Development of laminitis in horses has been clinically associated with numerous disease conditions, such as infections, metabolic derangements, ingestion of toxic substances, carbohydrate overload, ingestion of lush pasture, and excessive weight bearing. Several epidemiologic studies have been performed to investigate risk factors for laminitis and determine the incidence of laminitis in horses with comorbid disease conditions. In a multicenter hospital-based study, the risk for acute laminitis was highest in horses that were 5 to 7 years or 13 to 31 years old (compared with horses <5 years old), in breeds other than Thoroughbreds and Quarter Horses, and in mares (compared with geldings). However, in other epidemiologic studies, no significant associations between development of acute laminitis and horses' age, breed, or sex were detected.

In studies of horses in hospitals, disease conditions associated with an increased risk for acute laminitis included gastrointestinal tract disease, surgical colic, acute diarrhea, severe unilateral lameness (leading to laminitis in the contralateral limb), and duodenitis and proximal jejunitis. Laminitis was more likely to develop in horses weighing ≥550 kg (1,210 lb) with duodenitis and proximal jejunitis and those with hemorrhagic nasogastric reflux.

Although various gastrointestinal tract disorders have been identified as risk factors for development of laminitis, the exact mechanisms by which these and other systemic diseases induce lamellar damage in feet are not known. We believed that closer investigation of the signalment and comorbid disease states that appear to increase the risk for laminitis may provide insight that would direct further research and suggest more effective preventive measures. The poor prognosis for horses with severe laminitis, severe and chronic signs of pain associated with the disease, and financial and emotional expenditure of owners with laminitic horses all indicate that substantial effort should be directed at the prevention of laminitis rather than its treatment.

**Objective**—To identify risk factors for development of acute laminitis in horses during hospitalization for illness or injury.

**Design**—Retrospective case-control study.

**Animals**—73 horses that developed laminitis (case horses) and 146 horses that did not develop laminitis (control horses) during hospitalization.

**Procedures**—Case and control horses were matched in a 2:1 ratio by the date on which each horse was evaluated. Potential risk factors investigated included age, breed, and sex; highest and lowest values recorded during hospitalization for fibrinogen concentration, WBC count, PCV, and total solids concentration; and comorbid disease states, including pneumonia, endotoxemia, diarrhea, medically treated colic, surgically treated colic, pituitary adenoma, retained placenta or metritis, forelimb lameness, hind limb lameness, acute renal failure, and vascular abnormalities. A univariate screening of all potential risk factors was performed to determine which variables should be selected for further analysis. All factors found to be associated with development of laminitis were included in a multivariate conditional logistic regression model.

**Results**—Development of laminitis was marginally associated with lowest and highest fibrinogen concentrations, highest PCV, and lowest total solids concentration and significantly associated with pneumonia, endotoxemia, diarrhea, abdominal surgery for colic, and vascular abnormalities. In the multivariate analysis, only endotoxemia was significantly associated with laminitis.

**Conclusions and Clinical Relevance**—Endotoxemia is an important risk factor for development of acute laminitis in horses during hospitalization for medical or surgical conditions. Early recognition of endotoxemia, or the potential for it to develop in certain disease states, and initiation of treatment directed at endotoxemia or its consequences may help prevent laminitis in horses during hospitalization. (J Am Vet Med Assoc 2007;230:885–889)

**Abbreviations**

<table>
<thead>
<tr>
<th>TS</th>
<th>Total solids</th>
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<tr>
<td>COX-2</td>
<td>Cyclooxygenase-2</td>
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</table>

laminitis in the contralateral limb), and duodenitis and proximal jejunitis. Laminitis was more likely to develop in horses weighing ≥550 kg (1,210 lb) with duodenitis and proximal jejunitis and those with hemorrhagic nasogastric reflux. Although various gastrointestinal tract disorders have been identified as risk factors for development of laminitis, the exact mechanisms by which these and other systemic diseases induce lamellar damage in feet are not known. We believed that closer investigation of the signalment and comorbid disease states that appear to increase the risk for laminitis may provide insight that would direct further research and suggest more effective preventive measures. The poor prognosis for horses with severe laminitis, severe and chronic signs of pain associated with the disease, and financial and emotional expenditure of owners with laminitic horses all indicate that substantial effort should be directed at the prevention of laminitis rather than its treatment.
The purpose of the study reported here was to identify risk factors for the development of laminitis in horses at a tertiary care center. Risk factors included in the analysis were those for which information was easily obtainable from the caregiver or by physical examination and those that were considered comorbid states that could easily be detected during physical examination or derived from results of readily available laboratory tests. It was hoped that evaluation of such factors would make our findings clinically relevant to all equine veterinarians.

Criteria for Selection of Cases

Medical records for horses evaluated at the George D. Widener Large Animal Hospital at the University of Pennsylvania School of Veterinary Medicine from 1997 to 2004 were reviewed. A computer-generated search identified all horses with laminitis for use as potential case horses and all horses without laminitis for use as potential control horses. The medical records of the Massachusetts Medical General Utility Multi Programming System coded computer network provided storage and retrieval of hospitalized case horses and was used to recall case horses fitting the selection criteria during the 8-year period. The population of case horses was further refined by including only horses that did not have laminitis at admission but that subsequently developed laminitis during hospitalization. Including as controls only horses that were admitted to the hospital without signs of laminitis and that did not develop signs of laminitis during hospitalization further refined the population of control horses. Case and control horses were included only if they were hospitalized for at least 48 hours before discharge, death, or euthanasia and had a primary disease that was unrelated to laminitis. Case and control horses were matched by the calendar date on which each horse was evaluated at the hospital. Control horses were matched with case horses in a 2:1 ratio. Power calculations indicated sufficient power was achieved in our study by use of a 2:1 sampling ratio. The first control horse admitted within 1 week before a case horse and the second control horse admitted within 1 week after a case horse was admitted were considered as the matched control horses for each case horse. Thus, 2 control horses were chosen for each case horse matched by season.10

A diagnosis of acute laminitis was based on clinical examination findings (eg, including Obel lameness grade, increased intensity of digital pulses, and increased hoof wall temperature11,12) recorded in the problem list and corroborated by the examining clinicians (senior clinician and resident) in the medical record. The diagnosis was further supported radiographically (by the hospital radiologist) in horses that lived beyond the acute stage of the disease if rotation or distal displacement of the third phalanx was detected.11,12 Potential case and control horses were excluded if there was not a clear diagnosis of laminitis or if the horse could not clearly be determined to be free of laminitis at evaluation or during hospitalization from the medical record alone. Horses with evidence of a concurrent disease condition (eg, fever of unknown origin and an abnormal laboratory test result such as leukocytosis or hyperfibrinogenemia) that was not definitively diagnosed were also excluded.

Procedures

Potential risk factors were grouped according to 3 categories: signalment, results of laboratory testing, and comorbid disease states. Signalment included age, breed, and sex of the horse. Breed was categorized as either Thoroughbred or non-Thoroughbred. Laboratory testing included the highest and lowest values recorded for each horse during hospitalization for fibrinogen, WBC count, PCV, and TS concentration. Comorbid disease states included interstitial pneumonia and bronchopneumonia, endotoxemia, diarrhea, medically treated colic, surgically treated colic, pituitary adenoma, retained placenta and metritis, forelimb lameness, hind limb lameness, acute renal failure, and vascular abnormalities.

Interstitial pneumonia and bronchopneumonia were diagnosed on the basis of clinical signs (such as cough, nasal discharge, fever, inappetance, lethargy, and abnormal lung sounds) and radiographic or ultrasonographic findings that were consistent with pneumonia. Endotoxemia was diagnosed on the basis of clinical signs (such as hyperemic mucous membranes and hyperemic perivascular gingiva) and supportive laboratory findings (neutropenia and toxic changes in neutrophils). Diarrhea was diagnosed on the basis of clinical signs (feces with increased fluid content in which the volume, frequency, or both were also increased).

Horses with medically treated colic included those with signs of abdominal pain that were treated by medical management, which may have included IV or oral administration of fluids, administration of nonsteroidal anti-inflammatory drugs or other analgesic medications, sedation, and nasogastric decompression. Horses with surgically treated colic were those with signs of abdominal pain in which treatment for colic included exploratory celiotomy. Pituitary adenomas were diagnosed on the basis of laboratory findings, including abnormal serum insulin, ACTH, and cortisol concentrations. Dexemethasone suppression tests were not routinely performed.

Retained placenta and metritis were diagnosed on the basis of history and ultrasonographic confirmation of placental retention and endometritis. Lameness was defined clinically as abnormal ambulation not of neurologic origin and localized to a forelimb or hind limb. Acute renal failure was diagnosed on the basis of clinical signs (polyuria and polydipsia) and laboratory findings (increased serum creatinine and urea nitrogen concentrations, abnormal fractional excretion of sodium, decreased renal urinary concentrating ability, and increased γ-glutamyltransferase-to-creatinine ratio). Vascular abnormalities were defined as inflammation of a vein (phlebitis) or artery (arteritis) and were confirmed ultrasonographically.

Statistical analysis—Data were analyzed by use of statistical software.4 A final multivariate model was chosen through a forward variable selection procedure as described by Hosmer and Lemeshow.10 For continuous variables (age, highest and lowest fibrinogen concentration, PCV, and TS concentration), a Student t test for
comparison of means was used. Odds ratios were used as a measure of association between the development of laminitis and each independent variable by use of conditional logistic regression, with case horses matched to control horses according to the date of hospital admission. All exposures associated with the development of laminitis in the univariate model with a P value < 0.20 were included in the multivariate conditional logistic regression model. Values of P < 0.05 were considered significant.

Results

Seventy-three case horses and 146 control horses fit the selection criteria. Mean age of all horses was 5.8 years (median, 4.0 years; range, 1 to 24 years). Thoroughbreds comprised 51% (112 horses) of the study group; the remaining 49% of the study group included Standardbreds (28/219 [13%]), Quarter Horses (23/219 [10.5%]), Warmbloods (18/219 [8%]), Arabians (15/219 [7%]), and various breed crosses (23/219 [10.5%]) with no clear breed dominance. Males and females were fairly equally represented; 46% (101/219) of horses were mares, 38% (83/219) were geldings, and 16% (35/219) were stallions.

Of the potential risk factors analyzed with the univariate model, associations with the development of laminitis were detected for 9 variables (Table 1). The following laboratory indices recorded during the period of hospitalization were marginally (P < 0.20) associated with the development of laminitis in the univariate model: lowest fibrinogen concentration, highest fibrinogen concentration, highest PCV, and lowest TS concentration.

The final multivariate model was a stepwise selection and included the previous 9 variables. The fit of this model was assessed by use of the standardized residual plots described by Hosmer and Lemeshow11 and by use of likelihood ratio tests. When fitting the multivariate model, only endotoxemia had a significant association with laminitis after controlling for the laboratory indices (highest and lowest fibrinogen concentration, highest PCV, and lowest TS concentration) and diseases (pneumonia, diarrhea, abdominal surgery for colic, and vascular abnormalities). A significant (P = 0.015; odds ratio, 5; 95% confidence interval, 1.37 to 18.19) association between endotoxemia and development of laminitis was detected by use of the multivariate model (Table 2). On the basis of the medical records, the exact time of onset between endotoxemia and the development of clinical laminitis could not be determined; however, evaluation of the clinical examinations performed for each case

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Table 1—Results of univariate conditional logistic regression analysis for risk factors associated with development of acute laminitis in horses during hospitalization.

<table>
<thead>
<tr>
<th>Risk factor</th>
<th>OR</th>
<th>95% CI</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lowest TS concentration*</td>
<td>0.66</td>
<td>0.482–0.912</td>
<td>0.011</td>
</tr>
<tr>
<td>Highest fibrinogen concentration*</td>
<td>1.002</td>
<td>1.000–1.004</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Lowest fibrinogen concentration*</td>
<td>1.003</td>
<td>1.001–1.006</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Highest PCV value*</td>
<td>1.1</td>
<td>1.024–1.114</td>
<td>0.002</td>
</tr>
<tr>
<td>Abdominal surgery for colic†</td>
<td>2.9</td>
<td>1.039–8.130</td>
<td>0.042</td>
</tr>
<tr>
<td>Interstitial pneumonia or bronchopneumonia†</td>
<td>3.2</td>
<td>1.041–9.782</td>
<td>0.041</td>
</tr>
<tr>
<td>Diarrhea†</td>
<td>5.1</td>
<td>2.244–11.496</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Vascular abnormalities†</td>
<td>5.3</td>
<td>1.693–16.673</td>
<td>0.004</td>
</tr>
<tr>
<td>Endotoxemia†</td>
<td>10.1</td>
<td>4.236–24.283</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

*Lowest or highest value recorded during hospitalization. †Clinical sign detected during initial evaluation or hospitalization. Only endotoxemia was a significant risk factor for the development of laminitis in the subsequent multivariate analysis.

OR = Odds ratio. CI = Confidence interval.

Table 2—Results of multivariate conditional logistic regression analysis for risk factors associated with the development of acute laminitis in horses during hospitalization.

<table>
<thead>
<tr>
<th>Variable</th>
<th>No. of case horses*</th>
<th>No. of control horses†</th>
<th>Adjusted OR</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Highest fibrinogen concentration†</td>
<td>NA</td>
<td>NA</td>
<td>1.001</td>
<td>0.999–1.000</td>
</tr>
<tr>
<td>Lowest fibrinogen concentration†</td>
<td>NA</td>
<td>NA</td>
<td>1.002</td>
<td>0.997–1.01</td>
</tr>
<tr>
<td>Highest PCV value†</td>
<td>NA</td>
<td>NA</td>
<td>1.014</td>
<td>0.949–1.10</td>
</tr>
<tr>
<td>Lowest TS concentration†</td>
<td>NA</td>
<td>NA</td>
<td>0.849</td>
<td>0.517–1.40</td>
</tr>
<tr>
<td>Interstitial pneumonia or bronchopneumonia†</td>
<td>8</td>
<td>5</td>
<td>0.376</td>
<td>0.061–2.33</td>
</tr>
<tr>
<td>Diarrhea†</td>
<td>21</td>
<td>9</td>
<td>0.811</td>
<td>0.211–3.11</td>
</tr>
<tr>
<td>Vascular abnormalities†</td>
<td>12</td>
<td>6</td>
<td>2.67</td>
<td>0.577–12.3</td>
</tr>
<tr>
<td>Abdominal surgery for colic†</td>
<td>10</td>
<td>8</td>
<td>2.032</td>
<td>0.402–10.3</td>
</tr>
<tr>
<td>Endotoxemia†</td>
<td>34</td>
<td>11</td>
<td>5.00</td>
<td>1.37–18.2</td>
</tr>
</tbody>
</table>

*Horses admitted to the hospital without laminitis that subsequently developed laminitis during hospitalization. †Horses admitted to the hospital without laminitis that did not develop laminitis during hospitalization. ‡Lowest or highest value recorded during hospitalization. §Detected during initial evaluation or hospitalization. NA = Not applicable. See Table 1 for remainder of key.
horse revealed that the onset of clinical laminitis was within 4 hours of detection of endotoxemia. A case horse could have been admitted as a horse with surgically managed colic and developed diarrhea as a concurrent clinical problem or risk factor.

Discussion

In the study reported here, the principal finding that clinically recognizable endotoxia is a significant risk factor for development of laminitis was not unexpected. Garner et al.13 and Moore et al.14 implicated endotoxin as a causal factor for laminitis in horses more than 25 years ago. The effects of endotoxin on equine digital vasculature and concentrations of endotoxin in the circulation of horses with laminitis have subsequently been investigated in numerous studies.15-22 However, to our knowledge, this is the first case-control study confirming that endotoxia is a significant risk factor for development of acute laminitis. In our study population, the odds of a horse with clinically evident endotoxia developing laminitis during hospitalization were 5 times those of a horse with no clinical signs or evidence of endotoxia on routine laboratory testing. This finding verifies that endotoxia is often associated with development of laminitis, which has been the clinical experience of equine practitioners for decades. The disease states or clinical conditions most often associated with endotoxia in horses include acute diarrhea, surgically managed colic, interstitial pneumonia and bronchopneumonia, and retained placenta and metritis in postpartum mares. Detection of a significant association between these disease states and development of laminitis in the present study was, therefore, expected. However, after multivariate analysis, the only clinical condition determined to be significantly associated with development of laminitis was endotoxia.

One explanation for this apparent paradoxical finding that disease states typically associated with endotoxia did not significantly increase a horse’s risk for developing laminitis is that although endotoxia is a common sequela in these disease states, it is not universal or an inevitable consequence of any of these conditions. For example, it is possible for a horse to have pneumonia or diarrhea without developing clinical signs of endotoxia.

Another explanation is that many horses with comorbid disease states may have had endotoxia, but it was not clinically apparent with the diagnostic tools and criteria used in the study. One of the objectives in designing this study was to use diagnostic tools and criteria that are available to any equine practitioner. If dose or duration of endotoxin exposure is important in terms of laminitis risk, as results of several studies14,15,23,24 indicate, a brief period or subclinical level of endotoxia may not significantly increase a horse’s risk for developing laminitis.

Although experimental administration of endotoxin does not predictably cause laminitis in horses, our findings indicated that clinically identifiable endotoxia is a significant risk factor for the development of laminitis. Results of our study suggested that an important line of investigation for the prevention of laminitis is the effective treatment or prevention of endotoxia.

Results of a study by Rodgerson et al.19 indicate an increase in COX-2 expression in cultured equine digital artery smooth muscle cells exposed to endotoxin. Authors of that study suggested that upregulation of COX-2 synthesis may be at least partially responsible for the vasoactive events detected during development of laminitis.19 Inhibition of COX-2 activation may thus be a worthy line of investigation in the prevention of endotoxin-induced laminitis. However, although various studies18,20,23,25,26 have supported the role of vasoconstrictive and microthrombotic elements in the development of laminitis in horses, the biochemical and vascular changes occurring in the equine foot that culminate in laminitis are numerous and complex.

In the study reported here, most horses that developed clinical signs of endotoxia were treated aggressively for endotoxia. Treatment varied and included administration of low doses of flunixin meglumine, polymyxin-B, and in some horses, hyperimmune plasma. Associations between the development of laminitis and any single treatment for endotoxia were not investigated in our study. Such a study, focusing on the clinical outcome of treatments associated with the development of laminitis, would be a reasonable next step.

Endotoxia, as detected through physical examination and routine laboratory testing, significantly increased the risk for laminitis in horses during hospitalization. Further research on treatment and prevention of endotoxia in horses is needed, as prevention or early detection and effective treatment of endotoxia may be essential in protecting susceptible horses from the devastating effects of laminitis.

References


**Selected abstract for JAVMA readers from the American Journal of Veterinary Research**

Efficacy of tiludronate in the treatment of horses with signs of pain associated with osteoarthritic lesions of the thoracolumbar vertebral column

Virginie Coudry et al

**Objective**—To evaluate the efficacy of tiludronate for the treatment of horses with signs of pain associated with lesions of the thoracolumbar vertebral column.

**Animals**—29 horses with clinical manifestations of pain associated with lesions of the thoracolumbar vertebral column and abnormal radiographic findings indicative of osteoarthritis of the articular processes—synovial intervertebral joints.

**Procedures**—Horses were initially examined in accordance with a standardized protocol, which included radiographic, ultrasonographic, and scintigraphic examinations. Fifteen horses were randomly assigned to receive tiludronate (1 mg/kg, IV, as a slow-rate infusion), and 14 horses received a control substance (day 0). Horses were monitored for the subsequent 120 days. Clinical evaluations were performed on days 60 and 120. Horses that had no evidence of clinical improvement on day 60 were administered tiludronate. Statistical analyses were performed to compare efficacy at day 60, improvement of dorsal flexibility at day 120, and dorsal flexibility before and 60 days after administration of tiludronate.

**Results**—Horses treated with tiludronate had significant improvement in dorsal flexibility between days 0 and 60, compared with control horses. Clinical improvement in dorsal flexibility was still evident at day 120. The percentage of positive responses was higher in the tiludronate group at 60 days.

**Conclusions and Clinical Relevance**—Tiludronate had efficacy in the treatment of horses with signs of pain induced by osteoarthritic lesions of the thoracolumbar vertebral column, causing a significant improvement in dorsal flexibility. Tiludronate may offer a treatment option for the management of horses with intervertebral lesions and associated pain. (*Am J Vet Res* 2007;68:329–337)