Multinodular pulmonary fibrosis in five horses

David M. Wong, DVM, MS, DACVIM; Rodney L. Belgrave, DVM, MS, DACVIM; Kurt J. Williams, DVM, PhD, DACVIM; Fabio Del Piero, DVM, PhD, DACVIM; Cody J. Alcott, DVM; Steven R. Bolin, DVM, PhD; Celia M. Marr, DVM, PhD; Rose Nolen-Walston, DVM, DACVIM; Ronald K. Myers, DVM, PhD, DACVP; Pamela A. Wilkins, DVM, PhD, DACVIM, DACVECC

A 532-kg (1,170-lb) 12-year-old Thoroughbred gelding (horse 1) was examined at Iowa State University’s Veterinary Teaching Hospital for a 1-month history of decreased appetite, weight loss, fever, cough, tachypnea, and respiratory distress. Clinicalopathologic abnormalities detected by the referring veterinarian included lymphopenia (0.640 × 10³ cells/µL; reference range, 1.3 to 4.5 × 10³ cells/µL) and hyperfibrinogenemia (1,000 mg/dL; reference range, 100 to 400 mg/dL). Prior to referral, phenylbutazone (1.87 mg/kg [0.85 mg/lb], PO, q 12 h) and trimethoprim sulfamethaxazole (30 mg/kg [13.6 mg/lb], PO, q 12 h) were administered with no improvement detected. On physical examination, the horse was quiet and responsive with a rectal temperature of 37.8°C (100.1°F), heart rate of 52 beats/min, and respiratory rate of 22 breaths/min. The horse was in thin body condition (body condition score, 3/9). Moderately increased bronchovesicular sounds were present bilaterally upon auscultation of the thorax. A CBC, serum biochemical profile, and arterial blood gas analyses were performed; abnormalities included leukocytosis (20.1 × 10³ cells/µL; reference range, 5 to 11 × 10³ cells/µL) characterized by mature neutrophilia (18.1 × 10³ cells/µL; reference range, 2.1 to 6.7 × 10³ cells/µL), monocytes (1.2 × 10³ cells/µL; reference range, 0 to 0.5 × 10³ cells/µL), lymphopenia (0.6 × 10³ cells/µL; reference range, 1.3 to 4.3 × 10³ cells/µL), hyperfibrinogenemia (1,200 mg/dL), hypogalactoaminemia (2.7 g/dL; reference range, 3.3 to 4.6 g/dL), and hypoxemia (Pao₂, 81.3 mm Hg; reference range, 85 to 95 mm Hg). Thoracic radiography revealed a severe diffuse, uniformly distributed nodular interstitial pattern (Figure 1). Differential diagnoses included fungal pneumonia, interstitial pneumonia, and pulmonary neoplasia. Transtracheal wash aspirates were collected and submitted for bacterial and fungal culture. Endoscopy of the airway subsequently revealed a mild accumulation of mucus on the ventral aspect of the trachea. Ultrasonographic examination of the lungs revealed multiple well-defined 1- to 2-cm nodular lesions on the surface of the lungs (Figure 2). Bronchoalveolar lavage was performed, and a fluid sample was submitted for

Case Description—5 horses were evaluated because of decreased appetite, weight loss, fever, cough, tachypnea, and respiratory distress.

Clinical Findings—Tachycardia, tachypnea, increased respiratory effort, lethargy, fever, poor body condition, and nasal discharge were detected in various combinations on initial physical examination. Evaluation of the lower portion of the respiratory tract via radiography and ultrasonography revealed a severe nodular interstitial pattern. Histologic examination of lung tissue revealed interstitial expansion of alveolar parenchyma with collagen, intraluminal accumulation of neutrophils and macrophages within the alveoli, and occasional intranuclear inclusion bodies within alveolar macrophages. Equine herpesvirus type 5 was detected in samples of lung tissue, bronchoalveolar lavage fluid, or both via polymerase chain reaction assay in all cases. A diagnosis of equine multinodular pulmonary fibrosis (EMPF) was established.

Treatment and Outcome—Horses were provided supportive treatment and were administered a variety of medications including corticosteroids and acyclovir. Two horses survived and returned to their previous level of activity. Three horses were euthanized because of either deterioration of clinical condition (n = 2) or failure to improve within 4 weeks of initiation of treatment (1).

Clinical Relevance—EMPF should be considered as a differential diagnosis for adult horses with interstitial pneumonia and should be suspected on the basis of characteristic radiographic, ultrasonographic, and histopathologic findings. Equine herpesvirus type 5 is found in association with EMPF; although the exact pathogenic role this virus plays in EMPF is unknown, equine herpesvirus type 5 may be an etiologic agent or cofactor in the development of EMPF. (J Am Vet Med Assoc 2008;232:898–905)

Abbreviations

EHV Equine herpesvirus
BAL Bronchoalveolar lavage
EMPF Equine multinodular pulmonary fibrosis
cytologic examination; mild purulent inflammation characterized by 60% to 75% nondegenerate to slightly degenerate neutrophils, 25% to 40% vacuolated macrophages, and scattered mast cells was reported. Multiple lung biopsy specimens were collected from the left and right lung lobes via ultrasonographic guidance and a biopsy needle and submitted for bacterial and fungal culture. No growth was obtained from the transtracheal wash aspirate or lung biopsy specimens under aerobic and anaerobic conditions. Additional lung biopsy specimens were fixed in formalin; embedded in paraffin; and stained with H&E, periodic acid-Schiff, Gram, Giemsa, and acid-fast stains. Polymerase chain reaction analysis with general herpesvirus primers, primers to gamma herpesviruses, and EHV-2– and EHV-5–specific primers was performed on DNA extracted from sections of paraffin-embedded lung tissue as described.1 Polymerase chain reaction analysis was also performed on BAL fluid. The horse was hospitalized pending histologic results.

Histologically, the alveolar septa were mildly to moderately expanded by collagen, and alveoli were lined by indistinct low cuboidal epithelium. Type 2 pneumocyte hyperplasia was variably present (Figure 3). Many of the air spaces had large numbers of neutrophils within the lumen admixed with fewer alveolar macrophages and eosinophilic proteinaceous material. A histologic diagnosis of chronic purulent bronchointerstitial pneumonia with type II pneumocyte hyperplasia, fibrosis, and goblet cell metaplasia was made. No infectious agents were identified at this time. The owner was instructed to administer trimethoprim-sulfamethaxazole (30 mg/kg, PO, q 12 h for 21 days) and dexamethasone (0.037 mg/kg [0.017 mg/lb], IM, q 24 h for 5 days, then the same dose every other day for 12 doses) and return the horse for reevaluation in 3 weeks.

The horse’s attitude was brighter at recheck examination 35 days after initial evaluation, but the horse weighed 29 kg (64 lb) less than previously. Rectal temperature was 37.3°C (99.2°F); tachycardia (48 beats/min) and tachypnea (36 breaths/min) were evident. Auscultation of the lungs revealed the same findings as previously: Leukocytosis, neutrophilia, lymphopenia, anemia (Hct, 29.2%; reference range, 34% to 45%), and hyperfibrinogenemia were evident. No improvement was detected in hypoxemia (Paco, 82.2 mm Hg). Radiography of the thorax revealed moderate resolution of the nodular interstitial pattern involving the dorsocaudal lung field.

Figure 1—Lateral radiographic views of the thorax of a horse with multinodular pulmonary fibrosis. A—View obtained at initial examination; notice the severe, diffuse nodular interstitial pattern throughout the lung field. B—View obtained 101 days after initial examination; notice the mild diffuse bronchointerstitial pattern.

Figure 2—Ultrasonographic image of the left lung of the horse in Figure 1; notice 2 focal nodular lesions. Numerals 1 represents the thickness of the thoracic body wall (2.2 cm); numerals 2 and 3 represent nodular lesions involving the lung measuring 1.1 and 0.9 cm, respectively.
with minimal changes from initial radiographs involving the ventral lung field. Results of PCR analysis were positive for EHV-5 for the previously obtained lung tissue and BAL fluid (in contrast, 7 BAL fluid samples collected from horses without evidence of interstitial pneumonia, during the time frame when all 5 cases of this report were investigated, yielded negative results of PCR assay for EHV-5). A diagnosis of EMPF was made on the basis of clinical, radiographic, and pathologic findings.\textsuperscript{1} Acyclovir (20 mg/kg [9.1 mg/lb], PO, q 8 h) and prednisolone (1 mg/kg [0.45 mg/lb], PO, q 24 h) were prescribed, and the owner was instructed to return the horse in 4 weeks for reevaluation.

Sixty-two days after initial evaluation (27 days after the second examination), the horse was bright and alert and had gained 39 kg (86 lb). Results of physical examination, including auscultation of the thorax with a rebreathing bag in place, were unremarkable. A CBC revealed mild leukocytosis, neutrophilia, lymphopenia, and anemia. Hypoproteinemia and hypoalbuminemia persisted; PaO\textsubscript{2} was within reference limits. Radiographically, a moderate bronchointerstitial pattern was detected involving the caudodorsal lung field, whereas the caudodorsal lung field was only mildly affected with this pattern. The nodules previously observed were absent. Acyclovir, as prescribed, and prednisolone (1 mg/kg, PO, q 48 h) were administered for 39 more days.

One hundred one days after initial evaluation, the horse had gained an additional 33 kg (73 lb) of weight (575 kg [1,265 lb]) and no abnormalities were detected on physical examination or via CBC, serum biochemical profile, and urinalysis. The urine \gamma-glutamyltransferase–to–creatinine ratio was 24.56 U/g (reference limit, ≤ 25 U/g),\textsuperscript{2} and arterial blood gas analysis revealed a PaO\textsubscript{2} of 98.8 mm Hg. A mild diffuse bronchointerstitial pattern, predominately involving the ventral lung field, was still present radiographically (Figure 1). The horse was discharged with instructions to the owner to discontinue acyclovir administration and slowly discontinue prednisolone (1 mg/kg, PO, q 4 d for 4 doses) administration. The horse was reported to be doing well 10 months after initial evaluation.

An additional 4 cases (horses 2 to 5) of EMPF were recognized, and the horses underwent treatment over the next 6 months at 3 veterinary medical referral hospitals. Horse 2, an 8-year-old Thoroughbred gelding, was examined for a 3-week history of intermittent fever (41°C [105.8°F]), cough, and weight loss. Prior to referral, the horse was administered a variety of antimicrobials for treatment of presumed bacterial pneumonia and was administered flunixin meglumine (1.1 mg/kg [0.5 mg/lb], IV) as needed to control fever. Clinical findings included rectal temperature of 37.9°C (100.2°F), heart rate of 52 beats/min, and respiratory rate of 24 breaths/min. A mild but visible increase in abdominal effort was evident on expiration. Hematologic and serum biochemical abnormalities included neutrophilic leukocytosis, hyperfibrinogenemia, and anemia. Moderate bilateral diffuse roughening of the pleural surface was observed via thoracic ultrasonography; multiple superficial discrete nodular lesions (5 to 8 cm in diameter) were observed in the middle and cranioventral aspects of both hemithoraces and in the left caudodorsal lung field. The pulmonary parenchyma of the cranioventral portion of the lung appeared hypoechoic, suggestive of lung consolidation of both hemithoraces. A severe, primarily midventrally to cranioventrally distributed nodular pattern was observed on thoracic radiographs. Thick purulent fluid was recovered from transtracheal wash fluid; results of virus isolation for EHV-1 and aerobic and anaerobic bacterial and fungal cultures of the aspirate were negative. An inflammatory exudate, with approximately 90% mildly degenerate neutrophils, was detected cytologically. The horse was discharged and treated with penicillin G PO, and fungal cultures of the aspirate were negative. An additional intermittent fevers were reported at recheck examination 18 days after initial evaluation. Multiple lung biopsy specimens were obtained with ultrasonographic guidance from the right lung field with a spring-loaded biopsy needle.\textsuperscript{b} Pulmonary fibrosis with type II pneumocyte hyperplasia, mucous metaplasia, and suppurative inflammation was noted histologically. Occasional hyaline amorphophilic intranuclear inclusion bodies were also observed in alveolar macrophages. A sample of lung tissue was submitted for detection of EHV-5 via PCR assay; results were positive for EHV-5. A diagnosis of EMPF was made, and acyclovir and a tapering course of prednisolone were administered for 7 weeks.

Figure 3—Photomicrographs of sections of the lungs of horses with multinodular pulmonary fibrosis. A—Photomicrograph of biopsy section of lung in horse 1. Neutrophils and a few macrophages are contained in a small bronchiole (lower left). Adjacent alveolar septa are thickened and some alveoli contain neutrophils. Type II pneumocyte hyperplasia increased the thickness of the septa. H&E stain; bar = 70 \mu m. B—Photomicrograph of a section of lung lined by pneumocytes and containing macrophages and neutrophils are present. H&E stain; bar = 120 \mu m. C—Photomicrograph of a section of lung in horse 4. Within the lumen of an effaced alveolus, there are foamy macrophages, and 1 macrophage contains an intranuclear amorphophilic viral inclusion associated with chromatin margination (arrow). H&E stain; bar = 50 \mu m.
The horse was reevaluated 70 days later and had normal results of physical examination. Fever had resolved within 72 hours of commencing acyclovir administration. Results of thoracic radiography, ultrasonography, and auscultation were improved. Bronchoalveolar fluid yielded negative results of PCR assay for EHV-5, and cytologic findings were unremarkable. Hyperfibrinoginemia persisted. Acyclovir and prednisolone administration was continued for a further 4 weeks. Eight months after initial evaluation, the horse was reported to be doing well.

Horse 3, an 8-year-old Oldenburg gelding, was also examined for a 4-week history of intermittent fever and weight loss. Prior to referral, phenylbutazone was administered, as needed, to control fever, and trimethoprim-sulfamethoxazole was administered with no effect. Clinical findings included rectal temperature of 40°C, heart rate of 52 beats/min, and respiratory rate of 28 breaths/min. Hematologic abnormalities included mild anemia, lymphopenia, and hyperfibrinoginemia, although, unlike horses 1 and 2, neutrophilic leukocytosis was not present. Except for subjective dilation of the pulmonary artery (3.3 cm), results of thoracic radiography and ultrasonography were similar to those in horse 2.

Endoscopy revealed mucopurulent exudate in the trachea. Cytologic examination of transtracheal wash fluid revealed approximately 90% degenerate neutrophils. An Enterobacter sp was cultured from the aspirate. Results of virus isolation for EHV-1 and fungal culture of the tracheal fluid were negative. Penicillin G potassium, gentamicin, metronidazole, a tapering course of dexamethasone, flunixin meglumine, and clenbuterol were administered. Nebulization with cef timorfur (150 mg, q 12 h for 5 days) also was performed. Despite treatment, intermittent fever was still observed. Multiple percutaneous lung biopsy specimens were obtained from the right lung 10 days after initial evaluation, and the histopathologic diagnosis was EMPF. Samples of lung tissue yielded positive PCR assay results for EHV-5. Additionally, bacterial culture of the lung tissue yielded a pure growth of an Enterobacter sp; antimicrobial susceptibility was limited to amikacin. Bronchoalveolar lavage fluid yielded positive results for EHV-5 via PCR assay. A diagnosis of EMPF was made.

Bacterial pneumonia was made on the basis of clinical, radiographic, and pathologic findings. Treatment was consistent with EMPF. Biopsy specimens were obtained from the right caudodorsal lung field; histologic examination revealed lesions diagnostic for EMPF (Figure 3). Results of aerobic and anaerobic cultures of a biopsy specimen and serum antibody titers for Blastomyces, Coccioidoides, Histoplasma, Aspergillus, and Cryptococcus spp were negative. Lung biopsy specimens and BAL fluid yielded positive results for EHV-5 via PCR assay. A diagnosis of EMPF was made.

Initial treatment consisted of flunixin meglumine, acyclovir, and prednisolone. The horse was discharged 3 days after evaluation with instructions to the owner to administer doxycycline, acyclovir, and prednisolone. The horse was returned 39 days after initial evaluation because of continued weight loss (40 kg [88 lb]), tachycardia, and dyspnea. Physical examination revealed tachycardia, tachypnea, and hyperemic mucous membranes. Hyperfibrinoginemia and high serum creatinine concentration were detected along with hypoxemia. Radiography of the thorax revealed minimal improvement. Because of the lack of improvement, the horse was euthanized, and a postmortem examination was performed. Severe diffuse multinodular pulmonary fibrosis was confirmed. Tissues yielded positive results for EHV-5 via PCR analysis.

Horse 5, a 13-year-old Thoroughbred mare, was examined for acute onset of respiratory distress. Two days prior to admission, clinicopathologic abnormalities included neutrophilic leukocytosis, anemia, hypo-
albuminemia, hyperfibrinogenemia, and high concentration of serum amyloid A (249 mg/L; reference range, 0 to 20 mg/L). Tracheal aspirate cytologic evaluation revealed degenerate neutrophils. Aerobic and anaerobic bacterial culture of transtracheal wash fluid yielded no growth. Treatment with procaine penicillin, gentamicin, phenylbutazone, and clenbuterol had been instituted prior to referral with no improvement detected.

At evaluation, the horse was lethargic, had severe respiratory distress, and was in poor body condition. Heart and respiratory rates were high. Widespread inspiratory crackles were evident via thoracic auscultation, and bilateral nasal discharge and intermittent cough were observed. Hypoxemia also was present. Transtracheal wash was repeated; bacterial culture results were negative, and cytologic evaluation revealed a predominance of neutrophils. Thoracic ultrasonography and radiography results were consistent with EMPF. Two-dimensional echocardiography revealed that the diameter of the aortic root (6.49 cm) was smaller than that of the pulmonary artery (7.33 cm; reference range, 5.2 to 6.94 cm), suggesting reduced cardiac output, pulmonary hypertension, or both.

Initial treatment consisted of intratracheal oxygen supplementation, enrofloxacin, sodium penicillin, flunixin meglumine, omeprazole, glycopyrrolate, furosemide, clenbuterol, and dexamethasone. Indirectly measured mean systemic arterial pressure (coccyeal artery) was decreased (44 mm Hg; reference range, 82 to 110 mm Hg) when measured 20 hours after admission. Polyionic fluids (IV) and sildenafil (PO) were administered on day 2. On day 3, the diameters of the pulmonary artery (6.5 cm) and aorta (6.83 cm) and the mean arterial pressure (60 mm Hg) had improved. Improvement of pulmonary artery and aortic measurements appeared to wane toward the end of the administration interval of sildenafil; consequently, administration was changed to every 8 hours.

The horse’s respiratory pattern and rate improved over the next 72 hours, as did hypoxemia. Intratracheal oxygen administration was discontinued, and by day 5, the horse’s demeanor and respiratory rate improved. At this time, administration of glycopyrrolate was discontinued, and on day 9, administration of sildenafil was discontinued and the route of administration of furosemide was changed to oral. Thoracic radiography performed 13 days after initial evaluation revealed moderate numbers of neutrophils; consequently, administration was changed to every 8 hours.

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The horse’s condition deteriorated the following day with marked tachypnea and widespread crackles involving both sides of the thorax. The horse was humanely euthanized 2 days after discharge.

Results of gross postmortem and histologic examination of the lungs were consistent with pulmonary edema and EMPF. Lung tissue yielded positive results for EHV-5 via PCR assay. A diagnosis of EMPF was made on the basis of clinical, radiographic, and pathologic findings.

Discussion

Interstitial pneumonia represents a heterogeneous group of pulmonary disorders that are uncommon causes of lower respiratory disease in horses and foals.5–10 Various etiologies, including pathogens,5,9,11 inhaled or ingested toxins,8,12–16 and hypersensitivity reactions,8,17 have been incriminated as potential causes of interstitial pneumonia. However, defining the exact etiologic agent is challenging because of the chronic insidious nature of the disease. Although a broad variety of etiologies may cause interstitial pneumonia, the lung has a limited range of morphologic responses to injury; the initial insult results in characteristic injury to the alveolar wall (alveolar epithelium, capillary endothelium, and basement membrane) resulting in acute alveolitis.8,18,19 During this exudative phase, proteinaceous fluid leaks into the alveolar space, and inflammatory cells accumulate within the alveolus and alveolar interstitium, resulting in loss of functional alveolar-capillary gas exchange units.5,8 This event is followed by a proliferative phase characterized by hyperplasia of type II pneumocytes, accumulation of fibroblasts and inflammatory cells, and changes in the extracellular matrix of the lung parenchyma.8,18 Response to the chronic injury will progress to the terminal event as pulmonary fibrosis. Reported clinical signs associated with interstitial pneumonia in horses are variable and range from the absence of overt clinical signs to severe respiratory distress.9,13 Fever, cough, inappetance, weight loss, nasal discharge, exercise intolerance, tachycardia, tachypnea, and dyspnea have been consistently reported in horses with interstitial pneumonia.7,10,20

Equine multinodular pulmonary fibrosis is a recently described fibrotic interstitial lung disease of horses that is associated with infection with EHV-5.1 Two distinct gross patterns of lesions are present at necropsy.7 The more common pattern involves multifocal coalescing nodules of fibrosis within the lung parenchyma. Grossly, nodules are firm and vary in size from < 1 cm to 5 cm and are pale tan to white. Little unaffected lung is typically present in this form of EMPF. A less common pattern involves multiple discrete nodules, varying in size up to 8 to 10 cm, separated by larger areas of grossly unaffected lung. The less common pattern may be a precursor to the more common diffuse pattern; in both patterns, the lungs fail to collapse at necropsy. Histologically, the lesions of EMPF are centered on the alveolar parenchyma. Briefly, the nodules within the lung result from marked interstitial expansion with collagen replacing alveoli. The adjacent alveoli are lined by cuboidal epithelial cells, and the lumens are filled with moderate numbers of neutrophils and macrophages. Rarely, alveolar macrophages are enlarged and have large eosinophilic intranuclear viral inclusion bodies. The role, if any, that pulmonary infection with the gamma herpesvirus EHV-5 has in the development of EMPF remains to be determined.

Both EHV-2 and EHV-5 belong to the subfamily Gammaherpesvirinae, although it has only been during the past 20 years that EHV-5 has been recognized as a separate pathogen from EHV-2.21,22 The pathogenic roles of EHV-2 and -5 in equine respiratory disease are presently incompletely understood. Infection with EHV-2 has been associated with disease of the upper (pharyngitis) and lower (pneumonia) portion of the respiratory tract, lymphadenopathy, keratoconjunctivitis,
general malaise, and poor performance. However, experimental infection with EHV-2 has yielded variable results, and the virus can be isolated from a high percentage of sick and healthy horses worldwide. Unfortunately, even less is known about EHV-5 and its role in causing disease. One of the earliest reports of EHV-5 isolation was from horses with disease of the upper portion of the respiratory tract in Australia. Subsequently, EHV-5 has been detected in horses in Switzerland, Germany, New Zealand, England, and the United States and prevalence appears to be variable, depending on the specific region. 

Description of EMPF has been limited to postmortem findings. In the present report, the clinical findings in 5 horses with EMPF are detailed. No breed or sex predilection could be determined. However, mean age of affected horses was 13 years (range, 8 to 24 years), similar to the initial description of EMPF in which the mean age of 24 affected horses was 14.5 years; no breed or sex predilection was observed in that study. Historical similarities in the 5 cases reported here included weight loss (n = 4), fever (4), cough (2), and tachypnea (2). One horse (horse 5) had acute respiratory distress. Tachycardia (n = 5), tachypnea (5), increased respiratory effort (4), lethargy (2), fever (2), and nasal discharge (1) also were detected on physical examination of the horses of the present report. Auscultation of the thorax revealed variable findings, from normal lung sounds to increased or diminished bronchiovesicular sounds. Crackles and wheezes were auscultated in 2 horses. Unfortunately, these findings are nonspecific and consistent with other reported cases of equine interstitial pneumonia. 

A marked inflammatory response was often detected in the affected horses. Neutrophilic leukocytosis and hyperfibrinogenemia were common findings. Serum amyloid A concentration, a marker of acute inflammation following tissue injury, infection, or inflammation, was persistently high in horse 5. Lymphopenia, a common finding in the acute stages of viral infection in horses, was detected in 3 of 5 horses at initial evaluation and intermittently throughout the course of the disease. Lymphopenia has not been reported in most cases of equine interstitial pneumonia in the literature. The horses reported here, this may have been caused by persistent infection with EHV-5 or may have been secondary to administration of corticosteroids. Horse 1 survived and had a lymphocyte count within reference range at day 101; however, horses 3 and 4, both euthanized, had persistent lymphopenia. Other clinicopathologic findings observed included mild anemia. Hyperfibrinogenemia and neutrophilia have been reported in other cases of interstitial pneumonia, but anemia has been less commonly reported. 

As a result of a decreased number of functional alveolar-capillary gas exchange units, various degrees of hypoxemia were observed in the cases reported here. Alterations in serum biochemical values were minimal but included hypalbuminemia. Examination of tracheal and bronchial fluid aspirates consistently revealed purulent inflammation with nondegenerate to degenerate neutrophils, similar to another study of interstitial pneumonia in which substantially more neutrophils were observed in respiratory secretions, compared with healthy horses. Increased numbers of macrophages have been reported in respiratory secretions and bronchial lavage samples from horses with interstitial pneumonia, compared with healthy horses, but this was not observed in the cases reported here. No characteristic cytologic features of respiratory aspirates and EMPF could be established. Bacterial and fungal cultures of transtracheal aspirates yielded no growth except for horse 3, in which an Enterobacter sp was cultured.

A severe nodular interstitial pattern was observed radiographically among affected horses. Slow radiographic resolution of the nodular interstitial pattern may occur over time and served as a prognostic indicator in the horses described here. In the 2 horses that survived, a mild residual broncho-interstitial to alveolar-interstitial pattern was observed, suggesting that permanent radiographic changes may occur with EMPF. Discrete nodular lesions, ranging in size from 1 to 7 cm, were detected during ultrasonographic examination of the lungs in several horses. As with thoracic radiography, ultrasonographic examination of the lungs may allow evaluation of the progression of disease over time.

Antemortem, EMPF was suspected on the basis of characteristic radiographic findings and microscopic evaluation of lung biopsy specimens. All 5 horses had positive results for EHV-5 via PCR assay, including 3 of 4 BAL fluid samples obtained from horses 1 to 4 and 5 of 5 lung tissue specimens. In contrast, 7 BAL fluid samples collected from horses without evidence of interstitial pneumonia yielded negative results of PCR assay for EHV-5. The single negative PCR result was from a BAL sample from horse 2 that was obtained well after treatment with corticosteroids and acyclovir was undertaken. It is possible that PCR assay of BAL fluid for EHV-5 may prove to be a useful diagnostic test for EMPF but more work needs to be done to confirm the role of EHV-5 and investigate the sensitivity and specificity of PCR assay on BAL fluid for diagnosis of this disease. In a report of the pathologic findings associated with EMPF EHV-5 was identified in 24 of 24 affected horses via virus-specific PCR assay, whereas positive results were obtained from none of 23 age-matched controls.

As with other forms of equine interstitial pneumonia, treatment of the horses reported here included the use of corticosteroids. Dexamethasone and prednisolone were administered to decrease the inflammatory response and progression of fibrosis within the lung. Corticosteroids may effectively suppress airway inflammation by inhibiting synthesis of inflammatory cytokines and mediators. However, caution must be exercised when using corticosteroids in horses because of their immunosuppressive effects. Treatment with dexamethasone has experimentally resulted in profound reduction in T and B lymphocyte concentrations and has also been associated with recrudescence of equine infectious anemia virus and EHV-1 viremia in experimental studies in horses. Use of corticosteroids has also been associated with induction of laminitis, but prevalence appears to be low. Previous reports indicate that orally and IV administered dexamethasone (0.1 mg/kg [0.045 mg/lb], q 24 h) and orally administered
prednisolone (0.5 to 1 mg/kg [0.23 to 0.45 mg/lb], q 12 h) have been used in horses with interstitial pneumonia. In 1 report, 7 prednisolone was administered for 1 year (1 mg/kg, PO q 12 h); after discontinuation of corticosteroid treatment, the horse was able to compete as a jumper. The use of corticosteroids in cases of interstitial pneumonia may be associated with a positive outcome as indicated by 1 report 8 of bronchointerstitial pneumonia in foals. In that report, 10 of 13 affected foals were treated with corticosteroids, and 9 survived. Suppressing or eliminating infectious etiologies, when known, is another principle of treatment of interstitial pneumonia. The use of acyclovir in the cases reported here was entirely speculative because the susceptibility of equine gamma herpesviruses to acyclovir is unknown and the oral absorption of acyclovir is inconsistent because of poor bioavailability. 9,10 The efficacy of acyclovir against 2 human gamma herpesviruses, Epstein-Barr virus and human herpesvirus type 8, has been evaluated via flow cytometric assay systems. 11 In that study, 11 acyclovir effectively inhibited Epstein-Barr virus but not human herpesvirus type 8. In 4 of the horses reported here, acyclovir was administered for variable periods of time at a dose of 20 mg/kg, PO, every 8 hours. In an experimental study, 46,47 single-dose administration of acyclovir at 10 or 20 mg/kg (4.5 or 9 mg/lb) resulted in poor bioavailability and high variability in serum concentrations. Despite this, acyclovir has been used in clinical cases of equine herpesvirus myeloencephalopathy (20 mg/kg, PO, q 8 h) and has reportedly achieved adequate antiviral concentrations in some horses. 99 More recently, the pharmacokinetics and pharmacodynamics of the acyclovir prodrug valacyclovir have been described. 50 If antiviral treatment appears to be indicated on the basis of future studies of this disease, valacyclovir may be a better choice than acyclovir because of its much greater bioavailability when administered orally.

Although pulmonary pressure was not directly evaluated in any of the horses reported here, pulmonary hypertension was suspected in horses 3 and 5 on the basis of radiographic and echocardiographic findings, respectively. Pulmonary artery dilation was confirmed at postmortem examination in horse 3. We speculate that evidence of pulmonary hypertension is a poor prognostic indicator in horses with EMPF, and pulmonary artery diameter (in comparison to aortic diameter) and pulmonary artery pressure should be determined if possible. Pulmonary hypertension and right ventricular dilation have been described in a previous report 6 of interstitial lung disease in horses. Sildenafil, used in neonatal foals with pulmonary hypertension, and furosemide were administered in horse 5, and decreased pulmonary artery diameter was detected. 31

To our knowledge, this case series represents the first clinical description of EMPF. The long-term prognosis for horses with EMPF described here was fair to poor. Although 3 of 5 horses were euthanized because of deterioration of condition or failure to improve within a few weeks of instituting treatment, 2 of 5 horses responded favorably to treatment. Horse 1 resumed regular training 6 months after initial evaluation and was reportedly competing 10 months after initial evaluation, and horse 2 had resumed training 6 months after initial evaluation and did not have exercise intolerance or cough. We would suggest, on the basis of the cases described here, that treatment of horses with EMPF should be undertaken for at least 6 weeks, if possible, before evaluating efficacy of treatment and likely prognosis.

References