Impact of donor epidemiology and screening strategies on the safety of blood and plasma for fractionation

Yoshihiko Tani, MD, PhD

Japanese Red Cross Osaka Blood Center

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**Blood and Law**

<table>
<thead>
<tr>
<th>Blood and Blood components</th>
<th>Prescription Drugs Specified Biological Products</th>
</tr>
</thead>
<tbody>
<tr>
<td>Plasma derivatives (Alb, IVIG, etc)</td>
<td>=</td>
</tr>
</tbody>
</table>

- **AS PRESCRIPTION DRUG**
  - Pharmaceuticals and Medical Devices Act
  - GMP, GQP, GVP...
  - Quality Management System
  - Risk Management Plan

- **AS SPECIFIED BIOLOGICAL PRODUCTS (Human Blood)**
  - Law Concerning Securing Stable Supply of Blood Product (Blood Law)
  - Minimum Requirements for Biological Products
  - Standards for Biological Materials

Pharmacovigilance is implemented to blood components

Haemovigilance
# Blood Service and Regulation

## National Government (Ministry of Health, Labour and Welfare)

<table>
<thead>
<tr>
<th>Policy Making</th>
<th>Authorization</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Promotion of Blood donation</td>
<td>• Blood collection</td>
</tr>
<tr>
<td>• Domestic demand/supply of blood</td>
<td>• Manufacturing of blood components</td>
</tr>
<tr>
<td>• Promotion of appropriate use</td>
<td>• Marketing</td>
</tr>
<tr>
<td>• Secure stock of source plasma</td>
<td></td>
</tr>
</tbody>
</table>

## Blood Establishment (Japanese Red Cross Society)

<table>
<thead>
<tr>
<th>Blood Establishment</th>
<th>Regional Blood Centers</th>
<th>Block Blood Centers</th>
<th>Blood Service Headquarters</th>
</tr>
</thead>
<tbody>
<tr>
<td>Blood collection</td>
<td>Distribution</td>
<td>Manufacturing (testing, preparation)</td>
<td>Marketing Authorization Holder in charge of manufacturing</td>
</tr>
</tbody>
</table>

**Pharmaceuticals and Medical Devices Agency (PMDA)**

- Regulation Review
- Post-Marketing Safety Measure

**Supervision**

**Assessment**

- Application, ADR reports

**Approvals Licensing Statutory**
Blood Safety Measures

Voluntary Donor
- Personal Identification
- Questionnaire (Archive for 41 yrs)
- Reference of test records

Donated Blood
- Specimen storage
  - Sep 1996 (for 11 yrs)
- Call back

Plasma for Fractionation
- Pre-donation diversion
- Serological Tests
- NAT (Individual)

Blood for Transfusion
- Pre-storage leukocytes reduction
- Inventory hold (for 6 mo)
- Post donation information
- Inventory hold for FFP (for 180 days)

Hospitals
- Lookback study
- TTI Report

Patients

Plasma Pool
- Virus Removal/Inactivation
- NAT

Plasma Derivatives

JRCS⇒JBPO

※Relief System for Infections Derived from Biological Products
# Measures to Ensure Safety of Blood Supply

## Safety Measures

<table>
<thead>
<tr>
<th>Reception upon Blood donation</th>
<th>Safety Measures</th>
<th>Target Pathogens</th>
</tr>
</thead>
<tbody>
<tr>
<td>Blood collection</td>
<td>ID confirmation, Interview, Questionnaires</td>
<td>bacteria, WNV, Malaria, vCJD, Chagas, etc</td>
</tr>
<tr>
<td>Tests</td>
<td>Thorough skin disinfection, Diversion of initial blood</td>
<td>Resident skin bacteria</td>
</tr>
<tr>
<td>Preparation</td>
<td>Serological testing/NAT for pathogens, ALT</td>
<td>HBV, HCV, HIV, HTLV-1, Syphilis, B19/ HBV, HCV, HIV</td>
</tr>
<tr>
<td>Distribution</td>
<td>Leukocytes reduction prior to storage</td>
<td>bacteria such as Yersinia enterocolitica</td>
</tr>
<tr>
<td>Transfusion</td>
<td>Inventory holds(fresh frozen plasma) : 6 months</td>
<td>Information on infections of blood donor</td>
</tr>
<tr>
<td></td>
<td>Collection of information on adverse reactions/infections, Retrospective surveys</td>
<td></td>
</tr>
</tbody>
</table>
Screening of blood donations

1. **Serological Test (CLEIA)**
   - HBsAg
   - HBcAb*
   - HCV-Ab
   - HIV-1/2-Ab
   - HTLV-1-Ab
   - TP-Ab
   - ParvoB19-Ag
   - (selective CMV-Ab)

2. **Individual NAT** (since Aug. 2014)
   - HBV, HCV, HIV
     - (investigational HEV : Exclusive in Hokkaido)

3. **Biochemical test**
   - ALT (Ineligible above 101 IU/L)

4. **Blood type**
   - ABO typing, Rh typing
   - Irregular antibodies
     - (HLA typing)

---

### Criteria for HBcAb and HBsAb

<table>
<thead>
<tr>
<th>HBsAb</th>
<th>Criteria</th>
<th>HBcAb</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;200mIU/mL</td>
<td>eligible</td>
<td>1&lt; C.O.I ineligible</td>
</tr>
<tr>
<td>&lt;200mIU/mL</td>
<td>eligible</td>
<td>1&lt; C.O.I ineligible</td>
</tr>
<tr>
<td>&lt;200mIU/mL</td>
<td>eligible</td>
<td>1&lt; C.O.I ineligible</td>
</tr>
</tbody>
</table>

(since Aug. 2012)
Blood Donation

Whole Blood
- 200mL RBC-1
- 400mL FFP120
- 400mL RBC-2
- 400mL FFP240

Apheresis
- PC+PPP
  - PC
  - PPP
- PPP

Plasma for Fractionation
FFP (Fresh Frozen Plasma)

- **FFP 120mL, 240mL from Whole Blood**
  Prepare within 8 hours after collection

- **FFP 480mL from Apheresis**
  *(PPP: Platelet Poor Plasma)*
  Prepare within 6 hours after collection
Plasma for fractionation

- **Category C (for coagulation factors)**
  - Fibrinogen, FVIII, FIX, etc
  - good for 1 year after collection

- **Category N (for non-coagulation factors)**
  - Albumin, γ-globulin, etc
  - good for 4 years after collection
Annual Changes in volume of Plasma

x10^3 L

FFP  Plasma for fractionation

JRCS Tracing System

◆ Haemovigilance: Since January 1993

◆ Medical Representatives nationwide: 150 persons

◆ Repository Samples: Since September 1996
  6 mL, frozen, 11 years

◆ Nucleic amplification tests:
  Target viruses: HBV, HCV, HIV, Parvovirus B19, HEV, CMV, HTLV-1, Dengue etc.

◆ Storage of source plasma and FFP:
  Source plasma: since July, 2000
  FFP: since Jan., 2004

◆ Serological tests
◆ Microbiological tests
Specimen Storage:
minus 30 °C
for period of 11 years
(10 years + 1 years)
Flow of Transfusion ADR case reporting

Pharmaceuticals and Medical Devices Agency (PMDA) → Ministry of Health, Labour and Welfare (MHLW)

ADR case reporting

Voluntary Report
- JRC Regional Blood Centres
  - ADRs TTIs
  - Information acquisition
  - Analysis report

Mandatory Report
- JRCS Blood Service HQ Safety Vigilance Division
  - ADRs TTIs
  - Analysis results

Statutory
- JRCS Central Blood Institute
  - Investigation/analysis

JRC Regional Blood Centres
- Information acquisition
- Analysis report

Medical Institutions/Hospitals

Literature & Academic conferences

Mandatory Report
- Severe ADRs TTIs

Severe ADRs TTIs

Voluntary Report
- ADRs TTIs
Transition of the number of adverse reactions and infectious diseases

Non-hemolytic
Hemolytic
GVHD (doubt)
Infection (doubt)

<table>
<thead>
<tr>
<th>Year</th>
<th>Non-hemolytic</th>
<th>Hemolytic</th>
<th>GVHD (doubt)</th>
<th>Infection (doubt)</th>
</tr>
</thead>
<tbody>
<tr>
<td>2008</td>
<td>1.554</td>
<td>28</td>
<td>3</td>
<td>2</td>
</tr>
<tr>
<td>2009</td>
<td>1.541</td>
<td>25</td>
<td>2</td>
<td>1</td>
</tr>
<tr>
<td>2010</td>
<td>1.579</td>
<td>26</td>
<td>2</td>
<td>1</td>
</tr>
<tr>
<td>2011</td>
<td>1.597</td>
<td>14</td>
<td>6</td>
<td>3</td>
</tr>
<tr>
<td>2012</td>
<td>1.595</td>
<td>12</td>
<td>2</td>
<td>6</td>
</tr>
<tr>
<td>2013</td>
<td>1.515</td>
<td>21</td>
<td>23</td>
<td>13</td>
</tr>
<tr>
<td>2014</td>
<td>1.451</td>
<td>21</td>
<td>81</td>
<td>1</td>
</tr>
<tr>
<td>2015</td>
<td>1.533</td>
<td>1</td>
<td>28</td>
<td>2</td>
</tr>
</tbody>
</table>
(1) **Non-hemolytic adverse reactions**
- anti-HLA antibody
- anti-platalet antibody
- anti-granulocyte antibody
- anti-plasma protein antibody
- Plasma protein deficit

(2) **Hemolytic adverse reactions**
- ABO group and irregular antibody
(3) **Bacterial infection**
- Blood culture test
- Bacterial identification test
- Endotoxin quantification test

(4) **Viral infections**
- NAT
- Serological test

(5) **Post-transfusion GVHD**
- Micro-satellite DNA test
- Chimerism test on recipient blood
TT-Viral Infections
Annual changes in the number of suspected TTI reported cases

- **2000 50p-NAT**
- **2003 Look-back Study**
- **2004 20p-NAT**
- **2008 CLEIA method New 20p-NAT**
- **2012 HBcAb criteria revised**
- **2014 ID-NAT**

### Cases by Year and Pathogen

- **HIV**
- **HCV**
- **HBV**
- **Others**
- **Bacteria**

**Graph Details:**
- **X-axis:** Year (2001 to 2015)
- **Y-axis:** Number of cases (0 to 300)
- **Legend:**
  - Orange: Others
  - Grey: Bacteria
  - Light Blue: HIV
  - Yellow: HCV
  - Red: HBV

**Notes:**
- **2000 50p-NAT**
- **2004 20p-NAT**
- **2008 CLEIA method New 20p-NAT**
- **2012 HBcAb criteria revised**
- **2014 ID-NAT**
<table>
<thead>
<tr>
<th></th>
<th>Cases</th>
<th>Information Sources</th>
</tr>
</thead>
<tbody>
<tr>
<td>HBV</td>
<td>96</td>
<td>Report from medical institution, Look back, Follow-up research etc.</td>
</tr>
<tr>
<td>HCV</td>
<td>7</td>
<td>Report from medical institution, Look back, Follow-up research</td>
</tr>
<tr>
<td>HEV</td>
<td>19</td>
<td>Report from medical institution, Look back / Post-donation information</td>
</tr>
<tr>
<td>HAV</td>
<td>1</td>
<td>Post-donation information</td>
</tr>
<tr>
<td>HIV</td>
<td>1</td>
<td>Look back</td>
</tr>
<tr>
<td>H.Parvovirus B19</td>
<td>6</td>
<td>Report from medical institution</td>
</tr>
<tr>
<td>Bacteria</td>
<td>12</td>
<td>Report from medical institution</td>
</tr>
</tbody>
</table>
Transition of the number of TTI in Japan (donation year)

The number of cases derived from the same donated blood is excluded.
Annual TT-HBV confirmed cases by screening method and infectious status of donors

(cases/year)

<table>
<thead>
<tr>
<th></th>
<th>20p-NAT(old)</th>
<th>20p-NAT(new)</th>
<th>HBcAb criteria change</th>
<th>ID-NAT</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>48months</td>
<td>49months</td>
<td>23months</td>
<td>24months</td>
</tr>
<tr>
<td>8.0 cases</td>
<td>3.0</td>
<td>4.7</td>
<td>2.6</td>
<td>0.5</td>
</tr>
<tr>
<td></td>
<td>3.2</td>
<td>2.7</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>0.3</td>
<td>0.5</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>0.5</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

20p-NAT(old) Nat: 20p-NAT(new) Nat: HBcAb criteria change Nat: ID-NAT
### 95% LOD NAT screening

<table>
<thead>
<tr>
<th>Virus</th>
<th>LOD (IU/mL)</th>
<th>Sensitivity ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>HBV</td>
<td>64</td>
<td>4.3</td>
</tr>
<tr>
<td>HCV</td>
<td>248</td>
<td>3.0</td>
</tr>
<tr>
<td>HIV-1</td>
<td>836</td>
<td>18.0</td>
</tr>
<tr>
<td>HEV</td>
<td>1020**</td>
<td>7.9</td>
</tr>
</tbody>
</table>

* Attached document  
* * in-house PCR by Hokkaido BBC
Viral load, LOD of NAT, and window period

- **HCV**:
  - Sensitivity x83
  - Window period shorten 2 days

- **HBV**:
  - Sensitivity x15
  - Window period shorten 10 days

(Quantities in IU/mL)

- ID-NAT
  - 3 IU/mL
  - 4 IU/mL

- 20 pool NAT
  - 248 IU/mL
  - 64 IU/mL

About 10 days

Infection

2 days
Incidence of Post-Transfusion Hepatitis

- Paid blood donation (50.9%)
- Transition period (31.1%)
- Establishment of a donation system (1969)
- HBs antigen test (1972)
- 400 mL donation & plasma/platelet donation (1986)
- Discovery of HBc antibody test (first generation) (1989)
- HCV antibody test (second generation) (1992)
- (500-sample pool) NAT (1999) 0.48%
- (50-sample pool) NAT (2004) 0.001%
- (20-sample pool) NAT (2000) 0.0007%
Annual changes of TT-HEV cases

- Genotype3
- Genotype4

2006- Investigational HEV-NAT exclusively in Hokkaido

2011 Health insurance reimbursement for IgA-HEV-Ab testing

( ) Look-back study derived cases

(all G4 cases were occurred in Hokkaido)
Summary of TT-HEV cases

- 20 cases in 14 years
- from medical institutions: 8, look-back study cases: 12
- Genotype 3: 17 cases, Genotype 4: 3 cases (only in Hokkaido)
- Recovered with seroconversion: 15 cases
- Persisted viremia: 5 cases (transplantation, hematological disorder)
- ALT > 1000 IU/mL : 2 cases
- No fulminant or fatal cases
- Ribavirin: effective
- Blood donors: early phase of infection without HEV-Ab
- Infection rate: 50%

(calculated from TT-HEV cases and look-back study in Hokkaido)
TT-Bacterial Infections
Safety measures for bacterial infection

◆ Donor interview （dental treatment, diarrhea, etc.）
◆ Skin disinfection
◆ Diversion Pouch (to remove very first flow containing skin bacterial flora) 2006-2008 gradually started
◆ Leukoreduction （to remove bacteria such as Y.enterocolitica from RBC component）started in 2007
◆ Shortest shelf life （4 days for PLT, 21 days for RBC, including collection day）
  : Use the unit with low bacteria concentration
◆ Visual inspection of Platelet for swirling before delivery and at transfusion site
## Transfusion transmitted bacteria cases

<table>
<thead>
<tr>
<th></th>
<th>Before diversion pouch/leukoreduction</th>
<th>For 10 years after diversion pouch/leukoreduction</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>RBC</strong></td>
<td>3 cases (0)</td>
<td>B. cereus</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Y. enterocolitica x 2</td>
</tr>
<tr>
<td><strong>PLT</strong></td>
<td>2 cases (2)</td>
<td>S. pneumoniae</td>
</tr>
<tr>
<td></td>
<td></td>
<td>S. aureus</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Year</th>
<th>component</th>
<th>Days incl. collection</th>
<th>Detected bacteria</th>
</tr>
</thead>
<tbody>
<tr>
<td>2008</td>
<td>IR-PLT-LR</td>
<td>4</td>
<td>Staphylococcus aureus</td>
</tr>
<tr>
<td>2008</td>
<td>IR-PLT-LR</td>
<td>4</td>
<td>Streptococcus dysgalactiae ssp. Equisimilis</td>
</tr>
<tr>
<td>2009</td>
<td>IR-PLT-LR</td>
<td>4</td>
<td>Serratia marcescens</td>
</tr>
<tr>
<td>2009</td>
<td>IR-PLT-LR</td>
<td>3</td>
<td>Streptococcus agalactiae</td>
</tr>
<tr>
<td>2011</td>
<td>IR-PLT-LR</td>
<td>4</td>
<td>Streptococcus dysgalactiae ssp. Equisimilis</td>
</tr>
<tr>
<td>2012</td>
<td>IR-PLT-LR</td>
<td>4</td>
<td>Streptococcus pyogenes</td>
</tr>
<tr>
<td>2013</td>
<td>IR-PLT-LR</td>
<td>3</td>
<td>Streptococcus dysgalactiae ssp. Equisimilis</td>
</tr>
<tr>
<td>2015</td>
<td>IR-PLT-LR</td>
<td>3</td>
<td>Escherichia coli</td>
</tr>
<tr>
<td>2015</td>
<td>IR-PLT-LR</td>
<td>4</td>
<td>Staphylococcus aureus</td>
</tr>
</tbody>
</table>

( ) : fatal case
血小板製剤を輸血する前に外観検査として、色調の変化、凝固物の有無、パックの破壊の有無などの異常がないか確認していただく。

血液センターで行っている主な外観検査

製剤の色調
血小板製剤は、瓶内に波動されると色調が変化することがあります。

凝固物の有無
血小板製剤は、まれにフィブリンが析出し、細菌により凝固物が生じることがあります。

スワリングとは、血小板製剤を頭光管にかざしてゆっくりと回転したときに見られる渦巻き状のバターンを指し、スワリングを目視で確認することは血小板の状態を観察的に評価する方法として国際輸血学会(ISBT)によりその有用性が認められています。

血小板の保存方法
血液センターでは、血小板の機能を良好に保つために、20〜24℃で振とう保存しています。

血小板製剤の輸血前の外観検査
輸血する前に、製剤の色調、凝固物の有無や製剤パックの破壊の有無等、外観に異常がないか確認してください。

注意: スワリング検査の判定には、熟練が必要ですので、医療機関でスワリングの有無を判定される場合は、十分に注意してください。
# Near miss cases of bacterial contamination

<table>
<thead>
<tr>
<th>FY</th>
<th>Facilities</th>
<th>Visual abnormality</th>
<th>Component</th>
<th>Days incl. collection</th>
<th>Bacteria/Pathogen</th>
</tr>
</thead>
<tbody>
<tr>
<td>2012</td>
<td>Blood center</td>
<td>Swirling negative</td>
<td>Platelet</td>
<td>4</td>
<td><em>Escherichia coli</em></td>
</tr>
<tr>
<td></td>
<td>Blood center</td>
<td>Aggregation</td>
<td>Platelet</td>
<td>4</td>
<td><em>Staphylococcus aureus</em></td>
</tr>
<tr>
<td></td>
<td>Hospitals</td>
<td>Aggregation</td>
<td>Platelet</td>
<td>4</td>
<td><em>Streptococcus agalactiae</em></td>
</tr>
<tr>
<td></td>
<td>Hospitals</td>
<td>Aggregation</td>
<td>Platelet</td>
<td>4</td>
<td><em>Staphylococcus aureus</em></td>
</tr>
<tr>
<td></td>
<td>Hospitals</td>
<td>Line Clogging</td>
<td>Platelet</td>
<td>4</td>
<td><em>Staphylococcus aureus</em></td>
</tr>
<tr>
<td>2013</td>
<td>Blood center</td>
<td>Aggregation</td>
<td>Platelet</td>
<td>4</td>
<td><em>Staphylococcus aureus</em></td>
</tr>
<tr>
<td></td>
<td>Blood center</td>
<td>Aggregation</td>
<td>Platelet</td>
<td>4</td>
<td><em>Klebsiella pneumoniae</em></td>
</tr>
<tr>
<td></td>
<td>Hospitals</td>
<td>Line Clogging</td>
<td>Platelet</td>
<td>4</td>
<td><em>Staphylococcus aureus</em></td>
</tr>
<tr>
<td></td>
<td>Hospitals</td>
<td>Aggregation</td>
<td>Platelet</td>
<td>4</td>
<td><em>Staphylococcus aureus</em></td>
</tr>
<tr>
<td>2014</td>
<td>Blood center</td>
<td>Aggregation</td>
<td>Platelet</td>
<td>4</td>
<td><em>Staphylococcus aureus</em></td>
</tr>
<tr>
<td></td>
<td>Blood center</td>
<td>Aggregation</td>
<td>Platelet</td>
<td>4</td>
<td><em>Lactococcus garvieae</em></td>
</tr>
<tr>
<td></td>
<td>Blood center</td>
<td>Aggregation</td>
<td>Platelet</td>
<td>4</td>
<td><em>Staphylococcus aureus</em></td>
</tr>
<tr>
<td></td>
<td>Hospitals</td>
<td>Aggregation</td>
<td>Platelet</td>
<td>4</td>
<td><em>Staphylococcus aureus</em></td>
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<tr>
<td></td>
<td>Hospitals</td>
<td>Aggregation</td>
<td>Platelet</td>
<td>4</td>
<td><em>Staphylococcus aureus</em></td>
</tr>
<tr>
<td>2015</td>
<td>Blood center</td>
<td>Aggregation</td>
<td>Platelet</td>
<td>4</td>
<td><em>Citrobacter Koseri</em></td>
</tr>
<tr>
<td></td>
<td>Blood center</td>
<td>Aggregation</td>
<td>Platelet</td>
<td>4</td>
<td><em>Lactococcus garvieae</em></td>
</tr>
<tr>
<td></td>
<td>Hospitals</td>
<td>Aggregation</td>
<td>Platelet</td>
<td>4</td>
<td><em>Staphylococcus aureus</em></td>
</tr>
</tbody>
</table>
Summary of the TT-Bacteria cases

◆ 9 cases in 10 years after implementation of diversion pouch and leukoreduction
◆ All cases were caused by platelet component (apheresis)
◆ No fatal cases
◆ No infectious case of RBC
◆ Visual inspection is effective, because bacterial contamination is unavoidable
I thank Drs. Rikizou Taira and Naoko Goto (Japanese Red Cross Society Technical Department Safety Vigilance Division) for supporting and preparing for this presentation.
Thank you for your attention.
Thank you for your attention.
Thank you for your attention.