# Immediate and Long-Term Complications in Peripheral Blood Stem Cell (PBSC) Donation Procedures

John Miller, MDPhD

16th International Haemovigilance Seminar

Barcelona, March 6, 2014

NATIONAL MARROW DONOR PROGRAM®

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# Learning Objectives

- Describe hemovigilance efforts for hematopoietic stem cell (HSC) donors
- Compare and contrast issues in HSC donation compared with blood, tissue and solid organ donation and necessarily how donor evaluation is different
- Understand the requirements and reporting of adverse events
- Review literature reports and registry data of adverse events in related and unrelated PBSC donors

# Differences Between HSC and Solid Organ and Tissue Transplantation

| | Tissue/Solid Organ | HSCT |
|---|---|---|
| Annual # of Events | More than 1,000,000 in the US alone | 30,000 alloHSCT/yr worldwide |
| Donor → Patient | 1:many (dozen to 100s) | Usually 1:1 |
| Donor Testing | Often cadaveric: no retesting possible | Alive and well; retesting can be done |
| Donor Assessment | Often very time limited (as little as hours) | Not severely time limited |
| Matching | HLA, lower resolution | HLA, allele level 8 loci |
| Product Release/Expiration | ASAP/Hours | ASAP/Hours or days or cryopreservation |

# Differences Between HSC and Blood Donors

| | Blood | HSCT |
|---|---|---|
| Annual # of Events | More than 20,000,000 in the US alone | 30,000 alloHSCT/yr worldwide |
| Donor → Patient | 1:1, 1:2, 1:3 whole blood | Usually 1:1 |
| Donor Testing | Day of Collection, strict release criteria | Up to 30 days prior to donation, flexible release criteria |
| Donor Assessment | HHQ, limited physical assessment | HHQ, complete H&P, labs, EKG, CXR and extended testing possible |
| Matching | ABO/Rh +/- RBC Ag | **HLA**, ABO, KIR Only/best match |

# Differences Between HSC and Organ, Tissue and Blood Donors

- HSC donors may be the best or only match for a patient
- While transplantation may be urgent clinically, there is time to do a complete donor health assessment
- The emergence of new blood-borne infectious diseases will most likely occur in the setting of the blood and tissue world given the sheer number of transfusion/transplant events
- Therefore, vigilance efforts should focus on donor and recipient adverse events and product quality issues to enhance donor and recipient safety

# NMDP Processes Enable AE Surveillance

- Key element: electronic data capture (EDC) system for AEs (FormsNet™)
  - **Capture** AE info across US HCT
    - Establish baseline event rates
    - Facilitate reporting via a familiar, widely used system
    - Create a single point of contact for AE reporting for *any unrelated* donor product, irrespective of NMDP involvement
  - **Analyze** for trends that might indicate a safety issue
    - Aggregates AEs otherwise too rare to be recognized if not captured through a single means
  - **Report** back to the transplant community

# Recipient Serious Adverse Event (SAE) Reporting for the NMDP Network

- SAEs associated with PBSC, marrow and cord blood must be reported promptly to NMDP
  - Report using FormsNet Form 3001
    - **Rationale** for seriousness (death, life-threatening, hospitalization, birth defect, permanent impairment or disability)
    - **Event type / severity** using CTCAE Terms and Grading
    - **Attribution**
    - Examples include:
      - Serious infusion reaction within 24 - 48 hrs
      - Recipient seroconversion within 6 months
      - Recipient bacteremia related to contaminated CBU
      - Recipient develops RCD within 6 months that is caused by or potentially caused by CBU
- N.B. Some events are not NMDP regulatory responsibility and info will be passed to the appropriate IND holder

# What Happens to AE Reports?

- Regulatory reporting by NMDP
  - DPSM (the NMDP's DSMB)
  - FDA when NMDP is the IND holder
    - Otherwise, NMDP passes through the report to the IND holder
  - HRSA and other US government stakeholders
- Other stakeholders
  - Pharma as applicable (e.g. for mobilizing agents)
- International
  - Reporting to WMDA when donor or product-related

# Areas of Focus for NMDP in Biovigilance

- Change manual processes to automated
  - Tracking and trending
- Expand scope of routine report generation
- Continue education efforts to reduce over-reporting of expected, non-serious AEs that “clog” the system, creating unnecessary work for reporters and NMDP

# International Efforts in Biovigilance in HSCT

- Project NOTIFY (notifylibrary.org)
  - Joint venture between WHO and the Italian National Transplant Center in collaboration with the European SOHO (**S**ubstances **O**f **H**uman **O**rigin) V&S project
  - Creates
    - a series of papers from working groups
    - a database of vigilance info publically available
- WMDA: S(P)EAR reporting for donor AEs and product-related issues
  - Consolidates data from independent registries: increases power to detect sentinel AE (Shaw, et al, BMT 2013)
  - Mandatory reporting for accredited registries, standard AE definitions and likely *attribution*

# International Efforts in Biovigilance in HSCT

Worldwide Network for Blood and Marrow Transplantation (WBMT) Consensus Statement

- Data should be collected for:
  - Related and unrelated donors including demographics
  - Product type including mobilization
  - Complications from the donation procedure; short (up to 30 days of donation) and long term (1,5 and 10 years)
- Reporting:
  - Acute AE within 30 days of donation: Standard definitions and attribution
  - Long term focus on survival, malignancies and autoimmune disease

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Halter, et al (2013);48:220-225

# Common Adverse Events in PBSC Donors:
## July 1999 - April 2004, n = 2408

blood

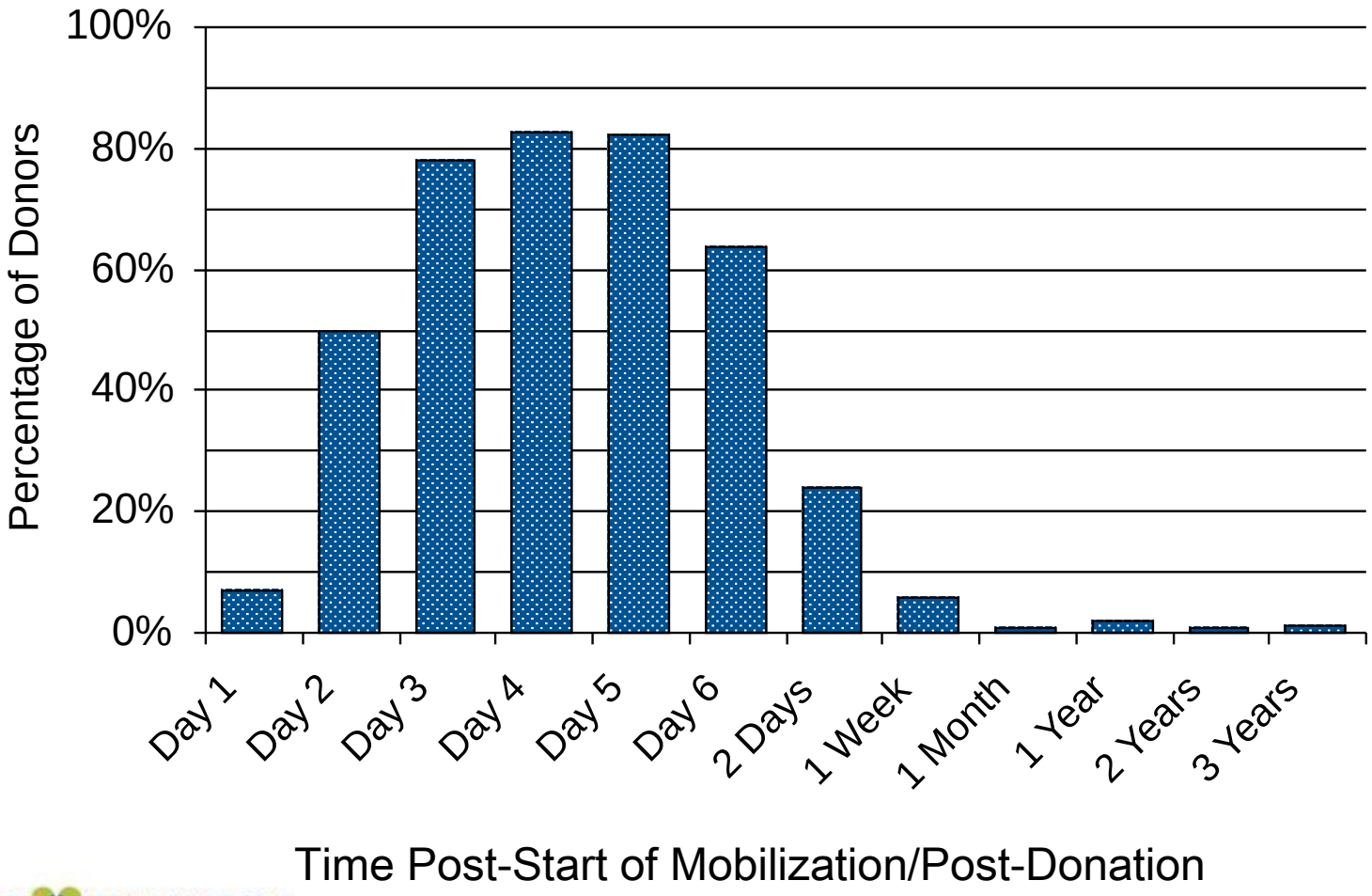
Prepublished online Feb 3, 2009;
doi:10.1182/blood-2008-08-175323

**Adverse events among 2408 unrelated donors of peripheral blood stem cells: Results of a prospective trial from the National Marrow Donor Program**

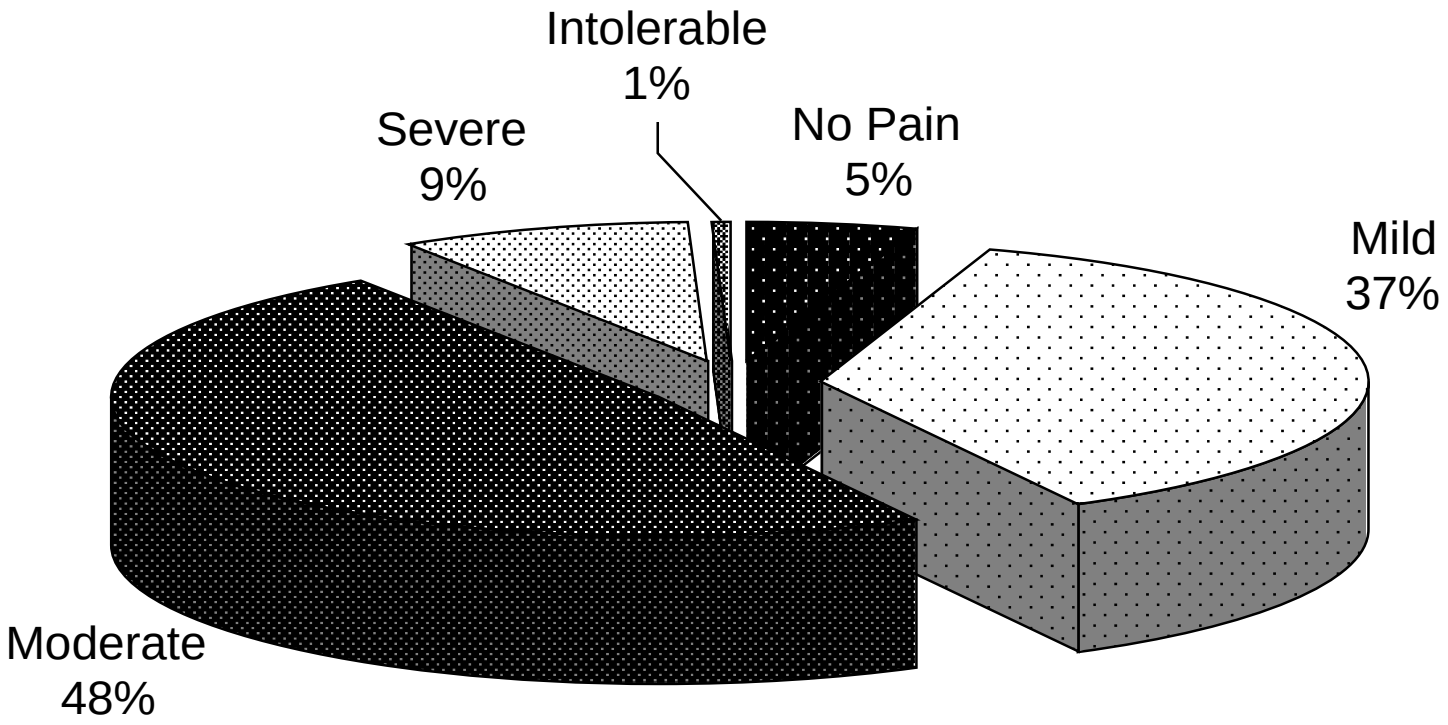
Michael A. Pulsipher, Pintip Chitphakdithai, John Miller, Brent R. Logan, Roberta J. King, J. Douglas Rizzo, Susan F. Leitman, Paolo Anderlini, Michael Haagenson, Seira Kurian, John P. Klein, Mary M. Horowitz and Dennis L. Confer

Data from 73 donor centers and 96 apheresis centers

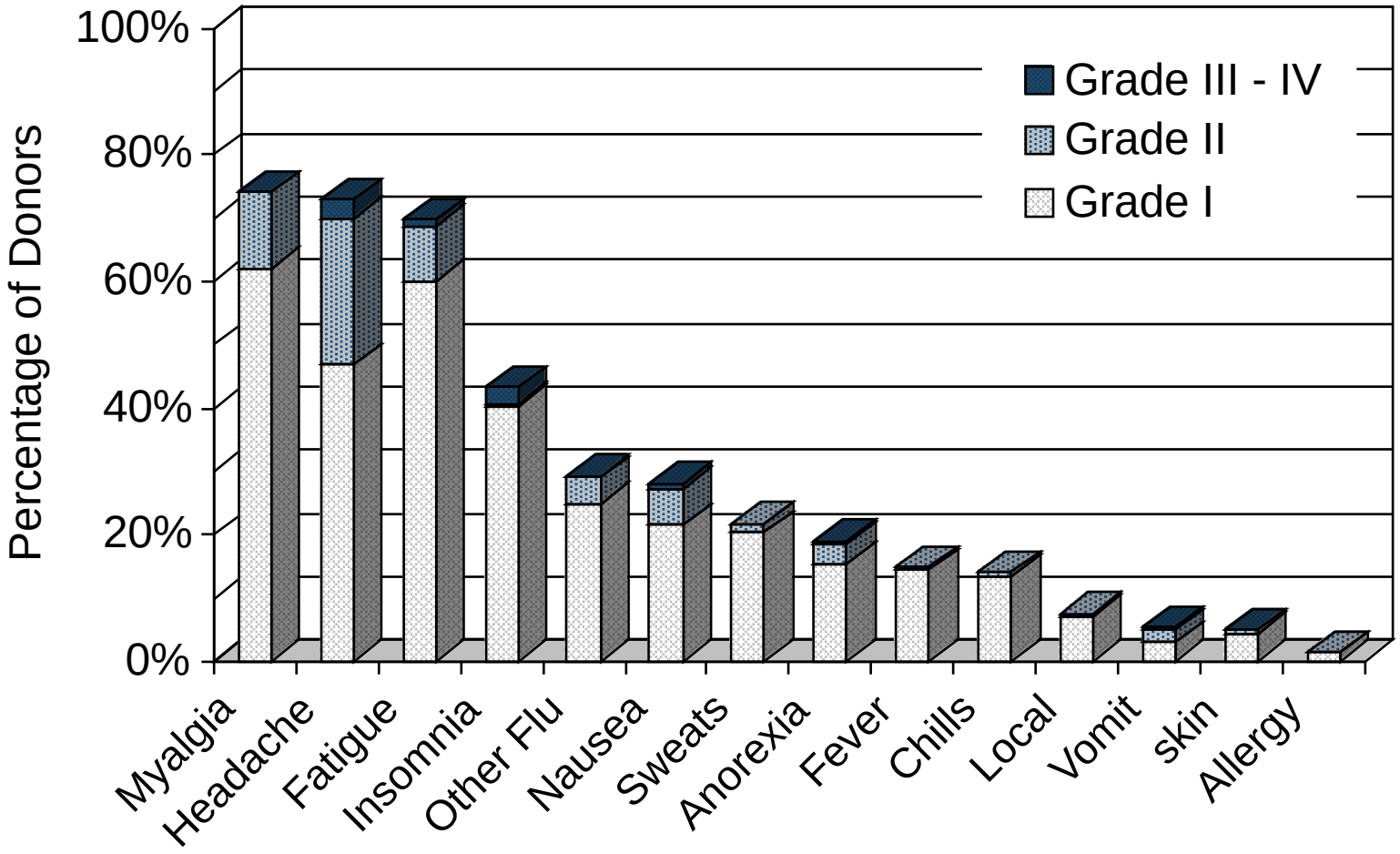
# Frequency of Bone Pain in PBSC Donors



# Maximum Bone Pain Severity for Donors



# Symptom Score During Mobilization



# The Donor Experience: Marrow vs. PBSC

blood

2013 121: 197-206
Prepublished online October 29, 2012;
doi:10.1182/blood-2012-03-417667

**Acute toxicities of unrelated bone marrow versus peripheral blood stem cell donation: results of a prospective trial from the National Marrow Donor Program**

Michael A. Pulsipher, Pintip Chitphakdithai, Brent R. Logan, Bronwen E. Shaw, John R. Wingard, Hillard M. Lazarus, Edmund K. Waller, Matthew Seftel, David F. Stroncek, Angela M. Lopez, Dipnarine Maharaj, Peiman Hematti, Paul V. O'Donnell, Alison W. Loren, Susan F. Leitman, Paolo Anderlini, Steven C. Goldstein, John E. Levine, Willis H. Navarro, John P. Miller and Dennis L. Confer

# The Donor Experience -1

- Donor Cohort 2004 – 2009; 6767 PBSC, 2726 marrow
- 61% male
- 86% general anesthesia
- 77% PBSC were one day collection
- CVC: 21% of female and 4% of male donors
- Thrombocytopenia in PBSC donors:
  - <150,000/mcL in 50% of donors
  - <100,000/mcL in 26% of donors
- All blood counts back to baseline at one month
- 0.5% of marrow donors received allogeneic blood

# The Donor Experience -2

- Bone Pain occurred in 80%, irrespective of donation type
- Timing of bone pain different, mobilization vs. post-collect
- Most pain was rated as mild or moderate
- Other symptoms were similar in both groups
- Bone marrow donors have more prolonged recovery and lower rates of complete recovery



Pulsipher, Blood 2013

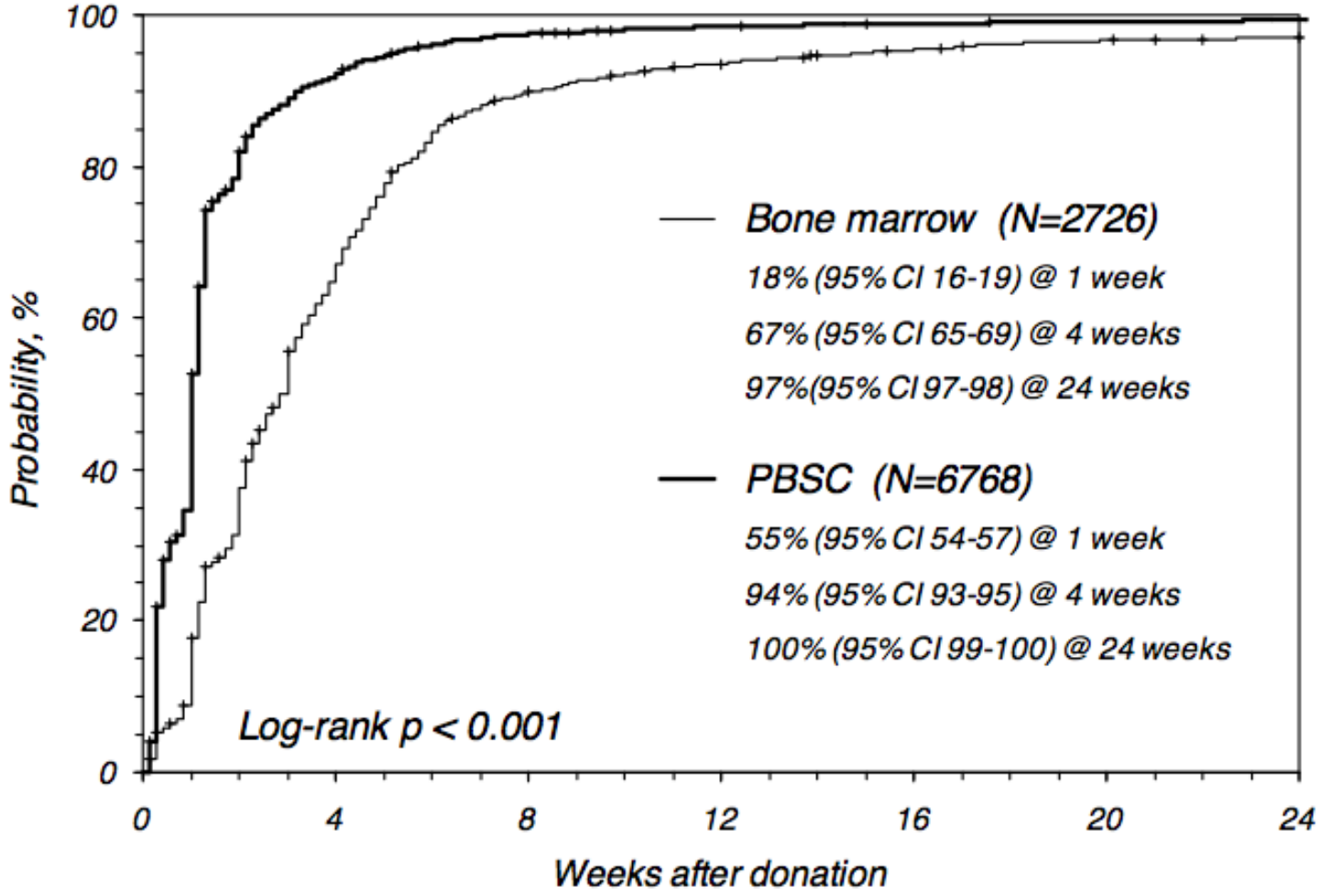
# The Donor Experience -3

- Overweight and obese PBSC donors have higher rates of grade 2-4 pain in the peri-collection period
- Female donors are more likely to report pain and other symptoms and are less likely to experience full recovery, regardless of donation type
- Older marrow donors are less likely to experience grades 2-4 skeletal pain in peri-collection period, but they are more likely to have pain at 1 week and 1 month



Pulsipher, Blood 2013

# Probability of Complete Recovery: Marrow vs. PBSC



# What About Serious Adverse Events?

- Life-threatening or fatal event
- Inpatient hospitalization or prolongation of existing hospitalization
- Persistent or significant disability / incapacity
- Required intervention to prevent permanent impairment/damage
- Congenital anomaly / birth defect
- Other at physician discretion

# Serious Adverse Events (SAE): NMDP Experience with Unrelated Donors

- Rates of SAE higher with bone marrow donation (2.4%) compared to PBSC donation (0.6%)
- Life threatening events are rare (0.1%)
- More life-threatening events, hospitalizations and long term disability with marrow donation
- The frequency of SAE are higher in female donors



Pulsipher, WMDA 2012

# SAEs in NMDP Donors: 1999-2007

42 Total SAEs in 5962 donors (0.7%)

- 37 Serious by virtue of hospitalization
  - 25 with symptoms: low $Ca^{2+}$, H/A, N/V, bone pain, chest pain
  - 4 Central line complications
  - 4 Low platelet counts
  - 2 Pneumonia
  - 1 Asthma
  - 1 DVT
- 5 Other Serious
  - 4 Cancer (renal, breast, lung, cervical)
  - 1 Low platelet count : ITP

# Serious/Unexpected AEs in NMDP Donors: 2008-2014

- 4 Head bleeds
  - 2 subdural
  - 1 intracranial
  - 1 subarachnoid
- 3 Cardiac Arrhythmias
- 3 Splenic bleeds
- 1 Pulmonary embolism
- 1 Hospitalization: RUQ abdominal pain, N/V
- 1 Cholecystectomy

# International Experience with SAE in Related and Unrelated Donors

- Retrospective survey of over 300 EBMT centers covering 1993-2005
- 51,024 first transplants
  - 27,770 marrow
  - 23,254 PBSC
- 37 SAE (0.0725%)
  - 12 marrow (0.043%)
  - 25 PBSC (0.1076) $p<0.05$
- Thromboembolic events more common in PBSC donors

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Halter (2009), Haematologica 94(1): 94-101

# International Experience with SAE in Related and Unrelated Donors (Halter, 2009)

| Adverse Event | Marrow = 12 | PBSC = 25 |
|---|---|---|
| Cardiac: MI | | 2 |
| Cardiac: arrest | 4 | |
| Cardiac: SVT | | 1 |
| Cardiac: New HTN | 2 | 1 |
| T-embolic: PE/DVT | | 7 |
| T-embolic: Stroke | 1 | |
| Pulmonary: TRALI | | 1 |
| Pulmonary: Edema | 1 | |
| Bleed: Subdural | | 1 |
| Bleed: Unspecified | 1 | 1 |
| CNS: Seizure | | 1 |
| Splenic Rupture | | 5 |
| Unspecified | 3 | 5 |

# International Experience with Fatal SAE in Related and Unrelated Donors

- 5 deaths within 30 days of donation (Halter, 2009)
  - All related donors
  - 1 marrow: DVT Dx followed by massive PE
  - 4 PBSC: 3 cardiac arrest and 1 subarachnoid hematoma

- At least 6 more cases (Confer, NOTIFY)
  - 2 cardiac events in related marrow donors
  - Stroke in related PBSC donor
  - Sickle crisis in PBSC donor
  - Cerebellar hemorrhage in 7 year old donor
  - Unspecified

# Related Donor Safety (RDSafe) Study

- There has been an increase in the number of transplants for older patients in recent years with both related and unrelated donors
- Related donors may have:
  - More comorbidities
  - More (or less) motivation to donate
- RDSafe study is a prospective, multicenter trail that includes donor assessments at specified timepoints:
  - Predonation
  - Day of donation (Day +5 of filgrastim)
  - 1 month
  - 1 year

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# Related Donor Safety (RDSafe) Study

- Compared with NMDP unrelated donors aged 41-60 yrs, older related donors (>60 yrs) have:
  - Higher rates of pain and other symptoms (Sx) at baseline
  - Lower rates of pain/Sx following mobilization, but the pain/Sx are of higher grade
  - Slower recovery; with more pain/Sx at one month after donation
- Female donors experience longer recovery times

# Long Term Donor Follow-up Study

## Primary Objective:

To describe the long-term incidence of malignant myeloid hematologic disorders in donors who received and in those who did not receive filgrastim.

## Secondary Objectives:

To describe the long-term incidence in donors receiving or not receiving filgrastim:

- Malignant hematologic disorders
- Non-hematologic malignant disorders
- Thrombotic events
- Autoimmune disorders

# Long Term Donor Follow-up Study

- Retrospective and Prospective cohorts
  - 1999-2015
- Expected Enrollment:
  - 10,956 unstimulated marrow donors
  - 21,172 filgrastim mobilized PBSC donors
- Enrollment began Oct 2010

# Summary -1

- Donor and Patient Risk varies amongst HCT, organ, tissue and blood donors
- Careful donor evaluation is necessary to ensure donor safety, but must be flexible to not exclude donors that are the best match for a patient (more later…)
- Symptoms related to the donation are common and rarely serious, SAE are rare
- Reporting of adverse events is essential to ensuring and promoting donor and patient safety

# Summary -2

Hemovigilance in HCT donors, products and recipients can help to achieve the following goals:

- Identify, evaluate causality, address corrective actions to help prevent or mitigate adverse events
- Enhance the quality and safety of HCT products
- More precisely define risk of HSC donation and transplantation for our donors and patients
- Increase awareness and reporting of adverse events