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Chapter 5

Spreading of Antibiotic Resistance with Wastewater

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Additional information is available at the end of the chapter

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Abstract

The recent statistics show that the world's population is rapidly increasing. This increase negatively affects the water resources and it increases the water demand progressively. Along with the increase in the world's population, the insensible use of water resources, pollution, and drought lead to the increasing reduction of water resources. Due to these factors, all countries, primarily developed countries, have started looking for new water resources. This search has been extended to extraterrestrial water. However, the existing technology and opportunities direct countries toward the purification of wastewater rather than searching for new water resources. For the reasons outlined above, purification and recycling of wastewater become important. In addition to the natural resistance of microorganisms against antibiotics, a resistance also arises because of the unconscious and overuse of antibiotics. This resistance spreads through wastewater progressively. Antibiotic resistance shows an increase according to the scientific data. In order to prevent the resistance, it is of capital importance to treat the wastewater in which the domestic pollution burden is high. In this study, the role of domestic wastewater in the occurrence and spread of antibiotic resistance will be revealed.

Keywords: antibiotics, spreading antibiotic resistance, water, wastewater, domestic wastewater

1. Introduction

Water contains millions of microscopic living beings within itself. The plenty amount of water is accessible on our planet for living beings to maintain their vital activities.

Along with 14 billion m^3 of water, 97.5% of it is salty water, 2.6% of it is freshwater, and 0.8% of the total amount of water is present as freshwater in the state of constant vaporization, precipitation, and flow. Water scarcity is indicated as one of the main problems of the twenty-first century in the whole world, and for this reason, lives of many people depend on the right usage

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of water. People need water primarily for civic, industrial, and agricultural areas. However, water is regarded as a limited source. For the fact that water resources become insufficient and decrease in quality creates serious concerns. The population increase, urbanization, agricultural practices, and industrialization increase the water demand. Wastewater treatment is built for the purpose of reducing the pollution by removing pathogens, nutrients, and biodegradable substances, and protecting public health and the environment. Furthermore, with the increase in water demand, the recycling of wastewater has been brought into question [1].

Wastewaters are divided into two groups such as domestic and industrial. Domestic wastewater can originate from house, workplace, and hospital because of its content. The complete treatment of this type of wastewater is impossible even if it goes through many stages. This situation causes many problems. The emergence and spread of antibiotic-resistant bacteria are the leading reasons for this problem and they make humans and animals sick.

According to American Centers for Disease Control and Prevention (CDC), antibiotic resistance constitutes one of the most important health problems of a country. In America, it is estimated that 2 million people become sick and 700,000 people die worldwide because of resistant bacteria. In a report of 2013, CDC indicated that the usage of antibiotics in the production of food animals causes the emergence of resistant *Campylobacter* that is contagious to humans. Resistance genes can be transferred between zoonotic bacteria types, among the bacteria species, through food chain and contact with feces of ill animals and contaminated environment [2].

Antimicrobial resistance causes many problems in humans and animals in the case of the spread through wastewater, spread wastewater treatment output's being low, and the usage of these waters in agricultural practices and irrigation fields, the emergence of many antibiotic-resistant microorganisms.

2. Significance of water

Water is an essential substance which is necessary for vital activities such as nourishment, circulation, respiration, excretion, and reproduction to occur in every period of human life. At the same time, water itself is a habitat as one of the basic elements in nature while forming a habitat. The presence of water in a habitat and its quality are extremely important for life [3].

As the most important one of all natural sources for all living beings, water is a habitat and it contains millions of microscopic living beings. It constitutes approximately three-quarters of the Earth [4].

Water is crucial for the life of living beings as the most common natural resource on the Earth. Seventy-five percent of the Earth's surface, seventy percent of the human body, and seventy-eight percent of the blood consist of water [5].

Ninety-seven percent of the water body on the Earth consists of oceans and seas, two percent of lakes, rivers, and underground waters, and one percent of glaciers and snows. Water has been used during the development of civilizations for many purposes such as personal hygiene, agricultural irrigation, industrial production, and electric power production [6].

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Water submerges more than 70% of the Earth as fresh and salty water and these environments are defined as aquatic environments [7]. Salty water constitutes more than 96% of the water on the Earth. More than 68% of the present freshwater is found in ice and glaciers. In this way, it is considered that water stays in stock. Thirty percent of freshwater consists of underground water. Two-thirds of underground waters are located deeper than 800 m. Surface freshwater sources such as rivers and lakes constitute 93,100 km^3 (22,300 cubic miles), which is 1/700 of 1% of all water on the Earth [8].

The minerals, salts, and sulfates contained in the water are very important along with its other characteristics. The presence of these substances in a certain amount in water is essential for life while their presence in small or greater quantities continually affects life in a negative way. At the same time, water is a habitat. The pollution of this environment creates danger for life [9, 10].

An increase in industrialization, urbanization, and population that started at the beginning of the twentieth century, and an increase in the use of natural resources have caused the emergence of the problems called the environmental pollution jeopardizing human life. An increase in the variety and amount of solid and liquid wastes that are disposed into the environment causes air and water pollution [6].

Water is a component which is significant for the life cycle of all living beings on the Earth. While three-quarters of the Earth is covered by water, two-thirds of the human body is covered by water. This rate significantly affects all living beings while being important for both the Earth and human beings. Water has many important roles from systems in the living organism to cellular functions. Even a small decrease in the amount of water can endanger life.

Since the existence of the Earth, all civilizations have settled in the places around or close to water. This shows us that water is a functional substance which is completely life-oriented. The decrease in the amount of water arises from both the environmental pollution and unconscious consumption. Because of this decrease, countries are in search of new sources and wars break out.

3. Water consumption

Population increase on the Earth leads to the decrease of water and pollution of clean and potable water. This will cause water scarcity in the future. Rivers and lakes constitute most of the water that people use daily. The pollution of these water sources will create water shortage. The amount of water that meets our needs is 0.25% of all water sources on the Earth [11].

About 97.39% of 1384.10^9 km^3 water on the Earth is found in the oceans and seas. The remaining 2.01% consist of glaciers and 0.60% consists of underground water, lakes, and rivers. This situation shows that the available freshwater supply constitutes quite a small amount of all water sources on the Earth [12].

The world's population that is approximately 6 billion is able to use 54% of the renewable surface and underground water supplies. It is considered that this rate will increase to 70% with the population's increase as the conditions of use remain the same. At the same time,

it is estimated that 90% of the present freshwater sources will be used with the increase of life standards and the increase of water usage per person. For other living beings, there will be 10% of the available water supply. It is indicated that there will not be enough water for environmental and ecological functions because of the population increase and unconscious use of water resources [13].

Water resources are also used in a sectorial aspect besides meeting daily needs. The usage of water is classified as agricultural, industrial, and domestic sectors [14].

Sixty-nine percent of the freshwater resources on the Earth are used for agriculture, twenty-three percent are used for industry, and eight percent are used for domestic purposes. These rates differ from continent to continent. For instance, while the rates of agricultural, industrial, and domestic usage of water in Africa are 88, 5, and 7%, respectively, these rates in Europe are 33, 54 and 13%, respectively [15].

Water consumption in the world has increased 10-fold since 1900. In the studies conducted, it is determined that water consumption will increase 17% in agriculture, 20% in industry, and 70% in domestic consumption in 2015. Moreover, it is told that 20% of 6 billion world population is deprived of clean water resources. The water amount per person decreased to 7300 m^3 in 2000 while it was 16,800 m^3 in 1950 [16–18]

While it is estimated that world population will be 8 billion, it is considered that water consumption per person will decrease to 4800 m^3 in 2025. This decrease in consumption will arise from water resources shortage. Furthermore, the present available water resources will be polluted in 2025 and then water will not be provided [19]. It is estimated that the curve of the increase in water demand and the curve of the decrease of clean water resources will intersect in 2023.

Recent studies show that population growth will increase the consumption of water. However, this situation is inversely proportional to the number of water resources. Due to the decrease of clean and available water resources, the quantity of water per person has decreased. The reason for these situations is water scarcity which arises from the unconscious use and pollution.

4. Water pollution

Water pollution has a negative effect on public health and ecology because of the degradation of water quality and natural balance. Water pollutants contain surplus metal, some radioactive isotopes, nitrogen, phosphorus, sodium, and other beneficial and necessary elements along with especially some faecal originated pathogenic bacteria, parasites, and viruses which can be human or animal originated.

Mixing of any organic, inorganic, radioactive, or biologic substance that inhibits or disturbs the usage of water resources by impairing their quality into water is called water pollution [20, 21].

The reasons of water pollution are particularly domestic, industrial, agricultural, physical, chemical, radioactive, and microbial pollution.

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Domestic wastewater contains organic and inorganic substances that are suspended, colloidal, and dissolved. Domestic wastewater consists of organic foods such as too much carbon, nitrogen, and phosphorus and highly concentrated microorganisms [22]. With the increase in urbanization, the flow of domestic waste into water through sewerage system also increased. In particular, detergents which are used in washing machines, oils poured out into lavabo, and the dispersion of wastes that should be accumulated in dustbins and recycled into the environment cause water pollution [23]. The characteristics of industrial wastewater differ from industry to industry [22].

Apart from domestic and industrial wastewaters that are discharged into water sources without being treated, the unconscious fertilization and unconscious usage of agricultural pesticides are also the reasons for pollution. These pollutants become crucial with negative effects on the water resources regarded as inadequate according to the world average, environmental, and public health and in terms of economy [6]. In the fields close to water, the incorrect ploughing mixes into water through the wind and causes pollution in water [3]. An increase in the usage of synthetic manure and pesticides in agriculture and industry and chemical substances that are used in the industry create a risk of water pollution [23].

Industrial establishments cause physical pollution. Power plants, steel, paper, car, plastic, and packing factories, which are big industrial establishments, throw environmentally hazardous solid and liquid substances. These substances are mostly toxic like arsenic, phenol, cyanide, chromium, and cadmium [24].

The chemical pollution of water began to cause critical health problems. It is estimated that in the future one of the most important water pollution problems will be the pollution caused by chemicals. Main metals causing chemical pollution are copper, zinc, mercury, nitrate, and phosphate [23].

Radioactive pollution in water can result from research agencies, hospitals, and some industrial fields. Radioactivity increases because of testing nuclear weapons. Therefore, rain water is getting dirty and, as a consequence, surface water is exposed to radioactive pollution [25].

Water might also be polluted by some pathogenic bacteria, parasites, and viruses that can originate from humans and animals [6]. Microorganisms that cause water pollution in terms of hygiene generally originate from diseases or human and animal excrements and urine being a porter [26]. An increase in bacteria population leads to bacterial pollution as a result of the decomposition of organic substances that are accumulated in the sea and inland waters or mixing of various pollutants apart from sewerage [25]. In stored waters, there is a lot of bacterial communities like the members of *Pseudomanas* sp., *Micrococcus* sp., *Achromobacter* sp., *Streptomyces* sp., and especially *Enterobacteriaceae.* The members of *Enterobacteriaceae* do not reproduce in clean water and their natural habitat is not potable water. Coliform bacteria are important in terms of human health and as an indicator of water pollution [24]. Their presence indicates that stool is mixed up with water through sewage directly or indirectly in one or more phases starting with the raw material to the transfer of water [27].

When it comes to water pollution, microbial pollution comes to mind first, even though there are many reasons of pollution. The most important of them is the pollution that arises from

domestic and industrial wastes. Since domestic wastewater contains sewage waters and detergents, it also causes the indirect microbial and chemical pollution.

5. Wastewaters and classification

Wastewaters are formed as a result of the pollution of water used in households and industrial establishments [28].

For the waters that are disposed by being used in households or industry, "wastewater" definition is used. Wastewaters demonstrate biological, chemical, and physical pollution. While biological pollution consists of bacteria, fungi, parasites, and virus particles, and chemical pollution consists of toxic substances, decomposed organic substances, and phosphor, physical pollution consists of color, scent, foaming, temperature increase, and suspended matters. Heavy metals contain colorants that belong to the group of chemical pollutants and include industrial wastes and some pesticides [29].

5.1. Classification of wastewaters

Wastewaters are classified into two groups as domestic and industrial.

5.1.1. Domestic wastewaters

Wastewaters that originate from the dirty water from households and workplaces and do not include the industrial content of factories are called domestic wastewaters. Although their pollution rate is low they contain a high level of oily compounds, proteins, particles, chemical oxygen demand (COD), and detergents. For this reason, domestic wastewaters have a complex structure (**Table 1**) [30].

Domestic wastewaters are the waters that contain dirty looking and colorful soluble and insoluble matters from food wastes, kitchen lavabos, bathrooms, washing, and dishing machines and the matters that have organic and inorganic content and 99% of water [31].

Physical properties	**Chemical components**			**Biological components**
	Organics	**Inorganics**	**Gases**	
Solid matters	Carbohydrates	pH	Methane	Living cells
Heat	Oil and grease	Nitrogen	Oxygen	Plants
Color	Pesticides	Phosphorus	Hydrogen	Single cells
Smell	Phenols	Alkalinity	Sulfur	Viruses
	Proteins	Chlorides		
	Surface active agent	Heavy metals		
		Sulfur		
		Toxic components		

Table 1. Physical, chemical, and biological components of domestic wastewater [32].

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Domestic wastewaters contain suspended, colloidal, and dissolved organic and inorganic substances. As well as this pollution arises from sewerages and detergents, it can also originate primarily from households and business enterprises. Moreover, domestic wastewaters contain pathogenic microorganisms such as bacteria, helminth, protozoa, and viruses. This situation increases the pollution rate of waters and indicates that water treatment is absolute. The indicator of the treatment's necessity is that some bacteria include R-plasmid. Since R-plasmid ensures antibiotic resistance to bacteria, untreated domestic wastewaters cause antibiotic-resistant bacteria to infect people and animals and create disease.

One of the most significant wastewaters that belong to domestic wastewaters is hospital-acquired wastewaters.

5.1.1.1. Hospital-acquired wastewaters

Hospital wastewaters contain micro and macro pollutants that come from various sources such as operating rooms, laboratories, investigation units, polyclinics, and drug use. The most important macro pollutants are bacteria and viruses while the most important micro pollutants are antibiotics, heavy metals (Hg, Pt, Gd, etc.), hormones and detergents/antiseptics. While microbiologic quality is determined for the usage of water, faecal pollution is identified by biologic and chemical indicators. In the content of biological indicators, there are total coliforms, faecal coliforms, faecal streptococcus, and *Clostridium perfringens*. Total coliforms are in the form of aerobic and facultative anaerobic, asporogenic and Gram-negative bacteria. Faecal coliforms, the marker of the pollution of water in which faecal coliforms and total coliform bacteria are found and which indicates the presence of pathogenic bacteria with human or animal excrements represent the presence of pathogenic bacteria and limited virus contamination. In hospital wastewaters, antibiotics such as ciprofloxacin, erythromycin, and sulfamethoxazole are found in high numbers in accredited adsorbable organic halide (AOX) and paracetamol. In municipal sewage, antibiotics such as ofloxacin and erythromycin are found in high numbers in AOX, paracetamol, and ibuprofen which is an analgesic [33].

In order for drugs to be stored longer and be easier to take, they must be quite durable and of high mobility quality in the liquid-phase while being produced. For this reason, active substances in drugs and biotransformation products lead to various factors by accumulating in the ecosystem. A lot of drugs such as antibacterial drugs, antibiotics, antifebrile, anodyne, synthetic steroids, cholesterol medicines, beta blockers and cytostatic drugs are the drugs detected in the ecosystem by studies performed [34].

Various drugs are used for various purposes during the treatment, protection, and development of human and animal diseases. These drugs cannot completely metabolize and they are removed from the body as they are or as a by-product in the form of ordure, urine, sweat, etc. [35].

In order for living beings to be treated, protected against microorganisms and infections and become resistant, many drugs should be taken. After the functions of these drugs in the body are over, they are removed through liver and kidneys. Medicine taken reaches the maximum level in the blood and when it starts to decrease the excretion also begins. While the excretion periods of drugs such as painkillers and antibiotics out of body are

different, antibiotics are not removed for a long time. Drugs are removed from the body as urine, ordure, or metabolized product. In this way, they mix into wastewaters through the sewer system.

Drugs mix into wastewaters not only through excretion. With the disposal of unused drugs in households and hospitals, they also mix into wastewaters through the sewage.

The medicines found in wastewaters cannot be completely refined through the refinement. One of the biggest reasons for this situation is that hospital wastewaters directly mix with domestic waters without pretreatment. This affects primarily potable waters, underground waters, lakes, and rivers in a negative way.

Medicine remnants that mix into the potable water as a result of the inadequate refinement of domestic wastewaters negatively affect living beings in many ways. This effect arises especially from antibiotics. Antibiotics that enter the body through water cause pathogenic microorganisms to become resistant.

Due to the negative outcomes on living beings, hospital wastewaters should be refined before they are transferred to domestic wastewaters.

5.1.2. Industrial wastewaters

Pollution in the environment that originates from unavailable or economically unvalued wastes in the industrial system is called industrial pollution. The accumulation of permanent and toxic organic substances in industrial wastewaters creates serious problems. The facts that these wastewaters are not discharged into the receiving environment, pollutants are not biodegraded, and they have a toxic influence upon living beings create many troubles [36].

Industrial wastewaters comprise of various resources such as refrigerant waters, process wastewaters, and domestic qualified wastewaters. Because of this content, the refinement of industrial wastewaters becomes crucial [11].

Since industrial wastewaters contain heavy metal content, they create the most crucial environmental problem of the present day. Wastewaters containing heavy metals are the waters that are generally acidic and have a low biochemical oxygen demand (BOD) value. Aquatic life is affected by mixing of wastewaters into the receiving environment. Because of this situation, expensive refinement systems are needed in order to use water resources as potable water sources. Heavy metals contained in wastewaters make the mud impossible to use for agricultural purposes by affecting the refinement efficiency of domestic wastewaters. For this reason, the discharge of industrial wastewaters with heavy metal content into the sewer system has an important role [37].

5.2. Wastewater treatment

The treatment of domestic wastewaters takes place in three stages as mechanic, biologic, and chemical.

Physical treatment covers the refinement of solid matters in wastewaters. This treatment stage comprises of four units as grid/sieve/grinder, sand catcher/oil slinger, preliminary settling, and flotation [38].

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The biologic treatment contains the stage in which organic matters contained in wastewaters are refined. This treatment happens along with the decrease in the organic matter amount by using and decomposing of organic substances as a nutrition substance by microorganisms. Domestic wastewater generally decreases nutrition and organic substances such as nitrogen and phosphorus contained in it. Biologic treatment helps microorganisms such as fungi, algae, protozoa, and metazoans and organisms belonging to bacteria and archaea. The most used processes in biologic treatment are activated sludge processes, air-conditioned lagoons, trickling filters, revolving biodiscs, and stabilization pools. Basic operations of this treatment are nitrification, denitrification, dephosphorization, waste stabilization and eliminating organics which are measured especially as BOD_5 and COD in wastewater [39, 40, 38].

Micropollutants that are common in water resources cannot be effectively eliminated with the present treatment systems and environmental impacts in the receiving environment. In particular, antibiotics and pharmaceutics are released into the environment after their production and consumption so they create a threat in the receiving environment. Conventional treatment processes, primarily biologic treatment systems, remain insufficient in the elimination of antibiotics. In order to remove antibiotics that are resistant to biodegradation, advanced oxidation processes with a high oxidation potential should be used [41].

In wastewater treatment establishments, antibiotics are generally removed from the environment by biodegradation and sorption with activated sludge. Antibiotic-resistant bacteria spread in nature thanks to the removing methods of activated sludge containing antibiotic-resistant organisms such as agricultural practices or burying into the pit [42].

Antibiotics are used to help the growth of animals along with the treatment of human and animal diseases. Antibiotics that enter the body are removed without being metabolized at the rates reaching 90%. For this reason, the main source of antibiotic pollution in nature is the antibiotics in human and animal faeces. In recent studies, it is determined that antibiotics are found in animal faeces and domestic wastewater sewage sludge besides various compartments. By regarding physical and chemical properties, antibiotics can reach sediments, soil, and underground water. It is determined that conventional treatment methods remain insufficient in the removal of low concentrated antibiotics in water. The high concentration of antibiotics in the environment causes the degradation of ecological balance by creating a toxic effect on microorganisms, and their low concentration causes pathogenic and nonpathogenic bacteria to gain antibiotic resistance. For this reason, in order to remove antibiotic pollution, alternative treatment methods are necessary [43].

Gao et al. [44] determined 14 antibiotics in total in the wastewater, and 18 antibiotics in the activated sludge in their study. In the activated sludge, floroquinons, and ofloxacin were determined at the highest rate. Wastewater treatment establishments cannot remove antibiotics completely and the removal rate ranges from 34 to 72%. The amount of antibiotics in water is determined to be higher in winter months in comparison with spring and fall months. At the same time, antibiotic remnants have an adverse effect on very different organisms in nature (they encourage reproduction). Because of the low treatment effect, wastewater treatment establishments are the major source of antibiotics in aquatic environments.

According to Li et al. [45], the removal activity of target antibiotics from water changed between 32 and 78% through conventional treatment. With the advanced treatment methods, the removal rate of target antibiotics became 85–100% and pollution probability of antibiotics decreased. In addition to this, in the risk assessment, the effects of ofloxacin and erythromycin on microorganisms in water are investigated by refining it. The majority of antibiotics cannot be absorbed or metabolized in the body. Moreover, the large part pass into the sewage system through urine and faeces and it comprises a significant part of the antibiotic source in nature.

In the study conducted by Zhang et al. [46], the elimination mechanism of three β-lactam, two fluoroquinolones, and two macrolide antibiotics was investigated in the wastewater treatment establishment, which has four different treatment methods among six wastewater treatment establishments in China, Dalian. In this study, fluoroquinolones and macrolide antibiotics were determined as dominant antibiotics at the exit of wastewater treatment establishment and in coastal waters. It is revealed that β-lactams are removed through biodegradation, for fluoroquinolones pretreatment is more effective than biologic treatment, and macrolide concentration increases dramatically after biological treatment. The reason for this is that macrolides that are covered by faeces particles are revealed [46].

Xu et al. [47] examined antibiotics and their resistant genes in a water treatment establishment in Beijing, China and the situation of the river into which water was discharged in their study. A total of 13 antibiotic resistance genes (ARGs) were examined. SuI-arg was found at the highest rate among all antibiotic resistance genes (ARGs). ARG quantity in the wastewater treatment establishment is higher than in the river. According to the correlation analysis, there is a positive relationship between tetracyclines and tetargs in water. This correlation could not be performed between suI-args and sulfonamides. A negative relationship was observed between the concentration of quinolone genes and enrofloxacin. When ARG abundance of the waters that are treated in the treatment establishment is examined, treatment establishment causes resistant genes to increase. Results show that treatment establishments have a function of a warehouse for resistance genes. As a result, treated water needs advanced treatment before it is sent to the natural aquatic environment. In the study, three antibiotic groups were studied as tetracycline, sulfonamides, and quinones that are known for their permanence in the aquatic environment. Tetracyclines are removed at the rate of 87.9% in sludge elimination establishments. In the elimination of tetracycline, biodegradation, and adsorption have an important role. In sludge elimination establishments, teta, tetm, tetw, and teto genes are the ones that are mostly found [47].

6. Antibiotics

Antibiotics are bioactive substances that kill or stunt the growth of the microorganism and have a high effect on synthetic or biological origin [48].

Antibiotics that are naturally obtained from plants and their extracts and are used for medical purposes have been brought into use as a result of Paul Ehrlich's studies in 1908. Paul Ehrlich revealed some chemical substances that are harmful to some bacteria and are less harmful to the host cells by investigating them [49].

Antibiotics are produced in nature by bacteria or fungi. The production of antibiotics by these living beings and their release into the environment result from their food competition with other species. Therefore, they produce antibiotics in their environment which extinguish other microorganisms or inhibit their growth. Antibiotics do not affect fungi, viruses, and protozoa since they are active only in bacterial infections. At the present time, antibiotics are produced synthetically. The microorganisms the production of which has provided the invention of antibiotics are fungi [50].

As antibiotics can be broad-spectrum affecting numerous bacteria, they can also be narrow-spectrum affecting limited bacteria. Furthermore, antibiotics with bactericide effect have an effect on bacteria by killing bacteria and antibiotics with bacteriostatic effect have an effect on bacteria by stopping their reproduction [51].

Although it has not been a long time since antibiotics have come into use, a rapid increase has been observed in their development. However, many problems have occurred during and after the consumption of these drugs. One of the main problems among them is bacterial resistance that develops against antibiotics.

There are a lot of reasons that bacteria develop resistance to antibiotics. The most important among them is that antibiotics are used without need and unconsciously.

Drugs that are used most frequently and in an excessive amount in the world are antibiotics. This usage also covers the unnecessary and unconscious use besides the proper use for treatment. The use for wrong purposes, misuse, and unnecessary use of antibiotics lead to bacterial resistance. For this reason, information about the usage of antibiotics should be given and the excessive and unnecessary usage should be prevented.

6.1. Classification of antibiotics

Antibiotics are separated into two groups according to their effect on microorganisms:

- **Classification according to antibiotic potencies**

1. Bacteriostatic: This type of antibiotics prevents the development and reproduction of bacteria without killing the cells.
2. Bactericide: This type of antibiotics destroys bacterial cells by causing heavy damage.

6.2. Mechanisms of action of antibiotics

6.2.1. The ones that inhibit cell wall synthesis

Bacteria are prokaryote microorganisms. They do not have real nucleus but they have cell walls. Cell walls protect bacteria from the external environment and antimicrobials. Cell wall contains pores 1–2 nm in diameter that is convenient to the transition of substances found in the external environment and nonselective. In short, they are not semipermeable. The transition of antimicrobials depends on the structure of the cell wall and molecular size of the drug.

Human cells have no cell wall. Thus, antibiotics (Penicillins and Beta-lactams) in this group cannot spoil the adhesion of human cells. These antibiotics affect either by adhering to Penicillin-Binding Proteins (PBP) or by spoiling the synthesis of cell wall without adhering to PBP (**Table 2**) [51].

The ones that inhibit the cell wall synthesis	**Beta-Lactams:**
	Penicillines
	Cephalosporins
	Monobactams (Aztreonam)
	Carbapenems (imipenem, Meropenem)
	Cycloserine
	Ristocetin
	Bacitracin
	Teicoplanin
	Vancomycin
The ones that inhibit cytoplasm membrane permeability	Polymyxins
	Gramicidin
	Nystatin
	Amphotericin B
	Candicein
	Ketoconazole and other antifungal imidazols
	Fluconazole and other antifungal trizols
	Hexachlorophene
	Cationic detergents
The ones that inhibit ribosome's protein synthesis	Tetracyclines
	Aminoglycosides
	Macrolides
	Amphenicols
	Lincosamides
	Fucidicasid
The ones that effect bacteria's genetic material break DNA and RNA	Fluoroquinolones
	Rifamycins
	Nalidixicasid
	Metronidazole
	Actinomycins

The ones that inhibit the cell wall synthesis	Beta-Lactams:
	Mitomycins
	Bleomycins
	Acyclovir
	Doxorubicin
	Daunorubicine
	Methotrexate
Bacterial antimetabolites	Sulfonamides
	Sulfones
	PAS
	Isoniazide (INH)
	Ethambutol
	Trimethoprim

Table 2. Classification of antibiotics [53].

6.2.2. The ones that inhibit the protein synthesis

These chemotherapeutic drugs are generally broad-spectrum and have a bacteriostatic effect. Tetracyclines which belong to this antibiotic group prevent the adhesion of t-RNA to ribosomes. As human ribosomes (60S + 40S) and bacterial ribosomes (50S + 30S) are structurally different, these antibiotics that show an effect by adhering to ribosomes do not affect human ribosomes and protein synthesis (**Table 2**) [51].

6.2.3. The ones that inhibit nucleic acid synthesis

The most important antibiotics which belong to this group are rifampicin and quinones. Rifampicin inhibits the transcription (RNA inhibition dependent on DNA). Quinones inhibit the formation of supercolid (DNA gyrase inhibitors).

Topoisomerases which are used in human DNA and RNA synthesis and enzymes which are used in the nucleic acid synthesis of microorganisms are different. For this reason, these antibiotics do not have a toxic effect on human cells (**Table 2**) [51].

6.2.4. The ones that increase cytoplasmic membrane permeability

These antimicrobials create an effect by splitting the membrane substances in bacteria, inhibiting sterol synthesis in fungi or spoiling the permeability by binding sterols.

The cytoplasmic membrane of human cell bears a resemblance with cytoplasmic membranes of bacteria and fungi. Therefore, these antibiotics can have a toxic effect on human cells when they are used in a systemic way (**Table 2**) [51].

6.2.5. The ones with antimetabolic activity

Antibiotics in this group are generally bacteriostatic. The ones that are broadly known are the drugs such as sulfonamides, sulfons, para-amino salicylic acid (PAS), ethambutols, and isoniazid. Sulfonamides and Sulfons stop the function of PAS and para-amino benzoic acid (**Table 2**) [51].

6.3. Basic antibiotic groups

6.3.1. Beta-lactams

Antibiotics containing beta-lactam circle which is found in the nucleus and is responsible for the antibacterial effect of molecules are called beta-lactam antibiotics. The beta-lactam circle is a saturated circle, which comprises one nitrogen and three carbons. Antibiotics in this group have bactericide effect by influencing the cell wall which consists of the murine of bacteria. Penicillin and Ampicillin are the most known antibiotics in the beta-lactam group [52].

6.3.2. Vancomycin

They have an effect on multiresistant bacteria [54]. These antibiotics inhibit cell wall synthesis by stopping RNA synthesis in bacteria, break the continuity of the peptidoglycan chain and spoil the cytoplasmic membrane structure. Vancomycin which has a narrow antibacterial spectrum affects Gram (+) cokes and *Clostridiums* [51].

6.3.3. Tetracycline

These antibiotics inhibit protein synthesis by adhering to 30S subunit of the microorganism ribosome. Tetracycline which affects both Gram (+) and Gram (-) bacteria is broad-spectrum and has bacteriostatic effect [55, 56]. Tetracycline affects numerous and various bacteria types. It is also effective against *Rickettsia* sp., *Chlamydia* sp., *Spirochaete* sp., *Mycoplasma* sp., *Leptospira* sp., and some protozoa [51].

6.3.4. Aminoglycosides

Aminoglycosides inhibit protein synthesis in ribosomes by adhering to 30S subunit of bacterial ribosomes. Moreover, they cause the misreading of genetic code that m-RNA has. These antibiotics are narrow-spectrum and have bactericide effect. They are effective only in aerobe bacteria as they are dependent on oxygen in the membrane cell [51].

6.3.5. Macrolides

These antibiotics inhibit protein synthesis that is dependent on RNA in bacteria. They provide this effect by preventing the continuity of the peptide chain and adhesion of t-RNA by binding 70S ribosome to 50S subunit. Bacteriostatic macrolides have an intense effect against Gram (+) cokes and bacillus [57].

6.3.6. Chloramphenicol

Chloramphenicol is the first broad-spectrum antibiotic. These antibiotics inhibit peptidyl transferase enzyme by binding bacterial ribosomes to 50S subunit and thus they inhibit pro-

tein synthesis in a reversible way. They are sensitive to coke, aerobe, anaerobe Gram (+) bacilli, and most of the Gram (-) bacteria. Furthermore, these antibiotics inhibit protein synthesis of bacteria in the tissue by transferring into the tissue [55, 58].

6.3.7. Quinolones

Quinolones affect bacteria by inhibiting DNA gyrase. This effect prevents DNA replication and creates bactericide impact. Moreover, the bacteria that are exposed to this antibiotic do not divide and die from stretching abnormally. They are effective in most Gram (-) bacteria and Gram (-) bacteria [59].

6.3.8. Trimethoprim-sulfamethoxazole

It is also known as cotrimoxazole. When Sulfamethoxazole (STX) is a sulfonamide, Trimethoprim (TMP) is a diaminopiriminid which inhibits bacterial dihydrofolate reductase competitively. They affect many Gram (+) and Gram (-) bacteria by causing unnoticeable synergistic bactericide effect when both drugs are used separately.

As a rule, the maximum synergistic activity of both antibacterial drugs, Trimethoprim (TMP), and Sulfamethoxazole (STX), occurs in bacteria types which are sensitive to both drugs. In the determination of the activity, sensitivity to TMP is more important [60].

6.4. Antibiotic resilience

Antibiotic resilience is simply the ability to resist against any antibiotic which spoils the reproduction function of a microorganism or causes its death. Resistance concerns the microorganism, patient, antibiotic, and environment or all of them. Resistance has no connection with virulence [61].

Antibiotic resistance spreads in three ways in bacteria:

1. Transfer of bacteria between people

2. Transfer of resistant genes between bacteria (generally through plasmids)

3. Transfer of resistant genes between genetic elements in bacteria [60]

The resistance that microorganisms show against antibiotics is classified in two groups as natural (phenotypic) and acquired (genotypic).

6.4.1. Natural resistance

Natural resistance is the situation that occurs when the microorganism cannot carry the structure affected by the drug as its quality or it cannot reach the target due to the structure of the drug. This resistance is not hereditary besides it is the key feature of bacteria and it is not related to the use of drugs.

For instance, microorganisms such as L-forms of bacteria and *Mycoplasma* that have no membrane have a natural resistance to antibiotics such as penicillin which inhibit the cell wall synthesis. Another example is that vancomycin cannot affect Gram (-) bacteria due to the fact that it cannot pass from adventitia [62].

6.4.2. Acquired resistance

Depending on the change in bacteria's genetic characteristic, it is the resistance which occurs as a result of taking DNA series that have resistance gene from another bacterium through transformation, transduction, or conjugation as it can be through mutations in a plasmid, chromosome, or transposon DNA. Furthermore, these bacteria can gain resistance against antibiotics to which they have been sensitive before [63]. Genetic originated resistance is examined in two groups as chromosomal and extrachromosomal.

6.4.2.1. Chromosomal resistance

It occurs as a result of mutations which happen spontaneously in the bacterial chromosome. Spontaneous mutations arise from some physical or chemical factors. Consequently, structural changes occur in the bacterial cell. In this situation, changes can happen in the drug's target in the cell or permeability of the cell to the drug can decrease [62].

6.4.2.2. Extrachromosomal resistance

Bacteria have extrachromosomal resistance plasmids that are called extrachromosomal elements, transposons that are active elements found on the chromosomes and bring chromosomes new antibiotic resilience, integrons, and antibiotics.

6.4.2.2.1.+ Plasmids

The structures that can be inside bacteria or outside the chromosomes in the DNA structure, bring some qualities to these bacteria and keep these qualities under control genetically are called plasmids.

Plasmids can have virulence factors besides resistance genes against antimicrobics and heavy metals. Plasmids which have resistance genes are called R-plasmids. R-plasmids transfer the resistant gene package by passing into other bacteria through transformation, transduction, and conjugation. Thus, they provide the spread of resistance [64].

6.4.2.2.2. Transposons

Transposons are the structures which can settle in different places in the bacterial chromosome or can be transferred from chromosome to plasmid, from plasmid to plasmid, from plasmid to DNA or bacteriophage. These structures are DNA series found over the replicon like a chromosome, plasmid or bacteriophage as they cannot replicate by themselves. They have an active role in the spread of the multiple drug resistant isolates of transposons by revealing them in a short time [62, 65].

6.4.2.2.3. Integrons

Integrons are active DNA elements which have the ability to capture genes, which codify antibiotic-resistant genes in enteric bacteria, with specific recombination. These genes that are captured

by integrons are called gene tapes. Gene tapes are active genetic elements which comprise of only one gene and recombination zone which is free, little-alkali and called the 59-base element. As well as these gene tapes may not present in integrons at all, there can be 100 of them [66].

6.4.3. Cross-resistance

It is the situation when some microorganisms are resistant both to some drugs and at the same time to other drugs that have a similar mechanism. This resilience can be seen between structurally similar drugs like erythromycin and kanamycin as it can be seen between completely different drugs like erythromycin and lincomycin [62].

7. Antibiotic resistance in aquaculture and agriculture

Antibiotic concentrations below curative doses cause antibiotic resistance in many patient groups especially in critically ill patients [67].

The emergence of antibiotic-resistant bacteria is seen as an important health problem. For, thousands of patients die because of resistant bacteria. All efforts are concentrated on the decrease of existing antibiotic-resistant bacteria and antibiotic usage [2].

Rapidly developing antibiotic-resistant bacteria force public health services and health centers. American Centers for Disease Control and Prevention and Food and Agricultural Organization stated that antibiotic resilience has seriousness over the world. According to the predictions, 700,000 people die because of antibiotic resistance in a year. With the changes in temperature and rain regime, climate-sensitive bacteria and diseases will increase and spread to new regions, consequently, the situation will worsen [68].

Determination frequency and antibiotic concentrations are generally higher in January and May. The reason for this is that low-flow and low-temperature conditions cause antibiotics to be trapped by sediments. Antibiotic quantities vary per region. The highest quantities are found in estuaries and places where sewage is disposed. Antibiotic usage is more than 100,000–200·000 tonnes over the world and more than 25,000 tonnes in China. 80–90% of these antibiotics are released into nature through human urine and faeces. Pharmacologically active compounds in animal manure are used as a fertilizer in agriculture, and in conclusion, these compounds are accumulated in soil or mix into surface or underground waters [69].

Antibiotics are used as an environmental pollutant, in the treatment of diseases in a broad sense, in the protection and treatment of diseases in veterinary, and as growth promotive in aquaculture and agriculture [42].

Veterinary drugs are used for the protection and treatment of animal diseases and are one of the important components of environmental pollution as a result of intensive agricultural and aquaculture actions. Veterinary drugs are among the potentials of chemical pollutants and they have a biological effect in low concentrations like other drugs. While the annual usage of veterinary antibiotics in the United States reaches 11,000 tonnes, China follows it by 6000 tonnes. These quantities contain not only drugs with therapeutic purposes but also

antibiotics which are used to promote production. In Europe, France leads these rates with 1064 tonnes, Holland follows it with 514 tonnes, and England with 403 tonnes. The most used antibiotics are tetracyclines, sulfonamides, β-lactams, and macrolides. The presence of veterinary antibiotics in nature causes the emergence of antibiotic-resistant bacteria and nontarget microorganisms are affected by drinking potable water that contains antibiotic remnants or by consumption of animal or herbal foods that contain antibiotics. Mixing of veterinary drugs into nature may cause the development of single, multiple, and cross-resistance in pathogens, commensals, and nonpathogens. Most of the veterinary drugs are feebly absorbed in the animal intestine. The remaining large quantity is removed with faeces. A small combination of these drugs removed undergoes a change, conjugates with polar molecules or remains the same. Consequently, these drugs can be detected in natural environments such as animal manure, soil, surface, and underground water resources. The major source of veterinary drugs in nature is biological remnants and the usage of dirty animal faeces in fertilization [70].

The usage of wastewaters for agricultural and other purposes by treating them provides many advantages such as the formation of alternative water resources, prevention of the pollution of surface and underground waters, and reduction of fertilizer usage. However, along with its advantages, it also has negative effects on public health and the environment. In order to minimize these effects, risks that origin from pathogens and chemicals that emerge from the wastewater usage should be evaluated well [71].

Waters that are polluted in many ways are treated by many methods with the progress of technology. The usage of wastewaters as irrigation waters by putting them through pretreatment or delivering into the land is one of these methods. Causing soil pollution by water pollution occurs in this method. Wastewaters from various resources pollute the soil and they have various effects on soil pollution [72].

Domestic wastewaters can be used in forests, pastures, lawns by being pretreated. The removal of wastewaters by using them in the irrigation of lands in this way creates serious health problems. Moreover, bacteria and pollutants in wastewaters are harmful to human health by being absorbed by the soil and reaching underground waters when the buffering effect decreases [72].

In the sector of aquaculture, antibiotics are intensively used to treat fish and protect it from diseases. Antibiotics that are applied to fish cause fish pathogens and zoonotic fish bacteria to gain resistance to antibiotics. Zoonotic fish bacteria which develop antibacterial resistance create danger for people and cause infections that are hard to treat [73].

The misuse of antibiotics affects human health directly or indirectly and complicates the treatment of fish diseases. Its direct effect is that fish bacteria and zoonotic fish bacteria gain resistance. These strains which are resistant create refractory infections when they infect people. The indirect antibiotic resilience occurs with the transfer of resistance plasmids in bacteria to human pathogens. In this way, human pathogens that gain resistance create resistant infections in people. Also in the studies conducted, it is revealed that multiple antibiotic resistance genes are transferred from fish pathogens to human pathogens [73].

In August 2011, 20 antibiotics that were taken from 20 different samples' regions taken from sediment and aquatic organisms in Dalian coastline were examined. Tetracyclines are dominant antibiotics in sea water. Sulfonamides are dominant antibiotics in sediment and aquatic organisms. Industrial aquaculture is the most significant reason for the pollution of coasts in developed and developing countries because of the intensive antibiotic usage. Antibiotic usage in China comprises the quarter of antibiotic usage over the world [74].

The state of 37 antibiotics was examined on 6 aquaculture farms around Hailing Island. Sulfamethoxazole, salinomycin, and trimethoprim were detected at the highest rate in water; ox tetracycline was detected at the highest rate in shrimp larva pools, enrofloxacin was detected at the highest rate in feed samples, and erythromycin was detected at the highest rate in sediment [75].

Wastewater usage in agriculture and land irrigations can be described as wastewater recycling. This usage brings many problems even if it is very economical. The usage of wastewater in agricultural activities by pretreating it is not enough to eliminate these results. Especially, domestic wastewaters constitute an enormous danger because of their content. Sewage and hospital wastewaters are the reasons for this danger. Antibiotics cause infections and antibiotic resistance in people besides the fact that they decrease the productivity in agriculture with the bacterial and parasite microorganisms they contain.

In aquaculture, which is a method used in fish farming, it is possible that bacterial and parasite infections occur. Therefore, antibiotics are used for the treatment and protection from infections. Antibiotic usage complicates treatment as well as it creates antibacterial resistance in fish and people.

8. Suggestion

Urbanization, an increase in industry and population, increases the water demand with each passing day. The most important need is water and nutrition's existence depends on water. For this reason, the amount of water, as well as its presence, is important for living beings.

The increase of water usage, its unconscious use, the involvement in pollutant activities, and not taking precautions against pollution have a negative influence on water amount. In this situation, people's awareness should be increased, and pollution pretending precautions should be taken. Besides these situations, water reutilization can be provided by treatment.

The reutilization of wastewater by treatment increases water amount and creates some sources for the use of living beings. This brings positive situations as well as many negative situations along with it.

Wastewater causes pathogenic factors in living beings because of its content as well as it causes antibiotic-resistant bacteria and the spread of pathogen microorganisms.

There are many ways for antibiotic resistance to occur and spread. The leading factors among them are the excessive and unconscious usage of antibiotics, the usage of broad-spectrum

antibiotics, its accumulation in sewers through taking it to the body and urinating it, especially giving hospital sewer's accumulation to treatment facilities without its pretreatment.

The result of the insufficient treatment of wastewater treatment facilities is that the amount of antibiotics remains and an increase occurs as well. Due to the chemical structure of antibiotics, it may not come to light before entering the wastewater treatment. Antibiotics have the tendency to hold on to sediments due to their structure. In the stages of wastewater treatment, as a result of the decomposition of sediments, antibiotics come out. In this situation, the problems of not treating antibiotics arise. The usage of these waters for agricultural purposes also causes antibiotic resistance to spread.

Antibiotics are used for the purposes of treating diseases in humans and also for the same purposes in animals. In this situation, this can cause the emergence and spread of antibiotic-resistant bacteria.

To prevent the emergence and spread of antibiotic-resistant bacteria, first the awareness of people of antibiotic use should be raised. The usage of antibiotics in human and animal treatment should be reduced. Other waters that belong to the group of all sewage and wastewater, especially hospital sewage, should be pretreated before being discharged to wastewater treatments with biological treatment. Mechanic, chemical, and thermal treatment processes are included in pretreatment. Many pretreatment processes such as the process of oxidation, thermophilic pretreatment, sludge disintegration, ozonation, photocatalytic pretreatment, physicochemical pretreatment, and ultrasonic method should be used. Since wastewater treatment systems used fall short in some cases, new systems and pretreatment systems for antibiotic treatment should be developed.

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