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Efficacy of Mass Antimicrobial Treatment of Foals with Subclinical Pulmonary Abscesses Associated with *Rhodococcus equi*

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Background: Mass antimicrobial treatment of foals with small subclinical ultrasonographic pulmonary lesions is empirical practice on many farms with endemic disease caused by *Rhodococcus equi*.

Hypothesis: Mass antimicrobial treatment of foals with subclinical ultrasonographic pulmonary lesions is unnecessary.

Animals: One hundred and eight foals on a farm endemic for infections caused by *R. equi*.

Methods: Controlled, randomized, and double-blinded prospective study. Foals with ultrasonographic evidence of pulmonary abscesses 5.0–10 cm in diameter (n = 108) were randomly allocated in 5 treatment groups: (1) tulathromycin IM; (2) doxycycline monotherapy PO; (3) doxycycline with rifampin PO; (4) azithromycin with rifampin PO, and (5) saline IM as a placebo. Physical examination and thoracic ultrasonography were performed by individuals unaware of treatment group assignment. Foals with evidence of disease progression were removed from the study and treated with azithromycin-rifampin.

Results: Overall, 22/25 (88%) foals in the placebo group recovered without the need for treatment. The proportion of foals that had evidence of disease progression did not differ significantly between the treatment groups ($P > .05$). Although the median duration of treatment was significantly ($P < .05$) shorter in foals treated with azithromycin-rifampin (46 days) compared with foals treated with the placebo (73 days), the time frame of ultrasonographic lesion resolution did not differ significantly between the treatment groups.

Conclusions and Clinical Importance: The majority of foals with subclinical pulmonary abscesses <10 cm in diameter recover without antimicrobial treatment and treatment of affected foals does not provide a clear benefit over administration of a placebo.

Key words: Azithromycin; Doxycycline; Equine; Foal; Pneumonia; Rifampin; Tulathromycin.

Introduction

Rhodococcus equi is one of the most important causes of pneumonia in foals and has a major financial impact on the equine industry. The clinical disease in foals is endemic and devastating on some farms and sporadic on others. Control of *R. equi* infections on many farms on which the disease is endemic often relies on early detection of disease by thoracic ultrasonography with antimicrobial treatment for all foals with pulmonary lesions >1 cm in diameter.[1–3] However, mass antimicrobial treatment of subclinically affected foals is costly and has the potential to select for antimicrobial resistance.[4]

The cumulative incidence of clinical signs of pneumonia attributed to *R. equi* on endemic farms that do not use ultrasonographic screening typically ranges between 5% and 20%,[5] whereas the cumulative incidence of foals with ultrasonographic evidence of pulmonary abscessation on *R. equi* endemic farms is generally between 30% and 70%,[1,2,6] suggesting that many subclinically affected foals recover without treatment.[7] In a recent double-blinded randomized placebo controlled study, many foals with small pulmonary lesions (sum of lesion diameters [or abscess score] of 1–10 cm; median 3 cm) recovered without antimicrobial treatment.[8] In addition, antimicrobial treatment of foals with small ultrasonographic lesions did not significantly hasten lesion resolution, compared with the administration of a placebo.[8] Currently, it is unknown whether foals with larger ultrasonographic lesions would also recover without treatment. Indeed, a recent consensus statement by the American College of Veterinary Internal Medicine identified validation of the value of ultrasonographic screening and establishment of better criteria to determine the necessity for treatment in subclinically affected foals as key areas of *R. equi* research.[9]

The objectives of this study were to determine the frequency of spontaneous resolution of larger subclinical pulmonary lesions (abscess score 5–10 cm) and if, at this larger lesion size, antimicrobial treatment conferred an advantage over the administration of a placebo. The final objective was to determine the relative efficacy, if any, of tulathromycin, azithromycin and rifampin in combination, doxycycline and rifampin in combination, and doxycycline monotherapy for the

Abbreviations:

AZM	azithromycin
DOX	doxycycline
RIF	rifampin
TUL	tulathromycin

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treatment of pulmonary abscesses on a farm with endemic infections caused by *R. equi*.

Materials and Methods

Study Population

The study was a controlled, randomized, and double-blinded clinical trial performed during the 2011 breeding season on a farm breeding Warmblood horses in Germany. The study was approved by the ethics committee of the state Mecklenburg-Vorpommern and informed consent of the owner was obtained. The farm had a history of recurrent foal pneumonia attributable to *R. equi*. Between 2003 and 2009, multiple studies performed on the farm confirmed that *R. equi* could be isolated from tracheobronchial aspirates of 39% (17/44) to 54% (118/217) of foals with ultrasonographic evidence of pneumonia.[10–13] In addition, postmortem examination of 24 foals from the same farm confirmed the presence of *R. equi* in the lung tissue of foals with ultrasonographic lesions.[14] All foals born on the participating farm that were older than 3 weeks of age at the beginning of the study were eligible for the inclusion. Standard housing, management, and preventative health-care practices as determined by the farm owner, manager, and veterinarian were used and were the same for all foals enrolled in the study.

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 thorough auscultation of the lungs. At the time of examination, blood was obtained by jugular venepuncture for white blood cell (WBC) counts. Foals with a temperature >39.5°C, a respiratory rate >80/min, coughing, abnormal lung sounds, or a WBC count >13.0 $\times$ $10^3/\mu L$ were examined by thoracic ultrasonography.

Thoracic ultrasonography was performed using a portable unit[a] with a 7.5 MHz linear transducer. The hair coat over the chest was wetted with alcohol and the entire surface of both lungs was imaged. For the purpose of the study, abscesses were defined as focal hypoechoic areas of consolidation with a diameter $\geq$1.0 cm. The number of abscesses noted during a given examination 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 5.0 and 10 cm and WBC $\leq$21.0 $\times$ $10^3/\mu L$ were enrolled for participation in the study, regardless of the presence or absence of clinical signs of respiratory disease. Foals with dyspnea, with abscess scores >10 cm, or with WBC $\geq$21.0 $\times$ $10^3/\mu L$ were excluded from participation in the study. Foals meeting criteria for inclusion in the study had been preassigned to one of 5 treatment groups using a computer-generated randomized sequence of the numbers 1 -5. Treatment groups were as follows: (1) weekly tulathromycin at a dose of 2.5 mg/kg body weight IM in the semimembranosus/semitendinosus muscles (TUL); (2) doxycycline monotherapy at a dose of 10 mg/kg PO q12h (DOX); (3) doxycycline at a dose of 10 mg/kg PO q12h in combination with rifampin at a dose of 10 mg/kg PO q12h (DOX-RIF); (4) azithromycin at a dose of 10 mg/kg PO q24h in combination with rifampin at a dose of 10 mg/kg PO q12h (AZM-RIF); and (5) weekly 0.9% saline (4 mL) IM (placebo). Foals were monitored daily for adverse reactions such as diarrhea or swelling at the injection site.

Each foal enrolled in the study was subjected to a weekly physical examination and thoracic ultrasonography until resolution of the lesions and discontinuation of treatment. Criteria for discontinuation of treatment were resolution of clinical signs and no evidence of consolidation upon thoracic ultrasonography for two consecutive weeks. Physical examination parameters were used to generate a clinical score based on respiratory rate (< or >80 bpm), presence and amount 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.[3,6] In addition, blood was obtained weekly by jugular venepuncture for the determination of WBC counts. The individuals responsible for thoracic ultrasonography, physical examination, and determining the need for treatment (diagnostic crew) were unaware of specific treatment group assignment for a given foal. All treatments were given by a completely different crew.

Criteria for Removal from the Study

The study protocol included a rescue mechanism to reduce the risk of death. Foals that developed dyspnea or an increase in the abscess score by $\geq$3.0 cm compared with their initial score were removed from the study protocol. Foals removed from the study were switched to the combination of AZM-RIF at the same dose as group 4, regardless of initial group assignment.

Additional Data Collection

For each foal enrolled in the study, data collected included sex, age, and body weight at the onset of clinical signs, clinical score, number of abscesses, and abscess score, as well as duration of treatment. 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 in the initial treatment at the time of removal from treatment and the duration of the 2nd treatment after the change were recorded.

Data Analysis

Normality of the data and equality of variances were assessed by the Shapiro-Wilk and Levene's tests, respectively. Comparisons of baseline (before initiation of treatment) and outcome variables between treatment groups were done by a one-way ANOVA. Data that did not meet the assumptions for parametric testing were compared by a Kruskal-Wallis test. When indicated, pairwise comparisons between each treatment group and the placebo group were done by Dunn's method. Student's t test or Mann Whitney's U test was used to compare the baseline variables of foals that responded to the initial treatment to those of foals that required a change in antimicrobial treatment. Comparison between proportions (eg, sex, percentage of foals that were removed from the study) was done by Fisher's exact test with Bonferroni adjustments for multiple comparisons. 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 the abscess score, the number of abscesses, and the WBC counts. Data that did not meet the assumptions for parametric testing were transformed to ranks before analysis. When indicated, pairwise comparisons between each treatment group and the placebo group were done by the Holm-Sidak test. For all analyses, significance was set at $P \leq .05$.

Results

A total of 108 foals had lesion scores between 5 and 10 cm and were included in the study. Baseline parameters at the time of initiating treatment with TUL, DOX, DOX-RIF, AZM-RIF, or the placebo for the 108 foals included in this study were not significantly different between the treatment groups (Table 1). Three foals in the DOX-RIF group developed hemolytic anemia and icterus 17–20 days after initiating the treatment. Treatment with DOX-RIF was discontinued at the onset of clinical signs. One of these foals was subjected to euthanasia. Necropsy revealed hyperemia of liver and spleen as well as an acute purulent splenitis and a chromoproteinemic nephrosis. The apical lung lobes showed areas up to 5-cm diameter of granulation tissue, chronic granulomatous inflammation, and moderate multifocal alveolar histiocytosis. The large colon showed a moderate diffuse chronic purulent colitis. After a 4th foal in the DOX-RIF group developed increased liver enzyme activities on day 9 of treatment, additional enrollment of foals to the DOX-RIF group was discontinued prematurely because of possible drug-related adverse effects. However, treatment with DOX-RIF was continued in foals that were already being treated with the combination (n = 13). The 4 foals in which treatment with DOX-RIF was stopped prematurely because of possible adverse effects were excluded from additional data analysis. Adverse effects attributable to treatment were not observed in the other groups.

There were no significant differences between the treatment groups in the proportion of foals that responded to the initial treatment, the duration of the initial treatment, the proportion of foals that were withdrawn from the study because they met the criteria for a change in treatment, and the number of days until the change in treatment (Table 2). Overall, 10 foals were removed from the study because of rescue criteria. All the foals that were withdrawn from the study responded to the treatment with AZM-RIF. The duration of the 2nd treatment did not differ significantly between the treatment groups (Table 2). However, the total duration of treatment was significantly shorter in foals treated with AZM-RIF compared with foals treated with the placebo. For all other treatment groups, total duration of treatment was not significantly different from that of the placebo group.

At baseline, foals that were eventually withdrawn from the study because they met the criteria for a change in treatment had a significantly higher abscess score, number of abscesses, and significantly lower WBC counts than foals that responded to the initial treatment (Table 3). In addition, foals that had to be withdrawn from the study were significantly younger at the time of initiation of treatment than foals that responded to the initial treatment (Table 3). There was a significant effect of time ($P < .001$) on WBC counts, abscess score, and the number of abscesses. The effect of treatment group and interactions between time and treatment groups for WBC count and abscess score were not statistically significant (Fig 1). There was a significant interaction between time and treatment group for the number of abscesses. After 1 week of treatment, the number of abscesses in the DOX-RIF group was significantly higher than in the placebo group. Differences between treatment groups at other time points were not statistically significant.

Discussion

In a recent study on the same farm, antimicrobial treatment of foals with smaller ultrasonographic lesions (abscess score 1–10 cm; median of 3 cm) did not provide any benefit over the administration of a placebo.[8] This study expands these findings by demonstrating that, despite selecting foals with more severe lesions (abscess score of 5–10 cm; median score of 6 cm), the proportion of foals that recovered without the need for a change in treatment was still not significantly different between foals treated with antimicrobial agents and foals administered a placebo. Despite enrollment of foals with more severe lesions, the proportion of foals in the placebo group that healed spontaneously without being switched to rescue antimicrobial treatment was significantly ($P < .001$)

Table 1. Baseline parameters in 108 foals at the time of initiation of treatment with tulathromycin, doxycycline, doxycycline-rifampin, azithromycin-rifampin, or placebo.

Variables	TUL (n = 25)	DOX (n = 24)	DOX-RIF (n = 13)[a]	AZM-RIF (n = 21)	PLACEBO (n = 25)	*P* Value
Males (%)	9 (36)	16 (67)	6 (46)	8 (38)	17 (68)	>.050
Females (%)	16 (64)	8 (33)	7 (54)	13 (62)	8 (32)	>.050
Clinical score	2 (1–2)[b]	2 (1–2)	1 (0–4)	2 (1–2)	2 (1–2)	.195
Abscess score (cm)	6 (5–9)	6 (5–8)	6 (5–8)	6 (5–9)	6 (5–9)	.951
Number of abscesses	3 (2–5)	4 (2–5)	3 (2–5)	4 (2–6)	4 (2–5)	.903
WBC ($\times 10^3/\mu L$)	15.0 (10.5–20.2)	16.2 (13.1–20.8)	15.0 (8.60–19.3)	13.7 (10.4–19.6)	14.4 (9.4–18.3)	.086
Age at diagnosis (days)	70 (47–135)	97 (42–135)	57 (36–112)	63 (38–138)	82 (47–145)	.175
Body weight at diagnosis (kg)	155 (114–235)	185 (128–221)	143 (107–198)	150 (113–223)	165 (114–247)	.397

TUL, tulathromycin; DOX, doxycycline; DOX-RIF, doxycycline rifampin; AZM-RIF, azithromycin-rifampin.

[a]Enrollment of foals to the DOX-RIF group was discontinued prematurely because of hemolytic anemia in 4 foals.

[b]Median (10th and 90th percentiles).

Table 2. Outcome variables in 104 foals treated with tulathromycin, doxycycline, doxycycline-rifampin, azithromycin-rifampin, or placebo.

Variables	TUL (n = 25)	DOX (n = 24)	DOX-RIF (n = 9)[a]	AZM-RIF (n = 21)	PLACEBO (n = 25)
Recovered without change in antimicrobial treatment (%)	19 (73)	24 (100)	9 (100)	20 (95)	22 (88)
Change in treatment (%)	6 (27)	0 (0)	0 (0)	1 (5)	3 (12)
Duration of treatment in foals that responded without change in antimicrobial (days)[b]	55 (41–103)	61 (38–92)	60 (39–100)	47 (41–122)	69 (30–132)
Days to removal from the study (days)[c]	7 (3–14)	NA	NA	4	15 (12–131)
Duration of second treatment after removal from the study (days)[c]	57 (21–70)	NA	NA	28	76 (35–98)
Total duration of treatment (days)[b,d]	58 (40–102)	61 (39–92)	60 (39–100)	46 (39–119)*	73 (40–140)

TUL, tulathromycin; DOX, doxycycline; DOX-RIF, doxycycline rifampin; AZM-RIF, azithromycin-rifampin; NA, not applicable.
[a]Excluding 4 foals in which treatment was changed because of a possible adverse effect of treatment rather than for treatment failure.
[b]Median (10th and 90th percentiles).
[c]Median (lowest and highest value).
[d]For the foals that were removed from the study, the total duration of treatment is the sum of the duration of the 1st and 2nd treatments.
*Significantly different compared with the placebo group ($P < .05$).

Table 3. Comparison of baseline parameters between foals that responded to the initial treatment and foals that were switched to a different treatment.

Variables	Responded (n = 94)	Change in Treatment (n = 10)[a]	*P* Value
Males (%)	43 (46)	5 (50)	1.00
Females (%)	51 (54)	5 (50)	1.00
Clinical score	2 (1–2)	1 (1–2)	.138
Abscess score	6 (5–8)*	7 (5–10)	.016
Number of abscesses	3 (2–5)	5 (3–5)	.006
WBC ($\times 10^3/\mu L$)	15.2 (11.9–20.1)	13.5 (3.71–18.6)	.011
Age at diagnosis (days)	82 (47–139)	54 (35–78)	.003
Body weight at diagnosis (kg)	169 (122–223)	135 (101–168)	.006

*Median (10th and 90th percentiles).
[a]Excluding 4 foals treated with DOX-RIF in which treatment was discontinued for possible adverse effects rather than for treatment failure.

higher in this study (22/25 or 88%) compared with that observed in the prior study involving foals with less severe lesions (14/32 or 44%).[8] This is likely explained by the fact that, in the prior study, there was a sense of apprehension regarding the risk of enrolling a placebo group. Although the members of the diagnostic crew were blinded with respect to treatment group, they were aware that a group of foals were receiving a placebo. As a result, there could have been an unintentional tendency to overreact and remove foals from the study prematurely. After being made aware that foals in the placebo group did not differ from treated foals in the 1st study (2010 season), it is probable that the diagnostic crew was less likely to overreact in this study (2011 season). The small subset of 10 foals that were withdrawn from the study because they met the rescue criteria were significantly younger, with lower WBC counts and higher abscess scores.

Although the proportion of foals with treatment failure was not significantly different between groups, the total duration of treatment was significantly shorter in foals treated with azithromycin and rifampin (median 46 days) compared with foals receiving a placebo (median 73 days). Although statistically significant, this finding might not be of clinical relevance because the ultimate outcomes, lesion resolution and survival, did not differ between groups. For all other treatment groups, total duration of treatment was not significantly different from that of the placebo group. As a result of the negligible effects of antimicrobial treatment and the limited statistical power of the study, the relative efficacy of the antimicrobial protocols evaluated could not be established. Data from

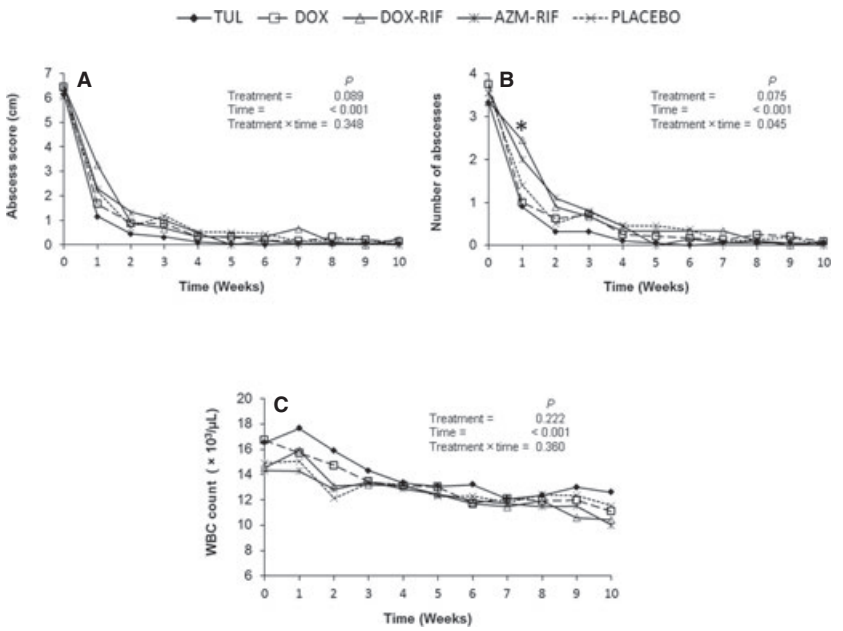

Fig 1. Mean abscess score, number of abscesses, and white blood cell counts over time in foals treated with tulathromycin (TUL, n = 25), doxycycline (DOX, n = 24), doxycycline-rifampin (n = 9), azithromycin-rifampin (AZM-RIF, n = 21), or the placebo (n = 25). *Indicates a significantly higher number of abscesses in foals treated with DOX-RIF compared with foals receiving a placebo at 1 week.

this study, combined with that from our previous study performed on the same farm, demonstrate that the majority of foals with pulmonary abscesses (abscess score <10 cm) recover without antimicrobial treatment and that treatment of affected foals does not provide a clear benefit over the administration of a placebo. The proportion of foals with abscess scores >10 cm that would recover spontaneously is unknown because these foals were excluded from participation to this study. Additional studies will be required to establish better criteria to determine the need for treatment in subclinically affected foals. 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, geographic region, and age at which ultrasonographic lesions are detected.

Recent evidence suggests that macrolide and rifampin resistance among *R. equi* isolates might be increasing.[4] In addition, emergence of widespread resistance to macrolides and rifampin has been documented on a farm where mass antimicrobial treatment with macrolides and rifampin was instituted after establishing an ultrasonographic screening program.[15] The best method to prevent or minimize the development of antimicrobial resistance is to limit the use of antimicrobial agents to individuals that clearly benefit from treatment.

The development of hemolytic anemia or increased liver enzyme activities in 4 foals treated with the combination of doxycycline and rifampin was unexpected because adverse effects were not detected in foals receiving doxycycline monotherapy and in foals receiving rifampin in combination with azithromycin. Despite the lack of data regarding efficacy, the combination of doxycycline and rifampin has been used in many foals with pneumonia caused by *R. equi* without apparent adverse effect. The combination of doxycycline and rifampin is used to treat brucellosis in humans with no similar adverse reactions reported.[16] Ultimately, it is unknown whether the hemolytic icterus and increased liver enzyme activity observed in this study was related to treatment or because of another disease process. Although not observed in this study, hyperthermia and diarrhea are common adverse effects of treatment with a macrolide and rifampin.[17] Thus, in addition to the cost and risk for selection for resistant bacteria, unnecessary mass antimicrobial treatment of foals with pulmonary lesions might lead to development of life-threatening adverse reactions in some foals.

In conclusion, this study has shown that the majority of foals with pulmonary abscesses recover without antimicrobial treatment and that treatment of affected foals does not provide a clear benefit over the administration of a placebo and might result in problems of antibiotic resistance in *R. equi*. Mass antimicrobial treatment of all foals with subclinical pulmonary abscesses (score of 5–10 cm) is unnecessary.

Footnotes

[a] Esaote Tringa Linear, Milano, Italy

Acknowledgment

Conflict of Interest: Authors disclose no conflict of interest.

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