THE BASICS OF PLATELET TRANSFUSION

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University of Toronto Transfusion Camp, Day 1

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St. Michael's

Inspired Care.
Inspiring Science.

Faculty Disclosure

- Clinical trials: F. Hoffmann-La Roche Ltd., Alexion – not relevant to this talk

- I am a member of the ICTMG, NAC and OBAC

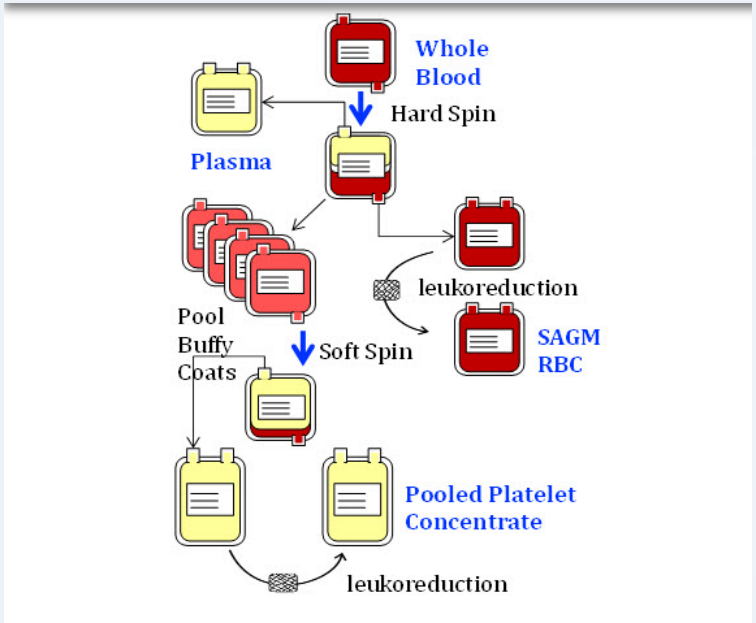
Learning Objectives

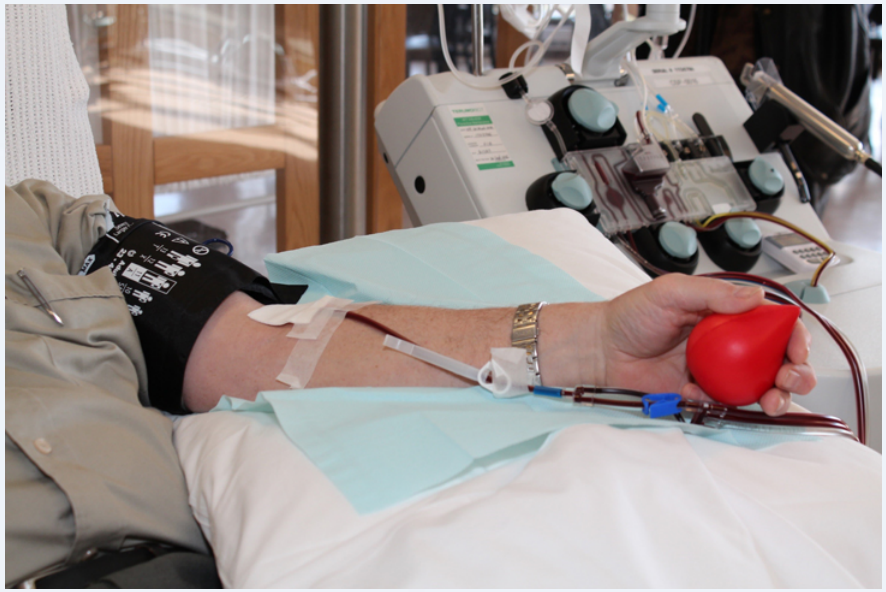
- Platelet Basics
  - Manufacturing, dose, storage, administration, and risks
- When platelets should be transfused?
- What platelets should be selected for transfusion?
  1. Special Requirements
  2. Role of ABO and Rh
  3. Apheresis vs. buffy coat pool platelets
  4. HLA selected platelets

Manufacturing, Administration and Risks of Platelet Transfusion

How are Platelets Made?

- From whole blood donations (70%)
- By apheresis (30%)





Platelet Transfusion

- 1 adult dose of platelets
  - **1 apheresis unit** (platelets + 250mL of plasma from a single donor)
  - **1 buffy coat pool** (platelets from 4 donors + 350mL of plasma from one of the male donors in the pool)
- Stored at room temperature, with constant gentle agitation
  - Do not place in cooler/fridge
- Administer over 60 minutes (max. 4 hrs)
- Shelf-life: 7 days
- All platelets are cultured (aerobic and anaerobic cultures) by the blood supplier to detect bacterial contamination
- All platelets are leukoreduced

Pathogen Reduced Platelets

- Intercept™ treatment damages DNA of leukocytes
  - Inactivates pathogens
  - Obviates irradiation requirement

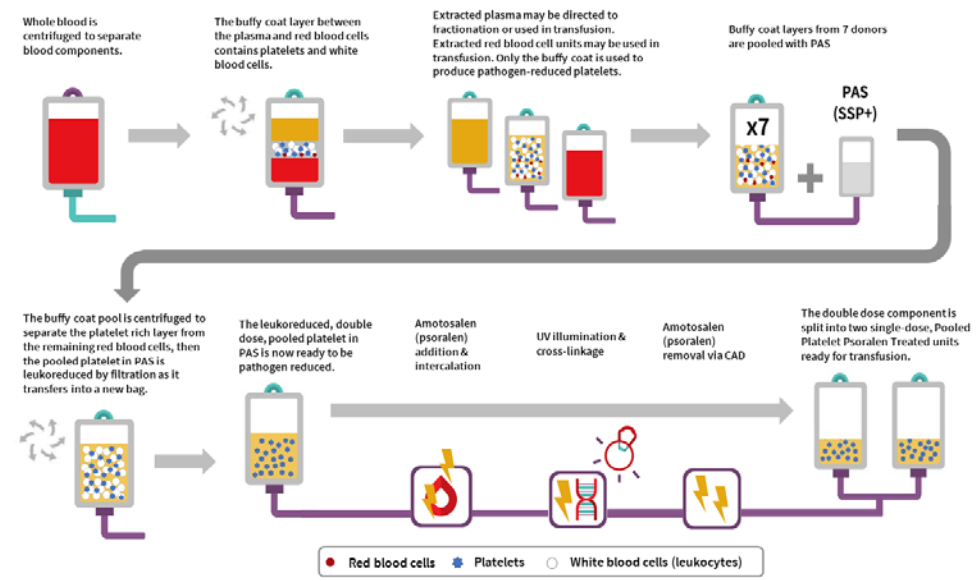


Figure 1: PPPT manufacturing at Canadian Blood Services.

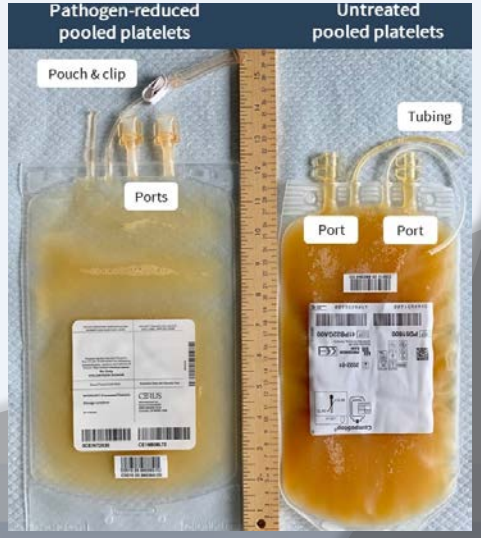
Check out Bug Free Platelets video at transfusionontario.org/en/information-on-pathogen-reduced-pooled-platelets-educational-video/

https://profedu.blood.ca/en/transfusion/publications/pathogen-reduced-buffy-coat-platelets

Pathogen Reduced Platelets

- Pooled platelets
  - Implemented in Ottawa January 2022 with national deployment to complete by end of 2023
  - Re-suspended in plasma and Platelet Additive Solution
  - 5 day shelf life (7 day shelf life expected to be approved early 2023)
  - Less volume (200mL) and less platelet yield
  - Lower post-transfusion platelet count increments
  - Limited long-term data on neonates

- Apheresis platelets
  - coming soon



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 10,000
  - Sepsis due to bacterial contamination of platelets: 1 in 100,000
- **HLA alloimmunization** (7% based on Seftel et al 2004)
- Others
  - TRALI
  - 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?

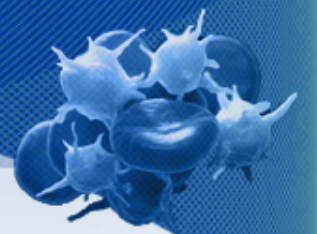
Platelet Transfusion

- 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

- Most recent platelet transfusion guidelines:
  - **ICTMG** (Nahirniak et al TMR 2015)
  - **AABB** (Kaufman et al Ann Intern Med 2015)
  - **BSH** (Estcourt et al BJH 2017)
  - **ASCO** (Schiffer et al JCO 2018) – patients with cancer only

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

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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

RCT, included 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 triggers 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)

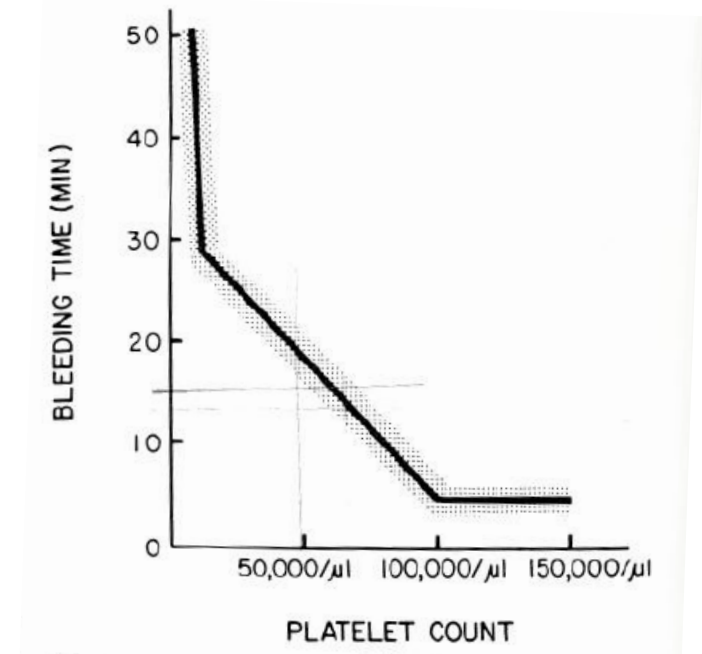


Fig. 26-1. The relation of platelet count to bleeding time (assuming normal platelet function). Not all observers feel the relationship is linear between 100,000 platelets/μl and 10,000/μl. (Adapted from Harker, L. A., and Slichter, S.J.: The bleeding time as a screening test for evaluation of platelet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

Triggers for Platelet Transfusion

PLT	Clinical Setting	Suggest
<20	Elective CVC 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

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
  - 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 ICH**: platelet transfusions increase risk of disability at 3 months (PATCH RCT, Baharoglu et al Lancet 2016)
  - **GIB**: platelet transfusions do not decrease re-bleeding, associated with higher mortality (observational, Zakko et al Clin Gastroenterol Hepatol 2017)

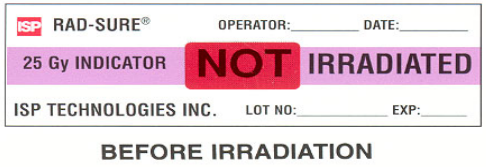
Do NOT…

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

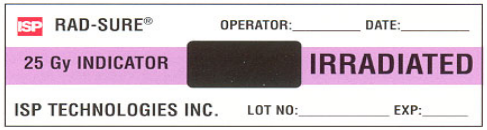
WHAT PLATELETS SHOULD BE SELECTED FOR TRANSFUSION?

Special Requirements

- Is irradiation required?
  - Irradiation aims to prevent transfusion-associated graft versus host disease
  - At risk:
    - immunocompromised patients OR
    - immunocompetent patients receiving a haploidentical blood component



BEFORE IRRADIATION



AFTER IRRADIATION @ 25 Gy

Special Requirements

- Is plasma reduction required?
  - For patients with recurrent plasma-related transfusion reactions or if unable to tolerate volume
- Are IgA deficient platelets required?
  - For patients with IgA deficiency, anti-IgA and history of allergic reactions to blood components/products
- Is HLA/HPA selection required?
  - For patients who are refractory to platelet transfusions due to anti-HLA/HPA antibodies

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 (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
- But…We have limited platelet inventory, shelf-life of platelets is short and the clinical need for platelets is often urgent
  - About 50% of platelet transfusions are non-identical
- How to mitigate patient risk?
  - Provide ABO compatible platelet transfusions
  - Titre O platelets to decide if safe for non-O recipient
  - Plasma reduction
  - Platelet additive solution

ICTMG
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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

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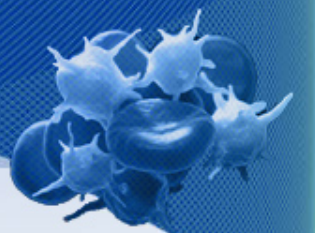
Nahirniak et al 2015

Apheresis vs. Buffy Coat Platelets



- ICTMG recommends:
  - When leukoreduced platelet products are available, whole blood derived platelets should be used as equivalent products to apheresis platelets

- When are apheresis platelets specifically indicated?
  - Special circumstances
    - HLA and/or HPA selected
    - IgA deficient

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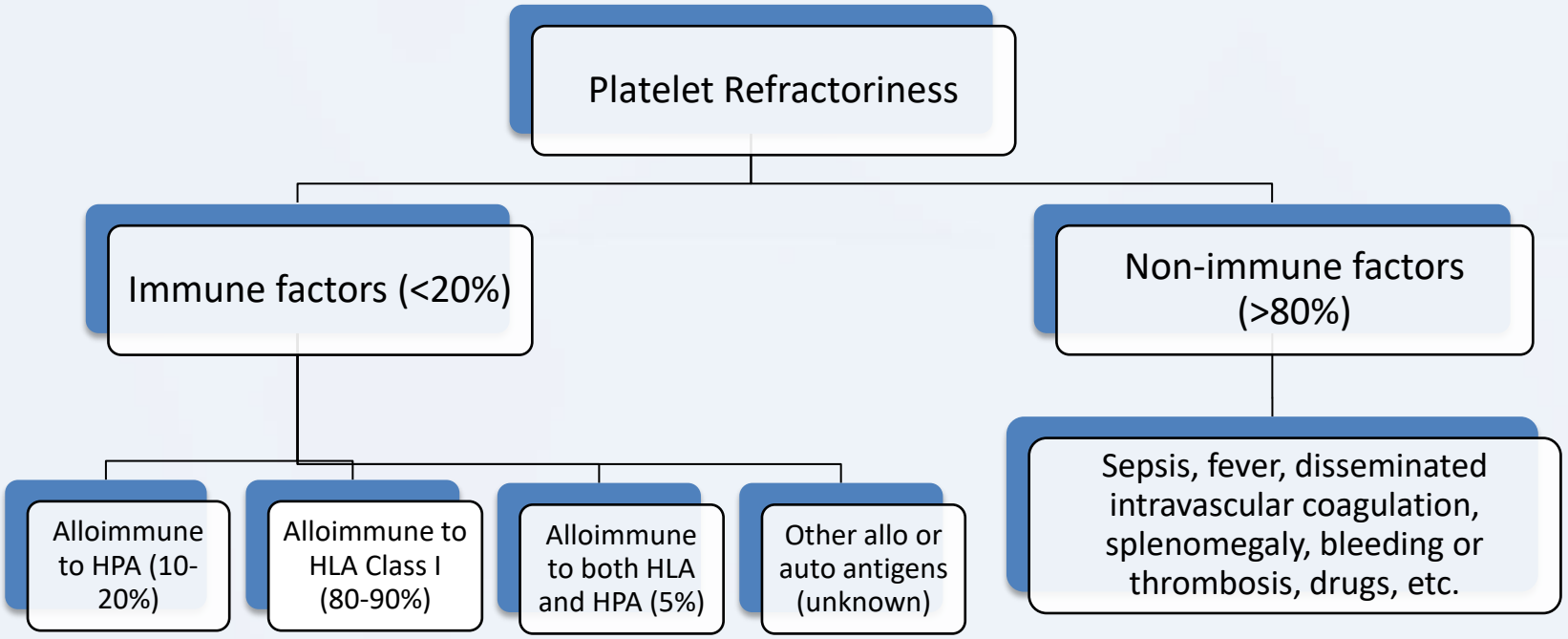
Nahirniak et al TMR 2015

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 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

Prevention of HLA Alloimmunization

- Multicentre RCT, n=603 patients

By 2008, 19 countries had implemented universal pre-storage leukoreduction (Bassuni et al 2008)

	Control: untreated pooled RDP	Study: LR pooled RDP	Study: LR SDP
# of patients	131	137	132
alloimmunization	45%	18% (vs. control p<0.001)	17% (vs. control p<0.001)
refractoriness	16%	7% (vs. control p=0.03)	8% (vs. control p=0.06)
alloimmunization and refractoriness	13%	3% (vs. control p=0.004)	4% (vs. control p=0.01)

The Trial to Reduce Alloimmunization to Platelets Study Group 1997

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 apheresis, ABO identical and younger platelets (3 days vs. 4-5 days): PLADO study

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

Slichter et al 2005; Triulzi et al 2012

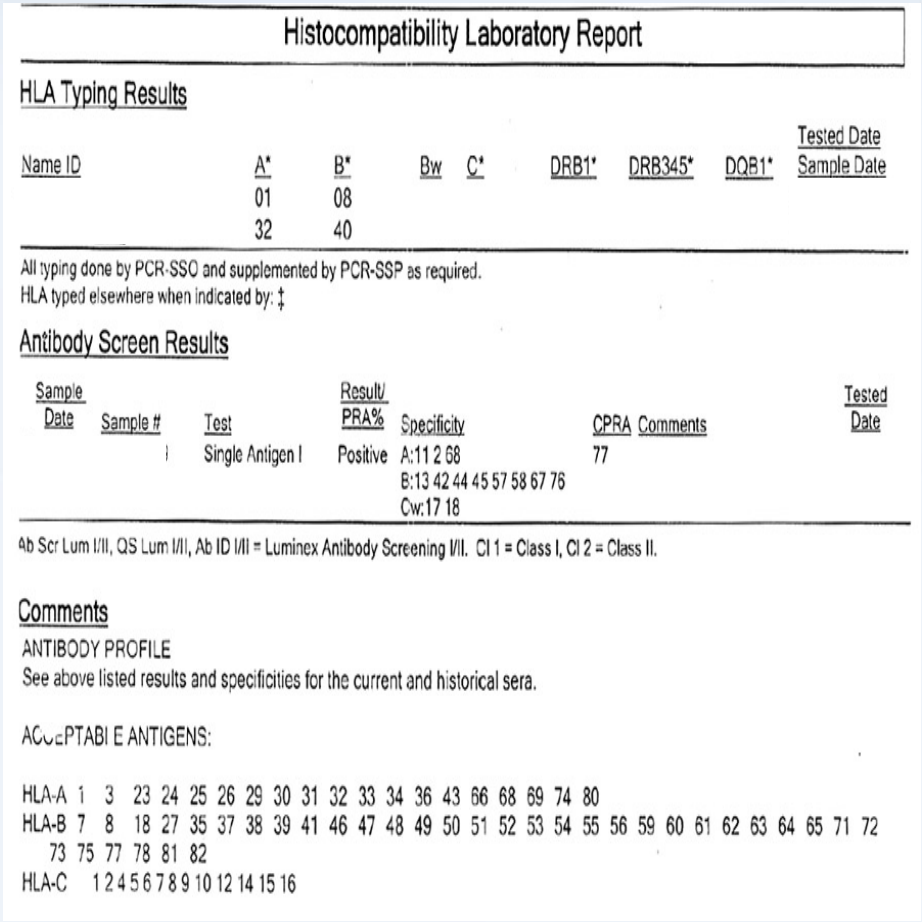
Diagnostic Workup for Refractoriness: 1 hr vs. 24 hr Post Transfusion PLT Count

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

Menitove and Duquesnoy 1981

Diagnostic Workup for Refractoriness

- Test patient **plasma** for presence of platelet antibodies and determine their specificity
  - Flow cytometry for HLA
  - ELISA/MAIPA for HPA
- Test patient's **white cells** to determine HLA and HPA type
  - Genotyping
- Testing takes 5-7 days



Histocompatibility Laboratory Report

HLA Typing Results

Name ID	A*	B*	Bw	C*	DRB1*	DRB345*	DQB1*	Tested Date / Sample Date
	01	08						
	32	40						

All typing done by PCR-SSO and supplemented by PCR-SSP as required.
HLA typed elsewhere when indicated by: ‡

Antibody Screen Results

Sample Date	Sample #	Test	Result/ PRA%	Specificity	CPRA	Comments	Tested Date
		Single Antigen I	Positive	A:11 2 68 B:13 42 44 45 57 58 67 76 Cw:17 18	77		

Ab Scr Lum I/II, QS Lum I/II, Ab ID I/II = Luminex Antibody Screening I/II. CI 1 = Class I, CI 2 = Class II.

Comments

ANTIBODY PROFILE
See above listed results and specificities for the current and historical sera.

ACCEPTABLE ANTIGENS:

HLA-A 1 3 23 24 25 26 29 30 31 32 33 34 36 43 66 68 69 74 80
HLA-B 7 8 18 27 35 37 38 39 41 46 47 48 49 50 51 52 53 54 55 56 59 60 61 62 63 64 65 71 72 73 75 77 78 81 82
HLA-C 1 2 4 5 6 7 8 9 10 12 14 15 16

Guidance on Platelet Transfusion for Patients with Hypoproliferative Thrombocytopenia

- Patients with hypoproliferative thrombocytopenia who are **refractory to platelet transfusions**:
  - **AND have class I HLA antibodies**
    - should probably receive **class I HLA-selected** or crossmatch-selected platelet transfusion to increase the platelet count (weak level of evidence, weak recommendation).
  - Due solely to nonimmune factors
    - should probably not receive HLA-selected or crossmatch-selected platelets (weak level of evidence, weak recommendation).

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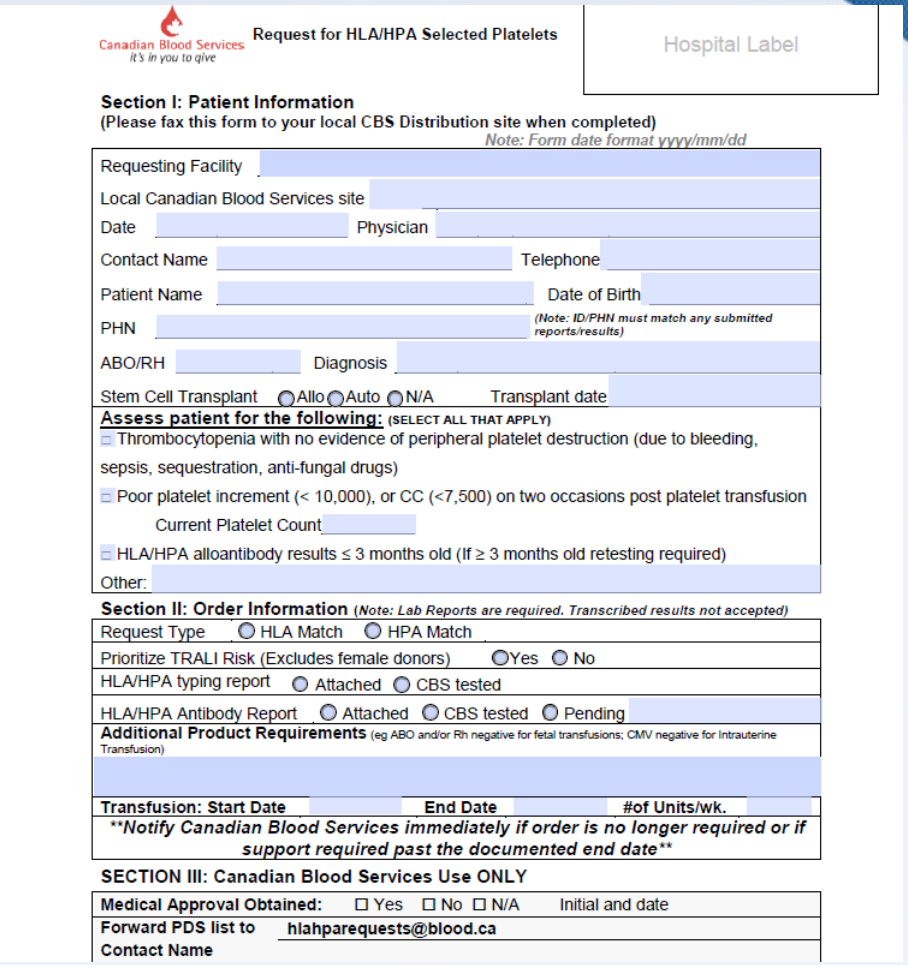
Nahirniak et al TMR 2015

Who needs HLA/HPA Selected PLT?

1. Hypoproliferative thrombocytopenia AND
2. Refractory to platelet transfusion AND
3. Alloimmunized: has anti-HLA (and/or anti-HPA) antibodies

CBS will send **antigen negative platelets** (i.e. platelets that will not react with patient's antibodies)



Canadian Blood Services
It's in you to give

Request for HLA/HPA Selected Platelets

Hospital Label

Section I: Patient Information
(Please fax this form to your local CBS Distribution site when completed)
Note: Form date format yyyy/mm/dd

Requesting Facility
Local Canadian Blood Services site
Date | Physician
Contact Name | Telephone
Patient Name | Date of Birth
PHN *(Note: ID/PHN must match any submitted reports/results)*
ABO/RH | Diagnosis
Stem Cell Transplant ◯Allo ◯Auto ◯N/A Transplant date

Assess patient for the following: (SELECT ALL THAT APPLY)
- Thrombocytopenia with no evidence of peripheral platelet destruction (due to bleeding, sepsis, sequestration, anti-fungal drugs)
- Poor platelet increment (< 10,000), or CC (<7,500) on two occasions post platelet transfusion
  Current Platelet Count
- HLA/HPA alloantibody results ≤ 3 months old (If ≥ 3 months old retesting required)

Other:

Section II: Order Information *(Note: Lab Reports are required. Transcribed results not accepted)*

Request Type ◯ HLA Match ◯ HPA Match
Prioritize TRALI Risk (Excludes female donors) ◯Yes ◯ No
HLA/HPA typing report ◯ Attached ◯ CBS tested
HLA/HPA Antibody Report ◯ Attached ◯ CBS tested ◯ Pending
Additional Product Requirements (eg ABO and/or Rh negative for fetal transfusions; CMV negative for Intrauterine Transfusion)

Transfusion: Start Date | **End Date** | **#of Units/wk.**

Notify Canadian Blood Services immediately if order is no longer required or if support required past the documented end date*

SECTION III: Canadian Blood Services Use ONLY

Medical Approval Obtained: ☐ Yes ☐ No ☐ N/A Initial and date
Forward PDS list to hlahparequests@blood.ca
Contact Name

While You Wait for HLA-selected Platelets

- Random donor platelets may be able to arrest bleeding in an alloimmunized, refractory patient
  - In 1996 Mazzara et al showed that incompatible platelet transfusions in alloimmunized, refractory patients could activate coagulation mechanisms, in the absence of an increase in the platelet count
- Do **not** hesitate to transfuse random donor platelets to a bleeding alloimmunized patient for whom HLA selected platelets are not readily available

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 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
- Special requirements

Writing Platelet Transfusion Order

- *Transfuse 1 adult dose of platelets for platelet count of 5 and minor mucosal bleeding over 1 hour*
- *Platelets must be irradiated (reason: allogeneic BMT 5 days ago)*
- *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 x10^9/L

D. > 100 x 10^9/L

Question 3

Her special requirements for platelet transfusion are (pick one best option)

A. Irradiated
B. Plasma reduced
C. IgA deficient
D. None of the above

Question 4

Platelets have all of the following antigens on their surface except

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

Question 5

Which of the following statements is correct?

A. Platelet transfusions have been shown to improve clinical outcomes in bleeding patients on anti-platelet medications
B. HLA selected platelet transfusions are indicated for thrombocytopenic patients with non-immune refractoriness
C. Group O platelets may lead to a hemolytic transfusion reaction if transfused to Group A patient
D. None of the above

Questions?