Recent Advances in Understanding Neonatal Hemolytic Disease

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Relevance of Hemolytic Disease to Neonatology Practice

OUTLINE
1. Mechanisms of senescence vs. hemolysis
2. Erythrocyte life span in neonates
3. Laboratory indicators of hemolysis
4. What’s new in ABO hemolytic disease?
5. What’s new in Rh hemolytic disease?

Erythrocyte Senescence = healthy clearance of RBC at the end of their productive life-span.
- Aged RBC are “tagged” for clearance in macrophages in the Spleen, Liver, Marrow.
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- Aged RBC are “tagged” for clearance in macrophages in the Spleen, Liver, Marrow.
- Aging-induced conformational change in CD47. CD47 switches from a signal of “phagocytosis suppression” to a signal of “phagocytosis promotion”.

Hemolysis = Pathological shortening of the normal RBC life-span.

Extrinsic (microangiopathic)

Extrinsic (oxidative damage)

Heinz bodies
Hemolysis = Pathological shortening of the normal RBC life-span.

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Extrinsic (oxidative damage)

Bite Cells

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Extrinsic (alloimmune, antibody-mediated)
Intrinsic (RBC structural abnormality)

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RBC Survival: Adult vs. Neonatal

RBC of adults 120 days
RBC of term neonates 85 days
RBC of “preterm” neonates 65-80 days

Classical Interpretation: characteristics intrinsic to the neonate’s RBC result in a shorter survival.
RBC Survival: Adult vs. Neonatal

● Newer testing: (biotin labeled autologous neonatal RBC and allogeneic adult RBC, transfused into VLBW neonates). Survival of neonatal and adult RBC was the same.

● Current interpretation: the circulatory environment of the neonate (not intrinsic RBC differences) is the primary determinant of the shorter RBC survival in neonates.

Laboratory Tests Indicating Hemolysis

Indirect Hyperbilirubinemia. Particularly when it is apparent on the day of birth.

Bhutani Normogram

Laboratory Tests Indicating Hemolysis

Indirect Hyperbilirubinemia. Urine analysis. Hemoglobinuria in the absence of RBC in the urine

Laboratory Tests Indicating Hemolysis

Indirect Hyperbilirubinemia. Urine analysis. Haptoglobin. Absent or falling value

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Laboratory Tests Indicating Hemolysis

- Indirect Hyperbilirubinemia.
- Urine analysis.
- Haptoglobin.
- End-tidal CO or carboxyhemoglobin.

- As hemoglobin is metabolized to biliverdin, CO is liberated.
- CO can be quantified in exhaled breath in ppm.

ABO Hemolytic Disease of the Fetus/Newborn

Mother is Blood Group O
and
Fetus is Blood Group A or B

Laboratory Tests Indicating Hemolysis

- Indirect Hyperbilirubinemia.
- Urine analysis.
- Haptoglobin.
- End-tidal CO or carboxyhemoglobin.

- For neonates on mechanical ventilation, an elevated carboxyhemoglobin, by co-oximetry, can recognize an elevated hemolytic rate.

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The ABO Blood Group Antigens (A and B) are sugars attached to the red blood cell surface. They attach to a sugar molecule called the H antigen.
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The A antigen is a galactosamine sugar attached to H

The B antigen is a galactose sugar attached to H

Textbook description of ABO hemolytic disease. Typically mild/moderate hyperbilirubinemia, but includes the possibility of the severe-end of the hemolytic spectrum, including:

- Hydrops with erythroblastosis fetalis
- Extreme hyperbilirubinemia (TSB > 25 mg/dL)
- Hospital readmission for jaundice
- Kernicterus (6% of USA kernicterus registry and 4 of 20 in Canadian report of kernicterus)

Problems:
1) None of the reports of severe-end ABO hemolytic disease are “post” AAP bilirubin screening/management guidelines (2004).
2) The risk of severe-end hemolysis from ABO hemolytic disease at Intermountain Healthcare, since 2004, is not known.

Hypothesis: We can judge the severity of ABO hemolytic disease at Intermountain by comparing specific outcomes of two groups of neonates born to group O(+) mothers since 2004.

Control Group… Babies of blood group O (not at risk)

Test Group… Babies of blood groups A and B (at risk)
Outcomes of Interest (Severe Hemolytic Disease):
1. Extreme hyperbilirubinemia (TSB ≥25 mg/dL)
2. Hospital readmission for jaundice treatment
3. Acute kernicterus
4. Hydrops fetalis with erythroblastosis

Summary of Findings
In 159,193 neonates born to group O(+) women:
1. Peak serum bilirubin higher in A and B than in O neonates (1 g/dL).
2. No difference in hospital readmission rate for jaundice treatment.
3. No difference in odds of bilirubin >25 mg/dL.
4. No difference in acute bilirubin encephalopathy (5 cases of kernicterus)
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3. No difference in odds of bilirubin >25 mg/dL.
4. No difference in acute bilirubin encephalopathy (5 cases of kernicterus).
5. No cases of hydrops/fetal anemia/erythroblastosis due to ABO.

Summary of Findings
In neonates born to group O(+) women and managed with “universal” bilirubin screening/management.
- Severe hemolytic disease is not more common than it is among controls.
- We doubt that ABO incompatibility causes hydrops/anemia/erythroblastosis. When such a case is seen, we look for other causes of hemolysis, in addition to ABO.

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Does IVIG add value in treating neonates with Rh hemolytic disease?

FINDINGS: Three studies, 189 infants. None randomized. Exchange transfusion was less in the IVIG treated neonates (typical RR 0.28, 95% CI 0.17 - 0.47; NNT 2.7).
CONCLUSION: Reduction in exchange transfusions but the applicability is limited. The number of studied infants is small. Further well designed studies are needed before routine use of IVIG can be recommended for the treatment of isoimmune hemolytic jaundice.

Smits-Wintjens et al. Intravenous immunoglobulin in neonates with rhesus hemolytic disease: a randomized controlled trial.
METHODS: Randomized, double-blind, placebo-controlled trial of IVIG (750 mg/kg) in neonates with Rh hemolytic disease.
RESULTS: 80 neonates. No difference in exchange transfusions between the IVIG vs placebo (17% vs 15%; P = 0.99) or duration of phototherapy (4.7 vs 5.1 days; P = 0.34), or maximum bilirubin levels (14.8 vs 14.1 mg/dL; P = 0.52).
CONCLUSIONS: IVIG is not effective in neonates with Rh hemolytic jaundice.
Van Klink JM et al. Immunoglobulins in neonates with Rhesus hemolytic disease of the fetus and newborn: long-term outcome in a randomized trial.

METHODS: Neurodevelopmental follow-up of 66 of the 80 children randomized, double-blind, placebo-controlled trial of IVIG (750 mg/kg) in neonates with Rh hemolytic disease.

RESULTS: No difference in cognitive scores or rate of neurodevelopmental impairment between the IVIG and placebo recipients.

Santos et al. The efficacy of the use of IVIG in Brazilian newborns with rhesus hemolytic disease: a randomized double-blind trial.

METHODS: Randomized, double-blind, placebo-controlled trial of IVIG (500 mg/kg) in neonates with Rh hemolytic disease.

RESULTS: 92 neonates. No difference in exchange transfusion (13% in IVIG group vs 15% in the placebo group, p=0.77). No differences in phototherapy time, peak bilirubin, or length of hospital stay.

CONCLUSIONS: IVIG is not effective in neonates with Rh hemolytic jaundice.

Figuras-Aloy et al (Barcelona) IVIG & necrotizing enterocolitis in newborns with hemolytic disease.

METHODS: Retrospective study over 16 years. 492 infants ≥34 weeks with severe isoimmune hemolytic jaundice Rh (n=91) or ABO (n=410) treated with phototherapy. 167 (34%) also received IVIG (500 mg/kg over 2 to 4 hours)

RESULTS: NEC diagnosed in 10 (6%) of the IVIG recipients and in 1 (0.3%) of the non–IVIG-treated group; OR: 31.7; 95% CI 3.3-309

Manotas et al (Cornell) Hemolysis after high dose IVIG in blood group A women with alloimmune thrombocytopenia.

PROBLEM: Hemolysis after IVIG dosing has been observed in clinical trials. Risk factors for hemolysis include having blood type A, B, or AB.

EXPLANATION: IVIG contains isohemagglutinins that coat red cells. Anti-A, Anti-B, and Anti-D titers are present in IVIG products at varying concentrations

Christensen RD, et al Increased hemolysis after administering IVIG to neonates with erythroblastosis fetalis due to Rh hemolytic disease.

2010

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#### Circulatory environment of the neonate

The circulatory environment of the neonate is the primary determinant of the shorter RBC survival in neonates.

- Elevated End tidal CO, or carboxyhemoglobin
- Haptoglobin absent or falling

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#### WAS IT FUN or BOARING?

**RECAP**

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Severity not significantly above control rates
WAS IT FUN or BOARING? 
BOTH?

Thanks for your kind attention!

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