Neonatal Septicemia - Pathology and Clinical Signs

Sarah Eaton[1]

[1]University of Arizona

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Abstract

Septicemia can be a tragic illness in neonatal and young foals. Sick foals may manifest a variety of clinical symptoms all related to a common infection and its systemic effects. While the pathogenesis of this disease is the same as for adult equids, the clinical signs seen can be very different. The rapid changes seen in foal are reflective of their low endogenous reserves of glucose and innate immune mediators as well as the poor ability to self-regulate their metabolism. The neonatal immune system is reliant on maternal antibodies at birth and development of the foal's own system takes a significant amount of time. This non-competent immune system changes how the foal responds to infection when compared to the adult. Clinical signs in septic foals include tachycardia, tachypnea, depression, anorexia, colitis, and fever. Less commonly, foals may show petechiation, swollen joints, anterior uveitis, and coma. This article is the first of a two part series on neonatal sepsis and will present a review on the neonatal immune system, the pathophysiology of sepsis, and the range of clinical signs seen in foals.

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Author: Sarah Eaton DVM DACT CVA DABVP-Equine; ORCID iD 0000-0002-9863-6968

Institutional Affiliation: College of Veterinary Medicine, University of Arizona, Tucson AZ

Summary and Keywords

Septicemia can be a tragic illness in neonatal and young foals. Sick foals may manifest a variety of clinical symptoms all related to a common infection and its systemic effects. While the pathogenesis of this disease is the same as for adult equids, the clinical signs seen can be very different. The rapid changes seen in foal are reflective of their low endogenous reserves of glucose and innate immune mediators as well as the poor ability to self-regulate their metabolism. The neonatal immune system is reliant on maternal antibodies at birth and development of the foal's own system takes a significant amount of time. This non-competent immune system changes how the foal responds to infection when compared to the adult. Clinical signs in septic foals include tachycardia, tachypnea, depression, anorexia, colitis, and fever. Less commonly, foals may show petechiation, swollen joints, anterior uveitis, and coma. This article is the first of a two part series on neonatal sepsis and will present a review on the neonatal immune system, the pathophysiology of sepsis, and the range of clinical signs seen in foals.

Horse, septicemia, colitis, neonate, pathophysiology

Main text

Pathology and Immunology

Septicemia is a life-threatening disease that can affect all horses; however, foals are very prone to illness when compared to adult horses. Commonly, foals are considered neonates when less than seven days old but in some studies foals are considered neonates until 30 - 60 days of age (Marsh and Palmer 2001; Wilson and Madigan 1989). Normal foals are very active and oscillate between nursing, sleeping, and playing.

Foals can become very ill rapidly (within hours), and as such prompt treatment is necessary. At birth, foals are immunologically naive and depend on two main methods of fighting infection, the innate and the adaptive immune systems (Mealey and Long 2018). Due to the equine placental structure (epitheliochorial, diffuse, microcotyledonary), no antibodies are passed *in utero* and as such foals depend on adequate amounts of colostrum intake for the antibodies needed for initial protection (Madigan 2013a; Senger 2005). These antibodies act as the acquired immune system until the foal is able to mount their own immune responses to pathogens. The colostral antibodies also help to opsonize neutrophils and make them more able to respond to infection (Mealey and Long 2018). The initial antibodies ingested by the foal from the dam's colostrum are assessed by measuring immunoglobulin G (IgG) levels in the blood (Madigan 2013a). Adequate levels of IgG are $>$ 800 mg/dL and this is considered "adequate passive transfer". Levels below 800 g/dL indicate complete or partial failure of passive transfer and make the foal more susceptible to infection (Madigan 2013a). Once the foal has absorbed immunoglobulins in the first 6 - 24 hours after birth they are used to fight against environmental organisms that may cause infection. Maternal, colostral-derived antibodies reach their lowest levels in the foal between one and two months of age due to usage consumption but can still interfere with a foal's endogenous antibody production. A foal will take weeks to months to develop a functional initial acquired immune system (Barton 2006). Specifically, IgGa starts being produced by nine weeks of age, but IgGb does not begin to rise until after four months of age. The effectiveness of IgG protection is also dependent on secondary signals from the inflammatory cascade which may not be mature enough to respond properly before four months of age (Mealey and Long 2018). The acquired (or adaptive) immune system is mediated by activation of B and T cell lymphocytes and develops due to exposure and recognition of the body to antigens. B cells are produced in the bone marrow after a 3 day maturation process and recognize antigens in solution or on cell surfaces. T cells are produced in the thymus and respond to antigens that are associated with self-molecules called major histocompatibility complex molecule, found on most cell surfaces. These exposures create primed cells that can rapidly respond when needed in the future by creating specific antibodies, cytokine, and cell proliferation responses in the form of plasma cells, memory B cells, CD4 T cells, or CD8 T cells (Mealey and Long 2018). This acquired response takes weeks to "learn" each new organism and the complete ability to respond to antigens in foals can take up to one year after birth (Perkins and Wagner 2015). An adult-level immune response using lymphoproliferation can be mounted starting at three months of age in foals. Prior to that major, histocompatibility complex II presentation may be compromised (Mealey and Long 2018). The innate immune system requires weeks to months to develop into full function (Perkins and Wagner 2015). Foals are born with neutrophils that are completely functional at birth, however for full effectiveness they require opsonization by colostral antibodies and as such may have reduced killing ability in the first two weeks of life (Mealey and Long 2018).

Cell-based molecules such as Toll-like Receptors recognize molecular patterns on the bacterial cell wall or viral structure and lead to an intracellular cascade which in turn signals the adaptive innate response as well as releasing pro-inflammatory cytokines. These cytokines stimulate the production of acute phase proteins from the hepatocytes, cause clinical signs of inflammation, and activate complement. The complement cascade activation leads to neutrophil chemotaxis, activation of mast cells, neutrophil degranulation, and the release of reactive oxygen species (ROS) from neutrophils. These ROS play a key role in bacterial and viral killing (Mealey and Long 2018). Band neutrophils are produced when the granulopoiesis in the bone marrow is not sufficient to keep up with the tissue demand and the cells are released prematurely (Webb and Latimer 2011). Band cells, which are immature neutrophils, have a longer half-life but are less effective against infectious organisms due to decreased phagocytosis and ROS production (Sheats 2019).

The adaptive immune response uses specific interactions between antigens and antigen-specific receptors on lymphocytes. In foals, it is incomplete through the first year of life, but an attempted immune response is seen to pathogens starting at three months of age. B and T cell lymphocytes have specific receptors that interact with cell surfaces either alone or in conjunction with the host's cell receptors to create antibodies against specific pathogens (Mealey and Long 2018). These lymphocytes have memory, which allows them to rapidly respond to previously recognized insults. If adequate, the immune system is able to eradicate the infecting organism without becoming uncontrolled. When there is an inadequate (whether excessive or

deficient) response, the uncontrolled immune response can turn against itself or allow an infection to flourish. Foals have been shown to have a reduced interferon levels in the prenatal period. This makes them more susceptible to intracellular organisms as interferon assists in the normal major histocompatibility complex response of T cells. (Mealey and Long 2018).

Sepsis and the Immune System

Sepsis, also known as septicemia, is defined as a dysregulated host systemic inflammatory response to infection (Sheats 2019). In neonatal foals, the most common causes of septicemia are Gram negative organisms such as *Escherichia coli (E.coli), Klebsiella pneumoniae, Pseudomonas aeruginosa, Salmonella* species, *Enterobacter*species, and *Actinobacillus* species, or Gram-positive organisms such as *Streptococcus* species, *Enterococcus* species, or*Staphylococcus* species (Frederick et al 2009; Taylor 2015). Limited studies are available evaluating sepsis in post-neonatal foals. When a horse is infected, key protective mechanisms include a physical barrier composed of epithelial cells, normal gastrointestinal flora, gastrointestinal mucus, phagocytic cells, and molecular defenses. These molecular defenses are soluble molecules such as cytokines, chemokines, and immunoglobulins which also may exist on cell surfaces such as antigen receptors (Barton 2006). The gastrointestinal tract has additional protection due to Mucosal Associated Lymphoid Tissues (MALT). The MALT are present close to epithelial surfaces for more rapid response. Microfold cells rapidly phagocytose and antigen present foreign organisms to B cells, leading to their more rapid differentiation. When the gastrointestinal mucosal barrier is breached pro-inflammatory chemokines, such as tumor necrosis factor ?, are produced. These chemokines attract neutrophils, monocytes, and mast cells. Neutrophils that have been activated after extravasation from the bloodstream release an oxidative burst of molecules that stimulate bacterial killing and attract more inflammatory mediators (Mealey and Long 2018). Mast cells increase vascular permeability, cause vasodilation, enhance epithelial secretion, and are phagocytic. Monocytes play a cell role as antigen presenting cells to cellular receptors (Figueiredo et al 2009). If the inflammatory response is uncontrolled it can lead to Severe Inflammatory

Response Syndrome (SIRS) and there is a risk of multiple organ failure due to the accumulation of neutrophils in organs causing secondary injury (Sheats 2019). As such, one of the main goals in the treatment of sepsis is the control of the inflammatory response (Werners 2016). The normal inflammatory response, as described above, has vasoactive and phagocytic components, mediated by inflammatory mediators. If these responses become uncontrolled, the activation of the inflammatory pathway exceeds the host's ability to regulate and contain that inflammation. Normal neutrophil response is to migrate to a site of infection/inflammation, then release inflammatory mediators and ROS. In sepsis, neutrophils lose their molecular compass and as such may attack host cells, have delayed apoptosis, and accumulate in organs (Sheats 2019). This leads to inappropriate activation of the innate immune system through pathogen associated molecular patterns or damage associated molecular patterns as well as activation of the complement and coagulation cascades. These released molecules also damage endothelial cells, leading to vasodilation and an increase in capillary permeability, causing fluid leakage (edema) and poor maintenance of intravascular pressure. The cytokines and other molecules released by the neutrophils change vascular perfusion due to endothelial cell damage, activation of protease cascades, and disrupt the coagulation system equilibrium (Wong and Wilkins 2015). The ROS become cytotoxic to host cells if uncontrolled (Mealey and Long 2018). Neuroendocrine responses stimulate central nervous system activity which in turn affects the function of organs distant to the site of inflammation as well as releasing neurotransmitters (Wong and Wilkins 2015). The number of organs affected have been correlated with the odds of six-month survival; with animals having three or more organs affected having a poorer survival rate (Sheats 2019). In horses the most common organs affected are the lungs, heart, kidney, and laminae of the hoof.

Enterocolitis

Enterocolitis, or inflammation of the gastrointestinal tract, can be a sequela to septicemia, a cause of septicemia, or can occur due to non-infectious causes (Mallicote et al 2012). Primary infectious diarrhea is caused by organisms colonizing and destroying the cells that line the gastrointestinal tract. Foals with systemic sepsis can develop secondary diarrhea due to mucosal hypoperfusion of the gastrointestinal tract and

the release of sepsis-related inflammatory mediators (Mallicote et al 2012). The translocation of enteric bacteria is possible but less common than gastrointestinal inflammation secondary to sepsis (Mallicote et al 2012). In foals with sepsis, 32 - 62% of foals showed signs of enterocolitis (Oliver-Espinosa 2018; Taylor 2015). Colitis occurs when there is an imbalance between the secretion by the crypt epithelium and the absorption by the surface epithelial cells of the colon. This balance is controlled by systemic hormones, the enteric nervous system, bacterial enterotoxins, and the immune system; all of which can be affected by pre-formed inflammatory mediators, such as those that occur with systemic infection. Reactive oxygen species are of specific concern as they can be cell damaging and increase mucosal permeability. One of the greatest risks to the gastrointestinal tract is damage to the tight junctions between epithelial cells. Damage to these tight junctions allows for solutes and inflammatory molecules to flow across a previously tightly regulated membrane (Mealey and Long 2018).

Clinical Signs Septic foals can range from symptomatic to comatose, and these clinical signs can progress rapidly. Unfortunately, septic foals often present with nonspecific signs, so suspicion of sepsis should be on the differential list for any abnormal neonatal foal. Owners may report that the foal is sleeping more than usual, difficult to rouse, or is not nursing. Upon examination, the only clinical evidence of the foal's anorexia may be an engorged udder or milk staining on the dam's hind legs. As the sepsis progresses, foals can show the classic signs of shock, cold extremities, mucous membrane abnormalities, hypothermia, and dehydration (McKenzie 2018). Other clinical signs seen may depend on the organ system affected. Respiratory infection often leads to tachypnea with subsequent acid-base disturbances that may mask the severity of disease (Taylor 2015). Clinically, foals with colitis can present with a range of symptoms from diarrhea to dehydration to depression to sudden death. Some organisms, such as certain *Clostridia spp.*, can cause acute colitis with toxemia and the foal may die acutely prior to physical evidence of diarrhea (Uzal et al 2022). Early in the disease foals often have physical examination findings consistent with colic or depression including, but not limited to, tachycardia, tachypnea, anorexia, bruxism, rolling, and pawing. Due to their small size and small glucose reserves, the foals can also develop weakness and ataxia from a lack of metabolizable energy (Oliver-Espinosa 2018). As the illness progresses into SIRS many foals show signs of cardiovascular shock in which they remain hypotensive despite adequate fluid resuscitation (Taylor 2015).

Foals are very prone to gastric ulcers when stressed. Septic or colitis cases can be stressed due to the pain from the inflamed gastrointestinal tract, fever, or anorexia. In self-propagating fashion, pain from the ulcers causes the foal to stop nursing, which causes more stress and more acid production. Gastric ulcers form from hydrochloric acid splashing upwards onto the squamous mucosa, leading to cell damage. This splashing can be due to movement, stress, or increased intra-abdominal pressure (Sykes et al 2015). Studies have shown the incidence of gastric ulcers in hospitalized foals to be between 3 and 51% (Furr et al 2012).

While it is less stressful for foals to be with their dams, colic may occur due to milk intake. Milk ingestion can cause physical discomfort due to gastrointestinal distention secondary to ileus or gas produced due to lack of lactose enzymatic digestion. As such, foals are sometimes muzzled, or the mare milked frequently to reduce foal intake for 12 - 24 hours allowing the gastrointestinal tract to rest (Oliver-Espinosa 2018). Inflammation of the foal gastrointestinal tract can lead to microvilli necrosis due to hypoxia secondary to changes in intestinal vascular perfusion (McKenzie 2018). This in turn reduces the foal's ability to break down and digest lactose, also known as lactose intolerance.

Foal-Specific Foci of Sepsis

In adult horses the umbilicus has atrophied as have the umbilical arteries, vein, and urachus. In foals, however, normal regression takes up to two weeks after birth (Whitcomb 2013). Until then the structures receive blood flow, although limited, and are exposed to the external environment at birth. This opening to the extracorporeal environment provides a good site for a nidus of infection to develop. In addition, ill foals can develop a patent urachus, in which a previously closed urachus reopens, providing another site for bacteria to enter the body (Knottenbelt et al 2004). Hematogenous spread of bacteria into the umbilical vessels can lead to abscessation of the vessels or the liver. Another area of foal-specific disease localization

is the joints and physes, as foals are predisposed to developing septic arthritis and epiphysitis compared to adult horses. This is due to the anatomy of the blood vessels in the subchondral bone of both the physis and the epiphysis which allows septic emboli to lodge therein (Knottenbelt et al 2004). Clinical signs of septic arthritis / epiphysitis are lameness, joint or leg swelling, and pain on palpation of the area. Finally, there is an increased incidence of bacterial meningitis in foals compared to adults secondary to sepsis (Knottenbelt et al 2004). This most likely occurs due to septic invasion into the central nervous system in cases with systemic sepsis as the bacterial causes are the same types of bacteria associated with neonatal sepsis. Clinical signs of meningitis include lethargy, recumbency, fever, cervical pain, and seizures.

Conclusion

Foals are not merely young horses, but have different environmental, nutritional, medical, and metabolic needs. Diseases in foals can progress extremely rapidly and treatment responses must occur just as quickly. Many of these differences in response can be attributed to the immature immune system of foals, which allow significant infection to become established in a short period of time. Education of owners and veterinarians on foal-specific clinical signs will lead to a more rapid identification of illness and hopefully successful outcome.

Declarations

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Ethical Animal Research

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