

Phenotypic Antimicrobial Resistance Dynamics Across Varying Clinical Severity Scores of Ovine Footrot Lesions

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Abstract: Antimicrobial resistance is an ancient phenomenon and an increasing global threat affecting animal, human, and environmental health. Its emergence is largely driven by the extensive use of antimicrobials in medicine and agriculture, while bacterial mutations, natural evolution, and horizontal gene transfer further promote the acquisition and spread of resistance genes. This study investigates the phenotypic antimicrobial resistance (AMR) dynamics of opportunistic Gram-negative (n=355) and Gram-positive (n=198) bacteria isolated from ovine footrot lesions, stratified across five clinical severity scores. For Gram-negative isolates, advanced Score 5 lesions exhibited alarming resistance rates to Ampicillin (89.2%) and Amoxicillin/Clavulanic acid (76.6%), while Imipenem maintained a static, high-resistance ceiling (76%-81%, $p = 0.442$) across the entire clinical spectrum. Among Gram-positive bacteria, Benzylpenicillin resistance reached an absolute saturation threshold of 100% in Score 5 lesions, a trajectory closely mirrored by Ceftiofur (92.6%) and Gentamicin (88.9%), signaling a highly prevalent methicillin-resistant phenotype. In contrast, Florfenicol (13%-24.2%) and Sulfamethoxazole (22.6%-33.3%) sustained the lowest and most favorable resistance boundaries, remaining statistically unaltered by clinical progression ($p \geq 0.05$).

Keywords: antimicrobial resistance; ovine footrot; clinical severity.

1. Introduction

The irrational use of antibiotics is a major contributor to the rise of antibiotic resistance and poses a global public health crisis. Measures are being implemented to promote the responsible use of these drugs, particularly in the agricultural sector [1]. The decreasing effectiveness of antimicrobials in treating infections has shown an upward trend in recent years; therefore, with the emergence of untreatable carbapenem-resistant *Enterobacteriaceae* strains, we can state that we are at the dawn of a post-antibiotic era [2]. Suboptimal drug doses promote the rapid selection of resistance, with mutations in microorganisms also contributing to this process, thereby providing mutant strains with a competitive advantage. In general, resistance genes are found on chromosomes, but increasingly they are also located on transmissible extrachromosomal elements. The resulting resistant clones—for example, methicillin-resistant *Staphylococcus aureus* (MRSA) USA300, *Escherichia coli* ST131, and *Klebsiella* spp. ST258—spread rapidly on a global scale [3]. Appropriate antibiotic use in sheep and goat farming is essential for effective herd health management and the maintenance of animal welfare standards [4]. Lameness is the most common welfare issue in many flocks and is typically caused by infectious foot diseases. These conditions are largely associated with bacterial infections, such as footrot, scald, and contagious ovine digital dermatitis, for which antibiotics have traditionally been the first-line treatment [5-7]. Antibiotic resistance in sheep and goats has a significant

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economic impact, reducing productivity by up to 15% due to the failure to effectively treat bacterial infections, which leads to increased morbidity and mortality [8]. Unfortunately, data on antibiotic resistance in sheep and goats in Romania are limited; therefore, this study aimed to provide an overview of the antibiotic resistance profile of bacteria isolated from sheep with podal diseases.

2. Materials and Methods

2.1. Sample collection

Swab samples were collected from 40 (n=40) sheep with clinical signs of footrot from three semi-intensive farms located in Transylvania. Clinical findings included lameness, erythema and inflammation of the interdigital skin, a characteristic foul odor of the affected hooves, and, in severe cases, separation of the hoof wall or sole from the underlying tissues. Following clinical examination, swab samples were collected from footrot lesions using sterile swabs with Amies transport medium (HiMedia Laboratories, Mumbai, India).

2.2. Bacterial isolation and identification

Each sample was initially inoculated into nutrient broth (Oxoid, Basingstoke, UK) and incubated aerobically at 37°C for 24 h. The cultures were subsequently streaked onto nutrient agar plates and incubated at 37°C for 24–48 h to obtain isolated colonies. Representative colonies were then subcultured onto Columbia agar supplemented with 10% sheep blood (BioMaxima S.A., Lublin, Poland) to obtain pure cultures.

Bacterial isolates were identified using the MALDI Biotyper® Sirius system (Bruker, Ettlingen, Germany), based on matrix-assisted laser desorption/ionization time-of-flight mass spectrometry (MALDI-TOF MS). Species identification was performed by comparing the acquired mass spectra with reference spectra included in the manufacturer's database, according to the manufacturer's instructions.

3.2. Antimicrobial Susceptibility Testing

Antimicrobial susceptibility testing was performed using the VITEK 2 system (bioMérieux, Marcy-l'Étoile, France). Pure colonies obtained after subculture were suspended in sterile saline, and the inoculum density was adjusted to a turbidity equivalent to a 0.5 McFarland standard.

The standardized inoculum was used to inoculate VITEK 2 AST cards for Gram-positive (GP79) and Gram-negative (GN96) bacteria, containing predefined concentrations of antimicrobial agents. The inoculated cards were loaded into the instrument, where incubation and continuous optical monitoring of bacterial growth were performed automatically.

Minimum inhibitory concentrations (MICs) were determined by the system software based on growth kinetics. The results were interpreted according to the European Committee on Antimicrobial Susceptibility Testing (EUCAST) guidelines [9], and isolates were classified as susceptible, intermediate, or resistant.

To evaluate the correlation between the clinical severity of footrot (expressed as ordinal scores from 1 to 5) and the phenotypic antimicrobial resistance rates, the Cochran-Armitage test for trend was performed. A p-value of less than 0.05 was considered statistically significant to confirm a linear trend across the clinical scores.

3. Results

3.1. Bacterial identification

A total of 553 (n=553) opportunistic bacterial isolates were recovered and identified from hoof samples collected from sheep presenting with different clinical stages of infectious pododermatitis. Gram-negative bacilli predominated, representing 64.20% (355/553) of all isolates, whereas Gram-positive bacteria accounted for 35.80% (198/553). The distribution of isolates was relatively consistent across the five clinical lesion scores, with 96 isolates recovered from Score 1 lesions, 109 from Score 2, 101 from Score 3, 121 from Score 4, and 126 from Score 5 lesions. Among the Gram-positive isolates (n=198), four major bacterial families were identified.

The family *Streptococcaceae*, represented by *Streptococcus* spp., was the most prevalent taxon in this group, accounting for 10.5% (n=58) of the total isolates. This was closely followed by the family *Enterococcaceae*, with *Enterococcus* spp. representing 9.0% (n=50) of the bacterioflora. Environmental and commensal stability was further represented by the family *Bacillaceae* (*Bacillus* spp., 8.5%, n=47) and the family *Staphylococcaceae* (*Staphylococcus* spp., 7.8%, n=43). Gram-positive bacteria demonstrated higher relative frequencies

during the initial stages of the disease, particularly in Score 1 (n=53) and Score 2 (n=54) lesions. The Gram-negative subpopulation (n=355) was heavily dominated by the family *Enterobacteriaceae*, which alone encompassed 44.8% (n=248) of all bacterial strains isolated in this study. Within this family, *Enterobacter cloacae* (*E. cloacae*) was the single most abundant opportunistic species identified overall, accounting for 13.2% (n=73) of the total bacterioflora. Other well-represented enterobacterial species included *Klebsiella pneumoniae* (*K. pneumoniae*; 11.4%, n=63), *Serratia* spp. (10.8%, n=60), and *Escherichia coli* (*E. coli*; 9.4%, n=52). Non-enterobacterial Gram-negative families were also identified as significant components of the secondary infection. The family *Pseudomonadaceae*, represented by *Pseudomonas* spp., accounted for 8.7% (n=48) of the total isolates, showing a marked proliferation in advanced necrotic tissues. Finally, the families *Aeromonadaceae* (*Aeromonas* spp., 6.5%, n=36) and *Moraxellaceae* (*Acinetobacter* spp., 4.2%, n=23) were recovered at lower frequencies. Notably, Gram-negative opportunistic bacilli exhibited a sharp, progressive increase in prevalence correlated with lesion severity, ultimately dominating the microflora in Score 4 (n=85) and Score 5 (n=101) clinical cases. The detailed distribution and percentage of each bacterial species across the five individual footrot lesion scores are summarized in Table 1.

Table 1. Prevalence and distribution of opportunistic bacterial isolates across footrot lesion scores in sheep

Bacterial Group / Opportunistic Species	Score 1 (N=96)	Score 2 (N=109)	Score 3 (N=101)	Score 4 (N=121)	Score 5 (N=126)	Total (N=553)
Gram-positive bacteria						
<i>Enterococcus</i> spp.	15 (15.6%)	12 (11.0%)	8 (7.9%)	10 (8.3%)	5 (4.0%)	50 (9.0%)
<i>Bacillus</i> spp.	10 (10.4%)	10 (9.2%)	12 (11.9%)	8 (6.6%)	7 (5.6%)	47 (8.5%)
<i>Staphylococcus</i> spp.	13 (13.5%)	15 (13.8%)	5 (5.0%)	5 (4.1%)	5 (4.0%)	43 (7.8%)
<i>Streptococcus</i> spp.	15 (15.6%)	17 (15.6%)	8 (7.9%)	10 (8.3%)	8 (6.3%)	58 (10.5%)
Gram-negative bacteria						
<i>Escherichia coli</i>	5 (5.2%)	8 (7.3%)	12 (11.9%)	12 (9.9%)	15 (11.9%)	52 (9.4%)
<i>Pseudomonas</i> spp.	3 (3.1%)	5 (4.6%)	10 (9.9%)	10 (8.3%)	20 (15.9%)	48 (8.7%)
<i>Klebsiella pneumoniae</i>	5 (5.2%)	12 (11.0%)	10 (9.9%)	18 (14.9%)	18 (14.3%)	63 (11.4%)
<i>Aeromonas</i> spp.	5 (5.2%)	3 (2.8%)	8 (7.9%)	10 (8.3%)	10 (7.9%)	36 (6.5%)
<i>Acinetobacter</i> spp.	7 (7.3%)	5 (4.6%)	3 (3.0%)	5 (4.1%)	3 (2.4%)	23 (4.2%)
<i>Serratia</i> spp.	10 (10.4%)	8 (7.3%)	12 (11.9%)	15 (12.4%)	15 (11.9%)	60 (10.8%)
<i>Enterobacter cloacae</i>	8 (8.3%)	14 (12.8%)	13 (12.9%)	18 (14.9%)	20 (15.9%)	73 (13.2%)
Total Isolates per Score	96 (100%)	109 (100%)	101 (100%)	121 (100%)	126 (100%)	553 (100%)

Note: N = total number of bacterial isolates obtained from feet within the specific lesion score; n = number of isolates of a specific bacterial species; % = percentage within the same lesion score column.

3.2. Antimicrobial resistance profiles

The phenotypic antimicrobial resistance profiles of the isolated Gram-negative opportunistic bacilli (n=355) exhibited high variability, with a clear, statistically significant trend toward increased resistance in advanced clinical footrot scores (Figure 1).

High resistance rates were recorded in Score 5 lesions for critical frontline antibiotics, most notably Ampicillin (89.2%), Flumequine (88.3%), and beta-lactamase inhibitor combination Amoxicillin/Clavulanic acid (76.6%). The Cochran-Armitage trend test mathematically confirmed that for these specific agents, as well as for Tetracycline and Enrofloxacin, the transition from mild pododermatitis (Score 1) to severe tissue necrosis (Score 5) is accompanied by a severe, linear escalation in resistance ($p < 0.001$ and $p = 0.003$, respectively).

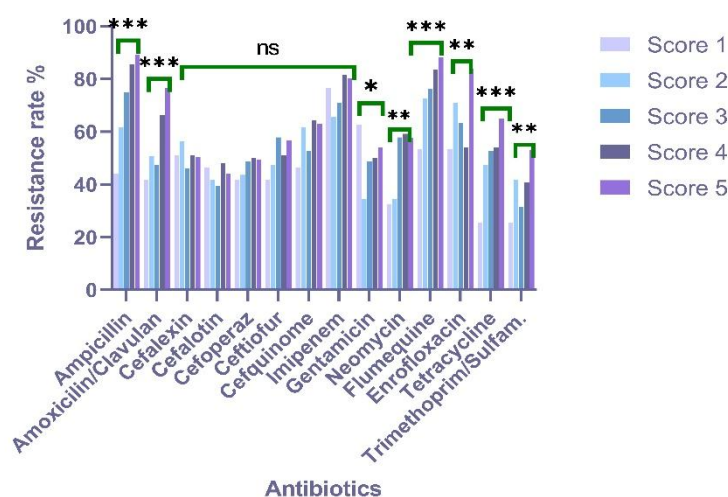


Figure 1. Phenotypic antimicrobial resistance rates (%) of Gram-negative bacilli ($n = 315$) isolated from ovine footrot lesions, stratified by clinical scores (1 to 5). Brackets indicate a statistically significant linear trend across the clinical scores determined by the Cochran-Armitage trend test: ns = non-significant ($p \geq 0.05$); * = significant ($p < 0.05$); = very significant ($p < 0.01$); *** = extremely significant ($p < 0.001$).

Conversely, Imipenem maintains a consistently high, ceiling-like resistance profile across the entire clinical spectrum, hovering around 76%-81% regardless of the lesion score ($p = 0.442$). In contrast to these highly dynamic or universally resistant agents, first- and second-generation cephalosporins (such as Cefalexin, Cefalotin, and Cefoperazone) demonstrate notable stability, with resistance rates remaining locked in a moderate 40%-50% plateau across all five scores. The phenotypic antimicrobial resistance rates of opportunistic Gram-positive bacteria ($n=198$), stratified across the five clinical footrot scores, exhibited distinct, highly variable dynamics. The Cochran-Armitage trend test statistically confirmed that the progression of digital lesions is strongly correlated with an upward, step-like increase in resistance across the majority of the tested frontline antimicrobial agents (Figure 2).

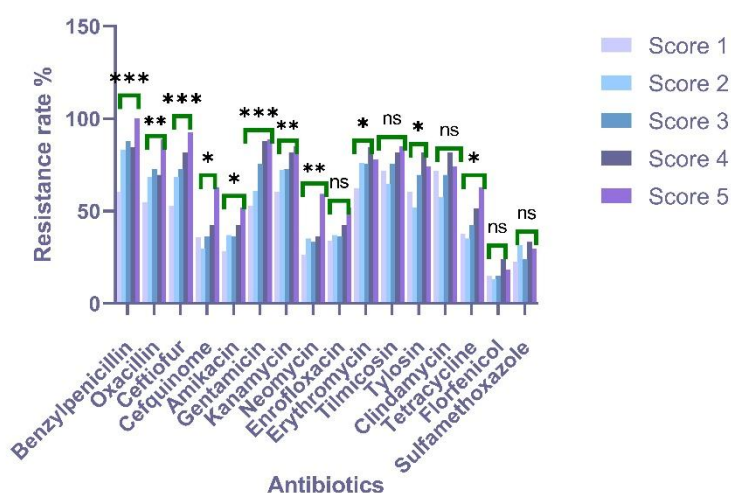


Figure 2. Phenotypic antimicrobial resistance rates (%) of Gram-positive bacteria ($n = 238$) isolated from ovine footrot lesions, stratified by clinical scores (1 to 5). Brackets indicate a statistically significant linear trend across the clinical scores determined by the Cochran-Armitage trend test: ns = non-significant ($p \geq 0.05$); * = significant ($p < 0.05$); = very significant ($p < 0.01$); *** = extremely significant ($p < 0.001$).

A dominant feature of the dataset was a massive, progressive surge in resistance from mild pododermatitis (Score 1) to severe necrotic stages (Score 5). An extremely significant linear trend ($p < 0.001$) was confirmed for Benzylpenicillin, Ceftiofur, and Gentamicin. Benzylpenicillin resistance started from a substantial baseline of 60.40% in Score 1, climbed steadily through the intermediate phases, and reached an absolute saturation threshold of 100% in Score 5 lesions. Ceftiofur resistance mirrored this severe trajectory, expanding from 52.80% (Score 1) and continuously escalating to peak at 92.60% in the final clinical stage. Gentamicin exhibited a highly robust upward trend, progressing from 50.80% in early-stage infections to a peak of 88.90% in advanced necrotic presentations.

A very significant progressive increase in phenotypic resistance ($p < 0.01$) was established for Oxacillin and two core aminoglycosides, Kanamycin and Neomycin. Oxacillin resistance rate expanded from 54.70% (Score 1) to 88.90% (Score 5), showing a temporary plateau between Scores 2 and 4 (68.50%-69.70%) before its final surge. Kanamycin and Neomycin resistance curves climbed substantially, moving from initial baselines of 60.40% and 26.40% (Score 1) to maximum peaks of 85.20% and 59.30% (Score 5), respectively. A moderate, yet statistically significant linear trend ($p < 0.05$) was observed for five antimicrobial agents, characterizing two distinct behaviors. Cefquinome, Amikacin, and Tetracycline resistance levels expanded steadily from relatively low or moderate initial baselines (35.80%, 28.30%, and 37.70%, respectively) to cross or reach structural peaks above or around the 50%-60% threshold in Score 5 (60%, 51.90%, and 60%, respectively). Erythromycin and Tylosin displayed high initial baseline resistance in Score 1 (62.30% and 60.40%), which grew further in intermediate scores but ultimately plateaued or fluctuated slightly in the advanced necrotic stages, finishing at 77.80% and 74.10% in Score 5.

In stark contrast to the dynamic shifts described above, five antimicrobials – Enrofloxacin, Tilmicosin, Clindamycin, Florfenicol, and Sulfamethoxazole – exhibited non-significant linear trends ($p \geq 0.05$), demonstrating that their phenotypic resistance remained statistically unaltered by the clinical progression of the footrot lesions. Enrofloxacin maintained a flat and statistically stable resistance baseline across Scores 1 to 4 (ranging closely between 34% and 42.40%), with a minor, non-significant increase to 51.90% in Score 5 ($p = 0.086$). Tilmicosin and Clindamycin presented a highly locked, high-resistance ceiling throughout the entire clinical spectrum, persistently hovering at elevated rates (64.80%-85.20% for Tilmicosin and 57.40%-81.80% for Clindamycin) regardless of lesion severity. Notably, Florfenicol and Sulfamethoxazole sustained the lowest and most favorable resistance boundaries in the study. Florfenicol resistance remained remarkably suppressed, fluctuating within a narrow, highly sensitive window of 13% to 24.20% across all five clinical stages, while Sulfamethoxazole stabilized effectively between 22.60% and 33.30%.

4. Discussion

The findings indicate that animal hooves are exposed to a diverse spectrum of microorganisms. These include opportunistic pathogens such as *Pseudomonas*, *Acinetobacter*, *Aeromonas*, and *Serratia* species, alongside commensal Gram-positive bacteria like *Streptococcus*, *Staphylococcus*, and *Bacillus* spp. Furthermore, Gram-negative fecal bacteria, specifically *E. coli*, *Klebsiella*, *Enterobacter*, and *Enterococcus* spp., are frequently prevalent within the hoof environment. Environmental factors, including poor hygiene, ambient temperature, and high humidity, interact with the structural integrity of the interdigital epithelium to dictate the pathogenic potential of this bacterial community [10]. Among the isolated Gram-negative bacteria, *E. cloacae* recorded the highest overall prevalence (13.2%), followed closely by *K. pneumoniae* (11.4%). Remarkably, both species demonstrated a progressive, score-dependent increase in isolation rates, peaking at Score 5 (15.9% for *E. cloacae* and 14.3% for *K. pneumoniae*). This accumulation of cases in the higher score tiers underscores the aggressive opportunistic profile of these *Enterobacteriaceae*, which are widely recognized in the literature for their capacity to harbor multidrug-resistance mechanisms and colonize critically ill or compromised hosts [11], [12]. A similar upward trajectory was observed for *Pseudomonas* spp. whose prevalence surged from a mere 3.1% at Score 1 to a peak of 15.9% at Score 5. This nearly five-fold increase in isolation rates suggests that *Pseudomonas* spp. plays a critical role in the microbial shifts associated with higher clinical severity, a phenomenon frequently attributed to its intrinsic resistance and biofilm-forming capabilities [13]. Furthermore, *E. coli* maintained a consistently high presence in scores 3, 4, and 5 (remaining around 11.9%), further reinforcing the hypothesis that *Enterobacteriaceae* and non-fermentative Gram-negative bacilli become predominantly established as case severity increases, consistent with the multicenter findings reported by Rhomberg et al. [14]. In sharp contrast to the trend seen in Gram-negative bacteria, Gram-positive pathogens demonstrated a marked trajectory. For instance, *Enterococcus* spp. decreased from 15.6% at Score 1 to just 4% at Score 5, while *Staphylococcus* spp. followed an almost identical decline (dropping from 13.5% to 4%). This inversion of the Gram-positive to Gram-negative ratio suggests an ecological niche shift or a

selective pressure, potentially driven by broad-spectrum empirical antimicrobial therapy, that favors the proliferation of Gram-negative bacteria in advanced stages, as highlighted in several recent epidemiological surveillance studies [15].

The linear escalation of antimicrobial resistance (AMR) aligned with the progression of pododermatitis severity highlights a critical challenge in clinical management. The data demonstrate that as tissue degradation advances from mild inflammation to severe necrosis, the therapeutic efficacy of frontline antibiotics precipitously declines. The Cochran-Armitage trend test statistically confirms a strong linear correlation between lesion severity and resistance rates for Ampicillin (89.2%), Flumequine (88.3%), and Amoxicillin/Clavulanic acid (76.6%) at score 5 ($p < 0.001$). This trajectory is also mirrored by Tetracycline and Enrofloxacin ($p = 0.003$). This can likely be attributed to chronicity and biofilm formation, as severe necrotic lesions provide an ideal anaerobic, structured environment for biofilm development. Bacteria with biofilms can exhibit up to 1,000-fold higher resistance to antimicrobials compared to their planktonic counterparts, severely limiting the efficacy of beta-lactams and fluoroquinolones [16]. Also, the prolonged courses of empirical antibiotic therapy that occur in patients with chronic injuries drive the selection of highly resistant clones, particularly against heavily utilized classes like tetracyclines and fluoroquinolones (enrofloxacin/flumequine) [17]. The exceptionally high resistance to Amoxicillin/Clavulanic acid (76.6% at Score 5) is particularly alarming, as beta-lactamase inhibitors are typically deployed to circumvent resistance. This suggests co-existence of alternative resistance mechanisms, such as penicillin-binding protein (PBP) alterations, porin loss, or overexpressed efflux pumps, which render the inhibitor combination ineffective [18].

Imipenem exhibited a consistently high and stable resistance profile throughout the clinical course (76%–81%, $p = 0.442$). Since carbapenems such as imipenem are strictly prohibited for use in livestock within veterinary medicine, this ceiling-like resistance pattern strongly indicates the presence of intrinsic resistance mechanisms inherent to the opportunistic Gram-negative bacilli colonizing ovine footrot lesions [19].

Cephalosporin stability across all five scores indicates that resistance to these agents is decoupled from disease severity. These antimicrobials maintain a moderate, predictable efficacy profile, suggesting that their resistance mechanisms are already widespread at a baseline level and are not actively enriched by the treatment or acute tissue injury.

Opportunistic Gram-positive isolates showed a progressive increase in resistance to Benzylpenicillin (60.4%–100%, $p < 0.001$), Ceftiofur (52.8%–92.6%, $p < 0.001$), and Oxacillin (54.7%–88.9%, $p < 0.001$) as the footrot lesion advanced, indicating a substantial risk of therapeutic failure. The attainment of complete resistance to Benzylpenicillin in Score 5 lesions suggest a total loss of efficacy of conventional penicillin-based therapies against secondary Gram-positive pathogens [19]. The concurrent rise in Oxacillin resistance points to the selection of a methicillin-resistant phenotype, commonly associated with *mecA/mecC*-mediated mechanisms that confer cross-resistance to most β -lactam antibiotics. This likely explains the high resistance levels observed for Ceftiofur and the significant increase in resistance to Cefquinome (60%, $p < 0.05$), indicating that advanced necrotic lesions favor the selection of multidrug-resistant Gram-positive strains [14].

The marked increase in resistance to Gentamicin (50.80%–88.90%), Kanamycin (60.40%–85.20%), and Neomycin (26.40%–59.30%) suggests strong selective pressures within severe lesions. The extensive tissue damage and exudative conditions in Score 5 lesions promote biofilm formation, which limits aminoglycoside penetration, reduces oxygen availability required for drug uptake, and facilitates horizontal transfer of aminoglycoside-modifying enzymes, contributing to the progressive increase in resistance [20]. Tilmicosin and Clindamycin maintained consistently high resistance rates (64.80%–85.20% and 57.40%–81.80%, respectively; $p \geq 0.05$), while Erythromycin and Tylosin also exhibited elevated baseline resistance, suggesting the presence of an established resistance background largely independent of lesion severity.

Among all antimicrobials tested, Florfenicol and Sulfamethoxazole exhibited the lowest and most stable resistance rates, with no association with clinical progression ($p \geq 0.05$). These findings indicate that resistance mechanisms against these agents have not yet become widely integrated into the multidrug-resistant populations involved in footrot, making them potentially valuable therapeutic options [21].

5. Conclusions

This study demonstrates a significant association between the clinical severity of ovine footrot and increasing phenotypic antimicrobial resistance among opportunistic bacterial isolates. The Cochran-Armitage trend test identified significant positive trends for resistance to several antimicrobial agents, indicating that resistance rates generally increased with higher clinical lesion scores. As lesions progressed from mild pododermatitis to advanced stages, both Gram-negative and Gram-positive isolates exhibited higher resistance rates to several commonly used veterinary antimicrobials, including ampicillin and

benzylpenicillin. These findings highlight the importance of considering disease severity when selecting antimicrobial therapy and support the need for continuous surveillance of antimicrobial resistance to guide evidence-based treatment strategies.

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