Case Studies in Chemical and Environmental Engineering 4 (2021) 100127

Contents lists available at ScienceDirect

Case Studies in Chemical and Environmental Engineering

journal homepage: www.sciencedirect.com/journal/case-studies-in-chemical-and-environmental-engineering

Sources of antibiotics pollutants in the aquatic environment under SARS-CoV-2 pandemic situation

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ARTICLE INFO

Keywords:
Antibiotics misuse
Wastewater detection
Aquatic environment pollution
Antibiotics for COVID-19

ABSTRACT

During the last decades, the growth of concern towards different pollutants has been increasing due to population activities in large cities and the great need for food production by the agri-food industry. The effects observed in specific locations have shown the impact over the environment in air, soil and water. Specifically, the current pandemic of COVID-19 has brought into the picture the intensive use of different medical substances to treat the disease and population intensive misuse. In particular, the use of antibiotics has increased during the last 20 years with few regulations regarding their excessive use and the disposal of their residues from different sources. Within this review, an overview of sources of antibiotics to aquatic environments was done along with its impact to the environment and trophic chain, and negative effects of human health due prolonged exposure which endanger the environment, population health, water, and food sustainability. The revision indicates the differences between sources and its potential danger due toxicity, and accumulation that prevents water sustainability in the long run.

1. Introduction

Aquatic environment is key to sustainable development for global society, these ecosystems are of great importance from an economic and environmental point of view [1]. Freshwater ecosystem holds 10% of the planet biodiversity (one third of vertebrates) and has come to a point where pollution, water scarcity and human usage have affected profoundly in the decrease of underwater living organisms [2]. The contamination of aquatic environments is mainly generated by anthropogenic activities making the pollution matrix so complex that it is composed of various substances such as domestic, industry and agricultural waste. Among these contaminants are found antibiotics, chemical substances that inhibit bacterial growth or decrease bacterial communities i.e. antibiotics used for medical and veterinary treatments [3]. Although a great effort is currently being made to improve wastewater treatment, it has been observed that current technology is not enough to remove the amount of antibiotics in the wastewater. In consequence a high load of antibiotics is discharged into bodies of water. Accumulation on aquatic environments has been evident and, on many occasions, it has also affected humans through the consumption and use of water. Recently, due to the pandemic caused by the SARS-CoV-2 virus, which causes the COVID-19 disease, the use of antibiotics to prevent and treat secondary diseases of a bacterial and fungal nature has increased in patients with COVID- 19. This has generated an alert since the increase in the use of these antibiotics, and their discharge into water bodies can have environmental consequences [4].

The projected scarcity of clean water is one of the biggest challenges to be addressed in the near future according to Ref. [5] number 6 (Clean water and sanitation) and the impact by interrelation to 1, 2, 3, 13, 14, and 15 SDGs [1]. The current availability of clean water is barely enough

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https://doi.org/10.1016/j.cscee.2021.100127
Received 29 October 2020; Received in revised form 23 August 2021; Accepted 25 August 2021
Available online 30 August 2021

to meet the requirements, only few locations in the world have full access and critical zones in Latin America [6], Sub-Saharan Africa, the Middle East and Central Asia [7,8]. Current studies estimate global population reached a crisis in the period of 1980 to 2016 [8] from where the goal of secure universal access to basic sanitation service by 2030 started.

The current technologies to enable water reuse are limited to low quality applications and few innovations can provide freshwater to be consumed by the population at a higher energetic and economic cost [9]. Some of the challenges to reach accessible prices in treated clean water are the availability of water reservoirs, distance, energy to transport, and quality [10]. Water pollution includes different contaminants of emerging concern, including a large list of antibiotics [11]. Paramount strategies to avoid the mentioned scene is by water reuse at a high percentage [1,2,9,10]. This work will focus on the identification of sources and types or groups of antibiotics found in aquatic streams and its adverse impact illustrated in Fig. 1. Furthermore, we will elaborate on the causes and impacts analyzed form the sustainable development goals and the COVID-19 pandemic situation.

2. Characteristics and main sources of antibiotics

Antibiotics are compounds that control bacterial infections in animals and humans. They kill or inhibits the growth or multiply of bacteria. by several mechanisms such as inhibiting the synthesis of a bacterial cell, synthesis of proteins, deoxyribonucleic acid (DNA), ribonucleic acid (RNA), by a membrane-disorganizing agent, or other specific actions [12]. Antibiotics are cytotoxic or cytostatic for bacteria, but they are partially metabolized and eliminated by the human body [13]. Antibiotics are used in an uncontrolled manner, moreover its consumption has increased rapidly in three sectors, domestic, industrial, and clinical as discussed in more detail in subsection 2.1, 2.2 and 2.3, respectively. Quantification of the use has been a challenge that recent years has been addressed by Wastewater Based Epidemiology (WBE) and current quantification of antibiotics has been recorded in high infrastructure countries from the beginning of the XXI century e.g., USA, Germany, Spain, Sweden, and Canada [11,14–17]. For instance, ESAC monitors and reports the data in continuum by survey from 2001 to 2003 [18], and quantification from wastewater biosolids sample were investigated USA nationwide to generate a baseline on pharmaceuticals and personal care products (PPCPs) by McClellan [11]. The data collection (in Table 1) is analyzed in the following subsections to understand the origin of the antibiotics.

2.1. Domestic misuse

During the 90's decade, the regulations for better practices have strengthened the accessibility to antibiotics where restrictions are in place the general population demand antibiotics to physicians, even though some countries have not followed the restrictions [23]. As a result of domestic misuse, the appearance of antibiotics on wastewater continues, for instance, the first reports where a baseline was screened in the USA shows how it is sustained during the period of six years from 2001 to 2007 [11]. On the other hand, countries like China have started the enforcement of antibiotic regulations from 2002 to 2016 with several measurements. The first was to include "The Administrative Measures for the Clinical Use of Antibacterial Drugs" in 2002 and the most recent National Action Plan to Contain Antimicrobial Resistance in 2016 [24]. The study presented by Zhang shows how a comparison between China, UK and USA resembles the abysmal gap between timely

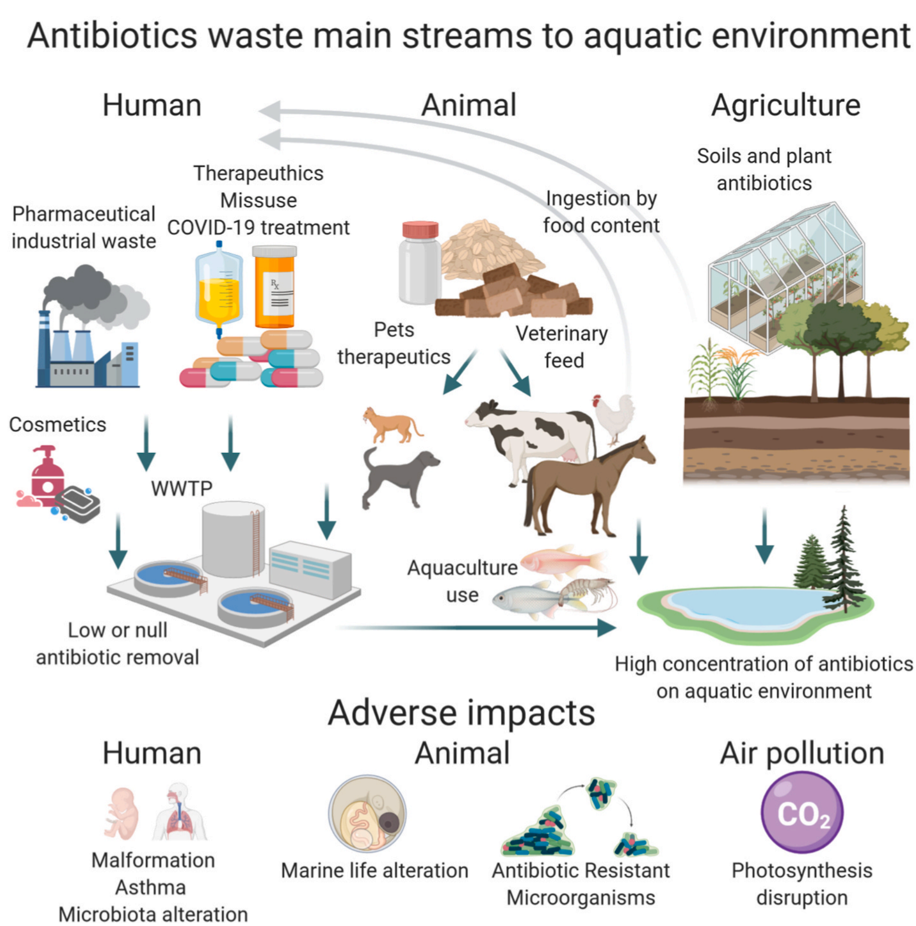
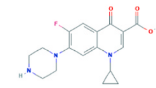
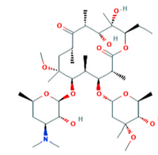
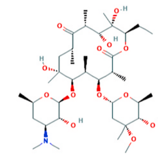
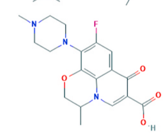
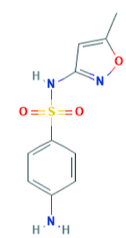
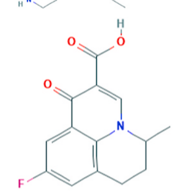
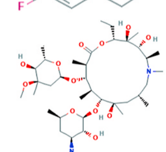
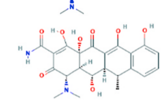
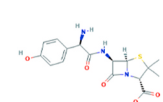


Fig. 1. Antibiotics waste main streams to aquatic environments and adverse impacts.

Table 1
Concentrations of antibiotics in wastewater and source.

Antibiotic	Mechanisms of action	Water source	Use	Country	Amount/ Concentration	Structure	Ref.
Ciprofloxacin	Inhibition of DNA replication	Hospital wastewater	Urinary and respiratory tract infections.	Switzerland	15700 ± 8000 ng L^{-1}		[19]
Clarithromycin	Inhibition of proteins synthesis	Hospital wastewater	Respiratory-tract, skin and soft-tissue infections.	Switzerland	1280 ± 840 ng L^{-1}		[19]
Erythromycin	Inhibition of proteins synthesis	Hospital wastewater Aquaculture ponds	Prevent bacterial protein synthesis.	Portugal Taiwan	575 ng L^{-1} 57.4 ng L^{-1}		[19] [20]
Ofloxacin	Inhibition of DNA replication	Hospital wastewater Domestic wastewater	Bacterial exacerbations of chronic bronchitis	Portugal China	6543 ng L^{-1} 2794 ug m^{-3}		[19] [21]
Sulfamethoxazole	Inhibition of dihydrofolate synthesis	Hospital wastewater Domestic wastewater	Urinary tract infections	South Korea China	25300 ng L^{-1} 2935 ug m^{-3}		[19] [21]
Norfloxacin	Inhibition of DNA replication	Domestic wastewater	Urinary tract infections	China	1813 ug m^{-3}		[21]
Flumequine		Aquaculture ponds	Veterinary medicine for the treatment of enteric infections as well as to treat cattle, swine, chickens, and fish.	Taiwan	331 ng L^{-1}		[20]
Azithromycin	Inhibition of mRNA translation	Domestic wastewater	To treat middle ear infections, tonsillitis, throat infections, laryngitis, bronchitis, pneumonia, sinusitis, non-gonococcal urethritis, and cervicitis.	Colombia	4120 ng L^{-1}		[22]
Doxycycline	Inhibition of protein synthesis	PEC data for the UK emergency hospital at Harrogate 95% treated Worst case scenario PNEC-ENV PNEC-MIC	COVID-19 treatment	UK	3 ng L^{-1} (Base line) 20 ng L^{-1} 25100 ng L^{-1} 2000 ng L^{-1}		[4]
Amoxicillin	Inhibition of cell wall synthesis	PEC data for the UK emergency hospital at Harrogate 95% treated Worst case scenario PNEC-ENV PNEC-MIC	COVID-19 treatment	UK	30 ng L^{-1} (Base line) 400 ng L^{-1} 600 ng L^{-1} 600 ng L^{-1}		[4]

[a]Note: PEC, Predicted Environmental Concentration Modelling tools; PNEC-ENV, Predicted No Effect Concentration, Environmental; PNEC-MIC, Predicted No Effect Concentration, Minimum Inhibitory Concentration. Chemical structures (ciprofloxacin CID: 2764; clarithromycin CID: 84029; erythromycin CID: 12560; ofloxacin CID: 4583; sulfamethoxazole CID: 5329; norfloxacin CID: 4539; flumequine CID: 3374; azithromycin CID: 447043; doxycycline CID: 54671203; amoxicillin CID: 33 613) were obtained from PubChem (https://pubchem.ncbi.nlm.nih.gov).

enforced policies and emerging ones. In general, China consumes 150 times more antibiotics than the UK. More in deep analysis the Chinese daily doses per inhabitant per day (DID) was from six to five times larger than the calculated for citizens of UK, USA, Canada and Europe [25].

Additionally, the waste disposal of domestic use antibiotics lacks in regulation. Even if a patient has been prescribed antibiotics and has access to the medicine it is not certain that the patient is going to use the antibiotics adequately and/or throw away the antibiotics leftover [26]. Furthermore, although there is adequate use of antibiotics by patients, research has indicated that antibiotics are poorly absorbed in the body, and about 30–90% of these compounds are excreted unchanged in urine or feces, and then flow into the domestic sewage system [21]. In addition to the use of antibiotics for medical treatments, at home, there are different PPCPs products such as soaps, shampoos, cleaning products, facial cleansers, sun creams, mouthwashes, and sterilizing agents for healthcare surfaces, which contain antimicrobial substances [27].

2.2. Industrial use

Agriculture industry is the main user of the total antibiotic production in the world e.g. China uses 52% of the total antibiotics to treat animals [25]. In agricultural use, the delay is notorious and just recently the Food and Drug Administration (FDA) in USA has issued a veterinary feed directive in contrast with European policy where the agricultural use of antibiotics reduced from 65% to 27% in the region [28]. In a similar way, aquaculture (farming of fish and other marine life) is a huge global enterprise, particularly in China as the largest aquaculture country producer in the world (with 58% of production 2016 [29] is an emerging activity for other countries. In this industry, the antibiotics are used to counteract the infections that marine animals can have when grown on an industrial scale [27]. Government authorities of some countries have issued strict regulations for the application and use of antibiotics. Lulijwa et al. [30], review revealed 67 antibiotic compounds used in aquaculture from 15 major producing countries (South Korea, China, India, Vietnam, Indonesia, Philippines, Egypt, Norway, Bangladesh, Brazil, Chile, Japan, Thailand, Myanmar, and Malaysia), between 2008 and 2018 and shown some of the antibiotics allowed and prohibited in the aquaculture industry [30].

Other industrial source of antibiotics is pharmaceutical and cosmetic products industry [31,32]. Antibiotic pharmaceutic production facilities are a major source of environmental contamination. Recent studies in some Asian countries had found antibiotic residues in wastewater discharged from pharmaceutical plants. These findings have raised the alarm because the concentrations of antibiotics were reported up to level of mg/L. The antibiotic concentrations measured in effluents were higher than the corresponding data measured in effluent samples from hospitals and aquaculture sites. This observation confirmed that pharmaceutical manufacturing plants are an important source of antibiotics in the aquatic environment [33].

2.3. Clinical waste

Much of the antibiotics administered to patients in hospital are partially metabolized in the body while the rest are added to the hospital effluents via excretion. Similarly, unused antibiotics are also dumped into hospital effluents. All these ultimately contribute to the residues of antibiotics in hospital-associated wastes. The amount of antibiotics in hospital wastewater depends on the size of a hospital, number of inpatients and outpatients, the bed density, the number and types of services, the number and the type of wards, the country, and the season. An emergent concern about hospital effluents is the chemicals without regulatory status, known as "emerging pollutants", whose impact on the environment and human health are poorly understood. Some hazardous substances produced in hospital facilities have a regulatory status and are treated as waste and are disposed of accordingly. However, concerns about substances such as antibiotics that don't have a regulatory status, have emerged [19].

2.3.1. COVID-19 treatment

During COVID-19 pandemic, the use of antibiotics has increased due to the need for treatment of 95% of COVID-19 patients, who have bacterial or fungal infection with regard to COVID-19 management. However, a high proportion of COVID-19 patients are being unnecessarily treated with antibiotics [34,35]. In the recent work done at UK hospital the outcome suggests a strategic use of antibiotics as doxycycline as first line and amoxicillin as second line. Additionally, it predicts the increment of release of drug residues to UK rivers and coastal waters from the WWTPs [4].

The use of antibiotics has also increased since many people have decided to self-medicate to protect themselves from the virus [36]. Macrolides are antibiotics used against Gram- positive bacteria that cause respiratory tract infections that have been shown immunomodulatory and anti-inflammatory effects and are presented as options for viral respiratory infections. Clinical trials have been conducted to evaluate efficacy and benefit-risk of azithromycin in combination to hydroxychloroquine in COVID-19 [37,38] Additionally, the use of antibacterial and disinfectants agents has increased, which contains biocides that will reach the wastewater [34,39].

The health systems sanitation recommended an extended and more frequent hands clean using soap, for instance, wash hands to at least 20 seconds [40] and be as frequent as every entry to buildings [41]. Some recent studies have explored the composition of the common soap and commonly used in cosmeceutical products along its destination into sewers showing a high concentration of triclosan, triclocarban and some parabens [42].

3. Impact of antibiotics on the aquatic environment and human health

Antibiotics have been detected in aquatic environments such as lakes, rivers, water reservoirs, wastewater treatment plants influent and effluent, groundwater, and even drinking water even though drinking water was treated [43]. As was mentioned before, the antibiotics found in the aquatic ecosystem, come from domestic, hospitals, the pharmaceutical industry, aquaculture, and agriculture activity. The presence of antibiotics in the aquatic environment is a serious concern because it may accelerate the proliferation of antibiotic-resistant pathogens, through genetic mutations and resistance vectors with high transfer rate between pathogens, thus lowering the therapeutic effect of antibiotics. In addition, antimicrobial resistance can be transferred between different organisms throughout the food chain. According to the World Health Organization [40], antimicrobial resistance is a significant challenge to global human and animal health, food safety, and development today, with the perspective of aggravation in the upcoming years, if adequate measures are not implemented. It was determined that detected levels of antibiotics in WWTP effluent samples exhibit an impact on the environment, especially in microbial communities in aquatic systems causing antibiotic resistance development [44,45].

The toxicity of antibiotics in aquatic organisms has been evaluated, finding that these compounds may have harmful effects on growth, development, reproduction or time of life [32]. A wide range of antibiotics such as macrolides and sulfonamides showed negative effects on the development and growth of algae [46]. Antibiotics also, can damage the photosystems of plant cells and can reduce the rate of carbon dioxide transformation [47]. Moreover, the residues of antibiotics in the aquatic environment can be spread widely due to the lack of proper wastewater treatment systems. The antibiotics present in water may enter the soil system affecting the function of native biota that plays an essential role in the biogeochemical cycling of elements [33,34,44].

Antibiotics present in the environment, in drinking water and in personal care products can harm humans through direct or indirect contact especially because its use is not properly regulated. The problem is so serious that it has been found that antibiotics such as triclosan can be transmitted to the fetus since they have been detected in cord blood samples in pregnant women. Moreover, it has even been found that this antibiotic transmission increases the risk of fetal malformation, decreased gestational age, weight and body length at birth [48–50]. The consumption of antibiotics alters the intestinal microbiota and resistome and increases the opportunistic pathogens abundance, creating problems in the gut and increases incidence of antibiotic resistant bacteria [51].

The chronic exposure to antibiotics by eating food or water provokes human health risk, for that it has been suggested to ban the use of antibiotics in the production of animals for food [52]. It is important to know that the veterinary antibiotics exposure can be of 1 μg/kg/d in children and in adults in some communities and that can affect three generations of the same family, being this exposure a public health problem [53]. This chronic exposure has even been associated with the development of diseases, for example, the preceding antibiotic exposure especially of amoxicillin is associated with the risk of asthma development in children [54].

4. Treatment and management strategies to remove antibiotics

Primary, secondary and tertiary treatments have been reported for treating effluents with high concentration drugs. Primary treatment reduces the chemical toxicity from hospital effluents and improves their biodegradability. Methods such as flocculation and coagulation using ozonation, photo-Fenton or both and a combination of ozone with UV and H_2O_2. In secondary treatment, membranes have been commonly used to remove pharmaceuticals and metabolites, in many countries the treatment was done by membrane biological reactor (MBR). Filtration adsorption, ozonation, and nanotechnological approaches were used as tertiary treatment [55].

Novel technology to treat emerging contaminants include the possibility to use microalgae as a polishing process coupled at the end of the usual water utilities operations. A comprehensive report was presented by a revision done in different conditions, from laboratory experiments and the application in real wastewater where the evaluation of the EC through the process is followed [56]. Major concerns are the fate of the EC and during this study identify three processes; bioadsorption, bio-uptake or bioaccumulation, and biodegradation. Another key point is the toxicity for the microalgae in real applications that have been overcome by the integration of consortiums and in some cases the presence of several EC's enhance the microalgae activity. Finally, this revision highlights the necessity of more real applications reported by this technology in the bioremediation of EC's [56].

Another technology group is the Advanced Oxidation Processes (AOPs) which includes mentioned technologies Ozone-based AOPs, UV-based AOPs, Physical AOPs and new promising technologies like Catalytic AOPs, Electrochemical AOPs. Within the Catalytic technologies it was found that the fenton, photo-fenton, photocatalysis and persulfate activation are some of the most promising technologies applied to eliminate the antibiotics in wastewater due to its high reactivity with most of the antibiotics [57]. In particular, the photocatalysis/persulfate-oxidation hybrid or PPOH can be classified in photo-assisted persulfate activation (PPA), persulfate-assisted photocatalysis (PAP) and oncurrent photocatalysis-persulfate activation (CPPA) systems. Advantages from this technology are high performance of mineralization of antibiotics, and PAP can be considered a greener process [57].

5. Conclusions and future recommendations

Antibiotics are chemical substances used to inhibit the growth of unwanted microorganisms and have been found in different aquatic ecosystems. These compounds are disposed in domestic wastewater, hospitals, and diverse industries such as pharmaceuticals, aquaculture, and agriculture. Most of the discarded antibiotics are not degraded in the wastewater treatment plants, and finally, they end up reaching aquatic ecosystems, causing damage to the development of microorganisms, animals, plants, and humans. Chronic exposure to antibiotics is a public health problem as it affects more than one generation in a specific location. Policies that regulate the release of antibiotics worldwide, to water sanitation systems, should be developed or strengthened, and implement new biotechnologies in wastewater treatment plants to eliminate this emerging pollutant. As well as greater awareness in the control of the use and disposal of antibiotics and their residues by the population, agri-food and pharmaceutical industry.

Currently, with the pandemic that is being experienced worldwide due to SARS-CoV-2, the health system is required to establish strategies for the specific administration of antibiotics in the treatment of COVID-19 patients. Studies to the development of an antimicrobial policy specific for COVID-19 is urgently needed. Specially to treat the wastewater effluent from hospitals that include some of the mentioned processes in section 4.

Funding

CONACYT is thankfully acknowledged for partially supporting this work under Sistema Nacional de Investigadores (SNI) program awarded to Juan Eduardo Sosa-Hernández (CVU: 375202), Elda M. Melchor-Martínez (CVU: 230784), Hafiz M.N. Iqbal (CVU: 735340), and Roberto Parra-Saldívar (CVU: 35753).

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Acknowledges

The authors acknowledge the support of the participant institutions for gaining access to scientific journal databases.

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