Review Article

The Battle against *Legionella*. Disinfection in Manmade Water Systems: A Systematic Review

Venia Stavrou, Ioanna Chatziprodromidou, Apostolos Vantarakis*

Environmental Microbiology, Department of Public Health, Medical School, University of Patras, Greece

***Corresponding Author:** Apostolos Vantarakis, Environmental Microbiology, Department of Public Health, Medical School, University of Patras, Greece, Tel: +30-2610-969875; E-mail: avanta@upatras.gr

Received: 10 August 2020; **Accepted:** 17 August 2020; **Published:** 04 September 2020

Citation: Venia Stavrou, Ioanna Chatziprodromidou and Apostolos Vantarakis. The battle against Legionella. Disinfection in manmade water systems: a systematic review. Journal of Environmental Science and Public Health 4 (2020): 244-266.

Abstract

Legionella constitutes the main cause of Legionnaires' disease (LD), a severe multisystem illness and life-threatening pulmonary infection. Manmade water systems are the main source of infection. Finding the most effective method is a matter of utmost importance. We conducted a systematic review to evaluate the effectiveness of disinfection methods against *Legionella* and the frequency of use of these methods. We recorded *Legionella* species and serogroups that are usually detected in manmade water systems, the building types and water systems where *Legionella* constitutes a problem. Literature search was conducted in two databases. Data were extracted from 141 studies that finally met the inclusion criteria. According to these studies, disinfection methods in manmade water systems were applied 259 times and the corresponding registrations were conducted in the data extraction form. *Legionella pneumophila* was the most common species detected in manmade water systems and *Legionella pneumophila* serogroup 1 the most common serogroup. The majority of studies dealt with *Legionella* in hospitals and in hot and cold water systems. Chemical disinfection methods had longer duration, while the combination of physical and chemical disinfection methods was more effective. Point – of – use filters, Cooper silver ionization and Hydrogen peroxide proved to be the most effective methods. Cooper silver ionization had

the lowest percentage of *Legionella* concentration increase, while ultraviolet light had a temporary duration of effectiveness against *Legionella* in the water system. No disinfection method has a 100% reduction of *Legionella* concentration, 100% decrease of colonized sites and duration of effectiveness all at the same time.

Keywords: *Legionella* spp.; *Legionella pneumophila*; Legionnaires' disease; Disinfection; Treatment; Prevention; Control; Management; Water system; Man-made water systems; Public health

1. Introduction

Legionnaires' disease (LD) is a severe multisystem illness and life-threatening pulmonary infection caused by *Legionella* spp.. [1, 2]. It is considered not to be transmissible from person to person and the environment, mainly manmade water systems, are the only source of infection [3]. Since the most famous outbreak, that took place at Philadelphia during a Legionaries' annual convention, *Legionella* has become a worldwide public health concern issue [4, 5].

The surveillance of LD carried out by the European Centre for Disease Prevention and Control reported 9,238 cases in 2017, of which 8,624 were classified as confirmed, by 30 EU Member States [6]. Regular checks for *Legionella* bacteria presence and appropriate control measures applied to engineered water systems may prevent cases of LD at tourist accommodation sites, healthcare facilities or other settings where populations at higher risk may be exposed [6], but disinfection of the water systems is the most effective preventive measure [7].

The first report of the implementation of a disinfection method that led to the reduction of LD cases in 1983 by the use of thermal disinfection is now known as 'heat and flush' [8]. Since then many disinfection methods to prevent *Legionella* in manmade water systems are used: chlorine, chlorine dioxide, monochloramine, hydrogen peroxide, biocides, ultraviolet light, Cooper - silver ionization, point – of – use filters, water temperature regulation in various ways etc. Many reviews comparing this methods are available in literature [7, 9, 10, 11]. Despite the variety of disinfection methods available for controlling *Legionella* in manmade water systems we are not aware of the optimal method. They all present advantages and disadvantages, related to the duration of their effectiveness, ease of implementation, cost and maintenance issues [2, 10]. At the same time LD remains an important cause of potentially preventable morbidity and mortality in Europe and there is no evidence for reducing problem [6]. Therefore, finding the most effective method is a matter of paramount importance.

To our knowledge there is no other systematic review evaluating disinfection methods for *Legionella* except a short one considering effective interventions in hospitals [2]. We conducted this systematic review in order to record the species and serogroups of *Legionella* usually detected in manmade water systems, the building types and the water systems where the bacterium exists, the frequency of use for each disinfection method according literature, the countries involved and finally to evaluate the effectiveness of disinfection methods.

2. Methods

2.1 Protocol and registration

In the present study we performed a protocol based on PRISMA statement [1], followed in all steps: literature search, study selection and analysis process.

2.2 Eligibility criteria

All study designs were included in the first step, irrespectively of the date of their publication. The literature search was conducted without language limitations, on the condition that an abstract in English existed reporting the information of interest. The inclusion and exclusion criteria were set as follows:

2.2.1 Inclusion criteria

- Primary studies
- Field
- Water systems where a new disinfection method is applied
- At least one of the following information was referred: *Legionella c*oncentrations, colonized sites, cases (before and after the implementation of the disinfection method), reduction of *Legionella* concentration, reduction of colonized sites, reduction of cases.

2.2.2 Exclusion criteria

- Wastewater
- Drinking Water Treatment Trains
- Pilot scale studies
- In vitro studies
- Letters to the editor
- Reviews

2.3 Information sources and literature search

The literature search was conducted in two databases: PubMed, Science Direct from February 21, 2019 to April 3, 2019, without date or language restrictions. We used the following search terms (adapted for each database): (Legionella) AND (disinfection OR treatment OR prevention OR control OR management OR intervention OR biocides OR antimicrobial OR copper silver OR UV OR ultraviolet OR chlorination OR bromination OR oxygen peroxide OR heat OR flush OR ozone OR ozonation OR filter OR monochloramine). The search of the terms was held in titles and abstracts for PubMed and in titles, abstracts and keywords for Science Direct.

2.4 Study selection

The selection of the studies to be included in the systematic review was implemented by two reviewers independently: (V.S. and I.C.). Mendeley was used to identify duplicated publications and include each article only once. A first screening was performed by titles and abstracts, using the inclusion and exclusion criteria. The potentially relevant articles were passed on to the next step for further assessment. A second selection of the relevant studies was conducted by the full text of the included publications. The authors independently reviewed the potentially relevant studies according to the eligibility criteria to determine which studies would finally be included in the review. Disagreements were solved by discussion with the third author (A.V.).

2.5 Data collection process

We developed a data extraction form using the Microsoft excel software, according to the requirements of the systematic review. We tested it by extracting the data from the first 20 randomly selected articles to be included in this systematic review.

During the process, the data extraction form was modified according to the arising needs.

2.6 Data extraction

The information extracted from the fulltext articles selected to be included in the study were:

- Publication year
- Location of the study
- Disinfection method
- Building type
- Water system type
- Reduction of *Legionella* concentration and/or
- Reduction of colonized sites and/or
- Reduction of cases of LD
- Species and serogroups involved and
- *Legionella'*s reappearance / increase of concentration in the water system

The variable "*Legionella'* s reappearance / increase of concentration" was added after the review started, since we observed that there are studies were *Legionella* recurred or its concentration was increased a while after the application of the disinfection method in the water system. The designed data extraction form was used in order to recover the extracted data. There are studies where a new disinfection method was applied more than once and met the inclusion criteria for each application. These studies report the application of different disinfection methods on the same building and same water system in the row or studies that report the application of one disinfection method in different building types or different water systems. For these studies we extracted data for each application of disinfection method and a registration in the data extraction form was held each time.

2.7 Classification of disinfection methods

A large number of disinfection methods as well as their combinations was used in the included studies of this systematic review. The data were too many that to export useful results. So, we decided to categorize disinfection methods. Initially we classified all methods to chemical, physical and combination of them. In a second step we categorized the disinfection methods applied in the studies in Chlorine - based methods, Ozonation, Temperature - based methods, point – of - use filters, Biocides, Cooper - silver ionization, Ultraviolet light, Hydrogen perogide, Mixed and Others. As Chlorine based methods defined: Chlorine, Monochloramine, Chlorine dioxide, Sodium hypochlorite, Hyperchlorination and as Temperature based methods: Heat and flush, Increase permanently temperature of hot water supply, solar pasteurization, pasteurizing, decrease water temperature below 20 ^{o}C and electric showers.

3 Results

3.1 Study selection

From the 4,031 articles that were identified after the search in the databases (3,075 articles from PubMed and 956 articles from Science Direct), 696 were duplicates and therefore 3,335 remained for further screening. Of the remained articles, 2,899 were discard after screening title and abstract as they did not meet the eligibility criteria. Then, 436 articles remained for full text evaluation. From those, 295 were discarded. In 28 articles we did not have access, 13 were reviews, 9 were letters to the editor, 14 were studies for disinfection in other means except water, 25 were dealing with disinfection in wastewater and drinking water treatment trains, 12 articles referred theoretically to disinfection methods, 39 studies used pilot scale models, 92 were in vitro studies and 63

articles did not meet the inclusion criteria. Finally, 141 studies met the eligibility criteria and were deemed eligible for inclusion in this systematic review [12-152]. Some studies applied more than once a disinfection method in the water system one after another. For each application, a registration to the excel took place. From these studies, 259 registrations were held in the data extraction form. The study selection is shown in Prisma flow diagram (Figure 1).

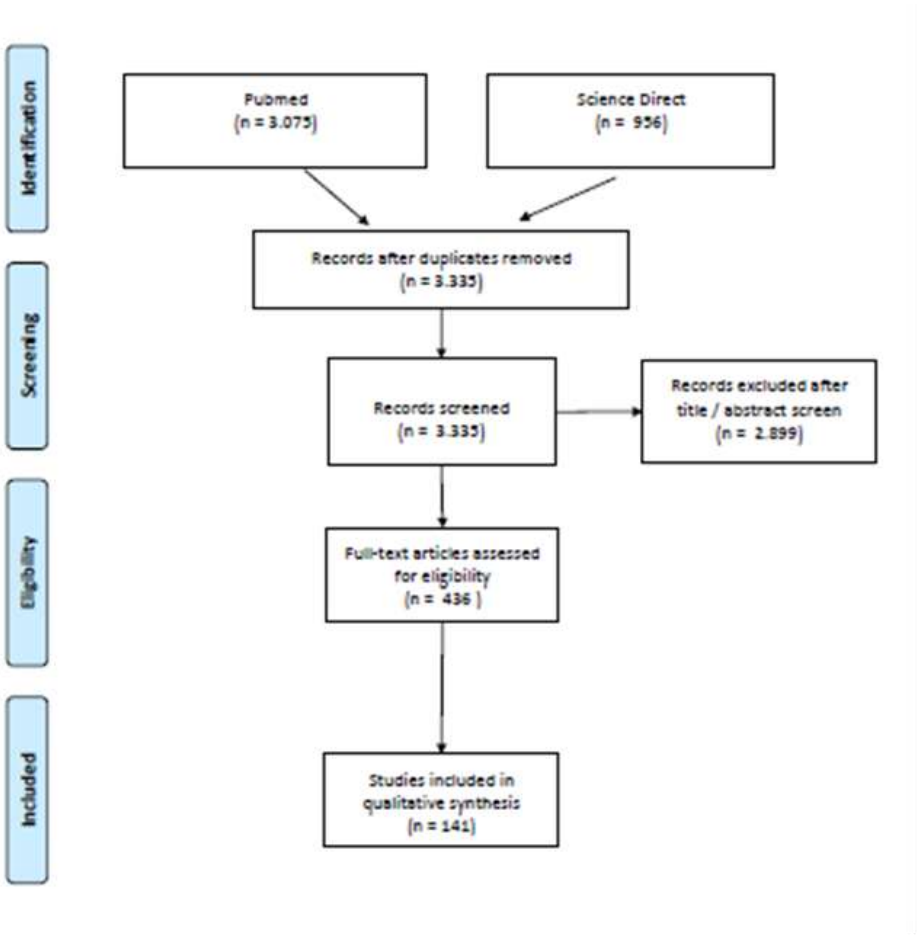

Figure 1: Flow chart diagram showing the procedure of study selection for this systematic review.

3.2 Study characteristics

The studies included in this systematic review were published from 1980 to 2019. Most studies (49, 34.8%) were published in the 2000s, while 45 studies (31.9%) were published in the 2010s. Twenty-nine studies were published (20.6%) in 1990s and 18 studies (12.8%) in the 1980s. Most studies were performed in USA (25.5%), Italy (15.6%), UK (12.1%), Germany (8.5%), Spain (6.4%), France (4.3%), Finland (3.5%), Japan (2.8%), China (2.8%), Sweden (2.1%), Canada (2.1%), Israel (1.4%), Czech (1.4%), Turkey (1.4%), Australia (1.4%) and other countries (8.7%). The studies deemed eligible for inclusion were related to disinfection in hospitals (75%), residents (6.8%), hotels (4.5%), dental clinics (3.8%), therapeutic spas (3.8%), industries (2.3%),

ships (1.5%), athletic venues (1.5%), and cultivation (0.8%). The included studies were focused on the application of disinfection methods in hot and cold-water systems (76.7%), cooling towers (11.6%), spas (3,4%), dental unit waterlines (2.7%), pools (1,4%) and other systems: humidifiers, buss tanks, rainwater, various systems checked on the same time (4.2%).

3.3 *Legionella* species and serogroups

At 93 (35.9%) of 259 registrations, at least one case of LD was diagnosed before the application of a new disinfection method. *Legionella pneumophila* was the most common species isolated from the water systems and *Legionella pneumophila* serogroup 1 the most common serogroup detected in the studies included in this systematic review. *Legionella pneumophila* occurred in 64.9% of registrations, *Legionella* spp. in 31.7% and *Legionella pneumophila* simultaneously with *Legionella* spp. in 3.5% of registrations of this systematic review. *Legionella pneumophila* serogroup 1 was detected in 48.4%, serogroup 2-14 in 38.7% and serogroup 1-14 in 12.9% of cases that *Legionella pneumophila* was present in the water system and serogroup was determined. In 85.71% of cases where other species were detected in water systems, specific species were not mentioned. The other species of *Legionella* that were identified are *Legionella anisa* (7.69%), *Legionella bozemanii* (3.30%), *Legionella iondiniensis* (1.10%), *Legionella micdadei* (1.10%) and *Legionella quaterensis* (1.10%).

3.4 Disinfection

In 23.6% of registrations more than one method was applied aiming to eradicate *Legionella* in water systems or reduce LD cases. In addition, in 19.7% of cases that a disinfection method was applied, more actions were necessary in order to reduce *Legionella* concentration: solving problems with dead-ends or dead-legs, replacement of shower heads or other apartments of the water system, removal of infrequently used showers and taps, disinfection of network components, periodic tap's flushing and network' s cleaning.

3.5 Frequency of use and effectiveness of disinfection methods

The application of chemical disinfection methods was slightly more common than physical, while in 10% of registrations chemical and physical methods were used in combination (Table 1). The combination of physical and chemical disinfection methods in a water system was more effective than using chemical or physical methods individually. Chemical disinfection methods had longer duration of effectiveness against the bacterium than the other methods (Table 1).

Disinfection method	**Frequency of used method (%)**	**Reduction of colonized sites (%)**	**Reduction of *Legionella* concentration (%)**	**Reduction of LD cases (%**	**Detectable again (%**
Chemical	49%	72.45±34.32	78.79±37.42	93.13±20.07	53.80%
Physical	41%	64.9±42.5	87.59±29.25	96.34±8.7	86.40%
Combination	10%	75.21±33.43	99.66±0.89	97.00±9.49	80.00%

Table 1: Frequency of application of chemical and physical methods and their combination in included studies and their effectiveness based on reduction of colonized sites, *Legionella* concentration, LD cases and reappearance of the bacterium in the water system after the application.

Chlorine – based methods and temperature – based methods were the most commonly used (Table 2). Hydrogen peroxide proved to be the most effective method in decreasing colonized sites in a water system (100%), while at the same time succeeding a high reduction on the concentration of *Legionella* (91.65%). Cooper - silver ionization presented the best results in reducing *Legionella* concentration (98.71%), and good enough in abating the colonized sites (71.91%). In some cases, Cooper - silver ionization reduced but not eliminated the bacterium. However, water systems that have been treated with Cooper - silver ionization showed the lowest percentage of recurrence or increase of *Legionella* concentration (25%). On the other hand, ultraviolet light reduces *Legionella* concentration by an average of 88.34%, but does not have the efficiency to decrease the colonized sites of the system and has a transient effectiveness since *Legionella* concentration increases after the application.

Disinfection method (categorized)	**Frequency of used method (%)**	**Reduction of colonized sites (%)**	**Reduction of *Legionella* concentration (%)**	**Reduction of LD cases (%)**	**Detectable again or increase of *Legionella* concentration (%)**
Chlorine based methods	24.3	72.25±34.00	77.57±37.79	89.53±25.71	54.50
Ozonation	2.3	62.00±52.15	77.50±43.66	NR	NR
Temperature based methods	24.3	61.09±43.74	85.71±31.93	92.28±7.26	84.20
Filter	8.5	89.66±24.44	93.18±24.89	NR	NR
Biocides	6.9	81.01±24.11	77.44±39.67	100±0.00	75.00
Cooper - silver ionization	11.6	70.67±36.36	98.71±4.21	96.84±9.31	25.00
Ultraviolet light	3.5	0.00	88.34±33.16	NR	100
Hydrogen perogide	0.8	100	91.65±11.80	NR	NR
Mixed	15,4	71.91±33.89	78.48±37.37	95.50±10.92	81.80
Others	2.3	NR	100±0.00	100	100

Table 2: Frequency of application of categorized disinfection methods in included studies and their effectiveness based on reduction of colonized sites, *Legionella* concentration, LD cases and reappearance of the bacterium in the water system after the application.

Finally, point – of - use filters seems to be the most effective measure to keep *Legionella* off a water system among physical disinfection methods (Table 2).

3.6 Use of disinfection in relation to the country

USA and UK showed a statistical significant preference for chemical disinfection methods over physicals (62.5% and 60.5%). On the contrary, Germany used more physical disinfection methods (59%) than chemicals, based on the registrations of this systematic review. UK used biocides to a greater extent than the other countries (28% of biocides were used by UK). Italy used 32% of chlorine based methods applied. While, 78% of application of Ultraviolet light was performed in Italy. Germany used point – of - use filters to a greater extent (45%) compared to other countries. Canada, France, Italy,

Spain and USA used mainly chlorine based methods (25%, 28.5%, 40%, 43.7%, 29.5% respectively) and temperature-based methods (50%, 57.1%, 20%, 25%, 16.4%) against *Legionella*. At the same time, USA used 34% of Cooper - silver ionization in a greater percentage in relation to other countries. Finally, Sweden applied only temperature - based methods according to the articles included in this systematic review.

3.7 Disinfection in relation to building type and water system type

The use of chemical disinfection methods prevailed over the application of physical and mixed methods in hotels (50%), industries (100%), ships (100%), and spas (50%). Physical disinfection methods were used at a higher frequency in cultivation (100%) and athletic venues (60%) in relation to chemical methods. In hospitals, residents and dental clinics chemical and physical methods were used approximately with the same frequency. Chlorine based methods and temperature based methods were used the most in the included studies. Chlorine based methods were applied in 100% at ships, 22.7% at hospitals, 23% at residents, 50% at spas and 40% at athletic venues while temperature based methods were used in 26.7% at hospitals, 46.15% at residents, 25% at spas and 60% at athletic venues, according to the registrations of this systematic review. Other disinfection methods: Cooper – silver ionization, point – of- use filters, Ultraviolet light, Ozonation and Hydrogen peroxide, were used mainly in hospitals, based on the extracted data of the studies included in this systematic review.

In hot and cold-water systems and dental unit waterlines chemical and physical disinfection methods were applied, approximately, in the same frequencies. Cooling tower's disinfection was performed mainly (87.9%) by applying chemical methods (42.2% biocides 27.2% chlorine based methods). According to the included studies biocides were used only in cooling towers and dental unit waterlines' disinfection. The most common methods for dental unit waterlines' disinfection were biocides (44,4%) and point – of – use filters (22.2%). Pools' disinfection was implemented both with chemical (33.3%) and physical (66.7%) disinfection methods (33.3% chlorine based methods and 66.7% point – of – use filters). Concerning spas, chlorine - based methods were applied in 37.5%, ozonation in 12.5% and temperature - based methods in 25% of registrations of this systematic review. For hot and cold water systems the most common methods proved to be temperature – based methods (27.3%), chlorine – based methods (24,2%) and Copper – silver ionization (15.5%).

4. Discussion

Some limitations exist in this systematic review: The dose and application period of disinfectants has not been considered. The applications of successive disinfection methods in some studies make it difficult to evaluate effectiveness due to the application of previous method or methods in the water system. We extracted different data from the studies that were used as units of measure to evaluate disinfection 's effectiveness. This fact makes effectiveness' comparison difficult: Cases before and after or cases reduction, *Legionella* concentration before and after or its reduction and/or colonized sites before and after or their reduction are studies' measures to express disinfection's effectiveness.

Proceeding with classification of disinfection methods we are not able to conclude which chlorine - based method or temperature - based method is the most effective against *Legionella.* At the same time, it is impossible to evaluate which combination of disinfection methods is more effective. So, a systematic review exclusively for chlorine - based methods and another one for temperature - based methods should probably be conducted.

From the results of this systematic review, studies are increasing over the years which suggests the growth of interest for *Legionella* free water systems. LD 's gravity is acceptable, but it considers to be a preventable disease, since controlling and eliminating the bacterium in water systems and other reservoirs prevents infection. LD has become a main concern of public health authorities and professionals involved with construction and maintenance of man-made water systems [5] which explains the increase in bibliography related to disinfection.

Most of the studies included in this systematic review were performed in USA and Italy. USA uses a National Notifiable Diseases Surveillance System (NNDSS) and a Supplemental Legionnaires' Disease Surveillance System (SLDSS). In 2017, 6,319 confirmed legionellosis cases were reported to SLDSS from 52 jurisdictions; 6,221 (98%) were LD cases [153]. Italy has a Surveillance System for LD [154] in contrary to other European countries. In 2017, the highest number of cases (2,013) and confirmed cases of LD (1,980) in the European Center were reported in Italy [6]. The high rates of LD cases in USA and Italy are probably explained by the fact that there is a good surveillance system and cases are detected and recorded. Surveillance system's existence and operation suggests that USA and Italy are seriously involved with LD and *Legionella*. These countries were expected to deal with disinfection methods, which is imprinted in bibliography.

Seventy-five per cent of the studies included were related to disinfection of man-made water systems of hospitals. A high rate of confirmed LD cases is healthcare-associated, are reported 21% of cases in USA in 2017 [153] and 9.3% of cases in Italy during the period of 2000 to 2011 [154]. Simultaneously, healthcare–associated LD can result in higher morbidity, mortality, and financial cost [155] than travel associated or community acquired LD. These are probably the causes that are focusing the interest of the studies in *Legionella* disinfection of hospital water systems.

Legionella pneumophila was the most common species of the registrations and *Legionella pneumophila* serogroup 1 the most common serogroup. *Legionella pneumophila* serogroup 1 is the most common identified pathogen causing LD [1, 6]. Consequently, in most studies is the pathogen that researchers are looking for in the systems. The fact that a high percentage of the included studies was implemented after the diagnosis of LD cases may increase the percentage of *Legionella pneumophila* serogroup 1 in our results.

We concluded that the combined application of physical and chemical disinfection methods has better results against *Legionella*, but chemical methods have longer duration of effectiveness. Sweden and Germany show a preference to physical disinfection methods. No disinfection method has a 100% reduction of concertation of *Legionella*, 100%

decrease of colonized sites and duration of effectiveness in the water system all at the same time. Among the physical methods, point – of use filters seems to be the most effective measure to keep *Legionella* off a water system. On the other hand, ultraviolet light reduces in a good percentage the concentration of the bacterium but does not eliminates it in the colonized sites and has the highest percentage of increase of *Legionella* concentration compared to the other methods. However, Cooper - silver ionization, comparatively to the other methods, seems to have a great effectiveness and simultaneously the lowest recurrence or increase of concentration of the bacterium. Hydrogen peroxide has even better results in terms of reducing colonized sites and concentration of *Legionella*, but there are no data for effectiveness' duration. It seems that other methods are effective too (use of paracetic, acid, improving water quality and system flushing) but the studies included are very few without being able to export safe conclusions.

Summarizing, we concluded that Cooper – silver ionization and Hydrogen peroxide gather all the desired features to a satisfactory degree compared to the other chemical disinfection methods, while point – of – care filters are the most effective among physical methods. Nevertheless, there is not yet a perfect disinfection method, effective enough to eradicate *Legionella* in a water system when used alone. That leads to application of combined methods or/and effort to solve problems in the water system. In order to choose the appropriate and most effective method or methods for a building type and a specific water system the characteristics of the system should be taken into account, certain information must be combined and a study of the system should be conducted. In addition, when selecting the method, except effectiveness and duration, other parameters must be capped in mind like cost, residual substances, safeness, ease of implementation, and maintenance issues.

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