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CONTEXT AND POLICY ISSUES:

In 2005, Canadian Blood Services (CBS) received approximately 850,000 units of whole blood from voluntary donors. All blood collected by CBS is routinely tested for known pathogens including syphilis, hepatitis B and C, human immunodeficiency virus 1 and 2, Human T-Cell lymphotropic virus I and II, and West Nile Virus. New and emerging pathogens, for which there are no known methods to detect, may cause concern in regards to blood supply safety. Pathogen reduction technologies (PRTs) can provide protection against many known and unknown pathogens.

PRTs, such as INTERCEPT Blood System™ and Mirasol® Pathogen Reduction Technology, have been approved for use in Europe. INTERCEPT was licensed for use in Europe in 2006 and Mirasol received European approval in 2008. Neither of these technologies is currently licensed in North America. These PRTs are effective against bacteria, parasites, leukocytes, lipid-enveloped viruses, and some non-lipid-enveloped viruses. Both INTERCEPT and Mirasol can be used for platelets and plasma, and Mirasol is being tested for use with red blood cells. Both systems use a photochemical treatment (PCT) approach which combines the blood products with a photoactive chemical [amotosalen and riboflavin (vitamin B2) for INTERCEPT and Mirasol, respectively] and expose the mixture to ultraviolet A light (UVA). The subsequent photochemical reaction results in the inactivation of the pathogens through cross-linking of the nucleic acids of the pathogens.

Both of the photochemical processes claim to inactivate the pathogens without adversely effecting the quality or safety of the blood products. This report will review the clinical and cost-effectiveness and guidelines for use of pathogen reduction technologies for blood products.
RESEARCH QUESTIONS:

1. What is the clinical effectiveness of pathogen reduction technologies for blood products?
2. What is the cost-effectiveness of pathogen reduction technologies for blood products?
3. What are the guidelines for use of pathogen reduction technologies for blood products?

METHODS:

A limited literature search was conducted on key health technology assessment resources, including PubMed, The Cochrane Library (Issue 3, 2009), University of York Centre for Reviews and Dissemination (CRD) databases, ECRI, EuroScan, international health technology agencies, and a focused Internet search. The search was limited to English language articles published between 2004 and September 2009. No filters were applied to limit the retrieval by study type.

HTIS reports are organized so that the higher quality evidence is presented first. Therefore, health technology assessment reports, systematic reviews, and meta-analyses are presented first. These are followed by randomized controlled trials, controlled clinical trials, observational studies, economic evaluations, and evidence-based guidelines.

SUMMARY OF FINDINGS:

Three randomized controlled trials (RCTs), one observational study, and four economic evaluations regarding the clinical and cost-effectiveness of the pathogen reduction technologies INTERCEPT and Mirasol were identified by the literature. No health technology assessments, systematic reviews, meta-analyses, controlled clinical trials, or evidence-based guidelines were identified.

Randomized controlled trials

Ambruso et al. (2009)\(^4\) conducted a RCT to evaluate the antibody formation to platelet neoantigens following platelet transfusion. The objective of this study was not to determine if the Mirasol PRT reduced potential pathogens in the donor platelets or if Mirasol-treated platelets were capable of improving hemostasis. Rather, the objective of this study was to determine if the chemical treatment of platelets during the Mirasol process modified the surface of the platelets in such a way that neoantigens (new antigens) were formed. The authors’ rationale was that the neoantigens could have triggered an unintended immune response by the recipient who received the Mirasol-treated platelets. A comparison was made between the Mirasol-treated platelets and control platelets (no treatment with PRT). Patients were included if they had a confirmed diagnosis of thrombocytopenia due to chemotherapy or hematopoietic stem cell transplantation. Patients who were refractory to platelet transfusions were excluded. The serum of 44 patients who received Mirasol-treated platelets and 22 patients who received control platelets over a 28-day study period was analyzed for the presence of neoantigens. No patients in either group had antibodies to platelet neoantigens. The authors concluded that neoantigen formation is not a side effect of the Mirasol treatment and therefore, the immunoreactivity of Mirasol-treated platelets was similar to that of control platelets. The study received funding from the manufacturers of Mirasol.
The results from a phase III RCT conducted by Mintz et al. were published in 2006. The objective of the trial was to compare fresh frozen plasma that had been photochemically-treated with amotosalen and UVA light with control fresh frozen plasma in patients with thrombotic thrombocytopenic purpura (TTP). Patients were included if they were over two years of age and had a diagnosis of acute TTP with a platelet count of less than $100 \times 10^9 \text{per litre (L)}$. The study took place in Finland. Thirty-five patients were randomly assigned to receive either PCT plasma ($n=17$) or control plasma ($n=18$). The mean age was $41.8 \pm 14.1$ [Standard Deviation (SD)] years in the PCT group and $38.9 \pm 18.3$ (SD) years in the control group. Females accounted for 82.4% and 77.8% of the patients in the PCT and control group, respectively. There were no significant differences in the baseline patient characteristics. The patients received plasma until a remission (defined as a platelet count of $150 \times 10^9 \text{per litre (L)}$ for two consecutive days) was achieved or for a maximum of 35 days. In the case of a relapse within 60 days of the last transfusion, the patient was eligible for a second and final cycle of treatment. Patients were observed for adverse events (AEs) for seven days after the last transfusion. The primary endpoint was the number of patients in remission within a 30 day period. Eighty-two percent of patients in the PCT group and 89% of patients in the control group were in remission within 30 days. There was no significant difference between groups in terms of the time to remission, relapse rate, time to relapse, total volume of plasma exchanged, and number of plasma units exchanged. The authors concluded that the effectiveness and the safety profile of PCT-treated fresh frozen plasma did not differ significantly from control fresh frozen plasma. The study received funding from Cerus, the manufacturers of INTERCEPT.

The results from the SPRINT trial, a randomized controlled phase III trial to evaluate the clinical effectiveness of PCT (amotosalen + UVA) treated platelets in patients with thrombocytopenia, was published in 2004 by McCullough et al. Patients were considered for inclusion if they were over six years of age and had a diagnosis of thrombocytopenia that required a platelet transfusion. Patients were excluded if they had a number of conditions including a history of clinical resistance, TTP, and acute promyelocytic leukemia. The platelets were collected and treated photochemically at each participating trial site. The patients were randomized to receive either PCT-treated platelets ($n=318$) or control platelets ($n=327$). The mean age of the patients in the PCT group was 47 years (54% male) and 46 years (51% male) in the control group. There were no significant differences in the baseline patient characteristics. The patients received platelets until they became independent of transfusions (seven days without transfusions) or for a maximum of 28 days. The primary endpoint was the proportion of patients with grade 2 bleeding (clinically significant bleeding that does not require a red blood cell transfusion) using the World Health Organization bleeding scale. The proportion of grade 2 bleeding did not differ significantly between the two groups (PCT, 58.5%; control, 57.5%). Significant differences in secondary endpoints between the two treatment groups were reported. These differences did not favour the PCT group. Before receiving transfusions, the platelet counts of the groups did not differ significantly (PCT group, $15.1 \times 10^9/L$; control group, $15.2 \times 10^9/L$). Patients receiving transfusions with PCT-treated platelets had lower post-transfusion platelet counts than patients in the control group ($36.5 \times 10^9/L$ versus $49.5 \times 10^9/L$). In addition, patients in the PCT group had a shorter interval time between transfusions than the control group (1.9 days versus 2.4 days) and required more transfusions than those in the control group (8.4 versus 6.2). The authors noted that the mean dose of platelets per transfusion was lower in the PCT group compared with the control group [$3.7 \times 10^{11}$ platelets per millilitre (mL) versus $4.0 \times 10^{11}$ platelets/mL]. Despite the differences in secondary outcomes, the authors concluded that the effectiveness of PCT platelets was similar to that of control platelets. The study received funding from Cerus, the manufacturers of INTERCEPT.
A follow-up paper was published in 2005 by Snyder et al.⁷ that described the safety profile of the PCT platelets used in the SPRINT trial in greater detail. AEs were categorized according to their relationship to the transfusion (probable relationship, possible relationship, or no relationship). The authors reported that the PCT group had significantly fewer acute transfusion-related reactions occurring within six hours of transfusion than in the control group. The patients in the PCT group experience significantly more minor hemorrhagic AEs including petechiae (broken capillaries), blood in the feces, and skin rashes. All other AEs, including those classified by authors as high-grade (anemia not otherwise specified, hyperglycemia not otherwise specified, febrile neutropenia, and thrombocytopenia), did not differ significantly between groups. The authors concluded that the safety profile of PCT platelets was comparable to that of control platelets.

**Observational studies**

A prospective cohort study was published by Osselaer et al. in 2008.⁸ The objective of the study was to evaluate the safety of INTERCEPT-treated platelet components in a broad patient population. Blood transfusion centres that used the INTERCEPT Blood System for routine production of platelet components were invited to participate in the study. Participating centres were located in Belgium, Norway, Spain, and Italy. To participate in the study, patients had to receive at least one INTERCEPT-treated platelet component transfusion. The authors stated that there were no other inclusion or exclusion criteria. Patients who received INTERCEPT-treated platelet components while in the hospital were monitored for AEs or 24 hours. Patients receiving transfusions in an out-patient clinic setting were monitored for six hours. AEs classified as related to transfusion included chills, fever, urticaria (hives), dyspnea (shortness of breath), nausea or vomiting, itching, flushing, and hypotension. A study report form was completed for all transfusions regardless of whether or not an AE occurred. Platelet components were collected from volunteer donors by apheresis or by whole blood-derived buffy coat procedures. Platelet components were leukoreduced and underwent the INTERCEPT process according to the manufacturer's instructions.

A total of 5,106 transfusions with INTERCEPT-treated platelets were performed in 651 patients over a period of approximately two years. The mean age of patients was 61.2 ± 17.0 (SD) years and 59.1% of the study population was male. Patients with hematological or oncological conditions accounted for the majority (58.1%) of the participants. The mean number of transfusions per patient was 7.8 ± 16.2 (SD) with a range of one to 156. AEs were reported in 55 transfusions [1.1%; 95% Confidence Interval (CI); 0.81 to 1.40] corresponding to 42 patients (6.4%). Three AEs were reported as serious. The authors reported that AEs occurred after a single transfusion and after multiple transfusions; therefore the authors suggested that repeated exposure to INTERCEPT-treated platelets did not increase the risk of a transfusion-related reaction. The authors reported that INTERCEPT-treated platelets were well-tolerated and that the AE profile of the patients receiving INTERCEPT-treated platelets was consistent with what was reported by other studies evaluating conventional platelet products. This study did not have a control group receiving un-treated (or conventionally-prepared) platelets. This represents a limitation of the study. The study received funding by the manufacturers of INTERCEPT (Cerus) and two of the study authors were employed by Cerus.
Economic evaluations

Janssen et al. (2006) performed a cost-utility analysis that evaluated the cost-effectiveness of a pathogen reduction technology (the particular brand was not specified) compared to an untreated sample diversion pouch. The diversion pouch collects the first 20 to 30 mL of blood which can contain the highest level of bacteria. The perspective was that of the health care system. A hypothetical population of 100,000 patients undergoing platelet transfusions was evaluated. The study took place in the Netherlands. The price year was 2002, the discounting rate was 4%, and costs are reported in US dollars. One-way and probabilistic sensitivity analyses were performed. The estimation of quality-adjusted life years (QALYs) was derived using a Markov model. The authors reported that the additional cost per QALY gained was $496,674 when using PRT with the sample diversion pouch compared with the sample diversion pouch alone. Results were most sensitive to the probability of sepsis and the probability of death given sepsis, the patients’ quality-adjusted life expectancy, and the probability of bacterial contamination. The authors concluded that given these unknown probabilities, the cost-effectiveness of PRT was uncertain.

Moeremans et al. (2006) conducted a cost-utility analysis to evaluate the cost-effectiveness of the INTERCEPT Blood System. The study compared a hypothetical population receiving INTERCEPT-treated platelets with a population that received control platelets that were prepared by conventional methods. The study populations included patients with hematological malignancies, breast cancer, and patients undergoing coronary artery bypass graft surgery. The study was conducted in Belgium and the costs were reported in Euros. The price year and the rate of discounting (if performed) were not reported. The time horizon was life long expectancy. With the assumption of an absence of an emerging virus, the incremental cost-effectiveness ratio (ICER) ranged from €195,364 to €3,459,201 per QALY. The authors concluded that the implementation of INTERCEPT could be considered cost-effective.

The cost-effectiveness of PRT for platelet transfusions was evaluated by Postma et al. in a study published in 2005. The study took place in the Netherlands and the costs were expressed in Euros. The price year was 2003 and future costs were discounted at a rate of 4%. The study took a societal perspective. Two main assumptions that were made were that the PRT was 100% effective in eliminating pathogens and that PRT-treated platelets were not associated with any AEs. Additional sensitivity analyses were performed taking in account various assumptions including risk of sepsis. The cost-effectiveness of PRT was €554,000 per life year gained. The authors concluded that PRT was cost-effective.

Staginnus and Corash (2004) conducted a cost-utility analysis comparing the INTERCEPT Blood System with control single-donor platelets. The study was conducted in Japan with a Japanese health care system perspective. The price year was not stated; however, resource use data was taken from studies that were published between 2002 and 2004. The costs are presented in Japanese Yen. Several hypothetical clinical scenarios were modeled and included patients that were undergoing progenitor cell transplantation, coronary bypass surgery, and hip arthroplasty. The time horizon was life long expectancy. A one-way sensitivity analysis was performed. The cost per QALY gained of using INTERCEPT-treated platelets compared with controlled platelets ranged from ¥1,076,000 (for hip arthroplasty) to ¥99,000 (for the treatment of acute lymphocytic leukemia with progenitor cell transplantation). The authors concluded that the treatment of platelets with the INTERCEPT Blood System was a cost-effective treatment.
strategy compared with other treatment strategies used in Japan including the use of nucleic acid testing to detect pathogens.

**Limitations**

The literature search for this review was limited to the last five years. It is possible that some studies were not included because they did not meet the date restriction.

No evidence from health technology assessments, systematic reviews, or meta-analyses was identified by the literature search. No evidence-based guidelines providing guidance on the use of pathogen reduction technologies were identified. All of the included clinical trials and the observational studies received funding support from the manufacturers of the pathogen reduction technologies. This may be a potential source of bias.

The outcomes of interest of the included studies were typically related to improvements in blood counts and safety. The literature search did not identify any studies evaluating the clinical effectiveness of Mirasol with respect to improvements in hemostasis. None of the studies included in this report evaluated whether patients treated with blood products prepared using either the INTERCEPT or Mirasol process became infected with any pathogens. This type of analysis would require long-term follow-up.

None of the economic evaluations included in this report were conducted in Canada. Therefore, it is not known whether the findings of these economic studies are generalizable to the Canadian health care system.

**CONCLUSIONS AND IMPLICATIONS FOR DECISION OR POLICY MAKING:**

Overall, the available evidence indicates that the INTERCEPT Blood System photochemical process (amotosalen + UVA light) does not adversely affect the clinical utility of the treated blood components, specifically plasma and platelet components. INTERCEPT-treated components were able to improve hemostasis in all of the included studies and had a comparable AE profile to conventionally-prepared plasma and platelet components.

One study examined the incidence of antibody development to potential neoantigens on Mirasol-treated platelets in blood product recipients. The study reported that none of the study participants that received Mirasol-treated platelets developed antibodies to neoantigens; therefore the authors concluded that neoantigen formation is not a potential side effect of photochemical treatment of platelets. The literature search did not identify any evidence relating to the clinical effectiveness of Mirasol in terms of improving hemostasis.

Three cost utility analyses and one cost-effectiveness study concluded that pathogen reduction technologies are cost-effective. None of these studies were conducted in Canada; therefore the generalizability to the Canadian health care system may be limited.

In addition to the effectiveness of INTERCEPT and Mirasol to improve hemostasis and the cost-effectiveness of these PRTs, other outcomes of interest for the current report were the risk of infection with pathogens following transfusion with products prepared using either of the PRTs and how PRTs compared to conventional methods in terms of the time it took to process the samples prior to transfusions. No information regarding these latter two outcomes was identified.
for inclusion by the literature search. In addition, no guidelines about the use of PRT were identified.

Given that these PRTs have had European approval for a limited time, the volume of evidence regarding their effectiveness may increase in the future if the clinical use of PRTs becomes more widespread and if INTERCEPT or Mirasol gain regulatory approval in North America. In addition, follow-up studies that investigate the long-term safety of transfusions with photochemically-treated blood products may become available. Such further evidence may be valuable for Canadian decision makers.

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