Article

Antibiotics in hospital effluents and their impact on the antibiotics resistant bacteria and remediation of the antibiotics: A review

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Abstract

Antibiotics since their inception are widely used for medical remedies for human and animals. Due to global economic prosperity, the consumption of antibiotics has increased during the last decade. The misuse, overuse, and application of antibiotics as manure has caused elevated development of multi-antibiotic-resistant bacteria posing environmental pollutant and causes serious risks to human and veterinary health. Antibiotics in the environment affect fundamental ecological processes, biogeochemical cycling and organic contaminant degradation via microbial communities. Antibiotics in the environment affect microbial community structure and function in two ways: direct (short-term) and indirect (long-term). The indirect effect causes the development of antibiotic-resistant bacteria and bacterial strains which can degrade them by metabolic or co-metabolic processes. This review presents the global occurrence of antibiotics in drinking water, sewage water, hospital effluents, river water, sediments, and manures. The results denote the concentration of antibiotics in water samples and soils are in the high range causing chronic toxicity in aquatic systems. This review also provides an overview regarding the antibiotics resistant bacteria and genes developed and regarding their remediation. As the use of antibiotics is expected to increase in the next decade due to the aging population and standard of living, the antibiotics will pose an additional environmental risk.

Keywords antibiotics; bacteria; hospital effluent; remediation; wastewater; phytoremediation.

1 Introduction

A number of crucial biological activities in the diverse ecological conditions are performed on the earth by the bacteria even long before humans made their presence on the earth. The humankind studied a number of the natural processes involving bacteria and advantageously used these processes for the welfare of society. A comparatively a small proportion of bacterial species are pathogens but some of these are responsible for infectious diseases that may have devastating impacts on human and animal health. The activities of antibiotic compounds, natural and synthetic, have been exploited by humans to fight bacterial infections since last

century. And with the invention of penicillin in 1927 antibiotics are used as the 'Panacea' for human and animal infection treatment. To manage the potential risk to human health caused by antibiotic-resistant bacteria and antibiotic-resistant genes, understanding the central role of the environment is very essential. Development of resistance in microbes to antimicrobial substances is a natural process and occurs throughout all of microbial evolutionary history. Anthropogenic activities underuse, overuse and misuse of antibiotics in medical therapy result in the development of antibiotic resistance in bacteria, an example of the ecological footprint (Frieri et al., 2017), describing the increase in impacts on natural processes. This review paper discusses the environmental contamination of antibiotics in hospital effluent, domestic effluent, wastewater treatment plants and in sewage sludge. The response by natural microorganisms to antibiotics in terms of resistance and remediation of antibiotics from natural sources is also reported.

2 Antibiotics in Hospital Effluent, Domestic Effluent, Wastewater Treatment Plants and in Sewage Sludge

Antibiotics with the invention of penicillin in 1927 are used for the treatment of infections in human, animals and as a food supplement to promote the growth of food animals (Sim et al., 2011). Annual worldwide production of antibiotics is more than one lakh tons (10^5 tons; Bbosa et al., 2014), out of which more than 50% are given to farm animals, fish and trees for disease prevention and growth promotion (Balzer et al., 2016). According to the IMS report, the human consumption of antibiotics in 2010 was 70 billion standard units (Van Boeckel et al., 2015), while global consumption of antibiotics for animals was 63151 tons which are expected to rise to 106000 tons by 2030 (Laxminarayan and Chaudhary, 2016). After consumption, the antibiotics are partially metabolized in the gut of human and/or animals and about 30-90% are excreted unaltered or as active metabolites via urine and feces and is released into the waste system, soils (Masse et al., 2014). Antibiotics are present as contaminants in a variety of environmental systems it is mainly due to disposal of expired medicine in the sewage system, excretions of un-metabolized pharmaceuticals from humans and animals, discharge of wastewater and surface runoff to receiving water, land application of biosolids (Sadek et al., 2013; Bole et al., 2013; Aali et al., 2014; Borecka et al., 2015; Rezka and Balcerzak, 2016; Kivits et al., 2018). Antibiotic compounds have a suspicious reputation among the class of pollutants referred to as 'emerging contaminants' as the biological activity of antibiotics is an intrinsic characteristic of their functional design.

Hospital wastewater is the wastewater generated from all the activities of the hospital (medical and non-medical) from the operating, emergency and first aid, laboratory, diagnosis, radiology, kitchen and laundry (Sadek et al., 2013; Prasad et al., 2018). The hospital wastewater is drained directly into the sewage system and the sewer water is generally used by the developing countries for crop irrigation. Some of the wastewater also reaches in animals' drinking water ponds. Pathogenic microorganisms (bacteria, viruses), residual of medicines particularly antibiotics and residual of chemicals from the laboratory are the harmful pollutants present in the hospital wastewater (Abd El – Gawad and Aly, 2011).

Antibiotics are present in the surface, drinking-groundwater in the number of countries, as per UN report (Aus der Beek et al., 2016a), sulfamethoxazole is present in 47 countries; trimethoprim in 29 countries; ciprofloxacin in 20 countries; norfloxacin in 15 countries and ofloxacin in 15 countries. Brown et al. (2006) reported that 58% of wastewater samples of Rio Grande (New Mexico) contain at least one antibiotic and 25% more than three and the hospital effluents contain four or more antibiotics. Antibiotics sulfamethoxazole, trimethoprim, ciprofloxacin, ofloxacin, lincomycin, and penicillin G were mainly found in the hospital effluents. The concentration of antibiotics in the residential and hospital effluent was up to 35500 ng/L while in the dairy the effluent was 700-6600 ng/L. Verlicchi et al. (2012) during their research found that urban waste water and hospital effluents contain antibiotics ng/L to µg/L. Ahmad et al. (2012) reported that the

concentration of antibiotics in the hospital effluent was 7.31 to 39.13 µg/L while in the municipal wastewater it was 0.26-0.43 µg/L. They also found that when hospital wastewater is mixed with municipal wastewater the concentration of antibiotics in municipal wastewater became 0.54 to 1.29 µg/L. Marathe et al. (2013) found that in India a wastewater plant which receives waste from approximately 90 drug manufacturing units releases 45 kg of ciprofloxacin daily in the nearby river.

Santos et al. (2013) during their work on the concentration of antibiotics in four hospitals effluent located in Coimbra (Portugal) reported that antibiotics fluoroquinolone, ofloxacin, ciprofloxacin, sulfamethoxazole and azithromycin were most prevalent and total antibiotics in the university hospital effluent (1456 beds) were 306 g/d; 155 g/d for general hospital (350 beds); 14 g/d for the pediatric hospital (110 beds) and 1.5 g/d for maternity hospital (96 beds). Similar results were also reported by other researchers during their studies on hospital effluents of Norway (Thomas et al., 2007), Switzerland (Kovalova et al., 2012; Verlicchi et al., 2012), China Taiwan (Duong et al., 2008), Germany (Ohlsen et al., 2003; Winker, 2014), and Sweden (Lindberg et al., 2004). The total amount of pharmaceuticals received in surface waters were in between 5 and 14 g/d/1000 inhabitants.

The average concentration of antibiotics in the wastewater of Sun Martin Hospital of Buenos Aires city (Argentina) was 10.05 mg/L/d (Magdaleno et al., 2014) which was three times higher than reported for hospital wastewater of Brazil (Berto et al., 2009). The antibiotics concentration in the Sun Martin Hospital effluent was 10 times than the predicted no effect concentration (PNEC) while the concentration of ciprofloxacin was 10000 times than PNEC for ciprofloxacin (Magdaleno et al., 2014). Dinh et al. (2016) during their studies found that in the hospital and domestic effluent of France, the antibiotics of eight classes were present, most of the samples contain fluoroquinolones, sulfonamides, macrolides and vancomycin (in hospital effluent only). Antibiotics concentration in hospital effluent ranged from 0.04 to 17.9 µg/L which was 10 times more than that presents in the domestic effluent (0.03-1.75 µg/ L) and hospital effluent contributes 90% of antibiotics inputs to the wastewater treatment plant. Lien et al. (2016) during their studies on antibiotics in urban and rural hospitals of Vietnam found that residue levels of antibiotics in the hospital, effluent depends on the amount used in hospitals. During their studies, they reported that 34 µg/L of antibiotics from rural and 32.4 µg/L of antibiotics from the urban hospital are released into the environment per month. They also calculated that approximately 61 g of antibiotics were released in the environment per month. Salukele et al. (2017) studied the concentration of antibiotics (ciprofloxacin, flucloxacillin, erythromycin, ampicillin, penicillin-V, amoxicillin, and cloxacillin) in ponds receiving effluents from students' halls of residence, staff quarters and hospital of Dares Salaam and found that in student's halls of residence, the antibiotics were in the range 0.2-1.47 µg/L while in hospital effluents was 0.98-7.10 µg/L. The concentration of antibiotics in influent and effluent of waste stabilization ponds ranged from 8.89 to 63.75 µg/L and 1.51 to 28.01 µg/L respectively and in sewage effluent, it ranges from 72.12 to 370 µg/L.

The average concentration of antibiotic globally in water bodies is ciprofloxacin 18.99 µg/L (with a maximum of 6500 µg/L), norfloxacin 3.457 µg/L (with a maximum of 520 µg/L), sulfamethoxazole 0.278 µg/L (with a maximum of 17.7 µg/L) and trimethoprim 0.037 µg/L (with a maximum of 13.6 µg/L) were the findings of Aus der Beek et al. (2016b) studies. Surface and groundwater samples of a drinking water catchment area of Germany contained antibiotics sulfadiazine, sulfapyridine, sulfamethoxazole, sulfadimidine, trimethoprim, dehydro-erythromycin, tylosin, and tetracycline (Burke et al., 2016) and trimethoprim was present in 74% of the studied water samples. Deng et al. (2016) found that in the river waters of Hong Kong antibiotics mainly detected were sulfadiazine, sulfamethoxazole, sulfapyridine, sulfadimidine, doxycycline and ofloxacin, and the total concentration of antibiotics in the river water were up to 580.4 ng/L, while the maximum concentration of antibiotics in sewage effluent was 360 ng/L. The total concentration of antibiotics

in domestic wastewaters and surface wastewaters ranged in between 0.3-150 ug/L, while in hospital effluents, aquaculture plants and pharmaceutical plants the concentration ranged from 100-500 mg/L (Zeynep and Merve, 2018).

Aydin et al. (2019) during their studies on the concentration of antibiotics in 16 different hospital effluents of Konya found that the concentration of the antibiotics in hospital effluent varied from 21.2-4886 ng/L in summer and 497-322735 ng/L in winter. They also reported that 3.46 g/d antibiotic in summer and 303.2 g/d in winter are passed in wastewater effluent which is 13-28% of total antibiotics concentration in wastewater.

The representative concentration of different antibiotics in sewage wastewater, hospital effluent, groundwater, aquaculture water, river water, sediments and manure/compost of previous studies are given in Table 1.

Table 1 Concentration of different antibiotics in sewage wastewater, hospital effluent, ground water, aquaculture water, river water, sediments and manure/compost.

Compound	Wastewater	Hospital Effluent	Freshwater	Riverwater	Aquaculture	Sediments	Manure/ compost mg/kg DW
Amoxicillin	0.54-1.29 ppb (Ataee et al., 2012) 172.6 ng/L (Mutiyar & Mittal, 2013) 62.5 ng/L (outlet) (Mutiyar & Mittal, 2013) 17.7 µg/L (Mutiyar & Mittal, 2014) 13.8 µg/L (Mutiyar & Mittal, 2014)	7.3-39.1 ppb (Ataee et al., 2012) 0.16-0.79 µg/L (Kimosop et al., 2016) 0.001-0.023 ppm (Liyange & Manage, 2016) 5.86 µg/L (Shokoohi et al., 2017)	622 ng/l (Waiser et al., 2011) 0.06-0.36 µg/L (Kimosop et al., 2016)	Nd-16.7 ng/L(Riva et al., 2015) 0.14-0.37 ng/L (Ataee et al., 2012)	0.0-0.06 µg/mL (Manage, 2018)	0.001-0.004 ppm (Liyange & Manage, 2016)	0.06-850.8 (An et al., 2015, Xie et al., 2016)
Ampicillin	139 ppb (Liyange & Manage, 2014)	131 ppb (Liyange & Manage, 2014) 0.09-0.54 µg/L (Kimosop et al., 2016) 0.001-0.024 ppm (Liyange & Manage, 2016) 1.24 mg/L (Verma et al., 2017)	nd-0.16 µg/L (Kimosop et al., 2016)		0.0-0.20 µg/mL (Manage, 2018)	30 ppb (Liyange & Manage, 2014) 0.001-0.003 ppm (Liyange & Manage, 2016)	
Azithromycin	160-1866 ng/L (Ghosh et al., 2016) 112-274 ng/L			1546 ng/l (Bartelt-Hunt et al., 2009)				

Compound	Wastewater	Hospital Effluent	Freshwater	Riverwater	Aquaculture	Sediments	Manure/ compost mg/kg DW
	(Ghosh et al., 2016)						
Carbamaze pine	0.65 µg/L (Metcalfe et al., 2003)						
Cefadroxil		3.24 mg/L (Verma et al., 2017)					
Cefixime		10.85 µg/L (Shokoohi et al., 2017)					
Cefpodoxi me		0.28 mg/L (Verma et al., 2017)					
Cefuroxime	0.6 µg/L (Mutiyar & Mittal, 2013) 1.7 µg/L (Mutiyar & Mittal, 2014)						
Ceftriaxone		60 µg/L (Diwan et al., 2009)					
Chloroamp henicol		0.06-0.59 µg/L (Kimosop et al., 2016)	Nd-0.08 µg/L (Kimosop et al., 2016)		5-32 ng/L (Baker et al., 2013); 45 ng/L (Impens et al., 2003)		
Chlortetrac ycline	44 µg/L (Awad et al., 2014)		2800 ng/L (Lin &Tsai, 2009)			16 µg/kg (Awad et al., 2014)	144 (animal-manure); 1.6 (soil); 6.38 (Sludge) (An et al., 2015) 0.40 (Aust et al., 2008) 0.1-46 (Martinez-Carballo et al., 2007) 1.1-26 (Hamscher et al., 2003) 0.4 (Karci & Balcioglu, 2009) 0.95-24.4 (Jacobson & Halling-Sorensen., 2006) 0.6-24.3 (Hu et al., 2008) 0.16-27.6 (Qian et al., 2016) 764 (Pan et al., 2011) 139 (Chen et al, 2012a)
Ciprofloxac in	100-160 ng/L (Renew & Huang, 2004) 0.2-1.4 µg/L (Batt et al., 2007)	237 µg/L (Diwan et al., 2010) 218-236 µg/L (Hughes et al., 2013)	6500000 ng/L (Peng et al., 2008) nd-0.06 µg/L (Kimosopetal., 2016)	1.3-124 ng/L (Ferrari et al., 2011)			

	1.5 mg/L (Mutiyar & Mittal, 2014) 1.4 µg/L (Mutiyar & Mittal, 2014) 231-371 ng/L (Ghosh et al., 2016) 258-398 ng/L (Ghosh et al., 2016) 3.0-5.45 mg/L (Hussain et al., 2016) 41 µg/L (Thai et al., 2018)	0.07-0.08 µg/L (Kimosop et al., 2016) 1.35 mg/L (Verma et al., 2017)	0.2 ng/L (Hussain et al., 2017)				
Clarithromycin	1129-3077 ng/L (Ghosh et al., 2016) 377-762 ng/L (Ghosh et al., 2016)			0.9-1497 ng/L (Calza et al., 2013)			
Cloxacillin		0.31 mg/L (Verma et al., 2017)					

3 Impact on Antibiotics Resistant Bacteria

The health of all ecosystem species is governed by the changes in the environmental conditions influencing the biological, chemical, physical and ecological processes. The survival of healthy populations of bacteria depends on their ability to adapt quickly to environmental stresses as humans adapt. All the bacteria have gene exchange characteristics. With the enhancement of stress to microbes in the environment due to increased human activities, the development of resistance and survival is according to Darwinian selection and survival. The response of organisms to environmental change depends on their survival capacity. The changes occurring at the cellular level in microbes reflect changes in the environmental scales, the mechanisms of development of antibiotic-resistant bacteria in biofilms lining the catheter tubes of a human are very similar to those in the wastewater treatment reactor. Resistance is a natural property of all the bacteria's (Angulo et al., 2004; Davies and Davies, 2010) and the term resistome is used to describe the framework that encompasses all forms of resistance and precursor elements (Olivares et al., 2013).

Application of animal manure, biosolids which contain un-metabolized antibiotics to agricultural land as fertilizer, use of sewage wastewater for agricultural land are the main sources of the release of antibiotics in the terrestrial environment (Williams and Adamsen, 2006; Liu et al., 2012; Kinney et al., 2009; Herklotz et al., 2010). Ohno et al. (2010) during their work found that environmental exposure to low concentrations of some antibiotic drugs has toxic effects in species *Daphnia magna*, *Selenastrum capricornutum* and Artemia.

Wastewater treatment plants have been described as hotspots' for antibiotics (Michael et al., 2013) and for antimicrobial resistance (Rizzo et al., 2013). Microorganisms become resistant either naturally (intrinsic) or by mutation or acquisition of plasmids or transposons (acquired). Gram-negative bacteria, bacterial spores and mycobacterium show intrinsic resistance, while both gram negative and gram positive bacteria shows acquired, plasmid-mediated resistance (Olowe et al., 2008). Low-level resistance helps in the survival of microorganisms at residual levels of antibiotics. As the resistant bacterium generally carries the transmissible gene, these genes are transferred through conjugation or transduction, the infection caused by such microorganisms is generally difficult to treat. The accumulation of antibiotic-resistant bacteria in the environment affects human most.

Antibiotic resistance is a problem that causes torment both for developed and developing countries, and the outlook it generates appear to be bleak due to rapidly rising costs of treatment, the threat of cross-resistance, as well as increased morbidity. Till last five years, the researchers have focussed only on the impacts of antibiotic-resistant microbes in human and veterinary medicines, the environmental microbes as reservoirs of resistance factors and the environmental side effects of antibiotic-resistant bacteria (ARB) were not studied. However, it is now known, that ARB and antibiotic resistance genes (ARGs) are omnipresent in nature (Saichang et al., 2013; Wang et al., 2014) and can occur in high concentrations in clinical, industrial, and communal wastewater (Segura et al., 2009; Liu et al., 2012; Sadek et al., 2013) as well as in animal husbandry (Heuer et al., 2008; Aali et al., 2014; Jiang et al., 2013; Yang et al., 2014). As these environments contain elevated levels of antibiotics and other pharmaceuticals these sites are considered as "sites of resistance evolution" (Kummerer, 2008; Kemper, 2008). In addition, liquid and solids discharged from these environments have been described as major sources of ARB in surface waters and soils (Martinez, 2009; Blasco et al., 2009).

Major factors causing antibiotic resistance are:

(1) Over-prescription of antibiotics by physicians
(2) Overuse of antibiotics in aquaculture and animal farming
(3) Poor hygiene, poor infection control in health care and inadequate sanitation
(4) Improper disposal of wastes produced by health care centers
(5) The non-discovery of new antibiotics

According to the World Health Organization (WHO) (2014), in the 21st-century antibiotic resistance is the biggest global threat and has identified it as one of the major global threat for the year 2019. Due to antibiotic resistance in the year 2014, about 700000 people have lost their lives and if proper care is not taken it is expected that by the year 2050 ten million people may lose their life (O'Neill, 2014). In Hyderabad (India) due to antibiotics resistant infections about 56,000 new-born babies die each year and multiple drug-resistant bacteria are found in the gut of 70-90% foreigners who travel to India. As per the WHO report in 2017 globally about 600000 TB patients became resistant to most effective drug rifampicin and 825 have multiple drug-resistant tuberculosis.

An overview of the literature reveals many exciting facts such as trace level concentrations of antibiotics in wastewater treatment plant effluents and surface waters. Long-term exposure of microorganisms to low concentrations of antibiotics in wastewater and surface water has the potential for the development of antibiotic resistance in these organisms (Chander et al., 2014; Devarajan et al., 2016). The concerns about antimicrobial resistance are increasing. A report presented to the House of Lords (UK) warns that the resistance to antibiotics and other anti-infective agents constitutes a major threat to public health and ought to be recognized as much more widely prevalent than it is at present (Eggen et al., 2011). In the environment, well balanced and important interdependencies are disturbed by the input of resistant bacteria and antibiotics (Fekadu et al., 2015).

Antibiotics affect microorganisms by reducing their numbers, biochemical activity, diversity and changing the microbial community structure (Luo et al., 2011; Marti et al., 2014). When toxic substances reached in the soil the first biota that undergoes direct and indirect impacts is soil micro flora. To assess the negative effects of antibiotics treatments and to evaluate the influence of chemicals on soil system (ecological tests), soil micro flora which due to its fast response to contaminants, ability size and recycling of elements act as a "biomarker" (Bailey et al., 2003).

According to one study in India, the number of carbapenems ((last resort antibiotic) resistant bacteria has increased from 2 to 52% in the last decade, it is due to the fact that bacteria are very quickly adapted to environmental conditions. Bacterial resistance occurs due to recombination and genetic mutation. The number of antibiotic-resistant bacteria is enhanced when the microbes are exposed to a very low level of biocide and metals due to cross-resistance. In China, the resistance to colistin (last resort antibiotic) was detected in 2015 in E. coli bacteria from pigs.

Antibiotic resistance has become a major clinical and public health problem within the lifetime of most people living today (Frieri et al., 2017). With the increasing amounts of antibiotics over the past 80 years, microbes turn resistant to antibiotics and became no longer susceptible to them. The resistance to microbes is not only due to antibiotics but also due to the spread of resistance genes and resistant bacteria. Due to molecular, operational, psychological, and economic factors, the dilemma of antibiotic resistance has become a multifaceted issue. Antibiotic resistance is the result of bacteria changing in ways that lead to the reduced effectiveness of antibiotics to cure or prevent infections. There are three main mechanisms through which resistance is acquired in bacteria: 1) Natural selection or the gradual scientific process by which biological traits such as resistance to antibiotics become common in a population (i.e. bacteria); 2) plasmids or independent circular pieces of DNA that may carry genes for antibiotic resistance that can be conferred between bacteria; and 3) mutations, or permanent changes in the DNA sequence of a gene that can lead to the formation of new traits such as resistance (Laxminarayan and Heymann, 2012). Furthermore, cross-resistance, or the possession of a resistance mechanism by a bacterial strain that enables it to survive the effects of several antibacterial molecules, may continue even after halting or reducing antibiotic use. As such, antimicrobial resistant bacteria may emerge under the selective pressure of antibiotics and become the dominant flora.

Hospital-borne infections are mainly caused by the bacteria carrying R-plasmid which is due to indiscriminate use of antibiotics causing selective pressure on antimicrobials enriching the MDR R+ strains. The situation has reached such an ugly state largely in developing countries like India, that a sizeable number of hospital strains have become resistant simultaneously to most of the available antibiotics (Magiorakos et al., 2011). Hospitalized patients become heavily colonized with R+ strains mainly in their gut (Dethlefsen et al., 2008). Infection with MDR bacteria may be transferred to other patients in the hospital resulting in cross-infections which are referred to as hospital-borne infections. The exact magnitude of hospital-borne infections is not precisely estimated for India but is expected to be around 10% and is much higher in intensive care units. Acquisition of MDR bacterial infections in hospitals may pose serious therapeutic difficulties. The transfer of R-plasmids has been shown to occur in the extra intestinal environment like the sewage system (Clemente et al., 2012). The dangers of infectious hospital waste received a great deal of attention in the last decade and the main emphasis on hospital solid waste, but liquid waste in the form of sewage has not received much attention.

The existence of antibiotic-resistant bacteria and their dissemination in the environment causes public health concern as when a patient came in contact of antibiotic-resistant microbes; the antibiotic-resistant infections are developed in the patient which is spread in the communities. The bacteria which survive in hospital wastewaters are exposed to a wide range of biocides causing the development of antibiotic resistance (Nuñez and Moretton, 2007). The resistant bacteria isolated were diverse in nature. Different studies have also

reported the co-resistance to antimicrobial agents among organisms, denoting that the untreated effluents pose a serious public health risk. The results of these studies also indicate that hospital wastewaters act as an environmental reservoir for the development of multidrug-resistant bacteria.

Waste effluent from hospitals contains high numbers of resistant bacterial strains and antibiotic residues at a concentration able to inhibit the growth of susceptible bacteria (Frieri et al., 2017). The numbers of resistant bacteria in the sewers which get hospital waste effluent increase due to selection for resistant bacteria and the introduction of resistant bacteria via hospital wastewater. Although sewage treatment reduces the number of bacteria in wastewater, the affluent generally contains a large number of both resistant and susceptible bacteria (Ghanem and Haddadin, 2018). The quantitative and qualitative studies of microbiological content of hospital and household waste denote that the hospital waste contains bacteria which are more harmful to humans as compared to household waste (Saini et al., 2004; Le et al., 2016). Studies on antibiotic residues in hospital effluent and in other environmental niches have been conducted mostly in well-developed countries, while studies in developing countries especially in low and middle-income settings are very few (Bole et al., 2013; Lamba et al., 2017). As untreated hospital effluents contain concentrated forms of infectious agents and antibiotic-resistant microbes which contaminate groundwater and surface water, in communities it causes water-borne diseases such as cholera, typhoid fever, dysentery and gastroenteritis (Sharma et al., 2010; Abdulaziz and Al-Ghamdi, 2011). A review of theliterature shows that hospital effluents regularly contribute antibiotic resistant genes to the aquatic environment at a significant level (Rowe et al., 2017)

In developing countries particularly in South Asia, there is a gradual decline in the availability of fresh water for agricultural purposes; therefore, sewage and other industrial effluents are being used for irrigation of agricultural fields particularly in peri-urban areas. As sewage effluent also contains hospital effluent which provides an environment conducive to MDR bacteria. Corcoran et al. (2010) during their research found that approximately 20 million hectares of land in 50 countries are irrigated by wastewater or partially treated wastewater containing antibiotics, their metabolites, antibiotics resistant genes and 10% of the world population consumes the food which is irrigated by wastewater. Budiati et al. (2013) isolated chloramphenicol and tetracycline resistant indices and plasmid carriage from catfish and tilapia from aquaculture production. de Kraker et al. (2011) reported increased human mortality and morbidity due to antimicrobial resistant bacteria such as *Escherichia coli*, enterococci, and salmonellosis. Profound resistance prevents effective chemotherapy of infected population. Bushnell et al. (2013) found that till today no antibiotics are available for carbapenems resistant bacteria. Presence of multidrug-resistant bacteria Escherichia coli and Staphylococcus aureus in untreated hospital wastewaters of South East Queensland, Australia was found by Katouli et al. (2012).

Makky et al. (2012) reported that twelve isolates obtained from three hospital drains in Cairo, Egypt were resistant to thirteen antibiotic as ceftazidime 91.7%, cefotaxime 91.7%, tobramycin 83.5%, cefoperazone 83.3%, vancomycin 75%, ceftriaxone 75%, gentamycin 58.3%, ampicillin-sulbactam 58.3%, cefepime 50%, cotrimoxazole 33.3%, imipenem 5%, amikacin 25%, and ciprofloxacin 8.3%.

The multiple antibiotic-resistant bacteria were 71% in the Hooghly River, 15.38% in the Kangabasti River and 8.33% in the groundwater and their prevalence was 73.58% in post monsoon period. 59.26% in winter and 53.57% in summer was the findings of Mohanta and Goel (2014).

Siddiqui et al. (2015) during their studies on hospital effluents of Jessore medical college and Jessore queens' hospital found that 75% of isolates were resistant to amoxicillin, 64% to ampicillin, 31% to chloramphenicol, 29% to gentamycin, 27% to nitrofurantoin and 23% to ciprofloxacin. *Salmonella* spp showed maximum resistance to these antibiotics.

Nunhez et al. (2016) during their research study found that hospital effluent constitutes a source of multiple antibiotics resistant enterococci which were resistant to ampicillin and erythromycin. Municipal wastewater also has strains which are multiple antibiotics resistant.

Ahn and Choi (2016) reported that nine genera isolated from hospital wastewater showed multidrug resistance and six genera were resistant to tetracycline, widely used as therapeutics in human and veterinary medicine.

Asfaw et al. (2017) found that treated and untreated hospital wastewater of Ayder referral hospital, Mekelle, North Ethiopia has 80% multidrug-resistant bacteria *E. coli*, *Staphylococcus aureus*, *Klebsiella* spp, and *P. aeruginosa.*

Vibhaw et al. (2017) studied antibiotic resistance bacteria in water discharges of a hospital in Patna and found that bacteria resistant to many broad-spectrum antibiotics are present in hospital effluents and these multidrug-resistant genes are transferred to city sewage bacteria.

Akhther et al. (2018) during their study on hospital effluents found that 10 isolates of *E. coli* at the level 100%, 80%, 80%, 70%, 30%, 20%, 20%, and 10% showed resistance to antibiotics ampicillin, ceftazidime, cefotaxime, tetracycline, chloramphenicol, gentamycin, ciprofloxacin, and azithromycin respectively. Earlier Islam and Uddin (2008) also found that all the isolates of *E. coli* from the hospital wastewater were resistant to more than 3 kinds of antibiotics.

Grenni et al. (2018) in their review studies found that antibiotics in the environment hampers microbial community structure and functioning in two ways direct (short-term) and indirect (long-term), bactericide and bacteriostatic actions with the disappearance of microbial populations and their ecological functioning are the direct effects. Development of antibiotic-resistant bacteria and bacterial strains are the long-term effects. These direct and indirect effects are influenced by the antibiotic's concentration, the exposure time, the ecosystem and the co-occurrence of other antibiotics. Antibiotics and resistant genes affect the structure and function of environmental microbial populations.

The bacteria which are highly resistant to antibiotics are given in Table 2.

Table 2 List of bacteria with high antibiotic resistance.

SN	Bacterium	Gram strain	Clinical infection	Problematic resistance
1.	*Acinetobacter baumannii (MDR)*	Negative	Pneumonia, UTI, septicaemia	All classes including carbapenem
2.	*Staphylococcus aureus and Methicillin–resistant Staphylococcus aureus*	Positive	Skin and soft tissue infections, nosocomial infections	β-lactam, glycopeptides and vancomycin
3.	*Streptococcus pneumonia (MDR)*	Positive	Pneumonia, bronchitis, meningitis	β-lactam, macrolides, quinolones
4.	*Clostridium difficile*	Positive	Diarrhoea, colitis	β-lactam, quinolones
5.	*Enterococci faecalis and Enterococci faecium* including vancomycin resistant enterococci (VRE)	Positive	UTI, surgical wound infections, endocarditis	β-lactam , glycopeptides and vancomycin

6.	*Escherichia coli*	Negative	UTI, haemolytic-uremic syndrome, renal failure	B-lactam,quinolones, aminoglycosides, fluoroquinolones, gentamycin
7.	Mycobacterium tuberculosis (MDR)	Positive	Tuberculosis	Rifamycin, quinolones, isoniazid, pyrazinamide, aminoglycosides
8.	*Pseudomonas aeruginosa (MDR)*	Negative	Skin and soft tissue infections, lung infection in cystic fibrosis, UTI	Susceptible only to polymyxins
9.	*Klebsiella pneumonia (MDR)*	Negative	Pneumonia, surgical wound infections	β-lactam, quinolones, aminoglycosides
10.	*Enterobacteriaceae and*Carbapenem-resistant E*nterobacteriaceae* (CRE)	Negative	Blood infections, wound infections, urinary tract infections and pneumonia, low blood pressure	β-lactam, quinolones
11.	*Neisseria gonorrhoeae*	Negative	Gonorrhoea	B-lactam, quinolones, tetracycline, macrolides

MDR= Multiple drug resistant.

4 Remediation of Antibiotics

Antibiotics in nature can be removed using biotic and abiotic methods (Shikha and Gaube, 2016; Jiang et al., 2010; Elmolla and Chaudhari, 2009; Onesios et al., 2009; Kummerer et al., 2009a, b), sorption, hydrolysis, photolysis, oxidation and reduction (Kim et al., 2010; Kummerer et al., 2009a) are the conventional methods used to degrade antibiotics, but as these methods are expensive, unsustainable and condition based, they] are not widely used. So, a less expensive biotic degradation method for remediating these antibiotics from the environment is an urgent need. Girardi et al. (2011) found that 0.9% of ciprofloxacin in the biotic soil system was mineralized after 93 days and degradation in soil was more than in water. It was also reported that under special artificial conditions ciprofloxacin is extensively degraded by fungi (Wetzstein et al., 1999; Wetzstein et al., 2009). To prevent the development of bacterial resistance Russell (2002) has suggested the rotation of disinfectants and antibiotics in hospitals and in the pharmaceutical, agricultural and food industries.

Derakhshan et al. (2016) during their review studies found that higher amount of antibiotics can be removed from water by using advanced treatment processes, ozonation, nanofiltration, advanced oxidation, activated carbon and reverse osmosis.

Bioremediation is the use of organisms (microorganisms and/or plants) for the treatment of polluted soils/water. It is a commonly used method of soil remediation because it is perceived to occur via natural processes and is a cost-effective method. Bioremediation technique is effective only when environmental conditions are favorable for the growth and activity of microbes. Bioremediation method controls the "Eutrophication" process in water. Although bioremediation is a non-disruptive method of soil remediation, it is usually time-consuming. In this technique enzymes produced by bacteria and fungi decompose antibiotics into less harmful chemical substances (Cajthaml et al., 2009).

A number of workers (Dolliver et al., 2007; Gujrathi et al., 2005; Farkas et al., 2007; Park and Choung, 2010; Kummerer et al., 2009b; Dhir et al., 2009; Nnenna et al., 2011) have studied the remediation of antibiotics by plants and /or microbes. Gujrathi et al. (2005) reported that *Helianthus annus* can degrade

tetracycline via reactive oxygen species present in the plant root. Farkas et al. (2007) showed that root exudates of maize produced glutathione-S-transferases removes the tetracycline from soils.

Park and Choung (2010) reported that glutathione-S-transferases activity is enhanced by the bacteria which significantly reduce the concentration of the antibiotic. Park et al., (2012) has also found that glutathione-S-transferases remove antibiotics in a bioreactor.

Harja and Ciobanu (2017) during their studies found that hydroxyapatite, a new alternative low-cost adsorbent, can remove the oxytetracycline from the wastewaters.

Phytoremediation is a tool of bioremediation that uses plants for the treatment of polluted soils. Phytoremediation method is mainly applied when the pollutants are within the root zone of the plant and cover a wide area. For removal of antibiotics from water sources, the phytoremediation is more effective and less expensive technology. As phytoremediation is a natural biological process remedial condition as pH, temperature, oxidation, and light are not required (Salt et al., 1998). Gujrathi et al. (2005) reported that *Myriophyllum aquaticum* (parrot feather) and *Pistia stratiotes* (water lettuce) in the hydroponic system can remove the TC and OTC, while CTC can be remediated by maize (Farkas et al., 2007). Results of Nnenna et al. (2011) denote that some bacteria and fungi from the aquatic environment can degrade the antibiotics.

Randhawa and Kuller (2011) found that cow dung / Gomeya can phytoremediate enrofloxacin antibiotics.

Carvalho et al. (2012) found that *Phragmites australis*, a perennial grass, remediate TC and other antibiotics from aqueous system. Vetiver grass extensively used for phytoremediation of heavy metals and toxic contaminants has also been used for phytoremediation of tetracyclines (Bansal, 2013; Datta et al., 2013). Bansal (2013) also reported that water lettuce, sunflower, and roots of water lettuce take up TC, OTC, and CTC from the aqueous medium. Indian mustard, tomato plant, and carrot plant remediate tetracycline (TC, OTC, and CTC) from soils.

Hoang et al. (2013) reported that native wetland plants *Acrostichum aureum* L. and *Rhizophora apiculata* Blume Fl. javae can photoremediate antibiotics ciprofloxacin and norfloxacin. The phytodegradation is enhanced by bacteria.

Makhijani et al. (2014) during their research found that plant *Cicer arietinum* (black chickpea) can remove tetracyclines from water and soils. *Cicer arietinum* remediates an average of 60% of ciprofloxacin (Shikha and Gauba, 2016).

Santosa et al. (2016) reported that *Moringa oleifera* seed preparations can remove tetracyclines from water naturally without damaging the environment.

Hirth et al. (2016) used microbial community containing the degrading strain *Microbacterium* sp C448 to remediate sulfamethazine from soils.

Li et al. (2017) during their work found that Goldfish algae and Vetiver grass can degrade norfloxacin and ciprofloxacin up to 44%. Ampicillin, tetracycline, oxytetracycline, and chlortetracycline can be degraded by *Pistia stratiotes* and *Eichhornia crassipes* (Chen et al., 2012b). Mangrove plants *Rhizophora stylosa* and the *Avicennia marina* can remove ciprofloxacin from the environment (Sun et al., 2017).

Neisi et al. (2017) during their studies found that antibiotic tetracycline can be removed from hospital wastewater by extended aeration activated sludge up to 98% in summer. Hybrid carbon membrane composed of 2D GO sheets, 1D CNT's and AC can effectively remove tetracycline from the water was the finding of Liu et al. (2017).

5 Conclusion

Antibiotics residues, which are originated from medical, agricultural and animal husbandry activities, are the latest environmental hazardous pollutants. The different studies of researchers have shown that antibiotics are

present in globally drinking water, sewage water, river water, hospital effluents. Though their concentrations at present are low (ng/L to ug/L) but if used unchecked their accumulation will pose a serious threat to human health and the ecosystem. After consumption, the antibiotics are partially metabolized in the gut of human and/or animals and a large amount is excreted unaltered or as active metabolites via urine and feces and is released into the waste system, soils. Antibiotics in the environment affect microbial communities directly with the inhibition of some microbial groups involved in key ecosystem functions or indirectly by acquiring resistance, generating genetic and phenotypic variability which influences physiological activities. Environmental microorganisms acquired the resistance genes which are transferred to human pathogens, as the resistance genes are not "degradable pollutants" but auto-replication elements, these changes affect the future of human health. Changes in microbial composition and communities due to stress or otherwise affect the ecosystem processes directly.

Antibiotics in the environment can be removed by biotic and abiotic methods, sorption, hydrolysis, photolysis, oxidation, and reduction are the conventional methods, as these methods are expensive, unsustainable and condition based are not widely used. The higher amount of antibiotics can be removed from water by using advanced treatment processes, such as ozonation, nanofiltration, advanced oxidation, activated carbon and reverse osmosis. Bioremediation and phytoremediation are the methods which are widely used for remediation of antibiotics from the environment.

As in the last decade, no new antibiotics have been developed globally and more and more diseases are becoming multiple drug resistant, if we do not prevent misuse/ overuse of antibiotics it will lead to doomsday.

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