7^ Conferenza Nazionale dei Servizi Trasfusionali
Vicenza | 24-26 maggio 2023
SIMTI

Le indagini piastriniche sierologiche e molecolari: dal laboratorio alla clinica

Antonella Matteocci

A.O. S. CAMILLO FORLANINI – ROMA

UOC MEDICINA TRASFUSIONALE E CELLULE STAMINALI

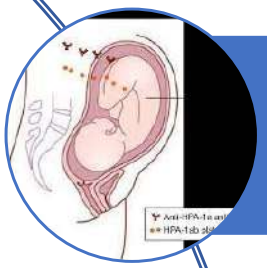
UOS Produzione Interaziendale Emocomponenti e Immunoematologia di II livello

La sottoscritta, **ANTONELLA MATTEOCCI** in qualità di Relatrice

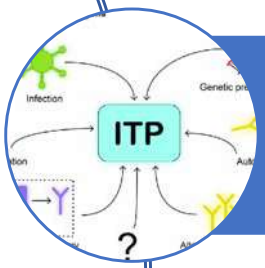
dichiara che

nell'esercizio della Sua funzione e per l'evento in oggetto, ***NON È*** *in alcun modo portatrice di interessi commerciali propri o di terzi; e che gli eventuali rapporti avuti negli ultimi due anni con soggetti portatori di interessi commerciali non sono tali da permettere a tali soggetti di influenzare le sue funzioni al fine di trarne vantaggio.*

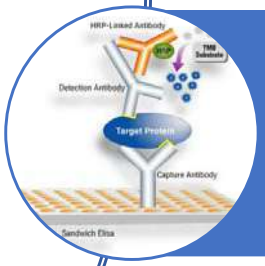
INTRODUZIONE



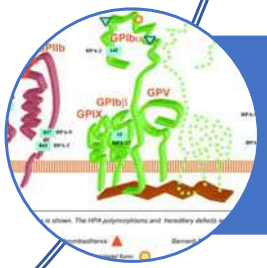
L’alloimmunizzazione contro gli antigeni piastrinici può causare complicanze nel setting trasfusionale o in ambito ostetrico/neonatale.



Le glicoproteine piastriniche sono implicate anche nelle piastrinopenie immuni (ITP) e farmaco-indotte (DITP).

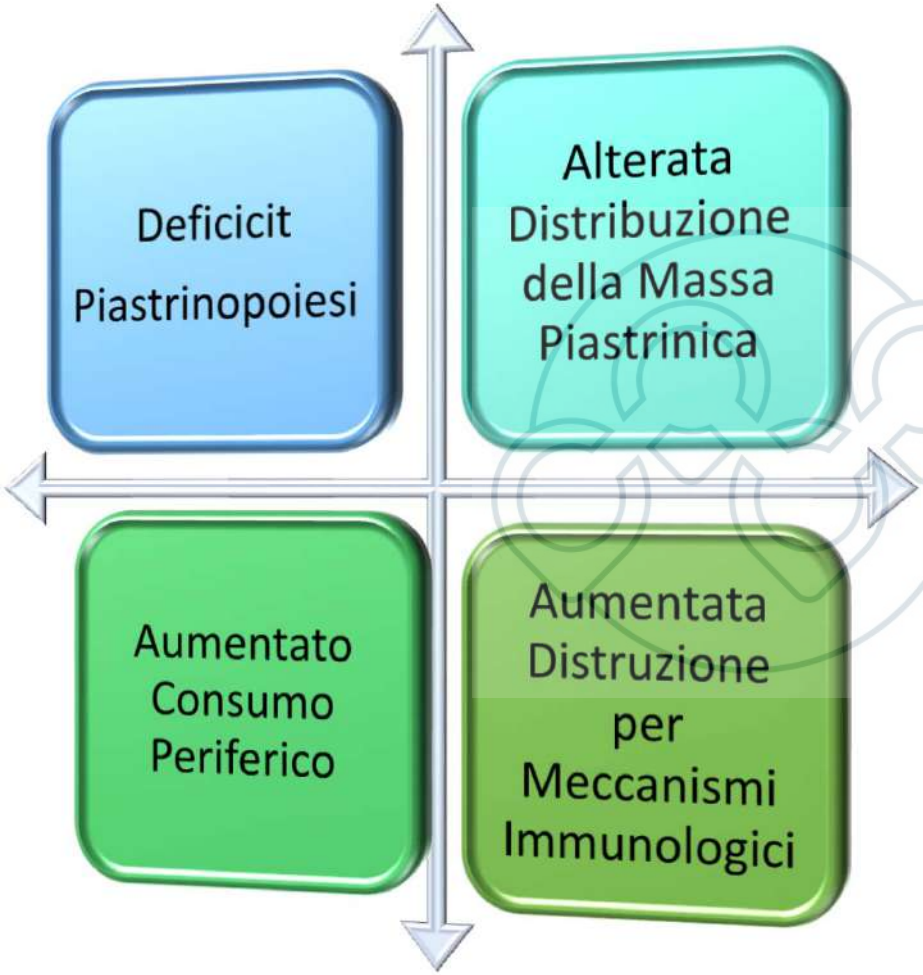


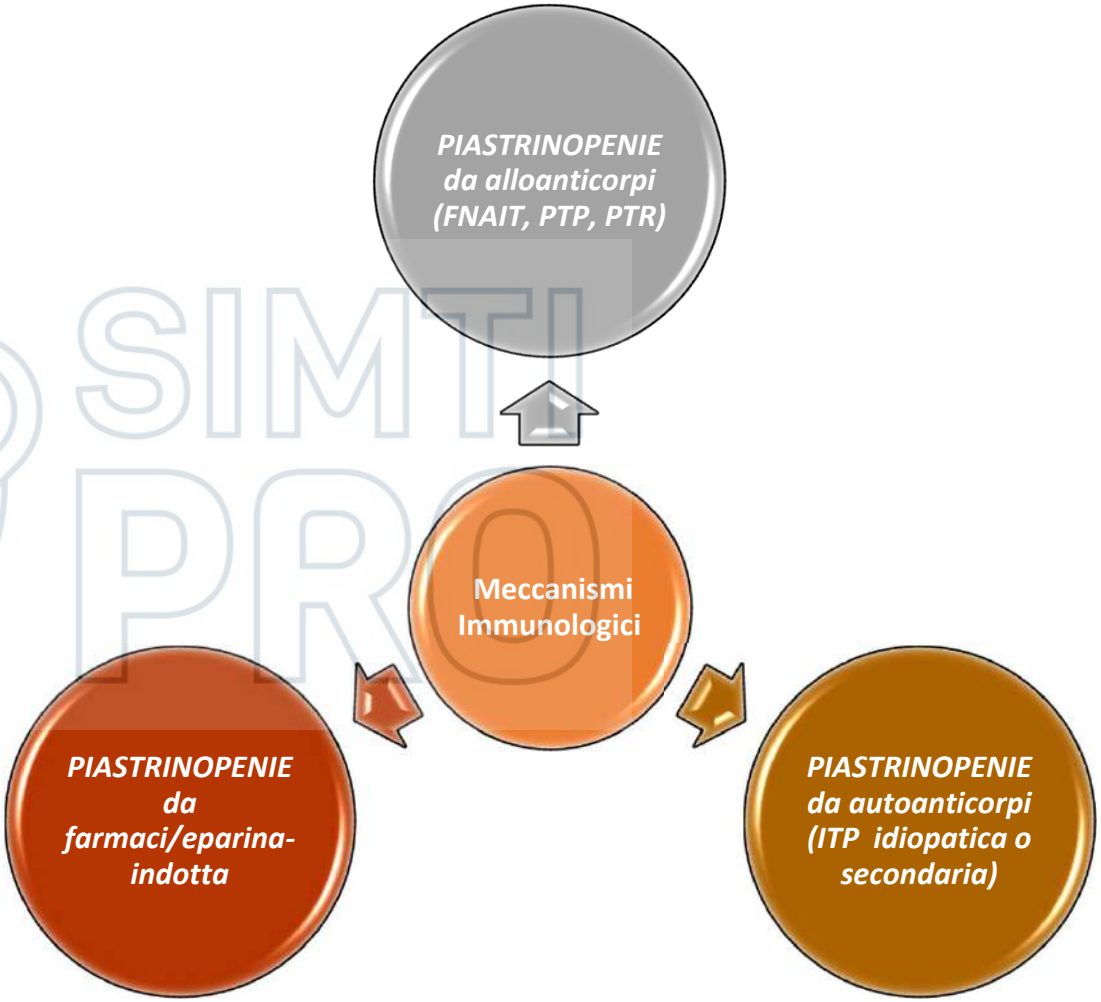
Le strategie diagnostiche si avvalgono di indagini sierologiche e molecolari che supportano il corretto inquadramento clinico delle piastrinopenie immuno-mediate e l’appropriata gestione terapeutica e trasfusionale.



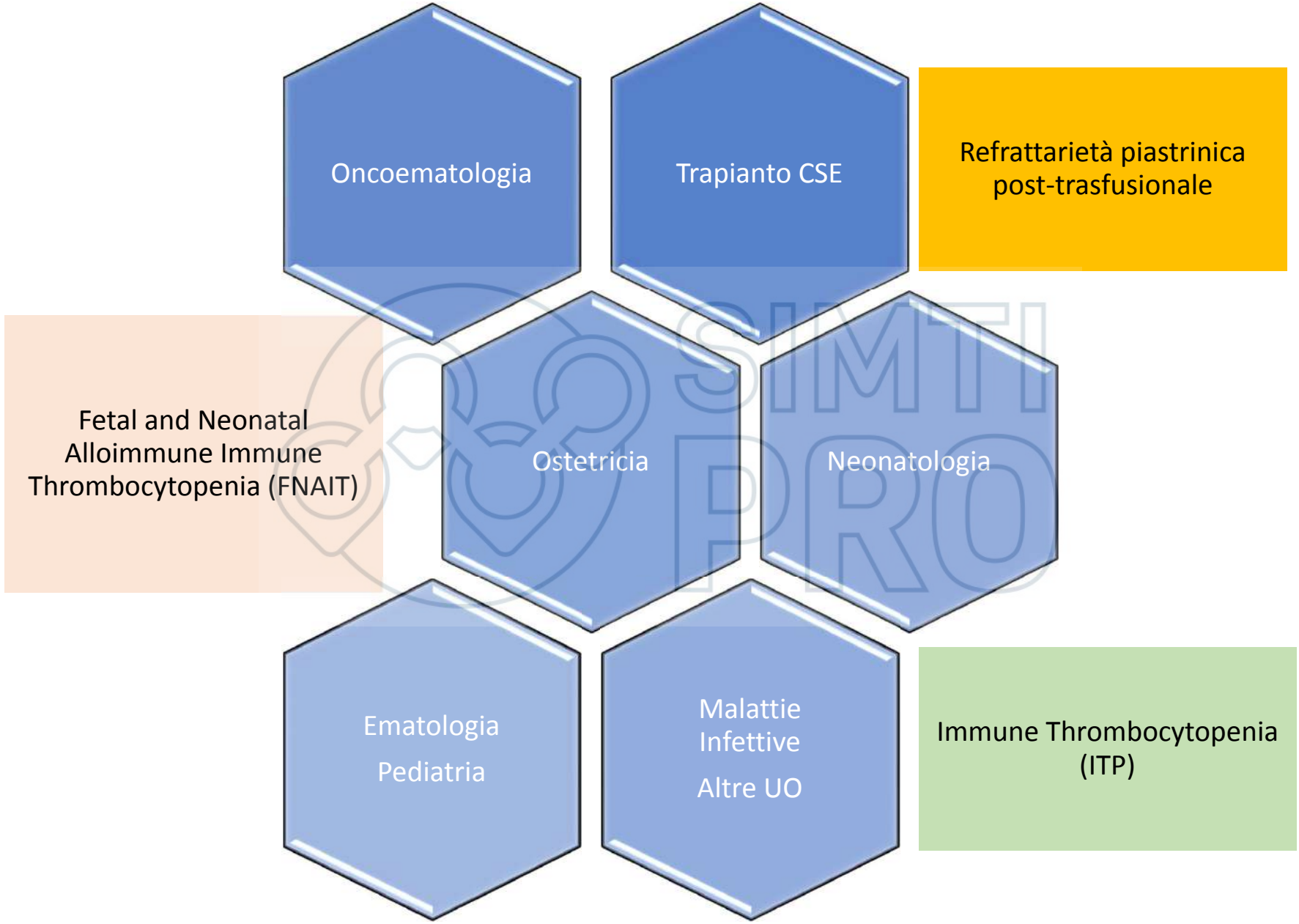
Gli algoritmi decisionali per gli esami diagnostici includono diverse tipologie di test da selezionare o integrare secondo il quesito clinico e l’urgenza della richiesta.

PIASTRINOPENIE IMMUNO-MEDIATE: CLASSIFICAZIONE





PIASTRINOPENIE DI INTERESSE IMMUNOTRASFUSIONALE



Antigeni in comune con eritrociti

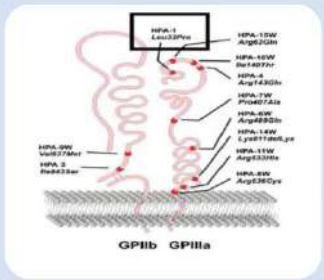
- ABO: espressi su tutte le GP, maggiormente sulla IIb,e sulle cellule endoteliali (molecole di adesione PECAM-1, CD31)
- A1: 2.100-16.000 molecole
- A2: non esprimono antigene A e considerati di gruppo O
- **"High Expressers":** 4-7% di soggetti con elevato numero di antigeni A e B **("Type II High Expressers")**

Antigeni in comune con leucociti

- HLA I classe A, B e di grado minore classe C
- Maggiore espressione degli antigeni HLA tra le cellule del sangue
- Circa 20.000 molecole/piastrina
- 30% donne immunizzate
- Anticorpi anti-HLA possono causare refrattarietà post-trasfusionle , FNAIT, TRALI, rigetto trapianti

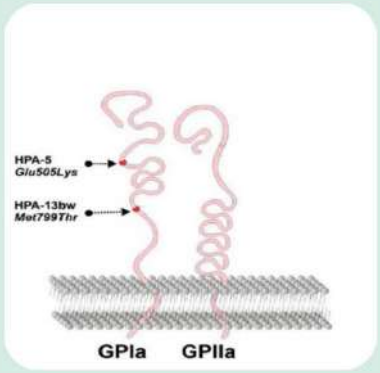
Glicoproteina IIb/IIIa

- GPIIb(CD41) e GPIIIa(CD61), geni su cromosoma 17 , circa 80.000 molecole/piastrina
- Presenti 26/35 sistemi HPA
- Recettore per fibrinogeno, fibronectina, vWF
- **Assenza complesso IIb/IIIa: Tromboastenia di Glanzmann**



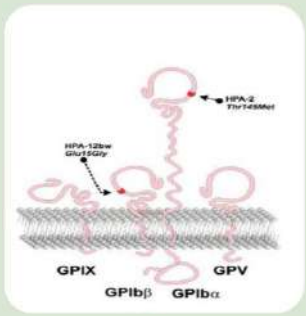
Glicoproteina Ia/IIa

- GPIa/IIa (CD49b/CD29), geni su cromosomi 5 e 9, circa 3.000-5.000 molecole/piastrina
- Presente HPA-5 e HPA -13b, HPA-18b, HPA-25
- Recettore per collagene



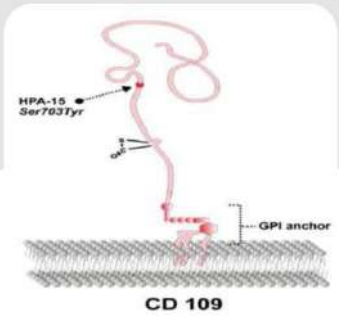
Glicoproteina Ib/V/IX

- GPIb(CD42c/b), GPIX(CD42a) e GPV(CD42d), geni su cromosomi 22,17, 3, circa 25.000 molecole/piastrina
- Presente HPA-2 e HPA-12b, HPA31
- Recettore per vWF
- Assenza complesso Ib/IX: sindrome di Bernard-Soulier



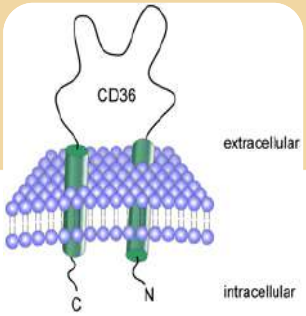
Glicoproteina CD109

- Glicosilfosfatidilinositolo (GPI), gene su cromosoma 6, circa 1.000 molecole/piastrina
- Espressa su piastrine e linfociti T attivati, cellule CD34+, cellule endoteliali, regola TGF-beta
- Presente HPA-15



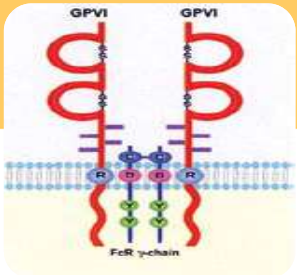
Glicoproteina IV

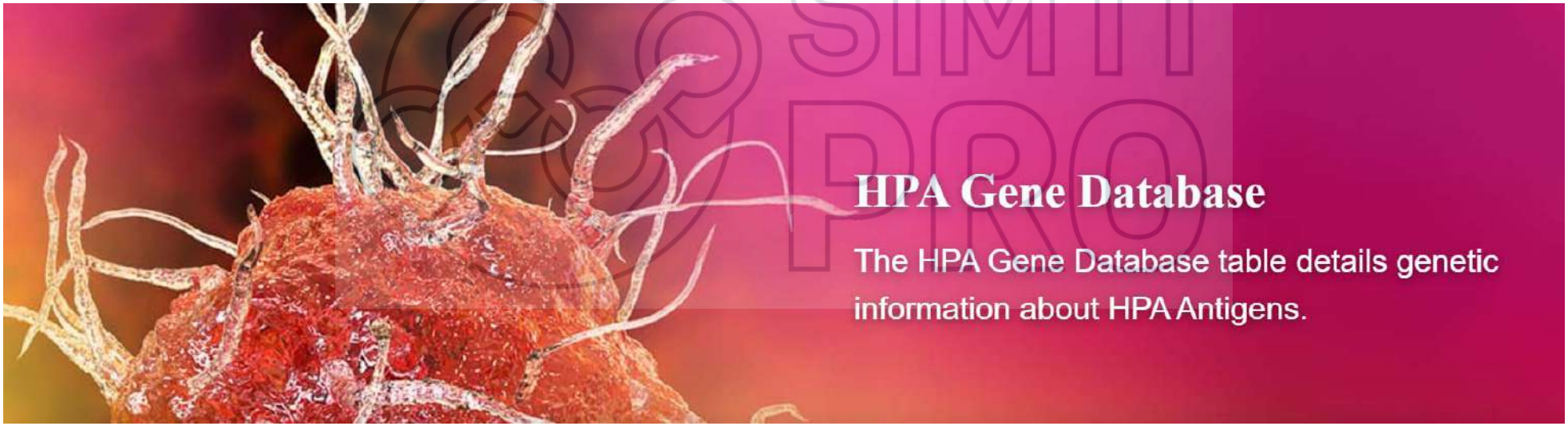
- CD36, espressa su piastrine, monociti/macrofagi, eritrociti nucleati, gene su cromosoma 7
- Recettore per colesterolo LDL, trombospondina, collagene
- Mutazioni geniche causano la perdita della proteina in popolazioni africane (2%) e asiatiche (5-10%).



Glicoproteina VI

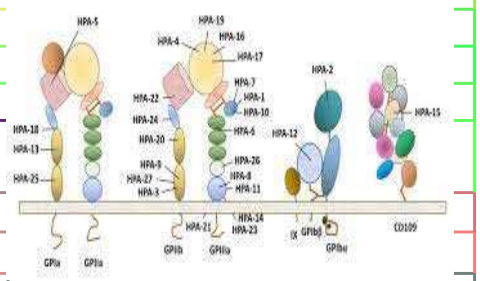
- Uno dei maggiori recettori per collagene (attivazione e aggregazione piastrinica), gene sul cromosoma 19,
- Non sono presenti HPA
- Autoanticorpi con "shedding" della GPVI e gravi emorragie



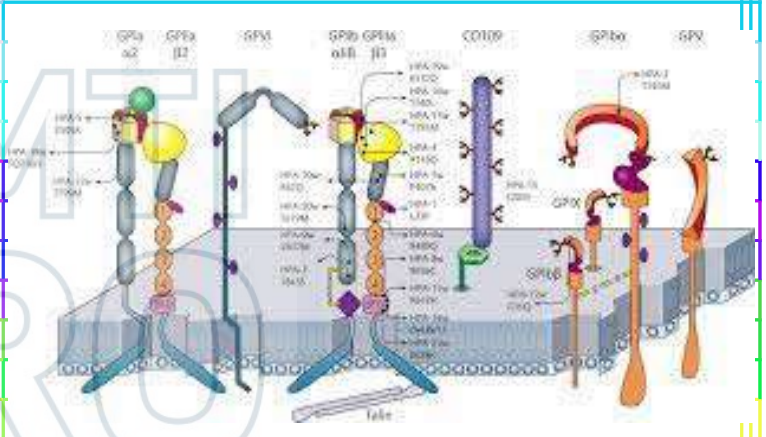


ISBT PLATELET IMMUNOLOGY WORKING PARTY:
35 SISTEMI HPA (6 bi-allelici), 42 ANTIGENI (molti a bassa frequenza-bw)

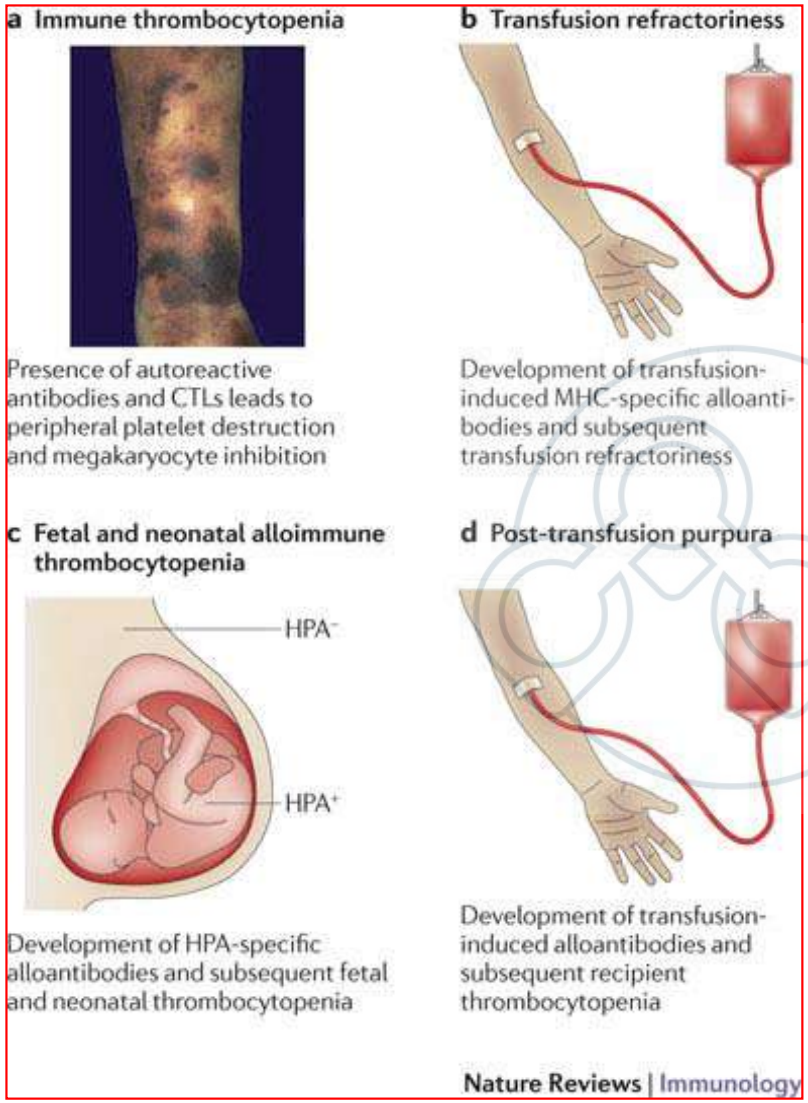
System	Antigen	Original names	Glycoprotein / SNP	CD	
HPA-1	HPA-1a HPA-1b	Zw^{a}, PI^{A1} Zw^{b},PI^{A2}	GPIIIa /L33P^{+}	CD61	
HPA-2	HPA-2a HPA-2b	Ko^{a}, Ko^{b}	GPIbα / T145M	CD42b	
HPA-3	HPA-3a HPA-3b	Bak^{a}, Lek^{a} Bak^{b}	GPIIb / I8435	CD41	
HPA-4	HPA-4a HPA-4b	Yuk^{b}, Pen^{a} Yuk^{a}, Pen^{b}	GPIIIa / R143Q	CD61	
HPA-5	HPA-5a HPA-5b	Br^{b}, Zav^{b} Br^{a}, Zav^{a}, Hc^{a}	GPIa / E505K	CD49b	
	HPA-6b	Ca^{a}, Tu^{a}	GPIIIa / R489Q	CD61	
	HPA-7b	Mo^{a}	GPIIIa / P407A	CD61	
	HPA-8b	Sr^{a}	GPIIIa / R636C	CD61	
	HPA-9b	Max^{a}	GPIIb / V837M	CD41	
	HPA-10b	La^{a}	GPIIIa / R62Q	CD61	
	HPA-11b	Gro^{a}	GPIIIa / R633H	CD61	
	HPA-12b	Iy^{a}	GPIbβ / G15E	CD42c	
	HPA-13b	Sit^{a}	GPIIIa / K611del	CD49b	
	HPA-14b	Oe^{a}	GPIIIa / K611del	CD61	
HPA-15	HPA-15a HPA-15b	Gov^{b} Gov^{a}	CD109 / S682Y	CD109	
	HPA-16b	Duv^{a}	GPIIIa / T140I	CD61	
	HPA-17b	Va^{a}	GPIIIa / T195M	CD61	
	HPA-18b	Cab^{a}	GPIa/ Q716H	CD49b	
	HPA-19b	Sta	GPIIIa / K137Q	CD61	
	HPA-20b	Kno	GPIIb/ T619M	CD41	
	HPA-21b	Nos	GPIIIa/ E628K	CD61	
	HPA-22b	Sey	GPIIb/ K164T	CD41	
	HPA-23b	Hug	GPIIIa/ R622W	CD61	
	HPA-24b	Cab2^{a+}	GPIIb/ S472N	CD41	
	HPA-25b	Swi^{a}	GPIa/ T1087M	CD49b	
	HPA-26b	Sec^{a}	GPIIIa / K580N	CD61	
	HPA-27b	Cab^{3a+}	GPIIb / L841M	CD41	
	HPA-28b	War	GPIIb / V740L	CD41	
	HPA-29b	Kha^{b}	GPIIIa / T33M^{+}	CD61	
	HPA-30b	Lab^{a}	GPIIb / Q806H	CD41	
	HPA-31b	Cab4^{b+}	GPIX / P123L	CD42a	
	HPA-32b	Dom^{b}	GPIIIa / N174S	CD61	
	HPA-33b	Bl^{a}	GPIIIa / D458G	CD61	
	HPA-34b	Bzh^{a}	GPIIIa / R91W	CD61	
	HPA-35b	Efs^{a}	GPIIIa / R479H	CD61	



HPA	HGNC	Chrom	SNP	Prec. Protein	Protein
HPA-1a/1b	ITGB3	17	176T>C	L59P	L33P
HPA-2a/2b	GP1BA	17	482C>T	T161M	T145M
HPA-3a/3b	ITGA2B	17	2621T>G	I874S	I843S
HPA-4a/4b	ITGB3	17	506G>A	R169Q	R143Q
HPA-5a/5b	ITGA2	5	1600G>A	E534K	E505K
HPA-6a/6b	ITGB3	17	1544G>A	R515Q	R489Q
HPA-7a/7b	ITGB3	17	1297C>G	P433A	P407A
HPA-8a/8b	ITGB3	17	1984C>T	R662C	R636C
HPA-9a/9b	ITGA2B	17	2602G>A	V868M	V837M
HPA-10a/10b	ITGB3	17	263G>A	R88Q	R62Q
HPA-11a/11b	ITGB3	17	1976G>A	R659H	R633H
HPA-12a/12b	GP1BB	22	119G>A	G40E	G15E
HPA-13a/13b	ITGA2	5	2483C>T	T828M	T799M
HPA-14a/14b	ITGB3	17	1909_1911delAAG	K637del	K611del
HPA-15a/15b	CD109	8	2108C>A	S703Y	S682Y
HPA-16a/16b	ITGB3	17	497C>T	T166I	T140I
HPA-17a/17b	ITGB3	17	662C>T	T221M	T195M
HPA-18a/18b	ITGA2	5	2235G>T	Q745H	Q716H
HPA-19a/19b	ITGB3	17	487A>C	K163Q	K137Q
HPA-20a/20b	ITGA2B	17	1949C>T	T650M	T619M
HPA-21a/21b	ITGB3	17	1960G>A	E654K	E628K
HPA-22a/22b	ITGA2B	17	584A>C	K195T	K164T
HPA-23a/23b	ITGB3	17	1942C>T	R648W	R622W
HPA-24a/24b	ITGA2B	17	1508G>A	S503N	S472N
HPA-25a/25b	ITGA2	5	3347C>T	T1116M	T1087M
HPA-26a/26b	ITGB3	17	1818G>T	K606N	K580N
HPA-27a/27b	ITGA2B	17	2614C>A	L872M	L841M
HPA-28a/28b	ITGA2B	17	2311G>T	V771L	V740L
HPA-29a/29b	ITGB3	17	98C>T	T33M	T7M
HPA-30a/30b	ITGA2B	17	2511G>C	Q837H	Q806H
HPA-31a/31b	GP9	3	368C>T	P123L	P107L
HPA-32a/32b	ITGB3	17	521A>G	D174S	D148S
HPA-33a/33b	ITGB3	17	1373A>G	D458G	D432G
HPA-34a/34b	ITGB3	17	349C>T	R117W	R91W
HPA-35a/35b	ITGB3	17	1514A>G	R505H	R479H



SPECIFICITA' ANTICORPALI E PIASTRINOPENIE



Piastrinopenie autoimmuni

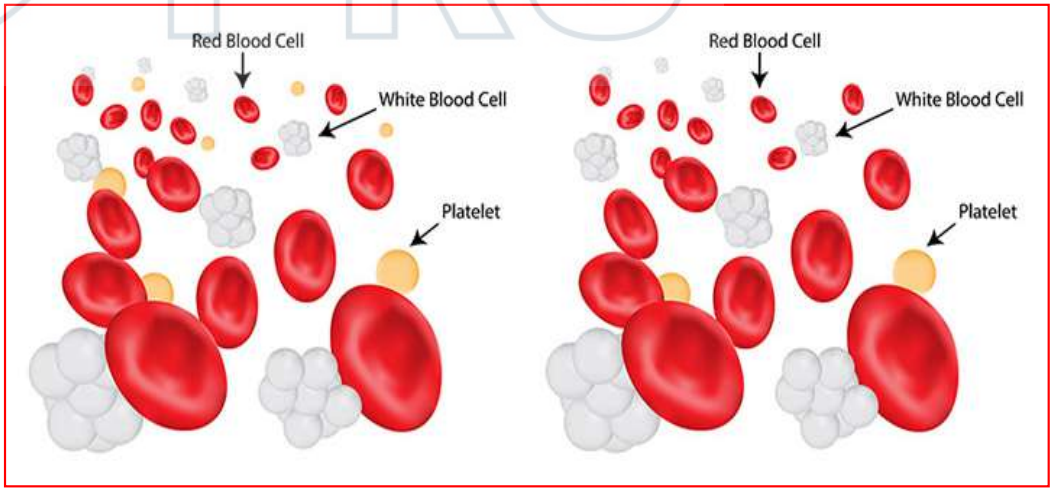
- Anti-GPIIb/IIIa
- Anti-GPIa/IIa
- Anti-GP Ib/IX

Piastrinopenie alloimmuni

- FNAIT: anti-HPA, anti-HLA, GPIV
- PTR: anti-HLA, anti-HPA
- PPT: anti-HPA

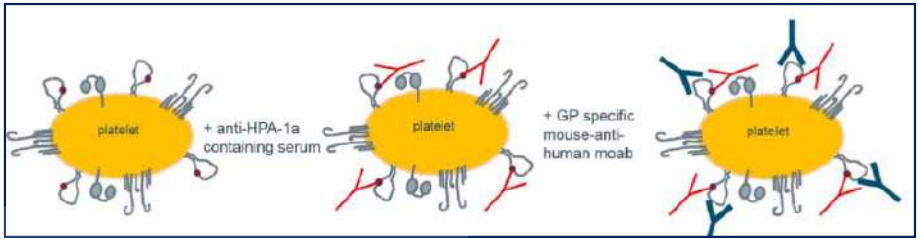
Piastrinopenie da farmaci

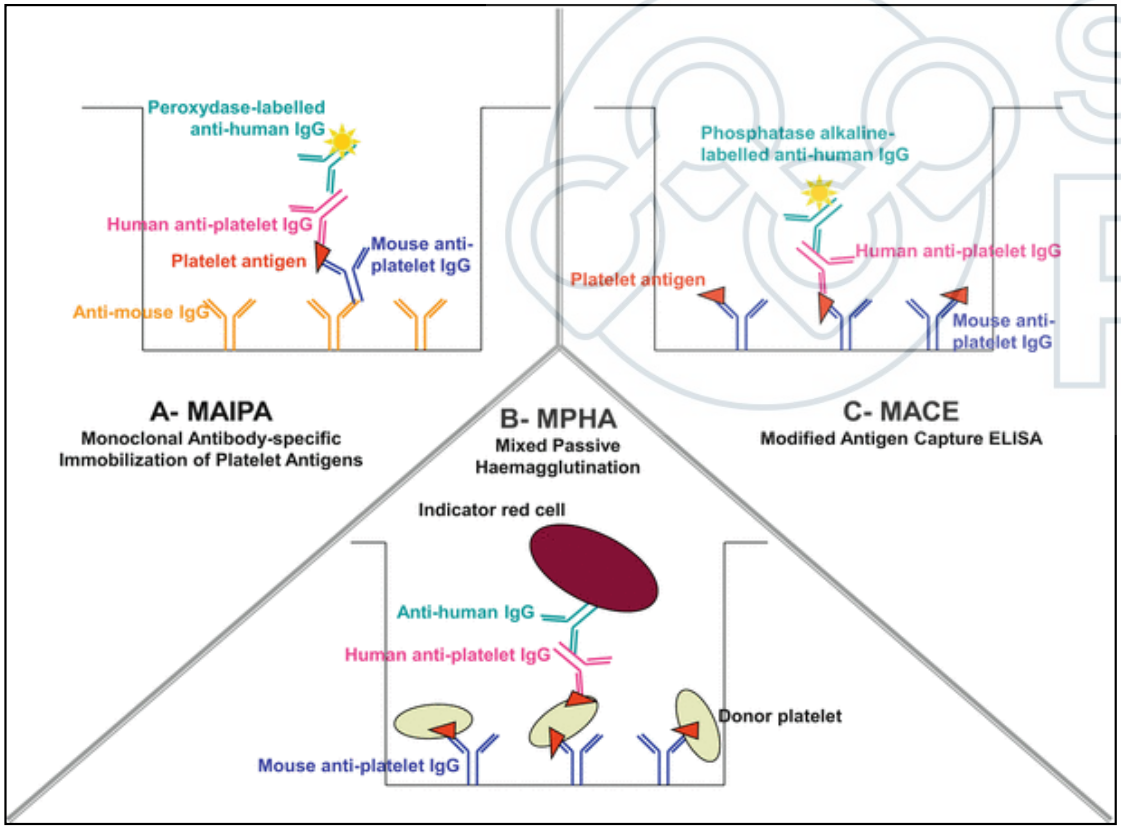
- DITP: Anti-GPIIb/IIa, Ib/IX
- HIT: anti complesso eparina-PF4

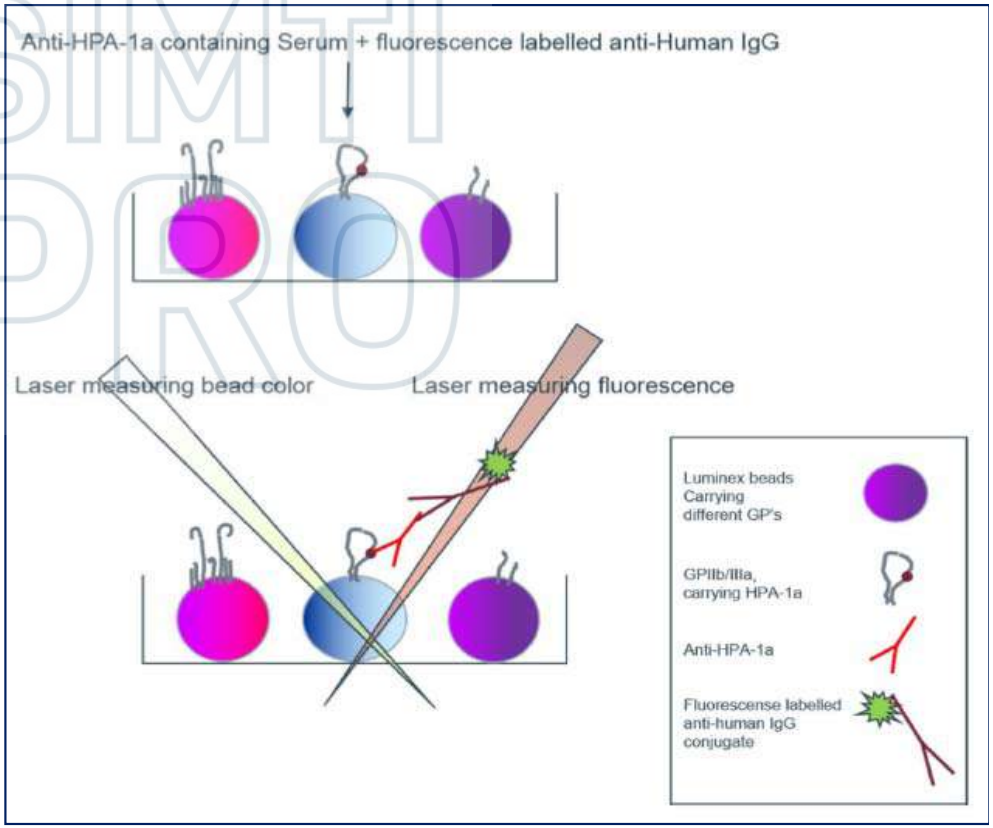


Sistemi diagnostici

- SPRCA (fase solida)
- ELISA: MACE, MAIPA
- Citofluorimetria
- Bead-Based Assay
- PCR SSP, Microarray fase solida e liquida







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CONGRESS REVIEW 2D-08-02

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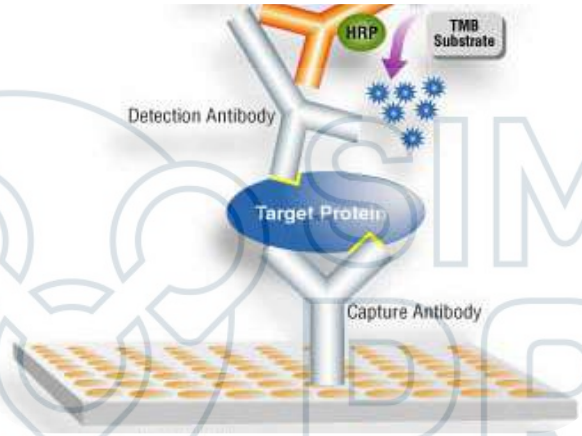
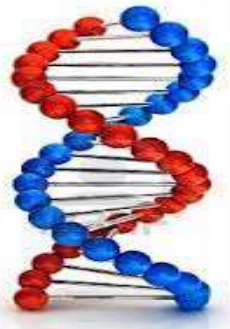
Serological and molecular typing in platelet alloantibody investigations





SPRCA

Citofluorimetria

- Test che utilizzano piastrine integre

ELISA

Bead-based assay

- Test (ELISA) che utilizzano glicoproteine specifiche da lisato piastrinico adese a supporto solido

PCR-SSP

DNA-Microarray

Bead-based suspension array

PCR –RT , NGS

- Test molecolari per tipizzazione HPA

PROGRAMMI DI PROFICIENCY TESTING PER INDAGINI SIEROLOGICHE E MOLECOLARI

APPLICAZIONI CLINICHE

SPRCA

PSFIT

- Screening allo e autoanticorpi nel siero (test indiretto) (NAIT, ITP, PTR)
- Screening autoanticorpi adesi (test diretto) (ITP)
- Cross-match piastrinici (PTR, NAIT)
- PSFIT: studio DITP

MACE

- Identificazione allo e autoanticorpi nel siero (test indiretto) (NAIT, ITP)
- Identificazione autoanticorpi eluiti (test diretto) (ITP)
- PF4 (HIT)

MAIPA

Bead Assay

- **MAIPA**: conferma test diretti e indiretti dubbi con ACE e MACE, titolo anticorpale (NAIT), DITP
- **Bead-Based Assay**: conferma test indiretti dubbi, MACE e MAIPA

PERCORSO DIAGNOSTICO PER ALLOANTICORPI

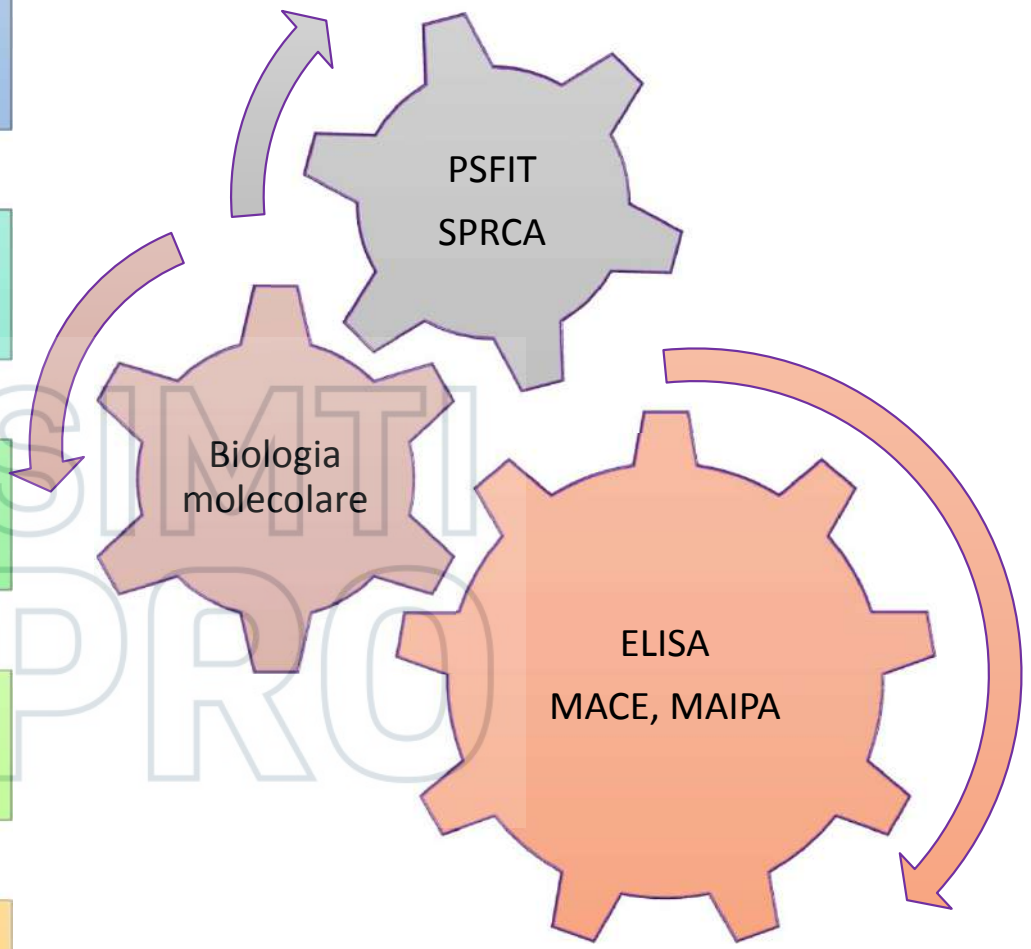
Screening SPRCA

Identificazione ELISA

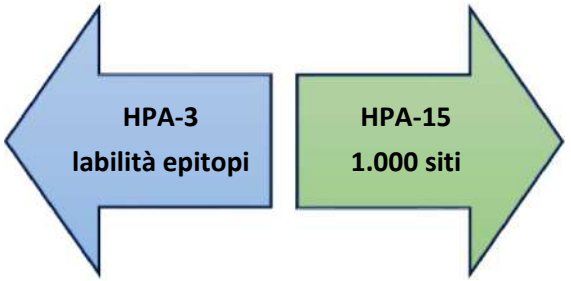
Identificazione Bead-based assay

Biologia Molecolare DNA Microarray

Cross-Match Piastrinici SPRCA



Falsi Negativi: basso titolo, IVIG, antigeni non presenti nei kit



TIPIZZAZIONE GENOMICA IN MEDICINA TRASFUSIONALE

Piattaforme convenzionali

Sequenziamento genico

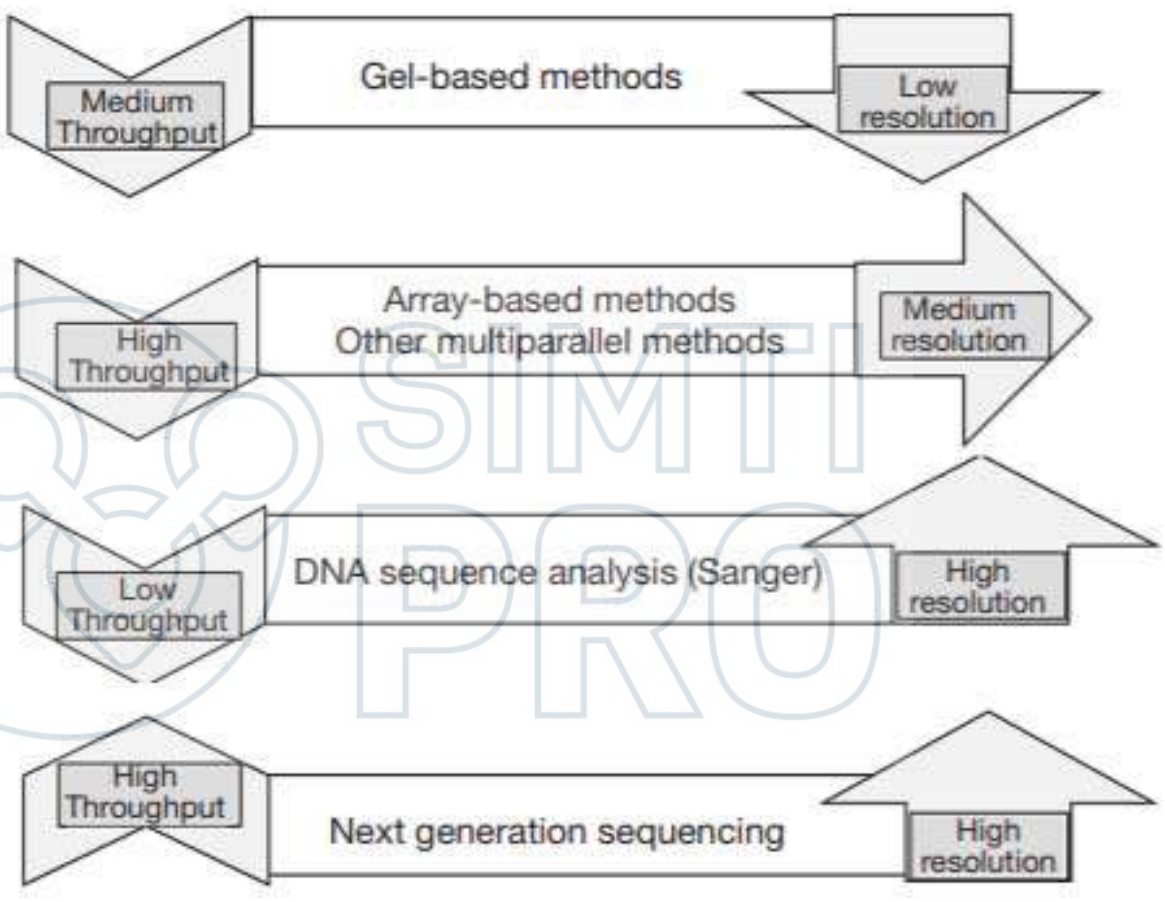
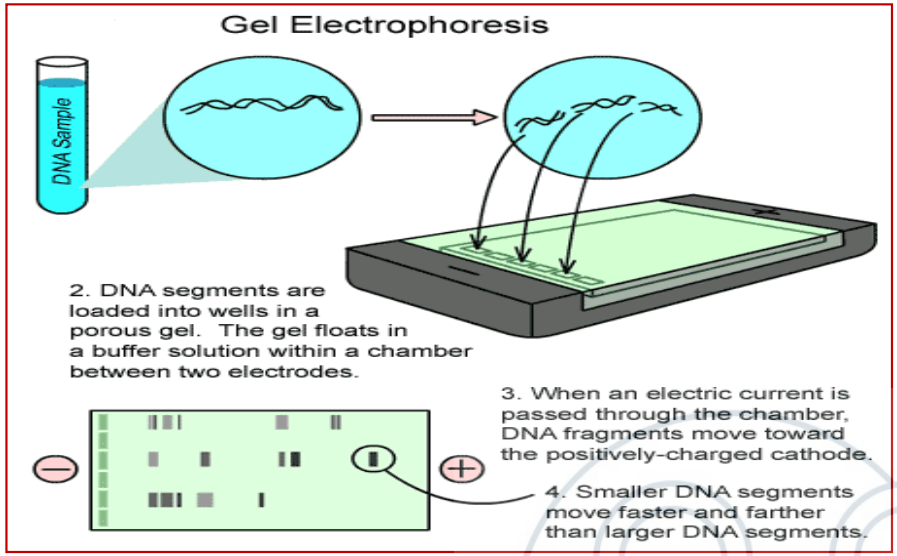


Figure 1 Throughput and resolution of molecular methods currently applied in diagnostics.

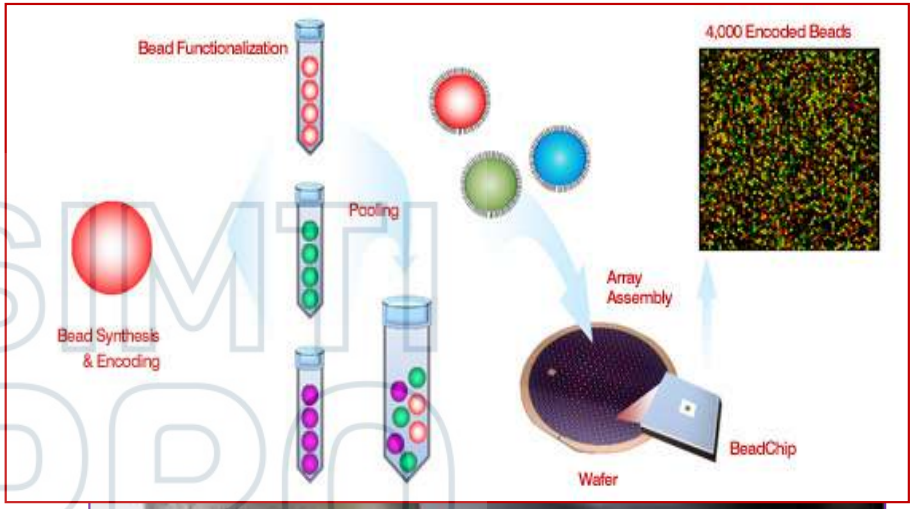
Ann Blood 2021;6:20

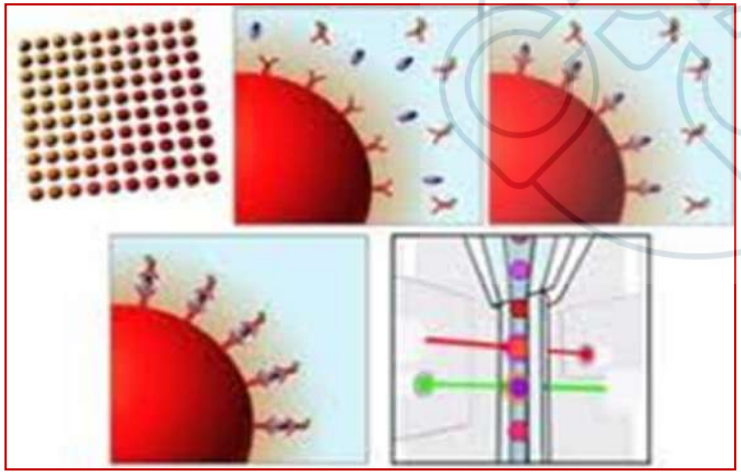
Metodi molecolari per tipizzazione HPA



PCR-SSP

HPA-1, 2, 3, 4, 5, 6, 9,15





Bead-Based Suspension Array

HPA-1 ,2 ,3, 4, 5, 6, 7, 8, 9, 10,11, 15

DNA-MICROARRAY

HPA-1 ,2 ,3, 4, 5, 6, 7, 8, 9, 11, 15

Laboratory testing for platelet antibodies

Nahla M. Heikal and Kristi J. Smock*

Am. J. Hematol. 88:818–821, 2013

TABLE I. Laboratory Tests Used to Detect Platelet Alloantibodies and Autoantibodies

Test	Description	Uses/Advantages	Limitations
I. Indirect platelet antibody tests	Identify platelet-specific antibodies in patient serum or plasma	Used for diagnosis of NAIT, PTP, & MPTR[a]	– Does not differentiate alloantibodies and autoantibodies – Not recommended for ITP (helpful in some cases)
a. ELISA	– Uses captured platelet glycoproteins from lysed platelets as source of known HPAs – Multiple methodologies (ACE, MACE, MAIPA) for glycoprotein capture	– Glycoprotein-specific (specific for antibodies to HPAs) – No reactivity from non-HPA antibodies (HLA, blood group) – Preferred for antibody identification in NAIT (using maternal serum)	– Results reported qualitatively – Clinical utility of antibody titer is controversial – Commercial kits detect only common platelet antibodies – Low titer and low avidity antibodies may not be detected
b. Flow cytometry	Uses intact platelets	– Detects some antibodies that cannot be detected by glycoprotein-specific tests – More sensitive for labile and low density antigens	– Less specific for antibodies to HPAs – May detect HLA, blood group antibodies
II. Direct platelet antibody tests	Detect autoantibodies attached to patient platelets	More sensitive and specific than indirect tests for autoantibody detection	– Does not identify specific antibody target – Sensitivity is compromised by severe thrombocytopenia – Not recommended for ITP (helpful in some cases)
a. ELISA	Detects glycoprotein-specific antibody by eluting bound antibody from patient platelets or using solubilized patient platelets with bound autoantibodies	Very specific	Low sensitivity (~50%)
b. Flow cytometry	Detects any platelet associated antibody	Very sensitive	Low specificity, often positive in non-ITP

[a] NAIT = neonatal alloimmune thrombocytopenia, PTP = post-transfusion purpura, MPTR = multiple platelet transfusion refractoriness, ITP = immune thrombocytopenia, HPA = human platelet antigen, ACE = antigen capture ELISA, MACE = modified ACE, MAIPA = monoclonal antibody immobilization of platelet antigens.

The results of antibody testing shown in this table can be further supported by identifying what antigen(s) are on the patient's platelets by phenotyping or genotyping methods (see text).

Confronto tra i diversi metodi diagnostici

Metodo	Durata	Vantaggi	Svantaggi
SPRCA	1 ora	Automazione, Identifica la maggior parte HPA, cross-match , sensibile	Non identifica anti-HLA, meno specifica
MACE	3-4 ore	Identifica la maggior parte GP, HPA e HLA , specifica, HIT molto sensibile	Non identifica HPA-15, poco sensibile, HIT poco specifica (IgG)
MAIPA	6-8 ore	Manuale, Identifica la maggior parte GP, HPA e HLA, titolo, alta sensibilità e specificità	Non identifica HPA-15, tempi lunghi di esecuzione
Citofluorimetria	2-3 ore	Molto sensibile, cross-match, DITP	No identificazione, poco specifica, strumentazione
Bead-Based Assay	2-3 ore	Identifica la maggior parte HPA e HLA, alta sensibilità, MFI	Non identifica HPA-15, costoso, strumentazione
Biologia Molecolare	6 ore	Tipizza la maggior parte HPA, test di conferma	Costoso, personale specializzato

Blood Reviews 59 (2023) 101038

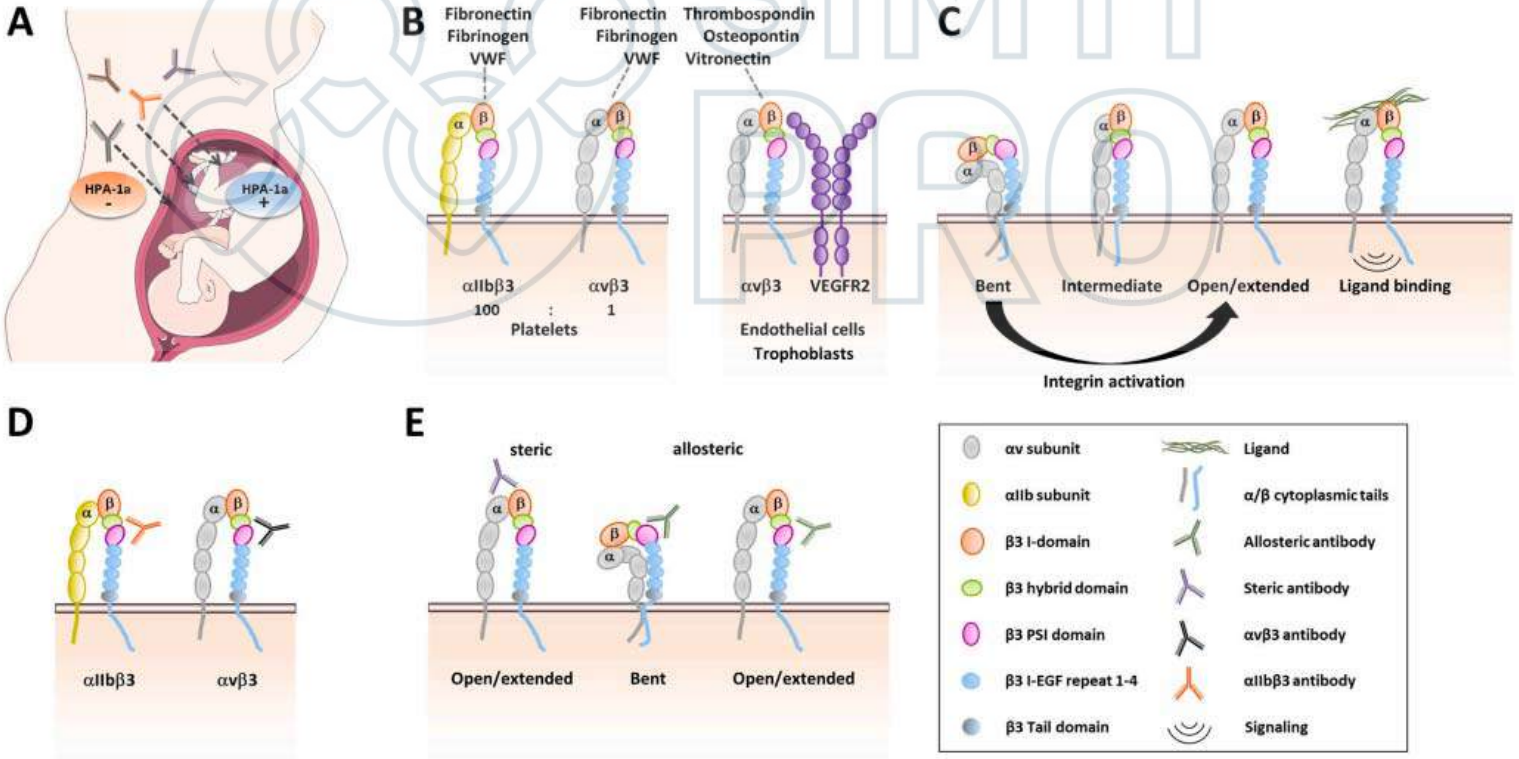
Contents lists available at ScienceDirect

Blood Reviews

journal homepage: www.elsevier.com/locate/issn/0268960X

Review

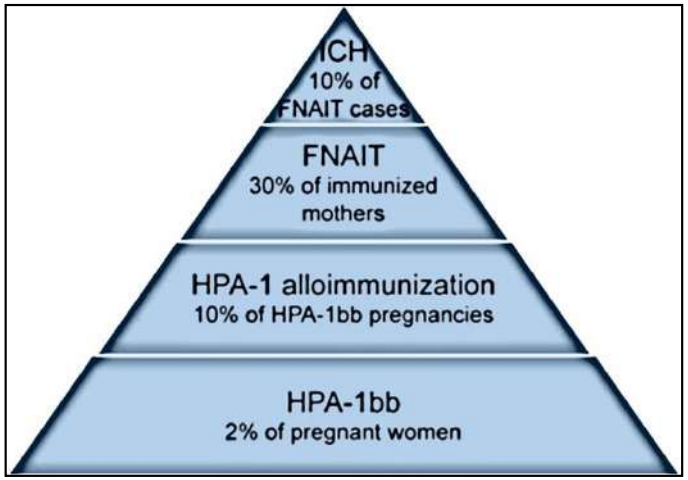
Fetal and neonatal alloimmune thrombocytopenia: Current pathophysiological insights and perspectives for future diagnostics and treatment

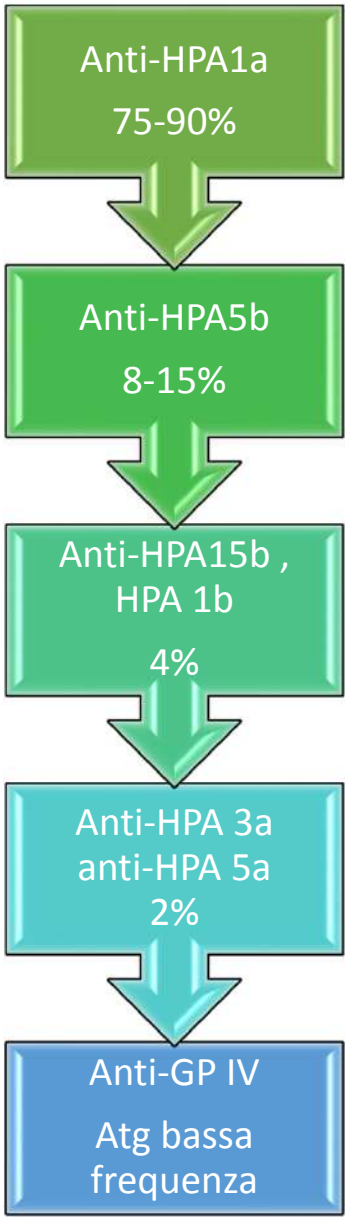


FNAIT

- La piastrinopenia alloimmune feto-neonatale (FNAIT) è una patologia rara (sottostimata) associata ad elevata morbidità e mortalità. Incidenza 1:1.000 – 2.000 neonati (>HPA1a).
- Causa emorragie severe, in particolare a livello intracranico (ICH) con incidenza di 1:10.000. Se precedente ICH: rischio ICH successiva gravidanza 70-80%; se precedente ICH, ma trattamento materno con IVIG: rischio ICH 11%. Mortalità ICH 9-48%.
- Richiede una diagnosi tempestiva e trattamento appropriato.
- Sono necessari algoritmi condivisi per standardizzare i test diagnostici ed identificare le gravidanze ad alto rischio (sono necessari screening).
- Sono state pubblicate recentemente le raccomandazioni dell'International Collaboration for Transfusion Medicine Guidelines (ICTMG)

British Journal of Haematology, 2019





2/3 dei casi di sospetta NAIT rimangono irrisolti

FNAIT: Algoritmo Diagnostico

Sospetta FNAIT in gravidanza: Neonato Piastrinopenico (<50x10^9/L)

Ricerca anticorpi >HPA, >HLA I (SPRCA, ELISA)

POS

Madre

Tipizzazione HPA (Microarray, PCR-SSP)

NEG

Padre

Raccomandazioni per l'impiego delle metodiche molecolari

Si suggerisce di avviare all'analisi molecolare dei sistemi HPA-1, 3, 4, 5, 15 donne in gravidanza con alloimmunizzazione HPA e con storia pregressa di feti/neonati con emorragia cerebrale e i loro partner, feti di donne nella suddetta condizione se il padre è eterozigote per l'antigene piastrinico coinvolto,

Neonato

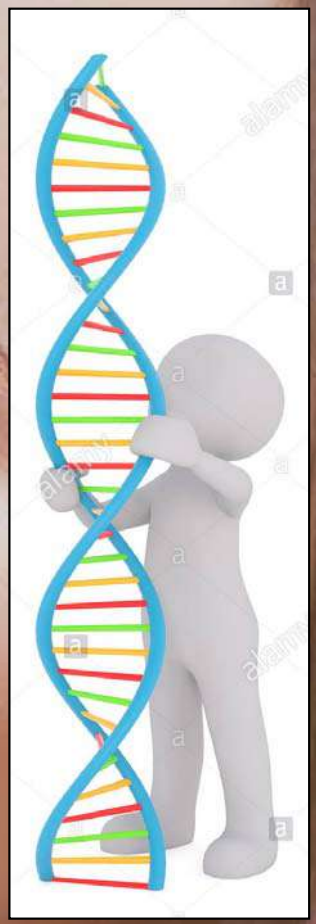
Cross-match (SPRCA)

Tipizzazione HPA

Se eterozigote genotipizzazione HPA fetale

Ricerca anticorpi >HPA, HLA I

Tipizzazione HPA



Transfusion and Apheresis Science 59 (2020) 102708

Contents lists available at ScienceDirect

Transfusion and Apheresis Science

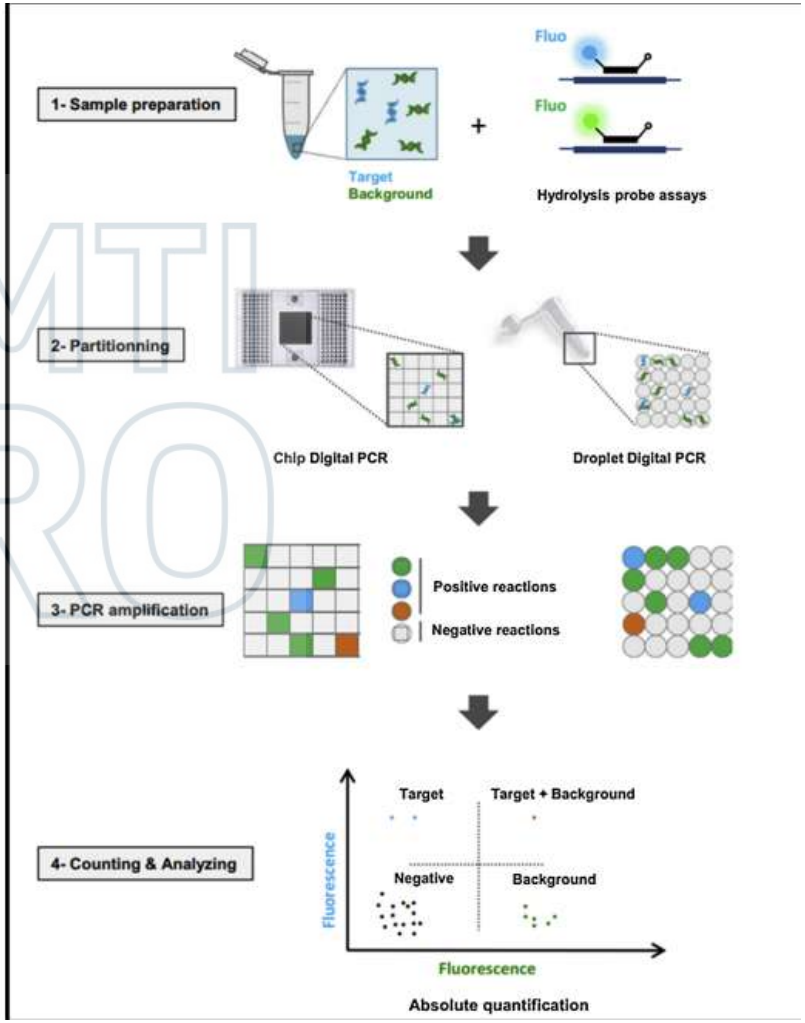
journal homepage: www.elsevier.com/locate/transci

Recent advances in non-invasive fetal HPA-1a typing

Overview of currently applied fetal HPA-1a genotyping methods.

	Method	Requirements	Earliest time	Advantages	Disadvantages
1	**Real-time PCR post-MspIdigestion**	Real-time instrument	2nd trimester 18 weeks	Sequence-specific restriction enzyme digestion of HPA-1b allele minimizes unspecific amplification	Requires pre-PCR processing with increased sample manipulation False positive results due to incomplete digestion
2	**Allele-specific Real-time PCR**	Real-time instrument	2nd trimester 18 weeks	Simple PCR assay Straightforward approach	Sufficient allele specificity difficult to achieve No internal control for fetal DNA
3	**PCR HRM**	Real-time instrument with Melting curve analysis software	2nd trimester 15 weeks	Simple PCR assay Low cost Unique intercalating dye No need for labelled probes	No internal control for fetal DNA
4	**COLD-PCR**	Real-time instrument	1st trimester* 12 weeks	Simple PCR assay Increased sensitivity compared to conventional real-time PCR assays	No internal control for fetal DNA
5	**Targeted Massive Parallel Sequencing**	Expensive NGS platforms	1st trimester* 13 weeks	Unbiased amplification of mother and fetal sequences Deep coverage Internal controls for presence of fetal DNA	High cost per sample Bioinformatics skills needed for analysis of the results
6	**Digital PCR**	Expensive microfluidic PCR device	1st trimester* 8 weeks	Low volumeof reagents Partitioning minimizes maternal allelecompetition High sensitivity High accuracy	Poor signal thresholding may lead to false positives Droplet volume variability affects accurate quantification

*Earliest time for its application only evaluated in a small number of samples. Further studies with a larger number of 1st trimester samples are required.

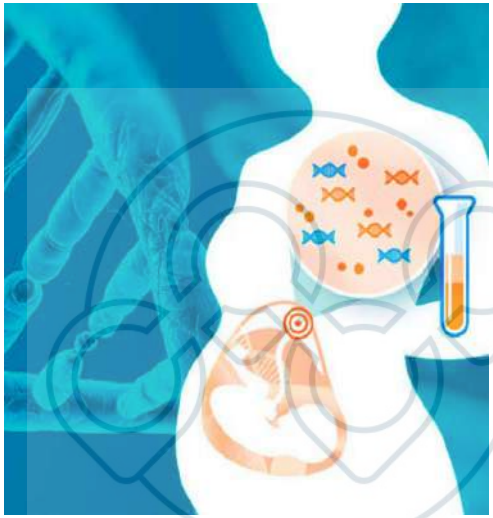


Journal of
Clinical Medicine

MDPI

Review

Noninvasive Prenatal Testing in Immunohematology—Clinical, Technical and Ethical Considerations



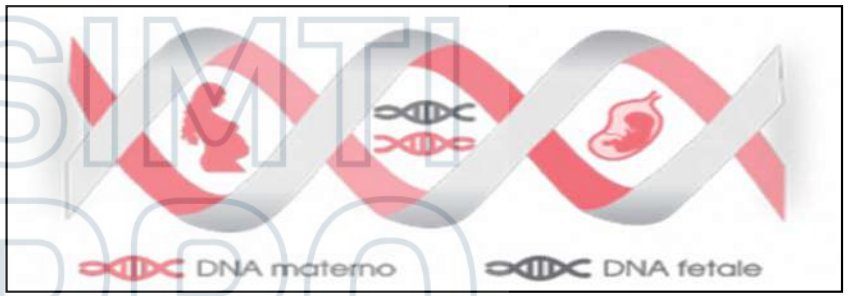


Table 2. Inhouse assays for fetal HPA-1 typing.

	Realtime PCR with Digestion of Maternal Allele	Cold PCR	NGS (Targeted Massive Parallel Sequencing)	Digital PCR
Use from gestational week	18	12	13	8
Control for cffDNA	no	no	yes	yes *
Cost	low	low	high	high
Turnaround time	Medium	Medium	Long	Medium
References	[52]	[54]	[56,57]	[59]

* can be included.

Transfusion and Apheresis Science 59 (2020) 102707

Contents lists available at ScienceDirect

Transfusion and Apheresis Science

journal homepage: www.elsevier.com/locate/transci

Foetal and neonatal alloimmune thrombocytopenia – The role of the *HLA-DRB3*01:01* allele for HPA-1a-immunisation and foetal/neonatal outcome

Jens Kjeldsen-Kragh[a,b,*], Maria Therese Ahlen[a]

[a] Department of Laboratory Medicine, University Hospital of North Norway, Tromsø, Norway
[b] University and Regional Laboratories Region Skåne, Lund, Sweden

ARTICLE INFO

Keywords:
Alloimmunization
Foetus
Neonate
Platelet
Pregnancy
HPA-1a
*HLA-DRB3*01:01*

ABSTRACT

Foetal and neonatal alloimmune thrombocytopenia (FNAIT) is the platelet counterpart of haemolytic disease of the foetus and newborn. Among Caucasians, around 80 % of FNAIT cases and some of the most severe cases, are caused by alloantibodies against the human platelet antigen 1a (HPA-1a). For around 3 decades it has been known that almost all HPA-1a immunised women are *HLA-DRB3*01:01* positive. The HLA molecule encoded by the *HLA-DRA/DRB3*01:01* genes seems to be of crucial importance for initiating the immune response against HPA-1a. The *HLA-DRB3*01:01* carrier status is not only important as a risk factor for immunisation, but does also have a significant impact on foetal/neonatal outcome. The possible role of *HLA-DRB3*01:01* typing as tool for risk stratification is discussed.

Women who are HLADRB3*01:01-positive have a 25 times higher risk of becoming HPA-1a immunized as opposed to those who do not carry this HLA type . Furthermore, those few HPA-1a and HLA-DRB3*01:01-negative women who become HPA-1a-immunized very rarely give birth to severely thrombocytopenic children, and, likewise, ICH is extremely rare in fetuses/newborns of HPA-1a and HLA-DRB3*01:01-negative women.

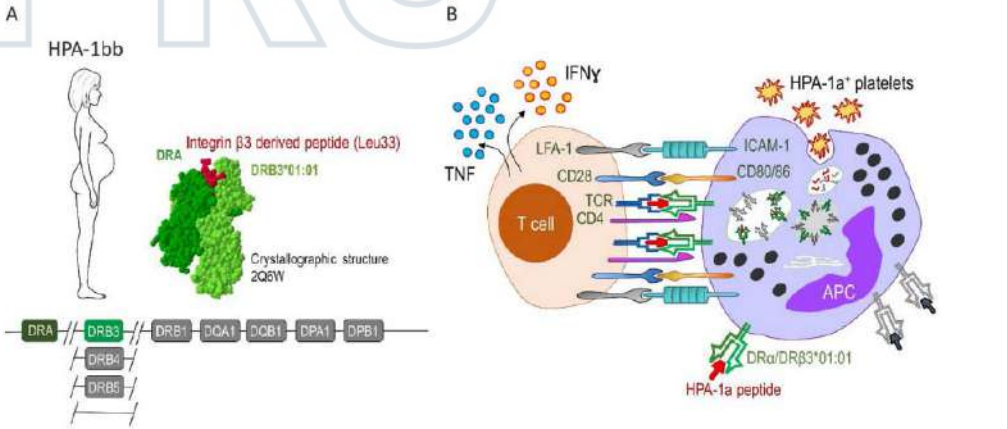


Fig. 1. (A) HPA-1bb women carying the *HLA-DRB3*01:01* allele are at risk of immunization, due to efficient presentation of the HPA-1a peptide derived from the foetal β3 integrin, by the HLA molecule encoded by *HLA-DRA/DRB3*01:01*. The illustration is made by Swiss-PDB viewer of structure 2Q6W from PDB [8]. (B) Processing and presentation of platelet antigens by an antigen-presenting cell. Efficient T cell activation depends on formation of an immunological synapse, by several TCR-peptide-HLA complexes and co-stimulatory and structurally supportive interactions.

Transfusion and Aphe

Contents lists a

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Foetal and neonatal alloimmune thromb
*DRB3*01:01* allele for HPA-1a-immunisa

Jens Kjeldsen-Kragh[a,b,*], Maria Therese Ahlen[a]

[a] *Department of Laboratory Medicine, University Hospital of North Norway, Tromsø, Norv*
[b] *University and Regional Laboratories Region Skåne, Lund, Sweden*

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ABSTRACT

Foetal and neonatal allo
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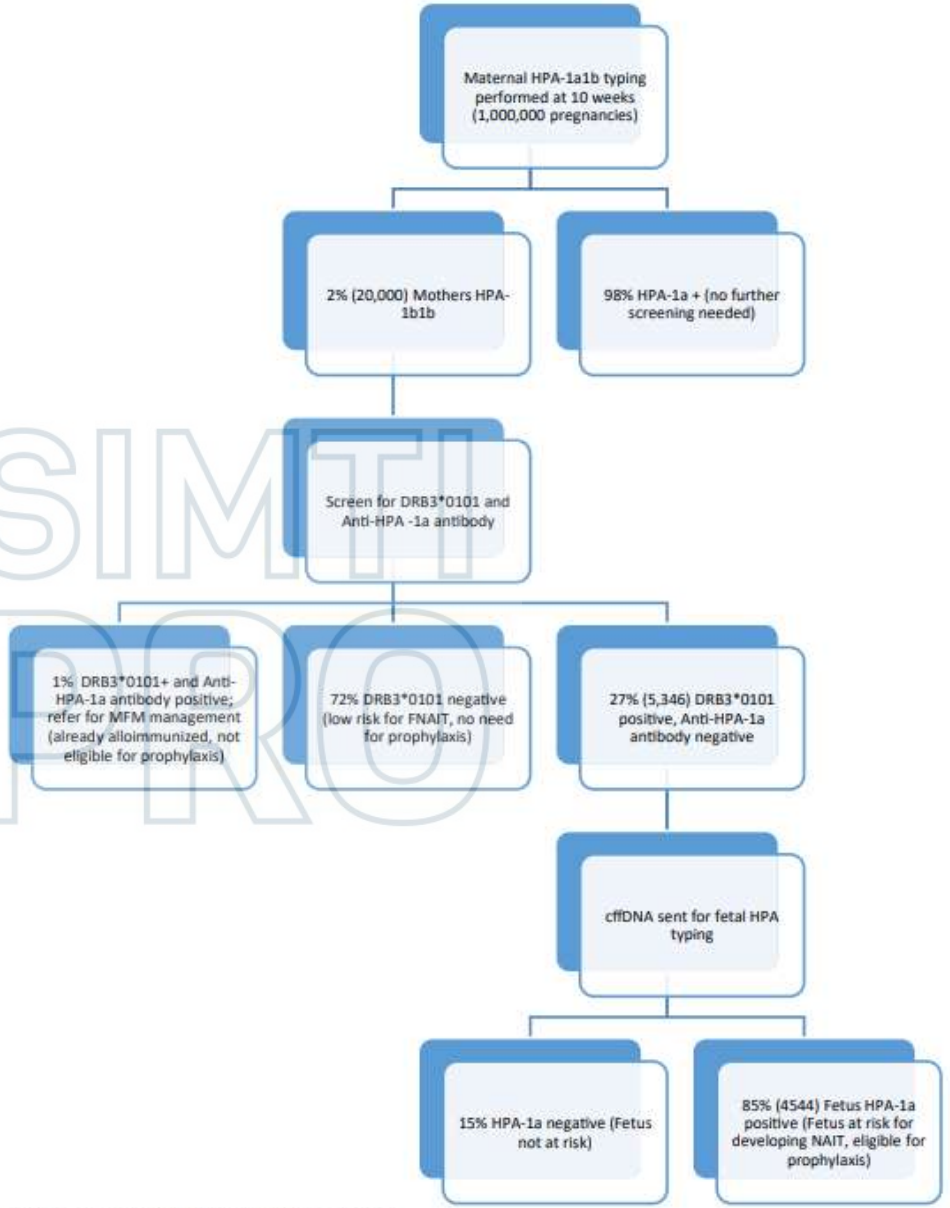
FIGURE 3
Theoretical screening process for FNAIT prophylaxis



FNAIT, fetal and neonatal alloimmune thrombocytopenia.
Estimated affected pregnancies per 1,000,000 deliveries.
Bussel. New developments in fetal and neonatal alloimmune thrombocytopenia. Am J Obstet Gynecol 2021.

Liu et al. Journal of Hematology & Oncology (2023) 16:4
https://doi.org/10.1186/s13045-023-01401-z

Journal of Hematology & Oncology

REVIEW Open Access

How we treat primary immune thrombocytopenia in adults

Xin-guang Liu[1†], Yu Hou[1†] and Ming Hou[1,2*]

European Journal of Internal Medicine 108 (2023) 18–24

Contents lists available at ScienceDirect

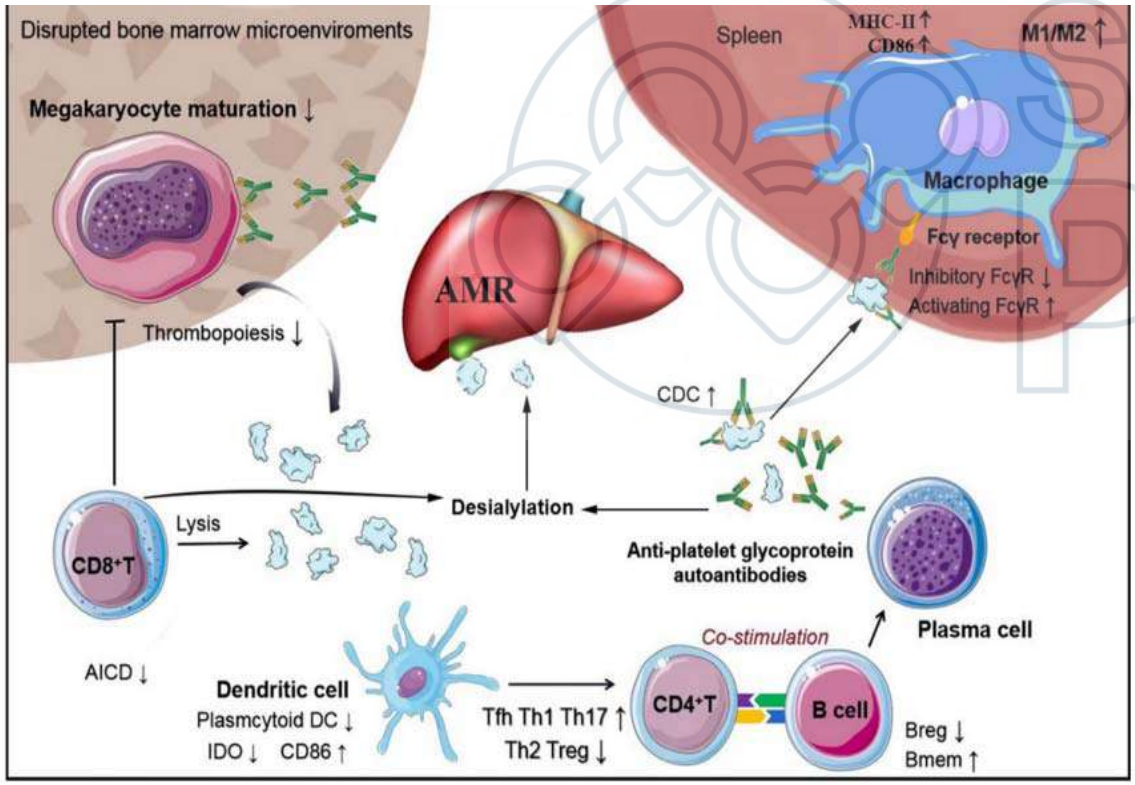
European Journal of Internal Medicine

journal homepage: www.elsevier.com/locate/ejim

Review Article

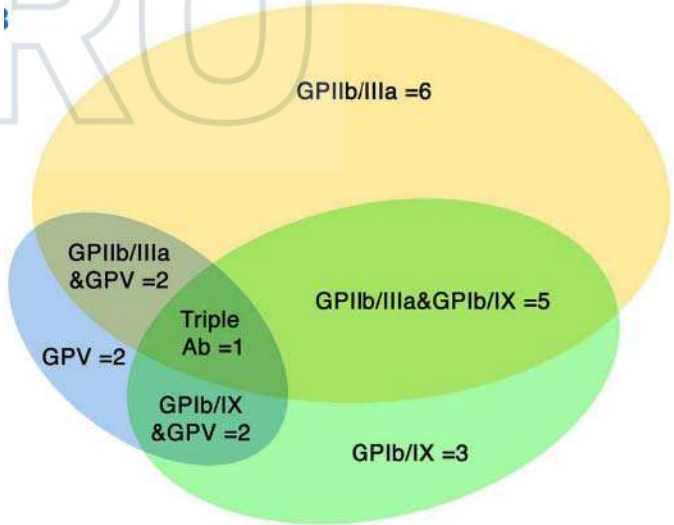
Current approaches for the diagnosis and management of immune thrombocytopenia

Anat Gafter-Gvili [a, b, c, *]



Antiplatelet antibody predicts platelet desialylation and apoptosis in immune thrombocytopenia

Haematologica | 107 September 2022



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Journal of
Hematology & Oncology

REVIEW Open Access

How we treat primary immune thrombocytopenia in adults

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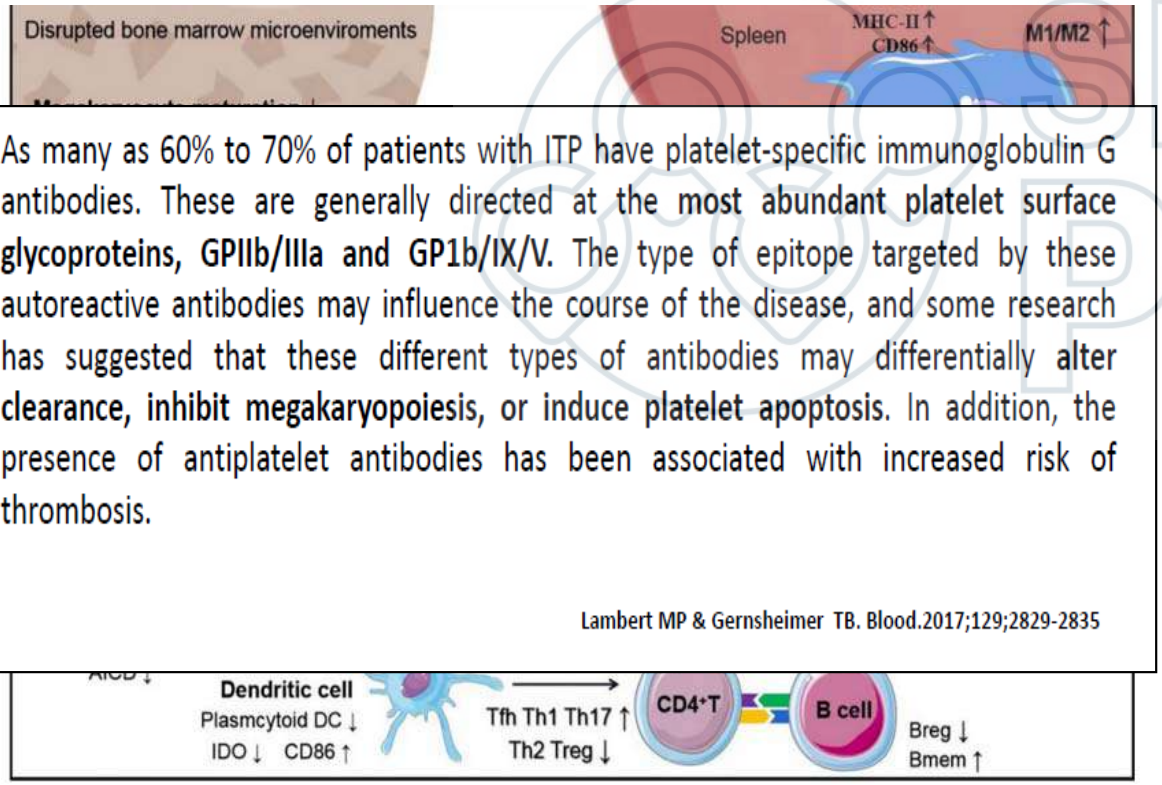
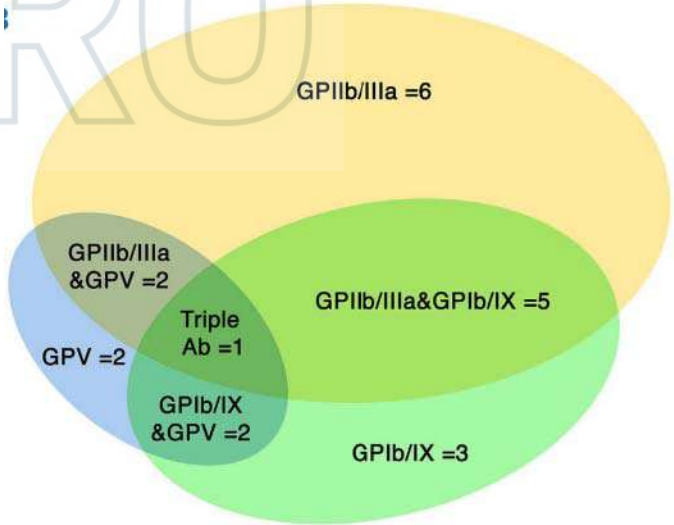


As many as 60% to 70% of patients with ITP have platelet-specific immunoglobulin G antibodies. These are generally directed at the **most abundant platelet surface glycoproteins, GPIIb/IIIa and GP1b/IX/V.** The type of epitope targeted by these autoreactive antibodies may influence the course of the disease, and some research has suggested that these different types of antibodies may differentially **alter clearance, inhibit megakaryopoiesis,** or induce **platelet apoptosis.** In addition, the presence of antiplatelet antibodies has been associated with increased risk of thrombosis.

Lambert MP & Gernsheimer TB. Blood.2017;129;2829-2835

Antiplatelet antibody predicts platelet desialylation and apoptosis in immune thrombocytopenia

Haematologica | 107 September 2022

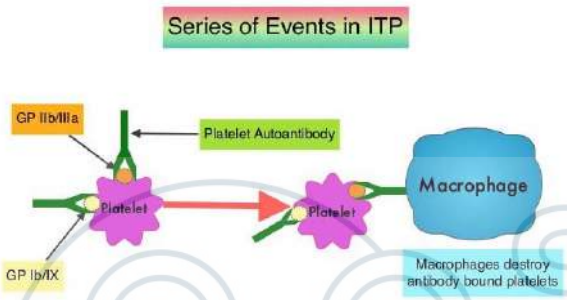


Trombocitopenia immune (ITP)

Piastrinopenia (<100x10^9/L) isolata, autoimmune, con aumentato rischio emorragico, causata da incremento della distruzione piastrinica e ridotta produzione

Diagnosi di esclusione,ITP primaria (80%) o secondaria (20%) a malattie autoimmuni, infezioni o neoplasie.

Colpisce tutte le età e gruppi etnici (tra 30-60 anni prevale nel sesso femminile)



Incidenza: 2-5 casi/100.000/anno

Prevalenza: 10 casi/100.000/anno

Nuova diagnosi (0-3 mesi), persistente (3-12 mesi), cronica (12 mesi).

Remissione nei bambini del 60-70% e negli adulti del 20-40% (decorso cronico).

Emorragie severe nei bambini (ICH 0.1-0.4%) e negli adulti (ICH 1.4%)

Conta piastrinica <30x10^9/L: 46% petecchie ed ecchimosi, 15% emorragie GI e menorragia, asintomatici nel 20-40%

- *Immune thrombocytopenia. NEJM 2019*
- *American Society of Hematology 2019 guidelines for immune thrombocytopenia. Blood Advances 2019*
- *An update on the pathophysiology of immune thrombocytopenia. Curr Opin Hematol. 2020*
- *Immune thrombocytopenia (ITP) World Impact Survey (I-WISh). Am J Hematol. 2021-*

CLINICAL GUIDELINES

blood advances

American Society of Hematology 2019 guidelines for immune thrombocytopenia

Cindy Neunert,[1] Deirdra R. Terrell,[2] Donald M. Arnold,[3,4] George Buchanan,[5] Douglas B. Cines,[6] Nichola Cooper,[7] Adam Cuker,[8] Jenny M. Despotovic,[9] James N. George,[2] Rachael F. Grace,[10] Thomas Kühne,[11] David J. Kuter,[12] Wendy Lim,[13] Keith R. McCrae,[14] Barbara Pruitt,[15] Hayley Shimanek,[16] and Sara K. Vesely[2]

[1]Division of Pediatric Hematology, Oncology, and Stem Cell Transplantation, Columbia University Irving Medical Center, New York, NY; [2]Department of Biostatistics and Epidemiology, Hudson College of Public Health, University of Oklahoma Health Sciences Center, Oklahoma City, OK; [3]Division of Hematology and Thromboembolism, Department of Medicine, and [4]McMaster Centre for Transfusion Research, McMaster University, Toronto, ON, Canada; [5]Division of Hematology-Oncology, University of Texas Southwestern Medical Center, Dallas, TX; [6]Department of Pathology and Laboratory Medicine, Perelman School of Medicine, University of Pennsylvania, Philadelphia, PA; [7]Centre for Haematology, Department of Medicine, Hammersmith Hospital, Imperial College London, London, United Kingdom; [8]Department of Medicine, Perelman School of

REVIEW ARTICLE

blood advances

Updated international consensus report on the investigation and management of primary immune thrombocytopenia

Drew Provan,[1] Donald M. Arnold,[2] James B. Bussel,[3] Beng H. Chong,[4] Nichola Cooper,[5] Terry Gernsheimer,[6] Waleed Ghanima,[7,8] Bertrand Godeau,[9] Tomás José González-López,[10] John Grainger,[11] Ming Hou,[12] Caroline Kruse,[13] Vickie McDonald,[14] Marc Michel,[9] Adrian C. Newland,[1] Sue Pavord,[15] Francesco Rodeghiero,[16] Marie Scully,[17] Yoshiaki Tomiyama,[18] Raymond S. Wong,[19] Francesco Zaja,[20] and David J. Kuter[21]

[1]Academic Haematology Unit, Blizard Institute, Barts and The London School of Medicine and Dentistry, Queen Mary University of London, London, United Kingdom; [2]McMaster Centre for Transfusion Research, Department of Medicine and Department of Pathology and Molecular Medicine, McMaster University and Canadian Blood Services, Hamilton, ON, Canada; [3]Division of Hematology/Oncology, Department of Pediatrics, Weill Cornell Medicine, New York, NY; [4]St. George Hospital, NSW Health Pathology, University of New South Wales, Sydney, NSW, Australia; [5]Department of Haematology, Hammersmith Hospital, London, United Kingdom; [6]Seattle Cancer Care Alliance, University of Washington, Seattle, WA; [7]Departments of Research, Medicine and Oncology, Østfold Hospital Trust, Grålum, Norway; [8]Department of Hematology, Institute of Clinical Medicine, Oslo University, Oslo, Norway; [9]Centre de Référence des Cytopénies Auto-Immunes de l'Adulte, Service de Médecine Interne, CHU Henri Mondor, AP-HP, Université Paris-Est Créteil, Créteil, France; [10]Department of Hematology, Hospital Universitario de Burgos, Burgos, Spain; [11]Department of Haematology, Royal Manchester Children's Hospital, Manchester, United Kingdom; [12]Department of Haematology, Qilu Hospital, Shandong University, Jinan, China; [13]Platelet Disorder Support Association, Cleveland, OH; [14]Royal London Hospital, Barts Health NHS Trust, London, United Kingdom; [15]Haematology Theme Oxford Biomedical Research Centre, Oxford University Hospitals NHS Foundation Trust, Oxford, United Kingdom; [16]Hematology Project Foundation, Affiliated to the Department of Cell Therapy and Hematology, San Bortolo Hospital, Vicenza, Italy; [17]Department of Haematology, University College London Hospital, Cardiometabolic Programme-NIHR UCLH/UCL BRC, London, United Kingdom; [18]Department of Blood Transfusion, Osaka University Hospital, Osaka, Japan; [19]Sir YK Pao Centre for Cancer and Department of Medicine and Therapeutics, Prince of Wales Hospital, The Chinese University of Hong Kong, Shatin, NT, Hong Kong; [20]SC Ematologia, Azienda Sanitaria Universitaria Integrata, Trieste, Italy; and [21]Division of Hematology, Massachusetts General Hospital, Harvard Medical School, Boston, MA

Table 3. Recommendations for the diagnosis of ITP in children and adults

Basic evaluation in all patients	Tests of potential utility in the management of an ITP patient	Tests of unproven or uncertain benefit*
Patient history	Glycoprotein-specific antibody (can be used in difficult cases, has poor sensitivity, and is not a primary diagnostic test)	TPO level
Family history	Anti-phospholipid antibodies (including anti-cardiolipin and lupus anticoagulant) if there are clinical features of antiphospholipid syndrome	Reticulated platelets/immature platelet fraction
Physical examination	Anti-thyroid antibodies and thyroid function	
CBC and reticulocyte count	Pregnancy test in women of childbearing potential	Bleeding time
Peripheral blood film	Antinuclear antibodies	Serum complement
Quantitative Ig level measurement†	Viral PCR for EBV, CMV, and parvovirus	
Blood group (Rh)	Bone marrow examination (in selected patients; refer to text)	
HIV‡	Direct antiglobulin test	
HCV‡	*H pylori*‡	
HBV		

CMV, cytomegalovirus; EBV, Epstein-Barr virus; PCR, polymerase chain reaction; PTT, partial thromboplastin time; Rh, rhesus; TPO, thrombopoietin.
*These tests have no proven role in the differential diagnosis of ITP from other thrombocytopenias and do not guide patient management.
†Quantitative Ig level measurement should be considered in children with ITP and is recommended in children with persistent or chronic ITP as part of the reassessment evaluation.
‡Recommended by the majority of the panel for adult patients in the appropriate geographic setting.

Updated international consensus report on the investigation and management of primary immune thrombocytopenia

Drew Provan,[1] Donald M. Arnold,[2] James B. Bussel,[3] Beng H. Chong,[4] Nichola Cooper,[5] Terry Gernsheimer,[6] Waleed Ghanima,[7,8] Bertrand Godeau,[9] Tomás José González-López,[10] John Grainger,[11] Ming Hou,[12] Caroline Kruse,[13] Vickie McDonald,[14] Marc Michel,[9] Adrian C. Newland,[1] Sue Pavord,[15] Francesco Rodeghiero,[16] Marie Scully,[17] Yoshiaki Tomiyama,[18] Raymond S. Wong,[19] Francesco Zaja,[20] and David J. Kuter[21]

[1]Academic Haematology Unit, Blizard Institute, Barts and The London School of Medicine and Dentistry, Queen Mary University of London, London, United Kingdom; [2]McMaster Centre for Transfusion Research, Department of Medicine and Department of Pathology and Molecular Medicine, McMaster University and Canadian Blood Services, Hamilton, ON, Canada; [3]Division of Hematology/Oncology, Department of Pediatrics, Weill Cornell Medicine, New York, NY; [4]St. George Hospital, NSW Health Pathology, University of New South Wales, Sydney, NSW, Australia; [5]Department of Haematology, Hammersmith Hospital, London, United Kingdom; [6]Seattle Cancer Care Alliance, University of Washington, Seattle, WA; [7]Departments of Research, Medicine and Oncology, Østfold Hospital Trust, Grålum, Norway; [8]Department of Hematology, Institute of Clinical Medicine, Oslo University, Oslo, Norway; [9]Centre de Référence des Cytopénies Auto-Immunes de l'Adulte, Service de Médecine Interne, CHU Henri Mondor, AP-HP, Université Paris-Est Créteil, Créteil, France; [10]Department of Hematology, Hospital Universitario de Burgos, Burgos, Spain; [11]Department of Haematology, Royal Manchester Children's Hospital, Manchester, United Kingdom; [12]Department of Haematology, Qilu Hospital, Shandong University, Jinan, China; [13]Platelet Disorder Support Association, Cleveland, OH; [14]Royal London Hospital, Barts Health NHS Trust, London, United Kingdom; [15]Haematology Theme Oxford Biomedical Research Centre, Oxford University Hospitals NHS Foundation Trust, Oxford, United Kingdom; [16]Hematology Project Foundation, Affiliated to the Department of Cell Therapy and Hematology, San Bortolo Hospital, Vicenza, Italy; [17]Department of Haematology, University College London Hospital, Cardiometabolic Programme-NIHR UCLH/UCL BRC, London, United Kingdom; [18]Department of Blood Transfusion, Osaka University Hospital, Osaka, Japan; [19]Sir YK Pao Centre for Cancer and Department of Medicine and Therapeutics, Prince of Wales Hospital, The Chinese University of Hong Kong, Shatin, NT, Hong Kong; [20]SC Ematologia, Azienda Sanitaria Universitaria Integrata, Trieste, Italy; and [21]Division of Hematology, Massachusetts General Hospital, Harvard Medical School, Boston, MA

Table 3. Recommendations for the diagnosis of ITP in children and adults

Basic						fit*
Patient						
Family						tion
Physica						
CBC a						
Periphe						
Quanti						
Blood						
HIV‡						
HCV‡						
HBV						

CMV,
*These
†Quar
‡Recommended by the majority of the panel for adult patients in the appropriate geographic setting.

Transfusion Medicine Reviews 34 (2020) 258–269

Contents lists available at ScienceDirect

Transfusion Medicine Reviews

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Evolution and Utility of Antiplatelet Autoantibody Testing in Patients with Immune Thrombocytopenia

Leendert Porcelijn [a,*], David E Schmidt [b], Gonda Oldert [a], Suzanne Hofstede-van Egmond [a], Rick Kapur [b], Jaap Jan Zwaginga [c,d,e], Masja de Haas [a,d,e]

VoxSanguinis
The International Journal of Transfusion Medicine

ISBT International Society of Blood Transfusion

Vox Sanguinis (2020) **115**, 323–333

DOI: 10.1111/vox.12894

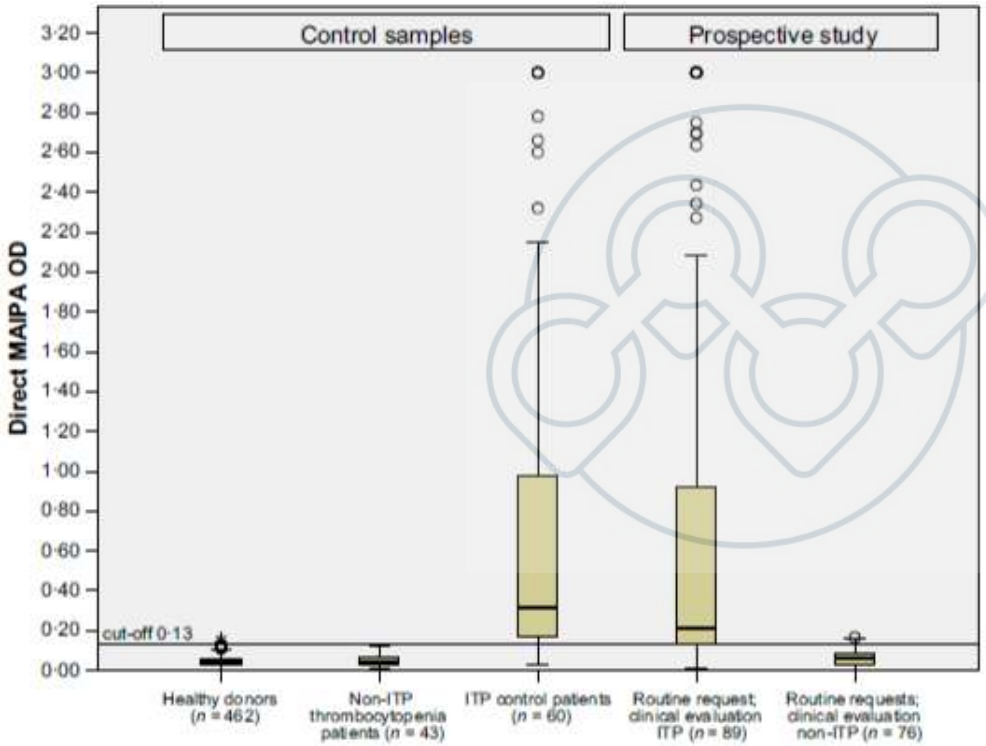
ORIGINAL PAPER

Anti-platelet antibody immunoassays in childhood immune thrombocytopenia: a systematic review

Cleveland, OH; [14]Royal London Hospital, Barts Health NHS Trust, London, United Kingdom; [15]Haematology Theme Oxford Biomedical Research Centre, Oxford University Hospitals NHS Foundation Trust, Oxford, United Kingdom; [16]Hematology Project Foundation, Affiliated to the Department of Cell Therapy and Hematology, San Bortolo Hospital, Vicenza, Italy; [17]Department of Haematology, University College London Hospital, Cardiometabolic Programme-NIHR UCLH/UCL BRC, London, United Kingdom; [18]Department of Blood Transfusion, Osaka University Hospital, Osaka, Japan; [19]Sir YK Pao Centre for Cancer and Department of Medicine and Therapeutics, Prince of Wales Hospital, The Chinese University of Hong Kong, Shatin, NT, Hong Kong; [20]SC Ematologia, Azienda Sanitaria Universitaria Integrata, Trieste, Italy; and [21]Division of Hematology, Massachusetts General Hospital, Harvard Medical School, Boston, MA

Detection of platelet autoantibodies to identify immune thrombocytopenia: state of the art

British Journal of Haematology, 2018, 182, 423–426



Performance characteristics of platelet autoantibody testing for the diagnosis of immune thrombocytopenia using strict clinical criteria

British Journal of Haematology, 2021, 194, 439–443

Key points

- The application of strict clinical criteria to classify patients with immune thrombocytopenia (ITP) increased the sensitivity of platelet autoantibody testing using the direct antigen capture assay by 16·4% (from 48.3–64.7%).
- With high specificity, the platelet autoantibody test may be useful to rule-in ITP; patients with the highest platelet autoantibody values had the highest likelihood of having ITP.

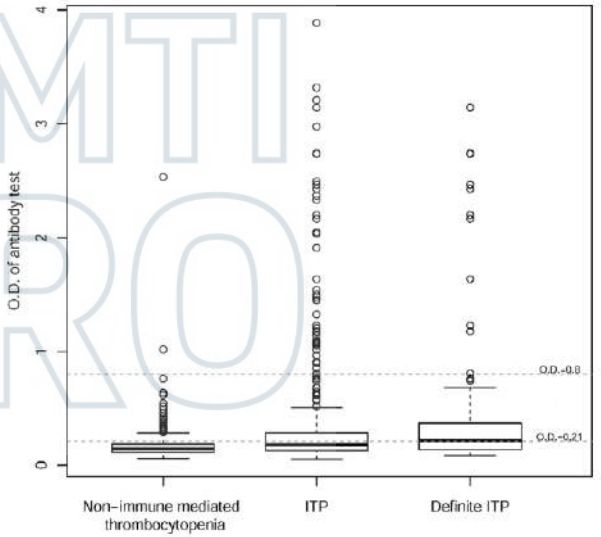


Fig 1. Box plot of optical density (OD) values for platelet autoantibody testing for non-immune-mediated thrombocytopenia patients [median 0·15; interquartile range (IQR) 0·12–0·20], all immune thrombocytopenia (ITP) patients (median 0·18; IQR 0·13–0·29) and for definite ITP patients (median 0·21; IQR 0·14–0·37).

Punti critici: piastrinopenia severa (<10x10^9/L), recente trasfusione piastrinica, anticorpi sequestrati, terapia cortisonica in atto, oppure meccanismi alternativi come la distruzione cellulo-mediata o anticorpi verso la trombopoietina o il suo recettore

Journal of Thrombosis and Haemostasis, **17**: 787–794 DOI: 10.1111/jth.14419

2019

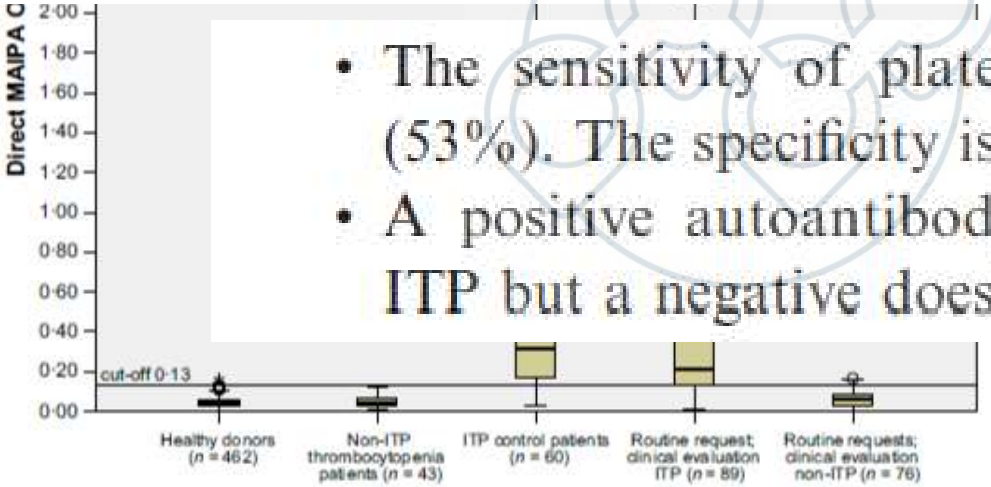
ORIGINAL ARTICLE

The sensitivity and specificity of platelet autoantibody testing in immune thrombocytopenia: a systematic review and meta-analysis of a diagnostic test

JOHN R. VRBENSKY,* JOYCE E. MOORE,* DONALD M. ARNOLD,*†‡ JAMES W. SMITH,* JOHN G. KELTON*† and ISHAC NAZY*†

*Department of Medicine, Michael G. DeGroote School of Medicine, McMaster University, Hamilton, Ontario; †McMaster Centre for Transfusion Research, Hamilton, Ontario; and ‡Canadian Blood Services, Hamilton, Ontario, Canada

- The sensitivity of platelet autoantibody testing is low (53%). The specificity is high (> 90%).
- A positive autoantibody test can be useful to rule in ITP but a negative does not rule out ITP.



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Current Status of and Global Trends in Platelet Transfusion Refractoriness From 2004 to 2021: A Bibliometric Analysis

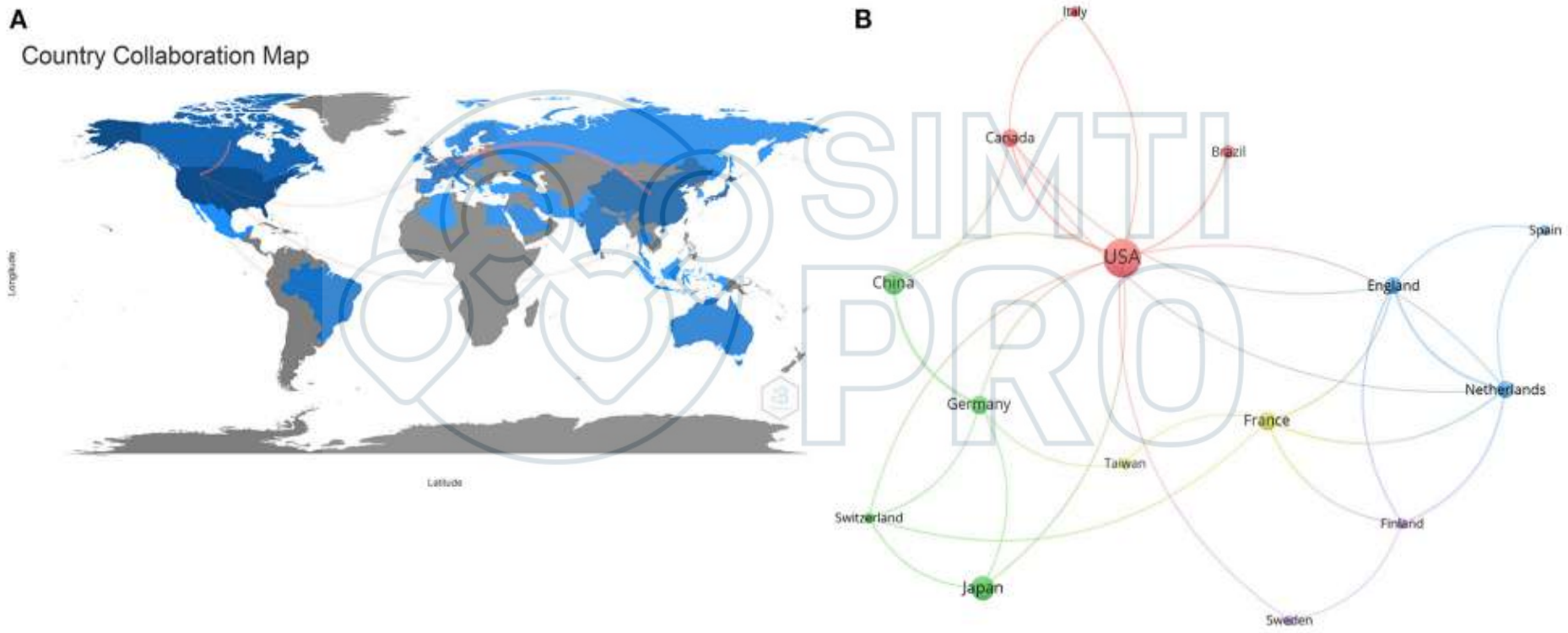
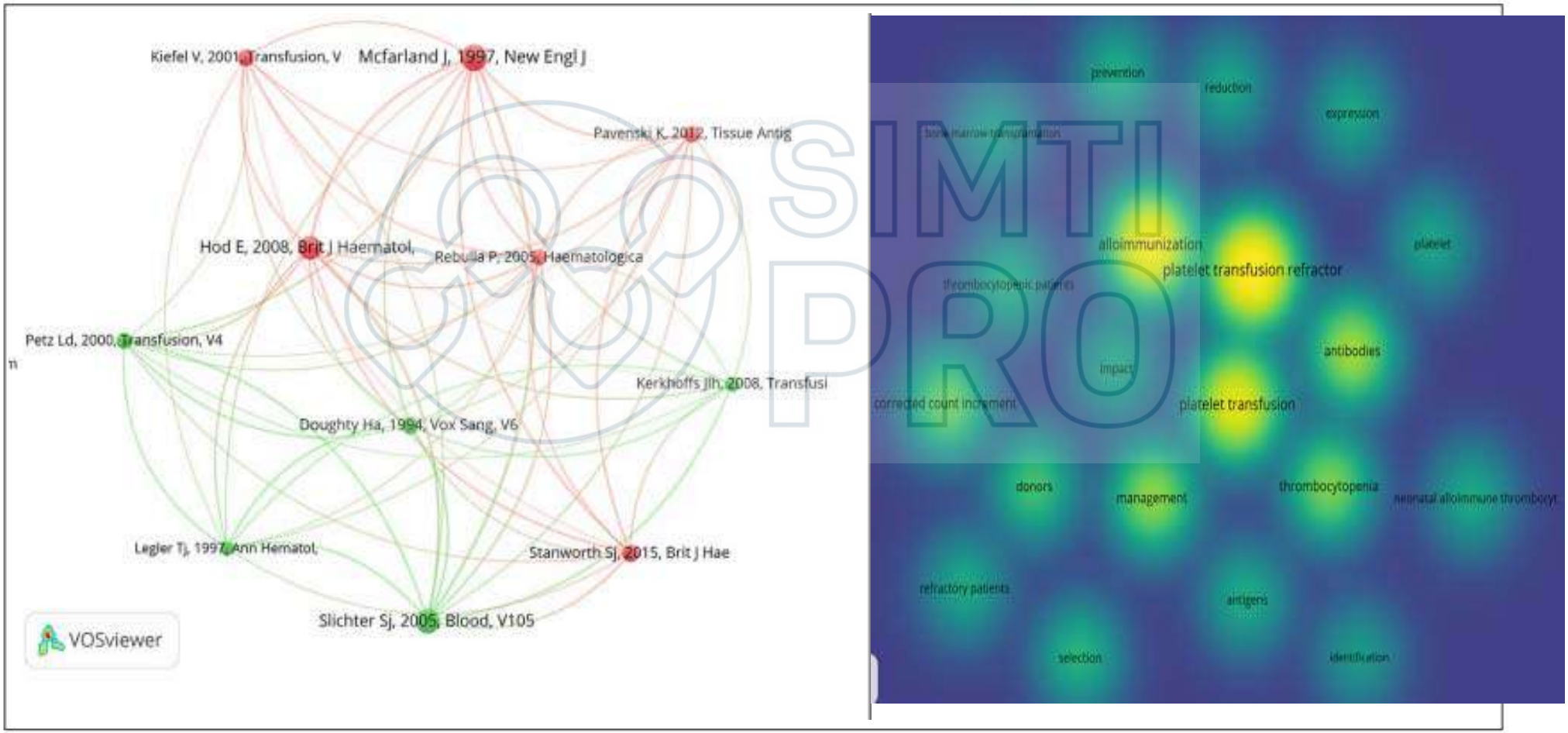


FIGURE 3 | Analysis of countries of publications in PTR research. **(A)** Coloring the distribution of countries with publications in PTR research. The line between countries shows their connection. **(B)** Network map of co-authorship between countries with more than five publications. The thickness of the line indicates the strength of the relationship.

Current Status of and Global Trends in Platelet Transfusion Refractoriness From 2004 to 2021: A Bibliometric Analysis



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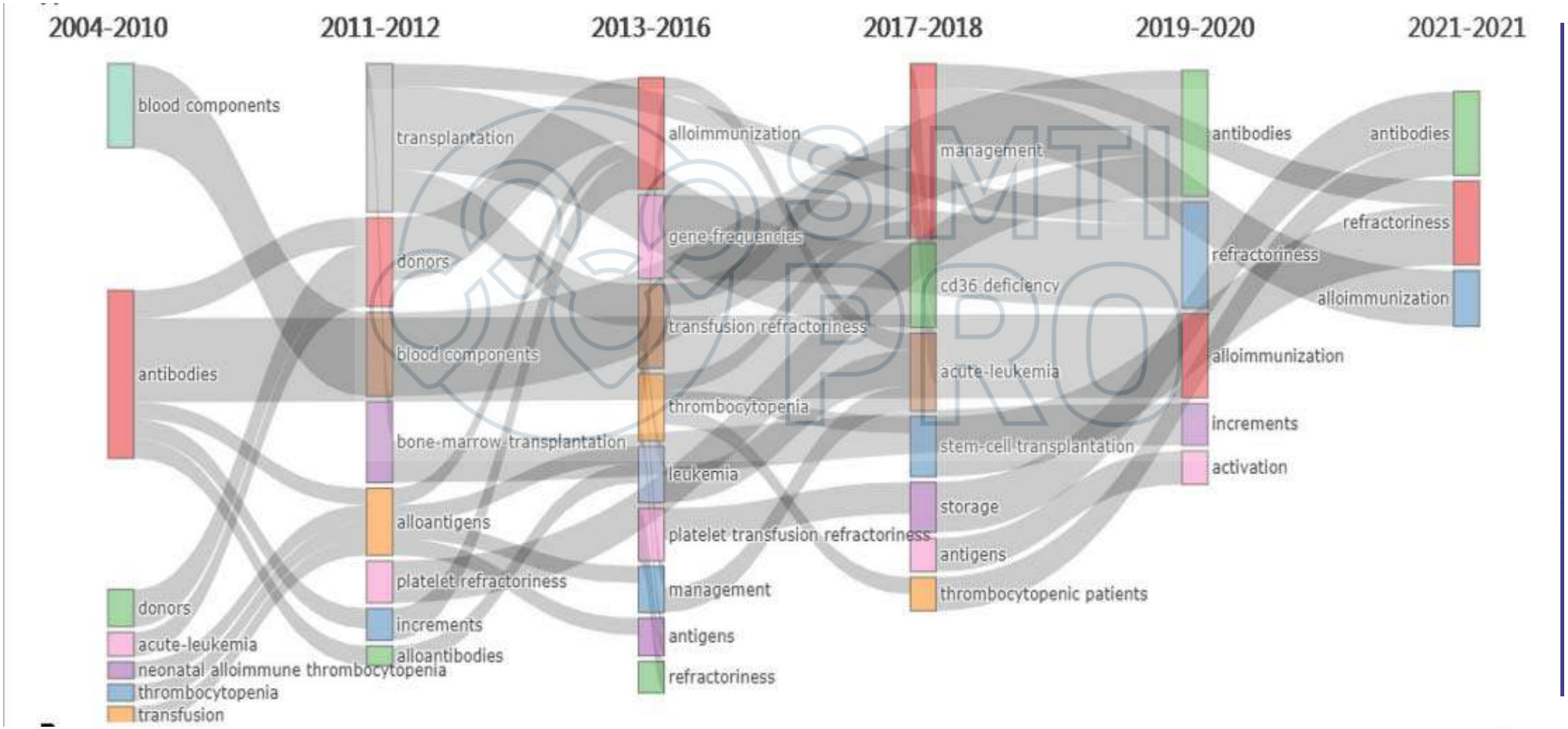


REFRATTARIETA' ALLA TRASFUSIONE PIASTRINICA

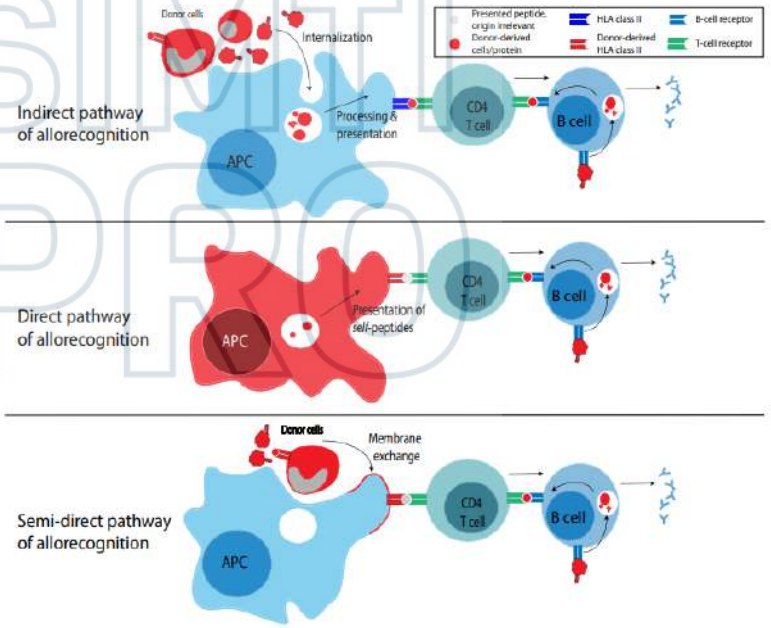
L'inefficacia alla trasfusione piastrinica si verifica nel 20-40% dei prodotti trasfusi

Refrattarietà: 5 – 14 % dei pazienti oncoematologici

Refrattarietà: mancato incremento in 2/3 episodi trasfusionali consecutivi

La refrattarietà piastrinica influisce in modo significativo sull'*outcome* (gg ricovero, rischio emorragie, ridotta sopravvivenza), sull'*utilizzo appropriato* (ricerca unità compatibili o elevato n. di unità assegnate random) dei concentrati piastrinici e sui *costi* ad essi associati. Spesso è misconosciuta e la gestione non è univoca, causa ritardi e sprechi, maggiore rischio per il paziente.

Am J Clin Pathol 2019;151:353-363



HLA-Mediated Platelet Refractoriness

An ACLPS Critical Review

Amy E. Schmidt, MD PhD, Majed A. Refaai, MD, and Myra Coppage, PhD

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ELSEVIER

Human Leukocyte Antigen Alloimmunization and Alloimmune Platelet Refractoriness

Anno Saris [a,1], Katerina Pavenski [b,*]

REFRATTARIETA' ALLA TRASFUSIONE PIASTRINICA

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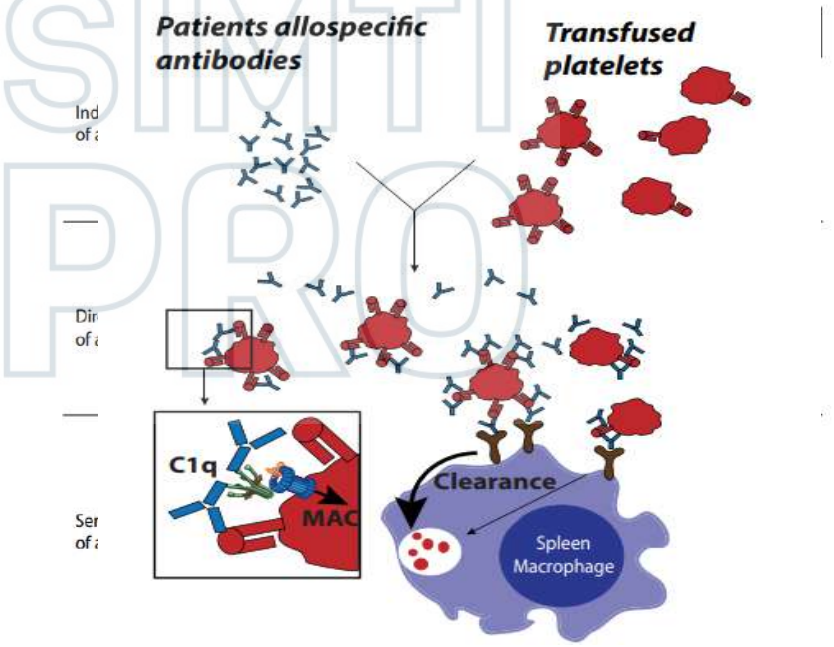

HLA-Mediated Platelet Refractoriness

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Human Leukocyte Antigen Alloimmunization and Alloimmune Platelet Refractoriness

Anno Saris [a,1], Katerina Pavenski [b,*]

Evaluation and management of platelet transfusion refractoriness

Blood Res 2022

Table 2. Etiology of platelet transfusion refractoriness.

Immune factors (<20%)	Non-immune factors (>80%)
Antibodies to HLA class I (80–90%)	Accerlerated platelet consumption (MAHA, DIC)
Antibodies to HPA (10–20%)	Active bleeding
ABO-mismatched platelets	Medications (Infectious disease agents; ampicillin, amoxicillin, cephalosporins, penicillin, piperacillin/tazobactam, rifampin, sulfonamides and vancomycinHistamin-receptor antagonists: cimetidine, famotidine etc., Analgesic; acetaminophen, fentanyl, ibuprofen, and naproxen chemotherpeutics and immunosuppressants: rituximab, and cyclosporin antithrombotics; heparin and GPIIb/IIIa antagonists)
Antibodies to drug-platelet glycoprotein complex	Graft-versus-host disease
Autoimmune (unknown)	Splenic sequestration
	Poor platelet quality

Abbreviations: DIC, diffuse intravascular coagulation; GPIIb/IIIa, glycoproteinIIb/IIIa; HLA, human leukocyte antigen; HPA, human platelet antigen; MAHA, microangiopathic hemolytic anemia.

Transfusion Medicine Reviews 34 (2020) 242–249

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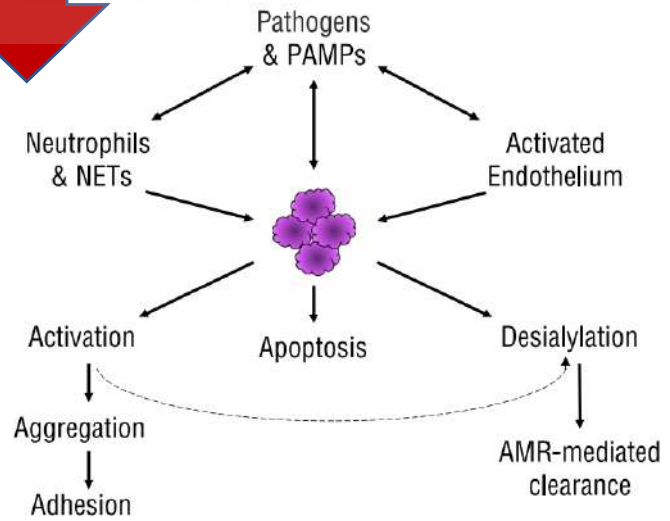
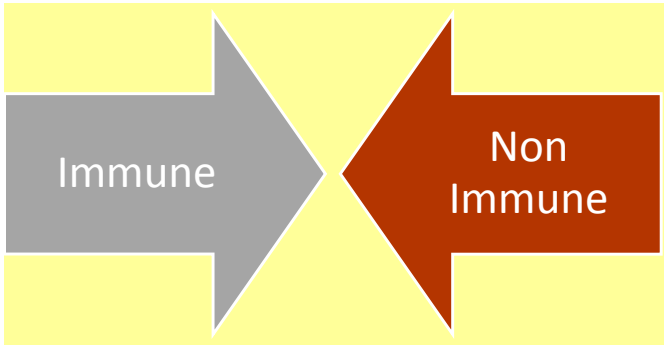
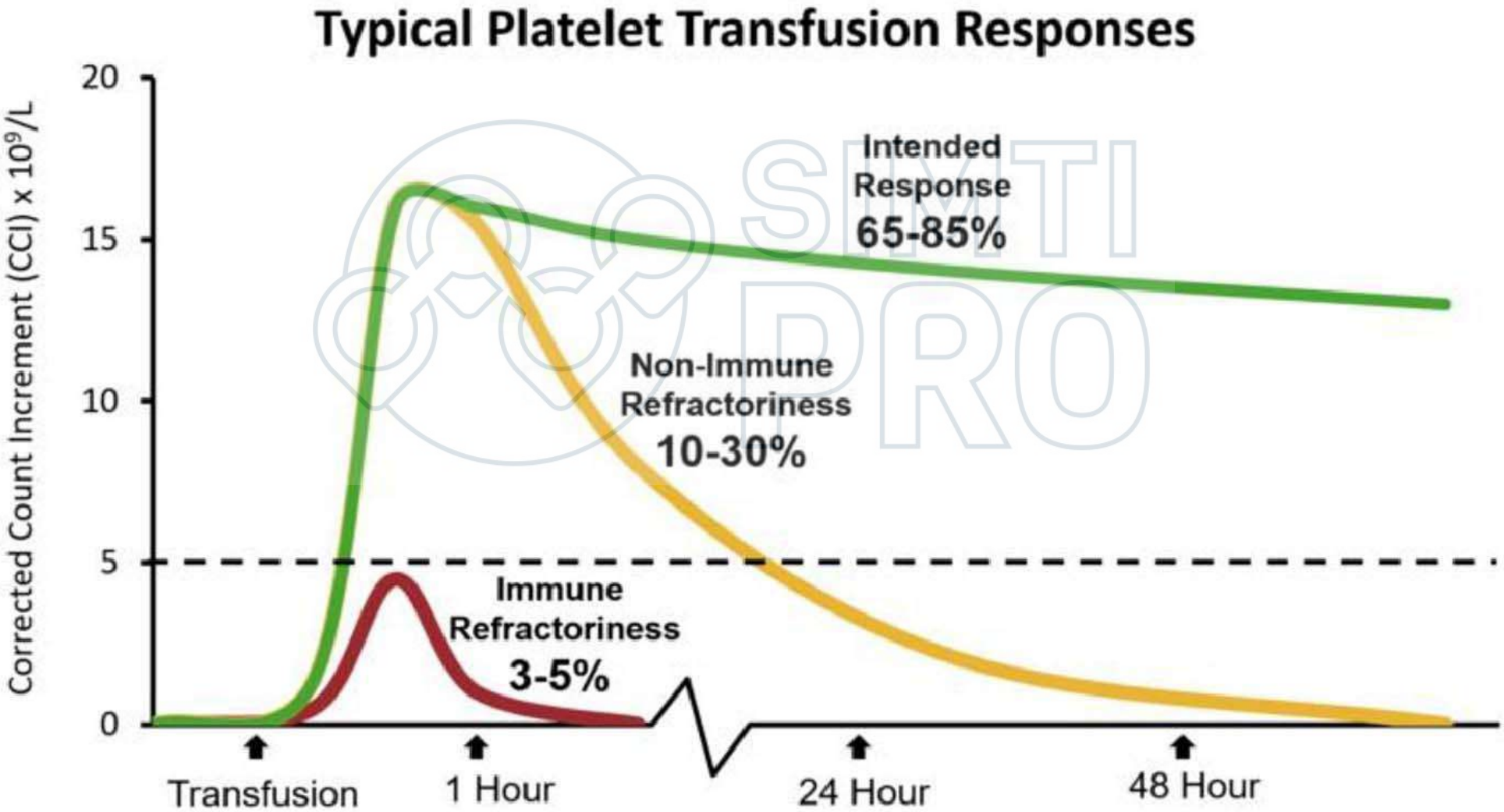
Non-Alloimmune Mechanisms of Thrombocytopenia and Refractoriness to Platelet Transfusion

Roger Belizaire [a], Robert S Makar [b,*]







Biol Blood Marrow Transplant 26 (2020) S96S255

Evaluation and management of platelet transfusion refractoriness

Blood Res 2022

Table 1. Various formula to assess platelet transfusion refractoriness (modified from Rebulla,1993).

Post-transfusion platelet increment (PPI) = (post-transfusion platelet count)-(pre-transfusion platelet count)

$$\textit{Corrected count increment (CCI)} = \frac{\textit{PPL (/μL)} \times \textit{BSA (m}^2\textit{)}}{\textit{Number of platelets transfused (10}^{11}\textit{)}}$$

>7500 1h; >4500 18-24 h

$$\textit{Percentage platelet recovery (PPR)} = \frac{\textit{PPL (/μL)} \times \textit{TBV} \times 100\%}{\textit{Number of platelets transfused (10}^{11}\textit{)}}$$

>20 % 18-24 h

Percentage platelet increment (PPI) = PPR/0.67 (0.67 accounts for splenic pooling)

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

Table 3. Comparison of methods used to identify compatible platelet units for alloimmunized patients

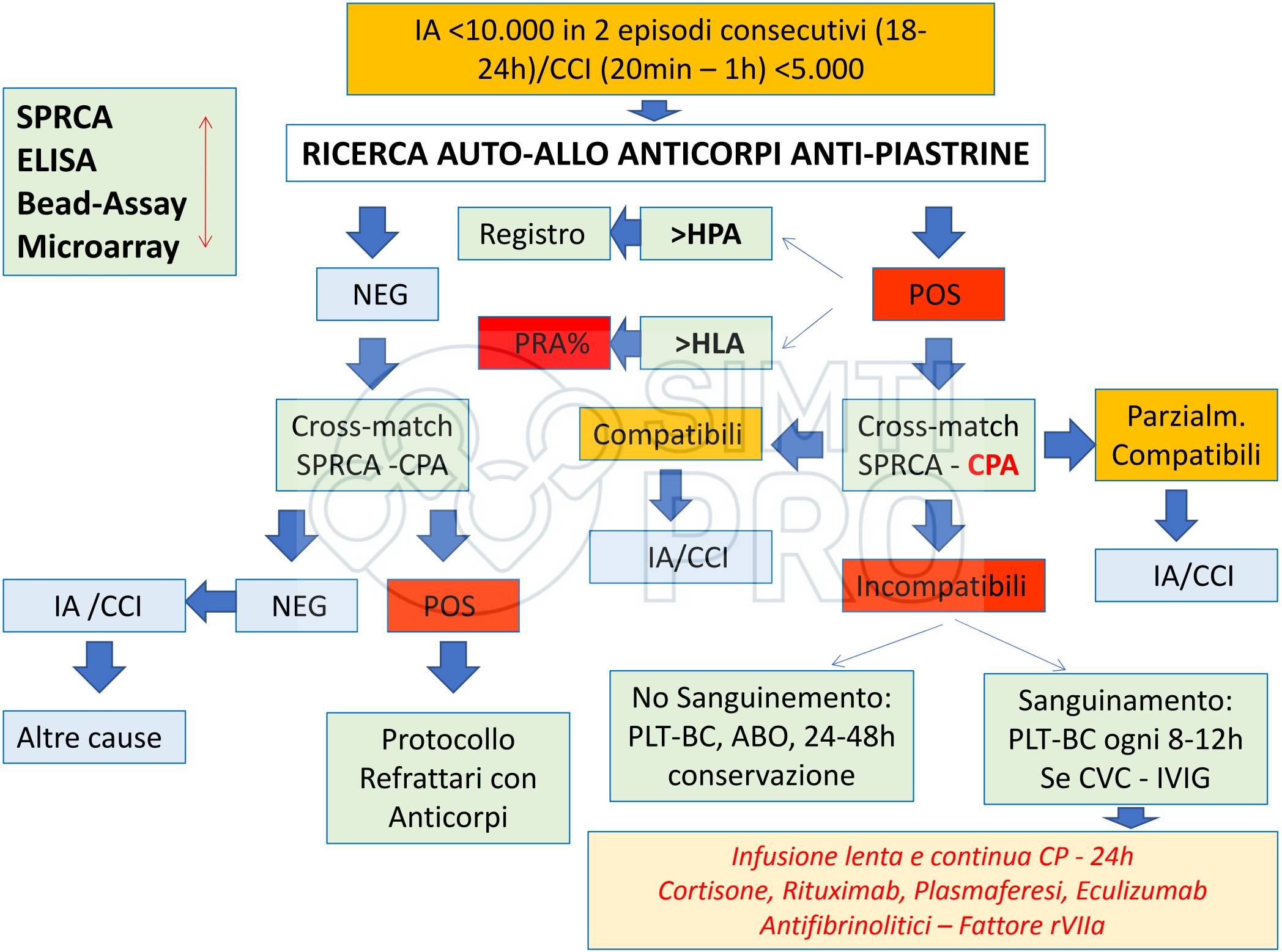
	Crossmatched	HLA matched	HLA compatible
Method	Test patient's serum against a panel of platelets to determine compatibility	Identify platelet donors with perfect (4/4) match for patient's HLA class IA and IB alleles	ASP: Use antibody specificities to select donor units that lack corresponding antigens
Pros	• Rapid turnaround-time	• 4/4 match ensures HLA compatibility	• Larger donor pool
	• Obtain compatible units without HLA genotype or HLA antibody testing	• Reduced risk of future alloimmunization	• Reduced risk of future alloimmunization
	• Compatible with HLA and HPA antibodies		
Cons	• Difficult to find compatible units for highly alloimmunized patients	• HLA genotyping required	• Not useful for HPA antibodies
	• Risk of alloimmunization for mismatched HLA antigens	• Limited donor pool for some patients	• HLA antibody testing required

Table adapted from Forest and Hod.[1]
ASP, antibody specificity prediction.

REGISTRO DONATORI AFERESI TIPIZZATI

Platelet transfusion refractoriness: how do I diagnose and manage?

Hematology 2020


IA <10.000 in 2 episodi consecutivi (18-24h)/CCI (20min – 1h) <5.000
SPRCA
ELISA
Bead-Assay
Microarray
RICERCA AUTO-ALLO ANTICORPI ANTI-PIASTRINE
Registro
>HPA
NEG
POS
PRA%
>HLA
Cross-match SPRCA -CPA
Compatibili
Cross-match SPRCA - CPA
Parzialm. Compatibili
IA/CCI
IA/CCI
IA /CCI
NEG
POS
Incompatibili
Altre cause
Protocollo Refrattari con Anticorpi
No Sanguinemento: PLT-BC, ABO, 24-48h conservazione
Sanguinamento: PLT-BC ogni 8-12h Se CVC - IVIG
Infusione lenta e continua CP - 24h
Cortisone, Rituximab, Plasmaferesi, Eculizumab
Antifibrinolitici – Fattore rVIIa

Porpora post-trasfusionale

Frequenza e anticorpi

- Evento raro (1:50.000-100.000 unità trasfuse)
- Piastrinopenia severa (<15x10^9/L dopo trasfusione GR/PLT (5-10gg) . ICH 5-10% casi
- Diagnosi differenziale con HIT, infezioni, farmaci, patologia ematologiche, splenomegalia
- *Case report*

Meccanismo patogenetico

- Pregresse gravidanze o trasfusioni
- Anticorpi anti-HPA-1a (più frequente), HPA-5b
- Immunocomplessi
- Adsorbimento di Ag solubile
- Autoanticorpi

Trattamento

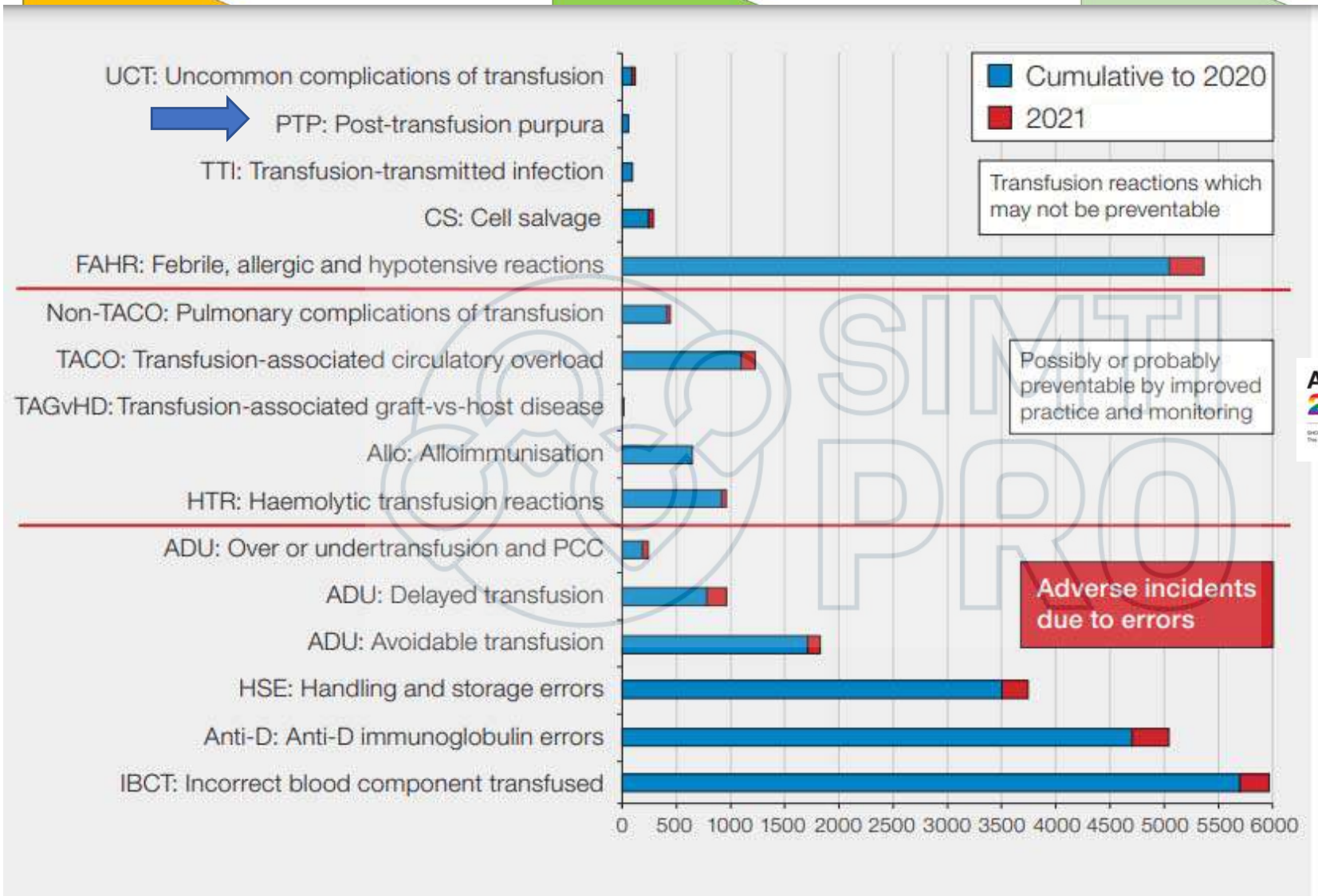
- IVIG (1g/Kg x 2gg) risposta entro 5gg
- Steroidi, pl
- NON INDIC
  TRASFUSIO
- Trasfusione GR antigene-neg lavate (?)
- TRASFUSIONI SUCCESSIVE: CP ANTIGENE-NEG (HPA)
- Prevenzione FNAIT (Card)

Open Access Full Text Article REVIEW

Post-Transfusion Purpura: Current Perspectives

Journal of Blood Medicine 2019:10 405–415

Porpora post-trasfusionale



Cumulative data for SHOT categories 1996-2021 n=27008

ANNUAL SHOT REPORT 2021

MHRA SHOT

Open Access Full Text Article

REVIEW

Post-Transfusion Purpura: Current Perspectives

Journal of Blood Medicine 2019:10 405–415

Diagnosi differenziale tra DITP e HIT

Trombocitopenia Eparina-indotta è causata da anticorpi che riconoscono il complesso Eparina-PF4 (in circolo per circa 100gg). Conta piastrinica <150.000, >50% di decremento della conta dopo 5-14 gg dall'assunzione. Colpisce 0.1-5% pazienti esposti. Disordine pro-trombotico (30-50%). Score 4T. Mortalità 20%. Test ELISA e funzionali.Riesposizione??

Trombocitopenia Farmaco-indotta (DITP) può avere diversi meccanismi immuni, 1 caso/100.000. Spesso nadir conta piastrinica inferiore 10-20.000/µL entro 1 settimana dall'assunzione delfarmaco.

Table 1. Mechanisms involved in different types of drug-induced immune thrombocytopenia (DITP).

Type	Mechanism	Examples	References
Hapten-induced antibody	Drug binds to platelet membrane and promotes antibody response	Penicillin and derivatives, cephalosporins	[13–16]
"Quinine-type" antibody	Drug binds to antibody Fab and/or membrane glycoprotein (GP), thereby enhancing antibody affinity and binding to platelet GP	Quinidine, quinine, antibiotics (vancomycin, rifampicin, sulfamethoxazol), anticonvulsants	[3–5,17,18]
Drug-specific antibody	Antibody recognizes the monoclonal antibody bound to its target	abciximab	[19–21]
Fibrinogen receptor antagonist-dependent antibody	Drug binds to GPIIb/IIIa inducing conformational changes, then recognized by antibody	tirofiban, eptifibatide	[22]
Autoantibody induction	Drug induces formation of autoantibody that binds alone to platelet GP	procainamide, gold salts, L-dopa, and likely several therapeutic monoclonal antibodies	[23–33]
Immune complexes	Drug binds to PF4 inducing antibodies that activate platelets via FcγRIIa receptors	heparin, protamine	[11,12,34–36]

DITP: drug-induced immune thrombocytopenia; PF4: platelet factor 4; GPIIb/IIIa: glycoprotein IIb/IIIa.

Diagnosi differenziale tra DITP e HIT

Tron
indo
anti
il complesso Eparina-PF4
(in circolo per circa 100gg).
Cont
>50%
cont
dall'
0.1-5% pazienti esposti.
Disordine pro-trombotico
(30-
Mor
funz

Comparsa trombocitopenia/Media conta piastrinica

DITP: ore-giorni, $10x10^9/L$

HIT: 5-10gg, $50x10^9/L$

conta piastrinica inferiore 10-20.000/µL entro 1 settimana

Manifestazioni cliniche/Test diagnostici

DITP: Emorragie, citofluorimetria o altro

HIT: Trombosi, ELISA o test funzionali

Trattamento/Persistenza anticorpi/Ri-esposizione

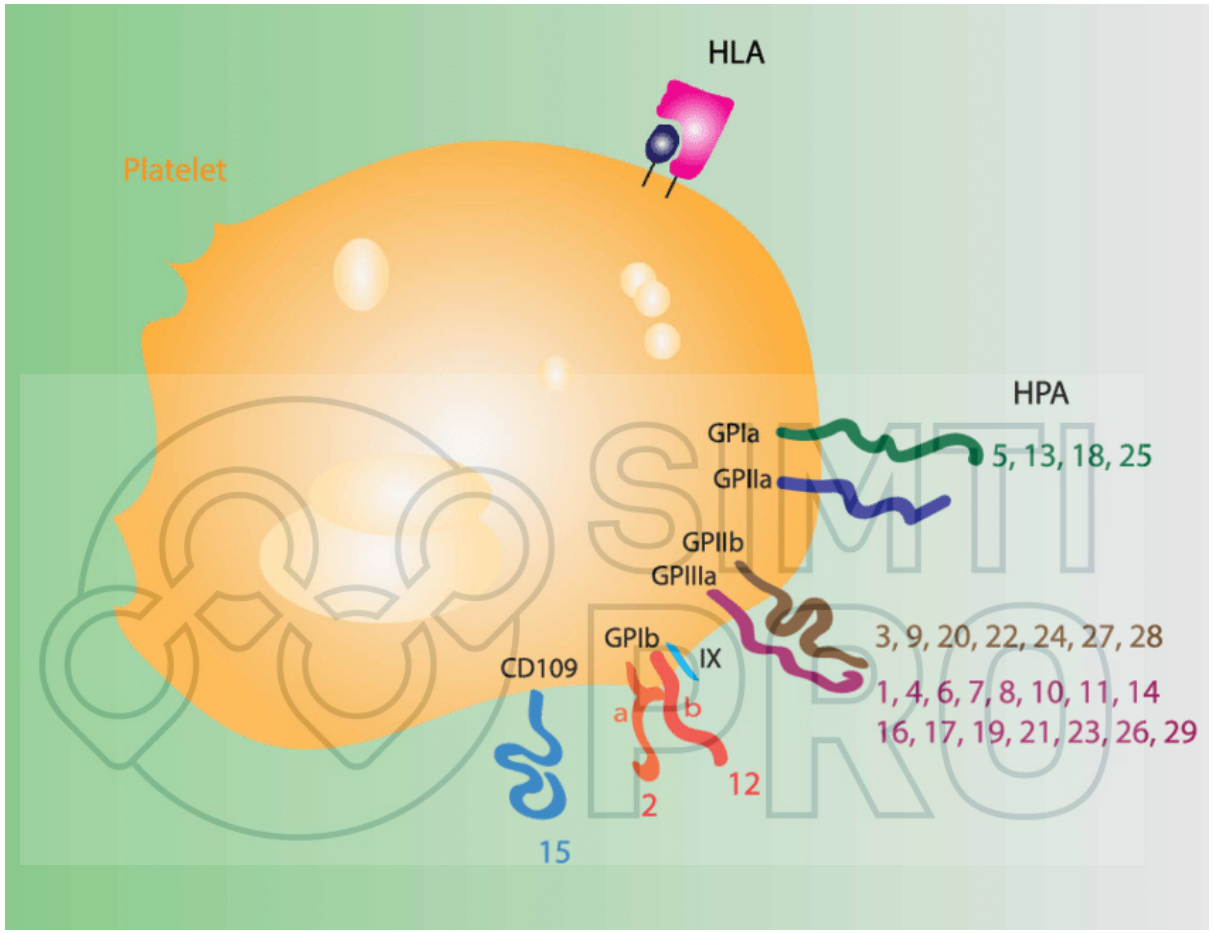
DITP: interruzione farmaco, persistenza non definita , no ri-esposizione

HIT: interruzione eparina , persistenza 50-80 gg , probabile ri-esposizione??

DITP).
erences
3–16]
cephalosporins
antibody response
Drug binds to antibody Fab and/or membrane glycoprotein (GP), thereby enhancing antibody affinity and binding to platelet GP
Quinidine, quinine, antibiotics (vancomycin, rifampicin, sulfamethoxazol), anticonvulsants
[3–5,17,18]
9–21]
[22]
3–33]
Immune complexes
Drug binds to PF4 inducing antibodies that activate platelets via FcγRIIa receptors
heparin, protamine
[11,12,34–36]
DITP: drug-induced immune thrombocytopenia; PF4: platelet factor 4; GPIIb/IIIa: glycoprotein IIb/IIIa.

CONCLUSIONI

- Come per la diagnostica immunoematologica eritrocitaria, anche per quella piastrinica è necessario avere a disposizione metodi diversi comprese le tecniche molecolari (Laboratori di Riferimento)
- I metodi PSFIT e SPRCA sono molto sensibili, ma meno specifici e sono quindi indicati per lo screening e i cross-match
- I metodi ELISA (tranne MAIPA) sono meno sensibili, ma permettono l'identificazione delle specificità allo e autoanticorpali
- Il Bead-Based Assay (metodo sensibile) è di recente applicazione
- Nella ITP è comunque utile eseguire i *test* come supporto alla diagnosi clinica
- Nella diagnostica della NAIT va considerato il tipo di incompatibilità HPA per approfondire la ricerca anticorpale (HPA-3, HPA-15)
- Algoritmo decisionale per RPT e monitoraggio efficacia trasfusionale
- Implementazione di programmi di Proficiency Testing



GRAZIE PER L'ATTENZIONE