THE BASICS OF PLATELET TRANSFUSION

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Inspired Care.
Inspiring Science.

Disclosures

- Y. Lin
  - Research funding from Canadian Blood Services and Octapharma
  - Consultant for Choosing Wisely Canada
- K. Pavenski
  - Participation in industry clinical trials: F. Hoffmann-La Roche Ltd., Sanofi – none are relevant to this talk

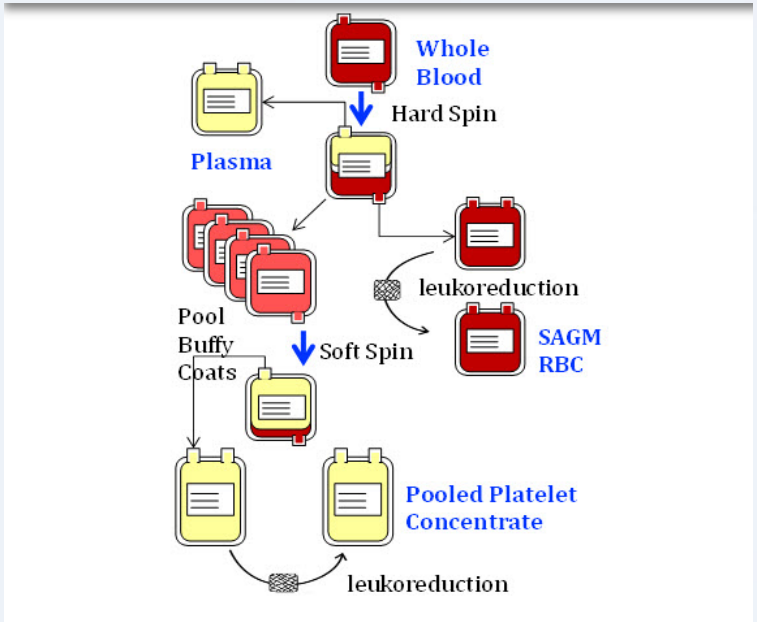
Learning Objectives

- Platelet Basics
  - Manufacturing, dose, storage, administration, and risks
- When platelets should be transfused?
- What platelets should be selected for transfusion?

Manufacturing, Administration and Risks of Platelet Transfusion

How are Platelets Made?

- From whole blood donations (platelet rich plasma or buffy coat)



Shown - buffy coat method

- By apheresis: single donor

Platelet Transfusion

- 1 adult dose of platelets
  - **1 apheresis unit** (platelets + about 250mL of plasma from a single donor)
  - **4-6 units of whole blood derived** platelets, each 45-65 mL (Rwanda)
  - **1 buffy coat pool** (platelets from 4 donors + about 350mL of plasma from one of the donors in the pool) (Canada)
- Stored at room temperature, with constant gentle agitation
  - Do not place in cooler/fridge
  - Can forgo agitation for short periods of time (ex. for transport)
- Administer over 60 minutes (max. 4 hours)
- Shelf-life: 5 days (Rwanda)
- May be leukoreduced upon request
- May be screened for bacterial contamination (pH) and cultured if fail screen (pH<6.2)

Risks of Platelet Transfusions

- Febrile non-hemolytic transfusion reaction per platelet pool (1 in 100)
- Minor allergic reaction (1 in 100)
- Bacterial contamination
  - Bacterial sepsis per pool of platelets: 1 in 10,000
- Transfusion-related lung injury (1 in 10,000)
- HLA alloimmunization
- Hemolytic transfusion reaction
- Major allergic reaction
- Thrombosis?
- Immunomodulation?

Bloody Easy 5; Ramirez-Arcos et al Transfusion 2017; Refaai et al Thromb Res 2011

WHEN SHOULD PLATELETS BE TRANSFUSED?

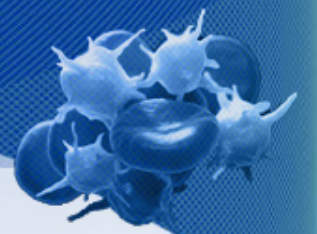
Platelet Transfusion

- Platelets are transfused to facilitate primary hemostasis in patients with **platelet deficiency or dysfunction**
  - To prevent or control bleeding
  - To raise platelet count
- One adult dose of platelets will raise platelet count by at least $15x10^9/L$
  - 1 adult dose of platelets is expected to raise platelet count by $30\text{-}40x10^9/L$ (Slichter 1997)
- Transfused platelets circulate for 4-5 days
  - Platelet survival is reduced in thrombocytopenic patients: $7.1x10^9/L$ are required daily to maintain vascular integrity (Hanson & Slichter 1985)

Platelet Transfusion

- Recent platelet transfusion guidelines/guidances/recommendations:
  - **ICTMG** (Nahirniak et al TMR 2015)
    - Update is in progress
  - **AABB** (Kaufman et al Ann Intern Med 2015)
  - **BSH** (Estcourt et al BJH 2017)

Prophylactic Platelet Transfusion



- In patients with **hypoproliferative thrombocytopenia** (thrombocytopenia due to failure of production of platelets by bone marrow - eg. post-chemotherapy)**, prophylactic platelet transfusions should be given**

- A threshold of **≤10×10^{9}/L** should be used for prophylactic platelet transfusion

iCTMG
International Collaboration for Transfusion Medicine Guidelines

Nahirniak et al TMR 2015

Is Prophylact
Indicated? Ye

Ann Intern Med. 2015;162(3)

d Hypoproliferative Thrombocytoper

	Effect	
	Odds Ratio (95% CI)	Absolute
	0.53 (0.32-0.87)	153 fewer bleeding events per 1000 (from 35 fewer to 257 fewer bleeding events)
	0.34 (0.22-0.52)	260 fewer bleeding events per 1000 (from 155 fewer to 361 fewer bleeding events)
	0.48 (0.12-1.92)	160 fewer bleeding events per 1000 (from 332 fewer to 162 more bleeding events)
	0.72 (0.30-1.55)	8 fewer deaths per 1000 (from 21 fewer to 16 more deaths)
	0.54 (0.09-3.10)	3 fewer deaths per 1000 (from 7 fewer to 15 more deaths)

Appendix Table 3. Prophylactic Platelet T

liferative Thrombocytopenia

Studies by Subgroup, *n*	Design	Risk of Bias	Inco		Effect Absolute	Quality	Importance
Grade 2 or greater bleeding: 3 (21, 24, 25)	Randomized trials	No serious risk	No s in	.87)	153 fewer bleeding events per 1000 (from 35 fewer to 257 fewer bleeding events)	Moderate	Critical
Grade 2 or greater bleeding, chemotherapy subgroup: 3 (21, 24, 25)	Randomized trials	No serious risk	No s in	.52)	260 fewer bleeding events per 1000 (from 155 fewer to 361 fewer bleeding events)	Moderate	Critical
Grade 2 or greater bleeding, autologous HPCT subgroup: 2 (21, 25)	Randomized trials	Serious‡	No s in	.92)	160 fewer bleeding events per 1000 (from 332 fewer to 162 more bleeding events)	Moderate	Critical
All-cause mortality: 4 (21, 24, 25, 63)	Randomized trials	No serious risk	No s in	.55)	8 fewer deaths per 1000 (from 21 fewer to 16 more deaths)	Low	Critical
Bleeding-related mortality: 4 (21, 24, 25, 63)	Randomized trials	No serious risk	No s in	.10)	3 fewer deaths per 1000 (from 7 fewer to 15 more deaths)	Low	Critical

HPCT = hematopoietic progenitor cell transplant
* Quality assessment evaluated risk of bias, incon
of CIs).
† Only 3/6 randomized, controlled trials reporte
‡ In Wandt et al (21), protocol deviations occurre
§ Stanworth et al (19) reported no deaths due to
‖ Wide CIs.
¶ Only 4/6 randomized, controlled trials reporte

zability of results), and imprecision (based on width

e data.

Prophylactic Platelet Transfusion: Trigger

Randomized controlled trial of adult patients with AML (excluded APL)

Results:

No difference in RBC transfusions, survival or length of hospitalization

Lower threshold strategy utilized 21.5% less platelet transfusions

Transfusion Strategy	PLT count <10×10^9/L OR 10-20×10^9/L + fever (>38°C), active bleeding, or invasive procedures (n=135)	PLT count <20×10^9/L (n=120)
Patients with major bleeding	21.5%	20%

Conclusion: two strategies produced **similar** outcomes

Rebulla et al NEJM 1997

Therapeutic Platelet Transfusion

- Evidence on transfusion thresholds is limited and of poor quality
- Low platelet count is associated with bleeding
- Preoperative platelet count is not significantly associated with intraoperative or postoperative bleeding (Bishop et al 1987)

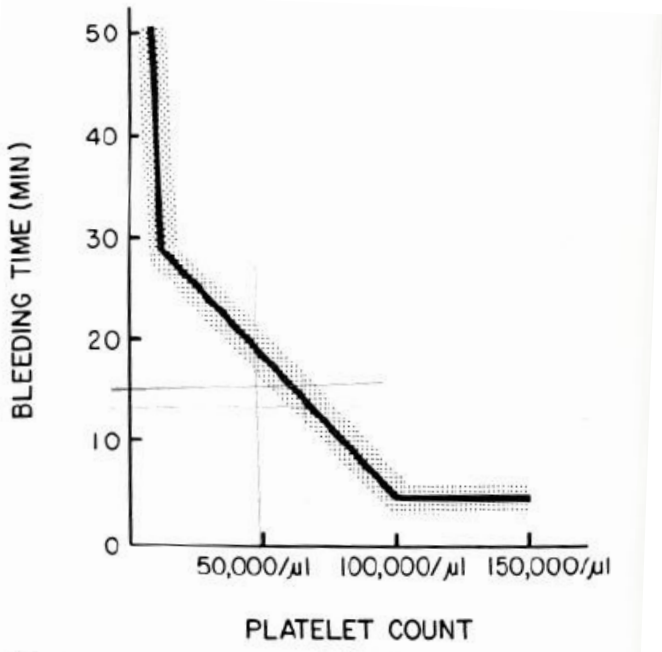


Fig. 26-1. The relation of platelet count to bleeding time (assuming normal platelet function). Not all observers feel the relationship is linear between 100,000 platelets/μl and 10,000/μl. (Adapted from Harker, L. A., and Slichter, S.J.: The bleeding time as a screening test for evaluation of platelet function. N. Engl. J. Med. 287:155, 1972.)

Triggers for Platelet Transfusion

PLT	Clinical Setting	Suggest
<20	Procedures not associated with significant blood loss (eg. Central line placement)	Transfuse 1 adult dose
<30	Patients on anticoagulants that should not be stopped	Transfuse 1 adult dose
20-50	Procedures not associated with significant blood loss	1 adult dose on hold, transfuse only if significant bleeding
<50	Significant bleeding Pre-major surgery, lumbar puncture, epidural anaesthesia	Transfuse 1 pool immediately before procedure
<100	CNS surgery, ICH, TBI	Transfuse 1 adult dose
Any	Platelet dysfunction *and marked bleeding* (e.g. post cardiopulmonary bypass, aspirin, or other antiplatelet agents)	Transfuse 1 adult dose

Platelet Transfusion for Dysfunctional Platelets

- Congenital platelet dysfunction
- Acquired platelet dysfunction post cardiopulmonary bypass
- Acquired platelet dysfunction due to anti-platelet therapy
  - *Traditionally, the following has applied…*

Medication	Platelet Dose to Reverse Effect
ASA	1 adult dose
Clopidogrel	2+ adult doses
ASA + Clopidogrel	2+ adult doses
Others	?

Platelet Transfusion for Dysfunctional Platelets Due to Antiplatelet Therapy

- No benefit
  - **Traumatic brain injury**: platelet transfusions do not improve outcomes (observational, Holzmacher et al Brain Inj. 2018)
- Evidence of harm
  - **Spontaneous, non-operative intracranial hemorrhage**: platelet transfusions increase risk of disability at 3 months (PATCH RCT, Baharoglu et al Lancet 2016)
  - **GI bleeding**: platelet transfusions do not decrease re-bleeding, associated with higher mortality (observational, Zakko et al Clin Gastroenterol Hepatol 2017)

Do NOT…

- Do not transfuse platelets to patients with thrombotic thrombocytopenias (example, thrombotic thrombocytopenic purpura) unless there is life, limb or organ threatening bleeding – **harm**
- Do not transfuse platelets to patients with immune thrombocytopenia unless there is serious bleeding – **futility**
- Do not transfuse platelets to bleeding patients without platelet deficiency or dysfunction - **futility**

WHAT PLATELETS SHOULD BE SELECTED FOR TRANSFUSION?

Platelet Immunology 101

Antigen on Platelet	Consequences
ABO(H)	Reduced post transfusion count increment with incompatible platelet transfusion
HLA (Human Leukocyte Antigen)	Platelet refractoriness
HPA (Human Platelet Antigen)	Platelet refractoriness FNAIT Posttransfusion purpura

Does ABO Matter?

- Minor incompatibility
  - **Plasma is incompatible** with recipient (eg. Group O platelets to group A recipient)
  - Potential for **hemolytic transfusion reaction**
- Major incompatibility
  - **Platelets are incompatible** with recipient (eg. Group A platelets to group O recipient)
  - Potential for **reduced post-transfusion platelet count increment**
    - But there is no definitive evidence that adverse events or mortality are different (with exception of rate of refractoriness)

Does ABO Matter?

- ICTMG recommends:
  - Platelet concentrates that are ABO identical should probably be used in patients with hypoproliferative thrombocytopenia, if available
- Platelet inventory is limited, shelf-life of platelets is short and the clinical need for platelets is often urgent
  - About 50% of platelet transfusions are non-identical
- If cannot give ABO identical, try to give ABO plasma compatible to reduce risk of hemolysis
  - In Canada, titres are done on the platelets to select low titre platelets, if possible for out of group transfusion

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Nahirniak et al 2015; Pavenski et al Transfusion 2010

Does Rh Matter?

- Platelet concentrates may contain residual RBC
  - Number of RBCs in apheresis platelets: less than 0.0002 mL per unit
  - Number of RBC in PRP WBD platelets: 0.4 to 0.6 mL of RBCs per unit
  - Number of RBC in BC WBD platelets: about 2 mL of RBCs per unit
- Risk of D alloimmunization is very low
  - ADAPT (Cid et al)
    - 7 (1.44%) of 485 D− recipients developed anti-D after transfusion of D+ platelets (no difference in the type of platelet product was observed)
- RhIg can prevent alloimmunization and is safe
  - Single dose of RhIg may cover multiple platelet exposures
    - Half-life is 21 days
    - 300µg dose eliminates 15mL of RBC

Nahirniak et al 2015

Does Rh Matter?

- Female children and females of child-bearing age/potential, with hypoproliferative thrombocytopenia, who are RhD negative should probably receive RhIg before, immediately after, or within 72 hours of receiving an RhD-positive platelet component

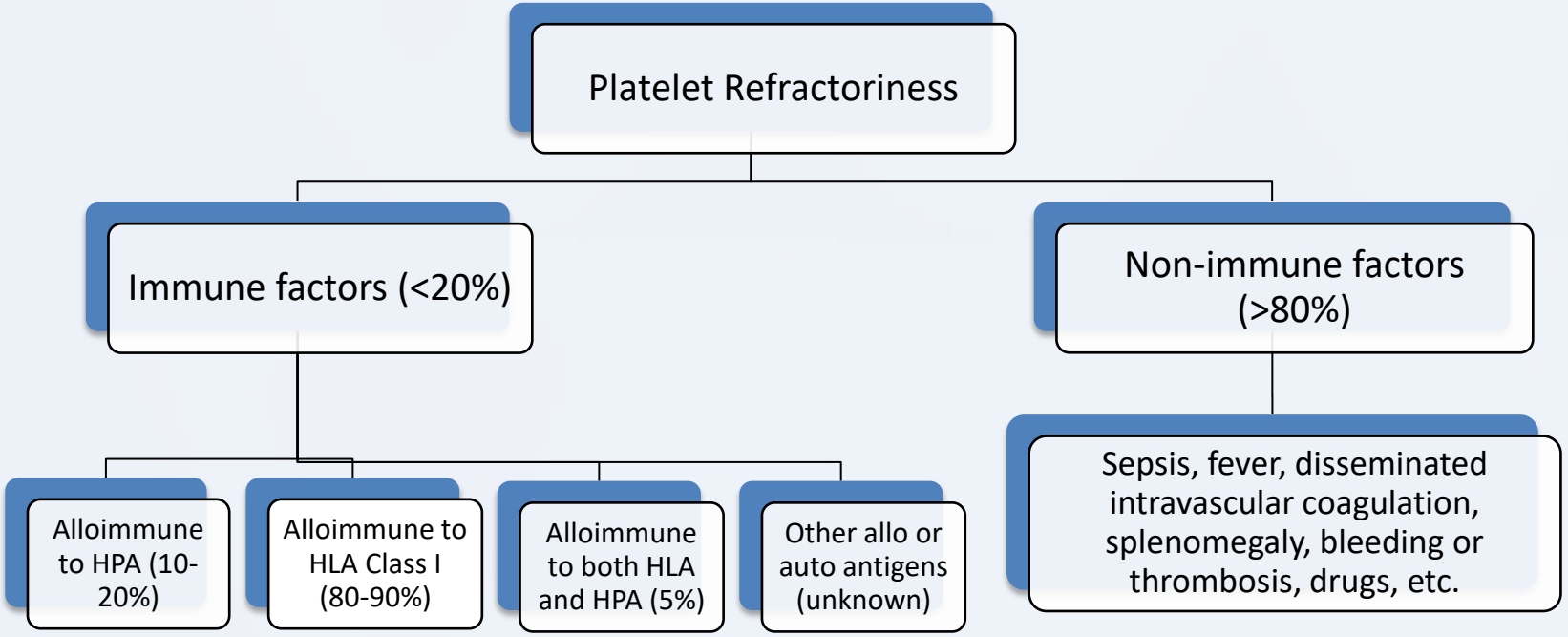
- Males and females who are not of child-bearing age/potential, with hypoproliferative thrombocytopenia, who are RhD-negative and are transfused with RhD-positive platelet components probably do not require RhIg

ICTMG
International Collaboration for Transfusion Medicine Guidelines

Nahirniak et al 2015

Platelet Refractoriness

- Platelet refractoriness is a persistent lack of post-transfusion platelet count increment



Modified from Pavenski et al Tissue Antigens 2012

HLA and HPA Alloimmunization

- HLA alloimmunization = IgG antibodies against HLA Class I antigens (A and B)
- HPA alloimmunization = IgG antibodies against HPA antigens
- Alloimmunization results from exposure to allogeneic blood – previous transfusions, pregnancies, transplants
  - Minority of alloimmunized patients will become refractory

Diagnostic Workup for Refractoriness

- Confirm refractoriness on the basis of at least 2 post-transfusion count increments
- Consider patient factors
  - Rule out non-alloimmune causes of platelet refractoriness
- Consider platelet factors
  - Better platelet increments with ABO identical and younger platelets

Transfuse fresh, ABO identical PLT and measure post-transfusion platelet increment at 10-60 min

Slichter et al 2005; Triulzi et al 2012

Diagnostic Workup for Refractoriness: 1 hr vs. 24 hr Post Transfusion PLT Count

- Poor 15 min-1 hour post transfusion platelet count is consistent with immune refractoriness

- Poor 18-24 hour post-transfusion platelet count (with adequate 1 hour count) is most often associated with non-immune (clinical) refractoriness due to increased utilization of platelets

Menitove and Duquesnoy 1981

Management of Platelet Refractory Patients

- Confirm refractoriness on the basis of at least 2 post-transfusion count increments
- Consider patient factors
  - Rule out non-alloimmune causes of platelet refractoriness
- Transfuse freshest, ABO identical platelets
- For alloimmunized, refractory patient the best treatment is HLA selected platelets
  - if not available, transfuse platelets only if the patient is bleeding with whatever platelets are available
  - even incompatible platelets in alloimmunized, refractory patients could activate coagulation (Mazzara et al 1996)

Alternatives to Platelet Transfusions?

- Topical thrombin
- Antifibrinolytic agents
- DDAVP
- rVIIa
- Fibrinogen concentrate
- FXIII

Caution…Evidence-Free Zone

Desborough et al Cochrane Database Syst Rev. 2016

Writing Platelet Transfusion Order

- Indication
  - What is the platelet count? Does patient have platelet dysfunction?
  - Is patient bleeding?
  - Is patient imminently going for a major invasive procedure?
- Dose
- Rate of administration: 1-2 hours
- Premedication

Writing Platelet Transfusion Order

- *Transfuse 1 adult dose of platelets over 1 hour, for platelet count of 5 and minor mucosal bleeding*
- *No pre-medications*
- *Dr. _____*
- *Date/time_____*

Test Your Knowledge

Question 1

28 year old female with leukemia, undergoing induction chemotherapy

- Clinically stable and not bleeding
- No procedures arranged
- Platelet count is $7 \times 10^9/L$

Is platelet transfusion indicated?

A. Yes
B. No

Question 2

24 hours following 1 adult dose, the platelet count should rise by:

A. 5-10 x 10^9/L

B. 15-50 x 10^9/L

C. 50-75 x10^9/L

D. > 100 x 10^9/L

Question 3

Platelets have all of the following antigens on their surface except

A. ABO(H)
B. D
C. HPA
D. HLA

Questions?