れ，機能している[2]．とくに，フランスでは1986年に提唱され，1995年にEC評議会において，加盟各国がヘモビジランスシステムを構築するよう決議された．これを受けて加盟各国はその取組みを開始した．1998年には，EU 15か国にスイスとノルウェーを加えて「ヨーロッパヘモビジランスネットワーク」が結成されている．EU加盟国の3分の2では，国が血液事業の責任主体とされており，ヘモビジランスも国のイニシアチブの下で運営されている．国あるいは赤十字を問わず，国内を一元的に管理した安全監視体制をもつ国として，フランス，イギリス，およびアイルランドなどが挙げられるが，ヘモビジランスにおいて取り扱われる報告は軽微なものから重篤なものまですべての有害事象とする国もあれば，死亡・重篤例のみあるいは感染症のみとする国もあり，様々である．

1. フランス

フランスは，世界に先駆けて1992年にヘモビジランスの実施に向けてその定義および概念を規定した[2]．1993年にはその全国的実施を法律で定めており，翌年から実施されている．フランスの基本方針は，有害事象を単に検出するだけではなく，それが国の保健医療のなかでもつ意味を理解できるよう疫学的に評価することにある．このため，医療機関と血液センターとを問わず，すべての有害事象を報告することを法律で義務付けている．有害事象症例は，ヘモビジランスコーディネーターおよび各医療機関などに配置されたヘモビジランス担当者を通して，当該医療機関および血液センターの連携のもとにその原因が調査されフランス血液局(AFSSAPS)に報告される．AFSSAPSはこれらの情報を管理し，その調査・研究に必要な対応を取るとともに，結果を学会誌や年報等で公表している．2004年の報告によると，輸血血液の年間供給数約255万中，有害事象の報告数は7,557件であった．このうち，輸血との関連が否定できないものが75%を占めている．また，全報告のうち，軽症例(grade 1)が75%，長期療養が必要なgrade 2が20%，生命の危険があったgrade 3が0.03%，死亡例(grade 4)が0.004%と報告している[3]．

2. イギリス

イギリスは1994年からヘモビジランスシステムの構築を準備し，ECの決議を受けて1996年から実施している．フランスとは対照的に，有害事象の報告は医療機関や血液センターから自発的に，かつ匿名で特別なルートを通してなされており，後に訴追されることがないよう配慮されている．また，イギリスの基本方針は，実際に輸血の現場で起きている有害事象のプロフィールを把握することにあり，人為的過誤の防止を安全監視の第一目標に掲げている．したがって，疫学的評価を目ざすものではない．イギリスにおけるヘモビジランスシステムは，SHOT(serious hazards of transfusion)と呼ばれ，国立臨床病理学者協会(Royal College of Pathologist)の下で運営されている．2005年は全403病院がSHOTに参加しており，609件の有害事象が報告された．このうち，IBCT (incorrect blood/component transfused；ABO型不適合輸血)79.6%，ATR(acute transfusion reaction；急性輸血反応) 11.1%，DTR(delayed transfusion reaction；遅発性輸血反応) 0.05%，TRALI 0.04%，TTI (transfusion transmitted infection, including bacterial contamination；輸血感染症)0.005%，PTP(post-transfusion purpura；輸血後紫斑)0.003%，TA-GVHD (transfusion-associated-GVHD；輸血関連GVHD)0%であった[4]．

このように，先進国のヘモビジランスとして最も大規模，充実したものとして，フランスのシステムがあり，またイギリスのSHOTは，重症の副作用に限って集計している．さらに，近年フランスとイギリスの両者を目指すアイルランドのシステムが注目されている．

日本のヘモビジランス

日本においては，1993年に，日本赤十字社が全国一律の医薬情報システムを組織し，副作用・感染症情報の収集を開始した．日赤では，医療機関から報告される「副作用・感染症報告」，献血後に献血者または検査データから得られた安全性に関する情報に基づく「献血者発の遡及調査」，製品または原料に由来する感染症に関する論文な

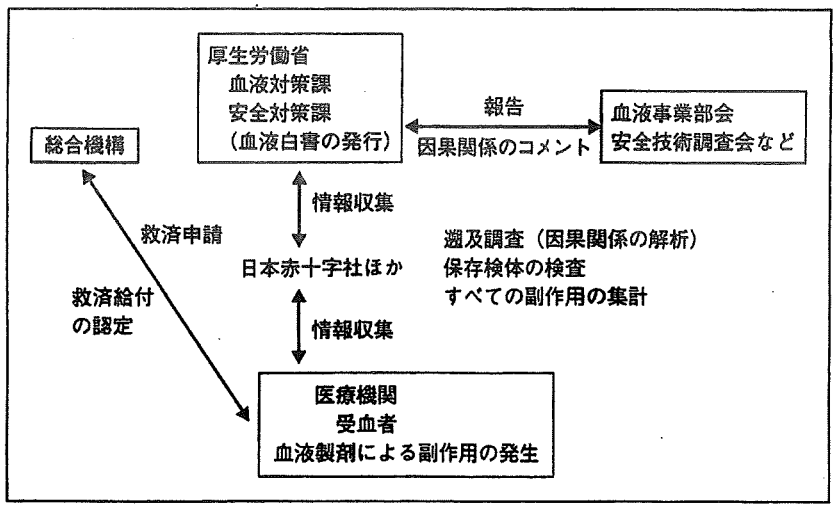

図1　日本のヘモビジランス(血液安全監視体制)の概要

どから得られた知見の評価に基づく「感染症定期報告」および，海外措置情報や研究報告に関する情報に基づく「海外措置・研究報告」などを対象にしている(図1)．1993年に収集された輸血副作用に関する症例数は228件であったが，2005年には1,882件を数えるまでになった．また，これまで約10年間の安全監視活動における最も大きな成果は，輸血後GVHD対策であろう．輸血後GVHDに対しては，1990年の全国調査を皮切りに毎年のように情報提供を行って医療機関の注意を喚起しつつ，かつ一方ではその予防策として輸血血液の放射線照射を進められた．2000年以降現在まで，輸血後GVHDは報告されておらず，わが国において輸血後GVHDは激減した．また，輸血感染症対策については，1996年に輸血血液の検体の保管を開始し，同時にHBV，HCV，HIVが核酸増幅検査が開始され，それ以降HCVおよびHIVの輸血感染も激減した．HBVについては年間数例の輸血感染を認めるが，その検証を可能としたのは検体の保管と核酸増幅検査である．これらの事実は，日赤の安全監視体制が成果を上げていることを示すものである．

こうした現状を踏まえて，平成15年度，第6回血液事業部会安全技術調査会〔2004(平成16)年3月8日〕で，輸血医療の安全性確保に関する総合対策として，「日赤と国と医療機関が連携して，ヘモビジランス体制を構築することを検討するべき時期に来ているのではないか」との意見が出されている．

日本のヘモビジランスの改善点

このように日本赤十字社の輸血副作用に関する集計が一定の成果を上げてきたが，さらに日本におけるヘモビジランスの体制をおしすすめる必要があろう．その理由として，副作用に関する情報は基本的には医療施設の自主申告であり，重症例に偏りがちである．2005年の日赤血液センターへの副作用報告は約1,882件であるが，実態はその10倍〔20,000件，輸血件数(100万)の2%前後〕であると推定されている[5]．また，いまだに院内採血が行われており，輸血後GVHDの発生の危険性が指摘されているが，今の日赤血液センターのヘモビジランス体制では副作用報告として上がってこない．

重症の副作用症例の詳しい情報解析およびその対策の必要性は論をまたないが，軽症の副作用報告の適切な積み重ねも重要である．平成16～18年度，厚生労働科学研究費補助金，レギュラトリーサイエンス研究事業で実施された高本滋教授らの免疫学的輸血副作用の把握とその対応に関する研究は示唆にとんでいる[5]．平成16年度，17年度の2年間において，特定5施設におけるMAP，FFP，PCの使用単位数，および輸血副作用について調査を行った．輸血副作用として溶血性副作用が1件認められたが，その他は，ほとんどが発熱，蕁麻疹，掻痒感などの軽症の免疫学的

表1　高本班で作成された輸血副作用症状の基準項目

1）発熱(℃) (≧38℃，輸血前値から≧1℃以上上昇)	9）腹痛・胸痛・腰背部痛 10）血圧低下 (収縮期血圧≧30 mmHgの低下)
2）悪寒・戦慄	11）意識障害
3）熱感・ほてり	12）血尿(ヘモグロビン尿)
4）掻痒感・かゆみ	13）動悸・頻脈 (成人：100回/分以上)
5）発熱・顔面紅潮	14）頭重感・頭痛
6）発疹・蕁麻疹	15）血管痛
7）呼吸困難 (チアノーゼ，喘息等)	16）その他
8）嘔気・嘔吐	
上記症状の初発時間(輸血開始後　　分)	

免疫学的輸血副作用の把握とその対応に関する研究
平成18年度報告書(主任：高本滋)より抜粋

副作用であることが判明した．さらに，この間に導入が図られた保存前白血球除去と輸血副作用の関連を解析したところ，保存前白血球除去は発熱などの低頻度副作用には有効なものの，蕁麻疹など高頻度アレルギー反応には無効なため，全体として，副作用の軽減に至っていないのではないかとする結論を導きだしている．このことは，輸血の副作用についての情報の集積は，単に有害および未知の事象についての分析・評価のみならず，安全性向上をめざして導入された保存前白血球除去がどの製剤でどの程度有効なのかという，評価のための貴重なデータにむすびつく可能性を示している．これらのことをふまえて，日本におけるヘモビジランスのさらなる充実を図っていくには，①輸血副作用の大部分を占める軽症の完全な把握を行う，②この際，各医療施設とも共通な認識のもとに副作用症状が統一された形で，情報の収集を図る，③インターネット上もしくは定期の刊行物として，輸血関連施設を含めて一般の多くの人を対象に情報の公開を行う，などが必要であろうと考える．例えば，輸血副作用症状の基準項目にしても，高本班で報告されているように，基準項目に診断項目は含めず，身体所見に限定し，観察者が簡便かつ容易に活用でき，各施設とも共通の認識のもとに副作用症状が統一された形で把握されることはとても有用であろう(表1)．

日本の“ヘモビジランス”将来構想

輸血副作用の大部分が症状のみの軽症にとどまること，さらに重症例でも必ず初発症状を呈することを考慮に入れると，軽症の輸血副作用の把握の意義は大きい．輸血副作用には輸血感染症と免疫学的輸血副作用とがあるが，その両方を総合的に統括，把握する必要がある．全国的なサーベイランス形成のためには，各医療機関の輸血療法委員会および都道府県合同輸血療法委員会，日本赤十字社，学会などの連携が不可欠である．非溶血性副作用などの輸血副作用の初発症状にも焦点をあてた，ヘモビジランス機能を医療機関，日赤血

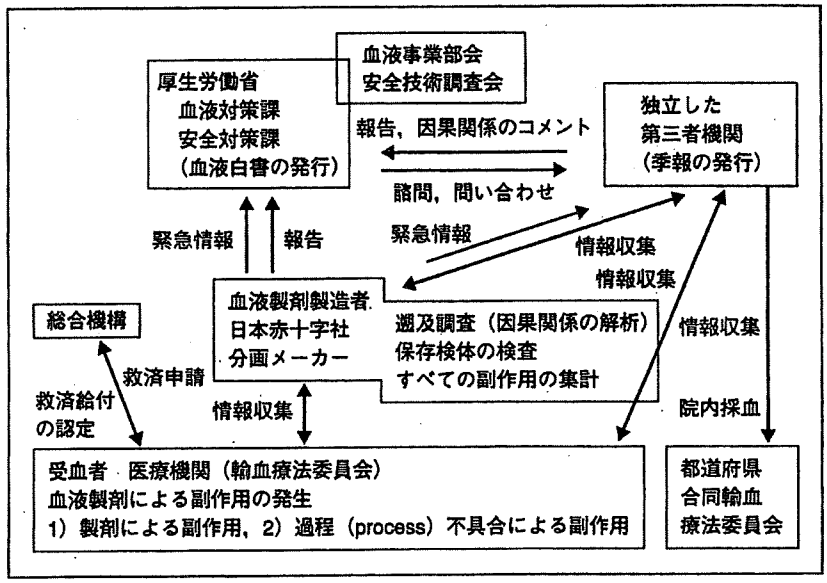

図2　日本の“ヘモビジランス”将来構想

液センターから独立した第三の組織が担い，これまで重症のサーベイを行ってきた日本赤十字社の事業を補完する形が望ましいと考える(図2)．

具体的なイメージとしては以下の通りである．輸血副作用症状の基準項目の作定を日本輸血・細胞治療学会が中心となって行い，実際の副作用事項の報告は各医療機関の限られた管理者によって，インターネットを利用した集計を行う．データの収集のやり方などを具体的に各医療機関に示し，医療機関間でのばらつきをなくす．また報告はリアルタイムではなく，一定期間内で集計してネット上，もしくは定期的に刊行物として報告する．したがって情報提供者にも，集計した情報のフィードバックを行うこととなる．当座の情報収集の主眼はトレンド解析であり，一定期間ごとまたは製剤ごとの非溶血性副作用を中心に情報の解析を行う．

現在，輸血にかかわる有害事象は一国内にとどまらず，どの国においても起こりうることであり，各国とも有害事象に対する共通の認識をもとうとしている．国際輸血学会のヘモビジランスワーキンググループなどを通して，日本でのヘモビジランスに関する情報が，各国と相互交換が行われ，国際協調が緊密になされる必要がある．

まとめ

2003(平成15)年に「安全な血液製剤の安定供給の確保等に関する法律」が制定され，国家レベルで血液製剤の安全性確保および安定供給，適正使用が実際に動き始めている．輸血の安全性をさらに高いレベルにまで引き上げるためにも，輸血血液および血液製剤による副作用の一貫した監視体制が構築されることが急務である．とくに全国の医療機関よりあまねく情報を収集し，統一した報告基準で解析を行う全国網羅のサーベイランスシステムの構築を行い，ヘモビジランスの強化を図っていくべきであろう．解析・評価された情報を医療機関などへフィードバックすることにより医療の安全への寄与に資する．このような一連の監視システムの充実を今後目指すべきである．

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Invited Review

Current Risks in Blood Transfusion in Japan

Hiroko Otsubo and Kazunari Yamaguchi*

Department of Safety Research on Blood and Biological Products, National Institute of Infectious Diseases, Tokyo 208-0011, Japan

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CONTENTS:

SUMMARY: Over the past decades, the incidence of transfusion-transmitted diseases has been dramatically reduced. These reductions have been due to a multifocal approach to the collection, processing, and release of blood components. The estimated risks of transfusion-transmitted hepatitis viruses are now extremely small, but the possibility of infections with emerging pathogens always exists because preventive measures may not be available for all cases. Thus, some patients may be harmed before preventive measures are introduced. Beside transfusion-transmitted infections (TTI), unsolved residual risks such as transfusion-related acute lung injury or incompatible blood components transfusion still exist as major concerns. Continuous efforts toward research on and the prevention of adverse reaction-related blood components must be made to ensure blood safety. The purpose of this article is to introduce the concept of the current risks of transfusion including TTI, review the preventive measures already implemented, and discuss future visions for transfusion safety in Japan.

1. Introduction

Transfusion safety is of the utmost concern, and much effort has been expended on measures to reduce the risk of transfusion-transmitted infectious agents. Since the onset of the human immunodeficiency virus (HIV) epidemic, effective screening tests have been implemented. Moreover, a multifocal approach to the collection, processing, and release of blood components has been added, and as a result remarkable improvements have been made in blood safety. However, the current strategy could not eliminate all transfusion-transmitted infectious agents, i.e., not only known pathogens but also unknown new agents, and some patients may be harmed before preventive measures are introduced. In Japan, the Japanese Red Cross (JRC), the sole provider of labile blood components in Japan, is responsible for blood products in accordance with the Pharmaceutical Affairs Law and has made much effort to improve blood safety.

*Corresponding author: Mailing address: Department of Safety Research on Blood and Biological Products, National Institute of Infectious Diseases, Gakuen 4-7-1, Musashimurayama, Tokyo 208-0011, Japan. Tel: +81-42-561-0771, Fax: +81-42-561-9722, E-mail: kyama@nih.go.jp

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Blood donors should answer many questions about their medical history and their risk factors. Their blood samples should be screened for indicators of infections such as syphilis, parvovirus B19, hepatitis B virus (HBV), hepatitis C virus (HCV), HIV types 1 and 2, and human T-cell lymphotropic virus (HTLV) types I and II. Blood is further tested for cytomegalovirus (CMV) antibody (Ab) before transfusion into patients who are at high risk for CMV disease. Similarly, hepatitis E virus (HEV) is screened as a trial in the Hokkaido district. Even though multifocal approaches to blood safety have been introduced in Japan, unresolved residual risks still exist. These include not only transfusion-transmitted infections (TTI) but also immunological adverse reactions such as transfusion-related acute lung injury (TRALI) and some allergic reactions. For the time being, transfusion components are derived from human blood; therefore, a "zero risk" blood transfusion is never possible. However, it is clear that the application of safety measures and a credible surveillance system which identifies the current transfusion risks will enable transfusion therapy to be safe. A continuous effort toward the research and prevention of adverse reaction-related blood components should be made.

The purpose of this article is to demonstrate the current transfusion risks, describe various approaches that have been implemented for blood safety, and discuss future visions about transfusion medicine in Japan.

2. History of transfusion medicine in Japan

The first transfusion experience in Japan was reported in 1918. Since then, most of the blood components derived from sold blood have been transfused. In 1964, a law came into effect and new JRC statutes were established. At the same time, the Cabinet made a decision that all blood components should be derived from donations, instead of blood sales, and all blood components have been supplied through donated blood since 1969. In 1972, the screening of hepatitis B surface antigen (HBsAg) was begun. The HTLV-I Ab test was added in 1986. In the same year, JRC also began to screen for HIV Abs as a measure to avoid an HIV epidemic.

In 1989, screening strategies for hepatitis B core antibody (HBcAb) and HCVAb were added. JRC established a hemovigilance system in their society and began to collect information on transfusion-related complications including TTI on a voluntary basis in 1993. As a part of the look-back system, JRC began to store 6-ml frozen repository samples from all blood donations in 1996 (1). Since 1999, nucleic acid amplification tests (NAT) for HBV, HCV, and HIV for labile blood products were introduced, and the pool size of NAT was reduced from 500 to 50 the following year (2,3). Since 2004, the pool size of NAT has been reduced from 50 to 20.

In order to investigate the causal relationship between blood components and incidents after transfusion, a look-back system regarding TTI was started nationwide in 2003, and the following year, 6-month-quarantine storage for fresh frozen plasma (FFP) was achieved. In 2005, pre-storage leukocyte-reduction for apheresis-derived platelets was started, and 2 years later, this approach was adapted for all labile blood components. In order to reduce the risk of bacterial contamination, diversion of initial blood flow was adopted in 2006.

Since 2005, people with a history of travel to some European countries, especially England, where bovine spongiform encephalopathy (BSE) is epidemic have been rejected as blood donors.

As noted above, more and more new technologies and/or additional interventions have been adopted over time to achieve the goal of "zero risk."

3. Current risks in transfusion

3-1. Transfusion-transmitted infectious diseases

3-1-1. HBV

Repository samples from all donors, which have been stored since 1996, made it easy to analyze the causal relationship between blood components and recipients. At present, approximately more than 10 cases per year are reported (4) in spite of various approaches to prevent transmission. The NAT-window period (5,6) and low titer of HBV DNA, which cannot be detected in occult HBV-carrier donors, are considered to be the main reasons for this (7-12). A JRC look-back survey reported that the risk of HBV infection caused by blood components from occult HBV carriers with low anti-HBc titers is more than 10-fold lower than the risk caused by donors in the NAT-window periods (6).

According to the JRC reports, it is estimated that the risks of HBV transmission range from 1 in 340,000 bags to 1 in 450,000 bags in Japan (13,14). Satake et al. estimated that the total number of HBV-TTI cases is 17 to 20 per year (1/0.27-0.32 million donations) in Japan out of 5.4 million annual blood donations. This implies that approximately 85% of the HBV infections are caused by donors in the NAT-window period (6).

3-1-2. HCV

Before the implementation of NAT screening, many suspected cases were reported every year. However, during the past few years, one case has been reported every year. The current rate of post-transfusion HCV infection from the donor is estimated to be 1 in 22 million donors, which corresponds to the risk of screening a test-negative, -individual-NAT-positive blood transfusion (13,14).

3-1-3. HIV

One case of HIV transmission due to whole blood transfusion was reported in 1997. Two cases of infected FFP and erythrocytes from the same donor also were reported in 1999. After the implementation of NAT, only one case of FFP-related HIV was reported in 2003. Therefore the risk of transmission is very low, estimated to be 1 in 11 million donors (13,14). However, the number of HIV-infected people in the population has been increasing in Japan. Also, the number of blood donors in which HIV is detected positively has been increasing gradually and finally exceeded 100 people per year in 2007 (Fig. 1) (15).

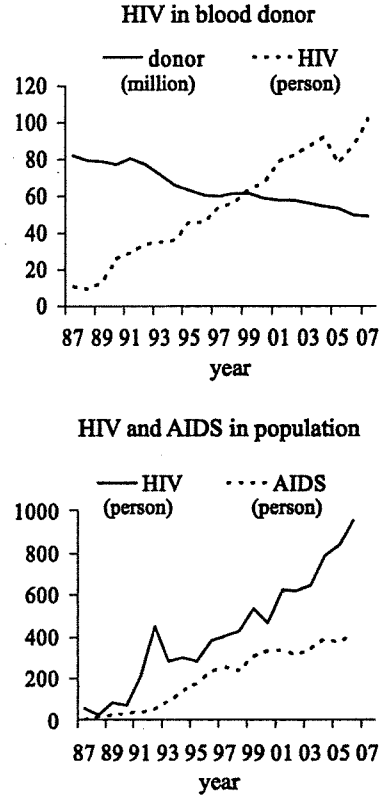

Fig. 1. Trends of the HIV infected rate in population and donation in Japan.

3-1-4. HTLV-I

HTLV-I, the first human retrovirus discovered, is well known as an etiologic pathogen of adult T-cell leukemia/lymphoma (ATL) and other associated diseases. It has been shown to have high seroprevalence in some endemic areas, especially Southwest Japan, the Caribbean islands, and parts of Africa. Its major routes of transmission are considered to be blood transfusion, breast milk feeding and sexual contact (16,17).

Table 1. Previously reported cases of confirmed bacterial contaminated blood components in Japan

Year	Detected bacteria species		Caused blood component
	Patient	Blood component	
1993	*Bacillus subtilis*	NT	RC-MAP
1994	*Serratia marcescens*	NT	PC
1995	*Acinetobacter calcoaceticus*	NT	RC-MAP
1996	*Staphylococcus aureus*	NT	PC
1996	G(+) rod	NT	RC-MAP
1998	*Morganella morganii*	NT	PC
2000	*Bacillus cereus*	*Bacillus cereus*	RC-MAP
2000	*Streptococcus pneumoniae*	*Streptococcus pneumoniae*	PC
2003	*Yersinia enterocolitica*	*Yersinia enterocolitica*	RC-MAP
2006	*Yersinia enterocolitica*	*Yersinia enterocolitica*	RC-MAP
2006	*Yersinia enterocolitica*	*Yersinia enterocolitica*	RC-MAP
2006	*Staphylococcus aureus*	*Staphylococcus aureus*	PC

RC-MAP, erythrocyte concentrate in mannitol-adenine-phosphate solution; PC, platelet concentrates; NT, not tested.

Therefore, preventive measures involving particle agglutination (PA) were implemented in 1986. Moreover, a second generation of PA methods was released for donor screening. Inaba et al. evaluated the efficacy of this screening and HTLV-I prevalence in blood donors after screening estimated the prevalence to be 1 in 45,560 (0.0022%) (18). No confirmed case transmitted by blood components has been reported to the JRC; however, its long latent period and transmission routes other than transfusion make the prevention rate uncertain.

3-1-5. Bacteria

Transfusion-transmitted bacterial contamination of platelets is the most common cause of fatality-related blood components, because the storage of platelets at room temperature to maintain its function is also suitable for bacterial growth. Therefore, numerous countries have introduced culturing-based screening methods to detect bacterial-contaminated platelets. However, after the implementation of these methods, death from bacterial sepsis has continued to be reported because erythrocytes are not screened for bacteria, and current screening methods based on culturing are not entirely satisfactory.

In the United States (US), before the implementation of culturing methods, an average of 11.7 deaths from sepsis per year were reported, whereas 7.5 per year were reported after these detection methods were introduced (19). According to the 6 years' experience of using the BacT/ALERT system in the US, between 0.03 and 0.12% of platelet concentrates (PCs) with a negative culturing test result were still contaminated with bacteria, i.e., false negatives were reported (20).

In Japan, screening methods for platelets have not yet been introduced. We evaluated the efficacy of DOX™ (Daikin Industries, Osaka, Japan), a commercially available system which has been developed to detect contaminated food by measuring the oxygen potential for contaminated PCs. Six species were inoculated into PC, and their dissolved oxygen potentials were measured consecutively (21,22). As a result, this system detected aerobic bacteria in PC within 20 h if their initial concentration was more than 10^1 CFU/ml.

Fatalities from bacterial sepsis are extremely rare and have been reported once every few years (23). However, we have experienced two fatalities from bacterial-contaminated platelet recently. One case was reported in 2000, caused by *Streptococcus pneumoniae* (24), and another case occurred in 2003, caused by a *Staphylococcus aureus*-contaminated platelet (25). In both cases, the patients suffered from malignant hematological diseases. Reported cases of bacterial contamination in Japan are described in Table 1. Since 2007, pre-storage leukocyte-reduction procedure and diversion of initial blood flow have been introduced in Japan. According to the JRC's report, nearly 6,000 blood aliquots from whole blood collected by either the conventional method or from the initial drawn blood flow were cultured using an automated culture system. As a result, the detected rate of bacterial contamination was remarkably reduced from 7 of 2,967 samples (0.24%) to 2 of 2,890 samples (0.07%) after implementation of the diversion (26).

National Blood Service (NBS) in the United Kingdom (UK) also reported that diversion together with improved donor arm disinfection has improved the reduction rate in contamination from 47 to 77% (27).

3-1-6. Prion and other emerging pathogens

Variant Creutzfeldt-Jacob disease (vCJD) was first identified in 1996 in the UK (28,29), and it is considered to be the result of human exposure to the BSE agent. Since then, vCJD patients have been identified in many European countries, especially in the UK. In 2004, the reports showed that vCJD can be transmitted by blood transfusions (30,31). The strategy for preventing trasmission through transfusion has been difficult because there is no effective screening method to determine if a blood donor is infected, and this disease has a long incubation period. Therefore, patients probably received blood products from donors who were asymptomatic at the time of donation. The US instituted a policy in which donations from people who spent at least 6 months in certain western European countries or 3 months in the UK between 1980 and 1996 were excluded. A similar policy has been applied to potential donors in many countries. In Japan, people who spent even one day in the UK from 1980 to 1996 and cumulative periods of 6 months in western European countries where BSE is epidemic were rejected as blood donors.

Consequently, donor deferral was roughly o 6% as a result of this policy. Recently, a number of companies have been developing prion removal filters. Asahi Kasei Medical Co., Ltd. (Tokyo, Japan) has developed an integrated filter which has the functions of prion removal and leukocyte reduction (32,33).

Pall Co., Ltd. (East Hills, N.Y., USA) gained a Council of

Europe (CE) mark for their device "Pall Leukotrap Affinity Prion Reduction Filter (LAPRF)," a new leukocyte reduction filter for the removal of infectious prion from erythrocyte concentrates in 2005 (34,35). Pathogen Removal and Diagnostic Technologies, Inc. (PRDT), which is a joint venture company of the American Red Cross and ProMetic BioSciences, established "P-Capt," which has high prion-binding affinity and also received CE mark in 2006, in cooperation with Macopharma (36).

Some pathogen agents carried by mosquitoes, such as chikungunya virus in the Indian Ocean, West Nile virus in the US, and malaria are widely known as transmitted infectious pathogens (37). Fortunately, this is not an issue of concerne in Japan at present, but potential donors move frequently throughout the world, and some materials imported from abroad may carry mosquitoes. We are collecting information carefully, and we have to manage them in the near future.

Similarly, HEV has been considered to be an imported infectious disease from its epidemic area in the developed countries. However, the epidemiologic study revealed that 2-14% of healthy populations were anti-HEV IgG positive (38), and approximately 13% of the non-A, -B, and -C acute hepatitis cases in Japan were caused by HEV (39). Moreover, the discovery in 2001 of an indigenous Japanese strain of HEV, JRA1, from a patient who had never been abroad, had a great impact on blood safety in our country (40,41). Under these circumstances, HEV screening using a real-time reverse transcription (RT)-polymerase chain reaction (PCR) system has continued as a trial in the Hokkaido district, northern part of Japan.

Blood is also tested for CMV Ab and provided to patients who are at an increased risk for CMV disease in Japan.

3-2. Non-infectious reactions

3-2-1. Hemolytic reactions

Hemolytic reactions are classified into acute hemolytic reactions and delayed hemolytic reactions. Most important hemolytic reactions involve incorrect blood components (IBCT). IBCT has rarely been reported to JRC as an adverse reaction, because it is regarded as a transfusion error. The surveillance of ABO-incompatible blood transfusions was conducted based on an anonymous questionnaire by the Japanese Society of Blood Transfusion for 5 years from 2000 to the end of 2004 (42). This surveillance targeted 1,355 hospitals in Japan, and data were obtained from 829 hospitals among them (61.2%). According to the data, 60 cases of ABO-incompatible transfusion were reported, and 31 of them involved erythrocyte concentrates. Of 31 cases, 22 were due to major mismatches, and others were due to minor mismatches. The current incidents collection system used by JRC is based on voluntary reporting; therefore, the number of reported IBCT cases might be underestimated.

3-2-2. Non-hemolytic reaction

Minor allergic reactions such as urticaria, fever, and dyspnea make up a major portion of non-hemolytic reactions. These include transfusion-associated graft versus host diseases (TA-GVHD) and TRALI.

3-2-3. TA-GVHD

Once TA-GVHD occurs, it is almost always fatal with a very rapid and fulminant course. The mechanism of this condition involves the activation of donor lymphocytes against recipient human leukocyte antigens (HLA). The risk increases in proportion to the degree of HLA haplotype-sharing between donors and patients. In Japan, this condition is a serious problem. Indeed, its incidence is 5-10 times higher than in European countries (43,44). JRC collected information and conducted a national survey in 1991, and a microsatellite DNA assay to identify TA-GVHD has also been developed (45-47). Consequently, JRC has begun the practice of irradiating the blood components supply throughout the country. Since 2000, no confirmed TA-GVHD case has been reported to JRC.

3-2-4. TRALI

TRALI is a serious clinical syndrome involving shortness of breath, hypoxemia and non-cardiogenetic pulmonary edema, associated with HLA/Abs or neutrophil antigens. JRC has gathered information on TRALI since 1997. As knowledge of TRALI has grown, the number of reported TRALI cases has increased. However, the definition of TRALI remains controversial, and it is likely that only a portion of TRALI cases are collected. Other similar serious symptoms which are not included in the definition occur, and treatments have not been developed. Supportive diagnostic evidence includes identifying neutrophil or HLA Abs in the donor or recipient plasma. Among the blood donors, multiparous women frequently have these antibodies. Therefore, in many developed counties, women are not permitted to be plasma donors. In Japan, however, this policy has not been applied.

4. Traceability of causal relationship between blood components and incidents by JRC

JRC has conducted the following tests on residual blood products, plasma derivatives, and recipient blood to identify the causes of adverse reactions and infectious diseases. The contents of the current tests to trace such causes are described in Table 2 (48).

Table 2. Currently conducted tests to identify the causal relationship between blood products and adverse reaction after transfusion according to the classification of reaction type

1. Transmitted infectious diseases
A. Virus
1. Serological test: serological markers related to suspected infections
2. NAT: (1) Detection of suspected viral genome
(2) Evaluation of viral genome sequence homology
B. Bacteria
1. Detection of bacteria by methods based on blood culturing
2. Identification of bacterial species by Gram's stain
3. Detection of endotoxins of Gram-negative bacteria
2. Non-infectious diseases
A. Non-hemolytic adverse reaction
1) Allergic reaction
1. Anti-human leukocyte antigen antibody
2. Anti-platelet antibody
3. Anti-granulocyte antibody
4. Anti-plasma protein antibody: against 6 plasma proteins, including anti-haptoglobin (HP) antibody and anti-immunoglobulin A (IgA) antibody
5. Plasma protein deficiency
2) TA-GVHD
1. Micro-satellite DNA assay
2. Chimerism test on recipient blood
B. Hemolytic adverse reaction
1. Re-check of the blood group and Coombs test
2. Detection of irregular antibody

NAT, nucleic acid amplification tests; TA-GVHD, transfusion-associated graft versus host diseases.

5. Detection strategy versus pathogen reduction for transmitted diseases

At present, detection strategies such as screening tests for known pathogens for which the methods have already been developed are added yearly to maintain the blood components' safety. However, the current strategy does not prevent all of the transfusion-transmitted pathogens. Considering that the use of human blood as a raw biological source is unsafe, screening tests alone cannot exclude all of the potential pathogens. Therefore, we have to consider the introduction of some alternative or additional preventive measures. Some pathogen reduction systems to damage pathogen nucleic acids to proliferate have been developed and some are now under development. Pathogen inactivation (PI) technology using methylene blue plus visible light or solvent-detergent treatment for plasma has been introduced in some European countries and has a track record of more than 10 years (49-51). Similar technologies involving amotosalen (S-59) plus ultraviolet (UV) A light have recently become available for plasma (52). Only amotosalen and riboflavin UV light treatment have obtained the CE mark in Europe, and they have been under evaluation for use with platelets (53,54). With regard to these methods, concern remains regarding cost, process operation changes, ability to inactivate, and ineffectiveness against prions, non-enveloped viruses, spore-formed bacteria and viruses which exist in exceedingly high concentrations in blood. Damage to the products which results in reduction of coagulation factor activities, deterioration of platelets, toxicity, and mutagenicity in recipients is also controversial (55-57). These residual risks are still a major concern to the public, politicians, regulatory agencies, and blood component providers. A recent consensus conference recommended that PI should be implemented when a feasible and safe method to inactivate a broad spectrum of infectious agents is available (58-60).

In Japan, the delegates on behalf of the Japanese Society of Transfusion Medicine and Cell Therapy (JSTMCT) visited some European countries and collected the current information. Additional detection strategies and undeveloped pathogen reduction technology will be extensively debated over the next few years. But it is obvious that TTI is not static and new agents continue to emerge; therefore, we have to carefully watch the circumstances and collect worldwide information.

6. Hemovigilance

Since the AIDS epidemic, developed countries, especially in Europe, took swift action to try to keep records related to transfusion therapy to help ensure blood safety. One method for doing so is called hemovigilance, which is a system for collecting information on unexpected events from donors after drawing blood to the adverse reactions of the patients after transfusion. Various hemovigilance models are usede around the world, depending on social security and national priorities (61-64). JRC has collected transfusion reaction and infectious disease transmission data since 1993, in accordance with the Pharmaceutical Affairs Law. Reporting by medical institutions is voluntary and targets relatively moderate to severe adverse events.

In 2007, JSTMCT established a hemovigilance committee to cooperate with medical institutions and JRC. Seven university hospitals agreed to report all adverse transfusion events

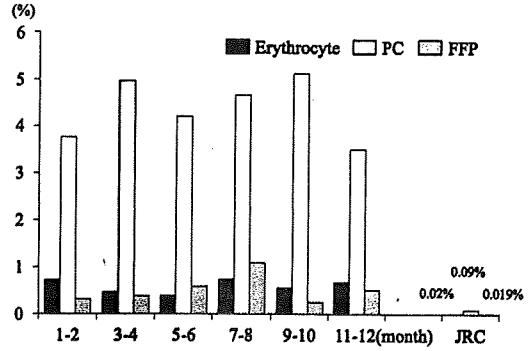

Fig. 2. Bimonthly variability in the reporting rate according to the responsible blood components. PC, platelet concentrates; FFP, fresh frozen plasma.

bimonthly through an anonymous, secure, online portal. Participants also entered the total number of blood products issued over each reporting period. Online access and data entry were made easy, with 16 categories of symptoms and 8 diagnoses. Adverse event rates were calculated automatically and were provided to the participants continuously. As a result of this pilot study, the total number of blood products issued corresponded to about 1% of the total issued in Japan. Six hundred seventy-five transfusion-related adverse events were reported in 2007 by 7 hospitals. Most of them were non-hemolytic transfusion reactions. The reported reaction rates were 0.54 and 0.63% for erythrocytes and plasma, respectively, and 3.4% for PCs in this trial. On the other hand, 0.02% for erythrocytes, 0.018% for plasma, and 0.09% for PCs were nationally reported to JRC (Fig. 2). Hemovigilance such as in this system by a third-party service through an anonymous online portal revealed a high incidence of adverse events, including relatively mild reactions, which physicians previously thought unnecessary, meaningless, or bothersome to report to JRC. Easy online access, anonymity, and the motivation of participating institutions likely contributed to this outcome. This system and the preexisting JRC hemovigilance will complement each other, or rather achieve a better harmonization for future hemovigilance systems (65,66).

7. Conclusion

Current multifocal approaches to blood safety have dramatically reduced the risks related to blood transfusion. However, residual low risks are still a major concern, and we are under pressure to maintain blood product safety. Current approaches have had limited success, and the source of the blood products is raw human blood. In order to improve the safety of blood products, we need to adopt safer alternatives and/or additional preventive measures. Each country has its own circumstances, such as politics, manufacturing, medical resources, and social services, related to transfusion medicine, and each country must develop its most suitable solution.

Consequently, one action taken in one country would not necessarily be an appropriate procedure in another country. It is important to share information and develop standards in transfusion medicine worldwide. However, it is important to remain focused on blood product safety and to track the effectiveness of our policies at all times.

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ヘモビジランス(血液安全監視体制)とは

浜口 功*

はじめに

ヘモビジランス(haemovigilance：血液安全監視体制)はもともとファーマコビジランス(pharmacovigilance)という薬剤の副作用のモニタリングから出てきた言葉であり，血液製剤も薬剤と同様にその副作用をモニタリングするべきという考え方に基づいている．ヘモビジランスで取り扱う血液製剤は原料がヒトの血液であり，ウイルスの安全性の観点からも，特段の注意を払う必要がある．また輸血を受ける側だけでなく，血液を提供する供血者側の安全性，特に採血の際の問題まで含めた監視体制が必要になる．さらには輸血用バッグなど，血液本体以外の品質保持にかかわる問題もモニターするような動きも含まれるようになってきている．

このように，採血から輸血までの一連の過程を監視することでより安全な輸血医療に貢献することが可能となる．すなわちヘモビジランス(血液安全監視体制)は“献血者の選択から患者の追跡調査に至るまでの輸血の全過程を前向きに監視することによって，有害および未知の事象を検出し，その原因を分析・評価し，必要な対応策を示しあるいは事前に警告を発するなどによって有害事象の再発および被害の拡大を防ぐこと”と定義できる．

海外の状況

ヒト免疫不全ウイルス(human immunodeficiency virus，HIV)感染症の発見以降，特にヨーロッパでは輸血・血液の安全性対策が図られ，ヘモビジランスが国レベルで確立され，機能している[1]．特に，フランスでは1986年に提唱され，1995年にEC評議会において，加盟各国がヘモビジランスシステムを構築するよう決議された．これを受けて加盟各国はその取り組みを開始した．1998年には，EU 15か国にスイスとノルウェーを加えて“ヨーロッパヘモビジランスネットワーク”が結成されている．EU加盟国の3分の2では，国が血液事業の責任主体とされており，ヘモビジランスも国のイニシアチブの下で運営されている．フランス，イギリスを始め，多くの国で，国あるいは赤十字を問わず，国内を一元的に管理した安全監視体制が確立されつつある．ヘモビジランスにおいて取り扱われる報告は，軽微なものから重篤なものまですべての有害事象とする国もあれば，死亡・重篤例のみ，あるいは感染症のみとする国もありさまざまである．

次に主な海外のヘモビジランスがどのように動いているか，例を挙げて紹介したい．

1．イギリス

イギリスは1994年からヘモビジランスシステムの構築を準備し，ECの決議を受けて1996年から実施している．有害事象の報告は医療機関や血液センターから自発的に，かつ匿名で特別なルートを通してなされており，後に訴追されることがないよう配慮されている．また，イギリスの基本方針は，実際に輸血の現場で起きている有害事象のプロフィールを把握することにあり，人為的過誤の防止を安全監視の第一目標に掲げている．したがって，疫学的評価を目指すものではない．

イギリスにおけるヘモビジランスシステムは，SHOT(Serious Hazards of Transfusion)と呼ばれ，国立臨床病理学者協会(Royal College of Pathologist)の下で運営されている．また毎年のSHOTの報告には，単なる統計的な数字だけではなく，それらの集計をもとに今後どのような改善を図ることができるかを“Key message and recommendation”という形で，輸血にかかわるすべての関係者向けに発信している．

2．フランス

フランスは，世界に先駆けて1992年にヘモビジランスの実施に向けてその定義および概念を規定した[2]．1993年にはその全国的実施を法律で定めており，翌年から実施されている．フランスの基本方針は，有害事象を単に検出するだけではなく，それが国の保健医療のなかでもつ意味を理解できるよう疫学的に評価することにある．

このため，医療機関と血液センターとを問わず，すべての有害事象を報告することを法律で義務付けている．有害事象症例は，ヘモビジランスコーディネータおよび各医療機関などに配置されたヘモビジランス担当者を通して，当該医療機関および血液センターの連携の下にその原因が調査され，フランス血液局(Agence française de sécurité sanitaire des produits de santé，AFSSaPS)に報告される．AFSSaPSはこれらの情報を管理し，その調査・研究に必要な対応を取るとともに，結果を学会誌や年報などで公表している．副作用の報告率は約0.3%であり，わが国に比べるとかなり高い．2004年からは“e-fit”と呼ばれるオンラインによる報告システムが導入されている．

3．アイルランド

アイルランドでは1999年からNHO(National Haemovigilance Office)がヘモビジランスを始めているが，報告率は0.1%程度である．特に輸血過誤の防止対策として，国レベルでニアミスプロジェクトを施行している．輸血の副作用として患者に起こる副作用より，なんらかの過誤による副反応がより問題となっている国々での新たな取り組みとして注目に値する．

4．アメリカ

アメリカではEU諸国のヘモビジランスの動きに反応する形で国レベルでの監視体制を輸血医療，細胞移植，臓器移植など移植医療全般に広げて構築しようとしている．2009年からは輸血による副作用と供血者の副作用に関してアメリカ血液銀行協会(American Association of Blood Banks，aaBB)，ならびにアメリカ疾病予防管理センター(Center for Disease Control and Prevention，CDC)が中心となってシステムを稼働しようとしている．

このように，EU諸国はもちろんのこと，そのほかの輸血医療のレベルが高い国々ではヘモビジランスシステムが既に導入されている．それぞれの国により体制の違いはあるが，他の国のシステムを参考にしながら，各国で自分の国にあったシステムを構築している状況である．

わが国のヘモビジランス

わが国においては，1993年に日本赤十字社が全国一律の医薬情報システムを組織し，副作用・感染症情報の収集を開始した．1993年に収集された輸血副作用に関する症例数は228件であったが，2007年には1,651件を数えるまでになった[2]．また，これまで約10年間の安全監視活動における最も大きな成果は，輸血後移植片対宿主病(graft versus host disease，GVHD)対策であろう．輸血後GVHDに対しては，1990年の全国調査を皮切りに毎年のように情報提供を行って医療機関の注意を喚起しつつ，かつ一方ではその予防策として輸血血液の放射線照射が進められた．2000年以降現在まで，輸血後GVHDは報告されておらず，わが国における輸血後GVHDは激減した．

また，輸血感染症対策については，1996年に輸血血液の検体の保管を開始し，同時にB型肝炎ウイルス(hepatitis B virus，HBV)，C型肝炎ウイルス(hepatitis C virus，HCV)，HIVを対象とした核酸増幅検査が開始され，それ以降HCVおよびHIVの輸血感染も激減した．HBVについては年間数例の輸血感染を認めるが，その検証を可能としたのは検体の保管と核酸増幅検査である．これらの事実は，日本赤十字社の安全監視体制が成果を上げていることを示すものである．

こうした現状を踏まえて，2003年度，第6回血液事業部会安全技術調査会(2004年3月8日)で，輸血医療の安全性確保に関する総合対策として，“日赤と国と医療機関が連携して，ヘモビジランス体制を構築することを検討するべき時期に来ているのではないか”との意見が出されている．

これまで日本赤十字社の輸血副作用に関する集計が一定の成果を上げてきたが，今後わが国におけるヘモビジランスの体制をさらに完備する必要がある．その理由として，副作用に関する情報は基本的には医療施設の自主申告であり，重症例に偏りがちである．2005年の日赤血液センターへの副作用報告は約1,882件であるが，実態はその10倍〔20,000件，輸血件数(100万件)の2%前後〕であると推定されている．また，いまだに院内採血が行われており，輸血後GVHDが発生していることが指摘されているが今の日赤血液センターのヘモビジランス体制では副作用報告として上がってこない．

重症の副作用症例の詳しい情報解析およびその対策の必要性は論をまたないが，軽症の副作用報告の適切な積み重ねも重要であることが，2004～2006年度，厚生労働科学研究費補助金，レギュラトリーサイエンス研究事業，高本班「免疫学的輸血副作用の把握とその対応に関する研究」で示された[3]．輸血の副作用についての情報の集積は，単に有害および未知の事象についての分析・評価のみならず，安全性向上を目指した評価のための貴重なデータに結びつく可能性を示している．

これらのことを踏まえて，わが国におけるヘモビジランスのさらなる充実を図っていくには，以下の点が必要であろうと考える．

①輸血副作用の大部分を占める軽症の把握を行う．

②この際，各医療施設とも共通な認識のもとに副作用症状が統一された形で，情報の収集を図る．

③インターネット上もしくは定期の刊行物として，輸血関連施設を含めて一般の多くの人を対象に情報の公開を行う．

例えば，輸血副作用症状の基準項目にしても，高本班で報告されているように，観察者が簡便かつ容易に活用でき，各施設とも共通の認識のもとに副作用症状が統一された形で把握されることはとても有用であろう．さらには，世界的な動向に注意を払いながら，わ

が国のシステムの良いところを世界の国々と共有し，今後もヘモビジランスで収集できたデータを有効に利用し輸血医療の安全性向上，供血者の安全性向上につなげていくよう，さらなる努力が必要である．

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（＊国立感染症研究所血液・安全性研究部
〒208-0011 東京都武蔵村山市学園4-7-1）

髄液中のアポリポ蛋白Eの臨床的意義

山内一由（やまうちかずよし）＊

▨髄液中に存在する中枢神経組織由来のアポリポ蛋白E

1．アポリポ蛋白Eとは

アポリポ蛋白(アポ)Eは299個のアミノ酸からなる分子量約34 kDaの糖蛋白であり，低比重リポ蛋白(low density lipoprotein，LDL)リセプターあるいはLDLリセプター関連蛋白(LDL receptor related protein)のリガンド蛋白として脂質の輸送および細胞内への取り込みといった機能を担っている[1]．一般的に，アポEには独立した対立遺伝子(ε2，ε3，ε4)によってコードされるアポE2(Cys^{112}，Cys^{158})，アポE3(Cys^{112}，Arg^{158})，アポE4(Arg^{112}，Arg^{158})の3種類のアイソフォームが存在し，それらの組み合わせによって，ホモ接合体3種類(アポE2/E2，E3/E3，E4/E4)，ヘテロ接合体3種類(アポE2/E3，E2/E4，E3/E4)，計6種類の表現型(フェノタイプ)が存在する．

アポEの主要な産生臓器は肝臓であるが，アストロサイトやグリア細胞をはじめとする脳神経組織でも豊富に産生され，髄液中の主要アポ蛋白として存在する[2]．脳神経組織由来の髄液中のアポEは体循環系のアポE，すなわち，肝臓由来のアポEと完全に独立しており脳血液関門(blood-brain barrier)を通過しない．このことは，肝臓移植後の患者で血中のアポEフェノタイプはドナー型に変わったのに対し，髄液中のアポEのフェノタイプは移植前と変化していなかったというLintonら[3]の知見が裏付けている．

また，髄液中には主要なアポ蛋白の一つであるアポBが存在しないことも特徴であり，そのことから，髄液中のアポEは血中のアポEと同様に脳神経組織における脂質代謝においてLDLレセプターのリガンドとして機能していると考えられている．また，髄液中のアポEは神経細胞の維持，修復などにも関与していること[4]が知られているが，その機能は完全に明らかになっているわけではない．

2．髄液中のアポEの性状

アポEは血中と同様に髄液中においてもリポ蛋白粒子として存在しており，ゲルろ過クロマトグラフィー法により血清高比重リポ蛋白(high density lipoprotein，HDL)とLDLの中間のサイズをもつ，アポAIも含有するリン脂質に富むHDL_1様の粒子として検出される．アガロース電気泳動において，血清アポEがpre-βとslow-α位に泳動されるのに対し，髄液アポEはfast-α位に泳動されることからもHDL_1様の粒子であることがわかる．

さらに，髄液中のリポ蛋白は超遠心法により，VLDL($d<1.006$)，HDL_2($d=1.063\sim1.125$)，HDL_3($d=1.125\sim1.21$)それぞれに相当する比重に分画されるが，興味深いことにLDLに相当する比重($d=1.006\sim1.063$)にはリポ蛋白は検出されない．これは血中でLDL粒子を構成しているアポBが髄液中には存在しない事実を反映した結果と考えられる．各リポ蛋白分画を電子顕微鏡下で観察すると，いずれも球状の粒子であり，血清リポ蛋白と同様に比重によるサイズの違いが認められるが，その差は血清リポ蛋白ほど大きくなく，また，サイズの異なる粒子が観察され，多様性に富んでいることがわかる．

髄液中のアポEは，ウエスタンブロット解析上，基本的には血中のアポEと同様にアイソフォームを反映したパターンを示すが，髄液に特有な性状もいくつか認められる．特に髄液中のアポEでは，アポEモノマーより若干分子量の大きいシアル化されたアポEと思われるバンドが多く検出される．実際，等電点電気泳動後のウエスタンブロット法で解析すると髄液中のアポEは血清のアポEに比べて高度にシアル化されていることが一目瞭然である[5]．

▨髄液中のアポEの測定とその臨床的意義

1．髄液中のアポEの測定法

臨床的に髄液中のアポEの測定法としては，酵素免疫測定法(enzyme-linked immunosorbent assay，ELISA)に基づく定量法[6]と，常法に従って処理した

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Haemovigilance for the optimal use of blood products in the hospital

H. W. Reesink, S. Panzer, C. A. Gonzalez, S. Gimbatti, E. Wood, M. Lambermont, V. Deneys, D. Sondag, T. Alport, D. Towns, D. Devine, P. Turek, M.-K. Auvinen, T. Koski, C. K. Lin, C. K. Lee, W. C. Tsoi, E. Lawlor, G. Grazzini, V. Piccinini, L. Catalano, S. Pupella, H. Kato, S. Takamoto, H. Okazaki, I. Hamaguchi, J. C. Wiersum-Osselton, A. J. W. van Tilborgh, P. Y. Zijlker-Jansen, K. M. Mangundap, M. R. Schipperus, D. Dinesh, P. Flanagan, Ø. Flesland, C. T. Steinsvåg, A. Espinosa, M. Letowska, A. Rosiek, J. Antoniewicz-Papis, E. Lachert, M. B. C. Koh, R. Alcantara, M. Corral Alonso & E. Muñiz-Diaz

Haemovigilance systems (HSs) have been established in many countries (see Vox Sang 2006; 90: 207–241). The main purpose so far has been the registration of all incidents and untoward effects related to blood transfusion. However, the question has arisen whether the optimal use of blood should be included in the HS. For this international forum, information was obtained on the opinion of the relevant authorities concerning this aspect of haemovigilance and how it should be organized. To obtain this information, the following questions were sent to representatives in the various countries.

Question 1

Has a HS been established in your country?

- If so, is the optimal use of blood products in the hospital part of the system?
- If not, do you feel that this aspect of haemovigilance should be included in the system and, if so, do you intend to include it in the future?

Question 2

If the optimal use of blood products in the hospital is part of your HS, or is expected to be so in the future, how will this part of the HS be organized, e.g.

- via a haemovigilance officer in the hospitals;
- audit methods in the hospital to check the use of these products and compliance with guidelines;
- other methods.

We obtained 16 contributions to this forum. A national HS has been established in all but three of the participating countries. In Argentina, although there is no official HS, the creation of hospital haemovigilance committees is promoted, and the blood banks are legally obliged to report all data concerning blood transfusion to the Ministry of Health, but because these data are not properly analysed, it is not considered to be a national HS. In Japan, where there have been local activities since 1993, a national HS is being organized, and in Australia, where there is an HS in some of the states/territories, a national system is on its way.

All HS were initially set up to record all transfusion incidents and adverse reactions and have led to the institution of transfusion committees (TCs) and transfusion officers (TOs) in the hospitals.

The opinion that the optimal use of blood products should be part of the HS, or that at least it should be actively propagated, is almost general. At present, it is already an integral part of the national HS in Belgium, Ireland and the Netherlands. In these countries, there are TCs and TOs in the hospital, and national guidelines for the optimal use of blood are available. In Poland, it will be included in the national HS as soon as possible. In Finland, this aspect of transfusion medicine is a separate project in which the five university hospitals and five other larger hospitals participate. In most of the other countries, where the optimal use of blood products is not (yet) part of the HS, there is much local activity to promote it. In Canada, New Zealand and Australia, the optimal use of blood products is not expected to become part of the HS.

The measures taken, or that are expected to be taken, to control the optimal use of blood products are the creation of TCs and the appointment of TOs in the hospitals, the availability of guidelines in which the proper medications for blood products are outlined and the education and training of clinicians and laboratory personnel and audits. An interesting scheme has been on trial in Hong Kong: an abbreviated form of the guidelines for the use of a blood product is printed on it. Any requests outside the guidelines must be supported by clinical justification. This policy has been successfully applied already, saving blood products.

Many of the answers we obtained are extensive and contain many interesting details, which can only be appreciated by reading the answers.

It can be concluded that there is much interest in including the optimal use of blood products in the national HS, and in some countries, this aspect is already an integral part of the HS, while in others, it is expected to become part of the HS in the near future. Hospital TCs and TOs and the education of clinicians and laboratory personnel play or will play an essential role in controlling this important aspect of transfusion medicine.

H. W. Reesink
Academic Medical Center
Department of Gastroenterology and Hepatology
Amsterdam, the Netherlands
E-mails: internationalforum@kpnplanet.nl;
h.w.reesink@amc.nl

S. Panzer
Department of Blood Group Serology and Transfusion Medicine
University of Vienna
Währinger Gürtel 18-20
A-1090 Vienna, Austria
E-mails: internationalforum@kpnplanet.nl;
simon.panzer@meduniwien.ac.at

C. A. Gonzalez & S. Gimbatti

Question 1

Our country does not have a haemovigilance national system. The technical and administrative standards in Argentine [1] promote the creation of haemovigilance hospital committee. Based on a tree-monthly standard form, all blood banks are legally obliged to send all data concerning blood transfusion to the Argentine Ministry of Health. Because the data are not fully analysed or reported throughout the country, we do not consider this as a haemovigilance system.

Undoubtedly, any system of haemovigilance should include between its parameters the control of the optimal use of blood products, co-ordinating its activities with the Hospital Transfusion Committee, without overlapping activities.

Question 2

The deficiencies in knowledge of prescription, administration or identification of transfusion recipients may impact on patient safety and, in some cases, result in death. This point was consistently demonstrated by audits of clinical transfusion practices [2]. Another significant contributing factor to this problem may be the limitations of budgets, inadequate facilities and insufficient numbers of experienced trainers make it impossible to meet the training needs.

In many developing countries, the lack of proper testing and understanding effects blood safety still is considered as a major problem in acquiring life-threatening transfusion-transmitted infections [3,4]. Another significant contributing factor to this problem may be the presence of fragmented and hospital-based blood transfusion system.

Buenos Aires city has the more complex health system in Argentina, and there is no doubt that is in great need for highly qualified, skilful, trained healthcare staff members, to provide an up-to-date, high-quality blood transfusions service.

In Buenos Aires City, the hospital transfusion committee was created by Resolution 135/SS/02 [5] that contained the first public clinical guidelines. The implementation of this ministerial resolution demanded a highly efficient training programme as one of the most important prerequisites.

The most challenging part was developing training courses for staff members of hospital blood banks aiming to improve technical competence and laboratory practice to check the use of blood products and compliance with guidelines between the most important objectives to learning.

This culture change involves making decisions with the best scientific evidence available in Transfusion Medicine and Immunohematology. This entails a great effort by all members of blood banks team, in the conviction that no permanent change is possible without education.

For these reasons, those courses are necessary, not as a palliative of inadequate training, but as a real tool for transforming the practice of transfusion medicine.

In our experience, those training courses could be the necessary first step before implementing the haemovigilance programme.

C. A. Gonzalez
Nélida Noemi Lena
Pablo Muntaabski
Dirección General Adjunta Redes de Servicios de Salud
Ministerio de Salud - GCBA
Medrano 350
Buenos Aires
Argentina
E-mail: carlos.gonzalez@speedy.com.ar

S. Gimbatti
Dirección General Adjunta de Asuntos Jurídicos
Ministerio de Salud - GCBA
Carlos Pellegrini 313
Buenos Aires
Argentina

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E. Wood

Question 1

Australia is working towards a national haemovigilance system [1]. At the present time, systems exist covering one or more Australian states/territories (jurisdictions) for identifying, reporting, reviewing and responding to transfusion-related patient adverse events and near-misses [2,3]. There is now agreement that these jurisdictional systems will provide validated data periodically for a national report, using an agreed data dictionary and with event classification and imputability assessments based on International Society of Blood Transfusion/International Haemovigilance Network definitions. The Australian Red Cross Blood Service also receives reports of recipient adverse events where special product support or reference testing is required, or where there are product recall or donor management implications, as well as capturing adverse events relating to donors and blood donation [4].

Formal surveillance for optimal use of blood is not part of the current jurisdictional haemovigilance activities or planned national system, although this could be an important area for future consideration. The current systems usually capture contributory factors such as transfusion decisions that did not conform to hospital or national clinical practice guidelines, or where procedures for appropriate transport, storage and handling were not followed.

Question 2

In Australia, the role of the transfusion practitioner is now well established as a key element in hospital transfusion safety. Most transfusion practitioners have a nursing background. This role works in partnership with other members of the transfusion team such as transfusion medicine specialists, haematologists, laboratory scientists and other clinical counterparts. Transfusion practitioners provide education and training (including to promote optimal use of blood), procedural review and implementation, investigation and follow-up of adverse events and near-misses, and clinical audit. Other audits and surveys relevant to optimal use of blood are conducted by transfusion laboratories, the Australian and New Zealand Society of Blood Transfusion, the jurisdictional transfusion practice improvement collaboratives and the Blood Service. Tools and reports of some of these audits are available online [2,5]. Patient blood management initiatives are also being actively developed in Australia at institutional, jurisdictional and national levels. The role of haemovigilance officer is not presently established in Australia separate from the role of transfusion practitioner. The Blood Service also has a transfusion medicine team (including transfusion nurses) whose role includes promotion of optimal use of blood.

E. Wood
Monash University
Melbourne, Vic., Australia
E-mail: woodericam@hotmail.com

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M. Lambermont, V. Deneys & D. Sondag

Question 1

A national haemovigilance system has been formally in place since November 2005 (implementation of the European directive 2002, 2005). The haemovigilance network includes a national cell depending on the Federal Agency for Medicines and Health Products (FAMHP) for notifications of adverse reactions and events associated with transfusions and donations. Haemovigilance data are collected by haemovigilance officers in each blood transfusion establishment and hospital.

In April 2002 (Royal Decree), transfusion committees were created in each hospital, in which all actors in the transfusion chain are represented: the medical director, three medical doctors with different specialities, the director of the blood bank, the director of the nursing department, the pharmacist, a representative from the blood transfusion establishment. Among the committee's various missions, optimal use of blood is clearly identified through the criteria of transfusion, the procedures for the whole transfusion process, the notification of adverse events and reactions, the evaluation of the efficacy of the transfusion and the patient's follow-up.

In collaboration with FAMHP, the Superior Health Council dependent on the Federal Ministry of Health elaborated recommendations for the optimal use of red-blood-cells, fresh frozen plasma and platelet concentrates based on international consensus conferences organized in Belgium. It has also published a transfusion manual to help transfusion committees to implement 'good transfusion practices'.

Question 2

The optimal use of blood products falls under the responsibility of the blood transfusion committee in close collaboration with the medical directors of the blood banks and the blood transfusion establishments.

The best method for evaluation is participation in clinical and benchmarking studies, audits (internal and external) and inspections by national authorities. The comparison of clinical transfusion practices is at the present time limited to a few hospitals.

All tools for implementing and maintaining a haemovigilance system, including optimal use of blood products, are being set up but are not yet optimally used because of a lack of resources.

M. Lambermont, V. Deneys & D. Sondag
Service du Sang, Belgian Red Cross
96, rue de Stalle, Brussels, Belgium
E-mails: xxxxx

T. Alport, D. Towns & D. Devine

Question 1

In Canada, primary responsibility for haemovigilance rests with the Public Health Agency of Canada who have developed the Transfusion Transmitted Injuries Surveillance System (TTISS Program). The mandate of the TTISS Program is:

- 'To establish a national surveillance system for transfusion, transmitted injuries (ie. infectious diseases and non-infectious adverse events); and
- To support target research to provide information for risk assessment to further reduce the risk associated with blood transfusion in Canada' (see http://www.public-health.gc.ca).

Participation in the programme is voluntary, but the programme does support the presence of hospital-based Transfusion Safety Officers, and there is good participation of all the provinces and territories.

In addition, Canadian Blood Services and Hema-Quebec, which operates the blood system in Quebec, have their own reporting requirements that are outlined in the Circular of Information (see http://www.blood.ca) and who, in turn, have a regulatory requirement to report significant adverse events to Health Canada. Provinces and hospitals often have their own systems for reporting adverse events and errors that are complimentary to the above.

Optimum use of blood products is not part of the Heath Canada mandate, and there are no current plans to include this as part of the formal haemovigilance programme. Consistent with the focus on consensus-driven practice change in Canadian medicine, it is unlikely that optimal use of blood products would become a mandated activity of a Canadian haemovigilance system. At the present time, the optimal use of blood products with respect to recommendations and guidelines is discussed by various groups including provincially based blood co-ordinating offices, which exist in some Canadian provinces, and the National Advisory Committee on Blood and Blood Products, which is a collaborative group of hospital-based transfusion medicine experts, representatives from Canadian Blood Services, and the government funders of the blood system. This loose system achieves a similar goal to the formal inclusion of optimal use of blood products in the haemovigilance programme.

Question 2

In Canada, utilization management occurs at a number of different levels in the system. As provinces (rather than the Federal Government) have primary responsibility for delivering health care, provinces and hospitals have developed their own systems to ensure optimal utilization of blood products. Some hospitals have transfusion safety officers or equivalent positions to support the appropriate use of blood products. Most provinces have active provincial blood co-ordinating offices with utilization management being a key mandate. The blood operators (Canadian Blood Services and Hema-Quebec) also provide educational information to hospitals and have staff specifically dedicated to working with the hospitals to monitor product use. For example, a formal disposition reporting system has recently been established to provide data on blood product use. The inter-provincial committee responsible for funding of the blood service also has a National Advisory Committee whose mandate includes developing guidelines and programmes to ensure optimal utilization of blood products.

There is collaboration among these groups as well as participation in international efforts to develop clear indications and guidelines for the use of blood products.

T. Alport, MD
Canadian Blood Services
Regina, SK, Canada
E-mail: Ted.alport@blood.ca

D. Towns, MD
Canadian Blood Services
Calgary, AB, Canada
E-mail: Dale.towns@blood.ca

D. Devine, PhD
Canadian Blood Services
Vancouver, BC, Canada
E-mail: Dana.devine@blood.ca

P. Turek

Question 1

Haemovigilance system has been established in the Czech Republic many years ago. In the year 2006, an older system has been modified to be fully compatible with EU Blood Directive. Use of blood components is included in the system only as regards organizational and technical matters (ordering, labelling of samples, mis-transfusions near misses etc.), indications and medical/clinical appropriateness are not included into the system. There is a discussion in the field on how optimal use of blood would be supported and controlled, but there is no intention to include this directly into the obligatory haemovigilance system.

Question 2

The 'optimal use of blood' is not included into our haemovigilance system, but possibilities and needs are discussed. Nowadays, we can hardly conceive it as a task of any specialized officer, self-audits and audits are already organized in some hospitals.

P. Turek
Thomayer Teaching Hospital
Videnska 800, 140 59 Prague, Czech Republic
E-mail: petr.turek@ftn.cz

M.-K. Auvinen & T. Koski

Question 1

The Finnish Red Cross Blood Service (FRCBS) is a financially and operationally independent unit within the Finnish Red Cross. It is a centralized organization providing nationwide blood services in Finland. Its tasks include organizing blood donor sessions and collecting blood as well as testing of donated blood, production of blood components and distribution of blood components to hospitals.

The Blood Safety Office (BSO) operates within the FRCBS and has been appointed by the Ministry of Social Affairs and Health to act as a co-ordinator between the various parties involved in the blood transfusion chain. Reporting serious adverse reactions and adverse events became mandatory at the beginning of 2006. In the same year, BSO was established within the FRCBS. Adverse events have been investigated in the FRCBS for years, but since 2006, all blood safety operations have been centralized in the BSO. BSO forwards reports on serious adverse events to the National Agency for Medicines, which then reports to the EC according to EU Directives. Mild adverse events can be reported to hospital blood centres or directly to BSO. In the case of mild events, sampling is usually unnecessary; a report will suffice. In practice, hospitals generally report mild adverse events on an annual basis to the BSO.

The number of adverse events is annually monitored to detect any noticeable increase in their incidence. Monitoring also helps to detect decreases in the number of adverse events resulting from changes or improvements. All data retrieved are used to improve training and operational instructions in hospitals and at the FRCBS.

The Programme for Optimal Use of Blood (VOK Programme) is a collaborative effort between the FRCBS and major Finnish hospitals to provide commensurate data on blood use in the participating organizations. It is not included in the haemovigilance reporting system and stands as a separate project as there are so many other aspects involved in optimal use of blood than adverse events. However, because both initiatives are run by FRCBS, the close information change and co-operation is possible.

So far, all five university hospitals in Finland and five other major hospital districts have joined the Programme, and the VOK Database now covers about 68% of the consumption of blood components in Finland (year 2007). The VOK Database currently includes data from 2002 to 2007.

Data for the VOK Database are collected from hospitals' administrative, laboratory, blood bank and operating theatre registers as well as from the Blood Service's Blood Donor Registry. Patient identifications are encrypted in the Database and cannot be traced back to the individual patient. The Database includes information about diagnoses, procedures, laboratory results and the transfused blood components. The Database allows analysis of differences in blood use and evaluation of clinical practices. The participating hospitals are also able to conduct specific analyses of data pertaining to their own organization. The ultimate aim of the VOK Programme is to improve patient safety and outcomes of patient care.

The reports are designed to compare blood use in participating hospitals and to illustrate changes from previous reports. FRCBS organizes 2–3 benchmarking events annually for clinical professionals involved with blood use in different hospitals. The benchmarking events typically consist of presentation of specific VOK reports and, most importantly, group discussions of differences in practices among hospitals. Lectures are given by the participants as well as invited experts. Experiences from the events are encouraging, and the benchmarking discussions have led to the adoption of best practices in several cases. It may be simple actions such as controlling the practice for blood reservations for operations. After such action, the blood use in orthopaedic interventions has decreased with 27%, whereas the total number of interventions has increased with 14% for the same period 2002–2007. Naturally, there are several other changes happening, and in the same time,

new techniques as well as medicines have been adopted, but we would like to believe that also the benchmarking activities play a role here.

Question 2

We don't have any national plans for establishing haemovigilance officers at the hospitals. Only a few hospitals have transfusion committees, and most of them are not active. This may reflect the fact that Finland has not had any major public mistrust in blood transfusions in the past compared with some other countries (a very low number of transfusion transmitted HIV, no BSE). Many of the practical issues have been solved between the clinicians and FRCBS directly.

For the follow-up of the transfusion triggers, some blood bank software programs show for the person ordering blood the latest haemoglobin and platelet levels of the patient. However, the possibility for automatic alarm when the laboratory values are above the predefined triggers has not been actively promoted. The alarms might be an inefficient way of guiding transfusions because the person facilitating the blood order at the ward rarely is a member of team transfusing the patients.

The laboratory technologists (and in some hospitals laboratory physicians) contact the clinic whether it is likely that the product or the number of units ordered is incorrect or unusual. The FRCBS requests that the physician consults if rarely used products are ordered (e.g. washed components, HLA-typed or volume reduced platelets).

Formal audits at the hospitals are rare because we don't have national guidelines for blood usage.

Locally, there are some guidelines that are only recommendations. Quality systems are increasingly implemented in the clinical wards, and blood usage and transfusion triggers are monitored at least in some hospitals e.g. in association with stem cell transplantations.

The adverse events of transfusions are reported as described in Q1. There are now an increasing number of hospitals using softwares for collecting and reporting data for severe adverse events and reactions in all fields of medicine. Ideally, the haemovigilance issues would be integrated in the same system. This would probably facilitate and increase the reporting of other haemovigilance issues than transfusion reactions leading to safer transfusions.

In the current economic climate, the cost-savings may be the most important driver for better practices in the transfusions field. This economic excuse may turn out to be beneficial for the patients if the decision to transfuse is made on a strictly medical basis and a decision not to transfuse is seen as an equally valid decision. Transfusion of blood may be a minor action in the whole process of treating a patient, but its economic impact is rather large. Any activities or excuses that attract the interest to evaluate the current practice are justified.

M.-K. Auvinen
Finnish Red Cross Blood Service
Kivihaantie 7
00310 Helsinki, Finland
E-mail: Marja-Kaisa.Auvinen@veripalvelu.fi

T. Koski
Department of Laboratory Haematology
Centre for Laboratory Medicine
Pirkanmaa Hospital District Centre
P.O.B 2000
FIN-33521 Tampere, Finland

C. K. Lin, C. K. Lee & W. C. Tsoi

Question 1

In Hong Kong, a haemovigilance system was established in 2001 among all public hospitals, which covered some 95% of health services and accounted for about 90% red cell utilization. The system, including a standardized reporting format, was implemented by the Central Transfusion Committee (CTC) of the Hong Kong Hospital Authority (HA), which is an organization responsible for the management of all public hospitals and outpatient clinics and the Hong Kong Red Cross Blood Transfusion Service (HKRCBTS). The CTC is a formal committee chaired by a senior executive who reports to the Chief Executive of the HA. Membership of the CTC includes all Hospital Transfusion Committee (HTC) Chairpersons and representative from the HKRCBTS. It took the CTC a year to implement the haemovigilance system that enables electronic reporting. Based on the consensus among CTC members and frontline clinicians, it was decided to categorize reporting into two major areas, namely, transfusion incidents and adverse transfusion reactions. The former mandates compulsory reporting of all incidents and near-miss events related to blood transfusion activities in hospitals. The severity of the incident is graded according to a 7-point scale, where 0 is equal to near-miss i.e. incident detected before transfusion took place and six means fatality as a direct consequence of transfusion.

For adverse transfusion reactions, the system encourages voluntary reporting of any adverse reactions happened during and after transfusion and adopts same severity grading scale as incident reporting. HTCs are responsible for the investigation and follow-up of local hospital issues and identify possible imputable relationship between adverse transfusion events and the blood components involved.

At half-yearly intervals, the HKRCBTS assists the CTC to collate and analyse the data that will be presented in a