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Mini-review Article

Why Do Antibiotics Fail? A Veterinary Perspective

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ABSTRACT

In both human and veterinary medicine, the failure of apparently appropriate antimicrobial therapy is a common and often exasperating clinical problem. Many factors are associated with the failure of antibiotic therapy, including an incorrect diagnosis of infectious disease, selection of the inappropriate antibiotic, and incorrect dosage. To achieve the best results, bacteriological diagnostics in the laboratory should be made. Even though the *in vitro* antimicrobial susceptibility testing guides the potentially suitable antimicrobials, the *in vitro* susceptibility obtained is not always the best *in vivo*. The clinician should be aware of other factors, including biofilm-forming bacteria, physicochemical conditions at the site of infection (such as perfusion rate, oxygen partial pressure, and pH value), or immunosuppression of the patient that can lead to treatment failure. This review summarized the main factors associated with antibiotic failure in a veterinarian practice. In a world where animal and human resistance to an antibiotic is rising every year, rational and efficient use of antibiotic therapy is of utmost importance. It is essential to continue with the education of veterinary practitioners in all aspects of antimicrobial resistance and treatment to improve future treatments and have a more rational use of antibiotics to reduce antibiotic resistance in animals and humans.

1. Introduction

According to the World Health Organisation, European Medicines Agency, Committee for Medicinal Products for Veterinary Use, and other agencies, there is a worldwide misuse and overuse of antimicrobials in veterinary and human medicine, leading to the increase of resistant bacteria worldwide[1–3].

Bacterial infections are a large percentage of the cases admitted to veterinary clinics. Therefore, optimization and rational use of antibacterial therapy are necessary to reduce the selection of resistant bacteria[2]. Veterinary practitioners must consider a variety of factors to prescribe antibiotic therapy, such as the severity of the disease, the etiological agent, drugs available on the market, additional therapeutic interventions, or symptomatic add-on therapy[2].

The clinical analysis can identify if it is a disease caused by infectious etiology. In the case of infection, animals usually present different symptoms, such as fever, leucocytosis, increased fibrinogen, and discopondylosis[1–3]. In the presence of any of these criteria, a correct laboratory diagnosis and subsequent antimicrobial susceptibility testing (AST) are important to achieve a good outcome.

In case it is not classified as an infection, preventive antibiotic therapy is only suitable in cases of strong suspicion of contamination or yearly infection[1,4].

In human medicine, the "90/60 rule" is based on the analysis that about 90% of bacterial infections respond positively to antimicrobial therapy if the antibiotic has been classified as susceptible *in vitro* tests[3].

In veterinary, this rule is not confirmed due to a few number of observations, so there are some limitations[2].

Treatment failure is usually detected by objective clinical criteria[4]. When the empirical antibiotic therapy fails, it is necessary to consider microbiological results, and if the first-line therapy chosen is inappropriate, the antibiotic should be changed immediately [4]. The antibiotic treatment sometimes seems to be falling because the

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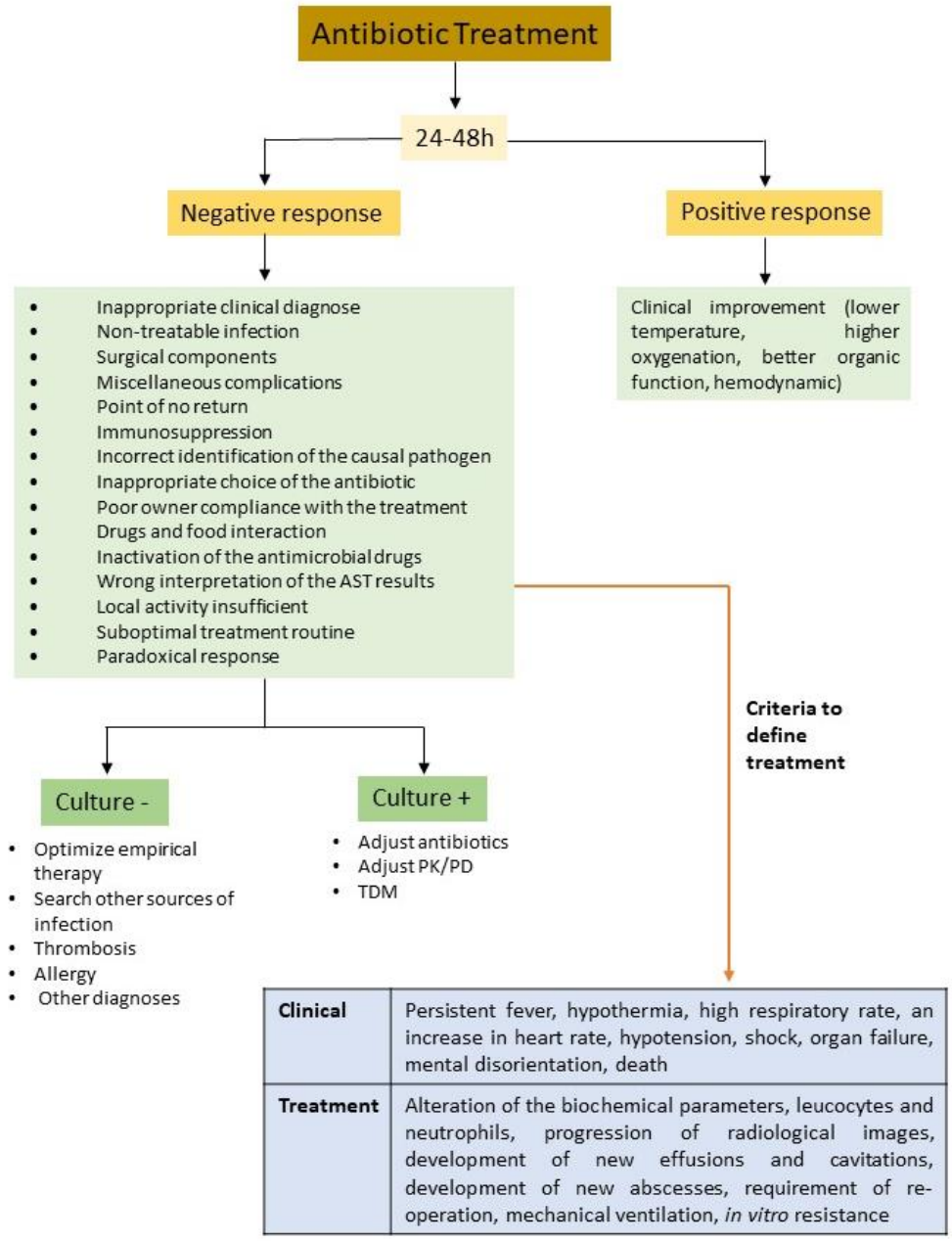

Figure 1. Algorithm to define antibiotic failure in the treatment of bacterial infections in animals

response is not immediate. Some patients can only show signs of response within 24-48 hours after the beginning of the treatment[5]. Figure 1 shows an algorithm to define antibiotic failure.

There are numerous factors associated with failure or insufficient response to antibiotic treatment in veterinary medicine. They can be grouped into two large groups as inappropriate diagnosis of bacterial infections and treatable infections with incomplete responses[4].

2. Inappropriate diagnosis of bacterial infections

2.1. Non-infectious disease that mimics infection

Some non-infectious diseases mimic infections because the organisms of vertebrates have a limited number of responses to aggression. For example, in a systematic inflammation (non-infectious), the patient presents a rise in the temperature, heart rate, respiratory, and white blood cell count. These parameters are also present in clinical infection cases, such as sepsis[5]. Several pathologies mimic symptoms of infectious diseases. Some examples are vasculitis, malignant hyperthermia, drug hypersensitivity, or adrenal insufficiency[5].

2.2. Untreatable Infectious diseases with antibiotics

Although considered infectious, viral, mycotic, and toxin-induced infections, these diseases should not be treated with antibiotic therapy[6]. Inappropriate diagnosis leads to the treatment with antibiotic therapy, which in

some cases appears to be working because some agents, such as azithromycin, have anti-inflammatory activity[5]. Unusual pathogens, such as *Rickettsia*, do not respond to the standard antibiotics used in clinic [6].

Before initiating the treatment, surgical components, such as abscess drainage, relief of obstruction, debridement of devitalized tissue, removal of foreign material/ prostatic material, and exclusion of persistent intravascular foci of infection are necessary in some cases[5]. Lung abscesses can drain themselves and are not necessarily surgically drained, but the remaining ones require their drainage surgically. If not drained, the patient will not recover. , without waiting for the antibiotic treatment to take effect, as waiting will not facilitate the process[5]. Clinicians should pay attention to the fact that in the early stages before the beginning of the treatment, metastatic abscess formation in other body sites, such as spleen, liver, subdiaphragmatic, and skeletal muscle[5] may occur in some cases (particularly immunosuppressed patients). Even if patients seem clinically stable, there is a possibility of them developing bacteremia despite negative microbial cultures. This can occur due to the release of specific components of the bacterial cell wall, such as endotoxins and exotoxins, into the bloodstream[6].

There are miscellaneous indirect complications of the inherent infection, including fever-drug hypersensitivity reactions, intravenous site infection, deep venous thrombosis, pulmonary embolism, urinary tract infection, atelectasis, aspiration, decubiti, adrenal insufficiency, myocardial infarction, unsuspected concurrent infection, and exacerbation of underlying disease[6]. Drug fever is another complication that can cause bradycardia and atypical lymphocytosis. Although all drugs have the potential to cause this problem, sulfonamides, penicillin, antiseizure, and diuretics medications are commonly associated with this phenomenon[5–7].

3. Treatable infections with incomplete responses

3.1. Incorrect identification of the causative bacterial pathogen

Correct identification of the agent is essential for a successful treatment[2,4,8]. The standard cultural media methods usually take at least 1-3 days. In severe cases, molecular techniques (PCR and nucleic acid lateral flow immunoassays are some examples) can offer faster and more accurate results[2].

It is crucial to establish the genus and species of the causative bacterial pathogen since many bacteria show intrinsic antimicrobial resistances (such as *Pseudomonas* spp.)[4].

For a veterinary practitioner's suitable identification of the pathogen, it is necessary to collect appropriate sample materials and communicate with the laboratory closely. Samples should be collected from acutely affected infections. An example is respiratory diseases, where samples collected from the trachea or a bronchoalveolar lavage will provide more precise results than those collected from the pharynx or nasal. The veterinary practitioners should give the diagnosis laboratory a sufficiently detailed report of animal species, age, sex, disease condition, sampling site, type of material, and any previous treatments. The laboratory should give detailed information on how to send samples, including sample volumes, preferred transport media, temperature (cooled or at room temperature), method of collection (aspiration, swab), and advice on the inexistence of antibiotic treatment at the moment of sampling and the three days before, no use anesthetics, such as lidocaine might exert antibacterial activity[2].

The misidentification or disregarding of a bacterial pathogen in polymicrobial infection cannot be discarded. Bacteria might not grow in the laboratory due to the culture conditions or be in a non-culturable stage although viable[2].

The isolation of an organism from a particular body spot does not mean it is responsible for the infectious disease process[2,7]. Epithelial mucosal and external body surfaces of animals are colonized by normal bacterial flora, constituted by bacteria and fungi[2,9]. These organisms are frequent contaminants of culture specimens. Some are always associated with colonization and only in very atypical cases with infectious processes, such as *Citrobacter*[7].

It is important to understand if the bacteria isolated in the culture is responsible for the infectious process. Pathogenic organisms are also frequent colonizers, which confuses their significance in cultures from clinical specimens. For example, in the case of Methicillin-resistant Staphylococcus aureus (MRSA) strains typically found in animals, most instances involve colonization, and only a small percentage of these cases lead to infection[2,7].

Colonization is generally not recommended for treatment because it is challenging to eliminate and attempting to do so may cause harm while also consuming valuable resources. Organisms that function as commensals in a specific body site are hard to eradicate because most antibiotics struggle to penetrate the secretions in which they reside, such as vaginal or nasal flora[7]. The treatment of commensal microorganisms can lead to side effects, such as hypersensitivity reactions, fungal superinfection, and antibiotic-associated diarrhea[7].

3.2. Uncertainties in antimicrobial susceptibility testing and evaluation of the results

A valid AST results allow clinicians to select the most efficient antimicrobial agent to which the causal agent is susceptible in *in vitro* conditions[2].

To obtain reliable results of AST, it is necessary to use appropriate methods in routine microbiological diagnostics, minimum inhibitory concentration, or disc diffusion, using guidelines from the veterinary Clinical and Laboratory Standards Institute (CLSI). Those guidelines allow a proper assessment of the AST results since they are veterinary-specific clinical breakpoints (VSCBs) and use quality

control ranges specific to veterinary. The VSCBs are specific for determined antimicrobial agents, bacteria, animal species, and organ systems[2], which are still limited in veterinary practice. *Ornithobacterium rhinotracheale, Riemerella anatipestifer, Bordetella avium, Avibacterium paraga-llinarum, Brachyspira* spp., *Lawsonia intracellularis,* and *Chlamydophila psittaci* are some of the agents for which no guideline is available[2]. In these cases, laboratories/clinicians often try to extrapolate from one animal species or similar bacteria[2].

The laboratory should point out the *in vitro–in vivo* disparity known to occur for some organisms. For instance, *Salmonella* spp. *in vitro* is susceptible to aminoglycosides but *in vivo* is not used, or *S. aureus* is susceptible *in vitro* to cephalosporins, but MRSA will not respond to treatment with these agents[5].

3.3. Discrepancies between in vitro and in vivo efficacy

3.3.1. Bacteria acquisition of resistance genes and development of mutations

It can rapidly acquire a resistance gene or develop a resistance-mediating mutation during therapy, mainly if subinhibitory doses of antibiotics are used or if an inducible resistance is encountered[2].

An infection generated by a multiresistant organism can flourish under the selective pressure of the prescribed antibiotic agent. Some bacteria have become resistant to many empiric treatments, and the prevalence and scale of this resistance will alter geographically[5].

3.3.2. Antibiotics not reaching the site of infection

Antibiotics administered per os can be ill-absorbed if there is a primary intestinal disease, bowel ischemia, superimposed ileus, edema, or interaction with food or medication (such as tetracyclines when administered with antacids or dairy products are inadequately absorbed)[2,7].

The central nervous system, eye, and prostate are protected anatomic locations because they have non-fenestrated capillaries[5]. Antibiotic agents cannot reach extravascular locations by passing between endothelial cells. These components can only pass directly through the cells[5]. Antibiotics that are lipid-soluble, such as chloramphenicol, rifampin, metronidazole, quinolones, doxycycline, and trimethoprim, can do that[5].

3.3.3. Antibiotics' inadequate local activity

Antibiotic inadequate local activity can be due to many factors, such as insufficient dosage, inactivation of antibiotics by low pH (aminoglycosides in abscesses or infected bone), inoculum size, incorrect route of administration, too short exposure to the antibiotic, effects of protein binding, low drug concentration in urine or bile, interactions with the immune system[5].

When tested *in vitro,* conditions are usually very different from the site of the infection. For *In vitro*, serum concentrations are used, and the concentration of an antimicrobial compound remains nearly constant during process[2]. During infections, the blood and tissue levels on the site fluctuate, and antimicrobial agents might accumulate on the infected tissue[2]. Moreover, *in vitro* tests are usually executed under aerobic conditions that can overestimate the susceptibility of the agent [2.] Usually, in the infected tissue, the conditions are microaerophilic or anaerobioses. The chemical composition of an agar medium regarding electrolytes, proteins, and folates is different from the infection site, can affect the antibacterial activity, and generally does not match the real conditions at the injection site[2].

Sub-inhibitory concentrations of antibiotics in the infection site can benefit phagocytosis, adherence, and intracellular killing[2,9].

3.3.4. Biofilm production

The biofilm formation is used in many serious infections, such as contaminated implants and medical devices, mastitis (*Streptococcus agalactiae*, *Staphylococcus aureus*), pneumonia (*Mannheimia haemolytica*, *Pasteurella multocida*), liver abscesses (*Fusobacterium necrophorum*), lymphadenitis (*Corynebacterium pseudotuberculosis*, *Streptococcus spp.*), enteritis (*Escherichia coli, Salmonella enterica*), and wound infections (*Staphylococcus aureus, Pseudomonas aeruginosa*)[2]. Biofilm production is not considered routine in the AST and has an impact on antibiotic therapy[2].

3.3.5. Presence of persisters

Persisters are subpopulations of bacteria that survive antimicrobial treatments without any resistance-conferring genetic changes. An example is in the lungs of patients with cystic fibrosis who select *Pseudomonas aeruginosa* with high-persister (hip) mutants[2]. They undergo a phenotypic switch to a dormant or protected state. They can be responsible for the development of chronic infections[2].

3.4. Inappropriate choice of antibiotic

Many compounds are not available in a suitable formulation in veterinary. Only certain veterinary medicinal products are authorized for determined animal species, depending on the national law. There is a restriction on the use of "Critical important Antimicrobials" from Group A from the categorization of antibiotics by the European Medicines Agency (EMA), which cannot be used in food-producing animals and only in exceptional circumstances administered to animals[1,10].

Due to the long waiting period for the microbiological and AST results, in many cases, veterinarians start the initial therapy of bacterial infections by empiric treatment. They are guided by the clinical presentation of the animal [8]. An example is the administration of antibiotics to production animals (chickens, rabbits) as prophylaxis in

farms and production[1].

Empiric selections should be made based on many factors, such as the location of the infection, understanding of the bacteria most prone to cause that type of infection, and data available on the resistance status of these bacteria (national and international resistance monitoring surveys)[1,8].

Samples for microbiological diagnosis should always be collected before initiating the treatment. The AST results will allow a fast shift to other antimicrobial agents that are more effective if the initial treatment is ineffective. The AST results allow the best selection of an antimicrobial agent that specifically targets the casual pathogen and reduces the selection of resistance in the pathogenic agent and the commensal bacteria[2,4].

Pharmacokinetic properties of the antibiotic are also important when choosing an antibiotic. Another factor is the improper use of bactericidal–bacteriostatic[5], toxicity factor of some agents (chloramphenicol is toxic given by the normal routes, and in veterinary is almost only used in topic applications), and antagonistic combinations, such as combinations of bacteriostatic antibiotic (tetracycline or chloramphenicol) and a bactericidal (penicillin)[7].

3.5. Insufficient therapeutic regimen and inappropriate handling of antimicrobial products

It is important to use the optimal antibiotic dosing regimens to avoid treatment failures and the selection of resistant subpopulations. In situations with a high bacterial density in the infection site, high doses of antibiotics should be given at the beginning of the treatment to exterminate susceptible and less susceptible subpopulations of bacteria and consequently increase therapeutic success[2]. Incorrect route administration can also affect the efficacy of the antibiotic on the infection site[7].

According to guidelines, the standard treatment duration is 3 to 7 days in acute infections, with some variation in some species, such as reptiles. The treatment should be extended to 15 days. Administering high doses of antibiotics for short periods can minimize the risk of developing resistant bacteria. More prolonged antibiotic therapies can sometimes be necessary, reliant on the patient's immune system status or the existence of other diseases simultaneously.

Clinicians should pay attention to the administration of animal owners at home. They sometimes administer low dosages; the dosing intervals are too long or too short for the treatment. The clinician should alert the owners about these problems[2].

The use of antibiotics as prophylactic should be used with awareness (such as before surgery or teeth extraction) because if the treatment begins too early, the sensitive flora of the target site is suppressed, and resistant strains can take over its place[7].

The inactivation of the active ingredients can occur due to pharmaceutical incompatibilities, poor storage, or use despite expiration[2].

3.6. Paradoxical response and the Jarisch-Herxheimer reaction

A paradoxical response to therapy is an immune reconstitution phenomenon exhibited by the apparent exacerbation of the infection, such as tuberculosis, where there is an expanding lymph node or pulmonary infiltrate. However, it improves immunologic responsiveness, and the temporary exacerbation can be treated with anti-inflammatory medications[2,5].

Jarisch–Herxheimer reaction can happen in spirochetal diseases (Lyme disease or leptospirosis), bacillary angiomatosis, and brucellosis. Fever, localized tissue damage, and myalgias, can occur due to the release of endotoxin or other pyrogens[5].

4. Conclusion

There are many possible causes of antibiotic therapy failure, from inappropriate choice of antimicrobial drugs, discrepancies between *in vitro* and *in vivo* efficacy, or non-infectious diseases wrongly diagnosed. The clinician should be aware of many factors when administering antibiotic treatment. When treatment fails, it is important to analyze the cause of the antibiotic failure by carefully evaluating the clinical case and using appropriate diagnostic tests and clinical history. It is essential to continue with the education of veterinary practitioners in all aspects of antimicrobial resistance and treatment to improve future treatments and have a more rational use of antibiotics to reduce antibiotic resistance in animals and humans.

Declarations

Competing interests

The authors declare that they have no competing interests.

Authors' contributions

Andreia Garcês conducted the research and prepared the manuscript.

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