

Platelet transfusion therapy

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January 23, 2007



The Eighteenth Century



Transfusions were done only sporadically, and were generally animal to human.

Transfusion was generally thought of as a cure for mental aberration or as a youth potion for the aged, rather than as a treatment for blood loss.

☺ Reciprocal transfusions were suggested as a cure for marital discord.

Blood was thought to carry the characteristics of the donor to the recipient: sheep blood would make a dog grow wool, hooves, and horns; cat blood would make a girl feline, etc.

“The Platelet”



- Size: 1.5-3 μ m
- Anuclear, discoid cell
- Circulating life span: 9-10 days, about 4-5 days when infused.
- Platelet count: 130,000 – 450,000
- 7000 – 10,000/uL are consumed daily for routine plugging of minor endothelial defects



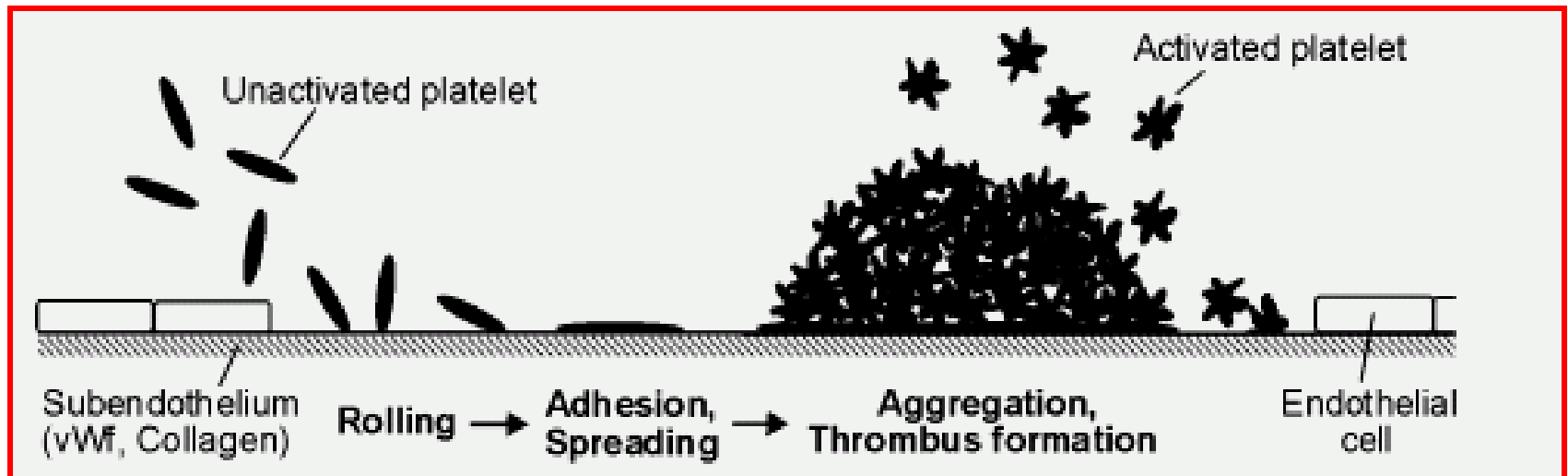
The Role of platelets in hemostasis



- Formation of the platelet and fibrin plug
 - Stages include
 - Platelet adhesion
 - Platelet activation and secretion
 - Platelet aggregation
 - Platelet associated coagulation
- Clot retraction and wound healing

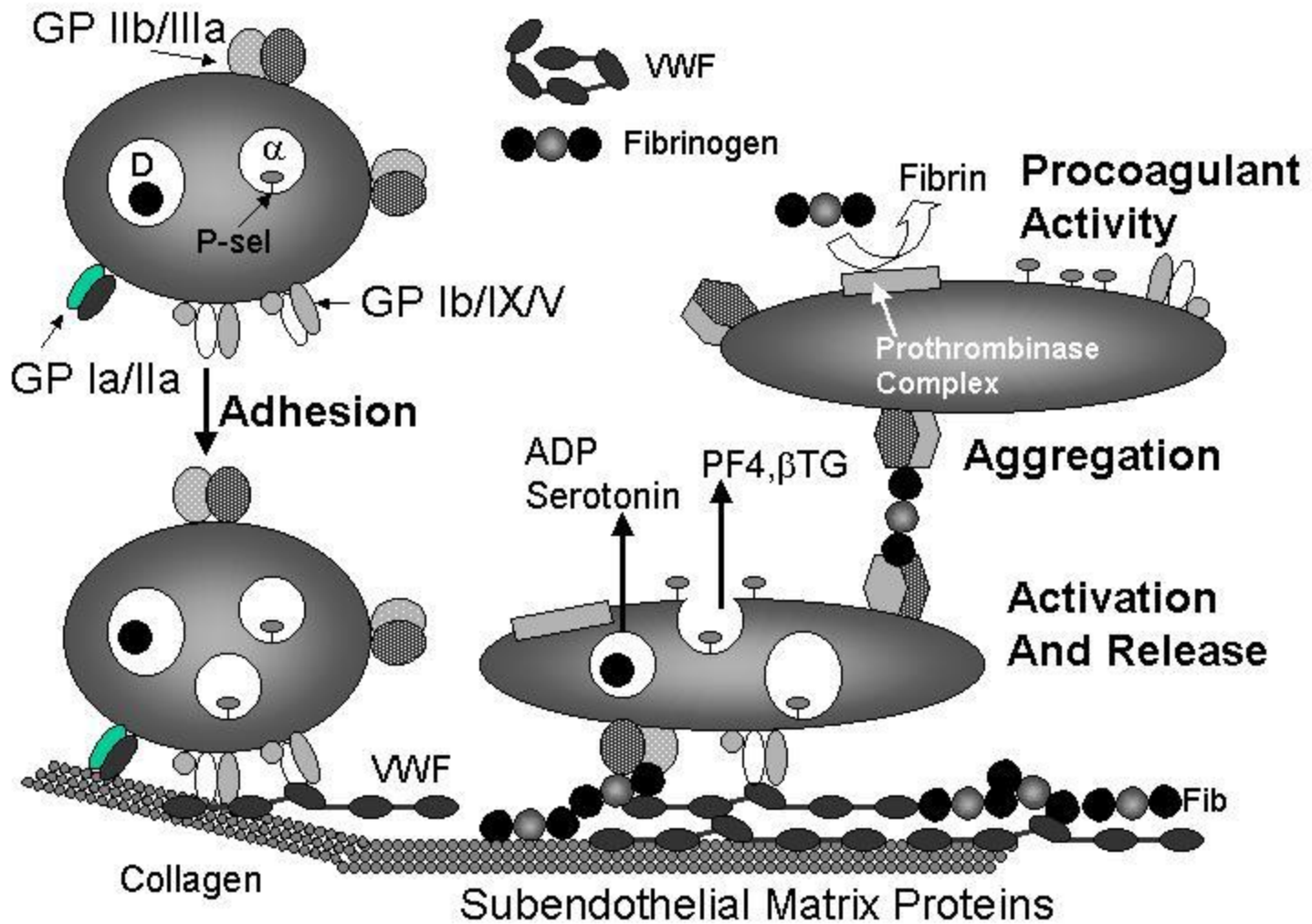


Platelet adhesion, activation, aggregation and thrombus formation on subendothelial surface at an injured blood vessel.

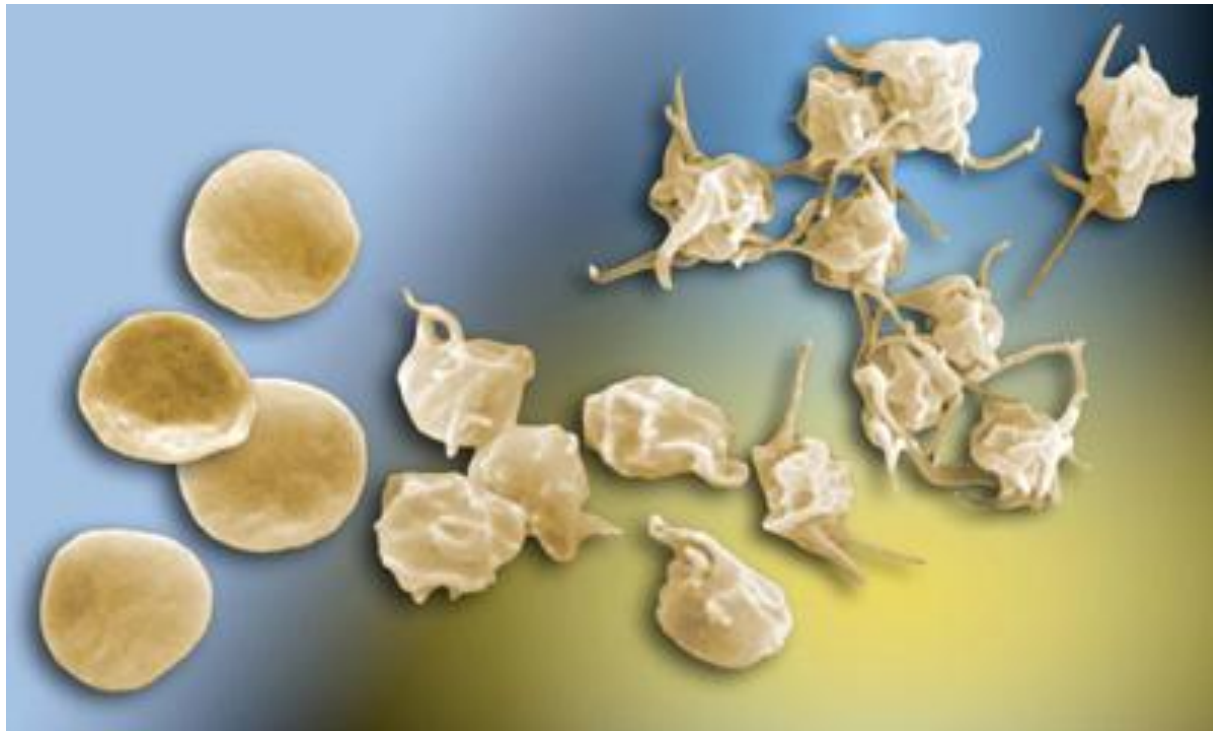




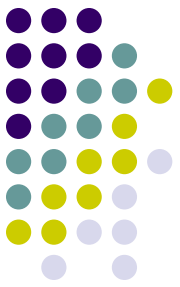
Platelet Activation



Platelet Activation

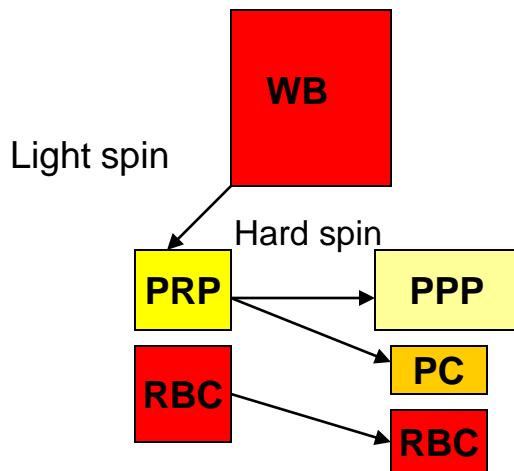


colorized scanning electron microscope image of platelets in various stages of activation



The platelet product

- 2 basic types
 - Whole blood derived (random donor platelets)
 - Platelet pheresis (single donor platelets)



Whole blood derived platelets



Apheresis
platelets



Random donor and Platelet pheresis

Random
donor

\$ \$

- **Minimum amount: 5.5×10^{10} /unit**
- **8×10^7 leukocytes, <1ml RBC**
- **volume: 45-60 ml**
- **Maximal availability, Easy to collect**
- **Dose escalation possible**
- **Multiple donor exposures**
- **Matching not practical**
- **High RBC and WBC content**

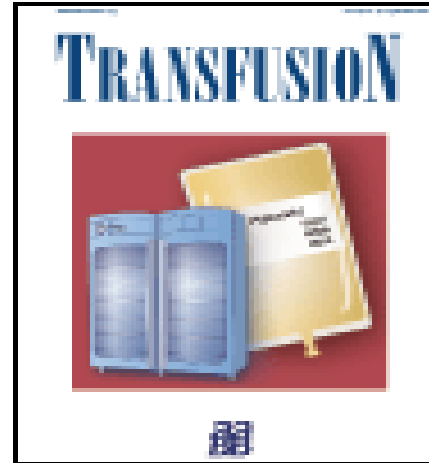
Platelet
pheresis

(Single donor)

\$\$\$

- **Minimum amount 3.0×10^{11} /unit**
- **$10^7 - 10^5$ leukocytes, rare RBC**
- **Volume: 200-300ml**
- **Single donor exposure**
- **Matching is possible**
- **Low RBC and WBC content**
- **Limits platelet dose**
- **Limited availability**
- **Inconvenient for donor**

Storage



Platelets were stored in the cold (1-6°C) in the 1950s and 1960s

- Cold temperatures decrease platelet survival after transfusion
- Platelets lose their discoid shape and become spherical when damaged by the cold
- Cooling causes clustering of the von Willibrand factor receptor complexes facilitating ingestion by hepatic macrophages



Storage

- Suspended in plasma and anticoagulant or platelet additive solutions.
 - Acid citrate dextrose is the anticoagulant of choice
- At 20-24 degrees
- Constant agitation
 - To prevent platelet activation and facilitate gas exchange
- Buffer to prevent drop in pH
- Permeable plastic containers
- Stored for 5 days

Infected platelet unit



<http://www.blood.co.uk/hospitals/services/Micro/Bact1.htm>

In attempt to prevent bacterial contamination...



- AAB- requires strategies to prevent bacterial inoculation and detection of bacterial growth during storage (since March 2004)
 - We use the pH test on random donor units
 - Blood center performs cultures on apheresis units

Platelet culture



<http://www.blood.co.uk/hospitals/services/Micro/Bact1.htm>



The platelet storage lesion

- Decreased recovery and survival
- Altered morphology- decreased MPV, loss of disc shape, fragments
- apoptosis
- Altered glycoprotein Ib
- Decreased content of α granules and dense bodies (due to platelet activation)
- Decreased function
- Lactic acid from glycolysis
- Decreased pH

The future of platelet storage



- Modifying platelets with galactose
- Use of inhibitors of actin filament assembly
- Use of calcium chelators
- Freezing
- Pathogen reduction technology

Selection of platelets for transfusion



- ABO antigens are weakly expressed on platelets
 - Can transfuse regardless of ABO type
 - Most adults will neutralize soluble antigenic A or B substances
 - ABO compatible units for smaller patients or repeated transfusions
 - ? Screen for anti A1 or anti B titers
 - Volume reduce



Rh compatibility

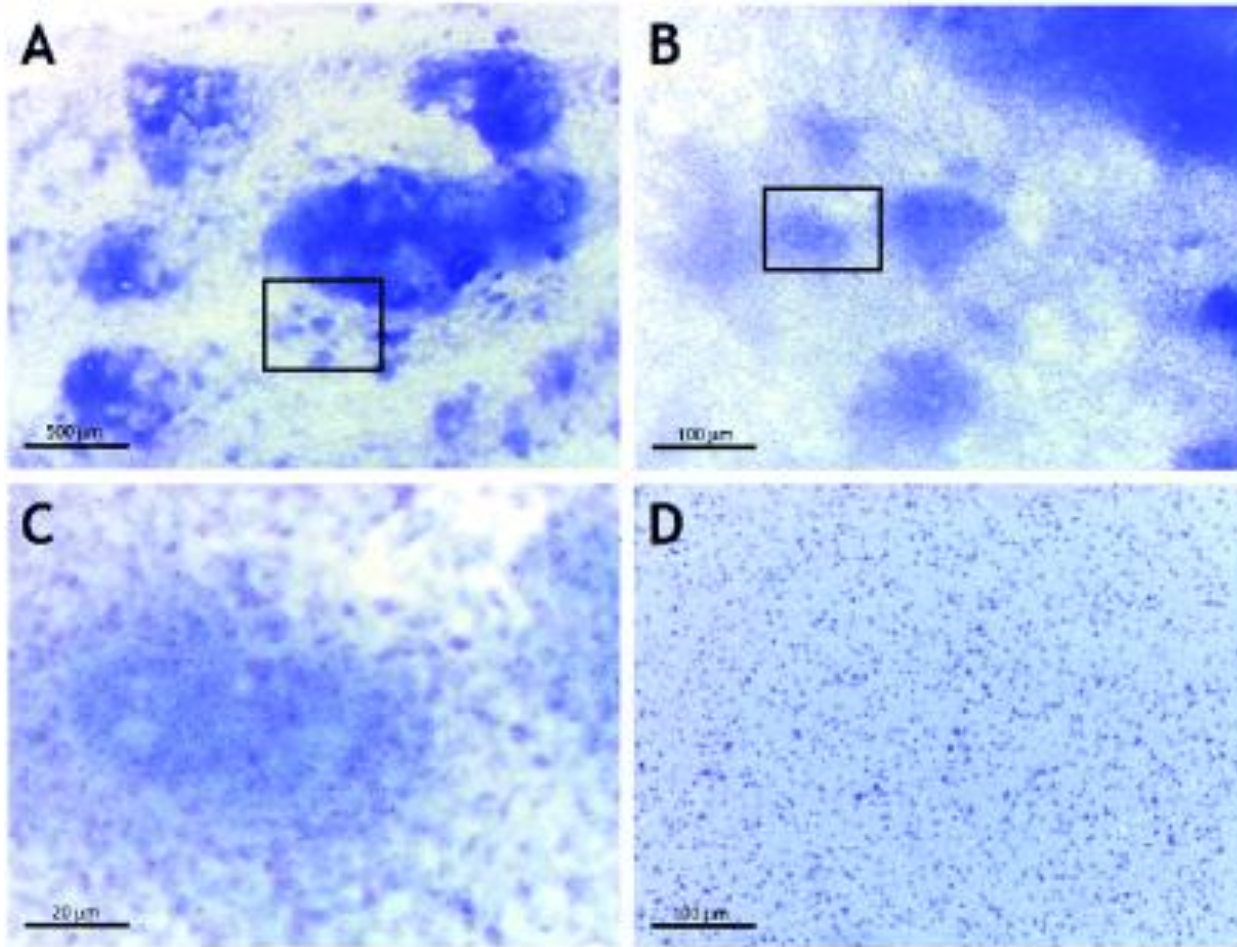
- Rh antigens are not expressed on platelets
- Passenger red blood cells may lead to alloimmunization to red cell antigens
- Adhere to Rh type in women of childbearing potential or issue Rh immunoglobulin

Selection of platelets for transfusion



- May need to pool random donor platelets
 - Must be transfused within 4 hours
- Other modifications
 - CMV reduced risk
 - Leukocyte reduced
 - Irradiated
 - Volume reduced
 - washed

Volume reduced platelets



Transfusion 45 (5), 651–651.

Indications for Platelet transfusion



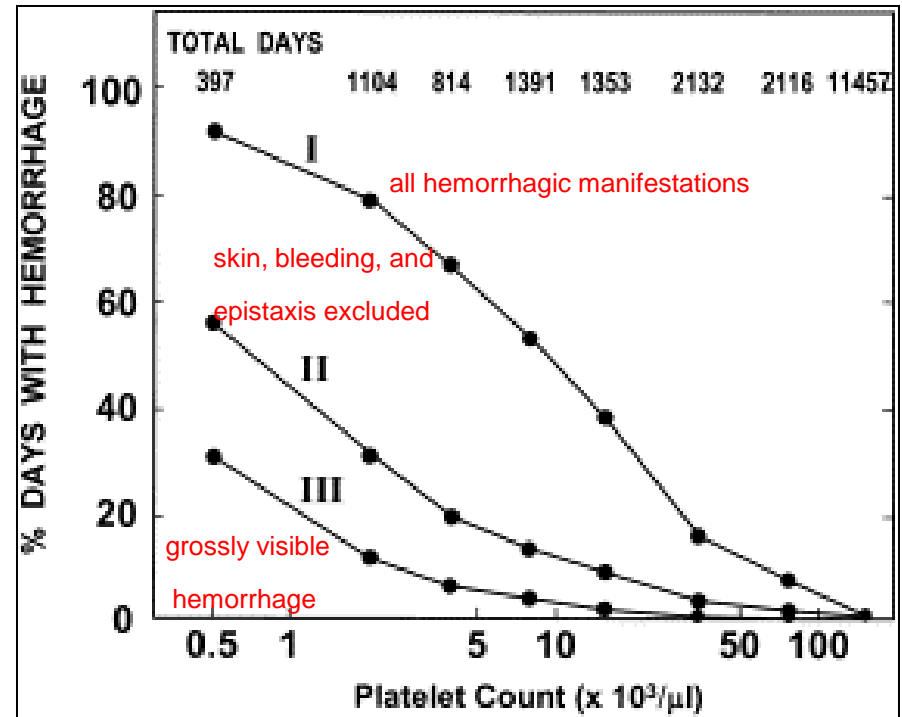
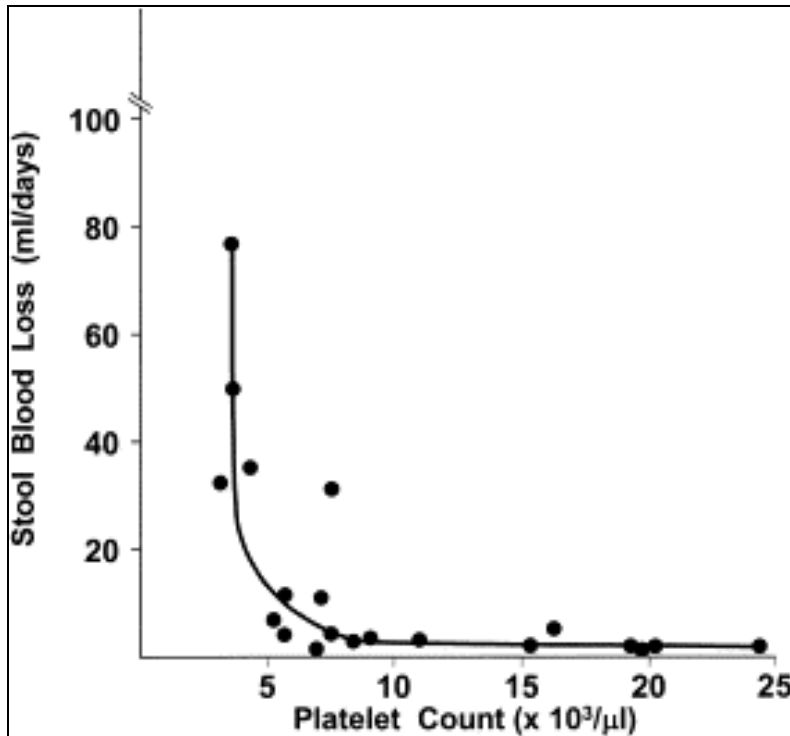
- Prophylactic transfusion
 - Severe thrombocytopenia
 - Before invasive procedure if thrombocytopenia is present
- Thrombocytopenic bleeding
- Dilutional thrombocytopenia
- Thrombocytopathy



Severe thrombocytopenia

- Most often seen in bone marrow failure
 - Acute leukemia
 - Acute promyelocytic anemia
 - Hematopoietic stem cell transplantation
 - After chemotherapy
 - Myelodysplasia
 - Aplastic anemia
- Numerous studies have been done to determine the threshold at which to transfuse platelets

Relationship between platelet count and bleeding risk in thrombocytopenic patients

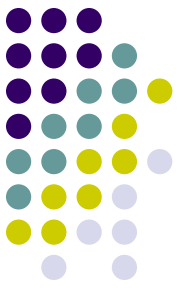


Some studies



First author	Patient population	20,000/ μ l threshold – bleeding	– 10,000/ μ l threshold – bleeding	<i>P</i> value	Other observations
Heckman ⁴²	Acute Leukemia	Median of two episodes per patient	Median of four episodes per patient	0.12	Fewer platelets transfusions per patient in the 10,000/ μ l arm; no bleeding deaths
Rebulla ⁴³	Acute myeloid leukemia	20% major bleeding	21.5% major bleeding	0.41	Fewer platelets given in 10,000/ μ l arm; 1 fatal bleed in the 10,000/ μ l arm
Zumberg ⁴⁴	Stem cell transplantation	17% major bleeding	14% major bleeding	0.66	No difference in platelet transfusions given in the two arms; no bleeding deaths

Optimizing platelet transfusion therapy*1.
Blood Reviews, Volume 18, Issue 3, Pages 149-165
J. Heal, N. Blumberg



Current practice

- Threshold of $10 \times 10^9/L$ in the absence of risk factors
 - Risk factors include sepsis, bleeding, use of antibiotics, other hemostatic problems
- Threshold of 20×10^9 if risk factors exist
- May need to manage on an individual basis in chronic stable thrombocytopenia



Invasive procedures

- Studies suggest that invasive procedures can be performed safely with a platelet count of 50,000/uL
- Higher threshold for neurosurgical and ophthalmic procedures (100,000/uL)
- Can perform bone marrow biopsies in patients with severe thrombocytopenia without platelet support

Thrombocytopenic bleeding



- Depends on site of bleed
- Higher threshold for CNS (100,000/uL)
- 50,000 or higher in other situations

Dilutional thrombocytopenia



- Occurs with massive transfusion
- Transfusion of colloids, crystalloids and RBC
- Replacement of one blood volume will reduce platelet concentration by half

Massive transfusion

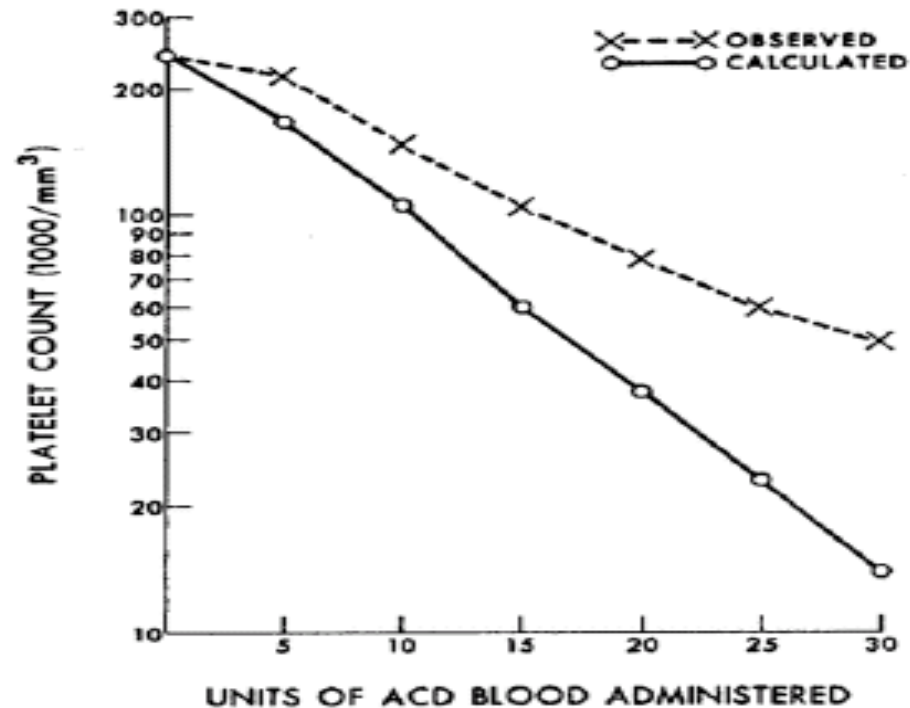


FIGURE 2 Calculated *vs* observed platelet counts in a person receiving platelet-free blood
Observed platelet counts are higher than those predicted by hemodilution alone: the observed platelet count after the administration of 25 units of blood is of the order of 60,000-mm⁻³ while hemodilution predicted a platelet count of approximately 20,000-mm⁻³. Reproduced with permission from *Miller RD, Robbins TO, Tong MJ, Barton SL. Coagulation defects associated with massive blood transfusions. Ann Surg 1971; 174: 794-801.*



Recommendations

- Only transfuse platelets if there is evidence of microvascular bleeding
 - In many cases platelets are given prophylactically

Thrombocytopathy



Congenital

Glanzman's
thrombasthenia
Bernard Soulier syndrome
Storage pool defects
Scotts syndrome
Platelet factor V
deficiency
Others

Acquired

Cardiopulmonary bypass
Uremia
Aspirin
Clopidogrel (Plavix)
Ticlopidine (Ticlid)
Tirofiban (aggrastat)
Abciximab (Reo Pro)
Epiibatide (Integrillin)

In hereditary platelet function disorders



- DDAVP will be useful in most defects
- Platelet transfusions especially if bleeding and thrombocytopenic, keep hematocrit above 35%
- Corticosteroids, ϵ -aminocaproic acid

Cardiopulmonary bypass



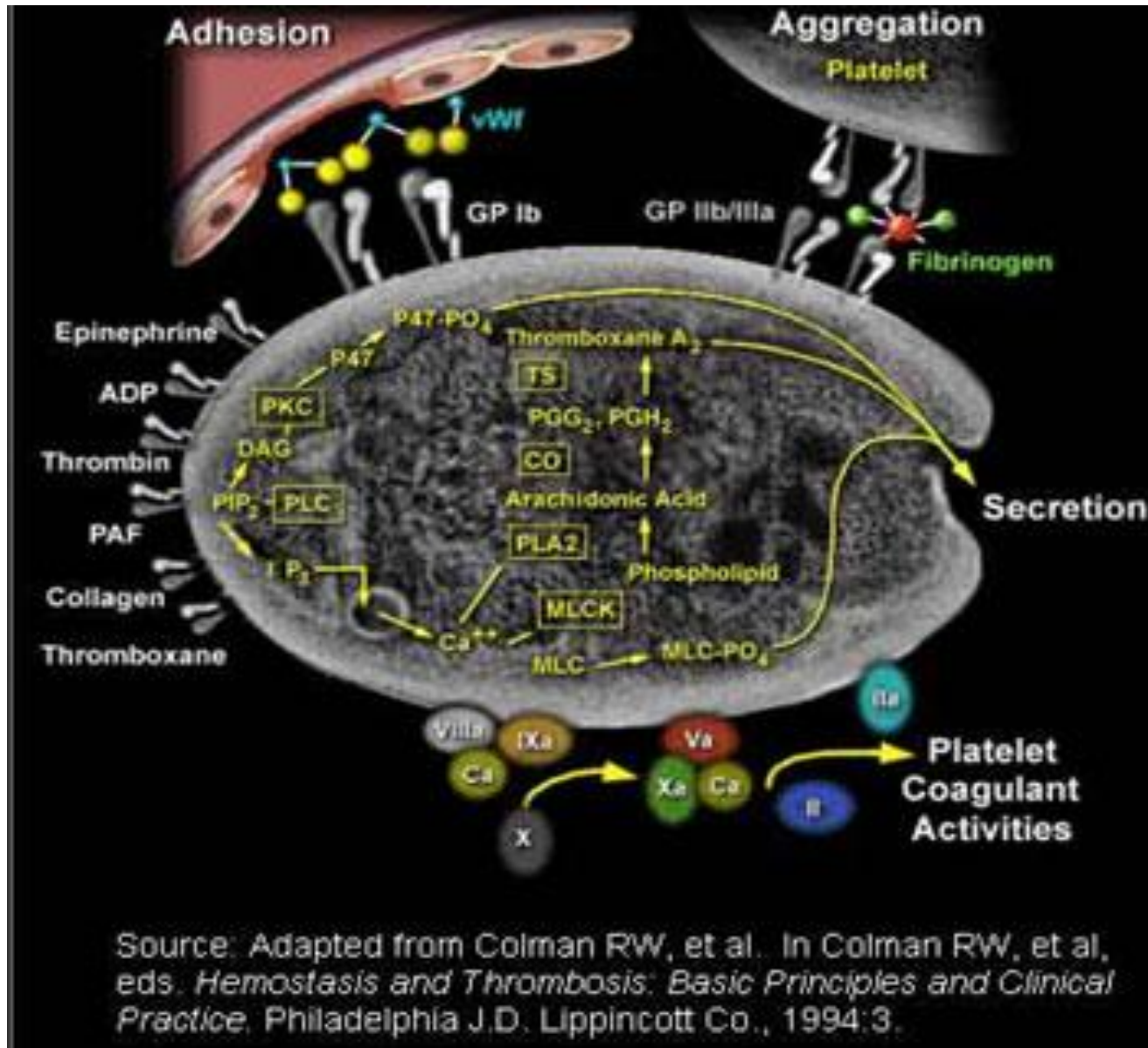
- Fall in platelet count
- Platelet function defect
- Studies do not support prophylactic transfusion, however, keeping the platelet count at 80,000- 100,000 may be beneficial



Uremia

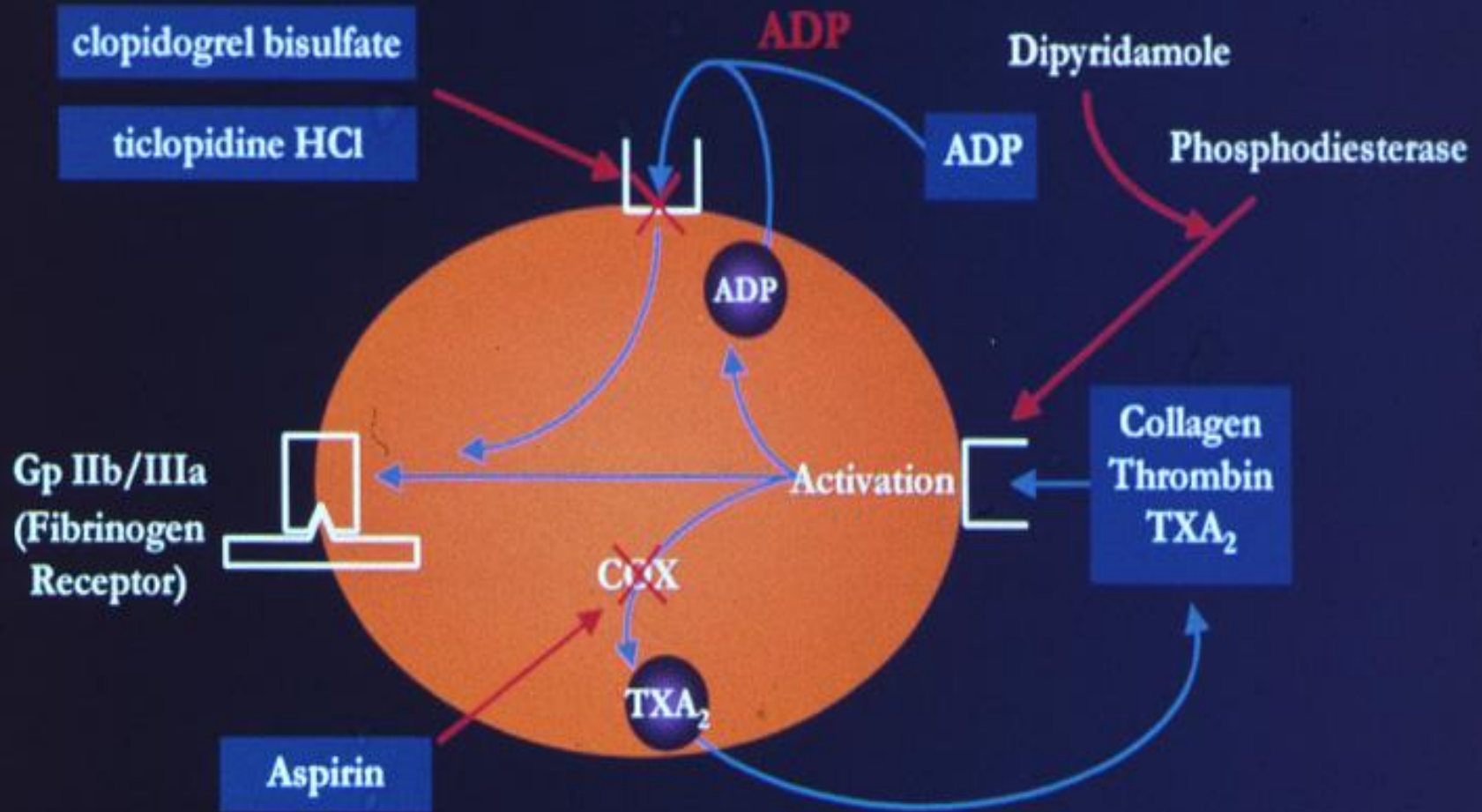
- Drop in platelet count
- Defect in platelet function
- Transfused platelets become defective
- Other therapeutic options available including DDAVP, cryoprecipitate, conjugated estrogens

Activators of Platelets.



ORAL ANTIPLATELET AGENTS

MECHANISM OF ACTION



ADP = adenosine diphosphate, TXA₂ = thromboxane A₂, COX = cyclooxygenase.
Schafer AI. *Am J Med.* 1996;101:199-209.

Aspirin



- Lack of Data but suggest platelet transfusion in bleeding due to aspirin
- Suggest stopping aspirin 3-10 days before surgery
 - Studies have shown that people who went into surgery less than 3 days after stopping aspirin used more blood products

Plavix

(inhibits ADP induced aggregation)



- No consensus on when to stop the drug before surgery
- Patients with bleeding due to Plavix may have normal platelet counts
- Active metabolite persists after cessation of drug
 - Therefore in a bleeding patient, may need platelet transfusions 4-5 day after stopping the drug

Ticloid

(inhibits ADP induced aggregation)



- Half life – 4-5 days
- Effect on platelet is irreversible
- Delay elective surgery for several days if possible
- May use more blood products if drug is still present

Platelet glycoprotein IIb/IIIa receptor antagonists



- Aggrastat, ReoPro, Integrillin
- Do not permanently impair platelets
- Platelet function returns within several hours for aggrastat and integrillin and 24- 48 hours for Reo Pro
- May need platelet transfusion in emergencies

Selective Serotonin Reuptake inhibitors



- Used to treat depression and other mood disorders
- Case reports of increased bleeding risks
 - Decreased platelet binding affinity
 - Blockade of intraplatelet calcium mobilization
 - Reduced platelet secretion in response to collagen
- Due to changes in the serotonin intraplatelet and plasma levels

Bleeding associated with SSRIs



- Usually not profound, superficial locations, Rarely require transfusions
- Hematomas, petechiae, bruising, epistaxis
 - Intracerebral, GI, retroperitoneal bleeding has been reported
- Increased risk of perioperative bleeding

Splenomegaly

- May cause platelet sequestration
- Platelet transfusion rarely indicated



Immune thrombocytopenic purpura



- Platelet transfusion may be indicated in hemorrhagic emergencies (may need to hypertransfuse)

Contraindications to Platelet transfusion



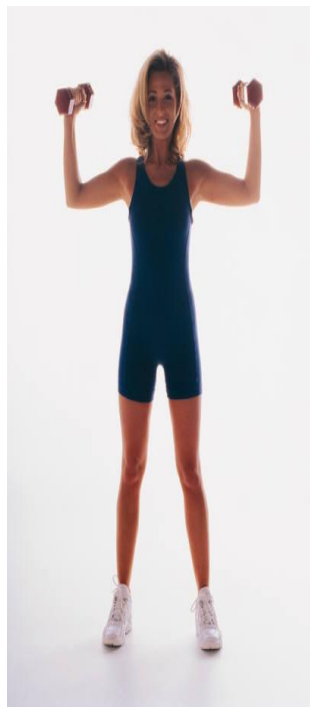
- Autoimmune idiopathic thrombocytopenia purpura
- Thrombotic thrombocytopenia purpura
- Heparin induced thrombocytopenia
- Coagulopathy only
- Anatomic bleeding only



Standard Platelet doses

- Infants: 10ml/kg body weight
- Children: 1 unit (whole blood derived) for every 10-15kg body weight
- Adults: 4-8 units pooled or 1 unit pheresis

Expected Increment



	1 unit	4 units	6 units
50lb	22,000/uL	88,000/uL	132,000/uL
100lb	11,000/uL	45,000/uL	66,000/uL
150lb	7,400/uL	30,000/uL	44,000/uL
200lb	5,500/uL	22,000/uL	33,000/uL



Assessment of response

- Cessation of hemorrhage
- Post transfusion count
 - Dependent on size
 - Initial platelet count
 - Dose given
 - One third transfused platelets will remain in the spleen



Corrected count increment (CCI)

- Takes into account the body surface area of the patient
 - Need to obtain platelet count within 10 minutes to 1 hour of transfusion

$$\text{CCI} = \frac{\text{platelet increment/uL} \times \text{BSA (m}^2\text{)}}{\text{number of platelets transfused}(x10^{11})}$$

CCI

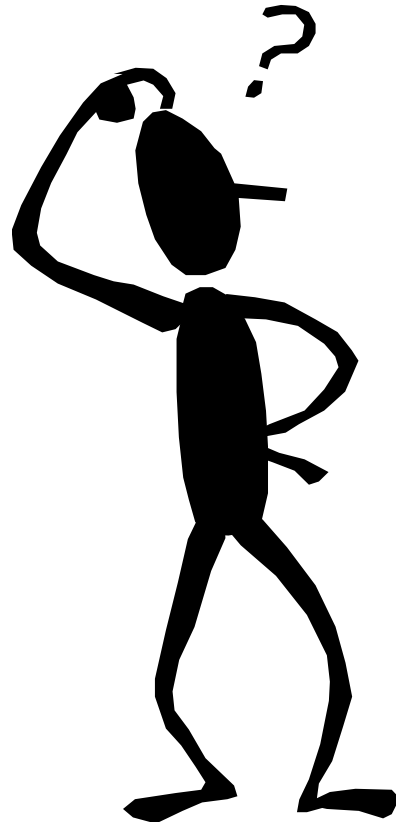


- Expected CCI should be > 7500
- If less than 7500 on at least 2 occasions, the patient is declared refractory to platelet transfusions

Platelet refractoriness



Immune



Non Immune



Non Immune Causes

- Platelet quality: dose, washed, filtered
- Platelet age: slightly better increments with fresh platelets
- Massive bleeding
- Splenomegaly
- DIC
- Fever
- Bone marrow transplantation
- Graft vs host disease
- Amphotericin
- TTP
- Other drugs



Immune causes

- ABO incompatibility
- HLA incompatibility
- HPA incompatibility
- Autoantibodies
- Drug induced antibodies
- Passively acquired antibodies



HLA Alloimmunization

- Platelets bear ~70% of whole blood load of class I HLA-A and HLA-B antigen
- Do not express class II antigens
- Donor leukocytes (have both class I and II) provide a source of antigen presenting cells
 - Hence the usefulness of leukocyte reduction!



TRAP Study

- Population: patients with newly diagnosed AML

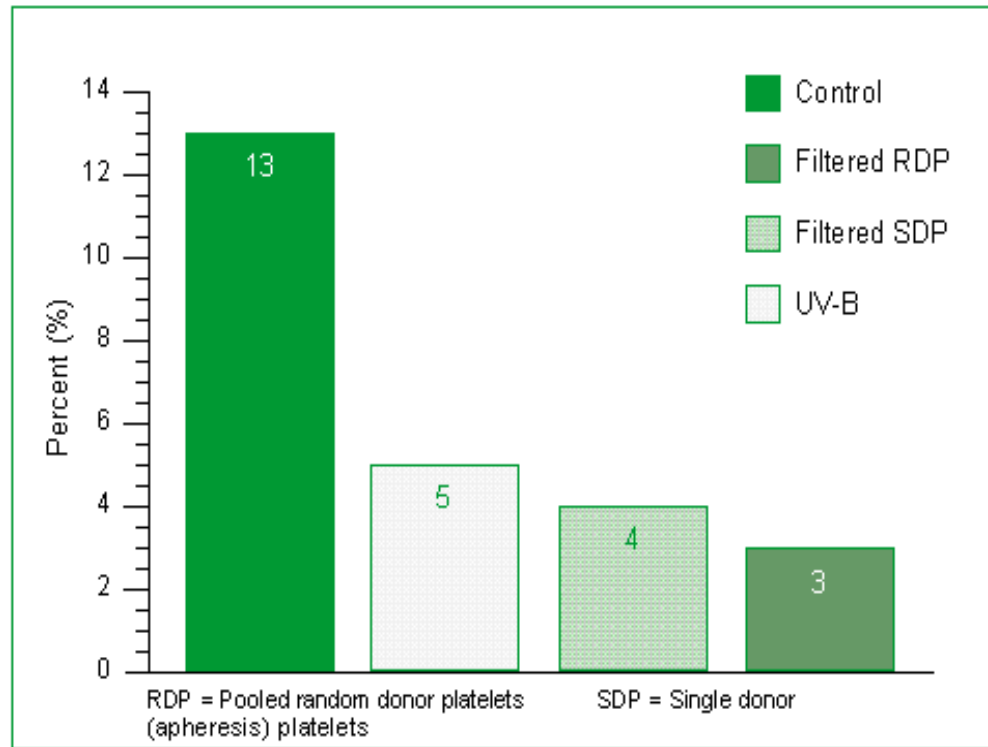
Control group

- received random platelets

Treatment group

- Pooled platelets leukocyte reduced by filtration
 - Pooled platelets with ultraviolet irradiation
 - Apheresis platelets- leukocyte reduced
-
- All RBC units were leukocyte reduced

TRAP study



www.pall.com/medical

- ✓ Less HLA alloimmunization in all treatment groups compared to the control group
- ✓ No differences between study groups
- ✓ Low incidence of bleeding in all groups
- ✓ Recommend filtered components for all AML patients



Leukocyte reduction

- Achieved by filtration or UV irradiation
- Less than 5×10^6 leukocytes
- Filters will remove 99.9% leukocytes



www.pall.com/medical

Management of Platelet refractoriness



- Non Immune
 - Treat or eliminate cause
 - Transfuse platelets only if necessary

Management of Platelet refractoriness



- Immune causes
 - Give ABO compatible platelets
 - HLA alloimmunization
 - HLA matched platelets
 - HLA antigen mismatch
 - Platelet crossmatch
 - Unselected platelets



ABO compatible platelets

- Especially a problem in recipients with high titers of anti A or anti B
- ABO density on platelets might be a contributing factor
 - A2 platelets contain 40 fold less of A antigen
- Pathogenesis: formation of immune complexes with soluble A and B substance
- Try ABO compatible



HLA alloimmunization

- Usually occurs 3-4 weeks after first transfusion
- Following pregnancy



HLA matching

- Improves platelet recovery
- Need to know patient and donor HLA type
- antibody specificity
- Can grade HLA matching based on number of antigens matched
- 80% patients will benefit

HLA antigen mismatch

- Characterize patient antibody
- Give platelets negative for the antigen



Return to unselected platelets



- HLA antibodies may disappear after one week to several months



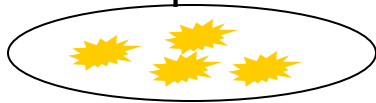
Platelet crossmatch

- Can select concentrate irrespective of nature of alloimmunization
- Use ABO compatible platelets
- Can select from a larger pool of donors
- Found to be equivalent to HLA matching
- Several methodologies available
 - Solid phase red cell adherence, flow cytometry, immunofluorescence, complement fixation

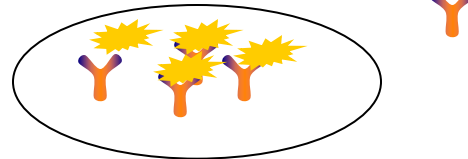
Platelet crossmatch using solid phase technology



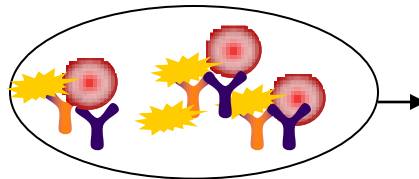
Donor platelets



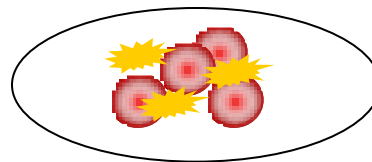
Add patient plasma



Add antibody coated RBC



Positive crossmatch



Negative crossmatch

When all fails in HLA alloimmunization



- Other causes ?
- If you tried HLA matched, try crossmatched or the reverse
- Antifibrinolytics
- Massive platelet transfusion
- IVIG
- Plasmapheresis?
- Immunoabsorption
- Immunosuppressive therapy
- HLA stripped platelets
- Thrombopoetin and platelet growth factors

Alternatives to Platelet Transfusion



- Cytokines
 - Recombinant human thrombopoietin
 - Human recombinant IL-6
 - Interleukin 3
 - Interleukin 11
 - Amifostine
- Antifibrinolytics



Platelet substitutes

- Lyophilized or freeze dried fixed platelets
 - Undergoing phase I and II studies
- Infusible platelet membrane
 - Can reduce bleeding time, under development
- Modified autologous rbc with covalently bound fibrinogen or peptide sequences
- Fibrinogen coated albumin microcapsules (synthocytes)
- Polyamide microcapsules

Complications of Platelet transfusion



- Disease transmission
 - Bacterial
 - Viral
 - Others
- Immune related
 - Febrile non hemolytic transfusion reaction
 - Allergic reactions
 - Transfusion related acute lung injury
 - Transfusion associated graft versus host disease



Summary

- Different platelet products available
- Storage time is a limitation for availability
- Transfusion thresholds exist but may vary with the patient
- Refractoriness can limit effectiveness
- Leukoreduction can reduce the risk of alloimmunization
- Several drugs can cause platelet dysfunction