Neonatal Transfusion
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I. Anemia in a neonate: both physiological and iatrogenic

(Note: unless otherwise noted, a "neonate" refers to an infant <4mo of age)

A. Neonates typically undergo physiologic anemia of infancy due to reduced erythropoietin production, reaching a minimum Hgb of ~9g/dL around 10-12 weeks of age. This decline may occur earlier and faster in premature infants, reaching about 7g/dL or less.

B. Anemia of prematurity is further exacerbated by laboratory draws during hospitalization

C. In general, the smaller the neonate, the more likely transfusion would be needed.

II. Pre-transfusion Testing

A. Neonate's immune system not fully functional, almost all antibodies are of maternal origin at birth

B. Usually a sample is drawn from both mom and infant to check for ABO/Rh type. Reverse type not done on the infant due to lack of endogenous ABO antibody production.

C. Maternal serum checked also for unexpected non-ABO antibodies.

- If negative: no additional compatibility testing (including crossmatching) is required during that hospital stay as long RBC given is group O negative, or ABO/Rh compatible with both mom and the infant
- If positive for non-ABO alloantibodies:
  - Can use maternal serum for subsequent compatibility testing
  - Units negative for the appropriate antigen needs to be selected

III. Selection and modification of blood products

- Age of the RBC Unit:
  - Ideally RBC units are less than 7-10 days of age("fresh") to avoid transfusing high levels of K+ and lactate.
  - This is less crucial in routine transfusions, but more so in massive transfusions (>15-20ml/kg of body weight)
- Aliquoting from designated unit
  - Aliquots of small volume transfusions can be removed from the same designated parent unit over days or weeks to reduce donor exposure over time.
  - When assigning a unit to an infant, the parent unit should be <7-10 days (depending on institutional policy) at the time of the first aliquot.
- CMV risk reduction:
  - Premature infants considered at increased risk of CMV infection

- AABB recommends give CMV safe products for infants under **1200g** when mom or infant is CMV negative or serostatus unknown
- CMV negative products should also be considered for patients who are immunosuppressed (congenital, iatrogenic), and born to CMV negative or HIV positive mothers.
- It is not unreasonable to provide CMV safe products for all neonates regardless of mom's serostatus(Infant loses protective maternal antibodies overtime anyways.) or birth weight.
- Leukoreduced products can be used as an alternative to CMV seronegative products
- No evidence that using CMV-negative AND leukoreduced products further improves safety

♦ Prevention of TA-GVHD
- There is concern that the immature immune function may put neonates (especially those with low birth weight) at higher risk for TA- GVHD
- Irradiated cellular products are indicated for:
  - intrauterine/neonatal exchange transfusions
  - infants with known immune deficiencies
  - premature neonates weighing <1200 g.
  - Infants receiving cellular products from blood relatives or HLA matched directed donors
- Debatable if larger or full-term infants need to receive irradiated products routinely.
- Currently there is no universally accepted standard. Legal and logistic considerations may strongly influence practice at each institution. Not uncommon practice to irradiate cellular products for all neonates.

♦ Leukoreduction
- Well-justified when goal is to prevent CMV infections
- Not well-justified if the goal is to :
  - Prevent FNHTR – these reactions are rare in neonates
  - Prevent alloimmunization – neonatess rarely make anti-HLA (or alloantibodies against RBC antigens)
  - Prevent TA-GVHD – Leukoreduction is not adequate. Irradiation is needed
  - Prevent immune modulation – no good evidence that immune modulation occurs in neonates.

♦ ***Ideally HgS negative RBCs should be used for neonates:***
- RBCs from sickle trait positive individuals may sickle and produce 'sickle crisis" under extreme hypoxia and acidosis
  - Blood bank can do a quick screening test on the donor unit (Sickle-dex) prior to issue

IV. Blood Administration

- For routine transfusions, usually only a small amount is needed. A single unit could be designated for an infant and then split into aliquots (multiple packs, syringes). This also reduces donor exposure. Adsol preserved unit can be reserved for a patient and be used over a 42-day period
- If sterile connections used during aliquoting, parent unit expiration date unchanged. But aliquot must be used within 4hrs after aliquoting.
  - Use small tubing sets to minimize wastage
  - Use infusion pump to control the rate of transfusion
  - Large volume RBC transfusion (>15ml/kg):
    - Large volume transfusion situations: exchange/intrauterine transfusion, cardiac surgery, trauma, cardiac bypass. ECMO etc
    - Blood warmer can be considered for transfusion of larger volumes
    - Fresh units preferred due to lower K+ content
    - CPDA preserved unit considered safer than AS units. (The latter has mannitol and higher concentrations of adenine)

V. RBC Transfusions:

A. Neonates may require simple transfusion to correct anemia/blood loss, or exchange transfusion for hyperbilirubinemia

B. Decision to transfused should be based on
  - Symptoms: lack of weight gain, fatigue during feeding, tachycardia, SOB
  - Labs: Hgb/hct, reticulocyte count, nucleated RBCs on peripheral smear
  - No universally accepted guidelines. One example
    - Transfuse if symptomatic, hct 23-25%
    - If moderate heart/lung disease, or undergoing surgery, transfuse if hct is below 30%
    - Severe cardiopulmonary disease, or younger than 24 hours, transfuse if <40%
  - Standard dose: 10ml/kg -> raise Hgb 1-2g/dL

C. Exchange Transfusion
  - Indications: hyperbilirubinenia, HDN most common.
    - Have been also done for DIC, polycythemia, hyperammonemia, toxin removal, sickle cell disease in neonates.
  - Substantial risks involved.; considerable attention has been devoted to establishing indications and trigger for exchange transfusion
  - For hyperbilirubinemia: cord indirect bilirubin level >4mg/dL, or serum indirect bilirubin >20mg/dL within the first 72 hours often used. Rate of bilirubin rise is also a consideration
  - Technical issues
    - Usually via umbilical vessels, or peripheral vein if possible

- If using umbilical vessels:
  - Can use both umbilical vein and artery to perform isovolemic exchange
  - If only vein available: use a three-way stopcock, and "pull-push" discontinuous exchange. Each withdrawal should not exceed 5-10% of the patient's blood volume
- One blood volume exchange should remove about 65% of the original intravascular constituent, 2 blood volumes: 85%
- Takes 1-1.5 hours
- The initial Hgb, the target Hgb, the volume intended will determine the hct of the blood used for the exchange. Formula available to calculate the necessary adjustments
- Replacement RBC can be reconsituted by adding 5% albumin if it is desired to lower the hematocrit – albumin can also bind bilirubin and improve the hyperbilirubinemia
- RBC can also be reconstituted in FFP if coagulopathy needs to be corrected
- Need to monitor
  - Ca: citrate used in the exchange can lower Ca level
  - Glucose: transfused unit may have high glucose content, cause insulin release and subsequent rebound hypoglycemia

VI. Platelet Transfusions

A. Indications for neonates: Same as adults plus:
   - neonatal alloimmune thrombocytopenia (NAIT)
   - Infection-related thrombocytopenia
   - Thrombocytopenia due to maternal problem (ITP,SLE, PTP)
   - Congenital diseases: Wiskott –Aldrich etc

B. "Triggers" for neonates: higher than in adults: Infants born < 37weeks with co-morbidities especially prone to have platelet dysfunction and thrombocytopenia, hence higher risk for intracranial bleeding. Guidelines used at UCLA:
   - Small infants (gestational age <34 weeks):
     - Platelet count <50,000/mm3 in a stable infant with no evidence of severe illness
     - Platelet count <100,000/mm3 with evidence of severe illness. (e.g., severe respiratory disease, sepsis, NEC, or cardiac disease).
   - Larger infants (gestational age >34 weeks or birth weight >2000 gm):
     - Platelet count <50,000/mm3 with active bleeding or the need for an invasive procedure
     - Platelet count <20,000/mm3 regardless of clinical status.

C. Indications for children >6 mo, similar to adults:

- Platelet count <10,000-20,000/mm3 and no evidence of significant bleeding, but bone marrow failure/ hypoplasia, or factors that increase the risk of bleeding (e.g., active infection, liver disease with abnormal clotting test results, renal failure).
- Platelet count <50,000/mm3 and significant active bleeding , or patients who are in trauma, perioperative, about to undergo invasive procedures.
- Active bleeding, regardless of platelet count, in patients likely to have qualitative/functional platelet defect. *However patients with qualitative platelet defects should NOT receive platelets unless they exhibit bleeding or are to undergo an invasive procedure.*
- Acute, massive bleeding in any patient regardless of clotting studies with the following guidelines:
  - The 1st transfusion may be urgent and given without further justification during treatment of massive blood loss (>1 blood volume in <8 hours documented in medical record).
  - To justify additional platelet transfusions during the following 24 hours, clotting studies (PT, PTT, fibrinogen, platelet count) should be done within 6 hour before or after the transfusion and the platelet count should be documented to be <50,000/mm3.

D. Dose: several ways to determine:
   - 10 ml per kg of body weight- most common. This should increase platelet count by 30,000 -50,000/μL
   - One unit of platelet concentrate (PC) per 10 kg body weight
   - Four units of PC per square meter of BSA

E. If higher dose required to achieve higher post count, or when ABO incompatible platelet (plasma) is transfused, units can be centrifuged to reduce volume. Transfuse neonates with ABO-compatible platelets whenever possible.

F. Avoid Rh(D) sensitization. If not possible, keep in mind that:
   - Alloimmunization is rare in neonates.
   - May consider using RhIg if Rh negative infant exposed to Rh(D) RBCs. Each dose should cover 15 ml of RBCs.
     - Platelet concentrate: contains about 0.5ml RBC
     - Aphereis platelet unit: contains <<0.5ml of RBC

G. Aliquots can be prepared from a plateletpheresis unit to be used by the same patient over the shelf-life of the unit (5days) to reduce donor exposure. If aliquot separated from the mother unit using an open system, the aliquot expires in 4 hours.

VII. Plasma /Cryoprecipitate Transfusions

A. Plasma (including fresh frozen plasma, frozen plasma, and thawed plasma) primarily used in the treatment of coagulation disorders when specific factor concentrates are not available, or contraindicated. Not recommended for treating hypovolemia or providing "nutritional support".

B. In neonates, plasma transfusions are mostly for patients with liver failure, DIC or dilutional coagulopathy in neonates.

C. Note: newborn infants have moderagely decreased levels of vitamin K-dependent clotting factors (II, VII, IX and X) within the first 72 hours of birth, which can lead to spontaneous bleeding. This is prevented by giving all infants a prophylactic dose of IM vitamin K after birth in the U.S. Premature infants may require IV vitamin K and repeat doses.

D. Thawed plasma and frozen plasma can have lower levels of heat labile factors such as FV and FVIII. For this reason, many centers avoid giving thawed plasma to neonates.

E. Dose of plasma transfusion: 10-15ml/kg. This dose should increase factor levels 15-20% with ideal recovery and achieve hemostatic factor levels for most patients.

F. Cryoprecipitae is a concentrate source of fibrinogen. Although it is also a concentrate of FVIII and vWF, it is no longer the first line treatment for FVIII or vWF deficiency.

G. Although in general cryoprecipitate transfusion does not need to be ABO compatible due to the small volume of plasma involved, neonates should be given ABO compatible units due to their small body volume whenever possible.

H. Dose of cryoprecipitate
   - Number of units needed can be calculated using the fibrinogen increment desired, patient body weight, and assuming that each unit contains 250mg of fibrinogen.
   - Rule of thumb: 1-2 units cryoprecipitate per 10kg of body weight, should raise fibrinogen level by 60-100 mg/dL. In most neonates, a single unit is usually sufficient.

VIII. Granulocyte Transfusions:

A. May be considered for septic and neurtopenic neonates. Efficacy not fully established.

B. Characteristics of granulocyte concentrates:
   - Collected from G-CSF and steroid-stimulated donors
   - Store at room temperature without agitation
   - Transfuse as soon as possible after collection within 24 hours.
   - Must be ABO compatible because each unit has a large amount of WBCs
   - Each unit is about 200ml in volume, contains at least $1x10^{10}$ WBCs
   - Contains a significant amount of platelets as well, and may have added benefits for thrombocytopenic patients.
   - Should be irradiated (why?), but not leukoreduced
   - Due to the presence of WBCs, risk of CMV infection is increased. Should use CMV seronegative donors whenever possible.

IX. Transfusion Consideration for Patients Undergoing Extracoporeal Membrane Oxygenation (ECMO)

A. What is ECMO?

- A form of cardiopulmonary bypass used to support patient with reversible/temporary pulmonary or cardiac disease
- Requires venoarterial or veno-venous access
- See schematic diagram below.
- To prevent thrombosis and platelet activation, patients are heparinized, thus are at higher risk for bleeding

B. Transfusion support

- Most centers have standard protocols
- ECMO is akin to massive RBC transfusions, so RBCs should be < 7days old, and in CPDA preservative preferably. (Adsol units have higher content of mannitol)
- For priming: 2-3 units of PRBC regardless of patients Hgb level Platelet count maintained above 100,000-150,000
- Hemoglobin maintained at 12-15 g/dL
- FFP and cryoprecipitate transfused to correct coagulopathy. PT and PTT unreliable since patient is heparinized. Activated clotting times may be used.
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Image taken from:
http://www.gla.ac.uk/departments/surgicalpaediatrics/ecmoinfo.htm