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Review Article

Sepsis-Induced Acute Kidney Injury in Equine: Current Knowledge and Future Perspectives

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ABSTRACT

Sepsis in equine describes a broad range of disorders with different underlying causes and often different prognoses. The syndrome can rapidly progress to septic shock and can result in hypoperfusion with subsequent multiple organ dysfunction including acute kidney injury (AKI). Despite extensive research and progress have been performed in several fields in equine medicine, the incidence as well as the mortality rate of sepsis-induced AKI remains unclear. Although sepsis is considered as the leading cause of AKI, the underlying pathophysiologic mechanisms are not completely understood and still a subject of ongoing debate. The aim of this article is to provide a comprehensive review of the pathophysiology of sepsis-induced AKI, and to outline the diagnostic as well as the therapeutic potentials of the disease.

1. Introduction

The bacterial infection continues to be one of the most common causes of morbidity and mortality, especially in adult horses and neonatal foals due to the development of sepsis, which arises from the host response to infection [1,2]. Therefore, the outcome from sepsis usually depends on the viability of invading pathogen, which can cause direct toxic and destructive changes to tissues, and even more so the host response, which may be rant and result in collateral organ and tissue damage [3].

The term systemic inflammatory response syndrome (SIRS) has been used to describe global inflammation that may be caused by several infectious agents including bacteria, fungi, viruses, etc or noninfectious causes like trauma, burns, toxins, acidosis, etc [1,4,5]. When SIRS is the result of infection, it is termed sepsis [5]. The most common infectious agents associated with sepsis are bacteria [1]. If bacteria are present in the blood, the term bacteremia is used. Although it has been suggested that septicemia should be eliminated from the current usage because it does not adequately describe the spectrum of organisms that invade the blood, it is defined as bacterial infection in the blood along with a state of SIRS [5].

In equine practice, there have been several clinical entities that are frequently associated with the development of sepsis and have the potential to develop into more severe forms such as severe sepsis, multiple organ dysfunction (MODS), and septic shock [1]. The term severe sepsis is defined as sepsis associated with hypoperfusion, hypotension, or organ dysfunction [5]. A frequent complication of SIRS is the development of organ system dysfunction, which is called MODS syndrome. If a patient with severe sepsis is hypotensive despite adequate fluid resuscitation,

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the term septic shock is used [1,5]. However, the term endotoxemia refers to a clinical condition characterized by circulation of a Gram-negative bacterial lipopolysaccharide (LPS) in the blood stream [6,7]. It has been found that the prevalence of endotoxemia is greatest for horses with colic, intestinal strangulation, obstruction (small intestinal or large colon volvulus, incarceration), enteritis (colitis, proximal enteritis), and septic peritonitis [7,8].

Bacterial endotoxin has been reported to be a complex glycolipid composed of three parts, each of which has important biologic characteristics [9], the innermost portion is hydrophobic lipid A moiety that anchors the molecule to the outer membrane, the middle region is a core oligosaccharide chain, which is well conserved in Gram-negative bacteria and links the inner portion to the outermost portion which is hydrophilic an O-antigen polysaccharide chain, which is quite diverse and responsible for the serological differentiation among bacterial species [10]. Lipid A has been reported to be a unique phosphoglycolipid [11]. Its structure is highly conserved among Gram-negative bacteria, it imparts the toxic and deleterious effects of the endotoxin molecule [12,13], but modifications exist that allow bacteria to evade recognition by host innate immune receptors and resist host-derived antimicrobial peptides and administrated antibiotics [10]. It has been reported that lipid A could be the major culprit in initiating the endotoxic symptoms. This component of endotoxin stimulates the release of tissue tumor necrosis factor (TNF) and can also activate the complement pathway [14]. Lipopolysaccharide derived from some bacterial species are poorly recognized by the immune system [10]. Thus, LPS from different bacterial strains stimulate different inflammatory mediator profiles [15]. Lipid A derived from *Escherichia coli* is a potent activator of innate immune responses in many species including the horse [16].

The cecal fluid of horses harbors large quantities of Gram-negative bacteria and approximately 80 μg/mL free endotoxin of clinically normal horses, as little as 1 μg/mL LPS in systemic circulation is sufficient to induce fever and leucopenia in equine [17,18]. Likewise, endotoxin can be liberated into the systemic circulation during rapid proliferation of the bacteria or cell lysis because LPS is an integral component of the outer cell wall of Gram-negative bacteria [11], or can gain access to the blood as soon as disrupted intestinal mucosal barrier that prevents systemic absorption [19]. It is of interest to note that nonpathogenic gastrointestinal flora could provide a continuous low level of LPS acting as hormonal signals to promote the development and enhance the function of the entire immune system. Endotoxins are antigenic because of their polysaccharide nature, and through their diversity they can elicit antibodies capable of neutralizing their function and limiting their immunotoxic and dysregulatory actions on the body systems [20].

As mentioned earlier, sepsis has been considered as a severe and dysregulated inflammatory reaction to infection, which can develop into septic shock and MODS, with initial dysfunction in the cardiovascular system, followed by involvement of the respiratory, hepatic, gastrointestinal, renal, and nervous systems [21]. Acute kidney injury (AKI) is a frequent and serious complication of sepsis in human patients [22]. Despite extensive research and progress have been conducted in several fields in equine medicine, the incidence as well as the mortality rate of sepsis-induced AKI remains unclear and warrants further investigations. Hence, most of the available literature are extrapolated from humans and laboratory animal models. In that regards, there is a strong evidence that sepsis and septic shock are the most important causes of AKI in critically ill patients, account for 50% or more of cases of AKI in intensive care units (ICUs) [23]. In addition, there is a growing evidence suggesting that even less severely ill patients with the infection have a significantly higher incidence of AKI [24].

2. Definition of Acute Kidney Injury

The term AKI has been introduced in humans, and subsequently small animal medicine with limited information in equine, to increase awareness of subclinical renal damage in patients with decreased renal blood flow (RBF) and glomerular filtration rate (GFR). Acute kidney injury has been defined as an increase in serum creatinine levels (SCr) of 0.3 mg/dL or a 50% increase from the baseline value, yet SCr may remain within the reference range. Hemodynamically-induced AKI is often associated with oliguria (urine output <0.5 mL/kg for 6 hours), whereas urine production with nephrotoxin-associated AKI often remains normal (nonoliguric AKI) [25].

To date, sepsis-induced AKI represents a complex disorder that lacks a widely accepted definition. This dilemma has impeded comparisons of articles in the literature and has limited the ability to develop effective approaches to prevent and treat AKI. It is, therefore, imperative to have a uniform standard for the diagnosis and classification of AKI. A consensus-based definition and classification system have been proposed, whereby diagnostic criteria, based on alterations in SCr levels and/or urine output, are used to classify different levels of injury [26]. In general, AKI has been found to be a common sequel of sepsis in human ICU with scarce information in equine medicine. It has been shown that the alterations in kidney functions with a rapid decrease in renal excretory function should be captured for early detection, diagnosis, and intervention, as any minor deterioration in GFR, and kidney dysfunction should be diagnosed as the presence of kidney damage or injury [27,28].

3. Recognizing Acute Kidney Injury

Although the available data used to recognize horses with AKI is still scarce, there have been three separate staging criteria currently used in humans to recognize and categorize AKI [29–31]. These classifications include the staging of renal dysfunction based on SCr concentration as well as urine output. The RIFLE (Risk, Injury, Failure, Loss, End Stage) classification of AKI has been originally established to standardize the severity of AKI in humans and found to correlate with morbidity and mortality in a stepwise manner, thereby providing an important tool for scientific research [29]. Despite having the ability to predict the outcome, RIFLE criteria are not taken into account the cause of AKI or the need for renal replacement therapy (RRT). Other limitations include issues surrounding the