Blood Systems
Blood Centers Division

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

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

Jonathan Hughes, MD, Medical Director
BloodSource – Blood Systems, USA

About BloodSource

- **California, USA based not-for-profit since 1948**
  - ~225,000 units/year
  - Part of Blood Systems (2016)
- **<u>Additional details:</u>**
  - 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

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

CFR 630.10

Donor Qualification – EU Criteria

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

Directive 2004/33/EC

**CoE Recommendation No R(95)15*

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

- **<u>Donation Frequency:</u>**
  - **Infrequent plasma donors:**
    - Once every 4 weeks
      (i.e., max 13 times per year)
  - **Frequent plasma donors:**
    - At least 2 days (48 hours) apart, <u>and</u>
    - 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

Donor Weight	Max Plasma (Collection) Volume	Max Plasma Loss / 12 months
110 - 149 lbs	625 mL (690 mL)	65 L
150 - 175 lbs	750 mL (825 mL)	78 L
≥ 175 lbs	800 mL (880 mL)	83.2 L

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

US: Source Plasma Collections

- **<u>Infrequent Donors</u>**: Eligible every 4 weeks

Donor Weight	Max Plasma (Collection) Volume	Max Plasma Loss / 12 months
< 175 lbs	**	12.0 L
≥ 175 lbs	**	14.4 L

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

21 CFR 630.3

EU: Apheresis Plasma Collections

Regulatory	Frequency	Collection Volume
Council of Europe Recommendation No R(95)15	≤ 33/year ≥ 48 h between	≤ 16% TBV **and** ≤ 750 mL# (unless replacement) ≤ 25 liters/year
National Authorities	Variable	Variable
France	≤ 24/year ≥ 2 wk. between	≤ 750 ml/donation (≤ 16% TBV)
Germany	2x/week; ≥ 48 h between ≤ 45/year	≤ 850 ml*/donation (if ≥176 lbs) ≤ 28.5 liters/year

** = Including anticoagulant; # = Excluding anticoagulant*

US: Additional Oversight

- **Medical supervision**
  - Onsite physician (MD) or physician substitute
  - Review of accumulated data every ≤ 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: ≤ 12.0 – 14.4 liters

Source Plasma Safety

Donor Health and Safety

- **<u>Supported by:</u>**
  - 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

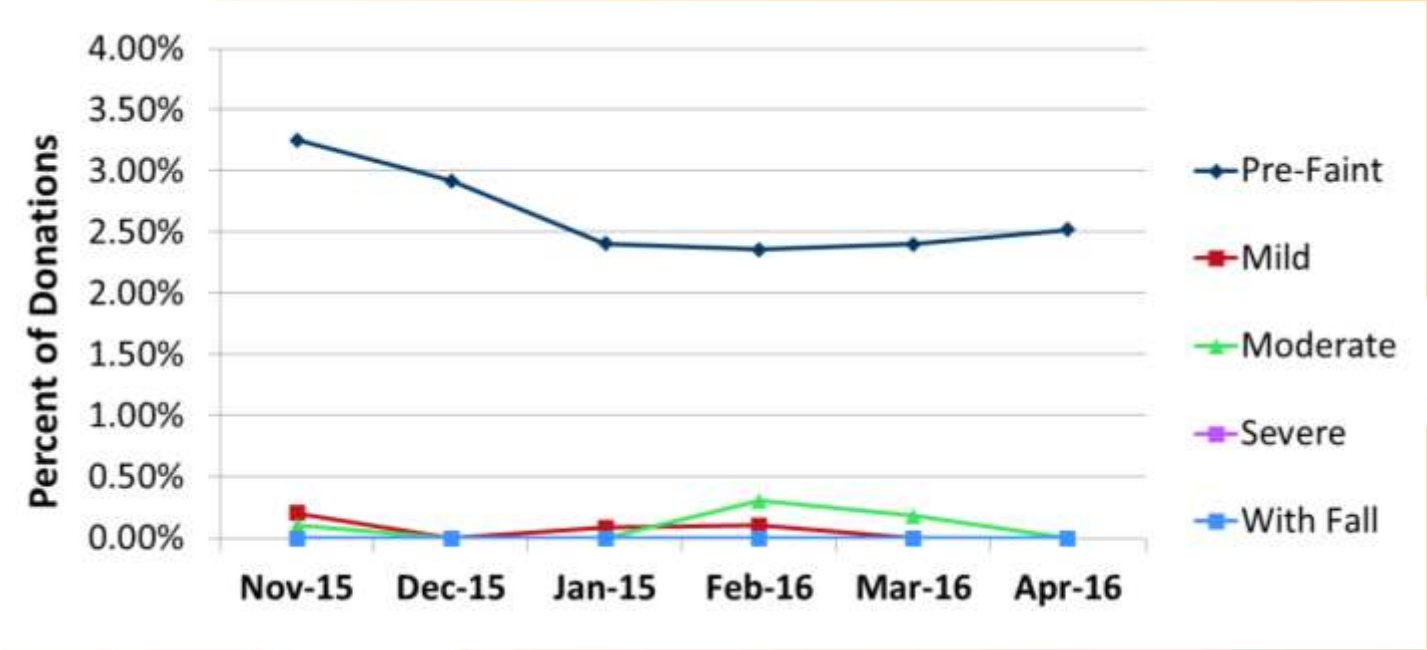
US: Informed Consent

- **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

RBC Loss	Donor Deferral
≤ 200 mL	Single incident deferral not required ** second incident in 8 weeks → 8 week deferral
> 200 mL	8 week deferral

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

Protein	Half-Life
Retinol binding protein	12 hours
IgA and AGP	< 5 days
HPX and TRF	7 and 8 days
HSA and IgG	15 and 23 days
IgG1, IgG2, IgG4	20-21 days
IgG3	7 days

- 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**