



How To Manage Platelet Refractoriness

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1

Overview

Introduction

Triggers and Indications for platelet transfusion

Platelet transfusion response monitoring

Risks associated with Platelet Transfusion

Platelet Refractoriness

Etiology

Diagnosis

Management

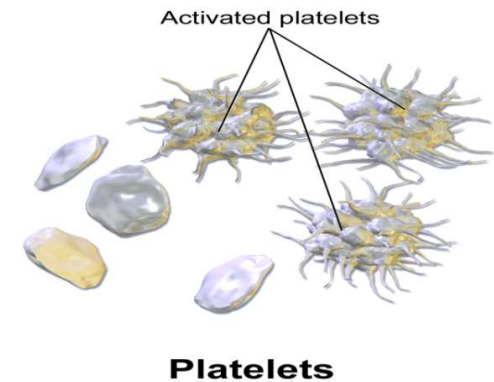
Practical Approach: Case Discussions

Introduction

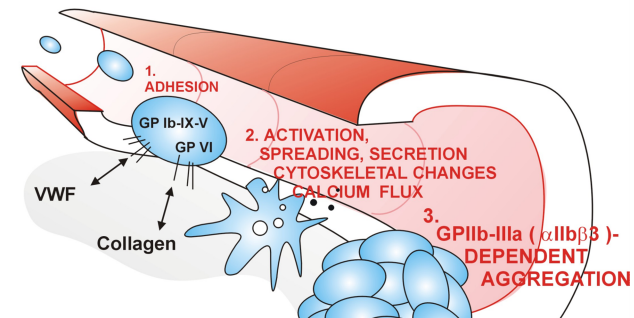
Platelet transfusion refractoriness is defined as a lack of adequate response in post-transfusion platelet increment after two or more consecutive platelet transfusions of an adequate dose of platelets

Introduction

- Platelets are essential for normal hemostasis
- Platelets are transfused into individuals with thrombocytopenia or platelet dysfunction for two indications:
 - To stop bleeding (therapeutic platelet transfusions)
 - To prevent bleeding (prophylactic platelet transfusions)



Platelet Adhesion Receptors and Normal Haemostasis



Indications for platelet transfusion

Recommendation	Platelet count	Grade
Prophylactic	<10,000	Strong recommendation; moderate-quality evidence
Elective central venous catheter placement	<20,000	weak recommendation; low-quality evidence
Elective diagnostic lumbar puncture	<50,000	weak recommendation; low-quality evidence
Major elective non-neuraxial surgery	<50,000	weak recommendation; low-quality evidence
Surgeries involving the central nervous system	<80,000- 1,00,000	Low-Quality evidence

Assessing the effectiveness of platelet transfusion

- Standard dose of platelets:
 - Six units of RDP or one apheresis platelet unit (SDP)
- Expected post-transfusion increment of about 30,000 to 60,000 platelets/ μ L -1 hour after platelet transfusion (AABB 20th ed.)
- To assess the response 2 things done :
 - Whether bleeding has stopped
 - Measuring post-Tx increment
- The post Tx increment measurement different formulae
 - Post-transfusion increment (PI)
 - Percent platelet recovery (PPR)
 - Corrected count increment (CCI)

Platelet transfusion response-monitoring

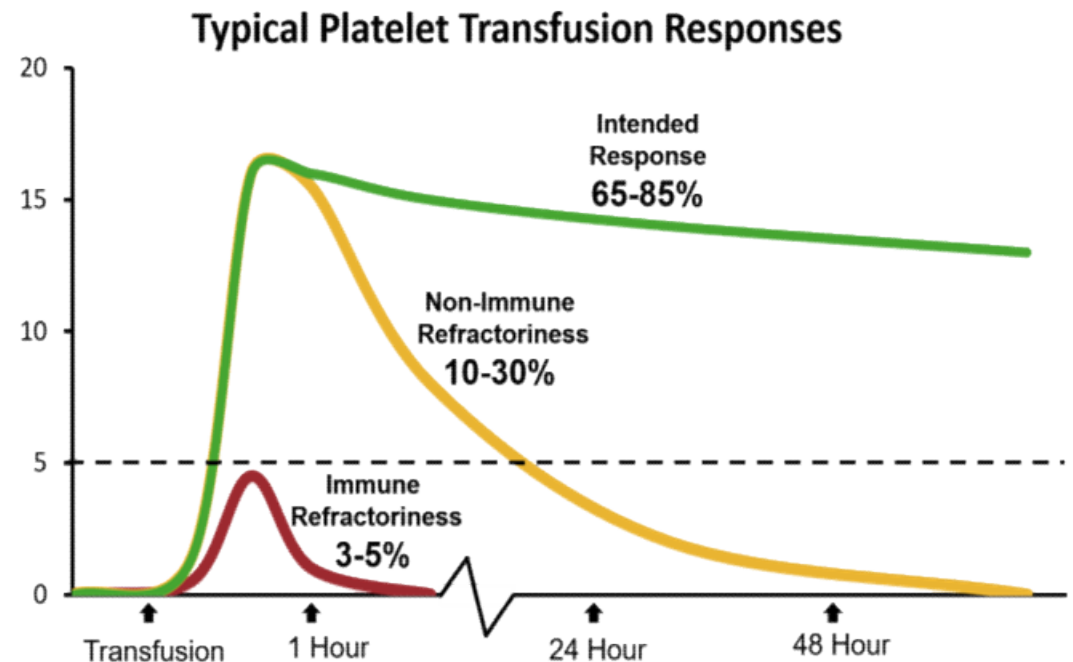
- Calculation of either a Corrected Count Increment Post-transfusion Platelet Recovery
 - 10-60 minutes and
 - 20-24 hours after transfusion

$$CCI = \frac{(\text{post-transfusion platelet count}/\mu\text{L} - \text{pretransfusion platelet count}/\mu\text{L}) \times \text{body surface area (m}^2\text{)}}{\text{No. of platelets transfused} \times 10^{11}}$$

$$PPR = \frac{(\text{post-transfusion platelet count}/\mu\text{L} - \text{pretransfusion platelet count}/\mu\text{L}) \times \text{total blood volume} \times 100\%}{\text{No. of platelets transfused} \times 10^{11}}$$

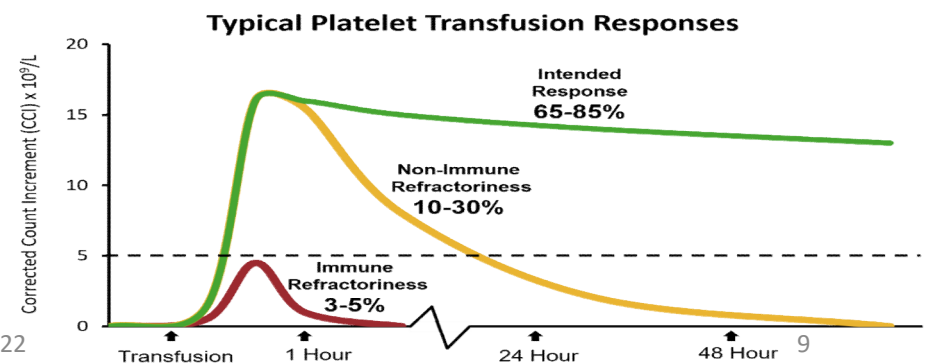
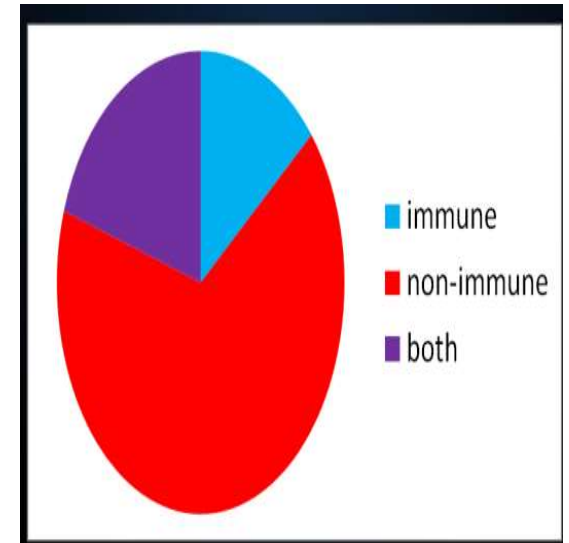
Response to Platelet Transfusion

- The intended response of a platelet transfusion is a substantial increase in CCI within 1 hour of transfusion and good survival of platelets for about two days
- If the transfused platelets lead to a sufficient 1-hour CCI but do not survive until the next day patients are said to be “non-immune refractory.
- When there is insufficient recovery of transfused platelets this leads to inadequate 1-hr CCIs in 3-5% of transfusion recipients and they are said to be immune refractory due to alloimmunization



Platelet Transfusion Response

- Some patients **do not achieve desired therapeutic effects** despite adequate dose and product quality
- Causes for inadequate response
 - Immune causes
 - Nonimmune causes
 - Both



Risks associated with platelet transfusion



Alloimmunization



Transmission of infection



Allergic reactions



Bacterial Infections



Refractoriness to platelet transfusion

Refractoriness and Alloimmunization

Refractoriness to platelet Tx may be defined as a consistently inadequate response to platelet Tx.

Alloimmunization → development of alloantibodies that have the potential to produce an inadequate response to platelet Tx

It is erroneous to use these terms interchangeably, patients who are refractory to platelet Tx are not necessarily alloimmunized & patients who are alloimmunized may respond well to platelet Tx.

Criteria for refractoriness

DGHS

- Patient is said to be refractory to platelet transfusion if increment in platelet count at one hour after transfusion is less than 20% of the expected increase in value on 2 occasions

BCSH

- Post transfusion platelet corrected count increment (CCI) of less than $7.5 \times 10^9/L$ at 1 hour and $4.5 \times 10^9/L$ at 20-24 hours

AABB

CCI at 1 hour post transfusion of <5000 to 7500 after two sequential ABO compatible platelet transfusion

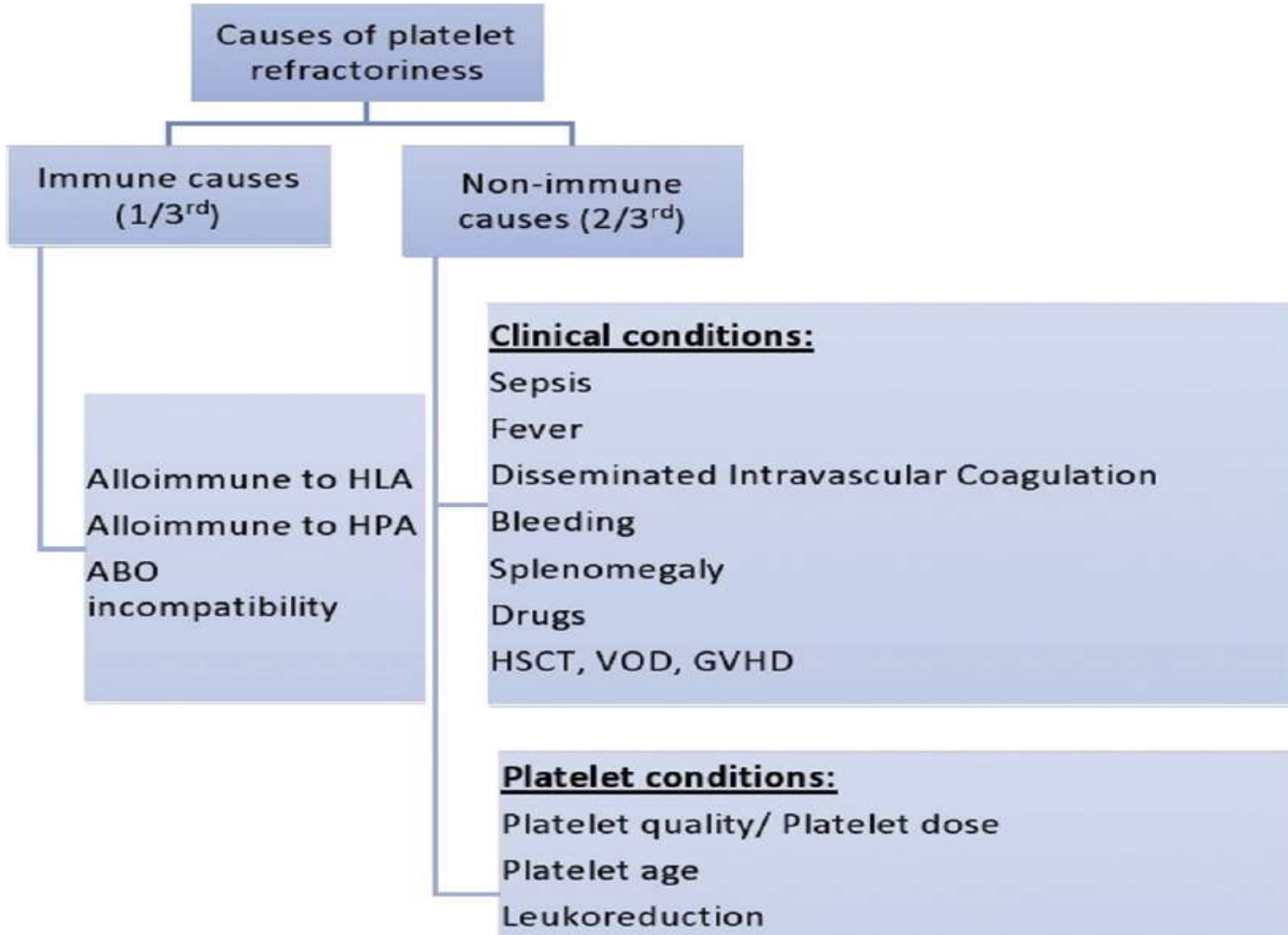
(AABB 20th ed.)

Clinical implications of Platelet Refractoriness

Platelet refractoriness is associated with several adverse outcomes including:

- Increased risk of bleeding (Toor *et al* , [2000](#); Kerkhoffs *et al* , [2008](#))
- Decreased survival (Kerkhoffs *et al* , [2008](#))
- Longer hospital stays (Meehan *et al* , [2000](#))

Etiology of Platelet Refractoriness

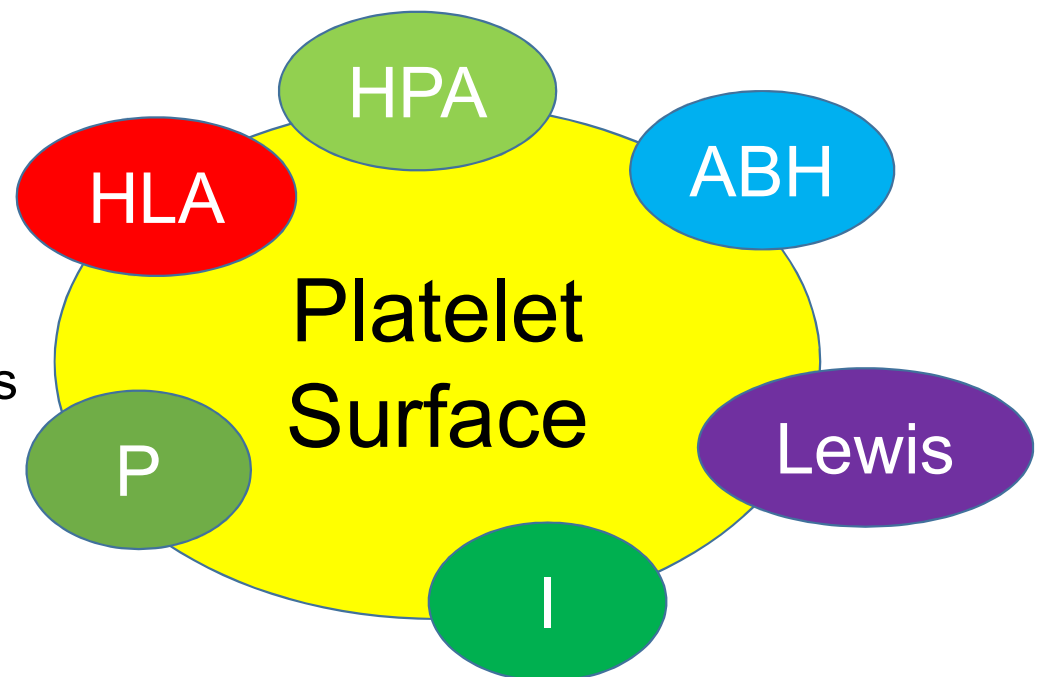


Etiology of Platelet Refractoriness

- **Immune-mediated platelet refractoriness** is due to antibodies made by the patient that recognize an epitope on the transfused platelets, most commonly HLA class I
- **Non-immune-mediated refractoriness** is due to a process other than platelet allo-antibodies which significantly decreases the circulation time of transfused platelets

Immunology of Platelets

- Platelets express a variety of immunogenic markers on the cell surface
- Some are shared with
 - all nucleated cells in the body as (in case of HLA antigens),
 - whereas others are observed to be essentially platelet specific.



Antigens on Platelet surface

Immunisation to HLA antigens

- Alloimmunization is a significant issue in patients who require multiple platelet transfusions; (e.g. hematological malignancies)
- Incidence: HLA alloimmunization among patients receiving multiple transfusions ranges from 20% to 71% (AABB technical manual 18th Edi.)
- Antibodies to class I significantly affect the recovery and survival of transfused platelets
- Risk of HLA alloimmunization is influenced by several patient and blood component factors
 - Underlying disease
 - Number and type of platelet product
 - Transfusion of RBC

Immunization to Platelet Specific Antigens

- In some patients poor response of platelet transfusion despite HLA matching indicates that perhaps PSA are involved
- The incidence of platelet-specific antibodies varies from 2% to 11% and leucoreduction does not affect this incidence
(Kickler et al, 1990; Godeau et al, 1992; Slichter, 1997)

Table 11-2. Platelet Alloimmunization in Multitransfused Patients Receiving Non-Leukocyte-Reduced Blood Components*

Study	No. of Patients	Anti-HLA [†]	Anti-PSA [‡]	Loss/Decrease in Antibody
Seftel et al (2004) ⁵⁷	315	61/315 (19%)		
TRAP (1997) ⁵⁶	131	59/131 (45%)	11/131 (8%)	
Atlas et al (1993) ⁵⁸	134	95/134 (71%)		43/95 (38%)
Meenaghan et al (1993) ⁵⁹	106	37/106 (35%)	45/106 (42%)	29/45 (64%)
Godeau et al (1992) ⁶⁰	50	13/50 (26%)	4/50 (8%)	
Pamphilon et al (1989) ⁶¹	49	20/49 (41%)	11/49 (22%)	12/20 (59%)
Murphy et al (1987) ⁶²	154	55/154 (36%)	5/154 (3%)	30/55 (54%)

Rossi's Principles of Transfusion Medicine 4th edi

Immunization to ABO blood group antigens

ABO-identical versus nonidentical platelet transfusion: a systematic review

TRANSFUSION Volume 49, November 2009

Nadine Shehata, Alan Tinmouth, Gary Naglie, John Freedman, and Kumanan Wilson

- ABO is expressed at low levels on platelet membrane
- Clinical trials comparing ABO identical to unmatched platelets in patients with cancer have suggested higher rates of refractoriness in in unmatched transfusions (AABB 18th Edit.)

BACKGROUND: The significance of ABO matching for platelet (PLT) transfusion has not been clearly defined. The primary objective of this report is to assess whether ABO-identical PLT transfusion is associated with improved mortality and/or morbidity for patients with hematologic/oncologic disorders.

STUDY DESIGN AND METHODS: A systematic review to January 2009 was conducted. Data on mortality, morbidity, PLT refractoriness, and PLT increment after transfusion were abstracted.

CONCLUSION: ABO-identical PLT transfusion results in a higher PLT increment. Randomized controlled trials are required to definitely determine the effect of ABO-identical PLT transfusion on survival, bleeding events, or transfusion reactions.

How To Manage Platelet Refractoriness??

Managing need of Platelet Transfusions

- Careful evaluation of clinical factors and possible risk factors for immunization
- Transfuse to minimize spontaneous bleeding and to treat on-going bleeding
- Fresh ABO-identical platelets transfused to exclude role of ABO antibodies or impaired platelet quality
- In presence of factors associated with increased platelet consumption (fever, sepsis or DIC) → frequent transfusion of platelets rather than increased dosages per transfusion recommend because of impaired platelet survival.
- In splenomegaly → low recovery of transfused platelet but normal survival → increase the platelet transfusion dose
- If consistent poor response to platelet transfusion without clear cause → suspect possibility of drug-induced antibodies. Correlate onset of thrombocytopenia with administration of drug and replace the offending

Managing need of Platelet Transfusions

- For Immune refractoriness
 - Three strategies:
 - HLA matched platelets
 - Antigen specificity prediction
 - Platelet crossmatch

HLA Matched platelets

- Requires HLA matching of both donor and recipient
- HLA-matched donors can be found either among **family members** or **HLA typed donor registry**
- Traditionally, recipient and donors are **matched for HLA - A and B antigens**
- The post transfusion **increment** depends on **degree of match**
- Selection of platelet donors with antigens in the same "cross-reactive groups" (**CREGs**) as the patient's antigens, has been demonstrated to be nearly as successful in supporting alloimmune platelet refractoriness as HLA-matched transfusions (Grade B1X or B2UX)
- **Irradiation before transfusion of HLA matched donor unit**

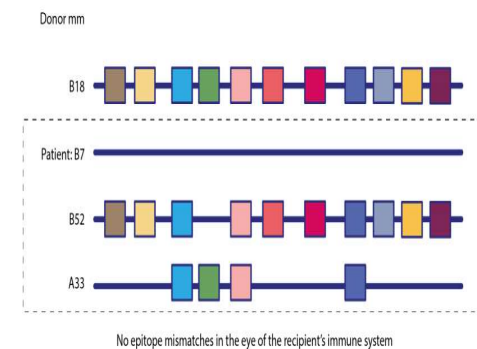
Table 11-3. Classification of Donor/Recipient Pairs on the Basis of HLA Match

A	All four antigens in donor identical to those in recipient.
B1U	Only three antigens detected in donor; all present and identical in recipient.
B1X	Three donor antigens identical to recipient; fourth antigen cross-reactive with recipient.
B2U	Only two antigens detected in donor; both present and identical in recipient.
B2UX	Only three antigens detected in donor; two identical with recipient, third cross-reactive.
B2X	Two donor antigens identical to recipient; third and fourth antigens cross-reactive with recipient.
C	One antigen of donor not present in recipient and non-cross-reactive with recipient.
D	Two antigens of donor not present in recipient and non-cross-reactive with recipient.

Rossi's Principles of Transfusion Medicine 4th edi

Newer approach: Epitope matching protocol

- Another alternative is to provide platelets from donors matched at HLA epitope level
- This is based on the concept that, **HLA antibodies are produced against epitopes** that can be structurally defined as eplets, which are present on different HLA alleles.
- HLA antigens have multiple epitopes that can be recognized by antibodies
- Epitopes are short sequence linear of amino acid residues that form a cluster on a molecular surface
- Thus instead of matching for HLA types, **matching can be performed for epitopes**
- The computer program used to perform epitope based matching
- Virtual crossmatch is done by determining the acceptable and unacceptable mismatches –HLA Matchmaker



Jas et al., Hum Immunol 2006

<http://www.HLAMatchmaker.net>

Antibody specificity prediction HLA-antigen negative "compatible" platelets

- An alternative method is the selection of platelets **according to the patient's HLA antibody specificity**, called the antibody specificity prediction (ASP) method.
- This is a similar approach to the technique used to provide compatible RBCs for patients who have RBC antibodies.
- In this method, **donors lacking the antigen** to the antibody that the patient has are selected
- The patient is HLA -A and B typed, the specificities of the patient's HLA antibodies are determined, entered in computer for search of compatible donors

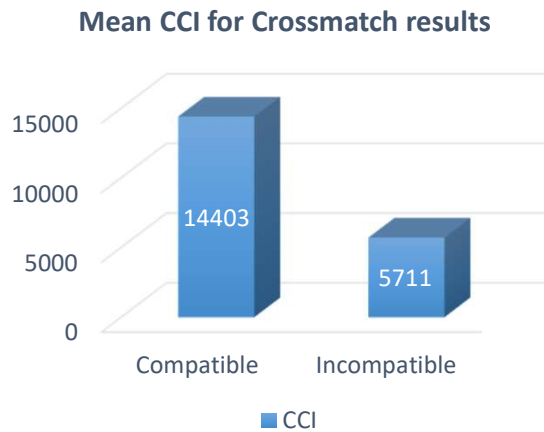
Limitations: HLA-matched platelets

- Requires **large pool** of HLA matched donors
- **Daily requirement** of HLA matched donors for several weeks seems impossible to support
- Costly, Time consuming,
- Up to 25% -40% of HLA-matched transfusions fail to give satisfactory post-transfusion platelet increment (*Dahlke MB, Weiss KL: Platelet transfusion from donors mismatched for crossreactive HLA antigens. Transfusion 24:299,1984*)

Platelet Crossmatch

- An alternative approach is to identify compatible units by cross-matching with the patient's plasma
- Different methods available
 - Enzyme-linked immunosorbent assay (ELISA)
 - Flow cytometry
 - Solid-phase procedures (SPRCA)
- Quick, Relatively low cost, Convenient
 - test can be completed before the availability of patient's HLA type and HLA antibody testing
 - Need for large pool of donors can be avoided
- Along with HLA, HPA compatibility can also be identified

Platelet crossmatch



Compatibility and CCI

Crossmatch result	CCI		Total	P value
	Adequate	Inadequate		
Compatible	34 (87.2%)	5(12.8%)	39	0.000* *p value
Incompatible	2(18.2%)	9(81.8%)	11	
Total	36	14	50	

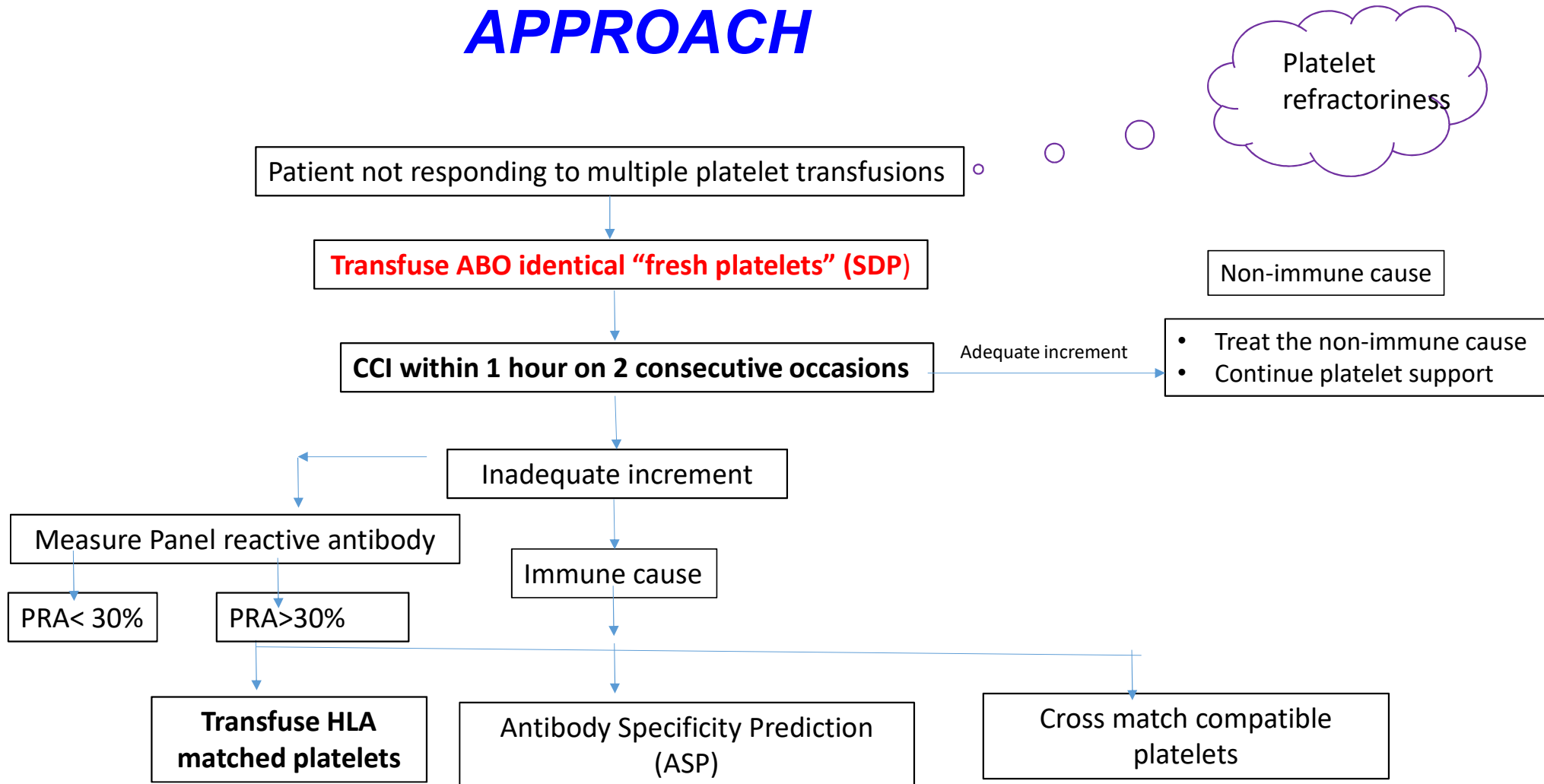
Correlation of platelet crossmatch results by Solid Phase Red Cell Adherence Assay (SPRCA) with post-transfusion platelet count increment in adult hemato-oncology patients of a tertiary care oncology centre in India

P. Desai*, P. Sontakke, S. Rajadhyaksha, A. Navkudkar
 Department of Transfusion Medicine, Tata Memorial Hospital, Homi Bhabha National Institute, Dr E Borges Road, Parel, Mumbai, India

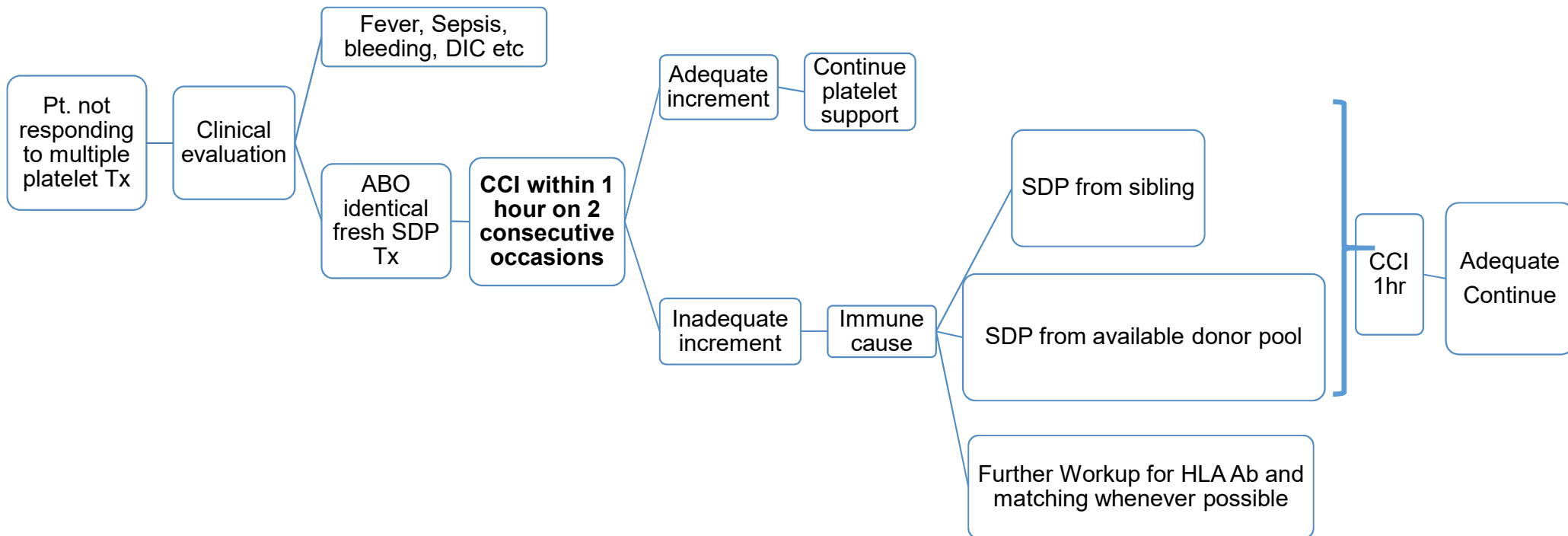
- Statistically significant association was found between crossmatch compatibility and CCI, compatibility being the best predictor of CCI.
- The time required to perform the crossmatch test by SPRCA assay was around two to three hours
- **The SPRCA assay is a rapid and effective method to select the compatible unit from the inventory and is feasible for an oncology set up to cater the requirement of multiple platelet transfusions to patients of hematological malignancies**

Advantages	Disadvantages
<i>ABO identical platelets</i>	
Easily available	Not useful in refractoriness due to HLA/ HPA antibodies
<i>Cross-matched platelets</i>	
Useful in refractoriness due to HLA and HPA antibodies	Multiple crossmatches required
Feasible, cost-effective	
<i>HLA-matched platelets</i>	
Useful in refractoriness due to HLA antibodies (Cause of immune refractoriness in majority of cases)	Expensive, time-consuming, labour intensive
	Requires large number of HLA typed donors
<i>Epitope-matched platelets</i>	
Antibodies are produced against epitopes and not complete antigens	Requires large number of epitope typed donors
Accurate matching	Virtual crossmatching

APPROACH



Practical Approach- TMH



Still If The Platelet Response Is Poor..... Then?

- Treat the underlying non-immune cause
- Check the interference of platelet transfusions with ongoing drugs
- Continue using ABO identical fresh platelets (< 48hours)
- Increase the platelet dose
- Platelet drip: Dose of platelet concentrate is infused slowly over a four-hour period (moderate success)
[Rossi 5th ed]
- Rheological effect: Raising the hematocrit to 30% if the patient is anemic
- Use of TEG (to check for other coagulation derangements)
- Antifibrinolytic agents (e-Aminocaproic acid)
- If unsuccessful, regular random-donor units should be used

Summary

- Platelet refractoriness is suspected when there is failure of platelet increment on two occasions
- Platelet refractoriness management is challenging
- Case history, clinical correlation and communication with clinical team is crucial in supporting patients
- It is important to hasten investigation and management to reduce morbidity and mortality

Prevention: Always better than cure!

- **Avoid prophylactic platelet transfusions**
- **Leukoreduced platelets:** Studies observed that leukocyte depletion below 5×10^6 per transfusion is effective in the prevention of primary HLA alloimmunization (TRAP trial)
- **Reduction of donor exposure:** Primary HLA alloimmunization occurs at a median of 3–4 weeks after the first transfusion in a recipient of multiple transfusions. Reduction of donor exposure using apheresis single-donor platelets (whenever possible) showed that alloimmunization was postponed. ^a
- **ABO-identical platelet transfusion:** To patients requiring ongoing platelet support yields better increments, a reduction of overall platelet requirement, and a decrease in platelet refractoriness. ^b

a: Gmür J et al. Delayed alloimmunization using random single donor platelet transfusions: A prospective study in thrombocytopenic patients with acute leukemia. Blood 1983;62:473-9

b: Heal JM, Rowe JM, McMican A, Masel D, Finke C, Blumberg N. The role of ABO matching in platelet transfusion. Eur J Haematol 1993;50:110-7

Thank You!!!!

