in developing an integrated PI technology for all blood components. Research initiatives should be directed toward a PI technology suitable for implementation in developing countries.[5,78]

Mathematical modeling should be used to develop credible scenarios for the unknown (emerging) pathogen risk; for example, what are the "break-even" threshold conditions and are they consistent with a worst-case scenario? Several different models might be constructed based on the extensive database developed during the HIV epidemic, which included a pathogen with an extended "silent period," high morbidity and mortality, secondary spread, surrogate testing, and clinical screening, contrasted with an agent such as WNV, which became clinically apparent quickly and involved limited morbidity and mortality and for which a screening test could be readily developed and introduced. These models could be used in economic analyses of candidate PI technologies to support decisions about PI implementation and investments for the research agenda.

Large, well-designed, randomized clinical trials should be performed to evaluate and/or confirm the effectiveness of any new PI technology. Postlicensure Phase IV studies should be integrated with hemovigilance systems to enhance the ability to detect adverse events.

Introduction of PI technologies might have unanticipated consequences for the health-care system. For example, the development and widespread availability of screening tests for new agents might be compromised.

Prion diseases have not been addressed by current PI technologies. New PI technologies should be investigated to address these and other resistant agents. Research should address the relative risks and benefits of PI pooled components versus PI single-donor components.[79]

CONCLUSION

PI or removal technologies hold considerable promise as a means of improving the safety of the blood supply, particularly against newly emergent or not-yet-discovered infectious threats. A number of PI technologies have already been adopted in different countries and some are expected to become available within a relatively short time in Canada. Implementation of PI will be complicated by considerations of efficacy, availability, logistics, cost-effectiveness, toxicity, and risk-benefit issues. Further, the extensive battery of screening assays for testing blood donations that has been developed since the mid-1980s greatly reduces the currently appreciated risk of blood transfusion. The success of this strategy has reduced the apparent benefit of PI. PI represents a prospective approach to blood safety that could add an important additional layer of safety to a nation's blood supply, however.

This consensus statement emerged from a consensus development process that involved experts and stakeholders in a variety of disciplines and a variety of roles in the process. The statement endeavors to answer six questions posed to the Consensus Panel by the conference organizers that address a number of the issues posed by the imminent availability of PI technologies. The Panel has prepared this statement in the anticipation that it will prove useful, not only to Canadian Blood Services and Héma-Québec, but also to the other stakeholders in Canada, and to planners and policy makers involved in blood services in other countries.

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No. 37

医薬品 研究報告 調査報告書

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研究報告の概要

○よりよい患者治療のための日本のヘモビジランスの有用性

日本赤十字社(JRC)が全国的ヘモビジランス体制を導入してから14年が経過した。報告された輸血副作用症例数は年間約2000例で、過去3年間はほぼ一定数である。非溶血性輸血副作用は報告症例の約80%を占めており、これには輸血関連急性肺障害(TRALI)やアナフィラキシーが含まれる。過去3年間でTRALI症例92例、TRALI疑い症例44例を記録した。TRALIに関係した献血者の約40%に白血球抗体を認めた。非溶血性輸血副作用を起こした患者の血漿タンパク質の抗体と欠損のスクリーニングを継続し、2006年にハプトグロビン欠損者を新たに3例特定した。輸血感染症(TTI)の報告数は、2004年293例、2005年265例、2006年191例と年々減少しているが、献血者の保管検体のID-NATで感染が確認された症例数はこれよりかなり少ない。TTIリスクを低下させる新たな戦略として、2004年から、HBV/HCV/HIV NATのプールサイズ縮小と、受付時の本人確認が実施されている。近年、輸血伝播HEV感染が問題となっており、北海道では最近4症例を記録した。北海道地方ではブタの内臓を十分加熱せずに食べることがあるため、これが献血者に発現したHEVの原因と考えられる。現在北海道で研究的HEV NATを実施している。また、細菌感染も問題となっている。2006年には細菌感染症例を3例認めた。死亡例1例はStaphyloccocus aureusに汚染された濃厚血小板製剤、非死亡例2例はYersinia enterocoliticaに汚染された濃厚赤血球製剤に関連した。日本では、濃厚血小板の保存期間はわずか72時間であり、細菌検査は行っていない。2007年に全ての血液製剤について白血球除去と初流血除去を開始した。3つ目の問題はvCJDである。2005年には日本で最初のvCJD症例が診断された。厚生労働省は、輸血によるvCJD感染を防ぐために、特定の期間ヨーロッパに滞在した人を献血から除外することを決定した。JRCのヘモビジランスは病院の自発報告に基づいている。ヘモビジランスの向上には、病院と血液センターとの相互協力が不可欠である。

報告企業の意見	今後の対応
日本赤十字社の輸血副作用とヘモビジランスに関する報告である。	日本赤十字社では、薬事法に基づき輸血に関連する副作用・感染症症例を報告している。また、「血液製剤等に係る遡及調査ガイドライン」(平成17年3月10日付薬食発第0310009号)に基づき、輸血副作用・感染症の調査を行っている。輸血副作用・感染症に関する新たな知見等について今後も情報の収集に努める。次世代NATの導入に向けた準備を進めている。(2007年11月、血小板の有効期間を本文中の72時間から4日間に延長した。)

使用上の注意記載状況・その他参考事項等

合成血「日赤」
照射合成血「日赤」
合成血-LR「日赤」
照射合成血-LR「日赤」

血液を介するウイルス、細菌、原虫等の感染
vCJD等の伝播のリスク

Simultaneous Session 13: Haemovigilance in Patients

3B-S13-2

TRANSFUSION-ASSOCIATED GRAFT-VERSUS-HOST DISEASE (T-A G-V-H D)

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Transfusion-associated graft-versus-host disease may occur when viable lymphocytes in a blood component engraft in a susceptible recipient and reject the patient/host. It has the features of classical graft-versus-host disease, e.g. like that after an incompletely matched (allogeneic) bone marrow or stem cell transplant, with the added complication of bone marrow failure. The latter is responsible for the high mortality after T-A G-v-H D where death is usually due to sepsis and/or bleeding. Patients at risk of T-A G-v-H D may have cellular immunodeficiency states, either congenital or acquired, or may be immunocompetent when the right combination of HLA antigens occurs on the lymphocytes in the transfused blood component. Patients at risk include those with acute leukemia, lymphoma, stem cell transplants, and those on intense, immunosuppressive chemotherapy, especially those receiving drugs like fludarabine and 2CDA, or undergoing radiation therapy. Non-immunosuppressed patients may be at risk when the blood component comes from a donor homozygous for HLA locus antigens for which the patient is heterozygous. The relative risk of the latter is increased when components are from blood relatives or from the same ethnic group as the patient and have limited HLA diversity. HLA matched components for patients who have become refractory to random donor platelets may increase the risk of T-A G-v-H D. Prevention is the key to obviating T-A G-v-H D as treatment is limited and rarely effective in obviating death. While inactivation of lymphocytes in blood components is most often carried out using irradiation, pathogen inactivation (PI) processes similarly inactivate transfused white blood cells. Radiation may be carried out using cobalt 60 sources but is more conveniently performed with dedicated irradiators with a cesium 137 source or specialized X-ray irradiators. The latter instruments are expensive to purchase but easy to maintain while being convenient to use. Quality control of irradiation involves a method to map the absorbed dose periodically and a device (usually a radiosensitive label) to verify that the dose of irradiation has been delivered to the cellular blood component. Standard operating procedures (SOPs) are set up to ensure that patients at risk of T-A G-v-H D receive irradiated or PI blood components. Irradiated components are not radioactive and may be given to patients who do not require irradiated components. The main effect of the irradiation is to cause minimal ongoing hemolysis and increased potassium leakage of red blood cells, so RBCs have a dating period of 28 days after irradiation.

3B-S13-3

THE BENEFITS OF THE JAPANESE HAEMOVIGILANCE SYSTEM FOR BETTER PATIENT CARE

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The Japanese Red Cross (JRC) blood service headquarters is the one and only blood service institution in Japan. There are 69 blood centers and 116 blood donation rooms collecting almost 60% of all blood. Mobile units, on the other hand, collect 40% of all blood. There were about five million donations in 2006, which consisted of 400 mL of whole blood donations (50%), and 200 mL of whole blood (30%) and apheresis donations (20%). We issued 3.3 million bags of red cell concentrate, 0.7 million bags of apheresis platelet concentrate, and 1.3 million bags of fresh frozen plasma in 2006. Fourteen years has past since the JRC implemented the haemovigilance system nationwide. The number of reported cases is around 2000, which has been almost the same for the past three years. Non-hemolytic transfusion reactions account for 80% of reported cases, which include transfusion-related acute lung injury (TRALI) and anaphylaxis. In the last three years, we recorded 92 cases of TRALI and 44 cases of possible TRALI. We found leukocyte antibodies in around 40% of donors implicated in TRALI. We continued the screening of plasma protein antibody and deficiencies in patients showing non-hemolytic transfusion reactions and found three more cases of haptoglobin deficiency in 2006. The number of reported cases of transfusion-transmitted infections (TTI) gradually decreased yearly: 293 in 2004, 265 in 2005, and 191 in 2006, although the numbers of cases confirmed by ID-NAT of repository samples from implicated donors are much lower than these. New strategies to reduce the risk of TTI have been implemented since 2004, that is, the reduction of HBV/HCV/HIV NAT pool size from 50 to 20 and the implementation of the regulation regarding donor identification at the reception. Transfusion-transmitted HEV (TT-HEV) infection is our most recent concern. Recently, we have recorded four cases of TT-HEV infection in Hokkaido, which is the largest island north of Japan. The cause of the presence of HEV in donors is probably the local practice of eating rare pork innards in the Hokkaido area. We now implement investigative HEV NAT in the Hokkaido region. Bacterial contamination is another concern. In 2006, we encountered three cases of bacterial contamination. One fatal case was associated with a platelet concentrate contaminated with *Staphyloccocus aureus*. Two non-fatal cases were associated with red blood cell concentrate contaminated with *Yersinia enterocolitica*. In Japan, the storage period of platelet concentrate is only 72 hours without the need for bacterial examination. We started to implement universal leukoreduction and diversion of initial blood flow for all blood products from early 2007. The third concern is vCJD. The first vCJD case was diagnosed in Japan in 2005. The Ministry of health, labour and welfare decided to exclude donors who have traveled to Europe during a certain period to prevent vCJD infection via transfusion. Our haemovigilance system is based on voluntary reports from hospitals. Mutual cooperation between hospitals and blood centers is essential for improving the haemovigilance system.

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DETECTION OF HPDEL AMONG THAIS, DELETED ALLELE OF HAPTOGLOBIN GENE THAT CAUSES CONGENITAL HAPTOGLOBIN DEFICIENCY

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Background: Congenital haptoglobin deficiency is a risk factor for anaphylactic non-hemolytic transfusion reactions in Japan. The deleted allele of the haptoglobin gene (Hp), Hpdel, in which there is a deletion larger than 20 kilobases in Hp and the tandemly arranged haptoglobin-related gene (Hpr), were identified from the Japanese patients with congenital haptoglobin deficiency who experienced anaphylactic transfusion reactions. The Hpdel allele has also been observed in other Northeast Asian populations, such as Koreans and Chinese. The same distribution in another part of Asia, specifically Southeast Asian countries, is thought to be worth investigating.
Aims: To investigate the distribution of congenital haptoglobin deficiency in Southeast Asian countries, we analyzed haptoglobin among the Thai population.
Methods: Blood samples collected from 200 randomly selected healthy Thai volunteers were analyzed for serum haptoglobin and the haptoglobin gene. 1) Plasma haptoglobin concentration was measured to identify haptoglobin deficiency. 2) Haptoglobin phenotyping was performed using SDS-PAGE followed by Western blotting. 3) The presence of the Hpdel allele was determined using genomic DNA by an Hpdel-specific PCR method.
Results: There were no haptoglobin-deficient subjects detected among the 200 Thais. Their haptoglobin phenotypes were as follows: Hp 1-1 in 10, Hp 2-1 in 81 and Hp 2-2 in 109. Six individuals heterozygous for Hpdel were

