers the cost to implement the strategy including labor and overhead. In the case of bacterial culture, costs are not incurred for all components as screening is conducted only on PLTs. PLTs comprise 10-15% of all components transfused in Canada.[22] We used a currency converted, inflation-adjusted cost estimate for bacterial culture from the Netherlands[9] to determine a cost of $25 for bacterial culture per PLT preparation.

The potential risks of riboflavin-based PRT include cytotoxicity, genotoxicity, and reduced efficacy of components. It is possible processing mistakes such as under- or over-exposure to UV light may lead to these consequences, but available laboratory and animal model studies conducted to date have found only minimal evidence of these adverse events.[23] It is expected that RBC and PLT efficacy could be reduced by the treatment process, but the one available clinical study of PLTs treated with riboflavin-based PRT did not demonstrate increased transfusion in the PRT treated compared to untreated arms of the trial.[24,25] Nonetheless, we included a component use cost factor in the model to account for potential additional transfusion of components due to the PRT treatment process. We reflected increased component use by assuming a 10% increase in blood component screening and preparation costs that would be necessary to achieve the same therapeutic efficacy in the PRT arm of the model. In sensitivity analysis we varied this additional cost factor between 0 and 20%.

Sensitivity analysis

Both one-way and probabilistic sensitivity analyses were conducted. All sensitivity analyses were performed using the overall (all ages) blood recipient population, age-specific sensitivity analyses were not conducted. In one-way analysis, the influence of a single model variable over the likely range of possible values for that variable is assessed with respect to its impact on cost-effectiveness. The one-way analyses have been aggregated into tornado diagrams, one for the whole blood version of the model and one for the PLTs-and-plasma model, showing the decreasing influence of model variables. The top 18 most influential variables specific to each model are included in each tornado diagram. Uncertain variable values and assumptions such as the residual risk of each adverse event, PRT risk reduction factors, and treatment costs were varied by ±50% of the baseline estimate. The costs of blood safety interventions including PRT and annual posttransfusion mortality were varied by ±25% indicating

TABLE 4. Costs and effects of current interventions, with PRT and incremental cost-effectiveness of PRT by transfusion recipient age group for whole blood PRT

Results category	Costs and effects: Overall (all ages)	0- to 39-year-old group	40 years or older group
Total costs for current screens/interventions ($CAD)	44.77	44.92	44.76
Effects with current screens/interventions (QALY)	7.885246	19.550197	7.311080
Total cost for PRT adoption ($CAD)	158.30	158.31	158.30
Effects with PRT adoption (QALY)	7.885335	19.550463	7.311161
Incremental cost of PRT ($CAD)	113.53	113.40	113.54
Incremental effectiveness of PRT (QALY)	0.000089	0.000266	0.000081
Incremental cost-effectiveness of PRT ($CAD/QALY) (95% CI approximation)	$1,276,000 ($600,000-3,313,000)	$426,000 ($197,000-1,173,000)	$1,405,000 ($653,000-3,693,000)

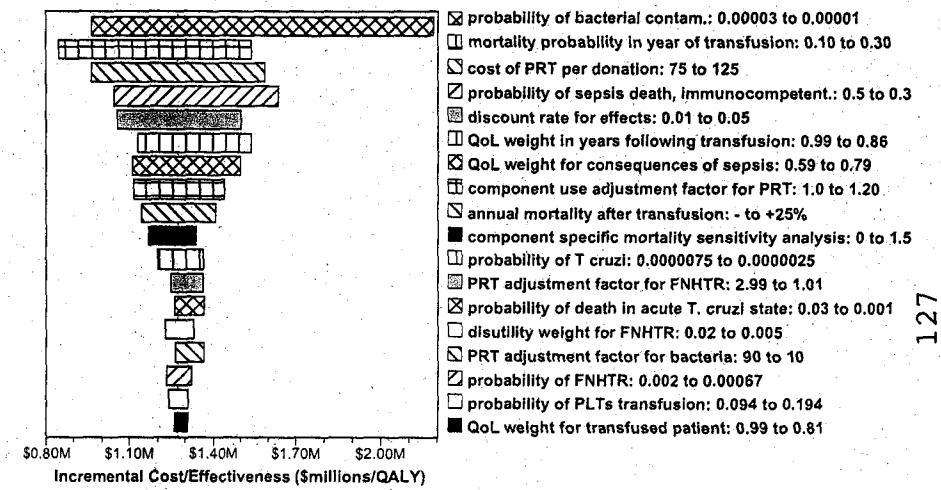

Fig. 1. Tornado diagram showing the range of values used and results from one-way sensitivity analysis of the most influential variables in the whole blood PRT model. Each horizontal bar reflects the range of adjacent values listed on the right. Ranges are provided from low to high or high to low in correspondence with the left and right ends of each horizontal bar. QoL = quality of life.

Several of the factors related to FNHTR, such as the probability of FNHTRs (attributable to residual white blood cells [WBCs] even in leukoreduced blood) and the assumed risk reduction, are influential in the whole blood PRT model. Evidence of the efficacy of UV light and photoactive compound PRT to reduce the occurrence of FNHTRs continues to emerge; both riboflavin-based and amotosalen-based PRT have demonstrated a decrease in these adverse events during active hemovigilance studies.[25,26] It is expected these benefits would be mostly limited to PLTs and RBC preparations. However, in order to assess the cost-effectiveness of PRT without considering a potential FNHTR benefit, we set the residual risk of this event to zero which removes this adverse event and associated costs from the model. The whole blood PRT result increased to $1,364,000/QALY representing nearly a 7% higher cost-effectiveness ratio.

Appropriate values for the current residual risk for pathogens that are not universally screened for are difficult to know with certainty. The influence of two infectious threats, bacteria and *T. cruzi*, was assessed jointly. If the underlying residual risk of bacterial infection for all components is 1 in 75,000 and for *T. cruzi* is 1 in 250,000, the cost-effectiveness ratio for whole blood PRT increases to $1,876,000/QALY (95% CI approximation, 812,000-5,295,000), representing a 47% higher cost-effectiveness ratio.

TABLE 5. Costs and effects of current interventions, with PRT and incremental cost-effectiveness of PRT by transfusion recipient age group for PLTs-and-plasma PRT

Results category	Costs and effects		
	Overall (all ages)	0- to 39-year-old group	40 years or older group
Total costs for current screens/interventions ($CAD)	44.37	44.55	44.36
Effects with current screens/interventions (QALY)	7.838611	19.458178	7.266893
Total costs for PRT adoption ($CAD)	72.43	72.55	72.42
Effects with PRT adoption (QALY)	7.838631	19.458243	7.266911
Incremental cost of PRT ($CAD)	28.06	28.00	28.07
Incremental effectiveness of PRT (QALY)	0.000020	0.000065	0.000018
Incremental cost-effectiveness of PRT ($CAD/QALY) (95% CI approximation)	1,423,000 (834,000-2,818,000)	429,000 (256,000-805,000)	1,579,000 (965,000-3,174,000)

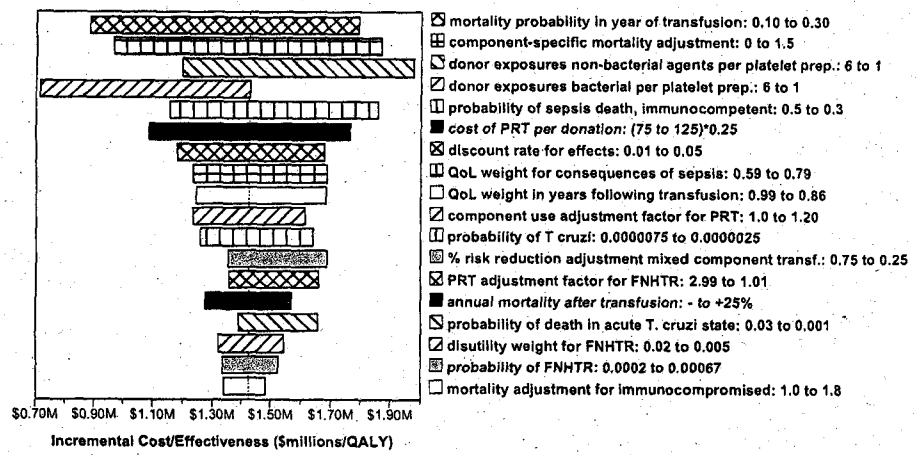

Fig. 2. Tornado diagram showing the range of values used and results from one-way sensitivity analysis of the most influential variables in the PLTs-and-plasma PRT model. Each horizontal bar reflects the range of adjacent values listed on the right. Ranges are provided from low to high or high to low in correspondence with the left and right ends of each horizontal bar. QoL = quality of life.

PLTs-and-plasma PRT

We report the costs and consequences of PLTs-and-plasma PRT compared to current screens and interventions used in Canada (Table 5). When evaluated on an all-transfusions basis, the incremental cost-effectiveness of PLTs-and-plasma PRT is $1,423,000/QALY (95% CI approximation, 834,000-2,818,000). The mean gain in quality-adjusted life expectancy is 11 minutes per patient; even though the incremental cost is also lower, the cost-effectiveness of PLTs-and-plasma PRT compared to current screens and interventions is less cost-effective than for whole blood PRT. This result is expected because of the decreased overall risk reduction achieved using PLTs-and-plasma PRT compared to whole blood PRT. The patterns of cost-effectiveness for older and younger transfusion recipients are similar to those seen for whole blood PRT with estimated cost-effectiveness of $429,000/QALY (95% CI approximation, 256,000-805,000) in transfusion recipients 39 years or younger in age.

PLTs-and-plasma PRT sensitivity analysis

In one-way sensitivity analysis, the factors that are influential in the PLTs-and-plasma PRT model in order of decreasing influence are mortality in the year of transfusion, mortality associated with type of blood components received, the number of donor exposures per pooled PLT preparation, the probability of death due to sepsis, the cost of PRT per donation, and the discount rate for effects (Fig. 2). We examined the sensitivity analysis results with respect to donor exposures in more detail by evaluating the influence of the percentage of single-donor PLT (apheresis) collections on the cost-effectiveness of PRT based when the pooled PLT method is either buffy coat or

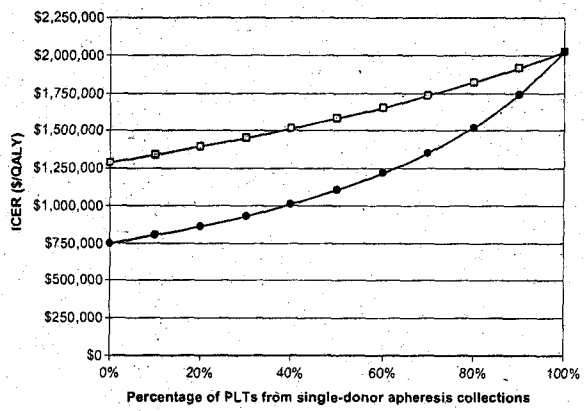

Fig. 3. Influence of the percentage of PLT preparations from single-donor apheresis collections on the incremental cost-effectiveness ratio (ICER) of PLTs-and-plasma PRT compared to current screens and interventions. (—□—) Buffy coat random-donor PLTs; (—●—) plasma-rich random-donor PLTs.

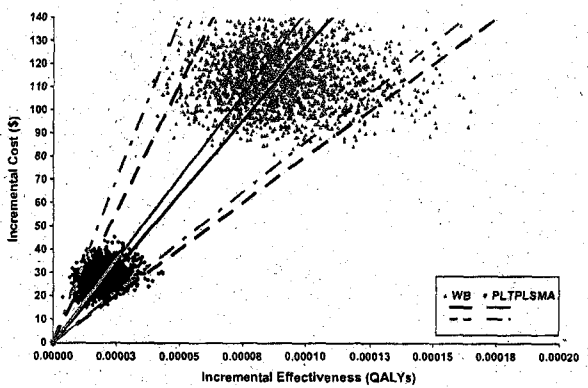

Fig. 4. Incremental cost and effectiveness scatterplots from 2000 probabilistic simulations for whole blood PRT compared to current screens and PLTs-and-plasma PRT compared to current screens. Solid lines represent the mean incremental cost-effectiveness ratio and dashed lines represent the 2.5 and 97.5% values of the cost-effectiveness ratios from the distributions of the simulations with points for whole blood PRT shown in gray and points for PLTs-and-plasma PRT in black; lines are in reverse grayscale so that they can be visualized on top of each corresponding cloud of points.

plasma-rich preparations (Fig. 3). When no PLTs are prepared using single-donor collection methods, the incremental cost-effectiveness of PLTs-and-plasma PRT is dependent on the pooled PLT preparation method. The residual risk of bacteria in plasma-rich PLT preparations is higher than in buffy coat or apheresis preparations; thus PRT treatment of PLTs prepared using this method yields greater benefit and a more favorable cost-effectiveness profile. As the percentage of single-donor apheresis collections increases, the cost-effectiveness ratio increases in a nonlinear manner, and at 100% single-donor collections, the ratio exceeds $2,000,000/QALY.

Probabilistic sensitivity analysis

The cloud diagrams of the incremental costs and effects, generated from probabilistic sensitivity analysis of whole blood PRT and PLTs-and-plasma PRT, provide an indication of overall uncertainty. As expected, the simulation result plots show that both the incremental cost and the incremental effectiveness of whole blood PRT are higher than for PLTs-and-plasma PRT (Fig. 4). In addition, the possible values for incremental effectiveness of whole blood are more uncertain than those for PLTs-and-plasma PRT as demonstrated by the greater horizontal dispersion of individual simulation results.

DISCUSSION

In this analysis, we assessed the cost-effectiveness of PRT for whole blood focused on the direct cost of blood safety interventions and medical care. While such a technology is currently unavailable, clinical studies of candidate technologies are under way. We estimated the cost-effectiveness of adding whole blood PRT in Canada to current screens and interventions to be $1,276,000/QALY. Recognizing that RBC risks would not be mitigated by currently available PRT, we modified the model and used it to estimate the incremental cost-effectiveness of adding PLTs-and-plasma PRT generating a result of $1,423,000/QALY compared to current screens and interventions. The cost-effectiveness of a PLTs-and-plasma PRT was most dependent on the PLT collection

and preparation methods used by blood centers. The most important factors driving better cost-effectiveness results are the risk of bacterial contamination and other infections resulting from higher donor exposures in pooled PLTs. Since Canadian blood centers collect and prepare PLTs via single-donor apheresis or buffy coat preparation methods PRT technology will be less cost-effective in Canada than in countries which primarily supply plasma-rich PLTs.

The analyses reported here with respect to the cost-effectiveness of PLTs-and-plasma PRT have focused on the mix of PLT preparation methods used by Canadian Blood Services. HemaQuebec, the other blood operator in Canada, which serves the Province of Quebec, uses a different combination of preparation methods. Approximately 80% of PLTs collected by HemaQuebec are from single-donor apheresis collections with the remainder of PLTs produced in 2007 being plasma-rich PLTs averaging five donor exposures. This combination of PLT preparation methods leads to a result of $1,389,000/QALY (95% CI approximation, 713,000-2,944,000) for PLTs-and-plasma PRT. The same percentages of single-donor apheresis collections and buffy coat–derived instead of plasma-rich PLTs as now used by HemaQuebec would lead to a result of $1,775,000/QALY (95% CI approximation, 1,021,000-3,364,000) for PLTs-and-plasma PRT.

On the one hand, if PRT were to be adopted it could be more cost-effective than reported here. The residual risk of transfusion-transmitted viruses of greatest concern is already very low, particularly in Canada, due to the efficacy of current screens and interventions, and in this analysis we did not assume that any of these screens or interventions would be discontinued or modified. However, it is likely that blood collection agencies would seek changes. Interventions that potentially could be eliminated include bacterial culture for PLTs and gamma irradiation. Interventions that could be modified include universal testing for WNV and HTLV. For example, with an available whole blood PRT, discontinuation of testing for WNV or elimination of outbreak season individual donation nucleic acid testing (NAT) might be possible due to the more than 5 logs kill achieved using riboflavin-based PRT,[27] and discontinuation of bacterial culture of PLTs also seems feasible for either a whole blood or a PLTs-and-plasma PRT.[28] Each of these changes would favorably alter the incremental cost-effectiveness of PRT. Avoidance of *T. cruzi* screening also seems likely given the observed ability of riboflavin-based PRT to inactivate this and other parasites.[29]

On the other hand, if PRT were to be adopted it could be less cost-effective than reported here. The potential for increased component use, adverse events for blood recipients, increased treatment costs, and increased total costs to the health care system could result from the use of riboflavin-based PRT. For example, the formation of neoantigens is possible. Based on other PRT methods that do not use riboflavin as the photoactive compound, this could be an issue for RBC units prepared from PRT-treated whole blood.[30] Another possible concern is for PLTs treated with PRT where clinical studies including the MIRACLE trial have shown that the corrected count increment (CCI) is lower for PRT-treated compared to untreated PLTs.[25] Lower CCIs could lead to increased risk of bleeding.

The current analysis does not consider other infections such as human parvovirus B19, *Babesia*, or the undefined value of PRT in preventing transfusion transmission of unknown or reemerging pathogens. The safety and health economic benefit of PRT in the face of an emerging agent could be considerable. Most infectious agents (except prions) would likely be at least partially susceptible to PRT. We elected not to include such an agent in this analysis because it is relatively easy to construct the set of assumptions regarding the pathogen so that results create a very attractive economic profile for PRT. Adopting PRT could be thought of as insurance against the risk of a future large epidemic of an unknown virus, bacteria, or parasite transmitted to transfusion recipients. In the face of a prevalent emerging pathogen it is highly likely that whole blood PRT would become much more cost-effective than PLTs-and-plasma PRT alone because of the reduction of the threat in all blood components.

The residual risk of many infectious or noninfectious threats is important for the cost-effectiveness of PRT, but limited data are available on objectively measured risks of many potential adverse events associated with transfusion. For example, the morbidity and mortality of bacteria-contaminated RBCs are not well defined. Quebec hemovigilance data report that bacterial contamination of RBCs occurs with a prevalence as high as 1 in 36,000,[22] whereas others have estimated the risk to be approximately 1 in 250,000 or lower.[31] The frequency with which such units result in detectable clinical morbidity or mortality affects the calculation of cost-effectiveness. In our analysis we assumed that the baseline residual risk of bacterial contamination was 1 in 50,000 and that 40% of nonimmunocompromised patients who received non–PRT-treated components containing bacteria would develop fatal infections. Active capture of data via hemovigilance may provide reliable estimates, but the availability of more precise data would improve the accuracy of the analysis of infectious risks across all blood component types. The importance of current residual risks of infection was also exhibited in other sensitivity analyses. When we reduced the risk of bacteria and *T. cruzi* at the same time, the overall cost-effectiveness ratio of whole blood PRT increased by 47%.

Our analysis of the cost-effectiveness of whole blood PRT has important limitations. To model the question of the cost-effectiveness of PRT we had to make several simplifying assumptions. In one simplification, we assumed

that transfusion episodes are one-time events with exposure to one whole blood unit or its equivalent components. This does not reflect clinical practice because transfused patients may receive multiple transfusions on different occasions, and even in the same transfusion episode patients could receive anywhere from 1 unit of any component type to dozens of units. The model does not account for transfusion of different numbers of components or multiple transfusion episodes. The survival of recipients of a large number of units in a single transfusion episode is significantly lower than recipients who receive a smaller number of units.[18,19] If we were able to account for this in our model, the cost-effectiveness ratio of PRT would be larger than reported here.

A key factor related to blood recipients that we cannot address in the analysis is the possibility that current post-transfusion survival across all component types, but particularly for PLT recipients, may be lower than the survival probabilities we used. Changes in practice patterns such as increased use of PLTs in patients with poor prognosis and reduced life expectancy would lead to larger cost-effectiveness ratios. While clinicians may recognize that current survival rates are lower for patients who receive specific blood components, only published longer-term survival data are appropriate to include in analyses of the cost-effectiveness of blood safety interventions. By necessity long-term posttransfusion survival data relies on transfusions that may have occurred as long as 20 years ago. Policy analyses that rely on posttransfusion survival data cannot circumvent this limitation.

Another potential limitation is the inclusion of some noninfectious adverse events such as postoperative infection that might occur as a result of TRIM. The debate is ongoing as to whether this is a real phenomenon leading to identifiable health consequences.[32,33] Nonetheless, assuming that the phenomenon is real the idea that TRIM is influenced by WBCs is less controversial. PRT will inactivate WBCs that are not removed by leukoreduction, preventing antigen presentation that could trigger recipient immune system responses. In this analysis, we assumed that PRT could achieve a 50% reduction in the residual risk of occurrence of TRIM. Moreover we modeled postoperative infection attributable to TRIM by assuming that the risk reduction could be as low as 1% or as high as a twofold increase. In sensitivity analyses, no aspect of TRIM was influential including the assumed risk reduction achieved using PRT.

Another possible limitation is that there is currently only emerging clinical data to support a reduced rate of FNHTR after the adoption of PRT. However, the mechanism for at least some FNHTRs is thought to include residual WBCs and PRT could reduce the frequency of FNHTR as has been observed in clinical studies. These benefits would be expected in components that carry higher risks of FNHTRs: PLTs and RBCs. In the model, FNHTRs are relatively high-probability and low-cost events that are somewhat influential. If FNHTR risk reduction is excluded from the model, for whole blood PRT the cost-effectiveness ratio increases by approximately 7% (meaning PRT is less cost-effective when FNHTRs are excluded). However, the 7% effect on the ratio shows that FNHTRs are not overly influential with respect to estimated cost-effectiveness.

The PLTs-and-plasma PRT model also has important additional limitations. Chief among them is that, except for donor exposures associated with PLTs, the model does not account for differential risks associated with different component types. For example, the model assigns the risk for plasma equal to that of PLTs for the transmission of enveloped viruses such as CMV or HTLV and for FNHTRs risk reduction. If other infectious or noninfectious threats differentially partition to specific labile blood components, then the model does not fully reflect these differential risks. However, we did account for one of the most important influences on the residual risk of bacterial contamination—the method of PLT preparation[34]—and showed that the cost-effectiveness of PLTs-and-plasma PRT varies depending on PLT collection and preparation methods.

Another important consideration is how we modeled the residual risk of each adverse event in the PLTs-and-plasma PRT analysis. The infectiousness of a blood component is dependent on multiple factors; these include the stage of donor's infection at the time of donation (viral load and antibody levels), the recipient's immune system, and the interaction between the two, among other factors.[35,36] An additional factor for component-specific use of PRT is also present and is related to the approach we used for modifying the residual risk of transfusion complications based on the combination of components transfused. For persons who receive transfusions that include both pathogen reduced and nonreduced components (RBCs), the residual risk of an adverse event is adjusted to reflect a blend of the lower risk in the pathogen-reduced component coupled with the residual risk of the nonreduced component.

Economic evaluations of similar PRT processes have previously been reported. For example, studies of the cost-effectiveness of amotosalen-based PRT for PLTs focused on patients with specific conditions requiring transfusion. A study conducted in the US setting reported results for four different patient groups (pediatric acute lymphocytic leukemia, hip arthroplasty, coronary artery bypass grafts, and adult non-Hodgkin's lymphoma) and with and without bacterial culture. Depending on the patient population, baseline results ranged from $4.8 to $23.0 million/QALY with bacterial culture and $1.4 to $4.5 million/QALY without bacterial culture for apheresis PLTs.[3] For pooled PLTs, the cost-effectiveness was $1.0 to $6.0 million/QALY under assumptions of low fatality attributable to bacterial

less uncertainty. All remaining model variables were varied within specifically defined ranges based on published literature or standardized methods.

Probabilistic sensitivity analysis (Monte Carlo simulation) allows for an overall assessment of the uncertainty given the range of possible values or probability distribution of each variable used in the model. We ran 2000 computer simulations of each analysis and obtained an approximation of the 95% Confidence Interval (CI) for the cost-effectiveness ratio, represented by the 2.5 and the 97.5 percentiles of the distribution of results from each simulation.

PLTs-and-plasma PRT

We modified the whole blood model to estimate the cost effectiveness of PRT for the technology that is currently approved for use in some European jurisdictions, PLTs-and-plasma PRT. To do so we added an additional section to the model focused on PLT preparation methods. As in the whole blood model, transfusions containing PLTs are separated from transfusions not containing PLTs; this design also allowed us to include the PLT preparation method (single donor or pooled PLTs). We assumed single donor PLTs represent 25% of the total preparations and buffy coat PLT preparations represent 75% of the total preparations (percentages that approximate the preparations issued by Canadian Blood Services). The baseline risk for PLTs in this version of the model applies to single donor preparations and a donor exposures factor is included to increase the baseline risk for each adverse event according to the number of donor exposures for recipients of pooled PLTs. In the PLTs-and-plasma analysis, except for bacterial contamination, we assumed that the risk of plasma was the same as that of PLTs and that PRT reduced those risks to the same degree in both products.

Except for transfusion episodes that include both PLTs and plasma, which are included in the PLTs arm of the model, transfusions that include plasma are considered in another separate arm of the model. PLTs and plasma account for approximately 25% of the components transfused in Canada[22] so the effective cost of PRT on an all transfusions basis would be approximately 25% of the cost of whole blood PRT if fixed costs are not considered. However, the risk reduction achieved for this cost is not 25% of the overall risk because different combinations of blood components are transfused to patients. To estimate the average expected effectiveness of PLTs-and-plasma PRT from the perspective of all components transfused, we adjusted the risk reduction achieved using whole blood PRT. We assumed that patients receiving RBC only transfusions would continue to have the same residual risk with no benefit from PRT. For patients receiving transfusions that are exclusively PLTs and/or plasma, representing nearly 15% of the transfused population, we assumed the risk reduction would be equivalent to the overall risk reduction achieved for whole blood PRT (Table 1). For the remaining 10% of the transfused patients receiving combinations of RBCs, PLTs, and/or plasma transfused, we assumed half of the current risk would be mitigated, meaning that the residual risks for recipients of RBCs with PLTs and/or plasma is the average of the current residual risk and the expected lower residual risk obtained by the use of PRT for PLTs and plasma.

RESULTS

Whole blood PRT

We report the estimated average quality-adjusted life expectancy for the transfused population overall and for specific recipient age groups, the average healthcare-related costs incurred per donation with current interventions, and incremental cost-effectiveness of whole blood PRT compared to current interventions used in Canada (Table 4). For all recipients, on average individuals are expected to gain approximately 47 quality-adjusted life minutes. In a cohort of 100,000 transfusion recipients this would represent a gain of approximately 9 quality-adjusted life years. The incremental cost-effectiveness of whole blood PRT compared to current screens and interventions is $1,276,000/quality-adjusted life-year (QALY; 95% confidence interval [CI] approximation 600,000-3,313,000). For transfused patients over 40 years of age, the incremental cost per QALY saved is higher, but similar to the overall result given that the average age of transfusion is approximately 65 years in Canada. However, for recipients 39 years of age or younger the incremental cost-effectiveness is $426,000/QALY (95% CI approximation 197,000-1,173,000).

Whole blood PRT sensitivity analysis

One-way sensitivity analyses are shown as a tornado diagram for the overall recipient population (Fig. 1). In order of decreasing influence, the model is most sensitive to the risk of bacterial contamination, annual mortality in the year of transfusion, the cost of PRT per donation, the probability of death due to sepsis, the discount rate for effects, and health state quality-adjustment preference weights for patients requiring transfusion in the years following transfusion. Bacterial contamination risk is the most influential variable and a low risk for bacteria (1:100,000) leads to a cost-effectiveness of nearly $2,200,000/QALY. The impact of posttransfusion mortality in the year of transfusion is shown in the second horizontal bar of the figure. Low annual mortality would lead to an incremental cost-effectiveness of whole blood PRT of $850,000/QALY, whereas high annual mortality would lead to an incremental cost-effectiveness of whole blood PRT of $1,550,000/QALY.

contamination and improved to $460,000 to $1.8 million/QALY assuming higher fatality due to bacterial contamination. Similar analyses for specific patient populations were conducted for Belgium, the Netherlands, and Japan.[4-6] Another study from the Netherlands found the cost-effectiveness of PRT for PLTs to be €2.8million/QALY (approx. $3.6 million/QALY) when added to bacterial culture and €382,000/QALY (~$497,000/QALY) without bacterial culture in random-donor PLTs for the average recipient.[9] The majority of these results suggest a cost-effectiveness of PRT that is less efficient than we report here. These previous analyses did not include the broad range of infectious and specific noninfectious threats that were included in our analysis. In addition, many other analysis assumptions were different, making direct comparison of our results to these studies difficult. Nonetheless, one common thread is apparent: bacterial contamination is the most important known adverse event that PRT addresses.

Our results also indicate that the age of the patient population is an important determinant of the cost-effectiveness of PRT. In the previously published cost-effectiveness studies of PRT for PLTs, the best incremental cost-effectiveness ratio was always evident for the pediatric population.[3-6] We conducted our analyses focused on different age groups to show that there are subgroups of transfused patients where PRT has a relatively attractive economic profile. These analyses are intended to indicate that for the expected benefits to accrue to subgroups of patients, it may be necessary to adopt PRT for all blood collections. Only if separate blood supply inventories were kept could recipient-specific use of PRT be an option. The complexity of maintaining separate inventories on such a large scale has not been carefully studied, but in many settings is likely not feasible.

Model variables related to the age and health status of the transfused population had important influence on cost-effectiveness results. In addition, the discount rate for effects was influential. Discount rates reflect time preference for health and money, with higher preference given to having health and money today as opposed to in the future. These model variables are not directly related to PRT and are often influential in analyses of any blood safety intervention. Moreover, the influence of life expectancy, quality of life, and discount rates is applicable to all cost-effectiveness analyses regardless of medical practice area. Both appropriately accounting for quality-adjusted life expectancy across broad population groups and determining what discount rates to use are unresolved methodologic controversies in health economics. While the influence of these variables in the analysis is evident, whether these variables have meaning with respect to decision making about PRT adoption is unclear.

Relative to the cost-effectiveness of interventions already in use in Canada and many other developed countries, such as minipool HIV and HCV NAT, which exceed $1.5 million/QALY in the United States,[37,38] the estimated preadoption cost-effectiveness of whole blood PRT and of PLTs-and-plasma PRT is consistent with established thresholds for value in blood safety. In developed countries that have very low risk of transfusion transmission of infectious diseases, even if some current screens or interventions are discontinued or modified, it is unlikely that any PRT will approach an incremental cost-effectiveness ratio threshold of $100,000/QALY. Although expensive on a cost-per-QALY basis in comparison to interventions adopted in other sectors of health care, given blood safety expectations that lean toward "zero risk" for infectious threats, commonly accepted thresholds that are regarded as cost-effective in clinical practice do not seem relevant. There continue to be multiple different hazards associated with transfusion including those considered in this analysis and other ones not amenable to the use of PRT such as transfusion-related acute lung injury and transfusion of the wrong blood type. This cost-effectiveness analysis provides additional information that was not previously available and may help to support decisions regarding this technology within the context of competing interventions and other threats to the safety of transfusion.

CONFLICT OF INTEREST

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SUPPORTING INFORMATION

Additional Supporting Information may be found in the online version of this article:

Technical Appendix. The cost effectiveness of pathogen reduction technology as assessed using a multiple risk reduction model.

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わが国における感染性因子低減化技術により生じる便益について（要約）

東京医科歯科大学大学院
医歯学総合研究科　環境社会医歯学系専攻
医療政策学講座　政策科学分野
河原　和夫

方法

輸血用血液製剤に感染性因子低減化工程を加えた時にいかなる費用便益を生じるかについて、感染性因子低減化技術が確立している血小板製剤を含むすべての輸血用血液製剤による感染を想定した。

経済計算は、疾病や障害を有する者の生存期間を無価値的に捉えたり結果が感覚としてわかりにくいQALY(Quality Adjusted Life Year)ではなく、具体的な金額により便益を算定した。

保管検体で陽性が確認された過去約10年間の感染性因子の件数から1年当たりの予想される感染事例を算定し、感染が成立した場合の予後の推移等をもとに「直接医療費」「休業損失」および「早世による遺失利益」を求めることにより便益を算定した。HBV、HCV、HIV、細菌感染、ヒトパルボウイルスB19、HEVが対象感染性因子である。

結果

平均的勤労者（平均年齢41.1歳、年収294.5千円）をモデルとすると感染性因子低減化技術の導入により削減できる年間の「直接医療費」は24,298,785円、「休業損失」は420,150円となった。加えて「早世による遺失利益」は1,083,669円となり、合計25,852,698円が便益となる。

考察

わが国ではHBV感染者が多いが、これは「直接医療費」と「休業損失」の大半がHBVを原因としていることにも表れている。成人のHBV感染の場合、慢性化しにくいことから1年目の医療費等の出費が増大するが、以後ほとんど影響を及ぼさない。HCVについては、慢性化する割合が高いものの、HBVに比べると絶対数が少ないことにより、同様に経済的影響は少ないものとなった。HIVについても同様である。他の感染性因子による感染が考えられる事例についても数が少なく慢性化しないものが多いことから便益は小額になったものと考えられる。

まとめ

本稿では新興・再興感染症の流行の問題を考慮していない。いかなる感染症まで対象を広げて経済計算を行うべきか、そして血液の検査や製造工程にどの程度の経済資源を投入すべきかについても議論が必要であろう。

わが国における感染性因子低減化技術により生じる便益について

東京医科歯科大学大学院
医歯学総合研究科　環境社会医歯学系専攻
医療政策学講座　政策科学分野
河原　和夫

緒言

高齢化により高騰する医療費をいかに抑制するかが、政府の主たる政策的課題であるが、医療技術の進歩も医療費を嵩じさせる要因の１つである。

現代の医療技術は、超音波、CT、MRI、PET などの診断治療技術と人工呼吸器、人工臓器、経静脈栄養、ICU などの延命的技術が主体となっている。対象疾患も長期・慢性の経過を示す生活習慣病である。治療期間が長いうえ、基盤は光学技術や電子工学などの最先端の技術で、しかも開発途上にあるため短期のサイクルで更新されていくものである。検査や血液製剤の製造技術も同様に高度かつ高価な技術基盤に基づくものである。NAT やウイルス等の感染性因子低減化技術もこうした技術に属する。しかも、旧来の検査・製造技術を併存しながら最新技術を付加しているのである。

血漿分画製剤の不活化は技術としてシステムとして確立している。論点は、輸血用血液製剤への感染性因子低減化技術の導入である。

検査技術としての NAT は、血液中のウイルスを高精度で検出する技術であり、血液製剤の信頼性の向上に大きく寄与している。しかし、費用便益面から考えると問題を有している。NAT という大規模技術の導入に当たっては医学面のみではなく経済的観点からの検討ならびに導入後の多角的評価が必要であった。しかし、それは十分にはなされてこなかった。感染性因子低減化技術も費用便益的観点からの分析・評価が十分とは言えない。こうした大規模技術は社会経済的インパクトが大きいにもかかわらず、医学的観点からの論議のみが先行し、そのほかの各分野の専門家、国民、行政、関係者を交えた議論の展開や合意の形成が欠落しているのである。

本稿は、感染性因子低減化技術などの最新技術を導入することが、医療や社会にどのようなインパクトをもたらし、導入した技術をシステムとして維持していくために検討を要する課題の一部を整理したものである。

輸血用血液製剤の安全性確保のために問診の強化や NAT が行われている。また、血漿分画製剤には不活化が製造工程で加えられ、安全性を飛躍的に向上させている。現在、これに加えて輸血用血液製剤に対しても不活化を行うべく議論が進んでいる。しかし、NAT をはじめとする新技術の導入は一般に高コストとなるものである。

そこで、輸血用血液製剤に感染性因子低減化工程を加えた時にいかなる便益を生じるかを調べた。但し、感染性因子低減化技術が確立している血小板製剤以外の製剤も含むすべての輸血用血液製剤による感染を想定した。

なお、経済計算を行っている多くの論文では、生活の質（QOL）で重みづけを行い生存期間に加えて生活の質の評価もできる QALY(Quality Adjusted Life Year)を求めている。しかし、QALY は健康な人が１年生きた場合の生存期間を 1QALY とするのに対し、脳卒中などで身体が不自由になった場合の生存期間を健常人が１年生きる価値があるのを 0.3QALY に補正するなど障害の重み付けに主観が入ることや、疾病や障害を有する者の生存期間を無価値的に捉える問題がある。加えて結果が感覚としてわかりにくいことから、本稿では多くの方が直観的にイメージしやすいように具体的な金額により便益を算定する方法を採用した。

方法

1. NAT を行っている HBV、HCV および HIV について

輸血用血液製剤の製造の際に感染性因子低減化工程を導入することは、NAT の検出感度以下の HBV、HCV および HIV の混入による患者への感染を防ぎ得たことによる不必要な医療費出費、外来や入院にともなう休業損失、早期死亡による遺失利益を減少させるという社会経済効果をもたらすものと考えられる。

日本赤十字社には輸血後感染症情報が医療機関等から寄せられ、保管検体をもとに原因ウイルスか否か同定することになる。これら報告のうち、検体陽性が確認された件数をもとにウインドウ期等のために NAT では検出できないケースが、これら３つのウイルスによる感染を引き起こすものと想定した（**表１**）。これらの感染は輸血用血液製剤に不活化工程を導入した場合、被害を防ぐことができるものとして社会的な観点から「直接医療費」「休業損失」および「早世による遺失利益」の計算を行った。具体的には、①感染により各段階に病態が進行した際の“直接医療費”、②外来や入院に費やす時間に起因する“休業損失”、そして③期待寿命を待たずして死亡した“早世による遺失利益”を社会的コストとして算定した。

HBV については急性肝炎のステージで病態が終息するとし、HCV については慢性肝炎、肝硬変、肝細胞がんへの移行確率を Markov 連鎖モデルをもとに算出した。

HIV については予後が近年著しく向上したことから、算定する今後 10 年間においては死亡がなく、定常的な状態にあるものとした。なお、これらウイルスの陽性血液を輸血された場合、必ず感染が成立するものとした。

また、2008 年８月より新 NAT システム（抽出・検出機器 cobas s401　試薬 TaqScreen MPX）により 20 プールで HBV、HCV、HIV に関する検査が行われている。それ以前の NAT の検出感度と現在のそれとの差を無視するが、2000 年～2010 年７月までの約 10 年

余の間に献血が原因と考えられる輸血後感染症は、HBV 95 例、HCV 3 例、HIV 1 例であった。これを年間発生数で表すと下記のようになる（**表1**）。計算は、年間発生件数を用いて行った。

表1　検体陽性数をもとに算定した年間感染件数

ウイルス名	2000 年～2010 年 7 月までの報告数	年間報告件数
HBV	95	8.98
HCV	3	0.28
HIV	1	0.09

(1)HCV 感染の Markov 連鎖モデル

HCV 感染後の患者は、急性肝炎→キャリアー→慢性肝炎→肝硬変→肝細胞癌という自然推移をとることが多いが、必ずしもそのような推移をとるわけではなく、中には慢性肝炎から肝硬変を経ずに肝細胞癌を罹患するという症例も見られる。また、肝硬変の症例は肝細胞癌を合併する前に死亡する例も見られることから、この推移は一義的ではない。このような疾患の自然推移をモデリングするために HCV 感染者の予後データ**[1]**、**[2]**、**[3]**、**[4]**をもとに Markov 連鎖モデルを用いて、NAT 後 10 年間の遷移確率を計算し、それぞれの状態において要する医療費を当てはめた。

Markov 連鎖は別名 Markov 過程とも呼ばれる確率過程のことである。すなわち、未来の挙動が現在の値だけで決定され、過去の挙動と無関係であるという性質を持つ確率過程である。例えば、ある慢性肝炎例が肝硬変を発症する確率が、その症例がどのように（例えばどの時点で）HCV に感染したかと無関係であるとき、この確率過程は Markov 性を有するという。

上記は数式により以下のように表すことができる。時点 i における集団の状態を、

$$\mathbf{S}_i = \begin{pmatrix} s_{i1} & s_{i2} & s_{i3} & s_{i4} & s_{i5} & s_{i6} \end{pmatrix}$$

とする。ここでベクトルの要素は疾患の推移（HCV 非感染、キャリアー、慢性肝炎、肝硬変、肝細胞癌、死亡）にそれぞれ対応する。次に、時点 i におけるそれぞれの状態の人数を、

$$\mathbf{L}_i = \begin{pmatrix} l_{i1} & l_{i2} & l_{i3} & l_{i4} & l_{i5} & l_{i6} \end{pmatrix}$$

とする。時点の経過とともに、ベクトルの各要素である各状態の人数は変動する。マルコフ連鎖モデルでは、この変動を推移確率行列という行列で確率的に規定する。

$$\mathbf{P} = \begin{pmatrix} p_{11} & p_{12} & 0 & 0 & 0 & 0 \\ 0 & p_{22} & p_{23} & 0 & 0 & 0 \\ 0 & 0 & p_{33} & p_{34} & p_{35} & 0 \\ 0 & 0 & 0 & p_{44} & p_{45} & p_{46} \\ 0 & 0 & 0 & 0 & p_{55} & p_{56} \\ 0 & 0 & 0 & 0 & 0 & 1 \end{pmatrix}$$

ここで、p_{ij} は i 番目の状態から j 番目の状態に推移する確率（推移確率）を意味する。例えば、p_{23} はキャリアーが次の時点に慢性肝炎を発症する確率を示している。上の推移行列では、疾患は進行するものの治癒することはなく（対角成分よりも下の推移確率が全て 0）、各時点で状態が推移する確率が時点によらず一定であることを仮定している。

上記のマルコフ連鎖モデルにより、時点 i におけるそれぞれの状態の人数は、$\mathbf{L}_0$ を初期状態の人数としたとき、$\mathbf{L}_i = \mathbf{L}_{i-1}\mathbf{P} = \mathbf{L}_0\mathbf{P}^i$ で表すことができ、マルコフ連鎖モデルにおける推移行列を下記のように定めることができる**[1]**。

たとえば、1 年単位の推移行列を下記のように推定すると、

$$\mathbf{P} = \begin{pmatrix} 0.99948 & 0.00052 & 0 & 0 & 0 & 0 \\ 0 & 0.977 & 0.023 & 0 & 0 & 0 \\ 0 & 0 & 0.957 & 0.03 & 0.013 & 0 \\ 0 & 0 & 0 & 0.923 & 0.043 & 0.034 \\ 0 & 0 & 0 & 0 & 0.697 & 0.303 \\ 0 & 0 & 0 & 0 & 0 & 1 \end{pmatrix}$$

この推移行列に対して、初期条件を $\mathbf{L}_0 = \begin{pmatrix} 1 & 0 & 0 & 0 & 0 & 0 \end{pmatrix}$ としたとき、年次の条件の推移は**表9、10**の通りである。この $\mathbf{L}_0$ に現時点での各病態の人数を代入すれば、将来における HCV の自然経過をモデル化できる。

2．輸血後副作用報告があったその他の感染症

日本赤十字社に報告があったその他の感染症として以下のものがある（**表2**）。

これらについても年間発生件数をもとに、「直接医療費」「休業損失」および「早世による遺失利益」の計算を行った。但し、「細菌」「ヒトパルボウイルス B19」「HEV」による感染は慢性化することなく、急性期で終息するものとした。

表２　輸血後副作用報告があったその他の感染症

（製剤陽性例　報告期間　1998～2007 年）

	確認件数	感染者数／年
細菌	8	0.8（うち死亡が 0.2）
梅毒	0	0.0
HTLV-1	0	0.0
ヒトパルボウイルス B19	10	1.0
HEV	5	0.5

仮定としては、感染性因子低減化工程を取り入れた場合と取り入れなかった場合を比較して、取り入れなかった場合に 1 年間に血液製剤を輸血され感染が成立した患者群を 10 年間追跡した場合の「直接医療費」「休業損失」および「早世による遺失利益」の総コストを算定し、これを便益とした。

また、計算の対象とした年齢は、わが国の標準的な勤労者とした。当該年齢の平均賃金は、男女計 294.5 千円(平均年齢は 41.1 歳)であった。

「休業損失」については、入院の場合 1 日、外来通院の場合 0.5 日の損失があったものと仮定した。

「直接医療費」については、「2005 年疾患別医療費データ」（津谷 2007 年）、平成 20 年の厚生労働省の「患者調査」、「社会医療診療行為統計」を用いて算定した。

「早世による遺失利益」については、死亡した時点から 65 歳（収入が得られる何らかの職業に従事している上限年齢を 65 歳に設定）までの間の残余年数を求め、昨今の経済情勢を加味して賃金上昇はこの期間ないものとして算定した。

これら 3 つの因子の今後 10 年間の値は、民事事件で損害額の算定に用いられるホフマン法を採用し、現在価値に置き換えた。ホフマン法については通常法定利息（割引率）5%を用いるところ、昨今の情勢に鑑み 3%として計算した **（注：参照）**。

注）ホフマン法

$$X = \sum_{n=1} A/(1+nr)$$

X：現在価格（手取額）

A：将来得ることが可能な利益

n ：利益が生じるまでの期間

r：利率（割引率）3%　（法定利率である 5%は昨今の経済状況から用いなかった。）

具体例）

$$X = 2{,}945{,}000/(1+0\times0.03) + 2{,}945{,}000/(1+1\times0.03) + 2{,}945{,}000/(1+2\times0.03) + \cdots\cdots$$

結果

1．直接医療費

HBV、HCV、HIV およびその他の感染症の医療費は「2005 年疾患別医療費データ」（津谷、2007 年）により算定した。その結果を**表３、４、５**に示している。

平均在院日数および平均外来日数は患者調査をもとに算定し、その結果は**表６、７、８**に示すとおりである。

さらに Markov モデルによる HCV の各病態への遷移確率と予想される人数を**表９、１０**に示している。

これらをもとに計算すると、今後 10 年間の「直接医療費」は**表１１**に示すように 242,987,846 円となり、1 年当たり 24,298,785 円となる。

表３　肝疾患の年間医療費（津谷　2007 年）

入院	円
急性肝炎	4,276,679
慢性肝炎	766,237
肝硬変	3,748,163
肝細胞がん	15,168,287
外来	**円**
急性肝炎	17,310,343
慢性肝炎	2,952,795
肝硬変	2,080,998
肝細胞がん	3,757,797

表４　HIV の年間医療費（津谷　2007 年）

	円
入院	14,900,000
外来	

表５　その他の感染症（細菌、ヒトパルボウイルス B19 および HEV）の年間医療費（津谷　2007 年）

入院	円
細菌感染	6,770,602
ヒトパルボウイルス B19	1,443,080
HEV	4,276,679
外来	**円**
細菌感染	1,341,824
ヒトパルボウイルス B19	6,019,502
HEV	17,310,343

- 細菌感染については、「その他の感染症および寄生虫症」、ヒトパルボウイルス B19 については「皮膚及び粘膜の病変を伴うその他のウイルス疾患」、HEV については HBV、HCV と同様に「ウイルス肝炎」の金額を用いた。
- HEV 感染については、重症化することなく急性肝炎で終焉したと仮定した。

表 6　肝疾患の平均在院日数および平均外来日数

入院	日
急性肝炎	14.2
慢性肝炎	35.5
肝硬変	40.7
肝細胞がん	22.4
外来	**日**
急性肝炎	36.7
慢性肝炎	50.0
肝硬変	44.0
肝細胞がん	38.0

表 7　HIV の平均在院日数および平均外来日数

入院	40.1
外来	25.0

表 8　入院および外来期間

入院	日
細菌感染	45.2
ヒトパルボウイルス B19	4.2
HEV	14.2
外来	**日**
細菌感染	23.3
ヒトパルボウイルス B19	36.1
HEV	54.5

表 9　HCV の向こう 10 年間の遷移確率

年	1年目	2年目	3年目	4年目	5年目	6年目	7年目	8年目	9年目	10年目
急性肝炎	1	-	-	-	-	-	-	-	-	-
慢性肝炎	0	0.023054753	0.023080453	0.034233965	0.045189093	0.055893239	0.066403804	0.076860411	0.086724170	0.096560112
肝硬変	0	0	0.000262277	0.000696621	0.001329091	0.002173249	0.003118031	0.004353039	0.005648790	0.007084631
肝細胞癌	0	0	0.000131138	0.000298552	0.000522581	0.000848925	0.001207338	0.001616098	0.002062628	0.002539370
死亡	0	0	0	0.000049758	0.000120826	0.000271656	0.000530051	0.000886248	0.001382899	0.001984550

表 10　HCV 感染者の実数（0.28 人）を代入した場合の向こう 10 年間の各病態の人数

年	1年目	2年目	3年目	4年目	5年目	6年目	7年目	8年目	9年目	10年目
急性肝炎	0.28	-	-	-	-	-	-	-	-	-
慢性肝炎	0	0.006455314	0.006462527	0.009585510	0.012652946	0.015650107	0.018593009	0.021464915	0.024282768	0.027036832
肝硬変	0	0	0.000073437	0.000195054	0.000372145	0.000608509	0.000890485	0.001218851	0.001581866	0.001983697
肝細胞癌	0	0	0.000036719	0.000083594	0.000146602	0.000237699	0.000338055	0.000452508	0.000577536	0.000711024
死亡	0	0	0	0.000013932	0.000033831	0.000076064	0.000148414	0.000248149	0.000387212	0.000565674

表 11　今後 10 年間の直接医療費

項　目	今後 10 年間の医療費（円）
HCV 医療費総計	2,214,000
HBV 医療費総計	193,851,458
HIV 医療費総計	11,883,782
細菌感染医療費総計	6,489,941
HPV-B19 医療費総計	7,462,582
HEV 医療費総計	10,793,511
総計	243,488,785

2．休業損失

今後 10 年間の休業損失総計は、4,201,504 円で 1 年当たり 420,150 円となる。数が多い HBV による損失が、この過半（2,751,410 円）を占めていた。

3．早世による遺失利益

過去に死亡例があったり、死亡を想定したものとして細菌感染と HCV があるが、これらの結果を**表１２**に示す。

表１２　遺失利益

項　　目	遺失利益（円）
HCV による遺失利益総計	57,768
細菌感染による遺失利益総計	10,778,922
総計	**10,836,690**

4．便益

以上より、不活化技術導入により得られる 1 年当たりの「直接医療費」「休業損失」「早世による遺失利益」を併せた便益は、**25,852,698 円**となる（**表１３**）。

表１３　不活化技術導入による便益

項　　目	便益（円）
直接医療費総計	243,488,785
休業損失総計	4,201,504
遺失利益総計	10,836,690
総合計（今後 10 年間）	258,526,979
総合計（1 年当たり）	25,852,698

考察

わが国では HBV 感染者が多いが、これは「直接医療費」と「休業損失」の大半が HBV を原因としていることにも表れている。成人の HBV 感染の場合、その約 98%が急性肝炎で推移し、ほとんど慢性化しないことから 1 年目の医療費等の出費が増大するが、以後ほとんど影響を及ぼさない。但し、近年の海外に起源を持つ HBV は慢性化すると言われているがここでは考慮しなかった。

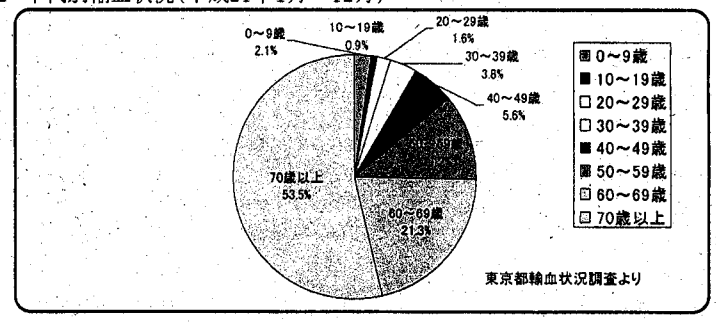
HCV については、慢性化する割合が高いものの、HBV に比べると数が少ないことにより、同様に経済的影響は少ないものとなっている。

HIV についても HBV 及び HCV に比して感染者自体が少ないことから、経済的影響は同様に少ないものと考えられる。

休業損失や遺失利益は就業者を対象にしたものであり、今回は勤労者の平均年齢を用いて便益を算定した。東京都の調査によると、輸血を受けている者の平均年齢は 64.6 歳と推計されることから、この平均年齢を用いると「休業損失」と「遺失利益」はほとんど生じないことになる。加えて原疾患の予後が不明であるが、健常人の生存曲線より減衰率が高いものと考えられる（**図１**）。したがって、これらのことを加味すると実際の便益は算定したものより少ないものと思われる。加えて今回の計算では、輸血によらない原疾患による輸血後の死亡のデータがないため計算できなかったが、これらを考慮すれば一層便益は低

下するものと思われる。一方、今回の計算では「感染性因子低減化技術」を 1 年間実施した場合の HCV の予後について 10 年間のみしか考慮しなかった。HCV の自然史経過は全体で 30 年間程度に及ぶことから、厳密には 30 年間の経済計算を行う必要があったと考える。しかし、30 年間の計算を行ったとしても、もともとの感染予想者の数値が小さいためその増分は僅かであり、結果にはほとんど影響を及ぼさないことと思われる。

図１　都内の輸血状況



＊　「東京都の血液事業（平成 21 年度）　東京都福祉保健局保健政策部　疾病対策課」によると、60 歳以上の患者に対する輸血が全体の 74.8%を占めている。そこで各年齢階級の中央値に年齢が集中していると仮定して、輸血を受けた者の平均年齢を求めると 64.6 歳と推計される。

まとめ

不活化導入コストについては、本稿で示した便益と比較して議論する必要もあろう。NAT はウイルスを検出することに主眼を置いているが、ウイルス等の病原微生物そのものの不活化が各国で行われつつある。S/D 処理による感染性因子低減化技術の経済性については A. Pereria**[7]**により行われたが、その結果は経済性が低いものであった。

また、本稿では新興・再興感染症の流行の問題を考慮していない。いかなる感染症まで対象を広げて経済計算を行うべきか、そして血液の検査や製造工程にどの程度の経済資源を投入すべきかについても議論が必要であろう。

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資料7

問診票

ID 1 1

以下の質問は、献血される方と輸血を受けられる方の安全を守るためにうかがうものです。
表現上、不快の念を抱かれる部分があるかもしれませんが、「責任ある献血」のために、何卒ご理解のほどよろしくお願いいたします。
エイズ検査目的の献血は、血液を必要とする患者さんの安全のためにお断りします。　注意）ご記入いただいた問診票及び献血申込書（診療録）の返却・廃棄はできません。

	質問事項	はい	いいえ
1	今日の体調は良好ですか。	☐	☐
2	3日以内に出血を伴う歯科治療(抜歯、歯石除去等)を受けましたか。	☐	☐
3	3日以内に薬を飲んだり、注射を受けましたか。 (　　　　)	☐	☐
4	次の育毛薬／前立腺肥大症治療薬を使用したことがありますか。 プロペシア・プロスカー等(1ヵ月以内)、アボダート・アボルブ等(6ヵ月以内)	☐	☐
5	次の薬を使用したことがありますか。 乾せん治療薬(チガソン)、ヒト由来プラセンタ注射薬(ラエンネック・メルスモン)	☐	☐
6	24時間以内にインフルエンザの予防接種を受けましたか。	☐	☐
7	1年以内にインフルエンザ以外の予防接種を受けましたか。 (　　　　)	☐	☐
8	次の病気や症状がありましたか。 3週間以内ーはしか、風疹、おたふくかぜ、帯状ほうしん、水ぼうそう 1ヵ月以内ー発熱を伴う下痢 6ヵ月以内ー伝染性単核球症、リンゴ病(伝染性紅斑)	☐	☐
9	1ヵ月以内に肝炎やリンゴ病（伝染性紅斑）になった人が家族や職場・学校等にいますか。	☐	☐
10	6ヵ月以内に次のいずれかに該当することがありましたか。 ①ピアス、またはいれずみ（刺青）をした。 ②使用後の注射針を誤って自分に刺した。 ③肝炎ウイルスの持続感染者（キャリア）と性的接触等親密な接触があった。	☐	☐
11	1年以内に次の病気等にかかったか、あるいは現在治療中ですか。 外傷、手術、肝臓病、腎臓病、糖尿病、結核、性病、ぜんそく、アレルギー疾患、 その他（　　　　）	☐	☐
12	今までに次の病気にかかったか、あるいは現在治療中ですか。 B型肝炎、がん(悪性腫瘍)、血液疾患、心臓病、脳卒中、てんかん	☐	☐
13	今までに次の病気にかかったことがありますか。 C型肝炎、梅毒、マラリア、バベシア症、シャーガス病、 リーシュマニア症、アフリカトリパノソーマ症	☐	☐

	質問事項	はい	いいえ
14	海外から帰国（入国）して4週間以内ですか。	☐	☐
15	1年以内に外国（ヨーロッパ・米国・カナダ以外）に滞在しましたか。 (国名　　　　)	☐	☐
16	4年以内に外国(ヨーロッパ・米国・カナダ以外)に1年以上滞在しましたか。 (国名　　　　)	☐	☐
17	英国に1980年（昭和55年）～1996年（平成8年）の間に通算1ヵ月以上滞在しましたか。	☐	☐
18	ヨーロッパ（英国も含む）・サウジアラビアに1980年以降、通算6ヵ月以上滞在しましたか。 (国名　　　　)	☐	☐
19	エイズ感染が不安で、エイズ検査を受けるための献血ですか。	☐	☐
20	6ヵ月以内に次のいずれかに該当することがありましたか。 ①不特定の異性または新たな異性との性的接触があった。 ②男性どうしの性的接触があった。 ③麻薬、覚せい剤を使用した。 ④エイズ検査（HＩV検査）の結果が陽性だった(6ヵ月以前も含む)。 ⑤上記①～④に該当する人と性的接触をもった。	☐	☐
21	今までに輸血（自己血を除く）や臓器の移植を受けたことがありますか。	☐	☐
22	今までに次のいずれかに該当することがありますか。 ①クロイツフェルト・ヤコブ病（CJD）または類縁疾患と診断された。 ②血縁者にCJDまたは類縁疾患と診断された人がいる。 ③ヒト由来成長ホルモンの注射を受けた。 ④角膜移植を受けた。 ⑤硬膜移植を伴う脳神経外科手術を受けた。	☐	☐
23	現在妊娠中または授乳中ですか。(男性の方は「いいえ」と回答してください) 6ヵ月以内に出産、流産をしましたか。	☐	☐

私は以上の質問を理解し、正しく答えました。

献血した血液について、梅毒、HBV（B型肝炎ウイルス）、HCV（C型肝炎ウイルス）、HIV（エイズウイルス）、HTLV−1（ヒトTリンパ球向性ウイルス−1型）等の検査が行われることを了解し、献血します。

署名

（注意）1．献血される方は、「はい・いいえ」欄の該当する方に ■ または ☐ 印をご記入願います。
2．それ以外の欄には、問診を行う者が、必要事項を記入いたします。

献血申込書（診療録）

☐ 初回　☐ 再来　☐（新規）

献血年月日　平成　年　月　日

採血センター

献血者コード

本人確認　採血種数　採血場所コード　便数

整理番号

手帳未携帯

ID 1 0

表彰区分　表彰規定回数

団体コード　（サブコード）

※太線枠内をご記入ください。裏面もご記入ください。

フリガナ（姓）　（名）

漢字氏名（姓）　（名）

性別：☐ 男　☐ 女

生年月日：☐ 昭和　☐ 平成　年　月　日　歳

身長　cm　体重　kg

旧名　登録　主登録センター

住所 〒　手帳者マーク

自宅電話　携帯電話

勤務先又は学校名

学年　電話1　電話2

OCR処理番号

職業：1☐ 公務員　2☐ 会社員　3☐ 高校生　4☐ 大学生　5☐ その他学生　7☐ 主婦　8☐ 自営業　9☐ その他

希望献血：1☐ 200mL　2☐ 400mL　3☐ 血漿　4☐ 血小板

希望採取血漿量　mL

既献血回数　回

採血（不採血）番号

血液型

受付特記：☐ 基準　☐ 通知　☐ 保留（問診回答変更）

検体の種類：☐ 血球計数　☐ 保管　☐ 生化学　☐ 血液型　☐ NAT

確認事項			
献血前に食事をとられた時刻　時頃	睡眠　約　時間	血液センターから必要に応じて献血協力のお願いをしてよろしいでしょうか。	☐ はい　☐ いいえ
B型、C型肝炎検査、梅毒検査、HTLV-1抗体検査の結果異常を認めた場合、通知を希望されますか。	☐ はい　☐ いいえ	検査サービス通知を希望されますか。	☐ はい　☐ いいえ

献血可能日：200mL　400mL　血漿　血小板

直近1年以内の献血回数　確認血液量　mL　血漿可能量　mL

直近1年以内の400mL献血日　年　月　日

前回情報：採血センター　種別　献血年月日　献血方法　血圧値(mmHg)　脈拍　/分　血色素量(g/dL)　比重　ALT　…　WBC　…　採血副作用　メモ　献血者　採血　特記　引継

血色素	測定者	著変	ヨード過敏症	血圧	脈拍	発熱	採血指示	指示採取血小板単位	採血適否	検診医
(g/dL)	左 右　外・正・内	有・無	☐ 有　☐ 無	mmHg /	/分	有・無　体温　℃	☐ 1 200mL　☐ 2 400mL　☐ 3 PPP　☐ 5 PC　☐ 6 PC+PPP	単位　指示採取血漿量　mL	☐ 適　☐ 否	署名

備考

特記・処置

検体採取指示　☐ 交差用HLA　☐ 登録用HLA

採血時OCR

著変：穿刺 有・無　抜針 有・無

左 右　外・正・内

採血担当者

採血特記

問診該当1の内訳：05☐　12☐　13☐　17☐　18☐　19☐　20☐　21☐　22☐

採血不適：1☐ 血色素　2☐ 血圧　3☐ 服薬　4☐ 問診該当①　5☐ 問診該当②　6☐ 事前検査　9☐ その他

記入例：■ または ☐　出力記録：

日本赤十字社

2010.10

献血後のお知らせ（検査結果）

献血いただく前に、検査結果通知のご希望の有無をお伺いしています。（結果は献血後1ヶ月以内に親展にてお届けします）

(1) お知らせしている検査項目

●血液型検査、生化学検査　●血球計数検査

(2) 検査で異常を認めた場合にお知らせする項目

●B型、C型肝炎ウイルス検査
●梅毒検査　●HTLV-1検査（エイズ検査ではありません）

より安全な輸血医療のために

エイズや肝炎は、主に性交渉により若い世代に感染が拡がっています

エイズウイルス（HIV）や肝炎ウイルス（HBV、HCV）を保有している人との性交渉や、注射器を共用し麻薬などを使用した場合に、エイズや肝炎のウイルスに感染する恐れがあります。
下記はいずれもこれらの危険性が高い行為です。過去6ヵ月以内に該当する場合は献血いただけません。

(a) 不特定の異性または新たな異性との性的接触　(c) 麻薬、覚せい剤を使用した
(b) 男性の方：男性との性的接触　(d) (a)～(c)該当者との性的接触

検査目的の献血をお断りする理由

エイズウイルスや肝炎ウイルスの感染初期には、強い感染力を持つにもかかわらず、最も鋭敏な検査方法を用いても検出できない期間があります。
エイズウイルスなどの感染に不安があり、検査により確認しようとすると、患者さんにウイルスを感染させてしまうことになります。

エイズ検査施設

エイズ検査をご希望の方は最寄りの保健所にお問合せください。保健所ではエイズ検査を匿名、無料で受けることができます。
「HIV 検査・相談マップ」(http://www.hivkensa.com)
では、保健所などの検査機関の情報が掲載されています。

何らかの病気や感染症にかかっているとわかった場合はご連絡ください

献血後、健康診断や医療機関などでB型・C型肝炎の疑いがあると診断された場合等には、血液センターまでご連絡ください。（又は主治医に献血した旨をお伝えください）

ご協力ください

・輸血を受けられた患者さんについて、感染症などの報告があった場合、輸血医療の安全性向上と献血された方ご自身の健康管理のため、検査用血液の採血を再度お願いする場合があります。
・献血された方に「輸血を受けられる患者さんのために」という印刷物をお渡しします。
これをよくお読みになって、思い当たる場合は、必ず献血当日中に血液センターへお電話ください。

日本赤十字社 Japanese Red Cross Society

人間を救うのは、人間だ。 Together for humanity

献血へのご協力に心から感謝いたします。

このチラシをよくお読みいただき、内容を了承されたうえで、献血受付にお進みください。

お願い！

献血していただいた血液は、輸血や分画製剤として患者さんの治療に用いられます。
患者さんが安心して輸血を受けられるように安全な献血をお願いします。

以下に該当する方は献血をご遠慮ください

❶ **渡航歴について**
- 海外から帰国（入国）して4週間以内の方
- 昭和55年（1980年）以降，ヨーロッパ・サウジアラビアに一定期間滞在された方（国名・期間等は受付におたずねください）

❷ **この3日間に出血を伴う歯科治療（抜歯・歯石除去等）を受けられた方**

❸ **輸血や臓器の移植を受けたことがある方**

❹ **ヒト由来プラセンタ注射薬を使用したことがある方**

❺ **エイズ感染が不安で，エイズ検査を受けるための方**

❻ **この6ヵ月以内に下記に該当することがある方**
- 不特定の異性または新たな異性との性的接触があった
- 男性どうしの性的接触があった
- 麻薬、覚せい剤を使用した

❼ **梅毒，C型肝炎，マラリア，シャーガス病注）にかかったことがある方**

注）シャーガス病は中南米地域においてサシガメ（昆虫）が媒介する感染症です。中南米居住歴のある方は検診医にお申し出ください。

※ 上記に該当されない方でも、検診医の判断で献血をご遠慮していただくことがあります。
※ 医薬品を服用されている方は、必ず検診医にお申し出ください。

献血に際して取得した皆様の個人情報は、血液センターにおいて厳重に管理されます。

献血前にお読みください

以下の内容をよくお読みになり、ご了承のうえ、献血申込書（診療録）にご記入ください。

献血前に

■お名前、生年月日、住所、電話番号等は正確にお書きください。
■ご本人の確認のため、運転免許証などの提示をお願いすることがあります。
■問診票の質問には正確にお答えください。
■プライバシーは厳守いたします。
■献血後に高所作業や激しいスポーツ、自動車の運転等をされる方は献血前にお知らせください。特に乗り物の運転をされる方は、献血後に十分な休憩（30分以上）を取っていただく必要があります。
■副作用予防のため、献血前に水分（スポーツドリンク等）を補給してください。

献血時は

■200mL・400mL献血では10分から15分位、成分献血では40分から90分位の採血時間がかかります。
■血圧や血色素量（ヘモグロビン濃度）を事前に測定します。
■採血針は、一人ずつ使い捨てとなっています。

採血副作用と注意

■採血に伴う副作用が生じることがあります。
採血中や採血後に、気分不良、吐き気、めまい、失神などが約0.9%（1/100人）の頻度で発症し、まれに失神に伴う転倒が発生することがあります。また、針を刺すことによる皮下出血が約0.2%（1/500人）、神経損傷（脱力や痛み）が約0.01%（1/10,000人）の頻度で発生します。
■採血針を刺した箇所に針跡が残ることがあります。
■針を刺した時に、強い痛みがある場合や痛みがいつまでも続く場合は、直ちに看護師、医師にお知らせください。また、皮下出血等も我慢せずにお知らせください。
■採血中に気分不良やめまいを起こした場合は、直ちに職員にお知らせください。また、採血後に同様の症状を起こした場合は転倒を防止するために、すぐにしゃがむか横になってください。
■献血によって健康被害が生じた場合に医療費等を補償する献血者健康被害救済制度が設けられています。詳しくは血液センター職員にお尋ねください。

献血していただいた血液は

■献血血液は、医療機関で血液を必要とする患者さんのもとへ届けられますが、以下のように有効利用させていただくことがあります。
- 血液型や輸血副作用の検査・研究のため、赤血球型、白血球型、血小板型及び血漿蛋白の遺伝子検査を実施する場合があります。
なお、その他の遺伝子検査をご本人の承諾を得ずに行うことはありません。
- 血液製剤の品質管理や輸血用の検査試薬製造のために使用することがあります。
- 輸血の有用性、安全性及び検査サービスの向上を目的とした研究のために血液を使用することがあります。

■次の検査を実施し、血液製剤の基準に適さないと判断した場合は輸血に使用しません。
血液型（ABO型、Rh型等）、不規則抗体、梅毒、B型肝炎ウイルス、C型肝炎ウイルス、エイズウイルス（HIV）、ヒトTリンパ球向性ウイルス-1型（HTLV-1）、ヒトパルボウイルスB19、ALT（肝機能）等
■血液の一部は少なくとも11年間冷凍保存し、輸血副作用・感染症などの調査のために使用します。
■献血血液が採血装置等の不具合・不良により輸血に使用できなくなることがあります。

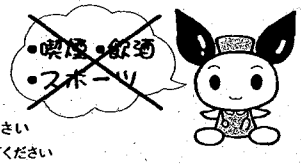
献血後の過ごし方

献血後は、水分の補給と休憩（少なくとも10分以上）をおとりください。
電車でお帰りの際、転落防止のため駅のホームでは線路の近くで電車を待たないでください。
（気分不良、失神などはじっと立っている時に発生しやすいといわれています）

＜献血当日は次のようなことをお願いいたします＞

ジュース（スポーツドリンク）、お茶などで十分補給してください

乗り物を運転される場合は、その前に十分な休憩（30分以上）をおとりください



・トイレ…採血直後の排尿は座位で行なってください
・エレベーター・階段…使用する際は、特に注意してください
・入浴…2時間以内の入浴と当日のサウナは避けてください
・飲酒・喫煙…献血直後は避けてください
・スポーツ…水泳、マラソンなど激しいスポーツは避けてください
・重労働…採血側の腕に強い力がかからないようにお願いします

気分が悪くなったら

緊張感の強い場合やその日の体調によっては、採血の数時間後、まれに気分が悪くなったりめまいがすることがあります。そのような場合はすぐにしゃがむか、横になってください。
通常は頭を低くして30分程度安静にするだけで軽快します。
また、採血後の腕の痛みなど何かご心配なときは、すぐに血液センターまでご連絡ください。

○○○赤十字血液センター（XXX-XXX-XXXX）

移動採血車の運行予定や献血ルームのご案内などはホームページでもご覧いただけます。
（http://www.○○○○.○○○）

献血ルームのご案内

・○○赤十字献血センター XXX-XXX-XXXX　・○○献血ルーム XXX-XXX-XXXX　・○○献血ルーム XXX-XXX-XXXX
・○○赤十字献血センター XXX-XXX-XXXX　・○○献血ルーム XXX-XXX-XXXX　・○○献血ルーム XXX-XXX-XXXX

ひと、くらし、みらいのために
厚生労働省
Ministry of Health, Labour and Welfare

資料 8－1

Press Release

平成22年11月12日
医薬食品局血液対策課
(担当・内線) 課長　三宅 (2900)
企画官 安田 (2901)
(代表電話) 03(5253)1111
(直通電話) 03(3595)2395
(FAX) 03(3507)9064

報道関係者 各位

フィブリノゲン製剤納入先医療機関の追加調査について

平成１６年１２月９日に公表したフィブリノゲン製剤納入先医療機関を対象として、平成１９年１１月７日付で実施した追加調査の結果について、平成２２年１０月１日までに回収した医療機関からの回答を取りまとめた状況をお知らせいたします。

１　回答状況

（１）追加調査実施期間　　平成１９年１１月７日～１２月５日（※１）
（ただし、現在も回収中）

（※１）（１）の調査以降、平成２０年８月２５日及び平成２１年１月１６日にも元患者の方へのお知らせ状況等について再度調査を行っており、（３）回答施設数以降はそれらの結果を反映したものである。

（２）追加調査対象施設数　　医療機関　６，６１０施設
（平成１６年公表施設のうち、所在地等が不明であった施設を除いた医療機関）

（３）回答施設数
- 平成１６年公表時に存続していた５，３９７施設のうち、５，２９１施設（98%）から回答があった。
- なお、このほか平成１６年公表時に廃院等していた１，２１３施設のうち、５０７施設から回答があった。

２　主な調査結果

（１）投与の年月について回答があった医療機関数と元患者数
医療機関数　９２５施設
元患者数　１３，７３８人　（投与年別は別表）

（２）上記以外に、過去に投与の事実をお知らせしたという記録が残されているが、現在では投与の年月は特定できないとする回答があった医療機関数と元患者数
医療機関数　９５施設
元患者数　３１２人

（３）（１）と（２）の合計
医療機関数　１，００１施設（※２）
元患者数　１４，０５０人

（※２）厚生労働省ホームページ「Ｃ型肝炎ウイルス検査受診の呼びかけ（フィブリノゲン製剤納入先医療機関名の再公表について）」の公表医療機関等リスト上の該当医療機関の「備考」欄に、「フィブリノゲン製剤を投与されたことが判明した元患者の方がいるとの報告あり。」と記載した。

（４）元患者の方への投与の事実のお知らせの状況

		元患者数
お知らせした		８，１１６人　(58%)　(※３)
お知らせしていない		５，９３４人　(42%)
理由	投与後に原疾患等により死亡	１，９７４人　(14%)
理由	連絡先が不明又は連絡がつかない	２，７５５人　(20%)
理由	肝炎ウイルス検査の結果が陰性	４２２人　(3%)
理由	今後お知らせする予定である	２２８人　(2%)
理由	その他（未記入含む）	５５５人　(4%)
合　計		１４，０５０人

（※３）元患者の方に一人でも投与の事実をお知らせした医療機関は８２７施設であった。

（５）診療録等の保管状況

平成６年以前の診療録等が次のいずれかにより保管されている施設数
（括弧内は調査対象施設数に対する割合）

２，０４１施設（31%）（※４）

（内訳）（※５）

診療録（カルテ）	１，４９８施設（23%）
手術記録あるいは分娩記録	１，５７６施設（24%）
製剤使用簿	１３５施設（ 2%）
処方箋	１４２施設（ 2%）
輸液箋あるいは注射指示箋	２７７施設（ 4%）
レセプトの写し	８３施設（ 1%）
入院サマリーあるいは退院サマリー	２９１施設（ 4%）
その他の書類	２９５施設（ 5%）

（※４）平成１６年の調査では「昭和６３年６月３０日以前にフィブリノゲン製剤を投与した記録（診療録、使用簿など）が保管されていますか。」との設問であったのに対し、今回の調査では、「平成６年以前のカルテ等の各種書類が保管されていますか。」との設問であったため、保管していると回答した施設の割合が異なったものと思われる。

（※５）厚生労働省ホームページ「Ｃ型肝炎ウイルス検査受診の呼びかけ（フィブリノゲン製剤納入先医療機関名の再公表について）」の公表医療機関等リスト上の「カルテ等の有無」欄に、平成６年以前のカルテ等の記録が一部でも保管されている場合、△印を付していたが、さらに保管されている記録の保管期間、保管状況等を記載した。

（別表）

投与の年月について回答があった元患者数の投与年別の内訳

投与年	人数
昭和３９年	０人
４０年	７人
４１年	８人
４２年	１２人
４３年	１６人
４４年	１８人
４５年	１９人
４６年	２２人
４７年	２５人
４８年	３４人
４９年	４８人
５０年	４８人
５１年	６７人
５２年	８８人
５３年	１２８人
５４年	１９８人
５５年	３２２人
５６年	４３１人
５７年	５６４人
５８年	９６３人
５９年	１，４８７人
６０年	１，７１６人
６１年	２，３７９人
６２年	２，９１３人
６３年	１，６８６人
平成　元年	２０６人
２年	１５７人
３年	９１人
４年	４３人
５年	２９人
６年	１３人
計	１３，７３８人

ひと、くらし、みらいのために
厚生労働省
Ministry of Health, Labour and Welfare

資料 8－2

Press Release

平成２２年１０月２５日（月）
医薬食品局総務課医薬品副作用被害対策室
室長補佐：信沢　（内線）２７１７
管理係長：内沼　（内線）２７１８
（直通）０３－３５９５－２４００

C型肝炎訴訟の和解について

本日、名古屋地方裁判所において、下記のとおり和解が成立しましたので、お知らせします。

平成２０年１月以降、同地裁に係属している原告（患者数２人）についての和解。
製剤はフィブリノゲン製剤。

上記の症状の内訳は、肝がん１人、無症候性キャリア１人である。

（参考）

○和解等成立人数※1　１６０６人

○新規提訴等人数※2　１７６４人　（１０月２２日現在）

※１「和解等成立人数」は、今回の和解成立者は含まず、これまでに和解が成立した人数（患者数）である。また、調停が成立した４人を含む。
※２「新規提訴等人数」は、救済法施行後に提訴等し、訴状等が国に送達された人数（患者数）である。このうち、１３９８人は既に和解等が成立している。

ひと、くらし、みらいのために
厚生労働省
Ministry of Health, Labour and Welfare

資料 8－3

Press Release

平成22年10月27日
医薬食品局血液対策課
（担当・内線）企画官　安田（2901）
課長補佐　難波江(2905)
（代表電話）03(5253)1111
（直通電話）03(3595)2395
（FAX）03(3507)9064

報道関係者　各位

平成２２年度フィブリノゲン製剤納入先医療機関訪問調査について

１　趣旨

フィブリノゲン製剤の納入が確認されている厚生労働省所管の医療機関及び国立大学法人の医療機関に対し、診療録等の保管状況を確認するとともに、投与事実の確認作業の実態等を把握するため、今年度は、以下の要領で訪問調査を実施する。

２　調査対象施設

フィブリノゲン製剤の納入実績等を踏まえて選定した３４医療機関
（別添参照）

３　調査のスケジュール

年度内を目途に訪問調査の結果をとりまとめ、公表を行う予定。

（参考）

フィブリノゲン製剤の納入が確認されている厚生労働省所管の医療機関への訪問調査は、平成２０年度に４６病院、平成２１年度に１５病院実施済みである。

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（別　添）

○調査対象施設

１．（独）国立病院機構病院
（１）北海道がんセンター
（２）函館病院
（３）高崎総合医療センター
（４）西埼玉中央病院
（５）名古屋医療センター
（６）京都医療センター
（７）神戸医療センター
（８）姫路医療センター
（９）兵庫青野原病院
（１０）呉医療センター
（１１）都城病院

２．（独）国立高度専門医療研究センター
（１）国立がん研究センター中央病院
（２）国立国際医療研究センター病院

３．労災病院
（１）中部労災病院
（２）神戸労災病院
（３）中国労災病院
（４）山口労災病院

４．社会保険病院
（１）札幌社会保険総合病院
（２）北海道社会保険病院
（３）社会保険船橋中央病院
（４）社会保険中央総合病院
（５）社会保険京都病院
（６）社会保険神戸中央病院
（７）社会保険下関厚生病院
（８）佐賀社会保険病院
（９）社会保険宮崎江南病院

５．国立大学附属病院
（１）東京医科歯科大学医学部附属病院
（２）東京大学医学部附属病院
（３）東京大学医科学研究所附属病院
（４）神戸大学医学部附属病院
（５）山口大学医学部附属病院
（６）佐賀大学医学部附属病院
（７）宮崎大学医学部附属病院
（８）鹿児島大学病院