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Environmental Evidence

SYSTEMATIC REVIEW PROTOCOL

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Diversity of antibiotics in hospital and municipal wastewaters and receiving water bodies and removal efficiency by treatment processes: a systematic review protocol

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Abstract

Background: Antibiotics are extensively discharged into the environment through sewages. These emergent contaminants cause health and environmental risks by toxicity, allergic impacts, non-biodegradability and more importantly advancing antibiotic resistance. Antibiotics are hardly removed by conventional treatment processes and frequently are being reported in aquatic environments. The systematic review outlined in this protocol will compile and synthesize literature on the variety and concentrations of antibiotics in wastewaters and receiving water resources. Also, the review will address the efficiency of treatment processes in elimination of antibiotics from aqueous solutions. Outcomes of the study could help wastewater treatment plant engineers with providing reliable design data and outline a road map for future researches.

Methods: The review will be performed according to the Collaboration for Environmental Evidence (CEE) guidelines for systematic review and evidence synthesis in environmental management, and will be reported according to ROSES reporting standards for systematic evidence syntheses. The published articles will be screened by considering the defined inclusion and exclusion criteria at the title, abstract and full-text levels. Included studies will be exposed to a critical appraisal for validity and quality assessment. The articles will be assessed on the susceptibility to bias and the studies with high bias will be excluded from the data synthesis. The data from included studies will be combined into a narrative synthesis. Random effect Meta-analysis will be conducted due to the likely range of underlying effects. If the heterogeneity exists, the source of heterogeneity will be sought by met-regression and subgroup analyses.

Keywords: Review, Protocol, Antibiotic, Pharmaceutical, Wastewater, Sewage, Hospital, Municipal, Removal efficiency

Background

Hospital wastewaters are one of the most toxic divisions of municipal wastewaters due to containing numerous hazardous and emergent micro-pollutants such as pharmaceuticals, heavy metals, adsorbable organic halogens, iodized X-ray contrast media, cytostatic agents, residual of chemical compounds used in laboratories, disinfectants, radioisotopes, and also variety of pathogenic microorganisms [1, 2]. Generally, hospital wastewaters is discharged into the publicy owned treatment works (POTWs) with or without pretreatment [1]. In POTWs, the trace contaminants could not be entirely removed by the conventional wastewater treatment technologies and then, are partially or completely discharged into the environment [3, 4]. Among the above listed contaminants,

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antibiotics are always considered with principal priority concerns due to the adverse effects on human health and deteriorating natural ecosystems [5]. Antibiotics are partially absorbed in the human body and the insufficient metabolism could change the chemical structure into more polar and soluble by-products [6]. Then, the main part of antibiotics is entered into the sewerages unchanged or as an active or inactive metabolites [7]. The major concern on antibiotics is generating bacterial resistant genes in the environment [8], which could cause increase in patients treatment period and extend hospitalization time and consequently more consumption of antibiotics and finally, increasing in health care expenditures [9, 10]. In the United States, antibiotic-resistant bacteria bring about at least two million cases of infection and 23,000 mortalities per year imposing an annual cost of 55–70 billion dollars [11]. According to the World Health Organization report on antimicrobial resistance surveillance system in 2014, microbial resistance is no longer a prediction for the future, and is now happening around the world and poses a serious threat to common infectious diseases. Then, without immediate and coordinated measures, the world would come back to the history before antibiotics and common infections and minor injuries could once again make happen terrible mortalities [12, 13]. On the other hand, the residue of antibiotics could advance adverse effects on the soil ecosystem, microorganisms, and crops and finally could enter food chain through irrigation with wastewater effluents and by land applications of biosolids [14, 15]. Antibiotics have been detected in hospital wastewaters [16], influent and effluents of municipal wastewater treatment plants [17, 18], soil, water resources and even drinking waters [19]. Meanwhile, antibiotics and their metabolites are not completely removed by the conventional wastewater treatment processes [20]. According to the literature, various quantities have been reported for elimination of antibiotics with physico-chemical [21], biological [22], and advanced oxidation processes [23, 24]. Removal of antibiotics by biological treatment processes are affected by the physicochemical properties of antibiotics such as water solubility, octanol/water partitioning coefficient, and principal plant design aspects including solids and hydraulic retention times and organic loading rates [8, 25–28]. In some studies in Italy, Iran, and China significant concentrations of ciprofloxacin (0.64 μg/l), clarithromycin (0.28 μg/l) [29], ofloxacin (1.43 μg/l), sulfamethoxazole (0.54 μg/l) [30], quinolones (4.91 μg/l), sulfonamide (2.91 μg/l), and macrolide (0.36 μg/l) [8] have been detected in the effluent of POTWs. Numerous studies have been conducted on the determination of concentration and fate of antibiotics in water resources and municipal and hospital wastewaters. Also, in plentiful investigations removal efficiencies of antibiotics by treatment processes have been evaluated. Then, a systematic review on the findings of these studies seems to be necessary to provide accurate and reliable data and optimize the design concepts for wastewater treatment plant designers and municipal planners and managers and outline a road map for prioritizing the future research subjects.

Objective of the review

The review will provide evidence based data on the variety and concentration ranges of antibiotics in hospital and municipal wastewaters and water resources. Also, the review will reveal accurate removal efficiencies of wastewater and or water treatment processes in reduction of antibiotics. The results could be used as design concepts in wastewater treatment plants. Finally, the systematic literature review will address the following primary and secondary main research questions:

Primary question

1. What is the type and concentration range of antibiotics in hospital and municipal wastewaters and receiving water bodies?
2. What are the comparative efficiencies of various wastewater treatment processes in the removal of antibiotics?

The PICO elements of these questions are provided in Table 4.

Secondary questions

1. What are the most abundant antibiotic members in hospital and municipal wastewaters and water resources?
2. How much are the averages and standard deviations of the concentration of various antibiotics in the hospital or municipal wastewaters or water resources?
3. How much are the effectiveness of conventional wastewater treatment processes in removing various groups of antibiotics?
4. Which design and operational conditions could affect the efficiency of treatment processes in the removal of antibiotics?
5. What is the best available technology regarding the performance in the removal of antibiotics from wastewater and water?

Methods

The review will be performed according to the Collaboration for Environmental Evidence (CEE) guidelines for systematic review and evidence synthesis in environmental management [31], and will be reported according to ROSES reporting standards [32]. This review protocol has been registered in the PROSPERO database. The protocol was prepared according to the ROSES form for systematic review protocol and could be find in an Additional file 1.

Search strategy

In order to determine a search strategy in electronic databases, the review team was asked to suggest the keywords using published reviews on the topic [33, 34]. In order to determine the content validity, search terms were re-reviewed by the members of the team. Then, in order to examine the maximum access to all papers related to the search terms, the initial search was conducted using selected keywords with high sensitivity in Embase, Web of Science, Science Direct, Scopus, and PubMed.

After the primary search of the papers, the first 50 articles were selected by relevance in terms of title, abstract and keyword and full text of the articles were reviewed by the colleagues to determine and finalize the search terms. After this step, the search strings have been revised to obtain an optimum level of both sensitivity and specificity. Sensitivity is the ability of a search to capture all relevant articles. Specificity refers to the ability of a search to accomplish only relevant articles and minimize irrelevant reaches. For the specificity, several repetitions of the keywords were used in search attempts until excluding a desirable level of irrelevant hits. To increase the sensitivity of the search it was later decided to broaden the scope of the search and not use any of the biases as search terms. Then, synonym terms will be applied and combined using the Boolean operator of "OR". Also, to prevent an increase in the number of unrelated articles in searching, the Boolean operator of "AND" will be used in combining the terms. The list of suggested search terms, search string, and how to use Boolean operators (AND, OR) are shown in Table 1. In addition, the asterisk (*) will be used to include the different search terms characters. The search strategy will be adjusted according to the instructions of each database.

Supplemental searches

The reference list of original and review articles found using search strategy will be skimmed to find any relevant articles. An email will also be sent to the authors whose paper information is incomplete to obtain any required information or in the case of not having access to the full text of the articles.

Language

A very high proportion of the research articles published worldwide currently appears in English. Then, this systematic review study will be limited to English articles that their full texts are available in the international databases. The period between 2010 and 2021 has been selected for the search time of published papers and reviewing the reference list in the articles.

Publication databases

The databases will be searched for relevant articles include:

- MEDLINE using PubMed (http://www.ncbi.nlm.nih.gov).
- EMBASE (http://www.embase.com).
- Web of Science Core Collection (https://webofknowledge.com)
- Scopus (http://www.scopus.com)
- Science direct (http://www.sciencedirect.com)

Assessing search comprehensiveness

The comprehensiveness of the search strategy was examined according to the method used by Bennett et al. [35]. First, 13 relevant papers were considered as "test set" that had the highest citation and have been published in valid journals that scored as *Q1* in Scimago Journal Ranking (SJR) site. Then, the bibliography of the "test set" articles was reviewed to determine if they are found through our search strategy, otherwise, the search strategy will be modified again (Table 2).

Update articles

If the process of systematic review is prolonged, the search will be updated by the same search strategies. In the new obtained articles, the duplicates will be removed and

Table 1 The proposed final search string for accomplishment of the searches

Search string
(water* OR wastewater* OR "waste-water*" OR sewage* OR effluent* OR influent* OR aqueous) AND (antibiotic* OR pharmaceutical*) AND (treatment* OR removal* OR elimination* OR reduction* OR degradation* OR mineralization*)

Table 2 The "test set" articles used in the comprehensiveness appraisal of the search strategy

NO	Citation	Years
1	Rashid [36]	2020
2	Verlicchi [29]	2012
3	Zhang [37]	2015
4	Rodriguez-Mozaz S [38]	2015
5	Verlicchi [39]	2015
6	Santos [40]	2013
7	Gros [41]	2013
8	Zhang [42]	2016
9	Hu 43]	2020
10	Cheng [44]	2018
11	Shahmahdi [4]	2020
12	Kovalova [45]	2012
13	Oller [46]	2011

screening will take place according to the three levels of title, abstract and full text appraisals.

Type of study

In this systematic review, the proposed study will include all descriptive and experimental articles which survey or examine presence or removing antibiotics by treatment processes from aqueous solutions such as hospital or municipal wastewaters, surface or groundwaters, tap or drinking waters or synthetic solutions. Review articles (literature reviews, systematic reviews, and meta-analysis) and letter to editor papers will be excluded. In some of these literatures valuable information could be found. However, published articles are the main references of the books. Also, books have a lag time of editing and publishing in comparison with the articles. On the other hand, most of the books are not available electronically and manual search of non-electronic resources are very time consuming.

Article screening and study eligibility criteria

Screening process

The obtained articles will be imported to a reference manager. Duplicate cases will be identified and removed. Then, the articles will be screened at three levels. Prior to the screening of the articles, a test of consistency will be performed between the reviewers to ensure the inclusion and exclusion criteria at all three levels of screening. Randomly, we will select 10% of all articles or 100 papers (whichever is greater) and two reviewers will screen the articles based on the criteria, and the consistency will be obtained using Kappa test. If the result is higher than 0.7 the consistency will be significant, otherwise, the inclusion criteria will be modified and the process will be repeated until to obtain an acceptable Kappa score. In addition to scoring, discussions will be continued between the group members to reach the highest agreement and the least disagreements.

The first level of screening will be based on the titles. The article inclusion and exclusion criteria that will be considered at level one are shown in Table 3. At the second level, the article abstract will be reviewed with additional criteria including population, intervention/exposure, comparator and the outcome based on research questions are shown in Table 4. For articles without abstract or with any unclear reason to exclude the review, it will be retained and moved to the next stage.

At the third level of screening, the exclusion criteria for the full-text review will be based on the same criteria as for the abstract level and in compliance with Collaboration for Environmental Evidence (CEE) guidelines that are presented in Table 5. At this stage, the articles will be evaluated by two reviewers and approved by the third one. Then, the last selected articles will be assessed very carefully to extract the needed data. Every reviewer will list the excluded articles along with the reasons in an

Table 3 List of exclusion/inclusion criteria at the stage of title screening

Inclusion
-Any study on hospital and municipal wastewater and water resources or synthetic aqueous solutions
-Any study on the presence of antibiotics in a hospital or municipal wastewater and water resources or synthetic aqueous solutions
-Studies on the application of any processes in reducing or eliminating of antibiotics or from the hospital and municipal wastewater and water resources or synthetic aqueous solutions
-Studies on analytical methodologies (with high-performance liquid chromatography coupled to mass spectrometry or tandem mass spectrometry and to a lesser extent by ultraviolet or fluorescence)
Exclusion
-Studies on the survey or elimination of pharmaceutical compounds in soils, sludge, and or food products
-Any study on antibiotic-resistant bacteria and genes determination in and elimination from soil, sludge, and or foods
-Studies on the presence of microbiological and chemical substances in wastewater, water, and other media
-Study on eco-toxicological risk assessment of wastewater contaminants

Table 4 List of exclusion/inclusion criteria at the stage of abstract screening

1. What is the type and concentration range of antibiotics in hospital and municipal wastewaters and receiving water bodies?	
Population	Type of aqueous solutions such as hospital and urban wastewater, lake, river, ground and surface water resources and drinking and tap water
Intervention	Is not applicable.
Comparator	Between concentration of antibiotic members in untreated and treated wastewater and water resources
Outcomes	Type, occurrence and concentration range of antibiotics in hospital and municipal wastewater and water resources
2. What are the comparative efficiencies of various wastewater treatment processes in the removal of antibiotics?	
Population	Type of aqueous solution such as; hospital and municipal wastewater, surface or groundwater, tap or drinking water and synthetic solutions
Intervention	Type of processes used for removal of antibiotics from aqueous solutions (including physicochemical, biological, advanced oxidation)
Comparator	No treatment and alternative treatment processes for elimination of different antibiotics
Outcomes	Removal efficiencies of the treatment processes and design criteria for the treatment processes

Table 5 List of exclusion criteria at the stage of full-text screening

✓Not on topic
✓No relevant population
✓No relevant intervention/exposure
✓No relevant comparator
✓No relevant outcome
✓Not quantitative
✓Topic specific reasons
✓Ambiguous data

Additional file 1 to reassessment again by the co-reviewers for any unwanted missing of important articles. In the case of unavailability of some data, the corresponding author will be contacted by email to provide the necessary information and if not, the paper will be removed.

Study validity assessment

Evaluating the quality of articles and bias will be done by combining and revising existing tools in the field of environmental sciences, including the criteria designed by Bilotta et al. which are derived from the Cochrane Collaboration's Risk of Bias Tool [47, 48] and the criteria defined by Schindler et al. will also be used [49]. The criteria in these tools will be reviewed by the research team based on the objectives of the study. Table 6 includes the desired criteria, assessment criteria like selection and performance, measurement of outcome, clarity and publication and the other biases. Each variable will receive a score based on the reviewers' comments. The papers will be divided into three groups based on their quality (low, medium, and high bias). Therefore, considering a range of normalized 0–100 for the quality score, studies with scores higher than 67 will be placed at high quality class, studies with scores 33–67 will be listed as a medium quality class and studies with scores less than 33 will be assigned at low quality class. Additionally, we will conduct a sensitivity analysis to seek the individual removing of each study. Then, studies that are classified with high bias will be excluded from the quantitative synthesis. It should be noticed that low quality article doesn't mean that the article is weak in its content, but the purpose of this classification is to increase the reliability of the study.

The reviewers will be provided with the necessary explanations and training before conducting the quality assessment and bias evaluation of the articles. This evaluation will be conducted on a random sample of 10% of the articles by two reviewers. Then the checklists will be compared and any disagreement on inclusion criteria at this stage will be discussed between the reviewers. Finally, all included articles will be controlled and confirmed by an expert.

Data coding and extraction strategy

A data extraction form will be used for studies that have passed the stages of screening, quality, and bias assessment. The information provided below (but not limited to) will be detailed in a datasheet:

- The bibliography of articles including authors, year of publication and type of study (bench, pilot or full scale studies, field survey)
- Type of antibiotic removal method (biological, physicochemical, absorption, membrane separation, advanced oxidation processes)
- Type of water or wastewater (hospital or municipal wastewater, surface or groundwater and synthetic solutions)
- Type of examined antibiotics

Table 6 Bias assessment framework of articles

Bias area	Study parameter	Characteristic	Bias assessment	Bias score
Selection and performance bias: study design	Sampling	Detection of antibiotic type and concentration	Total sample size > 10 (Temporal or spatial)	10
			Total sample size < 10 (Temporal or spatial)	5
			A single sample volume > 100 cc	10
			A single sample volume < 100 cc	5
			Replication of samples	10
			No-replication of samples	5
Assessment bias: measurement of outcome	Experimental design	Plant type	Full or pilot experiments with real wastewater	10
			Bench scale experiments with synthetic solution	5
		Antibiotic extraction method	Solid phase extraction	10
			Liquid–liquid extraction	5
		Antibiotic detection device	Gas or liquid chromatography coupled with mass spectrophotometry	10
			Gas or liquid chromatography	5
Bias linked to clarity and publication bias	Data analysis	Statistical analyses	Using and describing the statistical data analysis method	Yes [10] No [5]
			Clarity of the presentation of data quality/quantity or statistical analysis	Yes [10] No [5]
Other biases		Detection bias	Having significant differences in the results in before and after treatment process	Yes [10] No [5]
		Attrition bias	Same sample size in before and after treatment process	Yes [10] No [5]
			Same number of samples in before and after treatment process	Yes [10] No [5]

- Antibiotics extraction and detection methods and reported concentration range of antibiotics and statistical analysis
- Type, description and operation parameters of the treatment process,
- Experimental conditions (antibiotic initial concentration, reaction or exposure time, pH, chemical dosing rate and etc.)
- Antibiotic removal efficiencies
- Detected by-products
- Removal rate of biochemical oxygen demand (BOD), chemical oxygen demand (COD) and total organic carbon (TOC)

The results of the review are displayed in graphs, figures, tables, and text. A summary of statistics is used when the raw data are presented in the articles. If the article data are ambiguous, the author will be contacted and will be required to provide explanations. In order to reduce bias and error in data reporting, two reviewers will independently extract the data, and the same manner used in the screening stage will be used to evaluate the agreement between the two reviewers. In case of disagreement, researchers will be discussed or opinion of the third reviewer will be accepted. We will first interpret and integrate the findings to reach a "bottom line" message that incorporates the strengths, weaknesses, inconsistencies, and gaps in the evidence, as well as potential moderators such as populations, study designs, and contextual factors; and we will then report this message together with a brief summary of the evidence that supports the message. Narrative synthesis works with both numeric data and qualitative data.

Potential effect modifiers/reasons for heterogeneity

Useful outcomes and data on interventions and other potential effect modifiers will be extracted from included articles and recorded by the research team. The following is a list of possible elements that can cause variations to the effects between the studies and the data will be recorded in an Additional file 1:

- Comparator type (spatial/temporal variations, extended variety in the type of antibiotics, type of examined wastewater and water resources and etc.)
- Sampling method (sample size, randomization of sample selection, number of replicates, etc.)
- Type of antibiotics extraction and detection methods
- Variability in the type and operational parameters of the treatment processes
- Different operation parameters of the treatment process
- Various experimental conditions such as antibiotic initial concentration, reaction or exposure time

This list is not thorough, and a conclusive list of effect modifiers and causes of heterogeneity will be determined as the review proceeds.

Data synthesis and presentation

After extracting the required data from the assessed articles, narrative synthesis will include summarizing the results and presenting them in the form of tables and figures. Quantitative analysis will be performed to categorize data according to the type of antibiotics classes and performance of the various treatment processes in the elimination of antibiotics. Then, all the quantities of antibiotics that are present in the hospital and municipal wastewater and water resources will be presented as mean and standard deviation. In the absence of data on the efficacy of treatment processes for antibiotic removal, it will be calculated using antibiotic concentration at the inlet and outlet of the treatment processes. If studies show sufficient data of similar results, meta-analysis can be used to analyze the data. Random effect Meta-analysis will be conducted due to the likely range of underlying effects. If the heterogeneity exists, the source of heterogeneity will be sought by met-regression, and subgroup analyses may be performed according to the effects of variables of the studies, such as sample size and volume, type of extraction and instrumental analysis, and the type of antibiotic. A funnel plot will be used to check the publication bias.

In order to compare removal efficiency of each antibiotic amongst the treatment processes, the data will be converted into standard removal efficiency (SRE) based on equation $\mathrm{SRE} = (x - \mu)/\sigma$ ($x =$ antibiotic removal efficiency by each treatment process, $\mu =$ the average removal efficiency of antibiotic by all purification processes, and $\sigma =$ the standard deviation of removal efficiency by all treatment processes) [50]. The average SRE for each treatment option will be calculated and analyzed for significant differences in the average SREs using randomizations without replacement. This method is well suited for examining differences between study effect sizes, and has been effectively utilized to analyses similarly structured datasets exploring toxicological processes. The randomizations will be performed using Excel software, by calculating the differences in the average of all SREs among the treatment processes, and then randomly recasting the data to the different groups and recalculating the differences.

Supplementary information

Supplementary information accompanies this paper at https://doi.org/10.1186/s13750-020-00201-z.

Additional file 1. ROSES form for systematic review protocol of Diversity of antibiotics in hospital and municipal wastewaters and receiving water bodies and removal efficiency by treatment processes.

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Authors' contributions
The authors of the present protocol declare that they have cooperated in the idea and writing of the protocol. All authors read and approved the final manuscript.

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Consent for publication
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Competing interests
The authors declare that there is no conflict of interest in the present study.

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