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Update on passive transfer of immunoglobulins in the foal

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Summary

Foals are born essentially agammaglobulinemic and rely on the absorption of colostral IgG for protection against infectious agents during the first few weeks of life. A mare produces colostrum during the last 2 to 3 weeks of gestation and once the foal suckles, it is rapidly depleted. Colostral quality is directly related to its specific gravity and the amount of immunoglobulin it contains can be estimated with an equine colostrometer or sugar or alcohol refractometers. Foals whose dams do not have adequate colostrum need to be supplemented with a substance rich in immunoglobulin. Equine colostrum is highly preferred as a substitute over bovine colostrum or commercial immunoglobulin products because the IgG is most readily absorbed. Failure of passive transfer can be estimated in the foal as early as 8 to 10 hours of age. There are a variety of assays that may be used in the field to rapidly estimate the immunoglobulin content in the foal. Foals with low serum IgG concentrations should receive additional IgG within the first 3 days of life. The well-being of foals with failure of passive transfer will depend greatly on the farm environment. Foals living in a clean, well ventilated barn that is not crowded are less likely to become ill than foals born into dirty, crowded conditions.

Keywords: equine, foal, immunology, passive transfer, immunoglobulins

Eine Übersicht zum Immunglobulintransfer auf das Fohlen

Bei der Geburt weisen Fohlen eine Agammaglobulinämie auf und sind zum Schutz vor Infektionen während der ersten Lebenswochen von einer Absorption von kolostralem IgG abhängig. Die Stuten produzieren in den letzten 2 bis 3 Trächtigkeitswochen Kolostrum, und sobald das Fohlen anfängt zu saugen, ist es schnell verbraucht. Die Kolostrumqualität ist direkt von dem spezifischen Gewicht abhängig und der Immunglobulingehalt kann mit Hilfe eines equinen Kolostrometers oder eines Zucker- oder Alkoholrefraktometers bestimmt werden. Fohlen, deren Mütter kein Kolostrum von ausreichender Qualität besitzen, müssen mit einer mit Immunglobulinen angereicherten Substanz zugefüttert werden. Als Substitution wird equines Kolostrum vor bovinem Kolostrum oder kommerziellen Immunglobulinen bevorzugt, weil dessen IgG am schnellsten absorbiert wird. Eine ungenügende passive Aufnahme kann bei Fohlen bereits im Alter von 8–10 Stunden abgeschätzt werden. Es gibt eine Vielzahl von Tests, die in der Praxis verwendet werden können, um schnell den Immunglobulingehalt beim Fohlen zu bestimmen. Fohlen mit niedrigen IgG-Serum-Konzentrationen sollten zusätzlich IgG innerhalb der ersten drei Lebenstage bekommen. Das Allgemeinbefinden von Fohlen mit einer ungenügenden Aufnahme von Kolostrum hängt stark von den äußeren Haltungsbedingungen ab. Fohlen, die in einem sauberen, gut belüfteten, nicht überfüllten Stall gehalten werden, werden seltener krank, als Fohlen, die in einem schmutzigen, überfüllten Stall aufwachsen.

Schlüsselwörter: Pferd, Fohlen, Immunologie, passive Aufnahme, Immunglobuline

Introduction

Foals are born essentially agammaglobulinemic and rely on the absorption of colostral IgG for protection against infectious agents during the first few weeks of life. Failure of passive transfer of immunity (FPT) at birth is highly associated with sepsis during the first week of life and therefore, is of great concern to horse owners and veterinarians *(McGuire et al. 1977; McGuire et al. 1975)*. This article reviews the pathophysiology, diagnosis and treatment of failure of passive transfer.

Production and absorption of colostrum

Colostrum is produced in the last few weeks of pregnancy under the influence of estrogen and progesterone. It contains a number of soluble substances such as immunoglobulins, cytokines, growth factors, hormones and enzymes. Colostrum also contains cells, including lymphocytes, macrophages, neutrophils and epithelial cells *(Sellon 2000)*. These factors are likely important in the development of local gastrointestinal immunity and modulation of the newborn's response to antigens. At this time, though, only colostral immunoglobulins have been linked specifically to passive immunity and susceptibility to infection in the foal.

Normal foals suckle colostrum within 1 to 3 hours of birth, and maternal immunoglobulins are detectable in the foal's serum within 6 hours. Colostral proteins and macromolecules are absorbed non-selectively by specialized cells in the small intestine. This process is called pinocytosis. Macromolecule absorption is maximal soon after birth and decreases rapidly to less than 1% by 20 hours *(Jeffcott 1971; Jeffcott 1974)*. The amount of colostrum ingested and when it is ingested by the foal after birth influences the timing. Foals that suckle large quantities of colostrum within 1 to 2 hours of birth experience "gut closure" sooner than foals that are weak, that are orphaned

at birth or that suckle colostrum with a low immunoglobulin content. Absorption of macromolecules ceases by 24 hours after birth. This phenomenon results from a rapid turnover of absorptive cells and may be triggered by the high level of adrenal corticosteroids present in the foal's circulation in the first 24 hours of life *(Nathanielsz et al. 1972)*.
Serum immunoglobulin concentration declines rapidly during the first 4 weeks of life, largely because IgG is catabolized and diluted in the increasing plasma volume of the growing foal. The half-life of maternal IgG in foals is approximately 20 to 30 days. As maternally derived immunoglobulin wanes, the foal begins to produce its own immunoglobulin. This results in colostrum-fed foals having low serum IgG concentrations between 1 and 3 months of age with concentrations gradually increasing to adult levels by 6 months of age. In colostrum-deprived foals, there is an earlier and more rapid increase in autogenous immunoglobulin synthesis, detectable as early as 2 weeks of age *(Jeffcott 1974)*.

Measurement of colostral IgG concentration and storage

There are three potential causes of FPT in foals:
1) failure to ingest sufficient quantities of colostrum;
2) failure to absorb colostral immunoglobulins from the gastrointestinal tract; and
3) ingestion of colostrum with low immunoglobulin concentrations.

Colostral immunoglobulin concentration varies widely between mares. It can be estimated by measuring specific gravity, glutaraldehyde coagulation, refractometry and by single radial immunodiffusion. Colostral specific gravity is directly related to colostral IgG concentration *(LeBlanc et al. 1986)*. Colostrum with a specific gravity $\geq$ 1.06 has more than 3 G of IgG/L. Foals that suckle colostrum with a specific gravity $\geq$ 1.06 have serum IgG concentrations that are > 400 mg/dl at 24 hours of age *(LeBlanc et al. 1992)*. Foals that suckle colostrum < 1.06 have a 50% likelihood of having inadequate serum IgG concentrations at 24 hours of age ($\leq$ 400mg/dl) The immunoglobulin content in colostrum can be estimated with an equine colostrometer, sugar refractometer or an alcohol refractometer *(LeBlanc et al. 1986; Chavatte 1998)*. The equine colostrometer measures specific gravity and samples with a specific gravity > 1.06 has more that 3 G of IgG/L. Colostrum that contains $\geq$ 60g/L of IgG has a refractive index of $\geq$ 16% when measured with an alcohol refractometer or $\geq$ 23% when measured with a sugar refractometer. The alcohol refractometer is used to measure the degree of alcohol in wine by wine makers and is readily available in Europe.
Colostrum collected for banking should be taken from mares < 15 years of age and have a specific gravity > 1.06. Mean colostral specific gravity of older mares (> 15 years) is lower than that of younger mares and there is a higher incidence of FPT in foals from older mares *(LeBlanc et al. 1992)*. Therefore, taking colostrum from older mares may subject their foals to FPT. Mares produce between 2 and 3 L of colostrum and the IgG content drops rapidly if the foal suckles vigorously. By 8 hours after foaling, colostral IgG content has dropped by 60–75% *(Jeffcott 1974; Massey et al. 1991; Pearson et al. 1984)*. If colostrum is to be banked, it should be collected immediately after the foal first suckles. Approximately 250 ml of colostrum can be collected from a mare without harming her foal. Colostrum can be stored frozen for 18 months without measurable loss of IgG and can be thawed in either a warm water bath or in a microwave oven set on defrost cycle. Banked colostrum needs to be evaluated by a laboratory that performs modified blood typing to ensure that it does not contain antibodies against the factors Aa or Qa on red blood cells.

Diagnosis of failure of passive transfer

Failure of passive transfer has been defined variably as a serum IgG concentration at 24 hours of age of < 200 mg/dl, < 400 mg/dl and < 800 mg/dl. Foals that are completely colostrum deprived (IgG <200 mg/dl) are at extremely high risk for sepsis even when management practices are optimal *(McGuire et al. 1977; McGuire et al. 1975)*. However, partial FPT (IgG concentration of 200–800 mg/dl) is not always associated with increased prevalence of illness or death that suggests that environmental conditions and management practices, in combination with even minimal ingestion of colostrum, may be important in preventing sepsis.
There are many rapid field tests currently available for evaluating FPT *(Madigan 1990)*. The modified zinc sulfate turbidity test and the serum glutaraldehyde coagulation test are reliable, fast (10 minutes) and inexpensive, non-commercial, semi-quantitative techniques for detecting 400 mg/dl of IgG in neonatal foals. The major problem with both tests is that hemolysis of a serum sample may result in over estimation of IgG concentration. The enzyme immunoassay test, is a convenient, semi-quantitative, reliable diagnostic assay that is easy to perform. It determines serum IgG concentrations of < 200, 200–400, and >800. Many veterinarians prefer it to other tests because of its greater specificity and commercial availability, even though it is more expensive. Immunoglobulin screening tests are accurate at identifying foals with complete FPT, but their accuracy in detecting marginally deficient foals is variable. When there is doubt about test results, the value should be confirmed with the Single Radial Immunodiffusion test.
Serum IgG concentration can be measured in foals as early as 8 to 12 hours after birth since IgG peaks in serum at 12.2 ± 2 hours (Mean ± SD) in foals that suckle vigorously *(Massey et al. 1991)*. By measuring serum concentrations in foals at 8–12 hours, foals with low serum IgG concentration can be supplemented orally with colostrum prior to gut closure.

Prevention and treatment of failure of passive transfer

Foals that are less than 18 hours of age with serum IgG concentrations between 200 and 400 mg/dl and foals whose dams have poor quality colostrum (colostral specific gravity < 1.06) should be supplemented with at least 250 ml of colostrum that has a specific gravity > 1.06 within the first 18 hours of

life. Orphan foals, foals whose dams prematurely lactate, or foals with serum IgG concentrations < 200 mg/dl may need 1–2 liters of colostrum that has a specific gravity > 1.06. On a weight basis, foals require approximately 1 gm of colostral IgG/kg of body weight to attain an IgG concentration of 800 mg/dl serum *(Massey et al. 1991)*. Supplementation with colostrum should begin when the foal is 1 to 2 hours of age and should be given in volumes of 200 to 400 ml per feeding. If good-quality equine colostrum is not available, bovine colostrum or one of a variety of equine IgG supplements may be administered orally *(Lavoie et al. 1989; Holmes and Lunn 1991)*. Bovine colostrum does not provide protection against equine specific pathogens (i.e. Actinobacillus equuli) and therefore must be used with caution. Serum IgG concentrations attained after administration of purified IgG products have been disappointing *(Vivrette et al. 1998; Franz et al. 1998)*. This may result from these products lacking the cellular and soluble components that are present in colostrum.

Therapies for foals > 24 hours of age with FPT include intravenous plasma, purified IgG products and antibiotics. The dose of plasma required by a foal with FPT depends on the IgG content in donor plasma, the degree of IgG deficiency in the foal, the foal's body weight and whether or not it is ill *(LeBlanc 1987)*. Farm management and the cleanliness of the farm also needs to be considered. Foals with serum IgG concentrations between 200–400 mg/dl that are born on highly maintained, clean farms do not commonly become septic, whereas foals with > 800 mg/dl of IgG may develop sepsis in a dirty, overstocked environment. Recommended doses range from 20 to 200 mg/kg of IgG for healthy foals and up to 500 mg/kg of BW for ill foals with FPT *(McGuire et al. 1975; LeBlanc 1987)*. Because it is difficult to predict the magnitude of the rise in serum IgG following treatment, blood should be collected 24 hr after plasma is administered to measure serum IgG. A liter of plasma should increase serum IgG concentration by approximately 200 mg in a clinically healthy foal with FPT, whereas the increase in IgG in ill foals varies greatly *(LeBlanc 1987)*. Plasma will most likely need to be re-administered often to ill foals because serum IgG declines rapidly due to catabolism, equilibration between the intra- and extra-vascular spaces and use in immune interactions. An IgG concentration of 600 mg/dl or greater is considered optimal in ill foals but may be difficult to maintain.

The ideal plasma donor is an adult horse with serum IgG concentrations > 1500 mg/dl that has been blood typed and found free of isoantibodies to the equine major blood types (universal donor). There are several commercial sources of equine plasma. These products are convenient and relatively safe because donors are screened for major alloantigen or alloantibody problems and infectious diseases and are vaccinated against common equine pathogens. Alternatively, plasma can be obtained from donor horses housed in the same environment as the foal to be treated. This has the advantage of increasing the likelihood of providing optimal immunoglobulin concentrations against pathogens unique to the foal's local environment.

Lyophilized, purified, equine immunoglobulin products have been used for oral or intravenous use to treat FPT *(Vivrette et al. 1998; Franz et al. 1998)*. The advantages of purified equine IgG is that a small volume can be administered orally or intravenously. The major disadvantage, similar to commercially obtained plasma, is that it may not contain immunoglobulin that will protect the foal against environmental pathogens. These products are safe but do not appear to be as efficacious as colostrum in increasing serum IgG concentrations in foals with failure of passive transfer. They are also costly. Two products currently available are Lyphomune® (Diagnon Corp, Rockville, MD) and Seramune® (Shawnee Mission, KS). Doses of 50 to 70 gm of Lyphomune® that were fed or given intravenously to Thoroughbred and Arabian foals (n = 18) resulted in peak serum IgG concentrations ranging from 350 to 480 mg/dl at 10 hrs after birth *(Franz et al. 1998)*. Interestingly, when 10 of these 18 foals were fed colostrum at 24 hr after birth, serum IgG concentrations rose an additional 125 mg/dl. Administration of two 150 ml doses of Seramune® orally within 4 hrs of birth resulted in mean serum IgG concentrations of 105 $\pm$ 2.6 mg/dl in 12 foals *(Vivrette et al. 1998)*.

To treat or not to treat foals with FPT should be left up to the discretion of the veterinarian and farm management. However, hypogammaglobulinemic foals may be unable to respond adequately to bacterial challenge. Serum IgG is needed to maximize neutrophil phagocytosis and to neutralize bacteria. Foals with IgG concentrations < 400 mg/dl have significantly lower opsonic activity (binding capacity) than adults or foals with IgG concentrations > 600 mg/dl *(LeBlanc and Prichard 1988)*. By providing these foals with supplemental IgG, opsonization of bacteria will be enhanced.

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