Cefotetan-induced hemolytic anemia and potentially life threatening reactions to transfused blood products

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December 9, 2016
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Agenda

• Case reports of Cefotetan-induced immune hemolytic anemia at SCMC
• Hemolytic transfusion reactions, immediate and delayed
• TRALI
• TACO
• TA-GVHD and indications for irradiated blood
• Interference of Daratumumab in antibody detection

Cefotetan-induced immune hemolytic anemia case reports

Case 1:
39 year old woman, laparoscopic removal pelvic/colonic endometriosis. Hx PCN allergy (rash)
2 g. Cefotetan given perioperatively.
Post-op Hct 34.1%, EBL 200ml.
9 days later: fatigue, jaundice, dark urine, H&H 5.9&15.7%, DAT positive, LDH high, haptoglobin low, Bili high. Autoimmune hemolysis suspected.

Case 2:
85 year old man, laparoscopic coelectomy for colon cancer. Allergy to Codeine, no others known.
2 g. Cefotetan given perioperatively.
H&H 10&30% post-op day 3, discharged on post-op day 5.
Returned 2 weeks later: Fatigue, H&H 4.1 & 14.3%, DAT positive, LDH 853, haptoglobin 3, Bili 4.3. Autoimmune hemolysis suspected.
Case 2:
Treated with steroids and transfused with 5 units RBCs over 2 days, stabilizing his condition. Anti-Cefotetan antibodies high titer >1:50,000, found in testing done at American Red Cross, Portland. Cephalosporins (and PCN) added to his known allergies in EMR

Drug-induced immune hemolytic anemia (DIIHA)

Drug-dependent mechanisms:
1. Drug binds to proteins on RBC membrane. Pt makes IgG antibody to the drug, binding to the coated RBCs, interacting with histiocytes, causing Fc-mediated extravascular RBC destruction. Detect this by testing the Pt’s serum, or an eluate from the RBCs, against drug coated RBCs (prepared in vitro).
2. Drug-dependent antibodies that primarily activate complement can cause acute severe intravascular hemolysis & sometimes DIC, renal failure and death. Can’t make in vitro drug-coated RBCs in this group of drugs. The antibodies are only detected by mixing the drug with the Pt’s serum (containing drug antibody) and RBCs.

Drug-induced immune hemolytic anemia

- Recognition: Important that the Pt does not get more of the drug causing the antibodies. Typical presentation with anemia, jaundice, dark urine, fatigue, possible fever 7-21 days after perioperative prophylactic Cefotetan, or other cephalosporin.
- Treatment: Stop, or refrain from giving more of the drug. Support with RBC transfusions as needed. Steroids can be used.
- Evaluate for immune hemolytic anemia, Direct Coombs test (DAT), send for anti-Cefotetan antibodies to confirm. R/O delayed hemolytic transfusion reaction if the Pt got blood.

Drug-induced immune hemolytic anemia

- 85 cases Cefotetan-induced HA reported by FDA from 1985-1997
- 18% fatalities
- 8% renal dysfunction
- 59% got Cefotetan for prophylaxis, and 50% were associated with surgery
- Only 18% had a history of previous Cefotetan
- Other Cephalosporins and penicillin should be avoided in the future for these Pts

Drug-induced immune hemolytic anemia

Most commonly associated drugs currently: cefotetan, ceftriaxone, and piperacillin.
Prevalence: Rare, estimated 1 in 1 million of the population.
Mechanisms of action:
1. Drug-dependent antibodies
2. Drug-independent antibodies
3. Non-immune protein adsorption

Drug-induced immune hemolytic anemia

Drug-independent mechanism:
1. Drug affects the immune system, causing production of RBC autoantibodies. Drug is not required to further cause hemolysis driven by these autoantibodies. Remission is associated with discontinuing the drug.

Non-immunologic adsorption of proteins onto RBCs:
1. RBCs exposed to the drug adsorb IgG, C3, albumin, etc. Macrophages can interact with these RBCs to destroy them.
Adverse reactions to transfusion

- Febrile non-hemolytic transfusion reaction
- Allergic reaction, rarely anaphylaxis
- Hypotensive reaction
- Acute hemolytic transfusion reaction
- Delayed hemolytic transfusion reaction
- Transfusion-related acute lung injury (TRALI)
- Transfusion-associated circulatory overload (TACO)
- Transfusion-associated dyspnea (TAD)
- Transfusion-associated sepsis (TAS)
- Transfusion-associated graft vs host disease (TA-GVHD)
- Post-Transfusion purpura

The 3 leading causes of transfusion-related deaths, based on data reported to US FDA

- TRALI
- TAS
- ABO HTR

Acute hemolytic transfusion reaction

**Immune mediated**: Positive DAT for anti-IgG or anti-C3 and positive elution test with alloantibody present on transfused RBCs.

e.g.: Pt has a pre-existing alloantibody corresponding to an antigen on transfused RBCs.

ABO incompatibility, other antibodies not detected before transfusion.

**Non-immune mediated**: Serologic testing is negative, and physical cause (e.g. thermal, osmotic, mechanical, chemical) is confirmed.

Acute hemolytic transfusion reaction

- Signs and symptoms: occurs within 24 hours of transfusion, may occur during the first 15 minutes. (Important to stay with patient in 1st 15 minutes)
- New onset of any of the following:

  Back/flank pain, Chills/rigors, DIC, Epistaxis, Fever, Hematuria, Hypotension, Oliguria/anuria, Pain and/or oozing at the IV site, Renal failure

  And, 2 or more of: Decreased fibrinogen, Decreased haptoglobin, Elevated bilirubin, Elevated LDH, Hemoglobinemia, Hemoglobinuria, Spherocytes on blood smear
### Acute Hemolytic Transfusion Reaction - Treatment

- **Stop the transfusion.**
- Keep Normal saline IV running
- Telemetry monitoring/Strict urine monitoring
- Return blood products/send post-transfusion blood samples for investigation
- Possible need for mechanical ventilation
- Possible need for dialysis
- Possibility of DIC
- **Do not restart** that unit

### Delayed hemolytic transfusion reaction

- Recipient develops antibodies to RBC antigens between 24 hours and 28 days after the transfusion.
- **And** positive elution test with alloantibody present on transfused RBCs,
- **Or** newly identified RBC alloantibody present in recipient serum,
- **And either** inadequate rise in post transfusion H&H, or rapid fall back to pretransfusion H&H,
- **Or** otherwise unexplained appearance of spherocytes

### Transfusion related acute lung injury (TRALI)

- **Abrupt onset** of hypoxemia and chest X-ray with bilateral infiltrates in the absence of circulatory overload.
- No evidence of acute lung injury prior to transfusion, and onset of acute lung injury **within 6 hours** of cessation of transfusion.
- Hypoxemia defined by **any of these** methods: ratio PaO2/FiO2 <or= 300 mgHg, O2 sat <90% on room air, or other clinical evidence. **And** Radiologic evidence of bilateral infiltrates. **And** no evidence of left atrial hypertension (no circulatory overload).

### TRALI

- Risk factors for ALI not related to transfusion: sepsis, pneumonia, aspiration of gastric contents, drug OD, burns, DIC, near drowning, fracture of long bones and massive transfusion.
- TRALI is defined as ALI developing within 6 hours of transfusion in the absence of these other risk factors. The new ALI must be mechanistically related to the transfusion in order to confirm TRALI.

### TRALI

- Symptoms are clinically identical to ALI not related to transfusion. Severe bilateral pulmonary infiltrates, severe hypoxemia, **fever**, tachycardia, cyanosis, and hypotension.
- With prompt and vigorous respiratory support about 80% of Pts with TRALI improve both clinically and physiologically within 48 to 96 hours.
- One of the leading causes of transfusion-related fatalities in the USA (38%) in FY 2011-2015.

### TRALI

- Increased awareness has led to increased reporting of TRALI cases.
- Evenly distributed Male vs Female.
- All age groups, including children and elderly.
- Underlying illness may increase risk, but healthy experimental subjects given plasma with HLA Class II antibody have developed it.
- Plasma containing HLA/HNA antibodies implicated, leading to deferral of donors with known HLA/HNA antibodies (exposed from previous pregnancy, transfusion or transplantation).
### TRALI
- **Differential Dx:**
- **Circulatory overload** (TACO or other fluids): Respiratory distress, tachycardia, hypertension.
- **Anaphylactic transfusion reaction:** Respiratory distress and cyanosis related to laryngeal edema and bronchospasm, not pulmonary edema. Urticarial eruption, hypotension occurring rapidly at onset of transfusion.
- **Bacterial contamination:** Fever, hypotension, and vascular collapse, usually 1-2 hours after contaminated transfused products (platelets, RBCs).
- R/O other causes of resp. distress & pulm.edema.

### TRALI Prevention
Prevention is focused on limiting exposure to donors who are most likely to precipitate TRALI:
- Donors implicated in TRALI permanently deferred from future donation.
- Multiparous donors screened for HLA or granulocyte antibodies, deferred if present.
- Minimize transfusion of high plasma-volume components (i.e. don't use FFP to reverse Warfarin).
- Minimize inappropriate transfusion of blood components.

### Transfusion Associated Circulatory Overload (TACO)
- New onset/exacerbation of 3 or more of the following within 6 hours of transfusion:
  - Acute respiratory distress
  - Elevated brain natriuretic peptide (BNP)
  - Elevated central venous pressure (CVP)
  - Evidence of left heart failure
  - Evidence of positive fluid balance
  - Radiologic evidence of pulmonary edema

### TACO
- Not always recognized as a “transfusion reaction”. Probably under-reported.
- Should be reported to the blood bank so we don’t miss TRALI or other reactions, and it can be tracked.
- TACO was the 2nd leading cause of transfusion-related fatality (24% of fatalities reported to US FDA from 2011-2015).
- Up to 21% of TACO cases are life-threatening, resulting in increased ICU and hospital stays.

### TACO
- Fluid overload resulting in cardiogenic pulmonary edema.
- Incidence 2-6%, recent studies.
- Risk factors: Recipient age <3 yrs or >60 yrs, CRF, CHF, critically ill adults, multiple units transfused, rapid rate of transfusion. Intraoperative TACO can occur, especially in vascular, transplant and thoracic surgeries. Non surgical Pts age 80 and above have 4X the risk than Pts younger than age 50 (7.4% vs 2.0% respectively).
**TACO Treatment**

- Distinguish this from TRALI.
- **Stop the transfusion, report to blood bank.**
- Provide O2, place Pt upright, monitor O2 sat.
- Consider CPAP or BiPAP, if not contraindicated.
- Get early critical care consult.
- Consider diuretics, if not contraindicated.
- Consider transfer to ICU, if mechanical ventilation needed in severe cases.

**TACO Prevention**

- Avoid unnecessary transfusion.
- Identify underlying risk factors.
- Diuretics before transfusion may or may not be helpful.
- Decrease transfusion volume and rate of infusion. Try one unit and assess before next.
- Avoid use of Plasma to reverse Warfarin; consider use of 4-factor PCC.
- Monitor during transfusion for early detection.

**Transfusion-associated Graft vs Host Disease**

- Introduction of immunocompetent lymphocytes into susceptible hosts. The allogenic lymphocytes engraft, proliferate and destroy host cells.
- Clinical syndrome occurs 2 days to 6 weeks after transfusion. Characteristic rash, diarrhea, fever, hepatomegaly, liver dysfunction, marrow aplasia, pancytopenia. And characteristic skin or GI biopsy findings.

**GVHD histology in colon biopsy**

![GVHD histology](image)

**Irradiated Blood Product Indications (to prevent GVHD)**

- Bone marrow transplant
- Congenital cellular immune deficiency
- Hodgkin's disease
- Treatment with purine analogs
- Aplastic anemia with immune suppression
- Directed donation from blood relatives
- HLA matched platelets

**Irradiated Blood Products Possible Indications (to prevent GVHD)**

- Leukemia
- B cell malignancy with treatment-induced severe lymphopenia
- Premature low birthweight newborns

Irradiated blood is used to prevent GVHD by inactivating lymphocytes in the unit. It does not reduce the risk of other transfusion reactions.
Daratumumab interference in cross matching

- Cancer treatment drug Daratumumab (Darzalex) third-line multiple myeloma treatment.
- Preliminary studies show some effect in B-cell leukemias and lymphomas. More future use.
- Interference with antibody screening in cross matching. **False positive antibody screen can mask underlying real antibodies (panreactivity).**
- Drug binds to CD-38 Ag present on RBCs.

Summary:

- Drug-associated immune hemolytic anemia cases have occurred after perioperative Cefotetan. Recognize and avoid more exposure to the drug.
- Life-threatening reactions to blood products include Hemolytic Reactions, TRALI, TACO, and GVHD.
- Monitor during transfusions for early detection, and report suspected reactions to the blood bank. Avoid unnecessary transfusions.
- Notify the blood bank when your Pt is taking Daratumumab for Myeloma; do prescreening for antibodies before starting therapy.

Resources for Transfusion Information

- **Mabel Adams, MT(ASCP)SBB**
  - Blood Bank Supervisor
  - St. Charles Medical Center Bend
  - 541-706-4928 (Office) | 541-706-6918 (Fax)
  - maadams@stcharleshealthcare.org

- **Jason Brazelton, M.D**
  - Central Oregon Pathology Consultants
  - 541-693-2664 (Office)

References

- Paxton,A. On guard against daratumumab interference, CAP Today 2016 vol.30(10),1&38-44

Daratumumab interference...

- Pre-treatment testing with antibody screen to identify pre-existing antibodies, possibly do genotyping.
- **Inform blood bank that the Pt is taking Daratumumab.**
- Consider an automatic EMR alert from pharmacy when Pt is taking this drug.
- Blood bank can use 0.2M dithiothreitol (DTT) to denature CD38 on the RBCs used for cross match.