EQUINE ENDOTOXEMIA: ANY NEW THERAPIES IN THE HORIZON?
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Endotoxemia background:
Endotoxemia is a leading cause of morbidity, mortality and economic loss to the equine industry. Colic is the most common cause of endotoxemia in horses. Lipopolysaccharide (LPS), a component of the outer cell membrane of Gram-negative bacteria, stimulates the release of mediators of inflammation, including prostaglandins, histamine, serotonin, kinins, platelet-activating factors and others. Initially LPS binds to a soluble cell membrane binding protein (LPS-BP), which transfers LPS to the macrophage cell wall receptor CD14-MD2 complex and in turn transfers the signal through transduction Toll-Like-Receptor (TLR4) into the cell. The stimulation of TLR4 activates genes responsible for production of pro-inflammatory mediators. Massive inflammation results which in turn is responsible for cardiovascular depression, pulmonary hypertension and arterial hypoxemia that lead to decreased tissue perfusion and peripheral hypoxia and eventually, multiple organ dysfunction and death.

Treatment approach for endotoxemia:
Initial treatment for endotoxemia in horses with colic is to treat the underlying cause in order to eliminate the source of LPS. A strangulated intestinal segment should be removed in a timely manner. The second level of treatment intervention is to eliminate LPS prior to its interaction with the host’s receptors sites or block the LPS receptors. Once the inflammatory cascade has been initiated, the use of anti-inflammatory agents is indicated. After the endotoxemic cascade has been activated, the core therapy is directed at supportive fluid therapy targeted mainly to ameliorate cardiovascular deterioration.

Treatment modalities:
Polymyxin B
Polymyxin B (PB) is a cationic cyclic polypeptide antimicrobial drug that at low doses acts as a chelating agent by binding to the Lipid A moiety of LPS, removing endotoxin from the vascular system and by that preventing the pro-inflammatory cascade of endotoxemia. The Lipid A portion of LPS is highly conserved in gram-negative bacteria and thus PB is effective regardless the gram-negative bacteria isolated. In a study in foals administered endotoxin, PB ameliorated clinical signs and decreased concentrations of TNFα and IL-6. In a recent study PB was safe and effective in treating endotoxemia in adult horses.

Hemofiltration
One novel treatment approach to sepsis in human medicine involves circulating the patient blood through an external filter, thereby adsorbing the pro-inflammatory cytokines and improving survival rates. The use of hemofiltration was reported in horses and yielded no significant improvement in clinical and hematological response to LPS challenge. A more specific hemofiltration involves filtration of the blood through a column containing bound PB, removing LPS by adsorption. A recent systematic literature review found this method effective in improving hemodynamic and oxygenation status and even more importantly, increasing
survival rates in septic human patients. This highly effective, elegant, method may have an important role in the future of equine endotoxemia therapy.

**Detergent (Tyloxapol)**

Tyloxapol is a nonionic liquid alkyl aryl polyether alcohol which has a similar chemical structure to bile acids and acts like bile acids a detergent. Bile acids play a critical role in the body’s defense mechanism against infection by binding LPS. In a recent study, pre-treatment with Tyloxapol IV was effective in preventing fever, leucopenia and pulmonary hypertension in horses thus Tyloxapol may have a place in treatment of equine endotoxemia.

**Phospho-Lipid Emulsion:**

Protein-free phospholipid-rich emulsion (PLE) has been shown to bind and neutralize endotoxin in humans and prevent clinical signs of endotoxemia. Pre-treatment with PLE preventing the majority of the detrimental effects of LPS in horses but hemolysis occurred thus its clinical application may be limited.

**Lipid A analog E5564:**

E5564 or Eritron is a synthetic Lipid A analog that blocks TLR4 and by doing so effectively negates endotoxemia in in-vivo studies in rodents as well as in human. In the horse Eritron has shown some promise by reducing production of inflammatory mediators in ex vivo equine blood.

**Flunixin meglumine**

Flunixin meglumine (FM) is a potent NSAID that is considered one of the mainstays in anti-endotoxemic treatment in horses. Flunixin meglumine inhibits cyclooxygenase breakdown of arachidonic acid to prostaglandins which play a critical role in the systemic effects of endotoxemia including arterial hypoxemia, vasodilation, cardiovascular shock, and diarrhea. Studies have shown that pre-treatment with FM in horses administered endotoxin effectively prevents clinical signs related to endotoxemia. Other studies however, have conclusively shown that FM has detrimental effects on the small intestine by decreasing the Transepithelial-Electric-Resistance (TER), increasing the influx of endotoxin from the intestine and may actually paradoxically exacerbate existing endotoxemia.

**Firocoxib**

Firocoxib is a selective cox-2 inhibitor recently developed for use in horses. A study by Cook et al. 2008, demonstrated the visceral analgesic effects of firocoxib, while as opposed to FM it did not have deleterious effect on small intestinal mucosal permeability.

**Dimethyl Sulfoxide**

Dimethyl sufoxide (DMSO), an oxygen-free radical scavenger and potent anti-inflammatory agent was one of the most commonly used drugs against endotoxemia in a survey among clinical equine specialists. Nevertheless, evidence to support its alleged anti-endotoxic effect in the horse is lacking. In a recent study DMSO therapy did not show significant positive effect on horses with induced endotoxemia. Since low dose DMSO showed beneficial effects in an ischemic equine small intestine model, it can be recommended for clinical use.
Lidocaine

Lidocaine is a local anesthetic drug that exerts this effect by blocking sodium channels and by that prevents action potential propagation. Lidocaine decreased LPS influx after induced ischemia in the jejunum and negated the deleterious effects of flunixin meglumine (FM) on Transepithelial-Electric-Resistance (TER) and LPS influx. In a recent study, lidocaine effectively attenuated clinical signs and inhibited TNFα in horses with induced endotoxemia.

Ketamine

Ketamine is a dissociative anesthetic which blocks the N-methyl-D-aspartate (NMDA) receptors. Ketamine completely abolished endotoxic shock when given prior to administration of LPS in rats. Nevertheless, in a recent study by Alcott et al., ketamine failed to show positive effect on induced endotoxemia in horses.

Plasma

Fresh Frozen Plasma is often included in the treatment of endotoxemia in horses. In addition to providing albumin that improves plasma oncotic pressure, plasma provides a variety of molecules active in the clotting cascade such as fibronectin, antithrombin, complement and other factors. A current study by Forbes et al. found that plasma did reduce circulating TNFα but did not improve clinical signs after induced endotoxemia in horses.

Pirfenidone

Pirfenidone is an experimental drug used successfully in humans as an anti-fibrotic and anti-inflammatory agent. Studies in rodents showed promise for Pirfenidone as a potent anti-endotoxic drug however results in a preliminary study in horses have been disappointing.

Hyperbaric Oxygen Therapy (HBOT)

HBOT improved cell viability in an ischemic intestinal injury study in rats, in horses however HBOT failed to show a positive effect in an induced endotoxemia model.

Fluid Therapy

Fluid therapy is the mainstay, supportive therapeutic strategy to combat the hemodynamic effects of LPS. Nearly all endotoxemic patients are dehydrated and thus balanced crystalloid solutions are an essential part of the initial stabilization therapy. Endotoxemia leads to alternation in vascular and mucosal permeability leading to protein loss and reduced colloid oncotic pressure. Colloid therapy is indicated to increase the colloid oncotic pressure and arrest the vicious cycle of protein loss. Hypertonic saline (7-7.5 % Na-Cl, HS) provides immediate improvement in tissue perfusion and has been shown to exert some anti-endotoxemic effects. In a controlled prospective study, HS and hetastarch administered to endotoxemic horses failed to abate the hemodynamic effects of LPS.

Antibiotics

The use of antibiotic (AB) therapy in the management of endotoxemia is controversial. Administration of AB to horses with endotoxemia may exacerbate the condition by further killing gram negative bacteria and releasing more endotoxin. This is a concern in septic human patients and can cause clinical deterioration. However, since the immune system in
endotoxemic patients is overwhelmed and dysfunctional, AB administration may protect against opportunistic infections.

**Summary:** Many of the pharmacologic agents mentioned in this article can, to some extent, block the effects of endotoxin. In the clinical situation this may be the difference between survival and demise in colic patients. It must be emphasized that good scientific clinical data is lacking on many of the treatment modalities presented in this article. Nevertheless, this review presents our current knowledge of these agents and hopefully more information will be forthcoming soon.

**References:**