Transfusion Medicine

Jill Johnsen, MD
Associate Member, Bloodworks
Associate Professor, University of Washington

Bloodworks Northwest

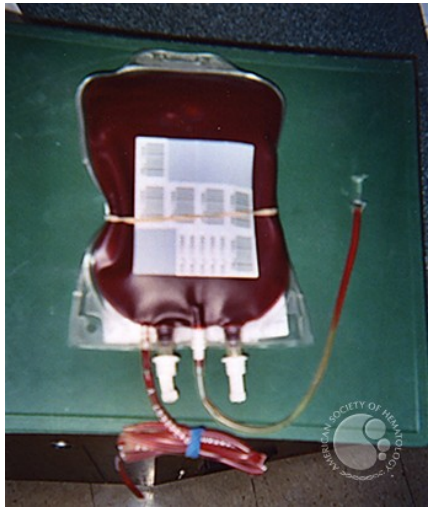
Seattle Cancer Care Alliance
Fred Hutch · Seattle Children's · UW Medicine

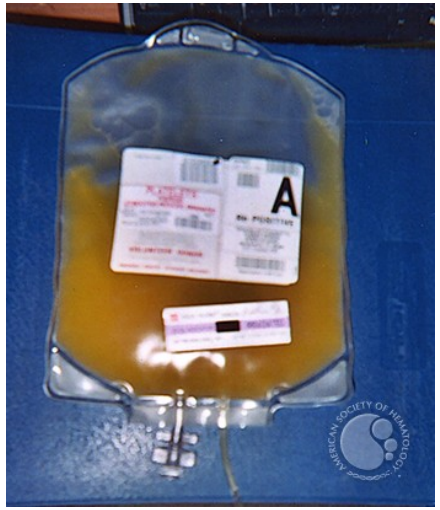
Transfusion

Transfusion is one of the most common inpatient procedures[1]

Transfused *daily* in the U.S.[2] :

- 36,000 U red blood cells (RBCs)
- 7000 U platelets
- 10,000 U plasma





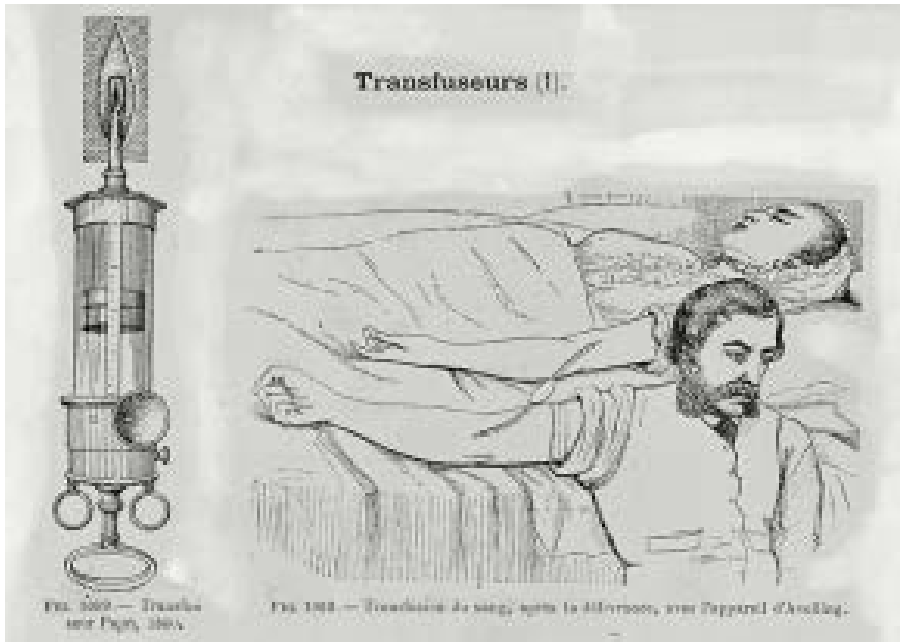
Source: ASH Image Bank.

1. Delaney M, Wendel S, Bercovitz RS, et al; Biomedical Excellence for Safer Transfusion (BEST) Collaborative. Transfusion reactions: prevention, diagnosis, and treatment. *Lancet.* 2016;388(10061):2825-2836.

2. American Red Cross. Blood needs & blood supply. Available at: https://www.redcrossblood.org/donate-blood/how-to-donate/how-blood-donationshelp/blood-needs-blood-supply.

Transfusion: Progress from a potentially lethal procedure to a now largely safe and common treatment

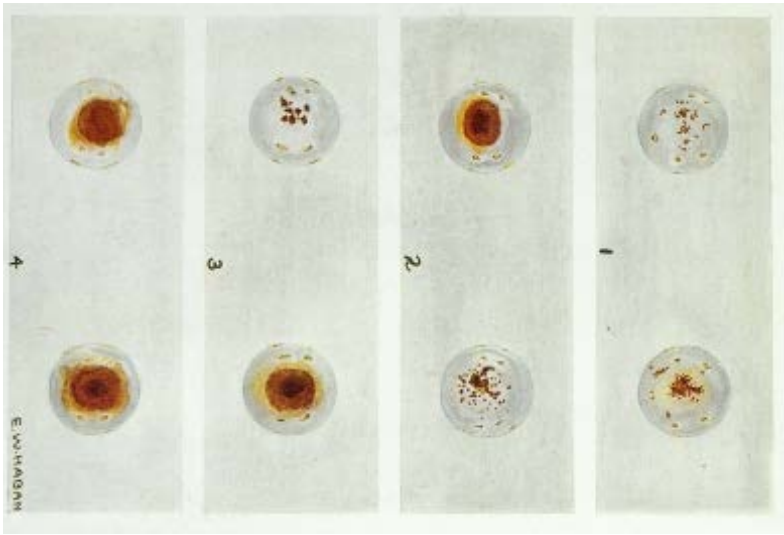
A patient having blood let from his right arm, while the blood of a dog is transfused into his left arm. Engraving, ca.1692.
Wellcome Library, London



Blood transfusion used during childbirth, including instruments. From Gustave-Joseph Alphonse Witkowski's Histoire des accouchements, ca. 1887. *Wellcome Library, London*

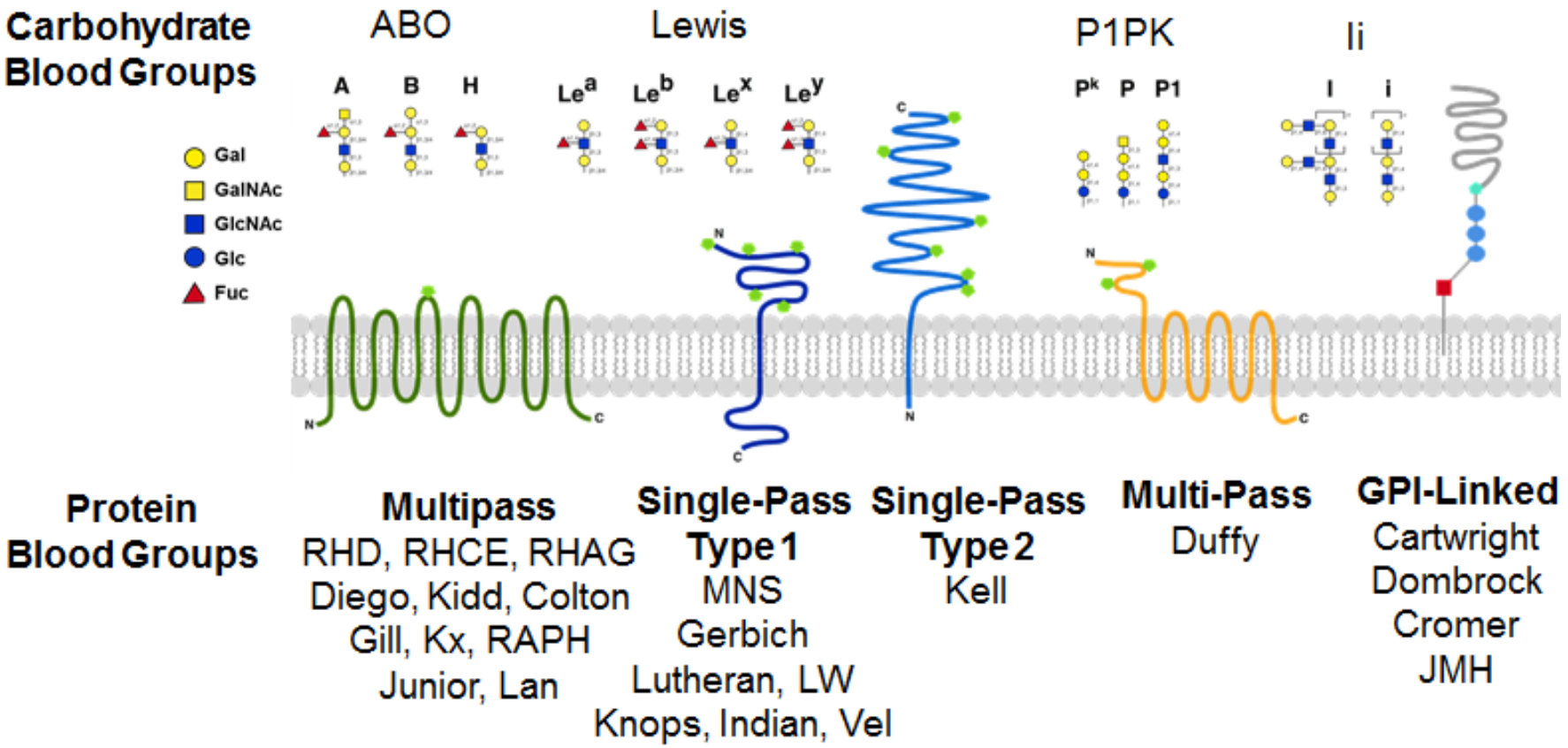
Discovery of ABO made safe transfusion possible

	ABO Blood Group			
RBC Antigens	O 	A 	B 	AB 
Alleles	OO	AO or AA	BO or BB	AB
Anti-A	✳		✳	
Anti-B	✳	✳		



The four blood groups. From Laurence H Snyder's Blood Grouping in Relation to Clinical and Legal Medicine, 1929. *Wellcome Library, London*

Now over 300 known red cell blood group antigens[1]



1. Johnsen J. Hematology (ASH Education Program). Dec 5;2015(1):168-76

Patient may need a transfusion? - order a “type and screen”

“**TYPE**” is a test to determine blood type

ABO and RhD (D) are considered in all transfusions

Extended typing tests for other blood groups (next most common: C,E,K)

Forward type: detects antigens on the patient’s RBCs using reagent antibody

Reverse type: detects antibodies in plasma/serum using reagent RBCs

“**SCREEN**” is a test to identify presence of anti-RBC antibodies

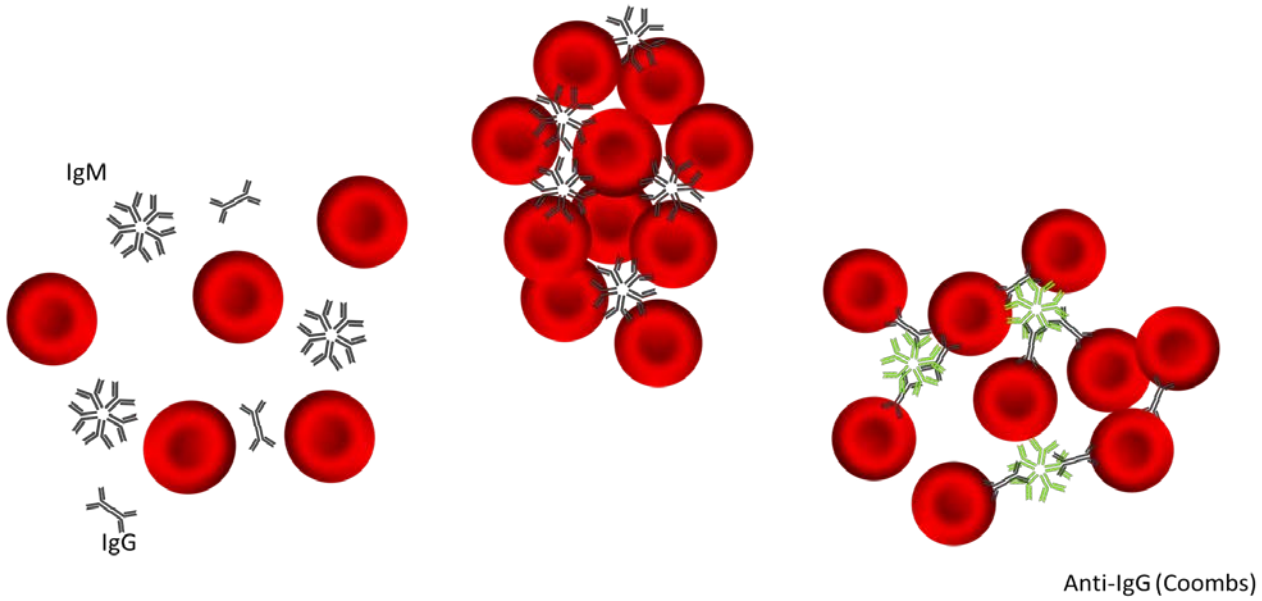
(Ordering a type and screen is a good time to consider IV access)

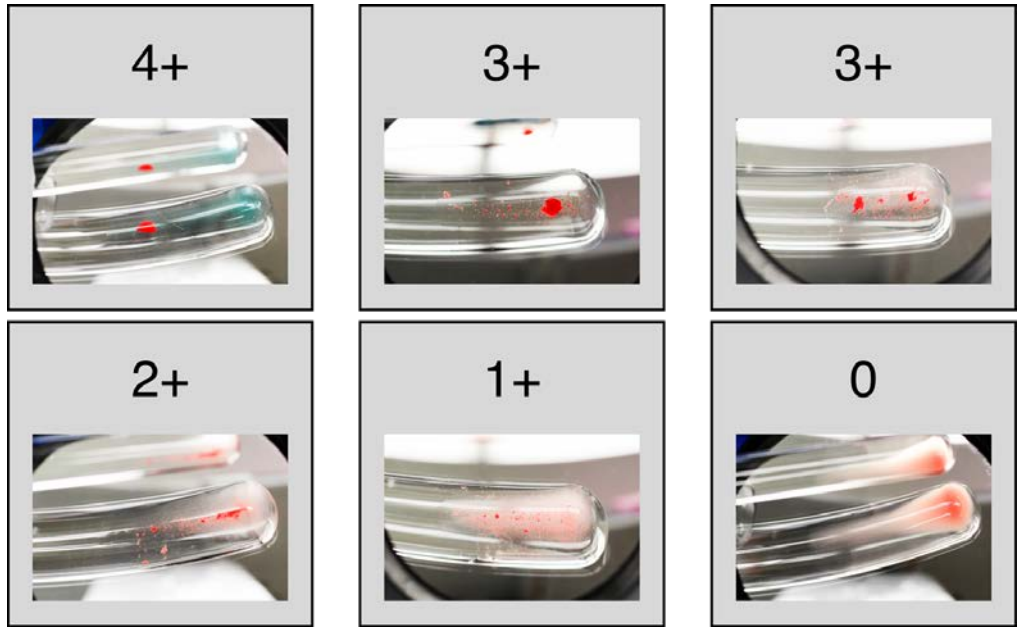
TYPE: Routine blood group testing is based on interaction of RBCs with anti-RBC antibodies

All transfusions: ABO, D.

Higher risk transfusions: C, E, K, potentially others

Genotyping can also be done, can test more blood groups at once





Tube testing image courtesy of Kerry Lannert

SCREEN: test for anti-RBC antibodies

Incubation of patient plasma/serum with red cells from 2-3 very well characterized “reagent” blood cell donors

- Collectively, these donors present the non-ABO blood group antigens likely to provoke allosensitization and transfusion reactions

PANOSCREEN
Master List

IMMUCOR, INC. Norcross, GA 30071 USA
US LICENSE NO: 886
LOT NO: 23502
EXPIRES: 2014/08/15

412-10

PANOSCREEN

VIAL	Donor	Rh - Hr							Kell						Duffy		Kidd		Lewis		P	MN				Luth-eran		X_g
		D	C	c	E	e	V	C^w	K	k	Kp^a	Kp^b	Js^a*	Js^b	Fy^a	Fy^b	Jk^a	Jk^b	Le^a	Le^b	P_1	M	N	S	s	Lu^a	Lu^b	Xg^{*a}
I	R1R1 B8691	+	+	0	0	+	0	0	0	+	0	+	0	+	+	+	+	+	+	0	+	+	0	+	+	0	+	+
II	R2R2 C4281	+	0	+	+	0	0	0	0	+	0	+	0	+	0	+	+	0	0	+	+	0	+	+	0	0	+	0
III	rr G1239	0	0	+	0	+	0	0	+	+	0	+	0	+	+	0	0	+	+	0	+	0	+	0	+	+	+	+	+

* Indicates those antigens whose presence or absence may have been determined using only a single example of a specific antibody.

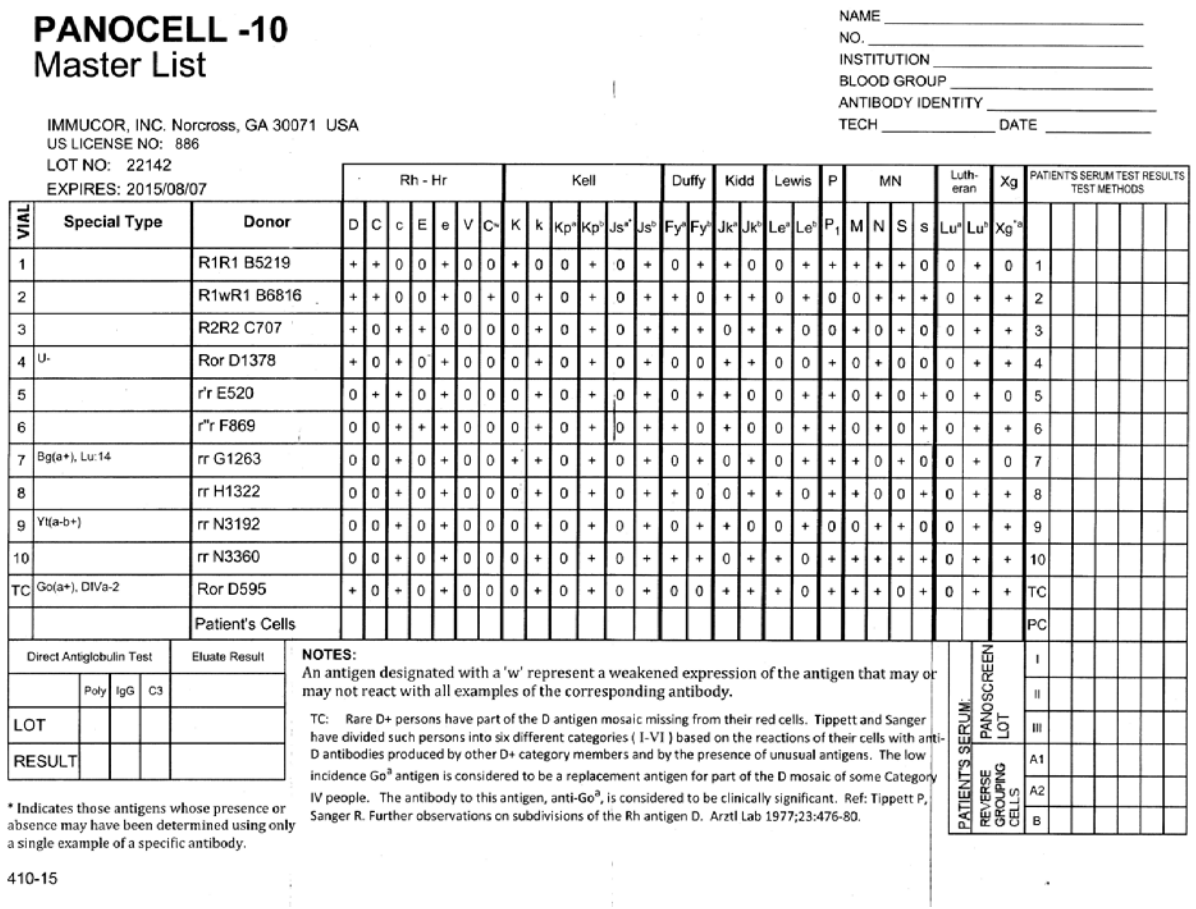
Antibody screen positive? Next step: Antibody identification

Antibody identification

A logic puzzle

Tests agglutination against a panel of 10-16 human red cells that express blood group antigens in different combinations

- Can take hours to days to solve
- Can be confounded by interfering agents (e.g. warm antibodies, some drugs)



PANOCELL -10
Master List

IMMUCOR, INC. Norcross, GA 30071 USA
US LICENSE NO: 886
LOT NO: 22142
EXPIRES: 2015/08/07

NAME _____
NO. _____
INSTITUTION _____
BLOOD GROUP _____
ANTIBODY IDENTITY _____
TECH _____ DATE _____

VIAL	Special Type	Donor	Rh - Hr						Kell						Duffy		Kidd		Lewis		P	MN				Luth-eran		Xg	PATIENT'S SERUM TEST RESULTS TEST METHODS
			D	C	c	E	e	V	C^w	K	k	Kp^a	Kp^b	Js^a	Js^b	Fy^a	Fy^b	Jk^a	Jk^b	Le^a	Le^b	P_1	M	N	S	s	Lu^a	Lu^b	Xg^{a*}	
1		R1R1 B5219	+	+	0	0	+	0	0	+	0	0	+	0	+	0	+	+	0	0	+	+	+	+	+	0	0	+	0	1
2		R1wR1 B6816	+	+	0	0	+	0	+	0	+	0	+	0	+	+	0	+	+	0	+	0	0	0	+	+	+	0	+	+	2
3		R2R2 C707	+	0	+	+	0	0	0	0	+	0	+	0	+	+	+	0	+	+	0	0	+	0	+	0	0	+	+	3
4	U-	Ror D1378	+	0	+	0	+	0	0	0	+	0	+	0	+	0	0	+	+	0	0	+	0	+	0	0	0	+	+	4
5		r'r E520	0	+	+	0	+	0	0	0	+	0	+	0	+	0	+	+	0	0	+	+	0	+	0	+	0	+	0	5
6		r''r F869	0	0	+	+	+	0	0	0	+	0	+	0	+	+	0	+	0	0	+	+	0	+	0	+	0	+	+	6
7	Bg(a+), Lu:14	rr G1263	0	0	+	0	+	0	0	+	+	0	+	0	+	0	+	0	+	0	+	+	+	0	+	0	0	+	0	7
8		rr H1322	0	0	+	0	+	0	0	0	+	0	+	0	+	+	0	0	+	0	+	+	+	0	0	+	0	+	+	8
9	Yt(a-b+)	rr N3192	0	0	+	0	+	0	0	0	+	0	+	0	+	0	+	+	0	0	+	0	0	+	+	+	0	0	+	+	9
10		rr N3360	0	0	+	0	+	0	0	0	+	0	+	0	+	+	+	0	+	+	0	+	+	+	+	+	0	+	+	10
TC	Go(a+), DIVa-2	Ror D595	+	0	+	0	+	0	0	0	+	0	+	0	+	0	0	+	+	+	0	+	+	+	0	+	0	+	+	TC
		Patient's Cells																											PC

Direct Antiglobulin Test				Eluate Result
	Poly	IgG	C3	
LOT				
RESULT				

* Indicates those antigens whose presence or absence may have been determined using only a single example of a specific antibody.

NOTES:
An antigen designated with a 'w' represent a weakened expression of the antigen that may or may not react with all examples of the corresponding antibody.

TC: Rare D+ persons have part of the D antigen mosaic missing from their red cells. Tippett and Sanger have divided such persons into six different categories (I-VI) based on the reactions of their cells with anti-D antibodies produced by other D+ category members and by the presence of unusual antigens. The low incidence Go^a antigen is considered to be a replacement antigen for part of the D mosaic of some Category IV people. The antibody to this antigen, anti-Go^a, is considered to be clinically significant. Ref: Tippett P, Sanger R. Further observations on subdivisions of the Rh antigen D. Arztl Lab 1977;23:476-80.

PATIENT'S SERUM:	
REVERSE GROUPING CELLS	PANOSCREEN LOT
	I
	II
	III
	A1
	A2
	B

410-15

Patient needs a transfusion: order a "Type and Cross"
TYPE, SCREEN, and Crossmatch

CROSSMATCH: identifies blood components for transfusion in *this* patient

If negative antibody screen:

- **Electronic Crossmatch** (most common!)
- Immediate Spin Crossmatch
  - Rapid mixing of patient serum with donor RBCs for ABO compatibility

If positive antibody screen:

- **Full Crossmatch**
  - Requires incubations and Coombs reagent to test that the patient's serum does not react with donor RBCs
  - Takes ≥45 minutes
  - Takes *a lot* longer if there is an antibody to a high incidence (very common) antigen

Blood components are from blood donors

- **Volunteer blood donors**
- Complete a health assessment and questionnaire
- Meet minimum physiologic criteria
- Blood is sampled for testing
  - **Blood groups:** minimum **ABO and D** (including testing for weak D)
    - Other blood groups in recurring donors and/or for special situations
  - **Blood borne pathogen testing:**
    - Serology: HIV-1/2, HCV, HTLV-I/II, HBc, HBsAg, syphilis
    - Nucleic acid testing: HCV RNA, HIV-1 RNA, WNV RNA, HBV DNA
    - At least once: serology negative for *Trypanosoma cruzi*
    - More recent additions: Zika, *Babesia microti*

Blood components for transfusion

- **Red cells** (packed red blood cells, or PRBCs): increase Hgb ~1 g/dL*
  - Hct 65-80% in 225-350mL, stored at 4C, *shelf life 42 days*
- **Platelets** (160-400 mL in plasma): increase platelets ~40-50 K/uL*
  - single donor (pharesis) or pooled (4-6 donors from whole blood centrifugation)
  - stored at RT, *shelf life 5 days*
- **Plasma** (albumin, coag factors, fibrinolytic proteins, Igs, others): 200-250mL
  - fresh plasma or fresh frozen plasma (FFP)
  - stored frozen, shelf life one year; *thawed shelf life 24 hours*

<u>Further manufacturing:</u>

- **Cryoprecipitate** (insoluble cold precipitate of plasma):
  - fibrinogen, VWF, factor VIII, factor XIII
- Prothrombin complex concentrates (thrombin, FIX, FX, FVII), IVIg, Albumin, etc.

*in average-sized adults

Infectious risks of transfusion

Transfusion-Transmitted Infection	Residual Risk Per Transfused Component
HIV	1 in 1,467,000
Hepatitis C	1 in 1,149,000
Hepatitis B	1 in 282,000
West Nile Virus	Uncommon
Cytomegalovirus	50-85% of donors are carriers. Leukocyte reduction is protective.
Bacterial Infection	1 in 2-3,000 (mostly platelets)
Parasitic Diseases Babesiosis, Chagas, Malaria	Relatively uncommon

Weinstein R. Red Blood Cell Transfusion: A Pocket Guide for the Clinician. American Society of Hematology. November, 2016.

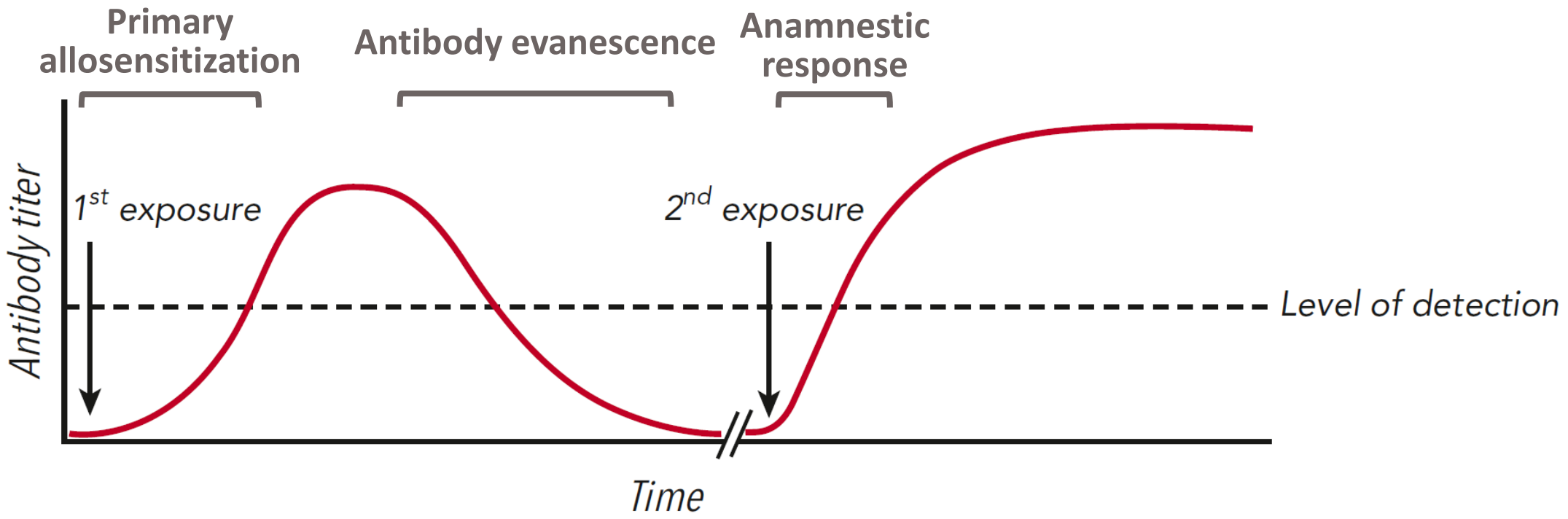
Immediate immunologic complications of transfusion

- **Hemolytic transfusion reaction (HTR)**
  - Destruction of RBCs by anti-blood group antibodies, life-threatening
- **Immune-mediated platelet destruction** (alloantibodies: HLA or platelet)
- **Febrile non-hemolytic reaction** (anti-WBC antibodies, cytokines)
  - Anti-pyretics can offer symptom relief; if recurrent consider leukocyte reduction
    - Incidence <1% leukocyte reduced RBCs, 5% leukocyte reduced platelets
- **Transfusion-related lung injury (TRALI)**
  - Acute hypoxemia, non-cardiogenic pulmonary edema within 6 hours
  - Due to donor anti-WBC antibodies, pro-inflammatory molecules in stored components
- **Allergic reactions** (1-3% of plasma-containing components)
  - Common, mild, self-limited urticarial reaction, usually responsive to antihistamines
- **Anaphylactoid/anaphylactic reactions** (rare, IgA-deficient patients high risk)
  - If refractory to meds, consider washed cellular components to reduce plasma exposure

Delayed immunologic complications of transfusion

- **Delayed hemolytic transfusion reaction** (destruction of RBCs)
  - Similar to HTR: hemolysis due to either anamnestic or new alloimmune response
- **Alloimmunization** to (donor) antigens (any blood cell antigens or plasma proteins)
  - Blood components contain things not on the label (*e.g. in platelets*: some RBCs, WBCs)
- **Post-transfusion purpura (PTP)**
  - Rare, dramatic, self-limited purpura 7-10 days later
  - Platelet specific antibody destroys autologous and allogeneic platelets, IVIg can treat
- **Transfusion-associated graft-vs-host disease (TA-GVHD)** (rare)
  - Transfused allogeneic T-cells (from any component with viable T-cells)
  - Risks for TA-GVHD: severe cellular immunodeficiency, purine analagues (e.g. fludarabine), haploidentical HLA to a homozygous donor
  - Irradiated components are indicated for patients at risk for TA-GVHD

Model of events leading to delayed hemolytic transfusion reaction (DHTR)[1]



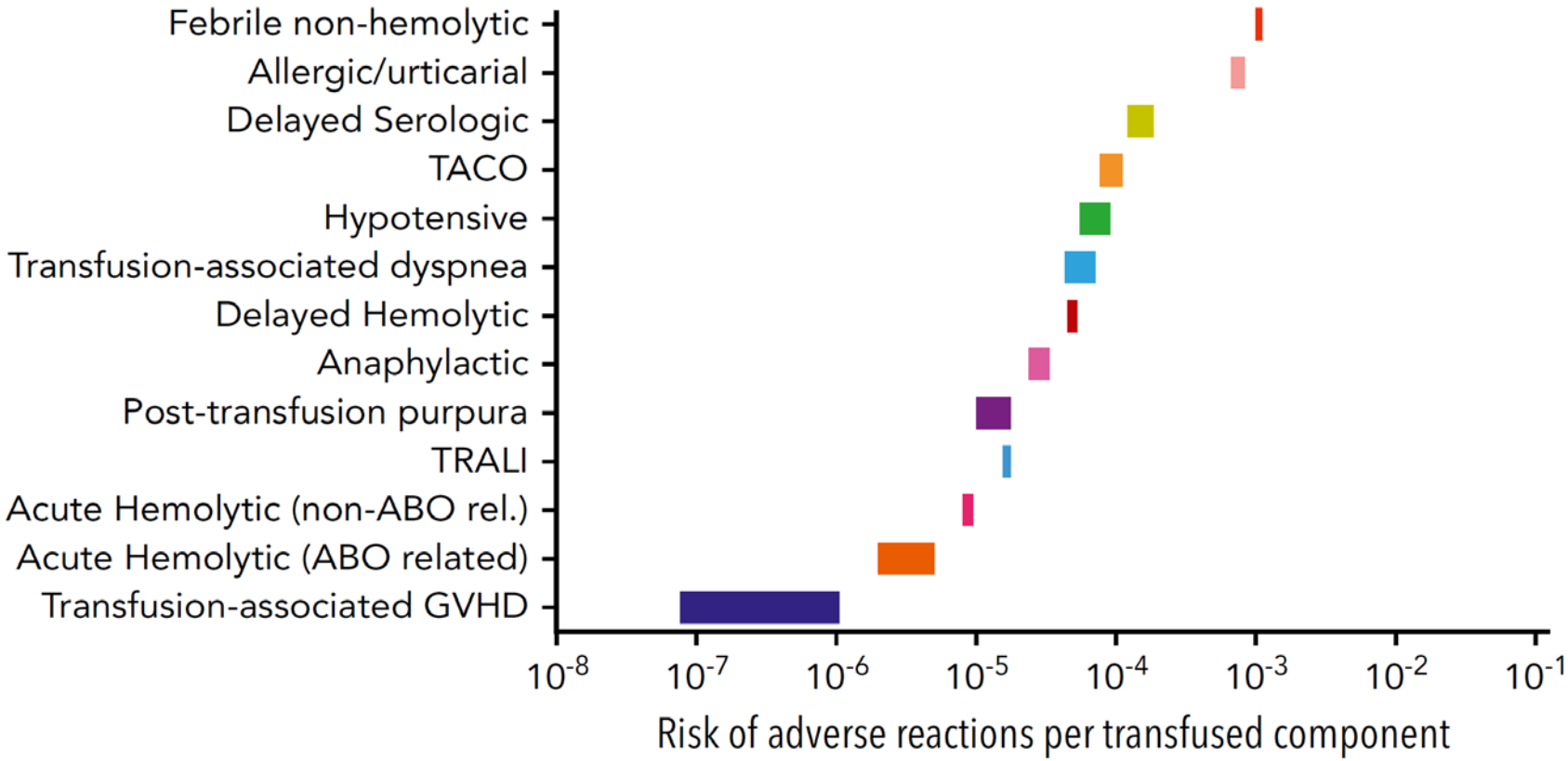
1. Tormey C. and Hendrickson J. Transfusion-related red blood cell alloantibodies: induction and consequences. *Blood* 2019;133(17);1821-1830. (2019)

Other (non-immune) complications of transfusion

- **Transfusion-associated circulatory overload (TACO)**
  - From excessive volumes or excessively rapid rates: treat pulmonary edema, reduce fluids
- **Hypothermia: from infusing large volumes of cold components**
  - Risks arrhythmia/arrest and coagulopathy: mitigated by blood warmers
- **Metabolic complications: usually with large volume / rapid transfusions**
  - Citrate "toxicity" : chelation of ionized calcium by the citrate anticoagulant in blood components
- **Iron overload**
- **Donor-transmitted infectious agents**: Viruses, bacteria, parasites, variant Creutzfeldt-Jakob
- **Bacterial sepsis or endotoxin rxns from contamination (infrequent, life-threatening):**
  - Most common culprit component is platelets
  - Treat aggressively with antibiotics and supportive care
- **Cytomegalovirus (CMV): can reside in donor WBCs**
  - Risks for immunocompromised patients and premature infants of seronegative mothers
  - Risks reduced by transfusing CMV-seronegative or leukocyte-reduced components

Noninfectious adverse outcomes per unit transfused[1]

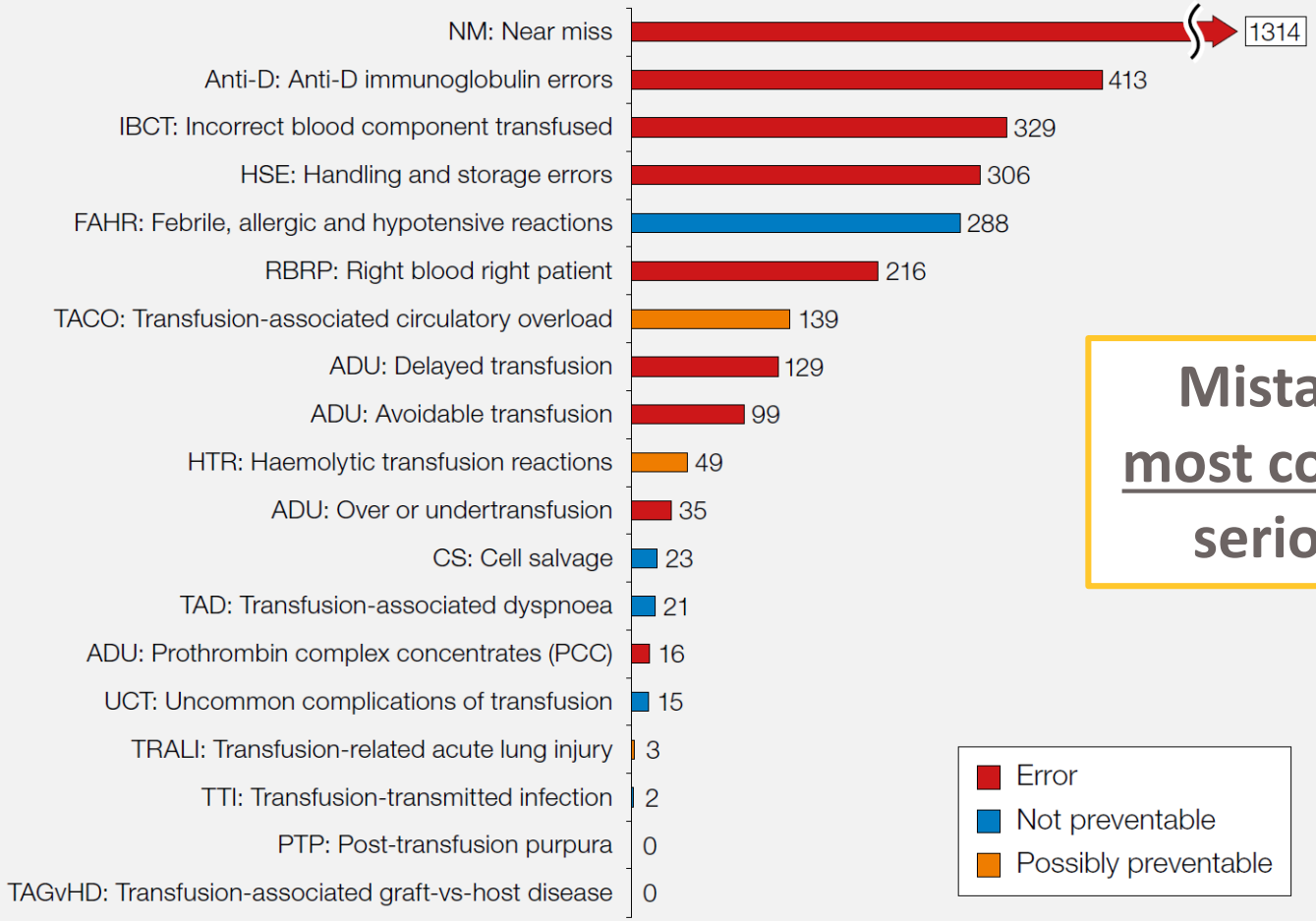
From National Blood Collection and Utilization Surveys 2011-2015



1. *In:* Goel R., *et al.* Noninfectious transfusion-associated adverse events and their mitigation strategies. *Blood* 2019 133: 1831-1839

Serious Hazards Of Transfusion (SHOT) 2019[1]

Summary data for 2019 (n=3397)



Mistakes are the most common of the serious hazards

1. *www.shotuk.org*

When to transfuse PRBCs?

Choosing Wisely®
An initiative of the ABIM Foundation

AABB Choosing Wisely (#1): Don't transfuse more units of blood than absolutely necessary.

ASH Choosing Wisely (#1): Don't transfuse more than the minimum number of red blood cell (RBC) units necessary to relieve symptoms of anemia or to return a patient to a safe hemoglobin range (7 to 8 g/dL in stable, non-cardiac in-patients).

- Transfuse for symptoms and/or hemoglobin
  - **Threshold 7.0-8.0g/dL** for most hospitalized, stable patients
  - **Threshold 8.0g/dL** for pre-existing cardiovascular disease
- Order one PRBC unit unless actively bleeding (use weight-based dosing in children)
  - Order more units only after re-assessment
  - Remember that *each unit of blood* carries risks
- **Liberal transfusion strategies do not improve outcomes compared to restrictive strategies**
- **Unnecessary transfusion generates costs and exposes patients to risks without likely benefit**

Adapted from *www.choosingwisely.org*

When not to transfuse: Asymptomatic iron deficiency anemia

Choosing Wisely®
An initiative of the ABIM Foundation

AABB Choosing Wisely (#2):

Don't transfuse red blood cells for iron deficiency without hemodynamic instability.

- Cheaper and safer alternatives to treat iron deficiency (*e.g.* iron treatment)
- Unless otherwise meet criteria for transfusion, *don't transfuse*

Adapted from *www.choosingwisely.org*

High risk for transfusion AEs: Sickle cell disease patients

Choosing Wisely®
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ASH Choosing Wisely (#7):

Don't routinely transfuse patients with sickle cell disease (SCD) for chronic anemia or uncomplicated pain crisis without an appropriate clinical indication.

- SCD patients are at higher risk for harm from unnecessary PRBC transfusion
  - alloimmunization to minor blood group antigens
  - iron overload
- Even most severe types of SCD (baseline hemoglobin 7-10 g/dl) usually tolerate further temporary hemoglobin reductions without symptoms.
  - IV fluids may contribute to a decrease in hemoglobin by 1-2 g/dL
  - routine transfusion in this setting should be avoided
- No evidence transfusion reduces SCD vaso-occlusive crisis pain!
- Guidance for transfusion in SCD is in the NHLBI 2014 guidelines

Adapted from *www.choosingwisely.org*

“Universal” blood and emergencies

Choosing Wisely®
An initiative of the ABIM Foundation

“Universal units”: O-negative RBCs, AB-positive (male) plasma

- Mitigate risks of ABO incompatibility
- Reduce risks of allosensitization to D

AABB Choosing Wisely (#5): Don’t transfuse O negative blood EXCEPT:

- **to O negative patients**
- **in emergencies for women of child bearing potential with unknown blood group.**

- O-negative PRBC units are in chronic short supply
  - Shortages are exacerbated by overutilization for patients who are not O-negative
  - Common practice during shortages to transfuse O-positive in males, use low titer anti-A plasma

Adapted from *www.choosingwisely.org*

Blood testing for transfusion: Monitoring recommendations

Choosing Wisely®
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AABB Choosing Wisely (#4):

Don't perform serial blood counts on clinically stable patients.

- Unless bleeding or otherwise unstable, transfusion (PRBCs or platelets) should use the results from the first labs of the day
- Multiple blood draws to recheck the transfusion threshold can lead to:
  - excessive phlebotomy
  - iatrogenic anemia
  - unnecessary transfusions

Limit blood draws!!

Adapted from *www.choosingwisely.org*

When not to use plasma and PCCs: Warfarin reversal

Choosing Wisely®
An initiative of the ABIM Foundation

AABB Choosing Wisely (#3):

Don't routinely use blood products to reverse warfarin.

ASH Choosing Wisely (#4):

Don't administer plasma or prothrombin complex concentrates for non-emergent reversal of vitamin K antagonists
(i.e. outside of the setting of major bleeding, ICH, or emergency surgery)

- Rationale: blood products have risks, are costly, and are rarely indicated
- Most patients can be reversed with holding warfarin and/or vitamin K
- For serious bleeding or emergency surgery / invasive procedures only:
  - prothrombin complex concentrates (PCCs)
  - (plasma)

Adapted from *www.choosingwisely.org*

When to transfuse plasma

- Preoperative or bleeding patients who require replacement of multiple coagulation factors *(e.g.,* liver disease, DIC)
- Patients undergoing massive transfusion
- Patients on warfarin who are actively bleeding or in need of an immediate invasive procedure
- Patients with coagulation factor or plasma protein deficiencies, congenital or acquired, for which no specific products are available (e.g. FXI, C1 inhibitor)
- Thrombotic thrombocytopenic purpura (TTP)

See lectures on coagulation for underlying disorders and management

When to transfuse platelets?

- Thresholds for platelet transfusion are evolving: the general trend is towards more conservative use of platelet transfusion
  - PLADO trial
  - Pragmatic use of a scarce resource
- Thrombocytopenia: correction of quantitative defects
  - Prophylactic transfusion: historically PLT <10k, but PLADO trial used threshold < 5K
  - For invasive procedures, trauma, and active bleeding in patients with moderate to severe thrombocytopenia
  - Rapidly falling platelet count with active bleeding or significant consumption
- Platelet dysfunction: correction of qualitative defects
  - Consider functional platelet count to be the predicted post-transfusion platelet count

See lectures on thrombocytopenia for causes and management

THANK YOU!