CASE STUDIES IN CLINICAL APPLICATIONS OF THERAPEUTIC PLASMA EXCHANGE

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Objectives

- Explain the process of a therapeutic plasma exchange (TPE).
- List possible complications of TPE.
- List possible indications for TPE as defined by AABB.
- Explain benefits of TPE in antibody-mediated pathologies found in two cases.

What we will discuss today

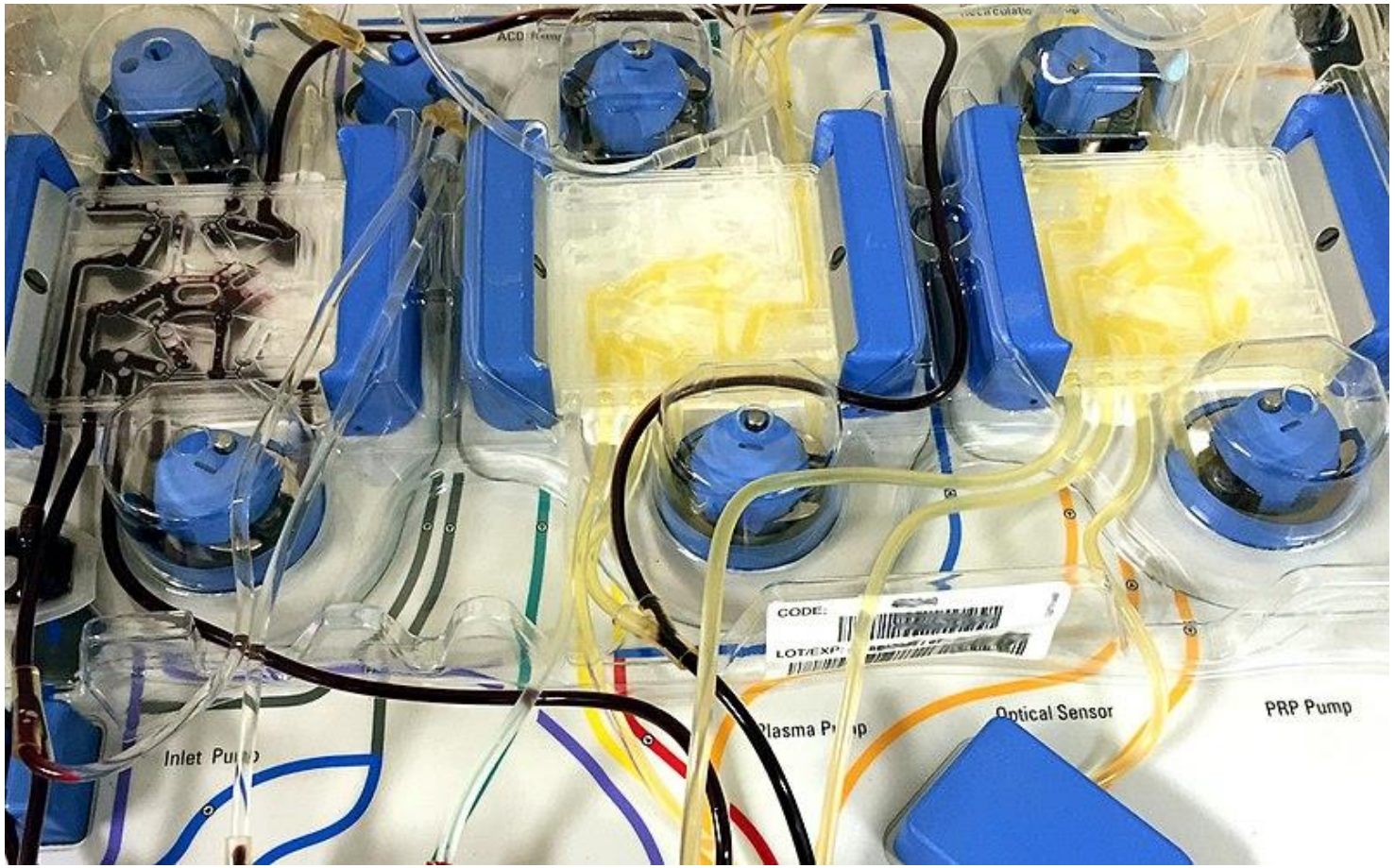
- Introduction and definition of Therapeutic Plasma Exchange (TPE)
- Applications of TPE, including AABB indications.
- Case 1: Stem Cell Transplantation
- Case 2: Autoimmune Hemolytic Anemia with monoclonal gammopathy.
- Questions, References, and Conclusion

What is a Therapeutic Plasma Exchange?

- Procedure (done by apheresis) to remove and retain the patient's plasma while returning cellular components to patient.
  - Usually replacing the plasma volume with a similar substance, either donor plasma or albumin, or a mix of both.
  - When albumin is used, it is usually blended with saline, unless patient becomes hypotensive.
- Prevents large loss of RBC volume while allowing for filtration of plasma.

- Why do we want to do this to a patient?

Apheresis machine



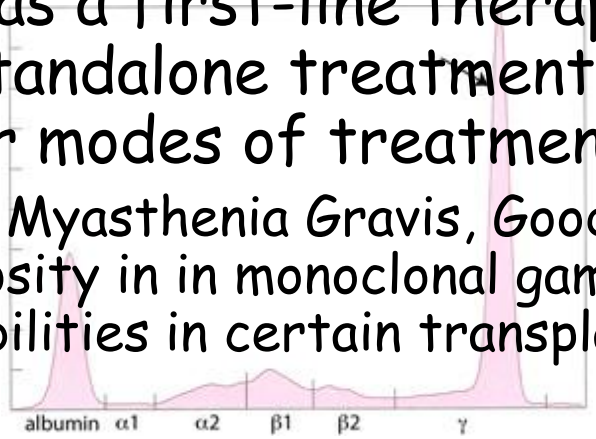
Source: National Institutes of Health

Uses of TPE

- Used first around 1952 to treat plasma hyperviscosity related to multiple myeloma (Bobati & Naik, 2017).
- Several uses and applications today.
  - AABB breaks these uses down into indications by four categories, explained later on the slide.
- Complications can include reduced coagulation factor availability and lowered fibrinogen levels, both of which may require transfusion management.

TPE Indications (per the AABB Technical Manual)

- **Category I**: "Disorders for which apheresis is accepted as a first-line therapy, either as a primary standalone treatment or in conjunction with other modes of treatment."
  - Examples: Myasthenia Gravis, Goodpasture syndrome, hyperviscosity in in monoclonal gammopathies, ABO incompatibilities in certain transplants, and more.



- **Category II**: "Disorders for which apheresis is accepted as a second-line therapy, either as a standalone treatment or in conjunction with other modes of treatment."
  - Examples: Major mismatch for stem cell transplantation, Antibody-mediated rejection of renal t lant, mushroom poisoning, and more.

TPE Indications (per the AABB Technical Manual), cont.

- **Category III:** "Disorders in which the optimal role of apheresis therapy is not established. Decision-making for patients should be individualized."
  - Examples: Autoantibody coagulation factor inhibitors, postpartum HELLP, Refractory immune thrombocytopenia, posttransfusion purpura., sepsis with multiorgan failure.

- **Category IV:** "Disorders in which published evidence demonstrates or suggests apheresis is ineffective or harmful. Institutional review board is desirable if apheresis treatment is undertaken in these circumstances.)
  - Examples: Lupus / SLE Nephritis, psoriasis, amyloidosis, antepartum HELLP.

Plasma exchanges at TUKHS

- Robust apheresis program for TPE, as well as WBC and RBC apheresis.
- Most at KU are done with albumin and saline, though some are done with undilute albumin (if patient becomes hypotensive).
- Less than 10% of cases are performed with donor plasma as the replacement.
- Increasing utilization
  - 2015: 655 TPE cases
  - 2016: 801
  - 2017: 915

Case study 1

- Patient history: Leukemia patient following up post bone marrow transplantation four months ago.
  - Recipient: O Pos
  - Donor: A Neg
- Chronically anemic. 23 units pRBCs administered since transplantation, with increasing frequency, presenting with a 5.7 g/dL Hemoglobin today.
  - WBC count normal, suggesting myeloid engraftment.

Anti-A	Anti-B	Anti-D	A1 Cells	B Cells
0	0	0	3+	4+

Where are our A Neg RBCs in the front type?

Case study 1: BMT, continuted.

- Major ABO Incompatibility between recipient and donor.
- Supported with O Neg RBCs, but anti-A1 still detectable in plasma, and no evidence of BMT donor being a subtype.
- Think: What would support the lack of complete conversion of blood type and the patient's chronic anemia?

- **Major ABO incompatibility** is defined as the presence of isoagglutinins in the recipient against a donor's A or B blood group antigens (Schwartz, et al., 2016)

Major ABO Incompatibility

- Serologically, we detected an antibody against the A antigen.
- This antibody has persisted even after the donor marrow has (mostly) engrafted.
- According to literature, persistent isoagglutinins against A or B antigens can delay RBC engraftment and destroy erythroid precursors, leading to pure RBC aplasia (Schwartz, et al., 2016)
  - Fits our patient, who has detectable anti-A in the backtype and is increasingly transfusion dependent.
- Isohemagglutinin titer performed:
  - Anti-A, 1:32

Case 1: Treated with therapeutic plasma exchange

	On Admission	After 2x Plasma Exchange	Most Recent Follow Up
Blood Type	O Neg*	O Neg*	A Neg
Isohemagglutinin Titer	1:32	1:4	Not done
Hemoglobin	5.7 g/dL	7.1 g/dL	12.2 g/dL

*- Resulted as "No Type Determined" due to incomplete transition to donor type

Case study 2

- Patient history: newly diagnosed lymphoma, Type 2 Diabetes, Acute Kidney Failure.

Lab Value	Patient Result	Reference Range
Hemoglobin	5.0 g/dL	13.5-16.5 g/dL
Hematocrit	15.9%	40%-50%
Reticulocyte %	1.5% (uncorrected) 0.5% (corrected)	0.5%-2.0%
Absolute Reticulocyte Count	5.9 x 10^3/uL	30-94 x 10^3/uL

Case study 2, continued

- Blood Bank Results, Type and Screen

Anti-A	Anti-B	Anti-D	Mono Control	A1 Cells	B Cells
4+	4+	4+	4+	4+	4+

Gel SC I	Gel SC II	Gel AC	Solid Phase SC I	Solid Phase SC II	Solid Phase SC III
3+mf	3+mf	3+mf	4+	4+	4+

Case study 2, continued

- Blood Bank Results, DAT

Poly	Anti-IgG	Anti-C_3b, -C_3d	Saline Control
3+	3+	3+	3+

- Antibody workup resulted in no specificity
- Cold agglutinin present
- Warm washing cells performed to resolve type and DAT discrepancies.

Case study 2, continued

- Blood Bank Results, Warm Washed RBCs used, Type and DAT

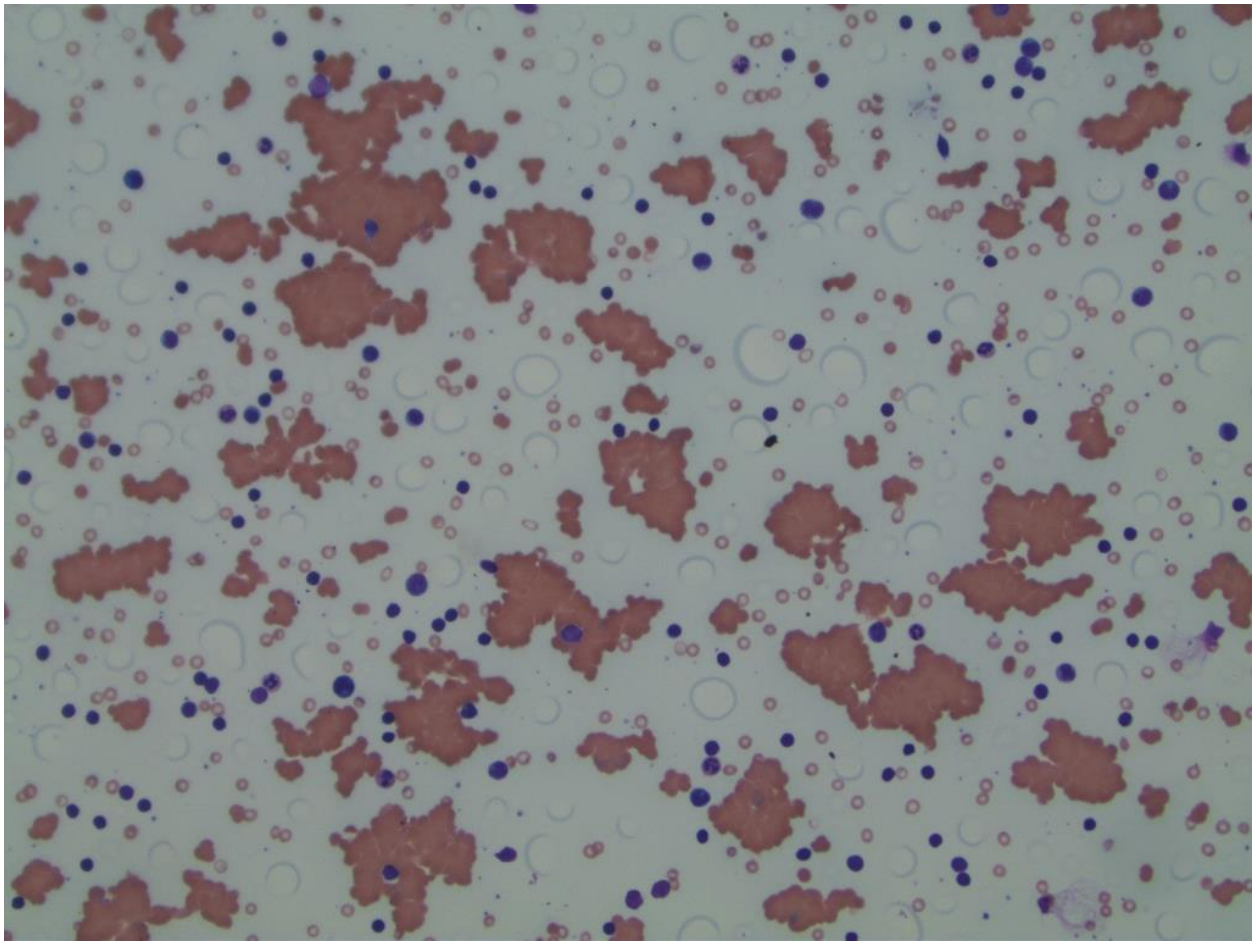
Anti-A	Anti-B	Anti-D	Mono Control	A1 Cells	B Cells
0	0	3+	ND	4+	4+

Poly	Anti-IgG	Anti-C_3b, -C_3d	Saline Control
2+	(+)	2+	0/0

- Serologic findings: Indeterminate antibody present (warm and cold autoantibodies identified, referred out for alloadsorption and further evaluation).
- Prewarm techniques seem to circumvent reactivity with unit crossmatches.

Case study 2, cold agglutinin

- Micrograph from peripheral smear



Case study 2, patient background, cont.

- Admitted 24 days ago to outside facility with critically low hemoglobin (4.1 g/dL).
  - 5 units pRBCs given, hemoglobin 7.2, discharged after a short stay.
- Admitted to another facility yesterday, noted to have hemolytic anemia and severe rouleaux.
  - Given immunosuppressants and folate
  - Transferred to TUKHS for evaluation of lymphoma and management of autoimmune hemolytic anemia
- On admission, further laboratory evaluation performed.

Case 2: Additional Labs

- IgG normal, IgA normal, but IgM above analytical range (>5000 mg/dL, normal 38-328).
- Reference lab cold agglutinin titer
  - 1:524288 (reference range 1:32)
- Protein electrophoresis
  - Elevated total serum protein (11.3 g/dL, ref 6.0-8.0)
  - Low albumin fraction (27.6%, normal 48-68%)
  - Beta/Gamma spike

Case 2: Piecing it all together…

- Likely as a result of patient's lymphoma, we are dealing with a (at least debatably) clinically significant cold autoantibody, along with a warm autoantibody we eluted off the RBCs (no allos, both cold and warm auto confirmed by our reference lab).
- Transfusion approach: Use blood warmers, keep patient warm to minimize impact of cold agglutinin, use prewarm technique when crossmatching units – units ended up compatible.
- Clinicians attempted to treat autoimmune response with multiple immunosuppressants, but patient was critically ill with severe anemia.

Case 2: TPE Time!

- Patient received two TPEs with albumin- first on day of admission, another a week later.
- IgM prior >5000, post TPE 1: IgM 2880 mg/dL
- IgM trended back up to 4800 mg/dL by day 6 after admission
- IgM reduced to 3260 mg/dL after second plasma exchange.
- Patient only required one unit pRBCs after both plasma exchanges- hemolytic anemia stymied.

- Patient was discharged and follows up with a clinician outside of our system.

Conclusion

- As evidenced in both cases, plasma exchanges can impact the blood bank in a variety of ways.
  - Our serological testing can be impacted by the pathologies these patients present.
  - We may be called upon to provide plasma either as the basis of the exchange or to replace depleted coagulation factors and fibrinogen
- These cases represent just a couple of the many conditions treated by therapeutic plasma exchange.
- A transfusion service and lab may have to support these cases in more ways than just administering cryo or plasma on a rare occasion.
  - For example, our use of isohemagglutinin titers, serum IgM levels, and more.

- Questions?
- Big thank you to Dr. Plapp at KU for his guidance in gathering material for this presentation today.

References

- Bobati, S. S., & Naik, K. (2017). Therapeutic Plasma Exchange - An Emerging Treatment Modality in Patients with Neurologic and Non-Neurologic Diseases. *Journal Of Clinical And Diagnostic Research, 11*(8), 35-37. doi:10.7860/jcdr/2017/27073.10480
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