TRANSFUSION MEDICINE—LECTURE 2

Transfusion Practice

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OUTLINE:

- Basics of Blood Component Use
  - Red blood cells
  - Platelets
  - Plasma
  - Cryoprecipitate
  - Granulocytes
- Special Transfusion Situations
  - Patients with autoantibodies
  - Support of bone marrow transplant patients
  - Hemolytic disease of the fetus and newborn

OBJECTIVES:

- Be able to describe the "practice guidelines" for the transfusion of red cells, platelets, plasma
- Be aware of the causes of iron overload and know what patients are at risk
- Be able to discuss the implications for a patient who becomes refractory to platelet transfusion and how this situation is manifest and treated
- Understand the mechanism of hemolytic disease of the newborn (HDFN)
- Be familiar with the procedures used to screen for HDFN and how to evaluate patients (both mothers and fetus/newborns) who are at risk

REFERENCES:

Extensive notes are provided to accompany the lectures on Transfusion Medicine

Transfusion Medicine

Lecture 2

Transfusion Practice

Jerry E. Squires MD, PhD

Lecture Outline

- Basics of Blood Component Use
  - Red Blood Cells
  - Platelets
  - Plasma
  - Cryoprecipitate
  - Granulocytes
- Special Transfusion Situations
  - Patients with Autoantibodies
  - Support of Bone Marrow Transplant Patients
  - Hemolytic disease of the Fetus and Newborn

Red Blood Cell Transfusion

- Component Review:
  - RBCs are the most commonly transfused blood product
  - Each RBC unit has a volume of 250 – 300 mL and is made up of red blood cells, suspended in anticoagulant (citrate), a preservative solution, and a very small amount of plasma

- **Basic Indication:**

" The primary indication for the transfusion of Red Blood Cells (RBCs) is to restore or maintain *oxygen-carrying capacity* to meet tissue demands."

AABB Technical Manual 2014

- **Patient Populations:**
  - Anemia
  - Active bleeding
  - Chronic transfusion
    - Sickle cell disease
    - Thalassemia

Red Blood Cell Transfusion--Anemia

- **Anemia**—even though "anemia" can be defined, not all patients who are technically anemic actually require a transfusion:
  - In "normal" circumstances, the oxygen carrying capacity of hemoglobin far exceeds tissue needs
  - In patients with anemia, the reduced capacity of the blood to carry oxygen is compensated for by:
    - Increased cardiac output
    - Redistribution of blood flow
    - Increase in RBC 2,3-DPG (which facilitates off-loading of O_2 to tissues)

- **When to Transfuse the Anemic Patient:**
  - The decision to transfuse should rely on the patient's symptoms:
    - Weakness, fatigue
    - Dyspnea, tachycardia
    - Worsening angina
  - Hemoglobin level is often used as a guideline for RBC transfusion, but it is a very poor indicator
  - Never transfuse RBCs if an asymptomatic anemia can be corrected medically (e.g. iron deficiency anemia in patient experiencing no symptoms—use oral or IV iron)

Red Blood Cell Transfusion--Anemia

- There are "Practice Guidelines" for the use of each blood component
- For RBCs, the practice guideline relies on the patient's hemoglobin level in the absence of any measure (including Hgb) with sufficient predictive power to discern anemia-related impaired tissue oxygen delivery (*Guidelines are **NOT** rules*)
- RBC Practice Guidelines:

Hemoglobin Level	Transfusion Recommendation
> 10 g/dL	RBC Txf. not generally indicated
6-10 g/dL	RBC Txf. based on patient symptoms and risk
< 6 g/dL	RBC Txf. generally indicated

- Transfusion of a single RBC unit to a non-bleeding adult should increase the hemoglobin by approximately 1 g/dL (or Hct by 3%)

Red Blood Cell Transfusion—Active Bleeding

- Active Bleeding Patient
  - Actively bleeding patients can occur in several specific settings
    - Medical bleeding (e.g. GI hemorrhage)
    - Surgery
    - Trauma
  - *The Hemoglobin level often does not provide an accurate or timely measure of patient status in this situation*
- When to Transfuse
  - Medical situations:
    - The decision to transfusion RBCs in these situations often rely on clinical experience, estimated blood loss, and the patient's symptoms
    - Estimated blood loss (*notoriously inaccurate procedure*):

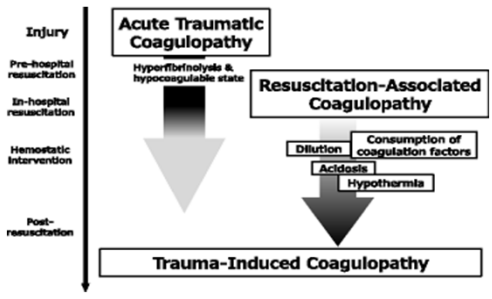
Class	Blood Loss	Symptoms	Replacement
I	<15%; <750 mL	Mild ↑HR	None
II	15-30%; 750-1500 mL	↑HR; cool, clammy skin; ↑Resp rate	Possibly RBC
III	30-40%; 1500-2000 mL	↓BP; ↑↑HR; Pale; Confused	Possibly RBC
IV	>40%; >2000 mL	↓BP; ↑↑Resp rate; Cool, pale skin	RBC; Volume replacement

Red Blood Cell Transfusion—Active Bleeding

- When to Transfuse-**Surgery**
  - Many surgical procedures are accompanied by significant blood loss
  - In general, the need for RBC transfusion is assessed by the surgeon and anesthesiologist and is based on patient vital signs and observed blood loss
  - Many hospitals have established *Maximum Surgical Blood Ordering Schedules (MSBOS)* which provide recommendations for the number of units of RBCs that should be ordered prior to each type of surgical procedure
- Reducing the need for RBC transfusion during **surgery**
  - Anemia should be corrected medically prior to surgery (patients going to surgery with anemia are more likely to be transfused and generally have poorer outcomes)
  - **Normovolemic hemodilution**—whole blood can be collected from the patient at the start of surgery and replaced with saline. The blood can then be re-infused at the end of surgery
  - **Intraoperative blood salvage**—blood lost during surgery can be collected, filtered and returned to the patient at the end of the procedure

Red Blood Cell Transfusion—Active Bleeding

- When to Transfuse-**Trauma**
  - Many trauma patients require large numbers of blood products
  - The decision to transfuse is based on the patient's signs and symptoms and the clinical experience of the trauma surgeons
  - Most major trauma programs have established "Massive Transfusion Protocols" to facilitate the management of these situations
- **Trauma Resuscitation**
  - One of the major complications in trauma resuscitation is the coagulopathy of trauma which may be a specific syndrome itself but is probably exacerbated by hypothermia and platelet/coag factor dilution.



Red Blood Cell Transfusion—Active Bleeding

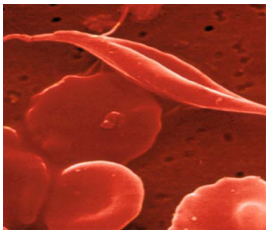
- Massive Transfusion Protocols:
  - Transfuse RBCs: Plasma: Platelets in a 1:1:1 ratio
    - There is accumulating evidence that transfusion these 3 products in a pre-assigned ratio significantly improves patient survival
    - Use group O RBCs until patient's blood type is known; platelets: any type; plasma group A
  - Whole blood use in trauma
    - Group **O Whole Blood** is now being used more frequently in trauma resuscitation even when the patient's blood type is not yet known
      - Even though the use of the 1:1:1 ratio of Plasma to RBCs to Platelets seems to be an improvement over "random" component transfusion in massive transfusion programs, it is cumbersome, slower, and possibly less effective than the use of Whole Blood
      - Experience is showing that the more quickly transfusion support is provided in a trauma situation, the better the outcome.
      - Whole blood can be provided to trauma patients quickly and can even be carried in the ambulance or helicopter and transfused before the patient even arrives at the hospital.

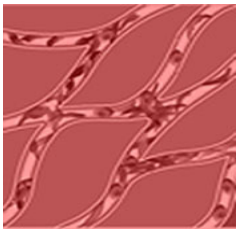
Red Blood Cell Transfusion—Chronic Transfusion

- Chronic RBC Transfusion
  - Certain categories of patients benefit from the chronic (scheduled) transfusion of RBCs regardless of hemoglobin level
  - The patients most commonly included are those with sickle cell disease and thalassemia
- **Thalassemia**
  - Results from a number of specific mutations affecting the synthesis of the α- or β-globin chains
  - All patients with thalassemia major require chronic transfusions to prevent the complications of anemia
  - RBC transfusion is generally required every 2-4 weeks

Red Blood Cell Transfusion—Chronic Transfusion

- Sickle Cell Disease (SCD)
  - SCD arises from a point mutation in the β-globulin chain of hemoglobin making deoxygenated hemoglobin susceptible to polymerization
  - These changes can distort RBC shape and ultimately lead to vaso-occlusive events





- Indications for RBC Transfusion:
  - RBC transfusion can be used to relieve the symptoms associated with vaso-occlusive, aplastic, and sequestration crises
  - RBC transfusion has also been used to reduce the risk of cerebrovascular events (strokes)
- Goals of transfusion in SCD:
  - Improve oxygen-carrying capacity
  - Decrease blood viscosity
  - Suppress endogenous erythropoiesis (reducing the production of the patient's HbS)

Platelet Transfusion

- Component Review
  - There are generally 2 types of platelet products:
    - Those derived from whole blood collections
      - These products have a volume of ~50 mL and because of the relatively small number of platelets, 4-6 products must be pooled together to make a single adult dose
    - Those collected by apheresis
      - These products have a volume of ~300 mL and each one represents a full adult therapeutic dose of platelets
- Basic Indications
  - Platelets are transfused to patients who are thrombocytopenic (or who have dysfunctional platelets) to prevent or stop bleeding
  - Practice Guideline:
    - < 10,000/µL Transfuse platelets
    - < 50,000/µL Transfuse platelets for invasivc procedure
  - Post-transfusion platelet increment:
    - The transfusion of 1 apheresis platelet to a non-bleeding, afebrile patient with a normal sized spleen should result in an increase in platelet count µof 30,000 to 40,000/µL

Platelet Transfusion—Refractory Patients

- Patients who are repeatedly transfused with platelets but fail to get the expected post-transfusion platelet increment (or certainly, less than 10,000/µL) are said to be ***refractory***
- There are several causes:
  - **Non-immune**
    - Enlarged spleen
    - Sepsis/fever
    - Certain medications (e.g. amphotericin)
  - **Immune (*Alloimmunized*)**
    - HLA or Platelet-specific (HPA) antibodies
- Patients generally become alloimmunized due to exposure to blood either through transfusion or pregnancy—many of these patients will develop HLA or platelet-specific antibodies
- Management of alloimmunized patients:
  - HLA-Matched platelet products:
    - Knowing the HLA type of the patient (HLA-A and HLA-B) allows us to identify potential platelet donors who have the same HLA type
  - Cross-matched platelet products:
    - These are serologic techniques that allow us to test the patient serum (containing antibodies) against a number of platelet donors to determine any might be "compatible"

Plasma Transfusion

- Component Review:
  - Plasma can be collected by apheresis, but is more commonly, the plasma removed from a whole blood donation when RBCs are produced
  - The primary benefit of plasma is that it contains hemostatic levels of all coagulation factors
  - Frozen plasma has a volume of ~250-300 mL and will require about 30 minutes to thaw prior to transfusion

- Basic Indications
  - Active bleeding due to **multiple** coagulation factor deficiencies (e.g. liver disease)
  - Patients with a single coagulation factor deficiency for which no manufactured coagulation factor is available (VIII, IX, VII are commercially produced factor concentrates)
  - Rapid reversal of Warfarin
    - Prothrombin complex concentrate (4-factor PCC) is now recommended for this purpose
    - Warfarin anticoagulation can be reversed in 24 hours simply by the use of IV Vitamin K

Cryoprecipitate Transfusion

- Component Review
  - Cryoprecipitate is prepared from plasma that has been frozen within 8 hours of collection
  - The proteins in cryoprecipitate are the "cold-insoluble" proteins in plasma
  - Cryo contains:
    - Factor VIII
    - Factor XIII
    - Von Willebrand Factor
    - Fibrinogen
  - Cryoprecipitate is stored frozen and requires 30 minutes to thaw prior to transfusion
- Basic Indications
  - Cryoprecipitate is used to treat:
    - Patients with decreased or abnormal fibrinogen (fibrinogen ≤ 100 mg/dL)
    - Some patients with von Willebrand Disease (type 3 and some type 2) who are not responsive to DDAVP
    - Rare patients who have a deficiency of Factor XIII
    - *While Cryoprecipitate has high levels of Factor VIII, it is **NOT** used to treat hemophilia A since a commercial (manufactured) concentrate of Factor VIII is available*

Granulocyte Transfusions

- Component Review
  - Granulocyte products are very rarely used due to difficulty in collection and their questionable efficacy
  - The products are collected by apheresis
- Basic Indications
  - Severely granulocytic patients who are septic (or have a serious infection) and who are currently being treated with antibiotics without success
  - These products seem to be successful ~30% of the time with bacterial infections

Special Transfusion Situations

- Now that we have discussed the use of the major blood components in general terms, there are several specific situations that should be reviewed:
  - Transfusion of patients with autoantibodies
  - Transfusion support for bone marrow transplant patients
  - Hemolytic Disease of the Fetus and Newborn (HDFN)

Special Situations—Patients with Autoantibodies

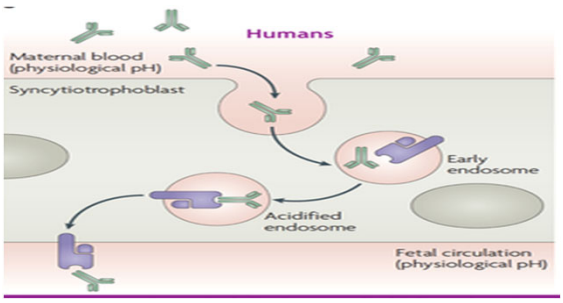
- Autoimmune hemolytic anemias can be caused by either IgG (warm AIHA) or IgM (Cold Agglutinin Disease)
- These diseases can either be indolent causing very little hemolysis or life-threatening anemia
- From a transfusion perspective it is important to know that the patient's RBCs will be coated with either IgG or Complement (CAS) causing a ***positive DAT***. In addition, the autoantibodies will be in the patient's plasma
- The autoantibodies in the patient's plasma will cause crossmatches to be incompatible
- Transfusing these patients will not necessarily worsen their hemolysis; the challenge is to determine whether or not the patient has other blood group antibodies (*alloantibodies*) such as anti-E, or anti-Kell, etc. which could cause a serious hemolytic transfusion reaction.
- In patients with *autoantibodies*, the blood bank must use special techniques to determine if *alloantibodies* are present prior to transfusion

Transfusion Support for Bone Marrow Transplants

- In solid organ transplantation (liver, heart, etc) ABO compatibility between the patient and the donor is essential
  - A and B blood group antigens are present on the endothelial cells of solid organs
- But for stem cell (hematopoietic progenitor cell; HPC) transplantation, ABO compatibility is not a barrier. This results in unique transfusion issues:
  - Blood product compatibility
    - There are specific compatibility guidelines for the pre-transplant, post-transplant, and engraftment periods for each of the various types of ABO incompatibilities between patient and stem cell product
  - Immunocompromised patients
    - All bone marrow transplant patients are ***immunocompromised*** and **must receive <u>irradiated</u> cellular products (RBCs, Platelets, and granulocytes)**

Hemolytic Disease of the Fetus and Newborn (HDFN)

- HDFN is defined as *anemia* and *hyperbilirubinemia* of the fetus and / or newborn caused by an incompatibility between maternal and fetal red cells.
  - HDFN is caused by maternal **IgG antibodies** that can be actively transported across the placenta; maternal IgM antibodies cannot cross the placenta and hence cannot cause HDFN:



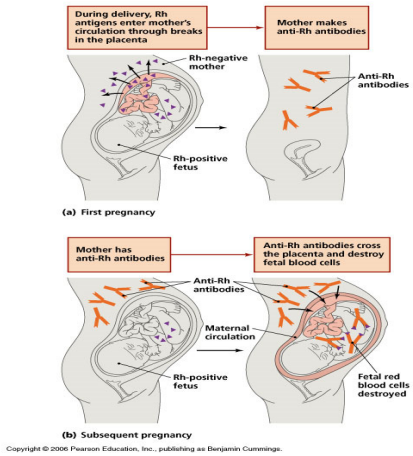
HDFN: 2 Categories of HDFN

- ABO-HDFN
  - 60% of cases of HDFN are caused by ABO incompatibility between fetus and mother
  - Most common: mother group O (her plasma contains anti-A and anti-B) and baby group A or B
    - **Why Type O mother?: Type O people tend to have relatively high levels of *IgG* anti-A and anti-B. Type A and B have very small amounts of IgG anti-A / anti-B (mostly IgM!!)**
  - Symptoms generally mild
    - ↑ postnatal bilirubin
  - Can affect *first* and *subsequent* pregnancies (due to "naturally occurring" anti-A or anti-B in mother)
- "Immune-antibody" HDFN (Rh or other antibody)
  - 40% of cases of HDFN are caused by "stimulated" or immune antibodies
  - Most common immune antibody causing HDFN is anti-D
    - ***Note: even though we will discuss "anti-D" as a cause of HDFN, other IgG antibodies that the mother may have can cross the placenta and possibly cause HDFN***
  - Symptoms can be severe
  - Generally affects only *"later"* pregnancies (2nd or later)

Hemolytic Disease of the Fetus and Newborn

- How do immune antibodies develop in the mother?
- Most frequently this occurs when an Rh negative mother is exposed to Rh positive blood (red cells that have a "D" antigen) which can occur in two ways:
  - **Transfusion:** Rh positive blood transfused to an Rh negative patient.
  - **Fetal-maternal hemorrhage** (FMH) during a "previous" pregnancy.
    - The risk of FMH increases at each "trimester" of pregnancy with the greatest risk at delivery

In either case Rh positive blood is introduced into the circulation of an Rh negative mother—or diagramatically…….



Hemolytic Disease of the Fetus and Newborn

- **Prenatal Presentation** (Erythroblostosis fetalis)
  - Anemia
  - High-output heart failure
  - Edema
    - Ascites
    - Pleural / pericardial effusions
    - Skin edema
  - Polyhydramnios (increased amount of amniotic fluid)

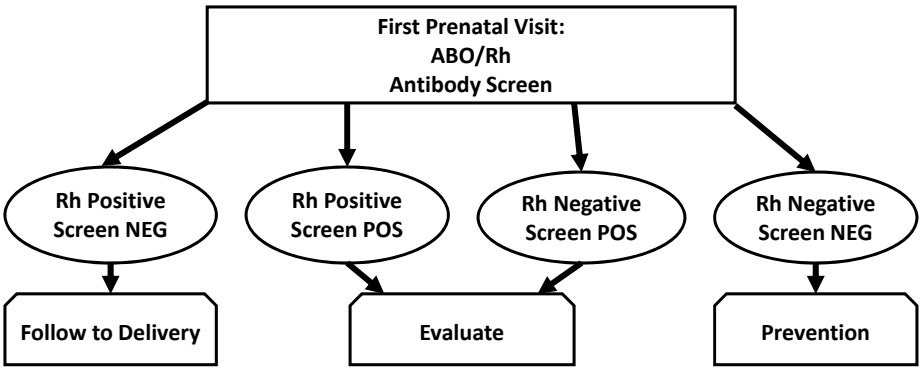
  (HYDROPS FETALIS)

Hemolytic Disease of the Fetus and Newborn

- **Postnatal presentation:**
  - Anemia
  - **Hyperbilirubinemia** (due to hemolysis of fetal RBC by maternal antibody)
  - **Kernicterus** (fetal liver is unable to conjugate bilirubin allowing the unconjugated bilirubin to pass through the blood-brain barrier; prenatally, the maternal liver will conjugate the bilirubin protesting the fetus from kernicterus)
  - **Neonatal demise** (~90%); severe neurological complications in survivors.

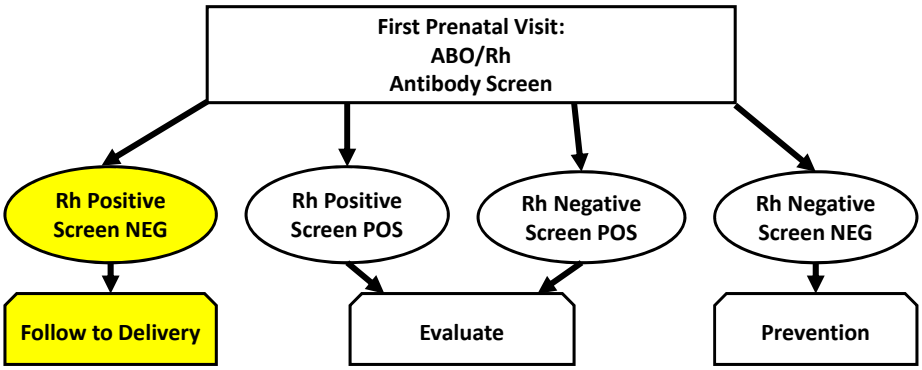
HDFN—Evaluation and Management

At the time of the first prenatal visit, a blood sample should be collected from the expectant mother for testing (*ABO/Rh and Antibody Screen*) which will yield 4 possible results:



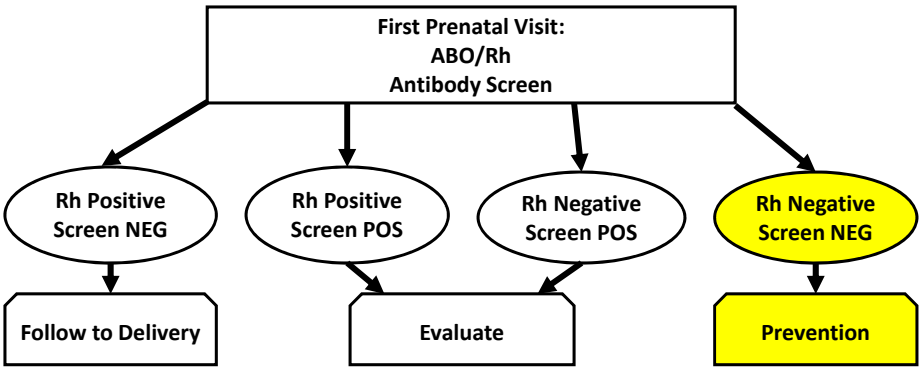
HDFN—Evaluation and Management

If the expectant mother is Rh positive and has a NEGATIVE antibody screen, she can simply be followed to delivery:



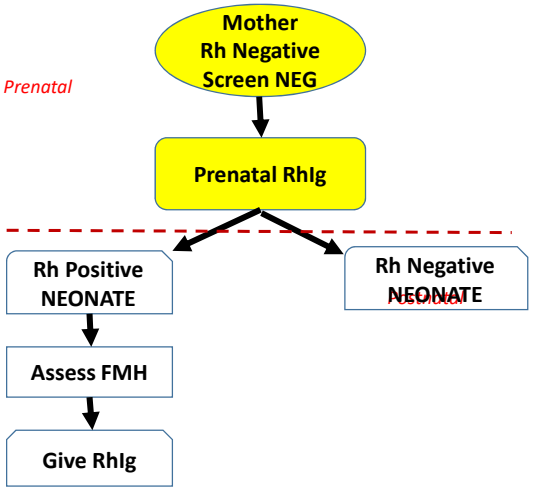
HDFN—Evaluation and Management

If the mother is **Rh negative but has no IgG antibody** that can cross the placenta, we want to make sure that she does NOT develop an anti-D if the fetus happens to be Rh-positive (*Prevention*)



HDFN—"Prevention"

- What do we mean by "prevention?"
  - Since Anti-D was such a common cause of severe HDFN, Rh-immune globulin (RhIg) was developed
  - **RhIg is a solution of antibodies to the "D" antigen that can prevent the development of immune anti-D in Rh negative individuals**
  - A "standard" dose of RhIg provides coverage for up to 30 mL of RhD positive blood
  - It should be administered within 72 hours of "exposure"
  - 1st dose given at 28 weeks gestation to Rh negative women *in case the fetus is Rh positive*
  - At delivery of an Rh-positive neonate, we have to calculate the appropriate dose (next slide…)

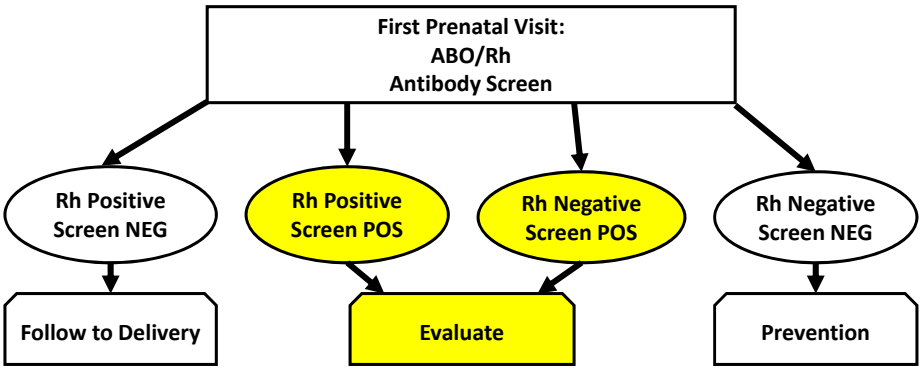


HDFN—"Prevention"

- **Assessment of FMH (*or* Fetal-Maternal Hemorrhage)**
  - Prior to 28 weeks a FMH is rare and will have a volume will be very small and certainly < 30mL—*So, one dose of RhIg will always be sufficient*
  - However, overall, 75% of all pregnancies have evidence of FMH; most FMH are small (<0.1mL); < 0.25% of pregnancies have FMH greater than 30mL.
  - In order to be sure to give enough RhIg, at delivery we must determine the approximate volume of FMH in case it is greater than 30mL:
    - Rosette test
      - This test is a simple test but can only say "big bleed" or "little bleed"
      - If the bleed is ***SMALL,*** one dose of RhIg is sufficient, BUT if the bleed is ***LARGE,*** we have to determine the approximate volume of the bleed……
    - Kleihauer-Betke test (to determine how many "doses" of RhIg are necessary)

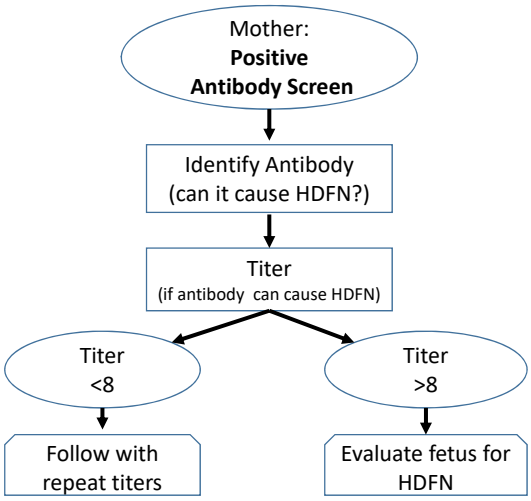
HDFN—Evaluation and Management

Finally, if the mother is Rh-positive ***OR*** Rh-negative, **BUT** has a ***positive antibody screen*** for an IgG antibody, we have to "Evaluate"



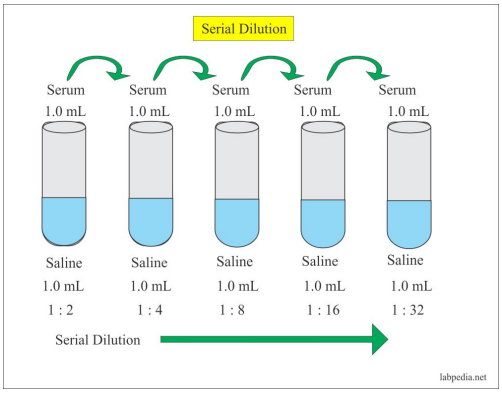
HDFN—"Evaluate"

- The concern: **the condition of the fetus**
- Evaluating potential HDFN
  - Antibody type
    - IgG versus IgM (IgG can cross the placenta, but IgM cannot!!!)
  - Maternal antibody **titer** if IgG antibody:
    - Serial dilutions of maternal plasma with **higher titers** corresponding to more severe HDFN *(diagram on next slide)*
  - Amniocentesis for hemolytic pigment
    - (NOT often used due to fetal risk)
  - **Fetal middle cerebral artery (MCA) systolic blood flow velocity (Doppler)**



HDFN—"Evaluate"

- **Antibody titers** (How much antibody is present????)
  - For patients who have a "positive" antibody screen for an IgG antibody
  - The higher the titer, the more likely that HDFN is severe
  - Repeat titer every two weeks during pregnancy
  - "Critical titer:" 1:8 to 1:16 (Note: this is actually the "dilution;" the corresponding "titers" are "8" and "16.")
    - At this titer, an MCA (*or other test)* to assess the status of the fetus should be done

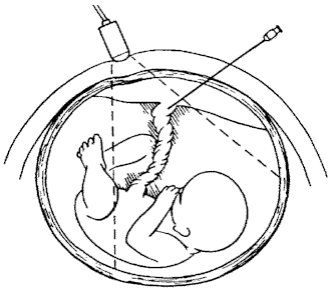


HDFN—Evaluation and Management

- If the titer is greater than 8, it is important to evaluate the fetus to determine how severely affected he/she is:
  - Amniocentesis
    - A sample of amniotic fluid is collected and scanned spectrophotometrically
    - Bilirubin derived from the breakdown of fetal RBC has an absorption peak at 450 nm
    - This "peak" is plotted on a Liley curve to estimate the severity of HDFN
    - This procedure is **not** often used since there is a small (~2%) fetal risk of fetal harm in doing the amniocentesis
  - Middle Cerebral Artery Mean Peak Velocity
    - This Doppler procedure is the more commonly performed procedure (no/minimal risk)
    - This procedures measures fetal blood flow and associates that with the degree of fetal anemia resulting from RBC hemolysis

HDFN—Management

- In the **prenatal period**, *if a fetus is thought to be severely affected by HDFN,* an intrauterine transfusion can be performed to increase the hemoglobin
- Blood for intrauterine transfusion should be:
  - Antigen negative for the offending antibody (*e.g. if anti-Kell is found to be causing HDFN, you must give Kell-negative blood*)
    - Crossmatch compatible with mother's serum
  - O negative
  - Irradiated (to prevent GVHD in fetus) CMV-safe (a fetus is NOT immunocompetent)
  - Blood lacking Hemoglobin S
  - Have a hematocrit of 75-85%
  - Blood < 5-7 days old "preferred"



HDFN--Management

- If the neonate is determined to be affected by HDFN, 3 options are available depending upon severity:
  - **Phototherapy *("mild")***
    - Oxidizes unconjugated bilirubin with oxidation products excreted in urine
    - Effective
    - Generally uses LED light source (wavelength 400-520; peak 460nm)
  - **IVIG**
    - Can be an adjunct to phototherapy
    - Probably ↓phagocytosis of RBCs by blocking Fc receptors and/or neutralizes mother's antibodies
  - **Exchange Transfusion**
    - Decreases bilirubin
    - Removes antibody-coated red cells
    - Removes maternal antibody
    - Corrects anemia
    - *Indications for exchange transfusion……*

HDFN--Management

- Exchange Transfusion
  - Indications:
    - Cord hemoglobin <10 g/dL
    - Rapidly rising bilirubin >.5 mg/dL/hour
    - Bilirubin > 20 mg/dL in term infant (*lower* in premature, hypoxia, acidosis, hypothermia)
  - Procedure:
    - Double volume exchanges replaces 85-90% of blood volume and removes 50% of bilirubin
  - Complications:
    - 12% adverse reaction rate
    - 0.5% mortality

Practice Exercises

In the table below, several "patient situations have been listed in the first column. For each of these "patients" suggest the blood product to be used and the transfusion guidance for the transfusion. *The patient's blood type for this exercise is **A.** The first patient problem is provided as an example*

Patient "Issue"	Blood Product	Guidance	Compatible Blood Product ABO Type(s)
Anemia; Hgb 5.0, with angina	*Red blood cells*	*Hgb ≤ 6.0; symptomatic*	*A, O*
Trauma; active bleeding			
↑PT and PTT; bleeding			
Thrombocytopenia: Plt Count 4,000/µL			
↓Fibrinogen; bleeding			
Sickle cell disease; painful crisis			

- Hemolytic Disease of the Fetus and Newborn:
  - *"The Jaundiced Baby" in-class exercise*

Patient "Problem"	Blood Product	Guidance	Compatible Blood Product ABO Type(s)
Anemia; Hgb 5.0, with angina	*Red blood cells*	*Hgb ≤ 6.0; symptomatic*	*A, O*
Trauma; active bleeding	Whole blood 1:1:1 ratio (plasma, RBC, plt)	Patient symptoms; clinical judgement	O (low titer O for WB) Patient's blood type when known
Thrombocytopenia: Plt Count 4,000/μL	Platelets	≤10,000—prophylactic ≤50,000—invasive proc.	Any type but A or AB preferred
↓Fibrinogen; bleeding in	Cryoprecipitate	Fibrinogen ≤100 mg	Any type
Sickle cell disease; painful crisis	Red blood cells	To resolve crisis	A, O
Patient actively bleeding believed due to Factor V deficiency	Plasma	Calculated to raise factor V to hemostatic levels *(NOT discussed in lectures!!)*	A or AB