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Antibiotic Resistant Genes in Natural Environment

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Abstract

The excessive use of antibiotics has contributed to emergence of antibiotic resistance in pathogenic bacteria. The environment and ecological habitats facilitate the transfer of the antibiotic resistance genes. To understand the pathogen ecology, it is now important to study antibiotic resistance in non-clinical natural habitats.

Keywords: Antibiotic resistance genes; Horizontal gene transfer; Ecosystem

Introduction

In early times, scientists considered antibiotic resistance in terms of adaptation to the toxic agents. For instance, Ehrlich worked on development of p-rosaniline resistance to *Trypanosoma brucei* as early as 1904. The resistance was observed during the treatment of trypanosome infections as the organisms emerged that were resistant to p-rosaniline. The drug inactivation was also discovered early as well [1]. In 1919, Neuschlosz reported *Paramecium caudatum* resistance to quinine and a dye that acquired the ability to destroy the toxic agent [1]. The emerging resistance in clinical isolates to penicillin was reported as early as 1941, resistance to sulfonamide in 1939 [2-4]. Miller and Bohnhoff observed resistance to streptomycin in 1947 [5,6]. The streptomycin was initially represented as the first breakthrough in the chemotherapy of tuberculosis [7]. However, relapses were soon observed with streptomycin-resistant *Mycobacterium tuberculosis* [8]. The resistance continued to develop for other antimicrobials as well. It was soon realized that resistance could emerge even in the absence of an antibiotic by transfer of antibiotic genes [1]. For instance, Hotchkiss demonstrated that penicillin resistance could be transferred to susceptible pneumococcus [1,9]. However, the most important step was to understand the prevalence of R-plasmids that help to better understand the resistance acquisition and dissemination [1]. The excessive usage of antibiotics in agriculture, aquaculture and livestock has resulted in selection for resistant bacteria [10]. The spread of antibiotic resistance genes by horizontal gene transfer via plasmids and mobile elements such as transposons has increased the acquisition of antibiotic resistance genes among species from antibiotic producers to commensal and pathogen bacteria [11,12]. Today, the focus is to understand the function of these resistance genes in their natural environmental hosts and understand the mechanisms involved in the emergence, and spread of antibiotic resistance.

Antibiotic Resistance Genes in Nature

One of the major concerns is distribution of antibiotic resistance in nature. Martinez [10] stated that "The analysis of bacterial isolates from pre-antibiotic era demonstrated that the copy number of different plasmids carried by pathogenic bacteria were essentially the same that can be found today". The pre-antibiotic plasmids did not carry the antibiotic resistance genes, therefore the acquisition and further dissemination among pathogenic bacteria is the consequence of strong antibiotic selective pressure as a result of antibiotic therapy [10]. Antibiotic resistance genes are mostly chromosomally encoded and are associated with mobile elements such as transposons. They can also be found in microbiotas that are not in contact with antibiotics [13,14]. The association of antibiotic resistance genes with mobile element has spread between bacteria of different species and genera via horizontal gene transfer (HGT). There is evidence that emergence of virulent strains of *Salmonella* in the food supply is linked to HGT [15,16]. The whole genome analysis has further shown that horizontal transfer has modified various genes, operons and islands within *Salmonella* chromosome [15]. However, the understanding of how HGT has altered the genomes of *Salmonella* pathogens can help to devise new risk evaluation strategies to detect this food borne pathogen [16,17]. The antibiotic resistance by horizontal gene transfer has a major role on the development and spread of antibiotic resistance genes.

The antibiotic resistance genes have originated in the environmental bacteria mostly as antibiotic producers. They are also known to have a physiological role [18,19]. One of the important examples is chromosomal penicillin binding proteins (PBP) that contribute to resistance to antibiotics [20,21]. The research literature has reported that PBP have evolved from transpeptidases that are physiologically involved in cell wall synthesis [18,22,23]. The resistance is commonly due to mutation or overproduction of PBP. For instance, *Enterococcus faecium* isolated from United States hospitals was shown to be highly resistant to ampicillin due to mutation or over production of the PBP5 [24,25].

Changes in Natural Ecosystem

The change in environment has affected our natural ecosystem. The chemical pollution, industrial activities, mining, intensive farming have resulted in selection of antibiotic resistance determinants in the environment. The selection is favored due to ecological advantage to the bacterium in its habitat [26]. They have acquired various mechanisms for adaptation to changing environment. The research study has reported that co-selection/cross-selection is frequently linked on the same plasmid [27]. The disposal of domestic and industrial waste has affected human health and environment. The toxic effects of heavy metals such as copper, cadmium, lead, zinc, nickel, mercury and chromium can be toxic to plants, animals, humans and aquatic life when accumulated in soils at higher concentration [28]. The presence of heavy metal in soils is also responsible for their persistence in the food chain. This could spread the antibiotic resistance genes among

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bacterial populations. For instance, bacterial strains isolated from tannery waste water such as Flavobacterium sp have shown tolerance to copper, zinc, mercury and lead [28,29]. The *Pseudomonas species* isolated from the waste showed tolerance against all antibiotics except ciprofloxacin. The *Pseudomonas species* also showed tolerance to heavy metals such as lead, copper, zinc, mercury and chromium [28-31]. The clearance of industrial waste has also caused contamination of rivers and lakes. The research study has shown that *Providencia stuartii* strain isolated from contaminated river has shown resistance to all antibiotics including carbapenems [32]. The use of several classes of antibiotics in aquaculture, including sulfonamides, quinolones, macrolides, tetracyclines and emamectin has increased considerable risk of release of antimicrobials into the environment and eventually the possibility of development of resistance in pathogenic bacteria [33,34].

Antibiotics in Agriculture

The excessive usage of antibiotics in agriculture, aquaculture and livestock may selects for resistant bacteria as large amount of antibiotics may find their way into natural habitats. The most commonly used antibiotic in agriculture is oxytetracycline and streptomycin [29]. The use of streptomycin has resulted in streptomycin-resistance strains of *Erwinia amylovora, Pseudomonas species,* and *Xanthomonas campestris*. The research study has reported that fraction of streptomycin-resistance genes in plant-associated bacteria are related to those found in bacteria isolated from humans, animals, and soil, and are associated with mobile elements [35]. The use of antibiotics such as avoparcin, which is a glycopeptide antibiotic, as a growth promoter on poultry and pig farms has resulted in increase in resistance to vancomycin [36-38]. The genetic modified organism needs to be carefully analyzed before they are introduced in the field as they may cause spread of antibiotic resistance genes in the population. The usage of *Burkholderia cepacia* for bioremediation and as promoter for crop growth need to be analyzed as it may also cause infection in immune compromised patients [39,40]. The regulations to curb the use of excessive antibiotics should be implemented to prevent the spread of resistances.

Conclusion

The ecological communities are the product of biotic and abiotic forces that are influenced by habitat and environmental conditions [41]. The study of transmission, intrinsic resistance to antibiotics and tendency to accumulate resistance genes are needed to understand the underlying mechanism [42]. However, pathogen ecology is not a part of current antibiotic treatment guidelines. The current drug regimen is mainly based on clinicians experience rather than on systematic evaluation of the trade-off between treatment success and resistance [42]. This can potentially increase the rate at which the resistance evolves and spreads to other bacterial populations. For instance, there is evidence suggesting that the rise of vancomycin-resistant enterococci in the United States during the 1980s was probably driven by excessive use of oral vancomycin for *Clostridium difficile* [37,42,43]. The emerging resistance in bacterial species makes it more important to understand the relationships between dosage, pharmacokinetics and therapeutic efficacy from the standpoint of bacterial resistance [42]. However, guidelines based on differences and diversity in ecological dynamics for the same bacteria in different habitats in the body could contribute to dramatically reduce the volume of antibiotics consumed and selection for resistance [44-46]. The study of antibiotic resistance in natural ecosystems is still underway. The most important question that is not yet answered is distribution of antibiotic resistance genes in nature.

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