Donor Safety, Including EU Requirements – Volumes, Frequency, Testing...

IPFA/BCA 3rd Global Symposium on the Future for Blood and Plasma Donations

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BloodSource – Blood Systems, USA
About BloodSource

- California, USA based not-for-profit since 1948
  - ~225,000 units/year
  - Part of Blood Systems (2016)
- Additional details:
  - IPFA member
  - EU certified
  - Volunteer donors
- Active apheresis program (long history)
  - Volunteer source plasma (2014) (non-immunized)
  - “Frequent” plasma
  - ~100% apheresis transfusable plasma (whole blood → recovered plasma)
BloodSource Source Plasma (SP)

**Donor demographics (2016)**
- Nearly **2,000 unique donors** (females 61%)
- Average donor age was **49 years**
- Average weight was **180 lbs (81.6 kg)**

**Collection details (2016)**
- Total = **9,400 liters SP** (26,000 liters recovered)
- Avg. repeat rate = **6.4 times per year** (5.0 in 2015)
- Avg. collection volume = **795 mL**
- 78% donors had average interval of ≥ **28 days**
Source Plasma Program
Source Plasma Donor Qualification

• Positive Donor Identification
• Donor Questionnaire
• Donor Assessment
  – E.g., vitals, weight, hemoglobin, total protein, entry physical
• Eligibility Determination
  – Ensure donor and patient safety

Similar to, yet unique differences from transfusable components
## Donor Qualification – US Criteria

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Requirement</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>≥ 16 or 17 (per state law; may require parent consent)</td>
</tr>
<tr>
<td>Temperature</td>
<td>Must not exceed 37.5°C</td>
</tr>
<tr>
<td>Blood Pressure</td>
<td>Systolic/Diastolic (90-180/50-100)</td>
</tr>
<tr>
<td>Weight</td>
<td>≥ 110 lbs; apheresis must weigh at each visit</td>
</tr>
<tr>
<td>Total Protein</td>
<td>6.0 – 9.0 g/dL at each donation (not required for infrequent plasma donors)</td>
</tr>
<tr>
<td>Hemoglobin</td>
<td>≥ 12.5 g/dl (female); ≥ 13.0 g/dL (male)</td>
</tr>
</tbody>
</table>

*CFR 630.10*
### Donor Qualification – EU Criteria

#### EU Criteria

**Directive 2004/33/EC**

*CoE Recommendation No R(95)15*

<table>
<thead>
<tr>
<th>Age</th>
<th>≥ 17 or 18 and ≤ 60 (first time donors) or 65 (repeat donors); subsequently eligible with medical assessment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Temperature; BP/Pulse</td>
<td>Not specified (optional)</td>
</tr>
<tr>
<td>Weight</td>
<td>≥ 110 lbs</td>
</tr>
<tr>
<td>Total Protein</td>
<td>Not required at each plasmapheresis</td>
</tr>
<tr>
<td>Hemoglobin (g/dL)</td>
<td>RBCs, PLTs: ≥ 12.5 (female); ≥ 13.5 (male) Plasmapheresis*: ≥ 12.0 (female); ≥ 13.0 (male)</td>
</tr>
</tbody>
</table>
Variation in Donation Limits

• Maximum plasma volume and donation frequency are regulated by national authorities and differ from country to country

• For apheresis plasma may range from:
  – Collection volumes: 400 to 800 ml/donation (anticoagulant excluded)
  – Donation frequency: 15 to 104 times/year

Vox Sanguinis (2010) 99, 220-231
US: Source Plasma Collections

• **Donation Frequency:**
  - Infrequent plasma donors:
    • Once every 4 weeks
      (i.e., max 13 times per year)
  - Frequent plasma donors:
    • At least 2 days (48 hours) apart, **and**
    • Eligible 2 times in any 7 days
      (i.e., max 104 times per year)

21 CFR 630.3
21 CFR 640.65
US: Source Plasma Collections

- **Frequent Donor**: Eligible twice per week

<table>
<thead>
<tr>
<th>Donor Weight</th>
<th>Max Plasma (Collection) Volume</th>
<th>Max Plasma Loss / 12 months</th>
</tr>
</thead>
<tbody>
<tr>
<td>110 - 149 lbs</td>
<td>625 mL (690 mL)</td>
<td>65 L</td>
</tr>
<tr>
<td>150 - 175 lbs</td>
<td>750 mL (825 mL)</td>
<td>78 L</td>
</tr>
<tr>
<td>&gt; 175 lbs</td>
<td>800 mL (880 mL)</td>
<td>83.2 L</td>
</tr>
</tbody>
</table>

*CBER Memorandum: Volume Limits for Automated Collection of Source Plasma; 1992*
US: Source Plasma Collections

• **Infrequent Donors**: Eligible every 4 weeks

<table>
<thead>
<tr>
<th>Donor Weight</th>
<th>Max Plasma (Collection) Volume</th>
<th>Max Plasma Loss / 12 months</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt; 175 lbs</td>
<td>**</td>
<td>12.0 L</td>
</tr>
<tr>
<td>≥ 175 lbs</td>
<td>**</td>
<td>14.4 L</td>
</tr>
</tbody>
</table>

**Volumes per donation should not exceed those for frequent source plasma donors

21 CFR 630.3
## EU: Apheresis Plasma Collections

<table>
<thead>
<tr>
<th>Regulatory</th>
<th>Frequency</th>
<th>Collection Volume</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Council of Europe</strong></td>
<td>( \leq 33/\text{year} )</td>
<td>( \leq 16% \text{ TBV and} ) ( \leq 750 \text{ mL}^# ) (unless replacement) ( \leq 25 \text{ liters/year} )</td>
</tr>
<tr>
<td>Recommendation No R(95)15</td>
<td>( \geq 48 \text{ h between} )</td>
<td></td>
</tr>
<tr>
<td><strong>National Authorities</strong></td>
<td>Variable</td>
<td>Variable</td>
</tr>
<tr>
<td><strong>France</strong></td>
<td>( \leq 24/\text{year} )</td>
<td>( \leq 750 \text{ ml/donation} ) ( \leq 16% \text{ TBV} )</td>
</tr>
<tr>
<td></td>
<td>( \geq 2 \text{ wk. between} )</td>
<td></td>
</tr>
<tr>
<td><strong>Germany</strong></td>
<td>2x/week; ( \geq 48 \text{ h} )</td>
<td>( \leq 850 \text{ ml}^*/\text{donation} ) (if ( \geq 176 \text{ lbs} )) ( \leq 28.5 \text{ liters/year} )</td>
</tr>
<tr>
<td></td>
<td>between ( \leq 45/\text{year} )</td>
<td></td>
</tr>
</tbody>
</table>

* = Including anticoagulant;  \# = Excluding anticoagulant
US: Additional Oversight

• **Medical supervision**
  – Onsite physician (MD) or physician substitute
  – Review of accumulated data every $\leq 4$ months

• **Physical exam**
  – Done by physician or physician substitute
  – Upon entry into program and then annually
US: Source Plasma Testing

- **Infectious disease testing**
  - Syphilis serology -- at least every 4 months
  - HIV, HBV, HCV -- every donation
    - anti-HIV 1/2, HBs-Ag, anti-HCV
    - HBV NAT, HCV NAT, HIV-1 NAT
  - Hepatitis A & Parvovirus B19 NAT
    - Donation or “In-Process Control” testing

*Do NOT* have to test for HTLV, WNV, Chagas, Zika, anti-HBc
US: Source Plasma Testing

• Non-infectious disease testing
  – Total protein -- every donation
    • (e.g., finger stick with refractometer)
  – Protein analysis -- initially then ≤ every 4 months
    • (i.e., plasma or serum protein electrophoresis or quantitative immunodiffusion)
      – Proteins should be within normal limits
      – Total protein must be ≥ 6.0 g/dL
EU: Source Plasma Testing

• **Infectious disease testing**
  – HIV, HBV, HCV -- every donation
    • Anti-HIV 1/2, HBs-Ag, anti-HCV
    • NAT and additional testing on voluntary basis or according to national requirements
  – “In-Process Control” testing -- on plasma pools
    • HBs-Ag, anti-HCV, anti-HIV, HCV NAT
    • B19 NAT and HAV NAT for specific products (or on voluntary basis on donations)

*European Pharmacopoeia Directive 2002/98/EC*
EU: Source Plasma Testing

• Non-infectious disease testing
  – Protein analysis -- initially then ≤ annually
    • (i.e., total serum or plasma protein and/or quantification of single proteins and/or protein electrophoresis)
      – TP must be ≥ 6.0 g/dL
      – IgG is within reference range and ≥ 6.0 g/L

Directive 2004/33/EC
US: Source Plasma Exceptions

• Infrequent plasma donors
  – Do not need to:
    • Perform physical examination(s)
    • Perform tests for total protein
    • Perform additional protein analysis (i.e., SPE)

Infrequent plasma donors:
  - Eligible once every 4 weeks
  - Annual plasma loss: \( \leq 12.0 – 14.4 \) liters
Source Plasma Safety
Donor Health and Safety

• **Supported by:**
  – Careful screening and evaluation of donors
  – Ensuring donors are prepared for collection and are comfortable during the procedure
  – Staff training and proficient apheresis collections
  – Monitoring apheresis donor data
    (e.g., donor chart review, adverse event trending)
Apheresis Adverse Reactions

• **Vasovagal reactions**
  - E.g., Dizziness, hypotension, syncope, nausea, anxiousness

• **Citrate reactions**
  - E.g., tingling, muscle cramps, metallic taste, parasthesia

• **Venipuncture issues**
  - E.g., bruising, nerve injury, vessel injury

• **Procedure-related complications**
  - E.g., hemolysis, air embolism, chills

• **Potential long-term complications**
  - E.g., bone density impact(?), iron deficiency, protein recovery
US: Informed Consent

• Physician or physician substitute must:
  – Obtain written informed consent prior to first donation and at an interval ≤ 1 year
  – Obtain informed consent at time of re-entry if no donations within 6 months

• Informed consent consists of:
  – Explanation of donation process and donor testing
  – Risks and hazards of the procedure
  – Opportunity to ask questions and refuse donation
Vasovagal Reactions

• Thought to be more likely to occur among:
  – Young, female, first-time, low-weight donors

• Generally reported to occur less frequently among apheresis donors
  – Apheresis includes fluid replacement and slower donation process compared to whole blood
BloodSource SP Syncopal RXNs

- Whole blood donors
  - Pre-faint: 16-17 year old: 6-8%
  - Pre-faint: first time donors: 4-9%
Iron Deficiency & RBC Loss

• RBC loss (small) with each plasmapheresis
  – Loss associated with routine donor testing
  – RBC retention in apheresis tubing
    • At conclusion of the procedure (mitigated with saline return) or as a result of technical difficulties

Example Loss (BloodSource):
  ➢ With saline rinse back kit residual RBC = 2 mL
  ➢ With samples the total RBC loss = ~ 18 mL
US: Source Plasma Collections

- Temporary deferral of donors who have lost red blood cells due to technical difficulties

<table>
<thead>
<tr>
<th>RBC Loss</th>
<th>Donor Deferral</th>
</tr>
</thead>
<tbody>
<tr>
<td>≤ 200 mL</td>
<td>Single incident deferral not required</td>
</tr>
<tr>
<td><strong>second incident in 8 weeks → 8 week deferral</strong></td>
<td></td>
</tr>
<tr>
<td>&gt; 200 mL</td>
<td>8 week deferral</td>
</tr>
</tbody>
</table>

Volume of loss is the total extracorporeal RBC volume described by the manufacturer
Iron Deficiency & RBC Loss

• Cumulative RBC loss with frequent donations
  – While ferritin may be lower in frequent donors, rates of iron store depletion or iron restricted erythropoiesis not consistently higher

Additional Oversight (BloodSource):
- 16-17 year old ferritin testing on all donations (including SP) with possible RBC deferral
  ➢ Female < 20 mcg/L → 12 month deferral
  ➢ Male < 30 mcg/L → 6 month deferral
Citrate Reactions

• Infrequent complication of apheresis donations
  – Even less frequent in source plasma as a significantly lower amount of citrate is returned to the donor compared to plateletpheresis
  – Most often a mild and self-limited reaction

• Acute citrate reaction may be addressed by:
  – Pausing and slowing reinfusion rate / increasing the blood to citrate ratio
  – Calcium supplementation (e.g., Tums®)
Long Term Effects of Citrate

• Cumulative impact on bone mineral density?
  – Conflicting/inconclusive data reported for plateletpheresis donors
  – Significance for frequent plasmapheresis donors is unknown as exposed to lower amts. of citrate

*BloodSource does address during our apheresis informed consent*
Post-Donation Protein Recovery

<table>
<thead>
<tr>
<th>Protein</th>
<th>Half-Life</th>
</tr>
</thead>
<tbody>
<tr>
<td>Retinol binding protein</td>
<td>12 hours</td>
</tr>
<tr>
<td>IgA and AGP</td>
<td>&lt; 5 days</td>
</tr>
<tr>
<td>HPX and TRF</td>
<td>7 and 8 days</td>
</tr>
<tr>
<td>HSA and IgG</td>
<td>15 and 23 days</td>
</tr>
<tr>
<td>IgG1, IgG2, IgG4</td>
<td>20-21 days</td>
</tr>
<tr>
<td>IgG3</td>
<td>7 days</td>
</tr>
</tbody>
</table>

• High frequency, high volume collects limit ability to return to normal physiologic levels

_Vox Sanguinis (2010) 99, 220-231_
Summary
Our Source Plasma Experience
Our Source Plasma Experience

• **Donor response has been VERY POSITIVE**

• **Have been happy with donor safety**
  – FDA/EU regulatory considerations
  – Appropriate donor screening, selection, & education
  – Staff training and medical oversight
  – Close monitoring of adverse event data

• **Ability to contribute towards patient need**