Managing the Patient Refractory to Platelet Transfusion

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BLOOD MATTERS 2019

Objectives

Causes and clinical significance of refractoriness

Non immune mediated platelet refractoriness

Approaches to caring for patients with platelet refractoriness

50 year old female AML, admitted to ICU with tumor lysis syndrome

She requires mechanical ventilation, vasopressors and begins chemotherapy

Develops pneumonia treated with broad spectrum antibiotics and antifungals

Remains febrile

Day 13, platelet count is 3 x 10(9)/L, she is not bleeding

24 hours following platelet transfusion, the count is 3 x 10(9)/L

The next step is to....

Repeat the platelet count 10 minutes-1 h after platelet transfusion

Request HLA typing & antibody screen as she is refractory

Administer fresh (<72 hours) platelets

Administer ABO identical platelets

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WHO grading of bleeding

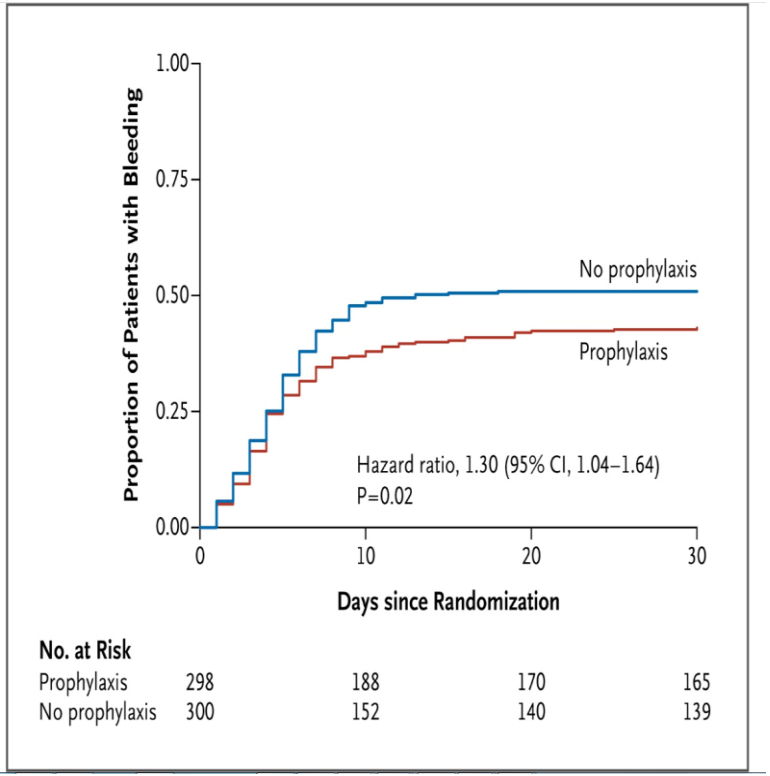
GRADE 1: petechiae, purpura localized to 1 or 2 dependent sites, epistaxis ≤30 min, oropharyngeal bleeding ≤30 minutes

GRADE 2: melena, hematemesis, hemoptysis, hematochezia, hemarthrosis

GRADE 3: Bleeding requiring RBC transfusion

GRADE 4: Fatal bleeding, bleeding with severe hemodynamic compromise (e.g. hypotension; >50mm/Hg fall or >50% decrease in either systolic or diastolic blood pressure)

Prophylactic platelet transfusion is intended to decrease the risk of hemorrhage



10-15% of platelets removed daily, predominantly by the spleen

7,000/µL for vascular integrity daily

1-hour post transfusion increment is ~30,000 to 60,000/µL

Shorter survival with lower counts: 7 days if 50 - 100,000/ µL vs. 5 days if < 50,000/ µL,

≤10,000/ µL is the prophylactic platelet count

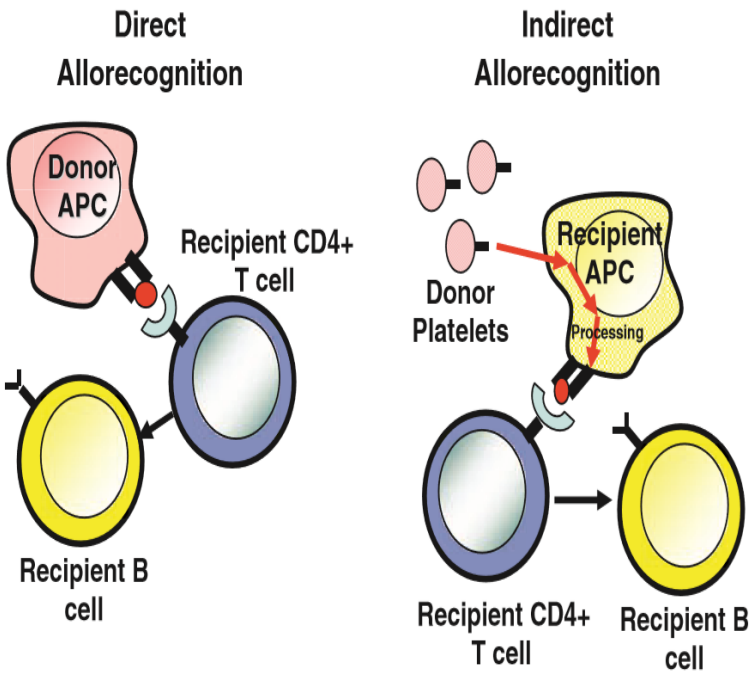
Stanworth S et al. N Engl J Med 2013;368:1771-80, Hanson S, Slichter S. Blood 1985; 66: 1105-09.

Platelet refractoriness is defined as

Increment <10,000/µl 10-60 minutes after transfusion ≥ 2 occasions

Lack of an increment within 60 minutes suggests an immune etiology secondary to antibody mediated destruction

If there is an increment >10,000/ µL it is non immune



O' Connell et al.Transfusion1988:28:66, Semple et al.Blood 1995;86:805-12. Gilson CR et al.Transfusion 2012; 52: 849. Pavenski K et al. Tissue antigens 2012;79: 237

Refractoriness is predominantly,80%,due to non immune factors

Recipient related

Platelet consumption

Fever ↓ 1.6 x 10^9/L (0.8,2.3)

Bleeding ↓ 1.7 x 10^9/L (0.6,2.8)

Splenomegaly ↓ 3.5 x 10^9/L (1.3,5.8)

Cytoreductive drugs/disease/antibiotics: e.g. linezolid, after 2 weeks of exposure in 2.4%

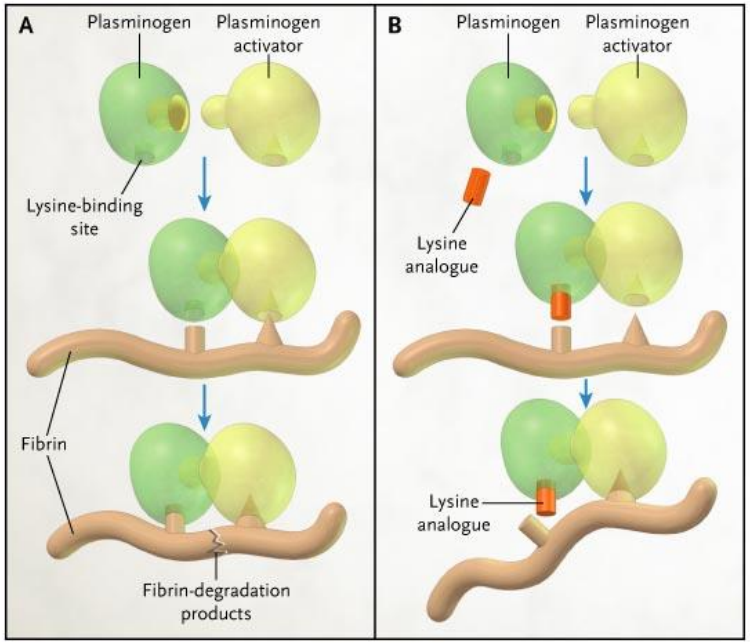
Platelet product related

Storage ≤ 48 hours ↑ 1.9 x 10^9/L (1.1, 2.7), recovery similar in well vs ↓ 80% with older platelets and bacterial infection

Pathogen reduction RR 2.9 (2.1 to 4.2)

Slichter S et al. Blood 2005;105: 4106–4114. Norol F et al. BJH 1994;86:125-129, Estcourt LJ et al. Cochrane Database Syst Rev 2017 30;7:CD009072, Arnold D et al. TMR 2013; 27: 137–145.

The inhibition of fibrinolysis by tranexamic acid to reduce the risk of bleeding may also decrease fibrinolysis



Plasmin activated from plasminogen causes degradation of fibrin

The process is facilitated by plasminogen binding to fibrin through lysine residues in fibrin that bind to lysine binding sites on plasminogen

In the presence of TXA these lysine-binding sites are occupied: inhibition of fibrin binding to plasminogen and impairment of fibrinolysis

Mannucci P and Levi M. NEJM 2007;356:2301-2311

Prophylaxis with antifibrinolytics appears to reduce platelet use: 4 ongoing studies will define their role

Study or subgroup	Tranexamic acid N	Mean(SD)	Placebo N	Mean(SD)	Mean Difference IV,Fixed,95% CI	Mean Difference IV,Fixed,95% CI
1 Induction chemotherapy						
Shpilberg 1995	16	6.2 (2.9)	22	4.5 (3.6)		1.70 [-0.37, 3.77]
2 Consolidation chemotherapy						
Shpilberg 1995	10	1.1 (1.4)	8	2.6 (2.2)		-1.50 [-3.25, 0.25]

Bleeding events/participant

1 Induction chemotherapy						
Shpilberg 1995	16	22.1 (13.2)	22	23.1 (11.7)		-1.00 [-9.11, 7.11]
2 Consolidation chemotherapy						
Shpilberg 1995	10	3.7 (4.1)	8	9.3 (3.3)		-5.60 [-9.02, -2.18]

Platelets/participant

-10 -5 0 5 10

Favours [tranexamic acid] Favours [placebo]

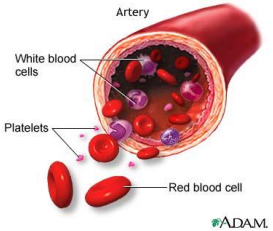
Estcourt LJ et al. Cochrane Database of Systematic Review 2016, Issue 3. Art. No.: CD009733

Aiming for higher hemoglobin targets to reduce bleeding remains an unresolved question

Supporting: Retrospective analysis of RCTs

Uhl et al, 2017 (n=1077): OR 4.9 (2.6, 9.9) of grade ≥ 3 bleeding with days with HCT ≤25% vs >29%

Webert et al, 2006 (n=255) 10g/L increase in Hb, RR 0.8 (0.6, 1.0)



Not supportive: Small RCTs

DeZern et al, 2016 (n=90) Hb 70 vs. 80 g/L: Frequency of bleeding, 32% vs. 37%

Tay et al, 2016 (n=300): Hb 70 vs. 90 g/L, no difference

Webert et al, 2008 (n=60): Hb 80 vs. 120 g/L, 86% vs. 90.3% had bleeding

Uhl L et al. Blood. 2017;130:1247,DeZern AE et al.Transfusion 2016; 56:1750, Tay J et al. Blood 2016 128:1032, Webert K et al. Transfusion 2008;48:81, Webert K et al. Haematologica 2006; 91:1530.

Thrombopoietin receptor agonists increase the platelet count

Eltrombopag and romiplostim

- Bind to the thrombopoietin receptor
- Used for ITP refractory to other therapies
- Improve normal megakaryopoiesis

Do they stimulate the growth of malignant blasts?

- Use in aplastic anemia suggests effect is on stem progenitor cells

Shastri A, Verma AK, Lancet Hematology
http://dx.doi.org/10.1016/ S2352-3026(17)30229-6

Thrombopoietin receptor agonists are useful for SAA, early days for MDS/AML

Severe Aplastic Anemia: 6 month overall response, 80-90% eltrombopag **vs.** 66% historically

Low risk MDS: terminated early, transient increase in peripheral blast count > 10%: romiplostim 15% **vs.** placebo 4%, AML 12% **vs.** 11% at 5 yrs

MDS (IPSS1,2,high risk): terminated early, no difference transfusion independence, eltrombopag 16% **vs.** 40% placebo, trend of disease progression 14% **vs.** 9%

High risk MDS/AML: (life expectancy 6 months, untreated), clinical events from thrombocytopenia 54% eltrombopag **vs.** 69% p=0.03, weekly platelet transfusions/PFS unchanged

Townsley TM et al.NEJM 2017;376:1540 Kantarjian HM et al. Lancet Haematol. 2018;5e117. Mittelman M al.Lancet Haematol 2018;5:e34, Dickinson M et al, Blood 2018 DOI 1182/

Platelet count after 1 hour was 10 x 10(9)/L, twice after fresh, ABO identical platelets, HLA antibody screen: cPRA is 20%

Request an HLA antigen negative product

The lack of response is not secondary to HLA antibody, request HPA antibody testing

The lack of response is not secondary to an HLA antibody,request partial splenic embolization

The lack of response is secondary to drugs, continue with the same product

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Immune (ALLO/AUTO) etiologies account for 20% of lack of a sustained platelet increment)

Alloimmune:

1. Class I HLA A, B antigens/epitopes

   Dependent on immune responsiveness, previous exposure to alloantigens by transfusion, pregnancy

   Leukoreduction: ↓ 18% alloimmunized, 3% refractory

2. Human Platelet Antigens (HPA) predominantly 1b, 5b

   Accounts for 2-8% of alloantibodies, refractoriness infrequent

3. ABO identical: ↑ 4×10^9/L

Autoimmune: Immune thrombocytopenia secondary to underlying disease e.g. lymphoma, leukemia or drugs

TRAP Study Group. NEJM 1997;337:1861-9., Shehata N et al. Transfusion 2009;49: 2442-2453. Kiefel V et al. Transfusion 2001;41:766-70.

Immune mediated thrombocytopenia resolves within days of discontinuation of implicated drug

E.g. piperacillin/tazobactam in ≤ 1%

The decline is 5 - 10 days after daily exposure, or within hours after re-exposure

Platelet count decline < 20×10^9/L

Rapid decline

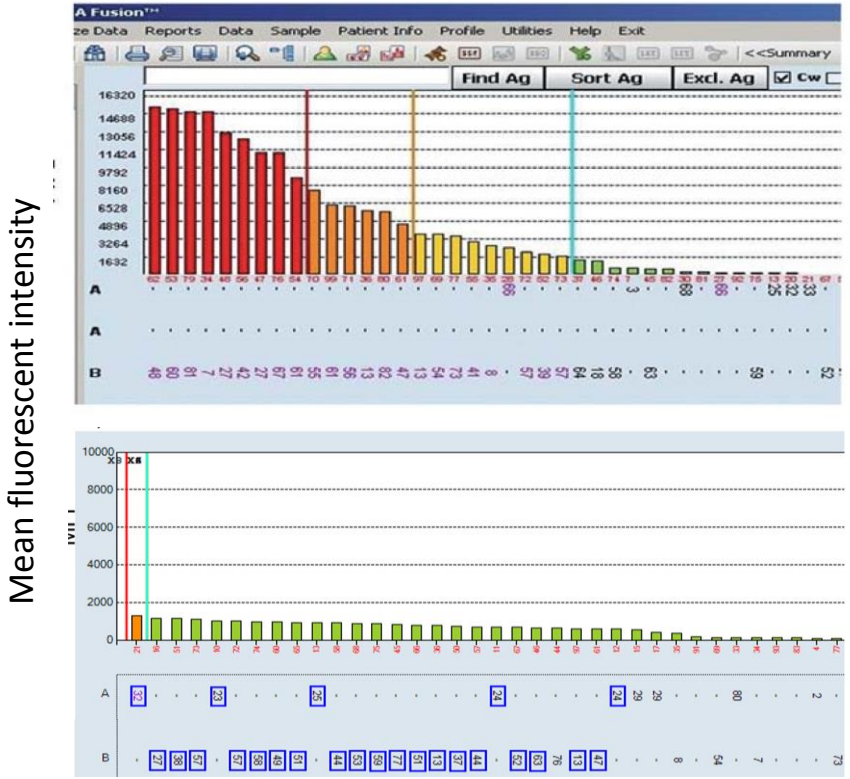
Mucocutaneous bleeding symptoms often occur

Arnold D et al. TMR 2013; 27: 137–145. :

Identifying platelet products for HLA alloimmunized

1. HLA epitope negative to the antibody:
   - **A.** Identify the antibody: detection of antibody by solid phase assays

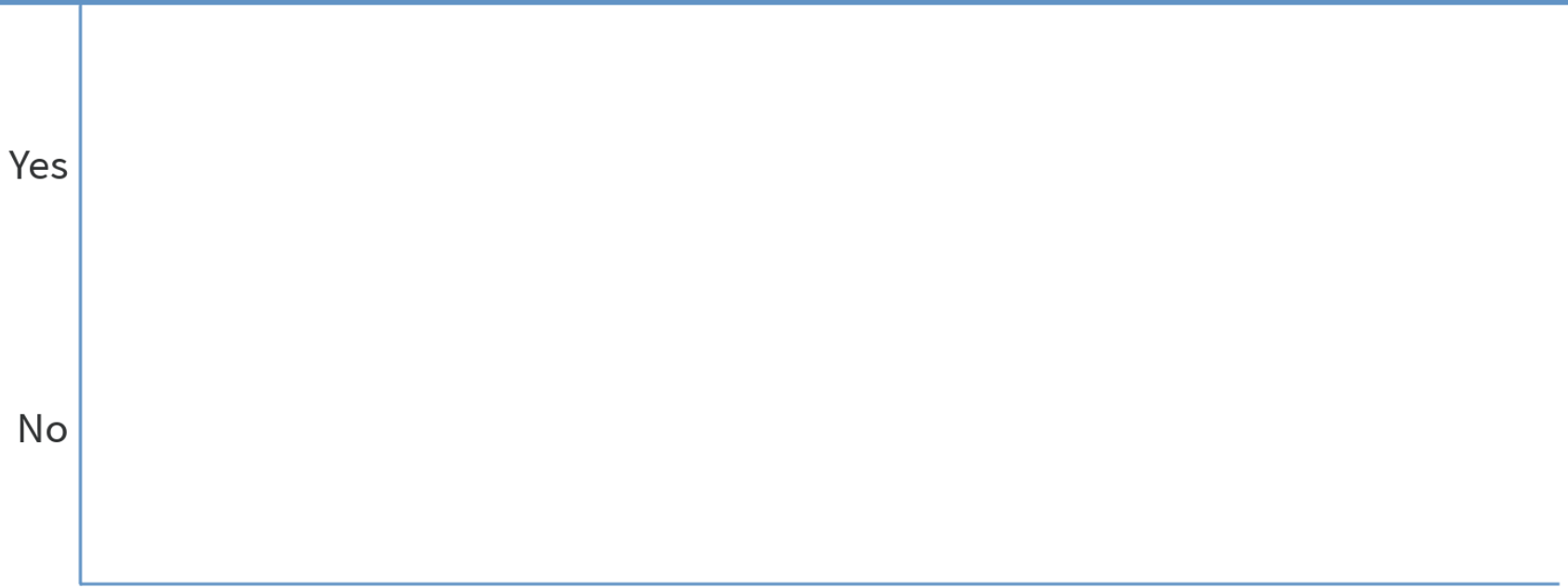
     Degree of HLA sensitization=Calculated Panel Reactive Antibody (cPRA): frequency of HLA epitope in the population/ incompatibility
   - **B.** Identify the epitope: molecular methods to detect epitopes +/- HLA Matchmaker
2. Crossmatching platelet products



Single antigen bead specificities

Kopko PM et al.Transfusion 2015;55:235, Duquesnoy R. Hum Immunol 2006; 67:847, Keirnan J et al. Curr Opin Organ Transpl. In press

She receives HLA antigen negative platelets to an antibody identified that result in minimal increases in platelet counts. She is not bleeding. Fever is resolved. Should daily platelet transfusion be discontinued?



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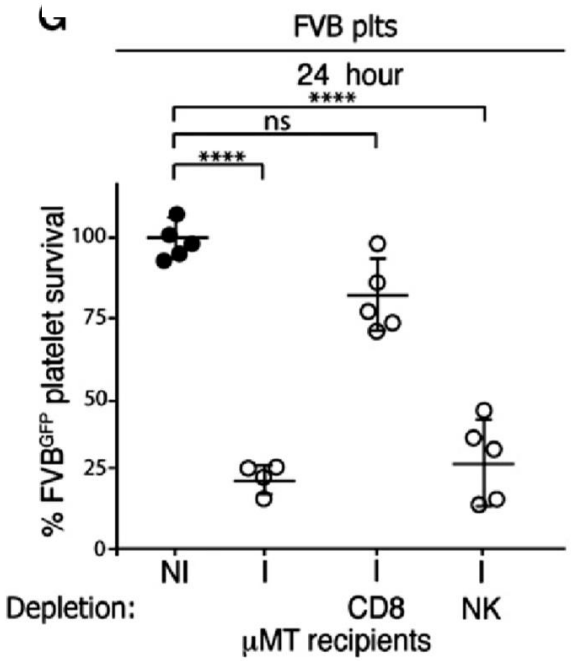
Up to 20% may continue to have refractoriness

Expanding HLA antibodies

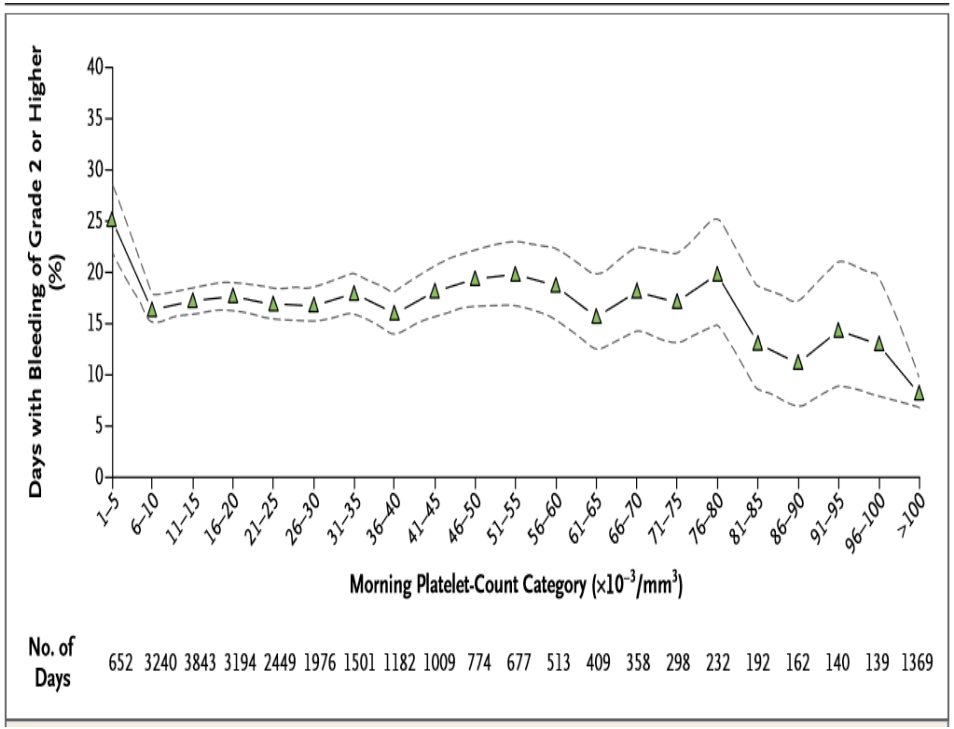
CD8+ T cells may mediate clearance independent of antibodies

IVIG does not appear effective (n=30) in immune refractoriness



Arthur CM et al.Blood. 2016;127:182 Kickler T et al. Blood 1990; 75:313. Lee E. J et al. Transfusion 1987 27:245, Schiffer CA et al. Blood 1984; 64:937,

Ongoing platelet refractoriness predisposes to bleeding: risk may differ according to disease



Bleeding: 25% of days with platelet ≤5000/µL vs. 17% when 6-80000/µL (p<0.001)

Autologous stem cell transplant

Similar bleeding rates in no prophylaxis (45%) vs. prophylaxis (47%) (Stanworth et al)

No grade 4 bleeding but grade ≥ 2: 8% prophylaxis vs. 28% therapeutic (p<0.001) (Wandt et al)

Slichter S et al NEJM 2010;362:600-13, Stanworth S et al. NEJM 2013;368:1771-80, Wandt H et al. Lancet 2012;380:1309-16.

Thrombocytopenia in critically ill patients may be a marker of prognosis

Platelet transfusion may not improve outcomes

- Organ failure scores may not be improved
- Mortality may not be improved
- Receive more RBCs

Warner M et al. Anesth Analg 2019;128: 288,
Shehata N, Fontes ML. 2013: 60; 621

Non Immune refractoriness (80% of platelet refractoriness)

Platelet count > 10, 10-60 minutes after a transfusion

Recipient/product related

ABO identical, fresh platelets (<72 hours)

Thrombopoietin mimetics for SAA

Remains refractory

Antifibrinolytics?

Immune refractoriness (20%)

<10 x 10(9)/L, 10-60 minutes

following transfusion

ABO identical, fresh platelet (<72 hours)

Remains refractory

HLA antibody detection and typing/crossmatching

Remains refractory

1. Expanding HLA antibodies 2. HPA antibody

3. Autoantibody 4. Drug related antibody

Anti-fibrinolytics?

Anticipated developments/answers

Refractoriness

The role of anti-fibrinolytics for reduction of bleeding

Cold stored platelets

Prophylactic vs no transfusion according to disease or bleeding risk e.g. autologous transplant

Non Immune: The role for thrombopoietin agonists in MDS/AML and AA

Immune: The immune response and targeted therapies