Enrofloxacin Use in a Long-Distance Transport Model of Equine Respiratory Disease

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Enrofloxacin, a fluoroquinolone antimicrobial agent with bacteriocidal activity and broad-spectrum efficacy, is labeled for use in cattle suffering from infectious pulmonary disease associated with transport. Although previous investigations have evaluated the use of this drug administered intravenously to horses, no studies have specifically evaluated its use in mature horses suffering from infectious respiratory disease.

INTRODUCTION
Infectious pulmonary disease develops in horses under various conditions, including after long-distance transport, as a complication of esophageal obstruction, or subsequent to immune suppression. Although a variety of management and treatment strategies have been used to reduce disease incidence, bacterial bronchopneumonia is still encountered in equine practice. Enrofloxacin offers an enhanced spectrum of antimicrobial activity with reduced risk of complication. This study investigated increasing doses of enrofloxacin (1.25, 2.5, 5.0, and 7.5 mg/kg) in the treatment of a model of transport-associated respiratory disease. Findings suggest that solo therapy with enrofloxacin may not be appropriate for the treatment of gram-positive pathogens in association with this transport model of equine respiratory disease.

Bacterial pneumonia in horses is frequently caused by gram-positive bacteria, and as such, empirical therapy should include antimicrobial agents with activity against this class of pathogen. However, gram-negative pathogens may coexist, which would make broad-spectrum antimicrobial coverage necessary. Because of potential drug-associated risks (e.g., nephrotoxicity in dehydrated patients, peracute colitis in racehorses), some antimicrobial agents may not be appropriate for empirical use. Enrofloxacin offers an enhanced spectrum of antimicrobial activity with reduced risk of complication. This study investigated increasing doses of enrofloxacin (1.25, 2.5, 5.0, and 7.5 mg/kg) in the treatment of a model of transport-associated respiratory disease. Findings suggest that solo therapy with enrofloxacin may not be appropriate for the treatment of gram-positive pathogens in association with this transport model of equine respiratory disease.

CLINICAL RELEVANCE
Bacterial culture and sensitivity testing of tracheal aspirates are not available at the time of treatment initiation in equine patients suffering from infectious respiratory disease; therefore, antimicrobial drug selection is based on knowledge of the most common pathogens associated with infectious pulmonary disease in horses. Contamination of the lower airway most commonly occurs with aerobic inhabitants of the oropharyngeal cavity,\textsuperscript{1,11,12} such organisms include Streptococcus equi subsp zooepidemicus, Pasteurella spp, Escherichia coli, and Actinomyces spp.\textsuperscript{12} Because horses with bacterial respiratory infection often have a polymicrobial infection,\textsuperscript{13–16} it is common to manage these cases with broad-spectrum antimicrobials. The combination of a β-lactam antibiotic and an aminoglycoside provides gram-positive and gram-negative spectrum coverage but is not always feasible because of the need for twice-daily administration (penicillin) and the risk of aminoglycoside-associated toxicity in debilitated, dehydrated, or endotoxic patients.\textsuperscript{17,18} Consequently, some equine clinicians choose enrofloxacin based on its once-daily administration and proposed effective antimicrobial activity.

Enrofloxacin primarily targets gram-negative bacteria, which have not historically been associated as the principal or sole pathogens in bacterial pneumonia in horses. Previous reports of equine pneumonia have determined that S. equi subsp zooepidemicus is the most common pathogen isolated from the equine lower airway\textsuperscript{19}; however, because other bacterial pathogens may also be involved in the pathogenesis of disease, broad-spectrum antibacterial coverage is needed in affected individuals. Of additional concern is the potential for antimicrobial resistance to develop among various bacterial species. Therefore, current recommendations suggest reserving enrofloxacin for use against susceptible bacterial microorganisms as reported by the American College of Veterinary Internal Medicine consensus statement.\textsuperscript{20} It was our aim to fulfill two main objectives with this investigation: first, to determine the efficacy of enrofloxacin for use in horses suffering from naturally occurring transport-associated respiratory infection, and second, to identify whether there was a dose–response relationship following intravenous enrofloxacin administration to horses with respiratory infection associated with long-distance transport.

### MATERIALS AND METHODS

The Kansas State University Institutional Animal Care and Use Committee approved all procedures performed on the horses during this investigation.

**Clinical Investigators**

Two equine veterinary clinicians were involved in this study. They collaborated with a microbiologist and microbiology laboratory for bacterial culture, pathogen identification, and establishment of minimum inhibitory concentration (MIC) values. The investigator responsible for daily scoring was blinded to treatment.

**Patient Management and Group Selection**

Eighty quarter horses and crossbred horses (42 mares, 13 stallions, and 25 geldings) were purchased at random from public auctions in
Veterinary Therapeutics • Vol. 7, No. 3, Fall 2006

Kansas and New Mexico and assessed for inclusion in the study. They ranged in age from 18 months to 20 years and in weight from 487 to 974 lb (221 to 443 kg). The criterion for selection was the absence of evidence of major illness or lameness. Horses were purchased in groups of 20 to 30 animals at a time until 80 horses were acquired. After being purchased, the horses were stressed by long-distance transport (1,000 miles) in an attempt to induce naturally occurring infectious respiratory disease. Each group of horses was transported in standard stock trailers containing no more than 15 horses. During transport, horses were not restrained or tied and were given access to water at 6-hour intervals; hay nets were available in the trailer free choice. On arrival at Kansas State University, horses were commingled (groups contained a maximum of 30 horses) and evaluated at 12-hour intervals for clinical score and rectal temperature until they either were enrolled in the study or had completed 7 days of evaluation.

Horses were enrolled in the study when they met the inclusion criteria of both a rectal temperature of 102.0°F (38.9°C) or higher and a total clinical score of 5 or higher. Clinical scores were the sum of scores assigned for nasal discharge, respiratory character, and depression (see box, left). After they were enrolled in the study, horses were randomly assigned to treatment groups (described below).

After the horses were assigned to a treatment group (day 1), blood was collected for complete blood count (CBC) and the fibrinogen concentration was determined using the heat precipitation method. Transcutaneous tracheal aspiration was performed with the horses under sedation (xylazine, 0.5 mg/kg IV). Samples were collected in a sterile fashion and placed in transport vials for subsequent aerobic culture. All horses enrolled in the study received either treatment or placebo for a minimum of 5 days; the horses were given a complete physical examination and their clinical score was recorded daily at the time the treatment or placebo was administered.

On treatment day 5, the horses were evaluated to determine whether they should remain in their treatment group or be removed from the study (treatment failure). Day 5 evaluation included CBC, determination of fibrinogen concentration, and transtracheal aspirate analysis. If a horse was deemed a treatment failure (clinical score ≥5 and rectal temperature ≥102°F), blinded study medication was discontinued and alternative antimicrobial therapy (procaine penicillin G [22,000 IU/kg IM q12h] and gentamicin [6.6 mg/kg IM q24h]) was administered. Horses not removed from the study at this time continued to receive daily treatment with either enrofloxacin or placebo through day 7; daily scoring and rectal temperature analysis continued until day 10. A final evaluation, which included estimated body weight, CBC, fibrinogen concentration,

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**Clinical Scoring**

Total clinical scores were the sum of scores assigned for the following characteristics:

**Nasal Discharge**
1 = No discharge
2 = Serous discharge
3 = Mucopurulent discharge

**Respiratory Character**
1 = No evidence of respiratory disease
2 = Respiratory rate >24 breaths/min with intermittent coughing
3 = Respiratory rate >40 breaths/min with paroxysmal coughing

**Depression**
1 = Normal
2 = Mild depression
3 = Moderate depression
4 = Severe depression
and transtracheal wash analysis, was conducted on day 10.

**Animal Management and Housing**

Horses were maintained in outdoor pens; each pen contained a loafing shed with straw bedding, and all horses were offered free-choice prairie grass hay and water. Neither vaccinations nor dewormers were administered during the prestudy or study period. Preconditioning was not implemented because the objective was to identify horses suffering from respiratory disease immediately on arrival at the Kansas State University–Animal Resource Facility. On arrival, horses were individually handled and haltered, and estimated body weights were obtained with a commercial weight tape. Each horse was numbered with marker paint on the haircoat, and the halters were likewise identified with permanent marker. After all the horses were numbered, blood was drawn for equine infectious anemia testing to confirm that the horses were free of this disease. Physical examination was performed, and the findings were recorded. Horses that met inclusion criteria on initial evaluation were enrolled in the study, whereas those that were not enrolled initially were evaluated at 12-hour intervals as described previously.

**Experimental Groups**

Thirty-three horses, 18 months of age or older, met the inclusion criteria and were enrolled in the study in one of two replicates (Table 1). Horses were enrolled as they met inclusion criteria for fulminate respiratory disease (described above). Age, gender, and breed were recorded, and subjects were randomized to the treatment groups in blocks of five (Table 1):

- **Group 1** (n = 6)—1.25 mg/kg/day enrofloxacin 10%; mean age, 3.4 years (range, 2 to 7.5 years)
- **Group 2** (n = 6)—2.5 mg/kg/day enrofloxacin 10%; mean age, 3.1 years (range, 1.5 to 8.5 years)
- **Group 3** (n = 8)—5 mg/kg/day enrofloxacin 10%; mean age, 4.2 years (range, 2 to 7 years)
- **Group 4** (n = 7)—7.5 mg/kg/day enrofloxacin 10%; mean age, 3.8 years (range, 2 to 10 years)
- **Group 5** (n = 6)—Placebo (0.9% NaCl); mean age, 2.1 years (range, 2 to 5 years)

Random assignment to treatment groups resulted in six horses being enrolled groups 1, 2, and 5; seven horses in group 4; and eight horses in group 3. Enrolled horses were separated from horses that did not meet inclusion criteria. Because this investigation was designed exclusively to investigate the efficacy of enrofloxacin for treatment of equine respiratory disease, concurrent antibacterial or antiinflammatory therapies were not administered.

**Treatment**

Horses meeting inclusion criteria of a clinical score of 5 or higher and a rectal temperature of 102°F or higher were assigned to treatment groups using a randomized block design. To determine a dose–response relationship, incremental doses of enrofloxacin 10% (1.25, 2.5, 5.0, and 7.5 mg/kg/day IV) were administered; the placebo group received 0.9% saline solution (administered by venipuncture) at a volume equal to that of the 7.5 mg/kg enrofloxacin dose.

**Side Effects/Adverse Reactions**

The investigators examined each animal daily for systemic and local (pain, swelling, host discomfort) adverse effects.

**Microbiology**

After a horse was enrolled in the study (day 1) but before enrofloxacin or placebo was ad-
ministered, a transtracheal wash was performed to collect tracheal secretions. The transtracheal wash samples were submitted as liquid in BBL Port-A-Cul transport vials (BBL catalog #221608, BD Diagnostics, Sparks, MD). Samples were held at 39.2˚F until they were shipped overnight to the Colorado Animal Research Enterprises facility in Fort Collins for aerobic culture. Bacterial colonies were evaluated specifically for enrofloxacin sensitivity and MIC evaluation. A loopful of transtracheal wash fluid was streaked separately to 5% sheep blood agar, phenylethanol agar, and MacConkey agar. Agar plates were incubated aerobically at 98.6˚F overnight and observed for bacteria growth. Additional incubation of the initial plate was performed at the discretion of the microbiologist. Presumptive identifications were confirmed to the species level via colony morphology, gram-stain characteristics, and Biolog identification (MicrologT 3 identification system, Biolog, Hayward, CA). The MIC of each isolate was determined by standard procedures and according to methods outlined by the Clinical and Laboratory Standards Institute. All isolates were tested in duplicate using separate plates for each replicate. The MIC was the lowest concentration of antibiotic for which no visible growth was observed or the pellet was 2 mm or less in diameter.

### Efficacy Parameters

The primary variable used to ascertain enrofloxacin efficacy was overall recovery (number of animals completely recovered based on the previously described scoring system), defined as a clinical score below 5 and a rectal temperature below 102˚F on days 5 and 10 of the study. Overall success was determined by the day 10 evaluation, which allowed an evaluation to be performed 48 hours after completion of antibiotic therapy. Other efficacy variables were evaluated via daily clinical monitoring throughout the study; these variables included rectal temperature, characterization of nasal discharge, malaise/depression, and respiration/dyspnea while animals received treatment for 7 days. Additional monitoring on days 5 and 10 included CBC, determination of fibrinogen concentration, and transtracheal wash analysis as previously described.

### Statistical Analysis

Outcomes were continuous observations over time, dichotomous (success), or scores. Total clinical score was considered a continuous outcome over time, and these data were handled in the mixed models analysis of variance (Proc Mixed, SAS Version 8, SAS Institute, Cary, NC). Dichotomous and score outcomes were handled in Proc Logistic (SAS Institute). Treatment, gender, age, weight, day, and baseline were used as fixed effects in the statistical model. Briefly, continuous outcomes were analyzed with mixed models analysis of variance (Proc Mixed). Clinical score means and 90% CIs were produced for each treatment group. When other independent factors (e.g., study

### TABLE 1. Horses Enrolled in Enrofloxacin Study and Outcome after Treatment

<table>
<thead>
<tr>
<th>Parameter</th>
<th>1.25</th>
<th>2.5</th>
<th>5</th>
<th>7.5</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. of horses/group</td>
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<td>6</td>
<td>8</td>
<td>7</td>
<td>6</td>
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<td>1</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>Day 10 failures</td>
<td>3</td>
<td>4</td>
<td>5</td>
<td>4</td>
<td>2</td>
</tr>
<tr>
<td>No. of horses successfully completing the study</td>
<td>2</td>
<td>2</td>
<td>2</td>
<td>1</td>
<td>1</td>
</tr>
</tbody>
</table>
day) interacted to change the treatment effect, means were examined for different levels of the interaction. The results for different dosages of enrofloxacin were each compared with the control (Dunnett’s adjustment for multiple comparisons). Dichotomous and score outcomes were analyzed with logistic regression (Proc Logistic). To best determine the treatment effect, all active treatments were compared with placebo. Enrofloxacin doses of 2.5 mg/kg and higher were compared with lower doses of antimicrobial treatment. Odds ratios and 90% CIs were produced. P-values < .05 were considered significant.

■ RESULTS

Evaluation of 80 horses resulted in enrollment of 33 horses, based on the criteria of a rectal temperature of 102°F or higher and a clinical score of at least 5. After completion of the investigation and based on the data generated, we established that eight of 33 (24.2%) horses completed the study and were deemed successes (Table 1 and Figure 1). These eight horses were evaluated during and after treatment with either enrofloxacin or placebo and had a clinical score less than 5 and a rectal temperature less than 102°F on days 7 and 10.

The day 5 evaluation revealed that seven of 33 (21.2%) horses were classified as treatment failures (Table 1), defined as horses having high clinical scores (≤5) and fever (rectal temperature ≥102°F); these horses were removed from the study and placed on alternative antibiotic therapy as described in Materials and Methods. After the day 10 evaluations, an additional 18 horses were classified as study failures based on a rectal temperature of at least 102°F or a clinical score of at least 5.

Treatment success on day 5 was greatest for the 2.5 mg/kg group (100% success; Figure 2). The active treatments had success rates of 71% and higher (rates of 83%, 100%, 88%, and 71% for enrofloxacin doses of 1.25, 2.5, 5, and 7.5 mg/kg, respectively). Success on day 5 was lowest for the placebo group (50% success). The only independent factor found to be associated with treatment success on day 5 was the contrast of active treatment and placebo injection: Horses receiving an active treatment were more likely to succeed than horses receiving placebo, but the difference did not achieve statistical significance ($P = .074$). It was concluded that treatment with enrofloxacin at any dose demonstrated a trend toward benefit for the horses, but there was no evidence of a dose–response effect. Overall success after day 10 evaluations revealed that success rates for increasing dosages of enrofloxacin from 1.25 to 7.5 mg/kg were 40%, 33%, 29%, and 20% and the success rate in the placebo group was 33% (Figure 1). None of the independent factors was found to be associated with overall study success on day 10.

One individual adverse event associated with drug administration was observed: One horse in the second replicate developed local celluli-
tis surrounding the site of injection. Warm compresses were applied daily, and no further inflammation was observed. By the completion of the study, no evidence of inflammation was detected. No other adverse events were observed during the investigation that could be attributed to drug administration, such as diarrhea or changes in appetite.

Total clinical score, respiratory character score, and nasal discharge score provided evidence of a treatment benefit. For total clinical score, each enrofloxacin treatment performed significantly better than the placebo treatment, with all P values < .0001. Total clinical score ranged from 3 to 9 during the trial without a dose-dependent effect being detected. The mean clinical score for placebo was 8.1 while that for active treatment was 5.7 or less. It was concluded that treatment with enrofloxacin improved total clinical score, although improvement was not dose related.

The treatment effect for respiratory score revealed that the group receiving the 7.5 mg/kg dose exhibited the lowest nasal scores compared with placebo (P = .001). Horses that received a lower dose of enrofloxacin did not demonstrate an improved respiratory score (P = .030). Therefore, treatment with enrofloxacin at 7.5 mg/kg improved nasal score.

Rectal temperature on day 1 tended to be slightly higher in the horses randomly allocated to the 5.0 and 7.5 mg/kg treatment groups, although high values were recorded in all groups. Throughout the study, rectal temperature ranged between 96.3°F and 105.9°F. Temperature change from day to day was not associated with treatment group, supporting the conclusion that there was no evidence of a treatment effect on rectal temperature.

Hematologic examinations were performed throughout the study period as described in Materials and Methods. Although variations from normal values were observed in select cases for leukocyte count and fibrinogen concentrations, it was concluded that no evidence of a treatment effect for either parameter was observed.

**Microbiologic Data**

Microbiologic data (bacterial species and MIC) were recorded as the specific bacterial species or “none” (negative result). Of the 99 samples collected throughout the course of the study, 70 (71%) were positive for bacterial growth. Four bacterial species were cultured: *Streptococcus equi* subsp *zooepidemicus*, *Mannheimia haemolytica* (MIC, 0.004 µg/ml), *Pasteurella* spp (MIC, 0.015 µg/ml), and *Streptococcus pneumoniae* (MIC, 1 µg/ml). Only *S. equi* subsp *zooepidemicus* was isolated from more than two transtracheal washes. *S. equi subsp zooepidemicus* was found in 94.5% of the positive culture results, with MICs of 0.5, 1, and 2 µg/ml being recorded in 19%, 78%, and 3% of the species’ isolations, respectively. There was a trend for a decrease in the number of positive isolations by day 10; however, because of the subjective interpretation of culture isolates, statistical analysis was not performed.
DISCUSSION

Based on the statistical evaluation of total clinical score, respiratory score, and nasal score, there was some evidence of therapeutic benefit following treatment with parenteral enrofloxacin in horses. Subjective analysis of culture results suggested a reduction in the number of positive samples by day 10 (Figure 3), indicating a need for further investigation. Treatment failures (seven of 33 horses; 21%) occurred in horses among all treatment groups, substantiating previous claims that enrofloxacin may not be an appropriate sole antimicrobial agent for use in horses with clinical evidence of respiratory disease that have positive Streptococcus spp culture on tracheal aspiration. However, enrofloxacin may be appropriate for combination therapy in some cases of polymicrobial respiratory infection.

Most surrogate indicators of clinical response to enrofloxacin administration (e.g., CBC, fibrinogen concentration) did not show evidence of a treatment effect. Overall evidence for treatment benefit was minimal; however, lack of statistical support may relate to the relatively small sample size for each treatment group. Eighty horses were evaluated for the development of respiratory disease, but the relatively low rate of morbidity resulted in a small sample size for evaluation of drug efficacy using this model. Our findings yielded data that supported the established belief regarding the use of enrofloxacin in horses with streptococcal respiratory infection.

Clinical examination revealed that some horses demonstrated evidence of respiratory disease at the time of presentation or within the first 5 days of evaluation. Respiratory disease was characterized by the measures of total clinical score and rectal temperature. Physical examination, clinical signs, hematology, and transtracheal aspiration for aerobic culture were the measures used to determine pulmonary pathology and bacterial isolation. During the selected 7-day observation period, we were able to identify and select all horses that were going to develop clinical respiratory disease. This conclusion was based on the fact that horses not meeting inclusion criteria were still monitored daily for the subsequent study period and that none of these horses developed respiratory disease after 7 days. Although most clinically abnormal horses were culture positive for respiratory bacterial pathogens, it is likely that respiratory pathogens included viruses in addition to bacteria, which may have contributed to the low level of complete disease resolution observed in the group of treatment horses. Virus isolation would have been an appropriate diagnostic test to perform in this investigation; however, support for the predominantly bacte-
rial nature of infection in treatment-failure horses was evidenced by their positive response to alternate antimicrobial therapy (i.e., penicillin and gentamicin) after they were removed from the study. The clinical response was rapid and complete: Clinical signs resolved within 5 days of treatment. It is possible that although viral disease may have been primary in some individuals, secondary bacterial contamination played a role in respiratory infection in some clinically affected individuals. An appropriate modification to this protocol would be to determine the frequency of viral infection in all clinically abnormal horses.

The overwhelming majority of isolates obtained from transtracheal wash cultures were *S. equi* subsp *zooepidemicus* (94.5% of positive isolates), yet *M. haemolytica* (3% of isolates), *Pasteurella* spp (1% of isolates), and *S. pneumoniae* (1% of isolates) were also isolated. *S. equi* subsp *zooepidemicus* is a gram-positive pathogen, and enrofloxacin is primarily recognized for its gram-negative efficacy. Therefore, it is not surprising that some individuals did not recover from clinical or microbiologic (i.e., culture positive at days 5 and/or 10) disease. Considering the current state of antimicrobial resistance among bacterial isolates, it is particularly important that clinicians consider the potential problems with such therapy. Enrofloxacin should be reserved for respiratory disease associated with gram-negative organisms if such treatment is supported by clinical (e.g., severe neutropenia, severe endotoxemia) or bacterial culture and sensitivity testing results.

Combination antimicrobial therapy including an agent with gram-positive activity may have resulted in improved disease recovery. This suggestion is supported by the fact that horses requiring alternative antimicrobial therapy (treatment failures) responded favorably to antimicrobial therapy that included activity against gram-positive organisms. Horses are particularly sensitive to development of streptococcal pneumonia in combination with other pathogens (particularly gram-negative organisms).

Because the data revealed evidence to suggest mild improvement in horses suffering from streptococcal respiratory disease after treatment with enrofloxacin, this class of antimicrobial agents should not be selected as sole therapy without consideration of the patient’s status and suspected (or confirmed) pathogenic bacteria. Enrofloxacin should be reserved for respiratory disease associated with gram-negative organisms if such treatment is supported by clinical (e.g., severe neutropenia, severe endotoxemia) or bacterial culture and sensitivity testing results. Enrofloxacin is not considered a primary therapy and, therefore, should be reserved for disease caused by bacteria with proven sensitivity to this antibiotic agent. Alternative antimicrobial therapies for management of equine respiratory disease, including β-lactam preparations with increased spectrum of activity (e.g., ceftiofur sodium), have been well described in the literature. However, anecdotal evidence has suggested that, in racetrack settings in North America, ceftiofur may be associated with the development of peracute colitis; therefore, alternative strategies should be considered when pathogens other than *Streptococcus* spp are encountered and ceftiofur sodium is not an appropriate therapeutic option. In select cases of equine respiratory disease, enrofloxacin may be chosen based on antimicrobial sensitivity data.
and clinical status of the patient (e.g., the need for gram-negative coverage in an azotemic patient) or for specific pathogens known to demonstrate susceptibility to this drug, such as staphylococcal pneumonia. Caution should be exercised when considering enrofloxacin in foals and young horses that have not yet reached maturity because of the potential for cartilage damage with this agent in immature animals.  

Based on the data generated from this investigation, it appears that enrofloxacin is unlikely to be curative for therapeutic management of equine respiratory disease associated with Streptococcus spp. Because gram-positive pathogens predominated in the lower airways of clinically diseased horses (e.g., pyrexia, nasal discharge, depression, positive culture results) exposed to this model of long-distance transport, we suggest that antimicrobial selection should include agents designed to cover this class of microorganisms under similar clinical settings. If clinical findings (e.g., endotoxemia, leukopenia, tachycardia) or microbiologic evidence reveals that gram-negative organisms are also playing a role in disease challenge, antimicrobial therapy providing coverage against this class of bacteria is also indicated. These data show that enrofloxacin appears safe for treatment of bacterial respiratory disease, but it is not recommended as the initial sole therapy without substantial evidence, such as bacterial culture and sensitivity data, to support its use.

**ACKNOWLEDGMENTS**

We thank Don Bade, Microbiological Investigator, Colorado Animal Research Enterprises, for his outstanding assistance with all microbiologic assays. Funding for this study was provided by Bayer Animal Health, Shawnee Mission, Kansas.

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