Dr. Nadine Shehata – Alloimmunization Secondary to Pregnancy and Transfusion in Women of Child bearing Age

Alloimmunization (the development of an antibody to a foreign red cell antigen) occurs in women who are exposed to foreign paternal antigens during pregnancy or to foreign red cell antigens from red cell transfusion as alloantibody development occurs when an individual does not have the antigen of which she is exposed. If the alloantibody is an IgG alloantibody, it can traverse the placenta (IgM antibodies do not traverse the placenta), bind to the cognate antigen on the red cells of the fetus causing destruction of red cells and thus fetal anemia (hemolytic disease of the fetus (HDF). Anemia can extend to the neonatal period (hemolytic disease of the newborn (HDN)).

The risk of development of an alloantibody is not only dependent on exposure but also on the immunogenicity of the red cell antigen, the volume of red cell antigen exposed (higher volumes of red cell antigen exposure is associated with higher the risk of developing alloantibodies during pregnancy), the gestational age when the antigen develops in utero (earlier in gestation is associated with increases the risk of developing alloantibodies during pregnancy) and the ability for the mother to develop a cytotoxic antibody.

Because of these factors, not all mothers develop an alloantibody that is capable of causing HDFN. Once a woman develops an alloantibody however, there is a risk of severe HDFN e.g. fetal anemia although some women do not have HDFN. The D, K and c antigen are associated with more severe HDFN.

Preventing alloantibody development prevents the risk of HDFN particularly severe disease. Prevention of alloimmunization is achieved by reducing exposure to paternal antigens and/or red cell antigens vua red cell transfusion. The only paternal red cell antigen exposure that can be prevented/reduced is exposure to paternal D antigen by administering Rh immune globulin (RhIG) to the mother prophylactically or when there is fetal maternal hemorrhage (entry of fetal blood into the maternal circulation) as occurs during normal pregnancy or risk of fetal maternal hemorrhage (as occurs with trauma during pregnancy).

RhIG is a plasma derived product from donors with high anti-D antibodies. It is administered prophylactically at 28 weeks gestation to D negative mothers and after delivery if the neonate is D+. The prophylactic dose at 28 weeks gestation administered to a D negative mother assumes the father is D+. RhIG is also given within 72 hours of a sensitizing event (from fetal maternal hemorrhage) but may be given up 10 days after such an event.

Reduction of exposure of red cell antigens from red cell transfusion is achieved by red cell transfusion avoidance unless necessary (e.g. bleeding or symptomatic anemia) or if red cell transfusion is required, by administering K antigen negative red blood cells (which can be requested from the blood bank) to women of child bearing age to prevent alloimmunization to the K antigen.

Red blood cell transfusion is often prescribed according to hemoglobin concentrations. During pregnancy the hemoglobin concentration decreases because of hemodilution (increased blood volume relative to red cell mass). As such, hemoglobin concentrations decrease in pregnancy to a maximum of approximately 15g/L by the third trimester. As there are no trials of hemoglobin transfusion thresholds for red cell transfusion during pregnancy, transfusion is administered with anemia in pregnancy if the mother is symptomatic or bleeding or if the fetus is symptomatic (e.g. fetal tachycardia). Nonetheless the most common cause of anemia in pregnancy is iron deficiency so that ensuring mothers are iron replete by using prenatal vitamins and checking CBCs at the end of the first trimester to ensure a mother is not becoming anemic potentially results in a reduction of anemia and need for transfusion. Iron deficiency anemia can be treated with iron salts during the entire pregnancy and iv iron (iron sucrose) in the second and third trimester.

Dr. Lani Lieberman, Neonatal and Pediatric Transfusions

Proposed NICU RBC Transfusion Thresholds

Respiratory status	Age of neonate	Hemoglobin Threshold
Ventilated	Age < 1 wk Age > 1 wk	Hgb < 120 g/L Hgb < 110 g/L
On O_2/ CPAP	Age < 1 wk Age > 1 wk	Hgb <100 g/L Hgb < 90 g/L
Stable and off O_2	Age > 1 wk	Hgb < 75 g/L

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RBC Threshold Guidelines for Children

Pediatric Patient type	Threshold	Evidence grade
PICU (stable, non-cyanotic)	70 g/L	1B
Oncology	70 g/L (typical practice) Insufficient literature	2C
Perioperative non-cardiac surgery (stable, non-bleeding)	70 g/L	1C
Chronic anemia (Diamond Blackfan anemia)	80 g/L Consensus based	2C

* Hemoglobinopathies

The following should be considered for children undergoing surgery with significant risk of bleeding:

Tranexamic acid (1B)

Red cell salvage (2C)

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Proposed NICU Platelet Transfusion Thresholds

Clinical status	Platelet threshold	Grade Comment
Major bleeding or requiring major surgery (e.g. neurosurgery)	< 100 x 10^9/L	No RCT in prems
Bleeding, current coagulopathy, sx, exchange transfusion	< 50 x 10^9/L	
No bleeding (including NAIT if no bleeding and FHx of ICH)	< 30 x 10^9/L	Grade 2C

Special considerations for NAIT – neonatal alloimmune thrombocytopenia

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Suggested platelet thresholds for platelet transfusion in children

Platelet threshold (x 10^9/L)	Clinical situation
< 10	Irrespective of signs of hemorrhage (excluding ITP, TTP/HUS, HIT)
< 20	Severe mucositis Sepsis Laboratory evidence of DIC in the absence of bleeding Risk of bleeding due to a local tumour infiltration
< 40	Prior to lumbar puncture
< 50	Moderate hemorrhage (e.g. GI bleeding) Surgery, unless minor (except at critical sites)
< 75-100	Major hemorrhage or significant post-op bleeding Surgery at critical sites: CNS including eyes

** expert opinion

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Clinical Pearls

- Laboratory reference ranges (hematology and coagulation) specific for neonates and children should be used
- Always consider the etiology of the anemia and thrombocytopenia prior to ordering a transfusion
- Order blood products using child's weight

Blood Products are ordered by weight (ml/ kg)

Product	Pediatric Dose (ml/kg)	Typical Adult Dose
RBC	10-15 ml/ kg	1 Unit ≈ 280-300 mL
Platelets	10-15 ml/kg	1 Unit ≈ 250-350 ml
Plasma	10-15 ml/kg	3-4 Units ≈ 750-1000ml
Cryoprecipitate*	1-2 U/10 kg	Adult Pool 150-200ml