PATHOPHYSIOLOGY OF IMMUNE HEMOLYSIS

Disorder	Etiology and Epidemiology	Pathophysiology and Presentation	Lab Findings and Diagnosis	Treatment
NEONATAL HEMOLYSIS				
MATERNAL ABO INCOMPATIBILITY	**Most common cause of hemolytic disease of the newborn.** Seen in type O mothers: IgG anti-ABO A, B, AB mothers: IgM 10% symptomatic Soluble neonatal ABH antigen neutralizes most maternal Ab Does not require primary immunization	**Extravascular Hemolysis** Fetal anemia Increased indirect bilirubin Harmless top fetus since it is eliminated by maternal portal circulation **Erythroblastisis Fetalis** Extramedullary Hematopoeisis Fetal hepatosplenomegaly Biliary obstruction **Hydrops fetalis**: edema, ascites, hepatic failure Kernicterus with indirect bilirubin > 20 mg/dL	Maternal anti-Rh antibody screen If elevated: **amniocentesis** Amniotic indirect bilirubin correlates with erythroblastosis fetalis and hemolysis	**In mild hemolysis**: delivery is sufficient to correct the anemia Simple transfusion Exchange transfusion Cord bilirubin > 5 mg/dL Hb < 12 g/dL Intrauterine transfusion UV phototherapy **Prevention** **Avoid transfusion of Rh+ve to Rh-ve mother** **Anti-Rh immunoglobulin** Used in all women at 28 wks Following abortion or transplancental hemorrhage Second bolus before delivery if fetus is Rh+ve
MATERNAL Rh(D) INCOMPATIBILITY	**Requires prior immunization** Transplacental hemorrhage Previous abortion of Rh+ve fetus Transfusion with Rh+ve RBCs Risk of immunization is maximal with ABO matched Rh-ve mother and Rh+ve fetus Incompatible ABO results in Immediate lysis of fetal erythrocytes			
AUTOIMMUNE HEMOLYSIS				
WARM AUTOIMMUNE HEMOLYTIC ANEMIA	Extravascular Hemolysis (spleen) IgG-mediated Associated with lymphomas, collagen-vascular disease, and drugs	No fixation of complement. Thus, intravascular hemolysis is rare	**PERIPHERAL SMEAR** Reticulocytosis No agglutination Spherocytes DAT: Positive for IgG and C3	**Corticosteroids** Downregulated macrophage Fc receptor expression Downregulated IgG secretion

	Involves many RBC antigens, predominantly Rh			**Splenectomy** If refractory to Prednisone **Rituximab**
COLD AUTOIMMUNE HEMOLYTIC ANEMIA	Extravascular (liver) and Intravascular Hemolysis Associated with infection (*Mycoplasma*, EBV), some lymphomas (e.g. Waldenstrom macroglobulinemia) **Involves the RBC Group I antigens**	May completely fix complement Hemolytic disease is determined by thermal amplitude of Ab Requires activity at > 28 deg **Cold Agglutinin Syndrome** Raynaud (vascular stasis in digits) Livido reticularis	**PERIPHERAL SMEAR** Reticulocytosis Agglutination Spherocytes DAT: positive fro C3, negative for IgG There is no DAT for IgM due to spontaneous agglutination	**Rituximab** **Plasmapherisis** **DOES NOT RESPOND TO splenectomy or corticosteroids**

TRANSFUSION HEMOLYSIS

General Features of Transfusion Biology

Anti-ABO antibodies are IgM in A, B, and B BUT IgG in O-type

However, all classes (IgA, IgM, IgG) may produce visible agglutination

A gene: enzyme catalyzes conjugation of N-acetyl-galctosamine

B-gene: enzyme catalyzes conjugation of galactose

Select identical ABO type for further antibody screening

In emergent trauma: transfuse with Type O RBCs (remove plasma)

Anti-Rh antibodies are IgG

The Rh(D) antigen is highly immunogenic: 50% of Rh-ve hosts will be immunized after first exposure

Exotic RBC antigen groups: Kell, Duffy, Kidd

Abs are only generated by immunization through transfusion or pregnancy

No screening is for these donor antigens and recipient Abs is performed before transfusion

However, testing is done in muliparous women and patients with previous transfusion

IMMEDIATE INTRAVASCUALR HEMOLYSIS	**ABO incompatible transfusion** Mortality is 10%	Onset is acute and severe Rigors and fever **Massive activation of complement** DIC: results from release of platelet PLs, and endothelial TF C3a, C5a → generate bradykinin and		

		trigger mast cell degranulation This results in peripheral vasodilation, increased capillary permeability, and hypovolemic shock NE → renal arteriolar vasoconstriction and AKI		
IMMEDIATE EXTRAVASCUALR HEMOLYSIS	IgG-mediated Typically involves Rh, Duffy, Kell, and Kidd antigens	Chills and fever due to acute phase reactants (response to cellular lysis)		
DELAYED HEMOLYSIS	Anamnestic response to transfusion RBCs Recipient is typically anergic to antigen. Exposure results in stimulation fo the humoral response and revives titres	Typically presents as gradually falling Hct and Hb IN THE ABSENCE OF BLOOD LOSS	DAT converts from positive to negative when donor cells are completely hemolyzed	
ANYPHYLAXIS and TRANSUSION TOXICOTY	**In 5% of transfusions** Non-self HLA expressed on leukocytes and platelets may elicit a generalized toxic reaction (fever). Urticaria: circulating antigens in donor blood (e..g after recent meal) Anaphylaxis: due to anto-IgA Abs in recipients with IgA deficiency Volumic and metabolic disorders: Hypocalemia, hyperkalemia, acidosis, fluid overload			
DRUG-MEDIATED HEMOLYSIS	**Immune Complex Absorption** Quinidine Deposition of immune complex on RBC membrane causes full activation of complement and **intravascular hemolysis** **Direct Drug Absorption**	PRESENTATION CAN BE PREDICTED based on site of hemolysis Typically, no findings in membrane-modification reactions (simply creates false-positive Coombs test) Most commonly: anemic symptoms with onset concurrent with new drug therapy	DAT demonstrates positive agglutination correlated with recent initiation of therapy	Discontinue drug therapy

	PCNs and cephalosporins IgG bindsto haptenic groups on RBC membrane, resulting in exposure of Fc and extravascular hemolysis **Membrane Modification** Cephalosporins Coating of the membrane causes non-specific absorption of plasma proteins. No hemolysis despite positive DAT **Cross-sensitization (autoimmunity)** A-Me-DOPA Inhibits T-reg cells (decrease secretion of IL-10 and TGF-β) → expansion of B cells and production of cross-reactign Ab IgG against Rh: extravascular hemolysis			