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Review Article

Microbial Resistance Due to the Use of Antimicrobials in Livestock and Agriculture

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Abstract

Antimicrobials are widely used in agriculture and livestock, nevertheless their large-scale and indiscriminate use contributes considerably to the development of microbial resistance. The intense commercialization of agricultural products accelerates the dissemination of pathogens that present resistance profiles, which characterize them as extremely harmful to plants and animals. Thus, there is an urgent need to control the use of antimicrobials in animal and vegetable food products in order to find new agents that are less able to develop resistance. It is essential the guidance of the professionals and the population about the rational use of antimicrobials in agriculture and livestock for the maintenance and protection of the human healthy and environment.

Keywords: Microbial resistance; Antimicrobials; Livestock; Agriculture

Introduction

The discovery of antimicrobials is one of the greatest achievements in medicine, these drugs allow the cure and treatment of various infectious diseases, preventing millions of premature deaths. Nevertheless, the microbial resistance to antimicrobials has emerged in a short time from the beginning of its use [1]. Microbial resistance can be acquired through several mechanisms and be established between microorganisms from the same population or in different populations, either from the animal or human microbiota [2].

The indiscriminate use of antimicrobials in the treatment of animals in livestock, as well as in agriculture, can make these plant and animal food products a source of microorganisms with resistance profiles to antimicrobial agents, inflicting serious hazards to the consumers. Another worrying factor is that the development of resistance by certain pathogenic microorganisms is faster than the ability of the pharmaceutical industry to produce new effective antimicrobial agents to combat these microorganisms [3].

Owing to the need to control the use of antimicrobials in livestock and agricultural products and to seek out new agents that have less ability to develop resistance, several countries are currently developing projects and creating new laws with the endeavour to establish programs that can diminishes the resistance to the conventional drugs. In this context, these projects intend to establish educational campaigns to guide the professionals and the population through surveillance and monitoring of the rational antimicrobial use [4,5].

Infections in animals

Enteric bacterial infections in animals, especially in pigs, have been growing significantly and are frequently observed in different age groups, causing a great impact for the pig industry worldwide [6,7]. In addition, some of these microorganisms able to infect animals may be potentially pathogenic to humans, pose serious public health risks. The main bacteria associated with the pathogenesis of enteritis are Escherichia coli, Clostridium perfringens Type A, Type C and Clostridium difficile, Salmonella spp., Yersinia spp. and Campylobacter spp. [7,8].

Among the groups of pathogenic microorganisms, Escherichia coli, part of the normal intestinal microbiota of numerous hosts, such as mammals, birds and reptiles, are one of the main pathogens species responsibles for the infections in animals. Infections caused by enterotoxigenic and enterohemorrhagic E. coli are a significant cause of diarrhea in animals, especially in piglets, calves and lambs, as well as in humans [9,10]. Enterohemorrhagic E. coli, causes hemorrhagic colitis and hemolytic uremic syndrome in infected humans [10,11]. In healthy cattle contaminated with enterohemorrhagic E. coli, the large intestine is the main reservoir of this agent. The ability of this microorganism to cause disease, colonize the bovine gastrointestinal tract and survive in the environment, requires the production of several virulence factors, including virulence plasmids [12-14].

Salmonellosis is one of the most relevant bacterial diseases in animals. Salmonella typhimurium can be isolated from swine for slaughter and Salmonella enteritidis is the main cause of egg contamination without causing a discernable disease process in infected birds [15,16]. Although Salmonella typhimurium infection in pigs can develop enterocolitis, the infection is usually asymptomatic [17,18]. Pigs that are infected with these bacteria can carry Salmonella spp. in your tonsils, intestines and lymphoid tissue associated with the gut for weeks or even months and eliminates them slowly. This causes an increased cross-contamination during transport and as consequence a higher level of pig carcass contamination [18,19].

Infections with Mycobacterium avium can cause tuberculosis and occur mostly among ruminants. After infection, the animal may present the absence of clinical signs for a long period. Afterwards, clinical signs, such as decreased milk production, significant weight loss and diarrhea can appear [20,21].

Another microorganism that is gaining projection is Campylobacter jejuni. These bacteria colonize the gut of a wide range of hosts, such as chickens, turkeys, ducks and pigs as a commensal. Notwithstanding, C. jejuni emerged as the major bacterial cause of foodborne diseases in several industrialized countries [22-24].

Infections in plants

Several pathogenic species of microorganisms are responsible for infections in plantations, which are considered one the main causes of considerable losses in agricultural production worldwide and source of food contamination with harmful toxins to human health [25,26]. Bacteria, viruses, fungi and oomycetes are among the major biological plant pathogens and can be disseminated through soil, irrigation water, air and insects, especially arthropods [27,28]. The menace of plant infections is caused by trade and transportation, intensified by resource-rich farming practices, potentiated by the adaptive ability of microorganisms and influenced by climate change [29,30].

Among the microorganisms that affect plants, the most important are the filamentous pathogens, oomycetes and fungi, the main responsible for the infections in plantations, causing great devastation and crop losses [31-33]. The most studied microorganisms are Phytophthora, Aphanomyces, Pythium, Zygomycetes, Ascomycetes, Basidiomycetous and Deuteromycetous [33,34]. Phytophthora cinnamomi is listed as one of the 100 most invasive plant pathogens and Phytophthora sojae is considered the second most destructive pathogen in soybean plantations [34,35]. The genus Phytophthora spp. assemble structures in the host plant called haustoria, this structure is able to secrete more than 1000 effector molecules that act in the cytoplasm of the cells and act mainly by the suppression of RNA silencing, which is considered the main virulence strategy of these pathogens [36].

Plant pathogens have in common the ability to evolve strategies to evade plant defense mechanisms, thus ensuring their reproduction [26,32]. One of the most common strategies used by these microorganisms is the suppression of the host immune response through the secretion of effector proteins that modulate the genetic transcription of the plant and control the influence of environmental factors, such as climate and temperature, promoting the progression of infection [26,31,37].

Microbial resistance due to the use of antimicrobials in livestock and agriculture

Since the beginning of the antimicrobial use, the levels of microorganism resistance have increased steadily, raising dramatically over the past 15 years. The primary mechanisms of resistance reported in the literature are: the enzymatic modification or destruction of the antimicrobial agent (eg. destruction of β-lactam agents by β-lactamase enzymes); the prevention of intracellular accumulation of antimicrobials by reducing their cellular permeability (eg. resistance of the bacterium Pseudomonas aeruginosa against imipenem) or the presence of efflux pumps in bacterial cells (eg. enterobacteria resistance against tetracyclines); changes in antimicrobial target molecules (eg, intrinsic resistance of Enterococcus bacteria against cephalosporins), and production of alternative target molecules that are not inhibited by the drug, while continuing to produce the original target molecules, thereby bypassing inhibition (eg, Staphylococcus aureus resistance to methicillin) [2,38].

Regarding antimicrobial consumption in livestock, in 2009, 80% of the total amount of antimicrobial consumed in the USA was employed for non-human use and 64% of them were administered in healthy animals [39]. It is estimated that in the US in the mid-1990s, antimicrobials were used in livestock for up to eight times the amounts allowed by legislation [40]. In a similar way, in Australia it is estimated that 55.8% of the antimicrobials used throughout the country were added to animal feeds as a non-therapeutic strategy [41]. From this excessive use of antimicrobials in livestock, high risks of selection and propagation of multidrug-resistant bacteria have been developed. The consequences range from the direct transfer of antimicrobial resistance genes to the animal population on farms and slaughterhouses to even indirectly transfer through dissemination by the ecosystem, water and soil [42]. In the US, antimicrobial-resistant bacteria cause more than 2 million diseases and at least 23,000 deaths each year [43].

Studies have shown that in countries where avoparcin, a vancomycin-like drug, has been used in animal production, there has been an increase in the amount of vancomycin-resistant Enterococcus in the intestinal microbiota of the animals treated with

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this drug, as well as in the fecal microbiota of healthy humans and domestic animals [44,45]. It was also possible to observe that the discontinuation of avoparcin use lead to a decrease in the level of microbial resistance in animal production in European Union countries [44-46].

Related to the consumption of antimicrobials in agriculture, it can be observed that the production of agricultural products, such as grains, has doubled in the last 40 years due to the modernization of agricultural technology, as well as there has also been a 20-fold increase in the use of pesticides in as a prophylactic and therapeutic strategy against emergency infections [29,47]. The unrestrained use of pesticides can cause serious toxic effects in humans and in the ecosystem itself [48-50]. It is estimated that the concentrations of pesticides used by farmers are often higher than those recommended by international regulatory agencies [51]. One of the major problems related to the excessive use of pesticides in plantations is the increase in pest outbreaks due to the antimicrobial resistance acquired by these pathogenic microorganisms, causing enormous crop losses [29]. In the last decade several studies have reported the resistance of many species of fungi and oomycetes to fungicides [50] through a review of the literature, have listed more than 25 types of fungi and oomycetes resistant to conventional fungicides, such as the genus Phytophthora, Cercospora and Fusarium resistant to the drugs mefenoxam, methyl benzimidazole and carbendazim, respectively.

Moreover, the intense global commercialization of agricultural products accelerates the dissemination of harmful pathogens to plantations and animals, introducing new microorganisms originating from different regions of the globe [52]. Several studies have shown that the exchange of genetic material between microorganisms, through horizontal gene transfer and hybridization, is able of give rise to new species of highly virulent and antimicrobial-resistant pathogens [3,32,53]. An example of a new microorganism derived from these genetic transfers is the ascomycete Pyrenophora tritici-repentis, responsible for the brown spots on wheat plantations, for the reduction of grain quality and for crop yield losses reach approximately 50% [54,55].

Due to the relevance for controlling the use of antimicrobials in livestock and agriculture, countries of the European and American continent, recently launched new projects and legislation that aim to establish programs to control the resistance to these drugs in agriculture. In Brazil, for example, this program was published in 2017 through a normative instruction from the Ministry of Agriculture, Livestock and Supply, which provides strategic interventions such as health education, epidemiological studies and surveillance and monitoring of antimicrobial use [5]. In the European continent, the Pesticide Use-and-risk Reduction in European Farming Systems with Integrated Pest Management (PURE) project was launched between 2011 and 2015. The main purpose of this program was to comprise methods and tools, through integrative research, for the implementation-based solutions for the management of agricultural pests [56].

In this context, the search for new antimicrobials for pest control in agriculture, which can be less toxic to humans and have a lower ability to develop resistance, is growing worldwide [57]. Among the different strategies that have shown promising results are the use of biological control agents, including compounds produced by fungi such as oligosaccharides, lytic enzymes and volatile compounds which demonstrate a great potential as effective biocontrol agents [57,58]. Another type of biological control agent is Bacillus velezensis which has been widely used as an alternative to conventional pesticides and can produce a variety of secondary metabolites that have a broad-spectrum antifungal activity. Nonetheless, this research area is still insipient and needs further studies to elucidate the mechanisms of action of these biological agents [49].

Conclusion

The antimicrobial resistance has become a major problem for both human and animal health, causing high rates of morbidity and mortality and great economic losses for the general population. The indiscriminate and inappropriate use of antimicrobial agents in agriculture and livestock as an alternative for infection control and reduction on crop production losses has contributed enormously to the emergence of resistant pathogens. Revisiting this issue, it is imperative that the indiscriminate use of antimicrobial agents for non-therapeutic purposes be discussed and reviewed by the population and by the health regulatory agencies, aiming to promote the rational use of these drugs in both human and animal health. Thus, it is necessary a more rigorous global control of the use of antimicrobials in agriculture and livestock, and the search for new antimicrobial agents that present a broad-spectrum activity at low dosages with low impacts on the environment.

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