Transfusion reactions and complications

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https://youtu.be/UrSGzkGb3jA

Classification options

- Acute (within 24 h) or delayed (beyond 24 h)
- Immune or non-immune (antibodies are involved in the reaction?)
- Infectious or non-infectious

Acute immune transfusion reactions

- Acute hemolytic transfusion reaction – AHTR (recipient antibody)
- Febrile non-hemolytic transfusion reaction – FNHTR (recipient antibody+donor cytokine)
- Allergic transfusion reactions– ATR, anaphylaxis (recipient antibody)
- Transfusion related acute lung injury – TRALI (donor antibody)

Acute non-immune transfusion reactions

- Hemolysis due to physical/chemical effects
- Transmission of infectious agent (bacteria, endotoxin) -> Transfusion associated sepsis (TAS)
- Transfusion associated circulatory overload – TACO
- Metabolic changes: hypocalcaemia, hyperkalaemia, citrate intoxication
- Hypothermia
- Coagulopathy

Delayed immune transfusion reactions

- Delayed hemolytic transfusion reaction – DHTR (recipient antibody)
- Transfusion associated graft versus host disease – TA-GVHD (donor cells)
- Post-transfusion purpura – PTP (recipient antibody)
- Immunomodulation

Delayed non-immune transfusion reactions

- Transfusion hemosiderosis (iron overload)
- Transmission of infectious agents (eg. HBV, HCV, HIV)

Positive patient identification

- No identification band, no blood transfusion.
- Whenever possible, the patient should be asked to confirm their identity.
- Positive identification of the patient must occur before blood sampling and transfusion of blood and blood products.

http://www.optimalblooduse.eu/content/4-adverse-events

To do-s under transfusion

- Biological test: always necessary, 25 ml rapid infusion than slower, observation for 15 min (infant: 1ml, child 3-5 ml)
- Monitor the transfused patient
  - Before starting the transfusion
  - 15 minutes after starting the transfusion
  - At least every hour during transfusion
  - Observe patient’s condition and vital signs (T, HR,BP, Sat, respiratory rate)
  - Recognise and respond appropriately to adverse event
  - Record outcome of transfusion
  - Observation of late reactions (2 hrs)
- If there is a change in the patient's condition or in the parameters, immediately call the doctor

http://www.optimalblooduse.eu/content/1-synopsis

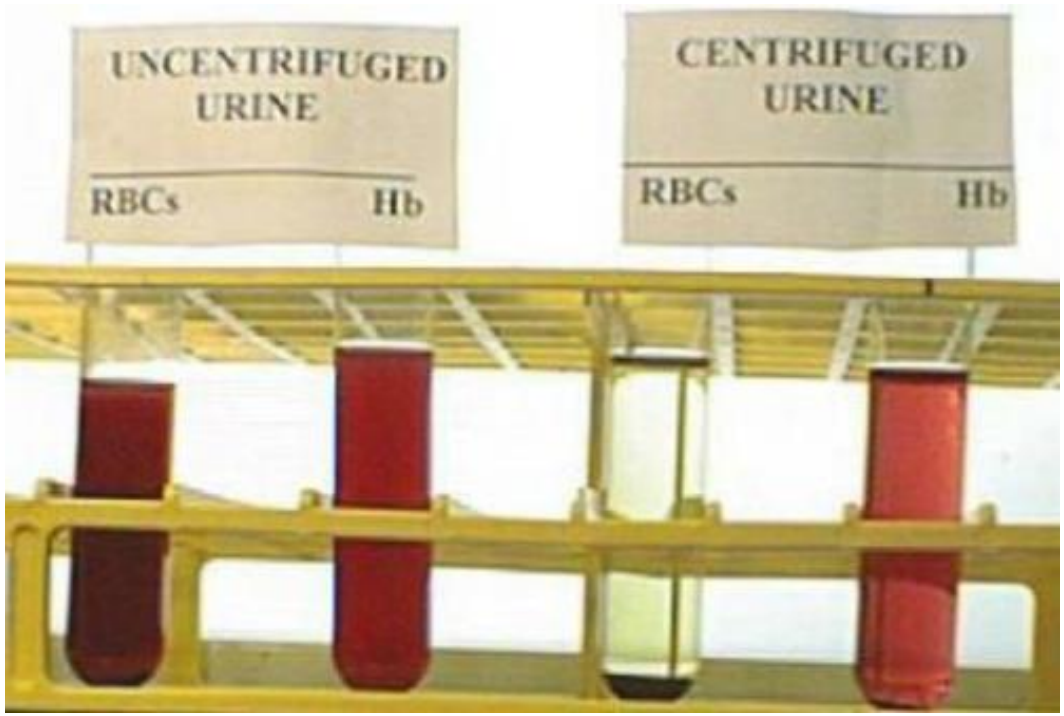
Acute hemolytic transfusion reaction – AHTR

- Life threatening reaction by acute intravascular hemolysis of transfused red blood cells (RBCs)
- Causes:
  - ABO-incompatible RBCs react with the recipient's anti-A/anti-B antibodies (major incompatibility)
  - Donor plasma with allo-antibodies against RBCs (minor incompatibility)
- Most commonly cause: human error
- Incidence: 1:38000-1:70000 transfusions, mortality: 1:630000-1800000 transfusions
- anti-ABO antibodies (predominantly IgM AB): intravascular hemolysis
- non-ABO antibodies (predominantly IgG AB): extravascular hemolysis

Separated normal versus hemolytic plasma

https://regi.tankonyvtar.hu/hu/tartalom/tamop412A/2011_0079_szarka_klinikai_kemia/ch01.html

Separated hematuria versus hemoglobinuria



https://quizlet.com/458023708/dsa-1b-anemia-of-blood-loss-and-hemolysis-flash-cards/

Clinical symptoms and signs of AHTR

- restless/agitated
- hypotension, tachycardia, dyspnea
- chest pain
- renal failure (oliguria, anuria)
- fever, chills, (rigors)
- skin flushing, anxiety, headache
- vomiting, nausea
- burning pain along transfusion site
- severe low back pain
- hemoglobinemia, hemoglobinuria
- uncontrollable bleeding (DIC)
- in patients under general anesthesia: hypotension, dark urine, uncontrollable bleeding

What should we do?

- Check again the patient's identity
- Check again the blood group of transfused blood and recipient (patient exchange may be at risk)
- Inspect the post-transfusion plasma and urine sample (hemolysis?)

What should we do?

- Take blood samples to the serology laboratory (repeat ABO/RhD typing, antibody screening, DAT, crossmatch on both pre- and posttransfusion samples) and to the clinical laboratory (serum: hemoglobin, haptoglobin, indirect bilirubin, lactate dehydrogenase (LDH), blood urine nitrogene (BUN), creatinine, fibrinogen, fibrin degradation products (FDP), urine: urobilinogen, hemoglobin)
- Inoculation due to the exclusion of sepsis
- Inform the responsible person for transfusion and competent transfusion department
- Send to the transfusion department: both pre- and posttransfusion samples, residue of blood (bag with assembly too), report with an exact description

Management of acute hemolytic reactions

- Discontinue the transfusion, keep open iv. line with infusion
- Hypotension: agressive fluid resustitation, vasopressors if indicated (for example dopamine)
- Prevent of acute tubular necrosis: diuretics (furosemid) and mannitol , dopamine: keep the renal output over 0,5 ml/kg/hour, alkalinization of the urine (Hb isn’t precipitate, easier empty)
- Hemodialysis may be necessary in the absence of diuretic response to fluid therapy

Management of acute haemolytic reactions

- Hypoxia: oxygen supplementation
- Treatment of metabolic acidosis
- Treatment of DIC is difficult. In case of bleeding: FFP, platelet transfusion
- In early phase: exchange transfusion?
- Further transfusions should be delayed until full serologic investigation is completed

Prevention of AHTR

- Prevention of of blood sample exchange
- Correct identification of the patient data.
- At the bedside after patient identification: labelling the blood sample
- Performing compatibility (pre-transfusion testing) at the bedside: both of patient blood and the issued blood unit
- Anew patient identification immediately prior to transfusion

Febrile non-hemolytic transfusion reaction (FNHTR)

- One of the most common complication
- Incidence:
  - All transfusion: 0,5-1 %
  - Non leuko-reduced platelet transfusions: 20-30%
  - Apheresis platelets: 5%
- Increase in body temperature of 1°C or more (body temperature >38°C) that occurs during or within several hours (2-8 hours) of transfusion and there is no other reason

Patomechanism of FNHTR

- 1. immunological cause: recipient antibodies (anti-HLA, anti-HNA allo-AB) bind to transfused leukocytes → monocyte activation → release of pyrogenic cytokines (IL-1, IL-6, TNF) → increase prostaglandin E2 production in hypothalamus → fever
- 2. non-immunogical cause: accumulation of pyrogenic cytokines and chemokines released from WBCs during storage – no antibodies in the reaction

Signs and symptomps of FNHTR

- chills and fever
- dyspnoea
- hypotension
- hypertension
- rigors
- nausea
- headache

Therapy of FNHTR

- Treatment: antipyretics (e.g. paracetamol, NSAID), corticosteroids, meperidine for severe rigors
- Prophylaxis: pretransfusion antipyretics
- Prevention: prestorage leukoreduction,

  remove additional leucocytes to a level < 5 × 10^6 per unit

Allergic transfusion reactions (ATR), anaphylaxis

- ATR can be mild, severe or life-threatening
- Incidence of ATR: one of the most common complication , 1-3% of plasma rich products
- Mechanism: immediate type I hypersensitivity reaction mediated by recipient IgE antibodies.
  - allergen-IgE complexes bind to recipient mast cells and basophil granulocytes → histamine release
  - allergen and antigen (plasma protein, drugs) may be present in the transfused blood product
- Signs and symptoms: mild allergic reaction, flushing, urticaria, itching (pruritus), angiooedema, wide range of cutaneous eruptions
- Treatment: antihistamines, prophylaxis as well
- Further transfusions: give washed RBC and platelet transfusion (especially in the case of anaphylaxis)

Anaphylaxis

- Life-threatening form: rare, RBC: 1:20000-1:50000, thrombocyta: 1:1600
- Predispisition: IgA deficiency (anti-IgA AB in the recipient's plasma, IgA in the transfused preparation)
- A few millilitres of blood cause
- Sign and symptoms: cough, dyspnoea, substernal pain, laryngeal oedema,circulatory collapse, bronchospasm, nausea, abdominal pain, shock
- Treatment: stop the transfusion, oxygen, adrenaline, infusion
- Prevention: give slow washed RBC and platelet transfusion, the person with IgA deficiency give IgA free preparation

Transfusion-related acute lung injury (TRALI)

- Incidence: 1:432 platelet transusion, 1:557000 RBC transfusion
- Mortality: 1:1,000,000 RBC
- ‚Classic' mechanism - 70-80%: anti-HNA or anti-HLA antibodies in donor plasma react with recipient neutrophils → accumulation and activation → neutrophil aggregates induce endothelial damage → vascular leakage → edema in the lungs
- ‚Alternative' mechanism (no antibodies) - 20-30%: Two-hit model: "first event": predisposing clinical condition (trauma, surgery, severe infection, massive transfusion)→ cytokine release → accumulation and priming of neutrophils "second event": transfusion of stored blood components containing biologically active lipids → neutrophil activation→ degranulation → endothelial damage → vascular leakage → edema in the lungs

Immunological complications of transfusions: hemolytic and non-hemolytic
Basics of transfusion medicine, 2019/2020. Tordai Attila

Symptoms and treatment of TRALI

- Symptoms: fever, chills, non-productive cough, dyspnea, cyanosis, hypo- or hypertension
  - within 1-2 hour (max.6 hrs) after transfusion
- Treatment: oxygen supplementation, respiratory support, mechanical ventillatory assistance, vasopressors

Hemolysis due to physical/chemical effects

- Acute non-immune transfusion reaction
- Causes:
  - Heat shock: frozen or overheated RBC
  - Mechanical damage (e.g. high pressure)
  - Inadequated manufacturing technique, incorrect storage, transport
  - Expired product
  - Bacterial contamination
  - Addition of incompatible of drugs, chemicals, infusions during transfusion
  - RBC damage by extracorporal devices (eg. pheresis, circulation/ventillation support (ECMO))

Signs and treatment of hemolysis due to physical/chemical effects

- Signs and symptoms: hemoglobinemia, hemoglobinuria, acute kidney injury, DIC
- Treatment: infusion, diuretics, alkalization of the urine (Hb isn’t precipitate, easier empty)

Hemolysis due to physical/chemical effects

- Laboratory signs of hemolysis (renal function, SeBi, LDH, haptoglobin, hemoglobinuria)
- Potassium level can be increased
- Direct Coombs is negative
- No irregular antibodies on serological evaluation
- Prevention: professional production, storage, transport of blood product, macroscopic inspection of blood product before transfusion

Sepsis

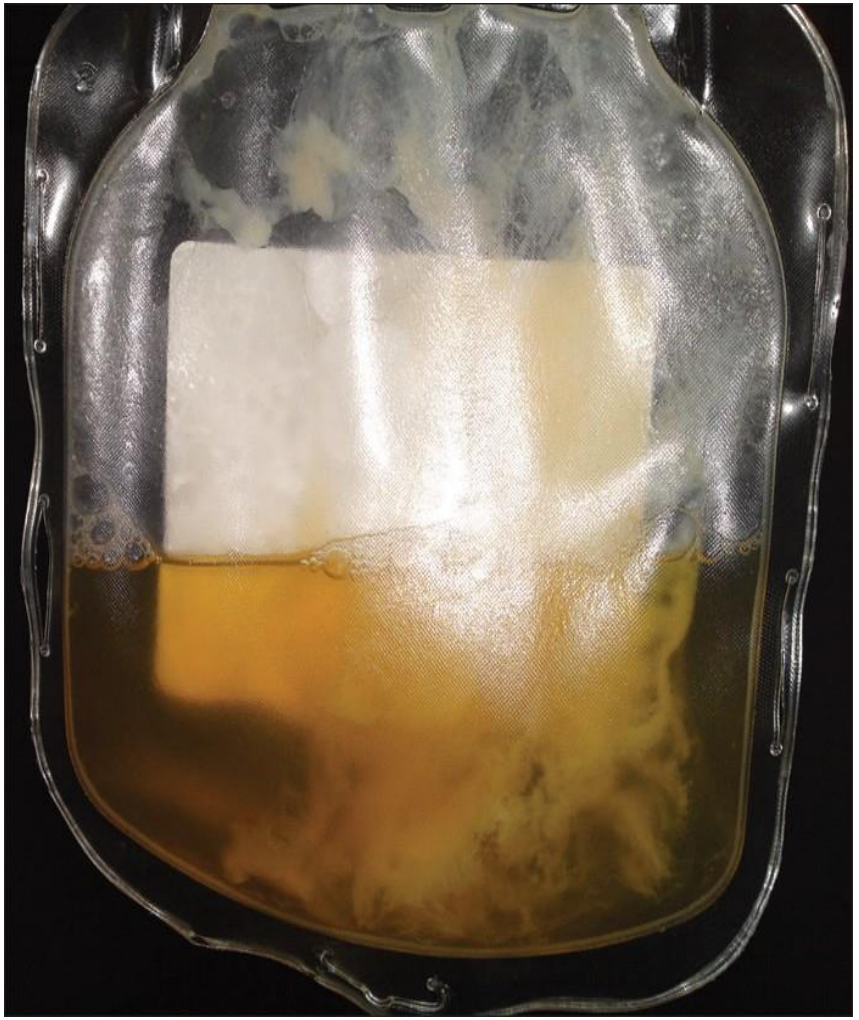
- Severe, immediate non-immune reaction during or just after the transfusion
- 10 % of transfusion related death
- In the blood product can be Gram-positive or/and negative bacterias or endotoxins
  - Donor (strict evaluation before donation)
  - Lack of asepsis during harvesting, processing, storage
- Temperature-fast bacterias, particularly in platelet products!

Signs, treatment and prevention of sepsis

- Signs: fever, hypotension, tachycardia, shivering, chills, vomiting, oliguria, septic shock, bleeding because of DIC
- Treatment:
  - immediately stop the transfusion
  - cultivation from the patient and the bags
  - immediately give broad spectrum antibiotic
  - vasopressors, infusion, treat the DIC
- Prevention:
  - appropriate donor selection
  - skin disinfection at the venipuncture site
  - diversion of the initial blood flow (the first 10-40 ml blood) into a diversion bag
  - compliance asepsis during harvesting, processing, storage
  - regular bacterial test of platelet concentrates
  - before transfusion check the product (hemolysis, fibrinous coagulation, turbidity, air bubbles)

Clot

Clot in RBC unit
https://professionaleducation.blood.ca/sites/msi/files/VAG_en.pdf



Large fibrinous coagulum in a platelet concentrate
https://www.ajts.org/viewimage.asp?img=AsianJTransfusSci_2012_6_2_139_98912_f1.jpg

Transfusion associated circulatory overload – TACO

- It is presents with acute or worsening pulmonary oedema within 6 hrs of transfusion
- Non-immunilogical complication
- Significant cause of death
- Incidence: 1:700-1:3000
- Cause:
  - give a large amount of transfusion at a time
  - too rapid infusion of blood products
- 1-2 units blood products may be enough
- Vulnerable patients: too young and elderly patients, patients with cardiac and/or renal diseases, pregnant woman, patients with severe anemia

Signs, treatment, prevention of TACO

- Signs: respiratory distress, tachypnoea, hypoxia, tachycardia, raised blood pressure, engorgement of neck veins, evidence of positive fluid balance
- Treatment:
  - stop the transfusion
  - give oxygen
  - diuretic therapy with careful monitoring
  - circulatory and respiratory support
- Prevention:
  - Observation, monitoring: HR, BP, CVP, SatO2
  - Slow rate
  - Patient with chronic anemia: max.2 units RBC concentration/day
- Differential diagnosis: TRALI

Hypothermia

- RBC concentrate is stored at +4-6°C
- Administration of one unit reduces body temperature by 0,25 °C
- Massive transfusion: rapid transfusion of large volumes (3000 ml citrated blood at 50 ml/min or more)
- Signs: hypotension, coagulopathy because of thrombocyte dysfunction and clotting factor interaction, bradycardia, arrhythmia, cardiac arrest

Prevent of hypothermia

- Warm the blood product before the transfusion to 20-37 °C
- Methods of warming blood:
  - Room temperature – passively
  - Disposable bedside electronic heat exchanger (small flow due to long tube)
- Do not use alternative methods (destruction of RBC and proteins)
- Monitoring of the patient body temperature, heat the hypothermic patient

Citrate toxicity

- Citrate is used for anticoagulation
- Citrate binds to ionized calcium $\longrightarrow$ $\downarrow$ ionized calcium $\longrightarrow$ hypocalcaemia
- Predisposing factors: massive transfusion, impaired liver function, exchange transfusion in newborn infants, large amount of FFP
- Signs: skeletal muscle spasm, tetania, paresthesia, arrhythmia
- Treatment: - give Ca (calcium-chloride or calcium-gluconate iv.)
- Prevention:
  - Monitoring of plasma Ca level
  - 10 ml 10% calcium-gluconate for every liter of citrated blood

Potassium toxicity

- During storage extracellular potassium is increase because of disintegration of RBC (from an initial level of 4 mmol/l to 30 mmol/l after 35 days)
- Irradiation also increase the potassium level
- Signs: arrhythmia (>7 mmol/l), carrdiac arrest (>10 mmol/l)
- Treatment:
  - give calcium-gluconate iv.
  - give insulin, β2-agonist (stimulates entry K from extracellular space to the cell $\longrightarrow$ decrease K level)
  - resonium (ion exchange resin) per os
  - give diureticum (furosemide)
  - dialysis (>7 mmol/l)

Prevent of potassium toxicity

- Electrolyte concentration and continuous ECG monitoring (especially incase of massive transfusion, kidney disease)

- Fresh (<1 week) products for:
  - Massive transfusion
  - Blood exchange in newborns
  - Premature infants

Air embolism

- Fatality rate: 1:38000
- Failing to expel air from the transfusion tubing
- Deaeration of transfusion set is obligatory

Microaggregates

- Cause: fibrin (from plts), leukocytes and platelets up to 200 µm
- The formation of microaggregates begin within 24 h
- Removal of buffy coat (PLTs and WBCs) is important in the prevention
- Tube contains filter standard pore size: 170 µm
- Massive transfusion – pulmonary microembolism, hypoxia
- WBC-depleted RBC product may decrease the risk
- Using fine microaggregate filters (40 µm)

Dilutional coagulopathy

- Severe bleeding + massive RBC transfusion + large volumes of crystalloids
- Dilution of coagulation factors and thrombocytes
- Diffuse bleeding
- Diagnosis: conventional laboratory parameters: INR, APTT, fibrinogen; point of care tests (POCT)
- Management:
  - Avoidance of hypothermia
  - Guided by the actually measured laboratory parameters: transfusion of RBC cc., PLT cc. and FFP and/or factor concentrates (prothrombin complex concentrate (PCC), fibrinogen, FVIIa)

Hypotensive reactions

- Signs: hypotension, vasodilatation, nausea, sweating and chest pain
- Etiology: inherited or acquired (eg. patients medicated with ACE inhibitors) abnormalities of bradykinin metabolism
- Pathophysiology: contact activation of FXII during WBC extraction→bradykinin↑→ vasodilation →hypotension

Transfusion hemosiderosis

- Iron overload occurs in patiens with transfusion dependent anaemia (aplastic anaemia, acquired refractory anaemia, myelodysplastic syndrome,myelofibrosis, thalassemia major, sickle cell anaemia)
- Repeated transfusions without bleeding $\longrightarrow$progressive increase of iron $\longrightarrow$toxic accumulation in many organ: in the heart (cardiomyopathia), liver (cirrhosis), endocrine organs (diabetes mellitus, sexual disturbances), skin (brownish discoloration)
- Main cause of death without control of iron overload; cardiac complication (restrictive CMP)
- Treatment: chelators: Desferrioxiamin (DFO, Desferal®) , Deferasirox (Exjade®)

Delayed hemolytic transfusion reactions (DHTR)

- Incidence: 1:5400
- DHTR is accelerated destruction of transfused red cells after an interval, during the recipient ready an immune response to an antigen carried by the transfused cells.
- The amount of antibody in the recipient's serum may be too low to effect rapid red cell destruction or even to be detected by sensitive compatibility tests.
- Common mechanism: re-exposure by an RBC antigen against which earlier sensitization occured but current antibody screening test are negative: "anamnestic response"
- Less frequently: the recipient is exposed to a foreign antigen for the first time and forms an antibody meanwhile the antigen positive RBCs are still in the circulation: "primary response"
- Antibody specificities: Kidd, RhD, Kell, Duffy

Signs, treatment, prevention of DHTR

- Signs and symptoms: fever, progressive anaemia, sometimes jaundice and/or haemoglobinuria, rare renal failure
- Laboratory investigation: repeat ABO/RhD, antibody screening (if positive: antibody identification), DAT
- Treatment: mostly not necessary , but if necessary same as AHTR: intravenous fluids, vascular support, close monitoring
- Prevention:
  - use of more sensitive antibody screening technology
  - transfusions should be minimized, if necessary: phenotype-identical blood
  - the importance of documentation, availability of transfusion history: nationwide IT systems, patient's card

Posttransfusion purpura (PTP)

- Uncommon syndrome with severe, isolated thrombocytopenia due to predominantly to anti-HPA antibodies
- Onset: 2 days to 2 weeks after RBC transfusion
- Incidence: 1:50000-1:200000, mortality: 5-10%
- Recipient's anti-platelet antibodies damage transfused antigen positive and recipient's own antigen-negative platelets.
- Patients have been immunized by previous transfusion or pregnancies.
- Signs and symptoms: fever, bronchospasm, purpura, epistaxis, gastrointestinal bleeding, hematuria, intracranial hemorrhage
- Treatment: first choice high-dose Intravenous Immunoglobulin (IVIG), plasmapheresis, corticosteroids
- Platelet transfusions should be avoided in acute phase and patients should only be transfused with platelets in emergencies in combination with IVIG

Transfusion associated graft versus host disease (TA-GVHD)

- Incidence: <1:1,000,000 (rare), but mortality >90%
- Onset: 4-30 days after transfusion
- Cause: recipient immune system unable to destroy transfused, immunocompetent T-lymphocytes
- Mechanism: cellular immune response by the surviving immunocompetent T-lymphocytes versus host tissues
- Signs and symptoms: fever, maculopapular rash, nausea, vomiting, watery, bloody diarrhea (enterocolitis), lymphadenopathy, pancytopenia (bone marrow aplasia), jaundice, hepatitis

Diagnosis, therapy and prevention of TA-GVHD

- Diagnosis: detection of donor DNA in the skin (skin and bone marrow biopsy)
- Therapy: supportive, immunosuppression; no specific treatment
- Prevention: irradiation of blood product (prevent T-lymphocyte proliferation)

Sources

- Mollison's Blood Transfusion in Clinical Medicine 12th edition, 2014
- Vezendi Klára: Transzfúzió, 2019, 2th edition
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- Tordai Attila: Immunological complications of transfusions: hemolytic and non-hemolytic

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Thank you for your attention!