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Early Recognition of the Septicemic Foal

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Take Home Message

Septicemia, defined as the systemic reaction caused by the presence of microorganisms or their toxins in the blood, is often cited as the most common reason for illness and death in the neonatal period. Knowledge of a combination of historical risk factors, physical findings, and simple laboratory diagnostics can be important aides in early recognition of septicemia.

Introduction

The actual incidence of septicemia in the general equine population is not well-known, relative to other, noninfectious causes of morbidity or mortality. “Serious” infection in the first 90 days of life was reported in 37 of 132 foals (28%) on a Standardbred farm in New York over the 1986 foaling season.1 In terms of neonatal mortality, septicemia was the reported cause of death in 26% of 334 foals less than 10 days of age born on a large farm in 1994 in Canada.2 A large-scale study of 167 farms in Texas in 1991, involving 2,468 foals, revealed that septicemia was responsible for 30% of the deaths in foals less than 7 days of age.3 In tertiary care centers, perinatal infection is consistently reported as one of the most common reasons for referral. At two referral university practices where blood is cultured from all foals that are admitted into their intensive care units, the reported incidence of positive blood cultures is 26% to 28%.4,5 At the University of Georgia, from 1986-2000, a review of 507 records on all foals that were less than 2 weeks of age revealed that 250 foals (approximately 50%) were ultimately diagnosed with infection, based on a positive blood culture, a positive sepsis score, or clinical or postmortem evidence of infection in 3 or more tissues.6 Considering that half of all admitted foals in the later study had evidence of significant infection, special attention needs to be focused on earlier recognition. Based on its definition, a positive blood culture is often considered the “gold standard” of diagnostic proof of septicemia. However, the inherent delay in obtaining the results of blood culture precludes a timely diagnosis, which is vital for a successful outcome. The main purposes of this session are to review physical findings and simple laboratory tests that can reliably alert the practitioner working in the field that septicemia is likely and to provide a general guide on which antimicrobial agents are most reliably efficacious.

The Physical Examination

Typically, the prodromal signs of sepsis are subtle and often are not recognized by the caretaker. Knowledge of normal foal behavior and physical parameters are paramount for early identification of septicemia. Normal physical findings of the newborn foal are listed in Table 1. In performing the physical examination, one should specifically try to identify potential primary
routes of infection, signs of a clinical response to infection, and signs of advanced infection into secondary sites.

**Table 1. Some practical facts on normal newborn foals.**

- **Time until sternal:** 1 to 2 minutes
- **Time to suckle reflex:** (to finger in mouth): 2 to 20 minutes
- **Time to stand:** average 1 hour. Longer than 2 hours is abnormal.
- **Time to nurse mare:** average is 2 hours. Longer than 3 hours is abnormal and puts foal at high risk of developing problems. *A healthy foal will nurse at least 4 times an hour.*
- **Time to pass meconium:** 4 hours. Some mild straining may be normal.
- **Time to first urination:** 9 hours
- **Temperature:** 99-101.5 F
- **Heart rate:** by 1 hour after birth, 80 to 120 beats/minute.
- **Respirations:** by 1 hour after birth, 30 to 40 breaths/minute.

Primary Sites of Infection

The skin, umbilicus, and digestive, respiratory and genitourinary tracts should be carefully examined as potential sites of primary bacterial invasion. Considering that Gram negative enteric bacteria, notably *Escherichia coli*, account for the majority of cases of septicemia in foals, it logically follows that the gastrointestinal tract is the most common primary site of infection. Diarrhea is never considered to be normal in the first few days of life and may be the only important clue of colonization and invasion of the gastrointestinal tract. Bruxism, anorexia, and colic also may be signs that indicate risk of bacterial translocation from the gastrointestinal tract.

External evidence of omphalophlebitis may not be grossly apparent for several days to one to two weeks after initial infection. Occasionally, despite significant infection of the umbilical vessels or urachus interior to the body wall, there will be no obvious evidence of disease in the external umbilical stump. Clinical signs that are consistent with infection of the umbilical remnants include heat, swelling, patentcy, pain of the umbilical stalk or discharge or moistness from or around the stalk.

Surprisingly, even severe infection of the respiratory tract may not manifest clinical signs in neonatal foals. Often the only signs of respiratory tract disease are the presence of unexplained tachypnea, nasal flare, or dyspnea. Other localizing signs, such as nasal discharge, cough, pleurodynia, or audible abnormalities, when present, are incriminating clues.

**The Clinical Response to Infection**

The foal’s response to sepsis can be highly variable, depending on the duration and intensity of the septic insult. The initial response to infection should evoke signs of decreased activity, malaise, increased periods of recumbency, inability to track the mare, decreased frequency of
nursing, and failure to gain weight. All of these signs often are associated with the onset of fever. The cyclic nature of fever necessitates serial evaluation, otherwise it may be overlooked. As the inflammatory response to infection intensifies, other signs of systemic disease appear including tachycardia, tachypnea, bilateral scleral injection, hyperemia of the coronary bands, unpigmented skin, and mucous membranes, petechial hemorrhages, and edema. Petechiae in the pinnae are a highly reliable indicator of sepsis in the foal and may develop as a result of either thrombocytopenia or vasculitis.

Identification of Secondary Sites of Infection

If the innate immune system is incapable of controlling the infection, as septicemia progresses, secondary sites of infection may develop. With the blood stream serving as the conduit, essentially all tissues of the body are susceptible to secondary infection. Tissues that receive a large portion of the cardiac output, and experience turbulent, slow, or unique blood supplies are targeted first and include physes, synoviae, the uveal tract, meninges, endocardium, liver, kidney, and skin/muscle. Any neonatal foal that has joint swelling, periarticular edema, lameness or prolonged recumbency should be carefully evaluated for sepsis. The cardinal signs of uveitis are blepharospasm, epiphora, miosis, aqueal flare, edema of the iris, and hypopyon. These signs most often manifest bilaterally in septic foals, though unilateral presentation can occur. Foals with meningitis will often have an altered mental status, ataxia, seizures, and a stiff, “guarded” neck and gait. Endocarditis is an infrequent complication of septicemia in foals. Tachycardia, tachyarrhythmia, lethargy, murmurs, jugular pulsation, and dependent edema may all be signs of endocarditis. Healthy neonatal foals will commonly have a low-grade systolic murmur over the semilunar valves over the left heart base. However, loud murmurs over the semilunar valves, murmurs over the mitral or tricuspid valves, or those that are accompanied by other signs of cardiac disease should be investigated further by echocardiography. Hepatic, splenic, and renal abscessation may occur secondary to septicemia, though secondary infection in these anatomic locations rarely cause localizing clinical signs.

When the systemic pro-inflammatory response to infection is uncontrolled and malignant, the clinical state of shock and MODS (Multiple Organ Dysfunction Syndrome) ensue. Septic shock is defined as hypotension that is accompanied by signs of hypoperfusion (altered mental status, hypothermia, hypotension, shivering, cold extremities, mucous membrane pallor, bradycardia or tachycardia, poor capillary or jugular vein refill, poor pulse quality, oliguria, and ileus) that is induced by the presence of sepsis, is the result of systemic vasodilation, and persists, despite adequate fluid resuscitation. The manifestations of MODS are vast and the signs reflect the organs that are predominantly affected. These may include mental deterioration, ataxia, seizures, oliguria, coagulopathy, dyspnea, tachypnea, tachycardia or bradycardia, colic, and/or ileus. Ultimately, identification of clinical signs or physical findings of secondary infection, shock, or MODS is significant. These conditions not only identify an advanced and improperly controlled disease state, but they are also associated with a poor prognosis.

Finally, when evaluating a neonatal foal for any reason, consider that any primary disease can induce a state of immunosuppression and/or cause loss of integrity of local protective barriers that subsequently welcomes infection. For example, other common diseases during the neonatal period, such as neonatal isoerythrolysis, neonatal encephalopathy, uroperitoneum, neonatal
asphyxia syndrome, meconium impaction, diarrhea, or any cause of colic, may be complicated by concurrent infection.

**Diagnosis of Septicemia**

**Laboratory Tests**

Laboratory tests that are statistically associated with sepsis include failure of passive transfer, hypoglycemia, changes in the morphology and numbers of circulating neutrophils, hyperfibrinogenemia, hypoxemia, and acidosis. Immunoglobulin G (IgG) plays a vital role in the innate immune system’s initial attack against microbial invasion. The lack of placental transfer of maternal immunoglobulin in foals and the short time during which colostral immunoglobulin can be effectively absorbed from the intestinal tract during the first few hours of life inherently puts the neonatal foal at high risk for infection. It is estimated that as many as half of all foals with failure of passive transfer of maternal colostral immunoglobulin become septicemic. Thus, use of a simple stall side test of passive transfer of colostral antibody that utilizes a drop of whole blood performed between 18 to 24 hours of age can be a very practical assessment of potential risk of infection.

Hypoglycemia develops as the combined results of reduced intake of milk, lack of sufficient glycogen stores in the neonate, and increased consumption by proliferating microbes. Extremely affordable stall side tests of blood glucose that utilize a drop of blood are readily available over the counter and like stall side IgG tests, are a simple test that can provide another important clue in the diagnosis of sepsis.

Addition of a complete blood count, including fibrinogen concentration, can be extremely valuable, though in most circumstances these tests cannot be performed stall side. However, results can be obtained rapidly with some portable whole blood analyzers or within hours, depending on the availability and proximity of laboratory facilities. The effect of sepsis on the circulating neutrophil count is variable. With appropriate stimuli from the soluble mediators of the acute phase response, neutrophilia with or without a mild left shift are expected. Overzealous production of cytokines in overwhelming or uncontrolled sepsis induces margination of neutrophils, extravasation into affected tissues, and/or apoptosis. In these scenarios, neutropenia, with or without a left shift occurs. The presence of toxic neutrophil morphology (vacuolization, basophilic cytoplasm, toxic granulation, Döhle bodies) is particularly helpful and is most intimately associated with endotoxemia or bacterial infection. Fibrinogen is an acute phase protein that reliably increases with any inflammatory insult in the horse. Significant increases in plasma fibrinogen concentration may be particularly useful in determining onset. Although constitutively present in the circulation, fibrinogen is synthesized by the liver during the acute phase reaction and significant increases indicate the presence of an inflammatory response of at least 24 to 48 hours duration. Thus increases in fibrinogen levels in foals less than 24 hours of age would be consistent with the presence of infection in utero.

Finally, reduced arterial oxygen content and metabolic acidosis typically reflect hypoxemia and hypovolemic shock with increased blood lactate concentrates in cases of advanced sepsis. Like glucose, stall side lactate concentration can be accurately estimated with a drop of blood.
The Sepsis Score

To facilitate rapid diagnosis of septicemia, Brewer and Kobert developed the Sepsis Score in the late 1980’s. Vigorously tested, retrospectively and prospectively in foals less than 12 days of age, the sepsis score system uses a practical combination of historical, clinical, and diagnostic parameters that are statistically associated with sepsis (see Table 2). A positive sepsis score (greater than or equal to 11) accurately identified sepsis in 93% (sensitivity) of the original cases studied, whereas scores below the cut-off value of ≤ 10 appropriately eliminated septicemia with a specificity of 88%. The sepsis score is not intended to replace clinical judgment or blood culture results, but its simplicity and speed of interpretation make it a useful diagnostic aide. With the exception of a CBC and fibrinogen concentration, the remaining parameters can be obtained by taking a history, doing a physical examination, and performing simple stall-side tests (i.e. IgG and glucose determinations). If the sepsis score is positive without inclusion of the results of a CBC, the practitioner in the field is appropriately alerted. The accuracy of the sepsis score and the prognosis are directly correlated with the score: scores > 23 are reported to have 100% diagnostic accuracy and are associated with mortality. In a recent retrospective study on 250 septicemic foals at the University of Georgia, the sepsis score was evaluated retrospectively against blood culture and necropsy results and the system remained diagnostically accurate. However, another recent study at the Marion duPont Scott Equine Medical Center in Virginia found lower sensitivity and specificity than originally reported with the modified sepsis score, indicating that the score system’s utility may vary based on the study population. Although the sepsis scoring system in foals is easy to use and practical, lower scores, or scores just below the cut-off should not be ignored. In general, the logic of “absence of proof is not proof of absence” and sound clinical judgment should prevail. Likewise, a positive score may not truly indicate septicemia, but does likely indicate that the foal has a systemic inflammatory reaction of some kind. Perhaps logic would dictate here to err on the side of presumed septicemia, until further diagnostics are secured.

Multi-site Infection

Although a sign of advanced disease, the presence of multiple local sites of infection clinically or on post-mortem examination is also considered a reliable indication of septicemia. With this in mind, it may be helpful to obtain additional ancillary diagnostics specifically aimed at identification of potential primary or secondary sites of infection. To this end, some clinicians prefer to routinely obtain thoracic radiographs, perform arterial blood gas analysis, and/or perform ultrasonography of the internal umbilical structures on neonatal foals with presumed septicemia. The information gained from these additional tests must be weighed against their cost. If lameness, periarticular edema, or joint swelling is present arthrocentesis is indicated for joint fluid analysis and culture. Radiography of joints may be helpful, but be mindful that radiographic changes of bone and articular surfaces lag behind clinical signs of septic arthritis. Occasionally lameness is present without obvious synovial distension, confounding localization of the affected joint or physis. In this situation, ultrasonography or computerized tomography may be helpful in detecting subtle changes in the synovia, articular surfaces, or physes of the affected limb. If neurologic signs are present, collection of CSF is indicated to rule out.
Table 2. The Sepsis Score: A positive blood culture or multisystem infection are definitive evidence of septicemia; however if neonatal septicemia is not aggressively treated before a positive blood culture is obtained or multisystem infection is apparent, the likelihood of a successful outcome is quite low. The “sepsis score” system uses historical facts, clinical findings, and laboratory data to predict the likelihood of septicemia in a neonatal foal. Because of its ease of application and rapid results, the sepsis score can be a powerful diagnostic tool. Each parameter is assessed and a score is assigned based on the table below. A total case score of 11 or greater has a 93% diagnostic accuracy for predicting septicemia in a foal < 12 days of age.

<table>
<thead>
<tr>
<th>PARAMETER</th>
<th>SCORE</th>
</tr>
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<tbody>
<tr>
<td>History:</td>
<td></td>
</tr>
<tr>
<td>1. Placentitis, vulvar discharge, dystocia, long transportation of mare, mare sick, induced, prolonged gestation (&gt; 365 days)</td>
<td>4: yes</td>
</tr>
<tr>
<td>Clinical signs:</td>
<td></td>
</tr>
<tr>
<td>2. Fever</td>
<td>4: &gt; 102F</td>
</tr>
<tr>
<td>3. Hypotonia, coma, depression, seizure</td>
<td>4: marked</td>
</tr>
<tr>
<td>4. Anterior uveitis, diarrhea, respiratory distress, swollen joints, open wounds</td>
<td>4: yes</td>
</tr>
<tr>
<td>Laboratory Data:</td>
<td></td>
</tr>
<tr>
<td>1. PMN count (per µl)</td>
<td>4: &lt; 2,000</td>
</tr>
<tr>
<td>2. Bands (per µl)</td>
<td>4: &gt; 200</td>
</tr>
<tr>
<td>4. Fibrinogen (mg/dl)</td>
<td>4: &gt; 600</td>
</tr>
<tr>
<td>5. Blood glucose (mg/dl)</td>
<td>4: &lt; 50</td>
</tr>
<tr>
<td>6. IgG (mg/dl)</td>
<td>4: &lt; 200</td>
</tr>
</tbody>
</table>

Total points for this case

Blood Culture

By definition, a positive blood culture is highly incriminating diagnostic proof of septicemia. However, approximately 10 to 40% of truly septicemic foals will have a negative blood culture. Despite this limitation, obtaining a blood culture at the onset of suspicious clinical signs in the high risk foal may prove to be extremely helpful in treatment that can ultimately be guided by specific antimicrobial sensitivity results. The hair over the site of venipuncture should be clipped and the skin surgically prepared. Use of sterile gloves and sterile handling of the venipuncture needle and syringe may reduce spurious skin contamination. The volume to be
cultured varies with the collection device, but typically it is recommended to obtain 12 to 20 mls of blood using a sterile technique. Exchanging the venipuncture needle with a new sterile needle prior to injection of the blood into the culture vials may also reduce contamination. Ideally, the blood should be split into two bottles. One bottle should be steriley vented for aerobic culture and the other bottle remains sealed for anaerobic culture. Alternatively, special anaerobic bottles may be used. The prevalence of positive blood cultures reported in foals that were ultimately diagnosed with septicemia based on clinical signs or necropsy findings varies considerably. Use of cation exchange resins that remove antimicrobials from the blood sample prior to culture has been shown to increase the positive blood culture rate in septicemic human patients. Some clinicians prefer to obtain serial blood cultures, though this practice can be costly.

Treatment of Septicemia

Septicemia in neonates requires an intense combination of therapies including treatment for failure of passive transfer, infection, inflammation, endotoxemia, hypotension, hypoxemia, coagulopathy, maintenance of appropriate glucose, nutrition, and fluid and electrolyte levels, and general supportive care. Early recognition and appropriate antimicrobial therapy are paramount for successful treatment of septicemia. Until cultures from blood or local sites of infection are available, antimicrobial therapy should logically be directed against the pathogens most commonly involved in equine neonatal septicemia. Before the 1970s, Actinobacillus equuli and β hemolytic Streptococcus were reported as the primary pathogens. Since the 1970s, Escherichia coli isolates predominate. Referral centers studies indicate that in the last two decades, Gram-negative bacteria account for the majority of isolates, with key players including E. coli, Salmonella, Klebsiella, Pseudomonas, Enterobacter, Citrobacter, and Actinobacillus spp..4,5,6,14-16 Despite the preponderance of Gram-negative isolates, in recent years it would appear that Gram-positive bacteria are on the rise. In one report, approximately 30% of the total isolates were Gram-positive and principally consisted of Streptococcus, Enterococcus, and Staphylococcus spp. In some cases, more than one bacterial species is isolated. Less commonly reported isolates include Rhodococcus equi, Listeria monocytogenes, Clostridium perfringens, Bacillus, Proteus, Pasteurella, Acinetobacter, Serratia marcescens, Bacteroides, and Morganella morganii.

Based on the above information, broad-spectrum antimicrobial therapy is required. Considering sensitivity data on isolates obtained at referral centers in the past 15 years, the most frequently recommended antimicrobial regimen is the combination of an aminoglycoside with a penicillin derivative. Since the 1990s, there have been increasing reports of gentamicin resistance among some E. coli and Salmonella isolates, thus amikacin (21-25 mg/kg IV q 24 hours) and penicillin (22,000-40,000 IU/kg, q 6 hours, IV) or ampicillin (22 mg/kg, q 6 hours, IV) are commonly used as the initial antimicrobial regimen for treatment of neonatal septicemia. This antimicrobial combination is projected to be effective against at least 90% of septic foal isolates. For single drug therapy against the major isolates, imipenem (10 mg/kg, q 6 hours, IV), ceftriaxone (25 mg/kg, q 12 hours, IV), ceftazidime (50 mg/kg, q 6 hours, IV infused slowly over 15 minutes), cefpodoxime (10 mg/kg, q 6-12 hours, PO), chloramphenicol (50 mg/kg, q 6 hours, PO), ceftiofur (5 mg/kg, q 12 hours, IV or IM), and tetracycline (5-10 mg/kg, q 12 hours, IV) are reported in decreasing order of efficacy from 99% to approximately 70%. More extensive listings of antimicrobial doses for use in the neonate are reviewed elsewhere.
Summary

Careful attention to the details of normal foal behavior in combination with a thorough physical examination, with particular attention to identification of potential primary and secondary sights of infection, can alert the equine practitioner to signs of septicemia. Evaluation of colostral IgG transfer, a complete blood count, and blood glucose concentration can be additional helpful tools to assess the risk of sepsis. Blood cultures should be obtained from high risk foals prior to instituting therapy, as they may ultimately provide guidance for appropriate choice of antimicrobials. For high risk foals, prompt intervention with broad spectrum antimicrobials is recommended.

Permissions

This review includes excerpts from previously published works of the author in Equine Internal Medicine: A case based approach, Mary Rose Paradis, ed. Elsevier Saunders, Philadelphia, PA, 2006 and DVM Magazine 2008.

References and Footnotes


   a. Snap Foal IgG™ Idexx Pharmaceuticals, Westbrook, ME.
   b. Accu-chek™ Roche Diagnostics, Indianapolis, IN.
   c. Accutrend Lactate™ Roche Diagnostics, Indianapolis, IN.
   d. ARD Antimicrobial Removal Device, Marion Scientific, Kansas City, MO.