The pathophysiology of endotoxaemia, a leading cause of death in the horse, is beginning to be understood in greater detail. Endotoxin may be absorbed into the systemic circulation in a number of different ways: most commonly the body’s normal defense mechanisms are disrupted or bypassed, or the normal clearance mechanisms overwhelmed. Following this widespread effects are observed, although the most significant are seen in the cardiovascular system. Fever, arterial hypoxaemia and signs of abdominal pain are also common. With increased understanding of the disease new therapeutic agents have become available, however, while the newer agents offer some advantages it is important to recognise that supportive care is the mainstay of treatment for endotoxaemia.

Supportive care consists of aggressive fluid therapy (crystalloid, colloid and hypertonic), the administration of non-steroidal anti-inflammatory drugs and, where appropriate, antimicrobials. The principles of supportive care are discussed in detail. Other therapies such as hyperimmune plasma, polymyxin B, pentoxifylline, dimethyl sulfoxide and heparin are commonly used in the treatment of equine endotoxaemia and their use is reviewed here. Furthermore, newer agents such as anti-tumour necrosis factor antibodies, detergent, activated protein C and insulin, which have yet to gain widespread acceptance but may have an important role in the treatment of endotoxaemia in the future, are examined.

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DMSO Dimethyl sulfoxide
ICU Intensive care unit
IL Interleukin
IM Intramuscular
IV Intravenous
LPS Lipopolysaccharide
NOSAD Non-steroidal anti-inflammatory drug
ROS Radical oxygen species
SC Subcutaneous
TNFα Tumour necrosis factor α

Endotoxaemia is a leading cause of mortality and morbidity in adult horses and foals. Colic remains the leading cause of death in the horse, while in foals septicaemia is the most common acquired disease and has the lowest survival rate of the acquired neonatal diseases. Tight mucosal junctions between epithelial cells, secretions from epithelial cells, and resident bacteria, all contribute to an effective defense mechanism that prevents absorption of large amounts of LPS into the circulation. In the normal animal a small amount of LPS may enter the portal circulation, however most is rapidly neutralised by circulating anti-LPS antibodies while the remainder is transported on specific proteins (LPS-binding protein) and cleared by the mononuclear phagocytic system of the liver.

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LPS may enter the systemic circulation by one of several ways. Firstly, if the amount of LPS entering the portal circulation is large enough, the clearance capacity of the liver can be overwhelmed. This may occur secondarily to a wide variety of conditions that compromise blood flow to the bowel, including many surgical gastrointestinal conditions, severe colitis and hypovolaemia. Alternatively, LPS that originates from sites in the body other than the gastrointestinal tract, such as the peritoneal cavity, pleural cavity or uterus, may bypass the portal circulation and directly enter the systemic circulation.

The effects of LPS on the cardiovascular system are dose dependent. At higher doses tachycardia with increased cardiac output and decreased systemic vascular resistance following peripheral vasodilatation (hyperdynamic shock), results. This problem is well described experimentally and closely reflects the clinical

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syndrome commonly seen. As a result of vasodilatation, a state of ‘relative hypovolaemia’ can occur in previously normovolaemic animals, due to an increase in the potential vascular volume. The relative hypovolaemia is often exacerbated by a true hypovolaemia due to either loss of fluids from gastric reflux or diarrhoea, or third spacing of fluids into the thoracic or abdominal cavities. Marked pulmonary hypertension and arterial hypoxaemia occur early in the disease process following activation of pulmonary intravascular macrophages.\textsuperscript{30-32} The combination of arterial hypoxaemia and decreased cardiovascular performance results in decreased oxygen availability at the tissue level, with cellular dysfunction, multiple organ disease and possibly death, resulting.

The clinical syndrome of endotoxaemia includes alterations in mucous membrane colour, tachycardia and dehydration secondary to the cardiovascular changes described above.\textsuperscript{20} Additionally, endotoxaemia is manifested by fever, decreased gastrointestinal motility, signs of abdominal pain and diarrhoea.\textsuperscript{35,34} Typically leukopenia and polycythaemia are seen early in the disease course, often followed by leukocytosis.\textsuperscript{33,35} Arterial hypoxaemia, metabolic acidosis and hyperlactaemia are also common.\textsuperscript{31}

**Current treatments**

In a recent review of 101 diplomates of the American College of Veterinary Internal Medicine and the American College of Veterinary Surgeons the most common treatments for endotoxaemia were IV fluid therapy, NSAIDs, broad spectrum antimicrobials, plasma and DMSO.\textsuperscript{36} Correspondingly the initial focus of this review is on the use of these therapies.

**Intravenous fluids**

Given the profound effects of LPS on the cardiovascular system, maintenance of circulatory volume in an attempt to optimise oxygen delivery to tissues is a fundamentally important goal of therapy in endotoxaemia. This is most commonly achieved with the use of isotonic, polyionic electrolyte solutions such as lactated Ringers solution or Normosol-R\textsuperscript{8}. These solutions are pH balanced and the predominant electrolytes are sodium, potassium and chloride. In relation to plasma they contain relatively low concentrations of sodium and chloride, and a normal concentration of potassium. KCl is commonly added to create a solution for long term use or maintenance. The addition of 20 to 40 mEq KCl/L of fluids is generally safe during the maintenance phase of fluid therapy. However, caution should be exercised to not exceed a maximum rate of 1 mEq KCl/kg/hour, as potentially fatal arrhythmias may occur.\textsuperscript{37} In general, the addition of KCl to fluids during the acute resuscitative phase is not recommended, to avoid an accidental excessive rate of administration. Colloids are also potentially beneficial as a component of fluid therapy for endotoxaemia. Colloids are large molecules which act to draw and retain fluid within the vascular space via osmotic forces. Colloids are useful during fluid therapy to ensure adequate colloid onotic pressure, thus maintaining vascular volume and minimising the development of tissue and pulmonary oedema. Colloids can be either natural, such as plasma, or artificial, such as large branched sugars (Hetastarch\textsuperscript{8}). Hypertonic saline may also be beneficial during the acute resuscitative phase and is readily available, cheap and easily stored and administered.

Detailed discussion of the use of IV fluids and electrolytes is beyond the scope of this review. However, it is vital to recognise that the provision of cardiovascular support is central to the management of endotoxaemia and it should form the cornerstone of therapy. Readers are referred to a recent review by Corley\textsuperscript{37} for more detailed discussion on the principles of IV fluid therapy and electrolytes in the horse.

**Non steroidal anti-inflammatory drugs (NSAIDs)**

The role of lipid derived pro-inflammatory mediators, and in particular the products of the cyclooxygenase pathway, is well recognised in equine endotoxaemia and many of the clinical signs of endotoxaemia are mediated, at least in part, via these products.\textsuperscript{30,36} The use of NSAIDs in the treatment of endotoxaemia is rational, because this class of drugs inhibits cyclooxygenase activity and the subsequent generation of the reactive metabolites described above.

Recently, in a study in humans, no overall effect on mortality was observed with the use of the NSAID ibuprofen in severe sepsis, despite decreased production of arachidonic acid metabolites and improvement in several clinical parameters.\textsuperscript{39} Appropriate placebo controlled clinical studies are lacking, and it is unclear whether NSAIDs improve survival in the horse. However, even if objective documentation of the ability to decrease mortality in equine endotoxaemia is lacking, their ability to ameliorate many of the clinical signs associated with the disease and improve patient comfort justifies their use.

The most commonly used NSAID in equine endotoxaemia is flunixin meglumine\textsuperscript{36} and it has been extensively studied in many models of equine endotoxaemia. Historically, concerns over toxicity and the ability of high doses of flunixin meglumine to mask the need for surgical intervention in colic led to investigation of lower doses.\textsuperscript{40,41} Pretreatment with 0.25 mg/kg of flunixin meglumine has been shown experimentally to decrease the period of inappetence, block the development of signs of abdominal pain and to blunt the rise in temperature that occurs following LPS administration.\textsuperscript{40,41} Pretreatment with 1.1 mg/kg is more effective at ameliorating tachycardia, tachypnoea and fever induced by LPS\textsuperscript{40,42} and has been shown to increase the time till death in fatal models of endotoxaemia in the horse.\textsuperscript{43,44} Flunixin meglumine at either dose does not prevent the development of leukopenia with initial exposure to LPS and both doses have been shown to be equally effective at decreasing the development of hyperlactaemia.\textsuperscript{40} Only the higher dose has been shown to alter the development of hypoxaemia and acidosis.\textsuperscript{42,45} Furthermore, 1.1 mg/kg has been shown to delay the onset of hypotension and hypodynamic shock and to decrease the magnitude of the reduction in blood flow to the brain, heart and large intestine.\textsuperscript{43-46} The LPS stimulated production of thromboxane B\textsubscript{2} and prostaglandin F\textsubscript{1a} are blocked effectively by 0.25 and 0.1 mg/kg respectively.\textsuperscript{40}

With regards to evaluating horses with signs of abdominal pain, the authors feel that the administration of 1.1 mg/kg of flunixin meglumine does not preclude accurate assessment of the need for surgical intervention. Other diagnostic procedures, such as examination per rectum, abdominocentesis, and the presence of borborygmi, as well as careful observation for subtle signs of pain, including depression and trembling, provide adequate information on which the decision for surgery can be based. With that in mind, and given the dose-dependent effects of flunixin meglumine, the use of 1.1 mg/kg every 12 hours may be superior to the traditional ‘anti-endotoxaemic dose’ of 0.25 mg/kg every 6 hours, in decreasing the severity of disease. Care should be exercised with higher doses in animals with circulatory compromise and adequate hydration must be maintained to minimise the likelihood of toxicity. Although not formally evaluated, the use of 0.5 mg/kg every 6 hours may offer some advantages to the standard
lower dose, while alleviating any residual concerns over masking the indicators of surgical colic and reducing the likelihood of toxicity.

Other NSAIDs including phenylbutazone, ketoprofen, and etenac are often used in horses with endotoxaemia, and each has been studied. In a direct comparison of phenylbutazone and flunixin meglumine, pretreatment with phenylbutazone at 2 mg/kg IV was shown to delay the onset of clinical signs of endotoxaemia. However, once developed, the clinical signs were unchanged compared with saline controls. Pretreatment with flunixin meglumine at 1 mg/kg IV almost completely ameliorated clinical signs. Flunixin meglumine also blocked the rise in plasma lactate whereas phenylbutazone did not. In contrast phenylbutazone has been shown to block the LPS induced decrease in blood flow to the intestines more effectively than flunixin meglumine. However, given the significant difference in the two drugs’ ability to alter clinical signs and cardiovascular effects of endotoxaemia, the authors believe there is little indication for the use of phenylbutazone as an anti-endotoxaemic treatment in the horse.

Flunixin has been proposed to have theoretical advantages over flunixin meglumine on the basis of partial inhibition of the leukotriene pathway and a higher therapeutic index. An in vitro comparison of the two drugs found no difference in the production of lipid derived mediators or TNFα following stimulation with LPS. The authors feel that its effectiveness is less well documented than flunixin meglumine, and it appears to offer no clear cut advantages. Flunixin meglumine remains the NSAID of choice for the treatment of equine endotoxaemia.

More recently etenac has been evaluated with promising results. Pretreatment with 0.5 mg/kg IV ameliorated the development of fever and pulmonary hypertension observed following LPS exposure. This effect was probably due to the complete blocking of LPS stimulated production of prostaglandin F2α and thromboxane B2. Although no effect was seen on LPS-induced changes in heart rate, systemic blood pressure and white cell count, etenac did block the rise in endogenous cortisol and adrenaline which were used as markers of stress. The authors believe that it is a potentially useful anti-endotoxic treatment worthy of further evaluation, but at this time offers no clear cut advantages over flunixin.

Antimicrobials

The use of antimicrobials in endotoxaemia is controversial. In animals with defined infections, such as pneumonia and metritis, antimicrobial therapy is clearly indicated. Importantly, dying bacteria may liberate LPS and potentially worsen the clinical picture, however release of LPS is dependent on the antimicrobial used. Antimicrobials effective against the bacterial cell wall, such as penicillins and cephalosporins, result in a greater release of LPS than those that affect microbial protein synthesis, such as the aminoglycosides. The LPS liberating effects of penicillins are blocked by the concurrent use of an aminoglycoside.

In horses with endotoxaemia originating from gastrointestinal disease, a clear indication for antimicrobials is less apparent. Bacterial translocation from the gastrointestinal system is well recognised as an important secondary problem in human sepsis, a disease condition which closely resembles endotoxaemia. In the authors’ opinion, broad spectrum antimicrobial therapy is indicated in severe cases of suspected endotoxaemia.

In most cases the use of penicillin and gentamicin is effective and safe, although care must be exercised in animals with renal disease or severe dehydration. Doses of penicillin ranging from 20,000 to 40,000 IU/kg IV every 6 hours and of gentamicin of 6.6 mg/kg IV once daily are generally adequate. In mature animals with suspected renal disease enrofloxacin at 5.0 mg/kg IV once daily is a viable alternative to gentamicin. Ceftiofur at 4 mg/kg IV or IM every 12 hours is another alternative, although care should be exercised because anecdotal evidence exists that the drug may be linked to a higher risk of antimicrobial associated colitis than other antimicrobials. The use of ceftiofur alone may also result in liberation of large amounts of LPS.

Hyperimmune plasma

The use of hyperimmune plasma has been studied in endotoxaemia in the horse. The rationale for the use of hyperimmune plasma is that anti-lipid A antibodies will bind LPS, preventing interaction with and activation of the mononuclear phagocyte system and subsequent induction of the pro-inflammatory response. Initial evaluation in an experimental model in adult horses and a clinical trial in foals found no significant difference in any of the parameters studied when compared with normal plasma. Subsequent evaluation found a significant improvement in behavioural abnormalities, including signs of abdominal pain and anorexia, observed following experimental LPS exposure in ponies. These results were supported by a double blinded, placebo controlled trial in adult horses where a significant decrease in mortality and a trend towards shortened recovery periods was observed in the treatment group. In contrast the administration of hyperimmune plasma to foals with experimental endotoxaemia has been associated with worsening of clinical signs and significant elevations in the key inflammatory mediators TNF and interleukin-6. The reasons for the inconsistency observed in the experimental and clinical trials are unclear. Based on the findings of the above studies, hyperimmune plasma may be beneficial in the treatment of endotoxaemia in adult horses but it should be avoided in foals because worsening of the clinical syndrome may occur. Regardless of the anti-endotoxic effect of hyperimmune plasma, it is important to recognise that fresh or fresh frozen plasma provides a readily available source of replacement protein that may be beneficial in maintaining colloidial oncotic pressure and thus vascular volume, as discussed above.

Dimethyl sulfoxide (DMSO)

DMSO is extensively used in the treatment of equine endotoxaemia, however the drug has not been studied in either experimental or clinical equine endotoxaemia. Free ROS are highly reactive and toxic oxygen products released during endotoxaemia. DMSO has been shown to have potent ROS scavenging capacities. Additionally, hypercoagulation in endotoxaemia results in microthrombi formation and ischaemia at the microvascular level and DMSO reduces platelet aggregation. Consequently it is reasonable to expect that DMSO may improve microvascular circulation and oxygen delivery at the tissue level and that it may be therapeutically advantageous in equine endotoxaemia. Administration of doses up to 1.0 mg/kg as a 10 to 20% solution, IV or enterally every 12 hours, may be beneficial in the treatment of endotoxaemia.

Polyoxin B

Polyoxin B is a cationic polypeptide with dose-dependent effects. At high doses the drug is a bactericidal antimicrobial with a predominately gram-negative spectrum of activity, while at lower doses the drug binds the lipid A component of LPS. In
addition to binding free LPS, polymyxin B has been shown to disperse LPS aggregates.64

The use of polymyxin B in the treatment of equine endotoxaemia has been studied experimentally. Ex vivo polymyxin B has a dose-dependent suppressive effect on TNF activity with doses of 1100 U/kg and 5200 U/kg expected to suppress TNF activity by approximately 75% for 3 and 12 hours respectively.65 These results are supported by an in vivo study that examined the effects of treatment with 6000 U/kg of polymyxin B prior to LPS exposure.68 Lower maximal TNF and IL-6 activities were observed and the increases in respiratory rate and rectal temperature seen following LPS administration were attenuated.68 Similarly, the use of a polymyxin B-dextran 70 conjugate at 50,000 U/kg of polymyxin B resulted in undetectable levels of TNF and IL-6 following LPS exposure and significant lowering of heart rate, respiratory rate and temperature.66 At this dose mild signs of toxicity were observed, however these were blocked by the concurrent administration of ketoprofen.66 Since polymyxin B relies on binding LPS and blocking its binding to mononuclear phagocytes, its effect may be significantly reduced in clinical endotoxaemia where LPS exposure has already occurred. The results of the above experiments indicate, however, that it may be a useful therapeutic modality under certain circumstances.

**Pentoxifylline**

Treatment of endotoxaemia with pentoxifylline has become popular recently. It improves cardiac output,67 oxygen delivery and tissue oxygen uptake,68, 69 in a wide number of experimental models of sepsis in laboratory animals, and improves survival in septic human neonates.70 Pentoxifylline inhibits, in a dose-dependent manner, TNF, IL-6 and tissue factor activity following in vitro exposure of equine whole blood to LPS.71 Important to the clinical setting, TNF production is inhibited by the addition of pentoxifylline after LPS exposure.

Unfortunately, attempts to reproduce these effects in vivo in the horse have been disappointing. The use of pentoxifylline alone subsequent to LPS exposure in two separate studies resulted in some positive effects on clinical signs, with lower rectal temperatures and respiratory rates, but no effect on TNF or IL-6 activity or on the haematological parameters measured other than whole blood recalciﬁcation times.72, 73 The use of pentoxifylline in combination with flunixin meglumine was demonstrated to reduce the magnitude of the flunixin meglumine induced decrease in PGF1α levels.73 The significance of this finding is unclear.

A likely explanation for the inability to reproduce the results of the in vitro experiments is that the effects observed in vitro were dose-dependent and were seen at concentrations of 10 mg/mL or greater. In a study on the pharmacokinetics of pentoxifylline at doses similar to those used in both in vivo studies, peak serum concentrations of only 3.5 mg/mL were achieved following IV administration.74 Similarly, administration of 7.5 mg/kg IV followed by an infusion of 3 mg/kg/h resulted in a brief peak blood concentration of 9.6 mg/mL with a steady state concentration of 3.4 mg/kg.75

As such, although pentoxifylline may be beneﬁcial in endotoxaemia and the potential usefulness of this has been demonstrated in vitro, it is unlikely to have any signiﬁcant effect when given IV at currently recommended doses. Furthermore the oral bioavailability of pentoxifylline has been demonstrated to be very poor and erratic74 and no accurate recommendations can be made regarding its oral use on the basis of currently available information.

**Heparin**

The presence of a hypercoagulable state in horses with endotoxaemia and severe gastrointestinal disease is well recognised. Several studies have demonstrated prolongation of clotting times and depletion of multiple coagulation factors in clinical cases involving both adults and foals.76, 77 Heparin is a potent anticoagulant and down regulator of the coagulation cascade. Although it may seem counterintuitive to administer an anticoagulant to an animal with prolongation of clotting times and bleeding tendencies, down regulation of an over activated system which is uncontrollably consuming clotting factors is a reasonable therapeutic goal. Heparin exerts its effect predominantly via inhibition of thrombin and by blocking the thrombin mediated positive feedback.78 It also results in the release of tissue factor inhibitor by endothelial cells and blocks platelet aggregation.79 80 The overall effect of heparin is down regulation of coagulation via inhibition of the extrinsic, intrinsic and common pathways, platelet aggregation and fibrinolysis.81

The pharmacokinetics of heparin in the horse has been described.81 Clearance occurs by a combination of saturable mechanisms and hepatic and renal, linear, first order metabolism and clearance. The combination of clearance mechanisms means that a linear dose effect is not observed and consequently a decreasing dosing regime is recommended. Based on titration of activated partial thromboplastin time and thrombin clotting time in normal horses, a dosing regime of a single loading dose of 150 U/kg SC, followed by 125 U/kg every 12 hours SC for six doses and then 100 U/kg SC every 12 hours until no longer required has been recommended.81

**Future treatment considerations**

**Anti-TNF antibodies**

Tumour necrosis factor is the principle mediator in endotoxin shock and its importance in the pro-inflammatory cascade is well recognised.82 It has been proposed that the use of monoclonal anti-TNF antibodies would decrease the severity of disease, and the administration of anti-TNFα antibodies has been shown to decrease the severity of disease and mortality in laboratory animals.83, 84 Initial evaluation of murine monoclonal antibodies in miniature horses given LPS suggested a positive effect, with decreased serum TNF activity, improved clinical scores, heart rates and white cell counts.85 However, these findings were not repeatable in a subsequent study using rabbit monoclonal antibodies in adult horses.86

In a review of the use of anti-TNF therapy in humans with sepsis Reinhart and Karzai87 concluded that meta-analysis of all randomised, controlled clinical studies demonstrated a modest improvement in mortality of approximately 3%. However, there is marked variation in the response of different subpopulations to anti-TNF therapy.87 Given the modest results from human clinical trials and the inconsistency of equine studies, it is unlikely that anti-TNF antibodies will be of significant benefit in clinical equine endotoxaemia.

**Tylovasol**

It has long been recognised that species which have a high density of pulmonary intravascular macrophages, such as horses and ruminants, have a dramatically increased sensitivity (100 to 1000 fold) to LPS when compared with other species, such as primates and murine species.88 In horses, pretreatment with an IV detergent, tylovasol, resulted in significantly lower pulmonary arterial pressures and complete amelioration of the leukopenia and fever.
observed following LPS exposure.88 Similar results have been reported in sheep, in which a greater than 90% suppression of TNF activity was also demonstrated.89 Although further pharmacokinetic work needs to be performed to establish an appropriate dosing regime, tyloxapin may be a useful treatment for endotoxaemia.

Activated protein C
In the 20 years preceding 2001, despite all the improvements in critical care, including the continual development of new antimicrobials with greater spectrums of activity, no single treatment had been demonstrated to result in a significant reduction in overall mortality due to sepsis in humans.90 However, in 2001 a novel therapeutic agent, recombinant activated protein C, was described.90 Activated protein C is an important down regulator of the coagulation cascade that has antithrombotic, anti-inflammatory and profibrinolytic properties.

In a recent randomised, double blind, placebo controlled, multicentre trial, recombinant human activated protein C was demonstrated to reduce the relative risk of mortality by nearly 20%.90 This equates to one extra life saved per 16 people entering the ICU. Decreased levels of protein C have been associated with a worsening of prognosis in horses, suggesting that a similar effect may be observed in the endotoxemic horse.91 A potential role for recombinant activated protein C in equine endotoxaemia has yet to be determined, but warrants further investigation, especially in neonatal critical care.

Insulin
More recently the regulation of blood glucose within normoglycaemic ranges in critically ill humans has been shown to result in a relative risk reduction for mortality of 32% when compared with a conventional permissive hyperglycaemia approach.92 Of potentially equal importance for veterinary medicine is that the intensive treatment group had a 46% reduction in secondary septicemia, decreased long term requirement for antimicrobials and shortened ICU stays.93 The pathophysiology and systemic manifestations of endotoxaemia in horses and sepsis in humans are very similar and the maintenance of normoglycaemia with the use of insulin in endotoxemic horses may contribute to a significant reduction in morbidity and mortality. With the use of controlled delivery pumps and regular blood glucose monitoring, maintenance of normoglycaemia with a constant rate infusion of insulin is an achievable goal in equine critical care, especially in neonates.

Conclusion
Given the significance of endotoxaemia to the equine industry an understanding of the basic pathophysiology and principles of treatment is important for all veterinarians. Most importantly treatment must involve aggressive supportive care. Crystalloid fluid therapy is the mainstay of treatment, although the use of colloidal or hypertonic fluids may also be beneficial. NSAIDs, especially flunixin meglumine, are of benefit in moderating the clinical signs of endotoxaemia, although their overall effect on mortality is unclear. Other treatments such as antimicrobials, DMSO, polymyxin B and heparin are either in common use or have been well described experimentally and when used judiciously may be of benefit in endotoxaemia. The use of hyperimmune plasma and pentoxifylline is less well justified based on currently available evidence. More recently activated protein C and insulin have been shown to have significant beneficial effects in human sepsis and their use may be of benefit in equine endotoxaemia, although further evaluation is required before recommending their widespread use in the horse.

References