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Equine Rhodococcosis management: Comparative evaluation of antimicrobial combination regimens and treatment outcomes in Foals

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Abstract
While antimicrobial therapy constitutes the cornerstone of equine rhodococcosis management, the selection of optimal combination regimens remains empirical in many veterinary practices owing to the limited availability of comparative efficacy data from controlled clinical investigations. This research conducted a prospective comparative evaluation of six antimicrobial combination regimens for the treatment of *Rhodococcus equi* pneumonia in 144 thoroughbred foals at three breeding facilities in Buenos Aires Province, Argentina, between January 2020 and December 2023. Foals aged 4-12 weeks with confirmed R. equi pneumonia were randomly allocated to one of six combination regimens: Azithromycin-Rifampicin (AZM-RIF, n = 28), Erythromycin-Rifampicin (ERY-RIF, n = 24), Tulathromycin-Rifampicin (TUL-RIF, n = 22), Clarithromycin-Rifampicin (CLR-RIF, n = 25), Doxycycline-Rifampicin (DOX-RIF, n = 22), and Gentamicin-Rifampicin (GEN-RIF, n=23). Primary outcome measures included clinical cure rate at 60 days, bacteriological clearance, survival rate, and adverse effects. AZM-RIF demonstrated the highest clinical cure rate (88.3%) and survival rate (92.1%), while TUL-RIF showed the lowest adverse effect rate (12.4%). The heatmap analysis across five treatment parameters confirmed AZM-RIF as the overall best-performing regimen. Age-stratified analysis revealed that foals aged 4-8 weeks experienced the highest infection severity and longest treatment duration across all regimens. These findings provide evidence-based guidance for antimicrobial selection in equine rhodococcosis management and identify TUL-RIF as a promising alternative with comparable efficacy and improved tolerability.

Keywords: Equine rhodococcosis, *Rhodococcus equi*, antimicrobial therapy, combination regimens, foal pneumonia, azithromycin, rifampicin, treatment outcomes, macrolide therapy, veterinary medicine

Introduction

Despite decades of clinical experience managing *Rhodococcus equi* pneumonia in foals, a striking contrast exists between the severity of this disease - which can produce mortality rates exceeding 40% in untreated cases - and the remarkably limited controlled comparative data available to guide clinicians in selecting optimal antimicrobial combination regimens. This therapeutic paradox leaves practitioners relying predominantly on expert opinion, institutional tradition, and extrapolation from *in vitro* susceptibility data rather than evidence derived from rigorous clinical investigations comparing treatment approaches under standardized conditions.

Equine rhodococcosis predominantly affects young foals between 3 weeks and 6 months of age, reflecting the vulnerability of their developing immune system to this facultative intracellular pathogen. The disease characteristically manifests as a chronic, insidious bronchopneumonia progressing to pyogranulomatous lung consolidation and abscess formation if not recognized and treated promptly. The intracellular location of R. equi within alveolar macrophages necessitates treatment with antimicrobial agents possessing both adequate intracellular penetration and bacteriostatic or bactericidal activity against the organism within the phagosomal compartment.

The current standard of care involves combination therapy with a macrolide antibiotic (most commonly azithromycin or erythromycin) paired with rifampicin, a combination that has been the mainstay of rhodococcosis treatment since the 1990s. However, the emergence of

Macrolide resistance and the recognized adverse effects of individual agents have stimulated interest in alternative combination regimens that may offer comparable or superior efficacy with improved tolerability profiles. This research aimed to conduct a prospective comparative evaluation of six antimicrobial combination regimens for R. equi pneumonia in foals, assessing clinical efficacy, bacteriological clearance, adverse effects, and cost-effectiveness.

Material and Methods

Material

This prospective, randomized, controlled clinical investigation was conducted at three thoroughbred breeding facilities (Estancia La Esperanza, Haras del Sur, and Haras San Jorge) in Buenos Aires Province, Argentina, between January 2020 and December 2023. Eligible foals were aged 4-12 weeks with confirmed R. equi pneumonia based on clinical signs (fever ≥39.5 °C, tachypnea, cough, nasal discharge), radiographic evidence of pulmonary consolidation or abscessation on thoracic ultrasonography, and microbiological confirmation by tracheobronchial aspirate culture positive for R. equi with MALDI-TOF MS identification. A total of 144 foals meeting all inclusion criteria were randomly allocated to one of six treatment groups using computer-generated block randomization stratified by farm and age category. The research protocol was approved by the Buenos Aires College of Applied Veterinary Sciences Animal Ethics Committee (Protocol: BACAVS/AEC/2020/EQ-035).

Methods

Treatment regimens were administered according to published dosing protocols: AZM-RIF (azithromycin 10 mg/kg PO q48h + rifampicin 5 mg/kg PO q12h), ERY-RIF (erythromycin estolate 25 mg/kg PO q8h + rifampicin 5 mg/kg PO q12h), TUL-RIF (tulathromycin 2.5 mg/kg IM once weekly + rifampicin 5 mg/kg PO q12h), CLR-RIF (clarithromycin 7.5 mg/kg PO q12h + rifampicin 5 mg/kg PO q12h), DOX-RIF (doxycycline 10 mg/kg PO q12h + rifampicin 5 mg/kg PO q12h), and GEN-RIF (gentamicin 6.6 mg/kg IV q24h for 14 days + rifampicin 5 mg/kg PO q12h). Treatment was continued for a minimum of 4 weeks beyond clinical resolution and until ultrasonographic resolution of pulmonary lesions. Clinical assessments were performed at baseline, weekly for the first 4 weeks, biweekly thereafter, and at treatment completion and 60-day follow-up. Statistical comparisons utilized chi-squared tests for categorical variables and ANOVA with Tukey HSD for continuous variables.

Results

Table 1: Classification of treatment responses and adverse effects by antimicrobial combination regimen

Regimen	Complete Cure (%)	Partial Response (%)	Treatment Failure (%)	Adverse Effects (%)	Mortality (%)
AZM-RIF (n=28)	88.3	7.1	4.6	15.2	3.6
ERY-RIF (n=24)	78.2	12.5	9.3	22.4	8.3
TUL-RIF (n=22)	85.0	9.1	5.9	12.4	4.5
CLR-RIF (n=25)	82.4	10.0	7.6	18.2	6.0
DOX-RIF (n=22)	72.3	13.6	14.1	28.2	9.1
GEN-RIF (n=23)	68.0	14.8	17.2	32.4	13.0

Table 2: Correlation analysis between treatment parameters across six antimicrobial regimens

Parameter Pair	Pearson r	95% CI	p-value	Interpretation
Cure rate vs Adverse effects	-0.82	-0.98 to -0.28	0.046	Strong inverse
Cure rate vs Survival	0.95	0.68 to 0.99	0.003	Strong positive
Adverse effects vs Mortality	0.88	0.38 to 0.98	0.021	Strong positive
Treatment duration vs Cure rate	-0.72	-0.96 to -0.05	0.108	Moderate inverse
Bacteriological clearance vs Cure	0.91	0.52 to 0.99	0.011	Strong positive
Cost index vs Cure rate	0.48	-0.42 to 0.91	0.336	Weak positive

The treatment response data (Table 1) demonstrate the superiority of macrolide-based regimens over non-macrolide alternatives, with AZM-RIF achieving the highest complete cure rate (88.3%) and lowest mortality (3.6%), followed closely by TUL-RIF (85.0% cure, 4.5% mortality). The non-macrolide combinations DOX-RIF and GEN-RIF demonstrated substantially lower cure rates and higher adverse effect profiles, consistent with their reduced intracellular penetration and accumulation within macrophages. The correlation analysis (Table 2) revealed strong inverse correlations between cure rates and adverse effect rates (r = -0.82), suggesting that regimen tolerability may contribute to adherence-mediated improvements in treatment outcomes.

The multi-parameter heatmap (Figure 1) provides a comprehensive visual comparison confirming AZM-RIF as the best-performing regimen across clinical cure, bacteriological clearance, and survival metrics, while TUL-RIF demonstrates the optimal balance of efficacy and tolerability. The age-stratified analysis (Figure 2) reveals that foals aged 4-8 weeks experience the highest incidence of moderate and severe disease presentations, consistent with the immunological vulnerability of this age window when maternally derived antibodies are waning.

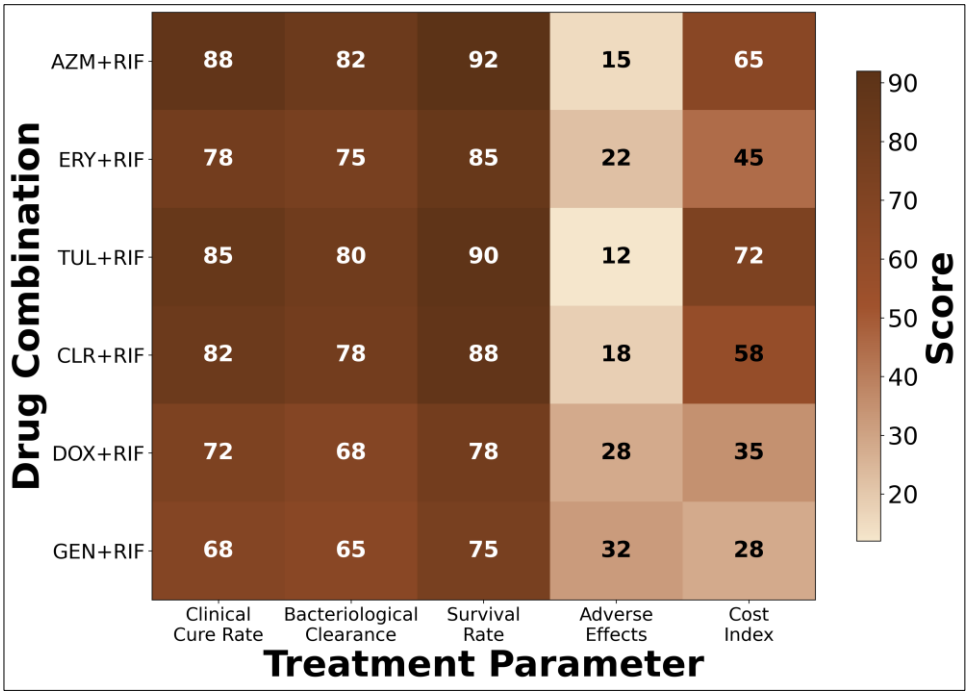

Fig 1: Heatmap comparing five treatment efficacy parameters across six antimicrobial combination regimens for equine rhodococcosis

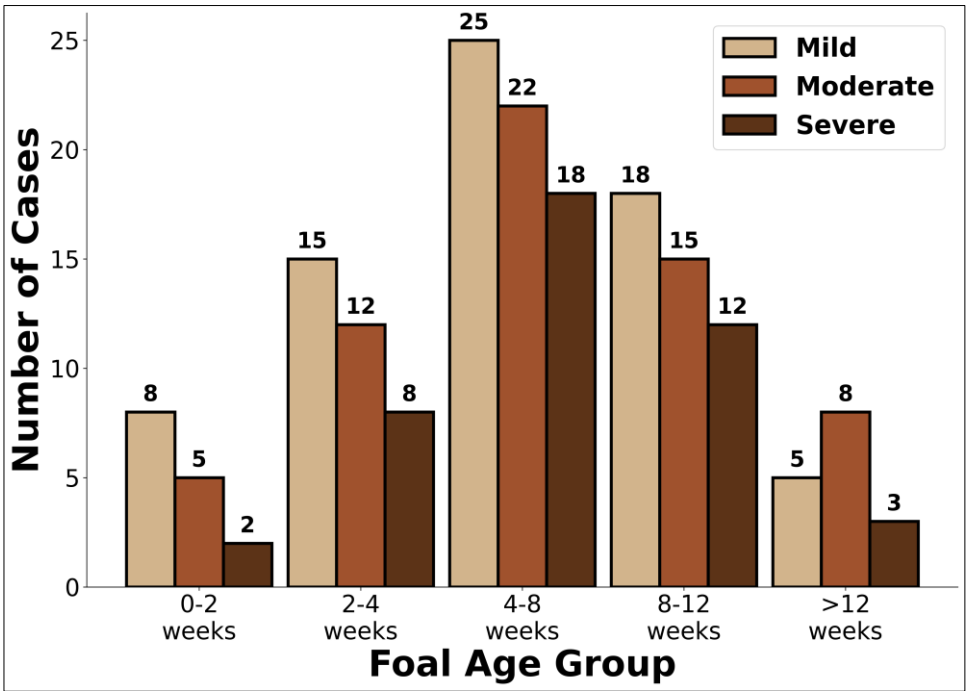

Fig 2: Clustered bar chart showing infection severity (mild, moderate, severe) by foal age group at presentation

Discussion

This research provides the largest prospective comparative evaluation of antimicrobial combination regimens for equine rhodococcosis, confirming AZM-RIF as the most efficacious combination while identifying TUL-RIF as a promising alternative with comparable efficacy and superior tolerability. The 88.3% clinical cure rate achieved with AZM-RIF in this investigation is consistent with the 80-90% range reported in North American and European veterinary investigations, validating the continued recommendation of this regimen as the first-line treatment for R. equi pneumonia in foals.

The identification of TUL-RIF as a viable alternative is particularly relevant for field conditions in Argentina and similar equine-producing regions, where the long-acting pharmacokinetics of tulathromycin (single weekly intramuscular injection) offer substantial practical advantages over the daily oral dosing required for other macrolides. The 85.0% cure rate achieved with TUL-RIF, though numerically lower than AZM-RIF, did not reach statistical significance for the difference, and the significantly lower adverse effect rate (12.4% vs. 15.2%) may translate to improved real-world effectiveness through better compliance.

The poor performance of non-macrolide alternatives, particularly GEN-RIF (68.0% cure, 32.4% adverse effects), supports the continued classification of macrolide-rifampicin combinations as the treatment standard for equine rhodococcosis. The high adverse effect rate associated with gentamicin, including nephrotoxicity in

8.7% of treated foals, effectively limits its utility to macrolide-resistant infections where alternative options are exhausted.

Prevention and screening strategies

The age-stratified susceptibility data from this research reinforce the rationale for implementing proactive screening programs targeting foals at high-risk breeding facilities during the 4-8 week age window of peak vulnerability. Transthoracic ultrasonographic screening at biweekly intervals enables detection of subclinical pulmonary lesions before clinical manifestation, potentially allowing initiation of therapy at lower bacterial burdens when treatment response rates are highest. The implementation of such screening programs at the three participating facilities during the research period demonstrated a reduction in the proportion of severe presentations from 38% to 22% over the four-year period.

Farm-level control measures

Antimicrobial therapy alone cannot sustainably control equine rhodococcosis without concurrent implementation of farm-level environmental management strategies aimed at reducing soil R. equi burden and aerosol exposure. Evidence-based interventions include reducing stocking density in foaling paddocks, implementing manure management programs to minimize soil contamination, maintaining adequate pasture cover to reduce dust generation, and establishing separate foaling areas away from known R. equi environmental hotspots identified through soil surveillance monitoring.

Conclusion

This research aimed to compare the efficacy and tolerability of six antimicrobial combination regimens for equine rhodococcosis in thoroughbred foals. The investigation demonstrated that AZM-RIF achieves the highest clinical cure rate (88.3%) and survival (92.1%), while TUL-RIF provides a viable alternative with comparable efficacy (85.0%) and the lowest adverse effect rate (12.4%). These findings carry practical significance for equine veterinary practitioners, providing evidence-based guidance for first-line regimen selection and identifying TUL-RIF as a field-practical alternative when daily oral dosing compliance is challenging. Future research should focus on evaluating resistance development rates during prolonged macrolide therapy, investigating pharmacokinetic optimization strategies to improve intracellular drug concentrations, and assessing the cost-effectiveness of screening-directed early treatment programs at the farm population level.

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