Platelets- To Transfuse or Not

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1

SECTION ONE

Evidenced-Based Platelet Transfusion Thresholds

2

Introduction

- All platelets and cryoprecipitate, most plasma, and rarely RBCs given for coagulation management.
- 5.9 million non RBC products US/year
  - Plasma – 2.7 million units
  - Platelets – 2.0 million doses
    - 10% given as 4-6 U pools
  - Cryo – 1.2 million units

2017 NBCUS

3

Benefit, Risk, and Cost

- Benefit – varies clinical situation
- Risk – at least 50,000 transfusion reactions year including small number deaths
- Cost – at least $2.5 billion just for products, more for handling …

Table 1. Approximate Risk Per-Unit Transfusion of Red Blood Cells (RBCs)

Adverse Event	Approximate Risk Per-Unit Transfusion of RBCs
Febrile reaction[1,2]	1:67[a]
Transfusion-associated circulatory overload[2,3,5]	1:100[b]
Allergic reaction[3,4]	1:250
Transfusion-related acute lung injury[2,5]	1:12 000
Hepatitis C virus infection[2,5]	1:1 149 000
Hepatitis B virus infection[2,5]	1:1 208 000 to 1:843 000[c]
Human immunodeficiency virus infection[2,5]	1:1 467 000
Fatal hemolysis[2,5]	1:1 972 000

JAMA 2016; 316: 2025-2035

4

Why do we believe we need to treat low platelets and long clotting times?

How did low platelet counts and long clotting times become a surrogate for bleeding risk?

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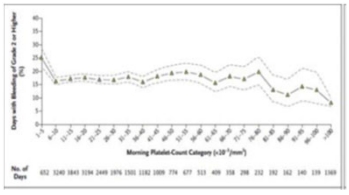
Risk of New-Onset Bleeding is the Same with Platelet Counts Between 5-80x10^9/L



N Engl J Med 2010;362:600-13

6

Blood Use

- About half of all components given in coagulation management are given prophylactically
- Prophylactic platelets in thrombocytopenic patients
- Prophylactic platelets and/or plasma before invasive procedures

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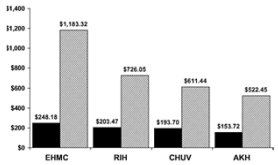
Patient Blood Management

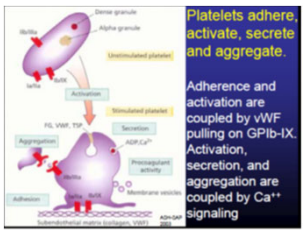
- Blood is expensive and not without risk
- Many patients receive blood in situations where evidence of benefit is poor
- Mounting evidence suggests that conservative use is associated with equivalent outcome



Transfusion 2010; 50: 753-65

8

How do Platelets Function?



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Where Do Transfusion Thresholds Come From?

- Randomized trials
  - 10,000/uL platelet transfusion threshold in cancer patients
- Expert opinion
  - Platelets- 50,000/uL platelet transfusion threshold for major surgery, 100,000/uL for optho & neuro
  - Plasma - > 2.0 INR
  - Cryoprecipitate-100 mg/dL fibrinogen threshold

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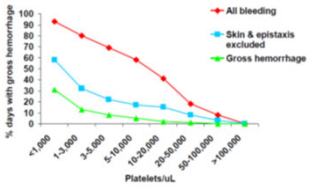
Relationship Between Platelet Count and Hemorrhage



Gaydos LA et al, New Engl J Med 1962; 266:905-9

11

RCTs comparing prophylactic platelet transfusion at 10K/uL vs. 20K/uL

	≤10,000/μL transfusion trigger			≤20,000/μL transfusion trigger		
First Author	# of patients	% major bleeding	Hemorrhagic deaths	# of patients	% major bleeding	Hemorrhagic deaths
Gil-Fernandez, 1996	103	12	3	87	14	4
Rebulla, 1997	53	22	1	52	20	0
Heckman, 1997	37		0	41		0
Wandt, 1998	58	18	0	47	17	0
Navarro, 1998	21	42	0	27	30	0
Lawrence, 2001	77	15		64	15	
Zumberg, 2002	78	14	0	81	17	0

Major bleeding generally indicated bleeding that led to transfusion

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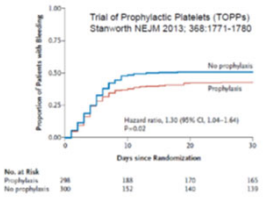
Are prophylactic transfusions needed?



- Randomized, open-label, noninferiority trial
- 14 centers in UK and Australia
- Randomly assigned receive, or not to receive, prophylactic platelet transfusions when morning platelet counts were < 10,000/uL
- Time to first bleeding episode significantly shorter no-prophylaxis group vs. prophylaxis group

13

TOPPs Conclusion

- Results of study support need for continued use of prophylaxis with platelet transfusion
- Showed benefit of such prophylaxis for reducing bleeding, as compared with no prophylaxis

N Engl J Med 2013; 368: 1771-1780

14

Platelet Transfusions AABB Clinical Practice Guidelines

- Literature search from 1900 to September 2014
- An expert panel reviewed data
- Developed recommendations using Grading of Recommendations Assessment, Development and Evaluation (GRADE) framework

Ann Intern Med. 2015;162:205-213

15

Recommendation 1

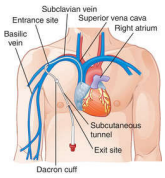
- Prophylactically count 10,000/uL or less
- Reduce the risk for spontaneous bleeding
- Hospitalized adult patients
- Hypoproliferative thrombocytopenia
- *Grade: strong recommendation; moderate-quality evidence*

Ann Intern Med. 2015;162:205-213

16

Recommendation 2

- Prophylactic platelet transfusion for elective central venous catheter placement with platelet count less than 20,000/uL
- *Grade: weak recommendation; low-quality evidence*



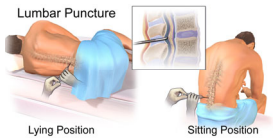
www.medical-dictionary.thefreedictionary.com 07/19

Ann Intern Med. 2015;162:205-213

17

Recommendation 3

- Prophylactic platelet transfusion for patients having elective diagnostic lumbar puncture with platelet count less than 50,000/uL
- *Grade: weak recommendation; very low-quality evidence*



www.enwikepedia.org 07/19

Ann Intern Med. 2015;162:205-213

18

Recommendation 4

- Prophylactic platelet transfusion for patients having major elective nonneuraxial surgery with a platelet count less than 50,000/uL
- *Grade: weak recommendation; very low-quality evidence*

Ann Intern Med. 2015;162:205-213

19

Recommendation 5

- Cardiopulmonary bypass (CPB)
- Perioperative bleeding with thrombocytopenia and/or evidence of platelet dysfunction
- *Grade: weak recommendation; very low-quality evidence*

Ann Intern Med. 2015;162:205-213

20

Recommendation 6

- The AABB cannot recommend for or against platelet transfusion for patients receiving antiplatelet therapy who have intracranial hemorrhage (traumatic or spontaneous)
- *Grade: uncertain recommendation; very low-quality evidence*

Ann Intern Med. 2015;162:205-213

21

Active Bleeding
No High-Quality Evidence for Guidance

Criteria	Platelet Count (/uL)
Thrombocytopenic Bleeding Patients	Often recommended maintain count above 50,000/uL

Some facilities use 100,000/UL for ophthalmologic, neurologic and pulmonary hemorrhage

AABB Technical Manual 19th ed. 2017

22

Thrombocytopathy

- Causes
  - Congenital (e.g., Glanzmann thrombasthenia)
  - Acquired as the result of disease (e.g., myelodysplasia)
  - Drug treatment (e.g., with aspirin or glycoprotein IIb/IIIa antagonists)
- Transfusion Decisions
  - Acceptable even at normal counts
  - Based upon patient's clinical status
  - Test platelet function

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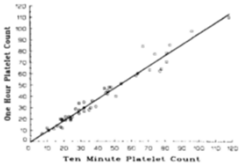
Platelets-Pre and Post Counts

- Platelet count should be obtained
  - Before
  - 10 to 60 minutes after transfusion
- Platelet count should increase by 30,000 to 60,000/uL
- Assess adequacy of response to transfusion



AABB Technical Manual. 19th ed. 2017
Transfusion 1988:28:66-67

24

Platelet Products Available

- Pooled platelets (Acrodose)- average 4-6 platelets per pool
- Apheresis Platelets 100% plasma
- Apheresis Platelets in PAS (platelet additive solution 65%, 35% plasma)
- Pathogen Reduced Apheresis Platelets (collected in PAS)

AABB Standards for Blood Banks/Transfusion Services 31st ed. 2018

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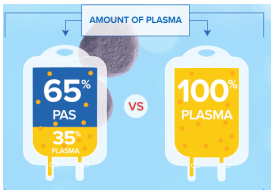
Apheresis Platelets in PAS (platelet additive solution 65%, 35% plasma)

- Standard apheresis platelet collected and upon finalization of collection
- 65% percent of plasma is removed
- Replaced with additive solution
- Solution added is InterSol Solution, Platelet Additive Solution 3 (also called PAS 3)



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Apheresis Platelets in PAS

- Study conducted at six sites 14,005 transfusions
  - Allergic transfusion reactions - 1.37% vs. 0.55%
  - Febrile nonhemolytic transfusion reactions - 0.66% to 0.40%
  - Removal of plasma, anti-A and anti-B titers may be decreased potentially reducing risk of hemolytic transfusion reactions that can occur with high-titer donors
  - Platelet viability and function is not affected
- Decrease in AB titer allows for products to be used interchangeably with patients with different ABO

Transfusion 2014; 54: 1927-1934
J Clin Apheresis 2012; 27: 93-98
Transfusion 2012; 52: 1237-1244

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27

Pathogen Reduction Technology (PRT) Mechanism of Action

- INTERCEPT® Blood System for Platelets uses amotosalen and UVA light to irreversibly cross-link nucleic acids
- Blocks replication of viruses, bacteria, parasites and T-cells; rendering them 'inactive'
- After processing, residual amotosalen is negligible

SCABB Presentation A Prichard 12/18

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28

Efficacy

- November 2010 - April 2016
- 469 hematology-oncology patients with chemotherapy-induced thrombocytopenia
- Randomized to 567 transfusion treatment periods
  - 283 control arm – platelets in plasma (PP)
  - 284 intervention arm (PRT)

Blood 2018; 132: 223-231

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29

Efficacy

- 3% absolute difference (51% PP vs. 54% PRT) significant (WHO classification - grade ≥ 2 bleeding) P=.012
- Transfusion increment parameters were lower and transfusion interval shorter- PRT arm
- There was no difference in proportion of patients developing HLA class I alloantibodies

Blood 2018; 132: 223-231

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30

Efficacy

- Other studies
  - Small losses in platelet function
- Effective eliminating transfusion-associated graft vs. host disease and the need for irradiation

ISBT Science Series. 2014; 9:44-50
Vox Sanguinis 2017; 112; 606-613

Conventional (left) and Psoralen-Treated (right) Apheresis Platelets

31

Platelet Components
Equivalent to 4-6 Whole-Blood Derived Platelets

	Apheresis Platelets- Includes Plasma, PAS and PRT	Prestorage Pooled Platelets (Acrodose)
Advantages	• Single donor exposure • HLA matching possible	• Closed system • Allows pooling 4-6 ABO identical units
Disadvantages	• Limited availability	• Matching impractical
Platelets	• $\geq 3.0 \times 10^{11}$ ($\geq$90%)	• $\geq 5.5 \times 10^{10}$ ($\geq$75%)/each unit

Transfusion Therapy. 3rd ed. 2011
Technical Manual. 19th ed. 2017
AABB Standards for Blood Banks/Transfusion Services 31st ed. 2018

32

Platelet Components

	Apheresis Platelets- Includes Plasma, PAS and PRT	Prestorage Pooled Platelets (Acrodose)
Leukocyte Reduction	• Prestorage	
Bacterial Detection	• Yes	
Shelf Life	• 5 days (7 days with point of release testing*)	• 5 days
Storage	• 20-24 C continuous gentle agitation	
Transport	• As close to 20-24 C-maximum time without agitation: 30 hours	
pH	• $\geq$ 6.2 end of allowable storage period ($\geq$90%)	

*Does not include PRT

Transfusion Therapy. 3rd ed. 2011
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33

Fiscal Years 2013-2017

- TACO - 32%
- TRALI and Possible TRALI- 30%
- Microbial contamination- 12%
- HTR due to non-ABO incompatibilities -11%
- Remainder- <10% each

Table 3: Transfusion-Associated Fatalities by Complication, FY2013 – FY2017

Complication	FY13 No.	FY13 %	FY14 No.	FY14 %	FY15 No.	FY15 %	FY16 No.	FY16 %	FY17 No.	FY17 %	Total No.	Total %
Anaphylaxis	–	0%	2	7%	1	3%	3	12%	3	8%	**11**	**6%**
Contamination	5	13%	1	3%	5	14%	5	32%	7	19%	**23**	**12%**
HTR (ABO)	1	3%	4	13%	2	5%	4	0%	1	3%	**12**	**7%**
HTR (non-ABO)	5	13%	4	13%	4	11%	1	2%	6	16%	**20**	**11%**
Hypotensive Reaction	–	0%	1	3%	1	3%	1	2%	0	0%	**3**	**2%**
TACO	13	34%	5	17%	11	30%	19	44%	11	30%	**59**	**32%**
TRALI	14	37%	13	43%	12	32%	8	19%	9	24%	**56**	**30%**

Note: FY2015-FY2017 only includes cases with an imputability of *Definite/Certain, Probable/Likely*, or *Possible*, and FY2013-FY2014 only include cases classified as transfusion-related.
*FY2013-FY2017 numbers combine both *TRALI* and *Possible TRALI* cases[22,23]

Fatalities Reported to FDA Following Blood Collection and Transfusion Annual Summary for FY2017

34

Transfusion Related Acute Lung Injury (TRALI)

Figure 1: TRALI Cases, FY2003 – FY2017

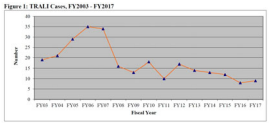
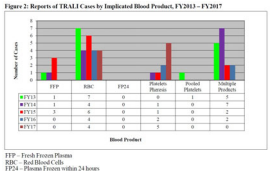


Figure 2: Reports of TRALI Cases by Implicated Blood Product, FY2013 – FY2017



	FFP	RBC	FP24	Platelets Pheresis	Pooled Platelets	Multiple Products
FY13	1	7	0	0	1	1
FY14	1	4	0	1	0	7
FY15	3	6	0	1	0	2
FY16	0	4	0	2	0	2
FY17	0	4	0	2	0	0

FFP – Fresh Frozen Plasma
RBC – Red Blood Cells
FP24 – Plasma Frozen within 24 hours

FDA Fatalities Report FY2017

35

SECTION TWO
Platelet Refractoriness and Patient Response

36

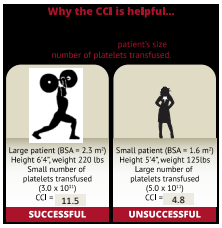
Corrected Count Increment (CCI)

$$CCI = \frac{\text{Platelet increment} \times BSA\ (m^2)}{\text{Platelets transfused}\ (\times 10^{11})}$$

Example: A patient with a BSA of 2.0 m^2 and a platelet count of 5000/μL receives a unit of apheresis platelets containing 4×10^{11} platelets, and the posttransfusion platelet count is 25,000/μL. The CCI may be calculated as follows:

$$CCI = \frac{20 \times 2.0}{4.0} = 10$$

Successful transfusion: ≥7.5
Refractory patient: Two or more transfusions with CCI <5.0



Transfusion Therapy. 3rd ed. 2011
Technical Manual. 19th ed. 2017

37

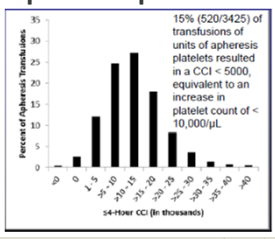
Refractory Patient

- Poor increments ≤ 10,000/uL on at least two posttransfusion counts

Technical Manual. 19th ed. 2017

38

Corrected platelet count increments after apheresis platelet units - PLADO study

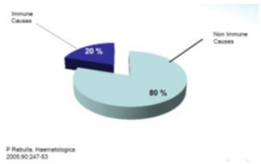


- Mean absolute increment 28,000/uL
- 95% CI 0-60,000/uL

N Engl J Med 2010;362:600-13

39

Alloimmune Platelet Refractoriness

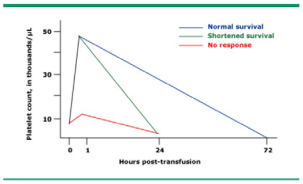


Nonimmune	Immune
Fever	HLA antibodies
Medications (eg, amphotericin, vancomycin)	ABO incompatibility
Splenomegaly	Human platelet antigen (HPA) antibodies
Sepsis	Drug-dependent autoantibodies
Disseminated intravascular coagulation	
Hemorrhage	
Veno-occlusive disease	
Graft-vs-host disease	
Prolonged platelet storage	

J McFarland AABB Webinar 03/12/14
AABB Technical Manual 19th ed. 2017

40

Patterns of response to platelet transfusion



UpToDate Graphic 82283 Version 2.0

41

ABO Compatible

- Some patients may be refractory from ABO
- Provide one or more transfusions of donor PLTs ABO compatible
- Monitor post-transfusion increments

Transfusion 2007;47:374-378

42

HLA antibody screening test
Panel-reactive antibody (PRA)

- Percent of HLA targets to which patient has made antibodies
- Different assays
  - Lymphocytotoxic assay (with or without antiglobulin enhancement)
  - Enzyme-linked immunoassay, or fluorescence-based assay
- Choice of assay not critical although serial assays are best done by the same method for ease of comparison

Transfusion 2007;47:374-378

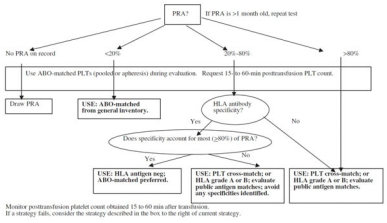
43

Undetectable PRA (0 percent sensitization)

- HLA matching will not be beneficial
- Other strategies should be tried (discussed later)
- For patients with positive PRA result, an algorithm can be used

44

Positive PRA - Decision algorithm for HLA-selected platelets used at Massachusetts General Hospital



Transfusion 2007;47:374-378

45

Strategies for HLA-selected Platelets

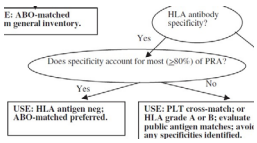
- HLA antigen avoidance
- PLT crossmatching
- HLA-matching

Transfusion 2007;47:374-378

46

HLA-Antigen Avoidance

- Identify HLA specificity that accounts for majority of PRA
- Most straightforward approach



Transfusion 2007;47:374-378

47

HLA lab is unable to identify specificity

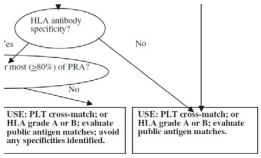
- Donor selection can proceed along two fronts

Transfusion 2007;47:374-378

48

Platelet Crossmatching - Fastest

- Transfusable units with higher survival rate *in vivo* can be located without need for HLA typed donors
- Patient HLA typing and/or HLA antibody identification is not required



Transfusion 2007;47:374-378

49

Platelet Crossmatching

- Strong HLA antibodies directed against antigens not found on PLTs will not be detected
- Lower costs to support mildly refractory patients or those with short to medium term matched platelet support
- Wide availability of some crossmatch methodologies

Transfusion 2007;47:374-378

50

Disadvantages of Platelet Crossmatching

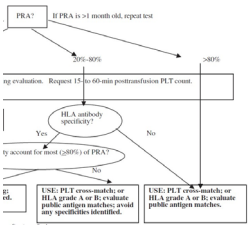
- Sensitivity to mediating antibodies varies depending upon which crossmatch methodology is utilized
- Highly alloimmunized patients may require numerous (e.g. ≥ 20) crossmatches to identify a compatible unit
- Logistical challenges posed by managing inventory of platelet units used in crossmatch testing

Transfusion 2007;47:374-378

51

High-PRA Patients

- While crossmatch–compatible PLTs are being tried
- Explore HLA matched platelets based on HLA-A and HLA-B types of recipient



Transfusion 2007;47:374-378

Degree of Matching (Duquesnoy Grades) for HLA Antigens HLA Class I A and B Loci

- "Standard" approach is to identify a donor whose four HLA-A and HLA-B antigens match those of the recipient (grade A match) -may be difficult to find
- Alternatives - grade A, B1u, B1x, or B2u matches,
- Most hospitals do not want to accept B2x matches or lower grades - much less likely to be successful

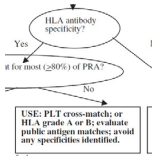
A	4 antigens match
B1U	3 antigens detected in the donor, all match
B1X	3 donor antigens match, 1 cross-reactive
B2U	2 antigens detected in the donor, both match
B2UX	3 antigens detected in the donor, 2 match and 1 cross-reactive
B2X	2 donor antigens match, 2 cross-reactive
C	1 antigen in donor not present in recipient and not cross-reactive
D	2 antigens in donor not present in recipient and not cross-reactive

Transfusion Medicine Self-Assessment and Review. 3rd ed. 2017

Transfusion 2007;47:374-378

HLA Public Antigens

- Consider not only the public groups of patient (public antigens to match)
- Public groups of target antigens that reacted in PRA (public antigens to avoid)



Transfusion 2007;47:374-378

HLA Public Antigens

- Public matching can often identify donor who gives good increment much more quickly than private antigen matching
- Strategy of matching for public antigens generally results in greater number of suitable donors

Transfusion 2007;47:374-378

55

Platelet Antigens

- Alloimmunization to platelet-specific antigens should be considered
- Sensitization to platelet-specific antigens may be cause of refractoriness when a donor product that is well matched for HLA fails to give an increment
- Identify antibodies to platelet antigens, test patient's serum with a commercially available enzyme assay

Transfusion 2007;47:374-378
Vox Sang 1998; 74(Suppl 2):359-63

56

Non-HLA

- Current era of leukoreduction, immune causes of refractoriness often reflecting a secondary immune response is particular problem with multiparous females
- Outside of this group nonimmune causes of PLT refractoriness are more common than immune-mediated causes and so refractory patients with a low PRA are often commonplace

Transfusion 2007;47:374-378
N Engl J Med 1997; 337: 1861-9

57

Drug-related thrombocytopenia

- Degree of thrombocytopenia is considered clinically unacceptable
- Serious paring down of medications, especially antibiotics, may be tried

Transfusion 2007;47:374-378
Curr Hematol Rep 2003; 2:158-64

58

What Does not Work-Shock and Awe

- Massive doses of platelets is rarely effective and for most patients
- Little more than an invitation to serious transfusion reactions
- Exception
  - Patient splenomegaly for whom double dose of platelets may be needed to achieve typical platelet increment

Transfusion 2007;47:374-378

59

What Does not Work- Treatments for Another Problem

- Platelet refractoriness not the same as autoimmune thrombocytopenia
- Treatments such as intravenous anti-D or high-dose intravenous immunoglobulin G fail to improve platelet increments among refractory patients

Transfusion 2007;47:374-378

60

What Does not Work- Voodoo drips

- Notion of a continuous drip of ineffective platelets has never made any sense largely “bad theater”
- Equally theatric is arranging for infusion of platelets to be simultaneous to performance of a bedside invasive procedure
- We simply do not do this!

Transfusion 2007;47:374-378

61

Local Bleeding–Local Treatment

- Appropriate hemostatic treatment for nonimmune refractory patient is local treatment
- For example, clinical team may be frustrated by continued oozing at site of insertion of central line despite repeated attempts to stop this with platelet transfusions
- This situation is better approached through use of topical agents at site of bleeding
- Topical fibrin glue or extra suture or two may be all that is needed

Transfusion 2007;47:374-378

62

Hemostatic Defects

- Hypofibrinogenemia, coagulation factor defects, or depressed von Willebrand’s factor
- Addressed with transfusion/pharmaceuticals

Transfusion 2007;47:374-378

63

Conclusions

- Prophylactic platelet transfusions remain standard of care
- Laboratory testing and donor selection are necessary steps in support of platelet transfusion refractory patient
- Many patients continue to require additional transfusion approaches and/or adjunctive therapy to treat and prevent bleeding

Transfusion 2007;47:374-378

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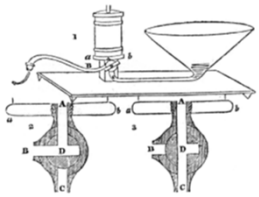
64

64

200th anniversary year of the first successful attempts at human-to-human transfusion



Transfusion Medicine Reviews 2018:
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65

65

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The End...Questions

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66