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Dosing equine antimicrobials: Ensuring clinical success and avoiding antimicrobial resistance

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Dosing equine antimicrobials: ensuring clinical success and avoiding antimicrobial resistance

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Running head: Dosing equine antimicrobials

Summary

Underdosing of equine antimicrobials is a global issue and may be contributing to antimicrobial resistance in horses. Recent research in Australia has identified that most antimicrobial use in peer reviewed literature is at a higher dose than that currently on the label for many common equine antimicrobials in the US, UK and Australia. These dosing regimens used are now considered the most appropriate doses to be using in horses and veterinarians treating equine patients should be aware of the contemporary dosing regimens.

Antimicrobial resistance is a global health emergency in people which is bringing antimicrobial use in animals under scrutiny, particularly in food animals. However, of all sectors of the veterinary profession, antimicrobial resistance in equine and companion animal patients appears to be a much bigger problem than in food animal species (Gibson *et al.* 2008; Platell *et al.* 2011; Abraham *et al.* 2016; Saputra *et al.* 2017). There are likely several contributing factors for this. Firstly, a wider range of antimicrobials are used in animals not destined for food (Hardefeldt *et al.* 2017b). Regulation is more restrictive for drug administration to food animals, mostly by the way of residue detection and setting of withholding periods. In addition, antimicrobials are more readily available for use off-label in companion animals and horses and, at least in the European Union, off label antimicrobials

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was most frequently reported by equine veterinarians (Committee for Medicinal Products for Veterinary Use 2017). Also, the economic factors that affect antimicrobial use in food animals are often less important in companion animals and horses, due to their high value or importance to animal owners, so newer, more important antimicrobials to human medicine, can be used despite their higher cost.

Secondly, antimicrobials are often prescribed “just in case” in equines such as those used prophylactically for clean surgical procedures (Hardefeldt *et al.* 2017a) or for horses with respiratory signs consistent with inflammatory airway disease (Weese and Sabino 2005) and in other conditions. A combination of factors may be driving veterinarians to prescribe to these horses including pressure, or perceived pressure, from clients and a fear of deterioration in a patient leading to litigation (Hardefeldt *et al.* 2018a). This overuse of antimicrobials is often seen as unlikely to cause harm however a change in mindset is required in the equine sector to recognise the role prescribing plays in the emergence of antimicrobial resistance that is affecting our patients and contributing to our loss of social licence as a profession.

Thirdly, under-dosing of antimicrobial agents has been well documented in prescribing to equine patients (Hardefeldt *et al.* 2017a). Appropriate dosing with antimicrobial agents is critical for effective treatment and also in the fight against AMR. All antimicrobial use can select for AMR, but exposure to subtherapeutic levels of antimicrobial agents may increase the rate of development of AMR, particularly when exposure is prolonged or recurrent (Guillemot *et al.* 1998; Gullberg *et al.* 2011; Liu *et al.* 2011). A predominant use of dose rates lower than those required to result in plasma concentrations of the antimicrobial above the minimum inhibitory concentrations required for efficacy against common equine pathogens is of particular concern to the equine industry and may be leading to the emergence of AMR affecting horses. Poor teaching of veterinary undergraduates is one potential reason for failure of veterinarians to administer appropriate doses of antimicrobial agents. Australian university equine veterinarians had 3.2 times higher odds of compliance with guidelines than general practitioners in the 2016 survey (Hardefeldt *et al.* 2017a). In addition, students in the final 2 years of study in Australia self-identified good knowledge of antimicrobial pharmacology (Hardefeldt *et al.* 2018c), similar data is not available for other jurisdictions. Thus, it seems unlikely that inappropriate university teaching is the primary reason for under-dosing of antimicrobial agents in equine and bovine practice. A second potential contributor to inappropriate dosing is the labelling of antimicrobials. Some of the

doses recommended on the labels for antimicrobials fall below those now recognised as appropriate. Recommended doses on the labels for procaine penicillin are lower than those currently recommended in the literature in Australia, the USA and UK and the label for gentamicin recommends doses that are lower than those currently recommended in the literature and dosing frequency higher than currently recommended in Australia. Gentamicin is only labelled for intrauterine use in the USA (Love *et al.* 1983; Bywater *et al.* 1985; Firth *et al.* 1986; ten Voorde *et al.* 1990; Uboh *et al.* 2000; Bauquier *et al.* 2015). While the dose recommended by the label is likely to be a factor influencing some veterinarians, the label is clearly not the only factor leading to inappropriate antimicrobial dosing. Respondents to an equine survey frequently used off-label (appropriate) doses of gentamicin in horses (89% of dose rates appropriate), but often used labelled (inappropriate) doses of procaine penicillin (32% of dose rates appropriate) (Hardefeldt *et al.* 2018b). Historical prescribing, and the culture of equine practice, is likely also playing a role with frequent anecdotal reports that the volume of intramuscular penicillin required for appropriate dosing was inhibiting the use of this drug at the recommended dose.

It is on this final point that our group has been particularly interested in. Our interest was primarily due to the out-dated dose recommendations on labels that accompany many antimicrobials in Australia. A problem that is also present in the UK and US. We undertook a content review of articles appearing in the major equine journals around the world (Equine Veterinary Journal, Equine Veterinary Education, Australian Veterinary Journal, Australian Equine Veterinarian, the Journal of Veterinary Internal Medicine and the Journal of Equine Veterinary Science) between January 2015 and August 2018 and searched for antimicrobial dosing regimens for the common equine antimicrobials (procaine penicillin G, gentamicin and trimethoprim sulphonamide) to assess the doses being used globally (Hardefeldt *et al.* 2019). In 83% of papers describing the use of penicillin a dose of 20-25,000 IU/kg administered every 12 hours was utilised (Hardefeldt *et al.* 2019), a dose used by only 29% of respondents to an Australian survey (Hardefeldt *et al.* 2017a). In 93% of papers describing the use of gentamicin a dose of 6.6 mg/kg administered every 24 hours was utilised (Hardefeldt *et al.* 2019), a dose used by 80% of respondents to an Australian survey (Hardefeldt *et al.* 2017a) but much higher than the labelled dose of 1.5-2 mg/kg (Australian Pesticides and Veterinary Medicines Authority). In all papers describing the use of trimethoprim sulphonamides a dose of 20-30 mg/kg administered every 12 hours was utilised

(Hardefeldt *et al.* 2019), a dose used by only 30% of respondents to an Australian survey (Hardefeldt *et al.* 2017a).

Many antimicrobials used commonly in equine practice have current dosing recommendations higher than in the past, based on advances in knowledge of drug pharmacokinetics, pharmacodynamics and target plasma antimicrobial concentrations. Procaine penicillin G should be administered at 22,000 IU/kg every 12 hours. Gentamicin should be administered at 6.6 mg/kg every 24 hours in adults and 8.8 mg/kg every 24 hours in neonates. Therapeutic drug monitoring for gentamicin should be considered, where possible, to aid in decisions on both dose and inter-dosing interval. Trimethoprim sulphonamide should be administered at 30 mg/kg every 12 hours. Veterinarians treating equine patients should be aware of the current recommended dose rates and inter-dosing intervals to ensure efficacy in therapy and to preserve the usefulness of these antimicrobials for the future.

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