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Estimation of urine volume in municipal sewage originating from patients receiving antibiotics at a private clinic in Crete, Greece

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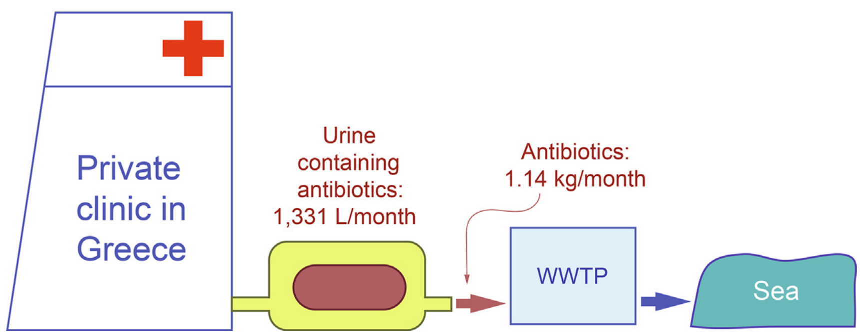
HIGHLIGHTS

- Estimation of urine volume in the wastewater from a private clinic in Greece.
- As high as 40.8% of the urine was produced by patients receiving antibiotics.
- Active substances in antibiotics behave like pollutants when enter the environment.
- Effluents from clinics should be treated before direct discharge into a sewer network.

GRAPHICAL ABSTRACT



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ABSTRACT

This study presents an estimation of the urine volume in the wastewater from a real, private clinic in Crete, Greece, during a seven-month period (01/06/2018 to 31/12/2018). Separate estimates were obtained for the volume of urine belonging to patients receiving antibiotics. It was found that the clinic disposed into the local municipal sewage network on the average 3,263 L/month of urine, from which 1,331 L/month (40.8%) belonged to patients receiving antibiotics. According to the pharmacy department of the private clinic, during the period of the study, the most frequently administered groups of antibiotics were on the average 779 g/month cephalosporins (68.1%), 108 g/month fluoroquinolones (9.5%) and others (11.2%), with various active substances including cefuroxime, ciprofloxacin, metronidazole and doxycycline. These active substances act like pollutants when disposed via the municipal sewer network into the environment.

1. Introduction

Antibiotics are widely used throughout the world for the reduction of common infectious diseases (Dinh et al., 2017a). Among the various available drugs, antibiotics are unique because they selectively target bacteria without any undesired effects to human cells and tissues. (Sköld, 2011). Within the human body, antibiotics undergo structural changes due to the presence of numerous

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microorganisms and enzymes (e.g., cytochromes), which exist within the intestine (Mendez-Arriaga et al., 2008). The metabolism of active substances occurs in the liver. Often the metabolites are more water soluble than the parent compounds, and thus they are easily excreted in the urine (Göbel et al., 2005). Also, the metabolites may be more toxic compounds than the parent compounds (Göbel et al., 2005). However, most of the antibiotics (55–80%) are excreted from a human body without any metabolism (Alcock et al., 1999; Al Aukidy et al., 2012; Jjemba, 2006; Verlicchi et al., 2012).

Antibiotics excreted from a human body often enter unprotected environmental systems. A significant proportion of these active substances as well as various pharmaceuticals are found in the environment in small concentrations (Dinh et al., 2017b). Consequently, they constitute a potential risk for the public health (Schwarzenbach et al., 2007; Fountouli and Chrysikopoulos, 2018).

Antibiotics are classified according to their chemical structure or mechanism of action. There are more than 250 active substances in the various registered antibiotics (Kümmerer and Henninger, 2003). A percentage of these active substances, their metabolites and transformation products eventually will enter and accumulate within environmental systems (surface and subsurface waters) with detrimental effects to numerous living organisms, various trophic levels in the food chain, and drinking water (Kümmerer, 2009). The active substances of antibiotics enter the environment through a variety of different sources (Heberer, 2002), such as the effluents from a private clinic on the island of Crete, Greece, which is known to release its wastewater, containing urine from patients receiving antibiotics, directly into the municipal sewer network.

Although the concentrations of active substances of antibiotics detected in the effluents of wastewater treatment plants may not be toxic to humans and the environment, there is a great concern about their long-term exposure effects to aquatic organisms and the entire food chain. The fate and transport of these active substances in the environment are of a particular interest, because the continuous exposure of bacteria to these substances leads to antibiotic resistant bacteria (Zaha et al., 2019). Certainly, this is a problematic issue, particularly in regions where treated (reclaimed) wastewater is reused (Gracia-Lor et al., 2012; Chrysikopoulos et al., 2010; Bungau et al., 2018). Consequently, recent research has focused to the development of effective antibiotics, which after their use are completely degraded in a very short period of time and are less toxic for the aquatic environment (Andra et al., 2018).

In contrast to other studies examining antibiotics in sewage effluents from healthcare units, this study was aiming directly at the source, which is the urine of patients who have received antibiotics. Furthermore, the quantities of the active substances of the various antibiotics administered to the patients, staff, and visitors of the clinic were also estimated.

2. Materials and methods

2.1. Description of the clinic

The private clinic used in this study is located in the island of Crete was founded in 1977 and operates 24 h a day. The wastewater produced in the clinic is disposed directly into the municipal sewer network of the city. For the needs of this study, the patients who visited a private clinic over the time period from 01/06/2018 to 31/12/2018 were monitored for the group and quantity of active substances present in the antibiotics administered to them. Subsequently, the total urine volume produced in the clinic was estimated. The patients were classified based on required hospitalization needs, on the type of medical services provided to them, as well as on their sex and their age. Additionally, they were classified as: overnight patients, short-term hospitalization patients, outpatient clinics, intensive care unit patients, and microbiology department. These classifications aided to efficient analysis of the urine volume produced by patients, staff, and visitors of the clinic, which was disposed directly in the local municipal sewer network. The urine volume from patients who received antibiotics was tracked separately.

Over the duration of this study, the patients of the obstetric, pathological, and surgical departments of the clinic, stayed hospitalized at list overnight (often more than 24 h). The patients of the chemotherapy, urology, and drug administration departments, as well as those who had a small-scale surgery operation at the clinic, remained hospitalized for less than 24 h. The visitors to the outpatient clinics used mainly the magnetic and axial tomography, surgical, cardiological, and orthopedic departments, as well as the emergency room and remained in the clinic only for just a few hours. The patients who continued their hospitalization at the intensive care unit of the clinic, remained in the clinic several days. The numbers of patients who visited the various departments of the clinic, over the time period of this study, are listed in Table 1.

The number of beds available to patients who stayed in the clinic, at least overnight, was 60. The beds available for patients who received brief hospitalization were 2, and the beds in the intensive care unit were 5. Therefore, the total number of available beds in the clinic was 67. The microbiology department had the capability of processing 40 urine specimens per hour. Also, the number of staff working in the clinic was 136 (41 men and 95 women).

2.2. Estimation of disposed urine and antibiotics

The desired data were collected using: (i) a questionnaire, (ii) the database of the private clinic with weekly and monthly compiled patient medical data, and (iii) personal interviews with the supervisors of the various departments of the clinic. Finally, the pharmacy of the private clinic, provided information about both the group and the quantity of the antibiotics as well as the associated active substances administered to the patients and the visitors of the private clinic. These data collection methods and procedures comply with the European Parliament's Directive 95/46/EC (1995), which protects individuals with regard to the processing of personal data. Clearly, there was no direct access and storage of personal data, but only numerical values were compiled.

The above sources of information provided enough data for accurate estimation of the urine volume (with and without prescribed antibiotics) produced and disposed of by the patients and staff in the various departments of the private clinic. The nationality of each patient hospitalized for more than 24 h in the private clinic was also a key information for the present research. Over the duration of this study patients from 18 different countries, including Greece, have visited the clinic.

In order to determine the number of patients who received antibiotics in the private clinic, medical records of patients in each individual department of the clinic were randomly checked. For at least two days per week selected at random, the number of patients receiving antibiotics in each department of the clinic were estimated. Subsequently, these data were carefully processed.

In order to determine the number of patients who received antibiotics prior to their scheduled urine examination, for at least two days per week randomly selected, the medical questionnaires filled by the patients prior to urine exams were inspected. Note that one question in the questionnaire inquired if antibiotics or other medication have been received prior to the examination. Subsequently, the data collected were carefully processed.

Table 1
Urine volumes disposed into the municipal sewer network from the various patient groups and staff of the clinic during the period June to December 2018.

Groups			Distribution						
			June	July	August	September	October	November	December
Overnight patients	Numbers of patients (–)	Men	126	105	160	83	104	80	53
		Women	121	127	137	189	208	175	158
		Sum	247	232	297	272	312	255	211
		Total				1,826			
		Receiving antibiotics				1,760			
		Average per month				261			
		Receiving antibiotics				251			
	Urine volume produced (L)	Total	1,143	1,066	1,397	1,227	1,412	1,151	945
		Receiving antibiotics	1,121	1,030	1,332	1,181	1,361	1,105	910
		Average per month				1,189			
		Containing antibiotics				1,149			
Short-term hospitalization patients	Numbers of patients (–)	Men	55	47	70	36	45	34	22
		Women	50	50	51	78	85	72	64
		Sum	105	97	121	114	130	106	86
		Total				759			
		Receiving antibiotics				235			
		Average per month				108			
		Receiving antibiotics				34			
	Urine volume produced (L)	Total	46	43	54	49	56	46	37
		Receiving antibiotics	15	14	16	15	17	15	11
		Average per month				47			
		Containing antibiotics				15			
Outpatient clinics	Numbers of patients (–)	Men	1,620	2,487	2,061	2,244	2,071	2,118	1,750
		Women	2,206	1,282	1,946	1,613	1,486	1,538	1,570
		Sum	3,826	3,769	4,007	3,857	3,557	3,656	3,320
		Total				25,993			
		Receiving antibiotics				3,955			
		Average per month				3,713			
		Receiving antibiotics				565			
	Urine volume produced (L)	Total	417	423	442	429	395	406	366
		Receiving antibiotics	62	64	66	67	62	64	52
		Average per month				411			
		Containing antibiotics				63			
Intensive care unit	Numbers of patients (–)	Men	8	10	11	9	7	5	8
		Women	2	2	4	0	1	3	2
		Sum	10	12	15	9	8	8	10
		Total				72			
		Receiving antibiotics				72			
		Average per month				10			
		Receiving antibiotics				10			
	Urine volume produced (L)	Total	78	98	108	88	69	49	78
		Receiving antibiotics	17	17	35	0	9	26	17
		Average per month				99			
		Containing antibiotics				99			
Microbiology department	Numbers of general urine examinations (–)	Sum	946	882	1,010	972	1,066	748	1,077
		Total				6,701			
		Receiving antibiotics				602			
		Average per				957			

(*continued on next page*)

Table 1 (*continued*)

Groups			Distribution						
			June	July	August	September	October	November	December
		month							
		Receiving antibiotics				86			
	Urine volume handled (L)	Total	57	53	61	58	64	45	65
		Receiving antibiotics	7	4	5	3	7	4	8
		Average per month				57			
		Containing antibiotics				5			
Staff	Urine volume produced (L)	Average per month				1,460			
Combined total	Urine volume produced (L)	Average per month				3,263			
		Containing antibiotics				1,331			

2.3. Preliminary evaluations

For the estimation of urine quantities produced by patients, visitors and staff of the private clinic, it was assumed that the clinic was operated 24 h per day, 365 days a year. Furthermore, it was assumed that men, women and minors produced different urine volumes. Here it was assumed that the average volume of urine produced over a 24-hour period by a man is 1.40 ± 0.56 L and by a woman 1.24 ± 0.44 L (Borghi et al., 1996), and people younger than 18 years old is 22.2 ± 2.0 mL per kg (Miller and Stapleton, 1989).

Based on the private clinic data collected over the duration of this study, it was estimated that overnight patients remained hospitalized on the average for 3.5 days, short-term hospitalization patients remained for 8 h, visitors of the outpatient clinics remained 2 h, and intensive care unit patients remained hospitalized on the average for 7 days, while the average urine specimens handled by the microbiology department was 0.06 L. These averaged values were employed for the estimation of urine quantities produced by the various patients of the private clinic.

3. Estimation of the number of patients and urine volume produced

3.1. Estimation of the number of patients hospitalized overnight

The distribution of the number of patients hospitalized in the clinic for more than 24 h, over the seven-month duration of this study, is presented in Table 1. Overall, the number of women hospitalized overnight was higher than that of men. In certain months, the number of women hospitalized overnight was more than twice as that of men. For example, during the month of September 2018, women accounted for the 69.5% of all patients, while men accounted for 30.5%. The highest activity in the clinic was observed during the time period August to October 2018 (297–312 patients). It should be noted that the months August and September, correspond to the peak of the tourist season on the island of Crete. The smallest number of patients hospitalized overnight at the clinic (211 patients) was during the month of December 2018, when the tourist activity is substantially lower from the peak months.

A large percentage of the patients hospitalized overnight at the private clinic had received antibiotics. On the average, the number of female patients hospitalized overnight and had received antibiotics was higher than the corresponding number of male patients. The urine volumes (with and without antibiotics) produced by the patients hospitalized in the clinic for more than 24 h, over duration of this study, are listed in Table 1.

It is evident from Table 1 that during the month of October 2018 the urine volume disposed of into the municipal sewage network was the largest (1,412 L), with 96.4% (1,361 L) produced by patients who had received antibiotics. On the average, 1,190 L/month of urine volume were produced by overnight patients, from which 96.6% (1,150 L/month) were produced by patients who had received antibiotics.

3.2. Estimation of the number of patients hospitalized for a short term

The numbers of patients who were hospitalized in the clinic for only a short term, for example, after chemotherapy, are presented in Table 1. Overall, the number of female patients hospitalized over a short term was higher than that of male patients. For example, during the month of December 2018, women accounted for the 74.4% of all patients, while men accounted for 25.6%. Furthermore, it is evident from the data of Table 1 that during the period August to October 2018 the number of short-term hospitalized patients was higher (114–130 patients), whereas the lowest (86 patients) was reported during the month of December 2018.

A substantial percentage of the short-term hospitalization patients of the private clinic had received antibiotics. On the average, the number of women hospitalized for a short term and received antibiotics was higher than the corresponding number of men. For example, during the month of December 2018, female patients accounted for the 69.2% of all short-term hospitalized patients, while male patients accounted only for 30.8%. Note that the highest number of short-term hospitalized patients in the clinic was during the period from August to October 2018 (121–130 patients), and the lowest was during the month of December 2018 (86 patients).

The time distribution of the urine volume (with and without antibiotics) produced by short-term hospitalized patients, over duration of this study, is presented in Table 1. As expected, during the month of October 2018 the urine volume produced by patients hospitalized for a short-term was the largest (56 L), from which 17 L (30.4%) was produced by patients who had received antibiotics. On the average, 47 L/month of urine were produced by patients hospitalized for a short-term, from which 31.9% (15 L/month) was produced by patients who had received antibiotics.

3.3. Estimation of visitors to the outpatient clinics

The distribution of the number of patients who visited the outpatient clinics (e.g., magnetic and axial tomography, surgery, cardiology) of the private clinic during the duration of this study, is presented in Table 1. The number of male patients who visited the outpatient clinics was on the average 8.6% higher than the corresponding number of female patients. For example, during the month of July 2018, men accounted for the 66% of all patients who visited the outpatient clinics, while women accounted for 34%. It is worthy to note that although the number of the patients who visited the outpatient clinics was highest during the month of August (4007 patients), the number of patients remained relatively steady over the duration of this study, with an average of 3654 patients per month.

The distribution of the urine volume produced by patients who visited the outpatient clinics over the study period is presented in Table 1. On the average, 411 L/month of urine were produced in the outpatient clinics, from which 63 L/month were produced by patients who had received antibiotics. Clearly, only a relatively small percentage (15.3%) of the patients who visited the outpatient clinics had received antibiotics. Also, it should be noted that the urine volume produced by patients who visited the outpatient clinics (with and without prescribed antibiotics) did not exhibit significant fluctuations over the duration of this study.

3.4. Estimation of the number of intensive care unit patients

The distribution of the number of patients hospitalized in the intensive care unit over the duration of this study is presented in Table 1. The number of male patients hospitalized in the intensive care unit was higher than that of female patients. For example, during the month of September 2018, only male patients were hospitalized in the intensive care unit. On the average, 10 patients per month were hospitalized in the intensive care unit, and all of these patients received antibiotics.

The distribution of the urine volume produced by patients who visited the intensive care unit over the period of this study is presented in Table 1. On the average, 98 L/month of urine were produced in the intensive care unit (81 L/month belonged to male patients and 17 L/month to female patients).

3.5. Estimation of urine volume handled by the microbiology department

The distribution of general urine examinations carried out at the microbiology department of the private clinic over the duration of this study is presented in Table 1. The number of urine tests remained relatively steady. On the average, 957 urine tests were conducted per month. The maximum number of urine tests (1,077 tests) was recorded during the month of December 2018 and the minimum number (748 tests) during the month of November 2018.

The distribution of the urine volume produced in the microbiology department from the various urine tests is presented in Table 1. On the average, 57.4 L/month of urine were produced, from which only 5 L/month (9.4%) were produced by patients who had received antibiotics. Worthy to note is that the urine volume produced (with and without prescribed antibiotics) was relatively steady over the duration of this study.

4. Nationalities of the patients visiting the clinic

The island of Crete is the largest of the Greek islands (260 km long and 56 km at its widest point) and one of the most popular tourist destination with approximately 4 million visitors per year from every part of the world. The permanent population on the island is 623,065 people (Region of Crete, 2019). According to the data provided by the private clinic, the patients who were hospitalized for at least one night, over the time period of this study, where nationals of Greece and from 17 other countries. Certainly, the majority of patients were Greeks. However, during the summer months the number of Greek patients was comparable to the combined number of patients from the other 17 countries. For example, during the month of August 2018 the percentage of the Greek patients hospitalized in the private clinic was 52.4%, and from all the other countries combined was 47.6%.

Among the foreign patients hospitalized in the clinic, the highest percentages belonged to Sweden (8.3%) in June 2018, United Kingdom (9.5%) in August 2018, and Denmark (11.4%) in September 2018. Also, as expected, after the peak tourist season the percentage of Greek patients increases. For example, during the month of November 2018, 91.7% of the patients were Greek. This observation that the majority of the patients were Greek is also evident from the combined results of the pie chart presented in Fig. 1, where the nationalities and percentages of the various patients hospitalized in the clinic over the duration of this study are illustrated. Clearly, the highest percentage corresponds to patients from Greece (73%), followed by patients from United Kingdom (3.6%), Denmark (3.4%), Netherlands (3.1%), and Norway (2.8%).

5. Active substances in antibiotics

Based on the data provided by the pharmacy department of the clinic, it was estimated that 7.98 kg of antibiotics (1.14 kg/month) were administered over the duration of this study. The most frequently used antibiotics can be classified mainly into the following groups (Alexy et al., 2004; Gros et al., 2010): cephalosporins (68.1%, 779 g/month), fluoroquinolones (9.5%, 108 g/month), aminoglycosides (4.3%, 48.8 g/month), carbapenems (3.8%, 43 g/month), oxazolidinones (1.5%, 17.3 g/month), lincosamides, (1.4%, 17 g/month), tetracyclines (0.1%, 0.7 g/month) glycopeptides (0.1%, 0.6 g/month) and other antibiotics (11.2%, 128 g/month). The major active substances in the antibiotics administered in the clinic as well as the form of antibiotics (tablet or injectable) are listed in Table 2. Furthermore, it should be noted that the antibiotics administered to patients of the clinic in liquid form were mainly (66.4%) cefuroxime, ciprofloxacin, metronidazole, and doxycycline, while in the form of tablets were only (100%) cefuroxime, ciprofloxacin and doxycycline.

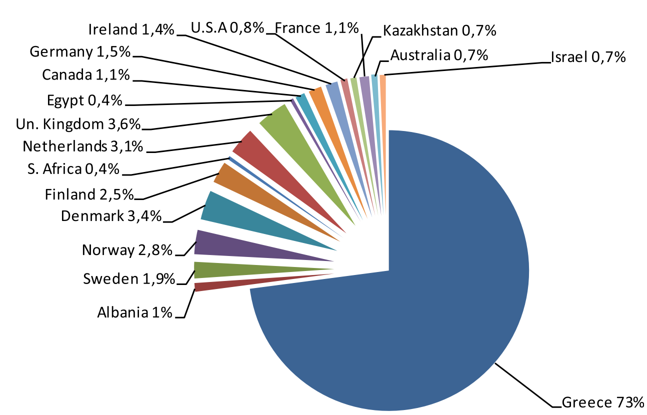

Fig. 1. Nationalities and percentage of combined number of patients hospitalized in the clinic from June to December 2018.

Table 2
Active substances in the antibiotics most frequently administered by the private clinic.

Active substance	Form		
	Tablet	Injectable	
	concentration (mg)	concentration (mg)	solvent volume (mL)
Amikacin	–	500	100
Cefuroxime	500	750	100
Ciprofloxacin	500	400	200
Clindamycin	–	600	100
Doxycycline	100	–	–
Levofloxacin	500	500	100
Linezolid	–	600	300
Metronidazole	500	500	100

6. Results

The monthly averaged urine volumes produced at the various departments of the clinic, which eventually were disposed of directly into the municipal sewer network during the period of this study are listed in Table 1. Note that both the total urine and the urine volumes containing antibiotics are also presented in Table 1. The monthly averaged total urine disposed of into the sewer network was 3,263 L, whereas the monthly averaged urine produced by patients who had received antibiotics was 1,331 L. Therefore, a substantial percentage (40.8%) of the urine disposed of directly into the municipal sewer network contained antibiotics. It should be noted that the volumes containing antibiotics are somewhat underestimated because the database of the clinic does not include information about staff members who had also received antibiotics. Also, it should be noted that due to incomplete documentation in the records of patients younger than 18 years old (e.g. body weight), this group, which constituted only 3.5% of the total number of patients of the clinic, was not treated separately.

It was estimated that patients who were hospitalized overnight at the private clinic received on the average of 38.1 g/day of antibiotics, which corresponds to 4.2 g/day of antibiotics per patient-bed. This consumption rate is similar to the literature values for a healthcare unit where the average consumption of active substances was reported as 4.27 g/day, for active substances in fluoroquinolones 3.8 g/day, and for active substances in other antibiotics 2.2 g/day (Dinh et al., 2017a).

The data collected suggested that the most frequently administered active substances in the clinic (89%) belonged to the groups of the antibiotics cephalosporins, fluoroquinolones and other antibiotics. These active substances have been reported to persist for a long time in the environment, due to their strong resistance to hydrolysis processes (Huang et al., 2001; Golet et al., 2002). It has been estimated that the active substances in cephalosporins persist in the environment from just a few days to over 200 days, while the active substances in fluoroquinolones persist in the environment, and particular in the aquatic environment, several hundred days (Kümmerer, 2001). Consequently, these substances are more likely to affect aquatic living organisms and particularly the fish, in the long run rather than the short run. Consequently, these active substances in the effluents from the private clinic, if eventually enter the aquatic environment, which is very likely to happen, will have some detrimental effects on the aquatic life over time.

The active substances in the group of the antibiotics cephalosporins are not only persistent, but also sorb poorly onto the soil particles and sediments. However, more active substances are expected to sorb onto suspended colloids than to soil surfaces because colloids have high surface area per unit mass (James et al., 2005). Therefore, pharmaceuticals in presence of colloids may migrate long distances within environmental systems (Xing et al., 2016), because colloid particles serve as carriers for the dissolved substances and consequently can significantly influence their migration (Abdel-Salam and Chrysikopoulos, 1995). Active substances in the group of the antibiotics fluoroquinolones, do not exhibit significant degradation in the marine sediments, which has been observed as low as 0.06% after 83 days. (Marengo et al., 1997).

7. Discussion

Evaluation of the effluents from five hospitals with different sizes in Germany, which offered similar services to patients as those reported in this study for a private clinic in the island of Crete, revealed that the healthcare units despite their great difference in size, produced almost the same concentrations of active substances found in common antibiotics (Kümmerer and Henninger, 2003). Furthermore, the average concentrations of ciprofloxacin and norfloxacin, which are present in the group of antibiotics fluoroquinolones were found to be at comparable levels in the effluents from healthcare units in Europe, America, and in developing countries, such as Vietnam (Brown et al., 2006; Duong et al., 2008). Therefore, healthcare units around the globe, almost regardless of their size produce effluent wastewater, with concentrations of active substances found in antibiotics which are relatively similar to those reported in this study for a private clinic in the island of Crete.

8. Environmental risk assessment

The results of this study reveal that numerous active substances of antibiotics received by the patients of a private clinic in the island of Crete are known to resist degradation in marine sediments and to persist for a long time in the environment. The active substances of antibiotics are disposed via the municipal sewer network into the aquatic environment of the city, without any special treatment for many decades. The seasonal influence is also an important issue because the loads of antibiotics were much higher in the summer than other seasons. Given that these substances act like pollutants, important questions are raised about existing and future concentrations of these active substances of antibiotics in the aquatic environment. The active substances of antibiotics have been identified as a possible future hazard for the region of Crete, and consist a possible threat to algae and fish that exist in the region (Pereira et al., 2015).

Certainly, long-term studies on the effects of antibiotics to the marine environment are of significant importance in order thoroughly evaluate their impact. Marine cyanobacteria tests are recommended, because these tests include bacterial species that account for variability and sensitivity between species such as *Anabaena* and *Synechocystis*, which are very sensitive to antibiotics (Halling-Sorensen et al., 2000; Hense et al., 2013).

9. Conclusions

The present analysis of the data from a private clinic in the island of Crete revealed that urine volume produced by the patients of the clinic, which is disposed directly into the municipal sewage network, contained active substances of antibiotics that are comparable to other health units throughout the globe. However, the active substances of antibiotics are practically environmental contaminants that significantly persist in the environment and particularly in aquatic systems with potential detrimental effects on aquatic living organisms. This study indicated that direct disposal into a sewage network should no longer be a recommended option, because it has been proven through studies that the use of on-site wastewater treatment plants can substantially reduce the concentration of antibiotics like fluoroquinolones, as is the case of ciprofloxacin in which has been reported to reach 86% reduction (Duong et al., 2008). This constitutes an effective solution, which in the long term could be environmentally beneficial and more cost effective (Pauwels and Verstraete, 2006).

Conflict of interest

All authors have participated in (a) analysis and interpretation of the data; (b) drafting the article or revising it critically for important intellectual content; and (c) approval of the final version.

This manuscript has not been submitted to, nor is under review at, another journal or other publishing venue.

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