Biovigilance in the US: A Hospital View

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Johns Hopkins Hospital

• Busy 900 bed academic medical center with 45,000 units of RBC, 15,000 units of SDP, and 16000 bags of FFP transfused annually
• Approximately 5% of samples need further immunohematologic studies
• Active and long standing transfusion monitoring programs for adverse effects- transfusion reactions, infectious complications, component misuse
• No formal “haemovigilance” program until 2009
“Haemovigilance” at JHMI

• Delayed hemolytic transfusion reactions

• Incorrectly labeled blood samples

• Septic platelet transfusion reactions
Delayed serologic transfusion reactions (DSTRs) and delayed hemolytic transfusion reactions (DHTRs) were studied in a large tertiary-care hospital. A DSTR was defined by the posttransfusion finding of a positive direct antiglobulin test (DAT) and a newly developed alloantibody specificity. A DHTR was defined as a DSTR case that showed clinical and/or laboratory evidence of hemolysis. Thirty-four cases of DSTR, 70 percent of which were due to anti-E and/or -Jka, were documented prospectively over a 20-month period. Retrospective review of the medical records found clinical evidence of hemolysis in only 6 (18%) of the 34. Thus, the incidence of DSTR was 1 (0.66%) of 151 recipients with posttransfusion samples available for testing, whereas the incidence of DHTR was only 1 (0.12%) of 854 patients tested. Fifteen of the 34 patients were followed for up to 174 days after reaction. Twelve of the 15 still demonstrated a positive DAT with anti-IgG only. Eluate studies indicated that the persistence of a positive DAT after DSTR or DHTR may involve several immunologic mechanisms, including the development of posttransfusion autoantibodies. This study indicates 1) that DSTRs are a frequent finding in multiply transfused patients, although most cases are benign and fail to meet rigid criteria for DHTR, and 2) that the persistence of a positive DAT after DSTR or DHTR is common.
<table>
<thead>
<tr>
<th></th>
<th>Pre-transfusion</th>
<th>Post-transfusion</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>- negative autocontrol/DAT</td>
<td>- positive autocontrol/DAT</td>
</tr>
<tr>
<td></td>
<td>- negative crossmatch</td>
<td>- newly developed alloantibody</td>
</tr>
<tr>
<td></td>
<td></td>
<td>in eluate and/or serum</td>
</tr>
</tbody>
</table>
Incidence of DSTR Per Patient

- DSTR cases = 34
- Number of transfused patients = 8,535
- Only 60% (5,121) had post-transfusion sample evaluations

\[
\frac{\text{DSTR}}{\text{Tested patients}} = \frac{34}{5,121} = 1:151 (0.66\%)
\]
## Clinical DHTR

<table>
<thead>
<tr>
<th>Patient</th>
<th>Diagnosis</th>
<th>Fever</th>
<th>Decreased HCT</th>
<th>Increased Bili</th>
<th>Renal dysfunction</th>
<th>Antibody</th>
</tr>
</thead>
<tbody>
<tr>
<td>4</td>
<td>Squamous Cell CA</td>
<td>No</td>
<td>Yes</td>
<td>No</td>
<td>No</td>
<td>Jk&lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
<tr>
<td>*10</td>
<td>Myelofibrosis</td>
<td>No</td>
<td>Yes</td>
<td>Yes</td>
<td>No</td>
<td>C&lt;sub&gt;,e&lt;/sub&gt;</td>
</tr>
<tr>
<td>11</td>
<td>Metast Breast CA</td>
<td>No</td>
<td>Yes</td>
<td>No</td>
<td>No</td>
<td>Jk&lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
<tr>
<td>12</td>
<td>Liver Transplant</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Jk&lt;sup&gt;a,E&lt;/sup&gt;</td>
</tr>
<tr>
<td>17</td>
<td>Coronary Disease</td>
<td>No</td>
<td>Yes</td>
<td>No</td>
<td>No</td>
<td>Jk&lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
<tr>
<td>*18</td>
<td>Sickle Cell Anemia</td>
<td>No</td>
<td>Yes</td>
<td>No</td>
<td>Yes</td>
<td>Jk&lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
</tbody>
</table>
Incidence of DHTR

\[
\frac{34}{5121} = 1:151 \\
\frac{6}{5121} = 1:854 \\
\frac{2}{5121} = 1:2561
\]

Clinically Reported
## Serologic findings in DHTR

<table>
<thead>
<tr>
<th></th>
<th>Traditionally-expected results</th>
<th>Previous study</th>
<th>Present study</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Initial findings</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>DAT</td>
<td>+</td>
<td>+ +</td>
<td>+</td>
</tr>
<tr>
<td>IgG</td>
<td>Usually</td>
<td>Seldom</td>
<td>Always</td>
</tr>
<tr>
<td>C3d</td>
<td>+/-0†</td>
<td>++</td>
<td>+/-0</td>
</tr>
<tr>
<td>MF⁺</td>
<td>Usually</td>
<td>Never</td>
<td>Rarely</td>
</tr>
<tr>
<td>Eluate</td>
<td>Alloantibody</td>
<td>Alloantibody</td>
<td>Alloantibody</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th><strong>Long-term findings (&gt; 14 days after transfusion)</strong></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>DAT</td>
<td>0</td>
<td>+</td>
<td>+/-0</td>
</tr>
<tr>
<td>IgG</td>
<td>0</td>
<td>+/-0</td>
<td>+/-0</td>
</tr>
<tr>
<td>C3d</td>
<td>0</td>
<td>++</td>
<td>+/-0</td>
</tr>
<tr>
<td>Eluate</td>
<td>0</td>
<td>Alloantibody</td>
<td>Alloantibody, Autoantibody, or nonreactive</td>
</tr>
</tbody>
</table>
## Delayed Hemolytic Transfusion Reactions: Evolving Concepts

<table>
<thead>
<tr>
<th>Feature</th>
<th>Traditional</th>
<th>Evolving</th>
</tr>
</thead>
<tbody>
<tr>
<td>Etiology</td>
<td>Anamnestic Response</td>
<td>Anamnestic; Can be primary</td>
</tr>
<tr>
<td>Incidence</td>
<td>Common</td>
<td>DSTR common; DHTR uncommon</td>
</tr>
<tr>
<td>Clinical Effects</td>
<td>Common</td>
<td>Uncommon</td>
</tr>
<tr>
<td>Serology</td>
<td>Traditional</td>
<td>Long term</td>
</tr>
<tr>
<td>Reactive Hemolysis</td>
<td>Not described</td>
<td>Not documented</td>
</tr>
</tbody>
</table>
Results of DHTR Studies

• Improved patient care by developing mechanism to identify patients, counsel them about future transfusions, provide early warnings to health care providers.

• Used clinical observation studies to develop research studies to re-define DHTR and its implications.

• Demonstrated importance of active surveillance to measure incidence rates.
THE JOHNS HOPKINS HOSPITAL
BLOOD BANK USE ONLY

Doe John

DATE 11.26.75

(LAST-FIRST NAME)

HIST. No. 111-22333 WARD ER

IDENTIFY YOUR PATIENT PRINT CLEARLY
<table>
<thead>
<tr>
<th>TABLE 1. Requirements for specimen labeling and rejection criteria*</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Required</strong></td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td><strong>Absolute rejection</strong></td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td><strong>Poor practice†</strong></td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td><strong>Acceptable</strong></td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td></td>
</tr>
</tbody>
</table>

* Patient’s hospital location and the date the specimen was drawn are required and may appear on the specimen label or requisition.
† Requires an incident report and consultation with the staff.
<table>
<thead>
<tr>
<th></th>
<th>Specimen typed</th>
<th>Discrepancies</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Correctly labeled</td>
<td>40,274</td>
<td>14</td>
<td>0.035</td>
</tr>
<tr>
<td>Mislabeled (rejected)</td>
<td>496</td>
<td>7</td>
<td>1.4</td>
</tr>
</tbody>
</table>
Elements of a Compatibility Testing System

- Patient identification
- Sample identification
- ABO/Rh/Ab screen
- Records check
- Unit selection
- Crossmatching
- Labeling
- Recipient identification

1/2,900 samples contains blood from the wrong patient

• Incidence of 1:4200 transfusions in oncology patients
• Septic reactions were more common with random donor platelet concentrates (RDP)
• Reactions were more common with longer periods of storage
• Source was skin contaminant in 4/7 cases; bacteremic donor in 3/7 cases
Study Design
JHMI SPTR Studies

• Beginning in 1986, all febrile transfusion reactions to platelets were prospectively studied by culture of the platelet bag.

• Confirmed SPTR were identified by isolation of the same bacteria from the bag and the patient’s blood, or positive cultures were confirmed by gram stain of the bag.
Septic Platelet Reactions

![Bar chart showing septic platelet reactions from 1987-88 to 1997-98 with two categories: SDP and RDP. The chart displays a significant increase in 1989-90 and a decline thereafter.]
Septic Platelet Reactions
Outcome

- Fatal
- Survived
JHMI Study Results

• Over a 12 year period, the usage of SDP increased from 51.7% to 99.4% with platelet transfusions increasing from 12708 to 14446 annual doses.

• The incidence of SPTR fell from 1 in 4818 Tx to 1 in 15098 Tx.

• If all Tx had been administered as RDP, the risk of SPTR would have been 1 in 1606 Tx.
## BaCon Study
### Kuehnert et al, 2001

<table>
<thead>
<tr>
<th></th>
<th>RBC</th>
<th>SDP</th>
<th>RDP</th>
</tr>
</thead>
<tbody>
<tr>
<td>Units</td>
<td>23,711,169</td>
<td>1,804,725</td>
<td>1,033,671</td>
</tr>
<tr>
<td>Cases</td>
<td>5 (3)</td>
<td>18 (4)</td>
<td>11 (2)</td>
</tr>
<tr>
<td>Cases per million</td>
<td>0.21</td>
<td>9.98</td>
<td>10.64</td>
</tr>
<tr>
<td>Deaths per million</td>
<td>0.13</td>
<td>2.22</td>
<td>1.94</td>
</tr>
</tbody>
</table>
Problems with BaCon Study

• Voluntary reporting
• Cases rates based on transfused denominator of participants but participation was nonuniform
• Strict (?unrealistic ) case definition excluded cases of SPTR
• Surveillance varied among sites
French BACTHEM

- Matched case control study on bacterial contamination conducted within the French Haemovigilance Network.
- Case accrual from 1996-1998
### Septic Platelet Reactions
#### Single Donor Platelets

<table>
<thead>
<tr>
<th></th>
<th>Ness et al</th>
<th>French Haemovig.</th>
<th>BaCon</th>
</tr>
</thead>
<tbody>
<tr>
<td>Units</td>
<td>134,140</td>
<td>282,848</td>
<td>1,804,725</td>
</tr>
<tr>
<td>Cases</td>
<td>10 (2)</td>
<td>9 (2)</td>
<td>18 (4)</td>
</tr>
<tr>
<td>Cases per million</td>
<td>74.5</td>
<td>31.8</td>
<td>9.98</td>
</tr>
<tr>
<td>Deaths per million</td>
<td>14.9</td>
<td>7</td>
<td>2.22</td>
</tr>
</tbody>
</table>
AABB Standards

• 5.1.5.1 The blood bank or transfusion service shall have methods to limit and detect bacterial contamination in all platelet components.

• To be implemented by March 1, 2004
Conclusions

• Transfusion complications can only be adequately addressed by an active prospective surveillance program; elements of bedside monitoring and blood bank review must be incorporated.
• Monitoring for transfusion complications is important as a means of improving patient care and designing research priorities.
• Haemovigilance requires an integrated approach involving clinical staff, the blood bank, and external reviews.
The Implementation and Utilization of Hemovigilance in a Large Academic Institution
A Brief History

• The U.S is the only developed nation that does not have an established method to track and monitor adverse events associated with blood transfusion on a national level.

• The Patient Safety and Quality Improvement Act 2005 – intends to improve patient safety by encouraging voluntary and confidential reporting of events that adversely affect patients.

• In 2006 the Department of Health and Human Services Advisory Committee on Blood Safety and Availability convened and recommended that a national system was needed.
Biovigilance

• Subsequently, AABB formed an Inter-organizational Task Force on Biovigilance, with representation from both governmental and non-governmental organizations in the U.S.

• It is the first and only national collaboration between government and non-government agencies designed to confidentially track adverse reactions and incidents associated with blood collection and transfusion as well as tissue, organ, and cell therapy
National Healthcare Safety Network (NHSN)

- A private-public partnership was established with the Center for Disease Control to use their NHSN secure reporting system.

- The Hemovigilance Module was the first release of the Biovigilance component of the NHSN.

- It is designed for Transfusion service staff in healthcare facilities.
Implementing Hemovigilance

- Digital Certificate- Hospital Administrator
- Annual Survey and Monthly Denominators
- Approval of Adverse Reaction criteria-TPC
- Integrate existing JHH systems with biovigilance system
- Creating new documentation forms
- Educating staff on Incident reporting
- Summary Data/Long report
Adverse Reaction

• The internal reporting process for clinical units did not change
• We simply added the Adverse Reaction form to our current process
• TM Attending responsible for classifying reaction, meets case definition criteria, grade the severity and relationship to transfusion and outcome.
• Approximately 80,000 blood products are transfused a year with 461 reactions reported.
Adverse reactions
Internal forms used by TM medical staff

The Johns Hopkins Hospital
Department of Pathology
Transfusion Medicine Division

Hemovigilance - Suspected Adverse Reaction Report

Facility ID # __________________________  Adverse Reaction # __________________________

Patient Information

Patient History #: __________________________  Gender: ☐ Male  ☐ Female  Date of Birth: __/__/____

Patient’s Blood Group: ☐ A pos  ☐ A neg  ☐ B pos  ☐ B neg  ☐ O pos  ☐ O neg  ☐ AB pos  ☐ AB neg

Reactions Details

Date reaction occurred: __/__/____  Patient Location: __________________________

Time reaction occurred: __:__:_ (HH:MM) or __ unknown: ___

Is this reaction associated with an incident? ☐ YES  ☐ NO  If YES, Incident #: __________________________

Signs and symptoms of the reaction (Check all that apply):

☐ Shock  ☐ Headache  ☐ Pain at infusion site  ☐ Dark urine
☐ Fever  ☐ Abdominal pain  ☐ Nausea/Vomiting  ☐ Chills/ rigors
☐ Anorexia  ☐ Back pain  ☐ Other pain sites  ☐ Hypovolemia
☐ Uricemia (Gives)  ☐ Chest pain  ☐ Shortness of breath  ☐ Hemoglobinemia
☐ Albinism ({} or no urine)  ☐ Flank pain  ☐ Diffuse hemorrhage  ☐ Hematuria
☐ Increased in Blood Pressure  ☐ Decrease in blood pressure  ☐ Other pain (Specify): __________________________

Component Details:

Date/time Transferred: __/__/____  Product Transferred: (Glob, Plasma..)

Product Unit #/Lot #: Product Exp date: Product Blood Group: Implicated in the adverse reaction?

[Table with data]

<table>
<thead>
<tr>
<th>Date/time Transferred</th>
<th>Product Transferred (Glob, Plasma..)</th>
<th>Product Unit #/Lot #:</th>
<th>Product Exp date:</th>
<th>Product Blood Group:</th>
<th>Implicated in the adverse reaction?</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>/</strong>/____</td>
<td><strong>/</strong>/____</td>
<td><strong>/</strong>/____</td>
<td><strong>/</strong>/____</td>
<td><strong>/</strong>/____</td>
<td><strong>/</strong>/____</td>
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<td><strong>/</strong>/____</td>
<td><strong>/</strong>/____</td>
<td><strong>/</strong>/____</td>
</tr>
</tbody>
</table>

Component code: __/__/____  Exp time: __/__/____

Component code: __/__/____  Exp time: __/__/____

Component code: __/__/____  Exp time: __/__/____

Hemovigilance - Suspected Adverse Reaction Report

Adverse Reaction (Select one):

☐ Allergic Reaction, including anaphylaxis
☐ Reaction to Blood Product
☐ Acute hemolytic transfusion reaction (AHTR)
☐ Immune Antibody
☐ Delayed hemolytic transfusion reaction (DHTR)
☐ Immune Antibody
☐ Delayed allergic transfusion reaction (DATR)
☐ Antibody

□ Febrile non-hemolytic transfusion reaction
□ Hypotensive transfusion reaction
□ Infection A: Bacterial (including sepsis)
☐ Viral
☐ Other B: Organism (specify):
Blood culture performed on patient: ☐ YES  ☐ NO
If YES, were any culture results positive? ☐ YES  ☐ NO
Blood culture performed on recipient/post-transfusion: ☐ YES  ☐ NO
If YES, were any culture results positive? ☐ YES  ☐ NO

Post Transfusion Purpura (PTP)

□ Transfusion associated circulatory overload (TACO)
□ Transfusion associated dyspnea (TAD)
□ Transfusion associated graft vs host disease (TA-GVHD)
□ Other:

Has the patient received any non-homologized blood products in the past two months? ☐ YES  ☐ NO

□ Transfusion related acute lung injury (TRALI)
□ Other:

(Optimal) Antibody studies performed:

Component: __/__/____  Exp time: __/__/____

<table>
<thead>
<tr>
<th>Component</th>
<th>Not Done</th>
<th>Negative</th>
<th>Positive</th>
</tr>
</thead>
<tbody>
<tr>
<td>Titer or ELA</td>
<td>☐</td>
<td>☐</td>
<td>☐</td>
</tr>
<tr>
<td>TRAP or ELA</td>
<td>☐</td>
<td>☐</td>
<td>☐</td>
</tr>
<tr>
<td>Immunoassay</td>
<td>☐</td>
<td>☐</td>
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</tr>
<tr>
<td>Immunoassay</td>
<td>☐</td>
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<tr>
<td>Antibody DNA</td>
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</tr>
<tr>
<td>Antibody DNA</td>
<td>☐</td>
<td>☐</td>
<td>☐</td>
</tr>
<tr>
<td>Other (specify): __________________________</td>
<td>☐</td>
<td>☐</td>
<td>☐</td>
</tr>
</tbody>
</table>

NO EVIDENCE of a TRANSFUSION REACTION

Date: __/__/____

Enter the following information in the Space at the bottom of the page:

□ Death: ☐ Major or long-term sequelae: ☐ Minor or no sequelae: ☐ Not Determined
□ If recipient died: relationship of transfusion to death:
☐ Definite  ☐ Probable  ☐ Possible  ☐ Doubtful  ☐ Ruled out  ☐ Not Determined

Enter forms into NHSS Hemovigilance Computer database by: __/__/____  Date: __/__/____

Page 1 of 2

Page 2 of 2

34
Biovigilance Data

Hemovigilance data: Percent of total reported adverse reactions by product transfused.

Matthew Karafin, MD
Incidents

- An accident or error that could lead to an adverse event affecting:
  - The safety, efficacy, or quality of blood, blood components, plasma derivatives
  - (or) the safety of recipients
Internal and External Incidents

- Specimen rejections (Summary Data)
- Staff errors and accidents (Long Form)
- Patient safety events (internal and external) (Long Form)
- Transfusion audit failures (Summary Data)
- Blood product wastage (Summary Data)
- Other transfusion events (Long Form)
Utilizing Our Data

National Healthcare Safety Network
Frequency Table for All Incident Data
As of: October 20, 2009 at 12:02 PM
Data Range: HWCID occurDate 07/01/2009 to 07/31/2009

RP 01 - Request for pickup on wrong patient!

UT 03 – Blood Product Wastage

Data contained in this report were last generated on October 20, 2009 at 11:53 AM.
Benefits/ The Future

• Participating facilities are able to independently analyze their data within NHSN.

• Data can be presented in many forms; reports, charts or graphs driven by date range, incident code, adverse reaction, etc.

• Will be able to compare our data with national aggregate rates in a confidential manner through NHSN in the future.

• Common definitions of adverse reactions and incidents will lead to better understanding of incidence and scope of transfusion complications.

• Results of data collected will help improve patient safety and help to change the face of healthcare.
Problems/ The Present

- System is voluntary so data are incomplete with potential for bias
- Surveillance methods are not specified; variable rates observed depending upon active surveillance or passive reporting
- Case definitions use measures often not used clinically- CVP, BNP, xrays
- Data are not aggregated by hospital demographics; data are not normalized.