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Hospital Antibiotics Usage: Environmental Hazard and Promotion of Antibiotic Resistant Bacteria

N. Chamkal[1,2], I. Lhlou[1,2], L. Bandadi[1,2], K. Ounine[1]

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Parole chiave: Antibiotici, reflui ospedalieri, pericolo, resistenza agli antibiotici

Abstract

Introduction. *Hospitals constitute a particular source of drug residues emission, especially antibiotics considered as the most critical therapeutic classes used in hospitals. Thus, the hospital wastewater can widely spread both types of emerging pollutants, antibiotic residues and antibiotic resistance bacteria. For this reason, antibiotics usage must be monitored. This study was conducted to investigate potential antibiotic compounds which can present potential environmental hazard and promote antibiotic resistance.*
Methods. *The consumption-based approach was adopted to calculate predicted antibiotic concentrations in hospital wastewaters. In the process, we assessed the antibiotics potential environmental hazard, with the hazard quotient between predicted concentrations and predicted no effect concentrations intended to be protective of ecological species. In order to evaluate the hospital contribution to antibiotic resistance bacteria promotion, we also compared predicted concentrations with predicted no effect concentrations as theoretical selective resistance bacteria.*
Results. *The highest expected concentrations in hospital wastewater were found for Penicillins and Cephalosporins being the most prescribed antibiotics in our context. We noted that among this class, Ampicillin is the most hazardous compound followed by Imipenem and Gentamicin as exclusive hospital use antibiotics, in spite of their low consumption. The results showed also that Ampicillin, Amoxicillin, and Ceftriaxone had a high ratio of potential antibiotic resistance bacteria promotion, confirming the correlation found previously between abundance of resistant bacteria and the corresponding effluent antibiotic concentrations. Nevertheless, the promotion of resistance selection can also be attributed to Imipenem and Ciprofloxacin as little-used antibiotics and occur at low to moderate levels in hospital wastewater.*
Conclusion. *This study identified the profile antibiotics consumption and their potential environmental hazard contribution and antibiotic resistant bacteria promotion. It can help decision-makers make appropriate management decisions, especially preventive measures related to antibiotic use pattern, as neither dilution nor treatment can eliminate antibiotic residues and antibiotic resistance genes.*

[1] *Laboratory of Biology and Health, Faculty of Science, Ibn Tofaïl University, Kenitra, Morocco*
[2] *Higher Institute of Nursing Professions and Technics of Health, Rabat, Morocco*

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Introduction

No aquatic environment is free of drug residues. Several compounds have been detected in sewage and surface, marine, and drinking waters (1-3). These micropollutants constitute a potential environmental hazard, although they are present at low doses (3-5). This hazard is because the adverse side effects that drug residues may have on wildlife and ecosystem health at low doses and long-term exposure are still largely unknown (3). Furthermore, organisms are rarely exposed to a single compound but rather to a cocktail of drug residues in varying concentrations (5). Besides, the potentially toxic effects of wastewaters could differ from the sum of the effects of individual compounds (3, 6).

The consumption phase is considered the most significant contributor to the emissions of drug residues into the environment (7). Once administered, drugs are metabolized to varying degrees and excreted in urine and feces as metabolites and unchanged parent compounds (3, 7).

The hospital sector constitutes a particular source of singular drug residue emission, leading to higher concentrations in wastewaters and a potential threat to the environment (8). Excreted drugs from patients find their way into hospital effluents (7). These effluents have a specific profile. They contain significant quantities of various drug residues, especially x-ray contrast media and antibiotic compounds (5). The antibiotic compounds should be of most concern regarding their persistence (9), and their relationship with increasing antibiotics resistance (10-13), and antibiotics susceptibility to accelerate the evolution and dissemination of antibiotic resistant genes in water (14).

The Hospital wastewaters (HWWs) widely spread both types of emerging pollutants, antibiotics residues and antibiotic-resistant genes (ARGs), associated with bacteria of clinical relevance and with antibiotics used mainly in hospitals (15). The HWWs raw and treated contribute to the spread of these emerging pollutants in the receiving environments (5, 7, 10, 15-17). Therefore, it is interesting to monitor antibiotics for the environmental risk assessment (6). Thus, the wastewaters characterization needs to be implemented in each country (18), since HWWs characterization can vary according to country, hospitals, and hospital specialties (6).

To our knowledge, nobody carried on investigations on drug residues in HWWs of Morocco so far, but only researches on physico-chemical, bacteriological and parasitological parameters. In addition, hospital effluents reach the wastewater sewer system without prior treatment, and no Moroccan standards on drug residues in hospital effluents have been promulgated (19, 20). On the other hand, the wastewater treatment sector in Morocco is expected to develop in the coming years (21). Furthermore, the Ministry of Health is also interested in the rational use of antibiotics in health facilities, combined with any treatment. The current study constitutes a preliminary investigation to identify antibiotic usage patterns, their expected concentrations in HWW, their potential environmental hazard, and their contribution to develop Antibiotic Resistant Bacteria (ARBs).

Materials and methods

The predicted antibiotic concentrations are determined based on their consumption. This approach is essential to identify compounds that may potentially require monitoring (8, 22) since the concentrations predicted, based on hospital antibiotics consumption data, showed good precision (23) and differed, for most cases, by less than one order of magnitude from the measured concentrations in the hospital effluents (8). At the same time, the prioritization of

which antibiotics should be measured is not a straightforward task (24). In addition, the required instrumental equipment is quite expensive, both to acquire and to maintain (25). Thus, nearly all water samples of studies conducted in Africa, except for South Africa, were analyzed in industrialized countries (26).

This study was carried at a Moroccan University Hospital, 781 beds with a 74.5% occupation rate. The total volume of water consumed in that hospital was 77,887 m3/ year, equivalent to 223.3 m3/day. The Department of Pharmacy provided the quantities of antibiotics consumed over three years (2016, 2017, 2018) at all hospital Departments. Only the antibiotics used during the three years were studied. Then, for each antibiotic, the total consumed was calculated as an average amount from data consumption.

To obtain the total amount of each compound, the concentrations of actives substances were converted into mass units. In the case of combined drugs, we considered only the weight of individual active substances.

The amount potentially released into the hospital effluents was calculated according to the compound excretion rates derived from peer-reviewed pharmacokinetic studies. We considered only the mean value compound excretion rate as the unchanged parent form. Then, the predicted HWWs' antibiotic concentrations (PCs) were calculated by dividing the amount released in the hospital effluent as unchanged form, by the volume of water consumed per day, multiplied by 10^6 as change factor unit g to µg.

$$\mathrm{PC}\ (\mu g/L) = \frac{Compound\ amount\ \left(\frac{g}{d}\right) * Excretion\ Rate/100}{Volume\ of\ Water\ consumed\ \left(\frac{L}{d}\right)} * 10^6$$

We performed The Spearman test, using the SPSS software, to study the correlation between antibiotic PCs in HWWs and their consumed quantity.

Table 1 - PNEC-Environment and PNECs for resistance selection values of studied antibiotics

Antibiotic compound	PNEC-Env	PNECs for resistance selection
Clavulanic-Acid	56	64
Amoxicilin	Nd	0.25
Ampicilin	0.87	0.25
Cefalothin	Nd	2
Cefipime	Nd	0.5
Ceftazidime	1.3	0.5
Ceftriaxone	10	0.032
Cefuroxime	0.84	0.5
Ciprofloxacin	0.45	0.064
Flucloxacillin	Nd	Nd
Levofloxacin	7.4*	0.25
Moxifloxacin	0.18*	0.125
Imipenem	0.41	0.125
Ertapenem	14	0.125
Gentamicin	0.2	1
Isoniazid	Nd	0.125
Linezolid	6.7*	8
Metronidazole	40.6*	0.125
Peperacillin	Nd	0.5
Sulbactam	Nd	16
Sulfadiazine	720	Nd
Tazobactam	44	Nd
Teicoplanin	Nd	0.5
Tigecycline	2	1
Vancomycin	Nd	8

Nd: No data; PNEC-Env (27); PNEC-Env* (28); PNECs for resistance selection (28)

To assess the Antibiotic potential environmental hazard, the HQ stated as the quotient between the PC and the predicted no effect concentration (PNEC): PC/PNEC was calculated (European Commission, 2003). For that purpose, the PNEC-Environment (PNEC-Env) values, intended to be protective of ecological species, were used (Table 1) (27, 28).

The quotients were classified into four risk levels: insignificant at PC/PNEC-Env ≤ 0.1, low at 0.1< PC/ PNEC-Env ≤ 1,

moderate at 1< PC/ PNEC-Env ≤ 10 and high at PC/ PNEC-Env >10 (29).

In order to evaluate the contribution of Hospital on ARB promotion, we compared PCs in HWW with the theoretical selective resistance bacteria values (PNECs) indicated in Table 1 (28).

Results

Profile of Antibiotics usage and their expected concentrations

The results revealed that the antibiotics use can reach 46 g/bed/y for a single type, while the totality of the antibiotic compounds represented an amount of 219 g/bed/y. As observed in Figure 1, the most consumed antibiotic was Ceftriaxone, followed by Ampicillin / Sulbactam in the same rank, and Amoxicillin as the third.

Lower consumption was observed among other antibiotic families. The amount consumed of the majority of Fluoroquinolone compounds didn't exceed 1kg/y and only Ciprofloxacin had an amount of 1.3392 kg/y. Similarly, Glycopeptides and Aminosides were consumed at low quantities, only 0.491 kg/y of Vancomycin was used in our context. Also, it was noted that only two compounds among Carbapenem, Ertapenem and Imipenem, were used with an amount exceeding slightly 2 kg/y for Imipenem.

The consumption leads to the emission of drug residues in HWW. The quantity excreted as unchanged form of antibiotics and reaching HWW was more than half (55.93%) of the amount of antibiotics consumed. Figure 1 revealed the highest values of PC in HWW for the most consumed antibiotics. It should be noted that Ampicillin and Sulbactam had a very high PC in HWW: 321.87 µg/L and 301.75 µg/L, respectively, followed by Amoxicillin at 172.76 µg/L.

Within Cephalosporin class, Ceftriaxone and Cefalothin were more consumed and

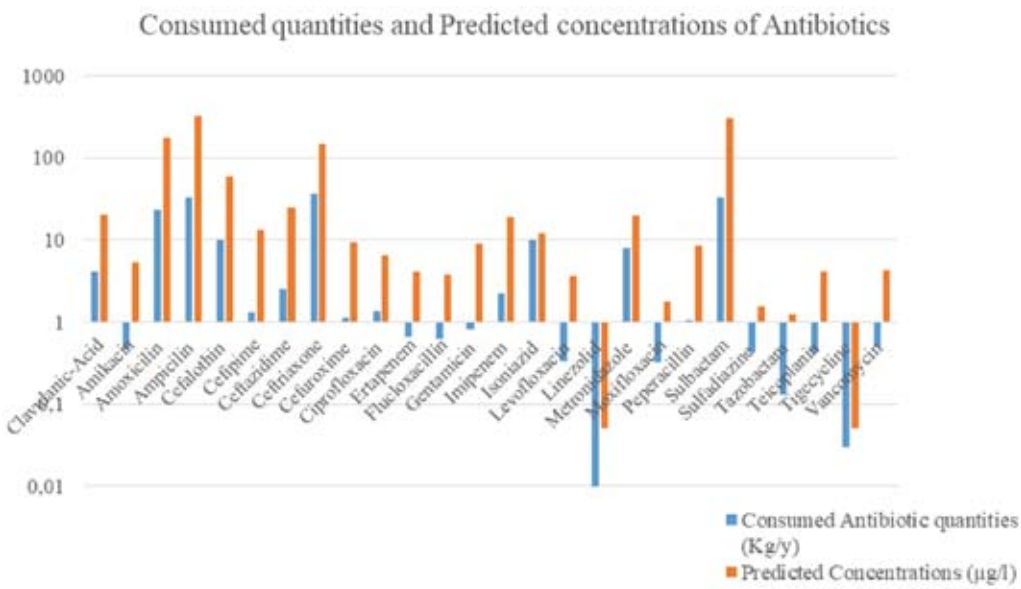

Figure 1- Antibiotic usage patterns and their Predicted concentrations in HWW

they were expected at high levels in HWW, with PC at 146.58 µg/L and 60.47 µg/L, respectively. For other Cephalosporin compounds, the PCs were estimated at moderate level in ascending order of weight for each one. Imipenem among Carbapenem compounds was expected at moderate concentration (19.05 µg/L) as well.

Considering other antibiotic classes, the findings showed low PCs for Fluoroquinolone compounds. Only Ciprofloxacin was estimated at 6.6 µg/L in HWW. The lowest concentrations were noted for Metronidazole and among Glycopeptides and Aminosides compounds, between 4.14 µg/L and 9.12 µg/L.

Overall, a significant correlation was found in the HWW between PCs of antibiotics studied and their consumed quantity (Spearman's test: $r = 0.956$, $p < 0.001$). Nevertheless, the PC depended not only on the quantity consumed, but also on the excretion rate of each compounds. Thus, Ceftriaxone consumed in greater quantity (36.2 kg) than Ampicillin (32.79 kg) had a lower concentration (146.578 µg/L) than the last one (321.872 µg/L). On the other hand, a higher PC was found for one antibiotic consumed less than another, for example 19.05 µg/L for Imipinem (2.22 kg) and 12 µg/L for Isoniazid (9.78 kg). We also found the same concentration for Cefuroxime and Gentamicin, which had different amounts consumed, 1.13 kg and 0.81 kg, respectively. Therefore, the association will be appropriately established for each antibiotic during a given period to demonstrate the link between its consumption and its PC in the HWW.

Environmental Hazard and Antibiotics Resistant Bacteria

Figure 2 shows the environmental HQ of the studied antibiotics whose PNEC-Env are available. It indicates that seven compounds had a high HQ, one compound presented a moderate hazard, and the remaining eight compounds were distributed equally at low and insignificant environmental hazard. The high level of HQ is attributed to Ampicillin and all Cephalosporin antibiotics particularly Ceftazidime and Ceftriaxone. Also the findings consider Gentamicin and Imipenem as highly hazardous antibiotics.

As regards the three Fluoroquinolone

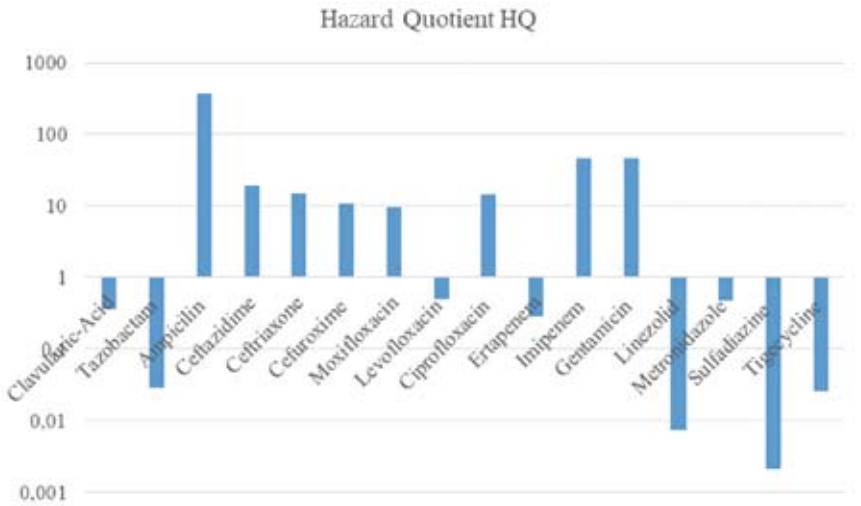

Figure 2 - Environmental Hazard Quotient of studied antibiotics

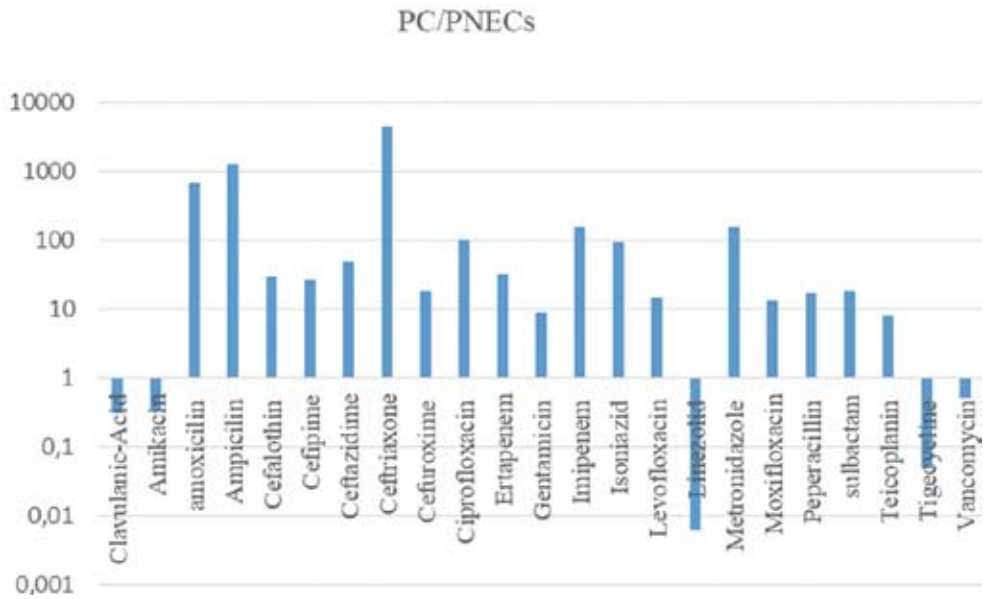

Figure 3 - ARB Quotient (PC/ PNECs for resistance selection)

antibiotics studied, they were distributed in low, moderate and high HQ, observed only for Ciprofloxacin.

In term of potential ARB promotion, the ARB quotient was higher for almost all of the antibiotics studied as indicated in Figure 3. Out of 18 antibiotic compounds evaluated, this quotient was more than 1,000 time for three compounds; more than 100 for four compounds, one antibiotic had 96. And for five antibiotics it varied between 8 and 50 times, while only five compounds had a PC less than PNECs. The Penicillin and Cephalosporin antibiotics had a high quotient of potential ARB selection. It was between 690 and 4,681 times for Amoxicillin, Ampicillin, and Ceftriaxone. For the Carbapenem class, PC for Imipenem occurred 150 times more than PNECs and only the Ciprofloxacin as part of the Fluoroquinolone antibiotics had a PC 100 times more than PNECs.

The lowest ARB quotients were noted among Aminosidic and Glycopeptide antibiotics, which had PCs not exceeding 10 times their PNECs for Gentamicin and Teicoplanin, and even less for Amikacin and Vancomycin.

Discussion

The most consumed antibiotics were Ceftriaxone, Ampicillin/Sulbactam, followed by Amoxicillin. These results were supported by previous findings which confirmed that Penicillins and Cephalosporins are the most prescribed antibiotics (30, 31). In this line, Ceftriaxone was classified as the most used (32). However, other studies attributed this rank to Piperacillin (22, 33), which is consumed slightly in our context. Also, Ampicillin and Sulbactam were classified within the first antibiotics used (2nd and 4th, respectively, among 20 antibiotics) (22). Some authors have identified Amoxicillin as the most used antibacterial, as it represents a treatment of choice for a number of bacterial infections (5, 33, 34). Contrary to what is observed in Brazilian Hospitals, where

it ranked 15th among the twenty antibiotics most consumed (22).

In contrast to our results and those reported by another study (35), the Fluoroquinolones class is described as highly consumed in other contexts, especially Ciprofloxacin (16). In the same way, Imipenem among Carbapenem, Glycopeptides and Aminosides, slightly consumed in our context. They are frequently used and most abundant in other sites (30): For example, 27.382 kg/y of Vancomycin was used in a Brazilian Hospital (22) while it didn't exceed 0.5 kg/y in our context.

In fact, the rate of excretion and the amount of the compound consumed can have a strong influence on the presence of the compounds in HWW (8). And the greater usage leads to higher load into the environment (36). The findings showed that the amount of antibiotic residues that reach the HWW as unchanged form was more than half of the amount of antibiotics consumed. In this line, previous results showed the significant correlation between the quantity of some antibiotics and their concentration in HWWs (16). It is revealed that Ampicillin and Sulbactam, being the most used, had the highest PCs. The same observation was raised for Ampicillin by (32). Also the highest concentration expected for Amoxicillin was supported by other studies (10, 37). But they differ from those found by (22), who identified its PC value at the low end of range [10, 100] µg/L, explained by the low consumption of this compound. This observation was noted for Piperacillin used slightly in our context, contrary to the results reported by (32), because it was more consumed.

The Ceftriaxone was expected at high level in HWW among Cephalosporin class, confirming the results found by (32). But in other contexts, it was predicted at moderate level [21.6-47.8] µg/L (10). Also the PC found for Ceftazidime was observed within the expected range of values presented by (10, 22).

In agreement with the reports of (32), the Fluoroquinolone compounds were expected at low concentration. Ciprofloxacin was expected at 6.6µg/L in HWW due to its high excretion rate as original form. Contrary to other contexts, among antibiotic families, Fluoroquinolones were detected at the highest concentrations, especially in hospital effluent samples (15, 16) with significant correlation with their quantity consumed (16).

Among Carbapenem compounds, Imipenem is expected at moderate PC within the range of predicted values [2.2-19.6] µg/L found by (10), and detected at 14.42 µg/L in Hospital effluent (17).

The lowest concentrations were noted among the lowest consumed antibiotics such as Glycopeptides and Aminosides compounds and Metronidazole. Contrary to other studies which showed that this last compound had high predicted and measured concentration in HWW as most consumed (15, 16, 22, 23, 38). In this sense a significant correlation was found between this antibiotic concentration in wastewater before treatment and its quantity consumed (16).

As mentioned above, it can be seen that the variations in the antibiotics administered in each facility may be reflected in antibiotic occurrence noted in HWW (17).

Environment Hazard assessment of antibiotics studied

The highest HQ is attributed to Ampicillin, similarly to assessment reported by (32). This compound is characterized by non-biodegradability, bioaccumulation and persistence (39). Also, Sulbactam and Amoxicillin may present a potential environmental hazard similar to Ampicillin, according to their highest PCs, although we cannot calculate their HQ in the lack of PNEC-Env. Because the environmental risk of a given

compound cannot be excluded, as there is no data to calculate the HQ and no ecotoxicity data are available (29). In this way, some studies suggest that Amoxicillin should be considered as a pollutant of high priority in the environment because the scientific knowledge is less than enough to fully assess the risks that it poses to the environment (13, 40).

In the same line, all Cephalosporin antibiotics studied had high level of HQ. They had been expected at high level of aquatic environmental risk by previous studies which suggest to monitor their usage and emission (32). This antibiotics class has great persistence independently of their amount when introduced into the environment. The results showed higher HQ of Ceftazidime and Ceftriaxone and can present an environmental risks. In Kazakhstan, it's confirmed that Ceftriaxone present the highest exposure indices in surface water (41). And the concentration of Ceftazidime has increased by approximately 74% in treated wastewater compared to raw hospital wastewater (17).

Our findings assessed also Gentamicin and Imipenem as high hazardous antibiotics. Previously, the usage patterns of all Carbapenem was assessed of high environmental risk, and ranked Gentamicin in medium level risk (32). In contrast, one study assessed Imipenem at low HQ (= 0.046) calculated with PNEC = 78 µg/L higher than the one used in our study (PNEC-Env) = 0.41µg/L). However, the authors concluded that this compound could contribute to a synergic toxic effect (30).

As for Fluoroquinolone compounds, Ciprofloxacin had high level of HQ. This compound was predicted had medium environmental risk (32). But assessed at high HQ based on measured concentration in HWW (6, 35). In sum, the hospital fraction of this compound presents a high risk to aquatic ecosystem. In fact, the measured concentration was close to the predicted concentration (38).

Finally, this study indicates that HWW studied is a potential source of environmental hazard, given that nearly half of the antibiotics studied have a high HQ. Some studies have shown that certain high-risk antibiotics in HWW were also those found at high levels of potential toxicity in influents and effluents from wastewater treatment plants (9). Furthermore, all antibiotics have high level of persistence (7). Consequently, the incomplete removal of antibiotics in Wastewater treatment plants severely affected the receiving water (15). Therefore, the HWW was considered to exhibit strong environmental and toxicological risks (6).

Assessment of Antibiotic Resistant Bacteria

The highest ARB quotient was registered among Penicillin and Cephalosporin family most used and expected in HWW study site especially for Amoxicillin, Ampicillin, and Ceftriaxone. In this sense, the significant correlation between abundance of resistant bacteria and the corresponding effluent antibiotic concentrations was reported (42). 60% of the isolates from the hospital effluents were resistant to up to six antibiotics, including molecules mostly used in the hospital such as Cephalosporin (30). And 62.83% of the isolates were resistant to Ampicillin (35). In addition, the results of study carried by (43) have shown that isolates bacteria encoding resistance to Ampicillin and Ceftriaxone were found in treated HWW more than 80% and 59%, respectively . Also, it is noted that more than half of *Enterobacteriaceae* and *S. aureus* isolates from HWW confer resistance to Ceftazidime (6).

On the other hand, the correlations between concentration of antibiotics and ARGs increase were showed (15). The ARGs conferring resistance to Cephalosporin (44)

and to b-lactams (17) were found in HWW. Such as bla genes (15, 45). This type of ARG often coexist with other antimicrobial resistance determinants and can also be associated with mobile genetic elements, increasing the possibility of multidrug resistance and environmental dissemination HWW as major source of environmental ARGs (45).

Within the Fluoroquinolone, the presence of Ciprofloxacin in the hospital effluent raised the question of potential selective pressure exerted on local microorganisms (35) although it was used slightly, similar to our findings. In this line, 27.3% of isolates from HWW confer resistant to Ciprofloxacin were detected (46). Such as *Klebsiella pneumonia* and the isolated *S. aureus* was susceptible (6). Moreover, the resistance to this antibiotic type was observed among bacterial isolates from untreated and treated wastewater (43). Furthermore, ARGs conferring resistance to Fluoroquinolone antibiotics were found (44), the reduced susceptibility to Fluoroquinolones was dominant, and its concentration increase after treatment (15, 35). And it is responsible for the dissemination of quinolone resistance markers detected among others, in *Klebsiella pneumonia and Klebsiella oxytoca i*solates (35).

Considering Carbapenem class, Imipenem presents high quotient of ARB selection even if it is used at low quantity. It is confirmed that this compound constitutes a real risk of selecting bacteria resistant (35) and the resistance is restricted to isolates from hospital effluents as exclusive antibiotic hospital use to treat patients with severe infections (31). Thus, 22.1% of the viable cells from biofilms formed in the hospital effluent were resistant to Imipenem (30) such as 80% of *P. aeruginosa* isolates (46).

Aminosidic and Glycopeptide antibiotics had the lowest ARB quotient. Nevertheless, in other contexts the resistance of Vancomycin and Gentamicin was observed respectively, among 50% and 100% of *S. aureus* (43, 46). The health risk raised by the presence of *S. aureus* resistant to Vancomycin is the transfer of these resistance genes to hospital strains (46). In our context, no resistance to Vancomycin has been found in strains of *S. aureus* involved in urinary tract infections (47).

In sum, the HWW studied contains high concentrations of antibiotics exceeded the PNECs. It can be concluded that the antibiotics use at the hospital study site can promote antibiotic resistance. In fact the high doses of antibiotics used in hospitals constitute a strong selective risk factor on the appearance and development of multiresistant bacteria (31) and contribute to the spread of ARB / ARG in the receiving environment, because neither dilution or treatment can remove these emerging pollutants (15, 17, 44, 48). By contrast, they can increase after HWW process treatment. In this line, previous studies have demonstrated the increase and persistence of the resistant bacteria proportion after treatment process (43, 49), such as the clinically relevant resistance genes to Vancomycin and Imipemem (31).

Conclusion

Having identified the profile of antibiotic consumption, the present study concludes that HWW constitutes a potential source of environmental hazard and promotes antibiotic resistance. Therefore, the decision-makers should make appropriate management decisions, especially in connection with preventive measures related to antibiotic use patterns, as neither dilution nor treatment can eliminate antibiotic residues and antibiotic resistant genes (ARGs).

Legenda

HWW: Hospital wastewater
ARB: Antibiotic Resistant Bacteria
ARGs: Antibiotic-Resistant Genes

PC: Predicted concentration
PNEC: Predicted no effect concentration
PNEC-Env: Predicted no effect concentration-Environment
PNECs: Predicted no effect concentration for resistance selection
HQ: Hazard Quotient

Riassunto

Utilizzo degli Antibiotici in Ospedale: Rischio Ambientale ed Incremento dell'Antibiotico-Resistenza

Premessa. L'ospedale costituisce una particolare sorgente di residui di farmaci, in particolare di antibiotici, i quali rappresentano la più critica delle categorie di farmaci usati in ospedale. Pertanto, i reflui ospedalieri possono rappresentare il serbatoio di due tra i più importanti inquinanti, gli antibiotici ed i geni batterici di resistenza ad essi associati. Il presente studio è stato condotto per identificare quei composti che possono rappresentare un pericolo per l'ambiente e promuovere l'emergere di resistenze batteriche.

Metodi. Un approccio basato sui consumi è stato utilizzato per stimare la concentrazione di antibiotici nei reflui ospedalieri. Da qui abbiamo valutato il pericolo potenziale degli antibiotici per l'ambiente, confrontando il quoziente di pericolo tra le concentrazioni effettive presunte e le presunte concentrazioni senza effetto sulle specie ambientali. Ulteriormente, per valutare il contributo dell'ospedale alla promozione delle specie batteriche antibiotico-resistenti, abbiamo confrontato le concentrazioni stimate nei reflui con le concentrazioni stimate che non influenzano la selezione dei batteri stessi.

Risultati. Le più elevate concentrazioni attese nei reflui ospedalieri sono risultate quelle di Penicilline e Cefalosporine, in quanto gli antibiotici più prescritti nelle nostre realtà. Abbiamo notato che, nella sua classe, l'Ampicillina è il composto più pericoloso, seguito da Imipenem e Gentamicina come antibiotici di esclusivo uso ospedaliero, a dispetto del loro limitato utilizzo. I risultati hanno anche mostrato che Ampicillina, Amoxicillina e Ceftriaxone possedevano un elevato potenziale tasso di promozione dell'antibiotico-resistenza, confermando l'associazione prima evidenziata tra l'abbondanza di batteri resistenti e le corrispondenti concentrazioni d'antibiotico nei reflui ospedalieri. Purtuttavia, la promozione della selezione alla resistenza può essere imputata anche ad Imipenem e Ciprofloxacina, che sono antibiotici scarsamente usati, con presenza limitata ed a basse concentrazioni nei reflui ospedalieri.

Conclusioni. Il presente studio ha identificato il profilo di consumo degli antibiotici ed il loro potenziale contributo al pericolo ambientale ed allo sviluppo dell'antibiotico-resistenza. Può aiutare i decisori a formulare decisioni gestionali appropriate, in particolare nel campo delle misure preventive nell'uso degli antibiotici, in quanto né la diluizione né un trattamento particolare possono eliminare i residui di antibiotici, né i geni dell'antibiotico-resistenza.

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Corresponding author: Nadia Chamkal, Laboratory of Biology and Health, Faculty of Science, Ibn Tofaïl University, Kenitra, Morocco
e-mail 1: nchamkal@yahoo.fr
e-mail 2: nadia.chamkal@uit.ac.ma