Equine neonatal sepsis: what is it, how should we treat it and where are we now?

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Introduction

Equine neonatal sepsis, defined as "life threatening organ dysfunction caused by a dysregulated host response to infection," is a major cause of death in foals less than 7 days old.[1] Septicemia carries a guarded prognosis and remains a major cause of equine neonatal morbidity and mortality.[2] A myriad of factors are involved in the pathophysiology of neonatal sepsis, including maternal disease, parturition complications, failure of transfer of passive immunity, animal husbandry and management practices and environmental exposure.[3] The clinical signs observed in sepsis overlap with many other non-infectious, life-threatening conditions. As sepsis is so multifaceted with non-specific clinical signs, diagnosis proves difficult until clinical signs become severe. Early initiation of therapy is imperative to improve clinical outcome. Despite improved survival with advances in veterinary medicine, neonatal sepsis and systemic inflammatory response syndrome (SIRS) remain significant contributors to morbidity and mortality in foals[1]. SIRS criteria have varying sensitivity for diagnosis and limited prognostic capabilities. Blood culture is the current gold standard to confirm sepsis,[4] however sensitivity (~41-50%) and long turn-around time (24-72 hours) are major drawbacks.[5] The need for a rapid and sensitive method for detection of bacteremia is imperative for the diagnosis and prognosis of sepsis/SIRS, as well as determining appropriate use of antimicrobials, but do we have one in the works? What is our best understanding of treatment today? Where are we now?

What is sepsis? And what about SIRS, NSIRS, MODS and MOF?

Sepsis is the number one cause of neonatal foal mortality and is most broadly defined by an overwhelming systemic inflammatory response syndrome (SIRS) triggered by infectious organisms.[6] SIRS is a host response characterized by alterations of temperature regulation, tachycardia, tachypnea (or hypocapnia) as well as alterations in peripheral leukocyte counts where ≥ 2 of these findings is often used to diagnose a patient with SIRS (**Figure 1**). The pathophysiology of SIRS and sepsis is complicated and involves the host's innate immune response in the face of infection or injury.[7] Full-term neonatal foals are born immunocompetent but immunonaive. They are largely protected from pathogens by the innate immune system and acquired colostral sourced immunoglobulins and soluble complement factors. Despite this, gastrointestinal origin of sepsis is a common route of bacteremia and subsequent sepsis during both the open gut phase (first 24 hours of life) or during inflammatory diseases (i.e. enteritis/enterocolitis), moreover, ascending infection via the umbilical remnant also occurs frequently. Regardless of the route, the host cell signaling responses and inflammatory cytokines produced lead to systemic inflammation. When the clinical manifestations of altered vital parameters and leukogram findings occur, this heralds the onset of SIRS. Activity during the inflammatory response intended to eliminate or contain infection can lead to host detriment in many ways ultimately leading to dysregulation of normal homeostasis. The severity of sepsis is also associated with survival. Multiple organ dysfunctions syndrome (MODS), progressing to multiple organ failure (MOF) are premonitory events before death. The

rapidity of progression is highly variable and as such early identification of sepsis or even an 'at risk' patient is essential to begin life preserving therapies. Recent studies show septic foals still have a high mortality rate (30-50%) further proving the need for early diagnosis in horses.[8,9,10]

How do we diagnose neonatal sepsis and SIRS?

Suspicion of neonatal sepsis should be considered based on a variety of historical information, physical examination findings and clinicopathologic derangements.[6] Relevant history includes details regarding the mare in late gestation (premature lactation, increased vaginal discharge, early parturition), abnormalities during foaling (unusual appearance of fetal fluids, meconium aspiration) and concerns following foaling (increased time to stand or nurse, failure of the transfer of passive immunity dullness). Physical examination findings described in cases of neonatal SIRS and sepsis include petechiation of mucous membranes or skin, injection of mucous membranes, inflamed joints and the presence of an enlarged umbilicus. For a recent example of a sepsis scoring system, see **Figure 1** below.

The SIRS concept in veterinary medicine was first employed in 1999 in a retrospective study of hypotensive, critically ill foals.[12] Parameters were based on human consensus statements and were applied to help retrospectively categorize neonatal foals with sepsis and septic shock. Use of the SIRS definition facilitated the categorization of patients into cohorts for research studies and investigation of the association of various blood parameters with systemic inflammation. A wide variety of laboratory findings have been identified in association with equine neonatal sepsis. Changes in white cell count with or without decreasing neutrophil count have long been considered important aspects for the diagnosis of sepsis, as well as increased potassium and creatinine, decreased lymphocytes, decreased IgG values, changes in blood glucose and elevations in blood lactate.[3,13] A more recent proposition for a specific neonatal SIRS (or NSIRS) score has been proposed, involving rectal temperature, heart rate, tachypnea, abnormal white blood cell count, blood lactate and blood glucose (**Figure 1**).[14] Importantly, variations in these parameters also share associations with other disease processes and are not specific to equine neonatal sepsis, and a widely accepted definition of SIRS has not been established within veterinary literature with which to diagnose sepsis.

An imperative component for the improvement of clinical outcome in human adult septic patients is the rapid detection of bacteremia and initiation of treatment, most often including antibacterial therapy.[11] Diagnostic blood culture has remained the gold standard for detection and isolation of pathogenic organisms, however, the diagnostic sensitivity remains low in septic neonates - reported incidence of positive blood cultures from ill neonatal foals at admission is between 25.8-36% of blood culture samples collected.[1] Limitations abound with sensitivity and time required for organism detection. Fastidious organisms as well as maternal and neonatal antibiotic treatment can significantly decrease sensitivity. The quantity of microbes present in the bloodstream during infection is often low in adults, and possibly even lower in neonates, and the gold standard blood culture is therefore limited in utility.

How do we treat neonatal sepsis? Are we successful?

Antimicrobials are a mainstay of treatment for equine neonatal sepsis, and cultutre and sensitivity is imperative in guiding treatment protocols. Interestingly, susceptibility of bacterial isolates from these foals varies between geographic regions.[15,16,17] Additionally, increased antimicrobial resistance of commonly used medications has been appreciated.[18] While awaiting the results of initial blood culture and sensitivity, the clinician's choice of antimicrobial tends to be based on personal or hospital experience prior to being adjusted as needed once the results of testing are obtained. If a culture reveals resistance, a clinician may opt to give the medication more time or change antimicrobials. This methodology yields a successful outcome in 65% of affected foals, while 35% fail to clinically improve despite implementation of test results.[19]

Some have theorized that treatment and exposure to hospital-acquired infections may cause selection pressures on initial bacterial populations and thus subsequent resistance, and revealed that repeat blood culture after 14 hours of hospitalization may be warranted.[15] One such study by Theelen et a., revealed that medications with an efficacy of >90% against bacteria isolated at hospital admission included amikacin + ampicillin (93.7%), amikacin + ceftiofur (93.7%), amikacin + penicillin (90.9%), ceftiofur (90.9%), and imipenem (94.1%), while none of these drugs or their combinations had a predicted efficacy of >90% against bacteria isolated from samples collected after ≥48 hours of hospitalization.

Additional recent studies investigating the influence of polymicrobiology, or infection with more than one pathogen, and have suggested that assessment of susceptibility patterns at a "whole foal" level rather than isolate level may be more useful for clinical decision making, particularly for veterinarians choosing initial antimicrobial treatment.[19] This study investigated blood culture results from foals admitted to a West Coast teaching hospital from 1990-2015; based on their results, the combination of amikacin and ampicillin appears suitable for empirical treatment in foals with sepsis. If all bacteria isolated from a single foal were susceptible to the initial antimicrobial treatment, the likelihood of survival was 65.4% Of note, 34.6% of the foals died despite receiving 'correct' antimicrobial therapy and 41.7% survived despite being treated with 'incorrect' antimicrobial drugs initially, illustrating a multifaceted influence on disease progression and role of the host immune response.

The future of equine neonatal sepsis: what does the ideal sepsis diagnostic test look like?

1. Rapid detection
2. Minimal invasiveness
3. High sensitivity
4. High specificity
5. Ease of integration into clinical workflow
6. Enable prognostic extrapolations
7. Levels reflective of disease severity

		Exact Number	4	3	2	1	0	This Case
CBC	**Neutrophil Count** (cells/μL)		<1000	<2000	2000-4000 or >12000	8000-12000	Normal	
	Band Neutrophil Count (cells/μL)		>500	>200	50-200		<50	
	Toxic Neutrophil Changes		Marked	Moderate	Slight		None	
	Lymphocyte Count[3,4] (cells/μL)			≤550				
	Fibrinogen (mg/dL)				>600	400-600	<400	
Other Lab Data	**Blood Glucose** (mg/dL)[1]				<50	50-75	>75	
	Blood Lactate (mmol/L)[2]		>10	>7	>5	>2.5	≤2.5	
	IgG (mg/dL)			200-400	400-800		>800	
	Creatinine (mg/dL)[4]			≥4				
Clinical Exam	**Petechia, scleral injection, hypopyon or anterior uveitis (not from trauma)**			Marked	Moderate	Mild	None	
	Diarrhea and/or swollen joint(s) and/or respiratory distress			Yes			No	
	Hypotonia, coma, lethargy, seizures				Marked	Mild	Normal	
Historical Data	**Prematurity** (gestational age)			<300	300-310	311-330	>330	
	Placentitis, vulvar discharge prior to delivery, dystocia, mare sick, foal induced, C-section, GA>365 days			Yes			No	
Presence of SIRS	See below for criteria		Yes				No	
Total								
Neonatal SIRS criteria	**Presence of at least 3 of the below criteria, 1 of which must be abnormal temperature or leukocyte count**							
		Birth–3d	**4-14d**	**This Case**				
	Temp (˚F)	>102.6F or <99.0F	>102.6F or <99.0F					
	Heart rate (beats/min)	>115	>120					
	Tachypnea (breaths/min)	>56	>56					
	Leukocytosis or Leukopenia (cells/μL)	>14.4 or <6.9	> 12.5 or < 4					
	Blood lactate (mmol/L)	>5.0	>2.5					
	Blood glucose (mg/dL)	<50	<50					

Figure 1: Wong et al. 2018, published this scoring system for sepsis which utilizes a cutoff value of 12 or above to define neonatal sepsis; this system has a sensitivity of 60% and specificity of 61% with an area under the curve of 0.71. The scoring system for NSIRS has a sensitivity of 42%, specificity of 76%, positive predictive value of 60% and negative predictive value of 61%.

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