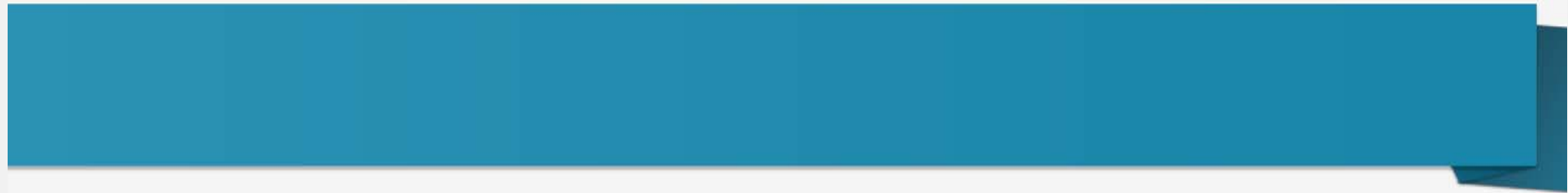


MANAGEMENT OF ADVERSE TRANSFUSION REACTIONS

13TH – 17TH MAY 2024





OBJECTIVES

- Get aware of the common transfusion reactions and/or risks
- Pathogenesis & Clinical presentation of those reactions
- Principles of management

INTRODUCTION

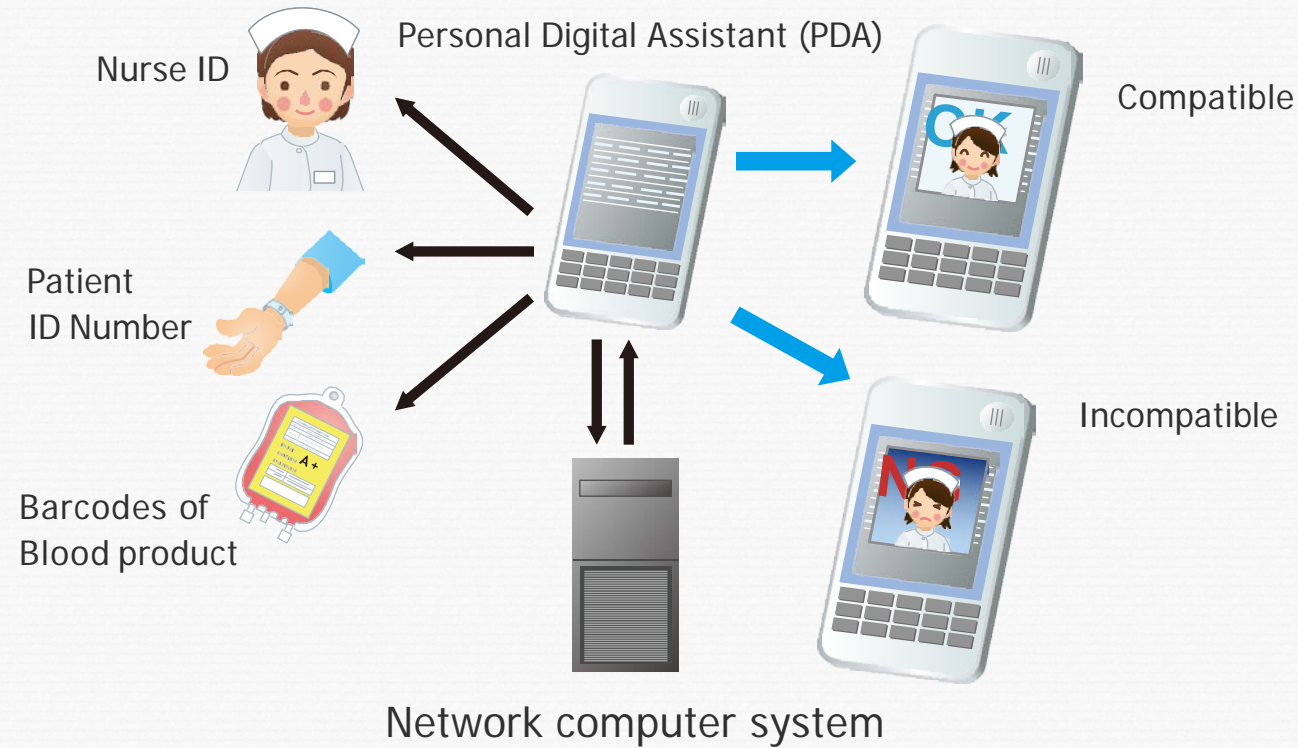
- The most common are febrile nonhemolytic and chill-rigor reactions
- The most serious with high mortality rates are transfusion-related acute lung injury (TRALI) and acute hemolytic reaction due to ABO
- Early recognition , proper management and reporting are essential

DEFINITION

- An adverse blood transfusion reaction is an undesirable response that occurs during or after the transfusion of blood or blood products.
- These reactions can be immediate or delayed and vary in severity from mild allergic reactions and fever to severe complications like anaphylaxis, hemolytic reactions, and infections.
- Acute reactions typically occur within 24 hours of the transfusion, while delayed reactions can manifest days to weeks later
(by NIH)

Common causes of TR

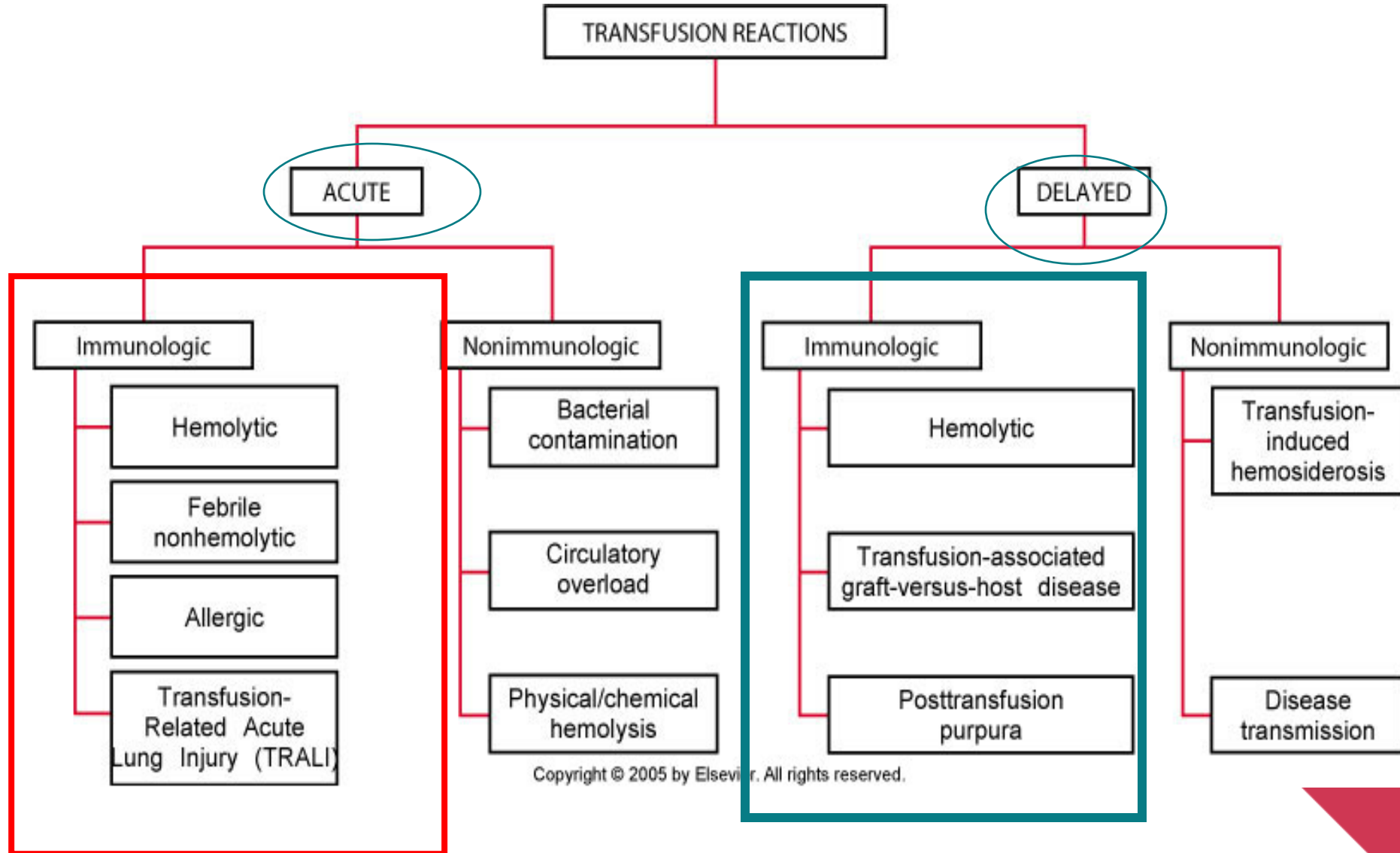
- Misidentification of the patient.
- Improper sample identification.
- Wrong blood issued.
- Administration error.
- Technical error.
- Storage error.



Electronic collation of blood product and patient at the bedside

The pre-transfusion check at the bedside is the most critical step in preventing mistransfusion. A bar code-based identification system is ideally suited to bedside check requirements. The label of blood products in Japan has a barcode showing ABO blood type and other information. The electronic collation of blood product and patient should collate the barcodes of the patient's wristband, the blood product, and operator identification number.

Classification of transfusion reactions



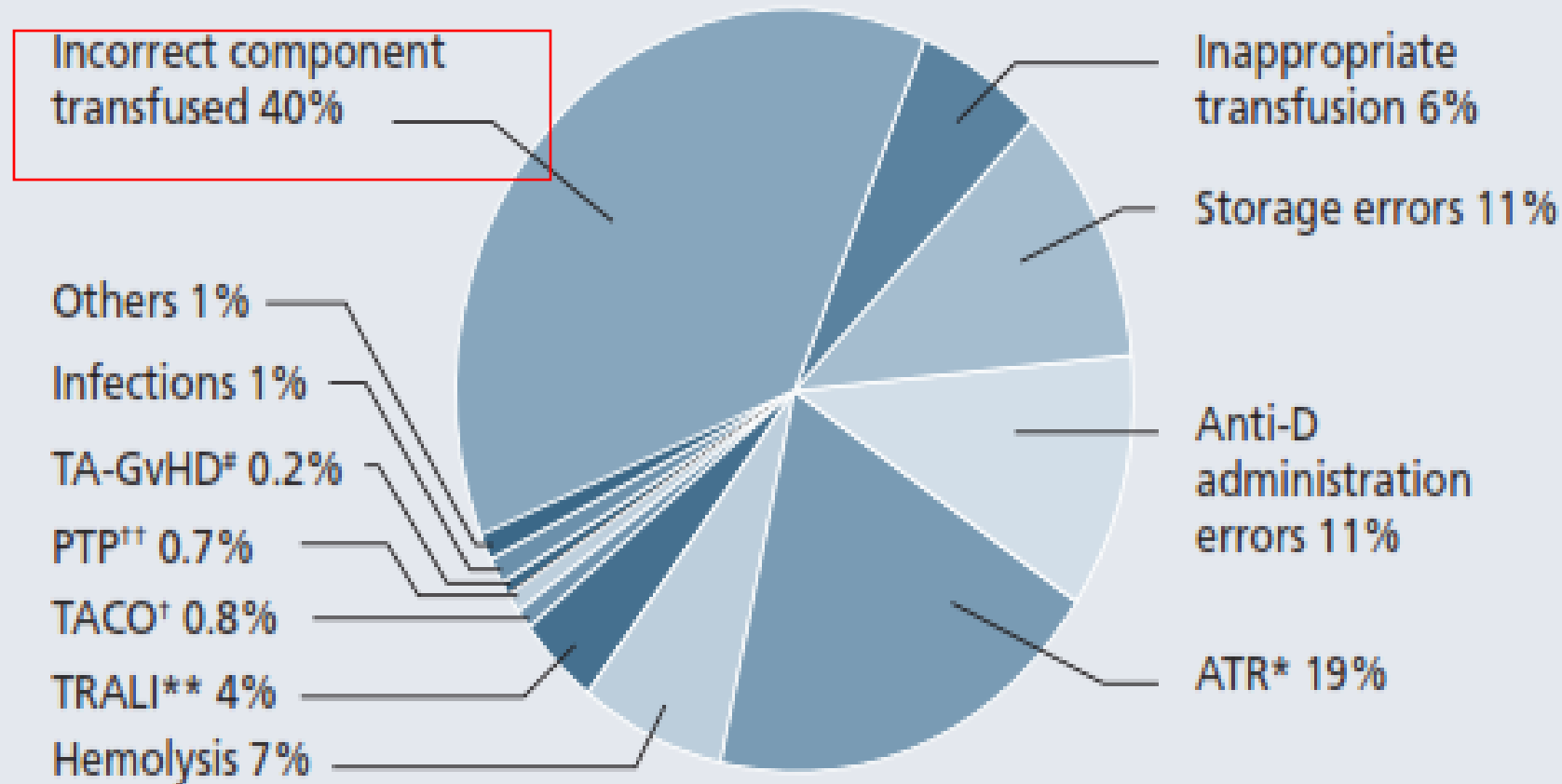
1. Acute Immunologic reactions

1.1 Acute Hemolytic Transfusion Reactions

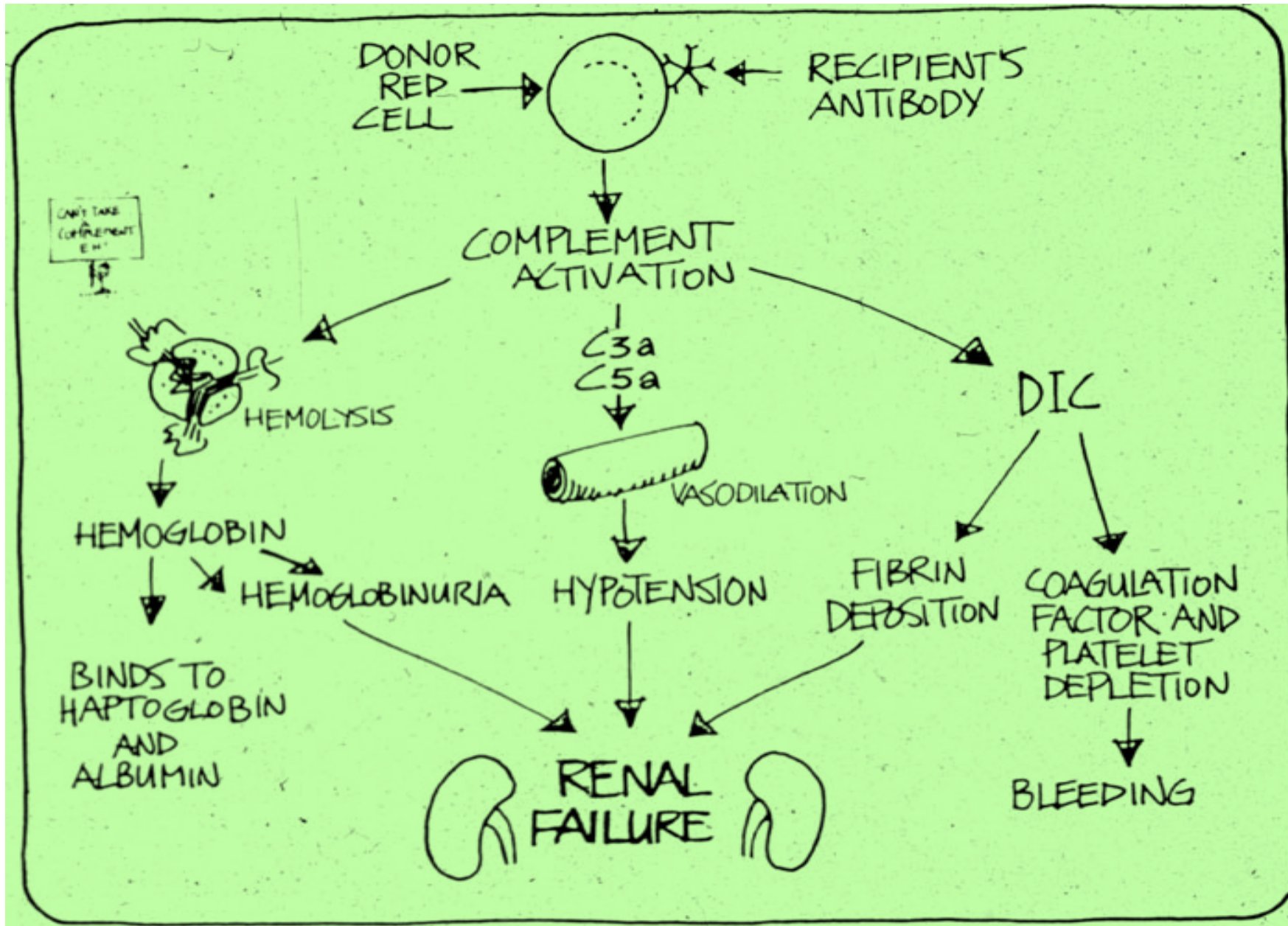
- Onset within 24 hours, usually immediate
- Most hazardous against foreign RBC's
- Hemolysis of donor RBC's can lead to ARF & DIC
- Mortality rate is 2%
- Leading cause is clerical error
- Most common antibodies that fix complement
 - ABO, Kell, Kidd, Duffy
- Rh antibodies do not fix complement but can cause serious hemolysis

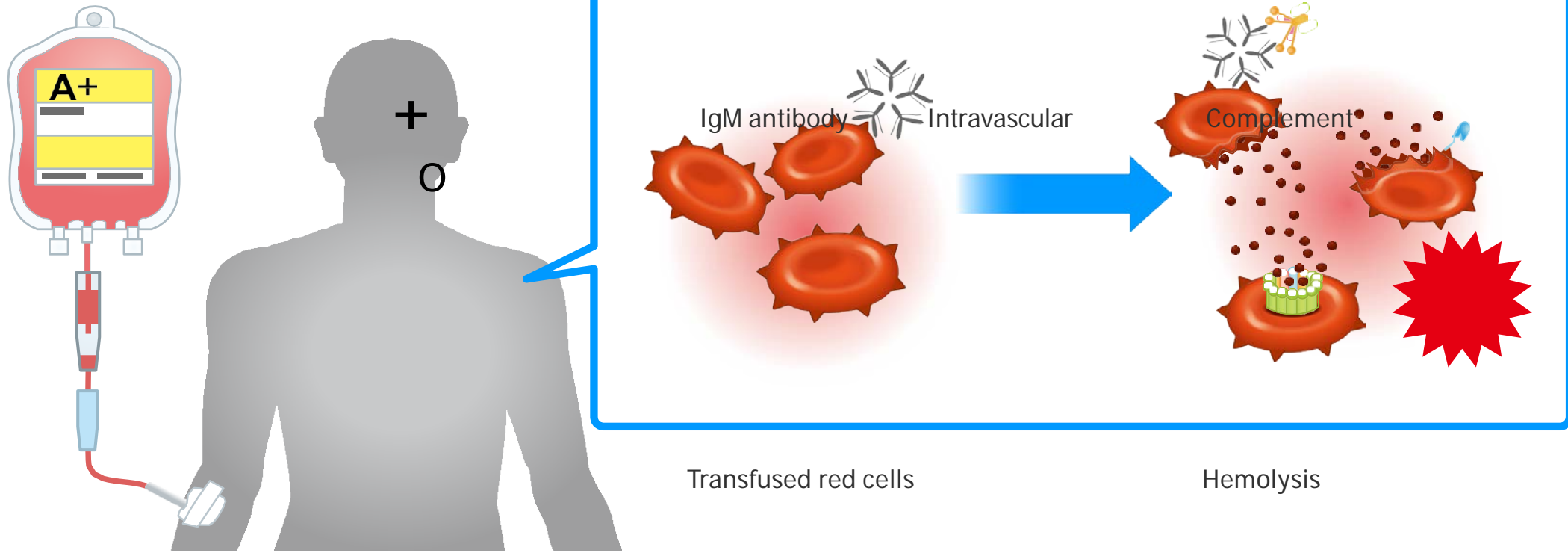
SERIOUS HAZARDS OF TRANSFUSION (SHOT), UNITED KINGDOM

MAJOR ADVERSE EVENTS REPORTED 1996-2009 (6653 REPORTS)⁴⁴



* Acute transfusion reactions (ATR) include fever, allergic, anaphylactic, hypotensive reactions





Pathophysiology of ABO-incompatible blood transfusion

Acute hemolytic transfusion reaction resulting from ABO-incompatible blood transfusion is usually due to the reaction of ABO antibodies with transfused red cells. Antibody-coated red cells activate the complement system, resulting in intravascular hemolysis.

Subsequently, over production of cytokines, hypotension, renal failure, and disseminated intravascular coagulation will appear.

Acute Immunologic reactions

1.1 Acute Hemolytic Transfusion Reactions

Clinical presentation:

- Fever, Chills, Rigors, Nausea
- Hypotension, dyspnea, tachycardia
- Chest Discomfort, Diarrhea
- Flank pain, Chest pain, pain up arm
- Burning at transfusion administration
- Hemoglobinuria (red/brown urine), oliguria with dark urine
- Bleeding, oozing at puncture sites (DIC?)....

Acute Immunologic reactions

1.1 Acute Hemolytic Transfusion Reactions

Lab work up:

- Obtain Blood and urine samples (inspect color)
- Check paper work
- Repeat cross Match
- FBC
- Direct Coombs' test
- DIC screen: PT,PTT, Fibrinogen, platelets
- BUN, Creatinin, electrolytes
- Haemolysis screen: LDH, Haptoglobin, bilirubin
- Blood culture if sepsis is suspected

Acute Immunologic reactions

1.1 Acute Hemolytic Transfusion Reactions

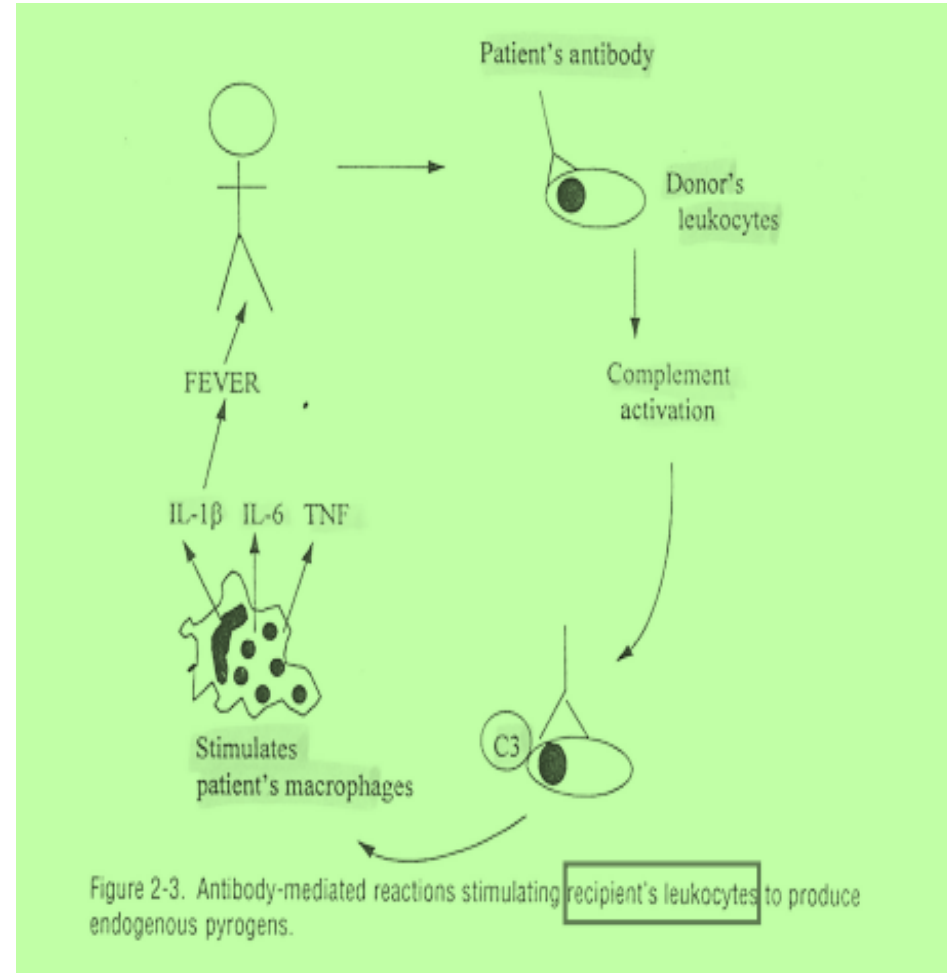
MANAGEMENT:

- **STOP transfusion IMMEDIATELY**
- Treat hypotension, maintain renal perfusion
 - IV fluids (NS), diuretic (IV furosemide: 1-2mg/kg)
 - Hydrocortisone may be considered
- Check for DIC
 - Component therapy as needed
- **CONTACT the Blood Bank**
 - Second patient may be at risk, if there was a switch in blood components
 - Outcome : Mortality ~ 10 %

Acute Immunologic reactions

1.2. Febrile Non Hemolytic transfusion reactions (FNHTR)

- HLAs or leukocyte Ag on the WBCs of the donor that react with the recipient antibodies previously formed
- Administration to the recipient of endogenous pyrogens accumulated during component storage.
- Onset during or within 4 hrs following transfusion



Acute Immunologic reactions

1.2. Febrile Non Hemolytic transfusion reactions (FNHTR)

Symptoms:

- Fever after 30-90 min
- \pm Rigors
- \pm Headache
- *No Hypotension*
- *No Bronchospasm*
- *No flank pain*
- *No Haemoglobinuria*

Acute Immunologic reactions

1.2. Febrile Non Hemolytic transfusion reactions (FNHTR)

MANAGEMENT:

- If Temp < 40 + Stable patient:
 - Stop transfusion
 - Antipyretics (paracetamol po)
 - Check the bag and cross match
 - Exclude red urine or red plasma
 - Resume transfusion at a slower rate
 - (If recurrent: Leucodepleted transfusion in the future)
- If Temp 40 or more + Unstable patient:
 - Stop transfusion
 - Manage as possible acute haemolytic reaction till lab. Confirmation or exclusion

Acute Immunologic reactions

1.3. Anaphylactic Transfusion Reaction

- Caused by allergenic substances in DONOR product
- Usually to an unspecified plasma protein (Ig A, haptoglobin,...)
- IgA deficient more likely at risk (1:300 – 1:500)
 - IgA deficient patients may make anti-IgA on exposure to normal plasma
 - When re-exposed to can get severe anaphylactic reactions & possible death

Acute Immunologic reactions

1.3. Anaphylactic Transfusion Reaction

Signs & symptoms:

- **Mild / Skin-restricted (1%)(ALLERGIC REACTION):**
 - Pruritus, Urticaria, No fever or Hypotension
- **Severe / Systemic (Anaphylaxis):**
 - As above +
 - Fever, tachycardia, widespread urticaria
 - Hypotension, cough, severe anxiety, shock
 - Bronchospasm, Respiratory Distr., Angio-edema
 - Cardiac arrest



Acute Immunologic reactions

1.3. Anaphylactic Transfusion Reaction

MANAGEMENT:

- **Mild / Skin-restricted :**
 - Stop transfusion temporary
 - Anti-histamines (Loratadine 10mg or cetirizine 10 mg Po)
 - Resume Transfusion
- **Severe / Systemic (Anaphylaxis):**
 - Stop transfusion
 - Anti-histamines (Loratdine, Cetirizine, promethazine 25-50 mg IV (Max rate 25 mg/min) if moderate
 - **Epinephrine**
 - Hydrocortisone 100 mg IV
 - Cardio-pulmonary support
 - Increased monitoring , eg BP every 15-30 min

Prevent the next one by reporting it to the BB

Acute Immunologic reactions

1.4. Transfusion Related Acute Lung Injury (TRALI)

- Acute respiratory distress hypoxemia, cyanosis, pulmonary edema within 6 hours (**usually 1-2h**) of transfusion of plasma or plasma containing cellular components
- Bilateral lung infiltrates
- Rare: 1/5000 transfusions

Acute Immunologic reactions

1.4. Transfusion Related Acute Lung Injury (TRALI)

- New onset
- Hypoxemia $SpO_2 < 90\%$ or $PaO_2/FiO_2 < 300$ mm Hg on room air, or other clinical evidence of hypoxemia
- Bilateral infiltrates on frontal chest X-ray



Chest X-ray of a patient before and during an episode of transfusion-related acute lung injury (TRALI)



Acute Immunologic reactions

1.4. Transfusion Related Acute Lung Injury (TRALI)

Pathophysiology:

- Anti-HLA or antigranulocytes containing donor's plasma
- React with receiver's WBC
 - Endothelial Cell activation → Increased adhesion of neutrophils to pulmonary endothelium
 - Neutrophil activation and release of cytokines
 - Pulmonary microvascular infiltration & damage: pulmonary edema

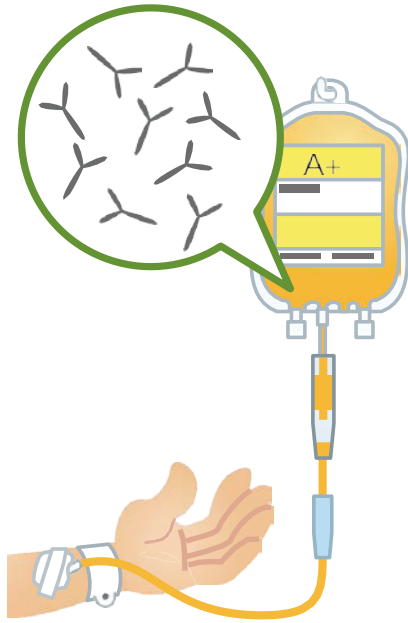
Acute Immunologic reactions

1.4. Transfusion Related Acute Lung Injury (TRALI)

Management:

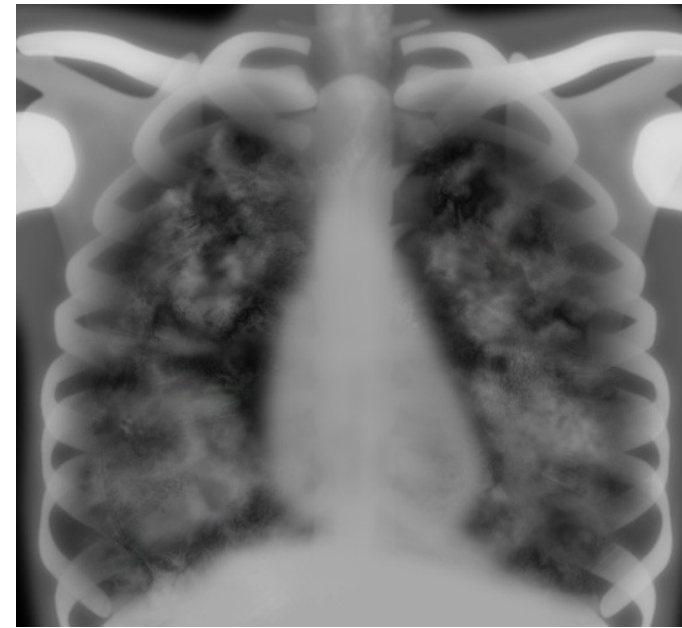
- STOP TRANSFUSION
- Oxygen, Mechanical ventilation
- Confirm diagnosis – pulmonary imaging, rule out alternative diagnoses
- IV Steroids

Mortality: HIGH!!!

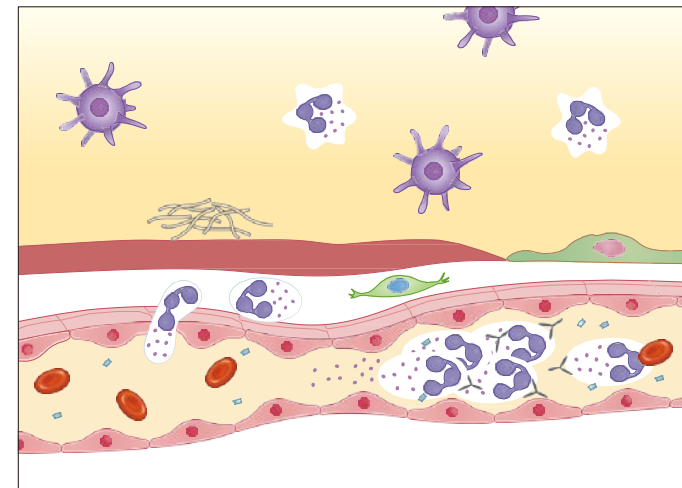


TRALI – causes
Anti-HLA or anti-HNA antibodies in donor blood

TRALI – pathophysiology
The interaction between anti-HLA or anti-HNA antibodies in donors and cognate antigens in recipient result in the increase of permeability of lung microvasculature endothelial cells and the aggregation of neutrophils.



TRALI
– Chest radiograph
Bilateral infiltrates on frontal chest radiograph



Delayed Immunologic reactions

1. Delayed hemolytic transfusion reactions:

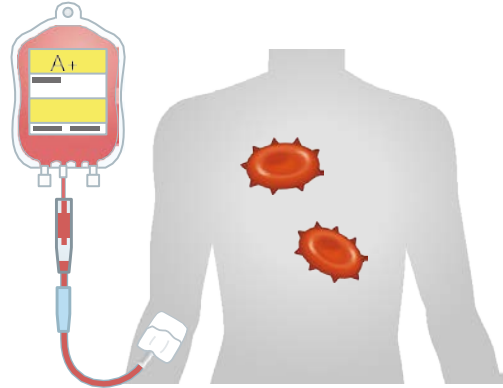
- Extravascular (intrasplenic)
- Delayed: 5-7 days after transfusion, may be up to 28 days
- Detected by inefficacious transfusion (drop of Hb)
- Causes:
 - Undetected irregular Ab in receiver's plasma

Delayed Immunologic reactions

Diagnosis of DHTR

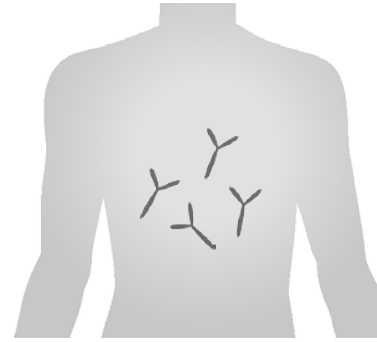
1. Irregular antibody test and crossmatch test in the recipient's serum before and after transfusion (pretransfusion: —, posttransfusion: +)
 2. Irregular antibody presence detected (one or more antibodies)
 3. Direct antiglobulin test results become positive (surviving transfused RBCs)
1. Some instances of antibody elution test results become positive
 2. Blood typing of transfused RBCs
 3. Hemolytic clinical findings (fall in Hb concentration, increase in LDH, total-bilirubin, hemoglobin-uria, etc.)
 7. Test requisition or consult in blood center

E Ag (+) RCC



Recipient with E antigen (-) has been immunized transfusion, or pregnancy.

Several weeks



Production of anti-E (immune memory)

Several weeks to several years

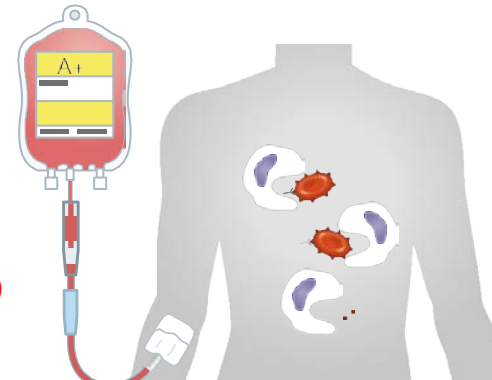


Low detection sensitivity of anti-E

Irregular antibody (-) and crossmatch test (-)



E Ag (+) RCC



Secondary immune response and clinical features of DHTR such as fall in Hb and fever etc.

Delayed Immunologic reactions

2. Graft- *versus*-Host disease (GVHD):

- Rare but life-threatening reaction
- 8-30 days after transfusion
- Mechanism:
 - Donor T cells engraft in recipient and react against the recipient's tissues
 - The recipient is unable to reject the donor lymphocyte because of:
 - *Immunodeficiency*
 - *Severe immunosuppression*
 - *OR share HLA antigens(parents)*

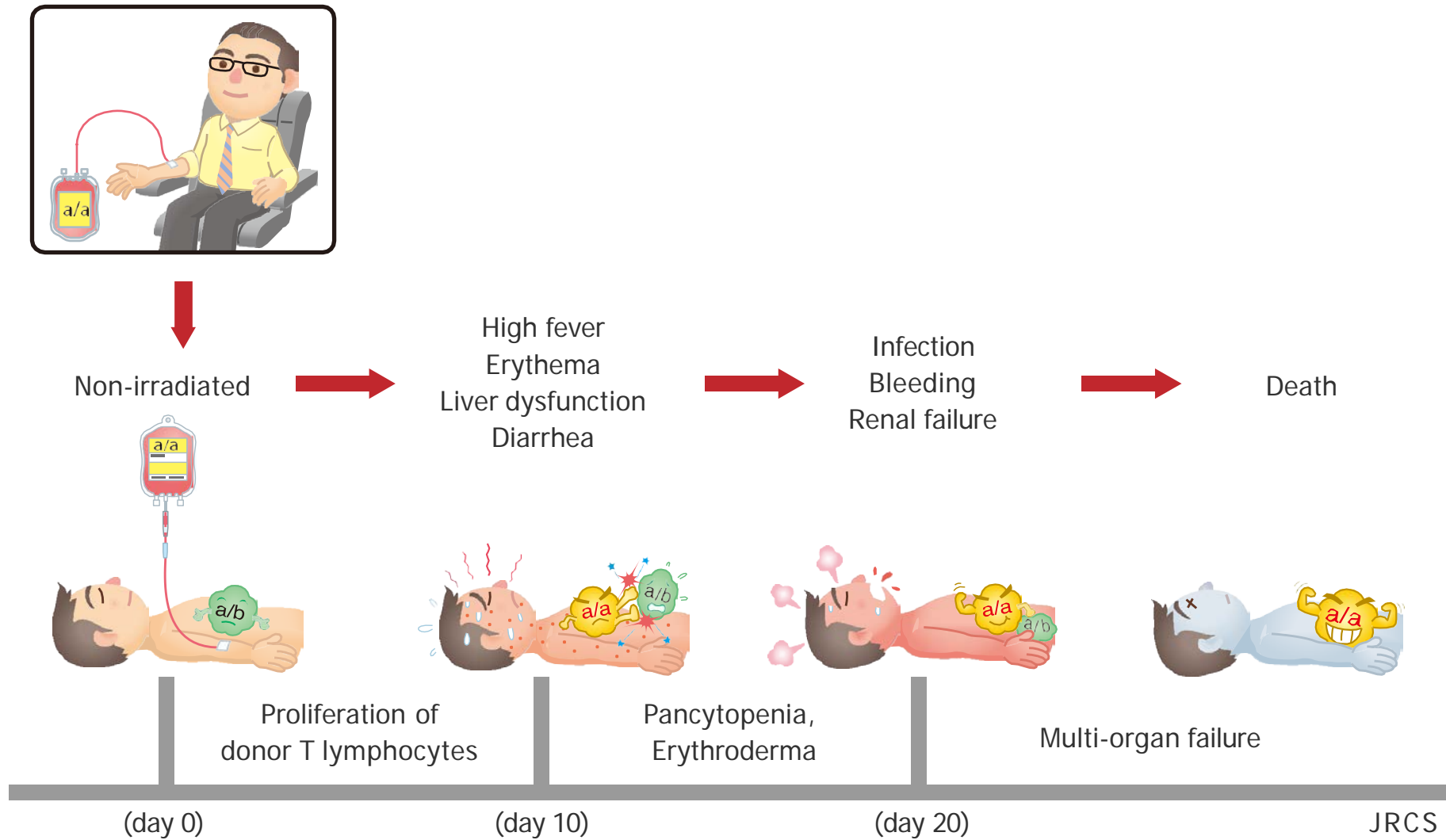
Delayed Immunologic reactions

2. Graft- *versus*-Host disease (GVHD):

- *Clinical presentation:*
 - *Fever, skin rash, hepatitis, diarrhea*
 - *Bone marrow suppression, infection, bleeding*
- *Management:*
 - *No treatment*
 - *Prevention:*
 - Irradiation of blood from directed donor for immunocompromised patients



FIG 2. An infant with SCID who had lethal GVHD from a nonirradiated packed RBC transfusion. Photograph courtesy of Dr Fred Rosen.



Post-transfusion graft-versus-host disease

PT-GVHD occurs when donor lymphocytes in transfused blood attack recipient organs and tissues recognizing recipient HLA and are not eliminated by host immunological defense.

2. Transmission of infectious agents

Transfusion transmitted-disease for which donors are tested:

- HIV
- HBV
- HCV
- Syphilis
- Others: HTLV, WNV, CMV, bacteria, Trypanosoma cruzi



2. Transmission of infectious agents

Transfusion transmitted-disease for which donors are not routinely tested:

- Malaria
- Viruses: HAV, Parvovirus B19, Dengue fever virus,
- Parasites: Babesia, leishmania, T. gondii...
- New variant of Creutzfeld-Jacob disease
- Bacteria: brucella,...

2. Transmission of infectious agents

Bacterial Contamination-related Sepsis:

- 1 in 25,000 platelets
- 1 in 250,000 PRBCs
- Relatively absent for FFPs

Results from bacterial contamination of blood products:

- Donor bacteremia: *Y. enterocolitica*, *C. jejunii*
- Inadequate skin disinfection: *Staphylococcus*
- Contamination during blood processing: *Pseudomonas*
- Contaminated bags(manufacture): *S marcescens*

2. Transmission of infectious agents

Clinical presentation:

- Fever and chills
- Shock
- Nausea, vomiting, abdominal pain, diarrhea
- Complications:
 - Acute Kidney injury
 - DIC
 - Death
- Differentials: Acute Hemolytic reaction (no Hbnuria), FNHR (less severe)



2. Transmission of infectious agents

Management:

- Stop the transfusion
- Broad spectrum antibiotics
- Supportive therapy

3. Other non immunologic and non infectious

1. *Transfusion associated Circulatory Overload (TACO):*

TRANSFUSION-ASSOCIATED CIRCULATORY OVERLOAD (TACO)⁷⁹

ETIOLOGY

- Circulatory overload results from:
 1. Impaired cardiac function, **AND/OR**
 2. Excessively rapid rate of transfusion

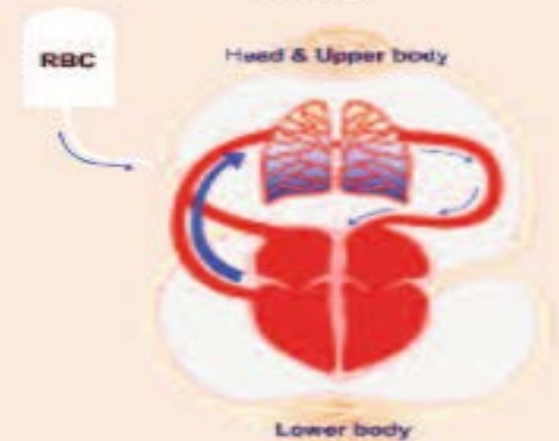
INCIDENCE

- Current estimate of the frequency of TACO is 1 in 700 transfusion recipients.
- In perioperative surgery setting in older orthopedic patients, incidence is much higher (1 in 100 patients).⁸⁰
- Patients over 60 years of age, infants, and patients with severe euvolemic anemia (hemoglobin < 50 g/L) are particularly susceptible.

CLINICAL PRESENTATION

- Clinical presentation includes: dyspnea, orthopnea, cyanosis, tachycardia, increased venous pressure, and hypertension.

Transfusion-associated circulatory overload (TACO)



3. Other non immunologic and non infectious

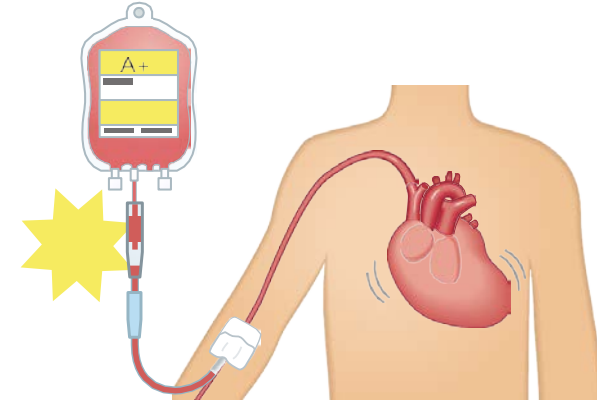
1. *Transfusion associated Circulatory Overload*

PREVENTION

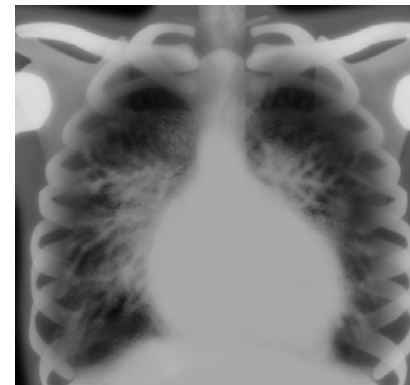
- Pre-transfusion assessment is important to identify patients at risk and management should be adjusted accordingly.
- Preventative measures include:
 - ◆ Avoid transfusing more than one unit at a time
 - ◆ Transfuse over longer periods (maximum 4 hours)
 - ◆ Pre-emptive diuretics
 - ◆ Components can be split into smaller aliquots to further reduce the speed of infusion without wasting product or increasing donor exposure

Transfusion-associated circulatory overload (TACO)

- Transfusion-associated circulatory overload (TACO) is one of the most severe complications of transfusion, which has been reported as early as 1940's. TACO has drawn much attention recently as a differential diagnosis of TRALI.
- TACO is basically a congestive heart failure with respiratory distress due to either volume overload or rapid infusion rate of blood products combined with underlying heart, renal or pulmonary disease.



TACO – causes
TACO is a congestive heart failure due to circulatory overload of blood products.



TACO – chest X-ray
Pulmonary congestion or edema on chest X-ray.

COMPLICATIONS OF MASSIVE TRANSFUSION

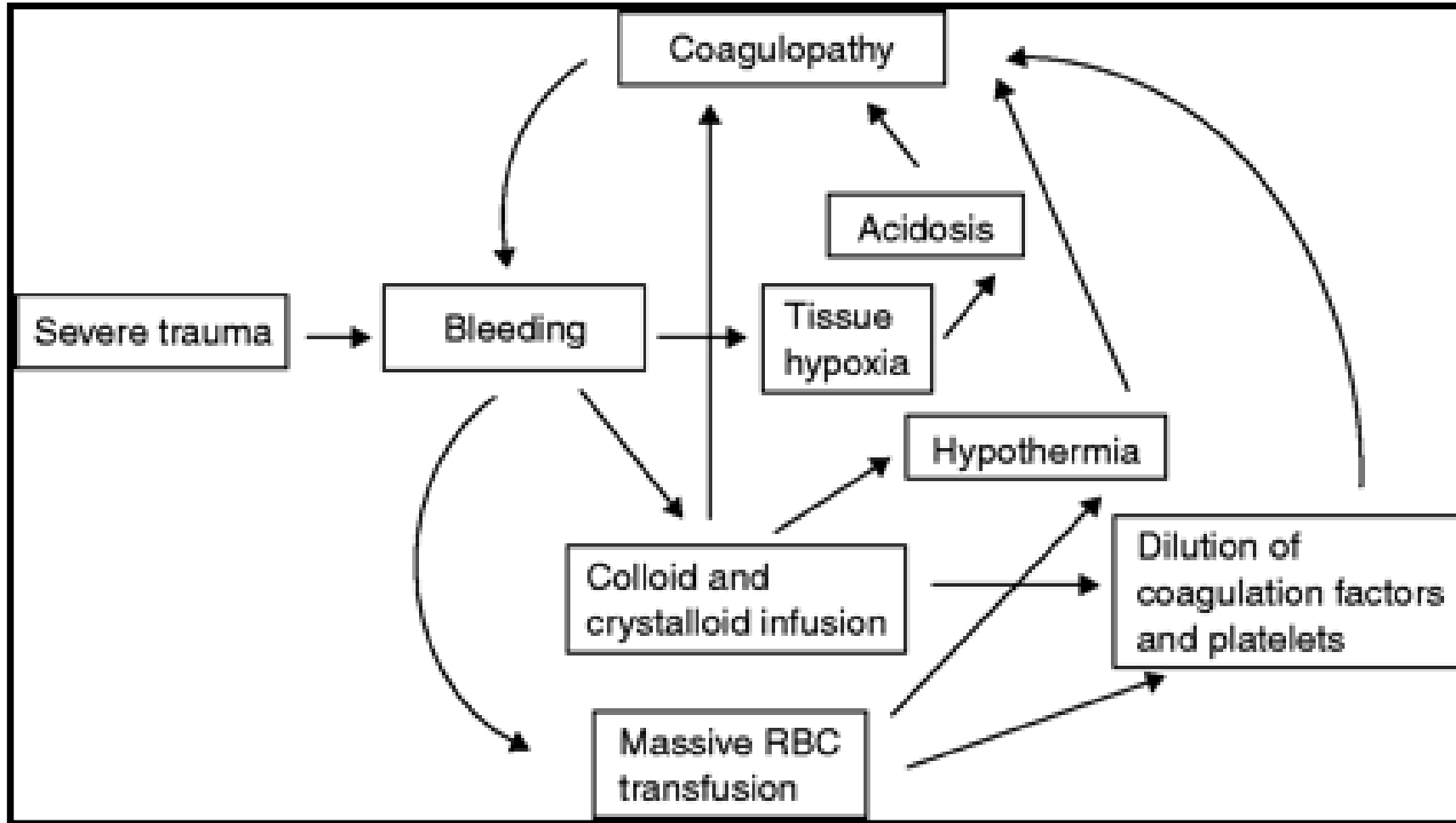
- **Immediate:**

- **Transfusion Associated Circulatory Overload:** due to rapid transfusion of blood or blood products (in elderly patients, small children and patients with compromised left ventricular function)
- **Interstitial oedema** due to increased hydrostatic pressure which may lead to abdominal compartment syndrome.

Immediate complications (Cont'd):

- **Dilutional coagulopathy** (blood loss causes fluid shift from the interstitial to the intravascular compartment that leads to dilution of the coagulation factors)
- **Citrate toxicity** (each blood bag contains approximately 3 g citrate , hypoperfusion or hypothermia associated with massive blood loss can decrease the rate of its metabolism leading to citrate toxicity)
- **Hyperkalaemia** (if underlying renal function, severity of tissue injury and rate of transfusion)
- **Hypothermia** (infusion of cold fluids and blood and blood products)
- **Hypomagnesemia** (Citrate also binds to magnesium)
- **Acidosis** (After 2 weeks of storage, PRBCs have a pH below 7.0)

Coagulopathy in massive bleeding:






Late complications

- Respiratory failure
- **Transfusion related acute lung injury (TRALI):** The risk of TRALI increases with the number of allogenic blood and blood products transfused.
- Sepsis
- Thrombotic complications.



Laboratory Investigation

- clerical verification
 - direct antiglobulin test on pre and post transfusion reaction blood specimen
 - visual inspection of pre and post transfusion reaction serum/plasma for hemolysis
 - ABO/Rh on pre and post transfusion reaction blood specimen
- 



```
graph TD; A[Transfusion reaction] --> B[Lab investigation]; B --> C[Preliminary test]; C --> D[Clerical check]; C --> E[visual check]; C --> F[serology];
```

Transfusion reaction

Lab investigation

Preliminary test

Clerical check

visual check

serology

CLERICAL CHECK:

- To identify the possibilities of ABO blood compatibility.
- Compare the component bag, label, paper work with patient sample and look for errors.
- If an error is found, the physician must be notified.
- Most common errors:
 - Misidentifications of patient when pre transfusion sample drawn.
 - Mix up of sample in the lab.
 - Not enough incubation time.

VISUAL CHECK:

- Plasma or serum reaction and compare with pre-transfusion.
- This step is done to examine the presence.
- This destruction of red cells and releasing haemoglobin will resulting a pink to red.
- The pink colour or red colour serum indicates into haemolysis.
- Thus the ABO testing must be repeated of post transfusion specimen.
- An urine examination of a post reaction helps in diagnosis of acute haemolysis.
- The free haemoglobin in the urine indicates the intravascular.

SEROLOGY CHECK:

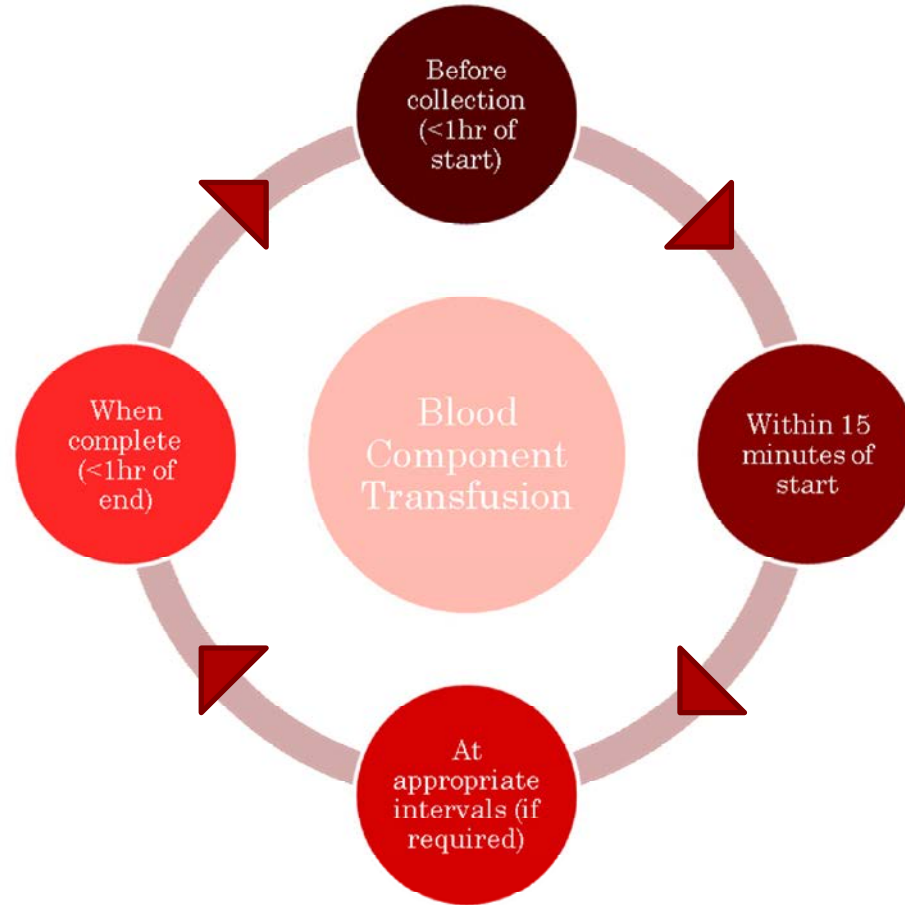
- On post transfusion sample redo the ABO test and perform the direct antiglobulin test (DAT).
- The sample post transfusion must be preserved in a EDTA preservation.
- If the DAT is positive on the post transfusion sample then one should be performed on the pre transfusion sample.
- If the result for the pre transfusion DAT is negative but the result for post transfusion is positive.

- If any of these three test above have positive and suspicious results, REDO test done before blood transfusion which are:
 - ABO &Rhesus grouping.
 - Antibody screening.
 - Repeat crossmatch.

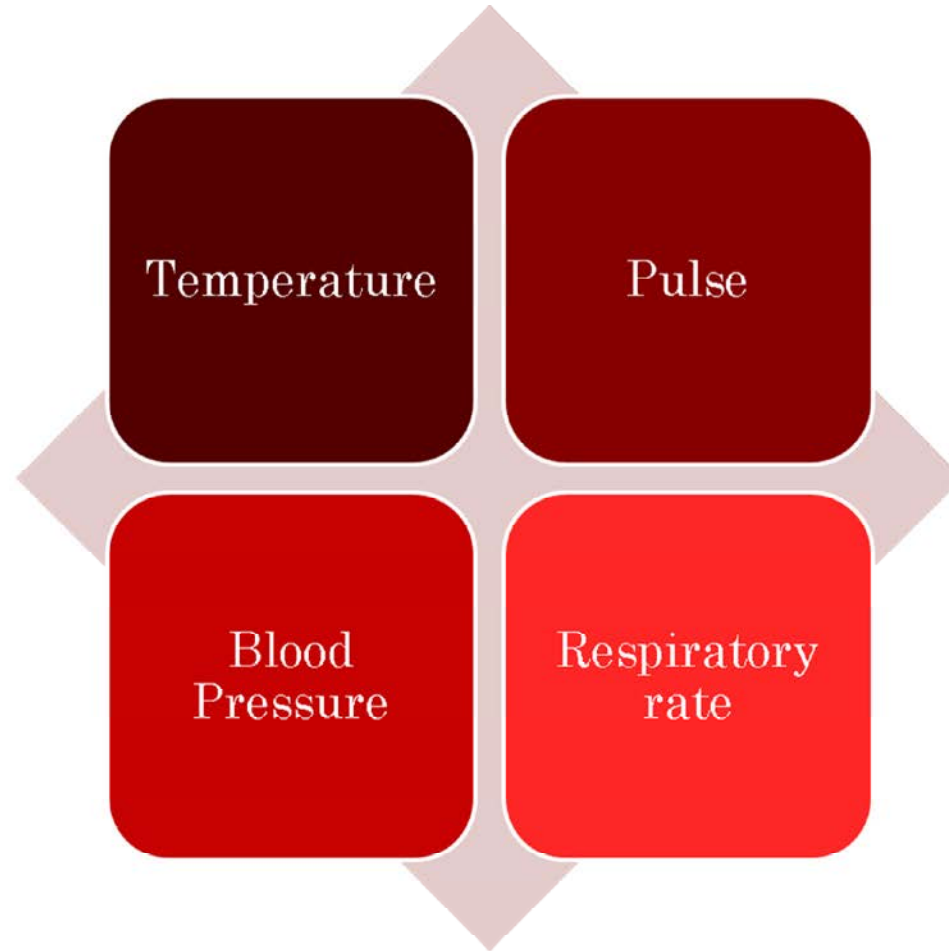
WHY DO WE TAKE OBSERVATIONS DURING A BLOOD COMPONENT TRANSFUSION?

- Administration problems
- Febrile reaction (<24 hrs)
- Allergic reaction (<24 hrs)
- Acute haemolytic reaction (<24 hrs)
- Bacterial contamination
- Transfusion-associated circulatory overload
- Transfusion-related acute lung injury
- Delayed haemolytic reaction (>24 hours)
- Post-transfusion purpura
- Transfusion-associated graft-versus-host disease

WHEN DO WE CARRY OUT OBSERVATIONS?



WHICH OBSERVATIONS DO WE DOCUMENT?



Exceptional healthcare, personally delivered

WHAT SHOULD HAPPEN IF YOUR PATIENT IS HAVING A SUSPECTED REACTION?

Stop

- Stop the transfusion if appropriate
- Maintain venous access
- Inform Nurse in charge / Doctor

Check

- Check and document patient observations
- Check correct unit given to patient

Test

- Take blood samples to identify type of reaction
- Return blood unit(s) to transfusion for further testing and microbiology



3.
in

ON BED TRANSFUSION REPORT				
Transfusing facility:	Service:	Patient #:	Age:	Sex:
Transfusuion Indication:	If RBCs: Hb: Hte:	If Platelets: PLT count:	If Plasma: PT: PTT: INR:	Pulse: T°: RR: BP:
Blood Component Donation ID:		Volume:	Expiry date:	
1. Is there adverse events during transfusion?: <input type="checkbox"/> No <input type="checkbox"/> Yes, Check all that apply				
<input type="checkbox"/> Urticaria (rash) <input type="checkbox"/> Pruritus (itching) <input type="checkbox"/> Headache <input type="checkbox"/> Fever (Oral T 38°C AND 1°C rise above baseline temp) <input type="checkbox"/> Chills (sensation of cold) <input type="checkbox"/> Rigors (involuntary shaking)	<input type="checkbox"/> Flushing <input type="checkbox"/> Skin rash other than urticaria <input type="checkbox"/> Restlessness/anxiety <input type="checkbox"/> Nausea/vomiting <input type="checkbox"/> Joint/muscle pain <input type="checkbox"/> Back pain <input type="checkbox"/> Chest pain	<input type="checkbox"/> Heat/pain at IV site <input type="checkbox"/> Dizziness <input type="checkbox"/> Jaundice <input type="checkbox"/> Red or brown urine <input type="checkbox"/> Oliguria	<input type="checkbox"/> Diffuse hemorrhage <input type="checkbox"/> Facial or tongue swelling <input type="checkbox"/> Dyspnea (shortness of breath) <input type="checkbox"/> Tachycardia (HR rise > 40bpm) <input type="checkbox"/> Hypertension <input type="checkbox"/> Hypertension (SBP drop > 30mmHg) <input type="checkbox"/> Shock <input type="checkbox"/> Other:.....	
If adverse events: Corrective action:				
2. Adverse events relationship to transfusion:				
<input type="checkbox"/> Definite	<input type="checkbox"/> Probable	<input type="checkbox"/> Doubtful	<input type="checkbox"/> Ruled out	<input type="checkbox"/> Not determined
3. Transfusion outcome:				
<input type="checkbox"/> Recovery	<input type="checkbox"/> Minor Sequelae	<input type="checkbox"/> Long term sequelae	<input type="checkbox"/> Death	
Notes:				
a) Bring this form to hospital laboratory, which in turn, send it to NCBT				
b) If any transfusion reaction, fill the form FRM_QMS_CPR_26_Transfusion Report Form and send it to NCBT as per the procedure QMS_CPR_26_Management of transfusion reactions				
Nurse reporting: Names: Date:		Signature:	Patient Physician: Names: Date:	
			Signature:	

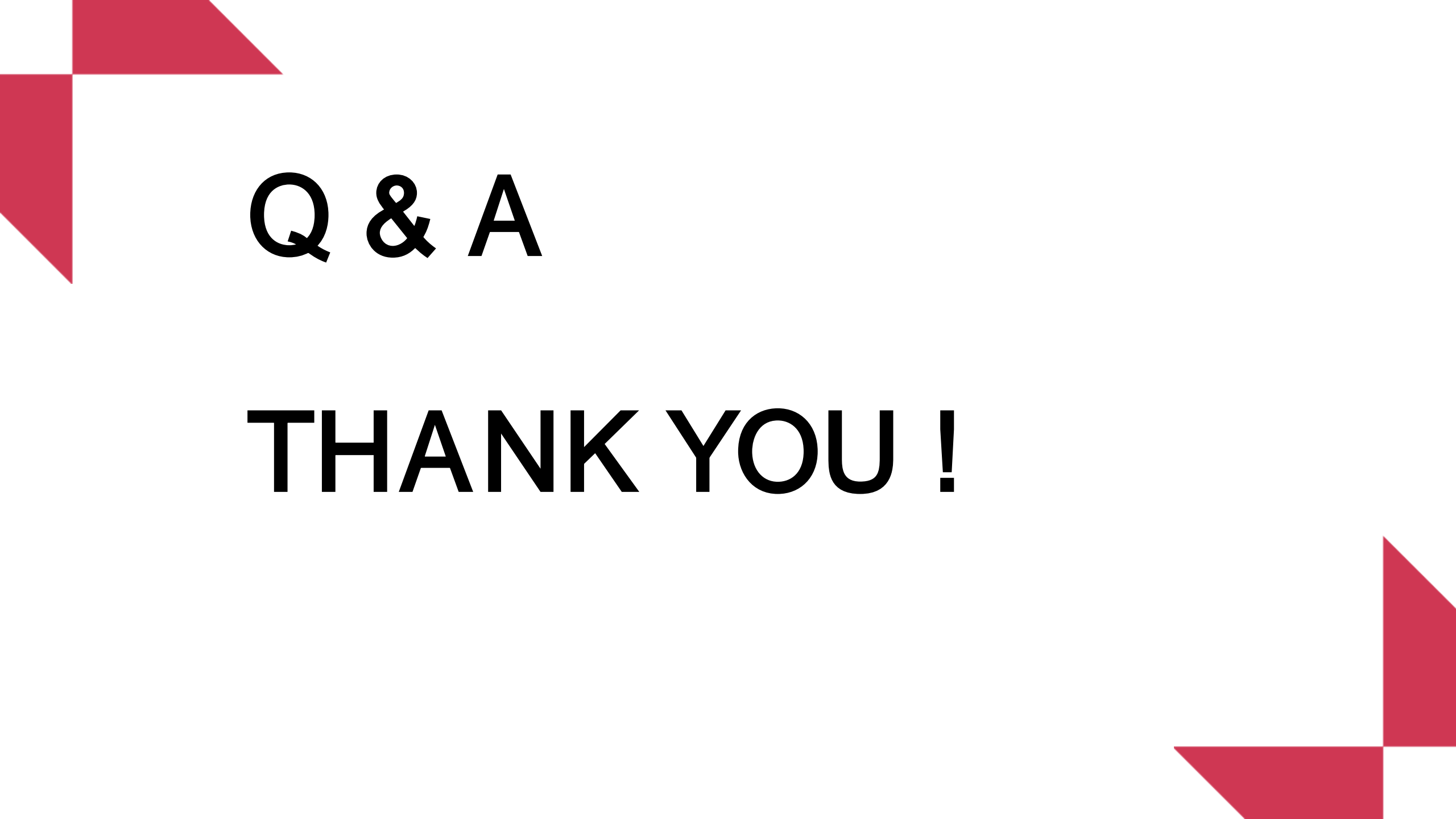
QUESTION 1

- A 25-year-old man is receiving blood after a road traffic accident. Vital signs are heart rate 72 bpm, blood pressure 122/75 mmHg, respiratory rate 16 breaths/min, and temperature 98.6F (37 °C). During the transfusion, he develops a fever and flank pain. The transfusion is immediately stopped. What is the next step in management?

- A. Insert a Foley catheter
- B. Fluid restriction
- C. O.1N HCL solution
- D. Isotonic fluids and furosemide

QUESTION 2

- An adult male admitted to the inpatient hematology unit repeatedly develops a fever following blood transfusions with leukoreduced red blood cells (RBCs). What is the most appropriate measure to prevent the recurrence of this reaction?
 - A. Administer freshly frozen RBCs.
 - B. Release 41-day-old RBC units collected in additive solution.
 - C. Use irradiated blood.
 - D. Wash red cells prior to transfusion

The image features a white background with two red geometric shapes. One is a square with a triangle cut out of its top-right corner, located in the top-left corner. The other is a square with a triangle cut out of its bottom-left corner, located in the bottom-right corner. The text 'Q & A' is centered in the upper half of the page.

Q & A

THANK YOU !