Equine Neonatal Sepsis: The Pathophysiology of Severe Inflammation and Infection

Marion duPont Scott Equine Medical Center
Leesburg, Virginia
H. C. McKenzie III, DVM, MS, DACVIM
M. O. Furr, DVM, PhD, DACVIM

ABSTRACT: Although the clinical syndrome of sepsis is a major problem in equine neonates, the pathophysiology of this condition remains incomplete. Because the term sepsis describes a broad range of disorders with different underlying causes and often different prognoses, the understanding of this process is further complicated. Continued progress is being made, however, in defining the syndromes associated with sepsis and in elucidating the mechanisms involved in these processes. Attempts at modulating the septic process by interfering with the action of bacterial toxins or the production or activity of individual mediators have not been successful, thereby reinforcing that this is a multifactorial response. Fortunately, the complex interactions of intra- and extracellular messengers leading to clinical sepsis continue to be defined. An increased understanding of the processes involved in the septic response may aid in the identification of patients with these syndromes as well as improve the effectiveness of treatment regimens.

One of the most challenging problems faced by equine veterinarians is the management of equine neonates with sepsis. Despite the substantial advances that have been made in the medical management of these foals, the mortality rate remains high. This is due to the fact that sepsis represents a systemic inflammatory response to infection or injury; therefore, it can rapidly progress to septic shock and death despite aggressive treatment. Traditionally, the term septicemia, which is used to refer to this process in equine neonates, describes a systemic disease process involving the presence of pathogenic microorganisms and/or their toxins in the blood. The classic presentation of sepsis was that of disseminated gram-negative bacterial infections; however, it has become apparent that an identical syndrome occurs in patients with gram-positive bacte-
rial infections, viral infections, trauma, hypovolemia, hemorrhage, and immunologic and drug reactions (Figure 1). 3–6

The abnormalities associated with the clinical syndrome of sepsis result from a nonspecific innate inflammatory response. This response, which has been termed the systemic inflammatory response syndrome (SIRS), is not necessarily associated with the presence of bacterial infection. 7,8 SIRS, which represents a common terminal phase of the inflammatory response characterized by malignant global activation of multiple proinflammatory pathways, 4 is defined by the presence of two or more of the following abnormalities: fever or hypothermia (rectal temperature greater than 39.2°C or less than 37.2°C), tachycardia (heart rate greater than 120 beats/min), tachypnea (respiratory rate greater than 30 breaths/min) or hypocapnia (partial pressure of arterial carbon dioxide less than 32 mm Hg), leukocytosis or leukopenia (leukocyte count greater than 12,500 or less than 4000 cells/µl), or increased numbers of immature forms of granulocytes (greater than 10% bands). 9,10 These manifestations of disease are the same as those previously used to define sepsis, and the appreciation that many different stimuli can induce this response has resulted in sepsis being redefined as SIRS due to infection (Box 1). 8

The changes associated with SIRS can lead to shock, which is characterized by severe hypotension not responsive to intravenous fluid therapy (Figure 2). Shock can result in hypoperfusion and organ dysfunction such that homeostasis cannot be maintained without intervention, a process termed multiorgan dysfunction syndrome (MODS). 5,8,9 MODS is a progressive syndrome with initial dysfunction in the cardiovascular system, followed by involvement of the respiratory, hepatic, gastrointestinal, renal, cardiac, and neurologic systems. 5,11 These processes result in the development of refractory hypotension, lactic acidosis, and oliguria, often progressing to death. 9,11

**PATHOPHYSIOLOGY OF SEPSIS**

Inflammation represents the response of tissues to either injury or the presence of microorganisms. It serves a vital role because it enhances the movement of phagocytic cells and defensive molecules (e.g., immunoglobulin, complement) from the bloodstream to the site of infection or injury. The first step in this process is the recognition of tissue injury or microbial invasion. Injured cells release preformed mediators (e.g., histamine) and synthesize proinflammatory substances, including eicosanoids (e.g., prostaglandins, thromboxanes, leukotrienes) and the cytokines (interleukin [IL]-1 and tumor necrosis factor [TNF]–α; Figures 2 and 3). These mediators are responsible for the initiation of a nonspecific inflammatory response. Microbial invasion

---

**Figure 1**—Relationships of systemic inflammatory response syndrome (SIRS), sepsis, and infection. Infection is not always associated with an inflammatory response; and SIRS can occur without infection. When SIRS occurs in association with infection, the response may be referred to as sepsis. 3

---

**Box 1**

**Terms Used to Describe Clinical Syndromes Associated with Systemic Inflammation** 9,10

- **Infection:** Inflammatory response to the presence of microorganisms or the invasion of normally sterile host tissue by microorganisms
- **Bacteremia/septicemia:** Presence of viable bacteria in the bloodstream
- **Systemic inflammatory response syndrome (SIRS):** Systemic response to an array of severe clinical insults
- **Shock:** SIRS-induced hypotension refractory to fluid resuscitation in association with hypoperfusion
- **Sepsis:** SIRS due to infection
- **Severe sepsis:** Sepsis associated with organ dysfunction, hypoperfusion, or hypotension
- **Septic shock:** Sepsis-induced shock
- **Multiorgan dysfunction syndrome (MODS):** Altered organ function in an acutely ill patient requiring intervention to maintain homeostasis
may result in tissue injury, thereby initiating this process, or specific bacterial cell components may be recognized by immune cells (macrophages), which result in the production of inflammatory mediators and the initiation of an inflammatory response. The bacterial cellular components that are recognized by the immune system include endotoxins (lipopolysaccharide; LPS) and exotoxins from gram-negative bacteria as well as peptidoglycans (PGs), lipoteichoic acids (LTAs), enterotoxins, and superantigenic exotoxins from gram-positive bacteria. Although bacterial infection may be responsible for the initiation of an inflammatory response, the inflammatory process itself results solely from the production of endogenous mediators.

Because of the predominance of gram-negative infection in foals with sepsis, LPS is commonly involved in the molecular mechanisms described. On entering the circulation, LPS is avidly bound to the LPS-binding protein (LBP); the LPS–LBP complex then binds to a receptor present on the surface of the mononuclear phagocyte (mCD14) or in the circulation (sCD14). CD14 also binds PG and LTA from gram-positive bacteria. This may represent a route of cellular activation in gram-positive infections. The LPS–LBP–
CD14 or PG–LTA–CD14 complex is then responsible for cellular activation of the mononuclear phagocyte via a toll-like receptor (TLR) that transmits the activation signal across the cell membrane (Figure 4). Numerous types of TLRs have been identified in mammalian species; evidence suggests that these different types of TLRs are responsible for recognition of different types of microbial pathogens.

Cellular activation may also occur because of the development of a nonspecific oxidative stress reaction within the mononuclear phagocyte following stimulation by proinflammatory stimuli such as TNF-α, endotoxin, or exotoxins (Figure 4). The development of an inflammatory response is dependent on the production—primarily by the activated mononuclear phagocyte—of numerous inflammatory mediators, including proinflammatory cytokines (e.g., TNF-α, IL-1, IL-6), proinflammatory enzymes (e.g., inducible nitric oxide synthase, phospholipase A₂, cyclooxygenase-2), and adhesion molecules (e.g., selectins, intracellular adhesion molecules). The transcription of many of the genes encoded for these mediators or the enzymes that produce them is dependent on the transcription activator nuclear factor–κB; therefore, this molecule may be a potential target for intervention in SIRS (Figure 4).

The initial changes that occur in an inflammatory response are primarily the result of local vasodilation and increased vascular permeability caused by the effects of vasoactive mediators released by the injured or infected cell (Figures 2 and 3). These factors include histamine, serotonin, kinins, eicosanoids, platelet activating factor, fibrin degradation products, and the complement products, C3α and C5a. Changes occur in the vascular endothelium under the influence of
molecules arising from the injured tissue (e.g., IL-1, TNF-α, histamine), resulting in neutrophil diapedesis and increased vascular permeability. On their arrival at the site of tissue injury, neutrophils and macrophages phagocytose foreign material and injured or dead tissue cells and destroy the phagocytosed material by oxidative mechanisms (neutrophils) or by both oxidative and nonoxidative mechanisms (macrophages). In addition, macrophages release a number of factors that augment the immune response, including the proinflammatory cytokines (e.g., IL-1, TNF-α, IL-6, IL-12, IL-18; Figure 3). The proinflammatory cytokines signal target cells, primarily neutrophils, to increase the production of secondary inflammatory mediators, including phospholipid derivatives (e.g., prostaglandins, thromboxane A₂, leukotrienes) and reactive oxygen species (singlet oxygen, superoxide anion, hydroxyl radical, hydrogen peroxide, NO, hypochlorite ion), further increasing the activity of the inflammatory response. The systemic manifestations of inflammation and/or infection (e.g., fever, lethargy, malaise, loss of appetite, cachexia) are primarily due to TNF-α and IL-1.

**Acute-Phase Response**

Interleukin-6, IL-1, and TNF-α initiate the acute-phase response, whereby the liver increases production of acute-phase proteins. These substances are important in many phases of the response to inflammatory stimuli, including complement activation, coagulation, fibrinolysis, transport of substances within the blood stream, inhibition of neutrophil proteases, and modulation of the inflammatory response (Figure 3). The acute-phase response is critical in inflammation, healing, and adaptation to noxious stimuli. Also included in the acute-phase response is a counterregulatory antiinflammatory component that normally functions to minimize and resolve the inflammatory response to localized stimuli. This counterregulatory response consists of antiinflammatory mediators that inhibit macrophage activation (e.g., IL-4, IL-10, IL-13, adrenal corticosteroids, transforming growth factor-β, prostaglandin-E₂), antagonists to the receptors for proinflammatory cytokines (e.g., IL-1 receptor antagonist), and soluble receptors of proinflammatory cytokines (e.g., soluble IL-1 receptor type II, soluble TNF receptors). The balance between these proinflammatory and antiinflammatory components is important in determining the characteristics of the inflammatory response because excessive activity of the antiinflammatory component may result in immunosuppression during or after a severe inflammatory response, which has been termed **compensatory antiinflammatory response syndrome** by Bone and colleagues.

**Systemic Inflammatory Response Syndrome**

In moderation, the changes associated with an inflammatory response are protective, resulting in enhanced killing of microbes by antigen-specific and nonspecific mechanisms, generalized immune stimulation, and increased activity of the systems required for the healing of damaged tissue. The excessive, malignant form of the inflammatory and acute-phase responses, termed SIRS, is characterized by the systemic activity of numerous proinflammatory mediators, including cytokines (e.g., IL-1, TNF-α, IL-6, IL-8), phospholipid derivatives (e.g., platelet activating factor, prostaglandins, throm-
These media-shock responses are impaired by the widespread activation of the clotting system, resulting in MODS. The initial systemic effect of these changes is pulmonary vasoconstriction leading to pulmonary hypertension likely caused by thromboxane A2. The initial hypertensive phase is followed by systemic hypotension caused by decreased arterial tone and results in decreased left ventricular preload, combined with venous vasodilation in the large-capacity vessels that decreases venous return. These effects are likely due to epoprostenol (PGI2; prostacyclin) and NO and can progress to the syndrome of hyperdynamic shock, with increases in heart rate and cardiac output developing as compensatory mechanisms to maintain tissue perfusion. This compensatory response is impaired by the reduction in left ventricular preload, combined with the decreased cardiac contractility resulting from myocardial depressants (e.g., NO, TNF-α, IL-1), decreased myocardial responsiveness to β-adrenergic stimulation, and decreased compliance due to myocardial edema.

Changes occurring in the microvasculature further contribute to the impairment of tissue perfusion. Arteriolar vasoconstriction develops due to the impairment of the normal autoregulatory systems (e.g., NO from endothelial NO synthase, PGI2 from cyclooxygenase-1) caused by inflammatory cytokines and endothelin-1 combined with the increased production of vasoconstrictive substances (e.g., endothelin-1, thromboxane A2). Adherence of neutrophils to the endothelium and endothelial cell swelling further reduce blood flow. Accumulation of fibrin and aggregation of platelets and erythrocytes secondary to activation of the clotting system results in occlusion of the vasculature, leading to tissue hypoperfusion. Arteriovenous shunting occurs in some tissues, whereas increased vascular permeability results in extravasation of fluids into the interstitial space, further contributing to hypotension and hypovolemia. Progressive alteration of the microcirculation leading to failure may represent the common final pathway of SIRS-related injury contributing to or resulting in MODS.

Activation of coagulation occurs primarily through the extrinsic pathway because of the production and surface expression of tissue factor (thromboplastin) on endothelial cells and mononuclear phagocytes under the influence of IL-6, the production of which is increased by proinflammatory stimuli (e.g., endotoxin, TNF-α, IL-1). Endothelial injury secondary to neutrophil degranulation results in decreased production of PGI2 and NO, leading to increased platelet adhesion. In the normal state, the accumulation of excessive amounts of fibrin would be prevented by the action of plasmin, the primary mediator of fibrinolysis. In the presence of SIRS, the fibrinolytic system is suppressed because of the increased plasma concentration of plasminogen-activator inhibitor type 1, the primary inhibitor of fibrinolysis. The widespread activation of the clotting system, combined with impairment of fibrinolysis and depression of the inhibitors of coagulation, can result in a consumptive coagulopathy potentially leading to disseminated intravascular coagulation.

**Shock**

The progression of these processes affecting the cardiovascular system ultimately results in shock. Shock occurs when cardiovascular function is severely impaired, such that hypotension cannot be corrected with intravenous fluid administration and requiring the use of inotropic and/or vasopressor agents. Shock represents severe cardiovascular dysfunction associated with SIRS and is a primary component of MODS. Septic shock is defined as shock associated with infection.

**Multiorgan Dysfunction Syndrome**

The development of MODS is likely the result of cardiovascular dysfunction, which leads to tissue hypoperfusion combined with changes in cellular metabolism that result in impairment of oxygen delivery and uptake, respectively. The presence of tissue hypoxia is manifested by metabolic acidosis and decreased oxygen extraction ratios. Pulmonary dysfunction is manifested by refractory hypoxemia, potentially caused by increased pulmonary vascular permeability,
Renal dysfunction is manifested by the development of azotemia and oliguria; acute renal failure is likely caused by alterations in the distribution of intrarenal blood flow arising from microvascular alterations with or without systemic hypotension.

Gastrointestinal dysfunction is primarily manifested by the presence of ileus but may also result in loss of the normal barrier function of the gastrointestinal mucosa. This loss of the mucosal barrier may further contribute to the pathogenesis of MODS due to bacterial translocation or endotoxin absorption. Hepatic dysfunction is manifested by the development of hyperbilirubinemia and, in some cases, increased serum activities of hepatic enzymes (sorbital dehydrogenase, aspartate aminotransferase). Hepatic dysfunction may result from hypoperfusion, particularly because of the high metabolic demands of this tissue, but may be heightened by the production of inflammatory mediators by the hepatic Kupffer's cells secondary to the actions of systemic mediators or stimuli derived from the gastrointestinal tract. Dysfunction of the central nervous system, which is frequently present, may manifest as depression but can progress to septic encephalopathy with extensive neuronal injury. The development of consumptive coagulopathy (disseminated intravascular coagulation) could also be considered a component of MODS rather than merely a pathophysiologic process contributing to the development of organ failure.

NEONATAL SEPTICEMIA

Risk Factors

A number of factors have been identified that increase the likelihood of septicemia and mortality in equine neonates. The risk factors for septicemia may include a history of placentalitis, prenatal vulvar discharge, dystocia, maternal illness, premature or delayed parturition, induced parturition, total failure of passive transfer, prolonged transport of the pregnant mare, and the presence of localized disease in the neonate (e.g., anterior uveitis, diarrhea, pneumonia, infectious arthritis, open wounds). Partial failure of passive transfer (serum IgG concentration 200 to 400 mg/dl) has been considered a risk factor for septicemia. However, this may not be the case because one study reported no statistical difference in duration or frequency of illness or survival when comparing foals with IgG concentrations of less than 400 or greater than 800 mg/dl. Risk factors for neonatal death may include maternal illness, premature or delayed parturition, induced parturition, prolonged duration of clinical signs, and decreased serum IgG concentration.

Routes of Invasion

Pathogenic organisms can infect equine neonates by numerous routes. While in the intrauterine environment, the fetus may be exposed to organisms that have invaded the placenta or that cross the placental–chorial barrier, gaining direct access to the foal's bloodstream. Bacteria associated with placental disease may enter the amniotic fluid and gain access to the respiratory and gastrointestinal tracts of the fetus. After birth, bacterial infection can be caused by contamination of the umbilical stump, ingestion or inhalation, or secondary to wounds.

Organisms Involved in Neonatal Sepsis

Blood culture remains the most definitive test for ante-mortem identification of septicemia in equine neonates. Blood culture should be performed—ideally prior to the administration of antimicrobial therapy—when any equine neonate presents with a clinical suspicion of sepsis. This test has been reported to have variable sensitivity in many species, including horses, with false-negative results obtained in up to 37% of cases of fatal septicemia. It is interesting to contemplate how much higher the false-negative rate might be in the less severely ill neonate that recovers with antimicrobial therapy. It has been recommended that multiple samples be collected to maximize the sensitivity of this test, but the majority of isolates have been reported to be present in the first culture sample. The need for immediate antimicrobial therapy usually results in only one sample being obtained. Because of the low sensitivity of blood culture, it is important to obtain bacterial cultures from suspected areas of infection during the course of treatment because the blood culture may be falsely negative or nosocomial infection may have developed during the course of treatment. The appropriate samples are dependent on the system affected but would include transtracheal aspirate; blood; urine; synovial, peritoneal, and cerebrospinal fluid; and umbilical remnants following surgical resection.

Although historically gram-positive organisms were most commonly associated with neonatal infections, over the past 20 years the most common bacteria isolated from infected foals have been gram-negative organisms (Table 1). Gram-positive organisms isolated from infected foals are typically present in mixed infections with gram-negative organisms; streptococcal species are most common. Other organisms associated with severe systemic inflammation in equine neonates include equine herpesvirus type 1 and Histoplasma capsulatum. It is also possible that severe hypoxia, which leads to hypoxic ischemic encephalopathy (also known as neonatal asphyxia, dummy foal syndrome), represents a causative factor for induction of SIRS in equine neonates.
Identification of Septic Neonates

Identification of septic neonates is of clinical relevance in ensuring that appropriate treatment is administered and in determining prognosis for survival. The identification of septic neonates remains problematic, however, because neonates that present with clinical abnormalities consistent with sepsis (SIRS) may be negative on blood culture with no evidence of a focal site of infection. Attempts to identify equine neonates with septicemia have included the development of a sepsis scoring system that combines historical information, objective data, and subjective measures to derive a numerical representation of the patient’s condition. The sensitivity and specificity of this scoring system were reported to be 93% and 86%, respectively. Unfortunately, the specificity and sensitivity may not always be this high. In addition, this scoring system must be adapted to each intensive care unit in which it is applied to achieve reasonably high levels of sensitivity and specificity.

Attempts to create sepsis scoring systems for human patients have encountered many of the same difficulties, likely resulting from the inherent limitations involved. The primary limitation arises from the fact that scoring systems strive to incorporate large amounts of clinically relevant data into a single representative numeric value. Although this may be beneficial in concentrating one’s attention on the most important components of the clinical situation, it also results in a loss of information. The second limitation arises from the fact that, as previously discussed, the pathophysiologic mechanisms operating in equine neonates with SIRS are consistent, regardless of the primary etiology. Therefore, the manifestations of disease that are subsequently incorporated into a scoring system inherently lack the precision required to differentiate various types of primary disease. As a result, no sepsis score can substitute for clinical judgment, and these scores should be used as a diagnostic aid in the identification of high-risk individuals with full consideration given to their limitations. Because of the difficulty of definitively identifying neonates with bacterial infection, it is appropriate to make the assumption that any high-risk neonatal foals presenting with clinical illness are septic. Aggressive therapy that includes antimicrobials is indicated. Although there are some risks associated with antimicrobial therapy, they are greatly outweighed by the risks associated with withholding antimicrobial therapy from a patient with sepsis secondary to bacterial infection.

CONCLUSION

The development of SIRS in equine neonates is a complex process that involves numerous initiating factors, inflammatory mediators, and variable degrees of organ dysfunction. Initially, it may be difficult to determine the underlying disease process when presented with a neonate with SIRS. Treatment of patients with SIRS requires the same basic supportive therapies (e.g., intravenous fluids, antimicrobials, antiinflammatory drugs) regardless of the etiology, but identification of the specific etiology will allow for more effective and appropriate application of both basic and adjunctive therapies. It is clear that the treatment of SIRS and its sequelae cannot focus solely on any single component of this process but must be directed at resolution of the initiating stimulus, modulation of the inflammatory response, and support and maintenance of organ function.

REFERENCES

5. Purvis D, Kirby R: Systemic inflammatory response syn-


---

**ARTICLE #4 CE TEST**

The article you have read qualifies for 1.5 contact hours of Continuing Education Credit from the Auburn University College of Veterinary Medicine. *Choose the best answer* to each of the following questions; then mark your answers on the postage-paid envelope inserted in *Compendium*.

1. The clinical condition of sepsis results from the activity of
   a. bacteria.
   b. viruses.
   c. fungi.
   d. host-derived mediators.
   e. all of the above

2. SIRS represents
   a. the clinical response to infection.
   b. the excessive activity of the antiinflammatory response.
   c. the result of cardiovascular dysfunction leading to tissue hypoperfusion.
   d. the excessive, malignant form of the inflammatory and acute-phase responses.
   e. a systemic disease process involving the presence of pathogenic microorganisms and/or their toxins in the blood.

3. The organisms most commonly involved in equine neonatal infections are
   a. gram-positive bacteria.
   b. gram-negative bacteria.
   c. equine herpesvirus type 1.
   d. mixed bacterial infections.
   e. anaerobic bacteria.

4. The excessive activity of endogenous antiinflammatory mediators may result in the
   a. MODS.
   b. SIRS.
   c. compensatory antiinflammatory response syndrome.
   d. systemic antiinflammatory response syndrome.
   e. septic shock.

5. The risk factors for equine neonatal septicemia include all of the following except
   a. unobserved parturition.
   b. gestational age.
   c. dystocia.
   d. induced parturition.
   e. maternal illness.

6. Blood culture samples
   a. are often contaminated with nonpathogenic bacteria.
   b. are rarely useful in guiding the clinical management of septic foals.
   c. must be collected before administration of antimicrobial agents.
   d. have very high sensitivity and specificity for septicemia.
   e. should be collected in all foals presented with a clinical suspicion of sepsis.

7. Antimicrobial therapy
   a. should be delayed pending the results of bacterial culture and sensitivity testing.
   b. should be initiated early in any high-risk clinically ill neonatal foal.
   c. is without major risk.
   d. will prevent the culture of organisms from blood cultures.
   e. should be reserved only for foals with clinically detectable infection.

8. Abnormalities used to define SIRS include all of the following except
   a. fever.
   b. tachypnea.
   c. leukocytosis.
   d. central nervous system depression.
   e. hypothermia.

9. Sepsis scoring systems are helpful in
   a. deciding if a foal should be treated with antimicrobials.
   b. monitoring the response to treatment.
   c. identification of high-risk individuals.
   d. assessment of passive transfer.
   e. determining the most appropriate antimicrobials for treatment of sepsis.

10. Organ dysfunction in equine neonates with sepsis may be manifested by all of the following except
    a. polyuria.
    b. hypotension.
    c. hypoxia.
    d. ileus.
    e. hyperbilirubinemia.