Efficacy of Gamithromycin for the Treatment of Foals with Mild to Moderate Bronchopneumonia

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Background: Gamithromycin is active in vitro against the bacterial agents most commonly associated with bronchopneumonia in older foals. However, the clinical efficacy and safety of this drug have not been investigated.

Hypothesis: Gamithromycin is effective for the treatment of bronchopneumonia in foals.

Animals: One hundred and twenty-one foals on a farm endemic for infections caused by *Rhodococcus equi*.

Methods: In a controlled, randomized, and double blinded clinical trial, foals with ultrasonographic evidence of pulmonary abscesses (abscess score 8.0–20 cm) were randomly allocated in 3 treatment groups: (1) gamithromycin IM q7 days (n = 40); (2) azithromycin with rifampin, PO q24h (n = 40); or (3) no antimicrobial treatment (controls; n = 41). Physical examination and thoracic ultrasonography were performed by individuals unaware of treatment group assignment. Foals that worsened were removed from the study.

Results: The proportion of foals that recovered without the need to be removed from the study was significantly higher for foals treated with gamithromycin (38 of 40) or azithromycin with rifampin (39 of 40) than for controls (32 of 41). Treatment with gamithromycin or with azithromycin-rifampin resulted in a significantly faster decrease in the clinical score and abscess score compared to the controls. Adverse reactions characterized by colic (n = 18) and hind limb lameness (n = 14) were observed only in foals treated with gamithromycin.

Conclusion and Clinical Importance: Gamithromycin was noninferior to azithromycin with rifampin for the treatment of bronchopneumonia in the study population but had a higher frequency of adverse reactions.

Key words: Macrolide; Pneumonia; *Rhodococcus equi*.

Pneumonia is a leading cause of morbidity and mortality in foals in the United States.[1] Gram-positive bacteria, such as *Streptococcus equi* subspecies *zooepidemicus* (*S. zooepidemicus*) and *Rhodococcus equi* are the most common causes of pneumonia in foals between 1 and 6 months of age.[2,3] Although *R. equi* can be cultured from the environment of virtually all equine farms, the clinical disease in foals is endemic and devastating at some farms and sporadic at others. Control of infections at farms endemic for *R. equi* often relies on early detection of disease using thoracic ultrasonography with antimicrobial treatment for affected foals.[4–6] Based on a consensus statement from the American College of Veterinary Internal Medicine, the combination of a macrolide (erythromycin or clarithromycin) or azalide (azithromycin) with rifampin is the recommended treatment for infection caused by *R. equi*.[7] These antimicrobial agents occasionally result in adverse effects such as hyperthermia and diarrhea.[8,9] Furthermore, their use requires multiple daily oral administrations, which is labor intensive, particularly when a large number of foals must be treated.

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Abbreviations:

AZM	azithromycin
GAM	gamithromycin
IM	intramuscular
MIC	minimum inhibitory concentration
RIF	rifampin

Gamithromycin is an azalide antimicrobial agent that has been approved recently for the treatment and control of bovine respiratory disease. Gamithromycin might be an effective alternative to antimicrobial agents currently used for the treatment of foal pneumonia owing to its accumulation in pulmonary epithelial lining fluid and phagocytic cells, as well as its in vitro activity against *R. equi* and *S. zooepidemicus*.[10] Intramuscular administration of gamithromycin to foals at a dosage of 6 mg/kg resulted in pulmonary epithelial lining fluid concentrations above the MIC inhibiting at least 90% of the isolates (MIC_{90}) of *S. zooepidemicus* and bronchoalveolar cell concentrations above the MIC_{90} of *R. equi* for approximately 7 days.[10] Availability of a long-acting antimicrobial agent providing sustained therapeutic concentrations at the site of infection would result in less frequent administration, which in turn would be less labor intensive and might improve client compliance. However, the lack of clinical efficacy and safety data precludes the rational use of gamithromycin for the treatment of pneumonia in foals.

The objectives of this study were to determine the relative efficacy and safety of GAM or AZM-RIF in combination for the treatment of foals with pulmonary lesions on a farm with endemic infections caused by *R. equi*.

Materials and Methods

Study Population

The study protocol was reviewed and approved in accordance to ethics guidelines of Hanover University and the German Animal Welfare Act. The study was a controlled, randomized, and double blinded clinical trial performed during the 2013 breeding season at a farm breeding Warmblood horses in Germany. The farm had a history of recurrent foal pneumonia attributable to *R. equi*. Between 2003 and 2009, multiple studies performed on the farm demonstrated that *R. equi* could be isolated from tracheobronchial aspirates of 39% (17/44) to 54% (118/217) of foals with ultrasonographic evidence of pneumonia.[11–14] In addition, postmortem examination of 24 foals from the same farm confirmed the presence of *R. equi* in lung tissue of all foals with ultrasonographic lesions.[15] All foals born on the participating farm that were older than 4 weeks of age at the beginning of the study were eligible for inclusion.

Monitoring of the Foals before Inclusion in the Study

From birth to 5 months of age, each foal was subjected weekly to a complete physical examination, including auscultation of the lungs. At the time of examination, blood was obtained by jugular venipuncture for white blood cell (WBC) counts. Foals with a temperature >39.5°C, a respiratory rate >80/min, coughing, purulent nasal discharge, abnormal lung sounds, or a WBC count >13.0 × 10³/μL were examined using thoracic ultrasonography.

Thoracic ultrasonography was performed using a portable unit[a] with a 7.5 MHz linear transducer. The chest was drenched with alcohol and the entire surface of both lungs was imaged. For the study, abscesses were defined as focal hypoechoic areas of consolidation with a diameter ≥1.0 cm. The number of abscesses noted during a given exam was recorded. In addition, the diameter of each abscess was added to generate a total abscess score in centimeters. For asymmetrical lesions, the average of the largest and smallest diameter was used for data analysis.

Criteria for Inclusion of the Treatment Study and Study Design

Foals with abscess scores between 8.0 and 20 cm and WBC ≤ 23.0 × 10³/μL were enrolled for participation in the study. Foals with dyspnea, with a WBC > 23.0 × 10³/μL or with abscess scores >20 cm were excluded from participation in the study. Foals meeting criteria for inclusion in the study had been pre-assigned to 1 of 3 treatment groups using a computer-generated randomized sequence of the numbers 1–3. Treatment groups were: (1) gamithromycin at a dose of 6.0 mg/kg body weight administered IM in the semimembranosus/semitendinosus muscles once a week (GAM; n = 40); (2) azithromycin at a dose of 10 mg/kg PO once daily in combination with rifampin at a dose of 10 mg/kg PO once daily (AZM-RIF; n = 40); and (3) no antimicrobial treatment (controls; n = 41). All the foals in each treatment group also received acetylcysteine at a dose of 10 mg/kg PO a day to provide the same daily manipulation of the foals in each group.

Foals were monitored daily for adverse reactions, such as diarrhea, lameness, colic, or swelling at the injection site. Each foal enrolled in the study was subjected to weekly physical examination and thoracic ultrasonography until resolution of the lesions and discontinuation of treatment. Physical examination parameters were used to generate a clinical score based on respiratory rate (< or >80 bpm), presence and type of nasal discharge (none, serous, purulent), submandibular lymph nodes (normal or enlarged), dyspnea (absent or present), and auscultation of the lungs and trachea (normal versus abnormal) as previously described.[6,16] In addition, blood was obtained weekly by jugular venipuncture for determination of WBC counts. Criteria for discontinuation of treatment were resolution of clinical signs and no evidence of consolidation upon thoracic ultrasonography for 2 consecutive weeks after a minimum of 40 days of treatment. The individuals responsible for thoracic ultrasonography, physical examination, and for determining the need for treatment were unaware of specific treatment group assignment for a given foal. All treatments were given by different individuals who had no control over treatment assignment.

Criteria for Removal from the Study

The study protocol included a rescue mechanism to reduce the risk of mortality. Foals that developed dyspnea or an abscess score >23 cm were removed from the study protocol. Foals removed from the study were switched to the combination of rifampin with azithromycin at doses 30% higher than those used in the study protocol.

Additional Data Collection

For each foal enrolled in the study, data collected included sex, age and body weight at onset of clinical signs, clinical score, number of abscesses and abscess score, duration of therapy, and adverse effects. For each treatment group, the proportion of foals removed from the study (rescue mechanism) was recorded. For foals that were removed from the study, the number of days into the initial treatment at the time of removal from treatment was recorded.

Data Analysis

Sample size analysis based on the ability to detect an estimated response rate of 97% in the GAM treatment group as being significantly superior from an estimated response rate of 70% in the control group with alpha set at 0.05 and power set at 80% indicated that 36 foals per group would be required. Sample size calculations for a noninferiority trial testing the null hypothesis that the response rate in the AZM-RIF treatment group is superior to that of the GAM treatment group was based on estimated efficacy of either treatment of 97%, statistical power of 80%, alpha of 0.05, and a noninferiority limit of 10%. The estimated number of foals required was 36 per group. We elected to enroll 40 foals per group to allow for potential losses to follow-up and variation in observed values from hypothetical values used for calculations.

Normality of the data and equality of variances were assessed using Shapiro–Wilk's and Levene's tests, respectively. Comparison of baseline and outcome variables between treatment groups was done using a Kruskal–Wallis ANOVA. Comparisons between proportions (eg, sex, percentage of foals that were removed from the study) were done using Fisher's exact test. A two way ANOVA with repeated measures was used to evaluate the effect of treatment group, time, and the interactions between treatment group and time on body weight, clinical score, abscess score, number of abscesses, and WBC counts of foals that responded to the initial treatment. Data that did not meet assumptions for parametric testing were transformed to ranks before analysis. When indicated, multiple pairwise comparisons were done using the Holm–Sidak method. For all analyses, $P < .05$ was considered significant.

Table 1. Baseline variables at the time of initiation of treatment with GAM, AZM-RIF. The control group did not receive antimicrobial treatment.

Variables	GAM (n = 40)	AZM-RIF (n = 40)	Controls (n = 41)
Males (%)	20 (50.0)	25 (62.5)	22 (53.7)
Females (%)	20 (50.0)	15 (37.5)	19 (46.3)
Clinical score	2 (1–3)[a]	2 (1–4)	2 (1–4)
Abscess score (cm)	10.0 (8.0–16.0)	10.0 (8.0–17.4)	10.5 (8.0–15.0)
Number of abscesses	7 (3–11)	7 (4–11)	6 (4–12)
WBC ($\times 10^9$/L)	14.2 (10.0–20.4)	14.0 (10.1–18.1)	14.9 (11.1–19.0)
Age at diagnosis (days)	120 (73–161)	117 (64–173)	127 (54–164)
Body weight at diagnosis (kg)	179 (141–222)	188 (140–225)	181 (132–232)

GAM, gamithromycin; AZM-RIF, azithromycin-rifampin.
[a]Median (10th and 90th percentiles).

Table 2. Outcome variables in foals treated with GAM, AZM-RIF, or in untreated controls.

Variables	GAM (n = 40)	AZM-RIF (n = 40)	Controls (n = 41)
Recovered without change in antimicrobial treatment (%)	38 (95)[*]	39 (98)[*]	32 (78.0)
Duration of treatment in foals that responded without change in antimicrobial (days)	45 (40–52)[a]	44 (40–52)[a]	44 (40–52)[a]
Days to change in treatment (days)	60 (58–61)[b]	59 (59)[b]	29 (1–61)[b]

GAM, gamithromycin; AZM-RIF, azithromycin-rifampin.
[a]Median (10th and 90th percentiles) unless otherwise indicated.
[b]Median (lowest and highest value).
[*]Significantly different compared to foals in the control group ($P < .05$).

Results

Baseline variables at the time of initiating treatment with GAM, AZM-RIF, or in untreated controls for the 121 foals included in this study were not significantly different between treatment groups (Table 1). The proportion of foals that recovered without the need for a change in treatment was significantly ($P < .048$) higher for foals treated with GAM (38 of 40; 95%) or AZM-RIF (39 of 40; 98%) compared for control foals (32 of 41; 78%) (Table 2). The proportion of foals that recovered without the need for a change in treatment in foals treated with GAM was not significantly ($P = 1.0$) different from that of foals treated with AZM-RIF. The difference in the percentage of efficacy of AZM-RIF versus GAM was 2.5% (90% CI = −0.0447 to 0.0947%), which did not cross the predetermined noninferiority limit of 10%. Therefore, GAM was noninferior to AZM-RIF within the predetermined noninferiority limit of 10%. The duration of the initial treatment was not significantly different between groups (Table 2).

There was a significant effect of time ($P < .001$) but no significant effect of treatment group ($P = .946$) or interactions between treatment group and time ($P = .862$) on body weight. There were significant interactions between time and treatment on clinical score, WBC counts, number of abscesses, and abscess score (Fig 1). The clinical scores, number of abscesses and the abscess scores after 1 and 2 weeks of treatment were significantly lower for foals treated with GAM or AZM-RIF compared to control foals (Fig 1).

The WBC count of foals treated with GAM was significantly higher than that of foals treated with AZM-RIF on week 3 of treatment (Fig 1B).

Overall, 23 of 40 foals (58%) in the GAM treatment group displayed signs of adverse reactions to the drug whereas adverse reactions were not noted in the other 2 groups ($P < .001$). Adverse effects consisted of signs of colic (n = 18; 45%) immediately after injection and lameness of the hind limb that was injected (n = 14; 35%). Signs of colic were mild in most foals and consisted of lying down and flank watching. Most episodes of colic were after the first and second injection of GAM. Four foals had severe episodes of colic after each injection. These foals were treated with 1 dose of a nonsteroidal anti-inflammatory agent during the episodes. In 12 foals, lameness was grade IV/V on the AAEP lameness scale the day after the first or and second injection and resolved progressively over the next 72 hours. In 6 foals, lameness was grade V/V the day after each injection and resolved progressively over the next 72 hours.

Discussion

This study demonstrated that GAM is effective for the treatment of foals with ultrasonographic lesion scores between 8 and 20 cm and is noninferior to treatment with AZM-RIF. For many years, control of *R. equi* infections at many farms at which the disease is endemic has relied on early detection of disease using thoracic ultrasonography with antimicrobial treatment for all foals with pulmonary lesions >1 cm
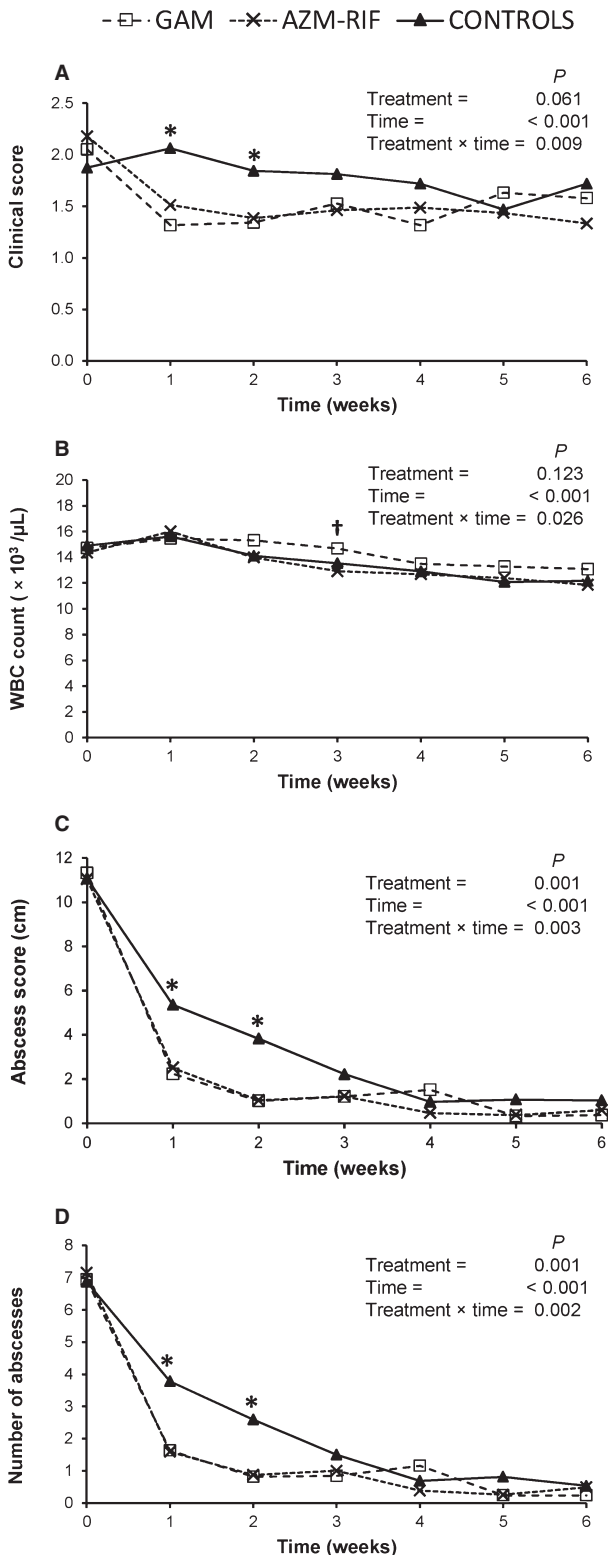
- ⊟- GAM   --✗-- AZM-RIF   -▲- CONTROLS

Fig 1. Least square mean clinical scores (A), WBC counts (B), abscess scores (C), and number of abscesses (D) over a period of 6 weeks in foals that responded to treatment with gamithromycin (GAM, n = 38), azithromycin-rifampin (AZM-RIF, n = 39), or in untreated controls (n = 32). *Indicates a significant difference between foals treated with GAM or AZM-RIF and untreated controls at a given time point (P < .05). †Indicates a significant difference between foals treated with GAM and foals treated with AZM-RIF at a given time point (P < .05).

cantly hasten lesion resolution, compared to administration of a placebo.[17,18] In contrast, treatment of foals with ultrasonographic lesion scores between 8 and 15 cm (median = 10 cm) with AZM-RIF provides a significant benefit compared to administration of a placebo.[19] These findings underscore the importance of a blinded controlled design in studies assessing the relative efficacy of various therapies. In the present study, weekly treatment with GAM was shown to significantly decrease the proportion of foals that developed more severe disease when compared to untreated controls. In addition, treatment with GAM resulted in a significantly faster decrease in the clinical score, number of abscesses, and abscess score compared to untreated controls. Administration of antimicrobial agents in this study did not decrease the total duration of treatment compared to the control group. However, these results must be interpreted with caution because the farm protocol imposed treatment for a minimum of 40 days, regardless of clinical signs or lesion resolution. The mandatory treatment duration of 40 days likely prevented a true and unbiased comparison of treatment duration between groups.

The definitive diagnosis of bronchopneumonia caused by *R. equi* should be based on bacteriologic culture or amplification of the *vapA* gene by polymerase chain reaction from a tracheobronchial aspirate obtained from a foal with (1) clinical signs of lower respiratory tract disease, (2) cytological evidence of septic airway inflammation, or (3) radiographic or ultrasonographic evidence of bronchopneumonia.[7] Although prior studies documented that *R. equi* could be cultured from most pneumonic foals at the farm, tracheobronchial aspirates were not performed in the present study. Although the etiology of the pulmonary lesions could not be determined, the presents study is an accurate reflection of what is occurring in clinical practice because tracheobronchial aspirates are not typically performed as part of ultrasonographic screening programs.[5] *S. zooepidemicus* and *R. equi* are by far the most common causes of pneumonia in foals between 1 and 6 months of age[2,3] and these microorganisms are typically susceptible to macrolides, azalides, and rifampin.[10,20]

Despite a statistically significant benefit of antimicrobial treatment in foals with abscess scores between 8 and 20 cm in the present study, the fact that 32 of 41 (78%) untreated control foals recovered indicates that many treated foals might have recovered without therapy. Indeed, the use of ultrasonography for

in diameter.[4–6] Recent double blinded randomized controlled studies have demonstrated that many foals with small pulmonary lesions (median abscess score ≤6 cm) recover without antimicrobial treatment and that antimicrobial treatment of these foals does not signifi-

screening to detect *R. equi* pneumonia was recently evaluated at another farm endemic for *R. equi* with personnel and veterinarians blinded to screening results.[b] Of 270 foals enrolled in the study, 216 (80%) developed sonographically visible pulmonary lesions whereas only 17% of foals developed clinically apparent *R. equi* pneumonia.[b] In the aforementioned study, resolution without clinically apparent illness or antimicrobial treatment occurred in 79% of foals with ultrasonographic pulmonary lesions.[b] Additional studies will be required to identify the optimal abscess score to predict the need for treatment on endemic farms. Nevertheless, treatment of foals with abscess scores between 8 and 20 cm, as reported in this study, has resulted in a considerable decrease in antimicrobial drug usage at the farm without concurrent increase in mortality compared to previous years when all foals with abscess scores >1 cm were being treated.

Previously, recommendations regarding the relative efficacy of antimicrobial agents for the treatment of pneumonia caused by *R. equi* were based exclusively on in vitro activity data, retrospective studies and comparisons to historical controls.[8,21–23] In the present study, GAM in monotherapy was noninferior to the combination of AZM-RIF. These results are consistent with those of a previous study performed at the same farm documenting that AZM alone had similar efficacy to AZM-RIF.[19] Although these data suggest that combination with RIF is not essential in the study population, these results must be interpreted with caution because the foals enrolled in both studies had either mild clinical signs of pneumonia or subclinical pulmonary disease. Therefore, the results might not apply to foals with advanced pulmonary lesions and severe signs of respiratory disease. The combination of a macrolide and rifampin is synergistic both in vitro and in vivo.[24,25] In addition, the use of the 2 classes of drugs in combination reduces the likelihood of development of resistance to either drug.[24–26] This is particularly important given the fact that the prevalence of macrolide resistance among *R. equi* isolates might be increasing.[27] A recent study documented emergence of widespread macrolide resistance at a farm after widespread use of these drugs was instituted for the treatment of foals with subclinical pulmonary lesions.[28]

The high frequency of adverse reaction after administration of GAM in the present study was unexpected. In a previous study, administration of a single dose of GAM by the same route to 6 foals did not result in adverse reactions.[10] The transient hind limb lamenesses observed in many foals the present study are likely the result of the irritating nature of the drug. Transient discomfort and mild to moderate injection site swelling are reported after subcutaneous administration of gamithromycin to cattle.[c] The absence of visible external swelling at the site of injection in the present study was likely because of the fact the drug was injected deep into the semimembranous/semitendinosus muscles. Treatment of foals with various macrolide and azalides antimicrobial agents has been associated with enterocolitis.[8,9] The signs of colic

observed in many foals in the present study might be the result of gastrointestinal disturbances caused by GAM. However, because signs of colic occurred almost immediately after injection and because none of the foals treated with GAM developed diarrhea, it is more likely that these signs were because of pain at the site of injection rather than to abdominal pain. Additional studies will be required to assess the pharmacokinetics and safety of the drug after administration via other routes.

In conclusion, the present study demonstrates that treatment of foals with ultrasonographic lesion scores between 8 and 20 cm with GAM or AZM in combination with RIF provides a significant benefit compared to untreated controls. In addition, these 2 treatments resulted in a significantly faster decrease in clinical score, number of abscesses and abscess score compared to untreated controls. The extent to which the results of this study may be extrapolated to other farms is unknown because the proportion of foals that recover without treatment may vary by farm, geographical region, and age at which ultrasonographic lesions are detected.

Footnotes

Acknowledgments

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