Case

- 22 mo female presents with a history of multiple episodes of thrush, fever, pneumonia, diarrhea, influenza A, and failure to thrive.
- Serum IgG 7 mg/dL, IgA <6 mg/dL, IgM <4 mg/dL

Case

- absolute CD3 98/uL (lower limit normal 1400)
- absolute CD4 70/uL (lower limit normal 900)
- absolute CD8 26/uL (lower limit normal 400)
- absolute CD19 1/ul (lower limit normal 600)
- absolute NK 238/uL (normal)

Case

- She is diagnosed with B-, T-, NK + SCID
- Adenosine deaminase mutation negative
- Pt is awaiting bone marrow transplant, meanwhile, suffers from recurrent fevers and infections including line infections, pneumonia, and recurrent resistant influenza A

TRANSPLANTATION OF HEMATOPOIETIC STEM CELLS AND LONG-TERM SURVIVAL FOR PRIMARY IMMUNODEFICIENCIES IN EUROPE: ENTERING A NEW CENTURY, DO WE DO BETTER?

Gennery et al
JACI September 2010

Objective

- Analyze long-term outcome of patients with SCID and non-SCID PID from European Centers treated between 1968 and 2005

Background

- Hematopoietic stem cell transplant (HSCT) curative since 1968
- It remains the only form of treatment for most patients with SCID or other primary immunodeficiencies (PID)

Background

- Since 1968
  - HLA-tissue typing refined
  - New stem cell sources available (umbilical cord blood)
  - Improved methods of isolating stem cells like CD34+ stem cell selection and CD3+/CD19+ depletion

Background

- Since 1968
  - More grafts using unrelated donors (URD)
  - Less toxic chemotherapy regimens have been developed → improved survival in very sick patients
  - Molecular detection of viral infection → pre-emptive antiviral treatment
  - Greater awareness of PID by pediatrician → earlier diagnosis and referral to specialist centers

SCETIDE registry

- Stem cell transplantation for Immunodeficiencies in Europe
  - Data derived from their database
- Patients with SCID and non-SCID PID treated in European centers between 1968 and 2005 were analyzed
- As many innovations in HSCT were introduced during the period of 2000 to 2005, authors explored whether better results were obtained compared with previous periods

Methods

- From1968 to 12/31/05 → 37 centers collected and recorded continuous and systematic relevant data on children undergoing HSCT for SCID and other PIDs
- Previous definitions of SCIDS and non-SCID PID as recently published by the International Union of Immunological Societies were used for consistency

Methods

- Donor and recipient HLA matching determined by:
  - Serology for earlier patients
  - Low-resolution class I with high-resolution class II molecular DNA typing in more recent patients
  - Methods dependent on each center's practice

Methods

- Genoidentical donors: HLA-identical sibling donors
- Phenoidentical donors: HLA-identical non-sibling family donors
- URD: Unrelated donor, HLA-matched (although some mismatched by 1 or 2 antigens)
- MMR: Mismatched related

Methods

- T-lymphocyte depletion performed by a number of different methods
- Since late 1990s, CD34+ stem cell selection rather than T cell depletion used
- If given, cytoreductive chemotherapy and GvHD prophylaxis (cyclosporine or tacrolimus), was given in accordance with the EBMT/ESID Inborn Errors Working Party treatment guidelines

Methods

- Survival times started from the date of last HSCT in statistical analysis
- Center effect explored, and analyses were adjusted for a center effect in multivariate analysis
  - Compared centers that transplanted more or less than 50 patients

Results

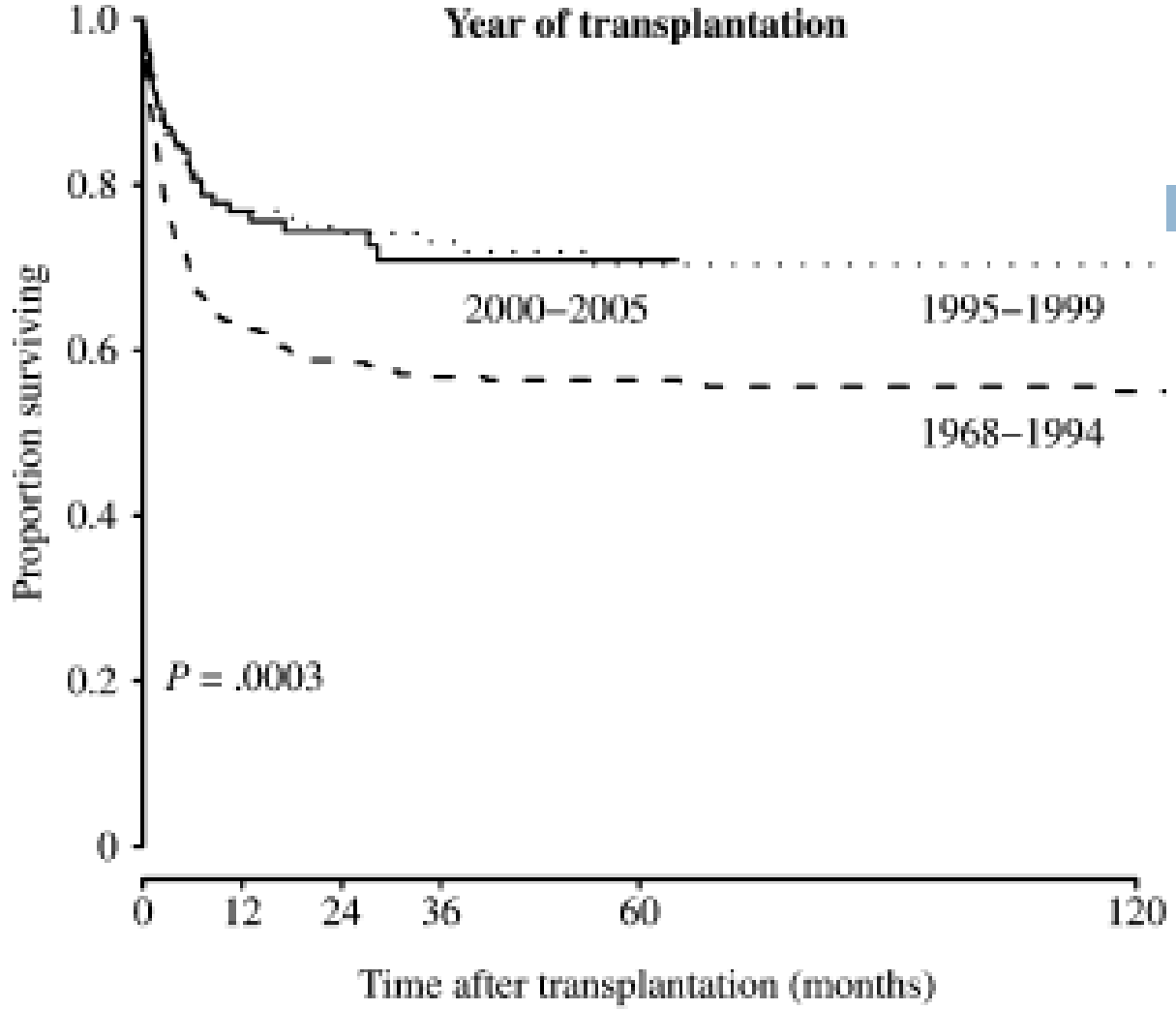
- Data on 699 patients with SCID collected
  - 49% had B+ SCID
  - 29% had B- SCID
  - 22% other forms of SCID
- The proportions of patients presenting with each diagnosis were unchanged over time

More URDS used a a proportion of total transplants over time reflects international registries and improved donor selection + harvesting procedures

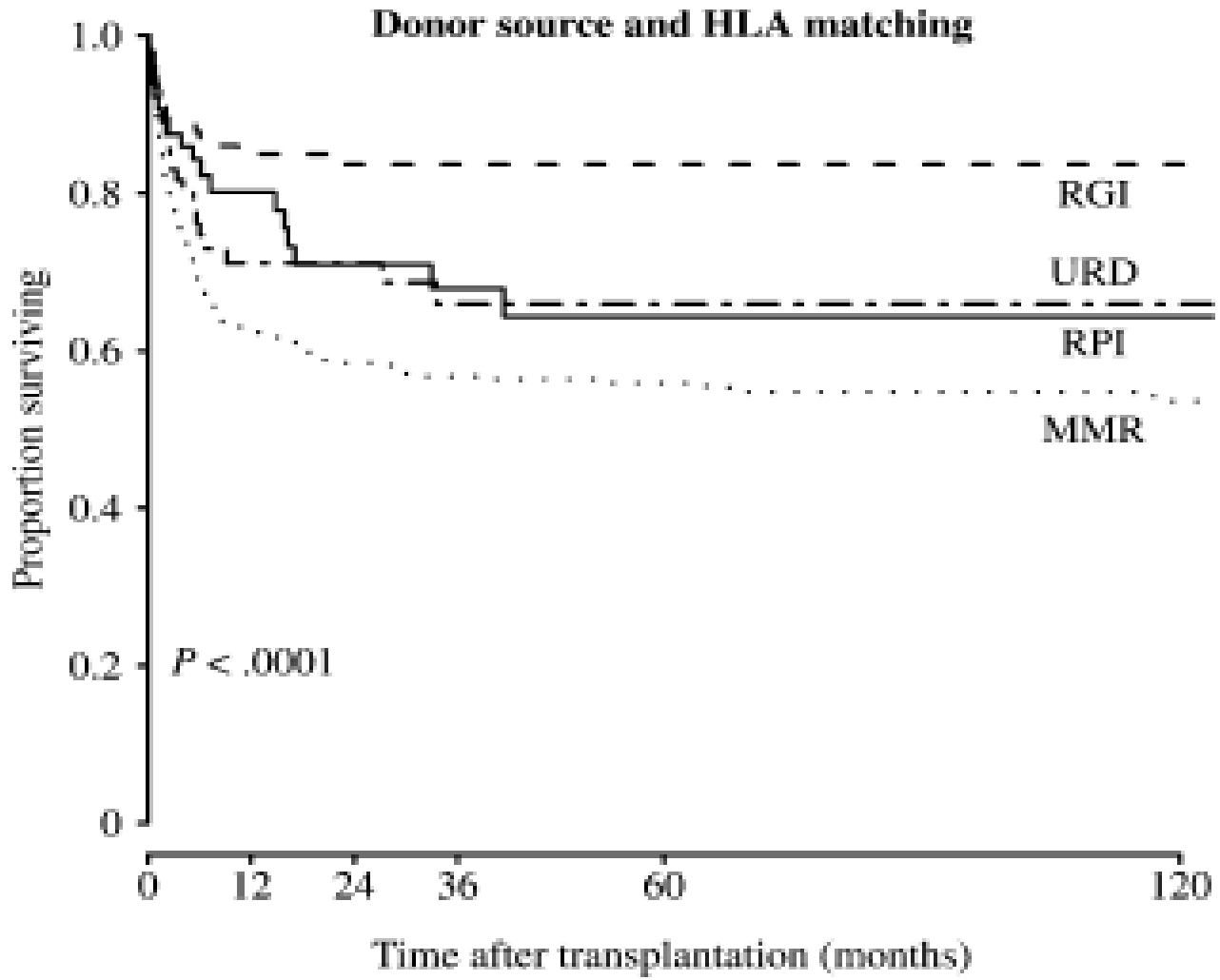
Diagnosis	n	Percent	Related donor			URD, n
			Genotypically HLA identical, n	Phenotypically HLA identical, n	HLA-mismatched, n	
SCID						
Years of graft <1995						
Total	361		84	33	229	15
Reticular dysgenesis	11	3	2	1	7	1
ADA deficiency	42	12	14	1	25	2
T- B−	105	29	29	14	60	2
T- B+	181	50	34	13	127	7
Other	22	6	5	4	10	3
Years of graft 1995-1999						
Total	157		26	21	90	20
Reticular dysgenesis	3	2	0	0	3	0
ADA deficiency	15	10	6	4	2	3
T- B−	46	29	3	11	25	7
T- B+	80	51	11	4	57	8
Other	13	8	6	2	3	2
Years of graft 2000-2005						
Total	181		25	14	96	46
Reticular dysgenesis	5	3	0	0	4	1
ADA deficiency	18	10	5	1	4	8
T- B−	55	30	7	5	32	11
T- B+	84	46	9	7	52	16
Other	19	11	4	1	4	10

SCIDS Results

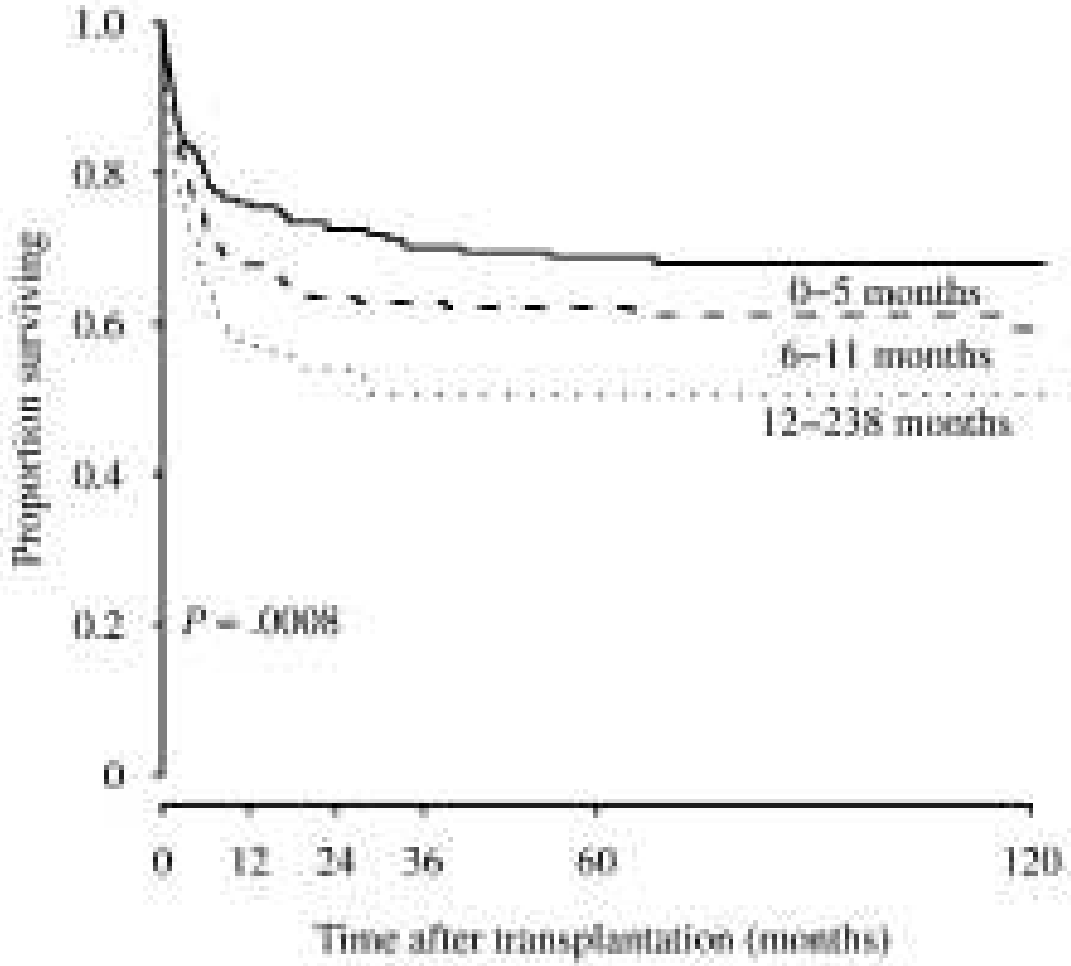
- 10 yr survival in patients with SCID has improved with time although no difference between ‘95-’99 and ’00-’05
- 10 yr survival better with sibling genoidentical donors
- Patients transplanted before 6 mo of age had a better overall survival than those transplanted at >12 months old



Months	0	6	12	24	36	60	120
Number at risk							
1968–1994	361	245	187	172	166	151	88
1995–1999	157	113	95	78	66	40	3
2000–2005	181	111	74	49	26	4	0



Months	0	6	12	24	36	60	120
Number at risk							
RGI	135	111	77	64	60	50	31
RPI	68	46	36	27	21	16	8
URD	81	53	36	33	23	18	6
MMR	415	259	207	175	154	111	46



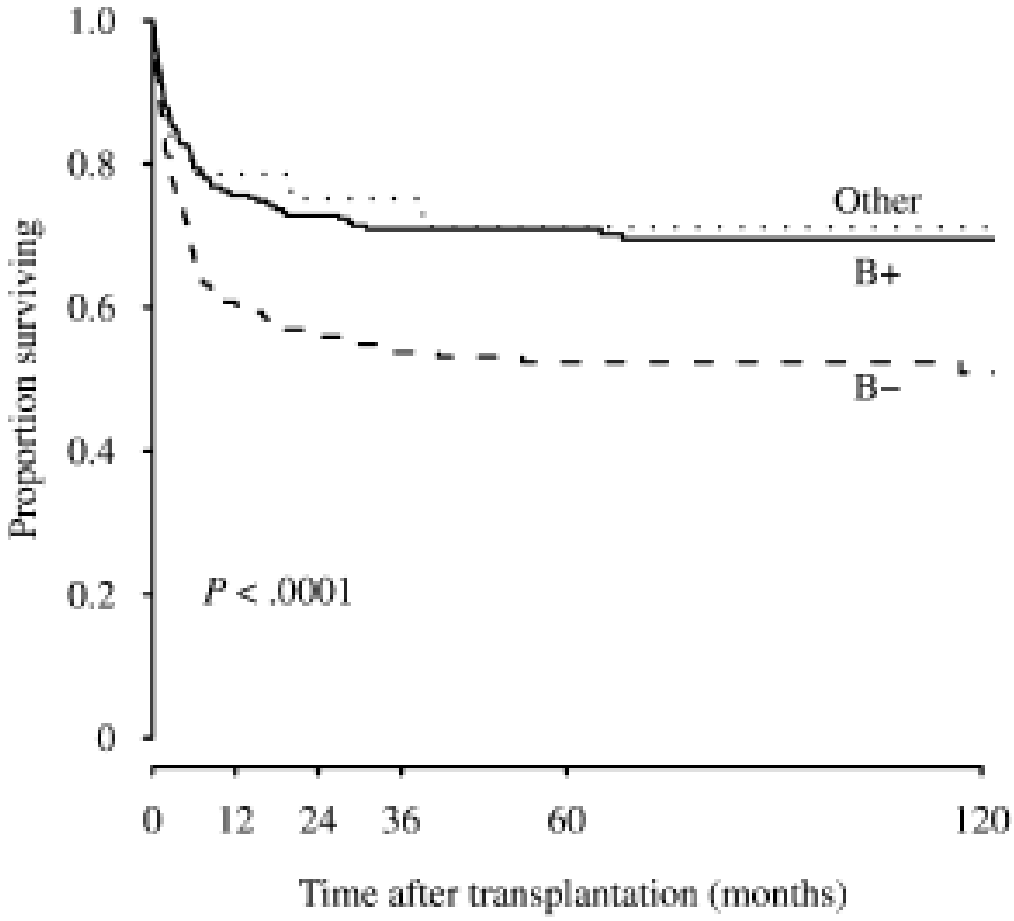
Months	0	6	12	24	36	60	120
Number at risk							
0–5 months	289	210	158	135	118	92	47
6–11 months	253	170	134	110	94	70	32
12–238 months	145	80	56	48	40	28	12

FIG E3. Cumulative probability of survival in patients with SCID after HSCT according to age at transplantation through all periods.

SCIDS Results

- Survival for patients with B+ and other forms of SCID remained better than B – SCID
- Worse outcomes associated with:
  - Pre-existing respiratory impairment
  - Pre-existing septicemia
  - Liver impairment
  - Meningeal infection
  - Malnutrition

Cumulative probability of survival in patients with T-B- or T-B+ SCID after HSCT through all periods



Months	0	6	12	24	36	60	120
Number at risk							
B+	345	247	195	168	147	111	55
B−	300	184	135	109	91	69	33
Other	54	38	26	22	20	15	3

SCIDS Results

- Significantly associated with outcome (multivariate anaylsis):
  - Age at time of transplant
  - SCID phenotype
  - Recipient/donor compatibility
  - Pre-existing respiratory infection
  - Protected environment
  - Antibiotic prophylaxis
  - Presence or absence of T-lymphocyte depletion

TABLE II. Factors affecting outcome after stem cell transplantation

Outcome factors	Univariate analysis				Multivariate analysis	
	Absolute number of patients	Absolute number of deaths	10-Year survival % (95% CI)	*P* value	Hazard ratio (95% CI)	*P* value
SCID						
Years of graft						
2000-2005	181	41	71 (63-80)*	.0003	1	
1995-1999	157	40	70 (63-79)*		1.0 (0.6-1.7)	.97
<1995	361	153	56 (51-62)*		1.5 (1.0-2.2)	.06
Age at transplantation (mo)						
<6	289	79	68 (62-74)	.0008	1	
6-11	253	92	59 (53-67)		1.3 (0.9-1.9)	.11
>12	145	61	51 (42-61)		2.4 (1.6-3.5)	<.0001
SCID phenotype						
B^+	345	92	70 (64-76)	<.0001	1	
B^-	300	128	51 (45-58)		2.2 (1.6-2.9)	<.0001
Other	54	14	71 (58-87)		1.2 (0.7-2.2)	.55
Recipient/donor compatibility						
Related genotypically identical	135	20	84 (77-91)	<.0001	1	
Related phenotypically identical	68	18	64 (52-80)		2.6 (1.3-5.3)	.009
URD	81	23	66 (55-79)		4.1 (2.1-8.1)	.0001
Related HLA-mismatched	415	173	54 (48-60)		8.9 (4.6-17.2)	<.0001
Respiratory impairment						
No	379	123	63 (58-69)	.006	1	
Yes	247	102	55 (48-62)		1.6 (1.2-2.2)	.002
Septicemia						
No	563	197	61 (56-65)	.003	1	
Yes	53	27	46 (33-63)		1.8 (1.1-2.8)	.013
Viral infection						
No	432	144	63 (58-68)	.002	1	
Yes	191	81	52 (45-61)		1.4 (1.0-1.9)	.041
T-cell depletion						
Yes	422	160	57 (52-63)	.011	1	
No	266	71	69 (63-76)		2.0 (1.3-3.3)	.004
Protected environment						
Yes	613	199	63 (59-67)	.004	1	
No	55	26	50 (37-66)		2.0 (1.2-3.2)	.005
Prophylaxis†						
Yes	503	173	62 (57-67)	.021	1	
No	88	40	54 (44-66)		1.9 (1.3-2.8)	.0007

TABLE E1. Clinical characteristics of patients according to year of graft

Clinical characteristic	Related donor			URD
	Genotypically HLA identical	Phenotypically HLA identical	HLA-mismatched	
SCID				
Years of graft <1995				
Total	84	33	229	15
More than 1 stem cell transplantation	8	3	43	4
Median age at transplantation (mo)	5.8	6.2	7.2	13.1
<6	46	15	87	2
6-11	20	17	98	2
12-18	8	0	27	6
>18	8	1	15	5
Years of graft 1995-1999				
Total	26	21	90	20
More than 1 stem cell transplantation	3	2	17	2
Median age at transplantation (mo)	6.6	4.5	6.9	10.1
<6	12	11	34	6
6-11	6	4	40	8
12-18	5	2	6	2
>18	2	3	8	3
Years of graft 2000-2005				
Total	25	14	96	46
More than 1 stem cell transplantation	0	2	23	5
Median age at transplantation (mo)	4.9	4.2	7.5	9.5
<6	16	9	33	18
6-11	5	2	41	10
12-18	2	0	6	7
>18	2	3	13	11

SCIDS Results

- Use of chemotherapy conditioning did not significantly affect survival (p=0.53)

Treatment	N	10 yr survival
Chemotherapy	280	61%
No chemotherapy	399	63%

Non-SCID Patients

- Data on 783 patients with non-SCID PID collected
  - After 1995, the numbers and proportion of patients with inborn errors other than Wiskott-Aldrich syndrome (WAS) increased
- T-lymphocyte deficiencies
  - 34% Omenn syndrome
  - 6% Purine nucleoside phophorylase deficiency
  - 32% HLA class II deficiency
  - 18% CD40 ligand deficiency
  - 10% undefined

Non-SCID Results

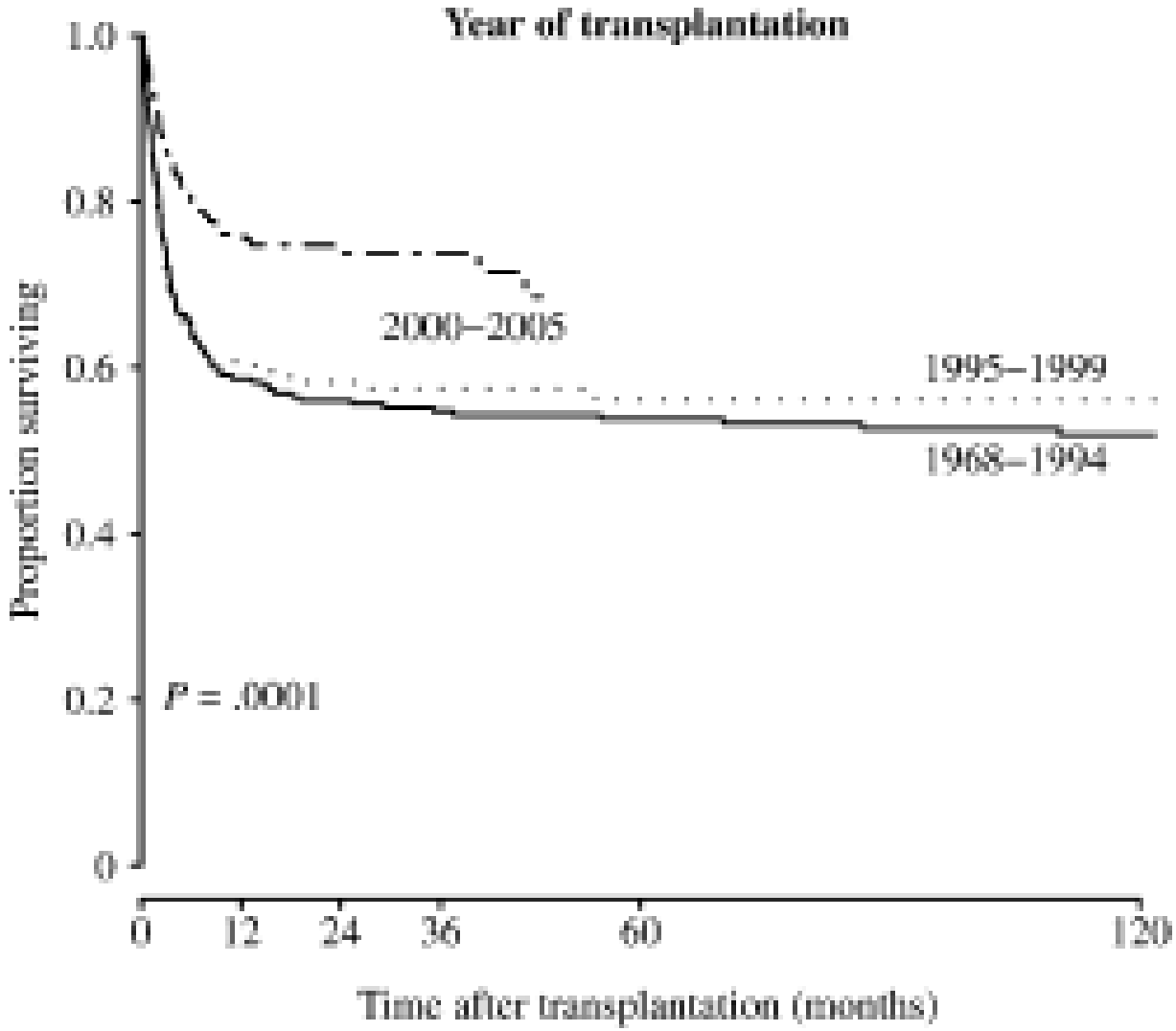
- Phagocytic cell disorders
  - Agranulocytosis
  - Chronic granulomatous disease
  - Leukocyte adhesion deficiency
- Hemophagocytic syndromes
  - 62% Familial lymphohistiocytosis
  - 16% Chediak-Higashi syndrome
  - 10% Griscelli Syndrome
  - 12% X-linked lymphoproliferative disease

Type of immunodeficiency according to donor origin, HLA matching, and year of graft

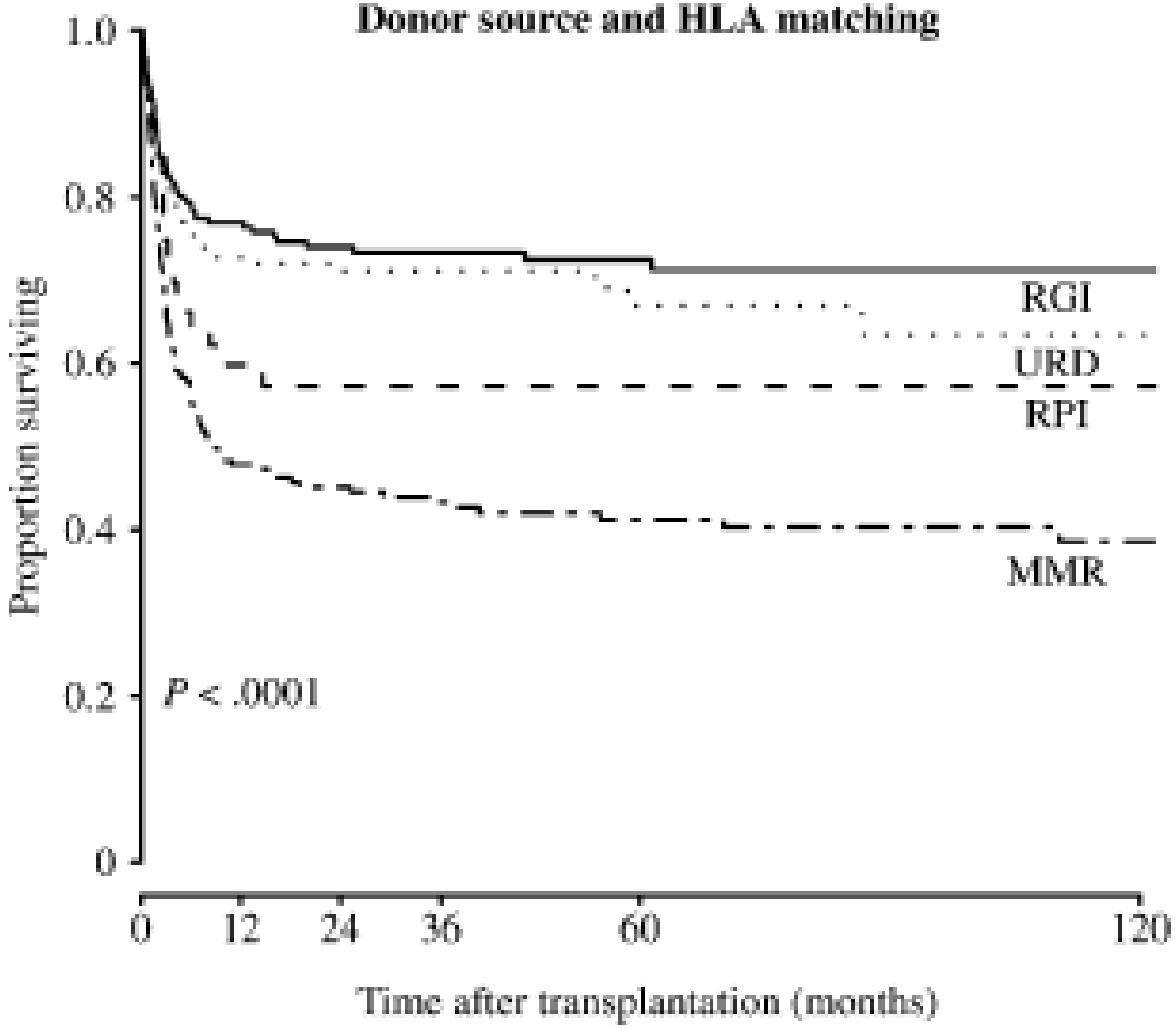
Diagnosis	n	Percent	Related donor			URD, n
			Genotypically HLA identical, n	Phenotypically HLA identical, n	HLA-mismatched, n	
Non-SCID						
Years of graft <1995						
Total	278		103	17	130	28
Years of graft 1995-1999						
Total	238		75	25	66	72
Years of graft 2000-2005						
Total	267		73	23	47	124

Non-SCID Results

- 4 year survival showed a marked improvement from 2000 to 2005 (not seen in SCID)
- Survival was better in URDs than phenoidentical tranplants
- Survival using an URD was almost the same as using an genoidentical donor



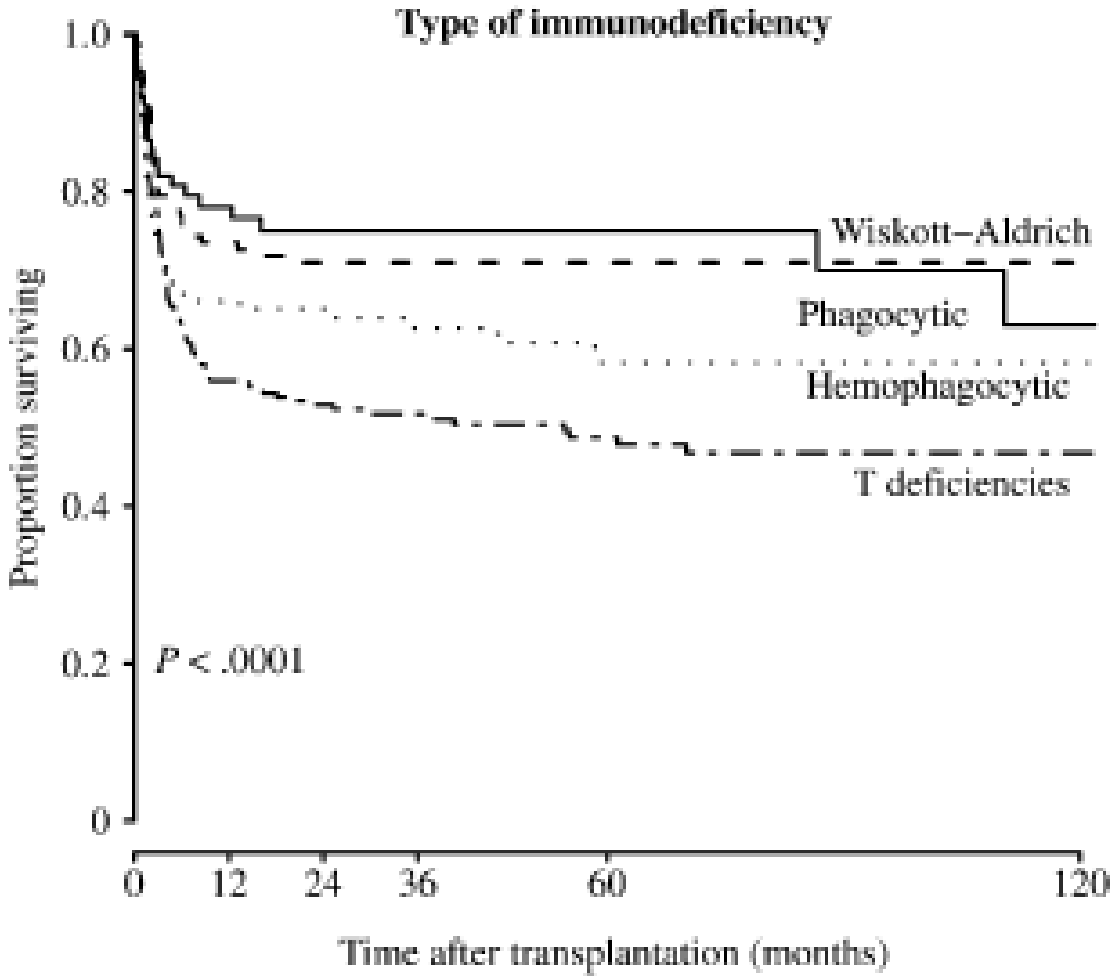
Months	0	6	12	24	36	60	120
Number at risk							
1968–1994	278	179	135	129	125	114	52
1995–1999	238	137	109	79	61	36	5
2000–2005	267	185	123	79	44	0	0



Months	0	6	12	24	36	60	120
Number at risk							
RGI	251	186	138	110	90	67	29
RPI	65	36	25	18	13	9	2
URD	224	151	110	81	60	31	9
MMR	243	128	94	78	67	51	17

Non-SCID Results

- 10 yr survival was significantly better for patients with WAS and phagocytic and hemophagocytic disorders than for patients with T-lymphocyte deficiencies when examined by univariate analysis but NOT by multivariate analysis



Months	0	6	12	24	36	60	120
Number at risk							
T deficiencies	326	181	140	103	82	54	19
Phagocytic disorders	92	71	54	39	30	25	8
Hemophago–cytic syndromes	159	98	69	57	45	22	7
Wiskott–Aldrich syndrome	168	124	91	79	70	55	23

Discussion

- Largest cohort study on the outcome of HSCT for PID with the longest follow-up
- Transplantation with genoidentical sibling donor now gives survival of:
  - 90% (95% CI 77% to 100%) for SCIDS pts
  - 79% (95% CI 69% to 89%) for non-SCIDS PID pts

Discussion

- Lack of improvement of survival in SCIDs transplant patients from 2000 to 2005
  - Difficult to transplant because younger at the time of transplant and often have severe opportunistic infections?
  - Immature organs in young patients more susceptible to GvHD?

Discussion

- Why is survival better in B+ SCID patients?
  - ? Effect skewed by artemis-deficient patients in B- group as associated with poorer outcome
  - ? Predisposition to development of autoreactive T cells after engraftment
  - ? Effect of NK cells (data not collected on NK cells as imcomplete)

Discussion

- Role of chemotherapy conditioning unclear
  - Survival similar, whether chemotherapy conditioning used or not
  - Reduced-intensity chemotherapy conditioning advantageous for pts with significant pre-existing organ damage
  - Further study needed on long-term survival, quality of immunoreconstitution, long-term effects of GvHD, neurodevelopmental outcomes and fertility

Discussion

- Few studies have examined long-term immunoreconstitution
- Critical to examine long-term outcome for disease-specific groups
- Next stage is to carefully analyze individual disease categories so that the prognosis after HSCT for the different genetic conditions may be better understood

Key messages

- Transplantation for primary immunodeficiency before 6 months of age is associated with improved outcome and supports the use of newborn screening programs to facilitate the early diagnosis of SCID.
- Prognosis after HSCT for PID is multifactorial, including molecular defect, disease status, donor, stem cell source, and conditioning regimen, and it is important now to analyze the long-term outcome for disease-specific groups.