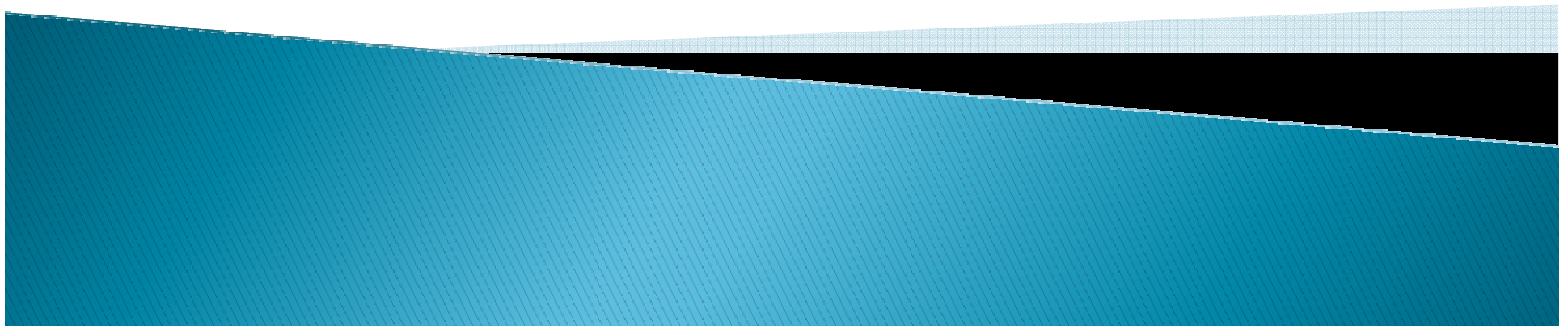


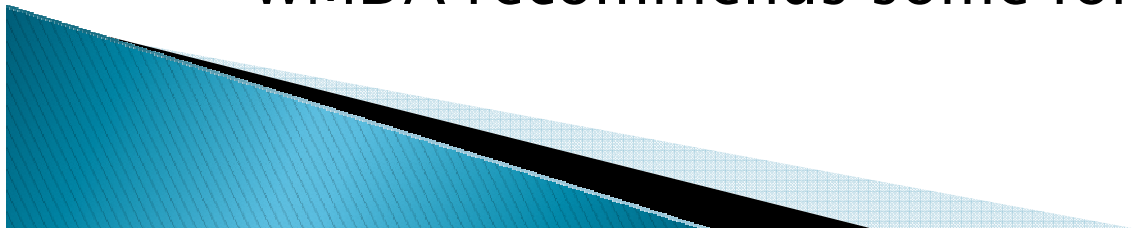
Pediatric Hematopoietic Stem Cell Donors: When and How can Children Ethically Donate?

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Associate Professor
University of Utah School of Medicine



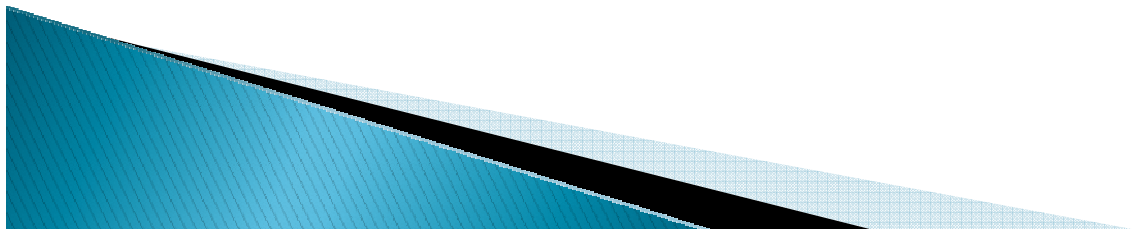
Special Considerations for Pediatric Donors

- ▶ Limited and changing ability to perform informed consent
 - Consent age 18, assent age? (7–17?)
- ▶ Without ability to consent, some type of advocacy is needed
 - Parents generally considered sufficient
 - Parents conflicted because they are deciding between two children
 - Some countries/states require court-appointed advocates
 - WMDA recommends some form of advocacy



BM Harvesting of Pediatric Sibling Donors is Ethically Permissible

- ▶ Procedure has been performed for >30 yrs
- ▶ Generally considered safe
- ▶ PBSC harvests have also been performed on young children with a reasonable safety record
 - Some countries/states do not allow PBSC collection because of concern about possible long-term effects of G-CSF



EBMT: Demographics and Risks of SC Collection in Pediatric Donors

Unpublished data, Styczinski, Peters

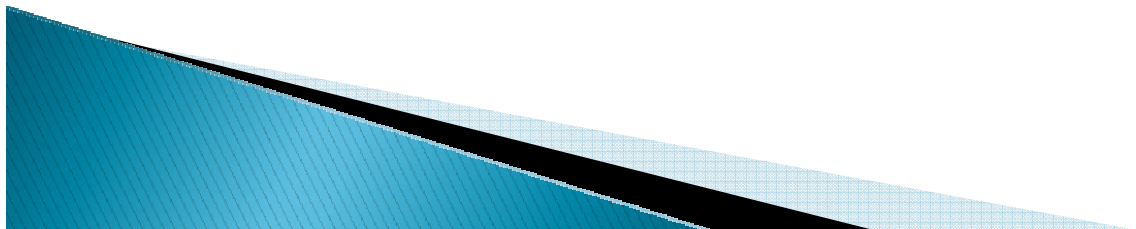
Variable	Total	BM donors	PBSC donors	P-value
Donor	n=453	n=313	n=140	
Gender				0.154
female	206 (45.5%)	148 (47.3%)	58 (41.4%)	
male	247 (54.5%)	156 (52.7%)	82 (58.6%)	
Age (median, range) yrs	9.6 (0.7-18.0)	8.3 (0.7-18.0)	12 (1.3-17.6)	<0.0001
Weight (median, range) kg	32 (8-114)	29 (8-100)	42 (12-114)	<0.0001
Age groups				<0.0001
< 4 yrs	58 (12.8%)	52 (16.6%)	6 (4.3%)	
4-8 yrs	114 (25.2%)	92 (29.4%)	22 (15.7%)	
> 8 yrs	281 (62.0%)	169 (54.0%)	112 (80.0%)	
Weight groups				<0.0001
< 20 kg	92 (20.3%)	79 (25.2%)	13 (9.3%)	
20-40 kg	194 (42.8%)	137 (43.8%)	57 (40.7%)	
> 40 kg	167 (36.9%)	97 (31.0%)	70 (50.0%)	

EBMT: Pain, transfusions, hospitalizations in pediatric donors

Variable HR	Total donors	BM donors	PBSC donors	P-value	(95%CI)
	n=453	N=313	n=140		
Pain (not related to G-CSF)					
No	237 (52.3%)	118 (37.7%)	119 (85.0%)	<0.0001	
Yes (no analgesics)	50 (11.0%)	38 (12.1%)	12 (8.6%)		
Yes (non-narcotic analgesics)	166 (36.7%)	157 (50.2%)	9 (6.4%)		
Blood allo-transfusion					
No	368 (81.2%)	229 (73.2%)	131 (93.6%)	<0.0001	5.3 (2.5-11.8)
Yes	85 (18.8%)	84 (26.8%)	9 (6.4%)		
days spent in hospital after collection					
0	118 (26.1%)	12 (3.8%)	106 (75.7%)	<0.0001	
1	265 (58.5%)	240 (76.7%)	25 (17.9%)		
2 or more	70 (15.4%)	61 (19.5%)	9 (6.4%)		

EBMT: Multivariate Analysis of Risk

- ▶ Children <4 had an increased risk of pain and hgb <8 after the procedure.
- ▶ Children <8 had an increased risk of requiring a blood transfusion.
- ▶ Donors having $>20\text{cc/kg}$ harvested had a 26 fold increased risk of low hgb and requiring a blood transfusion
- ▶ One BM donor had severe laryngospasm, one PBSC donor had a pneumothorax



**Safety and Efficacy of Allogeneic
PBSC Collection in Normal Pediatric
Donors: The Pediatric Blood and
Marrow Transplant Consortium
Experience (PBMTTC) 1996-2003**

Michael Pulsipher, MD

John E. Levine, MD

Robert Hayashi, MD

Ka Wah Chan, MD

Peter Anderson, MD, PhD

Reggie Duerst, MD

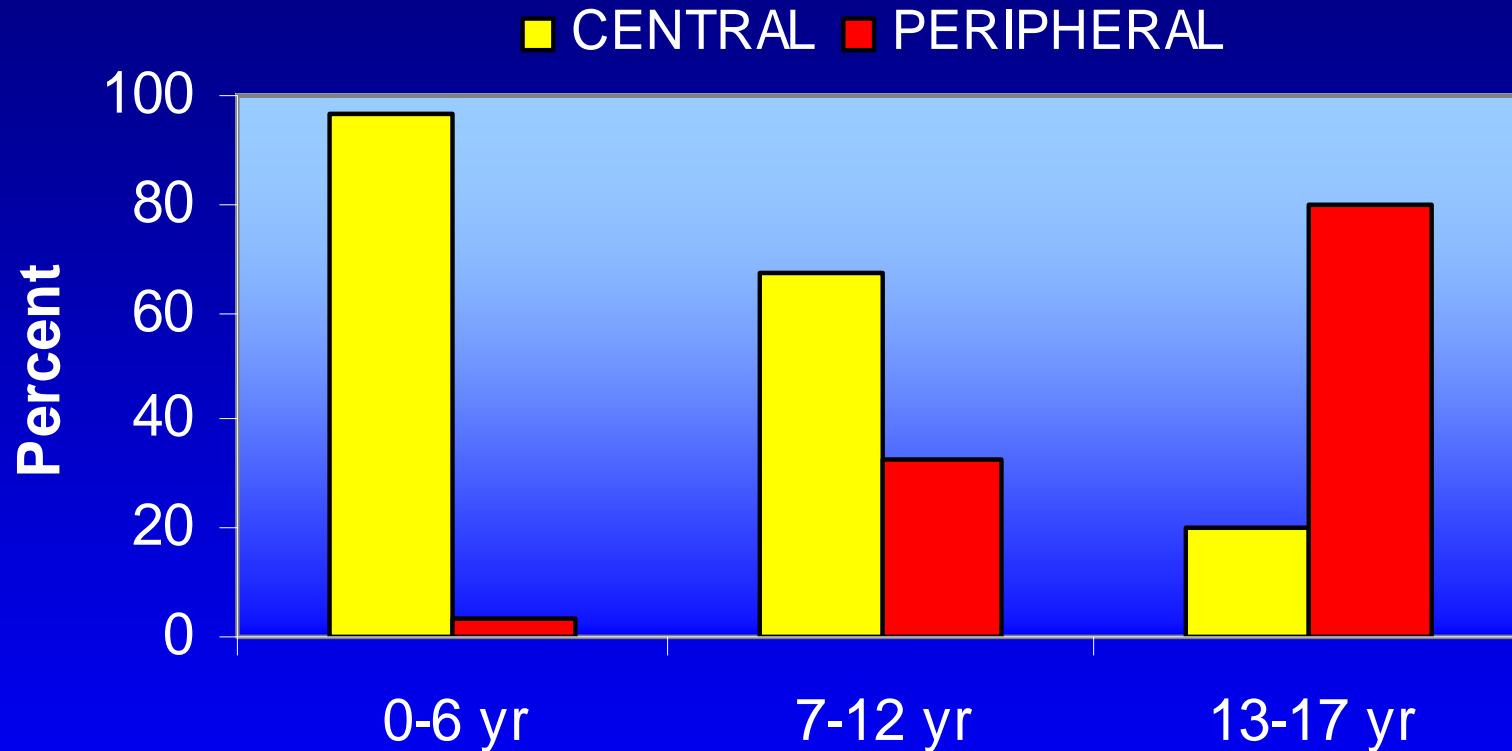
Stephen Grupp, MD, PhD

for the PBMTTC STC0212 Committee

Cytokine Treatment

<i>(n)</i>	<i>0-6 yr</i> <i>(36)</i>	<i>7-12 yr</i> <i>(74)</i>	<i>13-17 yr</i> <i>(87)</i>	<i>p</i> <i>value</i>
<i>Cytokine</i> <i>days</i>	4.4 (3-7)	4.3 (1-7)	4.5 (1-9)	NS
<i>G-CSF</i> <i>alone</i>	97%	97%	95%	NS
<i>Analgesia</i> <i>needed</i>	0%	11%	15%	0.06
<i>Narcotic</i> <i>needed</i>	0%	0%	1%	NS

Venous Access By Age



	0-6 yr	7-12 yr	13-17 yr
Femoral	26/38 (68%)	33/56 (59%)	9/21 (42%)
Subclavian	12/38 (32%)	23/56 (41%)	12/21 (58%)
/IJ			

Complications of Apheresis

<i>(n)</i>	<i>0-6 yr (28)</i>	<i>7-12 yr (74)</i>	<i>13-17 yr (95)</i>	<i>p value</i>
<i>Bleeding requiring transfusion</i>	0%	0%	0%	NS
<i>Bleeding requiring pressure</i>	0%	0%	2%	NS
<i>Symptomatic hypocalcemia</i>	7%	4%	8%	NS

Red Cell Priming/Transfusions

Blood used to prime apheresis machine:

Donor	<20kg	92%
	20-30 kg	6%

Autologous platelet transfusions (platelet rich plasma)

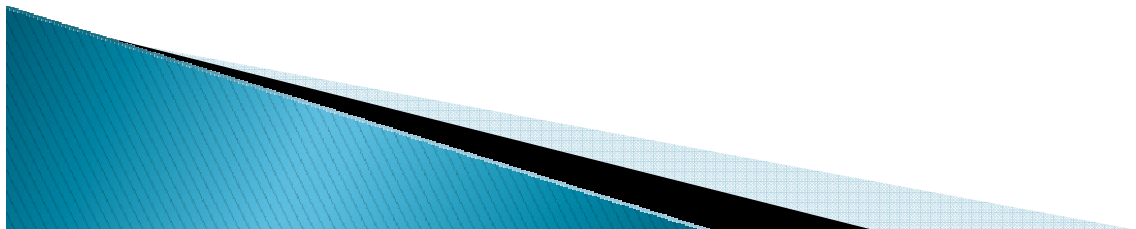
0-6	0/39 (0%)
7-12	3/80 (4%)
13-17	8/94 (9%)

Conclusions

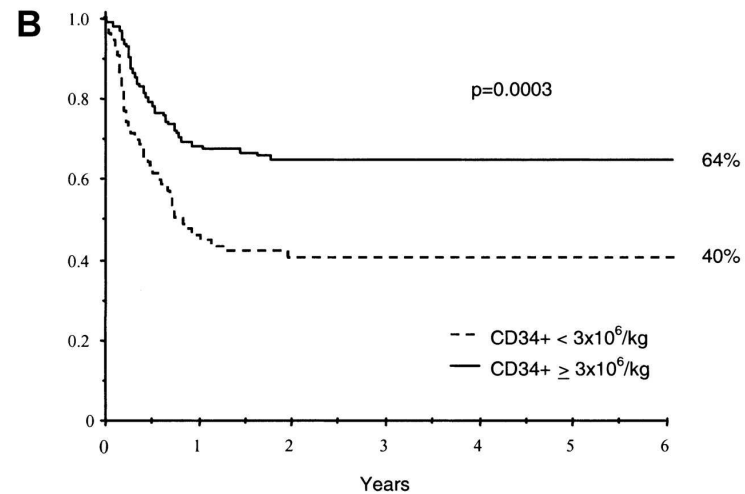
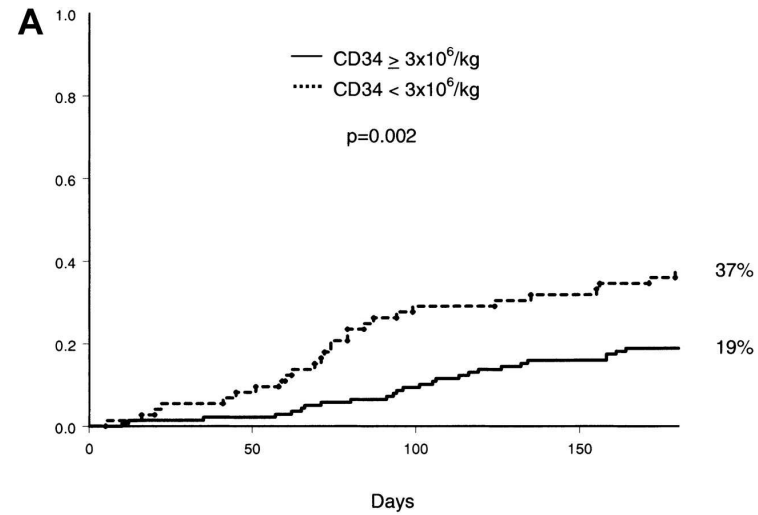
- PBSC collection from healthy child donors is associated with a low rate of complications and yields high numbers of CD34+ cells.
- After adjusting for covariates, more days of apheresis, younger age, and male gender were associated with higher yields.
- Donors under 20 kg were regularly exposed to blood products.
- Younger patients utilized more hospital resources

Challenges with Young/Small Donors

- ▶ Anesthesia—Pediatric specific approaches needed for intubation and management
- ▶ Access—small PBSC donors need central lines
- ▶ Apheresis priming—children <20kg need apheresis machines to be primed
 - Risk of blood exposure
- ▶ Too much blood—when donor/recipient sizes are discrepant, run the risk of harvesting too much
 - Recipient at increased risk of rejection/slow engraftment, donor at risk of needing transfusion



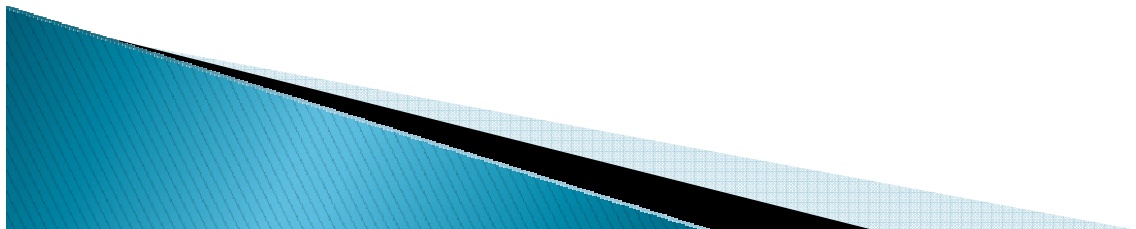
TRM and survival. Cumulative incidence of TRM at day 180 (A), and Kaplan-Meier estimate of overall survival (B) according to CD34+ cell dose.



Bittencourt H et al. *Blood* 2002;99:2726-2733

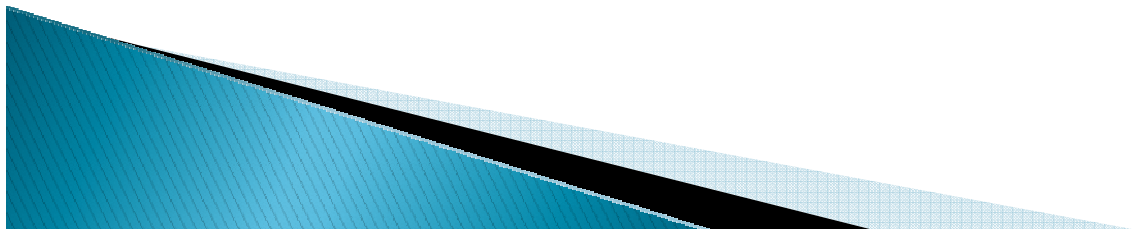
Good Practice for Pediatric Donors

- ▶ Harvest a maximum of 20cc/kg donor weight
- ▶ If major ABO incompatibility exists
 - Goal 15cc/kg
- ▶ If no major ABO incompatibility
 - Goal 10cc/kg



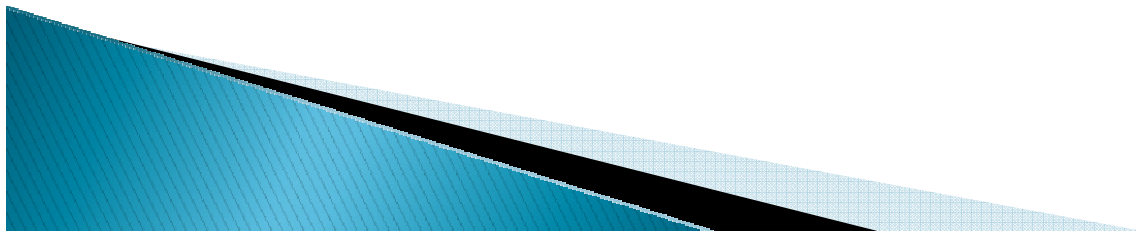
Rules of Thumb for Smaller Donors

- ▶ Harvests reported on children 3 months old
 - 6–8+ months old is preferred.
 - Collect and infuse cord blood if possible
- ▶ Alternative methods to increase CD34+ cells if donor/recipient weight ratio <0.5
 - G-CSF primed BM (more than doubles CD34 content) Frangoul Blood 2007 110: 4584–7
 - PBSC (high CD34 yields even when size discrepancy exists) Pulsipher Bone Marrow Transplant 2005 35:361–7
 - Consider using an alternative donor

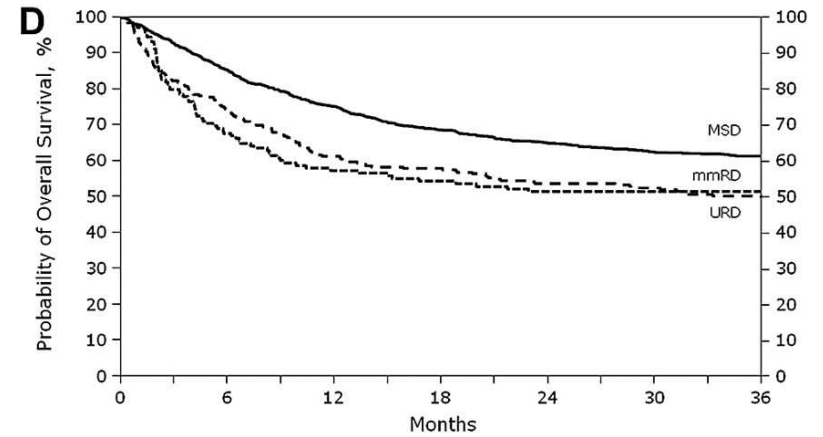
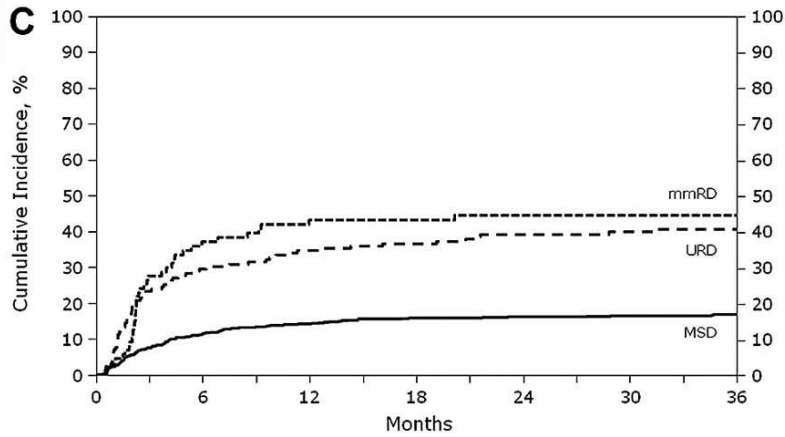
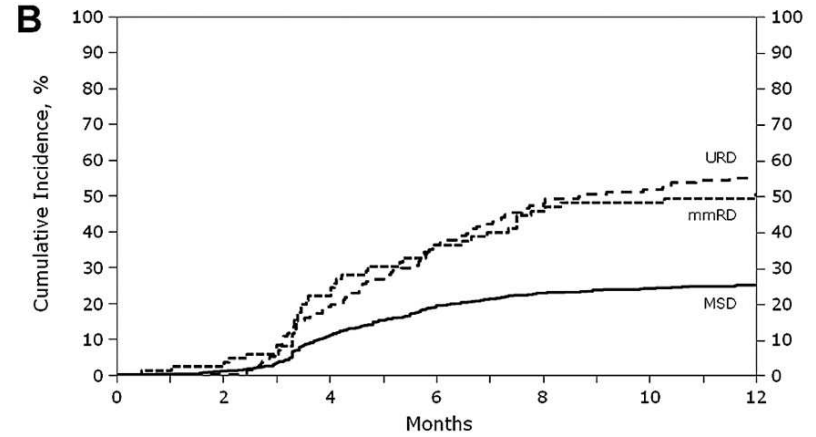
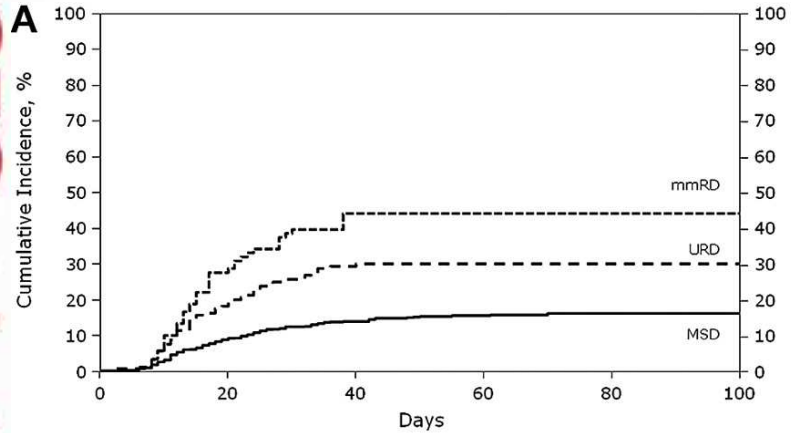


When is it appropriate for a child to donate HSCs?

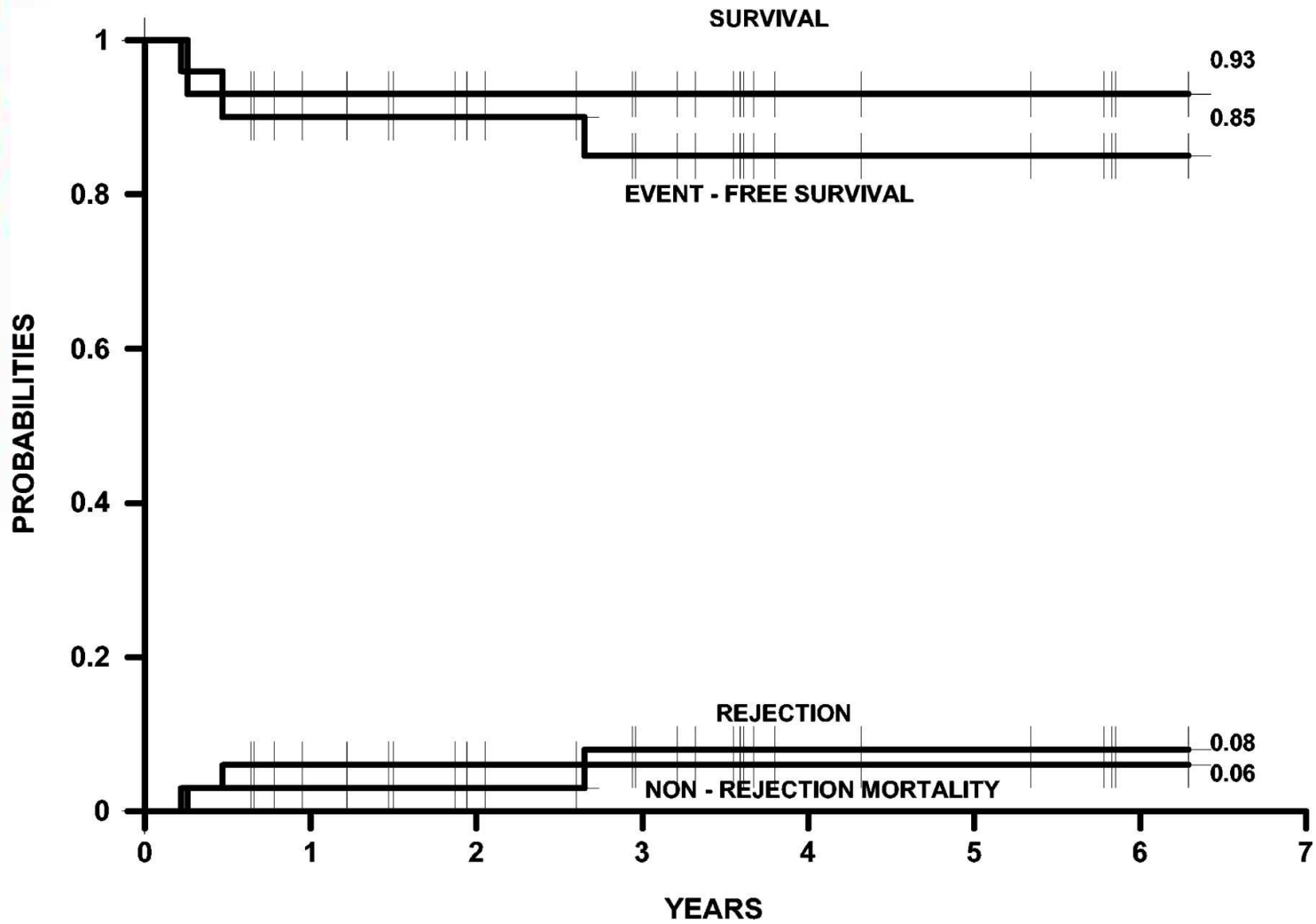
- ▶ American Academy of Pediatrics Statement:
 - (1) there is no medically equivalent histocompatible adult relative who is willing and able to donate
 - Fully matched sibling
 - Partially matched sibling/haploidentical



Unadjusted curves of acute GVHD grades 3-4, chronic GVHD, TRM, and OS by donor types.



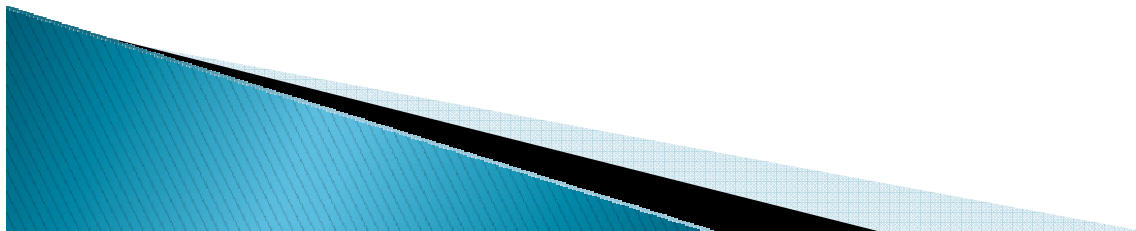
Shaw P J et al. Blood 2010;116:4007-4015



Sodani P et al. Blood 2004;104:1201-1203

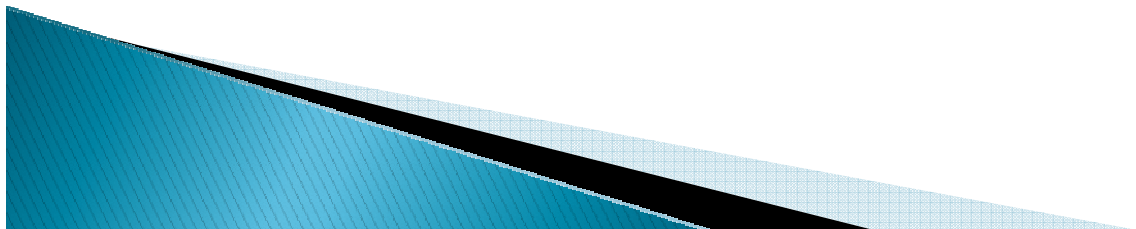
If multiple donors are available . . .

- ▶ CMV status
 - Negative donor/negative recipient—better outcome
- ▶ Gender
 - Gender mismatch (F to M) effect very small in children
- ▶ Blood type
 - For MA approaches, small effect in children
- ▶ Size matching
 - Better outcome with $>4 \times 10^6$ CD34 cell/kg or about 3×10^8 TNC/kg (roughly 10cc/kg from donor)
 - We do not have data to suggest a size of a donor compared to recipient that is too small
- ▶ Major issues—health of donor, age (ability to assent), willingness



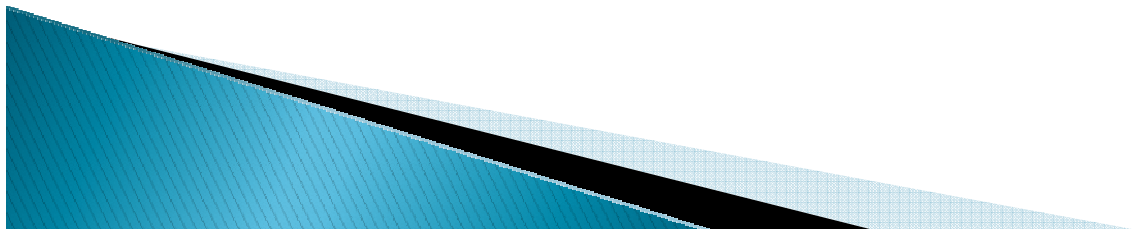
Examples

- ▶ Two siblings, one age 4 and a second age 11 are HLA matched
 - Recipient CMV–, 4yo CMV–, 11yo CMV+
 - Would choose the 4yo to decrease CMV risk
 - Recipient weighs 80kg, 4yo—15kg, 11yo 40kg
 - Choose the 11yo—max of 300cc of marrow is only 3.75cc/kg—risk low cell dose
 - Recipient age 8, both donors same CMV, blood type, both donors willing
 - Choose 11yo—all things equivalent the 11yo is more capable of assent



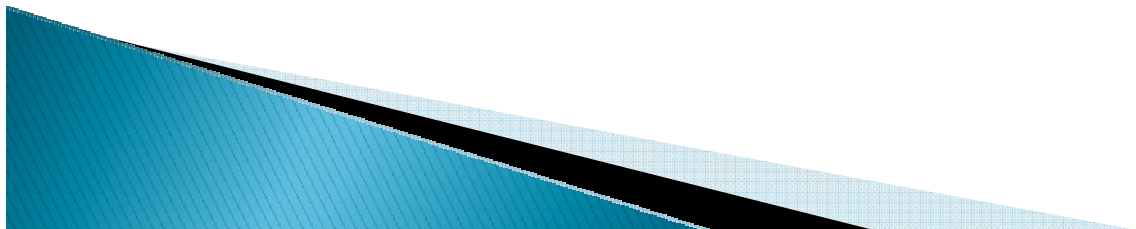
AAP Recommendations (Cont.)

- ▶ (2) there is a strong personal and emotionally positive relationship between the donor and recipient
 - Much controversy about this statement
 - Related donation has occurred between two siblings who have been raised separately and do not know each other
 - The key issue is that no coercion is involved
 - Many individuals willing to perform acts of kindness to strangers or those that they don't have a positive relationship with, but they must do this willingly



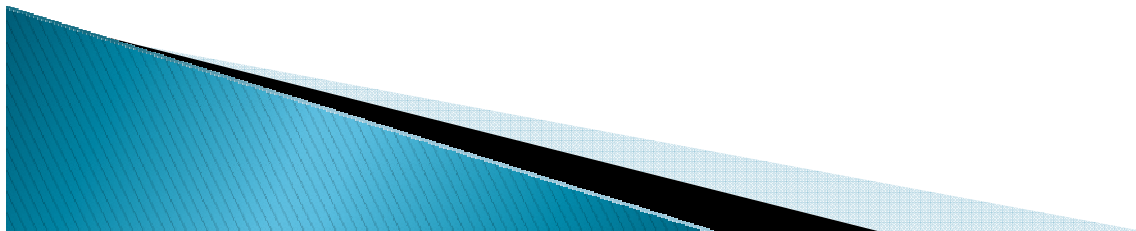
AAP Recommendations (Cont.)

- ▶ (3) there is some likelihood that the recipient will benefit from transplantation
 - Some consider a chance of success $<10\%$ to be an appropriate cut off
 - This may vary by family and be influenced by the ability of donor to assent



AAP Recommendations (Cont.)

- ▶ (4) the clinical, emotional, and psychosocial risks to the donor are minimized and are reasonable in relation to the benefits expected to accrue to the donor and to the recipient
 - every effort to minimize risk to the donor must be made
- ▶ (5) parental permission and, where appropriate, child assent must be obtained

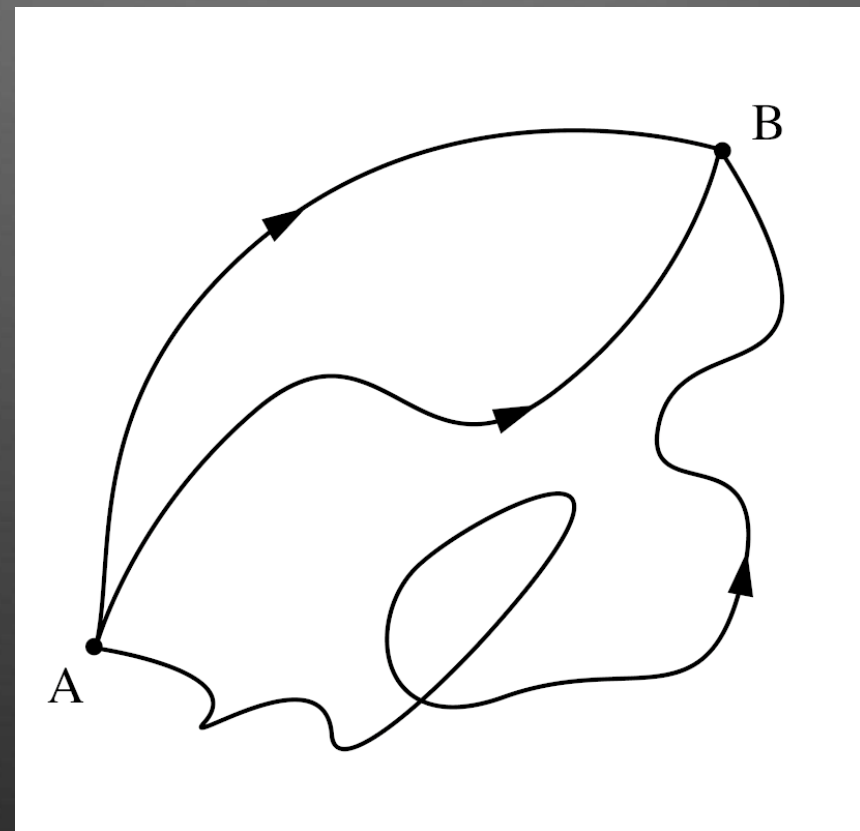


What about Research into Stem Cell Donation in Children?

- ▶ Declaration of Helsinki Principles Apply
 - respect for persons
 - autonomy
 - informed consent
 - voluntary nature of participation
 - Children are a “protected” population
- ▶ Extra “Coercive” Elements Apply to Donors
 - Parents advocating for both donor and recipient
 - Recipient has a life-threatening illness

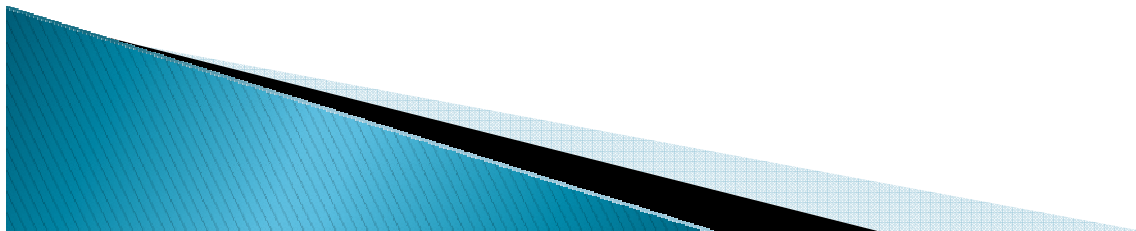


Studies on Children: 3 Paths



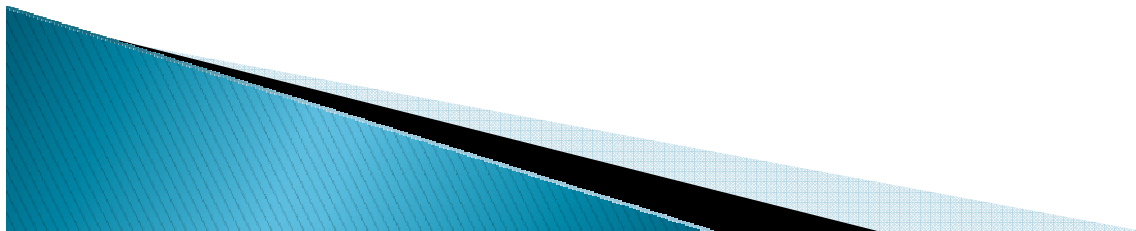
Studies on Children: 3 Paths in US Law

- ▶ 45CFR § 46.405 prospect of direct benefit
- ▶ 406 minor increase over minimal risk
- ▶ Neither 405 or 406 applies, but “the research presents a reasonable opportunity to further the understanding, prevention, or alleviation of a serious problem affecting the health or welfare of children.”
 - Refer to federal panel—this is a 407



Pediatric HSC Donation: Conclusions

- ▶ Countries/States must establish a legal framework to allow a minor to donate
 - BM and PBSC procedure considered safe
 - Individuals may have risk and assent issues
 - An independent advocate is desirable
- ▶ Special considerations for size issues
 - Smaller children at higher risk
 - Stem cell dose issues must be addressed
- ▶ Ethical guidelines
 - Older donors should be used if two are equal
 - Research designs protect safety



Acknowledgements

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SCT

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