# Transfusion Medicine

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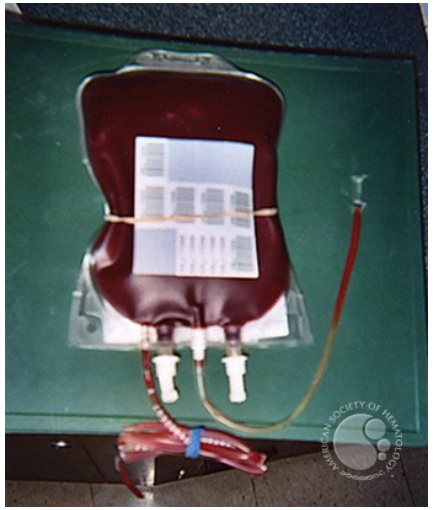
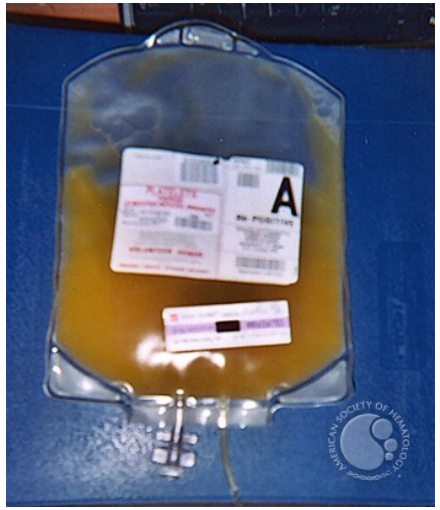
# Transfusion

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





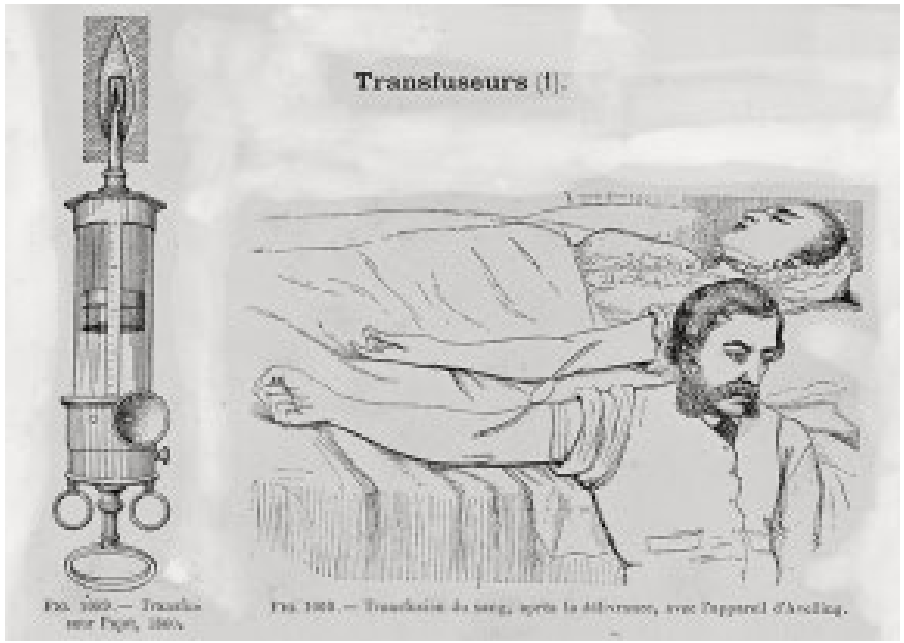

***Source: ASH Image Bank.***

**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.

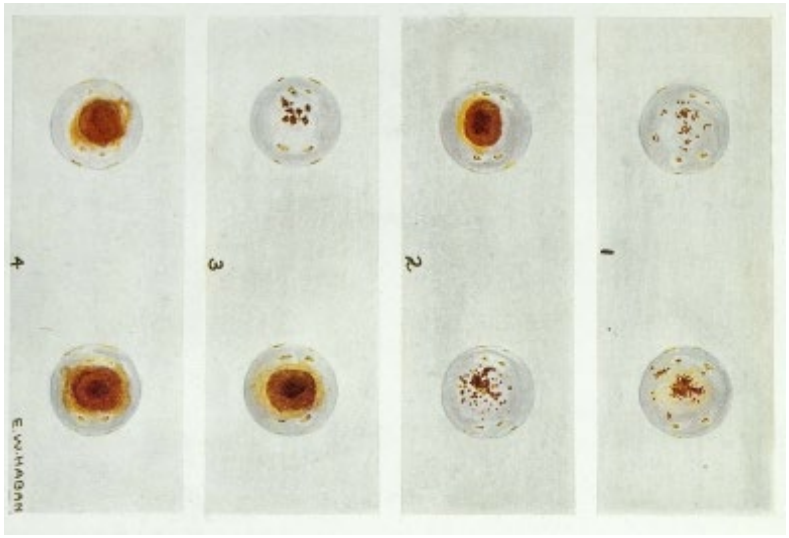
# Transfusion: Progress from a potentially lethal procedure to a now largely safe and common treatment

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*

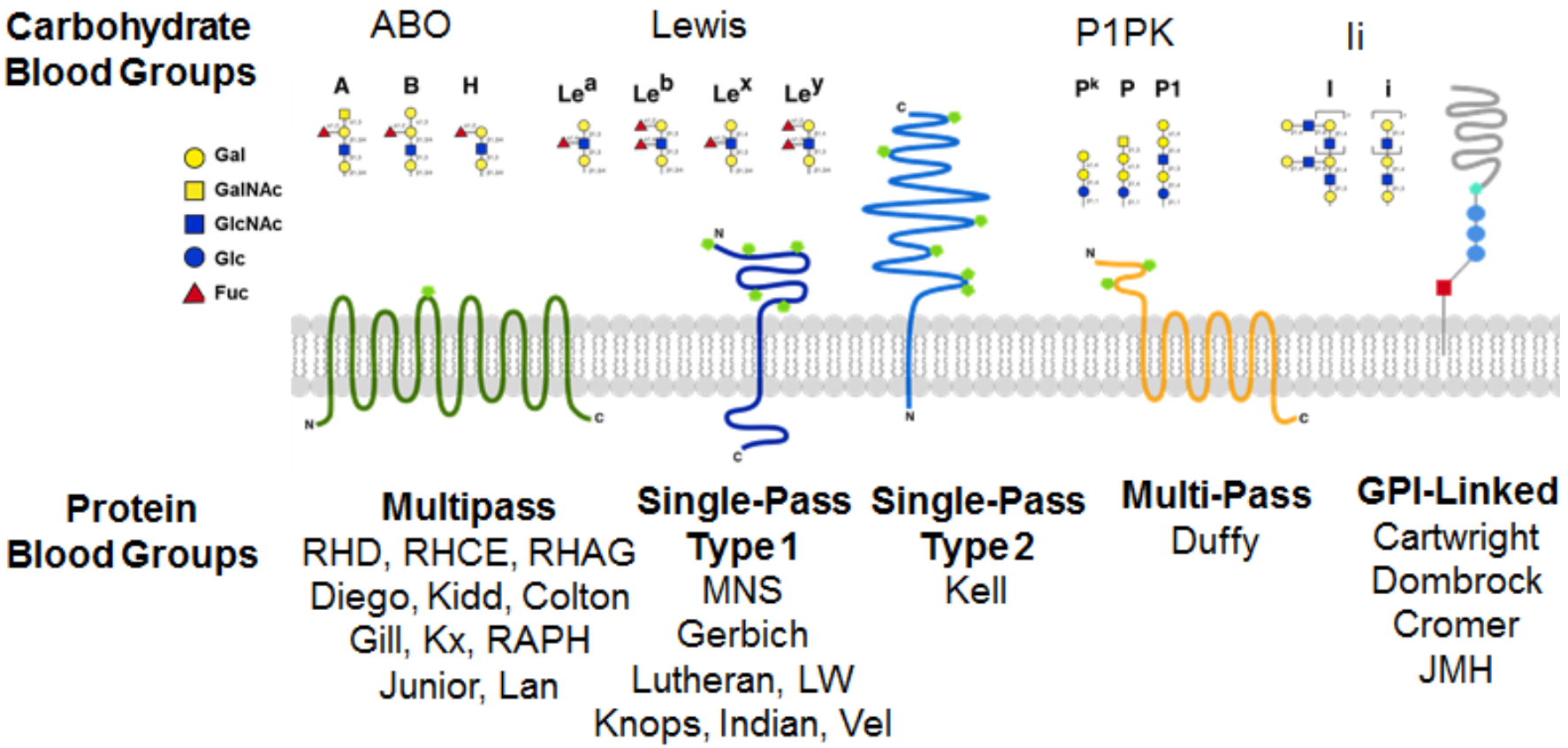
# Discovery of ABO made safe transfusion possible




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

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

# 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

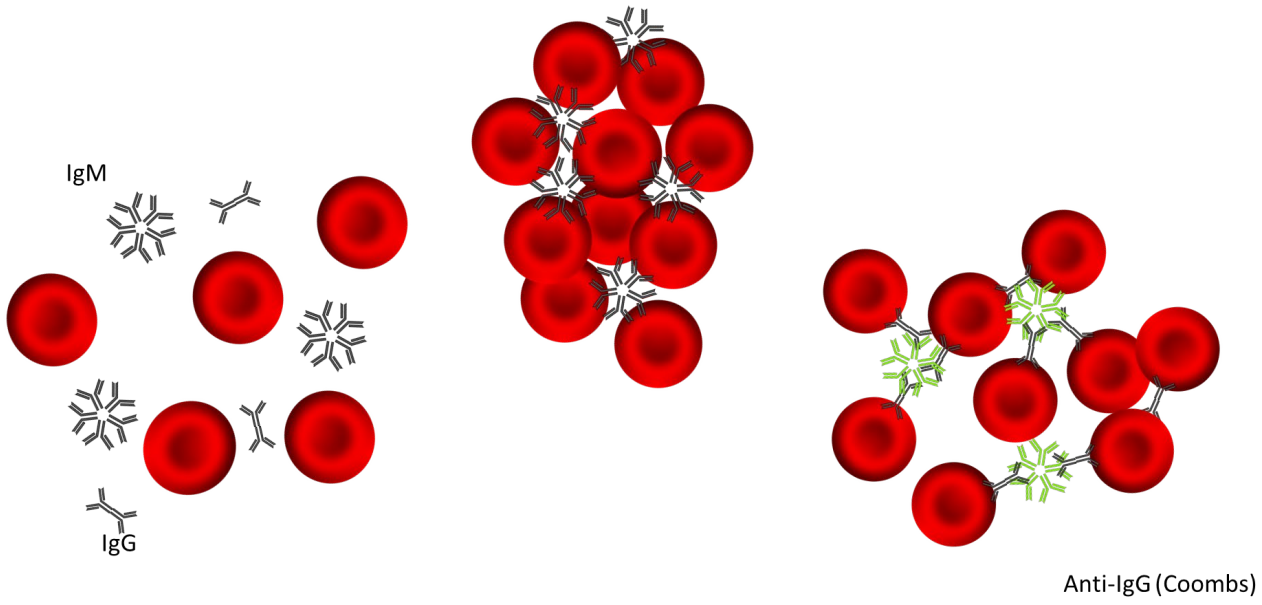
(Ordering a type and screen is a good time to consider IV access)

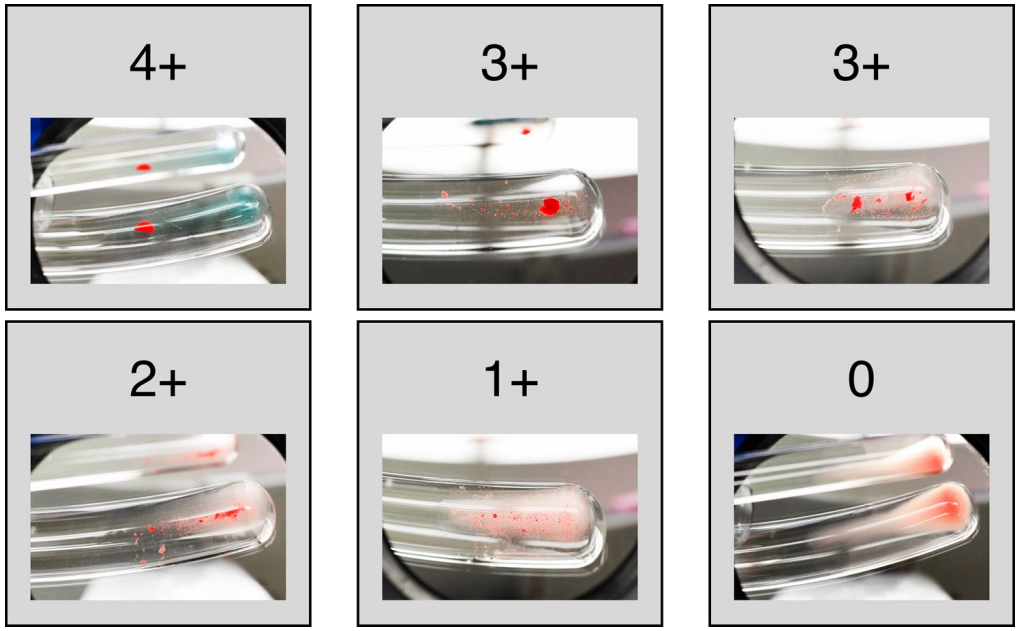
# TYPE: Routine blood group testing is based on interaction of RBCs with anti-RBC antibodies

All transfusions: ABO, D.

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

*RBC genotyping can also be done, testing more blood groups at once*



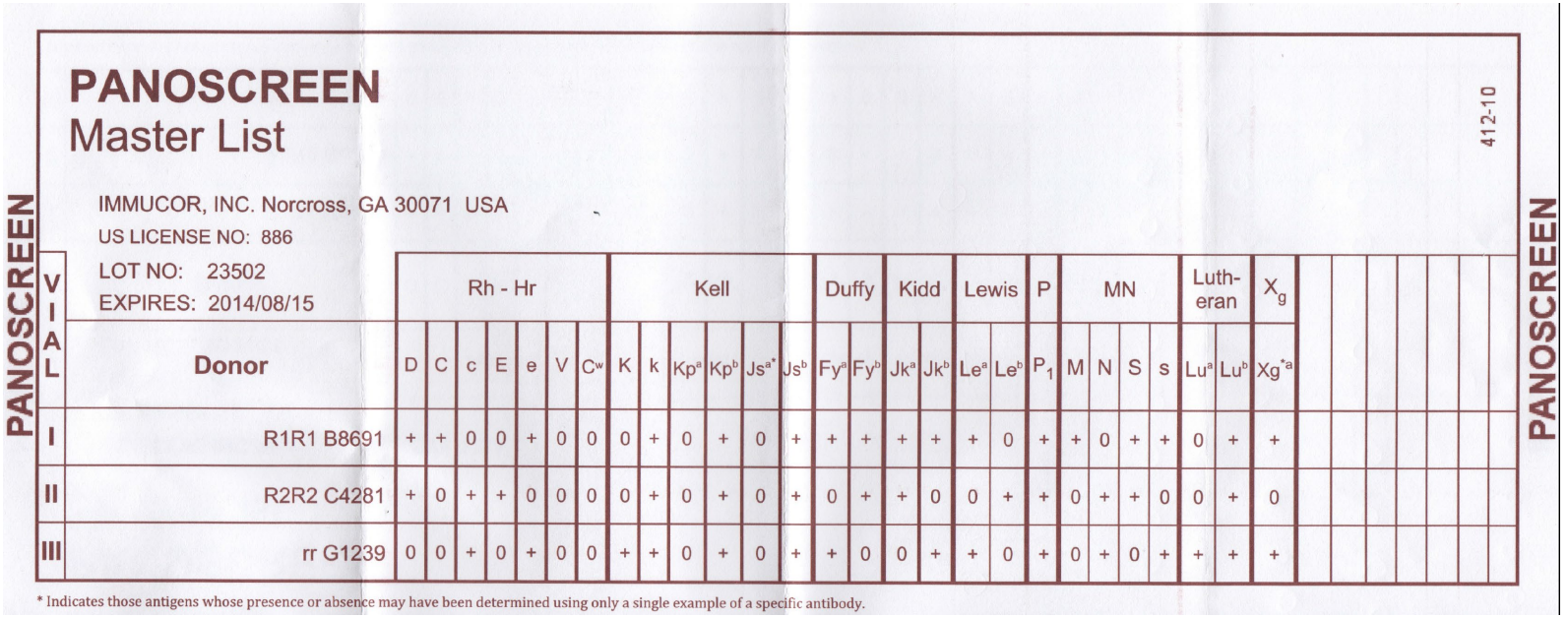




*Tube testing image courtesy of Kerry Lannert*

# 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

412-10

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

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

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)

Multiple specialized other tests may be needed

- Antibody characterization
- RBC genotyping

**PANOCELL -10**
Master List

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

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

| 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 | + | + | 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 | 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 | | | | |

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

* 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.

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
  - Autoantibodies
- Immediate Spin Crossmatch
  - Rapid mixing of patient serum with donor RBCs to search inventory for compatible units

# 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)
    - May test 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: *Babesia microti*
    - *Zika requirement recently discontinued*

# 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

# Counseling the patient on risks of transfusion[1]

| Transfusion Reaction or Infection | Estimated rate among Transfused Patients |
|---|---|
| Allergic (mild) | 1:20 |
| Fever/chills (nonhemolytic) | 1:50 |
| Transfusion-associated circulatory overload (TACO) | 1:100 |
| TRALI | 1:12,000 |
| Acute hemolytic (mistransfusion) | 1:40,000 |
| Acute hemolytic (incompatible plasma) | 1:50,000 |
| Delayed hemolytic | 1:50,000 |
| Septic reaction (apharesis platelets) | 1:100,000 |
| Anaphylaxis | 1:500,000 |
| HIV, HBV, HCV | 1:1,500,000 – 1:3,000,000 |

1. A Compendium of Transfusion Practice Guidelines. American Red Cross. Ed 4.0. January 2021.

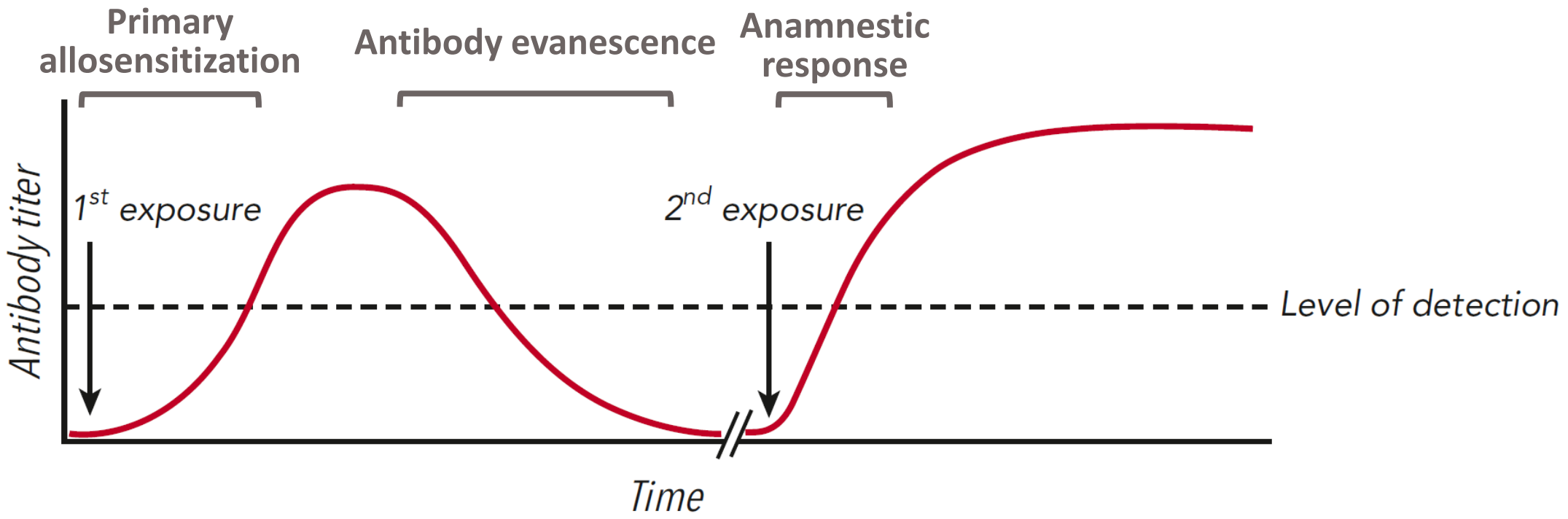
# *Immediate* immunologic complications of transfusion

- **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 analogues (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]



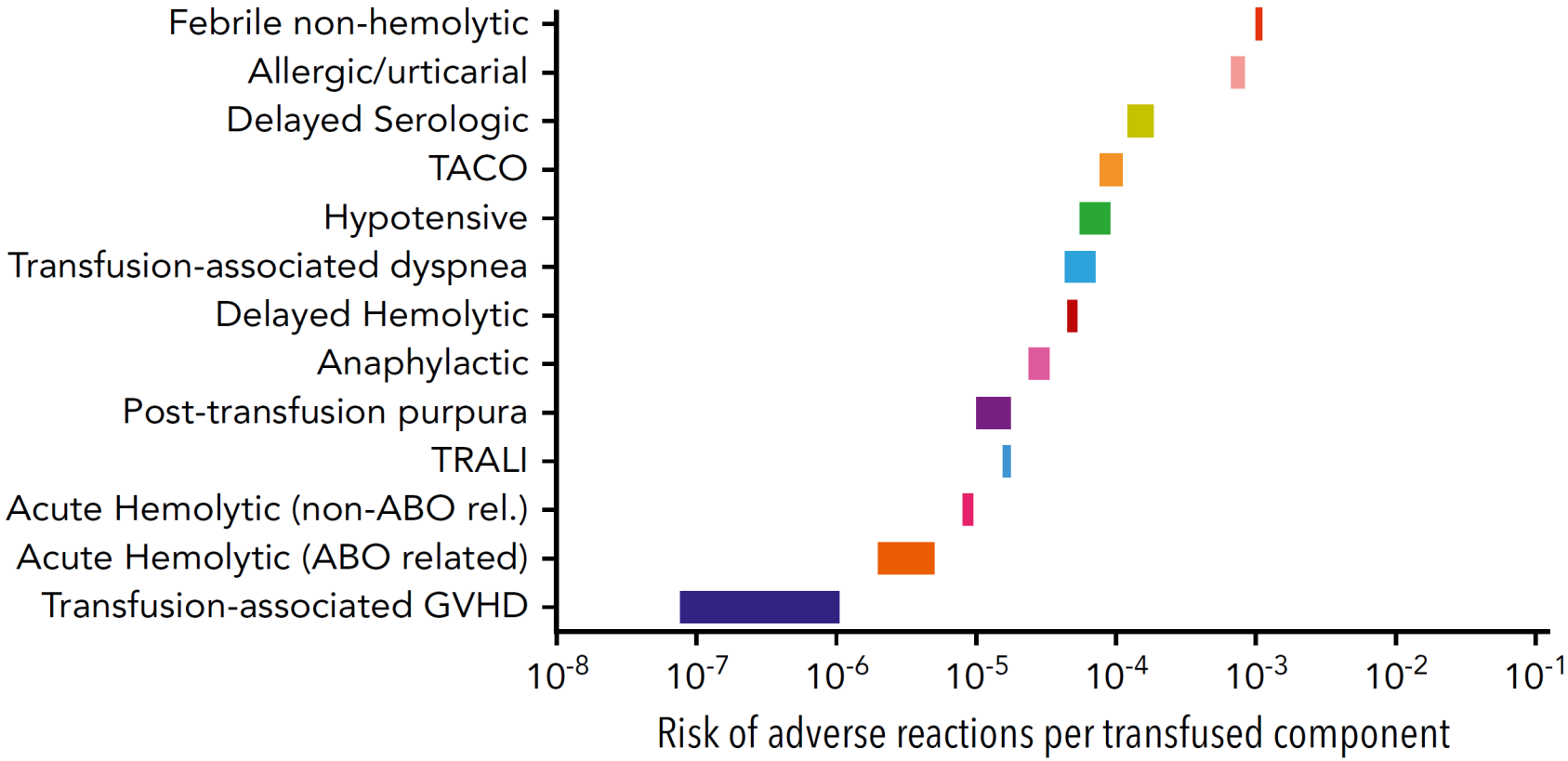

**1.** Tormey C. and Hendrickson J. Transfusion-related red blood cell alloantibodies: induction and consequences. *Blood* 2019;133(17);1821-1830. (2019)

# 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]

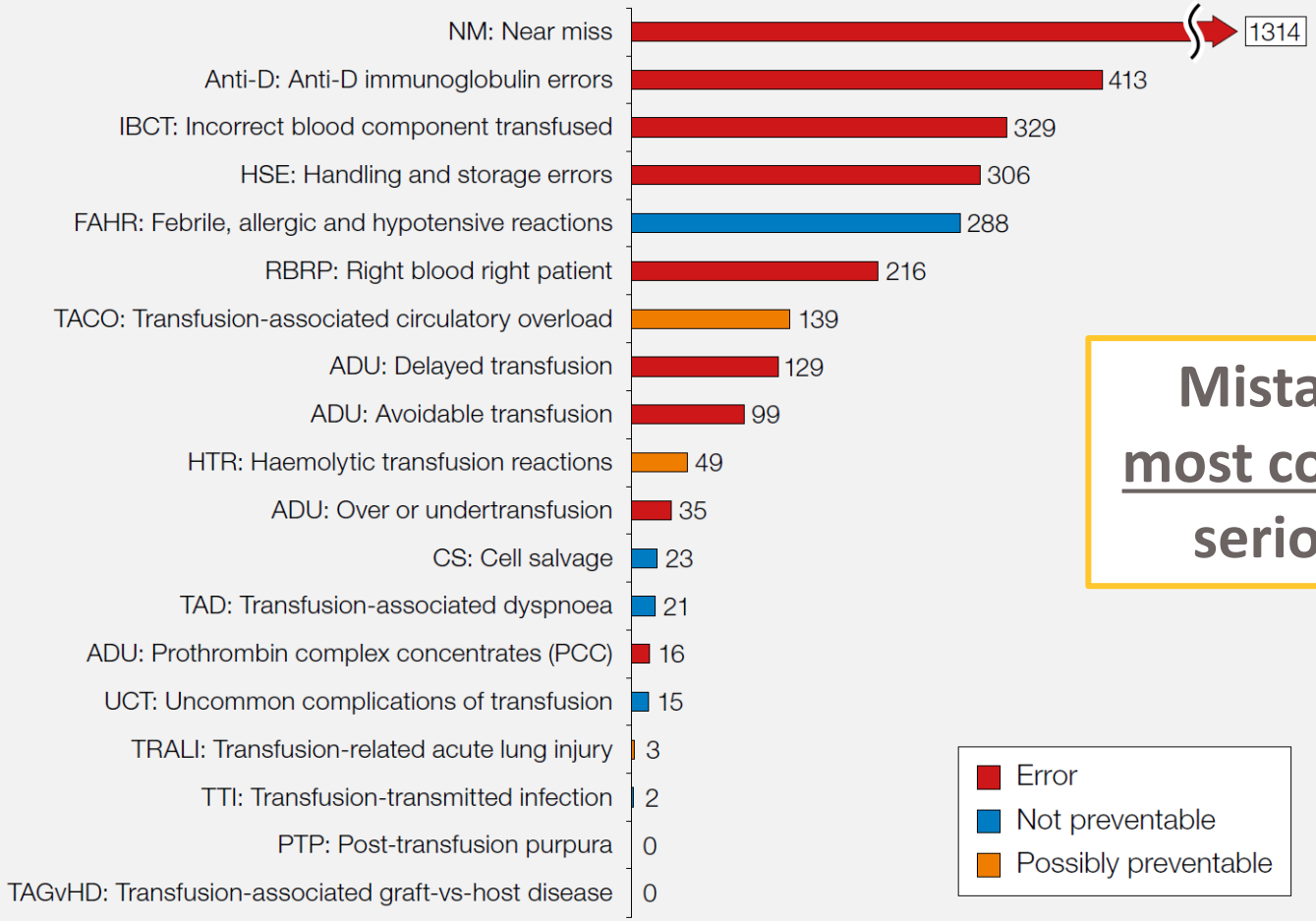
## From National Blood Collection and Utilization Surveys 2011-2015




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®
An initiative of the ABIM Foundation

## 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 and ASH 2020 guidelines

*See lecture on sickle cell disease for when to consider exchange transfusion*

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 or females of non-childbearing potential

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, (use inventory needed for other patients,) 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 use plasma

- Preoperative or bleeding patients who require replacement of multiple coagulation factors *(e.g.,* liver disease, DIC)
- Patients undergoing massive transfusion with coagulopathic bleeding
- 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. FV, FXI, C1-inhibitor)
- Thrombotic thrombocytopenic purpura (TTP) – plasma exchange (plasma if unavail)

*See lectures on coagulation for underlying disorders and management*

# When to use cryoprecipitate

- Acquired fibrinogen deficiency and bleeding
- Massive transfusion protocols
- DIC with severe hypofibrinogenemia (<100-150 mg/dL) that persists despite FFP replacement

- Not recommended for congenital factor deficiencies (fibrinogen, hemophilia A, VWD, factor XIII deficiency) unless specific factor replacement is unavailable

*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
  - Pragmatic use of a scarce resource
  - Reduce risk of allosensitization
- Thrombocytopenia: correction of quantitative defects
  - Prophylactic transfusion: most recent consensus guidance[1]
    - **Stable, non-bleeding patient**: maintain >10,000/uL
    - **Unstable, non-bleeding patient**: maintain >20,000/uL
    - **Active bleeding** or undergoing **major invasive procedures** or surgery: maintain >50,000/uL
- 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*

1. A Compendium of Transfusion Practice Guidelines. American Red Cross. Ed 4.0. January 2021.

# THANK YOU!