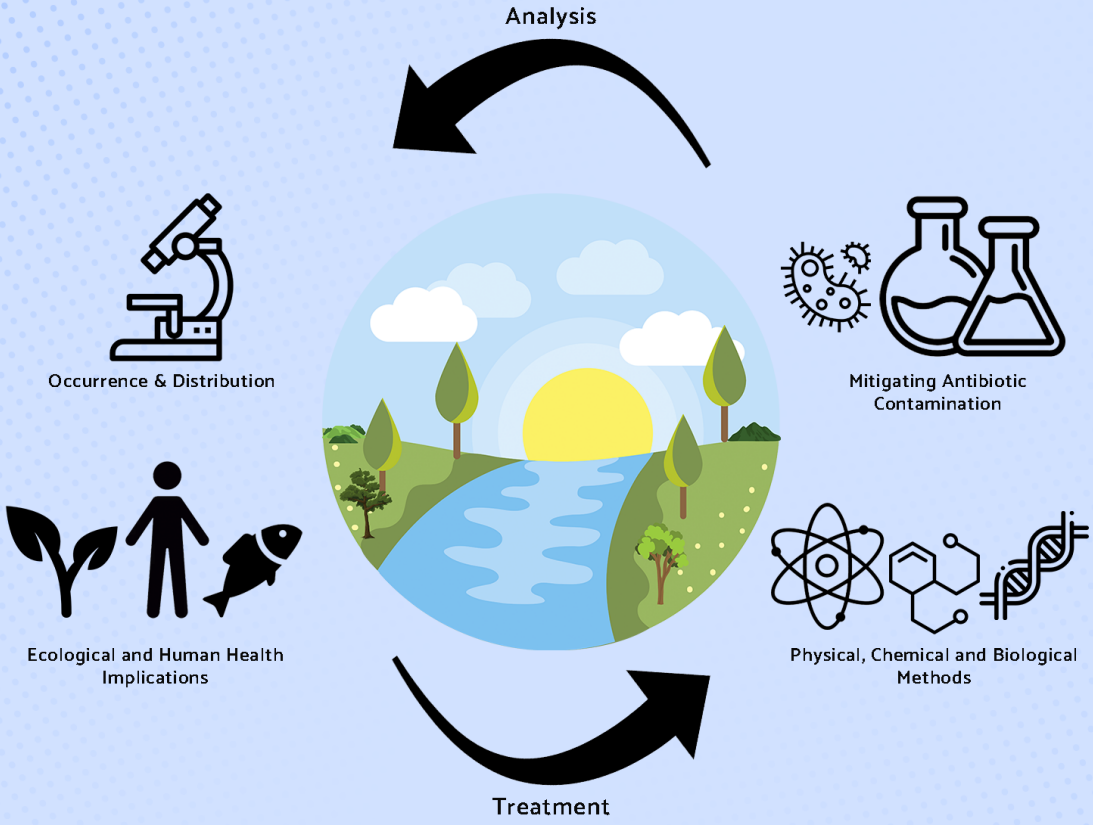
Antibiotics Found in Water Bodies and Treatment Methods



Felipe Oliveira da Silva | Aline Frumi Camargo | Helen Treichel

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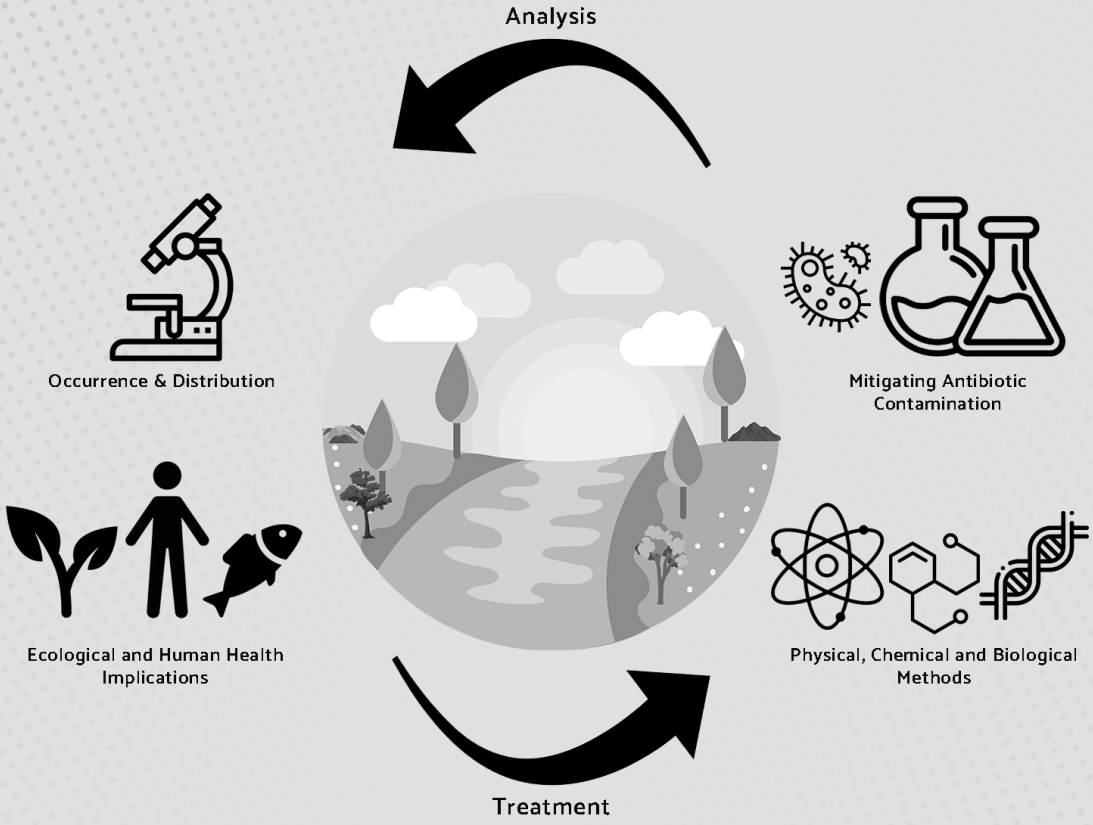

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Antibiotics found in water bodies and treatment methods

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This book provides an in-depth analysis of the occurrence and distribution of antibiotics in aquatic ecosystems, investigating their resistance capacity and characterizing them. It also explores the potential ecological and human health implications associated with antibiotic residues in water bodies. Recognizing the importance of mitigating antibiotic contamination in water bodies, this review devotes substantial attention to the various available treatment methods, encompassing diverse physical, chemical, and biological strategies. In addition, it will compare the legislation in force in Brazil, the European Union, and the USA.

KEYWORDS: Drug resistance, Antibiotics, Remediation Techniques, Human and Ecological Health.

SUMMARY

INTRODUCTION

In a world where the abuse and misuse of antibiotics pose a growing threat to global health, a worrying issue has emerged from an unexpected source: our water supply. Antibiotics, once considered miracle drugs that saved countless lives, are now becoming silent threats as they enter rivers, lakes, and drinking water sources. This water contamination with antibiotics and antibiotic-resistant bacteria has raised significant concerns about potential impacts on human health and the environment.

With the revolution in medicine, caused by the discovery of antibiotics, came large-scale consumption that had widespread effects on the microbial biosphere. Analyzes by Van Boeckel et al. They showed that humans' worldwide consumption of antibiotics reached 54 billion units – whether pills, capsules, or ampoules – in 2000 and increased by 36% in 2010 [1]. These authors also stated that this type of medicine in animals for food, supposedly higher than in humans, was more excellent than 63 million kg in 2010 [1]. Such significant and still increasing amounts of antibiotics overwhelm natural production, increasing selection pressure on bacterial populations in exposed environments [2]. The use and misuse of antibiotics in medicine, agriculture, and aquaculture are associated with the emergence of resistant bacteria in these environments [3,4,5]. Most antibiotics are expelled unchanged, being introduced into the territory directly or through waste and water streams [6].

As the development of this work delves deeper into the panorama of antibiotic pollution in waterways, it is intended to provide a critical assessment of the methods available for removal, weighing their advantages and limitations. By understanding the implications of these methods, we hope to contribute to the ongoing discourse on preserving water resources and protecting the health of ecosystems and communities.

ANTIBIOTICS

Despite the miraculous label, antibiotics are increasingly being misused. Their unsystematic use and disposal have led to resistance to various drugs among the microbiota. In case of reinfection, these antibiotics become useless for therapy. Their increasing use in the clinical, agricultural, and veterinary sectors is analogous to the growing resistance of bacteria to these frequently used antibiotics [7,8]. Antibiotic resistance has been established to be transmitted in the gut of warm-blooded animals [9,10,11]. Studies by Larsson and Fick [12] and Laxminarayan and Heymann [13] described the daily infiltration of about 45 kg of Ciprofloxacin from factories into nearby water bodies. The spread of environmental pollution has led to the discovery of antibiotic-resistant bacteria in uninhabited lands such as Antarctica [14,15].

Prolongation of illness due to a shortage of antibiotics or excessive use of antibiotics in circumstances where their use is not mandatory has become common. The use of antibiotics has skyrocketed in recent years. Sales of cephalosporins increased by 60% from 2005-2009, and sales of other last-line antibiotics increased sixfold from 2005 to 2010 [16,17].

Drug-resistant coliforms are the most commonly infecting bacteria, and the infection is contracted by exposure to unclean food, water, bacteria, or their carriers and reckless use of antibiotics [18]. Hanna et al. [19] investigated the association of drug-resistant E. coli infections with epidemiological factors: demographic variables, diet, health, and use of antibiotics and found a positive correlation between E. coli infection and contact with infected people, contaminated food, outpatient visit, misuse of antimicrobials, prolonged medication and frequent consumption of meat with self-prescribed medication. Overconsumption of antibiotics kills the beneficial bacteria in our system, increasing the growth of pathogens that may be insensitive to antibiotics and becoming resistant [19]. The antimicrobial susceptibility with the production of Extended Spectrum Beta-Lactamases (ESBL) among coliform isolates is cause for concern, as it renders therapy with beta-lactam antibiotics ineffective [20-23].

Mishra et al. [24] worked on the prevalence of antibiotic-resistant *E. coli* in the Mahanadi River. The water there involuntarily experiences the influence of varying composition. NMP, modified Eijkman test, biochemical fingerprinting, antimicrobial susceptibility testing, and 16S rDNA ribotyping methods were employed to isolate, enumerate, and identify coliform isolates such as *E. coli* with established resistance to beta-lactam antibiotics, carboxypenicillin coupled with β-lactamase, glycopeptides, carbapenems, macrolides, up to fourth generation fluoroquinolones, cephalosporins. Resistance rates of isolates against 42 antibiotics used with MAR indices ranging from 0.51 to 0.90 were also reported, which indicate severe pollution and risk to public health.

El-Zanfaly [25] reported that antibiotic resistance could increase during sewage treatment processes; his study applied enumeration, antimicrobial susceptibility, granular

activated carbon test, and transfer of antibiotic-resistant character tests to characterize ampicillin, sulfaguanidine penicillin, 2-sulfanilamide pyrimidine-resistant coliforms, tetracycline, chloramphenicol, neomycin, and streptomycin. The application of activated charcoal in a pilot experiment at a water treatment plant showed its prevalence with easy resistance transfer. The work insists on including antibiotic resistance in coliforms as a decisive criterion for judging water quality standards [25].

Characterization of the types of antibiotics found in water bodies

According to their chemical structures, antibiotics are classified into several groups, including macrolides, beta-lactams, tetracyclines, quinolones, fluoroquinolones, sulfonamides, phenols, and penicillins [26].

The tendency of antibiotics to be present in different environments - such as water, soil, and atmosphere - depends on their physicochemical properties, octanol/water split coefficient (Kow), distribution coefficient (Kd), separation constants (pKa), vapor pressure, and Henry's law constant (KH) [27].

According to the literature, the groups and types of antibiotics found in water bodies worldwide are expressed in Table 1.

Table 1. Classes of antibiotics are found in water bodies around the world.

Groups	Antibiotic Names	Symbol	Molecular Formula
Macrolides	Erythromycin	ERY	$C_{37}H_{67}NO_{13}$
	Azithromycin	AZI	$C_{38}H_{72}N_2O_{12}$
	Clarithromycin	CLA	$C_{38}H_{69}NO_{13}$
	Roxithromycin	ROX	$C_{41}H_{76}N_2O_{15}$
Tetracyclines	Tetracycline	TET	$C_{22}H_{24}N_2O_8$
	Doxycycline	DXC	$C_{22}H_{24}N_2O_8$
	Oxytetracycline	OTC	$C_{22}H_{24}N_2O_9$
	Chlortetracycline	CTC	$C_{22}H_{23}ClN_2O_8$
Fluoroquinolones	Ofloxacin	OFL	$C_{18}H_{20}FN_3O_4$
	Ciprofloxacin	CIP	$C_{17}H_{18}FN_2O_{12}$
	Norfloxacin	NOR	$C_{16}H_{18}FN_3O_3$
	Enoxacin	ENX	$C_{15}H_{17}FN_4O_3$
	Enrofloxacin	ENR	$C_{19}H_{22}FN_3O_3$
Sulfonamides	Sulfamethizole	SMZ	$C_9H_{10}N_4O_2S_2$
	Sulfathiazole	STZ	$C_9H_9N_3O_2S_2$
	Sulfamerazine	SMR	$C_{11}H_{12}N_4O_2S$
	Sulfaquinoxaline	SQX	$C_{14}H_{12}N_4O_2S$
	Sulfapyridine	SPY	$C_{11}H_{11}N_3O_2S$
	Sulfamethoxazole	SMX	$C_{10}H_{11}N_3O_2S$
	Sulfadiazine	SDZ	$C_{10}H_{10}N_4O_2S$

Amphenicols	Chloramphenicol	CHP	$C_{11}H_{12}C1_2N_2O_5$
	Thiamphenicol	TAP	$C_{12}H_{15}Cl_2NO_5S$
	Florfenicol	FF	$C_{12}H_{14}Cl_2FNO_4S$
β-Lactams	Amoxicillin	AMO	$C_{16}H_{19}N_3O_5S$
	Ampicillin	AMP	$C_{16}H_{19}N_3O_4S$
	Cephalexin	CEP	$C_{16}H_{17}N_3O_4S$
	Cefazolin	CEZ	$C_{14}H_{14}N_8O_4S_3$
	Penicillin G	PEN	$C_{16}H_{18}N_2O_4S$

MACROLIDES

The word macrolide is derived from “macro,” meaning large, and “olideo”, meaning lactone. They are compounds of the second most crucial antibacterial class used in human treatment after the β-lactamases family. For 40 years, they have been used to treat different types of infections. It has been used, especially in patients allergic to penicillins.

This class of antibiotics has activity against Gram-positive, Gram-negative, and anaerobic bacteria. Due to their intracellular concentration in several types of cells, such as macrophages, they can treat infections caused by intracellular pathogens. This class of antibiotics is used in human and veterinary medicine [28].

Macrolides are subdivided into two groups: those of natural origin and those of semi-synthetic origin. The latter can still be divided into three subgroups according to the chemical modification carried out in the core of Erythromycin. In the first subgroup, we have Roxithromycin and Clarithromycin. In the second subgroup, there is Azithromycin.

Finally, in the third subgroup, the ketolides [29].

Erythromycin is a bacteriostatic antibiotic produced by a strain of *Saccharopolyspora erythraea* (formerly *Streptomyces erythraeus*) and belongs to the macrolide group of antibiotics. It was initially discovered in 1952. Erythromycin is widely used to treat various infections, including those caused by gram-positive and gram-negative bacteria. It is available for administration in several forms, including intravenous, topical, and eye drop preparations.

Erythromycin is indicated for treating infections caused by susceptible strains of various bacteria. Erythromycin indications were summarized by the following body systems: respiratory infections, skin infections, gastrointestinal infections, and genital infections/ sexually transmitted infections.

In patients with normal liver function, erythromycin concentrates in the liver and is then excreted in the bile. Less than 5% of an orally administered erythromycin dose is excreted in the urine. A high percentage of absorbed erythromycin is not accounted for but is likely metabolized [30].

Azithromycin is a semi-synthetic macrolide derived from erythromycin by inserting nitrogen into the lactone ring. It is considered the first antibiotic of the azalide subclass [31,28].

It has a broader spectrum of action against Gram-positive microorganisms, high participation in the tissue, stability in an acid medium, and low metabolism rate, which make it more widely used than erythromycin.

Since most azithromycin is eliminated unchanged in the feces, significant active amounts of this compound can appear in sewage treatment plants. Its slow metabolism indicates poor degradation in treatment plants. Its active presence, along with its incomplete degradation in water treatment plants, is a facilitating factor in the development of antibiotic resistance in these stations and in the environment in general and its susceptibility to bind to the soil. Biliary excretion of azithromycin, mainly as an unchanged drug, is the primary route of elimination. Approximately 6% of the administered dose is found as a whole drug in the urine for one week [31].

Clarithromycin, a semi-synthetic macrolide antibiotic derived from erythromycin, inhibits bacterial protein synthesis by binding to the 50S ribosomal subunit. Binding inhibits peptidyl transferase activity and interferes with amino acid translocation during protein translation and assembly. Clarithromycin can be bacteriostatic or bactericidal, depending on the organism and drug concentration.

Because it is more stable in an acid medium, its bioavailability is better than erythromycin, and gastrointestinal intolerance is less [31]. Its metabolism takes place in the liver. Between 30 and 40% of an oral dose of clarithromycin is excreted unchanged through the urine, and the rest is excreted in the bile.

After a 250 mg tablet every 12 hours, approximately 20% of the dose is excreted in the urine as clarithromycin. In contrast, after a 500 mg tablet every 12 hours, urinary excretion of clarithromycin is slightly higher, approximately 30% [32].

Roxithromycin is a semi-synthetic macrolide that derives from and resembles erythromycin, differing in its prolonged half-life. It is active against Gram-positive and Gram-negative. It has excellent stability in an acid medium. Its metabolization in animals and humans and biotransformation have not yet been well elucidated [33].

Roxithromycin is a semi-synthetic macrolide antibiotic structurally and pharmacologically similar to erythromycin, azithromycin, or clarithromycin. It is most effective against certain Gram-negative bacteria, particularly *Legionella pneumophila*. Roxithromycin exerts antibacterial action by binding to the bacterial ribosome and interfering with bacterial protein synthesis. Used to treat respiratory, urinary tract, and soft tissue infections. Roxithromycin is only partially metabolized in the liver, with more than half of the parent compound excreted unchanged.

TETRACYCLINES

Tetracyclines were discovered in 1948 as the natural fermentation products of a soil bacterium, Streptomyces aureofaciens. The first chemically purified tetracycline was chlortetracycline (1954). Currently, three groups of tetracyclines are available: natural tetracycline products, semisynthetic tetracycline compounds, and chemically modified tetracyclines (CMTs). The literature suggests tetracyclines acting as antibiotics may also affect inflammation, immunomodulation, cell proliferation, and angiogenesis.

Due to their broad spectrum of action and the ease of administering them orally, tetracyclines were widely used in all countries. This led to the development of resistance by microorganisms, mainly through efflux mechanisms and modification in the ribosome.

The widespread production and use of natural tetracyclines in human and animal medicine in the decades following their discovery led to resistance mechanisms and decreased efficacy as first-line antibiotics [34].

Tetracyclines are drugs indicated mainly in the treatment of rickettsial diseases, chancroid, lymphogranuloma venereum, non-gonococcal urethritis, psittacosis, trachoma, cholera, atypical pneumonia caused by mycoplasma and chlamydia, recurrent fevers, tularemia, rat-bite fever, and plague.

Tetracyclines are broad-spectrum antibiotics used to treat infections caused by many aerobic gram-positive and gram-negative bacteria. Urethral and prostatic diseases due to chlamydia and mycoplasma have, in tetracyclines, the drug of choice for treatment.

Urethral and prostatic infections due to chlamydia and mycoplasma have, in tetracyclines, the drug of choice for treatment. This drug is not metabolized but is concentrated by the liver in the bile and excreted in the urine and feces in high concentrations in a biologically active form.

Doxycycline is a member of the tetracycline class of antibiotics and has been used clinically for over 40 years. It is a well-tolerated bacteriostatic drug that acts by inhibiting bacterial ribosomes. It is well absorbed and generally has good tissue penetration. The main side effects are gastrointestinal and dermatological, and it is usually contraindicated in pregnancy or childhood due to concerns about discoloration of developing teeth and possible impact on growing bones [35].

It has activity against many organisms, including Gram-positive, Gram-negative, and atypical bacteria. Furthermore, it has some potentially clinically useful anti-inflammatory properties [35].

Tetracyclines, including doxycycline, are concentrated in the bile by the liver and excreted in the urine and feces in high concentrations and a biologically active form. Kidney excretion of doxycycline is about 40%/72 hours in subjects with creatinine clearance of about 75 ml/min. This percentage can drop as low as 1-5%/72 hours in individuals with creatinine clearance below 10 mL/min.

Oxytetracycline is a broad-spectrum antibiotic that works by inhibiting protein synthesis in bacteria. Like other tetracyclines, it treats many common and rare infections. In penicillin-sensitive patients, it is sometimes used to treat spirochetal infections, clostridial wound infections, and anthrax. Oxytetracycline treats respiratory and urinary tract infections, skin, ear, eye, and gonorrhea. However, its use for these purposes has declined recently because of significantly increased bacterial resistance to this class of drugs. The drug is beneficial when penicillins and macrolides cannot be used due to allergy. It can be used to treat Legionnaires' disease as a replacement for a macrolide or quinolone [36].

Chlortetracycline was the first tetracycline to be identified. It was discovered in 1945 at Lederle Laboratories under the supervision of Subbarow and Duggar, who recognized the antibiotic as the product of an actinomycete grown from a soil sample collected at Sanborn Field at the University of Missouri. The organism was named *Streptomyces aureofaciens*, and the isolated drug, Aureomycin, because of its golden color [37].

It is combined with a triamcinolone acetonide cream for treating infectious, allergic dermatitis in humans. In veterinary medicine, chlortetracycline is commonly used to treat conjunctivitis in cats, dogs, and horses. It also treats infected wounds in cattle, sheep, and pigs and respiratory tract infections in calves, pigs, and chickens.

Chlortetracycline is not known to undergo significant metabolism. Chlortetracycline is mainly eliminated in the feces. Renal function does not affect the elimination rate [38].

FLUOROQUINOLONES

Fluoroquinolones are highly effective antibiotics with many advantageous pharmacokinetic properties, including high oral bioavailability, large volume of distribution, and broad-spectrum antimicrobial activity. With widespread use, antimicrobial resistance to fluoroquinolones has increased. In addition, fluoroquinolones risk serious adverse effects (e.g., Clostridioides difficile infection, tendinopathy, neuropathy) and have multiple drug interactions. Thus, fluoroquinolones are usually reserved for cases where the benefits outweigh the risks [39].

Ofloxacin is a quinolone antibiotic used for the treatment of various bacterial infections. When taken by mouth or injected into a vein, they treat pneumonia, cellulitis, urinary tract infections, prostatitis, plague, and infectious diarrhea. Other uses, along with other medications, include the treatment of MDR-TB. An eye drop can be used for a superficial bacterial infection of the eye, and an eye drop can be used for otitis media when a hole in the eardrum is present [40].

Ofloxacin is also sometimes used to treat other types of infections, including Legionnaires' disease (a type of lung infection), certain sexually transmitted diseases, bones and joints, and disorders of the stomach and intestines. Ofloxacin can also treat or prevent anthrax or plague (serious infections that can be transmitted intentionally as part

of a bioterrorist attack) in people who may have been exposed to the germs that cause these airborne infections. Ofloxacin may also treat or prevent traveler's diarrhea in certain patients.

Its metabolization takes place in the liver. Ofloxacin is eliminated primarily by renal excretion, where between 65% and 80% of an orally administered dose of ofloxacin is excreted unchanged in the urine within 48 hours of administration. About 4-8% of an ofloxacin dose is excreted in the feces, and the drug is minimally subject to biliary excretion.

Ciprofloxacin is a broad-spectrum antibiotic of the fluoroquinolone class. It is active against some Gram-positive bacteria and many Gram-negative bacteria. It works by inhibiting a type II topoisomerase (DNA gyrase) and a topoisomerase IV, which is needed to separate bacterial DNA, thereby inhibiting cell division. Fragmentation of bacterial DNA occurs due to enzyme inhibition [41, 42].

Ciprofloxacin was patented in 1980 and introduced in 1987. It is on the World Health Organization's List of Essential Medicines. The World Health Organization classifies ciprofloxacin as extremely important for human medicine. It is available as a generic drug [40].

Ciprofloxacin treats various infections, including bone and joint infections, endocarditis, gastroenteritis, malignant external otitis, respiratory tract infections, cellulitis, urinary tract infections, prostatitis, anthrax, and chancroid.

CYP1A2 primarily metabolizes Ciprofloxacin. The primary metabolites oxociprofloxacin and sulciprofloxacin comprise 3-8% of the total dose. Ciprofloxacin is also converted to the minor ethylene metabolites ciprofloxacin and formylciprofloxacin. These four metabolites represent 15% of the entire oral amount. There is a lack of available data on the enzymes and types of reactions involved in forming these metabolites [43-45].

Norfloxacin is a synthetic broad-spectrum fluoroquinolone antibiotic with variable activity on gram-positive and gram-negative bacteria. It is indicated in the treatment of uncomplicated urinary tract infections (including cystitis), complicated urinary tract infections (restricted use), uncomplicated urethral and cervical gonorrhea (however, this indication is no longer considered adequate by some experts due to bacterial resistance), and *Escherichia coli* prostatitis [46, 47].

Its metabolism is via the liver and kidney. Norfloxacin is eliminated by metabolism, biliary excretion, and renal excretion. It is expected to undergo glomerular filtration and tubular secretion during renal excretion, as demonstrated by its high renal clearance rate of approximately 275 mL/min [48].

Enoxacin is a broad-spectrum fluoroquinolone oral antibacterial agent structurally related to nalidixic acid used to treat urinary tract infections and gonorrhea. It has recently been shown to have a cancer-inhibiting effect [49].

It is indicated for the treatment of adults (≥18 years of age) with the following infections caused by susceptible strains of the designated microorganisms: uncomplicated urethral or cervical gonorrhea due to *Neisseria gonorrhoeae*, uncomplicated urinary tract infections

(cystitis) due to *E. coli*, *Staphylococcus epidermidis* or *Staphylococcus saprophyticus* and complicated urinary tract infections due to *E. coli*, *Klebsiella pneumoniae*, *Proteus mirabilis*, *Pseudomonas aeruginosa*, *Staphylococcus epidermidis* or *Enterobacter cloacae* [50].

Its metabolism is hepatic. Some isoenzymes of the cytochrome P-450 hepatic microsomal enzyme system are inhibited by enoxacin. After a single dose, over 40% was recovered in the urine within 48 hours as an unchanged drug [51].

Enrofloxacin is an antibiotic agent of the fluoroquinolone family produced by Bayer Corporation. The FDA approves Enrofloxacin for veterinary use. Due to the identification of fluoroquinolone-resistant strains of Campylobacter, in September 2005, the FDA withdrew approval of enrofloxacin for use in water to treat poultry flocks [52].

The bactericidal activity of enrofloxacin is concentration-dependent, with cell death of susceptible bacteria occurring within 20 to 30 minutes after exposure. Enrofloxacin has demonstrated a significant post-antibiotic effect for Gram-negative and Gram-positive bacteria and is active in both the stationary and growth phases of bacterial replication [53].

SULFONAMIDES

Sulfonamide is a functional group (a part of a molecule) that is the basis of several groups of drugs called sulfonamides or sulfa. The original antibacterial sulfonamides are synthetic antimicrobial agents (not antibiotics) that contain the sulfonamide group. Some sulfonamides are also devoid of antibacterial activity, for example, the anticonvulsant sultiame. Sulfonylureas and thiazide diuretics are newer drugs based on antibacterial sulfonamides [54].

Sulfonamides were the first widely effective antibacterials to be used systemically and paved the way for the antibiotic revolution in medicine. The first sulfonamide, trade name Prontosil, was a prodrug. Experiments with Prontosil began in 1932 in the laboratories of Bayer AG, which was, at the time, a component of the substantial German chemical fund IG Farben. The Bayer team believed that coal tar dyes, which can preferentially bind to bacteria and parasites, could be used to attack harmful organisms in the body [55].

Many thousands of molecules containing the sulfanilamide structure have been created since its discovery (by one account, over 5,400 permutations in 1945), producing improved formulations with greater efficacy and less toxicity. Sulfa drugs are still widely used for conditions like acne and urinary tract infections and are receiving renewed interest in treating infections caused by bacteria resistant to other antibiotics.

Sulfamethizole is a sulfonamide antibiotic. Sulfonamides are synthetic bacteriostatic antibiotics with a broad spectrum against gram-positive and gram-negative organisms. However, many strains of an individual species can be resistant.

It is indicated for treating infections and inflammations in the urinary tract, cystitis, prostatitis, and gonorrhea. With rapid absorption, its metabolization takes place in the liver.

Sulfathiazole is a short-acting sulfonamide drug. It was a common oral and topical antimicrobial until less toxic alternatives were discovered. It is still used occasionally, sometimes in combination with sulfabenzamide and sulfacetamide.

Except for those formulated for vaginal use, the FDA has withdrawn its approval for all sulfathiazole-containing medications [56, 57].

Sulfathiazole is effective against a wide range of gram-positive and gram-negative pathogenic microorganisms. Although it is no longer used in humans, it is used in cattle and is associated with treating bacterial pneumonia and infections of the eyes and hearing aids.

Sulfamerazine is a sulfonamide that is an antibacterial agent used to treat various bacterial infections such as bronchitis, prostatitis, and urinary tract infections [58]. They lack information regarding their absorption and metabolism.

Sulfaquinoxaline is an antimicrobial for veterinary use, with activity against a broad spectrum of Gram-negative and Gram-positive bacteria. Sulfaquinoxaline is used to prevent coccidiosis and bacterial infections [59].

This antimicrobial is widely used in poultry production as a therapeutic or prophylactic agent because broiler chickens are raised in intensive industrial farming systems, whose stressful conditions can make these animals more susceptible to infectious diseases [60].

Sulfapyridine is a sulfonamide antibacterial drug. At the same time, it was commonly referred to as M&B 693. Sulfapyridine is no longer prescribed for treating human infections, so much so that it has been withdrawn from the market in several countries. However, it can treat linear IgA disease and has use in veterinary medicine. It is an excellent antibacterial drug, but its water solubility is very pH-dependent. Thus, there is a risk of crystallization in the bladder or urethra, which can cause pain or obstruction [61].

It was indicated for treating dermatitis herpetiformis, benign pemphigoid of the mucous membranes, and pyoderma gangrenosum. Its metabolization takes place in the liver.

Sulfamethoxazole is a bacteriostatic sulfonamide antibiotic that interferes with folic acid synthesis in susceptible bacteria. It is usually given in combination with trimethoprim, which inhibits a sequential step in the bacterial synthesis of folic acid.

These agents act synergistically to block two consecutive steps in the biosynthesis of nucleic acids and proteins needed for bacterial growth and division and use them together to help delay the development of bacterial resistance. In this combination, sulfamethoxazole helps treat various bacterial infections, including those of the urinary, respiratory, and gastrointestinal tracts.

Sulfamethoxazole is indicated in combination with trimethoprim, in various formulations, for the following infections caused by bacteria with documented susceptibility: urinary tract infections, acute otitis media in pediatric patients (when clinically indicated), acute exacerbations of chronic bronchitis in adults, enteritis caused by susceptible Shigella, prevention and treatment of pneumonia by *Pneumocystis jiroveci* and travelers' diarrhea caused by enterotoxigenic *E. coli* [62].

Sulfamethoxazole is metabolized in the human liver to at least five metabolites. These metabolites are N4-acetyl-, N4-hydroxy-, 5-methyl-hydroxy-, N4-acetyl-5-methyl-hydroxy-sulfamethoxazole and an N-glucuronide conjugate. The CYP2C9 enzyme is responsible for the formation of the N4-hydroxy metabolite. In vitro studies suggest that sulfamethoxazole is not a P-glycoprotein transporter (FDA) substrate.

Sulfamethoxazole is mainly excreted really by glomerular filtration and tubular secretion. About 20% of sulfamethoxazole in urine is the unchanged drug, 15–20% is the N-glucuronide conjugate, and 50–70% is the acetylated metabolite. Sulfamethoxazole is also excreted in human milk.

Sulfadiazine is an antibiotic of the sulphamide class. Used in conjunction with pyrimethamine, a dihydrofolate reductase inhibitor, it is the treatment of choice for toxoplasmosis caused by a protozoan parasite. It is a second-line treatment for otitis media prevention of rheumatic fever, chancroid, chlamydia, and Haemophilus influenzae infections. It is also an adjunctive therapy for chloroquine-resistant malaria and various forms of bacterial meningitis. It is taken orally and excreted mainly in the urine.

Sulfadiazine was approved for medical use in the United States in 1941. It is on the World Health Organization's List of Essential Medicines. Sulfadiazine is available as a generic drug [40].

AMPHENICOLS

Amphenicols are synthetic antibiotics with a broad spectrum of activity used mainly for treating severe bacterial infections in human and veterinary medicine. They exhibit a wide range of movement against gram-negative and gram-positive organisms, including Streptococcus spp., Staphylococcus spp., Pasteurella spp., Escherichia coli, Salmonella spp. and Bordetella bronchiseptica that cause respiratory and enteric diseases in cattle, through the inhibition of protein biosynthesis by binding to the ribosomal subunits of susceptible bacteria [63].

Amphenicols have been used in livestock for many years, being marketed under brands such as Nuflor®, Resflor Gold®, Florocol®, and Selectan®. However, its use has been questioned since the mid-1980s due to concerns related to hematological toxicity and the risk associated with human health by ingesting animal products contaminated with amphenicol. Furthermore, growing global concerns regarding the emergence of drug-resistant bacteria due to overprescribing antibiotics have led to their strictly regulated use in many countries, including the European Union, China, and the United States [63].

Chloramphenicol is a broad-spectrum antibiotic that is effective against various serious and susceptible bacterial infections but is infrequently used because of the high risk of bone marrow toxicity. It was discovered after being isolated from Streptomyces venezuelae in 1947. Its chemical structure was identified, and it was first synthesized in

1949. It is on the World Health Organization's List of Essential Medicines. It is available as a generic drug [64].

Chloramphenicol is a valuable antibiotic for treating various bacterial infections. This includes use as an eye ointment to treat conjunctivitis. It treats meningitis, plague, cholera, and typhoid fever by mouth or injection into a vein. It is only recommended orally or by injection when safer antibiotics cannot be used. Monitoring medication and blood cell levels every other day is recommended during treatment [65].

The FDA has withdrawn all oral medications containing chloramphenicol due to the high risk of fatal aplastic anemia associated with this specific route of administration. Metabolization occurs via the liver, with 90% conjugated to inactive glucuronide.

Thiamphenicol (also known as thiophenicol or dextrosulfenidol) is an amphenicol antibiotic. It is the methylsulfonyl analog of chloramphenicol and has a similar spectrum of activity but is 2.5 to 5 times more potent. Like chloramphenicol, it is insoluble in water but highly soluble in lipids. It is used in many countries as a veterinary antibiotic but is available in China, Morocco, and Italy for human use. Its main advantage over chloramphenicol is that it has never been associated with aplastic anemia. Thiamphenicol is also widely used in Brazil, mainly for treating sexually transmitted infections and pelvic inflammatory disease [66].

Unlike chloramphenicol, thiamphenicol is not readily metabolized in cattle, poultry, sheep, or humans but is predominantly excreted unchanged. The drug is excreted in pigs and rats as parent drugs and as thiamphenicol glucuronate.

Florfenicol is a synthetic fluorinated analog of thiamphenicol, used mainly in veterinary medicine. As a generic, it is now available worldwide [67].

In the United States, florfenicol is currently indicated for the treatment of bovine respiratory disease (BRD) associated with *Mannheimia haemolytica*, *Pasteurella multocida*, and *Histophilus somni*, for the treatment of bovine interdigital phlegmon (foot rot, acute interdigital necrobacillosis, infectious pododermatitis) associated with to *Fusobacterium necrophorum* and bacteroides melaninogenicus. Florfenicol is also used in aquaculture and is licensed in the United States to control enteric septicemia in catfish [68].

Since the early 2000s, it has been used in Europe, mainly treating primary or secondary colibacillosis in broilers and parent flocks. Not allowed in laying hens due to residues in the eggs. It is also indicated in Türkiye [69]. The use of florfenicol in horses, and probably other equines, commonly causes diarrhea. This has been reported to progress to lethal cases of acute colitis. Therefore, using this antimicrobial in the equine patient should be limited to issues where other safer options are unavailable [70].

B-LACTAM

β-lactam antibiotics (beta-lactam antibiotics) contain a beta-lactam ring in their chemical structure. Primarily, they act by inhibiting cell wall biosynthesis in bacterial

organisms and are the most widely used group of antibiotics. By 2003, when measured by sales, more than half of all commercially available antibiotics were β-lactam compounds [71].

The first β-lactam antibiotic discovered, penicillin was isolated from a strain of the fungus Penicillium rubens called Penicillium notatum at the time [72]. β-lactam antibiotics are indicated for preventing and treating bacterial infections caused by susceptible organisms. At first, β-lactam antibiotics were primarily active only against Gram-positive bacteria. Still, the recent development of broad-spectrum β-lactam antibiotics active against many Gram-negative organisms has increased their usefulness.

Bacteria usually develop resistance to β-lactam antibiotics by synthesizing a β-lactamase, an enzyme that attacks the β-lactam ring. To overcome this resistance, β-lactam antibiotics can be administered with β-lactamase inhibitors such as clavulanic acid [73].

Amoxicillin is in the family of beta-lactam antibiotics, a medication used to treat many bacterial infections. Amoxicillin was discovered in 1958 and was used in medicine in 1972. It was approved for medical use in the United States 1974 and the United Kingdom in 1977. It is on the World Health Organization's List of Essential Medicines. It is one of the most commonly prescribed antibiotics for children. Amoxicillin is available as a generic drug. In 2020, it was the 40th most prescribed drug in the United States, with over 15 million prescriptions [74, 75].

Amoxicillin alone is indicated to treat susceptible bacterial infections of the ear, nose, throat, genitourinary tract, skin, skin structure, and lower respiratory tract. Amoxicillin is given with clavulanic acid to treat acute bacterial sinusitis, community-acquired pneumonia, respiratory tract infections, acute bacterial otitis media, infections of the skin and skin structure, and urinary tract infections. Amoxicillin is given with omeprazole to treat the disease of *Helicobacter pylori* (*H. pylori*).

Incubation with human liver microsomes led to the detection of 7 metabolites. Metabolite M1 underwent hydroxylation, M2 underwent oxidative deamination, M3 to M5 underwent aliphatic chain oxidation, M6 underwent decarboxylation, and M7 underwent glucuronidation. Regarding its route of elimination, doses of 125mg to 1g of amoxicillin are 70-78% eliminated in the urine after 6 hours [76, 77].

Ampicillin is a semi-synthetic derivative of penicillin that functions as an orally active broad-spectrum antibiotic. It was discovered in 1958 and began to be used commercially in 1961. It is on the World Health Organization's List of Essential Medicines, classifying it as extremely important for human medicine. It is available as a generic drug [40].

Ampicillin is used to treat infections with many gram-positive and gram-negative bacteria. It was the first "broad-spectrum" penicillin with activity against gram-positive bacteria; activity against gram-negative bacteria includes *Neisseria meningitidis*, some *Haemophilus influenzae*, and some of the Enterobacteriaceae (although most

Enterobacteriaceae and Pseudomonas are resistant). Its spectrum of activity is increased by co-administration of sulbactam, a drug that inhibits beta-lactamase, an enzyme produced by bacteria to inactivate ampicillin and related antibiotics [78, 79].

It is indicated for the treatment of infections - respiratory, gastrointestinal, genitourinary, and meningitis - caused by *E. coli, P. mirabilis, enterococci, Shigella, S. typhosa*, and other Salmonella, *N. gononhoeae* that do not produce penicillinase, *H. influenzae*, staphylococci, streptococci, including streptococci.

Cephalexin is an antibiotic that can treat many bacterial infections. It kills gram-positive and some gram-negative bacteria by stopping bacterial cell wall growth. It is a beta-lactam antibiotic of the first-generation cephalosporin class [62, 80].

Cephalexin was developed in 1967. It was first marketed in 1969 and 1970 under Keflex and Ceporex, among others. Generic drug versions are available under other brand names and are inexpensive. It is on the World Health Organization's List of Essential Medicines. It is among the most prescribed drugs in the US, Canada, and Australia [81, 40].

Cephalexin is indicated for the treatment of certain infections caused by sensitive bacteria. These infections include respiratory tract infections, otitis media, infections of the skin and skin structures, bone infections, and genitourinary tract infections.

Cephalexin is not metabolized in the body. It is excreted in the urine by more than 90% after 6 hours by glomerular filtration and tubular secretion, with a mean urinary recovery of 99.3%. Cephalexin remains unchanged in urine [83, 83]

Cefazolin is a first-generation cephalosporin antibiotic used to treat various bacterial infections. Cefazolin was patented in 1967 and began to be used commercially in 1971. Medication. It is a generic drug [74].

Cefazolin is a broad-spectrum cephalosporin antibiotic used primarily to treat bacterial skin infections. It can also treat moderately severe bacterial infections involving the lungs, bones, joints, stomach, blood, heart valve, and urinary tract. It is clinically effective against infections caused by staphylococci and streptococci species of Gram-positive bacteria [40].

This drug is not metabolized. Cefazolin is present in deficient concentrations in the milk of nursing mothers. It is excreted unchanged in the urine within the first six hours. Approximately 60% of the drug is excreted in the urine and increases to 70%-80% within 24 hours.

Benzylpenicillin (penicillin G) is a narrow-spectrum antibiotic used to treat infections caused by susceptible bacteria. It is a natural antibiotic given intravenously or intramuscularly due to oral malabsorption. Penicillin G can also be used as prophylaxis against susceptible organisms.

Natural penicillins are considered the drugs of choice for many infections caused by susceptible aerobic gram-positive organisms, such as *Streptococcus pneumoniae*, Group A, B, C, and G Streptococci, Group D non-enterococcal Streptococci, Viridans group Streptococci, and Non-enterococcal staphylococci.

Natural penicillins can also be used as first- or second-line agents against susceptible aerobic gram-positive bacilli such as *Bacillus anthracis*, *Corynebacterium diphtheriae*, and *Erysipelothrix rhusiopathiae.* Natural penicillins have limited activity against gram-negative organisms; however, they can be used in some cases to treat infections caused by *Neisseria meningitidis* and Pasteurella. They are generally not used to treat anaerobic conditions.

About 16-30% of an intramuscular dose is metabolized to penicilloic acid, an inactive metabolite. Small amounts of 6-aminopenicillins acid have been recovered in patients taking penicillin G. A small percentage of the drug appears to be hydroxylated to one or more active metabolites, which are also excreted in the urine. The kidneys eliminate penicillin G. Non-renal clearance includes hepatic metabolism and biliary excretion to a lesser extent.

Explaining the resistance

The increase in bacterial resistance is associated with the number of antibiotics prescribed and the fact that the prescription instructions are not followed precisely (the treatment is not followed to the end). Underprescribing antibiotics occurs for various reasons, including patients asking doctors to prescribe them, doctors prescribing them without explaining why they are not needed, or why they define them cautiously and for medical or legal reasons [84, 85].

Resistance occurs in three ways: natural resistance of certain bacteria, genetic mutation, or a species acquiring resistance from another (Horizontal Gene Transfer – THG). Resistance can arise spontaneously through random mutations or, more often, after a gradual buildup over time and due to the misuse of antibiotics or antimicrobials. Resistant microbes are increasingly difficult to treat, requiring higher doses or alternative drugs that can be more expensive or toxic. Microbes resistant to multiple antimicrobials are called “multidrug-resistant” (MMR) or sometimes superbugs.

NATURAL RESISTANCE

Some bacteria are naturally resistant to antibiotics. One of the defenses of some bacteria is a substance that destroys the antibiotic molecule. When the antibiotic is close to the bacteria, they release their chemical defenses, so the antibiotic stops working. Another way to protect yourself is to change your proteins so that the antibiotic no longer touches the outside of the body, which are the cells. For example, many antibiotics try to bind to bacterial receptors, molecules that are outside the bacteria and receive signals. Some of these bacteria can change the shape of their receptors so that the antibiotic cannot attach to them. If it can't bind, it can't kill the bacteria.

GENETIC MUTATION

The likelihood that a mutation will confer an antibiotic resistance phenotype (variability) affects the mutation rate. The variability depends on the structure and number of genes where mutations can produce a selectable phenotype. The DNA structure of a gene is essential for variability. If all positions mutate equally, long genes may be more susceptible to mutation than short ones. However, the size of the gene is not the most critical factor in terms of its variability, as not every transformation in the gene encoding the antibiotic target leads to resistance. Resistance only occurs through permissive mutations (non-lethal, or more broadly, that do not cause an unacceptable loss of fitness) and can produce the resistance phenotype. The probability of an effective resistance mutation is proportional to the number of such positions. For example, in *E. coli*, changes in at least seven places in the gyrA gene have led to a quinolone resistance phenotype. Still, changes in as few as three positions in the parC gene lead to a resistance phenotype [86].

The mutation rate of the gyrA gene is expected to be higher than that of the parC gene; indeed, gyrA mutants are found more frequently than parC mutants. In contrast, in Streptococcus pneumoniae, resistance to quinolones is due to changes in two positions of gyrA. Still, it is due to changes in five parts of parC, and parC mutants are the most common. In the same organism, the gene encoding 2× PBP, whose mutations can confer resistance to β-lactams, has 13 positions for cefotaxime resistance but only 1 for penicillin resistance. This, together with the number of different targets for both antibiotics, may contribute to the higher mutation rate of cefotaxime resistance compared to penicillin resistance [87].

Furthermore, resistance to streptomycin is caused by an alteration of one or a few nucleotides in the gene encoding the ribosomal protein S12, and the rate of spontaneous mutations is low. The stability of the sequences containing the nucleotides associated with the mutant phenotype is also essential regarding variability. It has been reported that a single base-specific mutation can vary more than 10,000-fold, and long stretches of repeating bases are prone to deletions or additions due to sliding strand mismatch [88, 89]. Even the location of a gene on the bacterial chromosome affects the mutation rate, as genes located farther from the reproductive origin of the Enterobacteriaceae chromosome can have a mutation rate approximately twice as high as genes closer to it [90].

Since the antibiotic resistance phenotype can result from mutations at different bacterial loci, the emergence of an antibiotic-resistant mutant depends on the total mutation rate resulting from the combination of independent mutation rates in these genes. Classical genetic analysis shows that when mutations in one gene or another can cause antibiotic resistance, the total variation is the sum of the independent mutation values. On the other hand, if mutations in both genes are required to achieve the antibiotic resistance phenotype, the total variability results from separate mutation rates for each gene. We considered two genes that contribute independently to the antibiotic resistance phenotype with independence

values of 10-8. If mutations in any gene can produce an antibiotic resistance phenotype (see independent conversions below), the total variability is 2 × 10-8; thus, it is only slightly larger than if only one gene contributing to the resistance phenotype were mutated. On the other hand, when mutations in both genes are needed for resistance, the total mutation rate is 10 to 16, much lower than when only one gene is necessary [91].

List of the main factors that increase antibiotic resistance mutation rates according to Martínez & Baquero:

- Unstable sequences around bases relevant to the resistance phenotype
- Long distance from the R gene to the origin of replication
- Large number of sites in the R gene that can give rise to a resistant and permissive phenotype
- Wide variety of R genes
- Low or high copy number of each R gene, if the mutation is recessive or dominant, respectively
- Few independent antibiotic targets or targeted access routes
- Various independent protection mechanisms
- Multiple cooperative targets for antibiotic action or cooperative access routes
- Few cooperative elements in target protection mechanisms
- Bacteria under stress (starvation, antibiotic stress, pathogenic stress)
- Contingency R genes (hypermutable)
- Transposable elements in bacteria
- Bacteria with a hypermutable phenotype (mutator)
- Low-level expression of bacterial programmed cell death
- Pre-existing low-level R gene mutations
- Low biological cost of R gene mutations
- Antibiotic concentrations in the selective window
- Low concentrations of antibiotics or short exposure time
- Slow-killing ability of the antibiotic
- Small phenotypic delay for expression of R gene mutations
- Compartmentalized (structured) physical structure of the selective habitat

HORIZONTAL GENE TRANSFER

Horizontal gene transfer (THG) or lateral gene transfer (TLG) is the movement of genetic material between unicellular and multicellular organisms other than by ("vertical") transmission of DNA from parent to offspring (reproduction). Factor in the evolution of many organisms. THG influences the scientific understanding of higher-order evolution while significantly changing perspectives on bacterial evolution [92, 93].

Horizontal gene transfer is the primary mechanism for the spread of antibiotic resistance in bacteria. It plays an essential role in the evolution of bacteria that can degrade novel compounds [94], such as artificial pesticides, and in developing, maintaining, and transmitting virulence [95]. It often involves bacteriophages and temperate plasmids [96]. The genes responsible for antibiotic resistance in one species of bacteria can be transferred into another through various HGT mechanisms such as transformation, transduction, and conjugation, subsequently arming the recipient of the antibiotic-resistant genes against antibiotics. The rapid spread of antibiotic-resistant genes in this way is becoming a challenge in the medical field. Ecological factors may also play a role in the HGT of antibiotic-resistant genes [97].

Horizontal Gene Transfer Mechanisms:

- Transformation is a cell's genetic alteration resulting from the introduction, uptake, and expression of foreign genetic material (DNA or RNA). This process is relatively common in bacteria but less so in eukaryotes. Transformation is often used in laboratories to insert new genes into bacteria for experiments or industrial or medical applications [98].
- Transduction is the process in which bacterial DNA is moved from one bacterium to another by a virus (a bacteriophage or phage) [99].
- Bacterial conjugation involves the transfer of DNA via a plasmid from a donor cell to a recombinant recipient cell during cell-to-cell contact [99].
- Gene transfer agents are host-encoded virus-like elements in the alphaproteobacteria order Rhodobacterales [100].

OCCURRENCE OF ANTIBIOTICS IN WATER BODIES

Antibiotic compounds have different mechanisms in cells, such as suppression of cell wall synthesis, inhibition of nucleic acid synthesis, modification of cell membranes, suppression of protein synthesis, and DNA inhibition, depending on the different functions of the molecule [101].

Some antibiotic molecules are metabolized in the bodies of humans or animals, while the majority (70-90%) is excreted unchanged through feces and urine [102, 103].

Antibiotic molecules enter wastewater as major compounds or metabolites of effluents from hospitals, pharmaceutical companies, wastewater treatment plants (WWTPs), aquaculture, and livestock farms. The low removal capacity of WWTPs led to the transfer of large amounts of antibiotics to surface water, groundwater, and even drinking water. Marine environments are the main sites of antibiotic accumulation [104].

The widespread presence of antibiotics in high concentrations in surface water, groundwater, sediments, and biota around the world has made these polluting compounds an emerging concern; these concentrations have been reported as 'ng/L and μg/L' and 'ng/g and μg/ g' [105, 106].

The presence of these compounds in water bodies - especially in developing countries, where management practices for antibiotics and antibiotic-related waste are not addressed - raises concerns [107].

In different regions of the world, the spatial and temporal distribution of antibiotics in water sources varies significantly, and this difference is closely related to the local industrial structure, the mode of disposal of antibiotics in the pharmaceutical industry, and the way of use of antibiotics in livestock [107].

Generally, 50-80% of the total parent compounds are excreted via urine and feces. The highest excretion rates are observed for ciprofloxacin (50-80%) and tetracycline (80-90%), while the lowest excretion rates are observed for are kept for erythromycin (5 to 10%), 4 sulfamethoxazole (15 to 30%) or clarithromycin (25%) [108].

OCCURRENCE IN RIVERS

Antibiotic contamination in small rivers and streams is mainly due to wastewater discharge. Many rivers face severe problems due to antibiotic contamination. Antibiotics in aquatic environments cause the accumulation of these contaminants in the biota [109, 110].

The concentrations of pollutants (including antibiotics) in rivers that pass through urban and rural areas have increased, caused by sewage discharge into these sources. In addition, population density downstream of the river compared to upstream, dehydration, and insufficient continuous flow of seasonal runoff for dilution are the main factors of high concentrations of antibiotics in the lower reaches of the rivers [112].

Studies on the cognition and mechanisms of action of antibiotics in humans show that their function differs in fish, algae, birds, and other species living in rivers [111].

The reduction in antibiotic concentrations in rivers may be linked to dilution effects. Variable concentrations in wastewater and effluents are due to the chemical transformation of pollutants – which become metabolites – along with purification systems that have little impact on antibiotic removal [113].

OCCURRENCE IN LAKES

The entry of antibiotics into aqueous media occurs through several sources. Most wastewater treatment plants cannot remove antibiotics effectively, so their production can contaminate surface waters with antibiotics [114].

Lakes, unlike rivers with high water exchange, have low water circulation and are, therefore, more exposed to antibiotic contamination. Although lakes have a high potential for long-term antibiotic storage, information on antibiotic contamination in lakes is much scarcer than in rivers. The entry of effluents from human activities and aquaculture increases the concentrations of these pollutants in lakes [115].

Quantity vs. Legislation (BR, USA and EU)

According to the United Nations World Report on the Development of Water Resources, in all countries except for the most developed ones, most wastewater is released directly into the environment without adequate treatment, causing harmful effects on human health and the environment. The inadequate disposal of solid waste, the inefficiency of Sewage Treatment Stations, and the release of raw sewage into water bodies are the factors that most contribute to the entry of emerging pollutants into the environment [116, 117].

According to the United Nations (UN) for the environment, conventional sewage treatment processes cannot remove all antibiotics and water-resistant bacteria. Scientific evidence shows that microorganisms resistant to several drugs are found in wastewater and may represent foci for *developing* microbial resistance [118].

In Brazil, CONAMA resolutions nº 357/2005 and CONAMA nº 430/2011 establish conditions and standards for effluent discharge into water bodies to protect aquatic life. The current potability standard is *set* by Ordinance MS No. 2914 of December 12, 2011, which provides for the control and surveillance procedures for *water quality* for human consumption in the country. The preparation of this Ordinance considered the advances in technical-scientific knowledge in the area, international experiences, and the principles advocated in the World Health Organization Guides on Water Quality for Human Consumption as a systemic and integrated vision in water quality control. However, despite the current legislation listing several chemical and microbiological parameters, it does not establish standard limits for drugs, especially antibiotics, which are in low concentrations (in the order of micrograms and nanograms/L) and are constantly present in aquatic environments.

Brazil

In Brazil, the Ministry of the Environment, represented by the National Council for the Environment (CONAMA), is responsible for the *primary* legal references *for* water and environmental quality. This body draws up a series of resolutions at the national level that must be followed to preserve the quality of water resources in Brazil.

CONAMA Resolution No. 30 of 2011 completes and amends CONAMA No. 357 of 2005 and contains conditions, parameters, standards, and guidelines for *releasing* effluents. In general, these norms determine several physical-chemical parameters, organic and inorganic chemical substances, algae, and microorganisms in *monitoring* water quality, changing the concentrations established for each substance according to the category to which the water body belongs.

The Ordinance of the Ministry of Health - MS No. 2,914 of 2011, provides for the control and surveillance procedures for water quality for human consumption and its potability standard. Established parameters: microbiological standard; turbidity standard for post-filtration or pre-disinfection water; and potability standard for chemical substances that pose a health risk – Inorganic; organoleptic pattern of potability; pesticides; disinfectants and by-products of disinfection; cyanotoxins; radioactivity. This Ordinance was based on the WHO recommendations and several international standards. The guidelines that define the quality of water suitable for human consumption are established by an ordinance published by the Ministry of Health, and the monitoring of the quality of this water is also an attribution of that same Ministry through Environmental Health Surveillance.

Among the various activities that fall into the domain of water quality monitoring, there are gaps in legislation that threaten mandatory measures, such as monitoring of contaminants in drinking water - especially antimicrobials - and the release of sewage into water bodies, which is a problem substantial threat to water quality and a danger to human health and the environment.

European Union

In recent decades, the European Union (EU) has implemented various environmental regulations, significantly reducing air, water, and soil pollutants. Chemical legislation has been updated, and many hazardous or toxic substances have been restricted. This has led EU citizens to enjoy some of the highest quality water in the world, and over 18% of the land has been designated as protected areas for nature. The European Parliament and the Council of the EU work together to develop Directives that set quality standards for Member States to follow. In addition to the hydrological and ecological characteristics, several physical-chemical parameters are monitored to ensure compliance with European rivers' "good condition" standards. Standards have been defined to ensure that all these parameters are within competitive ranges.

Directive 60/2000/EC of the European Parliament and the Council established a framework for Community action in the field of water policy, and the EU Water Framework Directive, also known as the Water Framework Directive (WFD), was adopted. This Directive aims to safeguard and restore European water quality while ensuring its long-term sustainable use.

As a first step in implementing the strategy elaborated by the WFD, Decision 2455/2001/EC established the initial priority list of 33 substances, which had no concentration limit protected at the time. It was only in 2008 that the boundaries of the Environmental Quality Standards (EQL) were defined for these substances in discharge waters through Directive 105/2008/CE. These substances were selected based on a prioritization process based on scientific evidence and supported by extensive consultation with experts from Commission services, Member States, stakeholders, and the Scientific Committee on Health and Environmental Risks – SCHER. Substances included on the watch list should be chosen from the available information that suggests they may pose a significant risk to or via the aquatic environment and for which monitoring data are insufficient.

The first watch list of ten substances or groups of substances was established by Implementing Decision (EU) 495/2015, which included certain medicines such as the macrolide antibiotics Azithromycin, Clarithromycin, and Erythromycin.

The European Commission has adopted a strategic approach to pharmaceuticals in the environment, focusing on ecotoxicity - the presence of antimicrobials in the background; and the potential consequences of prolonged exposure in humans. The primary tool to guarantee the quality, safety, and efficacy of medicines for human and animal use and safeguarding the environment is the legislation on drugs.

In the EU, effective monitoring relies on surveillance programs implemented by Member States, with relevant data shared with the Commission. The guidelines were designed to reduce misuse, encourage responsible use of antimicrobials, and apply to all stakeholders involved in their use or prescription in Europe.

U.S

The Environmental Protection Agency (EPA) is responsible for observing and enforcing US drinking water laws and regulations to protect the environment and human health. The Clean Water Act (CWA) is the primary federal law governing water contamination [119].

The EPA/CWA has implemented programs to control pollution, including establishing industry wastewater standards and creating national recommendations for water quality criteria for pollutants in surface water. Concerning drinking water quality, the Safe Drinking Water Act (SDWA) was passed by Congress in 1974 and amended in 1986 and 1996 to protect the quality of all water currently or potentially used for human consumption, either from surface or groundwater sources. This Act authorizes the EPA to establish safe purity standards and obliges all owners or operators of public water systems to comply with standards set to protect human health [119].

The EPA oversees the release of hazardous substances from municipal and industrial facilities that treat wastewater and collect sewage, as well as stormwater discharges from industrial and municipal facilities. The objective is to protect human health and the

environment, as required by the National System for the Elimination of Pollutant Discharges (NPDES) - National System for the Elimination of Pollutant Discharges [119].

The SDWA directs the Agency to assess the health implications and prevalence data of unregulated pollutants when determining which contaminants to include on the list. The SDWA also specifies that the list should contain substances that present the most significant risk to public health in drinking water. The EPA uses the Drinking Water Contaminant Candidate List (CCL) to assist in regulatory decision-making and data collection to identify priority contaminants [119].

The Environmental Protection Agency (EPA) implemented the Unregulated Contaminant Monitoring Rule (UCMR) to track contaminants in drinking water that are not yet regulated under the Safe Drinking Water Act (SDWA). This program aims to collect data on suspected pollutants in drinking water, estimate the level of exposure, and identify the number of people at risk. By collecting this information, EPA can make informed decisions to protect public health. In addition, the EPA publishes a Contaminant Candidate List (CCL) of contaminants that are not currently regulated by national drinking water standards but may be found in public water systems. This list is updated periodically, with the last version published in 2016 (CCL4). The CCL includes a variety of waterborne pathogens, chemicals, and pharmaceuticals, such as erythromycin, which was also included in the previous version. Contaminants in the CCL are evaluated to determine if they meet SDWA regulatory criteria.

The CCL only includes a limited number of harmful substances found in drinking water that require further investigation into their potential health effects and the levels at which they occur. If sufficient data and information are available, a Regulatory Determination will be made to increase the level of a specific contaminant. The SDWA also requires the Agency to select at least five contaminants from the current CCL and determine whether they should be regulated with a Core National Drinking Water Regulation (NPDWR). In addition, the EPA must publish a new list of up to 30 unregulated contaminants to be monitored by public water systems every five years, which serves as the basis for future regulatory actions to protect public health [119].

DEGRADATION OF ANTIBIOTICS

Antibiotic pollution is becoming increasingly serious globally. Although countries with severe antibiotic pollution have introduced corresponding policies, they have come too late and are inadequate to address the problem.

Researchers are developing environmentally friendly alternatives to antibiotics to reduce their use. At the same time, due to their excessive content in aquatic environments, researchers have developed various treatment techniques to degrade antibiotics. These methods can be divided into the following categories: physical adsorption, chemical oxidation, photodegradation, and biodegradation [120].

Physical treatment is a water purification method based on the enrichment and transfer of pollutants by physical action. This section reviews the research applications of three approaches, adsorption, membrane filtration, and ionic resins, for removing antibiotics from water, including treatment efficiency, removal mechanisms, and influencing factors.

The term adsorption is the accumulation of matter from a gaseous or liquid phase to the surface of a solid phase and may involve physical and chemical adsorption. The components that bind to the surface are called adsorbates, while the solid phase that retains the adsorbate is called an adsorbent. The removal of substances from the surface is called desorption.

Adsorbent materials are fast, efficient, and economical in treating antibiotics. Due to the unique and superior physical properties of most adsorbent materials, such as higher specific surface area and higher porosity, they can provide more active adsorption sites for adsorbates, combined with van der Waals forces between adsorbents and adsorbates, electrostatics, bonding of hydrogen, П–П bonds and hydrophobic forces, which can efficiently adsorb and remove pollutants in water [121]

The most common process is the application of activated carbon to remove organic substances. Activated carbon can be granular or powder-based, and its application depends on the treatment needs and expectations of final water quality. Activated carbon filtration (ACF) is primarily used as a polishing step in water treatment processes. Recently, it has gained renewed focus for its effectiveness in removing emerging “ micropollutants “ contaminants [122].

Obtained from burning some types of wood, activated carbon is a form of carbon that contains pores between atoms. The material, mainly of plant origin, can be used in powder or granules and aims to remove impurities through its pores.

Powdered activated carbon has a large surface area and well-distributed pore structure, with a predominance of medium pores and macropores. It is mainly used in batch filtration processes. Among its applications, the purification of substances such as caffeine, fats, sodium carbonate, wines, fruit juices, alcoholic beverages, municipal water, sugar refining, soft drinks, and antibiotics stands out.

Granulated activated carbon, on the other hand, is used in columns with fixed or mobile beds through which the fluid is filtered and purified, being responsible for adsorption processes in the liquid or gaseous phase. Applications include filters to remove chlorine from drinking and industrial water.

Despite numerous applications, activated carbon retains impurities with carbon and chlorine at the base of the composition. Therefore, other substances like sodium and nitrates can pass directly through the product. In addition, its potential is limited. When all the pores are filled, an activated carbon filter stops working. This is because the adhesion area is compromised and does not allow impurities to settle, so it is recommended that the filter be changed for a new one.

Granular activated carbon (GAC) has been widely used to remove organic contaminants from water and wastewater (Sabio et al., 2006; Sotelo et al., 2012; Sotelo et al., 2014). It has high adsorption capacity and removal efficiency of certain organic substances. In some applications, the removal efficiency can reach 100%. In actual application, adsorption processes using activated carbon are carried out in column mode [126]. Furthermore, the United States Environmental Protection Agency (USEPA) has designated GAC as the best technology for treating many regulated organic pollutants [124].

Membrane filtration is a green, harmless, and efficient treatment method, widely used in the zero-emission research field and without harmful additives. Membrane separation technology uses micro and nanoporous membranes to trap or reverse the osmosis of antibiotics in water for purification purposes. In practice, membrane separation is commonly used with other methods to remove antibiotics from the aquatic environment [121].

The membrane filtration method has the advantages of high separation efficiency, wide application range, and simple operation. Standard membrane treatment processes include microfiltration membranes, ultrafiltration membranes, nanofiltration membranes, and reverse osmosis membranes [128].

Membrane technology is considered one of the most promising water treatment methods due to its high separation selectivity, low energy consumption, lack of additional chemical requirements, relatively easy sizing, and the possibility of continuous operation [127]. However, the membrane process also has some disadvantages. During filtration, the accumulation of contaminants on the surface and within the membrane's pores can lead to fouling of the membrane by blocking and rejecting the membrane [129]. Thus, its prolonged use can lead to a decrease in its performance. Furthermore, membrane separation is a physical process, so although contaminants such as antibiotics may be concentrated, they are not decomposed, making it difficult to remove the impurities [130].

Although membrane filtration effectively retains antibiotics, the retention efficiency depends on the antibiotic type and the solution's pH. Changes in pH can affect the degree of protonation of amine and antibiotic groups, the strength of membrane surface charge, and the presence of antibiotics.

Ion exchange is a chemical process to remove unwanted ions dissolved in water and wastewater. To remove the ions, they are exchanged for ions of similar charge. When positive ions are exchanged during water treatment, the cations that come into contact with the ion exchange resin are exchanged for other available positively charged ions (usually sodium) on the surface of the resin. During anion exchange, negatively charged ions are exchanged for other negative ions on the surface of the resin. These ions are usually chloride ions. Anion exchange is essential as the ions can remove contaminants such as nitrate, arsenic, sulfate, and fluorine. Ion exchange in water treatment involves removing unwanted ionic pollutants from water by replacing them with another ionic substance. The four ion exchange methods are water softening, deionization, demineralization, and dealkalinization.

It is essential to remove contaminants from water to make it safe. When removing impurities, the contaminant and the exchanged substance must be dissolved and carry the same type of electrical charge. The most common ion exchange is water softening, which reduces calcium and magnesium in the water.

Bound antibiotics also exist in the form of ions, and research with magnetic ion exchange resins has also begun to be used. The magnetic ion exchange resin structure contains a polyacrylic acid matrix, quaternary amine functional group, and magnetization components, which can act as a weak magnet [131].

Unlike traditional ion exchange resins, magnetic ones have smaller particle sizes and larger specific surface areas, which can quickly adsorb pollutants.

It was found by Wang et al. that compared with powdered activated carbon, magnetic ion exchange resin has a better adsorption effect on antibiotics, which can have 2 to 7 times greater impact than powdered activated carbon in certain antibiotics. In addition, it is noteworthy that anion exchange is the primary mechanism of the adsorption of antibiotics on the anionic resin, and the hydrogen bond formed between the antibiotics and the resin also enhances the adsorption.

In addition, the removal performance of the magnetic ion resin for antibiotics is also related to factors such as pH value and coexisting anions. The effect of the pH value is mainly based on the different degrees of protonation of the antibiotics under other pH conditions, which will affect the ion exchange with the ionic resin.

The chemical treatment method is based on the chemical reaction between chemical oxidizing agents or reactive oxides generated in the reaction process and pollutants, thus destroying the chemical molecular structure of the contaminants, further converting the pollutants into non-toxic and harmless small molecular substances or performing the complete mineralization and removal, and finally achieve the goal of pollutant degradation or harmless treatment. Standard chemical treatment methods include strong oxidizing oxidation and advanced oxidation.

The robust oxidant oxidation method mainly relies on the solid oxidizing property of the oxidant itself to attack the electrophilic group structure in the antibiotic, destroy the chemical structure of the antibiotic, and carry out the oxidative degradation of the antibiotic. Common strong oxidants include chlorination and ferrate oxidation. In addition to water disinfection, chlorination has been used to study antibiotic degradation [128].

Also known as the Advanced Oxidation Process (AOP), they depend on the in situ production of highly reactive hydroxyl radicals (·OH). These reactive species are the most potent oxidants that can be applied to water and can oxidize virtually any compound in the aqueous matrix, often at a diffusion-controlled reaction rate. Consequently, OH reacts non-selectively once formed, and contaminants will be quickly and efficiently broken down and converted into small inorganic molecules. Hydroxyl radicals are produced with the help of one or more primary oxidants (e.g., ozone, hydrogen peroxide, oxygen) and energy sources (e.g., ultraviolet light) or catalysts (e.g., titanium dioxide). Accurate and pre-programmed dosages, sequences, and combinations of these reagents are applied to obtain a maximum yield of •OH. In general, when used under proper conditions, POAs can reduce the concentration of contaminants from several hundred ppm to less than five ppb and, therefore, significantly reduce Chemical Oxygen Demand (DOQ) and Total Organic Carbon (TOC), which earned him the credit of “21st-century water treatment processes” [132].

Although oxidation processes involving ·OH have been in use since the late 19th century - such as Fenton’s reagent, which was used as an analytical reagent at the time - the use of such oxidative species in water treatment did not receive adequate attention until Glaze et al. al. suggest the possible generation of ·OH “in sufficient quantity to affect water purification” and defined the term “Advanced Oxidation Processes” for the first time in 1987 [133].

Biological treatment is an improved artificial natural treatment technology based on environmental self-purification. It uses the metabolic action of organisms in the environment to oxidize and decompose organic pollutants in water and convert them into stable and harmless inorganic substances. The mechanism for removing micropollutants is a process of biosorption and biodegradation.

Aerobic water treatment is a biological technique that uses oxygen to break down organic impurities and other pollutants, such as nitrogen and phosphorus. A mechanical aeration device, such as an air blower or compressor, continuously mixes oxygen into wastewater or sewage. The organic material in the water is subsequently consumed by aerobic bacteria, which convert it into carbon dioxide and biomass, which can be removed.

Aerobic wastewater treatment is a reliable, easy, and effective method of producing high-quality secondary effluents. The resulting sludge is odorless and can be sold as a high-quality agricultural fertilizer. Aerobic treatment systems ensure the total removal of pollutants and nutrients when used in conjunction with anaerobic treatment.

Aerobic treatment of wastewater and sewage can be accomplished using various technologies. Some examples are Conventional activated sludge, moving bed biofilm reactor, membrane bioreactor, and biological aerated filter.

Activated sludge is a collective term for communities of microorganisms and the organic and inorganic materials attached to them. It is used for antibiotic biosorption, antibiotic biodegradation, and flocculation. The complex organisms in the activated sludge form a complex food chain with organic nutrients in the effluent, and the degradation of antibiotics is achieved through the action of the microbial community. Composting with activated sludge removes contaminants through microbial adsorption and biodegradation [120].

Activated sludge for antibiotic degradation is usually derived from biopharmaceutical or hospital effluents and significantly reduces post-degradation toxicity after activated sludge treatment. However, this method is highly dependent on environmental factors such as pH, temperature, dissolved oxygen, nutrients, and toxic substances, as well as on the composition and proportion of microorganisms, which influence the degradation time. Under low dissolved oxygen conditions, irritating gasses such as ammonia or sulfur dioxide are quickly produced, and the nutrient ratio in wastewater needs to be adjusted frequently; otherwise, the degradation efficiency is low [120]. Furthermore, the performance of the activated sludge process in removing antibiotics is influenced by the chemical structure of the antibiotics, the nature of the sludge, and the operational conditions of the biological treatment process [128].

As for the operation of activated sludge, the organic matter is purified through a colony of heterogeneous microorganisms that form activated sludge in the presence of oxygen during the process, which occurs in different stages.

Coarse solids are removed and passed through the equalization tank and into the aeration tank. In this last tank, the whole process is aerobic, and the aeration serves to add oxygen that helps the aerobic bacteria to change the biochemical form of the organic matter, converting them into simple molecules (H_2O, CO_2...), thus forming a homogeneous mixture with the effluent undergoing treatment. Continuing, the effluent is sent to a secondary decanter that separates treated effluent and sludge through decantation; the solids settle due to the action of gravity, with the deposition of flakes at the bottom of the tank the effluent clarifies. The flakes decanted with live microorganisms can still decompose organic matter and, therefore, can be recirculated to the aerobic reactor. An activated sludge system has three modes: conventional aeration, extended aeration, and batch.

- Conventional Aeration: This modality has a primary treatment system, stabilizing the biodigester sludge. Part of the organic matter is removed before the aeration tank in a primary decanter. This system is designed to be able to handle a large BOD load.

- Prolonged Aeration: The biomass remains longer in the system in this mode and receives the same BOD load as in the previous way. There is less food available for the microorganisms, which results in less organic matter per unit volume of the aeration tank and per unit of reactor biomass.
- Batch: In this mode, aeration and decantation are carried out in the same tank, and the biological mass is sedimented at the bottom, treating the effluent. A part of the resulting sludge is discarded, and the other part is kept for new treatments.

The Moving Bed Bioreactor (MBBR) offers a solution for wastewater treatment if the "bulk" of the pollutant load needs to be disposed of (as a means of reducing costs) or if the applicable discharge regulations are not as strict. This process is used to remove organic substances, nitrification, and denitrification.

The MBBR system consists of an aeration tank (similar to an activated sludge tank) with special plastic carriers that provide a surface where a biofilm can grow. A wide variety of plastic carriers are used in these systems. These conveyors vary in surface area and shape, offering different advantages and disadvantages. The surface area plays a significant role in biofilm formation. Floating carriers allow biofilms to form on the surface, so a large internal surface area is crucial for contact with water, air, bacteria, and nutrients [135]. The carriers will be mixed in the tank by the aeration system and thus have good contact between the substrate in the influent wastewater and the biomass in the carriers. Today's most preferred material is high-density polyethylene (HDPE) due to its plasticity, density, and durability.

Hybrid MBBR systems have achieved higher biomass concentration in bioreactors where suspended and adhered biomass coexist, contributing to biological processes [137].

The membrane bioreactor (MBR) combines membrane processes such as microfiltration or ultrafiltration with a biological wastewater treatment process, the activated sludge process [138]. The two basic MBR configurations are a submerged membrane bioreactor (SMBR) and a lateral flow membrane bioreactor. In the SMBR configuration, the membrane is located inside the bioreactor and submerged in the effluent. In contrast, in a side-flow membrane bioreactor, the membrane is located outside the reactor as an additional step after the biological treatment.

Two main types of membrane materials are available on the market: organic-based polymeric membranes and ceramic membranes. Polymeric membranes are the most commonly used materials in water and wastewater treatment. In particular, polyvinylidene difluoride (PVDF) is the most popular due to its long service life and chemical and mechanical resistance [139]. The following tables demonstrate the types of materials that membranes can be made from and a comparison between the two types.

The main advantages of this type of process are:

- High-quality effluent: With the small pore size of the membrane, the effluent is clear and free of pathogens;

- Independent Control of Solids Retention Time (SRT) and Hydraulic Retention Time (HRT): Since all biological solids are contained in the bioreactor, the SRT can be controlled independently of the HRT;
- Small footprint: Thanks to membrane filtration, there is a high concentration of biomass contained in a small volume;
- Robust to load variations: MBRs can be operated with a wide range of operating conditions;
- Compact process: Compared to conventional activated sludge (CAS), MBRs are more compact.

The main disadvantages of an MBR are the complexity of the operating process and the cost, in addition to the membrane life, permeate flux, and the membrane air cleaning rate (air cleaning energy).

The BAF system is one of the latest advances in biofiltration treatment techniques. It is considered a future technology and the most promising development in biological processes for drinking water treatment. The media used for a BAF include fixed or aerated, submerged, or floating film reactors, where microorganisms in biofilms remove organic and inorganic matter, after which the suspended solids are filtered through the medium [139].

The BAF system design consists of a column or tank as the main reactor, the filter medium, and a set of aeration, backwash, and feed systems [140]. BAFs are widely used in European countries such as the Netherlands and Germany and are particularly advantageous for treating Fe, Mn, and ammonia in untreated water.

The BAFs are operated with a carrier medium, and the water flows into the reactor after the primary treatment (coagulation/flocculation). The carrier medium is used to accumulate microbial growth in biofilms. The treated water from the immediate treatment can pass through the BAF system from above or below, depending on the design of the water treatment plant. During operation, the air is diffused upwards using a compressor or air blower to oxygenate the biofilm for growth [139], as the process depends on autotrophic bacterial activity to oxidize Fe and Mn ions [141]. In addition, the air supply also supports the reaction of Fe and Mn ions with oxygen to form precipitates. Backwashing is necessary to ensure the BAF system's sustainability when maximum pressure loss is increasingly detected so that system performance can return to the original operating condition [142].

The BAF system is a flexible reactor that can remove chemical and physical pollutants (suspension solids), requiring little space for treatment. According to Zhang et al., a BAF system also offers high specific volumetric removal rates compared to a conventional activated sludge process. Previous studies by Fu et al. on the simultaneous removal of Fe and Mn ions showed that 90% and 99% removal rates were achieved using a BAF system. Hasan et al. studied Mn ion removal from heavily and lightly polluted drinking water using a BAF system and found Mn ion removal efficiency of 99.1% and 82.9% for both conditions,

respectively. The Fe ion removal efficiency for biological aeration filters was greater than 98% from the beginning and throughout the experiment.

Anaerobic wastewater treatment is a biological process in which microorganisms break down organic pollutants without oxygen. In a basic anaerobic treatment cycle, wastewater is fed into a bioreactor. The bioreactor contains a thick, semi-solid substance called sludge, which comprises anaerobic bacteria and other microorganisms. These anaerobic, or "anaerobic," microorganisms digest the biodegradable materials present in wastewater, resulting in sewage with lower biological oxygen demand (BOD), chemical oxygen demand (COD), and total suspended solids (TSS), and by-products of biogas.

Anaerobic wastewater treatment is used to treat a variety of industrial wastewater streams from the agriculture, food and beverage, dairy, pulp and paper, and textile industries, as well as municipal sewage sludge and wastewater. Anaerobic technologies are typically used for wastewater with high concentrations of organic material (measured as BOD, COD, or TSS), usually before aerobic treatment. Anaerobic treatment is also used for specialist applications, such as treating waste streams containing inorganic or chlorinated organics, and is suitable for treating hot industrial wastewater.

Anaerobic methods include Anaerobic Digestion, Upflow Anaerobic Sludge Blanket, Anaerobic Deflector Reactor, and Sequencing of the Batch Reactor.

Anaerobic digestion (AD) is a series of biochemical steps in which microorganisms break down organic matter such as sewage sludge, manure, and food waste in the absence of oxygen (hence the word "anaerobic"), producing primarily gases such as methane, carbon and carbon dioxide and the wet or residual organic mixture known as "digestate". Anaerobic digestion treats or stabilizes food and other organic wastes reduces greenhouse gas emissions from waste that would otherwise go to landfills, and produces renewable energy in biogas.

The anaerobic digestion process is used by several industries, including agriculture for processing manure, energy crops, and agro-industrial waste; food and food waste processing industries, slaughterhouse waste, pulp and paper waste, and biochemical waste; and waste and wastewater industries for treatment or management of municipal organic waste and sewage sludge.

In addition to anaerobic digestion, there are other methods to stabilize sewage sludge, such as alkaline stabilization (generally by adding lime), aerobic digestion, composting, and autothermal thermophilic digestion. However, anaerobic digestion is considered one of the most sustainable options, as it generates renewable energy and reduces the volume of sludge or organic matter.

During the anaerobic fermentation process, four main steps occur: Hydrolysis, Acidogenesis, Acetogenesis, and Methanogenesis, all carried out by a diverse microbial community without oxygen. While these are the main biochemical reactions that take place in a fermenter, it should be noted that other biochemical reactions take place in the fermenter that are not discussed below.

- Hydrolysis – the organic starting material contains compounds that must be accessed/ broken down before they are made available as food for microorganisms. Complex polymers such as proteins, carbohydrates (polysaccharides), and lipids must first be broken down into their simplest forms. This “breaking down” of polymers in a digester is usually accomplished by hydrolases secreted by the hydrolytic bacteria in the digester. Hydrolysis is often referred to as the rate-determining step in anaerobic digestion, meaning that it is the slowest step and plays an essential role in determining the residence time of the feedstock in the digester. For this reason, pretreatment methods for anaerobic digestion, such as heat treatment, focus on optimizing this step. The steps of acidogenesis and acetogenesis co-occur.

- Acidogenesis (fermentation) - In this step, acidogenic or fermentative bacteria present in the fermenter absorb some of the hydrolysis products and form volatile fatty acids or VFAs (also called short-chain volatile organic acids) such as propionate, butyrate, and alcohols. Protein-rich raw materials such as sewage sludge also produce a lot of ammonia when amino acids are broken down, which is known to hamper anaerobic digestion. In addition to ammonia, carbon dioxide and other gases, such as hydrogen sulfide, can also be produced.

- Acetogenesis - Acetate is formed from volatile/short-chain fatty acids in acidogenesis along with hydrogen and carbon dioxide.

- Methanogenesis - Methanogenic microorganisms in the digester consume the accessible intermediates produced during acidogenesis and acetogenesis (acetate, hydrogen, and carbon dioxide) to produce methane. This mainly occurs in two pathways: acetoclastic methanogenesis and hydrogenotrophic methanogenesis. Next to methane, carbon dioxide is the second most abundant gas produced in this last stage.

Upflow anaerobic sludge blanket (UASB) technology, often called a UASB reactor, is a form of anaerobic digestion used for wastewater treatment.

The UASB uses an anaerobic process, forming a blanket of granular sludge flooring in the tank. Wastewater flows upwards through the blanket and is processed (broken down) by anaerobic microorganisms. Upflow combined with gravity keeps the sludge blanket suspended with the help of flocculants. After about three months, the slime mat begins to mature. Small slime granules are formed, covering the surface with bacterial accumulations. Without a supporting matrix, flow conditions create a selective environment where only microorganisms capable of binding to one another survive and multiply. Eventually, the aggregates transform into dense, compact biofilms called “granules”.

The by-product is biogas with a high concentration of methane, which can be captured and used as an energy source to generate electricity for export and domestic use. The technology must be constantly monitored as it is deployed to ensure the sludge blanket

is maintained and not washed away (causing the effect to be lost). The heat generated as a by-product of electricity generation can be reused to heat the digesters.

The screening of the sludge allows a double solid and hydraulic (liquid) residence time in the digesters. Solids that require a high degree of digestion can remain in the reactors for up to 90 days. Sugars dissolved in the liquid waste stream can be rapidly converted to gas in the liquid phase, leaving the system in less than a day [143].

UASB reactors are generally suitable for dilute wastewater streams (3% TSS with a particle size > 0.75 mm). Anaerobic baffle reactors (ABR) are upgraded septic tanks with baffles along the treatment chamber. Upflow chambers provide enhanced organic matter removal and digestion. Like septic tanks, ABRs are based on physical (decantation) and biological (anaerobic digestion) treatments.

An ABR consists of a tank and reciprocating suspended and permanent baffles that divide the reactors and force the liquid to flow up and down from one chamber to the other, allowing better contact between the fresh effluent entering the reactor and the waste sludge containing the microorganisms responsible for the anaerobic digestion of organic pollutants. Compartmentalization separates solids residence time from hydraulic residence time, allowing anaerobic wastewater treatment with residence times as short as a few hours. Solids treatment rates are high, while total sludge production is characteristically low [144]. They are simple to build and operate and robust to hydraulic and organic shocks [145]. However, both sludge and effluent require additional treatment.

ABRs are suitable for a wide range of wastewater, including highly polluted industrial effluents, but their efficiency increases with higher organic load. Therefore, ABRs are ideal for influents with high levels of unsettled suspended solids and a narrow COD/BOD ratio (SASSE 1998). ABRs are typically used in DEWATS, often in combination with various other treatment stages. A typical DEWATS might be a five-component system consisting first of three anaerobic steps, i.e., a biogas decanter, an ABR, and an anaerobic filter, followed by an aerobic treatment unit such as a built-in swamp (Free-Water Surface CV, Horizontal Subsurface Flow CV or Vertical Flow CV) and a maturation pond [40]. BOD can be reduced by up to 90%, which is far superior to removal in a conventional septic tank.

The anaerobic digestion in an ABR consists of different groups of organisms. The first group of organisms is the hydrolytic-fermentative (acidogenic) bacteria that hydrolyze the complex polymeric substrate into organic acids, alcohols, sugars, hydrogen, and carbon dioxide. The second group is hydrogen-producing and acetogenic organisms, which convert the fermentation products of the previous step (hydrolysis and acidogenesis) into acetate and carbon dioxide. The third group is methanogens, which convert simple compounds like acetic acid, methanol, carbon dioxide, and hydrogen into methane. The four main steps that generally cause the reaction of organisms in an anaerobic process are Hydrolysis, Acidogenesis, Acetogenesis, and Methanogenesis [146].

The most significant advantage of ABR is its ability to separate acidogenesis and methanogenesis longitudinally of the reactor, allowing different groups of bacteria to grow under the most favorable conditions. This specific advantage also enables the reactor to behave as a two-phase system without the associated high costs and control problems. The two-stage operation allows acidogenesis to dominate in the first compartment and methanogenesis in the subsequent section. This can increase acidogenesis and methanogenesis activity by a factor of four, as separating the two phases results in better protection against toxic substances and more excellent resistance to changes in environmental parameters (i.e., pH, temperature, and organic loads) [147].

Batch Reactor Sequencing (SBR) is an activated sludge process for wastewater treatment. In batches, SBR reactors treat wastewater, such as fecal matter or effluent from anaerobic digesters or mechanical-biological treatment plants. Oxygen is blown through the mix of wastewater and activated sludge to reduce organic matter (measured as biochemical oxygen demand (BOD) and chemical oxygen demand (COD). Treated wastewater may be suitable for discharge into surface water or for application to land.

While there are different SBR configurations, the basic process is similar. The system consists of one or more tanks, which can be plug-flow or thoroughly mixed. The tanks have a “flow-through” system, with raw sewage (influent) entering on one side and treated water (effluent) leaving on the other. In multi-tank systems, one tank is in settling/draining mode while the other is aerating and filling. In some scenarios, tanks contain a section known as a selector, consisting of walls or baffles that direct flow from one side of the tank to the other or over successive baffles. In this way, the influent and returned activated sludge (RAS) are mixed, and the biological digestion process is started before the liquid enters the tank’s main body [147].

In its simplest form, the SBR system consists of a series of tanks that operate on a “fill and remove” principle. Each tank in the SBR system is filled for a certain period and then used as a batch reactor. After the desired treatment, the mixed liquid is allowed to settle, and the clarified supernatant is removed from the tank. The cycle of each tank in a typical SBR is divided into five distinct periods: Several filling and reaction periods vary depending on the aeration and mixing processes. Sludge removal can occur at the end of the reactor phase or during the sedimentation, discharge, or idle phases. A vital feature of the SBR design is using a single vessel for multiple aspects of wastewater treatment.

SBR technology is much more flexible than conventional activated sludge processes in adapting reaction times to the concentration and degree of treatment required for a given effluent. Thus, in addition to adjustments that can be made in an equivalent conventional process (e.g., sludge age and solids concentration in the operating mix liquid).

CONCLUSIONS

Therefore, antibiotics in water have evolved from a subtle environmental concern to an urgent global challenge. The presence of antibiotics in water sources, with their potential for ecological disruption and the development of antibiotic resistance, is alarming. As reviewed, several removal and treatment methods have been developed to mitigate this problem, each with advantages and limitations.

Activated carbon, advanced oxidation processes, membrane filtration techniques, and other methods have demonstrated their effectiveness in reducing antibiotic concentrations in water, offering promising solutions to reduce the spread of these pharmaceuticals in our ecosystems. Furthermore, combining multiple treatment methods can increase removal efficiency, providing a comprehensive approach to solving this complex problem.

However, it is essential to recognize that no method is a definitive solution. When choosing the most appropriate treatment approach, one must consider the specific antibiotics present, the source of contamination, and local environmental conditions. Furthermore, continued research and development efforts are needed to refine existing methods and explore new, more sustainable approaches to solving this problem.

The implications of antibiotic contamination in water go far beyond the limits of aquatic ecosystems. It extends to public health, agriculture, and the global fight against antibiotic resistance. Therefore, multidisciplinary collaboration and a holistic perspective are imperative to address this challenge effectively.

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FELIPE OLIVEIRA DA SILVA: Conceived and designed the study. He helped with writing and carefully revised the manuscript. Aline Frumi Camargo and Helen Treichel critically reviewed and supervised the development of the paper. All authors reviewed and approved the final manuscript.

Declaration of competing interests

There are no competing interests.

Consent for publication

All authors agreed with this publication.

Availability of data and materials

The datasets generated for this study are available on request to the corresponding author.

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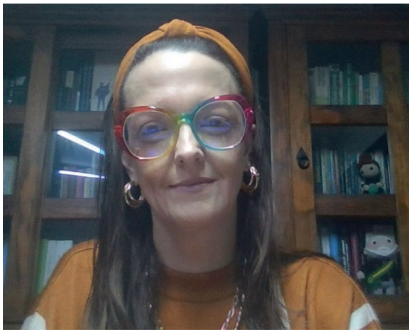

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