Neonatal Isoerythrolysis

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Neonatal Isoerythrolysis (NI) is an immune mediated hemolytic anemia of new born foals mediated by maternal anti-RBC antibodies absorbed from colostrum.

Conditions necessary for NI to occur

1) The foal must inherit certain RBC antigens from the sire that the dam does not have.

2) The dam has to be previously sensitized to these RBC antigens through:

   a. Placental bleeding from fetal membranes to maternal blood during previous pregnancies with same RBC antigens in foal's blood (most mares at risk are multiparous)

   b. Previous whole blood transfusion

   c. Equine biologics or plasma contaminated with RBC antigens

3) During the current pregnancy the mare is re-exposed, mounts an antibody response and concentrates the antibodies in her colostrum.

4) The foal must ingest and absorb the colostrum in sufficient quantities to cause disease.

The most common of the 32 blood group antigens in the horse to be involved is the Aa and the Qa locus which is thought to account for 90% of the reactions. The R and S groups are 3rd and 4th most common. The frequency of the genes for these antigens and thus the frequency that they are the culprits vary among breeds. Both agglutination and hemolysis may occur depending on the antibodies present in the colostrum. Both intravascular and extravascular hemolysis may occur.

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Frequency of Antigens and Risk of Antibody Production in Different Breeds

Breed	Antigen	% of mares without antigen (at risk)	Likelihood foal has inherited antigen
Thoroughbred	Aa	2%	85%
	Qa	16%	60%
Standardbred			
Pacers	Aa	22%	44%
Trotters	Aa	3%	82%
All Std	Qa		0%
Saddlebred	Aa	25%	50%
	Qa	68%	12%
Quarter Horse	Aa	25%	49%
	Qa	68%	18%
Morgan	Aa	18%	57%
	Qa		0%
Arabian	Aa	3%	82%
	Qa	72%	20%

from: Bailey, E. Prevalence of Anti-red Cell Antibodies in the Serum and Colostrum of Mares and Its Relationship to Neonatal Isoerythrolysis. Am J Vet Res (1982) 43:1917.

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Clinical signs

Onset occurs between 8 and 120 hours of age. The timing depends on amount of antibody absorbed as determined by the amount ingested, the titer in colostrum and efficacy of colostral absorption. The more antibody absorbed, the more rapid the onset and the more severe the disease (Note: this is one instance where FPT has its advantages).

There is a wide spectrum of disease which can be divided into 3 syndromes:

Peracute disease: Signs are caused by severe, acute anemia secondary to massive hemolysis. This causes severe anemic hypoxemia (lack of O_2 carrying capacity) resulting in tissue hypoxia leading to metabolic acidosis and MODS. These foals are normal at birth but have a sudden onset of weakness, tachycardia, tachypnea, collapse, neurologic derangement, fever or hypothermia, colic, cardiovascular collapse, shock, and death. All of this occurs within hours, often before they become icteric.

Acute disease: Signs are caused by moderate to severe anemia which results in recruitment of compensatory mechanisms which are sufficient to prevent tissue hypoxia (compensated fully except for the added demands of exercise or stress). Again, these foals are normal at birth but develop progressive weakness and icterus (which can become extreme), exercise intolerance, tachycardia, tachypnea, fever (secondary to hemolysis), and hemoglobinuria.

Subacute disease: Signs are secondary to hemolysis and mild anemia which is fully compensated even with moderate exercise or stress. These foals are normal at birth. The only sign may be icterus. They may be febrile, they can have brief hemoglobinuria, and mild tachycardia and tachypnea.

Laboratory Findings

Anemia is a constant finding. It may be mild to severe (can be as low as 4-8%). If the hemolysis has been present long enough, plasma may be very icteric. If intravascular hemolysis is ongoing, the plasma may be pink. Hyperbilirubinemia will be present, ranging from just above normal to 40 mg/dl with most being between 12 and 25 mg/dl which is primarily unconjugated. Although not often run, the direct Coomb's test will be positive.

I often cross match the mare and foal's blood to definitively identify the incompatibility. In this way agglutinins and hemolysins are identified if present. This can be run before the foal nurses but the hemolysin part of the assay will take

up to 3 hours so in cases at risk the foal will need to be kept from nursing the mare and fed bank colostrum while waiting test results. Since foals are often born late at night it also requires lab services available 24-7. The time, expertise and special reagents needed all make this test unsuited as a farm based test.

The Jaundice Foal Agglutination Test is a farm based test which only tests for agglutination and not hemolysins. Although this test does not detect hemolysins and thus will miss some cases (false negatives) many cases have both agglutinins and hemolysins or only agglutinins so there is a fairly good correlation of a positive test and presence on NI. The only special equipment needed is a centrifuge, which many large breeding farms have. The procedure is easy.

1) Make 1 ml serial dilutions of mare's colostrum 1:2 to 1:128 in saline

2) Add 1 drop of foal's blood (collected in anticoagulant)

3) Centrifuge 2-3 minutes a 300-500 g.

4) Decant the liquid

   a) Complete agglutination is indicated by tight pack of cells at bottom of tube

   b) Strong agglutination is indicated by cells remaining in large clumps

   c) Weak agglutination results in smaller clumps which run down the wall of tube

   d) A negative test results in the cells readily flowing down the side of the tube

5) Run a saline control (replaces colostrum) and a control using mare's RBC.

From: Bailey et al Proc 33rd AAEP 33:341, 1987.

Case Management

If signs occur during first 24 hours, milk colostrum from mare every 2 hours (*discard - do not feed to other foals*), separate foal from mare or muzzle foal and cover udder for first 36 hrs. An alternate source of colostrum should be found or the foal should be given plasma. Maintain adequate nutrition and hydration during this period. The foal can be allowed to nurse the mare after 36 hours if the mare has been milked every 2 hours.

It is very important is to minimize stress. This is often difficult since these otherwise normal foals need to be confined, not allowed to nurse the mare and frequent blood samples are needed.

Careful monitoring of the PCV is vital since new waves of hemolysis can occur at any time. Serial samples are needed. Observe closely for signs of hemolytic episodes such as fever, hemoglobinuria, tachypnea, tachycardia, and muscle fasciculations.

Make sure the foal has an adequate IgG level since these foals seem to be particularly susceptible to infections (may be because of reticuloendothelial system preoccupation with RBC fragments). Antimicrobial therapy should be routine in severe cases. Also watch kidney function which may become compromised with hematuria.

Treatment

A whole or packed cell blood transfusion is indicated when PCV is in the low teens and/or PCV is dropping rapidly. It is also indicated when signs of severe anemia are present despite the fact that the PCV is not extremely low. The mare can be used as a donor but her cells must be washed at least twice with saline. This takes a long time unless done at human blood bank. Alternately, a donor who is Aa and Qa antigen negative can be used since these are the antigens most likely to be causing the problem. Ideally, any donor should be cross-matched. The idea of cross-matching is to find a donor with major side compatibility (donor's RBCs don't react with foal's plasma). The minor side will always be incompatible because foal's RBC are already coated with Ab (from the colostrum) and will should either autoagglutinate or autohemolize. In fact, if this does not happen, the diagnosis should be reevaluated. Unlike older horses, transfused RBC in foals may have a nearly normal life span if they are a good match.

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Amount of blood transfused can calculate from:

$$\frac{\text{body wt (kg) X Blood vol (ml/kg) X (PCV desired - PCV observed)}}{\text{PCV of donor blood}}$$

Age	Blood Volume		Plasma Vol		RBC Volume		ECF Volume	
	ml/kg	S.D.	ml/kg	S.D.	ml/kg	S.D.	ml/kg	S.D.
2 days	151.2	32.8	94.5	8.9	58.3	25.8	394.1	28.8
2 weeks	99.1	15.7	70.2	9.2	29.0	7.6	364.9	52.7
4 weeks	93.0	10.2	61.8	5.9	29.5	5.1	348.0	44.7
12 weeks	82.0	6.0	52.8	3.1	29.2	3.0	276.9	26.7
24 weeks	69.3	8.8	44.9	6.9	24.1	2.8	291.7	35.6
Adult	72.0	11.0	48	6.0	25.0	6.0	234.0	22.0

from: Spensley et al AJVR 48:1703, 1987

General rule of thumb: need 2-4 l whole blood to raise PCV into mid 20's.

Prevention

If mare has had an NI foal before, she is at risk for having another. One approach to prevent future problems is to blood type the mare and stallion and breed based on blood groups. Although blood typing is commonly done for breed registries, it is rarely considered when breeding are planned. The blood type can be used to predict the likelihood of problem so that proper measures can be taken at birth.

Several options are available for use in late gestation or a birth before the foal nurses. The mare's sera can be tested in late pregnancy against the stallion's RBC. Alternately, the JFA test can be run before the foal nurses. Frequently once the mare has had a problem foal, it is assumed there will be a problem and protective measures are taken at birth such as covering the udder in late pregnancy in case of unexpected early foaling occurs, attending the birth so that before foal nurses it can be separated from mare or muzzled and the udder covered for first 36 hrs and the colostrum should be stripped from mare.

Sequela - Kernicterus and iron toxicity (from transfused incompatable RBCs) leading to acute liver failure (J Vet Intern Med 2008;22:1216-22).