This article discusses the different treatment modalities in the context of the pathophysiologic mechanisms with which they are associated.

**Treatment Based on Endotoxemia/Inflammation**

Because of their antiendotoxin and general antiinflammatory effects, NSAIDs have been one mainstay for treating laminitis for over two decades. However, a great deal of controversy exists regarding the importance of endotoxemia and inflammation in the laminitic process.

Laminitis most commonly occurs secondary to diseases associated with endotoxemia, and increased intestinal and circulating endotoxin levels have been reported in the carbohydrate model of laminitis.

1 Numerous other investigators (including myself) have failed to detect circulating endotoxin in multiple laminitis studies. One reason may be hepatic clearance (a report about cattle with grain overload detected endotoxin in the portal blood but not the general circulation). 2 It is likely that endotoxin is not the only bacterial toxin absorbed in these different disease processes; multiple toxins are likely to be absorbed in many of them. Using interleukin (IL)-1β as a marker for proinflammatory cytokine expression, my colleagues and I recently reported the expression of IL-1β by cellular components of the laminae and in the mesenteric lymph nodes in horses in the early prodromal stage of laminitis. 3 It is likely that exposure of the reticuloendothelial system to bacterial toxins leads to the expression and release of large amounts of proinflammatory cytokines into the general circulation.

Circulating cytokines may lead to the local digital expression of inflammatory mediators that stimulate expression of factors important in the
laminitic process, including vasoactive mediators, prothrombotic mediators, and metalloproteinases. Therefore, I think it is extremely important to aggressively treat horses at risk for laminitis with NSAIDs.

Nonsteroidal Antiinflammatory Drugs
Phenylbutazone and flunixin meglumine are the most commonly used NSAIDs for treating laminic horses. Flunixin has been shown to be more efficacious in combating signs of endotoxemia, whereas phenylbutazone is most commonly given to horses with clinical signs of laminitis (after the endotoxemic episode). Earlier work described a low dose of flunixin (0.25 mg/kg) that is commonly used to treat horses with endotoxemia. However, the horses on low-dose flunixin still exhibited signs of endotoxemia not present in the animals given the higher dose (1.1 mg/kg).2 Due to the documented presence of a systemic and local inflammatory process in the early stages of laminitis, I believe it is important to keep the animals on the high flunixin dose during the first 48 to 72 hours of a suspected endotoxemic episode. Renal function and hydration must be closely monitored with this dose.

It has been hypothesized that treatment with NSAIDs may break a pain–hypertension cycle (i.e., a pathologic cycle in which laminic horses responding to foot pain release catecholamines that further increase peripheral vasoconstriction and exacerbate the laminitis). However, a recent report demonstrated no improvement in laminar blood flow in horses with experimentally induced laminitis treated with phenylbutazone.3 This suggests that NSAIDs work by blocking the expression/release of deleterious mediators downstream of the cyclooxygenase (COX) enzymes versus merely working by decreasing the level of pain experienced by the animal.

Polymyxin B
Polymyxin B is a cyclic cationic polypeptide antibiotic that reportedly binds to a lipid A moiety of endotoxin and neutralizes its effect.4 The drug has been shown in vivo and in vitro to protect against endotoxin in horses. Due to its potential toxicity (especially to the kidneys) as it extravasates into the tissue, polymyxin B has recently been conjugated to dextran to keep the drug in the intravascular space. This polymyxin B–dextran conjugate was shown to effectively block the signs of experimental endotoxemia in horses.5 The use of polymyxin B is warranted in horses that show signs of endotoxemia but is not indicated in horses with laminitis if the endotoxemic period has already passed.

Endotoxin Antiserum
There are many conflicting reports regarding the efficacy of antiserum to endotoxin in treating endotoxemia in horses. There is a risk of anaphylaxis with the administration of these products; thus they should only be used as a replacement for polymyxin B therapy in horses with renal compromise.6

Treatment Based on Altered Digital Blood Flow Due to Vascular Tone
The majority of research points to two different vasoactive processes that may be involved in laminitis: vasoconstriction and arteriovenous (AV) shunting. There are convincing data that both processes occur and that the vasoconstriction is most likely a postcapillary venoconstriction in the digital microvasculature.8 However, some recent data using Doppler ultrasound probes to assess laminar blood flow have raised questions by demonstrating an initial decrease in laminar blood flow followed by an increase in laminar blood flow at the time of onset of clinical lameness.5 This may be due to AV shunting as the Doppler technique does not discriminate between AV and capillary blood flow. Thus it may still be beneficial to give vasodilators if the drugs induce a venodilation and increase the amount of previously shunted blood into the laminar capillaries. Recent data indicate a role for endothelin in the vasoactive processes in the laminic foot.9

Phenothiazine Tranquilizers
Phenothiazine derivative tranquilizers cause peripheral vasodilation via α-adrenergic blockade. Although this class of drugs is mentioned in numerous articles as part of the treatment protocol for laminitis, the majority of experimental data do not report any efficacy of acepromazine in inducing increased laminar blood flow.10–12 Therefore, the use of this entire class of drugs is questionable for laminitis therapy.

Isoxsuprine
Isoxsuprine is a β-phenylethylamine reported to have α-adrenergic antagonist properties and β-adrenergic agonist properties, both of which should result in vasodilation. Although peripheral vasodilation was reported in horses administered the drug intravenously, isoxsuprine failed to cause increased digital or laminar blood flow in normal horses when given orally at suggested doses.12 Thus there are little data to support the use of this drug in laminitis.

Nitroglycerin
Nitroglycerin is a donor of nitric oxide that is rapidly absorbed percutaneously. Nitric oxide causes potent vasodilation of both arteries and veins, although nitroglycerin is classically known as a venodilator. A study using near-infrared spectroscopy indicated increased laminar blood flow subsequent to the application of nitroglycerin.13 However, a study using Doppler ultrasound indicated no improvement in laminar blood flow in laminic horses treated with nitroglycerin.13 A preliminary study at the
University of Georgia demonstrated improved digital microvascular blood flow using intravascular administration of nitroglycerin in the extracorporeal perfused digit model in early laminitis.\textsuperscript{14} Thus objective data on the efficacy of nitroglycerin in the treatment of laminitis are limited and controversial. If used, it is important to realize that tolerance to nitrate therapy occurs rapidly in other species and most likely occurs in horses. Therefore, interval therapy is indicated with a drug-free period of 8 to 12 hours per day.

**Pentoxifylline**

Pentoxifylline is a methylxanthine derivative that acts as a phosphodiesterase inhibitor. It has hemorheologic properties that increase the deformability of blood-cell membranes, and therefore the drug increases blood flow due to decreased capillary friction (viscosity). Pentoxifylline was originally used to treat claudication in humans, a peripheral vascular disease in which arteriosclerotic lesions lead to decreased blood flow to the legs. Recent clinical studies report minimal no effect of pentoxifylline on claudication.\textsuperscript{15} In normal horses, suggested doses of pentoxifylline failed to increase digital or laminar blood flow.\textsuperscript{7} Pentoxifylline has been shown in experimental models to decrease tumor necrosis factor–α expression and therefore has been suggested as a treatment for septic shock/endotoxemia.\textsuperscript{16} Although the drug may have an indication for use in endotoxemia, there are little data to support its use as a hemorheologic agent.

**Treatment Based on Thrombosis**

Thrombi have been identified in vessels of laminitic digits in both experimental models and clinical cases. Experiments using radioisotope-labeled platelets demonstrated localization of platelets and platelet–neutrophil complexes to the digital microvasculature in laminitic horses.\textsuperscript{17,18} A recent study demonstrated efficacy of a new class of platelet-aggregation inhibitors in preventing experimental laminitis.\textsuperscript{19} The importance of thrombosis in laminitis suggests that new treatments related to platelet biology may become available for treating laminitis.

**Heparin**

Heparin is the most commonly used drug in laminitis therapy for inhibiting thrombogenesis. An earlier study demonstrated that heparin administration before carbohydrate overload decreased the incidence of experimental laminitis.\textsuperscript{20} However, two retrospective clinical studies involving horses with small intestinal colic and laminitis showed conflicting data regarding efficacy of heparin therapy.\textsuperscript{21,22} A major drawback of heparin in horses is autoagglutination of erythrocytes, which could further a decrease in microvascular blood flow if the agglutinated erythrocytes become trapped in capillaries. Low-molecular-weight heparin (LMWH) has been reported not to cause erythrocyte agglutination in horses while still maintaining the positive attributes of heparin therapy. Thus LMWH is a better candidate for treating laminitis, but the cost of these products may limit their use in equine medicine.\textsuperscript{23}

**Future Treatments**

Future and ongoing studies may support the use of COX-2–specific inhibitors (over the nonselective NSAIDs discussed), endothelin receptor antagonists, and proteinase inhibitors in laminitis. COX-2 inhibitors may produce fewer adverse effects associated with NSAID administration while maintaining the beneficial clinical effects. COX-2 has also been found to be important in homeostatic functions; therefore, COX-2 inhibitors must be assessed clinically and experimentally before they can be accepted as a superior drug to nonselective COX inhibitors in laminitis. My colleagues and I have recently found that equine digital vein smooth muscle cells undergo COX-2 expression when exposed to a much lower concentration of endotoxin than that reported to induce COX-2 in other species.\textsuperscript{24} Thus it is possible that the equine digital vasculature is very sensitive to COX-2 regulation.

With increasing evidence that endothelin-mediated vasoconstriction may be a component of laminitis, endothelin receptor antagonists are a current focus of interest in laminitis research and may be a treatment modality in the future.

Finally, reports of the involvement of metalloproteinases in the physical breakdown of the attachment of dermal and epidermal laminae (leading to coffin bone rotation) indicate that proteinase inhibitors may be a potent addition to the collection of drugs for treating laminitis in the future.\textsuperscript{25,26}

The numerous mediators and signaling mechanisms in laminitis make it unlikely that a silver bullet will be discovered to prevent or treat laminitis with a single drug. However, as scientists further detail the pathophysiologic events that occur in laminitis, they will be able to design a more accurate treatment regimen to counteract this devastating disease process.

**References**

4. Semrad SD, Hardee GE, Hardee MM, Moore JN: Low-dose flunixin meglu-


