We are IntechOpen, the world's leading publisher of Open Access books Built by scientists, for scientists

6,300

Open access books available

172,000

International authors and editors

190M

Downloads

Our authors are among the

154

Countries delivered to

TOP 1%

most cited scientists

12.2%

Contributors from top 500 universities

WEB OF SCIENCE™

Selection of our books indexed in the Book Citation Index
in Web of Science™ Core Collection (BKCI)

Interested in publishing with us?
Contact book.department@intechopen.com

Numbers displayed above are based on latest data collected.
For more information visit www.intechopen.com

Chapter

Effects of Antibiotics on Impacted Aquatic Environment Microorganisms

*Livia Caroline Alexandre de Araújo,
Sivoneide Maria da Silva,
Rafael Artur de Queiroz Cavalcanti de Sá,
Ana Vitoria Araujo Lima, Amanda Virginia Barbosa,
Jaqueline dos Santos Silva, Kaleen Massari Leite,
Wellenilton Jose do Nascimento Júnior,
Vladimir da Mota Silveira-Filho,
Carina Lucena Mendes-Marques,
Francisco Henrique Da Silva
and Maria Betânia Melo de Oliveira*

Abstract

Due to their mass production and intense consumption in human medicine, veterinary, and aquaculture, antibiotics have been widely detected in different ecosystems, leading to a growing worldwide concern. These and their byproducts are being continuously discarded in natural ecosystems via excretion of human and animal urine and feces, also domestic and hospital effluents. Residues of these drugs can persist in natural environments through bioaccumulation due to their difficult biodegradation. Also, they have a gradual deposition in sediments, aquatic surfaces, and groundwater. Studies have shown the presence of these drugs in aquatic environments, which can trigger severe changes in the composition and structure of the bacterial community, such as the ability to develop and propagate genes resistant to these pollutants. In this context, this review aims to address the effects of the antibiotics on microorganisms present in impacted aquatic environments.

Keywords: bacteria, resistance genes, pollutants

1. Introduction

Water, as an essential resource for the maintenance of life, must be ingested in significant amounts daily. However, when this substance does not correspond to levels suitable for human consumption, it can represent a means of transmitting diseases [1]. According to the World Health Organization – WHO (2016) [2],

approximately half of the developing world population will be affected by infections directly related to water outside the quality standards either-or with lack of adequate or even non-existent sanitation.

The inappropriate disposal of residential waste, industrial, and agricultural effluents cause an imbalance in natural aquatic ecosystems. The amount of pollutants interferes with the proper functioning of the fauna and flora of these environments and, consequently, cause damage to the man himself [3]. Among the polluting agents of these ecosystems are pharmaceutical products, which are called emerging contaminants, of which antibiotics have been the subject of studies [4, 5].

Antibiotics are natural, synthetic, or semi-synthetic compounds developed and widely prescribed for therapeutic and prophylactic use against microbial infections in humans and animals [6, 7]. Besides, they have been widely used to stimulate the growth and production of animal [8–10]. The consumption of these drugs has increased considerably in recent decades, which is considered an emerging contaminant increasingly present in several environments, such as water [11, 12].

Despite being found in low concentrations in aquatic environments, data from the literature show that the presence of these contaminants causes negative impacts on several non-target organisms, such as microbial populations [13–15]. Changes in these populations can affect the maintenance of biological processes and change the structure of the entire ecosystem [16].

These drugs are considered the main source of changes in natural environments and influence a diversity of processes, including the development of antibiotic resistance and the spread of genes through horizontal gene transfer (HGT) [12, 17, 18]. Thus, the aquatic environment is considered efficient for the selection of bacterial populations resistant to antimicrobials, through mobile genetic elements [8]. Increased resistance to antimicrobials is often associated with a high adaptive capacity of microorganisms, with bacteria being more susceptible to changes and gene acquisition [19, 20].

Constant monitoring of bacterial communities is a tool that can lead to an understanding of the complexity of this phenomenon and the impact of human activities on natural environments [21]. In this context, this review aims to address the effects of antibiotics on microorganisms present in impacted aquatic environments.

2. Antibiotics

Antibiotics can be either from chemical compositions, derived from natural sources, or synthetic or semi-synthetic formulations. Compounds capable of inhibiting the growth of the invading microorganism, are classified as bacteriostatic. However, those that promote their microbial destruction are bactericidal [22]. The most appropriate antibiotics for the treatment of infections, by any infectious agents, are those that exert their respective mechanisms of action, directly on the pathogen without causing damage to the host, in other words, they present selective toxicity. However, all of these medications can have side effects [23].

They are usually classified according to their respective spectra and mechanisms of action. Through the description and synthesis of new compounds, it was necessary to organize them into the following groups: inhibitors of cell wall synthesis, inhibitors of cytoplasmic membrane synthesis, protein synthesis inhibitors in ribosomes, alteration of nucleic acid synthesis, and alteration of cellular metabolism [24]. The main targets of antibiotic action can be seen in **Figure 1**.

Its prescription, often, considers the symptoms presented by the patients and has no basis in more accurate clinical diagnoses that indicate the need for certain antibiotics or the appropriate dosages for each case [25]. Generally, there are several

Figure 1.
 Classifying scheme of the action mechanisms of antibiotics.

independent factors associated with non-compliance with the guidelines for antimicrobial prophylaxis, such as the lack of well-defined protocols, the lack of knowledge and updating, the lack of communication or disagreement between the prescribing professionals and the absence of tax audits [26]. For this reason, all health institutions and clinical analysis laboratories must use the same procedures and interpretive criteria, especially in the case of bacteria producing carbapenemases [27].

The discovery of antibiotics, initially penicillin by Alexander Fleming in 1928, was a milestone in the history of medicine and represented one of the most important therapeutic interventions for the control of diseases caused by bacteria. Thus, until the early 1960s, more than 20 classes of antibiotics were marketed worldwide. However, since that period, only two new classes were added to this group of drugs [28].

Thus, the obtention of new effective active ingredients capable of reaching different bacterial targets has been significantly reduced, so that new therapeutic approaches are essential to minimize the damage generated to human health [29, 30]. Also, The search for new molecules that have at least one synergistic mechanism in association with drugs already known, thus enhancing their effects, have been highlighted and may help the therapy of infections caused by microorganisms [31, 32].

The diversity of resistance genes identified in pathogenic bacteria, it is pointed out as one of the main causes of the growing increase in antibiotic resistance. However, the prevalence of bacterial resistance both regionally and on a global scale is highly attributed to the mechanisms of dissemination of virulent bacteria, which can colonize and adapt in various environments, including the aquatic [33, 34].

3. Antibiotics in aquatic environments

The extensive and continuous consumption of antibiotics is directly related to their presence in the environment, and for this reason, they have aroused a growing worldwide concern [12, 35]. Also, it estimated that a few thousand tons of these drugs are produced annually, and part of them is introduced into various ecosystems, including aquatic ones [36–38].

It is known that antibiotics can occur naturally in the environment. However, anthropogenic activities are considered the major source of these pollutants. Among these activities, the use in human and veterinary medicine for the treatment and prevention of bacterial infections stands out [7, 39].

After the administration of these drugs, they are not fully metabolized and absorbed by the body of the human or animal, there about 90% of the residues of each dose is excreted in the urine, and 75% of the remainder eliminated in the feces [40, 41]. These non-metabolized compounds are discarded in domestic and hospital effluents, and they can be partially disposed of in water treatment plants, following until they reach natural aquatic environments, such as rivers, lakes, seas, and groundwater [42, 43].

Another important source of environmental contamination by these drugs is through aquaculture, which also contributes to the contamination of the surface, groundwater, and sediment due to the use of antibiotics as fish food additives to promote growth and prevent disease [44, 45]. The pharmaceutical industry can also be considered a relevant source due to the disposal of effluents generated during the synthesis, processing, and filing of these compounds [46–48].

The dynamics of these compounds in the environment is determined by various physical-chemical and biological processes in soil-water systems, being dependent on structural characteristics of antibiotics, properties of soil and water, as well as environmental parameters, such as geographic location, temperature, and pH [10, 49–52]. In aquatic environments, antibiotics are being detected in low concentrations (ng/L e µg/L) [53–55]. However, some of these drugs can persist in the environment due to their low biodegradation. Consequently, they trigger their bioaccumulation and biomagnification [46, 56].

The presence of antibiotics in the natural environment, even in low concentrations, can affect the survival, reproduction, metabolism of populations of organisms, in addition to changing the structure of communities and ecological functions of ecosystems [57–59]. In this context, several studies have shown that these drugs trigger toxic, acute, either-or chronic effects in organisms of different trophic levels, such as bacteria, fungi, algae, invertebrates, and fish [60–62].

4. Effects of antibiotics on microorganisms in aquatic environments

Antibiotics were strategically developed to act against pathogenic microorganisms, and their advantages for the control and treatment of infectious diseases are indisputable [62]. However, its bioactive properties, the increase in its presence in the environment, and its toxicity on non-target organisms have aroused growing concern worldwide [15, 63].

Among the different groups of organisms, microorganisms are considered the most sensitive and most affected by the action of these drugs [61, 64]. Their bactericidal and bacteriostatic effects can trigger changes in the structure of microbial populations and their ecological functions in the environment. Microbial biodiversity is essential for the maintenance of biological processes in aquatic and terrestrial environments, including biogeochemical cycles [16].

Studies have shown that the presence of antibiotics, even at low concentrations, can cause changes in essential microbial processes for the ecosystems, such as nitrogen transformation, methanogenesis, sulfate reduction, nutrient cycle, and degradation of organic matter [16, 59, 65].

Another widely discussed effect of this class of drugs on the environment, it is the contribution to the emergence of antibiotic-resistant bacteria (ARB), and genes of resistance to antibiotics (GRA) [66]. Antibiotic resistance may occur naturally in the environment, but the increase has been reported due to the overuse and inappropriate disposal of these drugs. According to WHO, the occurrence of BRA and GRA is recognized as one of the most worrying public health problems of the century, with GRA being considered an emerging environmental pollutant [12, 67].

Among the different ecological niches, the aquatic environment is considered the most efficient for the selection of resistant bacterial populations. This environment is prone to constant changes that can apply selective pressure, favoring the evolution of these microorganisms regarding the adaptation process to various antimicrobial agents [68].

Literature data have been reporting the presence of antibiotic-resistant opportunistic pathogens such as *Escherichia coli*, *Klebsiella pneumoniae*, *Acinetobacter* spp., *Pseudomonas* spp., *Shigella* spp. [69–71], in several urban rivers, lakes, and streams, which receive an untreated effluent discharge domestic, hospital, and industrial, or inefficient water treatment plants [72–74].

Studies have shown that ARBs are introduced in these environments mainly by contamination by enteric bacteria that are exposed to high concentrations of antibiotics in the gastrointestinal tract of humans and animals [75]. Among various sources of these bacteria, urban water treatment stations stand out due to their high microbial density and the high presence of contaminants such as antibiotic residues, pharmaceuticals, heavy metals, among others. The combination of these substances puts selective pressure on these microorganisms, amplifying the development of resistance and its dissemination [76–78].

These bacteria act as a source of resistance in natural environments and can spread GRAs present in the environment [79]. Literature data suggest that the increase in the frequency of resistant bacteria in the water is influenced by the spread of GRAs among bacterial populations through vertical gene transfer (VGT) and horizontal gene transfer (HGT). VGT is parental genetic transmission via reproduction, and mutations in bacterial DNA can occur. On the other hand, HGT consists of the exchange of genes between microorganisms, intra or inter-specific, through mobile genetic elements, such as plasmids and transposons encoding antimicrobial resistance [80–82].

As mentioned above, microorganisms present in these impacted aquatic environments can develop different resistance mechanisms to adapt to the stress caused by various contaminants, such as heavy metals. Studies suggest that contamination by metals in the natural environment may play an important role in maintaining and proliferating resistance to antimicrobials [83–85]. In these environments, the selective pressure exerted by metals can select resistant isolates in a similar way to antibiotics, since both resistance genes are often located in the same moving elements [86, 87].

Martins et al. [88] observed that *P. aeruginosa* isolate, obtained from a contaminated river in southeastern Brazil, presented a conjugative plasmid with co-resistance to tetracycline and copper, reinforcing that resistance to antibiotics can be induced by the selective pressure of heavy metals in the environment. Rasmussen and Sorensen [89] demonstrated an increase in the occurrence of conjugative plasmids in contaminated sites. They observed that the mercury and tetracycline resistance genes were located on the same plasmid. This data that corroborates with the study carried out by Araújo et al. [90], who verified genes for resistance to mercury and tetracycline in isolates of *K. pneumoniae* obtained from an impacted urban stream in Pernambuco, Brazil.

In this way, not only the indiscriminate use of antibiotics but also environmental contamination by other substances can pose risks and damage to the environment and human health, since resistance genes can be transferred horizontally from environmental microorganisms to human commensals [91, 92]. Given this problem, there is a clear need to develop research and technologies for monitoring and removing these substances in the aquatic environment, in order to reduce their impact on the environment and public health.

5. Conclusion

The presence of antibiotics in aquatic ecosystems, although considered less than other contaminants, can alter the microbiota of these environments and favor the emergence of multi-resistant bacterial populations. Considering the importance of water bodies for human subsistence and due to the risk of bacterial spread, strategies for controlling the disposal of these contaminants must be evaluated, as well as the other agents that impact aquatic environments.

Author details

Lívia Caroline Alexandre de Araújo¹, Sivoneide Maria da Silva¹, Rafael Artur de Queiroz Cavalcanti de Sá¹, Ana Vitoria Araujo Lima¹, Amanda Virginia Barbosa¹, Jaqueline dos Santos Silva¹, Kaleen Massari Leite¹, Wellenilton Jose do Nascimento Júnior², Vladimir da Mota Silveira-Filho³, Carina Lucena Mendes-Marques¹, Francisco Henrique Da Silva¹ and Maria Betânia Melo de Oliveira^{1*}

¹ Laboratory of Molecular Biology (BioMol), Biochemistry Department, Federal University of Pernambuco, Recife, Pernambuco, Brazil

² Laboratory of Food Engineering, Federal University of Pernambuco, Recife, Pernambuco, Brazil

³ Biology Department, University of Pernambuco, Recife, Pernambuco, Brazil

*Address all correspondence to: maria.bmoliveira@ufpe.br

IntechOpen

© 2020 The Author(s). Licensee IntechOpen. This chapter is distributed under the terms of the Creative Commons Attribution License (<http://creativecommons.org/licenses/by/3.0>), which permits unrestricted use, distribution, and reproduction in any medium, provided the original work is properly cited.

References

- [1] Mouly D, Gorla S, Mounié M, Beaudeau, Galey C, Anne Gallay A, et al. Waterborne Disease Outbreak Detection: A Simulation-Based Study. *International Journal of Environmental Research and Public Health*. 2018; 157: 1505.
- [2] WHO. Sanitation safety planning: manual for safe use and disposal of wastewater, greywater and excreta. World Health Organization, 20 Avenue Appia, 1211 Geneva 27. 2016.
- [3] Bashir I, Lone FA, Bhat RA, Mir AA, Dar ZA, Dar AS. Concerns and Threats of Contamination on Aquatic Ecosystems. Springer Nature Switzerland AG. 2020; 1-26.
- [4] Gaffney V, Cardoso V, Benoliel MJ, Almeida C. Emerging contaminants - pharmaceuticals: monitoring, environmental and human health risk assessment. *Água & Resíduos - APESB*. 2016; 1: 1-27.
- [5] Kraemer SA, Ramachandran A, Perron GG. Antibiotic Pollution in the Environment: From Microbial Ecology to Public Policy. *Microorganisms*. 2019; 7: 1-24.
- [6] Kümmerer K. Antibiotics in the aquatic environment—a Review-Part 1. *Chemosphere*. 2009a 75, 417-434.
- [7] Carvalho IT, Santos L. Antibiotics in the aquatic environments: a review of the European scenario. *Environment International*. 2016; 94, 736-757.
- [8] Von Wintersdorff CJH, Penders J, Van Niekerk JM, Mills ND, Majumder S, Van Alphen LB, et al. Dissemination of Antimicrobial Resistance in Microbial Ecosystems through Horizontal Gene Transfer. *Frontiers in Microbiology*. 2016; 7: 173.
- [9] Cycoń M, Mroziak A, Piotrowska-Seget Z. Antibiotics in the soil environment—degradation and their impact on microbial activity and diversity. *Frontiers Microbiology*. 2019; 8(10):338.
- [10] Zhao RX, Feng J, Liu J, Fu WJ, Li XY, Li B. Deciphering of microbial community and antibiotic resistance genes in activated sludge reactors under high selective pressure of different antibiotics. *Water Research*. 2019; 151, 388-402.
- [11] Liu JL, Wong MH. Pharmaceuticals and personal care products (PPCPs): a review on environmental contamination in China. *Environment International*. 2013;59:208-224.
- [12] Ben YJ, Fu CX, Hu M, Liu L, Whong MH, Zheng CM. Human health risk assessment of antibiotic resistance associated with antibiotic residues in the environment: a review. *Environmental Research*. 2019; 168, 483-493.
- [13] Minguez L, Pedelucq J, Farcy E, Ballandonne C, Budzinski H, Halm-Lemeille MP. Toxicities of 48 pharmaceuticals and their freshwater and marine environmental assessment in northwestern France. *Environmental Science and Pollution Research*. 2016; 23:4992-5001.
- [14] Straub JO, Gysel D, Kastl U, Klemmer J, Sonderegger M, Studer M. Environmental risk assessment for ancillary substances in biotechnological production of pharmaceuticals. *Environmental Toxicology and Chemistry*. 2012; 31:681-687.
- [15] Kumar M., Jaiswal S, Sodhi KK, Shree P, Singh DK, Agrawal PK, Shukla P. Antibiotics bioremediation: perspectives on its ecotoxicity and resistance. *Environment International*. 2019; 124, 448-461.
- [16] Grenni P, Ancona V, Caracciolo A. Ecological effects of

- antibiotics on natural ecosystems: a review. *Microchemical Journal*. 2018; 136, 25-39.
- [17] Qiao M, Ying GG, Singer AC, Zhu YG. Review of antibiotic resistance in China and its environment. *Environment. International*. 2018; 110:160-172.
- [18] Zhang T, Hu Y, Jiang, L, Yao S, Lin, K, Zhou Y, Cui C. Removal of antibiotic resistance genes and control of horizontal transfer risk by UV, chlorination and UV/ chlorination treatments of drinking water. *Chemical Engineering Journal*. 2019; 358:589-597.
- [19] Cho S, Nguyen HAT, McDonald JM, Woodley TA, Hiott LM, Barrett JB, et al. Genetic Characterization of Antimicrobial-Resistant *Escherichia coli* Isolated from a Mixed-Use Watershed in Northeast Georgia, USA. *International Journal of Environmental Research and Public Health*. 2019; 16: 3761.
- [20] Dai Z, Sevillano-Rivera MC, Calus ST, Santos QMB, Eren AM, Wielen PWJJ, et al. Disinfection exhibits systematic impacts on the drinking water microbiome. *Microbiome*. 2020; 8: 42.
- [21] Jutkina J, Rutgersson C, Flach CF, Larsson DG. An assay for determining minimal concentrations of antibiotics that drive horizontal transfer of resistance. *Science of the Total Environment*. 2016; 548-549.
- [22] Guimarães DO, Momesso LS, Pupo MT. Antibióticos: importância terapêutica e perspectivas para a descoberta e desenvolvimento de novos agentes. *Química. Nova*. 2010; 33: 667-679.
- [23] Fernandes R, Amador P, Prudêncio C. β -Lactams: chemical structure, mode of action and mechanisms of resistance. *Reviews in Medical Microbiology*. 2013; 24: 7-17.
- [24] Madigan MT, Martinko JM, Bender KS, Buckley DH, Stahl DA. *Microbiologia de Brock*. 14 ed. Porto Alegre: ArtMed. 2016.
- [25] Leekha S, Terrell CL, Edson RS. *General Principles of Antimicrobial Therapy*. Mayo Clinic Proceedings. 2011; 86: 156-167.
- [26] Calbo E, Álvarez-Rocha L, Gudiold F, Pasquau J. A review of the factors influencing antimicrobial prescribing. *Enfermedades Infecciosas y Microbiología Clínica*. 2013; 31: 12-15.
- [27] Eichenberger EM, Thaden JT. Epidemiology and Mechanisms of Resistance of Extensively Drug Resistant Gram-Negative Bacteria. *Antibiotics*. 2019; 8: 37.
- [28] Coates A, Halls G, Hu Y. Novel classes of antibiotics or more of the same? *British Journal of Pharmacology*. 2011; 163: 184-194.
- [29] Nogueira HS, Xavier AREO, Xavier MAS, Carvalho AA, Monção GA, Barreto NAP. Antibacterial: main classes, mechanisms of action and resistance. *Revista Unimontes Científica*. 2016; 18: 96-108.
- [30] Santos DVA, Oliveira GA, Pacheco LG, Faria LMO, Cunha JC, Mello TM. Antibiotics through the approach of mechanism of bacterial resistance. *Ciência Atual*. 2018; 11: 4-14.
- [31] Mabou FD, Tamokou JD, Ngnokam D, Nazabadioko LV, Kuiate JR, Bag PK. Complex secondary metabolites from *Ludwigia leptocarpa* with potent antibacterial and antioxidant activities. *Drug Discoveries & Therapeutics*. 2016; 10: 141-149.
- [32] Kobayashi J. Search for New Bioactive Marine Natural Products and Application to Drug Development. *Chemical and Pharmaceutical Bulletin*. 2016; 64: 1079-1083.

- [33] Rojas GC, Ulate L. A. Resistencia antimicrobiana: microorganismos más resistentes y antibióticos con menor actividad. *Revista Medica de Costa Rica y Centroamerica*. 2016; 621: 757-763.
- [34] Motlagh AM, Yang Z. Detection and occurrence of indicator organisms and pathogens. *Water Environment Research*. 2019; 91: 1402-1408.
- [35] Kümmerer K, Alexy R, Hüttig J, Schöll A. Standardized tests fail to assess the effects of antibiotics on environmental bacteria. *Water Research*. 2004; 38, 2111-2116.
- [36] Ji, X, Shen Q, Liu F, Ma J, Xu G, Wang Y, Wu M. Antibiotic resistance gene abundances associated with antibiotics and heavy metals in animal manures and agricultural soils adjacent to feedlots in Shanghai; China. *Journal of Hazardous Materials*. 2012; 235, 178-185.
- [37] Harnisz M, Korzeniewska E, Gołaś I. The impact of a freshwater fish farm on the community of tetracycline-resistant bacteria and the structure of tetracycline resistance genes in river water. *Chemosphere*. 2015a; 128, 134-141.
- [38] Al Aukidy M, Verlicchi P, Jelic A, Petrovic M, Barcelò D. Monitoring release of pharmaceutical compounds: occurrence and environmental risk assessment of two WWTP effluents and their receiving bodies in the Po Valley. Italy. *Science of the Total Environment*. 2012; 438, 15-25.
- [39] Berkner S, Konradi S, Schönfeld J. Antibiotic resistance and the environment—there and back again. *EMBO Reports*. 2014; 15, 740-1744.
- [40] Sarmah AK, Meyer MT, Boxall ABA. A global perspective on the use, sales, exposure pathways, occurrence, fate and effects of veterinary antibiotics (VAs) in the environment. *Chemosphere*. 2006; 65:725-759.
- [41] Zuccato E, Castiglioni S, Bagnati R, Melis M, Fanelli R. Source, occurrence and fate of antibiotics in the Italian aquatic environment. *Journal of Hazardous Materials*. 2010; 179 (1), 1042-1048.
- [42] Moldovan Z. Occurrences of pharmaceutical and personal care products as micropollutants in rivers from Romania. *Chemosphere*. 2006; 1808-1817.
- [43] Lapworth DJ, Baran N, Stuart ME, Ward RS. Emerging organic contaminants in groundwater: a review of sources, fate and occurrence. *Environmental Pollution*. 2012; 163, 287-303.
- [44] Pham-Duc P, Cook MA, Cong-Hong H, Nguyen-Thuy H, Padungtod P, Nguyen-Thi H, et al. Knowledge, attitudes and practices of livestock and aquaculture producers regarding antimicrobial use and resistance in Vietnam. *PLoS ONE*. 2019; 14(9): e0223115.
- [45] Hossain A, Nakamichi S, Habibullah-Al-Mamun M, Tani K, Masunaga S, Matsuda H. Occurrence, distribution, ecological and resistance risk of antibiotics in surface water of finfish and shellfish aquaculture in Bangladesh. *Chemosphere*. 2017;188:329-336.
- [46] Carvalho, E.V. et al. Aspectos legais e toxicológicos do descarte de medicamentos. *Revista Brasileira de Toxicologia*. 2009; 22 (1-2):1-8.
- [47] Américo, J.H.P. et al. Ocorrência, destino e potenciais impactos dos fármacos no ambiente. *Saúde e Biologia*. 2013; 8 (2):59-72.
- [48] Giri P, Pal C. Ecotoxicological aspects of pharmaceuticals on aquatic Environment. *American Journal of Drug Discovery*. 2014; 1:10-24.

- [49] Andreozzi R, Caprio V, Ciniglia C, de Champdoré M, Lo Giudice R, Marotta R, Zuccato E. Antibiotics in the environment: occurrence in Italian STPs fate, and preliminary assessment on algal toxicity of amoxicillin. *Environmental Science and Technology*. 2004; 38 (24), 6832-6838.
- [50] Lee YJ, Lee SE, Lee DS, Kim YH. Risk assessment of human antibiotics in Korean aquatic environment. *Environmental Toxicology and Pharmacology*. 2008; 26 (2), 216-221.
- [51] Brausch JM, Connors KA, Brooks BW, Rand GM. Human pharmaceuticals in the aquatic environment: a review of recent toxicological studies and considerations for toxicity testing. *Reviews of Environmental Contamination and Toxicology*. 2012; 218, 1-99.
- [52] Mitchell SM, Ullman JL, Teel AL, Watts RJ. pH and temperature effects on the hydrolysis of three β -lactam antibiotics: ampicillin, cefalotin and cefoxitin. *Science of the Total Environment*. 2014; 466, 547-555.
- [53] Batt AL, Kim S, Aga DS. Comparison of the occurrence of antibiotics in four full-scale wastewater treatment plants with varying designs and operations. *Chemosphere*. 2007; 68, 428-435.
- [54] Ma Y, Li M, Wu M, Li Z, Liu X. Occurrences and regional distributions of 20 antibiotics in water bodies during groundwater recharge. *Science of the Total Environment*. 2015; 15, 518-519: 498-506.
- [55] Krzeminski P, Tomei MC, Karaolia P, Langenhoff A, Almeida CMR, Felis E, et al. Performance of secondary wastewater treatment methods for the removal of contaminants of emerging concern implicated in crop uptake and antibiotic resistance spread: a review. *Science of the Total Environment*. 2019; 648, 1052-1081.
- [56] Pereira, L.C. et al. A perspective on the potential risks of emerging contaminants to human and environmental health. *Environmental Science and Pollution Research*. 2015; 22:13800-13823.
- [57] Loos R, Carvalho R, António DC, Comero S, Locoro G, Tavazzi S, et al. EU-wide monitoring survey on emerging polar organic contaminants in wastewater treatment plant effluents. *Water Research*. 2013; 47, 6475-6487.
- [58] Martinez JL. Environmental pollution by antibiotics and by antibiotic resistance determinants. *Environmental Pollution*. 2009; 157:2893-2902.
- [59] Martin-Laurent F, Topp E, Billet L, Batisson I, Malandain C, Besse-Hoggan P, et al. Environmental risk assessment of antibiotics in agroecosystems: ecotoxicological effects on aquatic microbial communities and dissemination of antimicrobial resistances and antibiotic biodegradation potential along the soil-water continuum. *Environmental Science and Pollution Research*. 2019; 26(18):18930-18937.
- [60] Rede D, Santos LHMLM, Ramos S, Oliva-Teles F, Antão C, Sousa SR, Delerue Matos, C. Individual and mixture toxicity evaluation of three pharmaceuticals to the germination and growth of *Lactuca sativa* seeds. *Science of the Total Environment*. 2019; 673, 102-109.
- [61] Brandt KK, Amézquita A, Backhaus T, Boxall A, Coors A, Heberer T, et al. Ecotoxicological assessment of antibiotics: a call for improved consideration of microorganisms. *Environment International*. 2015; 85, 189-205.
- [62] Luo Y, Xu L, Rysz M, et al. Occurrence and transport of tetracycline, sulfonamide, quinolone,

and macrolide antibiotics in the Haihe River Basin, China. *Environmental Science & Technology*. 2011; 45:1827-1833.

[63] Su H, Hu X, Wang L, Xu W, Xu Y, Wen G, et al. Contamination of antibiotic resistance genes (ARGs) in a typical marine aquaculture farm: source tracking of ARGs in reared aquatic organisms. *Journal of Environmental Science and Health, Part B*. 2020; 55(3):220-229.

[64] Petrovich ML, Zilberman A, Kaplan A, Eliraz GR, Wang Y, Langenfeld K, et al. Microbial and Viral Communities and Their Antibiotic Resistance Genes Throughout a Hospital Wastewater Treatment System *Frontiers in Microbiology*. 2020; 11: 153.

[65] Bielen A, Šimatović A, Kosić-Vukšić J, Senta I, Ahel M, Babić S, et al. Negative environmental impacts of antibiotic-contaminated effluents from pharmaceutical industries. *Water Research*. 2017;126:79-87.

[66] Bila DM, Dezotti M. Fármacos no meio ambiente. *Química Nova*. 2003; 26 (44):523-530.

[67] Zarei-Baygi A, Harb M, Wang P, Stadler LB, Smith AL. Evaluating Antibiotic Resistance Gene Correlations with Antibiotic Exposure Conditions in Anaerobic Membrane Bioreactors. *Environmental Science & Technology*. 2019; 53(7):3599-3609.

[68] Woodford N, Wareham DW, Guerra B, Teale C. Carbapenemase-producing Enterobacteriaceae and non-Enterobacteriaceae from animals and the environment: an emerging public health risk of our own making? *Journal of Antimicrobial Chemotherapy*. 2014; 69:287-291.

[69] Hladicz A, Kittinger C, Zarfel G. Tigecycline resistant *Klebsiella pneumoniae* isolated from Austrian

river water. *International Journal of Environmental Research and Public Health*. 2017; 14:11-13.

[70] Marathe NP, Pal C, Gaikwad SS, Jonsson V, Kristiansson E, Larsson DGJ. Untreated urban waste contaminates Indian river sediments with resistance genes to last resort antibiotics. *Water Research*. 2017; 124:388-397.

[71] Nishiyama M, Ogura Y, Hayashi T, Suzuki Y. Antibiotic resistance profiling and genotyping of vancomycin-resistant enterococci collected from an urban river basin in the Provincial City of Miyazaki, Japan. *Water*. 2017; 9:79.

[72] Karkman A, Pärnänen K, Larsson DGJ. Fecal pollution can explain antibiotic resistance gene abundances in anthropogenically impacted environments. *Nature Communications*. 2019; 10:80.

[73] Niestępski S, Harnisz M, Korzeniewska E, Aguilera-Arreola MG, ContrerasRodríguez A, Filipkowska Z, Osińska A. The emergence of antimicrobial resistance in environmental strains of the *Bacteroides fragilis* group. *Environment International*. 2019; 124, 408-419.

[74] Osińska A, Korzeniewska E, Harnisz M, Niestępski S. Quantitative occurrence of antibiotic resistance genes among bacterial populations from wastewater treatment plants using activated sludge. *Applied Sciences*. 2019; 9:387.

[75] Alonso A, Sánchez P, Martínez JL. Environmental selection of antibiotic resistance genes. *Environmental Microbiology*. 2001; 3:1-9.

[76] Zhang T, Shao M-F, Ye L. Pyrosequencing reveals bacterial diversity of activated sludge from 14 sewage treatment plants. *The ISME Journal*. 2012; 6:1137-1147.

- [77] Michael I, Rizzo L, McArdell CS, Manaia CM, Merlin C, Schwartz T, Dagot C, Fatta Kassinos D. Urban wastewater treatment plants as hotspots for the release of antibiotics in the environment: a review. *Water Research*. 2013; 47:957-95.
- [78] Rizzo L, Manaia C, Merlin C, Schwartz T, Dagot C, Ploy MC, Michael I, Fatta-Kassinos D. Urban wastewater treatment plants as hotspots for antibiotic resistant bacteria and genes spread into the environment: a review. *Science of the Total Environment*. 2013b; 447:345-360.
- [79] Davison J. Genetic exchange between bacteria in the environment. *Plasmid*. 1999; 42:73-91.
- [80] Ali Abadi FS, Lee SP. Antibiotic treatment for animals: effect on bacterial population and dosage regimen optimization. *International Journal of Antimicrobial Agents*. 2000; 14:307-313.
- [81] Wegener HC, Moller NF. Reducing the use of antimicrobial agents in animals and man. *Journal of Medical Microbiology*. 2000; 49:111-113.
- [82] Shao S, Hu Y, Cheng J, Chen Y. Research progress on distribution, migration, transformation of antibiotics and antibiotic resistance genes (ARGs) in aquatic environment, *Critical Reviews in Biotechnology*. 2018; 38(8):1195-1208.
- [83] Dickinson AW, Power A, Hansen MG, Brandt KK, Piliposian G, Appleby P, et al. Heavy metal pollution and co-selection for antibiotic resistance: A microbial palaeontology approach. *Environment International*. 2019;132:105117.
- [84] Dahanayake PS, Hossain S, Wickramanayake MVKS, Heo G-J. Antibiotic and heavy metal resistance genes in *Aeromonas* spp. isolated from marketed Manila Clam (*Ruditapes philippinarum*) in Korea. *Journal of Applied Microbiology*. 2019;127(3):941-952.
- [85] Gallo IFL, Furlan JPR, Sanchez DG, Stehling EG. Heavy metal resistance genes and plasmid-mediated quinolone resistance genes in *Arthrobacter* sp. isolated from Brazilian soils. *Antonie Van Leeuwenhoek*. 2019;112(10):1553-1558.
- [86] Zhang M, Wan K, Zeng J, Lin W, Ye C, Yu X. Co-selection and stability of bacterial antibiotic resistance by arsenic pollution accidents in source water. *Environment International*. 2020; 135:105351.
- [87] Ohore OE, Addo FG, HAN N, Li X, Zhang S. Profiles of ARGs and their relationships with antibiotics, metals and environmental parameters in vertical sediment layers of three lakes in China. *Journal of Environmental Management*. 2020; 255:109583.
- [88] Martins VV, Zanetti MOB, Pitondo-Silva A, Stehling EG. Aquatic environments polluted with antibiotics and heavy metals: a human health hazard. *Environmental Science and Pollution Research*. 2014; 21:5873-5878.
- [89] Rasmussen LD, Sorensen SJ. The effect of long-term exposure to mercury on the bacterial community in marine sediment. *Current Microbiology*. 1998; 36: 291-297.
- [90] Araújo LCAA, Purificação-Junior AF, Silva SM, Lopes ACS, Veras DL, et al. In vitro evaluation of Mercury (HG+2) effects on biofilm formation by clinical and environmental isolates de *Klebsiella pneumoniae*. *Ecotoxicology and Environmental Safety*. 2019; 169:669-677.
- [91] Baker-Austin C, Wright MS, Stepanauskas R, mcarthur JV.

Co-selection of antibiotic and metal resistance. *Trends in Microbiology*. 2006; 14(4):176-182.

[92] Touchon M, Sousa JAM, Rocha EPC. Embracing the enemy: the diversification of microbial gene repertoires by phage-mediated horizontal gene transfer. *Current Opinion in Microbiology*. 2017, 38:66-73.