# THE BASICS OF PLATELET TRANSFUSION

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**University of Toronto Transfusion Camp, Rwanda Edition**

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St. Michael's

Inspired Care.
Inspiring Science.

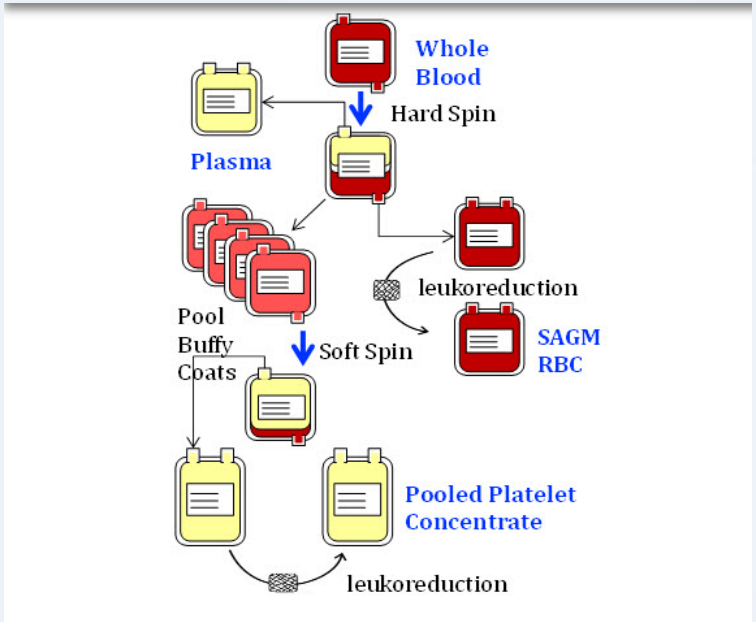
# Learning Objectives

- 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 (buffy coat OR platelet rich plasma)
- By apheresis




Shown - buffy coat method

# Platelet Transfusion

- 1 adult dose of platelets
  - **1 buffy coat pool** (platelets from 4 donors + about 350mL of plasma from one of the donors in the pool)
  - **1 PRP pool** (platelets from 4-6 donors + about 250mL of plasma from each donor in the pool)
  - **1 apheresis unit** (platelets + about 250mL of plasma from a single donor)
- 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
- 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 (1 in 20)
- Minor allergic reaction (1 in 100)
- Bacterial contamination
  - Bacterial contamination of platelets: 1 in 3,000 to 1 in 10,000
  - Sepsis due to bacterial contamination of platelets: 1 in 100,000
- HLA alloimmunization
- Transfusion-related lung injury
- Hemolytic transfusion reaction
- Major allergic reaction
- Thrombosis?
- Immunomodulation?

Bloody Easy 4; 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 decreased production of platelets by bone marrow - ex. 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 Prophylactic Platelet Transfusion Indicated? Yes!

**Ann Intern Med. 2015;162(3):205-213. doi:10.7326/M14-1589**

***Appendix Table 3.*** Prophylactic Platelet Transfusion Versus No Prophylactic Platelet Transfusion in Therapy-Induced Hypoproliferative Thrombocytopenia

| Studies by Subgroup, *n* | Quality Assessment* | | | | | | Patients, *n/N* (%) | | Effect | | Quality | Importance |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | Design | Risk of Bias | Inconsistency | Indirectness | Imprecision | Other Considerations | Prophylactic Platelet Transfusion | No Prophylactic Platelet Transfusion | Odds Ratio (95% CI) | Absolute | | |
| Grade 2 or greater bleeding: 3 (21, 24, 25) | Randomized trials | No serious risk | No serious inconsistency | No serious indirectness | No serious imprecision | Reporting bias† | 192/528 (36.4) | 258/519 (49.7) | 0.53 (0.32-0.87) | 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 serious inconsistency | No serious indirectness | No serious imprecision | Reporting bias† | 77/187 (41.2) | 115/169 (68.0) | 0.34 (0.22-0.52) | 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 serious inconsistency | No serious indirectness | No serious imprecision | None | 103/308 (33.4) | 128/313 (40.9) | 0.48 (0.12-1.92) | 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 serious inconsistency | No serious indirectness | Serious§‖ | Reporting bias¶ | 13/545 (2.4) | 16/531 (3.0) | 0.72 (0.30-1.55) | 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 serious inconsistency | No serious indirectness | Serious‖ | Reporting bias¶ | 3/544 (0.6) | 4/530 (0.8) | 0.54 (0.09-3.10) | 3 fewer deaths per 1000 (from 7 fewer to 15 more deaths) | Low | Critical |

HPCT = hematopoietic progenitor cell transplantation.
* Quality assessment evaluated risk of bias, inconsistency (based on heterogeneity among trials), indirectness (based on assessment of generalizability of results), and imprecision (based on width of CIs).
† Only 3/6 randomized, controlled trials reported this outcome.
‡ In Wandt et al (21), protocol deviations occurred in 30% of transfusions in the therapeutic group vs. 14% in the prophylactic group.
§ Stanworth et al (19) reported no deaths due to bleeding. We used the continuity correction (0.5 as event) to include this study in pooling the data.
‖ Wide CIs.
¶ Only 4/6 randomized, controlled trials reported this outcome.

# 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 <$10\times10^9$/L OR 10-$20\times10^9$/L + fever (>38°C), active bleeding, or invasive procedures (n=135) | PLT count <$20\times10^9$/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)

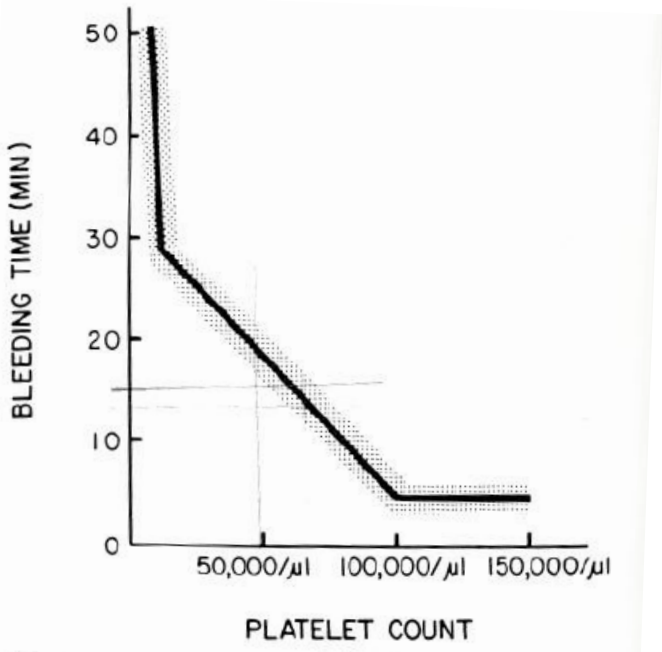



Fig. 26-1. The relation of platelet count to bleeding time (assuming normal platelet function). Not all observers feel the relationship is linear between 100,000 platelets/μl and 10,000/μl. (Adapted from Harker, L. A., and Slichter, S.J.: The bleeding time as a screening test for evaluation of platelet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

# Thresholds for Platelet Transfusion

| PLT | Clinical Setting | Suggest |
|---|---|---|
| <20 | Elective central venous catheter placement | Transfuse 1 adult dose (weak recommendation; low quality evidence) |
| <50 | Elective diagnostic lumbar puncture | Transfuse 1 adult dose (weak recommendation; very low quality evidence) |
| <50 | Major elective non-neuraxial surgery | Transfuse 1 adult dose (weak recommendation; very low quality evidence) |
| ? | Post-cardiopulmonary bypass bleeding with thrombocytopenia and/or evidence of platelet dysfunction | Transfuse 1 adult dose (weak recommendation; very low quality evidence) |
| Any | Intracranial hemorrhage on anti-platelet therapy | No recommendation |

Kaufman et al JAMA 2015

# Thresholds 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<br>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
  - Transfuse if major bleeding on:

| 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<br>FNAIT<br>Posttransfusion purpura |

# Does ABO Matter?

- Minor incompatibility
  - **Plasma is incompatible** with recipient (ex. Group O platelets to group A recipient)
  - Potential for **hemolytic transfusion reaction**
- Major incompatibility
  - **Platelets are incompatible** with recipient (ex. 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

ICTMG
International Collaboration for Transfusion Medicine Guidelines

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

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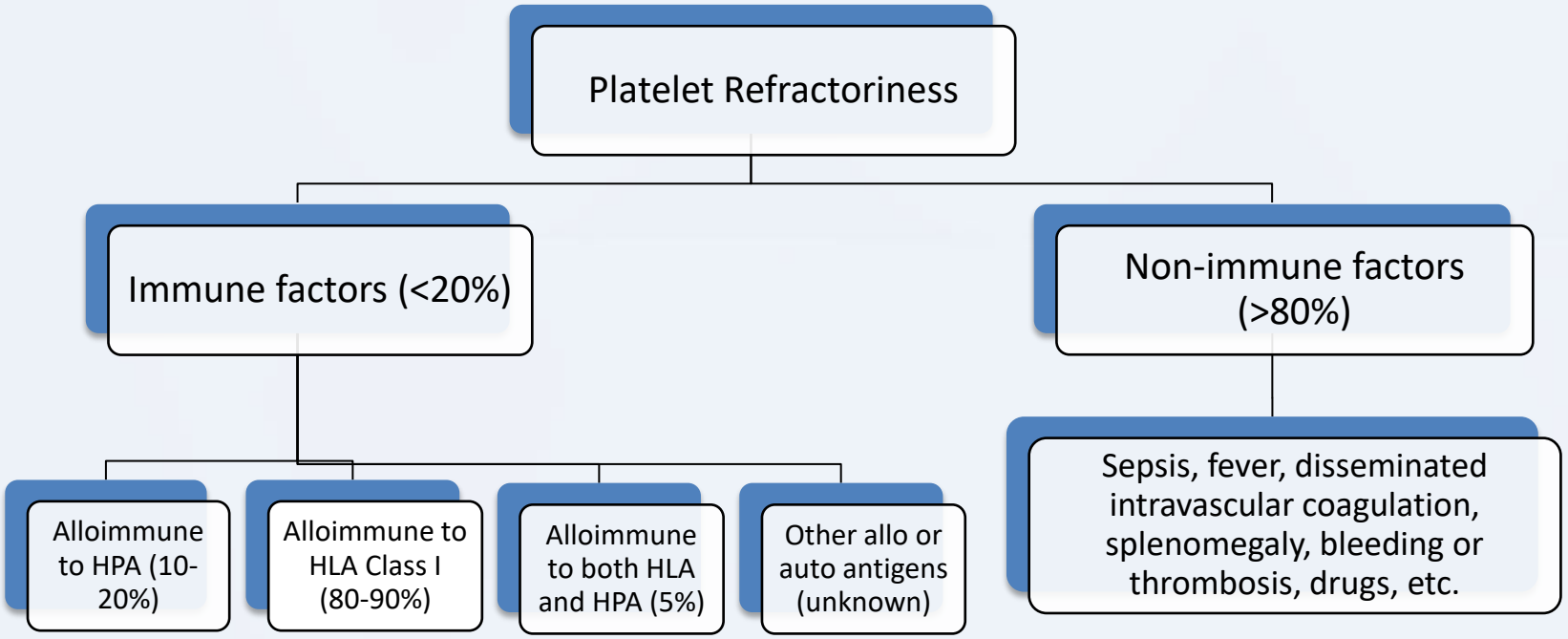
Nahirniak et al 2015

# Platelet Refractoriness

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




Modified from Pavenski et al Tissue Antigens 2012

# 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 (aka clinical) refractoriness due to increased utilization of platelets

Menitove and Duquesnoy 1981

# HLA and HPA Alloimmunization

- HLA alloimunization = 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

# 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 example, tranexamic acid – oral, intravenous, topical
- DDAVP

Desborough et al Cochrane Database Syst Rev. 2016

# Writing Platelet Transfusion Order

- Indication
  - What is a 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 for platelet count of 5 and minor mucosal bleeding over 1 hour*
- *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 platelet transfusion, the platelet count should rise by:

A. 5-10 x $10^9$/L

B. 15-50 x $10^9$/L

C. 50-75 x$10^9$/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?