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Review Article

Use of Antibiotics in Equines and Their Effect on Metabolic Health and Cecal Microflora Activities

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ABSTRACT

In the race against deadly diseases, multiple drugs have been developed as a treatment strategy in livestock. Each treatment is based on a specific mechanism to find a suitable drug. Antibiotics have become a fundamental part of the equine industry to treat bacterial diseases. These antibiotics have specific doses and side effects, and understanding each parameter allows veterinarians to avoid or limit the adverse effects of such drugs. Use of antibiotics causes microbial imbalance, decreased microbial diversity and richness in both cecal and fecal samples. Antibiotics reduced metabolites production such as amino acids, carbohydrates, lipids, and vitamins, increased multi-resistant microbes, and gives opportunity to pathogenic microbes such as *Clostridium perfringens* and *Salmonella* spp., to overgrow. Therefore, appropriate use of these antibiotics in equine therapy will reduce the adverse consequence of antibiotics on cecal microbiota activities.

1. Introduction

Since the development of veterinary medicine, antibiotics have played a pivotal role in the therapeutic management of equine diseases caused by bacteria. Unfortunately, the over-exploitation of some of the antibiotics causes not only the failure of the internal organs of the equines but also alters its metabolic functions, thereby generating short- and long-term consequences [1]. Antibiotics have different effect on equine health ranging from neurological abnormalities, emerging drug resistant microbes and digestive disturbances [30]. Currently, the indiscriminate use of antibiotics has contributed to the growth and emergence of antibiotic-resistant strains and this poses a challenge to the treatment of bacterial infections in equines [22]. Multi-drug resistant bacteria can cause severe infections in animals, which lead to difficulty in providing timely treatment for deadly diseases [2].

Varieties of strains have developed drug resistance and these strains contain plasmids that alter the cell genetically and escape from the antibacterial actions of drugs [3]. Khusro et al [30] reported on the impact of antibiotics on equine health and recommended that an appropriate dosage of antibiotics should be used due to their bacteriostatic and bactericidal traits. The bactericidal properties of antibiotics ought to be given great consideration in equine due to the role of microbes in their hindgut. While many studies have considered the impact of antibiotics on the overall health, little focus has been on digestive health especially on the hindgut microbes. In fact, the information on this aspect is scarce.

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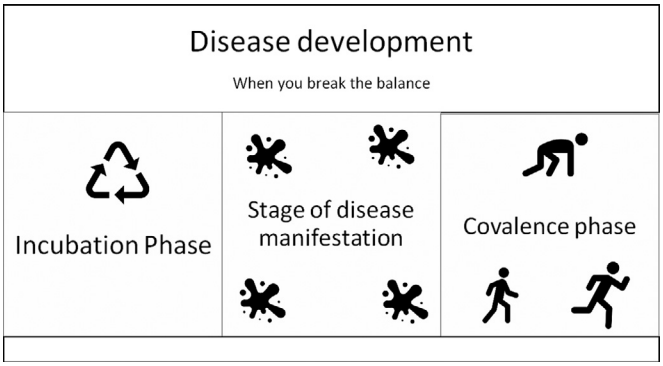

Fig. 1. Stages of disease development after equilibrium is broken in the patient.

The use of antibiotics should be based on a correct administration, knowledge of the drug, information of the infecting agent (s), the correct selection of the drug, and the formulation of an adequate administration protocol and dosage, as well as full awareness of the benefits or risks of the treatment applied to the patient [4]. Considering the above, and with the litle available information on this topic, this manuscript focuses on the use of antibiotics and their influence on metabolic health and cecal microbiota activities in equine.

2. Factors Affecting Disease Development

According to the World Health Organization, disease is known as the alteration or deviation from the physiological state in one or several parts of the body, due to known causes, in which specific symptoms or signs manifest, and whose evolution can be foreseen [33]. When the equilibrium that exists between the host and the bacteria that harbors it is broken, disease development is favored. Many factors contribute to the disruption of the equilibrium, including immunosuppression, poor administration of antibiotics, abrasive actions, malnutrition, etc. [6]. The development of diseases is based on three principles or stages, the incubation phase, the overt disease phase, and the covalence phase, as shown in Fig. 1 [7]. The incubation phase develops when the infecting agent enters the organism, incubates, begins its development, and the first manifestation of symptoms occurs. Subsequently, the period of overt disease develops to the point where clear symptoms and signs of the disease appear, during this stage, the disease is diagnosed, and timely treatment is started [8]. Once the previous stage is terminated, the covalence phase begins which is carried out from the moment treatment is given until recovery.

Equines submitted to surgical processes or that are likely to get invasive wounds are susceptible because such processes generate immunosuppressive effects and increase the possibilities of infection. Other factors like stress also increase susceptibility because they alter the mucous membranes in the equine, which reduces its ability to phagocytose and eliminate bacteria, thereby resulting in bacterial colonization of the mucous membranes, and the infections can be fatal [4].

Careful administration of drugs is very important in all species, however, the difficulty in administering such in equines suggests that caution is required [9]. The efficiency of the antibiotic is based on the mechanism of action of the drug, and its pharmacodynamic and pharmacokinetic properties depend on the state of the drug (liquid, solid or aerosol) and route of administration (Fig. 2). One of the important parameters to consider when choosing antibiotics is the absorption rate of the drug. Normally the absorption rate depends on the physicochemical characteristics of the antibiotic and the carrier involved [10].

The antibiotics passage through the tissue and blood is influenced by various factors such as size, the drug load, the degree of the binding and affinity, and its ability to cross the cell membranes that integrate the different tissues [3]. The choice of the appropriate antibiotic is primarily based on knowing the clinical condition. Not all antibiotics can be administered in the same way and in the same dose to all animals. Several factors that can be useful at the time of choosing an appropriate treatment [4,5]; these include dosage, dosing interval, route of administration, and duration of treatment. Furthermore, several factors are considered when using more than one antibiotic such as patient susceptibility, mixed infections, need for synergistic action, and side effects in patients [4].

3. Main Antibiotics Administered in Equine

There is a wide list of antibiotics used in the equine clinic (Table 1), however, few are used frequently. Furthermore, Table 2 describes the conflict that equine treating veterinarians may face and some limitations or consequences of their misadministration.

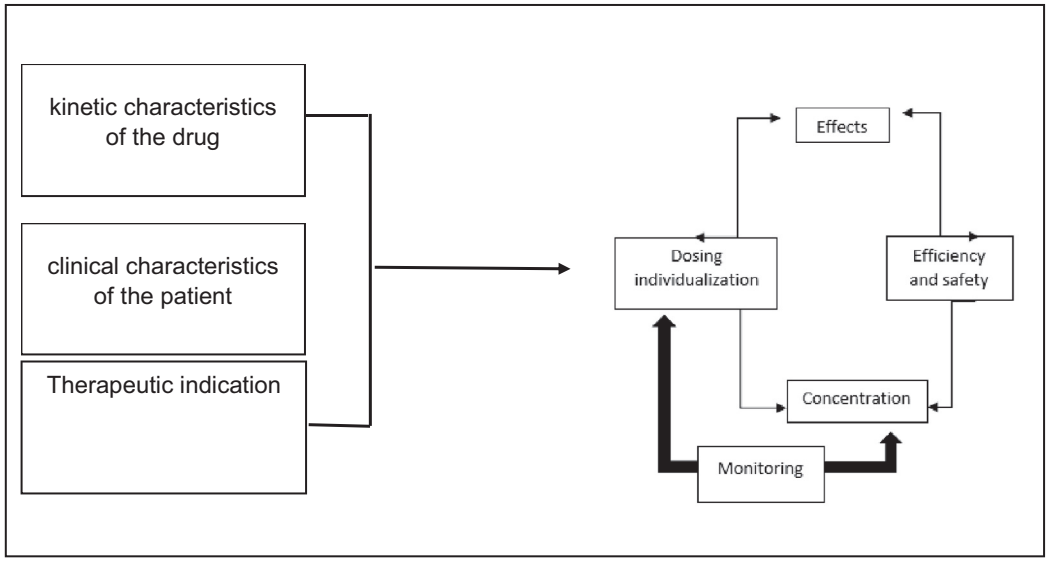

Fig. 2. Outline of parameters and characteristics considered in equine clinical therapy when prescribing antibiotics for bacteria induced infectious diseases.

Table 1
Dosage and antibiotics use in equine.

Drug	Doses and Route of Administration	Reference
Amikacina	In young horses and adults: 6 mg/kg BW[a], IV or IM a daily dose (around 3 ml/100 kg BW)	[4]
Ampicillin	6.6 mg/kg, a 10–20 mg/kg c/6–8 h. IM, IV	[4]
Amoxicillin	10–20 mg/kg, IM	[4]
Ceftiofur	2.2–4.4 mg/kg c/24 h. IM; Dosage 5–10 mg/kg c/12 h. IV, IM.	[2]
Enrofloxacin	5 mg/kg c/24 h. IV. IM; 7.5–10 mg/kg c/24 h.	[2]
Erythromycin	37.5 mg/kg c/12 or 25 mg/kg c/8 hr Colts: 5 mg/kg c 4–6 hr. IV	[4]
Gentamicin	Adults: 4–6.8 mg/kg IV, IM c/24 h.	[5]
Metronidazole	20–25 mg/kg c/ 8–12 h., o 15 mg/ kg c/ 6 h. Oral. Parenteral 20 mg/ kg c/ 8–12 h.	[5]
Penicillin G	Penicillin potassium 10,000 a 40,000 U/kg. c/ 6–8 h. IV. Penicillin sodium 10,000–40,000, U/kg. c/6–8 h. IV Procaine penicillin 20,000–24,000 U/kg. c/ 12–24 h. IM	[5]
Rifampin	2.5–10 mg/kg c/12–24 h. Oral	[2]

[a] BW, body weight; IM, intramuscular; IV, intravenous.

Table 2
Side effects of antibiotics on equine.

Drug	Side Effects	Reference
Amikacin	May irritate if administered intramuscularly; diarrhea from superinfection, the onset of prolonged treatments, mostly with broad-spectrum antibiotics.	[11,29]
Ampicillin	Susceptible in inactivation and is less active against Gram-positive in comparison to penicillium G; lethal enterocolitis.	[4,12]
Amoxicillin	Susceptible in inactivation and is less active against Gram-negative in comparison to penicillium G; vomiting and diarrhea.	[4,12]
Ceftiofur	Stable when found in a solution. One-time prepared. It has seven days functional lives. Freeze preserved for up to 8 wk; no direct side effects reported.	[2,11]
Enrofloxacin	Can generate defects in the process of maturation in the cartilage of the joints to equines; arthropathies.	[2]
Erythromycin	Can generate gastrointestinal problems and diarrhea; diarrhea can lead to the death of the equine.	[4,12]
Gentamicin	May irritate if administered intramuscularly; nephrotoxicity.	[5]
Metronidazole	Can generate neurological problems like weakness or depression; gastrointestinal disturbances, vomiting, and loss of appetite.	[4,5]
Penicillin G	Can generate agitation, attacks, salivation, colic, and in severe cases death; gastrointestinal disorders; poor absorption syndrome, and hypersensitivity reactions.	[4,12]
Rifampin	Elevated price; gastric discomfort.	[2,5]

Amikacin is an antibiotic that belongs to the family of semisynthetic aminoglycosides and is a derivative of kanamycin. It is the most administered aminoglycoside because it has the widest spectrum of antimicrobial activity and is resistant to the inactivating enzyme. It is not used in early or uncomplicated episodes [11]. It is mainly administered during severe infections that are caused by sensitive bacteria. Ampicillin is a semisynthetic amino penicillin with a longer half-life compared to penicillin G. It is potent and has great efficiency against gram-negative bacteria; however, against gram-positive bacteria, its activity is reduced. Ampicillin is less effective compared to penicillin for the treatment of *Streptococcus* infections and gram-negative bacteria resistance to these antibiotics has increased in recent years [4].

Amoxicillin is an amino penicillin that is commercially available in trihydrate form for equine administration, while sodium salt is used for parenteral application. Its activity is similar to ampicillin, but it is absorbed better and its serum concentration is higher [12].

Penicillin G is often used in the equine clinic due to its effectiveness against *Streptococcus* spp. Penicillin is an antibacterial agent with a broad-spectrum activity against gram-positive bacteria including many anaerobic bacteria. The mechanism of action is related to the interruption of peptidoglycan synthesis in the bacterial cell wall, which causes cell lysis. Because it is a drug with non-fat-soluble characteristics, it has a small volume of distribution and is eliminated through urine [4]. The increasing role of anaerobic bacteria in equine infections has led to the use of various combinationof specific antimicrobials, mainly against anaerobic bacteria. For examples, Metronidazole has an increased bactericidal power together with penicillin [4].

3.1. Therapeutic Use of Antibiotics in Equine

Bacterial localization in other organs in case of colitis is quite rare, it is recommended that in severely neutropenic animals, broad-spectrum antibiotics are used. However, antibiotics used for colitis caused by *Clostridia* are administered out of the recommendations of pharmaceutical companies ("extra-label use"). In these cases, antibiotics such as lincomycin, clindamycin, oxytetracycline, and low doses of erythromycin ethyl succinate have resulted in colitis [13,14]. Furthermore, in some cases, colitis has also been associated with the use of cloxacillin, florfenicol, ampicillin/sulbactam, chloramphenicol, metronidazole, and more recently ciprofloxacin [13]. Parenteral and oral antibiotics that have been temporally associated with the onset of diarrhea are tetracyclines, lincomycin, erythromycin, cephalosporins, and penicillin.

Metronidazole can be teratogenic; therefore, its use in pregnant mares should be restricted. Vancomycin should be reserved only for severe infections where bacteria are resistant to the other antibiotics mentioned. Di-tri-octahedral has been tested *in vitro* and found to bind toxins and inhibit *C. difficile* growth but has not been critically evaluated as an adjuvant in the treatment of equines with undifferentiated colitis or *C. difficile* colitis [13]. A dramatic re-

covery, as well as a decrease in mortality occurs when treatment with oxytetracycline is initiated within 24 hours of the onset of fever. Response to therapy is characterized by a decrease in body temperature, improvement in attitude, appetite, and increased bowel sounds; this is seen within 12 hours of initiating treatment [15].

The combination of erythromycin stolate and rifampicin are also effective when administered early in the course of the clinical case, but the response is not as rapid as when oxytetracycline is administered IV. The risk of altering the colonic flora must be taken into account whenever oxytetracycline is used [14].

3.2. Antibiotics on the Cecal Microflora Activities

Equines are herbivorous, they are also known as pseudo-ruminants because they have functional hindgut (caecum and colon microbiota) [34], which serve as fermentation chamber similar to the rumen enabling efficient forage utilization for optimal nutrition. The hindgut is rich in microbes and plays important role in nutrient digestion, health, welfare, and diseases in the host. These microbes residing in the colon, especially within the comparatively enlarged caecum help to degrade non-digestible cellulosic and hemicellulosic forage components to release bioavailable energy and other essential nutritional needs in horses [16]. These microbes also contribute to the stimulation of the immune responses, help protect against pathogens, neutralize toxins, and regulate gene expression in the host's epithelial tissues [17]. Due to the sensitivity of these hindgut microbes, disturbances leading to microbial imbalance through different means including diet and antimicrobial therapy may affect animals' health, nutrient derivation, and utilization [18,19,20].

Antibiotics are used in equine as both prophylactic and therapeutic to treat a variety of undesirable bacterial infections [21]. However, an increasing level of multi-resistance due to widespread use of antibiotics in equine has been reported [22]. Furthermore, the antibiotics usage in equines could disrupt hindgut microbiota balance affecting the fibrolytic activity and the intestinal immune balance, leading to diseases and it could give opportunities to pathogenic microbes to overgrow in the gut segment [23,24] causing allergic reactions and diarrhea [19]. Antibiotic administration can cause gastrointestinal disease in horses, creating a disruption of the normal population and function of bacteria found in the hindgut [25]. The use of antibiotics has been reported to cause decreased microbial diversity and richness, microbial instability, decreased *Lachnospiraceae* and *Ruminococcaceae* family members, decreased lactic acid utilizing bacteria; and decrease in butyrate-producing bacteria that have anti-inflammatory properties [31]. Furthermore, non-steroidal anti-inflammatory drugs such as phenylbutazone and firocoxib used in equine studies were reported to decrease diversity and caused alteration of microbiota profiles about ten days after its use and inferred metagenome [32]. This shows that if non-steroidal anti-inflammatory drugs are combined with antibiotics in equine at the same time, their usage may be catastrophic for the hindgut microbes. Costa et al [20] study on the use of trimethoprim sulfadiazine decreased the microbial richness and diversity, caused a drastic decrease of Verrucomicrobia - a beneficial microbe. Moreover, White and Prior [26] treated horses with oxytetracycline and reported a decrease in *Veillonella* spp., and an increase in pathogen *C. perfringens* which often outgrow beneficial microbes *like* the lactate-utilizers (e.g., *Veillonella* spp.), saccharolytic bacteria, proteolytic bacteria, cellulolytic bacteria, etc. [21]. Similarly, the use of trimethoprim-sulfadiazine and antibiotics decreased fecal cellulolytics and *Lactobacilli,* and increased *Salmonella* spp. and *C. difficile* [21]. Furthermore, application of metronidazole (15 mg/kg) in horses caused a significant decrease in microbial richness and evenness indices in both cecal, and fecal samples, such as *Actinobacteria, Spirochaetes, Lentisphaerae*, and *Verrucomicrobia* which correlated with clinical signs of gastrointestinal disease and reduced the metabolites such as amino acids, carbohydrates, lipids, nucleic acids, and cofactors and vitamins in the feces [25]. These results suggest that the administration of antibiotics in equine can disrupt hindgut microbes balance and allow the proliferation of pathogenic bacteria [27].

4. Adverse Effects on Equine Metabolism

The equine digestive and metabolic systems are complex. The intestinal microbiota found in the small intestine, helps the system to function properly, and improves digestion and nutrient bioavailability. The dermal surface and mucosa in the small intestine provide a protective barrier thath is composed of chemical, physical, and microbial defenses [35]. The intestinal microbiota contributes to protection against pathogens. However, at the same time, commensal bacteria coexist with the host without posing a health threat if they are within the normal range [28].

Antibiotics have two functions - positive and negative, and positive functions involve the elimination of harmful pathogens that develop the diseases. However, excessive use of antibiotics generates intestinal problems because it eliminates the intestinal microbiota, thereby triggering other problems (Table 2).

Nephrotoxicity is a well-identified side effect with the use of aminoglycosides. There are subclinical nephrotoxic effects after receiving drugs belonging to this family. However, clinical nephrotoxicity occurs more frequently in susceptible patients due to age or other diseases. Consequences recorded are renal or hepatic dysfunction, sepsis, and electrolyte alterations [5].

The toxicity of gentamicin has been associated with the concentrations at the time of administration of the drug dose, being more susceptible with high administration. There are reports that lethal enterocolitis can be induced with gentamicin. However, there are no clear references to the causative agent [12]. Erythromycin has occasionally been associated with acute colitis. Parenteral administration of the drug can induce severe diarrhea which is usually not fatal and stops with discontinuation of treatment [5].

During the administration of antimicrobials, there are common reactions thath are associated with inflammatory processes. Likewise, any antibiotic of beta-lactam class or others can provoke allergic reactions, presenting symptoms such as cutaneous rash, papular reaction, petechial, localized, or diffused. However, most of these conditions disappear with the suspension of therapy [2].

Anaphylactic reactions are rare, however, there are specific situations in the equine which are important to point out. Equines are especially susceptible to the effects of neomycin and this antibiotic can generate otic toxicosis, renal toxicosis or both [12]. Oral overdose induces a malabsorption syndrome and predisposes equines to develop superinfections caused by fungi which are manifested as fatal diarrhea [12].

It is important to point out that there is the possibility of facing an allergic reaction with any antibiotics. Among them are : allergy, where conditions such as dermatitis, urticaria, pharyngitis, and nervous reactions develop after long-term administration of treatment and cause symptoms such as convulsions or muscle tremors and local reactions [2].

The most serious complications are because these antimicrobials affect the microbiota and thus favor the proliferation of resistant pathogenic microorganisms. In horses treated with tetracyclines, severe and even fatal diarrhea can occur, especially if they are very sick or under a lot of stress. The elimination of the intestinal microbiota in monogastric animals reduces the availability and ability to synthesize vitamin B and vitamin K from the large intestine [12].

5. Conclusions

Several antibiotics such as amikacina, metronidazole, erythromycin, enrofloxacin, ampicillin, amoxicillin, rifampin, and gentamicin are used in equine and these antibiotics could cause microbial disruption. Notwithstanding, the overall use of antibiotics reduces fibrolytic activity of bacteria and the intestinal immune balance, gives opportunities to pathogenic microbes to overgrow in the gut segment, decreases microbial diversity and richness in feces and cecum. Antibiotics may be cause microbial instability which reduces the ability to produce or synthesize beneficial metabolites of amino acids, carbohydrates, lipids, nucleic acids, and cofactors, and vitamins. Thus, the mechanisms of action and conditions of the equines are important to choose the appropriate antibiotic for treating bacterial diseases.

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