

TROMBOSİT ALLOİMMÜNİZASYONU YÖNETİMİ

Dr. Onur KIRKIZLAR
Trakya ÜTF

- TROMBOSİT REFRAKTERLİĞİ TANIMI
- REFRAKTERLİK NEDENLERİ
- HAVUZ TROMBOSİT VS AFEREZ
- REFRAKTERLİK GELİŞEN HASTA YÖNETİMİ
- KORUYUCU vs TEDAVİ

- EN AZ 2 DEFA/ARDI ARDINA UYGULAMA
- ABO UYUMLU
- ÜRÜNLER <48-72 SAATLİK

Table 1 Definitions of platelet refractoriness



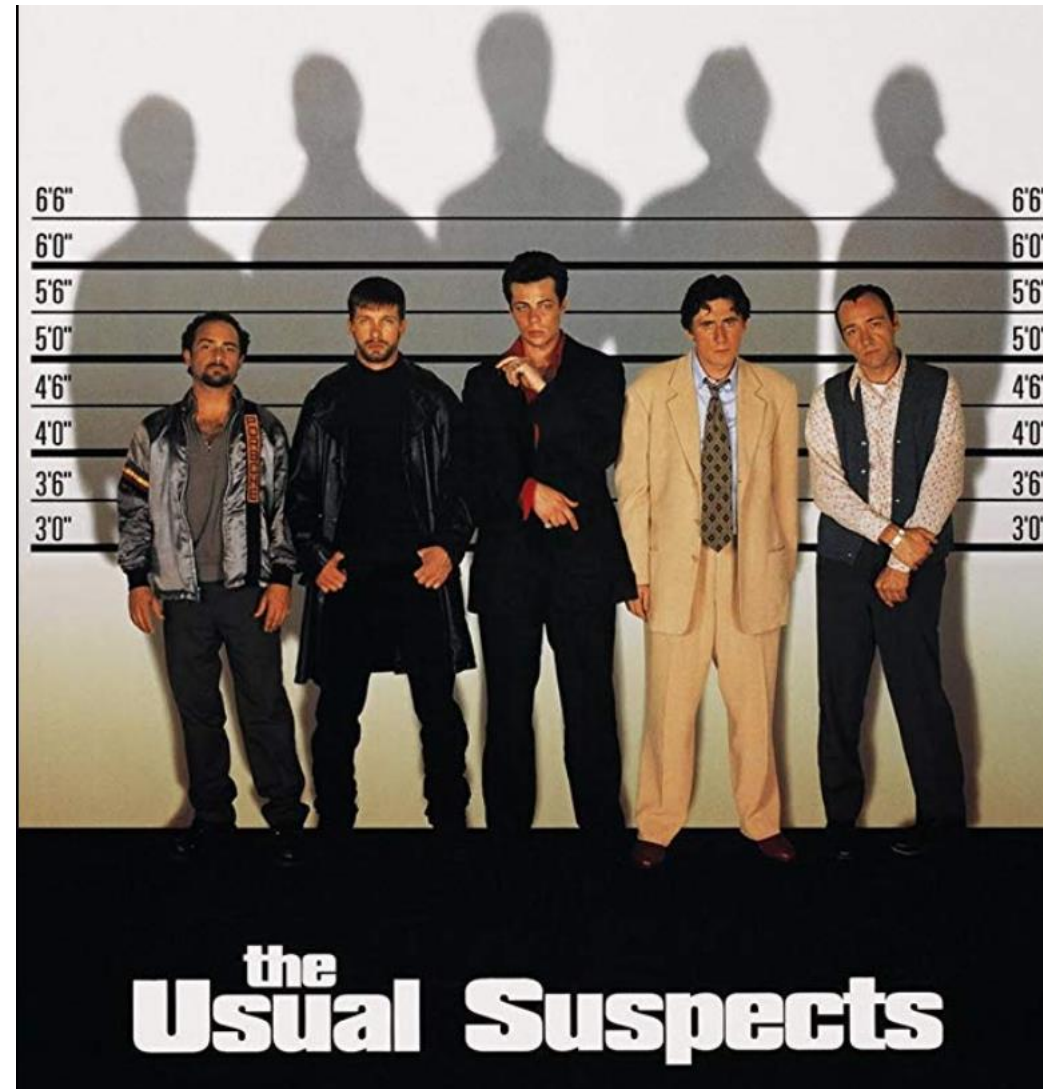
Measure of transfusion outcome	Formula	Values suggestive of refractoriness
Absolute count increment (ACI)	(post-transfusion platelet count)-(pre-transfusion platelet count)	At 60 min, ACI <5/ μ l per unit of whole blood derived platelets
Corrected count increment (CCI)	(ACI \times BSA)/(number of platelets transfused)	At 10–60 min, CCI <7500/ μ l At 18–24 h, CCI <5000/ μ l
Percent platelet recovery (PPR)	(100%) (ACI \times TBV)/(number of platelets transfused)	At 60 min, PPR <20% At 16 h, PPR <10%

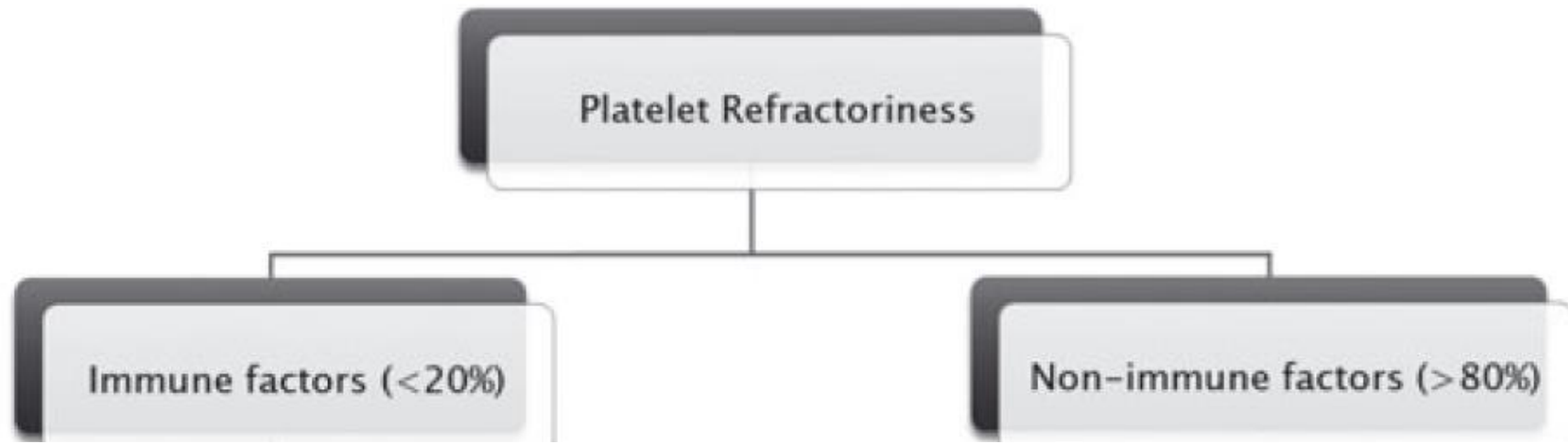
BSA, body surface area; TBV, total blood volume.



- TAHMİNİ SAYI?
- KAÇINCI GÜN?
- ÜRÜNÜN SAYIMI?

Pavenski et al., Tissue Antigens, 2012

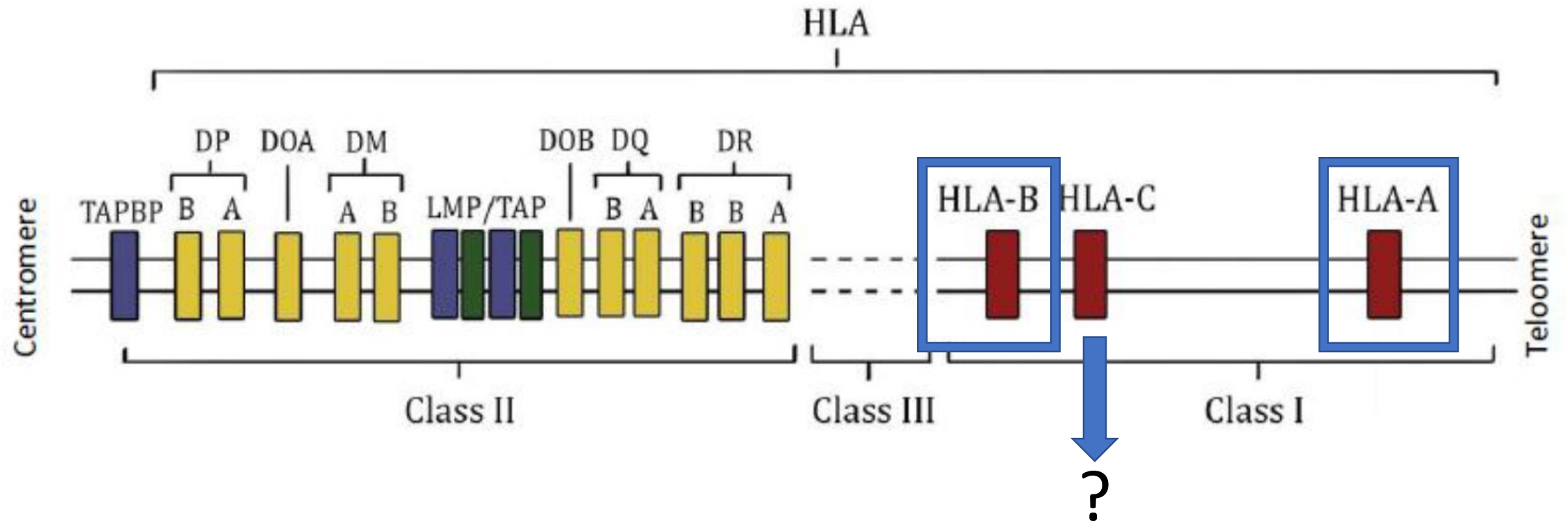




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TROMBOSİT ALLOİMMUNİZASYONU-HLA (%80)



TROMBOSİT ALLOİMMUNİZASYONU-HPA (%20)

EMBL-EBI

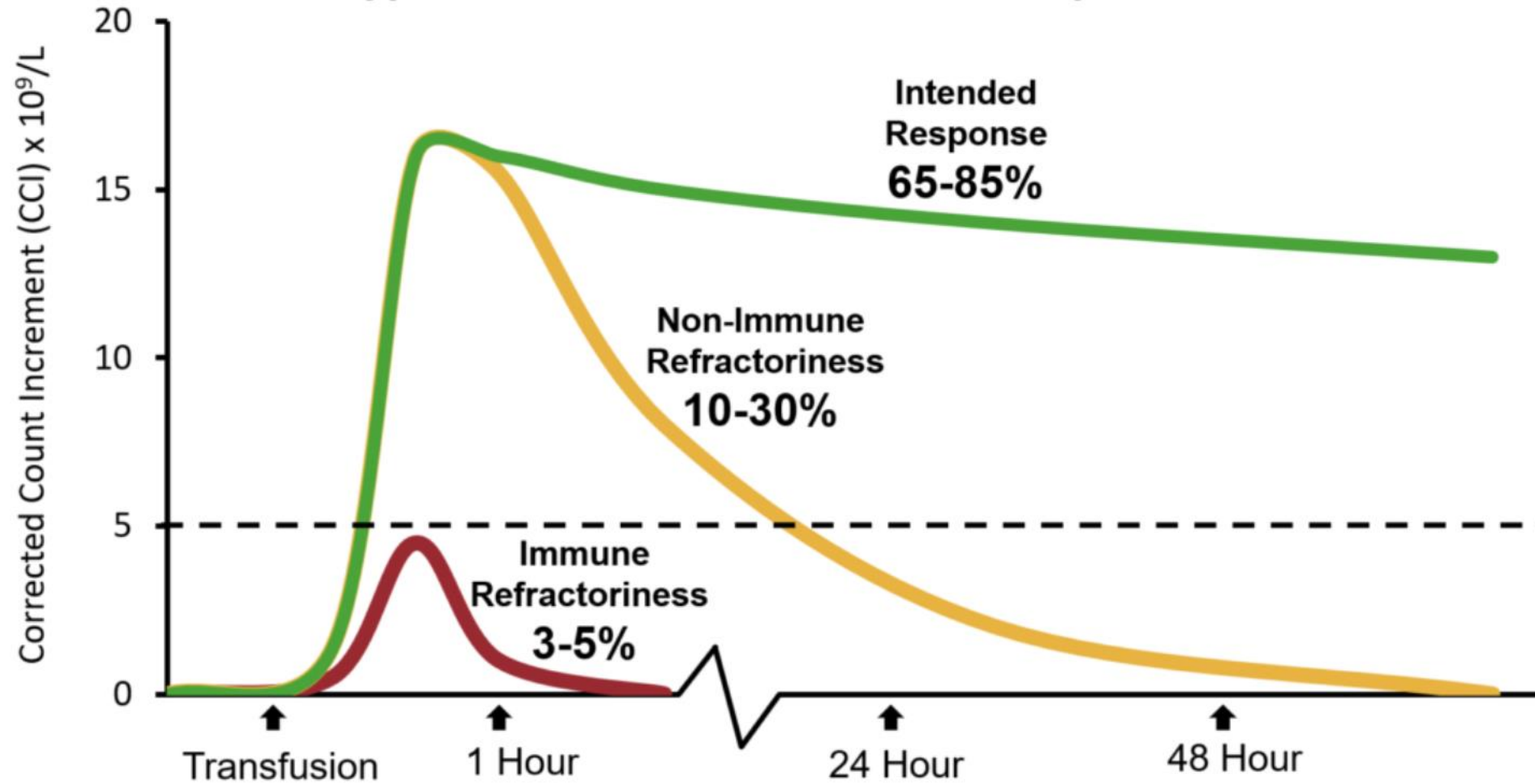
ServicesResearchTrainingAbout us

Immuno Polymorphism Database

OverviewIMGT/HLAKIRMHCHPAESTDABContactSupport

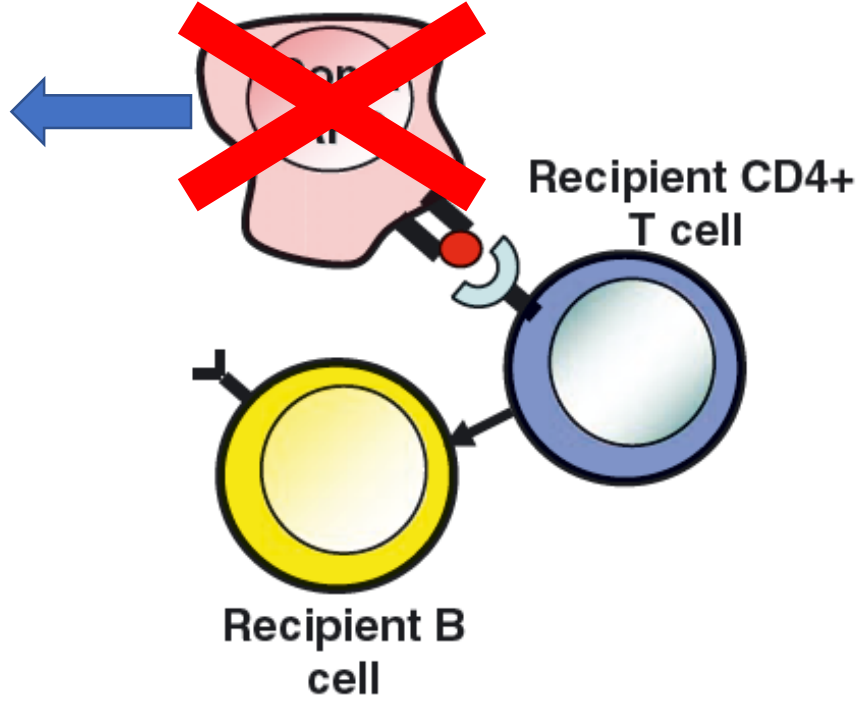
System	Antigen	Original names	Glycoprotein	CD	Reference	HPA-15	HPA-15a HPA-15b	Gov ^b Gov ^a	CD109	CD109	Kelton et al, Blood 75:2172-6 (1990) Smith et al, Blood 86:2807-14 (1995)
HPA-1	HPA-1a HPA-1b	Zw ^a , pI ^{A1} Zw ^b , pI ^{A2}	GPIIIa	CD61	van Loghem et al, Vox Sang 4:161-9 (1959) Shulman et al, J Clin Invest 40:1597-1620 (1961) van der Weerd et al, Vox Sang 8:513-30 (1963)						
HPA-2	HPA-2a HPA-2b	Ko ^b Ko ^a , Sib ^a	GPIbalpha	CD42b	van der Weerd et al, Proc. 8th Congress European Society of Haematology, Vienna 1961. Karger, Basel .P379 van der Weerd Thesis 1965, University of Amsterdam		HPA-16bw	Duv ^a	GPIIIa	CD61	Jallu et al, Blood 99:4449-56 (2002)
HPA-3	HPA-3a HPA-3b	Bak ^a , Lek ^a Bak ^b	GPIIb	CD41	von dem Borne et al, Vox Sang 39:113-20 (1980) Kickler et al, Blood 71:894-8 (1988)		HPA-17bw	Va ^a	GPIIb/IIIa	CD61	Kekomaki et al, Transfus Med 2:27-33 (1992)
HPA-4	HPA-4a HPA-4b	Yuk ^b , Pen ^a Yuk ^a , Pen ^b	GPIIIa	CD61	Friedman et al, Blood 65:1412-5 (1985) Shibata et al, Vox Sang 50:177-80 (1986) Shibata et al, Vox Sang 51:334-6 (1986)		HPA-18bw	Cab ^a	GPIa	CD49b	Bertrand et al, Transfusion 49:2076-83 (2009)
HPA-5	HPA-5a HPA-5b	Br ^b , Zav ^b Br ^a , Zav ^a , Hc ^a	GPIa	CD49b	Kiefel et al, Vox Sang 54:101-6 (1998) Kiefel et al, Blood 73:2219-23 (1989) Santoso et al, Br J Haematol 72:191-8 (1989)		HPA-19bw	Sta	GPIIIa	CD61	Peterson et al, Transfusion (2009)
	HPA-6bw	Ca ^a , Tu ^a	GPIIIa	CD61	Kekomaki et al, Br J Haematol 83:306-10 (1993) McFarland et al, Blood 81:3318-23 (1993)		HPA-20bw	Kno	GPIIb	CD41	Peterson et al, Transfusion (2009)
	HPA-7bw	Mo ^a	GPIIIa	CD61	Kuijpers et al, Blood 81:70-6 (1993)		HPA-21bw	Nos	GPIIIa	CD61	Peterson et al, Transfusion (2009)
	HPA-8bw	Sr ^a	GPIIIa	CD61	Kroll et al, Blood 76:2296-302 (1990)		HPA-22bw	Sey	GPIIb	CD41	Peterson et al, Transfusion (2012)
	HPA-9bw	Max ^a	GPIIb	CD41	Noris et al, Blood 86:1019-26 (1995)		HPA-23bw	Hug	GPIIIa	CD61	Peterson et al, Transfusion (2012)
	HPA10bw	La ^a	GPIIIa	CD61	Peyruchaud et al, Blood 89:2422-8 (1997)		HPA-24bw	Cab2 ^{a+}	GPIIb	CD41	Jallu et al, Transfusion (2011)
	HPA11bw	Gro ^a	GPIIIa	CD61	Simsek et al, Vox Sang 67:302-6 (1994)		HPA-25bw	Swi ^a	GPIa	CD49b	Kroll et al, Transfusion (2011)
	HPA12bw	Iy ^a	GPIIbeta	CD42c	Kiefel, et al, Vox Sang 69:250-4 (1995)		HPA-26bw	Sec ^a	GPIIIa	CD61	Sachs et al, Thromb Haemost (2012)
	HPA13bw	Sit ^a	GPIa	CD49b	Santoso et al, Blood 94:4103-11 (1999)		HPA-27bw	Cab ^{3a+}	GPIIb	CD41	Jallu et al, Transfusion (2013)
	HPA14bw	Oe ^a	GPIIIa	CD61	Santoso et al, Blood 99:1205-14 (2002)		HPA-28bw	War	GPIIb	CD41	Poles et al, published online (2013)
							HPA-29bw	Kha ^b	GPIIIa	CD61	Sullivan et al, Transfusion (2015)

Typical Platelet Transfusion Responses



Direct Allorecognition

EVRENSEL
LÖKOSİT
AZALTMA
ÖNLEMLERİ



LÖKOSİT
AZALTMANIN
ETKİNLİĞİ
YOK

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LEUKOCYTE REDUCTION AND ULTRAVIOLET B IRRADIATION OF PLATELETS TO PREVENT ALLOIMMUNIZATION AND REFRACTORINESS TO PLATELET TRANSFUSIONS

THE TRIAL TO REDUCE ALLOIMMUNIZATION TO PLATELETS STUDY GROUP*

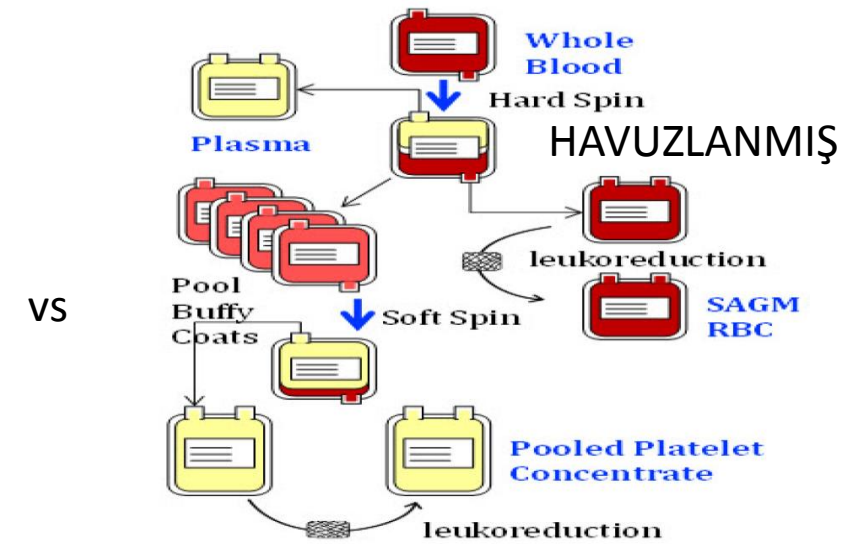


Table 1. Patient Donor Exposures in the TRAP Study.*

Variable	Unmodified Pooled Platelet Concentrates (Control)†	Ultraviolet B–Irradiated, Pooled Platelet Concentrates†	Filtered, Pooled Platelet Concentrates†	Filtered Platelets Obtained by Apheresis‡	Relative Increase in Donor Exposures
Platelets — no.					
Transfusions/patient	14±11	16±13	15±11	13±8	
Median donor exposures/patient	66	72	72	11	
Corrected count increment	12,800±4900	11,200±4600	12,700±5700	14,700±5200	
	↓	↓		↓	
TROMBOSİT REFRAKTERLİĞİ	%13	%7		%8	

Apheresis versus whole-blood-derived platelets: pros and cons

P.F. van der Meer

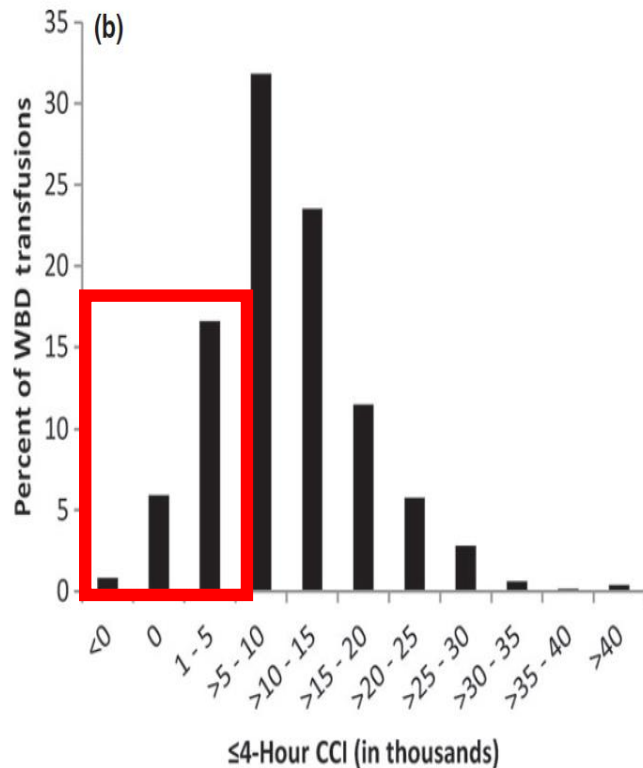
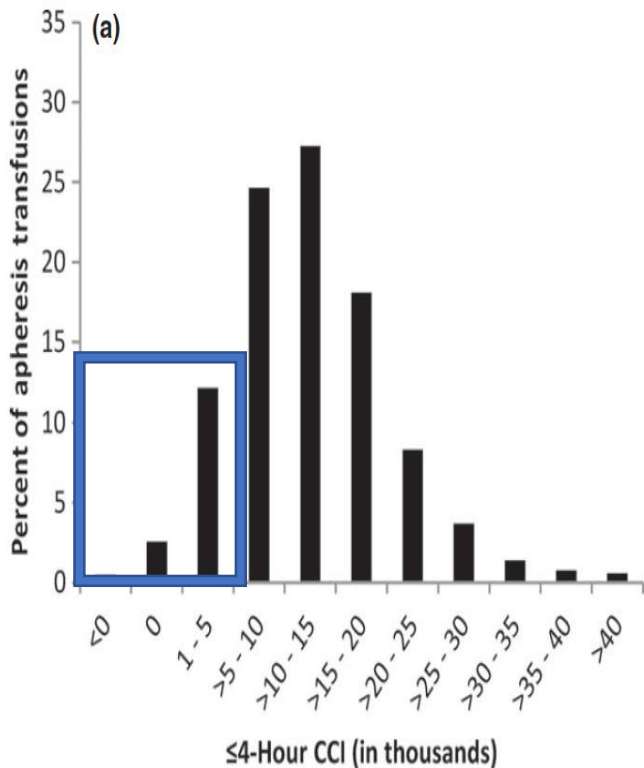
Sanquin Blood Bank, Department of Product and Process Development, Plesmanlaan 125, 1066 CX Amsterdam, PO Box 9713, 1006 AC Amsterdam, The Netherlands

	Whole blood		
	PRP method	BC method	Apheresis
Anticoagulant	Citrate-phosphate-dextrose	Citrate-phosphate-dextrose	(Acid)-citrate-dextrose
Centrifugation	Soft spin, followed by hard spin	Hard spin, followed by soft spin	In-process centrifugation
Pooling	Post-storage	Pre-storage	Not applicable
Storage	Single unit	Pooled	Single unit
Leukoreduction	Post-storage	Pre-storage	Pre storage
Number of units for one adult dose	4–6, sometimes up to 10	4 or 5	No pooling
Storage time	5 days	7 days	7 days
Risk of bacterial transmission	At least 2-fold higher as apheresis	Low	Low
Risk of viral transmission	At least 2-fold higher as apheresis	At least 2-fold higher as apheresis	Low
Risk of vCJD transmission	At least 2-fold higher as apheresis	At least 2-fold higher as apheresis	Low
Recovery and survival	Adequate	Adequate	Adequate
Corrected count increments	Adequate	Adequate	Adequate
Alloimmunization and refractoriness	Not different	Not different	Not different
Acute reactions, FNTR	Not different	Not different	Not different
TRALI	Not different	Not different	Not different
Donor adverse reactions	More	More	Few

ORIGINAL PAPER

Clinical and laboratory correlates of platelet alloimmunization and refractoriness in the PLADO trial

J. R. Hess,¹ F. L. Trachtenberg,² S. F. Assmann,² D. J. Triulzi,³ R. M. Kaufman,⁴ R. G. Strauss,^{3,5} S. Granger² & S. J. Slichter^{1,6}



Category	Reference Category	Odds Ratio (95% CI)	P-value
Platelet Factors			
Platelet Source			0.15 (1 df)
WBD	Apheresis	1.69 (0.83–3.44)	0.15
Treatment Dose ^a			0.04 (2 df)
Low Dose	Medium Dose	2.28 (1.03–5.04)	0.04
High Dose	Medium Dose	0.92 (0.37–2.33)	0.86
ABO Match ^b			0.06 (2 df)
Minor mismatch but no major mismatch	ABO-identical	1.73 (0.72–4.17)	0.22
Major mismatch	ABO-identical	0.60 (0.28–1.29)	0.19
Patient Factors			
Gender/Pregnancy			0.007 (2 df)
Female, nulliparous	Male	0.49 (0.11–2.29)	0.36
Female, ≥1 pregnancy	Male	2.78 (1.37–5.63)	0.005
Randomization			0.02 (2 df)
Stratum			
Auto/Syngeneic SCT	Allo SCT	0.66 (0.27–1.58)	0.35
Chemotherapy	Allo SCT	2.12 (0.96–4.70)	0.06
Age Group			0.75 (5 df)
0–19 years	50–59 years	0.55 (0.11–2.75)	0.46
20–29 years	50–59 years	1.07 (0.27–4.19)	0.93
30–39 years	50–59 years	1.07 (0.35–3.42)	0.91
40–49 years	50–59 years	1.58 (0.64–3.93)	0.33
≥ 60 years	50–59 years	0.86 (0.32–2.36)	0.77

KIZILAY-SAĞLIK MÜDÜRLÜĞÜ-TRAKYA ÜTF KAN ÜRÜNLERİ TEMİN SORUNLARI İLGİLİ TOPLANTI SONUÇLARI NİSAN 2019

ÜRÜN	İSTENEN	KARŞILANAN	YÜZDE
HAVUZ TROMBOSİT	871	775	%87
ERİTROSİT	8552	5620	%65
TDP	4265	4265	%100
AFEREZ TROMBOSİT	682	296	%40
KRİYO	490	435	%88

EN İYİ ALLOİMMUNİZASYON TEDAVİSİ= ALLOİMMUNİZASYON GELİŞMEMESİ

KORUYUCU ÖNLEMLER

1- EVRENSEL LÖKOSİT AZALTILMASI

The New England
Journal of Medicine

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LEUKOCYTE REDUCTION AND ULTRAVIOLET B IRRADIATION OF PLATELETS TO PREVENT ALLOIMMUNIZATION AND REFRACTORINESS TO PLATELET TRANSFUSIONS

THE TRIAL TO REDUCE ALLOIMMUNIZATION TO PLATELETS STUDY GROUP*

Table 2 Summary of results of the TRAP)

	Controls: untreated pooled random donor platelets	Leukoreduced pooled random donor platelets	Leukoreduced single donor apheresis platelets
Number of patients	131	137	132
Alloimmunization	45%	18% ($P < 0.001$)*	17% ($P < 0.001$)*
Refractoriness	16%	7% ($P = 0.03$)*	8% ($P = 0.06$)*
Alloimmunization and refractoriness	13%	3% ($P = 0.004$)*	4% ($P = 0.01$)*

Adapted from reference 40.

*as compared to control group.

Universal prestorage leukoreduction in Canada decreases platelet alloimmunization and refractoriness

BLOOD, 1 JANUARY 2004 • VOLUME 103, NUMBER 1

Matthew D. Seftel, Gershon H. Grove, Tanya Petraszko, W. Barrett Benny, Alan Le, Chao-Yong Lee, John J. Spinelli, Heather J. Sutherland, Peter Tsang, and Donna E. Hogge

ALLOİMMUNİZASYON

	Pre-ULR group* (%)	Post-ULR group* (%)	P
Overall	61/315 (19)	21/302 (7)	< .001§
Chemotherapy or supportive care	26/116 (22)	11/117 (9)	.011§
ALL	2/20 (10)	1/11 (9)	.99
AML	19/84 (23)		
Supportive care	5/12 (42)		
SCT	35/199 (18)		
ALLO RD	10/75 (13)		
ALLO VUD	11/39 (28)		
AUTO BM	7/39 (18)		
AUTO PB	7/46 (15)		
Nulliparous/nontransfused†	16/144 (11)		
Parous/transfused‡	39/154 (25)		
Parous only	7/46 (15)		
Transfused only	22/75 (29)		
Both	6/26 (23)	7/25 (28)	.75

- 1- LÖKOSİT AZALTMA
- 2- GEBELİK ÖYKÜSÜ
- 3- TRANSFÜZYON ÖYKÜSÜ
- 4- TEDAVİ TİPİ

REFRAKTERLİK

	Pre-ULR group* (%)	Post-ULR group* (%)	P
Overall refractoriness†	27/315 (40)	68/302 (23)	< .001§
Overall alloimmune refractoriness‡	44/315 (14)	12/302 (4)	< .001§
Chemotherapy or supportive care patients	19/116 (16)	8/117 (7)	.038§
ALL	1/20 (5)	1/11 (9)	.99
AML	13/84 (16)	7/97 (7)	.097
Supportive care	5/12 (42)	0/9 (0)	.045
SCT	25/199 (13)	4/185 (2)	.003§
ALLO RD	7/75 (9)	1/72 (1)	.063
ALLO VUD	8/39 (21)	2/32 (6)	.102
AUTO BM	5/39 (13)	1/24 (4)	.394
AUTO PB	5/46 (11)	0/57 (0)	.016
Nulliparous/nontransfused†	12/144 (8)	3/152 (2)	.021§
Parous/transfused‡	28/154 (18)	9/139 (7)	.005§
Parous only	5/46 (11)	5/59 (9)	.75
Transfused only	15/75 (20)	0/53 (0)	< .001
Both	6/26 (23)	3/22 (12)	.47

EN İYİ ALLOİMMUNİZASYON TEDAVİSİ= ALLOİMMUNİZASYON GELİŞMEMESİ

KORUYUCU ÖNLEMLER

2- TRANSFÜZYON EŞİĞİ/ TRANSFÜZYON YAPMA(MA)/PROFİLAKTİK TRANSFÜZYON


Guidelines for the Use of Platelet Transfusions A British Society for Haematology Guideline

GERİ DÖNEBİLECEK KEMİK İLİĞİ YETERSİZLİĞİ TABLOSU

- Give prophylactic platelet transfusions (platelet transfusions to patients who do not have clinically significant bleeding [WHO grade 0 or 1] and do not require a procedure) to patients with reversible bone marrow failure receiving intensive chemotherapy or undergoing allogeneic HSCT to maintain a platelet count at or above $10 \times 10^9/L$ (1B)
- Use only one adult dose (one unit) routinely for prophylactic platelet transfusions (1A)
- Consider not giving prophylactic platelet transfusions to well patients with no evidence of bleeding who have had an autologous stem cell transplant (2B)
- Consider increasing the threshold for prophylactic platelet transfusion to between 10 and $20 \times 10^9/L$ in patients judged to have additional risk factors for bleeding. Individual review is required. (2C)

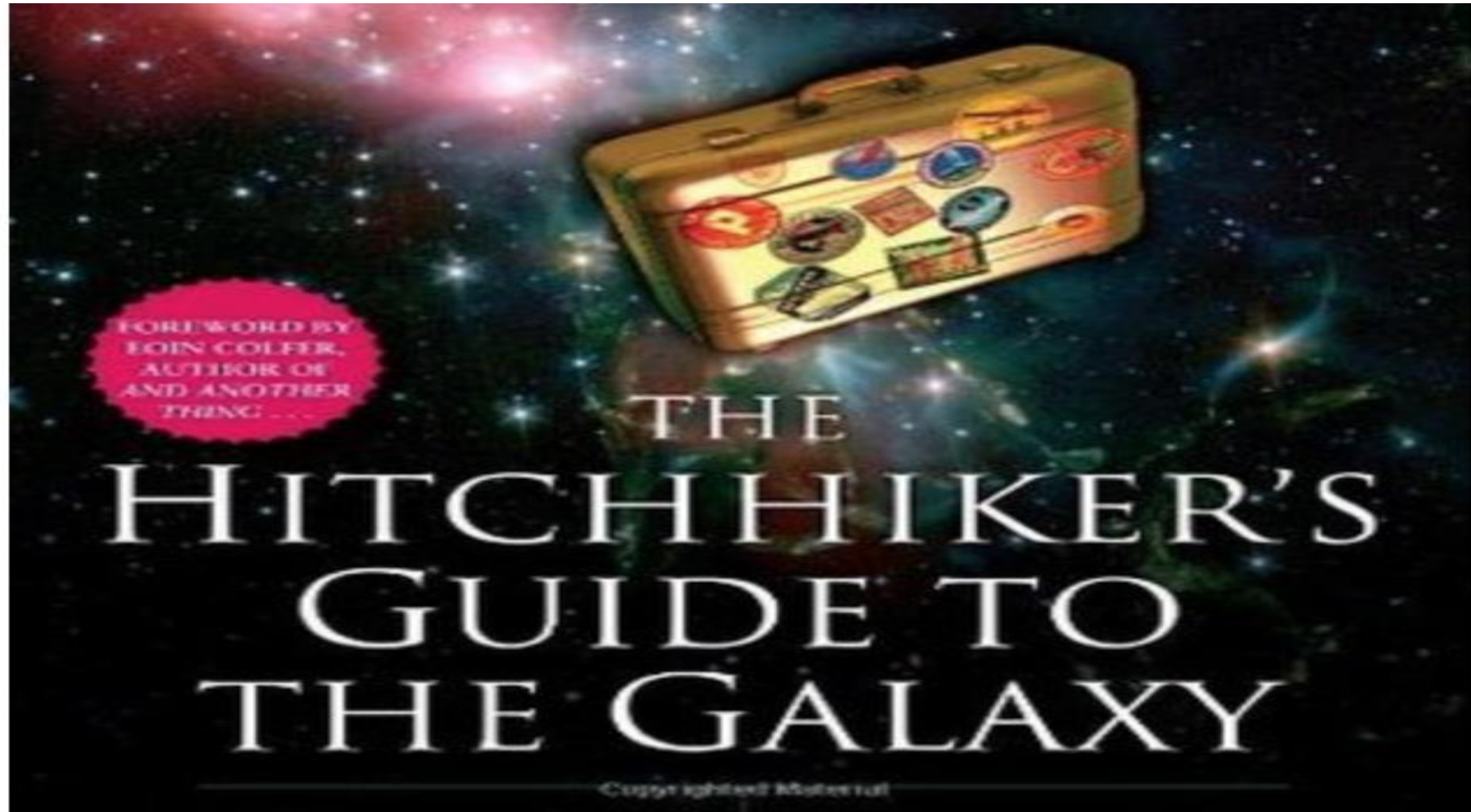
GERİ DÖNÜŞ BEKLENMEYEN KEMİK İLİĞİ YETERSİZLİĞİ TABLOSU

- Use a 'no prophylactic platelet transfusion' strategy for asymptomatic patients with chronic bone marrow failure (including those taking low dose oral chemotherapy or azacitidine) (2B)
- Give prophylactic platelet transfusions to patients with chronic bone marrow failure receiving intensive treatment (1B)
- Manage patients with chronic bleeding of WHO grade 2 or above individually, according to the severity of their symptoms and signs. Consider a strategy of prophylaxis (e.g. twice a week) (2C)

- 
- TROMBOSİT VERDİM YÜKSELMİYOR???
 - TAZE (<48 SAAT), ABO UYUMLU VER



DON'T PANIC!!!



Guidelines for the Use of Platelet Transfusions A British Society for Haematology Guideline

Lise J Estcourt¹, Janet Birchall (Writing Group Chair)², Shubha Allard (BCSH Task Force Member)³, Stephen J Bassey⁴, Peter Hersey⁵, J Paul Kerr⁶, Andrew D Mumford⁷, Simon J Stanworth⁸, Hazel Tinegate⁹ on behalf of the British Committee for Standards in Haematology.

Platelet Transfusion for Patients With Cancer: American Society of Clinical Oncology Clinical Practice Guideline Update

Charles A. Schiffer, Kari Bohlke, Meghan Delaney, Heather Hume, Anthony J. Magdalinski, Jeffrey J. McCullough, James L. Omel, John M. Rainey, Paolo Rebulla, Scott D. Rowley, Michael B. Troner, and Kenneth C. Anderson



Professional Education

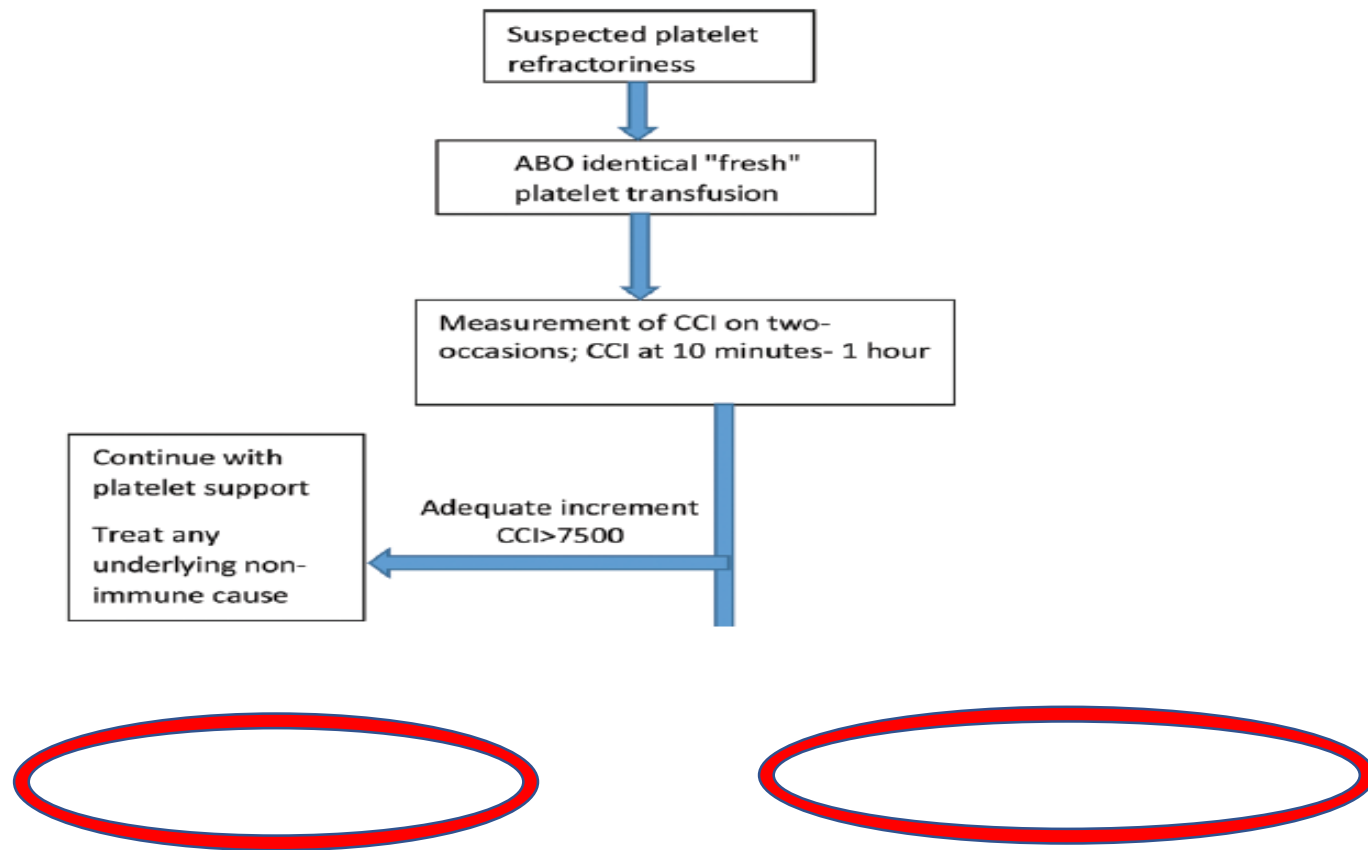
CLINICAL GUIDE TO TRANSFUSION

CHAPTER 18. PLATELET TRANSFUSION, ALLOIMMUNIZATION AND MANAGEMENT OF PLATELET REFRACTORINESS

Chapter 18: Platelet Transfusion, Alloimmunization and Management of Platelet Refractoriness

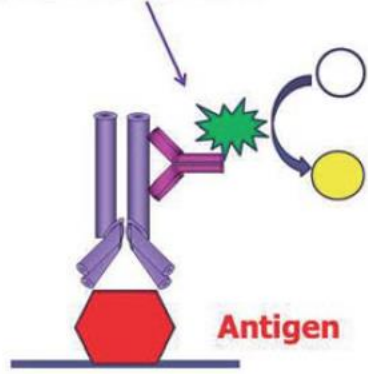
Platelet count increment $<5\text{--}10 \times 10^9$ cells per litre ~1h after transfusion, on 2 occasions

Consider etiology with history, physical, medication, etc.



ELISA

Enzyme labeled AHG

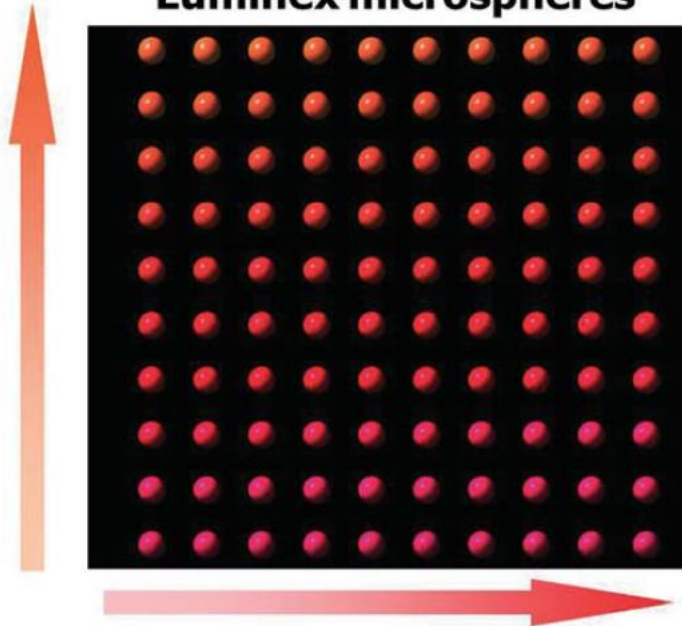


Antigen

Microtiter well

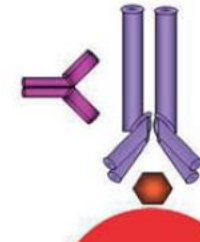


Luminex microspheres



Bead Assay

Fluorochrome labeled AHG



Purified antigen

Microsphere

HLA/HPA
NASIL TESPİT EDELİM?

Luminex Analysis



Table 1 HLA-match grade classification

Grade	Degree of matching
A	All 4 donor HLA loci are identical to the recipient
BIU	Only 3 antigens are detected in donor and all 3 detected antigens are identical to the recipient
BIX	2 HLA antigens are identical to the recipient and 1 HLA antigen is incompatibility

- 29 HASTA PLT ALLOIMMUNIZE
- 7000 DONOR HLA DATABASE
- SADECE 39 HLA UYUMLU (2A+2B)
- AMA 1426 PERMISSABLE MATCH

Petz et al, Transfusion, 2000

Asnok Nambiar, Rene J. Duquesnoy, Sharon Adams, Tingdong Zhao, Jaime Obitas, Susan Leitman, David Stroncek, and Francesco Marincola

BLOOD, 15 FEBRUARY 2006 • VOLUME 107, NUMBER 4

HPA systems on the ITGB3 gene

Exon #	3		4			5	10			11		12			
Nucleotide	176§	263	487	497	506	662	1297	1544	1818	1909-1911§	1942	1960	1976	1984	
Variation	T>C	G>A	A>C	C>T	G>A	C>T	C>G	G>A	G>T	AAG>deletion	C>T	G>A	G>A	C>T	
Amino acid	L59(33)P	R88(62)Q	K163(137)Q	T166(140)I	R169(143)Q	T221(195)M	P433(407)A	R515(489)Q	K606(580)N	K637(611)dele	R648(622)W	E654(628)K	R659(633)H	R662(636)C	
Antigen	HPA-1□	HPA-10w	HPA-19w	HPA-16w	HPA-4□	HPA-17w	HPA-7w	HPA-6w	HPA-26bw	HPA-14w	HPA-23bw	HPA-21w	HPA-11w	HPA-8w	

HPA systems on the ITGA2B gene

Exon	5	15	20	23	26		
Nucleotide	584	1508	1949	2311	2602‡	2614	2621‡
variation	A>C	G>A	C>T	G>T	G>A	C>A	T>G
Amino acid	K195(164)T	S503(472)N	T650(619)M	V771(740)L	V868(837)M	L872(841)M	I874(843)S
Antigen	HPA-22bw	HPA-24bw	HPA-20w	HPA-28bw	HPA-9w	HPA-27bw	HPA-3□

HPA systems on the ITGA2 gene

Exon	7 ^s	13	17	20	28
Nucleotide	759*¶†	1600	2235¶	2483	3347†
variation	C>T	G>A	G>T	C>T	C>T
Amino acid	Silent mutation	E534(505)K	Q745(716)H	T828(799)M	T1116(1087)M
Antigen		HPA-5□	HPA-18w	HPA-13w	HPA-25bw

HPA system on the CD109 gene

Exon	19
Nucleotide	2108
variation	C>A
Amino acid	S703(682)Y
Antigen	HPA-15□

HPA system on the GPIb α gene

Exon	2
Nucleotide	482
variation	C>T
Amino acid	T161(145)M
Antigen	HPA-2□

HPA system on the GPIb β gene

Exon	2
Nucleotide	119
variation	G>A
Amino acid	G40(15)E
Antigen	HPA-12w

- # Exons are referred to NG_008332.2
- s Not related to any alloimmune response
- § HPA-14 has both nucleotide changes
- Biallelic antigen systems
- ‡ HPA-9bw has both nucleotide changes
- * HPA-5a allele2
- ¶ HPA-18bw has both nucleotide changes
- † HPA-25bw has both nucleotide changes

TROMBOSİT CROSS-MATCH???

Strength of Reaction



PLT cross-match techniques

- Flow
 - Washed intact PLTs. Antibody detection by FITC-labeled anti-IgG

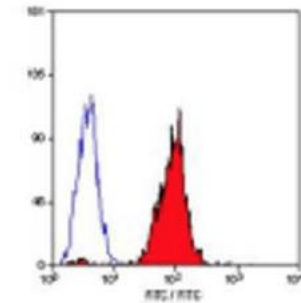


Table 3: Advantages and disadvantages of different methods to support platelet transfusions in refractory patients

Advantages	Disadvantages
ABO-identical platelets	
Easily available	Not useful in refractoriness due to HLA/HPA antibodies

HLA: Human leukocyte antigen, HPA: Human platelet antigen

CLINICAL GUIDE TO TRANSFUSION

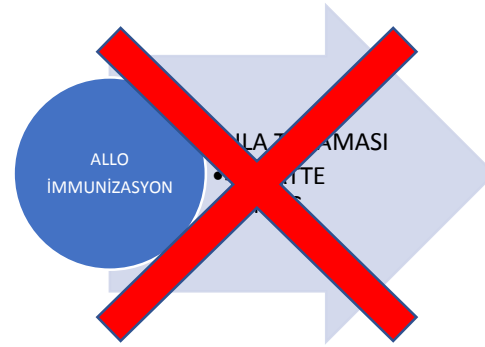
CHAPTER 18. PLATELET TRANSFUSION, ALLOIMMUNIZATION AND MANAGEMENT OF PLATELET REFRACTORINESS

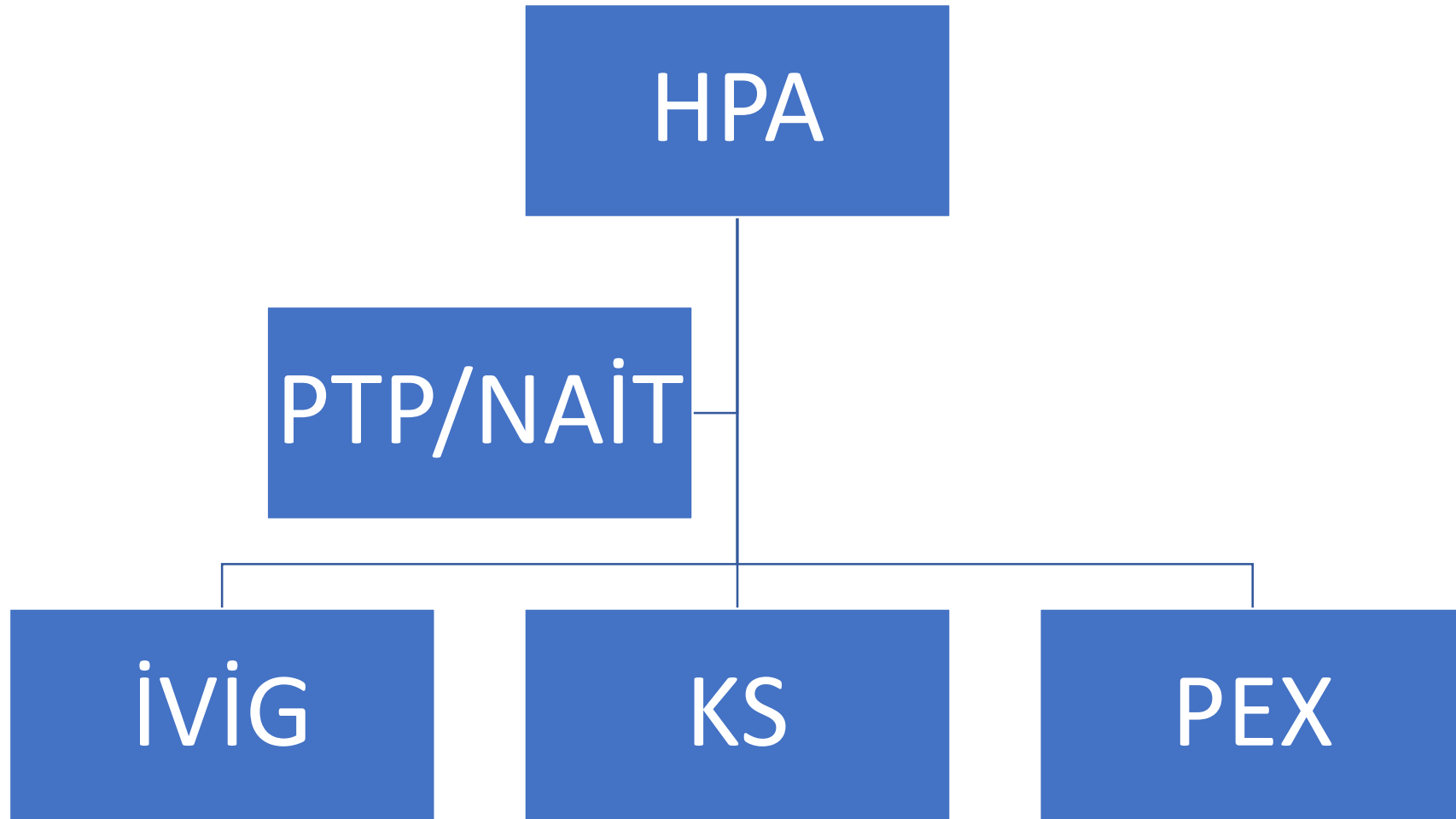
The International Collaboration for Transfusion Medicine Guidelines (ICTMG) made the following recommendations for management of patients with hypoproliferative thrombocytopenia who are refractory to platelet transfusions.⁴

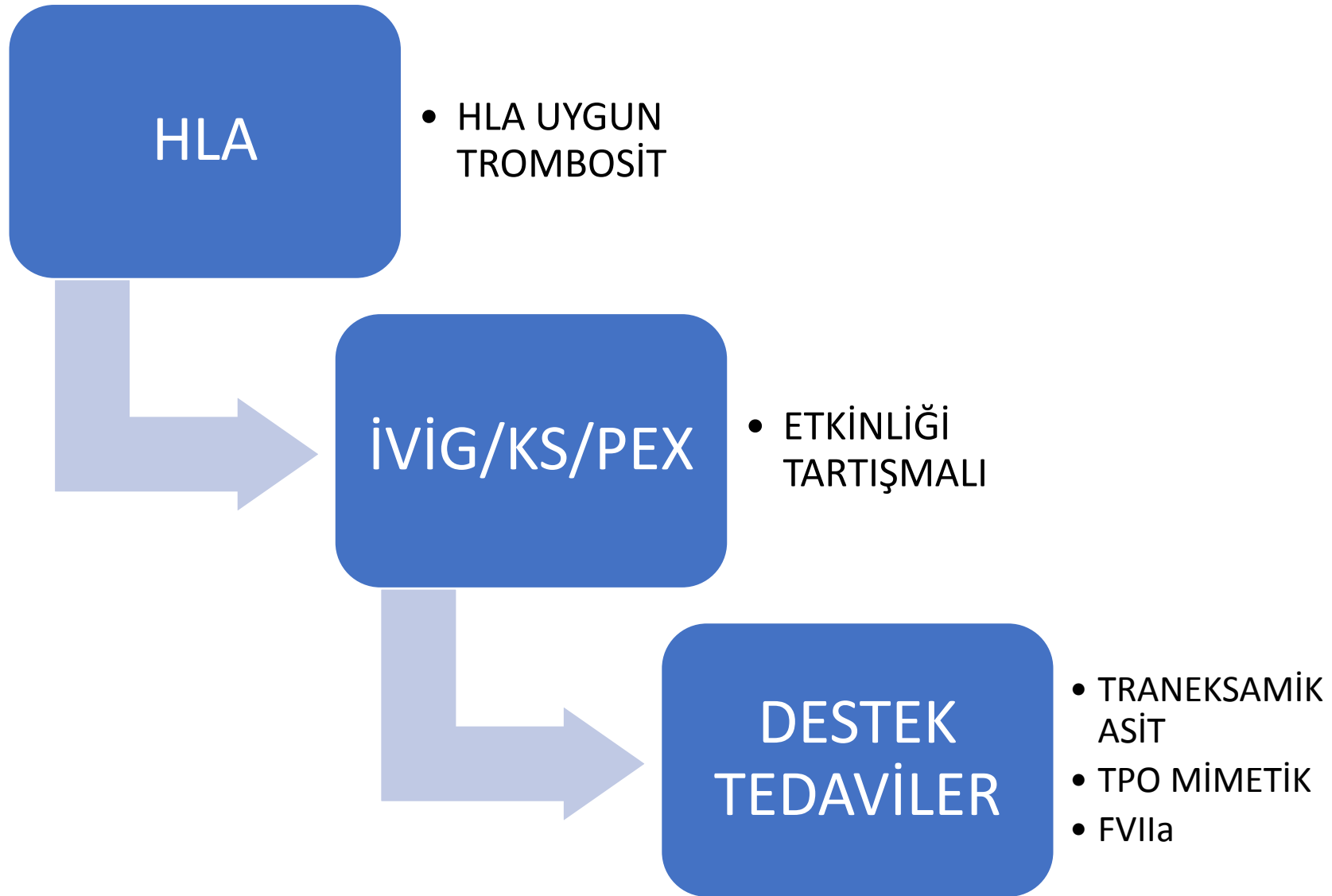
- In setting of class I HLA antibodies, should probably receive class I HLA-selected or crossmatch-selected platelet transfusions (weak level of evidence)
- In setting of HPA antibodies, should probably receive HPA-selected or crossmatch-selected platelet transfusions (very weak level of evidence)
- In setting of non-immune causes, should probably not receive HLA-selected or crossmatch-selected platelet transfusions (very weak level of evidence)

Platelet refractoriness – practical approaches and ongoing dilemmas in patient management

NHSBT practice is to provide HLA-selected platelet transfusions within hours of receipt of the sample/request. The laboratory tests (antibody screening and HLA typing) can be completed within 3–4 h and NHSBT has a pool of HLA-typed apheresis donors to select the appropriate product. In a situation of active bleeding, common practice if the patient has not been HLA typed or the antibody results are not available would be to transfuse ABO-compatible apheresis platelets. Some institutions and published guidance (Slichter, 2007; Hod & Schwartz, 2008) have suggested employing platelet ‘drips’, i.e. low dose continuous platelet infusion, to persistently refractory bleeding patients. However, the use of





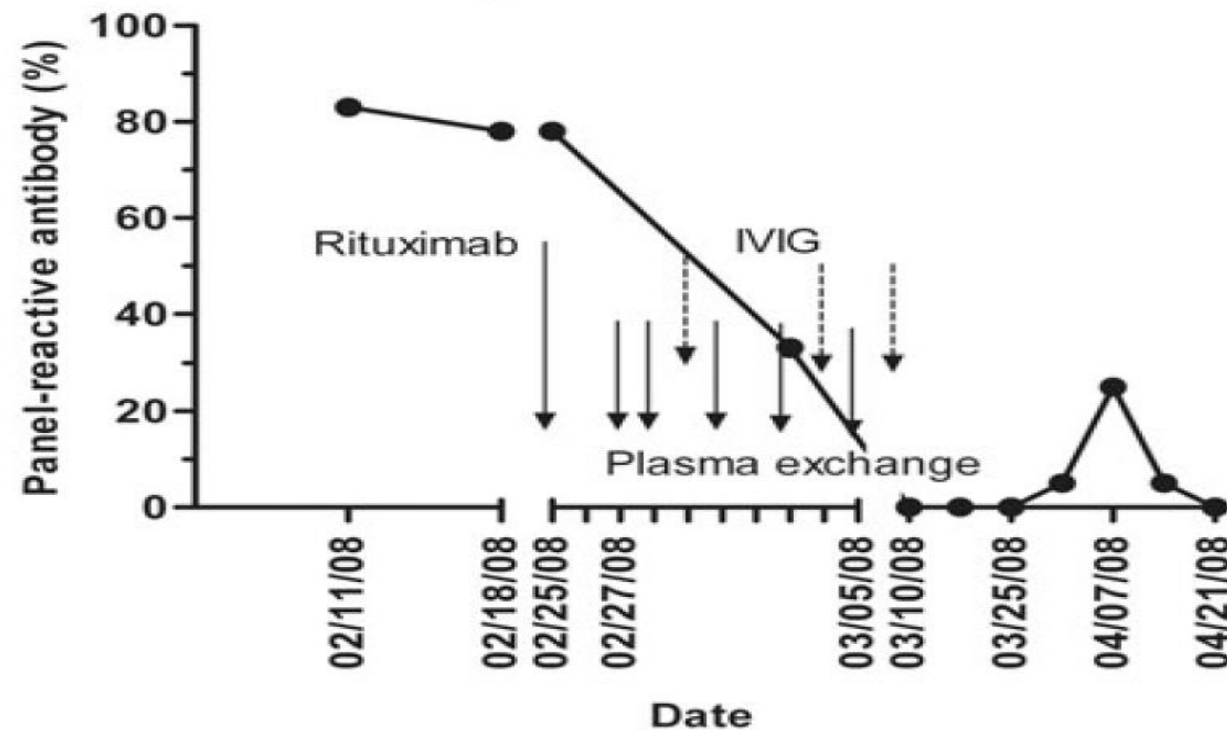


CASE REPORT

Rituximab, plasma exchange and intravenous immunoglobulins as a new treatment strategy for severe HLA alloimmune platelet refractoriness

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New treatment strategy for HLA immune PLT refractoriness





TEŞEKKÜRLER

