

Current perspectives on the dynamics of antibiotic resistance in different reservoirs

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Abstract

Antibiotic resistance consists of a dynamic web. In this review, we describe the path by which different antibiotic residues and antibiotic resistance genes disseminate among relevant reservoirs (human, animal, and environmental settings), evaluating how these events contribute to the current scenario of antibiotic resistance. The relationship between the spread of resistance and the contribution of different genetic elements and events is revisited, exploring examples of the processes by which successful mobile resistance genes spread across different niches. The importance of classic and next generation molecular approaches, as well as action plans and policies which might aid in the fight against antibiotic resistance, are also reviewed.

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1. Introduction

Many classes of antibiotics are not only clinically valuable in human medicine, but also in other fields such as veterinary medicine and animal food production, including aquaculture [1,2]. The agricultural setting also plays an important role in the spread of antibiotic residues in the environment due to

their use as additives and biocides in crops. Consequently, all adjacent natural environments consisting of water, soil and plants are environmental niches to be taken into consideration in the dynamics of antimicrobial resistance [3,4].

The use of antibiotics may have dangerous long-term effects that extend beyond selection of specific resistance mechanisms [5]. The selection pressure applied to bacterial communities via widespread discharge of antibiotic residues in the environment strongly contributes to the exposure of several niches to antibiotic-resistant bacteria (commensal and/or pathogenic) [6]. For example, use of animal manure may enhance viable antibiotic-resistant coliform bacteria in soil, increasing the frequency of detection of some antibiotic resistance genes [3]. These bacteria may reach the food chain, since vegetables are grown in soil [7]. Acquired antibiotic resistance is also frequent among isolates from wild animals

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which represents a niche of concern. Indeed, many reports point to wild animals as reservoirs of resistant determinants that commonly appear in other habitats, namely in human settings [8].

It should also be noted that bacterial resistance to antibiotics is related to soil and aquatic native microorganisms which may be producers of antimicrobial compounds [9,10]. Several other factors contribute to antibiotic resistance. Indeed, the existence of major anthropogenic actions such as international travel and global trade in foodstuffs strongly contribute to its amplification [11–14] (Table 1). A classical example of a vehicle for transmission of antibiotic-resistant bacteria is the human hand, which can become easily contaminated by environmental surfaces near patients in hospitals or animals in husbandry settings [15,16]. Consequently, the World Health Organization is strongly committed to making people aware of the problem of antibiotic resistance, and especially caretakers, namely through promoting hand hygiene for fighting antibiotic resistance [16,17].

Table 1

Antibiotic resistance is generated by several factors (adapted from [11–13]).

Factors depending on biological and physical influences:

Human activities
Animals (namely insects, birds, wildlife)
Water
Environmental changes
Wind
Changes in geographic localization of bacteria

Factors dependent on humans and their management of antibiotics:

Preservation of ecosystems (eventually bioremediation)
Intensive farming
Sanitation and hygiene measures
Runoff and leak
Manure
Demographic changes (increasing number of elderly people)
Anthropogenic contacts
Socioeconomic factors
Bioterrorism (biological war)
Travel of people and foodstuffs
Patient movement within and between medical institutions
Infection control measures (prevention of infection)
Appropriateness of use

Factors related to the antibiotic itself

Antibiotic use
Novel antibiotics
Dose of treatment
Duration of treatment
Antibiotic residues
Food additives
Selection of antibiotic resistant bacteria

Factors related to microorganisms

Wide spread of commensal bacteria
Extensive spread of old or new pathogens
Higher number of infections (opportunistic)
Increased number of host-pathogen contacts
Modification of microbial diversity

Factors related to the genetic basis of resistance

Cross selection
Non-antibiotic selection
Gene transfer
Clonal spread

There exists an urgent need to elucidate possible connections between antibiotics, environmental organisms and associated bacterial communities, as they may threaten diverse ecosystems and consequently human health [18]. In this review, we emphasize that these settings are linked and may constitute reservoirs of antibiotic resistance determinants, playing important roles in their dynamics.

2. Antibiotic residues versus resistomes in the environment

Before the antibiotic era, environmental antibiotic-resistant bacteria already existed, carrying genes that became critically important in medicine [19]. Indeed, for many years the environment consisted of an under-recognized reservoir of resistance genes that have the potential to be transferred and emerge in clinically important bacteria [20–22]. Groh et al. (2006) showed that homologues of multidrug resistance genes present in bacterial pathogens are essential for sediment fitness in non-pathogenic bacteria, by conferring an ecological advantage on these microorganisms [23].

Several reports have demonstrated the existence of antibacterial activity in extracts from different microorganism genera/species against distinct bacteria. A recent study showed that some antibiotic-resistant Gram-negative strains recovered from an industrial alpine location highly polluted with oil hydrocarbons had the ability to produce antimicrobial compounds active against Actinobacteria and Gammaproteobacteria. Thus, the selection pressure present in this environment could lead not only to high antibiotic resistance, but also to the capacity of this population to produce antimicrobial compounds [24]. LeBel et al. (2013) also demonstrated that the heat-stable bacteriocin nisin (naturally produced by *Lactococcus lactis*) displayed antimicrobial activity against the emerging zoonotic agent *Streptococcus suis* [25].

In fact, several studies have demonstrated that freshwater/marine bacteria are also able to produce antibacterial compounds that exhibit antimicrobial activity similar to standard drugs, which is the case for cyanobacteria [26]. In addition, it was demonstrated that extracts from *Anabaena* spp. were effective against vancomycin-resistant *Staphylococcus aureus* [27]. Some authors consider that cyanobacteria antibacterial activity is more effective against Gram-positive bacteria [28,29] than Gram-negative, attributed to the protection conferred by the lipopolysaccharide barrier of the Gram-negative cell wall [28]; however, some Gram-negative bacteria, including pathogenic species, are also affected by cyanobacterial compounds. The potential application of bacterial compounds to the development of new antimicrobials therefore appears to be a promising research area.

The relationship between bacteria and antibiotics may be approached in a variety of ways. In the case of cyanobacteria, considering their ubiquity and importance in the ecosystems [30], increasing concern has been attributed to the effects of environmental stressors in these bacteria. In fact, although cyanobacteria can easily adapt to different environmental conditions, they can also be severely affected by

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