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# Efficacy of treatment and survival rate of foals with pneumonia: Retrospective comparison of rifampin/azithromycin and rifampin/tulathromycin

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**Summary:** Rhodococcus equi (R. equi), a Gram-positive facultative intracellular pathogen is one of the most common causes of pneumonia in foals. The retrospective study compares the efficacy of rifampin/azithromycin versus rifampin/tulathromycin for the treatment of R. equi pneumonia in foals. Weekly medical data of foals born in the seasons 2012 to 2016 (i.e. five foaling seasons) that developed pneumonia were collected and analysed. Foals 21 days of age or older with a pulmonary consolidation of more than 1 cm (abscess score ≥ 1 cm) were enrolled for participation in the study. All foals meeting the criteria for inclusion were listed in a spreadsheet and 330 foals affected with pneumonia each year were randomly selected by an online research randomizer. Foals with incorrect or missing data and those that were included in previous treatment studies were excluded from the analysis, resulting in a total enrolment of 1544 foals with pneumonia. The farm established a screening program in 2003 in order to detect foals in the early course of pneumonia, so all foals were examined once weekly starting at the age of two weeks until four and a half months of age. A physical examination of the respiratory tract, body temperature, haematology and an ultrasonographic examination of the lungs were included. Sonography areas with visible consolidation were measured and added to calculate an "abscess score" which represents the extent of pulmonary damage. Weekly medical data were analysed retrospectively. The risk of therapy failure, which means either death or worsening of pneumonia requiring that the foal be switched to another therapy, showed in a univariate comparison of the two treatments, that there was a higher incidence of treatment failure in foals treated with RIF/AZM (32/353, 9.1 %) than in foals that were treated with RIF/TUL (19/406, 4.7 %; Pearson's $\chi^2$, $P = 0.016$). In a Kaplan-Meier analysis, there was also a significant difference between the two treatments with respect to their survival functions (Log-rank test, $P = 0.045$; Figure 1). The incidence of mortality due to R. equi pneumonia was higher in foals that were treated with RIF/AZM (8/353, 2.3 %) than in those that were treated with RIF/TUL (0/406, 0.0 %; Fisher's exact test, $P = 0.002$). After adjusting for year, age of foals at the beginning of treatment, and abscess score at the beginning of treatment, the risk of treatment failure was not significantly lower for foals that were treated with RIF/TUL compared to those that were treated with RIF/AZM [Hazard Ratio (95 % CI) = 0.75 (0.38, 1.5)]. Age of foals was negatively associated with treatment failure, with the risk of failure decreasing by 30 % for every one-month increase in age at the beginning of treatment [HR (95 % CI) = 0.70 (0.54, 0.91)]. Abscess score was positively associated with treatment failure, with the risk of failure increasing by 4 % for every one cm increase in score [HR (95 % CI) = 1.04 (1.01, 1.07)]. Year was also associated with the risk of treatment failure but it did not meet the proportional hazards assumption, so the model was adjusted for the effects of year by stratification. In conclusion Rifampin/tulathromycin is an effective therapy against mild to moderate R. equi pneumonia in foals as this treatment has similar survival rates compared to rifampin/azithromycin. In terms of costs and dosage form, the combination of tulathromycin with rifampin is an adequate therapeutic option for the treatment of foals with R. equi pneumonia.

**Keywords:** antibiotics, foal, pneumonia, Rhodococcus equi

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## Introduction

Rhodococcus equi (R. equi), a Gram-positive facultative intracellular pathogen is one of the most common causes of pneumonia in foals, in particular those between one and six months of age. Although R. equi can be cultured from the environment of many stables, the clinical disease in foals is endemic at some farms, sporadic at others, and unrecognized at many (*Cohen* 2014). On farms where the disease is endemic, costs associated with morbidity and mortality attributable to R. equi may be very high. The treatment of abscessing pneumonia in foals is challenging due to the emergence of resistant strains of the bacterium against standard antimicrobial drugs and the lack of alternatives for efficient treatment or preven-

tion (e.g. vaccination) (*Peters* et al. 2011, *Berlin* et al. 2016). Foals acquire R. equi infection by inhalation of dust and soil particles carrying virulent bacteria (*Vázquez-Boland* 2010). Compared to extracellular pathogens as Streptococcus equi subsp. zooepidemicus (S. zooepidemicus), the survival strategy of R. equi is based on the intracellular survival and reproduction especially within alveolar macrophages after phagocytosis (*Giguère* et al. 2012, *Muscatello* 2012, *Giguère* et al. 2015). Macrolide antibiotics are a major part of the standard therapy (*Muscatello* 2012), as they widely distribute into pulmonary compartments (*Gaynor* and *Mankin* 2003). In foals, macrolides show unique pharmacokinetic features such as rapid and extensive distribution and long persistence in pulmonary epithelial lining fluid (PELF) and in bronchoalveolar cells (*Villarino* et al. 2013). For all the macrolides, the rate of elimination is slow, and drugs tend to persist for a long period of time in bronchoalveolar cells when compared with PELF and plasma (*Villarino* et al. 2013).

The combination of macrolides with rifampin achieves a synergism in efficacy against R. equi in vitro as well as in vivo (*Prescott* and *Nicholson* 1984, *Nordmann* and *Ronco* 1992, *Giguère* et al. 2012). In addition, the use of the two classes of drugs in combination reduces the likelihood of development of resistance to either drug (*Prescott* and *Nicholson* 1984, *Nordmann* and *Ronco* 1992, *Berghaus* et al. 2013). It is known that the development of antimicrobial resistance to rifampin is relatively rapid when used in monotherapy treatment regimens (*Giguère* et al. 2010). This is particularly important given the fact that the prevalence of macrolide resistance among R. equi isolates is increasing (*Giguère* et al. 2010). Some studies describe the emergence of widespread macrolide and rifampin resistance at a farm as a consequence of wide-spread use of these drugs in subclinically affected animals (*Hoffman* et al 1993, *Burton* et al. 2013). The best method to prevent or minimize the development of antimicrobial resistance is to limit the use of antimicrobial agents to only those individuals that require treatment. (*Weese* et al. 2015)

The combination of erythromycin and rifampin (RIF) has become the standard treatment of foals with R. equi pneumonia in the 1980s and has dramatically reduced foal mortality since its introduction (*Hillidge* 1987, *Sweeney* et al. 1987). In recent years, clarithromycin or azithromycin (AZM), both newer generation macrolides, have replaced erythromycin in the combination with rifampin (*Giguère* et al. 2004). Compared to erythromycin, AZM has an increased stability at an acid pH, a longer half-life, and the ability to achieve high tissue concentrations by direct uptake and delivery via phagocytes (*Lode* et al. 1996). Clinical microbiology studies have shown that AZM has a broad spectrum of action against gram-positive and gram-negative aerobes and anaerobes because of its ability to inhibit protein synthesis at the 50s ribosome level (*Davis* et al. 2002). It is a good option in combination with macrolide antibiotics, as it acts synergistically with RIF (*Prescott* and *Sweeney* 1985, *Weinstock* and *Brown* 2002, *Giguère* et al. 2012). The dosage of RIF is given in a wide range in the text books: from 5–10 mg/kg once or twice daily (*Dowling* 2004, *Knottenbelt* and *Malalana* 2015, *Davis* 2018). A recent pharmacokinetic study has shown that a RIF dosage of 10 mg/kg per os once per day achieves concentrations above the minimum inhibitory concentration required to inhibit the growth of 90% of all organisms (MIC90) for R. equi in the pulmonary compartments (Epithelial Lining fluid (ELF), Bronchoalveolar Lavage Cells (BALC)) (*Berlin* et al. 2017). The antimicrobial effect of rifampin against R. equi acts bacteriostatic, time-dependent and is additionally characterized by a long post-antibiotic effect (*Giguère* et al. 2012).

Tulathromycin (TUL), a novel long-acting macrolide antibiotic of the triamilide group was introduced for treatment of bacterial respiratory infections of cattle and swine in 2004 (*Benchaoui* et al. 2004, *Traeder* and *Grothues* 2004). A single injection provides seven days of therapeutic concentrations in lung tissues of these species. After intramuscular administration, TUL is rapidly and nearly completely absorbed from the injection site. It is widely distributed and accumulates in lung tissue, but the plasma concentrations and the lung tissue concentrations are far below the MIC for R. equi, which brings into question the value of TUL as an alternative to treat pneumonia caused by R. equi in foals (*Villarino* et al. 2013). But as shown by in vitro studies, TUL accumulates also in leukocytes and macrophages to concentrations several times above the serum levels. Its elimination is extremely slow with half-lives of 4–6 days (*Benchaoui* et al. 2004, *Gáler* et al. 2004, *Nowakowski* et al. 2004). Results of a recent study reconfirmed that TUL is as effective as standard treatment with RIF/AZM (*Rutenberg* et al. 2017). The only observed side effect in a recent study were 12 minor (< 5 cm) swellings developed at the injection site after a total of 279 injections of TUL (*Venner* et al. 2007). So it is recommended to change injection side. Further advantages of TUL are the lower price, the small injection volume and the convenient frequency of administration (only a single injection per week).

The objectives of the present study are to evaluate the comparative efficacy and survival rate of foals with pneumonia and treated with RIF/AZM versus RIF/TUL.

## Materials and methods

*Study population*

The study was a retrospective analysis of data from a German breeding farm during 2012 to 2016. The farm has a history of endemic foal pneumonia attributable to R. equi. This pathogen was isolated from tracheobronchial aspirates of 39% (17/44) to 54% (118/217) of foals with ultrasonographic evidence of pneumonia in multiple studies performed at the farm (*Venner* et al. 2007a, *Venner* et al. 2007b, *Kilian* 2008, *Lämmer 2010*, *Hagist* 2016). 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 (*Weimar* 2006).

*Study design and criteria for inclusion in the treatment study*

Foals 21 days of age or older with an abscess score ≥ 1 cm (definition explained below) were enrolled for participation in the study. All foals born in the seasons 2012 to 2016 (i.e. five foaling seasons) meeting criteria for inclusion were listed in a spreadsheet, and 330 foals affected with pneumonia each year were randomly selected by an online research random-

izer[1]. Foals with incorrect or missing data and those that were included in previous treatment studies were excluded from the analysis, resulting in a total enrolment of 1544 foals with pneumonia.

From the age of two weeks to weaning, each foal was subjected to a physical examination and a white blood cell (WBC) count weekly. Findings of physical examination were recorded, given a score, and added to a clinical score adapted for foals with respiratory disorders (*Venner* et al. 2009). The clinical score is based on respiratory rate, tachypnoea, presence and type of nasal discharge (none, serous, mucus, purulent), mandibular lymph nodes (normal or enlarged), dyspnoea (absent or present) and auscultation of the lungs and trachea (normal versus abnormal) as described previously (*McCracken* and Slovis 2009, *Venner* et al. 2009).

Foals older than three weeks with signs of respiratory disease (cough, nasal discharge, abnormal lung sounds, dyspnoea, temperature > 39.5 °C) or with a WBC count > 13 G/L were subjected to thoracic ultrasonography using a portable unit[2] with a 7.5 MHz linear transducer. Pulmonary abscesses were defined as focal hypoechoic areas of consolidation of the lung tissue with a diameter larger than 1.0 cm. Furthermore, the number of pulmonary abscesses noted during an examination was documented in a lung sheet. The diameters of all consolidations detected in a foal were added to a so-called "abscess score" indicated in cm, which represented the extent of pulmonary damage. For lesions that appeared asymmetrical, the diameter was measured using the average of the largest and smallest diameter. Thoracic ultrasound examination was performed on each foal with clinical signs of respiratory disease once weekly. Furthermore, foals, with pulmonary lesions smaller than the treatment protocol requirements, were evaluated sonographically twice weekly, and closely monitored but not treated with antibiotics. Additionally, all treated foals were monitored daily for adverse reactions, such as diarrhoea, lameness, colic, or swelling at the injection site, if injections were given. A treatment duration of six weeks was set for all foals, for which treatment was deemed necessary. All foals with worsening pneumonia during the assigned treatment, either RIF/AZM or RIF/TUL, were switched to the opposite therapy. All treatments were given by different individuals not involved in monitoring and without influence on treatment assignment.

The recorded variables are summarized in Table 1.

*Data analysis*

Data were screened for aberrant values using range and logic checks. Foals with data errors that could not be corrected were excluded from the analysis. The distributions of continuous variables were graphically assessed using histograms and normal probability plots. Univariate comparisons of categorical variables were performed using Pearson's $\chi^2$ test, or Fisher's exact test if expected counts were less than five. The Mann-Whitney test was used to compare treatment groups with respect to continuous variables, and the Kaplan-Meier method with the log rank test was used for univariate comparisons of survival functions.

**Table 1** Descriptive evaluation criteria for a random subset of foals (n = 1,544) diagnosed with pneumonia between 2012 and 2016 on a single German breeding farm. | *Deskriptive Auswertungskriterien der randomisiert ausgewählten Fohlen (n = 1544) mit diagnostizierter Pneumonie zwischen 2012 und 2016 auf einem deutschen Gestüt.*

| Recorded variables | |
|---|---|
| General data | Sex<br>Date of birth |
| Health history | IgG level post colostrum |
| | Plasma transfusion and amount |
| | Died of R. equi infection (yes/no) |
| | If death from R. equi: pneumonia or extrapulmonary |
| | Cause of death (if not R. equi) |
| Clinical parameter | Highest recorded clinical score + date + age |
| | Signs of pneumonia (yes/no) |
| | Which signs (cough, tachypnoea, fever > 39.5 °C, nasal discharge) |
| | Dyspnoea (yes/no) + signs of dyspnoea, tachypnoea |
| | Clinical score onset of therapy |
| | Clinical score during first/second recurrence |
| Laboratory parameter | Transtracheal wash culture results |
| | Highest recorded WBC count + date + age |
| | WBC count onset of therapy |
| | WBC first/second recurrence |
| Ultrasound parameters | Initial ultrasound rationale |
| | Highest abscess score + date + age |
| | Highest number of abscesses |
| | Abscess score at the beginning of therapy |
| | Number of abscesses at the beginning of therapy |
| | Follow-up ultrasound rationale (e.g. WBC, weekly check-up,) clinic) + date |
| | Abscess score during the recurrence + number of abscesses |
| | Duration of abscesses and no treatment |
| Treatment data | Treated for pneumonia (yes/no) |
| | Treatment rationale (e.g. ultrasound score, clinic, WBC) |
| | Date of first lesion + age |
| | Date of initiation of therapy + age |
| | First drug (s) used |
| | Duration of first therapy (days) |
| | Switch (yes/no) – different drugs needed |
| | Second drug (s) used |
| | a.) Date second therapy stopped |
| | b.) Duration of second therapy |
| | Third drug (a+b) |
| | Fourth drug (a+b) |
| | Total duration of therapy |

Multivariable survival analyses were performed using the Cox proportional hazards model. Variables considered for inclusion in the multivariable analyses were year, sex, age, abscess score, clinical score, and WBC count. A manual backward elimination procedure was used for model selection, beginning with a maximum model that contained main effects for all variables that had $P < 0.20$ in the univariate analysis. Non significant predictors were eliminated from the maximum model in a stepwise manner until only variables having $P < 0.05$ remained. Treatment was included as a predictor in all models regardless of its significance, and all two-way interactions with the treatment variable were evaluated. If the removal of any variable resulted in greater than a 10% change to the estimated hazard ratio for treatment, that variable was considered an important confounder, and it was retained in the final model. Continuous variables were assessed as both continuous and categorical predictors, with Akaike's information criterion being used to determine which form of the predictor provided the best fit. The proportional hazards assumption was assessed by evaluating the slope of the scaled Schoenfeld residuals, and by evaluating the significance of an interaction between each of the covariates and a function of time. Variables that failed to meet the proportional hazards assumption were included in the analysis by allowing them to interact with a function of time in an extended Cox model, or they were included in the analysis as a stratification variable. Data were further screened for outliers and influential observations using index plots of the deviance residuals and delta-beta values.

All statistical tests assumed a two-sided alternative hypothesis, and values of $P < 0.05$ were considered significant. Analyses were performed using commercially available statistical software (Stata version 15.1, StataCorp LLC, College Station, TX).

## Results

Records of 1,544 foals were included in the study, with the number of foals for each of the five years ranging between 297 and 319. Seven hundred sixty-one (49.3%) foals were fillies, and 783 (50.7%) were colts. Seven hundred eighty-six (50.9%) of the foals were treated for R. equi pneumonia. Of the foals that were treated, 353 (44.9%) received rifampin and azithromycin (RIF/AZM) as their first treatment, 406 (51.7%) received rifampin and tulathromycin (RIF/TUL), and 27 (3.4%) received a different drug treatment combination. The proportions of foals receiving RIF/AZM or RIF/TUL varied by year ($P < 0.001$) but not by sex ($P = 0.52$; Table 2). At the beginning of treatment, foals receiving RIF/AZM did not differ from foals receiving RIF/TUL with respect to age ($P = 0.32$), clinical score ($P = 0.31$), or WBC count ($P = 0.20$), but foals receiving RIF/AZM did have a higher median abscess score ($P < 0.001$; Table 3).

Treatment failure was defined as a worsening clinical condition that required switching to a different drug treatment protocol, or death due to R. equi pneumonia. In a univariate comparison of the two treatments, there was a higher incidence of treatment failure in foals treated with RIF/AZM (32/353, 9.1%) than in foals treated with RIF/TUL (19/406, 4.7%; Pearson's $\chi^2$, $P = 0.016$). In a Kaplan-Meier analysis, there was also a significant difference between the two treatments with respect to their survival functions (Log-rank test, $P = 0.045$; Figure 1). The incidence of mortality due to R. equi pneumonia was higher in foals treated with RIF/AZM (8/353, 2.3%) than in those treated with RIF/TUL (0/406, 0.0%; Fisher's exact test, $P = 0.002$).

Results of a multivariable Cox regression analysis for treatment failure are summarized in Table 4. After adjusting for year, age of foals at the beginning of treatment, and abscess score at the beginning of treatment, the risk of treatment failure was not significantly lower for foals treated with RIF/TUL compared to those treated with RIF/AZM [Hazard Ratio (95%

**Table 2** Number (%) of foals treated with rifampin and azithromycin (RIF/AZM) or rifampin and tulathromycin (RIF/TUL) by year and sex. | *Anzahl (%) der Fohlen behandelt mit Rifampin und Azithromycin (RIF/AZM) beziehungsweise Rifampin und Tulathromycin (RIF/TUL) sortiert nach Jahr und Geschlecht.*

| | RIF/AZM (n = 353) | RIF/TUL (n = 406) | †P |
|---|---|---|---|
| Year | | | < 0.001 |
| 2012 | 33 (18.2) | 148 (81.8) | |
| 2013 | 138 (63.9) | 78 (36.1) | |
| 2014 | 36 (30.5) | 82 (69.5) | |
| 2015 | 98 (56.3) | 76 (43.7) | |
| 2016 | 48 (68.6) | 22 (31.4) | |
| Sex | | | 0.519 |
| Female | 163 (47.8) | 178 (52.2) | |
| Male | 190 (45.5) | 228 (54.5) | |

†P-value for Pearson's $\chi 2$ test

**Table 3** Clinical characteristics of foals treated with rifampin and azithromycin (RIF/AZM) or rifampin and tulathromycin (RIF/TUL) at the beginning of treatment. | *Klinische Parameter der Fohlen behandelt mit Rifampin und Azithromycin (RIF/AZM) beziehungsweise Rifampin und Tulathromycin (RIF/TUL) zu Beginn der Behandlung.*

| | RIF/AZM (n = 353) | RIF/TUL (n = 406) | †P |
|---|---|---|---|
| Age (days) | | | 0.320 |
| Mean (SD) | 106 (38) | 105 (30) | |
| Median (Min, Max) | 109 (26, 231) | 106 (33, 205) | |
| Abscess score (cm) | | | < 0.001 |
| Mean (SD) | 15.8 (9.8) | 11.7 (4.4) | |
| Median (Min, Max) | 13.5 (0, 64) | 11.0 (0, 30) | |
| Clinical score | | | 0.313 |
| Mean (SD) | 2.2 (1.1) | 2.1 (1.1) | |
| Median (Min, Max) | 2 (0, 6) | 2 (0, 6) | |
| WBC count × $10^3$ (cells/μL) | | | 0.198 |
| Mean (SD) | 15.0 (4.7) | 15.0 (4.4) | |
| Median (Min, Max) | 14.3 (4.2, 34.7) | 14.8 (3.8, 23.4) | |

†P-value for the Mann-Whitney test

CI) = 0.75 (0.38, 1.5)]. Age of foals was negatively associated with treatment failure, with the risk of failure decreasing by 30% for every one-month increase in age at the beginning of treatment [HR (95% CI) = 0.70 (0.54, 0.91)]. Abscess score was positively associated with treatment failure, with the risk of failure increasing by 4% for every one cm increase in score [HR (95% CI) = 1.04 (1.01, 1.07)]. Year was also associated with the risk of treatment failure but it did not meet the proportional hazards assumption, so the model was adjusted for the effects of year by stratification.

If foals required a second round of treatment for pneumonia after the end of the initial treatment period, they were considered to have had a recurrence. In a univariate comparison of the two treatments, there was a higher incidence of recurrence in foals treated with RIF/AZM (59/349, 16.9%) than in foals that were treated with RIF/TUL (28/399, 7.0%; Pearson's $\chi^2$, $P < 0.001$). In a Kaplan-Meier analysis, there was also a significant difference between the two treatments with respect to their survival functions (Log rank test, $P < 0.001$; Figure 2).

Results of a multivariable Cox regression analysis for recurrence of pneumonia are summarized in Table 5. After adjusting for year and age of the foals at the end of their initial treatment period, the risk of recurrence was 54% lower in foals treated with RIF/TUL compared to foals that were treated with RIF/AZM [HR (95% CI) = 0.46 (0.28, 0.76)]. Age of foals was negatively associated with recurrence, with the risk of recurrence decreasing by 65% for every one-month increase in age. The proportional hazards assumption was not met for year, so, the model was adjusted for the effects of year by stratification.

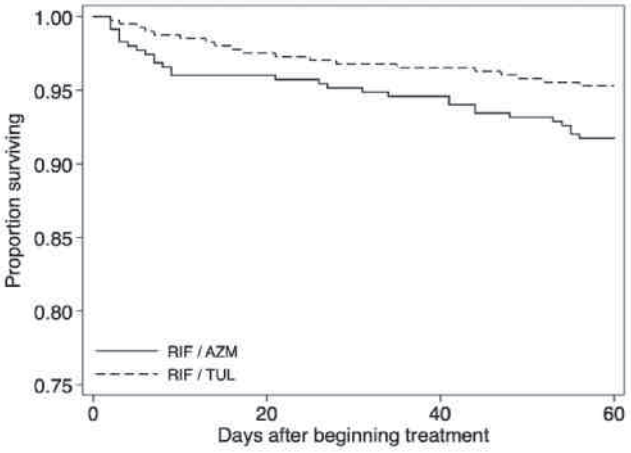


**Fig. 1** Kaplan-Meier graph illustrating time from the beginning of treatment until treatment failure in foals treated with rifampin and azithromycin (RIF/AZM) or rifampin and tulathromycin (RIF/TUL). Treatment failure was defined as a worsening clinical condition that required switching to a different drug treatment protocol, or death due to R. equi pneumonia. (X: Days after treatment onset, Y: Survival rate) | *Kaplan-Meier-Kurve zur Veranschaulichung der Zeit von Therapiebeginn bis Therapieversagen bei Fohlen behandelt mit Rifampin und Azithromycin (RIF/AZM) beziehungsweise Rifampin und Tulathromycin (RIF/TUL). Therapieversagen wurde definiert als Verschlechterung des klinischen Zustandes, der Therapieumstellung auf ein anderes Behandlungsprotokoll erforderte, oder den Tod durch R. equi Pneumonie. (X: Tage nach Behandlungsbeginn, Y: Überlebensrate)*

## Discussion

As results of previous studies have shown, RIF alone is insufficient as an R. equi therapy thus it should not be used alone due to emerging resistant strains (*Prescott* and *Nicholson* 1984, *Nordmann* and *Ronco* 1992, *Giguère* et al. 2010, *Berghaus* et al. 2013). The combination of RIF with a macrolide antibiotic has proved to be very effective in in vitro studies as well as in foals with natural infection with R. equi (*Sweeney* 1987, *Giguère* et al 2012. *Hildebrandt* 2015, *Rutenberg* 2017). The efficacy of several macrolides has been evaluated in the treat-

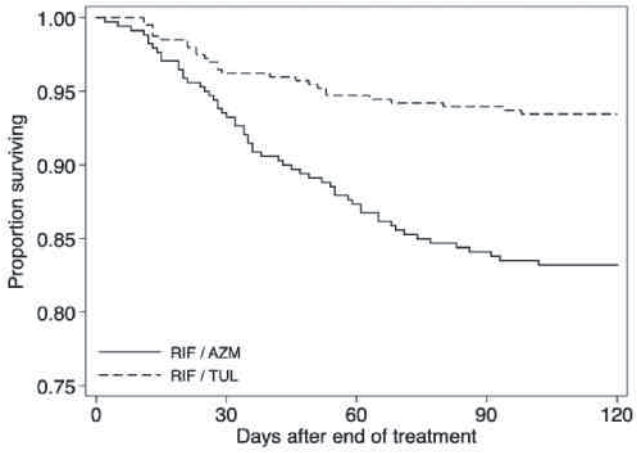


**Fig. 2** Kaplan-Meier graph illustrating time from the end of the initial treatment period until pneumonia recurrence in foals treated with rifampin and azithromycin (RIF/AZM) or rifampin and tulathromycin (RIF/TUL). (X: Days after treatment onset, Y: Survival rate) | *Kaplan-Meier-Kurve zur Veranschaulichung der Zeit vom Ende der initialen Behandlungsperiode bis zu einem Rückfall der mit Rifampin und Azithromycin (RIF/AZM) beziehungsweise Rifampin und Tulathromycin (RIF/TUL) behandelten Fohlen. (X: Tage nach Behandlungsbeginn, Y: Überlebensrate)*

**Table 4** Summary of a stratified* multivariable Cox regression model for time from the beginning of treatment until treatment failure in foals (n = 754) treated with rifampin and azithromycin (RIF/AZM) or rifampin and tulathromycin (RIF/TUL). Treatment failure was defined as a worsening clinical condition that required switching to a different drug treatment protocol, or death due to R. equi pneumonia. | *Zusammenfassung der stratifizierten* multivariablen Cox-Regression der Zeit von Therapiebeginn bis zum Therapieversagen der Fohlen (n = 754) behandelt mit Rifampin und Azithromycin (RIF/AZM) beziehungsweise Rifampin und Tulathromycin (RIF/TUL). Therapieversagen wurde definiert als Verschlechterung des klinischen Zustandes, der Therapieumstellung auf ein anderes Behandlungsprotokoll erforderte oder den Tod durch R. equi Pneumonie.*

| Variable | Coefficient (SE) | Hazard Ratio (95% CI) | †P |
|---|---|---|---|
| Treatment | | | 0.401 |
| RIF/AZM | Reference | Reference | |
| RIF/TUL | –0.287 (0.343) | 0.75 (0.38, 1.5) | |
| Age (months) at beginning of treatment | –0.355 (0.135) | 0.70 (0.54, 0.91) | 0.009 |
| Abscess score (cm) at beginning of treatment | 0.040 (0.015) | 1.04 (1.01, 1.07) | 0.007 |

*Stratified by year, †Wald P-value

**Table 5** Summary of a stratified* multivariable Cox regression model for time from the end of the initial treatment period until pneumonia recurrence in foals (n = 737) treated with rifampin and azithromycin (RIF/AZM) or rifampin and tulathromycin (RIF/TUL). | *Zusammenfassung der stratifizierten* multivariablen Cox-Regression der Zeit vom Ende der initialen Behandlungsperiode bis zu einem Rückfall der mit Rifampin und Azithromycin (RIF/AZM) beziehungsweise Rifampin und Tulathromycin (RIF/TUL) behandelten Fohlen (n = 737).*

| Variable | Coefficient (SE) | Hazard Ratio (95% CI) | †*P* |
|---|---|---|---|
| Treatment | | | 0.002 |
| RIF/AZM | Reference | Reference | |
| RIF/TUL | –0.784 (0.257) | 0.46 (0.28, 0.76) | |
| Age (months) at end of initial treatment period | –1.057 (0.106) | 0.35 (0.28, 0.43) | < 0.001 |

*Stratified by year, †Wald *P*-value

ment of R. equi pneumonia in foals in recent years. RIF/TUL appears to be an appropriate therapy of foals with R. equi pneumonia due to several reasons. From the antibiotics used in this study, TUL is the only drug licensed for veterinary use. In terms of the drug cascade, it should be the first choice of the veterinarian before using drugs only licensed for human medicine. Additionally, the therapy interval with injections every seven days is simple to manage, and is well tolerated by the foals (*Venner* et al. 2007). Minor side effects observed are rare and most of the time self-limiting. Furthermore TUL itself is less expensive than azithromycin and, because it is given parenterally, it is less likely to contaminate the environment than orally administered AZM. The data analyzed here shows that the number of foals treated with RIF/TUL was higher during some years compared to other periods, as seen in Table 3. This is due to the fact that the treatment protocols changed over the years due to results of several treatment studies or individual veterinary decisions. That makes it difficult to directly compare the efficacy of RIF/TUL and RIF/AZM even if statistical adjustments for abscess score, clinical score and age were made in the present study.

Nevertheless, the present analysis of a large data set suggests that for the treatment of mild to moderate R. equi pneumonia, the combination of RIF/TUL seems adequate and leaves the veterinarian with the powerful combination of RIF/AZM in reserve in the rare cases when the pneumonia worsens. Finally, the option of treating foals with different severity levels of pneumonia with an alternative antibiotic combination has a benefit for the foal and the owner.

In conclusion, rifampin/tulathromycin is an effective treatment for foals with mild to moderate pneumonia.

## Footnotes

[1] https://www.randomizer.org
[2] Esaote Tringa Linear, Milano Italy.

## Conflict of interest

The authors declare that there is no conflict of interest.

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