Severe sepsis in calves occurs most commonly in calves associated with failure of passive transfer (FPT). If the invading bacteria are not quickly controlled by the immune system, they can establish focal infections in areas such as the joints, meninges, heart valves, or growth plates. Septicemia refers to a bacterial infection of the blood associated with adverse systemic signs. If not successfully treated, this can lead to multiple organ dysfunction, septic shock, and death. Treatment is based on selecting an appropriate antimicrobial drug and dosage, anti-inflammatory therapy, and supportive therapy (including fluids). Prevention of FPT through good colostrum management is essential.

**Etiology and Pathophysiology**

Neonatal septicemia refers to a systemic disease associated with the presence of pathogenic bacteria and/or their toxins in the blood. The term implies that the animal has clinical signs of disease as compared to bacteremia which would simply refer to a bacterial infection of the blood. *E. coli* is the main bacterial pathogen associated with septicemia in calves. However, it is certainly not the only one as *Salmonella, Campylobacter, Klebsiella* and different *Staphylococcus* species have also been isolated from the blood of septic calves. Newborn calves are particularly at risk for developing septicemia since they are dependent upon colostral antibodies and cells (passive transfer of immunity) for immunity. Calves lack a normal adult intestinal flora and when born in a heavily contaminated environment, colonization of the GI tract with virulent bacteria may occur prior to the establishment of normal flora. Septicemia may also result from bacterial colonization of another site such as the umbilicus.

Bacterial infection and the host inflammatory response should be differentiated. The immune response, in combination with the reticuloendothelial system prevents the development of sepsis from an opportunistic or pathogenic invasion. However, this initiates an inflammatory cascade involving highly toxic mediators which if uncontrolled will eventually lead to the systemic inflammatory response syndrome (SIRS) and subsequent multiple organ dysfunction syndrome (MODS). There is a balance between an appropriate, yet effective, immune response and an overzealous response to the bacteria or their toxins.1,2

Endotoxin (lipopolysaccharide) is a component of the outer cell wall of Gram-negative bacteria. It is released following cell death or during periods of rapid bacterial growth. The interaction between endotoxin and the immune system triggers a complex inflammatory cascade involving cytokines and other inflammatory mediators. Initiation of the cascade results in the production of arachidonic acid metabolites, release of myocardial depressant factors, activation of the complement system, as well as the production and release of many other mediators of sepsis. The results include dehydration, tachycardia, pyrexia, leukopenia, hypotension, a decrease in systemic oxygen delivery and cardiac output, and generalized weakness.3
severe and complex pulmonary vasculature response to endotoxin leading to hypoxemia. Cattle are very sensitive to endotoxin and even small doses can produce severe lung injury. Severe endotoxemia is frequently associated with death from respiratory failure in both calves and adult cattle. Therefore NSAIDs are critical in blocking the formation of reactive metabolites (i.e. thromboxanes) and restoring lung function.

Exactly how bacteria get into the meninges is poorly understood. Specific mechanisms may include the development of a sustained and high grade bacteremia in the highly perfused dural venous system and choroid plexuses, adherence of fimbriae from some strains of *E. coli*, or the phagocytosis of the pathogens by circulating monocytes and endocytosis through the microvascular endothelial cells. Bacteria survive and proliferate in the poorly defended CSF. Complement is essentially nonexistent in CSF, which, when combined with low numbers of specific antibodies leads to inadequate opsonization of meningeal pathogens. The sequelae of meningitis are associated with the release of cytokines and the direct effects of bacterial invasion. Bacteria may release endotoxin, leading to inflammatory infiltrates that cause thromboses of the arachnoidal or subependymal veins. Congestion or hemorrhagic infarction may follow with subsequent necrosis of nerve cells. Inflammatory changes in the subarachnoid space may affect the choroid plexus, decreasing the absorption of fluid and potentially creating hypertensive hydrocephalus.

**Clinical Signs and Diagnosis**

Neonatal septicemia should be seriously considered whenever there is multiple organ dysfunction, or when severe cardiac and/or respiratory signs are encountered. Classic septicemia is described as a condition affecting newborn calves between 2 and 6 days of age. The progression is rapid and most often fatal. Very early in the disease, the clinical signs are vague, non specific and likely attributed to other disease. An alteration in mental status ranging from a mild depression to coma is commonly observed. Lack of suckling ability or enthusiasm towards nursing are early non-specific clinical signs. Abnormal rectal temperature (fever or hypothermia) is not consistent, however sustained tachycardia and eventually tachypnea develop. Hyperemia of the mucous membranes and scleral injection is frequently observed. Capillary fragility may initiate petechiation of the mucous membranes. Eventually, hypotension and clinical signs that are associated with poor cardiac output (slow capillary refill, diminished peripheral pulse, cold extremities and decreased urine output) become prominent. Dehydration usually develops. Diarrhea is not present in all cases but is common in the terminal stages of septicemia.

Early clinical signs of septicemia can be subtle and non specific. The presence of focal infection or a clinical picture consistent with infection increases the suspicion of sepsis and/or septicemia. However, the definitive diagnosis of septicemia can only be based on a blood culture. The jugular vein should be clipped and scrubbed prior to sampling. Ten ml of whole blood are drawn using a sterile syringe and needle and the blood is placed into a blood culture bottle using a new sterile needle. Some clinicians recommend taking 2 samples (from blood collected one hour apart) to increase the chances of isolating the bacteria and to facilitate the interpretation of results if opportunistic or contaminating bacteria are found in one sample. The bottle is then submitted to the laboratory for culture and susceptibility testing. If the bottle is not submitted immediately, it should be stored at room temperature or at 37°C. A negative blood culture must be interpreted with caution since many factors may interfere with bacterial isolation from a blood culture. Cultures of other body fluids such as joint, cerebrospinal, peritoneal, or
pleural fluids may be helpful for bacteriological diagnosis whenever the blood culture is negative.

Some laboratory findings may increase the suspicion of septicemia. Hematologic abnormalities of septicemia vary with the severity of the disease. Abnormal neutrophil count (neutrophilia and neutropenia) and increased immature forms (bands) are frequently seen. Fibrinogen concentration is often elevated. Thrombocytopenia may be present in severe cases. One study of suspected septic shock in calves found that 8 out of 12 calves had at least 3 abnormal coagulation parameters (most commonly APTT and PT). Hypoglycemia or less often hyperglycemia may be observed. A metabolic acidosis is also frequently present in septic calves. Lactic acidosis occurs as the disease progresses. Some calves will develop respiratory disease (respiratory distress syndrome) or pneumonia, and will suffer from hypoxemia and/or hypoventilation. Sepsis scoring systems have been developed for calves but are not consistently useful. Ultimately the presence of clinical signs including lethargy, pyrexia, diarrhea, tachypnea, polyarthritis, uveitis, omphalitis, and meningitis, along with documented presence of failure of passive transfer should make the clinician highly suspicious of septicemia. If multiple clinical signs are present, the likelihood of disease is increased.

Calves with meningitis are often presented because they have lost their suckle reflex and appear lethargic. Previous treatment for diarrhea is common. Fever is often present unless NSAIDs have been given or if the animal is in an extremely cold environment. The calves may have an extended head and neck and attempts to flex or reposition the neck can result in a tonic extension and thrashing of the limbs. Calves with meningitis almost always have abnormal mentation. As the diseases progresses, profound depression develops and eventually the animal becomes comatose and non responsive, or may develop seizures. Presumptive diagnosis of bacterial meningitis is based on demonstration of failure of passive transfer, presence of a septic focus such as omphalophlebitis or septic arthritis, and the presence of abnormal neurologic signs. However, the definitive diagnosis is based on an abnormal CSF analysis. Collection of CSF from the lumbosacral space is easy and safe in ruminants. The number of nucleated cells and the protein concentration is markedly increased. The proportion of neutrophils may reach as high as 80%. The ratio of CSF to plasma glucose concentration is <1 in animals with bacterial meningitis because of bacterial metabolism of glucose in the CSF. Xanthochromia (yellow color) is inconsistent. Free or intracellular bacteria may be observed in some cases.

Treatment

Neonatal septicemia is a severe disease with high mortality. The primary goals of treatment are to 1) control the infection, 2) modulate the inflammatory response and 3) support the animal during the disease. Antimicrobial therapy should begin as soon as possible in order to minimize the bacteremia. The choice and the dosage of antibiotic depend on several factors and personal preference, along with past experience are often important. It is generally accepted that the intravenous route is preferable whenever possible and that broad-spectrum drugs are preferred. Appropriate antimicrobial choices include: third or fourth generation cephalosporins (ceftiofur 5-10 mg/kg one to three times a day IM or IV), sodium ampicillin (10-20 mg/kg three times a day IV), and florfenicol, although even when given intravenously at the extralabel dosage of 20 mg/kg/BID it only exceeds the MIC90 value in plasma for one hour. Combinations of drugs can be used to broaden the spectrum of activity (such as ampicillin-ceftiofur or ampicillin-trimethoprim-sulfonamide). Fluoroquinolones can also be effective in countries where their use
is permitted. Once the pathogen has been identified and the susceptibility pattern determined (on
the individual or on the farm), the most appropriate antibiotic can be chosen.

As described above, the inflammatory response if uncontrolled often causes severe clinical
signs. Therefore NSAID therapy should be considered for ancillary treatment. Possible side
effects of aggressive NSAID treatment include abomasal ulcers and renal toxicity, particularly in
dehydrated animals. The duration of NSAID treatment is often limited to 2 to 3 days due to their
potential toxicity. NSAIDs should not be continued for any longer than they are considered
essential for survival.

Supportive treatments for septicemic calves include correction of secondary problems,
administration of fluids, plasma transfusion, oral or parenteral nutrition and oxygen
administration. Problems that must be addressed include: hypovolemia, hypoglobulinemia,
hypoglycemia, metabolic acidosis, electrolyte abnormalities and hypoxia. IV fluids (or oral as a
promise on the farm) should be administered. Dextrose (5%) combined with normal saline
(0.9%) should be administered at a rate of at least 50 mL/kg/24 hours. Nutrition is important and
septic calves either nurse reluctantly or are inappetant. As a result, they do not ingest an adequate
amount of milk. If the animal refuses to nurse, then tube feeding should be used to ensure that
the calf ingests at least 10% to 15% of its bodyweight of milk per 24 hours. The feeding schedule
may involve several feedings per day (3 to 5) and should be gradually increased in amount to
prevent abdominal distension. If the gastrointestinal system does not tolerate the tube feeding
regimen, parenteral nutrition should be considered. There is usually no need for total parenteral
nutrition since most animals will continue to nurse or tolerate tube feeding up to 5% of their
bodyweight. For calves with meningitis, convulsions can be treated with diazepam (0.1-0.2
mg/kg, IV). This can be repeated every 30 minutes until convulsions are controlled.9

Summary

Septicemia can be minimized by making sure colostrums management in adequate on farms.
Also careful inspection of the environment and management practices on the farm should be
investigated. Clusters of septicemia could be related to specific risk factors. As an example,
feeding heavily contaminated colostrum could be the origin of the septicemia on some farms.1,10
Prevention through excellent cleanliness and management practices is the most effective means
of controlling and preventing neonatal sepsis.

References
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