

Introduction to Transfusion



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Disclosures: None (co-PI K.I.T.E. CAR-T Cell Study)

Things I learned from my mentor:

Transfusing wrong blood to wrong patient is the fastest way to kill a stable patient.

Above usually occurs in pairs...

“Bad blood” is better than NO BLOOD, since patients with no blood will die!

All bleeding will eventually stop!

Transfusion

Products	Special Products	Tx Reactions	Blood Bank
RBC Tx	Leukopoor	Allergic	Type & Screen
FFP Tx	<u>Washed</u>	Febrile	Type & Cross
Platelet Tx	<u>Irradiated</u>	<u>Hemolytic</u>	Type & Hold
Cryo Tx	CMV Negative	Delayed <u>Hemolytic</u>	Phenotyping
		TRALI /TACO	

Case 1: *“Going for the mileage”*

A 75 yr old patient with autoimmune hemolytic anemia and CLL undergoing chemotherapy comes for outpatient transfusion after complaining of weakness and feeling lightheaded.

Patient feels fine after 1 unit of PRBC

Hemoglobin is up to 8.1 g/L after 1st unit

Patient's symptoms have resolved

Patient is on EPO

Transfusion criteria for additional units no longer met

Physician states patient was in for “topping off” before the weekend!

(if there were extenuating circumstances additional units could be Tx)

RBC Transfusion

1 unit of PRBC $\approx$ 300ml

- ONLY to increase O₂ Carrying capacity (NOTHING ELSE)
- 1 unit of blood increases Hgb by 1 gram/dl (+3% Hct) in adult
- 1%/mL/kg in a child
- Transfuse at Hgb of ≤ 7.0 /dl prophylactically
- Transfuse at higher hemoglobin if patient symptomatic
- Elective transfusion: order 1 unit and check Hct or comment.

Adults: Ordering 2 units for an elective transfusion is usually “flagged”*

** there may be circumstances that justify ordering more than 1 unit @ time*



Case 2: *Where is all the Volume Gone?*

54 yr old gentleman had uneventful elective colectomy for Crohn's disease this AM. Late afternoon BP drops to 70 x palpable; his abdomen is distended. US indicates fluid in abdomen.

Hgb 9.8 (previous 11.3g/L)

INR 1.9

PTT 49 sec (N= 42)

Pt taken back to OR, surgeon orders 3 **units** of FFP “on the way to OR”

What would you do?



Transfusion : Plasma

Fresh Frozen Plasma

- Made from one unit of donated blood or collected by machine
- Contains all clotting factors (I - XIII)
- Used to supply clotting factors.*
- **NOT TO BE USED AS A VOLUME EXPANDER!**
- To treat active bleeding with $\text{INR} > 1.6$
- To reverse anticoagulation.

Thawed Frozen Plasma

- Good for 5 days at 4°C
- Lacks factor V and VIII.

** Also contains all enzymes present in normal donors*



“My Resident wants FROZEN Plasma”

You must give me what I want!

Trauma surgeon just joined your the service:

“I will not operate in this hospital if I cannot get one unit of platelets for each unit of PRBC transfused”

Thoughts?



Transfusion: Platelets

PLATELETS ARE STORED AT ROOM TEMPERATURE (lifespan = 5 days)
Most likely source of transfusion associated bacterial infections!

Random “pooled” platelets

- Each unit made from a unit of donated blood.
- Six units are the usual dose for an adult “six-pack”
- Never given as single unit (unless pediatrics)
- Are being phased out but have made a come back (\$).

Single Donor Platelets

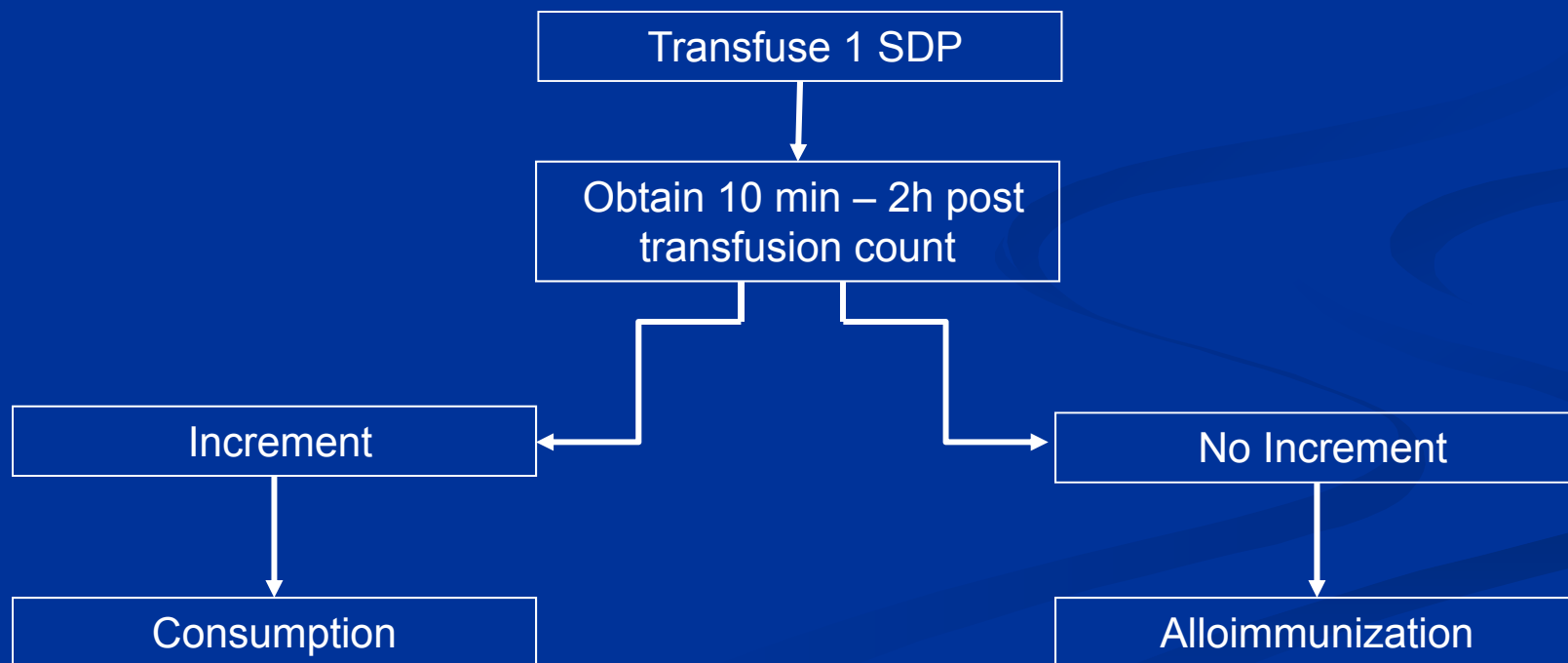
- Collected by machine and are equivalent to 6 units of pooled platelets
- Single donor = less exposure to HLA and risk of contamination
- Most hospitals in the US use SDP.
- Beware of older physicians who want a “six-pack” of SDP!



Transfusion: Platelets continued...

- 1 SDP should increase platelet count by 30 -60K / μ L in adults
- 5-10ml/Kg should increase platelet count by 50 – 100K / μ L (neonates)

Simple approach to platelet refractoriness:



Alloimmunization

Occurs when tissue from one individual is transferred to another through transplant, transfusion or pregnancy.



My Resident wants “Special Platelets”

- Alloimmunization: occurs due to exposure to allogeneic HLA antigens
 - Pregnancies
 - Multiple Transfusions
 - Soluble HLA antigens (???)

Platelet crossmatch (\$\$)

Patient's plasma vs platelet samples from multiple SDP

Goal: Find one that does not agglutinate.

Advantage: Readily Available

“Disadvantage”: Don't know name of antigen (who cares???)!

HLA matched platelets (\$\$\$\$)

- Need HLA type of recipient (patient) 1-2 days
- Consult Local & National Donor HLA phenotyping databases
- Fly Platelets over (2-3 days if not found locally)



Transfusion: Cryoprecipitate.

Contains: 150 -250mg of Fibrinogen

80-120 U of F-VIII

80 U vWf

40 -60 U of F XIII

Ordered in pools of 10 units for adults

One cryo pool (10 units) will raise fibrinogen by 50-100mg/dL.

Can also be used in uremic coagulopathy*

* Consider DDAVP.



Special Products: Leukoreduction

Leukopoor RBC's & Platelets*

- 99.99% WBC removed
- Less passenger WBCs
- Less HLA alloimmunization
- Less Transfusion Reactions
- “CMV Safe” (by FDA)

**Leukoreduction done at the blood center.*



Blood Filters

1st generation filters: Clot removing filters (170 -250 microns)

2nd generation filters: Cellular aggregate “microaggregate” filters
(40 micron pore size)

3rd generation filters: Leukocyte filters (removal of individual WBC)



Leukoreduction

Initial count (1 unit of blood) = 10^9

1 log removal: 100 million remain (10^8)

2 log removal: 10 million remain (10^7)

3 log removal: 1 million remain (10^6)

4 log removal: 100.000 remain (10^5)



Leukoreduction Methods

- Sedimentation
 - Centrifugation
 - Washing
 - Freezing / Thawing
 - Leukofiltration
-



Transfusion and Bacterial Infection

**Patient receiving blood that is not
Leukodepleted is more susceptible
to bacterial infection**

JO Bordin et al. Blood 84:1703, 1994



Special Products: Irradiation

The only reason to irradiate is to prevent GVHD!

Who is at risk ?

Congenital immunodeficiencies



- Severe Combined Immunodeficiency
- Wiscott-Aldrich Syndrome
- DiGeorge's Syndrome
- Other T-Cell defects

- All perinatal / intrauterine transfusions
- Premature infants
- Very low birth weight infants
- Hematological malignancies
- Bone Marrow Transplant recipients
- Directed Donations (familial)
- Granulocyte transfusions|.
- Anyone receiving Fludarabine



IS THERE ANY HARM IN IRRADIATING BLOOD / PLATELETS/ WBC's?



NOT REALLY!

K⁺ LEAKS FROM RBC'S AT 1mEq/day.

FDA limits irradiated blood storage to 28 days.



Transfusion: Washed Products

SOLE PURPOSE OF WASHING IS TO REMOVE PLASMA

Why?

- Severe allergic reactions
- IgA deficiency with antibodies

“The patient needs plasma but he keeps reacting to FFP, please wash it”



TRANSFUSION REACTIONS: ALLERGIC

- Urticaria
- Generalized pruritus
- Erythema
- Dyspnea
- Anxiety
- Wheezing
- Nausea
- Hypotension

Anaphylaxis and allergic reactions

Urticarial reactions : 1-3% of plasma tx

Anaphylactoid Rx : 1:1000 plasma tx

Anaphylactic Rx : 1: 20.000 to 1:50.000

Severe reactions can occur with as little as 10 to 50 ml (adult)



Transfusion Reactions: Allergic

- Most allergic reactions are mild
- Most allergic reactions are not anaphylactic
- The cause of most allergic Tx Rx is unknown

Histamine

Leukotrienes

Prostaglandins

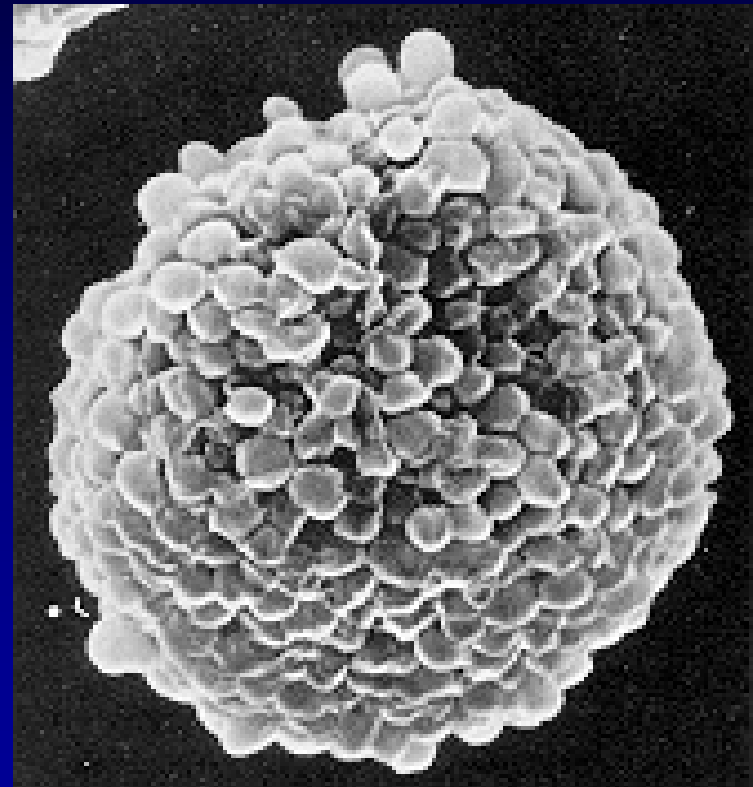
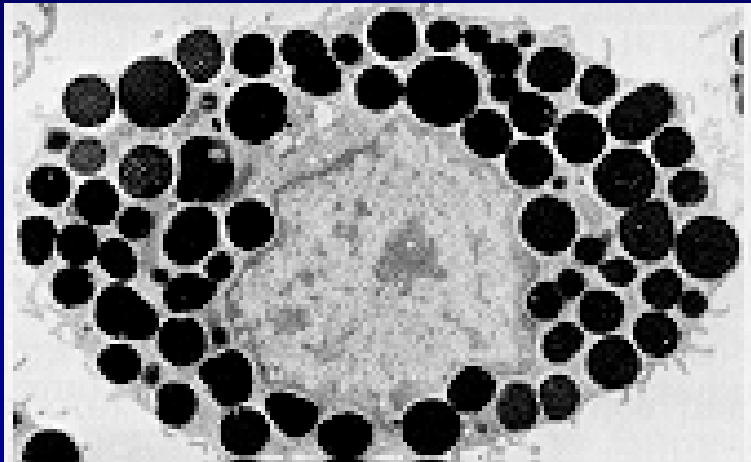
PAF

Tryptase



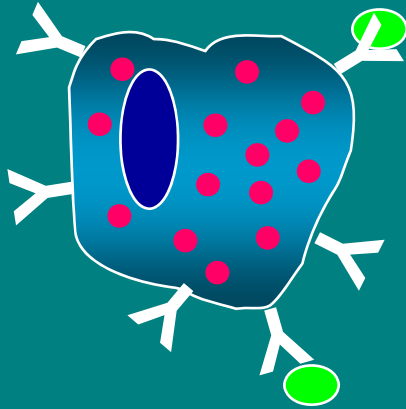
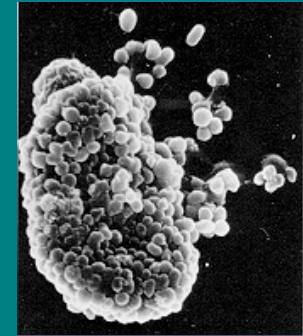
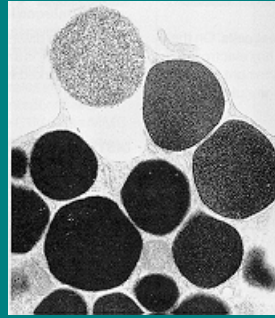
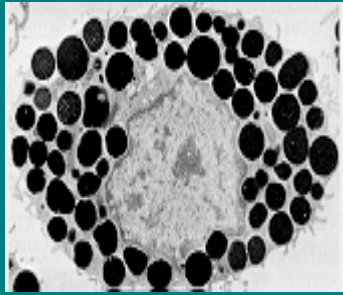
Transfusion Reactions: Allergic

Mast Cell (T.E.M.)



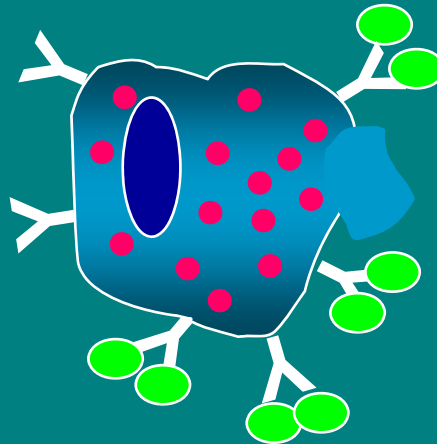
Mast Cell (S.E.M.)





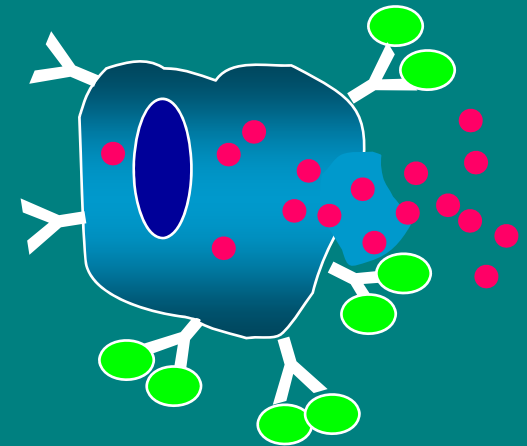
A

Antigens from plasma
bind to pre-formed IgE
attached to mast cells



B

Antigen binding causes
activation of histamine
release mechanism from
mast cells.



C

Histamine is released
from mast cells and
causes increase in
vascular permeability



Allergic Reaction : What to do ?

- 1) Stop transfusion
- 2) Keep venous access open
- 3) Treat symptoms
- 4) Do a Tx Rx workup

Do we need to do a Coombs test ?



Hemolytic transfusion Reactions

First described hemolytic transfusion reaction

As soon as the blood began to enter into his veins, he felt the like heat along his Arm, and under his Arm pits, which he had felt before. His pulse rose presently, and soon after we observ'd a plentiful sweat over all his face. His pulse varied extreamly at this instant, and he complain's of great pain in his kidneys, and that he was not well in his stomach, and that he was ready to choak unless they gave him his liberty... When he awakened,... e made a great glass full of Urine of a colour as black as if had been mixed with soot of chimneys.

Denis, 1668.

(Same patient died during next transfusion)



Hemolytic Transfusion Rx

Your worst nightmare...

What to do ?

- 1) Stop transfusion immediately !
- 2) Keep IV open !
- 3) Notify M.D. immediately ! (patient may go into shock or DIC)
- 4) Review all crossmatched units on the shelf
- 5) issue uncrossmatched group O units if needed
- 6) FDA must be notified .

OCCUR IN PAIRS: Wrong unit went to your patient!

Where is the unit that your patient should have received?



Intravascular Hemolysis

Fever	16
Chest Pain	19
Hypotension	6
Nausea	2
Flushing	2
Dyspnea	2
Hemoglobinuria	2

From : Pineda A, Taswell H et al Mayo Clinic Proceedings 1978;53:381



Hemolytic transfusion Reactions

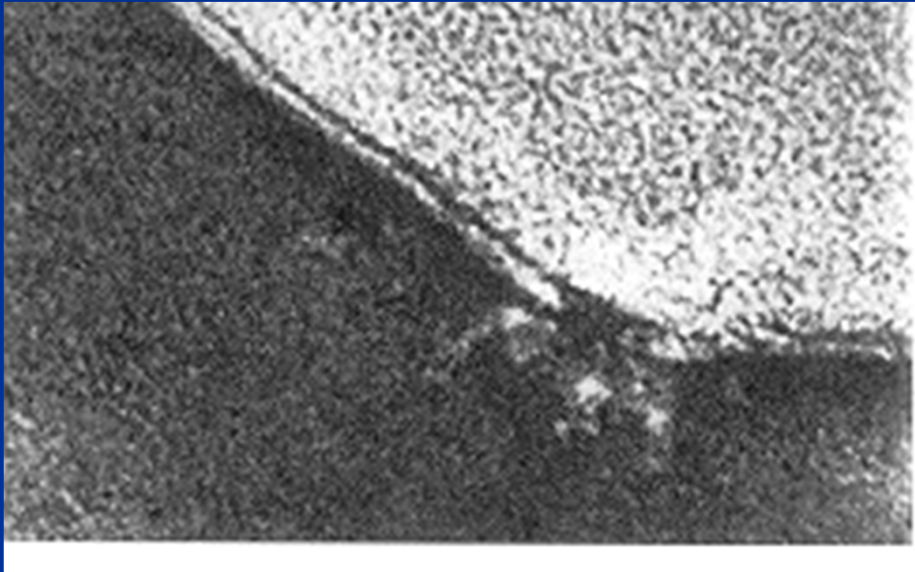
1: 1417 (Cook County 1961 - 1967)

1: 250.000 (1990)

Average : 1:40.000



Intravascular Hemolysis



Red Blood Cell Lysis as seen by transmission Electron Microscope.

(From Rossi E. "Principles of Transfusion Medicine" 2nd Edition)



Intravascular Hemolysis

Laboratory Diagnosis

Visual inspection of plasma.*
Coombs test.
Clerical check.

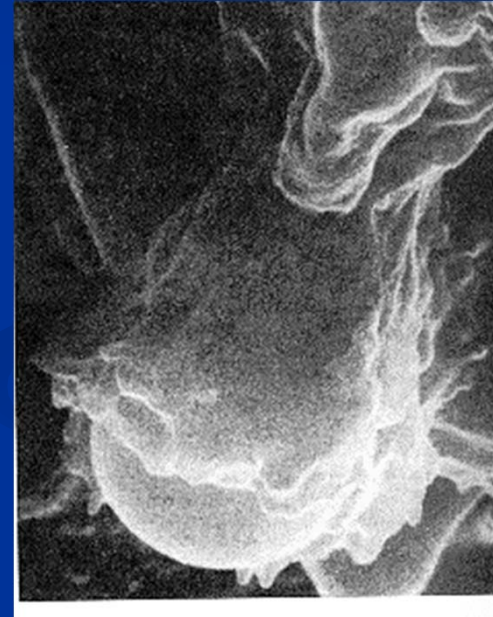
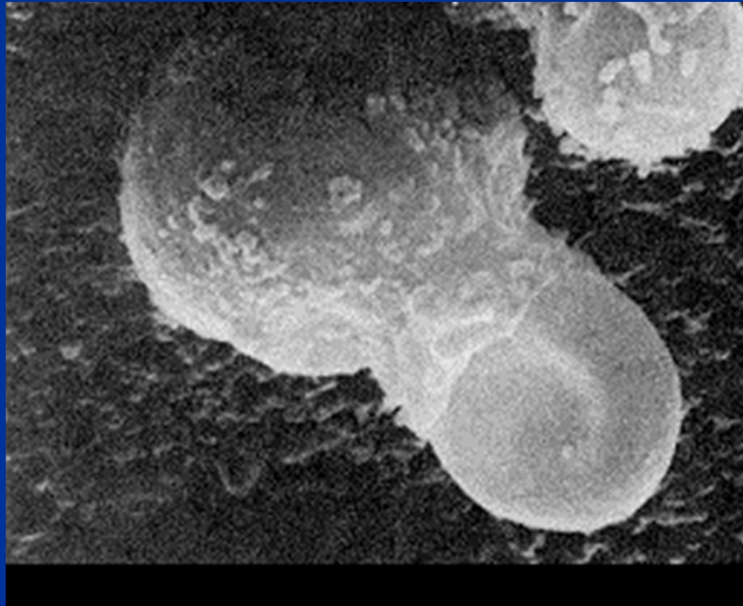
Lysis of 4 -10 ml of RBC's in a 70 Kg adult results in visually detectable hemolysis !



Delayed Hemolytic Transfusion Reactions

Extravascular Hemolysis: R.E.S removes IgG coated RBC's

Complement is not sufficiently activated to cause IV hemolysis



RBC phagocytosis (SEM)

(From Rossi E. "Principles of Transfusion Medicine" 2nd Edition)



Transfusion Reaction: Febrile

- Increase in temperature $> 1^{\circ}\text{C}$
 - 0.5% per unit transfused
 - More common with random platelets
 - Caused by breakdown products of leukocytes
-



Febrile Reaction: Etiology

Release of pyrogenic cytokines

Activation of thermoregulatory center (hypothalamus)

3 possible mechanisms:

- Presence of foreign granulocytes in transfused unit.
- Substance in transfused units causes degranulation of donor leukocytes.
- Presence of leukocyte breakdown products in transfused unit.

Removal of 75 to 90% of the WBC from concentrates significantly decreases the reaction rate in most patients.



Cytokines in FNTR

IL 1 β : Causes fever by production of PG E₂

TNF

IL6

IL1

Central mediators of inflammation

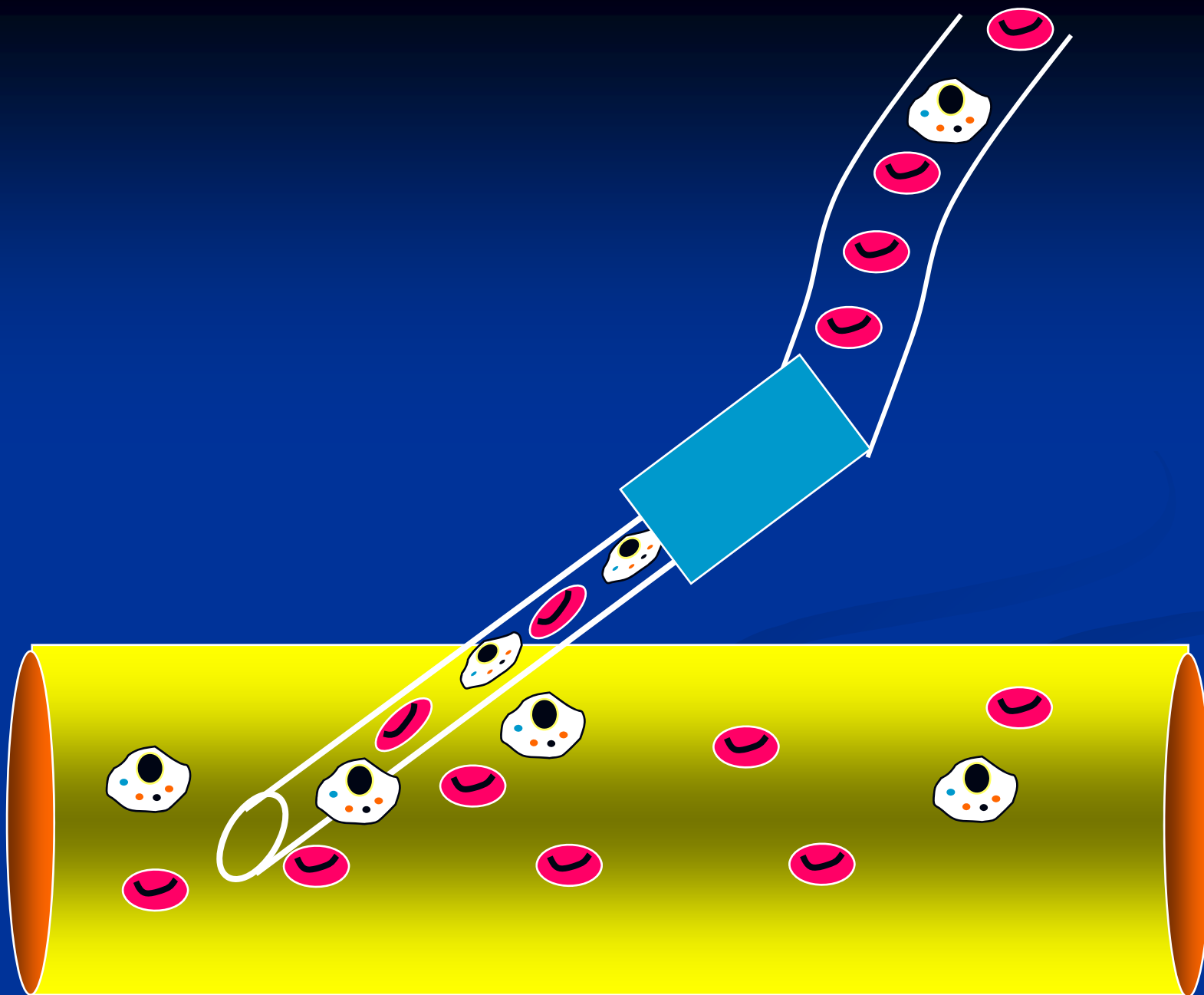


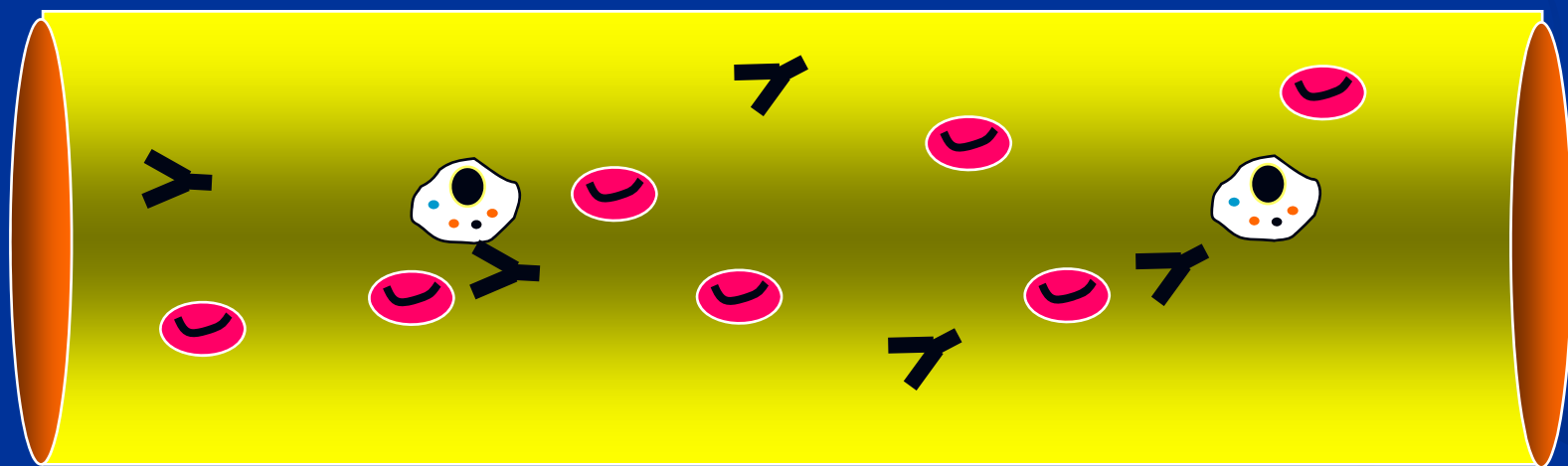
FNTR : Symptoms

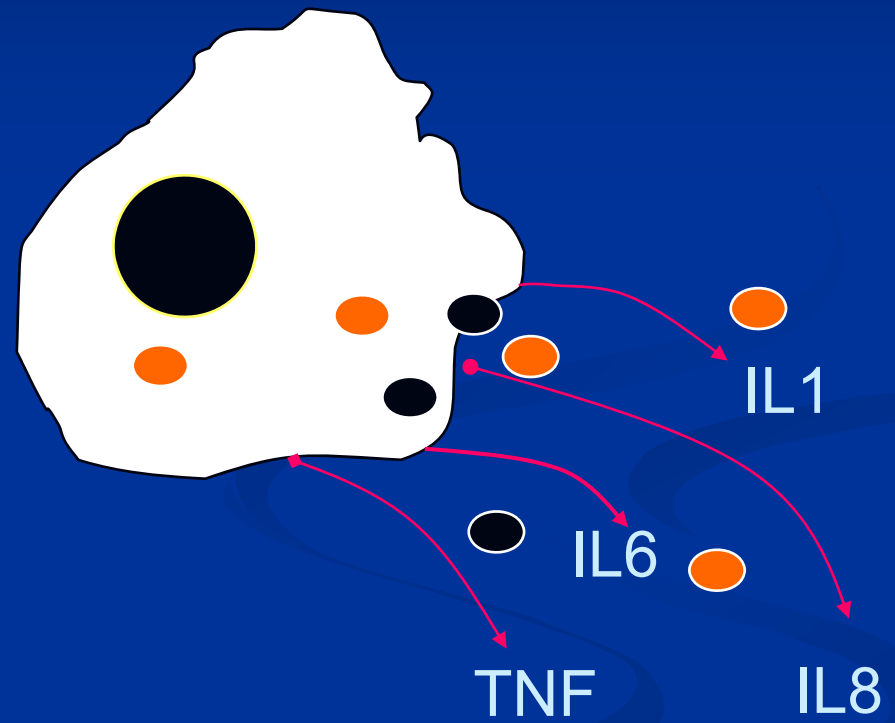
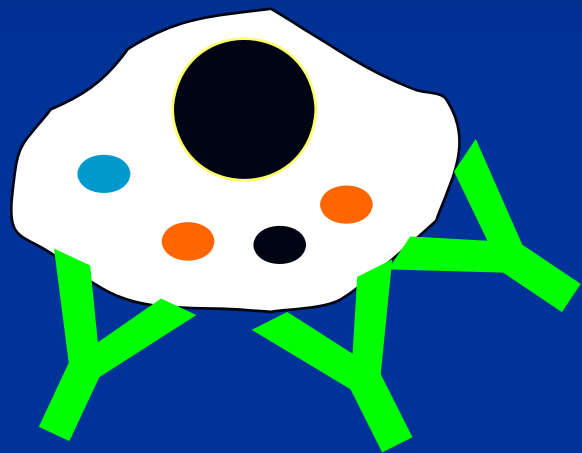
- Apprehension
- Chilliness
- Shaking Chill
- Fever
- Headache
- Flushing
- Rapid pulse
- Nausea, vomiting
- Shortness of breath

**CANNOT BE EASILY DIFFERENTIATED
FROM SYMPTOMS OF HEMOLYTIC Rx!**







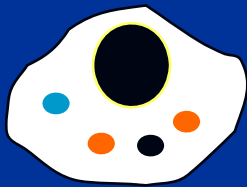


Febrile Reaction: Thresholds

5×10^8 WBC per unit will cause FNTR



5×10^6 WBC per unit will cause HLA sensitization



FNTR

- **Most common in :**
 - **Women (2:1)**
 - **Multiply transfused patients**
 - **Rare in children**
-



FNTR

- Transfusion reactions are more common in patients receiving platelets (30.8%) than in those receiving RBC products (6.8%)
 - Antipyretics prevent most fever but do not prevent chills or discomfort.
-



FNTR

**Reactions can also be elicited
by transfusing supernatant plasma
from stored platelets.**

(in the absence of cellular elements)



FNTR

**Likelihood of recipient reaction
increases with the length of storage
prior to transfusion**



Transfusion Reactions: Treatment

- **Stop transfusion !**
 - **Maintain venous access**
 - **Treat symptoms as necessary**
 - **Rule out other reaction causes**
-



Transfusion Related Acute Lung Injury

ONLY DIFFERENTIAL CLINICAL DX IS PULMONARY EMBOLISM

VERY RAPID ONSET : SCARRY!

- Chills
- Fever
- Acute Respiratory Distress
- Bilateral Pulmonary Edema
- Severe Hypoxemia
- Occurs 1 to 6 hrs post transfusion
- 5% mortality rate

MOST COMMON CAUSE OF TRANSFUSION ASSOCIATED MORTALITY!

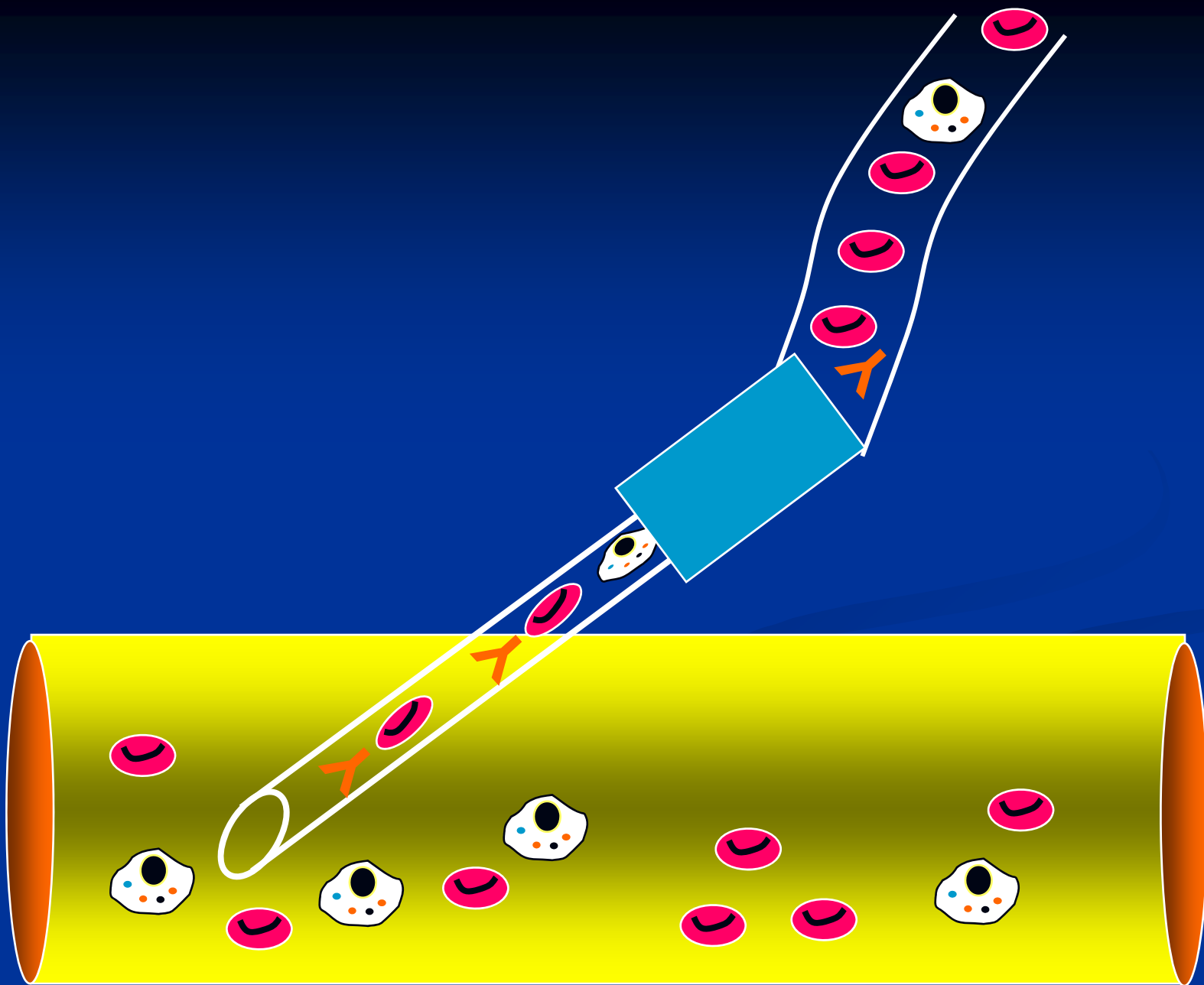
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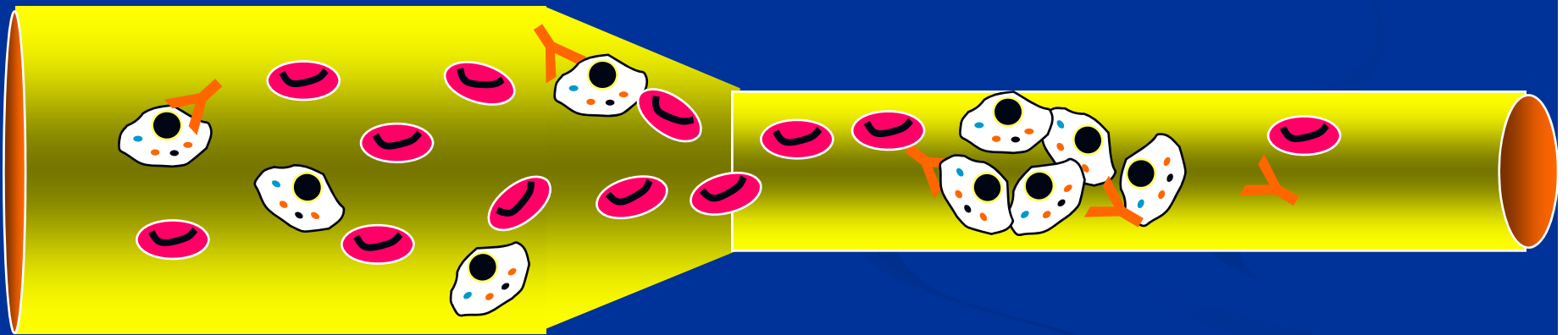
TRALI

Most often caused by transfusion of antileukocyte antibodies in the donor plasma (either anti-HLA or anti-granulocyte specific)





T.R.A.L.I.



Clumps of WBC form and get trapped in the pulmonary microcirculation.



TRANSFUSION ASSOCIATED CIRCULATORY OVERLOAD (T.A.C.O.)

Just a fancy term for fluid overload caused by transfusion...

DDX: TRALI

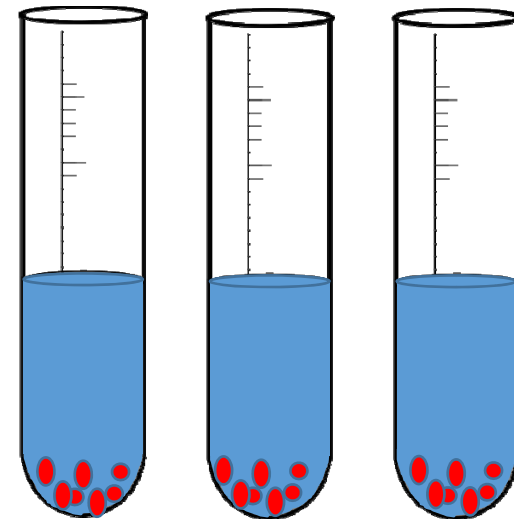
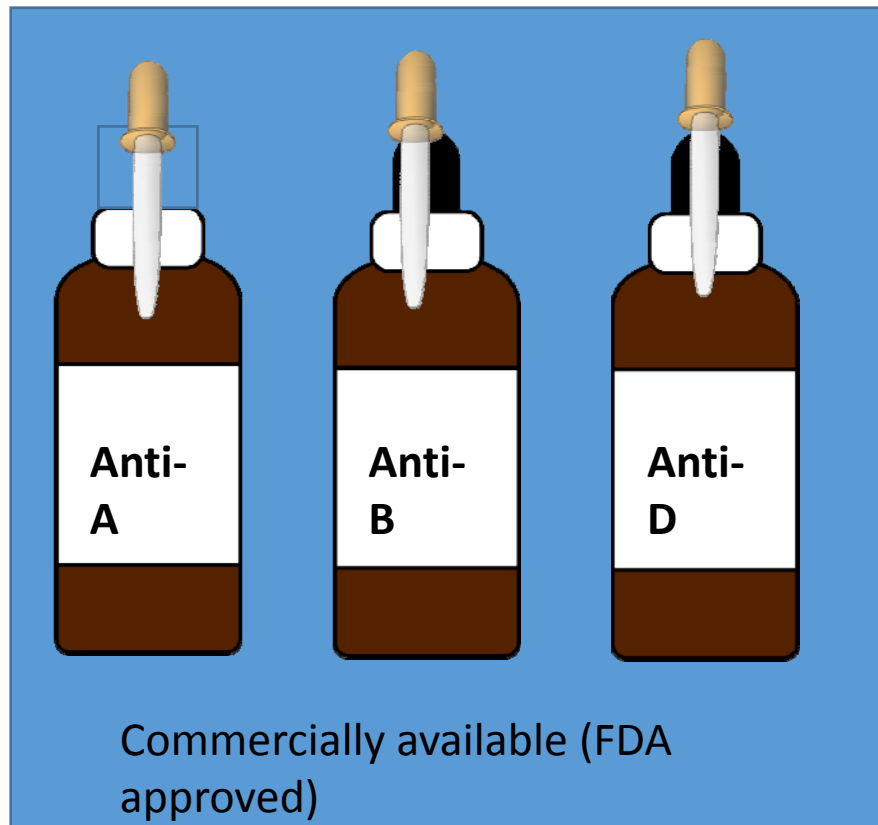
Typical case:

47 yr old female with Factor XI deficiency seen as an outpatient to receive 4 units of FFP for AM elective hysterectomy the next day. Patient is in a hurry and wants to attend an important social engagement on the day before surgery. 4 units of FFP were infused over 2:30 hours. Patient leaves Rochester on her way to the Twin Cities. 45 minutes later she is brought back by helicopter for pulmonary edema. BNP extremely elevated, patient is treated for fluid overload but misses the engagement. Surgery is postponed...

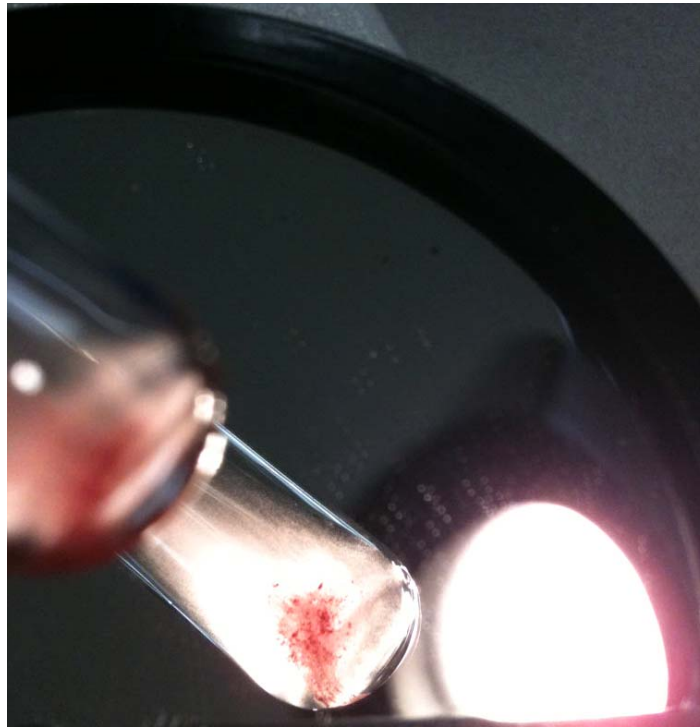
Testing prior to transfusion

- ABO & Rh type
- Antibody Screen
- Antibodies to common antigens
- Identification of antibodies to common antigens
- Crossmatching

How is blood group determined?



Centrifuge 5 min



“Gently shake”

Clumps= positive

Antibody Screen

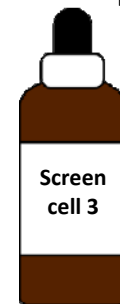
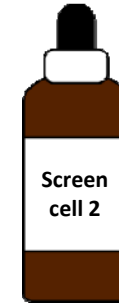
Add 2 drops of pt plasma



D	C	C	E	e	V	Cw	K	K	Kpa	Kpb	Jsa	Jsb	Jk a	Jkb	Lea	Leb	P1	M	N	S	S	Lua	Lub	Xg a	R T	3 7	
+	+	0	0	+	0	0	0	+	0	+	+	+	+	0	0	+	0	+	0	+	+	0	+	+	0		
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0	0	+	0	+	0	0	+	+	0	+	+	+	+	0	0	+	+	0	+	+	0	0	+	+	0		

Results

FDA approved typed commercial cell



Positive Antibody Screen

D	C	C	E	e	V	Cw	K	K	Kpa	Kp	Js	Js	Jk	Jkb	Lea	Leb	P1	M	N	S	S	Lua	Lub	Xp			
+	+	0	0	+	0	0	0	+	0	+	+	+	+	0	0	+	0	+	0	+	+	0	+	+	+		
+	0	+	+	0	0	0	0	+	0	+	+	+	0	+	+	0	0	+	0	0	+	0	+	+	+	+	
0	0	+	0	+	0	0	+	+	0	+	+	+	+	0	0	+	+	0	+	+	0	0	+	+	0	0	

“The patient’s plasma reacts against antigen(s) present on screening cell 1”

“The patient’s plasma reacts against antigen(s) present on screening cell 2”

The patient’s plasma does not react against any of the antigens present on cell 3

Type and hold

- Perform blood type & stop!

“I don’t anticipate transfusing, but just in case...”

If blood is needed we are that much ahead

Crossmatching

- Same as antibody screen but using an ABO compatible unit
- Blood Group O can be given to anyone as long as screen is negative

Computer Crossmatch

2 separate blood samples needed to establish "official" type
Antibody screen with 3 commercial phenotyped cells is negative
Computer has inventory & assigns ABO compatible unit to patient*

NO PHYSICAL CROSSMATCH IS DONE!!!

END of TRANSFUSION

