Antimicrobial Resistance in Environmental Microbiome: An Overview

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Abstract

Antimicrobial resistance (AMR) is a great concern worldwide distressing the health of humans and animals directly or indirectly, which is truly problematic for the clinicians in disease control. This chapter highlighted the manifestation and spread of AMR and AMR genes (ARGs) in the environment that resulted from the human intrusions. Natural environments were less reported for the outbreak of pathogenic microbes, but with the human interventions such as the effluents of hospital wastes, human and animal wastes, etc. converted them into hotspots for antimicrobial genes by providing suitable medium for the exchange of ARGs among the organisms. Moreover, they can also serve as vehicle for the transfer of pathogenic microbes between human and animals that resulted in a wider epidemiological issue. Therefore, proper surveillance of microbiological risks should be there to maintain a healthy microbiome. It is a huge task to functionally characterize environmental microbiomes by conventional isolation method, with advances in high-throughput sequencing and computational biology today permit researchers the exploration of even un-culturable microbes by using metagenomics approach, which have been used effectively not only in determining the diversity of microbes but also in the characterization of pathogenic and antibiotic resistance microorganisms that can be a great help in this regard.

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2.1 Introduction

Antimicrobial agents have been successfully used for the past many years to treat and reduce infectious microbial diseases. But in time, overuse and misuse of antibiotic in the past few decades has tremendously increased the number of resistant bacteria which accounts for thousands of human deaths every year (Jørgensen et al. 2017). It has been well reported that different microorganisms including bacteria, parasites, viruses, and fungus are well capable of developing resistance which infers that the antimicrobial agents have become less effective to that particular microorganisms (Alexander et al. 2013; Mediavilla et al. 2016).

Antimicrobial resistance (AMR) is when an antimicrobial agent becomes less effective to certain microbial pathogens by losing the ability to inhibit or kill the pathogens which were previously susceptible; this leads to the persistence of the particular disease in the body. This also increases the risk of spreading to others. Infections caused by AMR bacteria may lead to morality, prolong the hospital stay, etc. (de Kraker et al. 2011). AMR is a global concern as it is known as the major problem to human and animal health with significant impact on the economy (O'Neill 2017).

The occurrence of AMR is mainly due to the overuse and misuse of the antimicrobial agents for disease control, treatment, and prevention. Antimicrobials used for growth regulators in animals and the misuse of prescribed human medicine have highly contributed to the AMR (Brinkac et al. 2017). As the usages of antimicrobials have increased, the complexities on which the bacterial pathogens exhibit the resistance mechanisms have also increased. Scientists are struggling to have control against infections, but the development of new antimicrobial agent is not manageable to cope up with the rate of increasing resistance since microorganisms evolve to have better resistance mechanism (Krause 1992).

The genes encoded for their AMR are capable of moving to other microbes through vertical and horizontal gene transfer and further incorporated into the normal microbiota of human beings, animals, and environment which includes food, sewage, soil, and water. This underlying forces and development of AMR depend on the communication linkages connecting all these ecological, biological, and genetic entities (Baquero et al. 2019).

The transmission of AMR to human is well documented, and the natural environment serves as a major passage by which transmission has occur (Davies and Davies 2010). The level at which this transmission may occur remains uncertain. It is comparatively important to understand the role of environment for the transmission of antimicrobial bacteria to humans rather than the transmission through animal carriers, food, or the flow of AMR in healthcare and community settings (Huijbers et al. 2015).

AMR bacteria are most commonly found in infirmary settings which possibly reached to different environments such as wastewater treatment plants (WWTPs) via hospital wastes and the wastewater associated with this environment (Hocquet et al. 2016). The further route for these AMR bacteria is unknown that no trace in WWTPs (Flach et al. 2018) while a number of reports have been found on AMR bacteria conceivably of hospital origin which survive the treatment process and thereby are released into recipient waters (Rizzo et al. 2013).

There are certain monitoring surveillance program setup by different networks to monitor AMR bacteria which has increased the knowledge of dissemination of resistant bacteria, for example, the European AMR Surveillance Network (EARS-Net) (European Centre for Disease Prevention and Control 2017), ECO-SENS (Kahlmeter and Poulsen 2012), and Central Asian and Eastern European Surveillance of AMR (CAESAR) (World Health Organization 2015). This chapter highlighted an overview on the manifestation and spread of AMR and ARGs in the environment that resulted from the human interventions.

2.2 Antimicrobial

Antimicrobials remain the most significant pharmaceutical products in the management of bacterial infections, both humans and animals globally (WHO); this has become a global concern with the evolution of new pathogens. Moreover, it has played a key role in the development of sustainable livestock production by giving them healthy life besides serving as food preservatives and growth regulators; they also help in the control and management of the possible risks associated with infectious diseases that are zoonotic.

2.3 Antimicrobial Resistance (AMR)

The World Health Organization defined AMR as the resistance of a microorganism to an antimicrobial drug that was originally effective for treatment of infections caused by it. The overuse and misuse of antimicrobials has caused the occurrence of resistant microorganisms and therefore gave birth to the term AMR (Davies and Davies 2010). Microorganisms are extremely adaptive organisms even under unfavourable conditions; they can undergo mutations and are able to survive in several environmental stresses. Therefore, the rise in AMR is not a surprise rather it was much predictable with the invention of the first antimicrobials. The first antimicrobial-resistant strain *Staphylococcus aureus* was isolated from a patient in British hospital in the year 1948 which was found to be resistant against Penicillin (Barber and Rozwadowska-Dowzenko 1948). Later in the same year, *Mycobacterium tuberculosis* was observed to be resistant against streptomycin (Crofton and Mitchison 1948). After that in 1950s, a bunch of pathogenic bacteria such as *Escherichia coli*, *Shigella* spp., and *Salmonella enteric* showed AMR (Watanabe 1963; Olarte 1983; Cantas et al. 2013). Later on VRE (vancomycin-resistant

Enterococci), MRSA (methicillin-resistant *Staphylococcus aureus*) were found in the 1960s which leads to the idea of multidrug-resistant bacteria where the microbes are resistant to at least three antimicrobials (Marshall and Levy 2011).

2.4 Origin of AMR in the Environment

Different sources where the AMR is believed to be originated such as hospitals, waste water, animal farm, and agriculture (Fig. 2.1) have been reviewed and highlighted as described below. *Enterococci* was found to be the most dominant AMR organisms in the selected site followed by *S. aureus* and *E. coli.* Vancomycin resistance was found to be the most dominant antimicrobials in the selected study sites (Table 2.1).

2.4.1 Hospitals

Hospital-acquired infection which is also termed as nosocomial infections are of a serious concern with regard to AMR (Monnet et al. 1998). The normal bacteria usually commensal that becomes pathogenic when they multiply in normal sterile sites, such as the lower respiratory tract or the blood, are usually the type of bacteria that are responsible for nosocomial infection (Bonten and Weinstein 1996). For limiting nosocomial infection especially to reduce antibiotic-resistant bacteria, several measures have been taken up such as maintaining proper sanitation like frequently washing hands and barrier precautions within the hospital (Slaughter et al. 1996). The main transmission from one hospital to another hospital takes place when one hospital refers patients for various reasons to another hospital; in this way, the patient may transfer hospital-acquired pathogens between healthcare institutions.

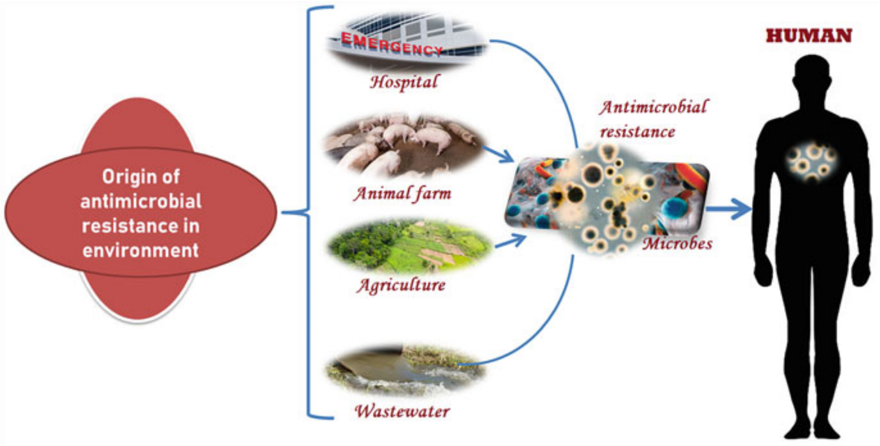

Fig. 2.1 Origin of AMR and their gene flow

Table 2.1 Selected common resistance microorganisms with antimicrobials and their origin

S. no	Origin of antimicrobial resistance	Microorganisms	Antimicrobials	References
1.	Animal farm (pig farm)	*E. coli*	Cephalosporin	Agersø and Aarestrup (2013)
2.	Animal farm (pig farm)	*E. faecium* and *E. faecalis*	Tylosin	Agersø and Aarestrup (2013)
3.	Animal farm (broiler farm)	*E. faecium*	Avilamycin	Aarestrup et al. (2001)
4.	Animal farm (chicken farm)	*E. coli* and *Salmonella enterica serovar Heidelberg*	Ceftiofur (a third-generation cephalosporin)	Dutil et al. (2014)
5.	Wastewater (hospital effluent)	*Enterococci*	Amoxicillin	Leclercq et al. (2013)
6.	Wastewater (hospital and community effluent)	*Enterococci*	Vancomycin	Caplin et al. (2008)
7.	Wastewater (sludge)	*Enterococci*	Vancomycin	Bates et al. (1994)
8.	Animal farm (poultry manure)	*Enterococci*	ESBL	Blaak et al. (2014)
9.	Soil (manure-amended)	*Staphylococcus aureus*	Methicillin	Huijbers et al. (2015)
10.	Soil (agricultural soil)	*Enterococci*	Vancomycin	Huijbers et al. (2015)
11.	Hospital (patient)	*Klebsiella pneumoniae*	Carbapenem	Zhao et al. (2019)
12.	Hospital (patient)	*Staphylococcus aureus*	Methicillin and vancomycin	Heinze et al. (2018)

Through the shared patients, different hospitals become connected (Donker et al. 2010) which eventually lead to the transmission of MDR (multidrug-resistant) pathogens like MRSA (methicillin-resistant *Staphylococcus aureus*), VRSA (vancomycin-resistant *Staphylococcus aureus*), etc. On the other hand, wrong or unnecessary prescription of antibiotics to patients by doctors is the major cause of AMR in hospitals. In 2010, India was the largest consumer of antibiotics when assessing total tonnage; however, their per capita usage (7.5 units per capita) was comparatively low as compared to Australia and New Zealand which recorded among the highest usage rates of 87 and 70 units per capita, respectively (Van Boeckel et al. 2014).

2.4.2 Wastewater

Wastewater coming from different sources could be a favourable habitat for resistant bacteria and resistance genes (Munir et al. 2011; Reinthaler et al. 2013). Resistant bacteria may reach the wastewater treatment plants (WWTPs) from hospital water as discussed above, since resistant bacteria are abundantly present in hospitals (Hocquet et al. 2016). Some studies have suggested the correlation between resistances rates among bacteria present in wastewater with corresponding to human population in that particular area. Therefore, basic research on the resistance rate of the indicator bacteria such as *E. coli* in wastewater is an important tool to observe the changes in the resistance pattern of the normal human intestinal microbiota (Blanch et al. 2006). For instance, *Enterococcus faecium*, i.e. a Swedish clone that carries ampicillin and fluoroquinolone resistance, could be traced from its hospital origin (Torell et al. 2003) to wastewater coming out from hospital (Iversen et al. 2002). The clone was further found in untreated water and the samples were still further found in receiving waters (Iversen et al. 2002), which is likely a source for hospital origin, antibiotic resistance bacteria colonization in human. In addition to this, a high bacterial population are found in biofilms from wastewater system especially from activated sludge of sewage treatment plants. Biofilms are also generated in surface water and drinking water distribution systems (Schwartz et al. 2003).

2.4.3 Animal Farm

Animal husbandry has extremely increased over the past five decades worldwide. According to FAO, 2018 global meat production has almost increased in fourfold, from 84 million tons in 1965 to about 335 million tons in 2018, and it is assumed that this is likely to be continued. Antimicrobials are used extensively in farm animals for the treatment of certain diseases as well as for growth regulators. Therefore, animal farms are zoonotic pathogen reservoirs, as well as sources of veterinary antimicrobials and ARGs. This kind of case happens in countries that produce antimicrobials in large amount without any essential regulation (Wellington et al. 2013). Stokstad and Jukes were the first to report the used of antimicrobials in farm animals after noticing a small doses of penicillin and tetracycline could enhance growth (Stokstad and Jukes 1950). After that, the use of antimicrobial agent in farm animals has increased. For instance, in China, antimicrobials have been used as low-dose feed additives for livestock and poultry since the mid-1970s; since then, China is currently the leading country in the production and consumption of antimicrobials for animals worldwide (Zhu et al. 2013). In many underdeveloped and developing countries, where the resources do not meet the requirement of the people, the use of antimicrobials is increasing rapidly due to the high demand for animal protein, shifting animal husbandry into large-scale industry. For example, BRICS countries were estimated to consume 99% increase of antimicrobials from 2010 to 2030 (Van Boeckel et al. 2019). In addition to this, the manure produced by these farm animals was found to constitute a great number of antimicrobial-resistant bacteria, where the genes associated with antibiotic resistance, ribosomal protection, and enzyme inactivation mechanisms were commonly detected in such manure and the soils where applied (Cadena et al. 2018).

2.4.4 Agriculture

The extensive use of antimicrobials in animal farm has increased the number of AMR as well as antimicrobial genes inside the animal body. Reports have shown that manures collected from such farms to fertilize the soil of agricultural land has introduced novel ARGs to the soil as well as enriched the naturally present ARGs (Yu et al. 2017). Even though, samples collected and analysed from an isolated soil have suggested that ARGs also occurs naturally in the soil (Miteva et al. 2004; Bhullar et al. 2012). But ARGs are more abundant as compared to the isolated native soil, which suggested the enrichment of agricultural soil with ARGs with the application of manures (Davies and Davies 2010). From agricultural land, it will be eventually transported through the waterways and will contaminate the water quality.

2.5 Resistance Transmission

The flow of AMR and the genes associated have been observed from microorganisms to microorganisms, animal to human, and environment to human.

2.5.1 Microorganisms to Microorganisms

Occurrence of one mutation to cause resistance on microorganism is well known. In addition to that, the new mutated genetic material can be exchanged between one microorganism to another which in turn may lead to the host cell and its progeny to have new AMR genes, following different mechanisms mostly through plasmid transmission (Walsh et al. 2011; Unemo et al. 2012). The emergence of AMR is influence by antimicrobials using a selective pressure, also by inducing transfer of resistance determinants between microbes (Beaber et al. 2004).

2.5.2 Human to Human

Transmission of resistance microbes may occur between human to human contact, and this type of transmission is one of the most common ways of transmission. In the community, faecal–oral transmission is the most common route of transmission which is often due to poor sanitation. This type of transmission plays an important part especially in the transmission of resistant Enterobacteriaceae (Wellington et al.

2013). In addition, sexual encounters may also lead to the transmission of resistant bacteria, for instance, *Neisseria gonorrhoeae*, which leads to a widespread distribution of resistant clones (Lewis 2013). Hospital or healthcare-associated infections also play vital role in the transmission, if proper sanitation is neglected. For example, healthcare workers' hand is an important mode of transmission of resistant bacteria such as methicillin-resistant *Staphylococcus aureus* (MRSA) if proper sanitation is not maintained (Chamchod and Ruan 2012).

2.5.3 Animals to Human

The transmission of antimicrobial-resistant microbes from animals to human beings, which is due to the use of antimicrobial growth promoters in farm animals, was first recognised in the 1960s (Anderson and Lewis 1965). Bacteria and mobile genetic elements consulting resistance may remain on animal skin and in faeces, and by any means, the mobile genetic elements may be transferred to bacteria, and eventually the bacteria will however direct to humans (Kruse and Sørum 1994). This intertwining of animal and human microbial population includes both commensals and opportunistic pathogens, which may include *E. coli*, *Enterococci*, and *Staphylococcus aureus*. There are certain evidences to support the transmission of resistant bacteria from animals to human beings. For instance, ESβL and AmpC-β-lactamase genes on plasmids and of *E. coli* possibly through food chain clones have been reported (Kluytmans et al. 2013).

2.5.4 Environment to Human

Environment such as soil, water, drainage system, etc. may also transmit resistant bacteria to human beings. The contribution of the environment to AMR transmission is a global concern. This existed to be confirmed by the isolation of AMR microbes in several sewage systems (Kristiansson et al. 2011). These opportunistic AMR pathogens have enormous chance of transmission to human beings. These indirect transmissions are not well studied and are a great area of research interests with the advancement of high-throughput metagenomic approaches.

2.6 Mechanism for the Development of AMR

AMR could be either innate or acquired in microorganisms. In some species of bacteria, resistance to any one class of antimicrobial agents are innate. In such cases, all the strains of that particular bacterial species are resistant to all the members of that antibacterial class. Since innate resistance is a naturally occurring process, it is of a lesser concern. The more serious concern is acquired resistance where microbes which were previously susceptible to a particular antimicrobial agent developed resistance, which means that antimicrobial agent has lesser effect on that microbe.

These resistant bacteria will proliferate and spread under the selective pressure of use of that agent. The mechanism includes the following: First step is the attainment of the genes encoding enzymes such as β-lactamases, capable of destroying antimicrobial agent before having an effect. Second step is the removal of antimicrobial agents out from the cell where the bacteria may acquire efflux pumps for forcing the antibacterial agent terminating its effect before reaching the site of action. Third step is the alteration of bacterial cell wall by acquiring several genes for a metabolic pathway modifying the binding site of that particular antimicrobial agent. There is also a possibility that bacteria may hamper the entry of antimicrobial agents inside the target cell via downregulation of porin genes by mutation. In this way, susceptible bacterial populations may attain resistance to antimicrobial agents through mutation and selection or by acquiring the resistant gene from other bacteria. Resistance to multiple classes of antimicrobial agents mainly occur due to the exchange of genetic information from one bacterium to other bacteria. Such kind of bacteria that shows resistant to at least three classes of antimicrobial agents are termed as MDR (multidrug-resistant) and have become the most critical issues and challenges, mostly in hospitals and other healthcare institutions where they tend to occur most commonly. Although a single mutation may not be enough to acquire resistance, it could reduce the susceptibility and may be the key to acquire additional mutations or additional genetic information resulting in full resistance to the antibacterial agent (McManus 1997).

2.7 Future Perspectives and Conclusions

The development of AMR is a great concern worldwide. This leads to search for alternative sources for drugs having potential to inhibit MDR pathogens. The major issue in the development of AMR is the misuse and overuse of antimicrobials. There is a need to understand the proper use of antimicrobials to avoid further development of AMR.

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Conflict of Interest The authors declare that there is no conflict of interest.

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