SEVERE APLASTIC ANEMIA TRANSPLANTATION

TEHRAN MARCH 2023

SEVERE APLASTIC ANEMIA CASE PRESENTATIONS:

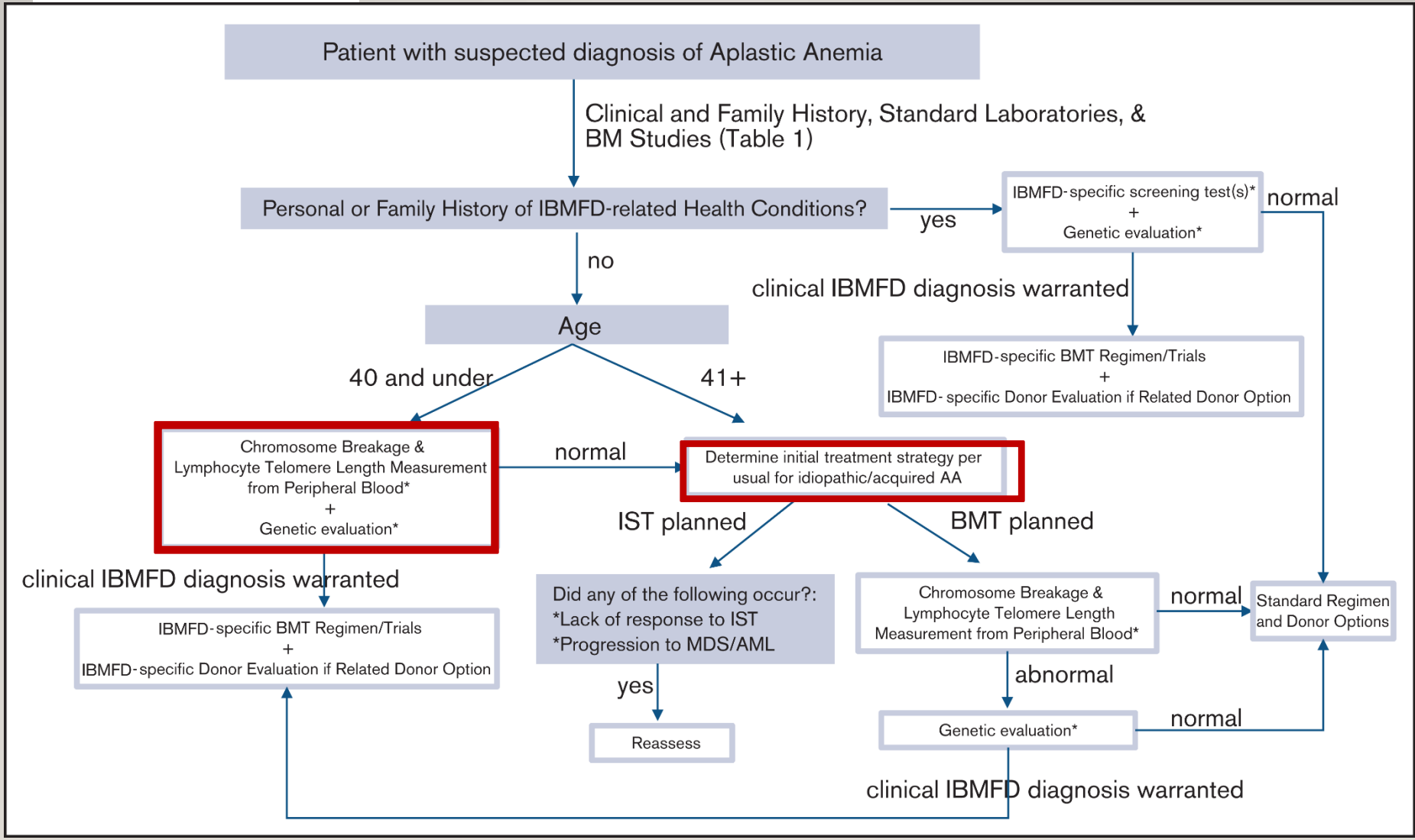
AGE/SEX	GRAFT SOURCE RECIPIENT STATUS	CONDITIONING GVHD PROPHYLAXIS	ENGRAFTEMENT /GVHD	OUTCOME
36/Male	MRD/Female 32 yr Limited blood products transfusions Transplantation in 4 months	CPM 120mg/kg,FLU 120 mg/kg,ATG 7.5 mg/kg CSA ,MTX Cell dose :3.5 X 10. 6/Kg T cell depletion: NO	Day. + 12 NO GVHD	14 months Chimeris m99%
33/Female	MUD/Female 32 yr No blood products transfusions Transplantation in 2 months	CPM 90mg/kg,FLU 120 mg/kg,ATG 7.5 mg/kg CSA ,MTX Cell dose 10 x 10 6/kg T cell depletion: YES	Day. + 14 NO GVHD	30months Chimeris m99%

SEVERE APLASTIC ANEMIA CASE PRESENTATIONS:

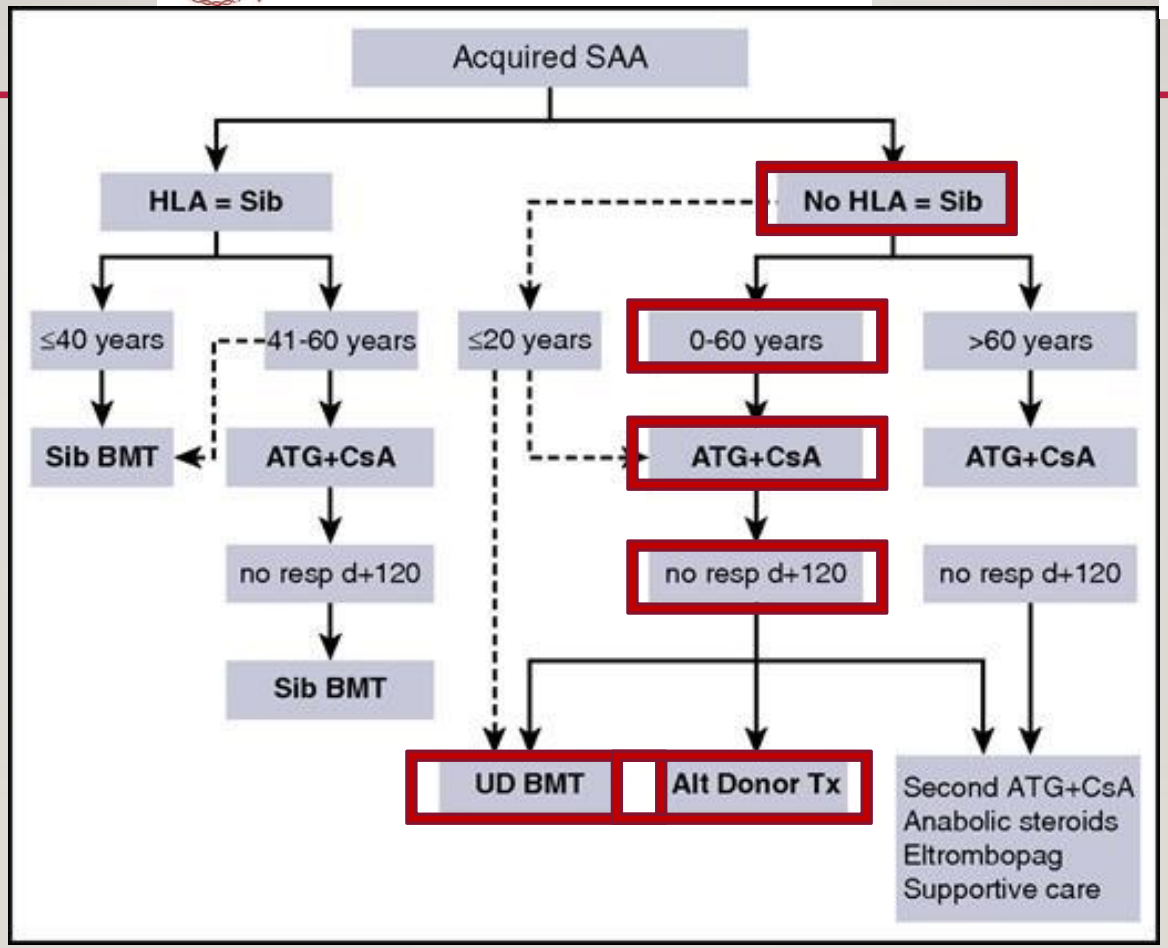
AGE/SEX	GRAFT SOURCE RECIPIENT STATUS	CONDITIONING GVHD PROPHYLAXIS	ENGRAFTEMENT /GVHD	OUTCOME
10/Female	MRCB Limited blood products transfusions hATG+CSA	CPM 90mg/kg,FLU 120 mg/kg,ATG 7.5 mg/kg CSA ,MTX TNC dose :3.19X 10. 7/Kg post thaw:2.93 x10 7/kg T cell depletion: NO	Day. + 21 NO GVHD	6years Chimeris m95%
20/male	HLA DR ,PermissiveDP MMUD /male Heavily transfused. Transplantation after 2 yrars IST hATG & r ATG Fungal infection +	CPM 90mg/kg,FLU 120 mg/kg,ATG 7.5 mg/kg CSA ,MTX,PTCP 50 mg/kg x2,cellcept Cell dose 9x 10 6/kg CD 3,169 T cell depletion: NO	Day + 15 NO GVHD	+60 Chimeris m99% BUT rejection on +180

blood advances

Blood Adv (2021) 5 (12): 2660–2671.



American Society of Hematology
Helping hematologists conquer blood diseases worldwide



6

Donor selection for SAA patients

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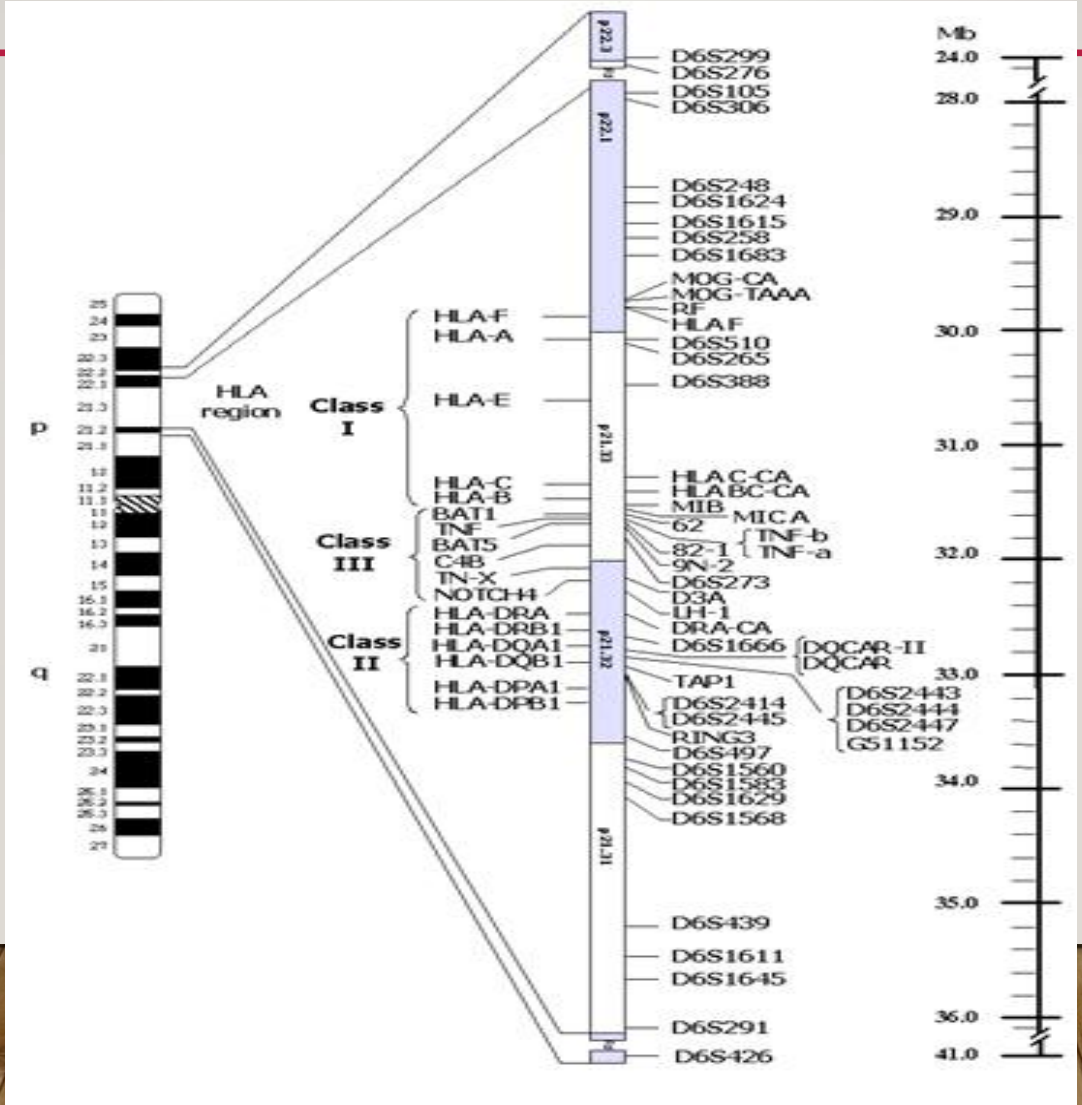
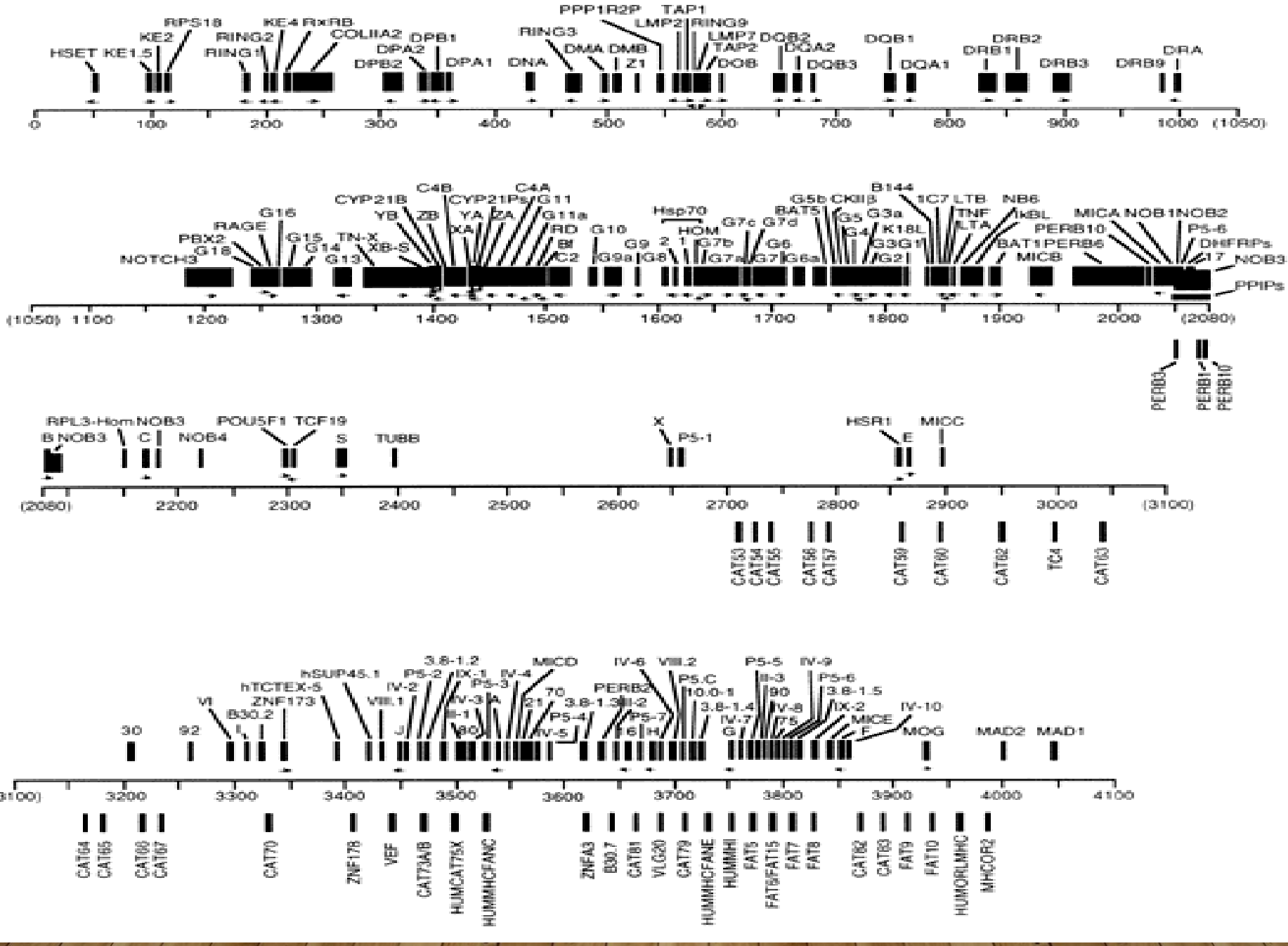
Associate Professor of Medical Genetics
Shahid Beheshti University of Medical Sciences

HLA GENES


p
q
HLA region
Class I
Class III
Class II
HLA-F
HLA-A
HLA-E
HLA-C
HLA-B
BAT1
TNF
BAT5
C4B
TN-X
NOTCH4
HLA-DRA
HLA-DRB1
HLA-DQA1
HLA-DQB1
HLA-DPA1
HLA-DPB1
D6S299
D6S276
D6S105
D6S306
D6S248
D6S1624
D6S1615
D6S258
D6S1683
MOG-CA
MOG-TAAA
RF
HLA F
D6S510
D6S265
D6S388
HLA C-CA
HLA BC-CA
MIB
62
MICA
82-1
TNF-b
TNF-a
9N-2
D6S273
D3A
LH-1
DRA-CA
D6S1666
DQCAR-II
DQCAR
TAP1
D6S2414
D6S2445
D6S2443
D6S2444
D6S2447
G51152
RING3
D6S497
D6S1560
D6S1583
D6S1629
D6S1568
D6S439
D6S1611
D6S1645
D6S291
D6S426
Mb
24.0
28.0
29.0
30.0
31.0
32.0
33.0
34.0
35.0
36.0
41.0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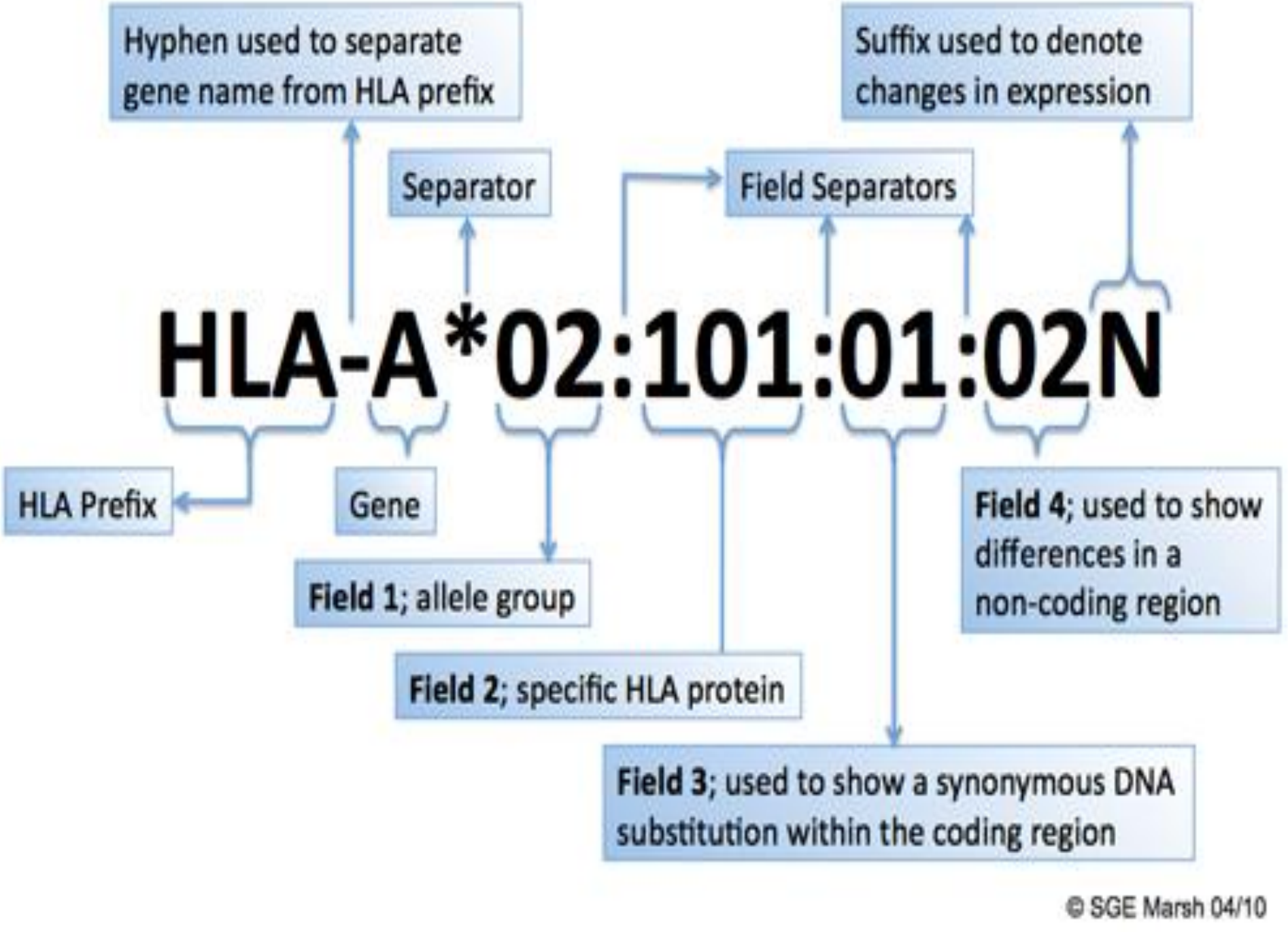
0 100 200 300 400 500 600 700 800 900 1000 (1050)
NOTCH3 PBX2 G18 RAGE G16 G15 G14 G13 TN-X XB-S CYP21B C4B YB ZB CYP21Ps C4A YA ZA G11 G11a RD C2 G10 G9a G9 G8 Hsp70 2 1 HOM G7c G7b G7a G7d G6 G7 G6a BAT5 G5b CKIIβ G5 G4 B144 G3a K18L G3G1 G2 tC7 LTB TNF LTA NB6 kBL MICB MICA NOB1 NOB2 PERB10 PERB6 BAT1 P5-6 DHFRPs 17 NOB3 PPIPs
(1050) 1100 1200 1300 1400 1500 1600 1700 1800 1900 2000 (2080)
PERB3 PERB11 PERB10
RPL3-Hom B NOB3 NOB3 C NOB4 POU5F1 TCF19 S TUBB X P5-1 HSR1 E MICC
(2080) 2200 2300 2400 2500 2600 2700 2800 2900 3000 (3100)
CAT53 CAT54 CAT55 CAT56 CAT57 CAT59 CAT60 CAT62 TC4 CAT63
30 92 VI B30.2 ZNF173 hTCTEX-5 I hSUP45.1 VIII.1 J IV-2 P5-2 3.8-1.2 IX-1 IV-3 II-1 90 P5-3 IV-4 MICD 21 70 P5-4 IV-5 PERB2 3.8-1.3 II-2 P5-7 e H IV-6 VIII.2 P5.C 10.0-1 3.8-1.4 G P5-5 III-3 90 IV-7 75 IV-8 IV-9 P5-6 3.8-1.5 IX-2 MICE F IV-10 MOG MAD2 MAD1
(3100) 3200 3300 3400 3500 3600 3700 3800 3900 4000 4100
CAT64 CAT65 CAT66 CAT67 CAT70 ZNF178 VEF CAT73A/B HUMCAT75X HUMMHCFANC ZNFA3 B30.7 CAT81 VLG20 CAT79 HUMMHCFANE HUMMHI FAT5 FAT5/FAT15 FAT7 FAT8 CAT82 CAT83 FAT9 FAT10 HUMORLMHC MHCOR2

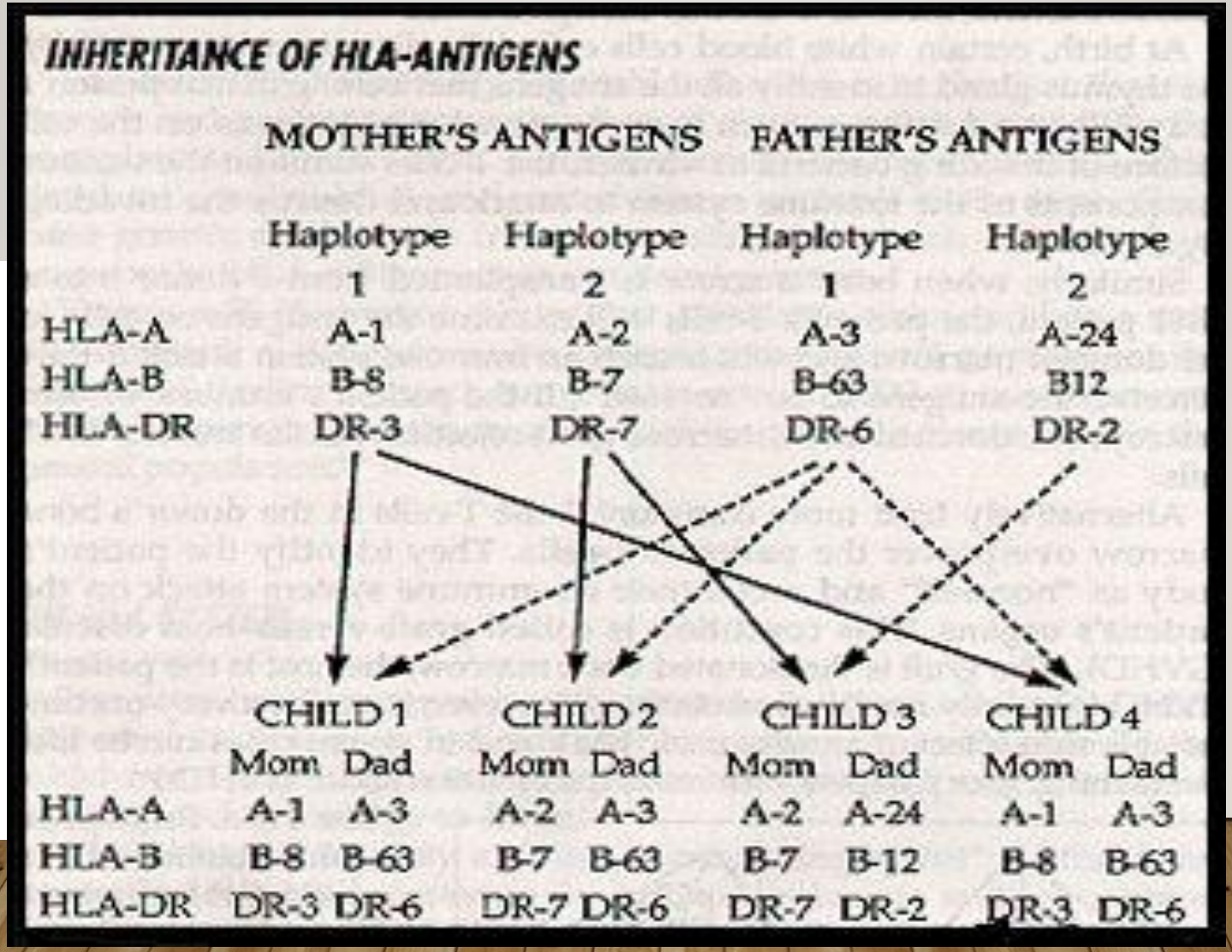
HLA ALLELES NUMBERS

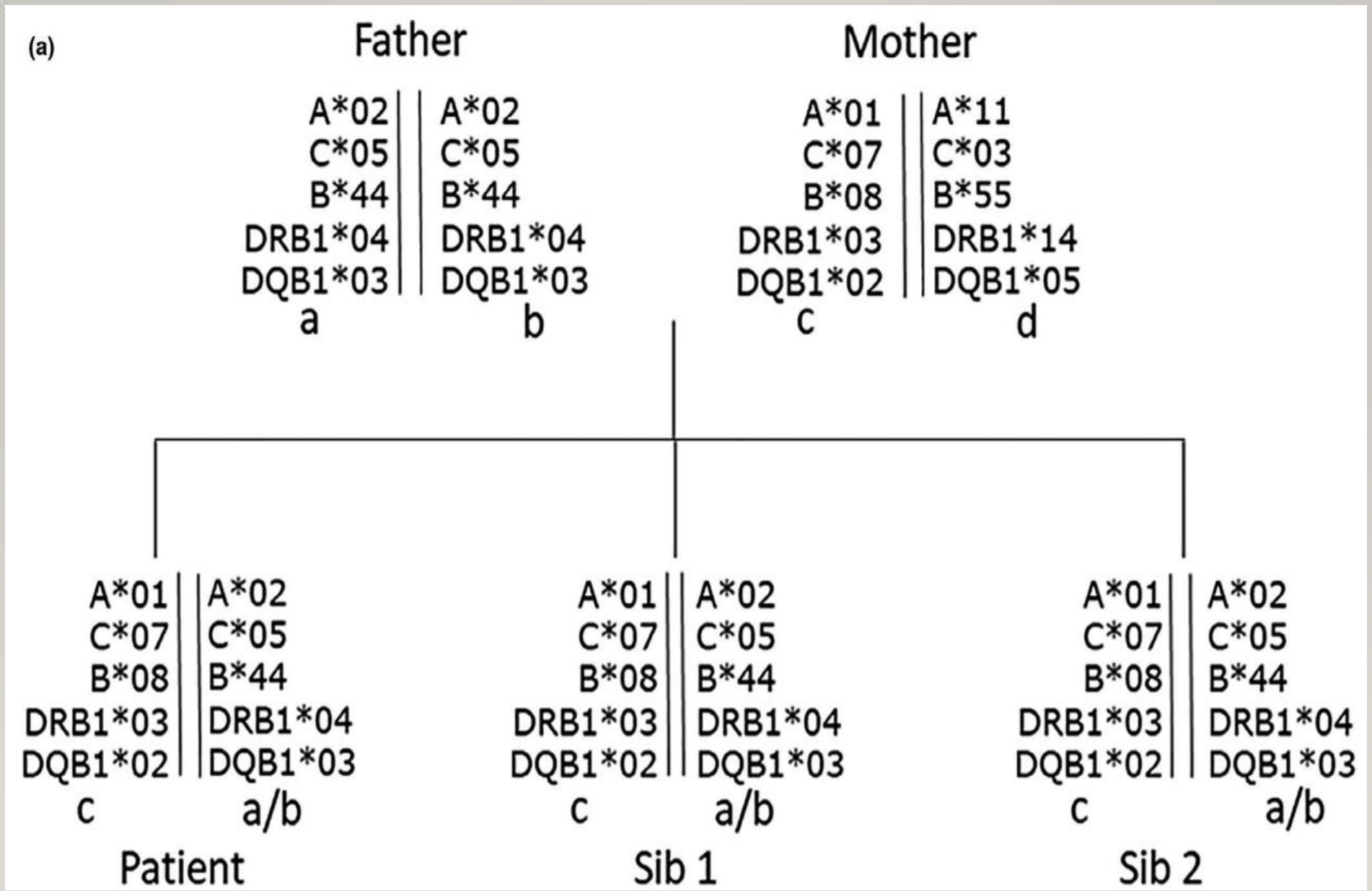
Numbers of HLA Alleles	
HLA Class I Alleles	25,019
HLA Class II Alleles	10,201
HLA Alleles	35,220
Other non-HLA Alleles	796

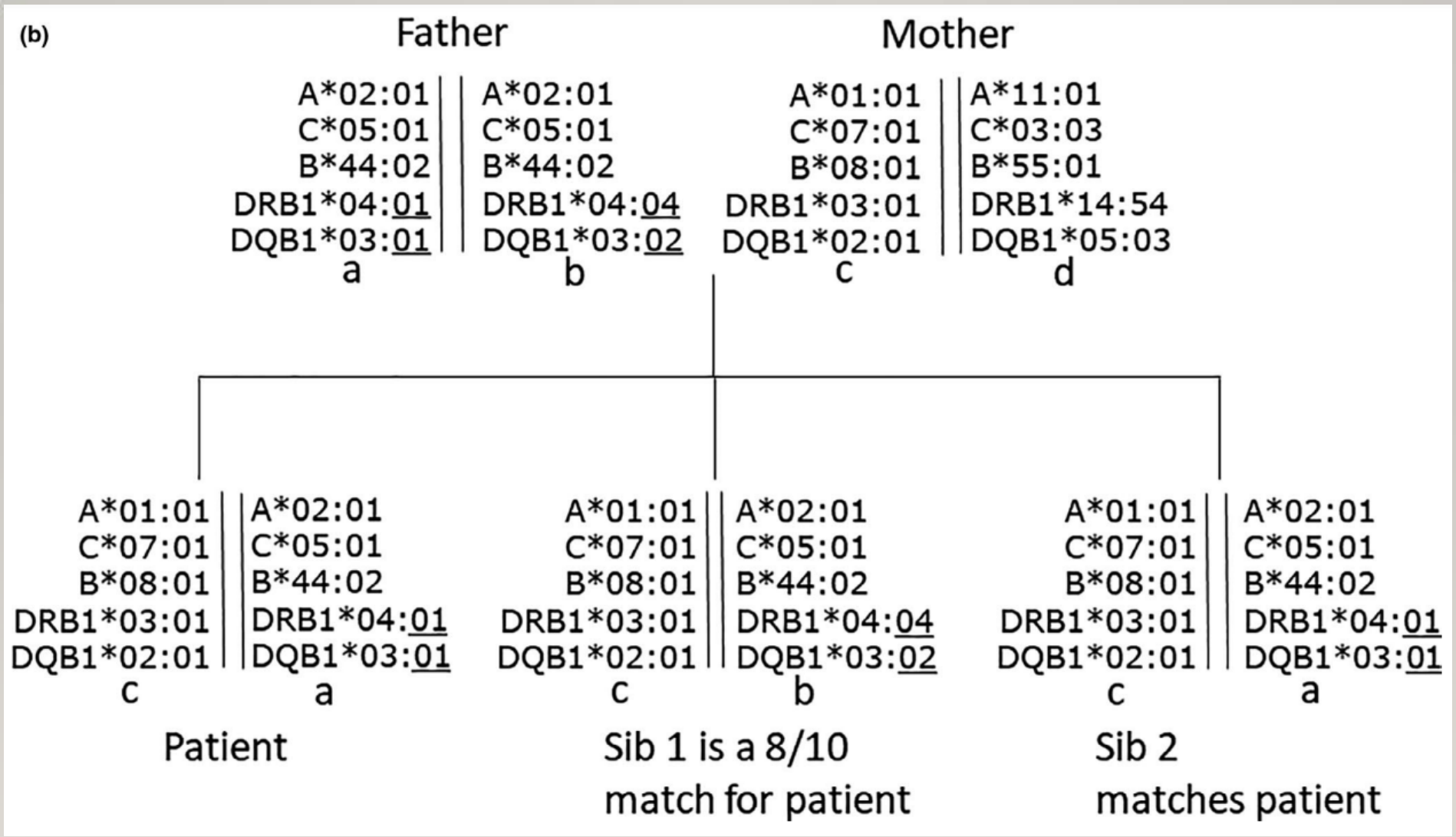

Hyphen used to separate gene name from HLA prefix
Suffix used to denote changes in expression
Separator
Field Separators
HLA-A*02:101:01:02N
HLA Prefix
Gene
Field 1; allele group
Field 2; specific HLA protein
Field 3; used to show a synonymous DNA substitution within the coding region
Field 4; used to show differences in a non-coding region
© SGE Marsh 04/10

HLA TYPING TECHNIQUE

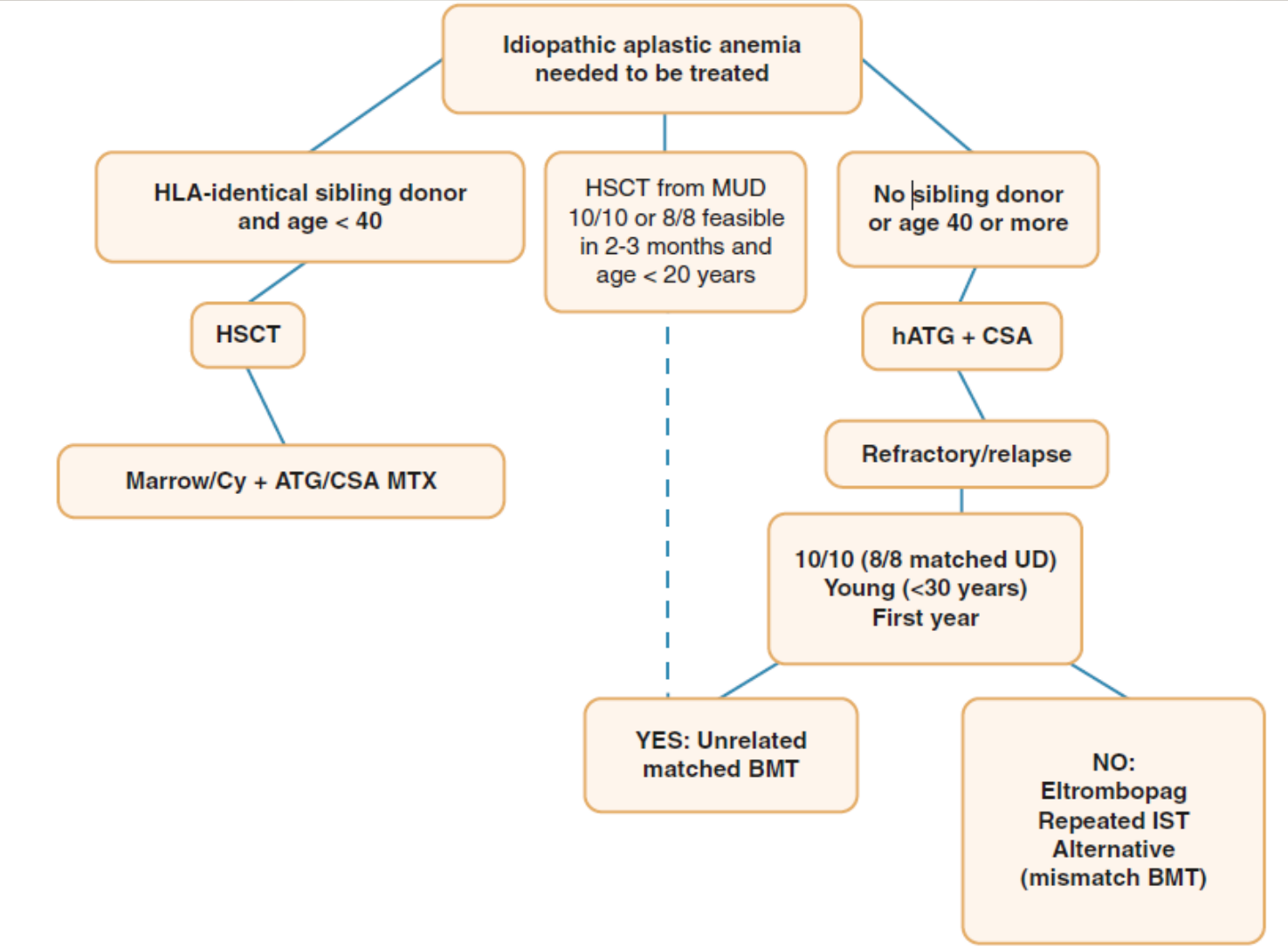
Haplotypes


INHERITANCE OF HLA-ANTIGENS
MOTHER'S ANTIGENS
FATHER'S ANTIGENS
Haplotype 1
Haplotype 2
Haplotype 1
Haplotype 2
HLA-A
A-1
A-2
A-3
A-24
HLA-B
B-8
B-7
B-63
B12
HLA-DR
DR-3
DR-7
DR-6
DR-2
CHILD 1
CHILD 2
CHILD 3
CHILD 4
Mom Dad
Mom Dad
Mom Dad
Mom Dad
HLA-A
A-1 A-3
A-2 A-3
A-2 A-24
A-1 A-3
HLA-B
B-8 B-63
B-7 B-63
B-7 B-12
B-8 B-63
HLA-DR
DR-3 DR-6
DR-7 DR-6
DR-7 DR-2
DR-3 DR-6


(a)
Father
Mother
A*02 A*02
C*05 C*05
B*44 B*44
DRB1*04 DRB1*04
DQB1*03 DQB1*03
a b
A*01 A*11
C*07 C*03
B*08 B*55
DRB1*03 DRB1*14
DQB1*02 DQB1*05
c d
A*01 A*02
C*07 C*05
B*08 B*44
DRB1*03 DRB1*04
DQB1*02 DQB1*03
c a/b
Patient
A*01 A*02
C*07 C*05
B*08 B*44
DRB1*03 DRB1*04
DQB1*02 DQB1*03
c a/b
Sib 1
A*01 A*02
C*07 C*05
B*08 B*44
DRB1*03 DRB1*04
DQB1*02 DQB1*03
c a/b
Sib 2


(b)
Father
Mother
A*02:01
C*05:01
B*44:02
DRB1*04:01
DQB1*03:01
a
A*02:01
C*05:01
B*44:02
DRB1*04:04
DQB1*03:02
b
A*01:01
C*07:01
B*08:01
DRB1*03:01
DQB1*02:01
c
A*11:01
C*03:03
B*55:01
DRB1*14:54
DQB1*05:03
d
A*01:01
C*07:01
B*08:01
DRB1*03:01
DQB1*02:01
c
A*02:01
C*05:01
B*44:02
DRB1*04:01
DQB1*03:01
a
Patient
A*01:01
C*07:01
B*08:01
DRB1*03:01
DQB1*02:01
c
A*02:01
C*05:01
B*44:02
DRB1*04:04
DQB1*03:02
b
Sib 1 is a 8/10 match for patient
A*01:01
C*07:01
B*08:01
DRB1*03:01
DQB1*02:01
c
A*02:01
C*05:01
B*44:02
DRB1*04:01
DQB1*03:01
a
Sib 2 matches patient

TREATMENT ALGORITHM



The EBMT Handbook, 2019,https://doi.org/10.1007/978-3-030-02278-5_77

MUD

- UK investigators reported an excellent estimated 5-year Failure-free survival (FFS) of 95% in 44 consecutive children who received a MUD HSCT; 40 of these children had previously failed IST (Samarasinghe and Webb 2012).
- ✓ Because of those excellent results, up-front MUD HSCT became an attractive first line option in children.
- Between 2005 and 2014, a UK cohort of 29 consecutive children with idiopathic SAA received UD HSCTs (including **five** patients with 1 Ag mm transplants) **as first-line therapy**. Results were excellent, with OS and EFS of 96% and 92%, respectively, low GVHD rates, and only one death (from idiopathic pneumonia) (Dufour et al. 2015b).
- This cohort was then compared with historical matched controls who had received (1) first-line MRD HSCT, (2) first-line IST with horse ATG + CSA, and (3) MUD HSCT post-IST failure as second-line therapy. Outcomes for the up-front unrelated cohort were similar to MRD HSCT and superior to IST and UD HSCT post-IST failure. Similar results were observed in another pediatric study (Choi et al. 2017).

CON …

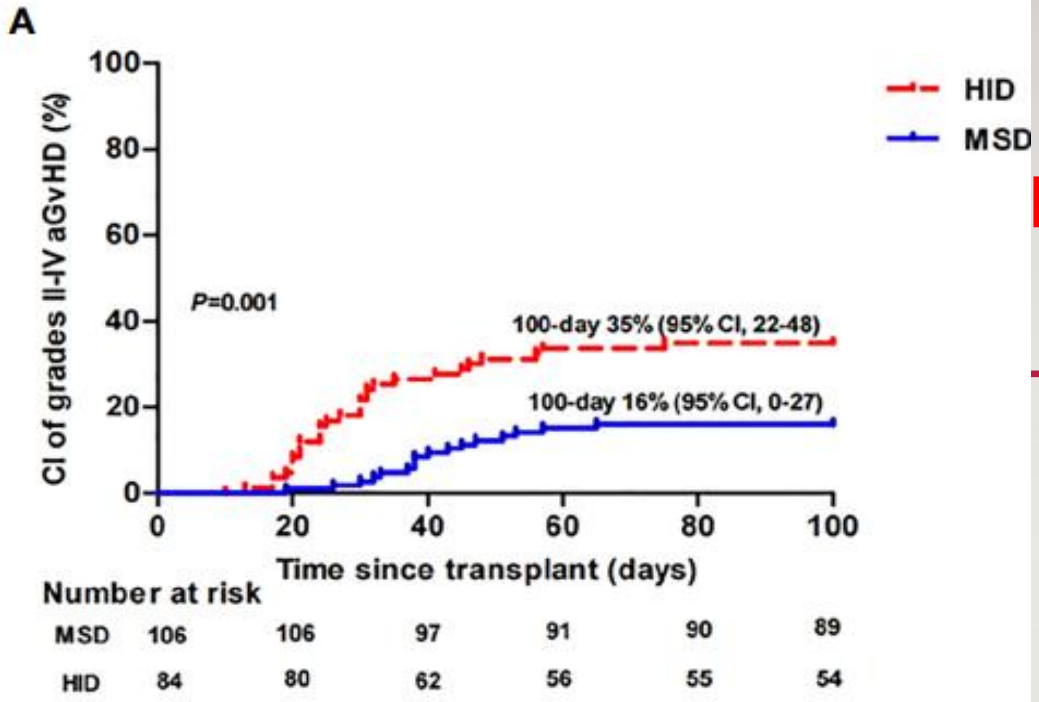
This is why MUD donor search ***should be started at diagnosis in young*** patients who lack a MRD.

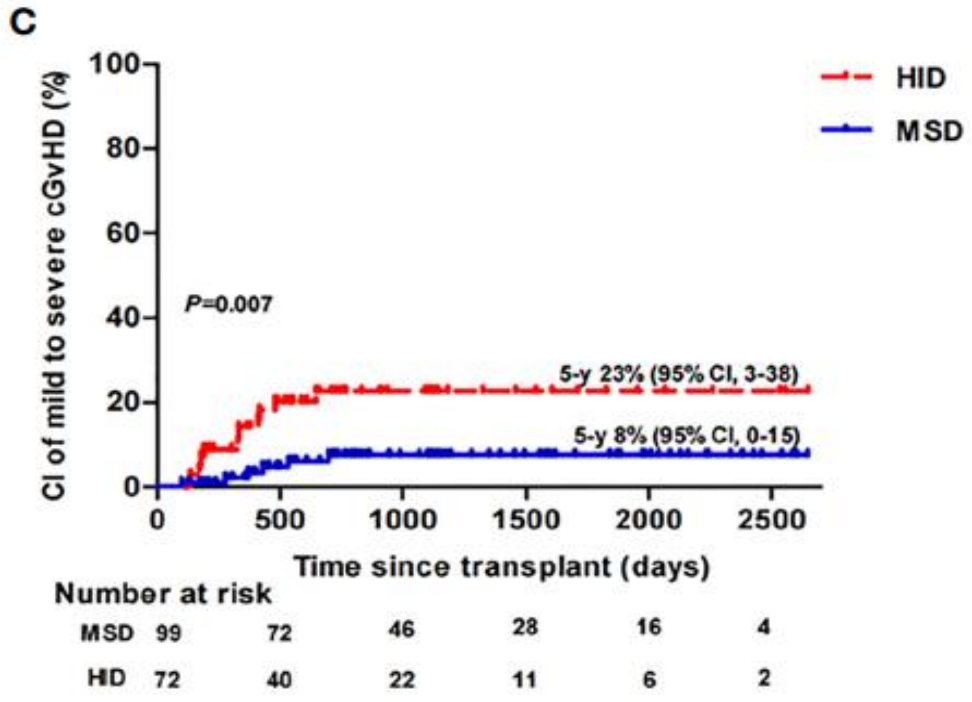
ALTERNATIVE DONOR TRANSPLANTATION IN SAA

- Alternative HSCTs (MMURD, CB, and haplofamily donors) are possible for individuals with no suitable MUD.
- Patient age, comorbidities, and alternative HSCT specificities are thus important issues in the decision-making process.

- Based on this, alternative HSCT can be considered a salvage option that needs to be carefully balanced with best supportive care.

RNATIVE DONOR

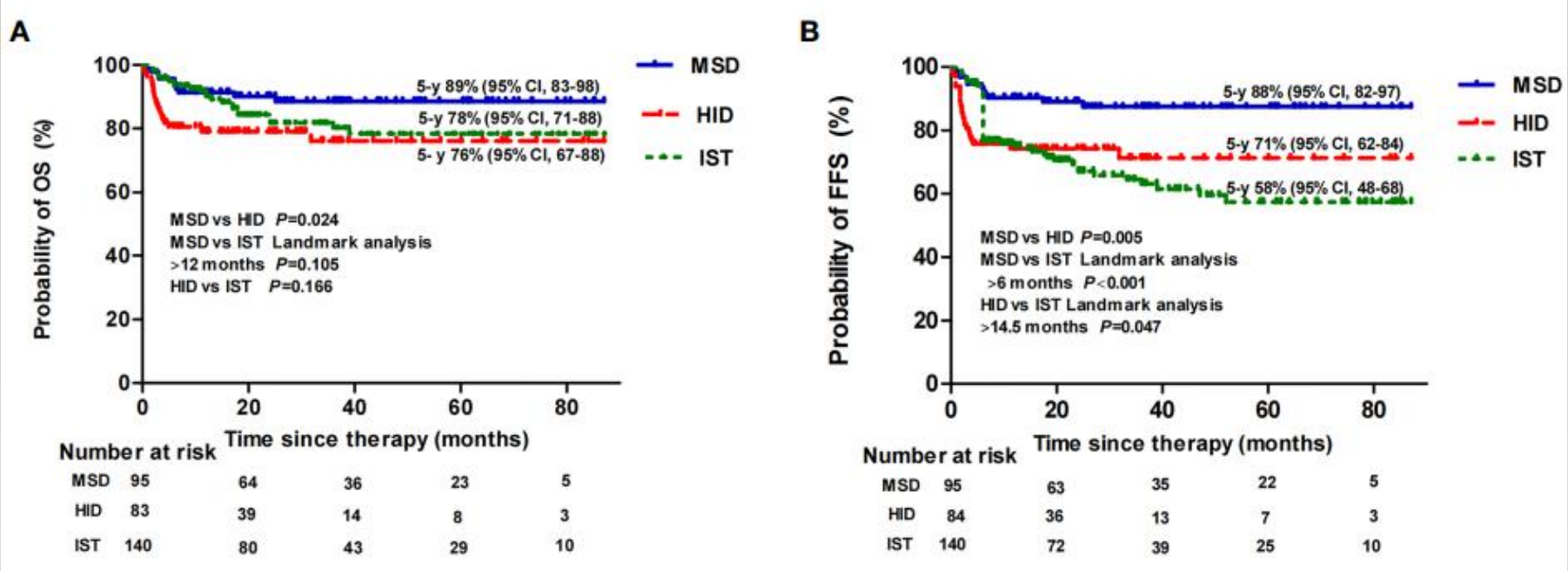




Comparison of Hematopoietic Stem Cell Transplantation Outcomes Using Matched Sibling Donors, Haploidentical Donors, and Immunosuppressive Therapy for Patients With Acquired Aplastic Anemia, Frontiers in Immunology, 2022.

(MSD) (n = 108) vs (HID) (n = 91) vs immunosuppressive therapy (IST) (n = 188) from 2014 to 2020 at China hospital

CON …


A
Probability of OS (%)
100
80
60
40
20
0
5-y 89% (95% CI, 83-98)
5-y 78% (95% CI, 71-88)
5- y 76% (95% CI, 67-88)
MSD
HID
IST
MSD vs HID P=0.024
MSD vs IST Landmark analysis
>12 months P=0.105
HID vs IST P=0.166
0
20
40
60
80
Time since therapy (months)
Number at risk
MSD 95 64 36 23 5
HID 83 39 14 8 3
IST 140 80 43 29 10
B
Probability of FFS (%)
100
80
60
40
20
0
5-y 88% (95% CI, 82-97)
5-y 71% (95% CI, 62-84)
5-y 58% (95% CI, 48-68)
MSD
HID
IST
MSD vs HID P=0.005
MSD vs IST Landmark analysis
>6 months P<0.001
HID vs IST Landmark analysis
>14.5 months P=0.047
0
20
40
60
80
Time since therapy (months)
Number at risk
MSD 95 63 35 22 5
HID 84 36 13 7 3
IST 140 72 39 25 10

CLASSIFICATION OF TRANSPLANT INDICATIONS

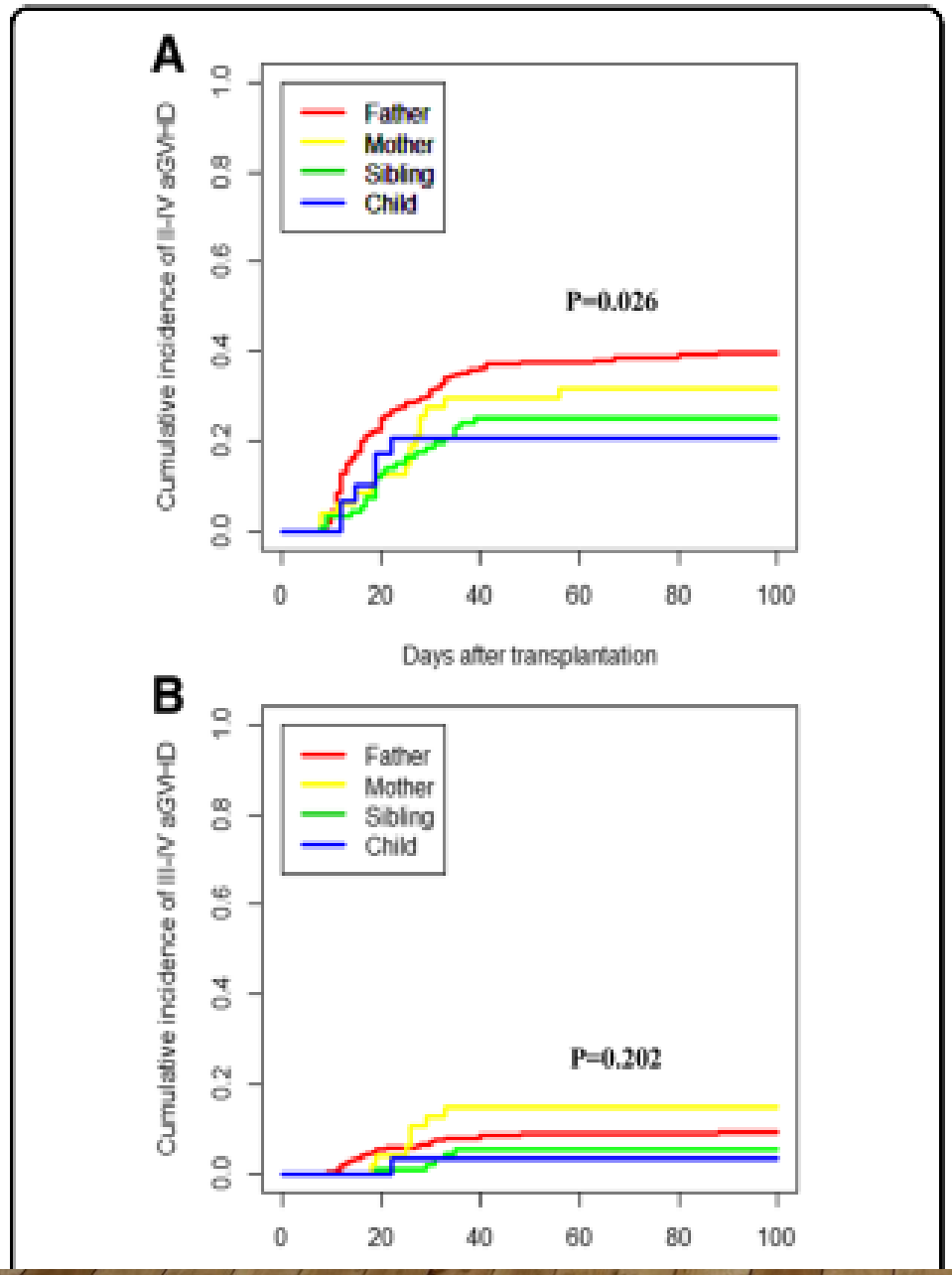
The eighth report from EBMT April 2022, [Indications for haematopoietic cell transplantation for haematological diseases, solid tumours and immune disorders: current practice in Europe, Bone Marrow Transplantation **(Springer Nature**) (2022) 57:1217–1239.]

Disease	Disease status	MSD allo	MUD allo	MMAD allo	Auto	CAR-T
SAA (for adult)	Newly diagnosed	S/II	CO/II	GNR/III	NA	
	Relapsed/ Refractory	S/II	S/II	CO/II	NA	
SAA (for children and adolescents)		S/II	S/II	CO/II	NA	

S: Standard of care (generally indicated in suitable patients), **CO:** clinical option (can be carried after careful assessment of risks and benefits), **GNR:** generally, not recommended, **NA:** not applicable.
Grade I: Evidence from at least one well-executed randomized trial.
Grade II Evidence from at least one well-designed clinical trial without randomization.
Grade II: Evidence from opinions of respected authorities based on clinical experience.

22 ALTERNATIVE DONOR

- "Who is the best HID in SAA?" Xu et al. designed a multicenter study based on a registered database of 392 SAA patients treated with HID HSCT and observed that transplantation from **mothers resulted in more cGvHD** than fathers (44.3% vs. 27.1%, P = 0.027). However, the survival rates were comparable among patients with different donors, and the **2- year OS** rates were 86.6, 87.1, 84.3, and 92.2% for recipients of **father, mother, sibling, and child** grafts (P = 0.706).
- These outcomes in SAA were **somewhat different from those in hematological malignancies**, in which **young, male, NIMA-mismatched** donors were preferred. The possible reasons for the difference between malignancies and SAA were as follows: first, disease category and conditioning regimens (especially Cy dose) were disparate; second, the sample size of the SAA cohort was relatively smaller. [Xu LP, Wang SQ, Ma YR, Gao SJ, Cheng YF, Zhang YY, et al. Who is the best haploidentical donor for acquired severe aplastic anemia? Experience from a multicenter study. J Hematol Oncol. 2019;12:87]



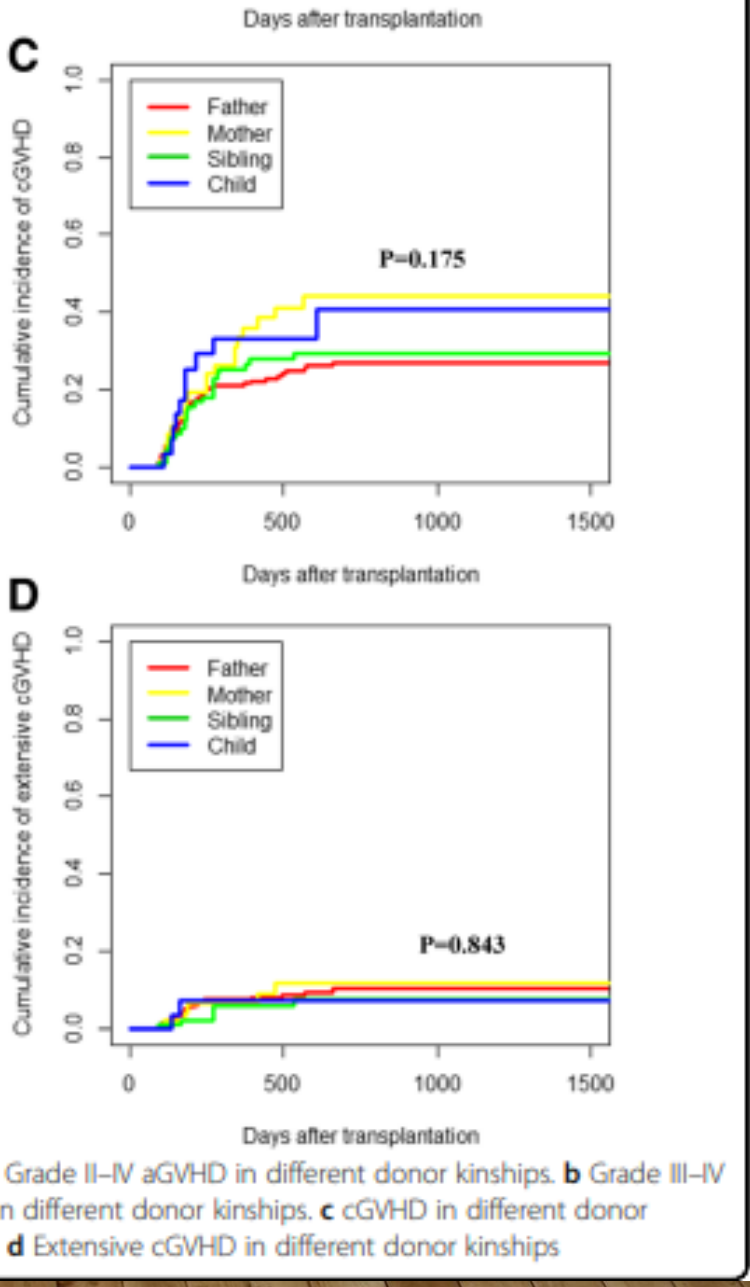
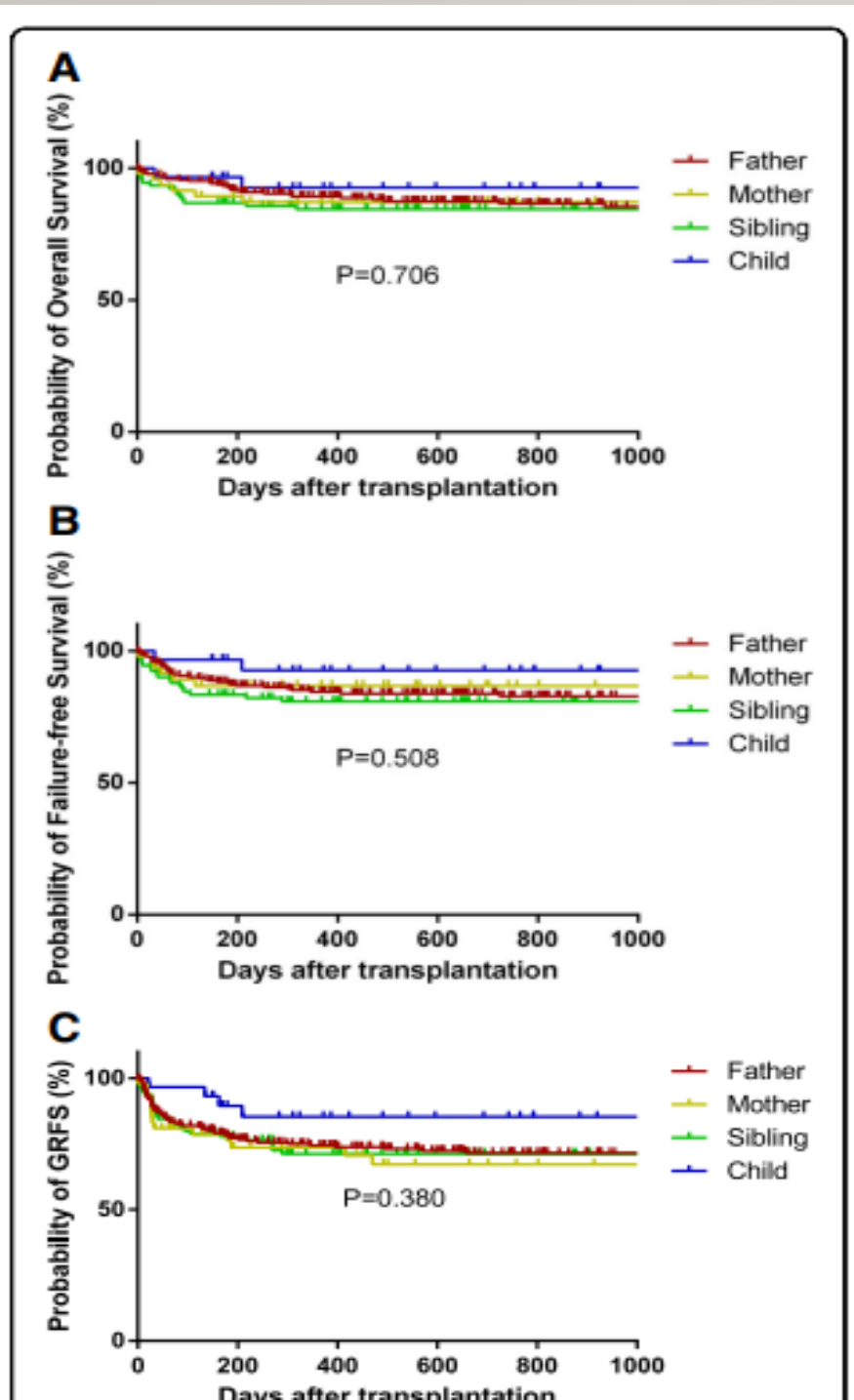
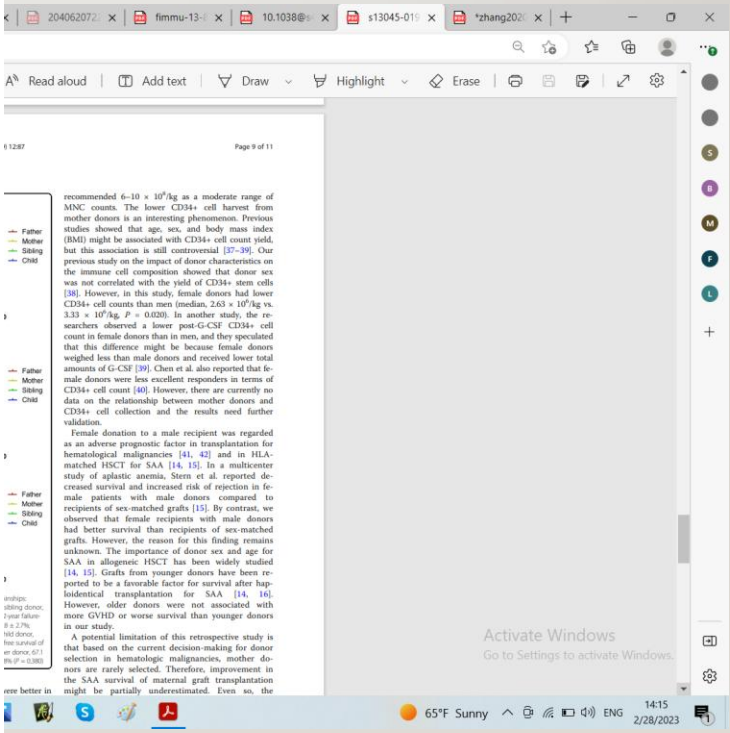


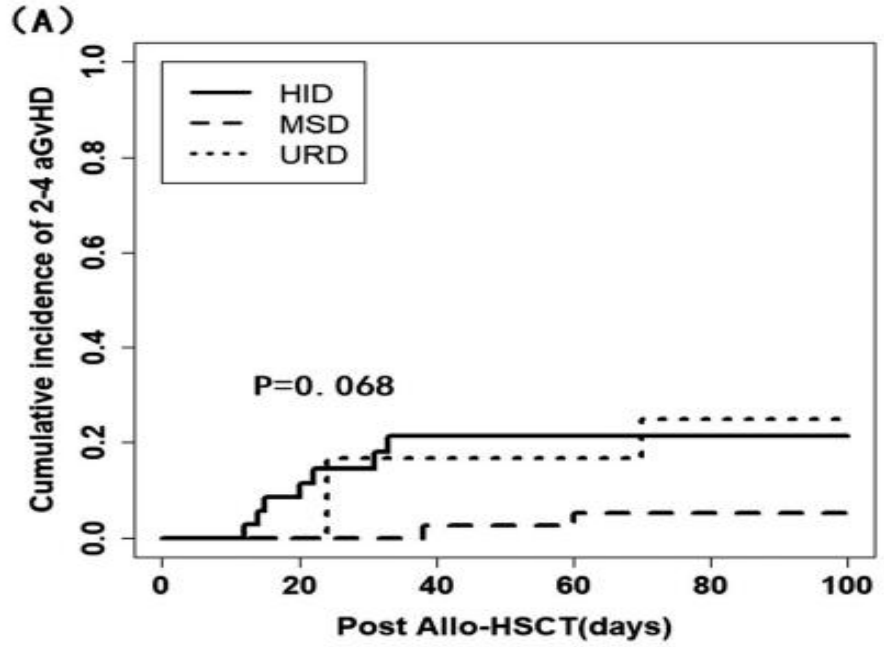
Fig. 1 **a** Grade II–IV aGVHD in different donor kinships. **b** Grade III–IV aGVHD in different donor kinships. **c** cGVHD in different donor kinships. **d** Extensive cGVHD in different donor kinships

[Xu LP, Wang SQ, Ma YR, Gao SJ, Cheng YF, Zhang YY. et al. Who is the best haploidentical donor for acquired severe aplastic anemia? Experience from a multicenter study. J Hematol Oncol. 2019;12:87]

CON …


A
Probability of Overall Survival (%)
100
50
0
0
200
400
600
800
1000
Days after transplantation
P=0.706
Father
Mother
Sibling
Child
B
Probability of Failure-free Survival (%)
100
50
0
0
200
400
600
800
1000
Days after transplantation
P=0.508
Father
Mother
Sibling
Child
C
Probability of GRFS (%)
100
50
0
0
200
400
600
800
1000
Days after transplantation
P=0.380
Father
Mother
Sibling
Child


Read aloud
Add text
Draw
Highlight
Erase
Page 9 of 11
recommended 6–10 × 10⁶/kg as a moderate range of MNC counts. The lower CD34+ cell harvest from mother donors is an interesting phenomenon. Previous studies showed that age, sex, and body mass index (BMI) might be associated with CD34+ cell count yield, but this association is still controversial [37–39]. Our previous study on the impact of donor characteristics on the immune cell composition showed that donor sex was not correlated with the yield of CD34+ stem cells [38]. However, in this study, female donors had lower CD34+ cell counts than men (median, 2.63 × 10⁶/kg vs. 3.33 × 10⁶/kg, P = 0.020). In another study, the researchers observed a lower post-G-CSF CD34+ cell count in female donors than in men, and they speculated that this difference might be because female donors weighed less than male donors and received lower total amounts of G-CSF [39]. Chen et al. also reported that female donors were less excellent responders in terms of CD34+ cell count [40]. However, there are currently no data on the relationship between mother donors and CD34+ cell collection and the results need further validation.
Female donation to a male recipient was regarded as an adverse prognostic factor in transplantation for hematological malignancies [41, 42] and in HLA-matched HSCT for SAA [14, 15]. In a multicenter study of aplastic anemia, Stern et al. reported decreased survival and increased risk of rejection in female patients with male donors compared to recipients of sex-matched grafts [15]. By contrast, we observed that female recipients with male donors had better survival than recipients of sex-matched grafts. However, the reason for this finding remains unknown. The importance of donor sex and age for SAA in allogeneic HSCT has been widely studied [14, 15]. Grafts from younger donors have been reported to be a favorable factor for survival after haploidentical transplantation for SAA [14, 16]. However, older donors were not associated with more GVHD or worse survival than younger donors in our study.
A potential limitation of this retrospective study is that based on the current decision-making for donor selection in hematologic malignancies, mother donors are rarely selected. Therefore, improvement in the SAA survival of maternal graft transplantation might be partially underestimated. Even so, the
Activate Windows
Go to Settings to activate Windows.
65°F Sunny
ENG
14:15
2/28/2023



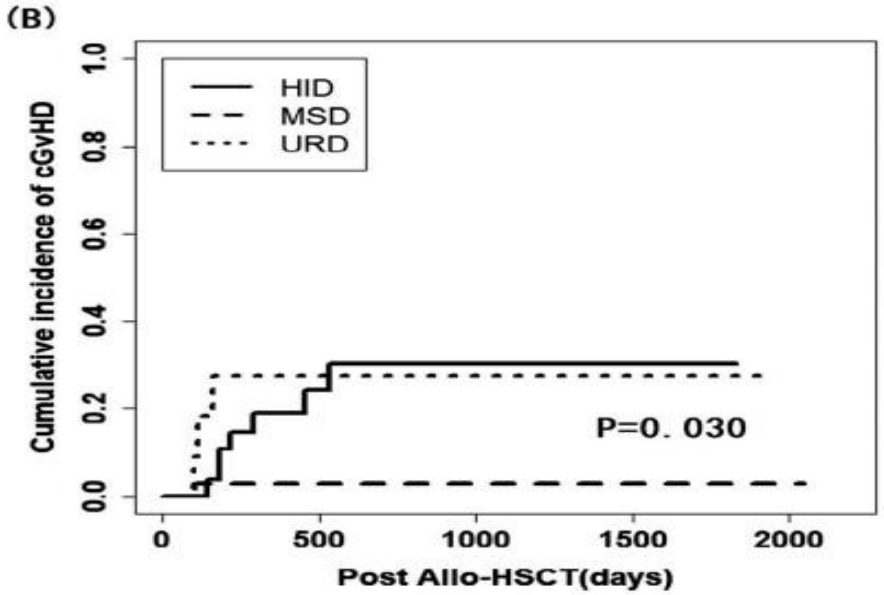


FIGURE 1 Cumulative incidence of graft-versus-host disease. A, Incidence of Grade II-IV acute graft-versus-host disease and B, incidence of chronic graft-versus-host disease

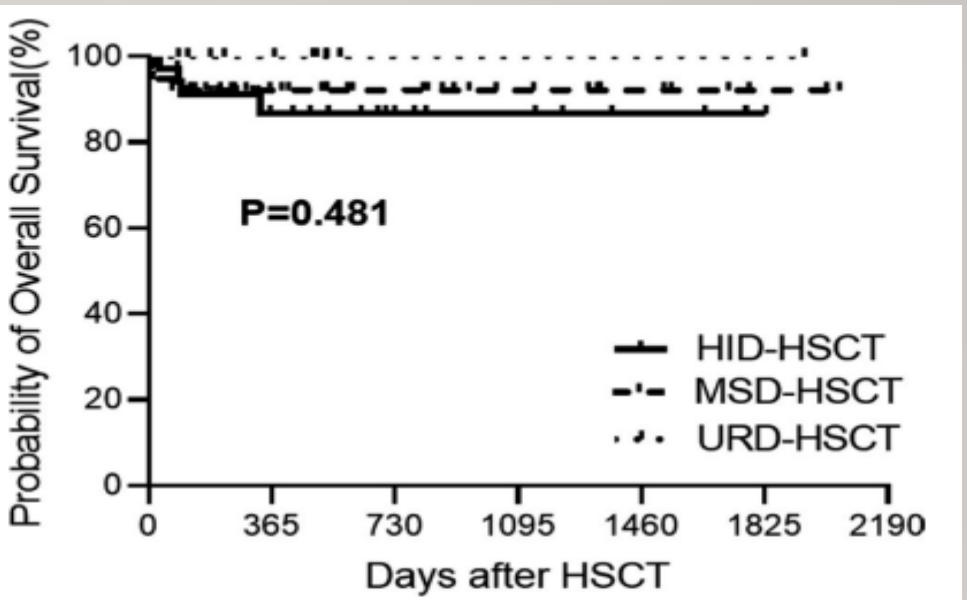


FIGURE 2 Probability of overall survival

Our results showed an encouraging survival outcome in SAA patients 40 years of age and older, and the transplantation outcome of HID-HSCT was comparable to those received grafts from MSD and URD. We confirmed that HSCT was an effective therapy for SAA patients in this age group, and HID-HSCT might be a feasible alternative choice when MSD was not available.

Zhang YY, Mo WJ, Zuo YY, Zhou M, Zhang XH, Wang Y, et al. Comparable survival outcome between transplantation from haploidentical donor and matched related donor or unrelated donor for severe aplastic anaemia patients aged 40 years and older: a retrospective multicentre cohort study. Clin Transplant. 2020: e13810]

ALTERNATIVE DONOR

- Huang et al. first led a prospective, multicenter study to compare the efficacy of HID and MRD transplantation as a salvage option. The data showed that HID HSCT (n = 101) could achieve 3-year OS (89.0% vs. 91.0%, P = 0.555) and failure-free survival (FFS; 86.8% vs. 80.3%, P = 0.659) comparable to contemporaneous MRD HSCT (n = 48) [Xu LP, Wang SQ, Wu DP, Wang JM, Gao SJ, Jiang M. et al. Haplo-identical transplantation for acquired severe aplastic anaemia in a multicentre prospective study. Br J Haematol. 2016;175:265–74].
- The group has recently conducted a retrospective multicenter study that aimed to compare outcomes of HID (n = 35), MRD (n = 38), and URD (n = 12) transplantation among SAA patients aged 40 years or older. The 3-year OS rates were 86.7, 92.1, and 100% in HID, MRD, and URD group (P = 0.481). The 3-year FFS rates were also similar (86.7, 92.1, and 87.5% for the HID, MRD, and URD groups, P = 0.866) [Zhang YY, Mo WJ, Zuo YY, Zhou M, Zhang XH, Wang Y, et al. Comparable survival outcome between transplantation from haploidentical donor and matched related donor or unrelated donor for severe aplastic anaemia patients aged 40 years and older: a retrospective multicentre cohort study. Clin Transplant. 2020: e13810]

DONOR–RECIPIENT HLA MATCH

- 10/10 , 9/10, haplo in HLA-A, -B, -C, -DRB1, -DQB1 (DPB1)

- CB:

Minimum of 8 high-resolution (HLA-A, HLA-B, HLA-C, and HLA-DRB1) for both patient and CB unit

>4/6 HLA-A and HLA-B antigen, HLA-DRB1 high-resolution (traditional match), and >4/8 high-resolution match (some centers investigating use of 4/6 and 3/8 units if adequate dose)

EBMT GUIDLINE

	Volume collected	Med CD34 content	Med CD3 content	Target cell dose
Bone marrow	10–20 mL/kg	2–3 × 10^6/kg[a]	25 × 10^6/kg	>2 × 10^8 TNC/kg
Peripheral blood	150–400 mL	8 × 10^6/kg	250 × 10^6/kg	5–10 × 10^6 CD34+/kg
Umbilical cord blood	80–160 mL	0.2 × 10^6/kg	2.5 × 10^6/kg	>3 × 10^7 TNC/kg

[a]Per kg recipient body weight

CB GUIDELINES FROM THE NMDP/CIBMTR:

TNC >2.5 * 107 /kg and CD34 cells >1.5 * 105 /kg

- For prioritization of **cell dose vs HLA match** (applies to single- and double-unit transplants), cell dose frequently needs to take priority over HLA match for adult and larger pediatric patients. HLA-match can take priority in children or smaller adults or those with common HLA typing who have multiple units with high cell dose. Optimizing HLA-match is very important in CB transplant for nonmalignant diagnoses. **In children with nonmalignant diagnoses, higher cell doses (>5 * 107 /kg)** should be selected. Further data are required as to how to balance cell dose against HLA match. A current guidance for consideration is as follows: **if high doses (eg, TNC >3 * 107 /kg and CD34 >2 * 105 /kg), consider optimizing high-resolution HLA match over cell dose**; if lower TNC and CD341 doses, optimize dose first and high-resolution HLA match second; and if units have similar cell doses, optimize high-resolution HLA match.

30

CHOICE OF CONDITIONING REGIMENS FOR BONE MARROW TRANSPLANTATION IN SEVERE APLASTIC ANEMIA

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ROYAN INSTITUTE

ALLOGENEIC TRANSPLANTATION

- Allogeneic transplantation with an HLA-matched sibling donor is widely regarded as first-line treatment for children and young adults with severe aplastic anemia.
- When an HLA-matched sibling is not available, treatment with immunosuppressive agents is the first-line therapy, and allogeneic transplantation from an unrelated donor is generally offered only after failure of immunosuppressive treatment.
- Several conditioning regimens can be used for BMT.

COMPLICATIONS OF SCT FOR ACQUIRED APLASTIC ANEMIA

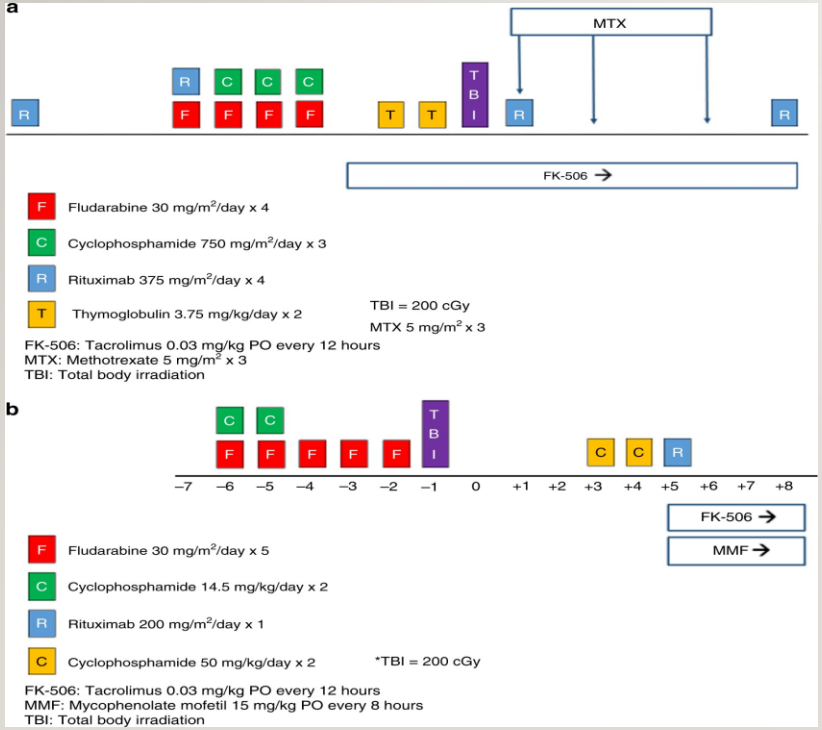
- The 2 major complications of SCT for acquired aplastic anemia are graft failure and GvHD.
- Graft failure remains an issue, more frequent than rejection in patients with acute leukemia.
- GvHD has no beneficial effect in AA patients, and particular care should be taken to reduce its incidence as much as possible: in vivo T cell depletion with anti-thymocyte globulin (ATG) or alemtuzumab (Campath) is one way to effectively prevent GvHD.

Conditioning regimen	Drug	Dose (total)	Time(d)	Transplantation type
International regimen				
Cy-ATG	Cy	200 mg/kg	−5 ~ − 22	HLA-matched sibling HSCT
	ATG	11.25 ~ 15.00 mg/kg	−5 ~ − 3, − 2	
FluCy-ATG	Flu	120 mg/m^2	−5 ~ − 2	HLA-matched unrelated HSCT
	Cy	120 mg/kg	−5, − 2	
	ATG	11.25 ~ 15.00 mg/kg	−5 ~ − 3, − 2	
Regimens in China				
mBuCyATG-SAA	Bu	6.4 mg/kg(ivgtt)	−7, − 6	Haploidentical-HSCT
	Cy	200 mg/kg	−5, − 2	
	ATG	10 mg/kg	−5 ~ − 2	
	or ATG-F	40 mg/kg	−5 ~ − 2	
mBuCyFluATG	Bu	6,4mg/kg(ivgtt)	−7 ~ − 6	Haploidentical-HSCT
	Flu	120 mg/m^2	−10 ~ − 7	
	Cy	200 mg/kg	−6 ~ − 3	
	ATG-F	20 mg/kg	−4 ~ − 1	
	or ATG	10 mg/kg	−4 ~ − 1	
FluCy-ATG	Flu	120 mg/m^2	−5 ~ − 2	Haploidentical-HSCT
	Cy	90 mg/kg	−3, − 2	
	ATG	10 mg/kg	−5 ~ − 2	

STANDARD CONDITIONING FOR MATCHED SIBLING TRANSPLANTS

- Under the age of 40 Cyclophosphamide 200mg/kg (CY 200) and ATG, as originally described.
- For older patients, current guidelines support the use of FLU-CY-ATG-low dose irradiation (FCA) or FLU-Cy alemtuzumab (CAMPATH) (FCC).
- The HLA matching between donor and recipient is relevant, and one should aim to identify an 8/8 HLA A,B,C,DRB1 matched unrelated donor.
- Rituximab 200mg on day +5 should be added in patients receiving alternative donor grafts.

NOVEL RITUXIMAB-BASED NON-MYELOABLATIVE CONDITIONING REGIMEN FOR HEMATOPOIETIC CELL TRANSPLANTATION IN SEVERE APLASTIC ANEMIA



- improved efficacy
- decreased toxicity
- decreased risk of infectious complications

https://doi.org/10.1016/j.bbmt.2017.12.766

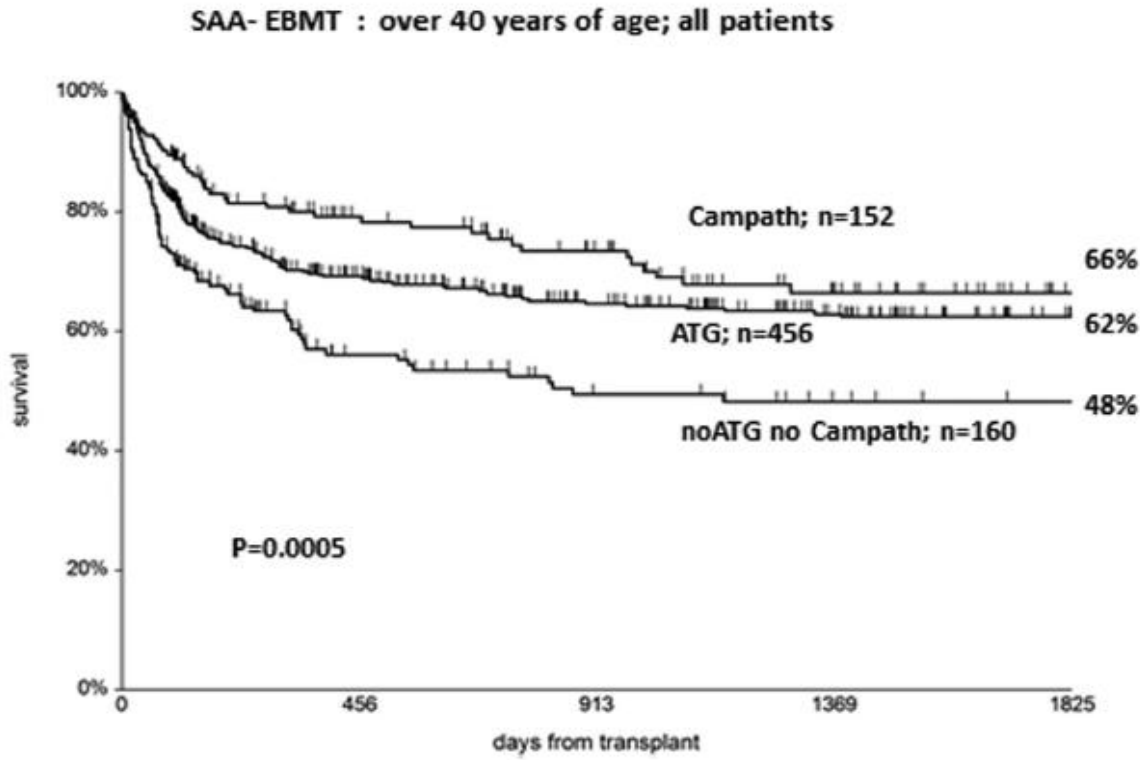


Figure 1. Actuarial survival of patients undergoing a SCT from HLA identical siblings or unrelated donors: shown is the effect of GvHD prophylaxis with Campath (alemtuzumab), ATG, or no Campath/ATG. The difference is highly significant.

CONDITIONING REGIMENS

- There are no randomized trials that have compared transplant-conditioning regimens.
- Cyclophosphamide (Cy) at 200 mg/kg or a lower dose and anti thymocyte globulin (ATG) with or without fludarabine (Flu) are most often used for HLA-matched sibling transplantation
- Low-dose total body irradiation is often added to Cy and ATG for URD transplantation.

ALLOGENEIC TRANSPLANTATION

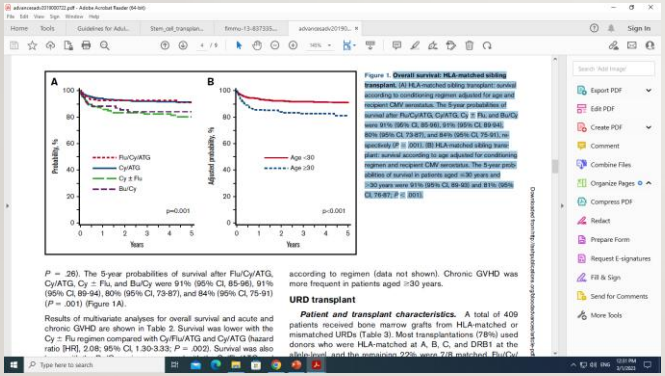
- Reports from the EBMT and the Center for International Blood and Marrow Transplant Research support bone marrow as the preferred graft choice for HLA-matched sibling and URD transplantation
- For adults aged >40 years, immunosuppression is typically first-line treatment, and allogeneic transplantation is reserved for those who do not respond to immunosuppression

HLA-MATCHED SIBLING TRANSPLANT

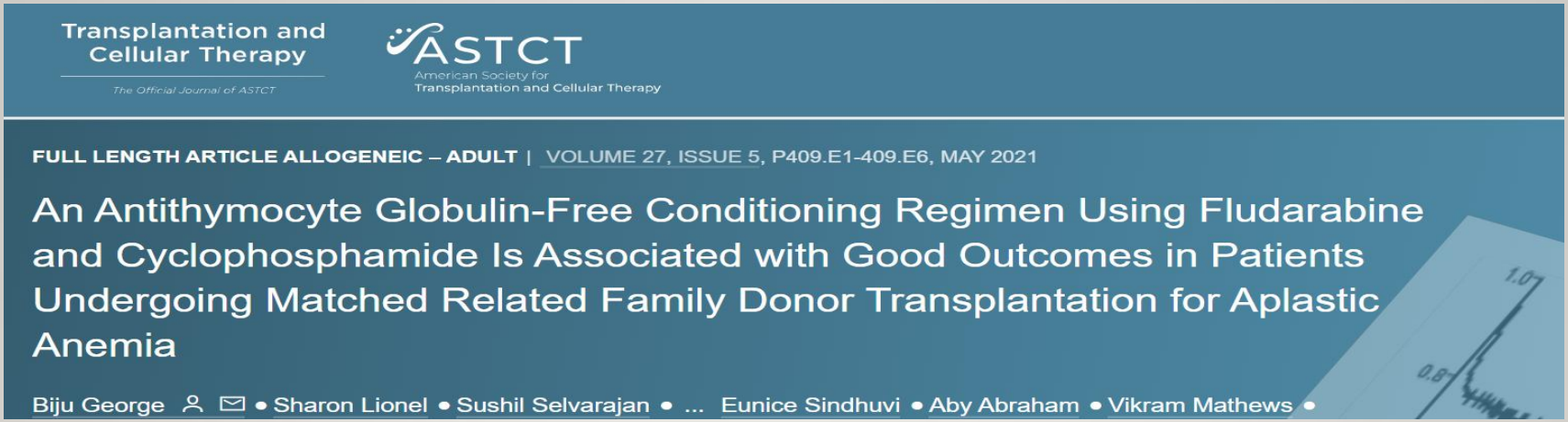
- Cy with ATG was the predominant regimen.
- Flu/Cy/ATG was the second most commonly used regimen.

- Although survival after an unrelated donor BMT did not differ between regimens, use of ***rabbit-derived ATG*** may be preferred because of lower risks of acute GVHD.

OVERALL SURVIVAL: HLA-MATCHED SIBLING TRANSPLANT



- (A) HLA-matched sibling transplant: survival according to conditioning regimen adjusted for age and recipient CMV serostatus. The 5-year probabilities of survival after Flu/Cy/ATG, Cy/ATG, Cy 6 Flu, and Bu/Cy were 91% (95% CI, 85-96), 91% (95% CI, 89-94), 80% (95% CI, 73-87), and 84% (95% CI, 75-91), respectively (P 5 .001).
- (B) HLA-matched sibling transplant: survival according to age adjusted for conditioning regimen and recipient CMV serostatus. The 5-year probabilities of survival in patients aged #30 years and .30 years were 91% (95% CI, 89-93) and 81% (95% CI, 76-87; P , .001).



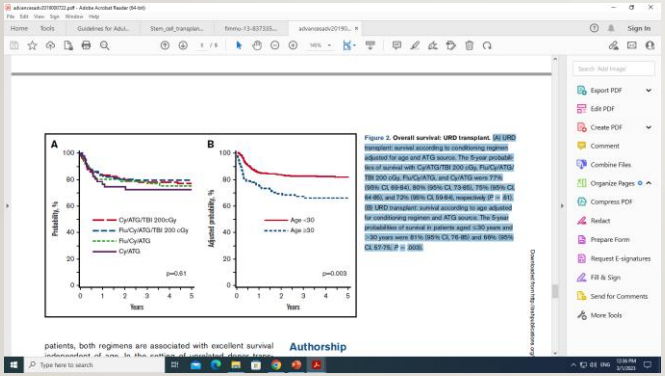
- An anti thymocyte globulin-free protocol using fludarabine and cyclophosphamide as conditioning for matched sibling donor transplantation in patients with aplastic anemia was evaluated.
- **Flu (30 mg/m2/day for 6 days) and Cy (60 mg/kg/day for 2 days)**
- Overall survival was reasonable at 75%, with >80% survival in patients age <20 years.
- The incidence of GVHD was low at 27.6% for acute GVHD and 41.6% for chronic GVHD.
- Most patients (80%) were free of immunosuppression at 5 years post-transplantation.
- The rate of long-term complications was very low.

UNRELATED DONOR TRANSPLANT

- Flu/Cy/ ATG/TBI 200 cGy
- Cy/ATG/TBI 200 cGy

were the predominant regimens

OVERALL SURVIVAL: URD TRANSPLANT



- (A) URD transplant: survival according to conditioning regimen adjusted for age and ATG source. The 5-year probabilities of survival with Cy/ATG/TBI 200 cGy, Flu/Cy/ATG/ TBI 200 cGy, Flu/Cy/ATG, and Cy/ATG were 77% (95% CI, 69-84), 80% (95% CI, 73-85), 75% (95% CI, 64-85), and 72% (95% CI, 59-84), respectively (P 5 .61).
- (B) URD transplant: survival according to age adjusted for conditioning regimen and ATG source. The 5-year probabilities of survival in patients aged #30 years and .30 years were 81% (95% CI, 76-85) and 66% (95%CI, 57-75; P 5 .003).

ATG PREPARATION

- Rabbit and equine ATG have different pharmacokinetics profile:
  - Rabbit ATG (rATG): 29.8 days
  - Horse ATG (hATG): 5.7 days
- Consequently :
  - rATG can deplete transplanted donor T cells in vivo much more efficiently as opposed to hATG
  - Can prevent acute GVHD but at the expense of possibly higher incidence of graft rejection and delayed immune reconstitution.

Bunn D et al. Clin Nephrol. 1996; 45(1):29–32
Vo PT, Pantin J, Hematol Oncol. 2015; 26;8:78

ALEMTUZUMAB CONDITIONING REGIMENS

- Alemtuzumab (CAMPATH) monoclonal Ab against CD52
- CD52, a GPI-linked membrane protein expressed on almost all WBC but not on CD34 HSC
- Potent lympholytic agent
- Detected in the plasma for several weeks after administration resulting in depletion of recipient auto reactive lymphocytes
  - Prevents GVHD by depletion of donor allo-reactive T-cells

Gandhi S,et al. Int J Hematol. 2013 May;97(5):573-80

Transplantation and Cellular Therapy
The Official Journal of ASTCT
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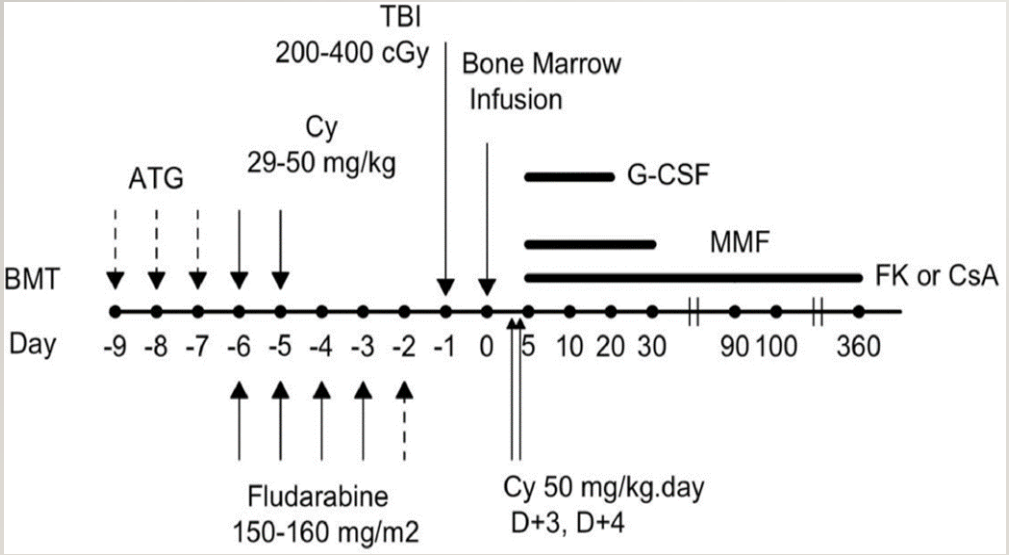
American Society for Transplantation and Cellular Therapy

BRIEF ARTICLES | VOLUME 26, ISSUE 9, E222-E226, SEPTEMBER 2020

A Case Series of Post-Transplantation Cyclophosphamide in Unrelated Donor Hematopoietic Cell Transplantation for Aplastic Anemia

Leonardo Javier Arcuri • Samir Kanaan Nabhan • Gisele Loth • ... Samantha Nichele • Renato de Castro Araujo • Carmem Bonfim • Show all authors

Open Archive • Published: June 03, 2020 • DOI: https://doi.org/10.1016/j.bbmt.2020.05.023 • Check for updates



Post-transplantation cyclophosphamide is feasible for patients with severe aplastic anemia undergoing unrelated donor hematopoietic stem cell transplantation

The toxicity of PTCy was low in patients with SAA undergoing URD HSCT.

The engraftment rate of URD HSCT for SAA is promising.

High total nucleated cell number was

CONCLUSIONS

- Flu/Cy/ATG and Cy/ATG regimens offer the best survival for matched-sibling BMT.
- In the setting of unrelated donor transplants, ATG/Cy/TBI 200 cGy and Flu/ATG/Cy/TBI 200 cGy are the predominant regimens with comparable survival, the exception being the use of Cy 150 mg/kg with the Flu/ATG/Cy/TBI 200 cGy regimen.
- Transplantation in patients aged >30 years is associated with higher mortality after matched sibling and unrelated donor BMT.

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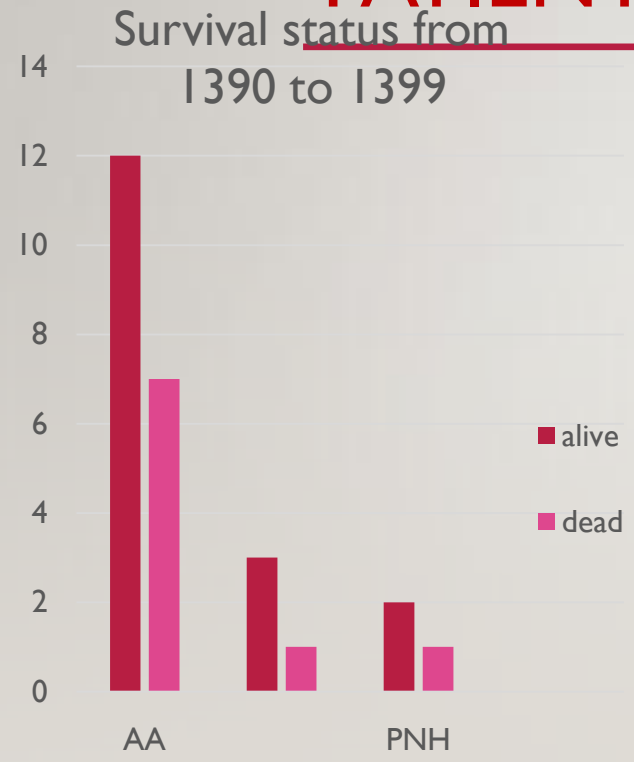
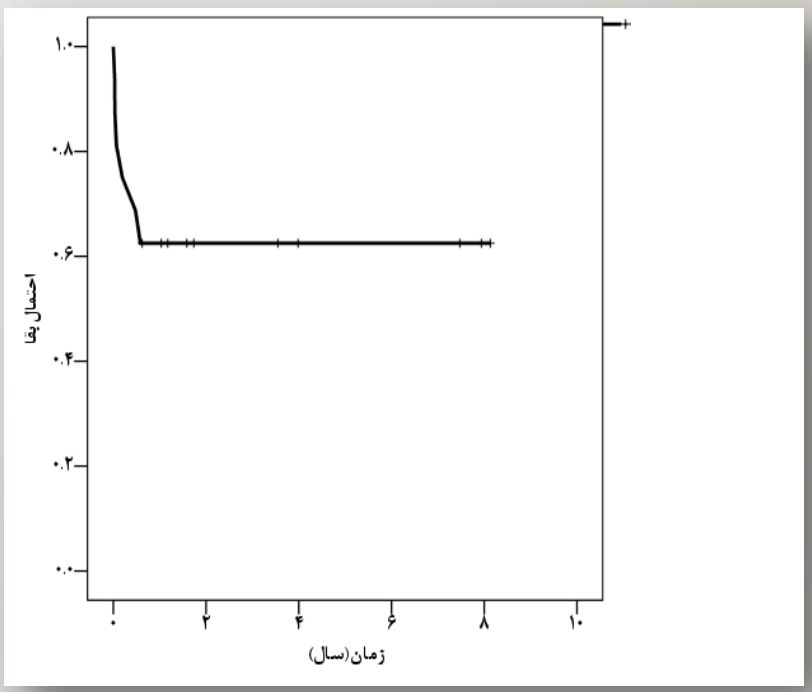
SURVIVAL STATUS OF OUR PATIENTS AFTER ALLO-HSCT

بقای ۶ ماهه و ۱ ساله





متغیر های معنی دار در سورویوال بیماران اپلاستیک آنمی

متغیر	مقدار	معنی دار
بروز سندرمSIIRS	2	S
فاصله زمانی تشخیص تا پیوند(سال)	1,82	S
زمان اینگرفتمنت wbc(روز)	14	s
عفونت سیستمیک قبل پیوند	+	s

متغیر های معنی دار در سورویوال بیماران اپلاستیک آنمی

متغیر	مقدار	معنی دار
سن	۳۱	NS
دوز سیکلوفسفامید		NS
خونریزی	+	
ترومبوز	+	

The Twelfth Annual
Medical and Nursing Congress
in Hematopoietic Stem Cell Transplantation
Tehran Heart Center Hospital, Conference Hall, Tehran, IRAN
March 02-04, 2023

THE ROLE OF HAPLOIDENTICAL TRANSPLANTATION IN APLASTIC ANEMIA

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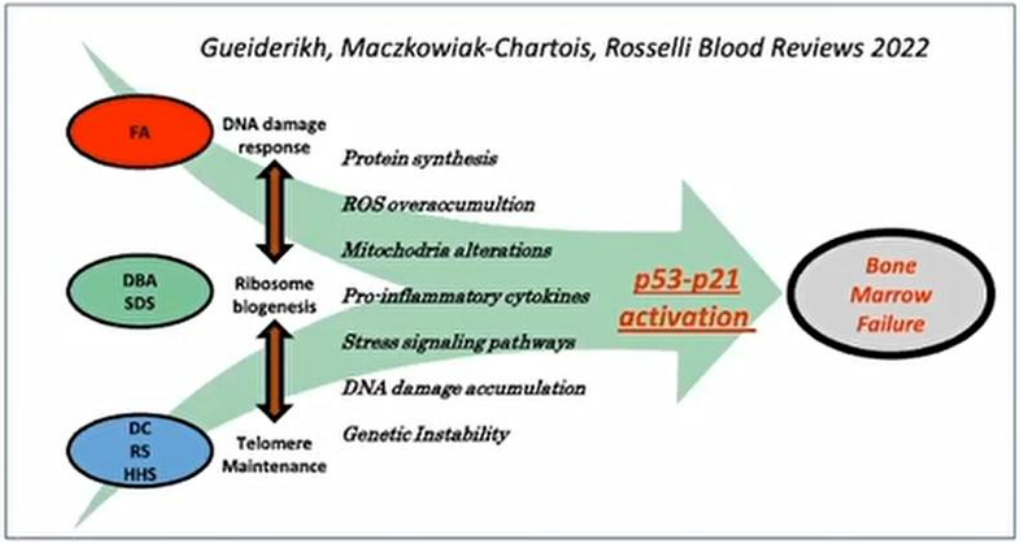
TEHRAN UNIVERSITY OF MEDICAL SCIENCES
SAAWP OF EBMT

HSCT is a cure for Aplastic Anemia



- Results are excellent for patients transplanted from unaffected matched related or unrelated donors
- Screen potential family donors
- Transplant strategies need to be modified for patients with FA /TBD and SDS
- Lifelong screening for cancer after transplantation and disease related issues

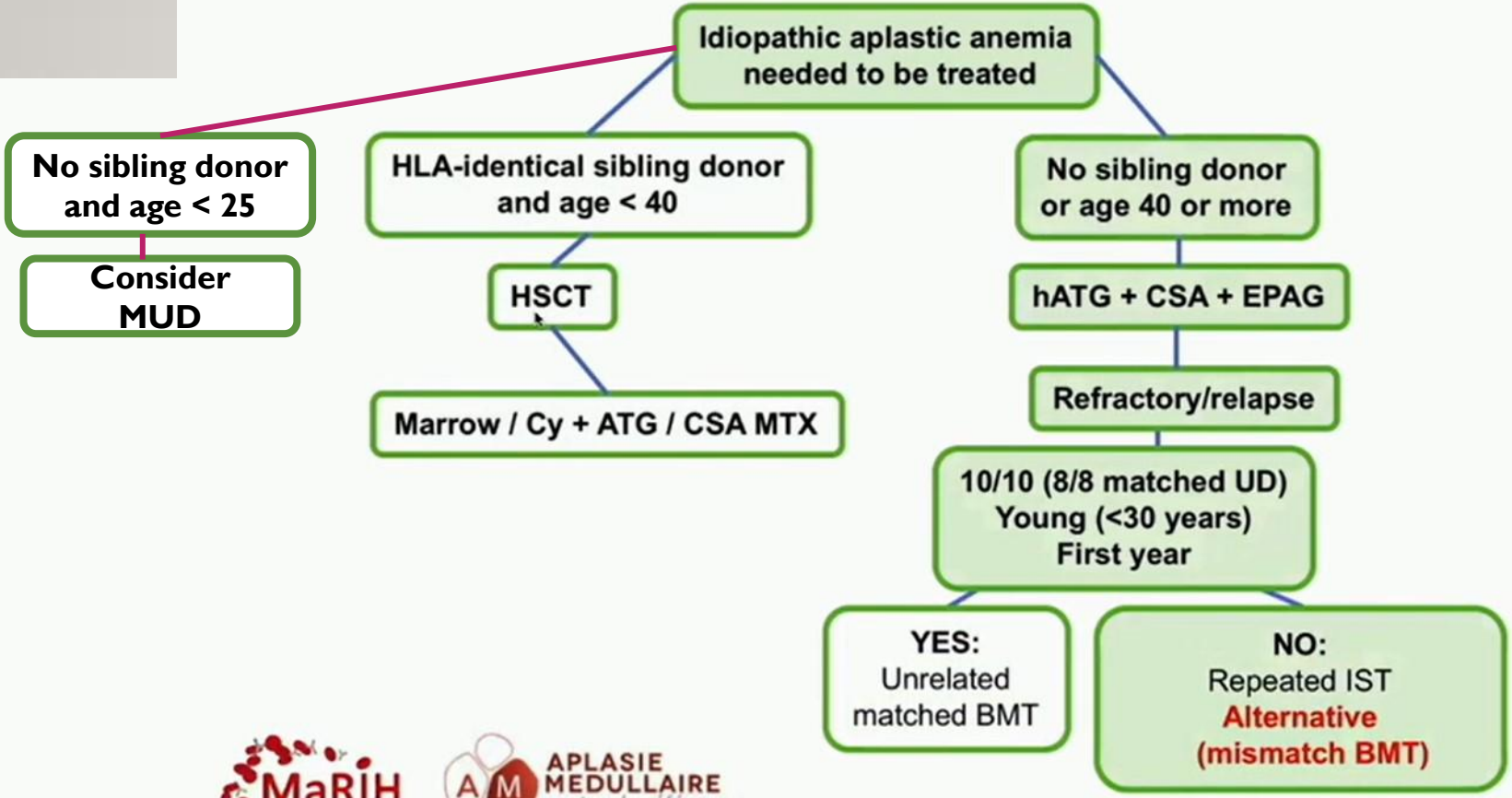
- For patients without matched donors, alternative donor transplantation is the next best option
  - Mismatched related or unrelated donor transplantation
  - Haploidentical cell transplantation

WHY HAPLOIDENTICAL ?

Table 1. Advantages of haploidentical hematopoietic stem cell transplantation

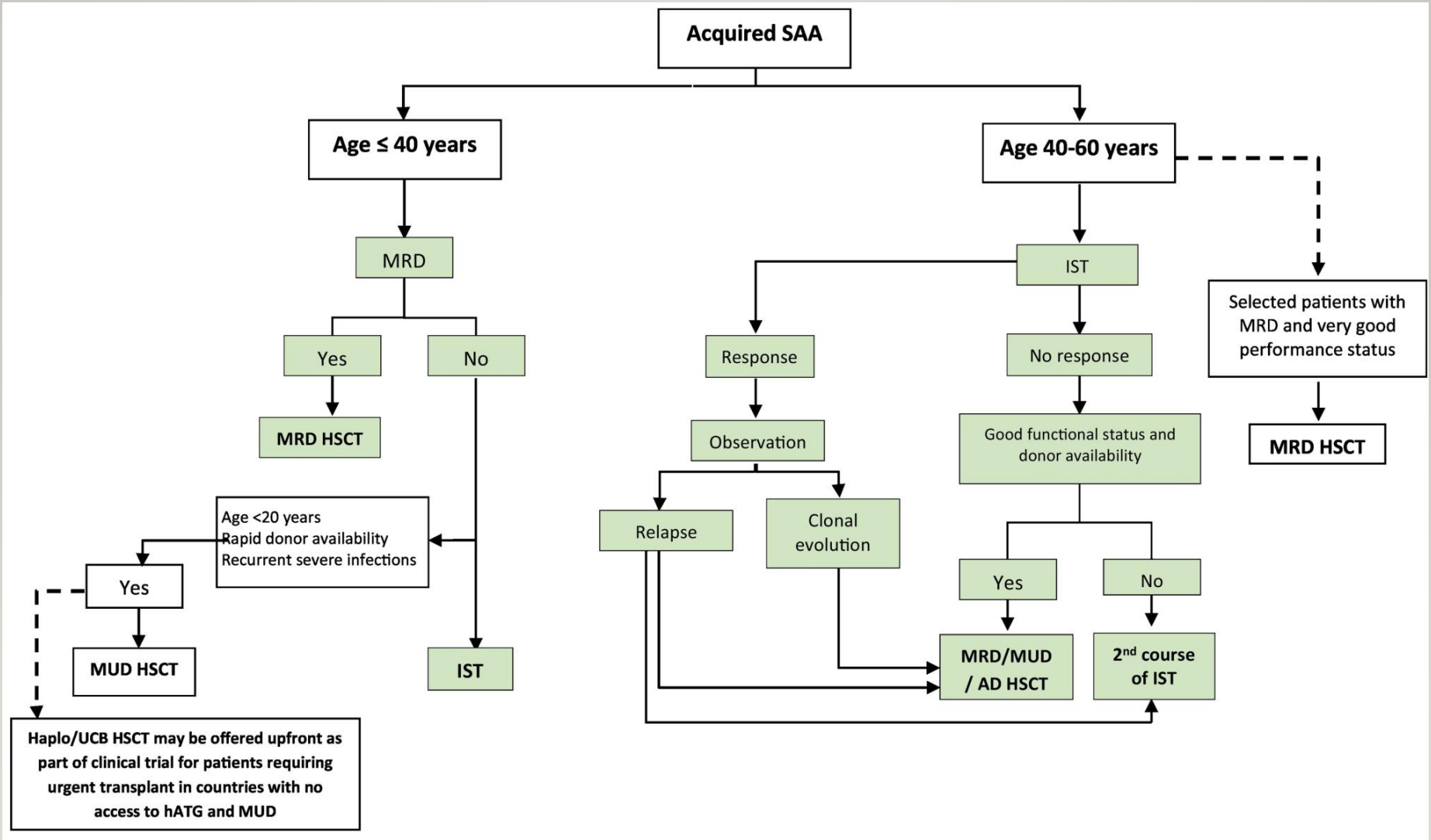
Availability for almost all patients
Immediate donor accessibility
No racial or ethnic restrictions
Multiple donors
Continued donor access

Treatment (guidelines)



MaRIH

APLASIE MEDULLAIRE centre de référence


Acquired SAA
Age ≤ 40 years
Age 40-60 years
MRD
Yes
No
MRD HSCT
Age <20 years
Rapid donor availability
Recurrent severe infections
Yes
MUD HSCT
IST
Haplo/UCB HSCT may be offered upfront as part of clinical trial for patients requiring urgent transplant in countries with no access to hATG and MUD
IST
Response
No response
Observation
Relapse
Clonal evolution
Good functional status and donor availability
Yes
No
MRD/MUD / AD HSCT
2nd course of IST
Selected patients with MRD and very good performance status
MRD HSCT

What you do ?
depends on where you live & your resources

Resources and access:

- To confirm the diagnosis of inherited aplastic anemia
- To look/find and pay for unrelated donor search/grafts worldwide
- To have access to specific drugs and T cell depletion techniques

MODERN HAPLO-HSCT

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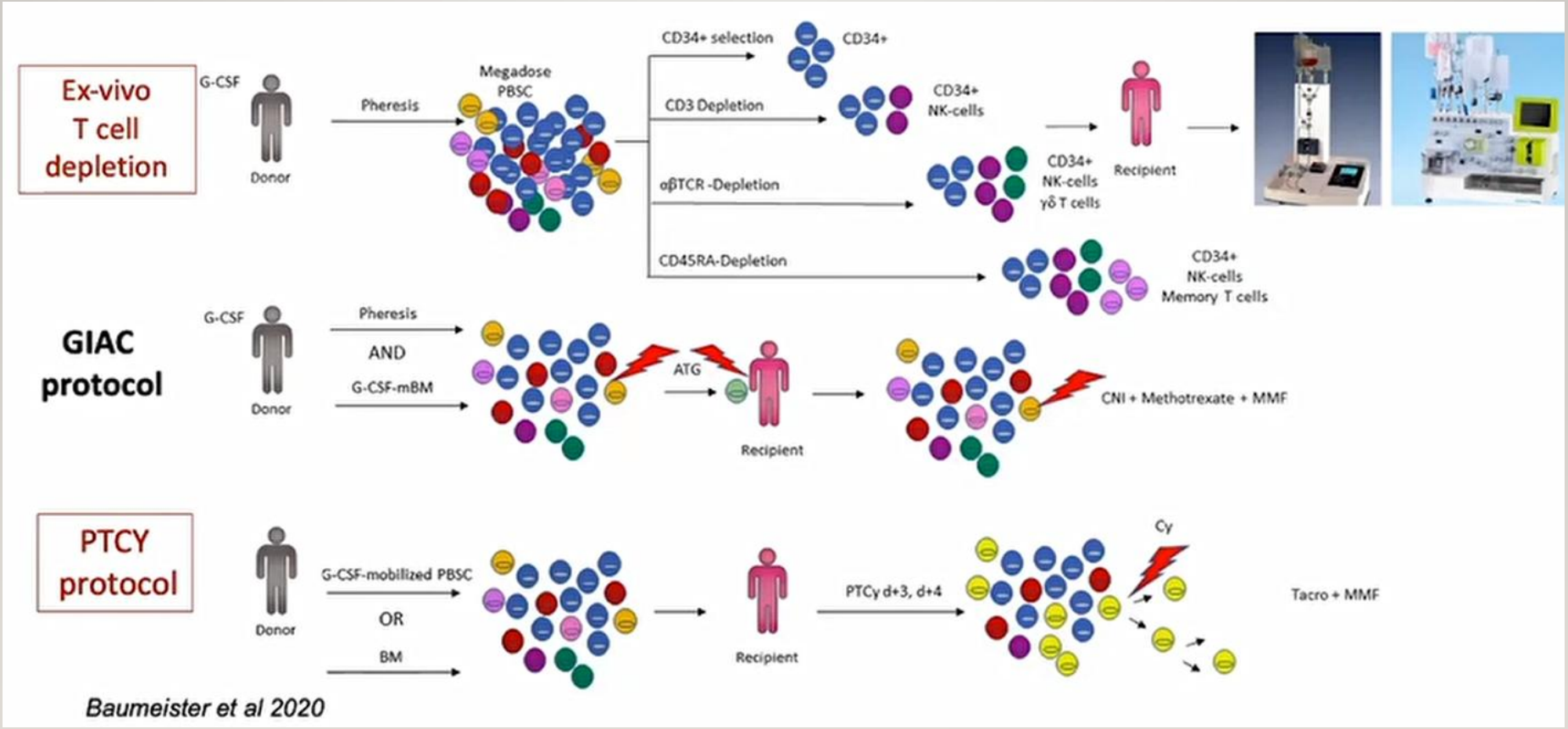
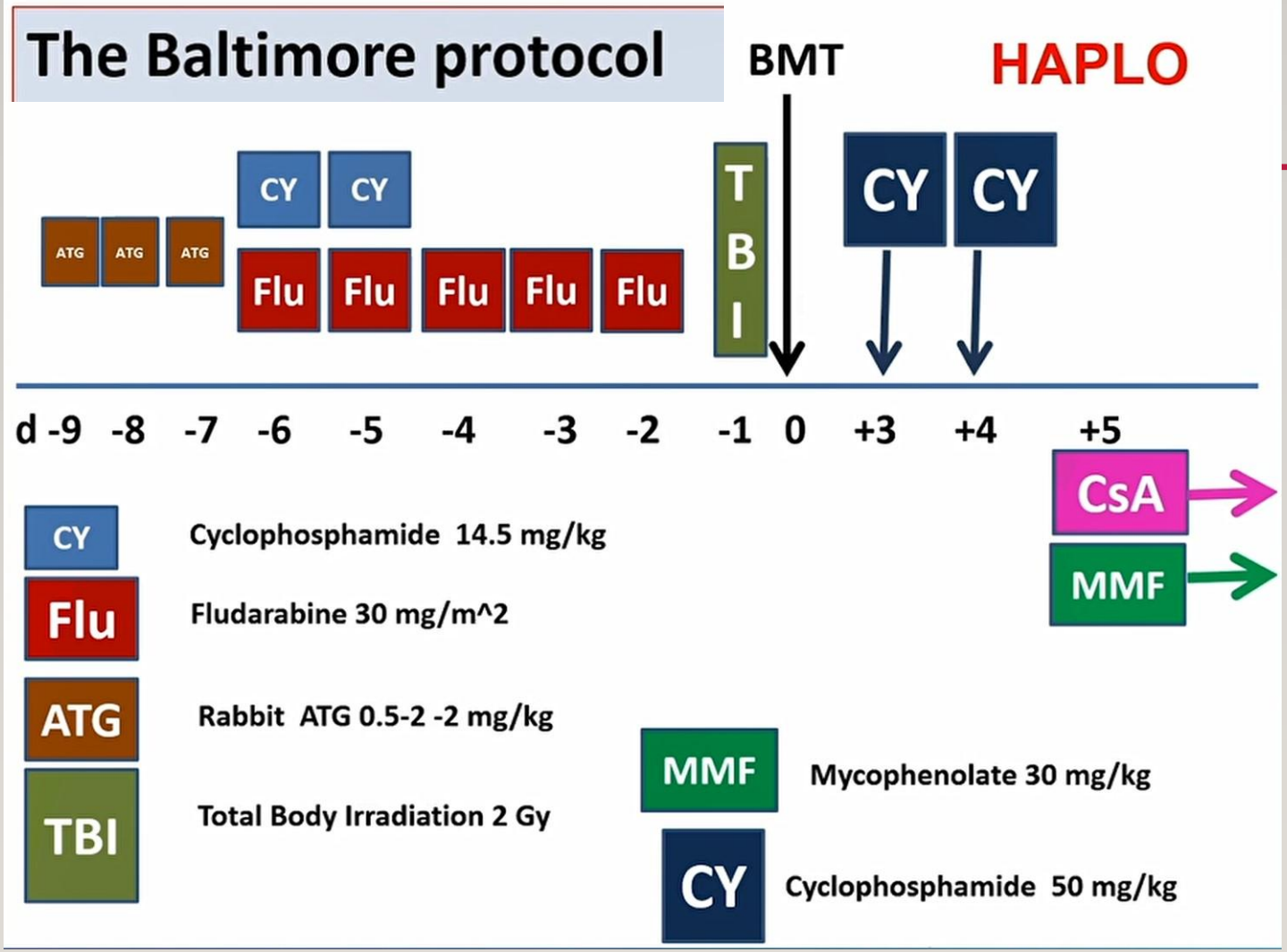
March 02-04, 2023



The Baltimore protocol



ELSEVIER

Biology of Blood and Marrow Transplantation

journal homepage: www.bbmt.org

Impact of CD34 Cell Dose and Conditioning Regimen on Outcomes after Haploidentical Donor Hematopoietic Stem Cell Transplantation with Post-Transplantation Cyclophosphamide for Relapsed/Refractory Severe Aplastic Anemia

N= 87 HAPLO Tx for SAA

BRASIL

Heavily transfused

All pts had failed IST

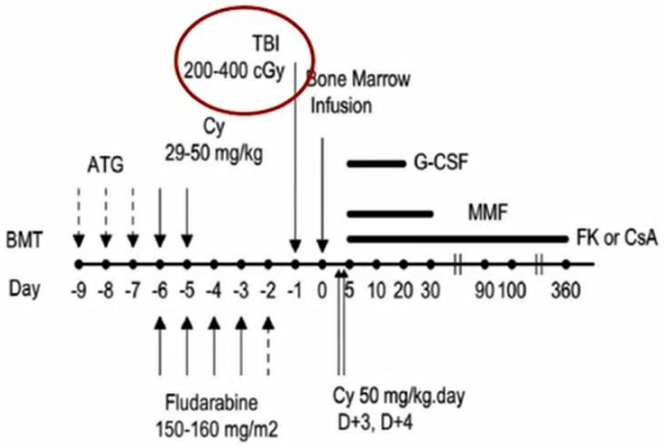
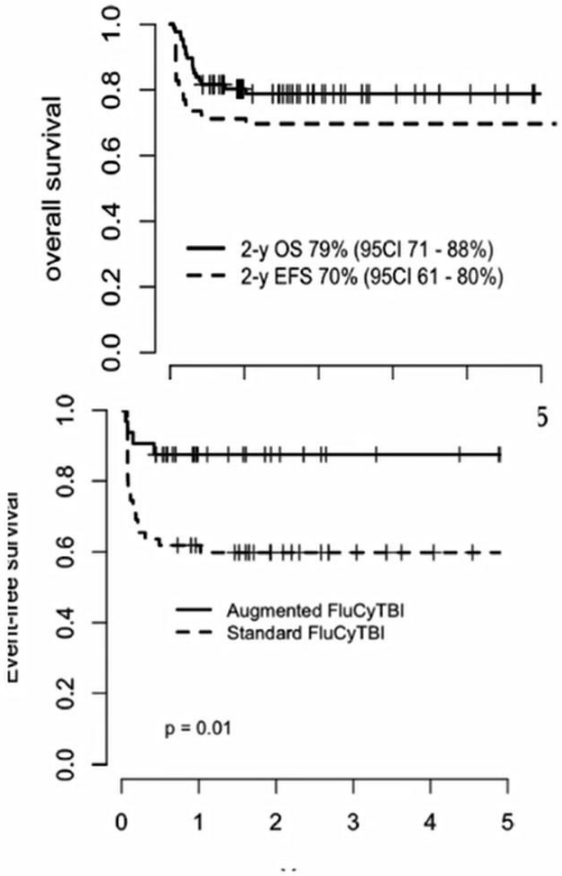
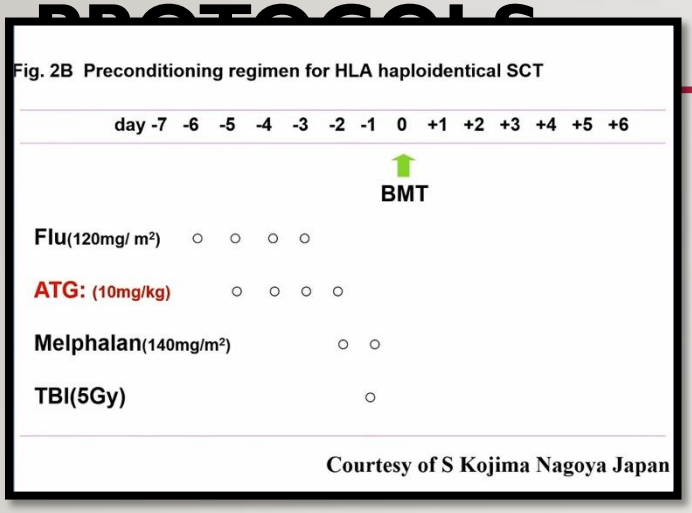
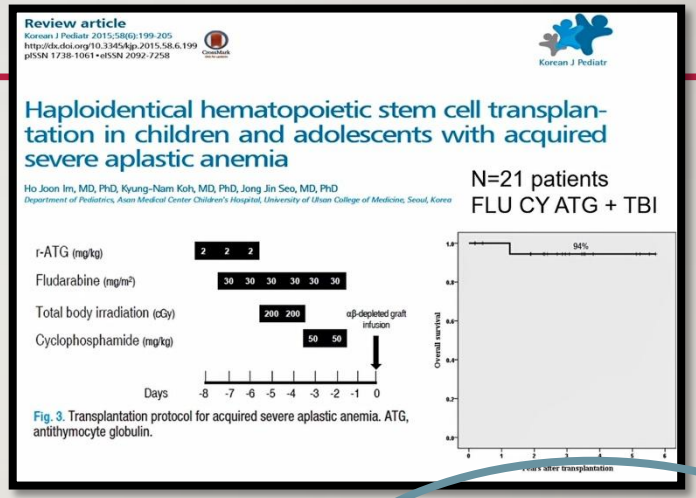


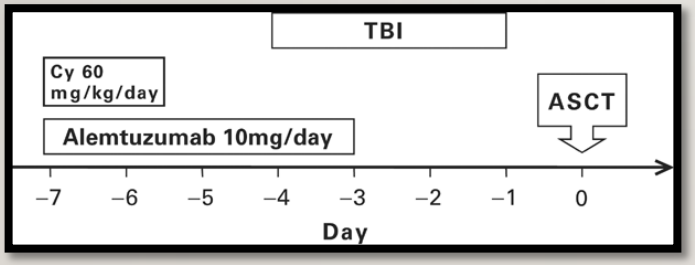
Figure 1. Conditioning regimens and GVHD prophylaxis.



ALTERNATIVE ACCEPTABLE PROTOCOLS







Conditioning

	HAPLO
CY	50mg/kg x4
ATG	2.5 mg/kgx4
BU	**3.2 mg/kgx4**

FLUCAB-Prime

Flu	(30 mg/m^2)	-7 to -3
Cy	(14.5 mg/kg)	-6 & -5
rATG	(5 mg/kg)	-6 to -3
Bu	(3.2 mg/kg/d)	-3 & -2

STRATIFICATION

Results of HAPLO transplants in SAA stratified by patients age.
Results of HAPLO transplants in SAA, stratified by intensity of the conditioning regimen.

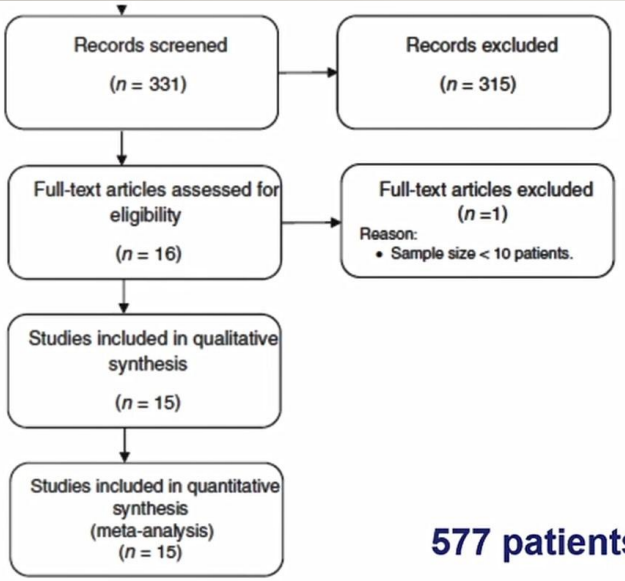
Ref	n.pts	Age (Years)	Conditioning regimen	GvHD Prophylaxis	SC source	Engraft	GvHD II-IV	Alive 1 y
NMA regimens								
Esteves [9]	16	17	Cy14.5 × 2, Flu30 × 5+TBI 200	Thymo10+MMF+CsA+PTCY	BMum	94%	13%	67%
DeZern [15]	16					0%	12%	100%
Li [12]	17					%	41%	76%
Clay [11]	8					%	12%	75%
Gao L [13]	26					%	12%	84%
Zhu [17]	13					0%	50%	78%
Subtotal	96					%	23%	80%
RIC regimens								
Im [10]	16					%	20%	94%
Im [10]	5							
Yamei [14]	40					%	26%	93%
Yamei [14]	37	11	(b) FLU 30 × 5+ CY30 × 4	Thymo 10+Basilix+Csa+MMF	GPB+GBMum+MSCuc			
Xu [19]	51	25	BU 3.2 × 2 + CY 200	Thymo10+CsA+MMF+MTX	GBM+GPB unmanip	98%	20%	88%
Xu [16]	89	25	BU 3.2 × 2 + CY 200	Thymo10+CyA+MMF+MTX	GBM+GPB unmanip	97%	30%	86%
Lu [18]	41	13	BU3.2 × 2+FLU30 × 4+CY30 × 4	Thymo7.5+FK+MMF+MTX	GPB+GBM	94%	44%	80%
Subtotal	279	16				95%	33%	87%
Total	375	19				94%	25%	83%

Results of HAPLO grafts in SAA according to GvHD prophylaxis.

GvHD Prophylaxis	GvHD-III-IV	Graft failure
ATG+CNI+MMF+MTX[13,16,17,18,19]	11%	1%
Basiliximab + ATG + CNI+ MTX + MMF [12,14]	12.5%	4%
Ex vivo T-depletion [10]	14%	4%
PTCY+ATG+ CNI+ MMF [9,11,15]	12.5%	7.5%

Haploidentical hematopoietic stem cell transplantation in aplastic anemia: a systematic review and meta-analysis of clinical outcome on behalf of the severe aplastic anemia working party of the European group for blood and marrow transplantation (SAAWP of EBMT)

Bone Marrow Transplantation (2020) 55:1906–1917
https://doi.org/10.1038/s41409-020-0897-2



577 patients

Engr 97%
GvHD II-IV , 26%
cGvHD 25%
TRM 7% per year
OS 70-95%

577 patients

Median age of studies

17 yy (5-32)

RIC vs NMA

- Engraftment (97.7% vs 91.7%, P = 0.03)
- aGvHD (29.5% vs 18.7%, P = 0.008)
- Similar cGvHD or mortality incidence

Other regimens vs MTX vs PTCY

- aGvHD (28.6%, 27.8%, and 12.8%, P = 0.02)
- CMV viremia (55.7%, 38.6%, and 10.4%, P < 0.001)
- CMV disease (2.1%, 33.0%, and 0%, P < 0.001)

Comparison of frontline treatment with intensive immunosuppression therapy and HLA-haploidentical hematopoietic stem cell transplantation for young patients with severe aplastic anemia – A meta analysis

Leukemia Research
Volume 88, January 2020, 106266

Pooled estimates	Pooling model	No. of studies IST/haplo-HSCT	IST (95% CI)	Haplo-HSCT (95% CI)	*p* value
Overall survival (OS)					
1-year	Fixed	3[28-30]/3[31,28,30]	0.92 (0.86,0.97)	0.88 (0.81,0.96)	0.543
3-year	Random	3[28-30]/4[26,31,28,30]	0.82 (0.70,0.94)	0.85 (0.76,0.93)	0.717
5-year	Random	5[7,27-30]/3[26,31,28]	0.81 (0.77,0.85)	0.83 (0.71,0.96)	0.822
10-year	Fixed	3[28-30]/2[31,28]	0.74 (0.65, 0.82)	0.89 (0.80, 0.97)	0.052
Failure free survival (FFS)					
1-year	Fixed	3[28-30]/3[31,28,30]	0.67 (0.58,0.76)	0.89 (0.82, 0.98)	0.002
3-year	Fixed	3[28-30]/3[31,28,30]	0.54 (0.44, 0.63)	0.89 (0.82, 0.96)	<0.001
5-year	Fixed	4[7,28-30]/2[31,28]	0.52 (0.45, 0.60)	0.91 (0.83, 0.99)	<0.001
10-year	Fixed	3[28-30]/2[31,28]	0.44 (0.34, 0.53)	0.91 (0.83, 0.99)	<0.001

DILEMMAS

- ✓ **RIC vs NMA**
- ✓ **GVHD prophylaxis comparison**
- ✓ **IST vs Haploidentical**

- ❑ **TBI vs non-TBI ?**

PROSPERO registered systematic review

HAPLOIDENTICAL HSCT (SINGLE ARM)

Location	Date	N	PRE BMT therapy	Median Age (Range)	Conditioning Regimen	GVHD Prophylaxis	Overall Survival	Median Follow-Up	Acute GVHD	Chronic GVHD
Studies Utilizing Post-transplant Cyclophosphamide as GVHD prophylaxis										
Brazil[36]	2010–2014	16	All R/R to IST; no IBMFS included	17 (5–39)	RIC: Flu, CY, TBI (200–600 cGy)	PTCy +3,4; MMF to D35 CSA/Tacro	67.1%	355 days	13 % grade II–IV	20% limited
United Kingdom[37]	Prior to 2014	8	4 R/R to IST; 4 failed to engraft after previous BMT	32 (19–57)	RIC: Flu, CY, TBI (200 cGy)	PTCy +3,4 MMF to D35 CSA/Tacro	75%	14.8 months (7.2–44.4)	1 Grade 2 aGVHD	0
****Baltimore**[34]	2011–2016	16 (13 haplo)	All R/R to IST; IBMFS included	30 (11–69)	RIC: rATG, Flu, CY, TBI (200 cGy)	PTCy +3,4 MMF to D35 Tacro	100%	21 months (3–64)	2 Grade 1–2 aGVHD	2 limited
Studies NOT Utilizing Post-transplant Cyclophosphamide as GVHD prophylaxis										
China[69]	2007–2010	26	All R/R to IST; no IBMFS included	25.4 (18–41)	RIC: rATG, Flu, CY	CSA to D180 MMF to D90 MTX D+1,3,6,11	84.6%	1313.2 days (738–2005)	12% grade II–IV	4% extensive
China[48]	2012–2015	89	None	22 (4–51)	RIC: Bu; CY; rATG	CSA to 1 yr MMF to D60 MTX D+1,3,6,11	86.1%	22.6 (7.1–47.6)	30.3% grade II–IV	3.4% extensive
****China**[38]	2012–2015	101	All R/R to IST; no IBMFS included	19 (2–45)	RIC: Bu; CY; rATG	CSA to 1 yr; MMF to D60; MTX D+1,3,6,11	89%	18.3 months (3–43.6)	33.7 % grade II–IV	10% extensive

UNMANIPULATED GRAFT

Author	n	Year	Place	Setting	Compare	Conditioning	GVHD prophylaxis	Worse in HID	Similar outcome
Xu LP et al.	158	2017	China, multicenter	Upfront SAA	MRD vs HID	BuCy + ATG	MTX + MMF + CSA	aGVHD, cGVHD	OS, FFS (3-y)
Xu LP et al.	101	2016	China, multicenter	Salvage	MRD vs HID	BuCy + ATG	MTX + MMF + CSA	aGVHD, cGVHD	OS, FFS (3-y) III/IV aGVHD
Zhang Y et al.	387	2022	China, single	Upfront SAA	MRD vs HID vs IST	FluCy + ATG BuCyFlu + ATG	NA	aGVHD, cGVHD OS, FFS (5-y) FFS better than IST	III/IV aGVHD OS similar to IST
Park SS et al.	89	2018	China, single	Salvage	MUD vs HID	BuCyFlu + ATG	MTX + MMF + CNI	aGVHD	OS, DFS, GFFS (3-y) cGVHD
Yang S et al.	49	2019	China, single	Upfront	MUD vs HID vs IST	Cy + ATG ± FluBu	MTX + MMF + CSA	FFS (3-y)	OS (3-y) GVHD
Liu L et al.	365	2020	China, multicenter	Upfront	HID vs IST	BuCy + ATG	MTX + MMF + CSA	FFS (4-y)	OS (4-y)
Li Y et al.	235		China, multicenter	Upfront	MRD vs HID	BuCy + ATG FluCy + ATG	MTX + CSA	aGVHD, cGVHD, OS, FFS (3-y)	PGF III/IV aGVHD

MANIPULATED GRAFT (COMPARATIVE)

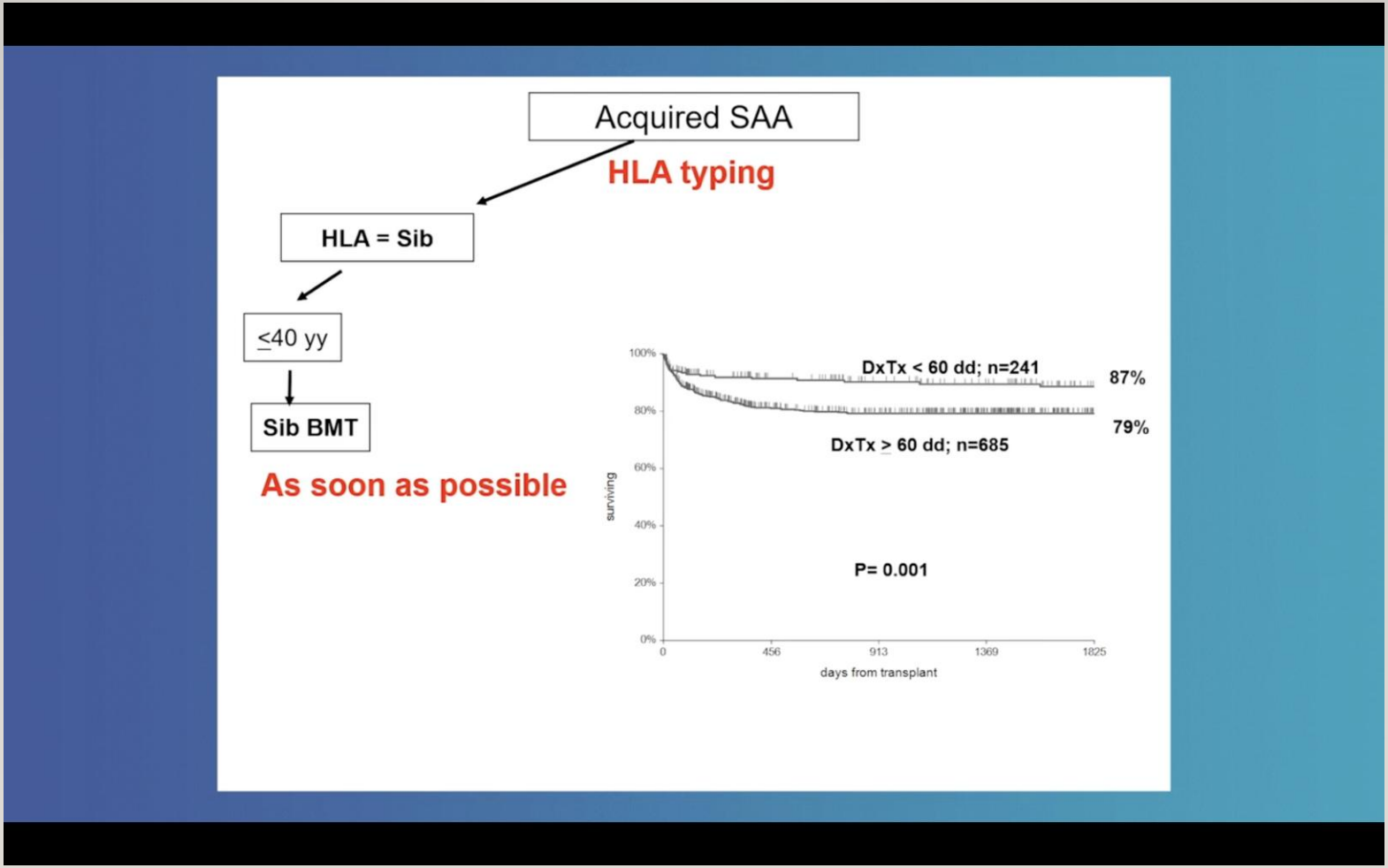
Author	n	Year	Place	Graft	Compare	Conditioning	GVHD prophylaxis	Increased outcome (HID)	Similar outcome
Kim H et al.	67	2018	Korea, single	CD3 depleted	MRD vs MUD vs HID	Cy + ATG ± TBI FluCy + ATG ± TBI	CNI + MTX CNI + MMF	ANC engraft	aGVHD, cGVHD OS, FFS (5-y)
Arcuri et al.	87	2021	Brazil, single	PTCY	HID (CD34 dose)	FluCy + TBI	PTCY	EFS (higher CD34)	N/A
Yang K et al.	29	2020	China, single	PTCY	HID	BuCyFlu	PTCY + MTX + CNI	--	--

Summary

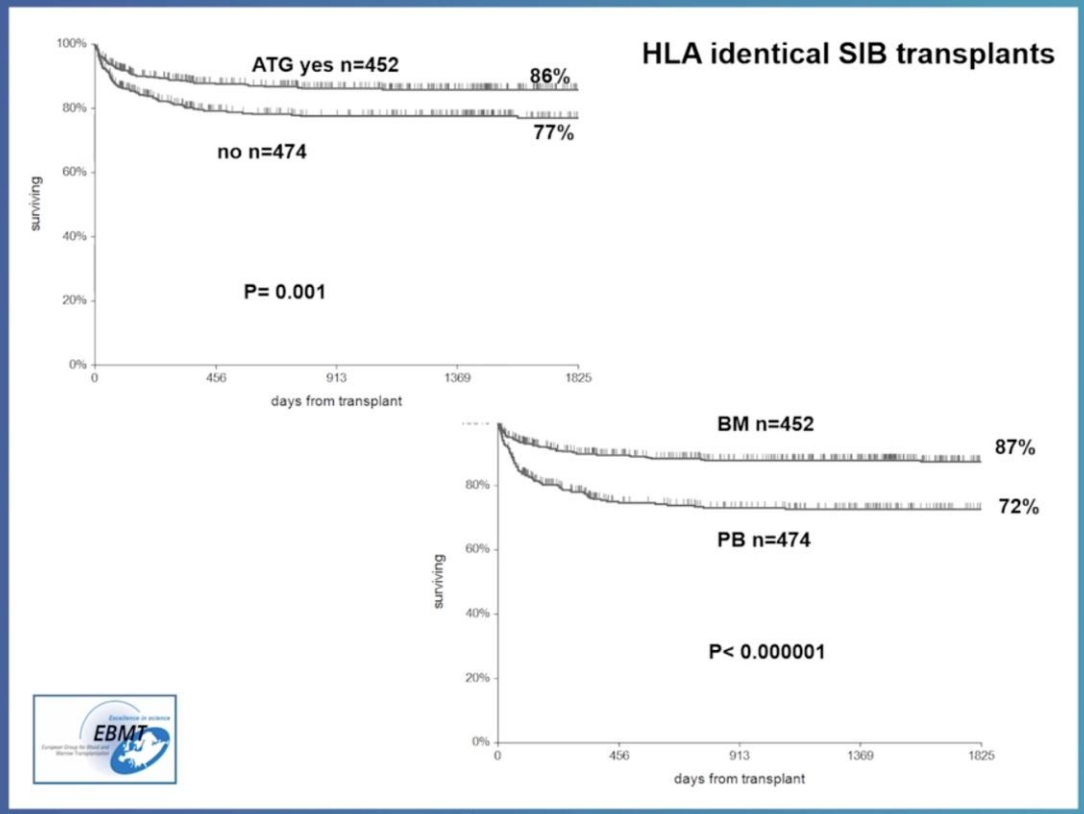
- **International collaboration (to augment scarce data)**
- **Timing, conditioning & GVHD prophylaxis choice**
- **For the time being HAPLO transplants for SAA should continue to be performed, preferably in the context of clinical trials, and reported in detail, in order to identify best transplant platforms.**
- **Preferentially within the framework of a local clinical protocol in a well-experienced center**

TAKE HOME MESSAGES OF THIS PANEL

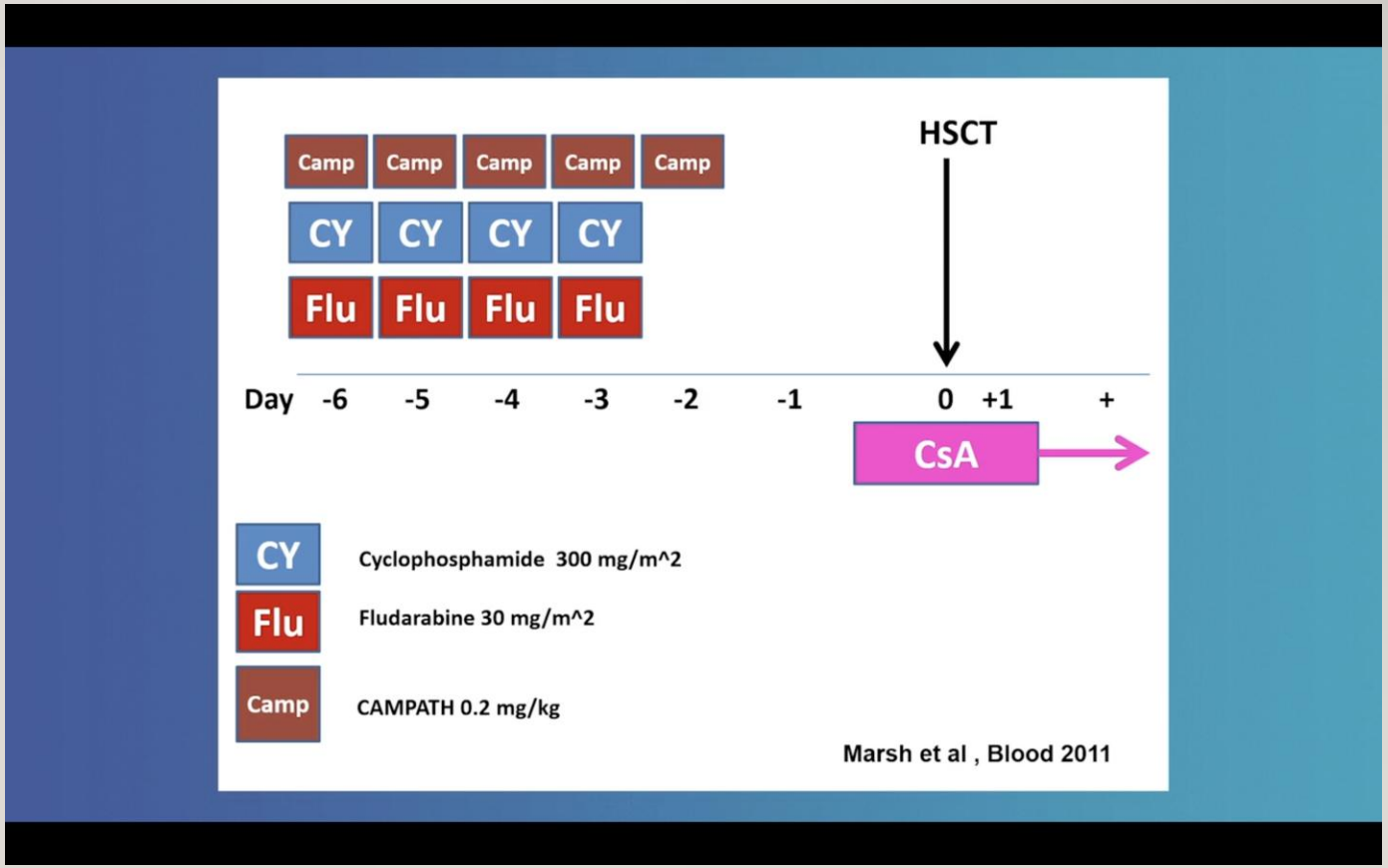
AS SOON AS POSSIBLE



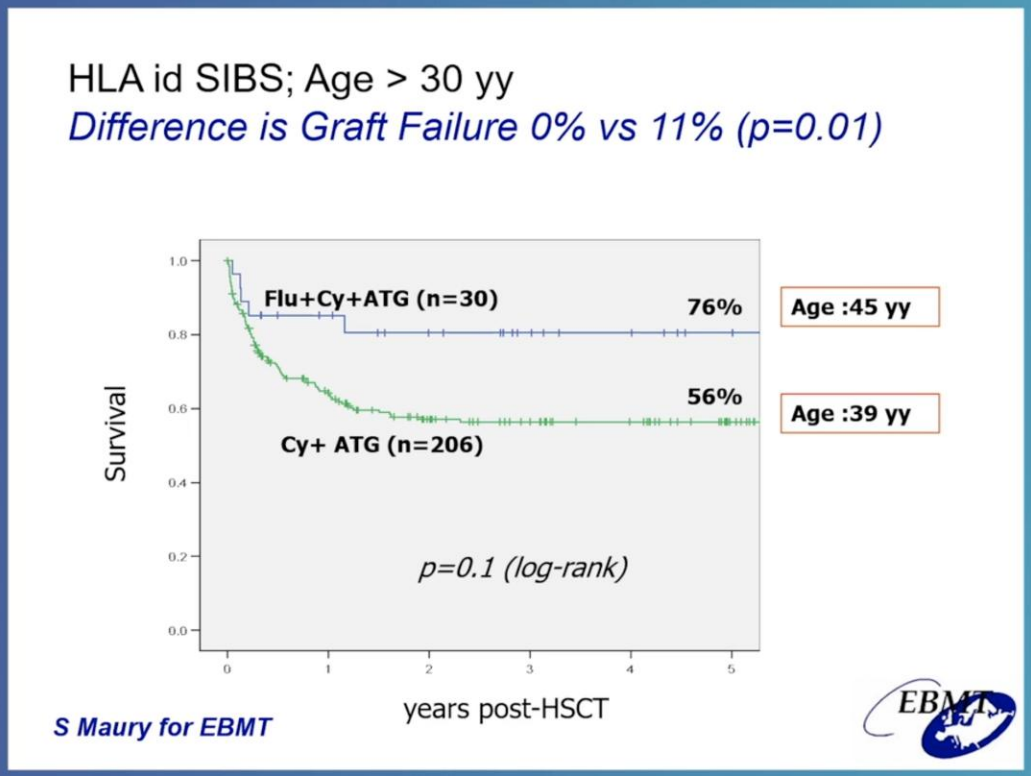
BONE MARROW SOURCE OF GRAFT & SEROTHERAPY IS RECOMMENDED



LESS C GVHD WITH ALEMTUZOMAB



BETTER OUTCOME WITH REDUSED DOSE OF CPM ESPECIALLY IN >30 YEARS



MUD ALLOTRANSPLANT IS BECOMING UPFRONT FOR YOUNG PATIENT WITH SAA

- strong considerationshould be given to first-line marrow transplantation for patients whoare younger than 30 years old with aplastic anemia if a 10/10 HLAmatchedunrelated donor is rapidly identified

- Your time is:4-6 weeks
- Unrelated donors with 9/10 high-resolution HLA matching may also be considered, but there are insufficient data to propose such donors for first-line treatment. Clinical

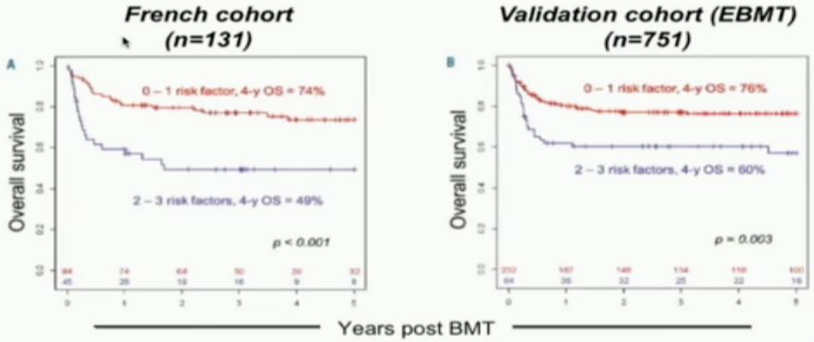
MUD ALLOTRANSPLANT IS BECOMING UPFRONT FOR YOUNG PATIENT WITH SAA

MUD for refractory patients: no change

Decision making process

3 Risk factors

- Age (30)
- MUD versus mismatch UD
- BMT in the first year post AA versus after



Bacigalupo, Blood 2016; Devillier R, *et al.* Haematologica. 2016;101:884-90.

CONSIDER RITUXIMAB IN UD TRANSPLANT CONDITIONING

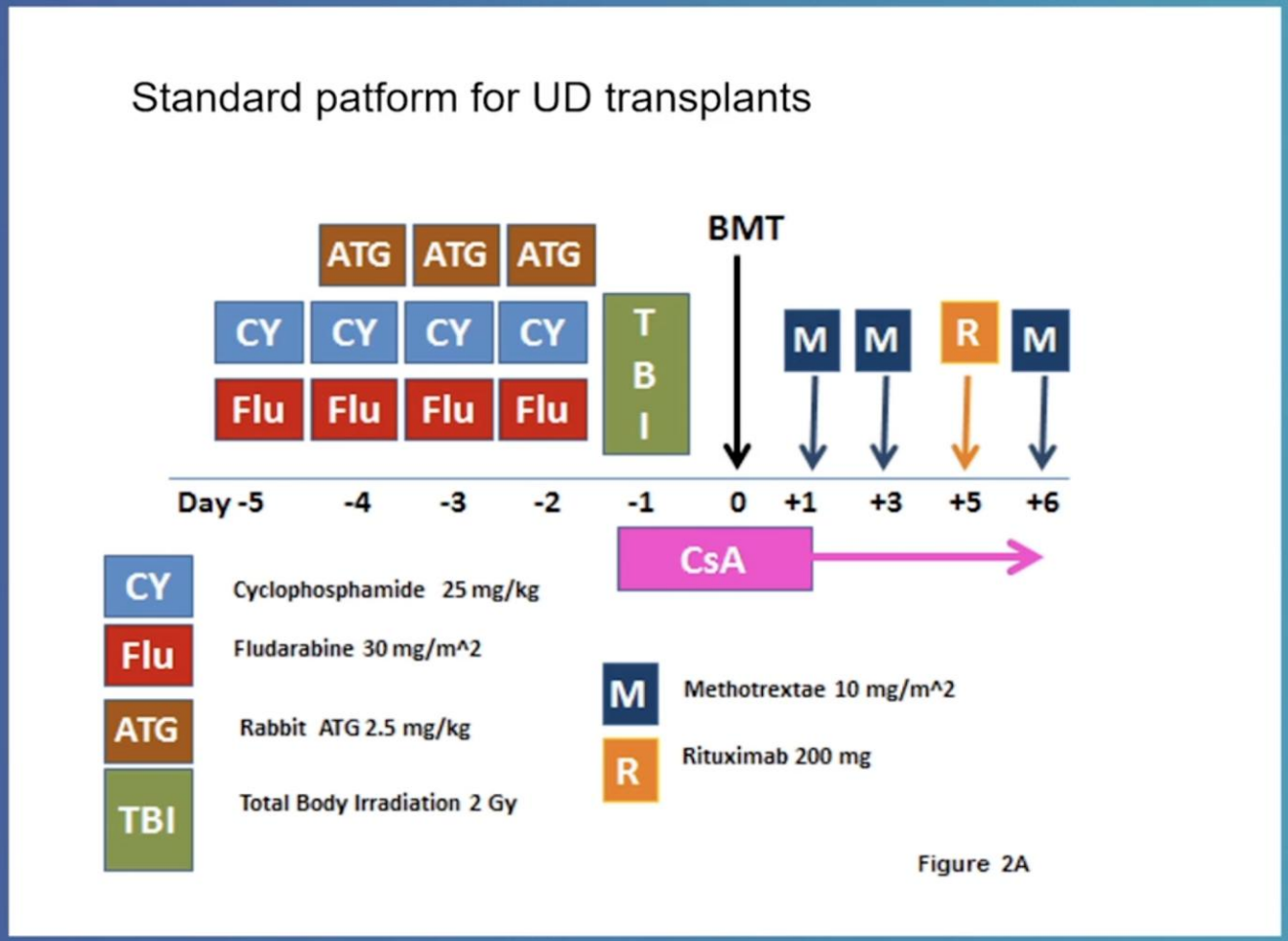
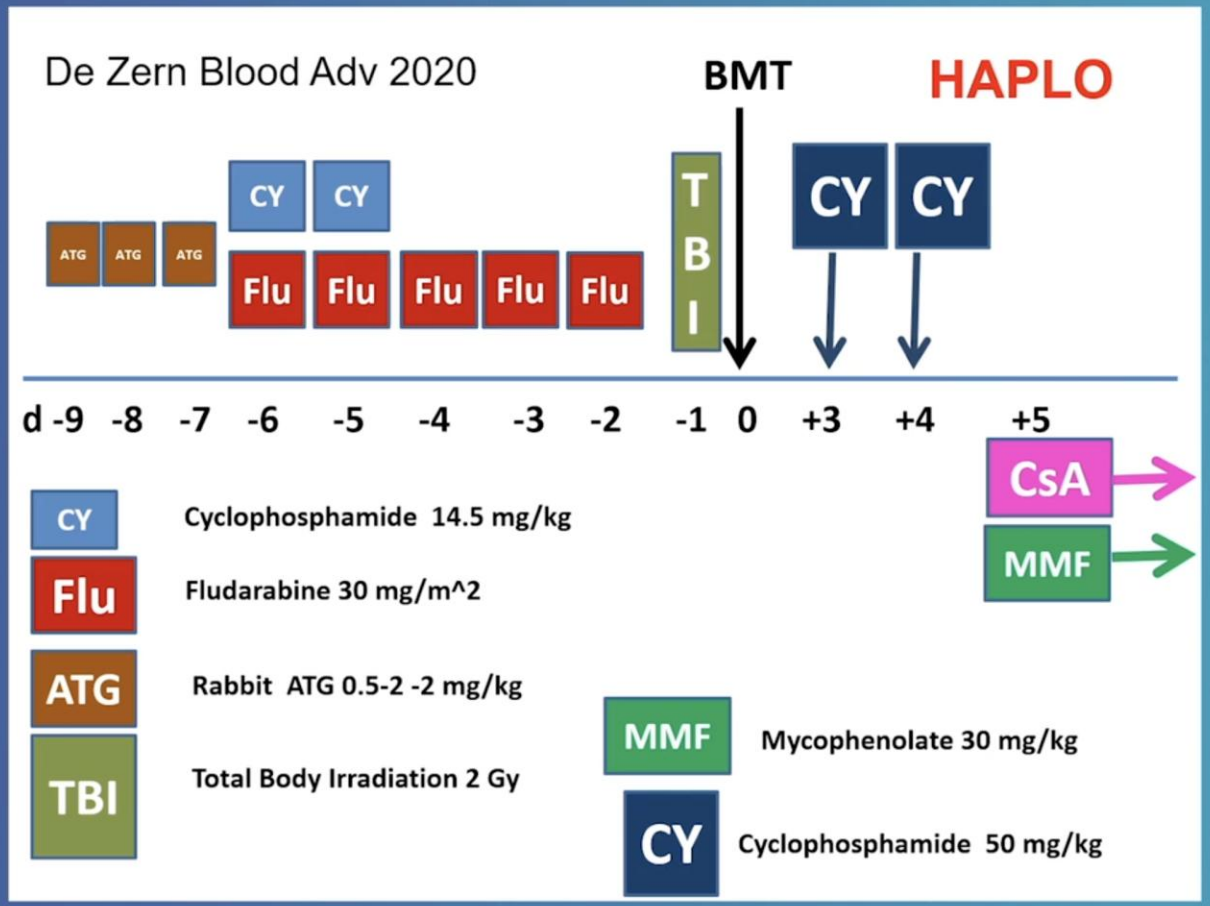
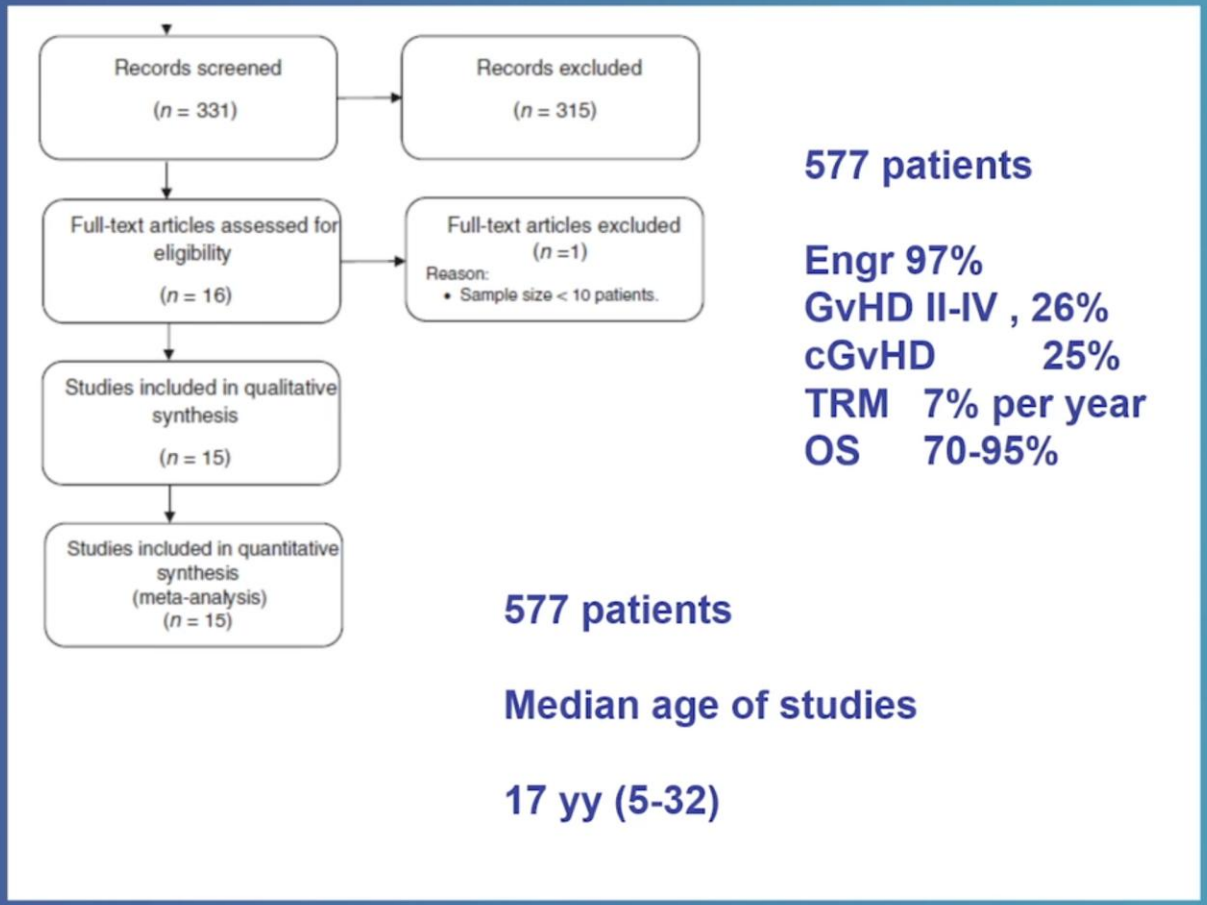


Figure 2A

BALTIMORE HAPLO PROTOCOL
EXCELLENT FOR EVERY WHERE



HAPLO TRANSPLANT IN SAA IS PROMISING BUT SHOULD BE MORE EVALUATED(FRONT LINE??)



SAA TRANSPLANTATION IN ERA OF ELTHROMBOPAG

- No difference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