Equine antibiotic resistance: epidemiology, regulation and strategies there of

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1. Introduction

Antimicrobial resistance is the ability of the microbe to endure and multiply within the body tissues in the presence of highest tolerated antimicrobial dose. This being a global healthcare threat, it has not just remained confined to humans but has successfully stretched its presence even in animals. Of the various antimicrobials used in veterinary practices, antibiotics are quite readily prescribed by the veterinarians against infections, becoming the basis of developing bacterial resistance in animals. However, it is only recently that the antimicrobial resistance in horses has started to receive due attention, at both, public and clinical levels.

Methicillin-resistant Staphylococcus aureus (MRSA) is no longer the only bacterial species that exhibits equine antibiotic resistance; many other bacterial species, notably gram-negative bacteria like E. coli, have also exhibited similar resistance in clinical settings. The four critical targets for any antibacterial agent in the bacterial cells are – inhibition of cell wall synthesis, prohibiting genetic material (DNA/ RNA) synthesis, preventing protein synthesis or disruption of a vital metabolic pathway.

1.1 Epidemiology in equine antibiotic resistance

Researchers have made efforts in understanding the epidemiology behind single or multi-drug resistance, particularly amongst MRSA and β-lactamase producing E. coli in equine samples using both phenotypic and genotypic methodologies.

1.2 Antimicrobial resistance against MRSA

MRSA carriage has been detected on the skin and mucous layers of the nasal chambers in horses. Though all MRSA colonization may not lead to clinical infections but may possess a threat for potential infections under certain circumstances, most likely during hospitalization of horses. With a 2.3-6.4% prevalence in hospitalized horses under normal circumstances, these values can go very high under an infection outbreak (1).

At molecular levels, the epidemiology is governed by the carriage of variably sized DNA fragments of the SCCmec gene cassettes. Within this, the mecA gene encodes PBP2a, an

alternative penicillin-binding protein, which has reduced affinity for β-lactam drugs like methicillin. This mechanism induces resistance in horses (2). Further, a narrow spectrum of resistance is offered by the encoding of the blaZ β-lactamase gene, which synthesizes penicillinase that breaks down the β-lactam penicillin's, majorly encountered in staphylococci from horses (3).

1.3 Antimicrobial resistance against *E. coli*

Resistance to all antimicrobials has been encountered in E. coli for horses. Faecal carriage of E. coli has been reported quite high in hospitalized horses (60.5-81.7%) compared to non-hospitalized community (13.4-24.5%) horses. Similar estimates and faecal carriage ratios are prevalent for multidrug resistant and extended spectrum β -lactamase (ESBL) producing E. coli isolates in hospitalized horses than in the community horses (4).

Due to inherent inability for penicillin penetration through E. coli's outer layers, there is an increasing resistance to β-lactam drugs primarily by producing inactivating β -lactamase enzymes like TEM-1, TEM-2, and SHV-1, or AmpC β-lactamases, which are all encoded by different bla resistance genes (5). Recently equine faecal samples of clinically normal horses have shown ESBL producing E. coli isolates, particularly the CTX-M-15 type from the ST131 gene sequence (6). Similarly, mild ciprofloxacin resistance was observed in equine samples due to an over synthesise of AAC(6')-lb-cr, an aminoglycoside modifying acetyltransferase enzyme along with over expression of efflux pumps due to qnr gene encoding towards fluoroquinolone resistance (4).

1.4 Antimicrobial resistance against other microbes

Intrinsically resistant to cephalosporins and aminoglycosides, vanA and vanB genes have been identified exhibiting resistance to vancomycin in enterococcal isolates from horses with sample prevalence of 6.7-9.6%. Similarly, equine enterococcal resistance to macrolides and tetracycline have been identified to be caused by erm(B) and tet(L) genes (4, 7).

With only limited antibiotics available to treat Pseudomonas caused sepsis, extensive multidrug resistance has been reported in foals (4). However, epidemiologically antimicrobial resistance against Pseudomonas (particularly P. aeruginosa), a major causative agent for various equine infections is lacking.

Salmonella, another significant causative agent for various equine diseases has shown multidrug resistance in equine faecal samples. Several ESBL genes (blaCTX-M-1, blaCTX-M-15, blaSHV-12), plasmid mediated ampC genes (blaCMY-2) and integrons associated genes (DT104) have been identified in equine Salmonella isolates (8, 9). Similarly, equine sulphonamide and trimethoprim resistance is observed due to over expression of aminoglycoside adenyltrasferase enzyme and several dihydrofolate reductase enzyme analogues from dfr genes respectively (4, 10).

Acinetobacter has significantly been understood for human diseases, however very restricted information is available epidemiologically in equine cases. A. baumannii has shown various aminoglycoside resistance genes. Similarly, various Acineobacter isolates have documented carbapenemase OXA-23 genes in horses that metabolize carbapenem (4).

1.5 European Medicines Agency (EMA) Approach in assessing antimicrobial resistance in veterinary medicine

The emerging instances of antibiotic resistance in veterinary practices has posed a global healthcare threat due to limited availability of therapeutic options in combatting any infections. Repeated exposure to antimicrobial drugs has caused the microbes to undergo changes (including genetic mutations) and stop them from being killed or inactivated by the treatment.

By supporting the responsible use of antibiotics and taking effective measures in order to minimise the development of antibiotic resistance in animals, including food-producing animals like horses, EMA has been following a steadfast approach.

Under the veterinary regulatory guidelines of the EMA, antimicrobial resistance in veterinary medicines section highlights the following key topics summarised as below:

1.5.1 Committee for Veterinary Medicinal Products (CVMP) strategy on antimicrobials

As a strategic plan for 2021-2025, CVMP is focusing on the implementation of the Veterinary Medicines Regulation provision along with a guideline on the demonstration of efficacy for antimicrobial veterinary medicines. Further, it also provides guidelines on the metaphylactic use of antimicrobics in animals at the verge of catching an infection.

1.5.2 Monitoring veterinary antimicrobial consumption

As horses are considered as food-producing animals, it is vital to monitor antimicrobial consumption that may lead to resistance and potential contamination in the food chain. Within the European Union (EU) member state, from 2010 EMA has initiated the 'European Surveillance of Veterinary Antimicrobial Consumption (ESVAC)' project which collects data on the use of antimicrobials in the EU and the European Economic Area (EEA). This data can be publicly accessed through the 'European database of sales of Veterinary antimicrobial agents.

1.5.3 Analysis of antimicrobial consumption and resistance

The EMA analyses the intake of antibiotics by animals and the development of resistance thereafter in close collaboration with the European Food Safety Authority (EFSA) and the European Centre for Disease Prevention and Control (ECDC). The results get published in the 'Joint Inter-agency Antimicrobial Consumption and Resistance Analysis' (JIACRA) report.

1.5.4 Recommendations on the use of antibiotics in animals

EMA along with other relevant EU authorities, involving EFSA, issues the RONAFA opinion based on the 3R's theme – reduce, replace and rethink. This joint opinion aims to reduce the rigorous use of antimicrobial agents in animal rearing. Previous reports from EMA, EFSA, ECDC and European Commission's 'Scientific Committee on Emerging and Newly Identified Health Risk (SCENIHR)' have pressed the need for not just the wise use of antimicrobics in animals but has also strongly recommended adherence to basic animal husbandry hygiene practices. Additionally, a sturdy approach towards monitoring of antibiotic resistance, fostering novel areas of research and strategies to overcome antibiotic resistance in animals are also advised.

1.5.5 Proposed methods for preventing antibiotic resistance in horses

Across the EU and the EMA, experts/ veterinarians propose strategic approaches towards preventing/ minimising or slowing down the antibiotic resistance in horses.

- Follow the prescribed regimen thoroughly.
- Never use one antibiotic amongst different horses. Doses or frequency of dosing are tapered according to individual horse's condition.
- Just like for humans, do not stop administering the prescribed antibiotic midway if the condition is seen improving in the horse.
- Never keep outdated antibiotics for later use.
- Never skip a dose.
- Always contact a clinical expert if no improvement is seen/ conditions worsen.
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Apart from the key advices on the use of antibiotic in horses to prevent resistance, basic good hygiene animal husbandry and biosecurity principles should be followed in preventing infections. Self-medication without a veterinarian's intervention should be avoided based on just visual inspection by the owner, which is quite common in parts with difficult access to vet clinics. Most of the times, especially in self-medication, viral infections can be misunderstood as bacterial infections and using antibiotics in viral infection may lead to severe antibiotic resistance.

2. Conclusion

Antibiotic resistance in horses is an alarming concept globally. For easy access and efficacy of antibiotic therapies, antimicrobial/ antibiotic stewardship must be embraced. Being a nexus with multifaceted approach, key emphasis must be given to the monitoring and education on the use of antibiotics in horses. Further, understanding the mechanisms causing the resistance is critical which would dictate the clinicians to effectively choose an antibiotic regimen against a particular infection. However, there is limited research work done on understanding the epidemiology of antibiotic resistance in various microbes in horses. A collaborative effort must be made between academician, industry, and regulatory bodies to foster this multifactorial research forming the basis of practicing antimicrobial/ antibiotic stewardship. Additionally, reporting and documentation of any antibiotic resistance observed in horses must be efficiently reported and must be well documented with the regulatory bodies. This would enhance evidence-based decision-making on antibiotic selection and direct the pathway towards development of more robust and novel antibiotic moieties.

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