Evolution and Future of Sepsis Treatment in Equine Emergency and Critical Care

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The approach to sepsis in the horse, both young and old, has evolved over the last 30 yr and has resulted in improved treatment approaches and outcomes, both for life and for function. Future improvements require the use of modern molecular techniques and prospective clinical studies. Author’s address: Department of Veterinary Clinical Medicine, College of Veterinary Medicine, University of Illinois, Urbana, Illinois 61802; e-mail: pawilkin@illinois.edu. © 2009 AAEP.

1. Introduction

The specialty of Veterinary Emergency and Critical Care has grown almost exponentially in the last 15 yr and has welcomed those interested in providing the best care possible to our horse patients, large and small. Much attention has been paid to the critically ill neonate by equine practitioners, and because of this, our knowledge regarding these small patients has expanded to the point where the profession may be in the opposite position described in 1986 when Dr. Jill Beech most appropriately noted that “When information was extrapolated from the adult horse to the foal, it became rapidly apparent that this was inadequate; neonatal foals are not just little horses.” Our knowledge regarding foals has increased so much, we must guard against extrapolating information from the care of the foal to the adult horse; adult horses are not just big foals. We must ensure our vision encompasses both the adult horse and foal in our consideration of what constitutes critical care in equine medicine.

Sepsis is an area of commonality between the two age groups and highlights the advances made in areas where new knowledge is changing practice.

2. Definitions

Sepsis is a serious medical condition characterized by a whole body inflammatory state (called a systemic inflammatory response syndrome [SIRS]) and the presence of a known or suspected infection. The body may develop this inflammatory response to microbes in the blood, urine, lungs, skin, or other tissues. An incorrect layman’s term for sepsis is blood poisoning, more aptly applied to septicemia. Bacteremia is the presence of viable bacteria in the bloodstream. Likewise, the terms viremia and fungemia simply refer to viruses and fungi in the bloodstream. These terms say nothing about the consequences of having these microorganisms in the body. Conversely, SIRS can occur in patients without the presence of infection, for example, in patients with burns, polytrauma, or the initial state in pancreatitis and chemical pneumonitis. Septicemia (also septicemia) is a related but deprecated (formerly sanctioned but not been sharply defined) term referring to the presence of pathogenic organisms in the bloodstream, leading to sepsis. The term has been inconsistently used in the past by medical professionals, for example, as a synonym of bacteremia,
causing some confusion. The present medical consensus is that the term should be avoided.2,5 Severe sepsis occurs when sepsis leads to organ dysfunction, low blood pressure (hypotension), or insufficient blood flow (hypoperfusion) to one or more organs causing, for example, lactic acidosis, hypoxemia, decreased urine production, or altered mental status. Patients with SIRS and acute organ dysfunction may be termed “severe SIRS.” Severe sepsis can lead to septic shock (severe sepsis with refractory hypotension non-responsive to fluid resuscitation), multiple organ dysfunction syndrome (MODS; formerly known as multiple organ failure), and death. Organ dysfunction results from sepsis-induced hypotension and diffuse intravascular coagulation (DIC), among other disease processes.

3. Discussion
In equine medicine, there are few reports describing the incidence and mortality associated with severe sepsis, despite the knowledge, from multiple studies, that conditions routinely seen in equine practice are infectious in origin—or associated with endotoxemia/toxemia—and have the potential to induce severe systemic inflammatory responses (SIRS).5–26 Horses do develop severe sepsis and, compared with other species, experimental data indicate that horses are exquisitely sensitive to the effects of endotoxins.13–15,17–19,22 Most equine practitioners are now aware of the pathogenesis and potential treatment of sepsis in horses because of advances made in the last 30 yr and the dedication of continuing education organizers and their focus on making those in practice aware of advancements. Progress in applicable treatments in equine critical care is slowed because of the relatively large size of the adult horse and economic factors that limit ready availability of funds to do hypothesis-driven large prospective studies. Most of what is known about sepsis and severe sepsis in horses is from studies performed on and in neonates, too numerous to list. Although studies in the adult horse are expanding in number, progressing from individual case reports to clinical case series to experimental multicenter prospective studies, much work remains to be done. The ultimate goal, of course, is to provide equine practitioners with guidelines and therapeutic options—aimed at our equine patients—to reduce mortality from severe disease.

Bacteria are the most frequent initiators of severe sepsis in horses. In young foals, neonatal bacterial sepsis is the most common presentation, often without a detectable primary site of infection.5,7,10–12,16,19,20,23,24,26 In adults, sepsis is commonly found during gastrointestinal disturbances (colic, proximal enteritis, colitis) and, whereas previously thought a result of excess circulating bacterial products, such as endotoxins, rather than true bacterial infection, evidence is mounting for circulating bacteria, or translocated bacteria located in gastrointestinal lymph nodes, playing a major role.6–8,21,27 Bacterial translocation across the gastrointestinal barrier, without bacteria entering the bloodstream, may initiate SIRS by induction of the inflammatory cascade at the level of the lymph node. Other conditions associated with sepsis in adult horses include severe bacterial pneumonia or pleuropneumonia, clostridial myositis, retained placenta, and metritis.

Horses presenting with severe SIRS have clinical signs that are obvious, and familiar, to equine practitioners: tachycardia, tachypnea, dark injected mucus membranes with or without a gingival toxic ring, altered capillary and jugular refill times, injected sclera, and fever or hyperthermia. Sepsis patients may be depressed, lethargic, or show signs of abdominal discomfort. However, early clinical signs may not be obvious and easily overlooked by a non-suspecting examiner. Clinical laboratory data abnormalities are common in patients with sepsis and SIRS, most commonly leukopenia with a left shift. Hypovolemia and pulmonary dysfunction may be reflected by increased packed cell volume (PCV), lactic acidosis, and arterial hypoxemia. Blood glucose alterations, such as hypo- or hyperglycemia, are common in foals but may also be seen in adult horses and are potentially associated—perhaps predictive—with outcome, similar to recent findings in critically ill humans.9,28 Changes in creatinine concentration and liver and muscle enzyme activities may reflect end organ dysfunction, damage, or hypoperfusion. Alterations of coagulation, including prolonged prothrombin time (PT) and activated partial thromboplastin time (PTT), decreased antithrombin III (ATIII) levels, thrombocytopenia, and increased fibrinogen degradation products (FDPs), have been recognized in adult horses and foals with sepsis, with more recent work evaluating tests of clotting function.29–34

The most important points in treating septic patients are early diagnosis, treatment of the primary disease process, and supportive care; this is especially true in equine medicine, given financial realities and limited large-scale clinical trials for determining good evidence-based protocols. Frequent and thorough patient monitoring, adequate fluid resuscitation, support of the cardiovascular function with inopressor therapy, use of appropriate antimicrobials, nutritional support, and a thorough search for existing or newly developing infectious foci are the current “best practice” approaches to sepsis in the horse, young or old.

Anti-Endotoxin Therapies
Because of the likely importance of circulating endotoxin in equine sepsis in initiating SIRS, therapeutic approaches directly targeting circulating lipopolysaccharides (LPSs) have been developed.19,35,36 Transfusing hyperimmune plasma containing antibodies against Re mutant Salmonella typhimurium or J5 mutant Escherichia coli is one of the earliest described approaches.37 Because
of the high economic cost of hyperimmune J5 plasma and because of potential complications associated with administration of plasma and other blood-derived products, large-scale controlled clinical trials with strict entry criteria for patient selection are needed before true evidence-based recommendations can be made.

The antimicrobial drug polymyxin B, known to bind circulating endotoxin and prevent activation of inflammation, has been advocated in the management of suspected endotoxemia. Experimental studies have shown that treatment with polymyxin B (3000–6000 IU/kg diluted slowly, IV, q 12 h) before endotoxin challenge resulted in improved clinical signs and decreased level of circulating pro-inflammatory cytokines.38,39 As with J5 hyperimmune plasma, critical evaluation of the potential benefits of polymyxin B in clinical cases is sparse, with much support being anecdotal.35

Non-Steroidal Anti-Inflammatory Drugs

One important effect of the initiation of inflammation and pro-inflammatory cytokines is activation of phospholipase A2 (PLA2) and cyclooxygenase (COX)-2 and production of eicosanoids, mediators of a variety of pathologic changes during inflammation. Blocking their production by using non-steroidal anti-inflammatory drugs (NSAIDs) is considered a logical step in the treatment of sepsis and is supported by experimental data in horses. Administration of flunixin meglumine (1.1 mg/kg) before administration of sublethal doses of endotoxin dramatically reduces the effects of experimentally administered LPS.40 A lower dose of flunixin meglumine (0.25 mg/kg; low-dose flunixin) was shown effective in preventing eicosanoid production and suppressing increases in blood lactate but not in alleviating the clinical signs of endotoxemia.41 Flunixin meglumine is apparently more effective than phenylbutazone in controlling the clinical signs of endotoxemia.42 Large controlled clinical studies are needed to uncover appropriate flunixin meglumine dosages and dose intervals for treatment in clinical sepsis cases. Despite a dearth of evidence-based protocols, use of NSAIDs most likely has its place in the treatment of sepsis in horses, as long as appropriate attention is given to potential untoward negative effects, including renal and gastrointestinal injury.

Early Goal-Directed Therapy

In critically ill human patients, there seems to be a narrow window where therapeutic interventions can stop the progression toward shock and death.43 Early goal-directed therapy (EGDT), developed at Henry Ford Hospital by E. Rivers, MD, is a systematic approach to resuscitation that has been validated in the treatment of severe sepsis and septic shock. It is meant to be started in the Emergency Department. The theory is that one should use a stepwise approach, having the patient meet physiologic goals, to optimize cardiac pre-load, afterload, and contractility, thus optimizing oxygen delivery to the tissues.44 A recent meta-analysis showed that EGDT provides a benefit on mortality in patients with sepsis.45 As of December 2008, some controversy around its uses remains, and a number of trials are ongoing in an attempt to resolve this.46

In EGDT, fluids are administered until the central venous pressure (CVP), as measured by a central venous catheter, reaches 8–12 cm of water (or 10–15 cm of water in mechanically ventilated patients). (In horses, this may require 3–4 l of isotonic crystalloid solution, rapidly administered, to a foal or 20–40 l to an adult, whereas ~4 l is common for human patients.) If hypotension is apparent, vasopressors or vasodilators are given as needed to reach the goal. Once these goals are met, the mixed venous oxygen saturation (SvO2), i.e., the oxygen saturation of venous blood as it returns to the heart as measured at the vena cava, is optimized. If the SvO2 is <70%, blood is given to reach a hemoglobin concentration of 10 g/dl, and inotropic therapy is added until the SvO2 is optimized. Elective intubation and mechanical ventilation may be performed to reduce oxygen demand if the SvO2 remains low, despite hemodynamic optimization. Urine output is also monitored, with a minimum goal of 0.5 ml/kg/h. In the original trial, early assignment of patients to a strict hemodynamic support protocol—with minutes to a few hours of admission to an emergency room—that mortality from 46.5% in the control group to 30.5% in the intervention group.44 The Surviving Sepsis Campaign guidelines has recommended EGDT for initial resuscitation of the septic human patient with a level B strength of evidence (single randomized control trial).45

Although similar studies, particularly those evaluating the benefits of rapid correction of fluid deficits, monitoring, and correcting abnormalities in blood pressure, blood lactate, central venous pressure, and central venous oxygen saturation, are not commonly reported in the adult horse or foal, this is one of the most important directions that clinical research is taking, and one that is intuitively attractive. Invasive monitoring is not routinely performed or easily accomplished, particularly in the adult, and the current emphasis is on evaluating more readily monitored, but related parameters, such as lactate concentrations. However, more invasive studies need to be undertaken in adults and foals so that precise recommendations may be given if these approaches are of benefit in horses. The equine internist/criticalist commonly initially extrapolates from human critical care guidelines; care must be taken to account for essential species differences.

Intensive Insulin Therapy

Hyperglycemia and insulin resistance are seen in equine critical care patients, although most commonly found and monitored in critically ill neonatal
foals. Although insulin therapy is common in some equine neonatal intensive care units, the goal of such therapy is usually to avoid gross hyperglycemia and not strict maintenance of normoglycemia. A few published studies are available regarding the frequency and implications of glucose alterations in acutely ill equine patients but, to date, no specific recommendations for treatment have been made, and no prospective clinical trials have been performed to evaluate the potential efficacy of tight glucose regulation in horses.54–56 Therefore, clinical trials are needed to evaluate the use of insulin therapy in critically ill foals and, at the least, clinicians should be aware of the potential importance of strict glucose control so that adequate monitoring and, if needed, adequate treatment be provided to critically ill equine patients. These studies are likely forthcoming, given recent reports evaluating various glucose meters in both horses and foals.46,47

Low-Dose Corticosteroid Therapy

The activation of the hypothalamic-pituitary-adrenal axis during acute illness is an important protective mechanism aimed at controlling the acute inflammatory response, and critically ill patients should normally present increased plasma cortisol concentration.48,49 This is not always the case, however, because some patients may instead present functional or relative adrenal insufficiency, which could contribute to poor outcome.50 Indiscriminate use of large doses of steroids should be avoided in severe sepsis.51–53 However, the question remains whether there is potential benefit of low doses of corticosteroids in patients with septic shock and shown adrenal insufficiency. Although low-dose therapy with hydrocortisone and fludrocortisone significantly reduced both 28-day mortality and duration of vasopressor administration in human patients with septic shock, especially those with documented adrenal insufficiency, similar work remains to be done in the horse.54 Some studies evaluating the potential for adrenal insufficiency in sick, septic foals have been performed, suggesting that some level of corticosteroid supplementation may also improve outcome in horses, although protocols for diagnosis need to be developed and tested prospectively, and, as yet, no recommendations for treatment have been made in the horse.54–56 A recent meta-analysis of steroid use during sepsis in humans suggested that benefit is associated with dose and disease severity.57 Low-dose steroid regimens (mean, 1200 mg total steroid dose—hydrocortisone equivalent—over treatment periods) versus high-dose regimens (mean, 23,975 mg total steroid dose—hydrocortisone equivalent—over treatment periods) seem to reduce shock in most patients with septic shock and decrease mortality in those patients with septic shock at highest risk of death.57 Low-dose steroid protocols unfortunately seem to increase mortality or have no effect in the least severely affected patients and are probably not indicated for this patient cohort. Trials performed before 1989 were the majority of studies in the high-dose group and had an associated greater incidence of harmful effects of steroid treatment.57 Duration of the course of treatment, in addition to total dose, may impact outcome because the earlier trials using higher doses had significantly shorter courses and may have led to harmful immunosuppression.57 The more recent lower-dose studies aimed at providing the ~300 mg of cortisol/day produced by the body in stressful circumstances. The lower-dose regimens do not seem to be immunosuppressive or to lead to other steroid-related adverse events, such as gastrointestinal bleeding and steroid-induced myopathy or neuropathy.57 In foals, this author has used 1 mg dexamethasone/foal/day, IV, in severe sepsis and severe SIRS cases with refractory hypertension and has also used 50–100 mg/foal/day, IV, methylprednisolone for that same purpose. The ultimate importance of adrenal insufficiency in acutely ill horses and the potential benefits for these patients of supplemental therapy remain completely unknown.

4. Conclusions and Future Directions

Sepsis develops in horses when the host response to the invading pathogens is not properly balanced according to the severity of the insult. Several clinical conditions frequently encountered in equine practice may be associated with the development of sepsis and have the potential to progress to more severe forms such as severe sepsis, MODS, and septic shock. Consequently, it is important for equine practitioners to be aware of the manifestations, pathophysiology, and treatment of sepsis. Although enormous progress has been made in recent years in our understanding of the pathophysiology of sepsis, more work remains to be done in improving basic critical care guidelines and basic monitoring in equine intensive care units and in critically evaluating potential equine sepsis therapy. Fortunately, we can learn from the important advances made recently in the treatment of human sepsis patients, and hence, rapid progress may be expected in the near future, especially as more veterinarians show interest in the discipline of equine critical care.

Evaluation and institution of species-appropriate EGDT will be an important “next step.” The evolution of and routine availability of high-throughput genetic and molecular techniques will further refine our understanding of severe sepsis and septic shock, essentially becoming the next step, allowing for appropriate therapeutic intervention, perhaps even targeted to each individual according to the state of their individual immune response at the time of treatment. Some of these ‘next steps’ have already been taken. There are investigations using molecular techniques to study inflammation,12,18,38–40 clinical infection, and application of PCR techniques to rapid identification of pathogens,61–63 including bacterial and viral
agents. Those studies should allow for rapid institution of appropriate treatment in the future.

References


