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REVIEW

A review on hazards and treatment methods of released antibiotics in hospitals wastewater during the COVID-19 pandemic

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Abstract Drugs and related goods are widely used in order to promote public health and the quality of life. One of the most serious environmental challenges affecting public health is the ongoing presence of antibiotics in the effluents generated by pharmaceutical industries and hospitals. Antibiotics cannot be entirely removed from wastewater using the traditional wastewater treatment methods. Unmetabolized antibiotics generated by humans can be found in urban and livestock effluent. The antibiotic present in effluent contributes to issues with resistance to antibiotics and the creation of superbugs. Over the recent 2 years, the coronavirus disease 2019 pandemic has substantially boosted hospital waste volume. In this situation, a detailed literature review was conducted to highlight the harmful effects of untreated hospital waste and outline the best approaches to manage it. Approximately 50 to 70% of the emerging contaminants prevalent in the hospital wastewater can be removed using traditional treatment strategies. This paper emphasizes the numerous treatment approaches for effectively eliminating emerging contaminants and antibiotics from hospital wastewater and provides an overview of global hospital wastewater legislation and guidelines on hospital wastewater administration. Around 90% of ECs might be eliminated by biological or physical treatment techniques when used in conjunction with modern oxidation techniques. According to this research, hybrid methods are the best approach for removing antibiotics and ECs from hospital wastewater. The document outlines the many features of effective hospital waste management and might be helpful during and after the coronavirus disease 2019 outbreak, when waste creation on all hospitals throughout the globe has considerably increased.

Keywords Hospital wastewater treatment · Antibiotics · Emerging contaminants · Advanced oxidation process · Biological treatment

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Introduction

Hospital wastewater poses a significant hazard to the safety of human health caused by its great susceptibility to the breakout of various infections and chemicals which are presented in it. Additionally, the COVID-19 pandemic outbreak required that viruses, other infectious organisms, and different pharmaceutical active ingredients which were used to treat the patients be monitored and eliminated in hospital wastewater on a global scale. In 2002 and 2003, an outbreak of severe acute respiratory syndrome (SARS) occurred in Guangdong Province, China. In 2012, after 10 years, MERS-CoV appeared in the Middle East countries, and the 2019 coronavirus (COVID-19) first appeared in Wuhan, China, 7 years later. The World Health Organization (WHO) declared the outbreak of COVID-19 as a global public health emergency (Mandal et al., 2020).

In March 2020, WHO declared COVID-19 as a global pandemic based on the alarming level of spread and severity of infection. Corona viruses have a gram-positive lipid envelope and single-stranded ribonucleic acid (RNA), and the five dominant types of this virus are alpha, beta, gamma, delta, and omicron (Kien & My, 2021).

The main way of transmission of COVID-19 is either through direct contact with an infected person or through respiratory droplets (McMinn et al., 2021). With the spread of the disease and hospitalization of patients in hospitals, the use of therapeutic drugs began. The ways of disposal of drugs used in the hospital are disposal by patients in the form of the main compound or the compound metabolized by the patients' body, disposal through urine and feces, and accidental entry by drug residues in containers and surfaces (Ben et al., 2019). If hospital waste materials are not properly managed, including pharmaceutical compounds such as antibiotics left in vials and injection syringes, etc., they will be introduced into the environment intentionally or accidentally, which will be a great risk, especially in epidemic and pandemic conditions. In many developing countries, hospitals do not have wastewater treatment plants, and hospital wastewaters are often discharged into municipal wastewater collection systems or absorption wells (Nasr & Yazdanbakhsh, 2008). In addition, treatment of hospital wastewater in an unmanaged manner also entails risks because the sludge and effluent produced during the treatment of hospital wastewater can carry the potential risk of transmission of infectious diseases in addition to chemical risks. Therefore, it is necessary to have accurate and correct information about the status of hospital wastewater and take the necessary measures to prevent hospital wastewater from entering the environment without treatment or incomplete treatment and to prevent their discharge into surface and underground waters that cause pollution (Jalilian et al., 2020; Nasr & Yazdanbakhsh, 2008; Ngigi et al., 2020).

Wastewater from hospitals and healthcare facilities is generally qualitatively similar to municipal wastewater, but may also contain potentially toxic and infectious substances and compounds. The most important pollutants in hospital wastewater include viruses and pathogenic bacteria, molecules from un-metabolized and unused medicinal substances, organic compounds and halogens from the significant use of sodium hypochlorite, and ionic compounds in disinfectants. The oxidation and reduction reaction (an atom or molecule or ion loses an electron during the reaction) between organic substances and disinfectants before the sedimentation and filter stage in the treatment plants leads to the production of organic compounds and halogens. These compounds are essentially stable, lipophilic, and toxic compounds and are very hazardous to the environment. In some cases, hospital wastewater may contain chlorine compounds or heavy metals such as mercury and silver (Nasr & Yazdanbakhsh, 2008; Wang et al., 2018a, b).

Furthermore, research reveals that hospital wastewater is challenging to treat using traditional biological treatment processes because its average biodegradability index (BOD/COD) is often lower compared to municipal wastewater (Carraro et al., 2016; Majumder et al., 2021; Sodhi & Singh, 2023). The presence of hazardous pollutant compounds that are also non-biodegradable, such as X-ray contrast agents, disinfectants, active pharmaceutical ingredients, and chemically stable antibiotics, reduces the ratio of BOD to COD in hospital wastewater (HWW) (Emmanuel et al., 2005; Shahavi et al., 2022; Verlicchi et al., 2010a, b). At low doses (g/L to ng/L), the majority of these pollutants, known as emerging contaminants (ECs), can be harmful to humans and other aquatic species. For hospital wastewater treatment, the use of biological processes is used, which is a more cost-effective process than chemical processes because the treatment is done without the use of chemicals and with the use of microorganisms in the wastewater itself, but since hospital wastewaters contain different concentrations of organic substances such as antibiotics and laboratory chemical compounds and pathogens, they are considered toxic and growth-inhibiting substances, and the use of biological processes alone has low efficiency (Buelow et al., 2018, Sodhi & Singh, 2022). On the other hand, since the ratio of BOD to COD is small in many hospital wastewaters (due to the presence of man-made organic compounds that have little biological degradability), the discussion of using non-biological methods alongside biological processes, especially advanced oxidation processes, is raised (Esplugas et al., 2007; Khansary et al., 2020).

Today, one of the methods used in the treatment of wastewater containing resistant pollutants is the use of integrated (hybrid) methods (Lee et al., 2017). So far, various physical and chemical processes such as chemical precipitation (Freitas et al., 2015), physical absorption (Yagub et al., 2014), and oxidation with oxidizing compounds such as chlorine and ozone (Malik et al., 2017) have been used for more effective and advanced treatment of hospital wastewater. In this regard a study by Ouarda et al. indicated in 2018 that by combining biological processes and advanced oxidation, the effective treatment of hospital wastewater is possible (Ouarda et al., 2018). Furthermore, modern biological methods such as up-flow anaerobic sludge blanket (UASB), sequencing batch reactor (SBR), moving bed biofilm reactor (MBBR) are used increasingly instead of conventional biological treatment methods such as activated sludge (Ouarda et al., 2018). In 2021, M. Kumar et al. presented an account of decay in the genetic material loading of SARS-CoV-2 during up-flow anaerobic sludge blanket (UASB) treatment of wastewater and application of polyethylene glycol (PEG) and ultrafiltration as virus rejection methods from wastewater for SARS-CoV-2 genes. They reported a $> 1.3 \log_{10}$ reduction in SARS-CoV-2 RNA abundance utilizing UASB treatment in the presence of PEG, and the RNA was not detected at all in the final effluent (Kumar et al., 2021). Nadeem A. Khan et al. represented a study on sequencing batch reactor (SBR and MBR) in treating hospital wastewater. The SBR resulted in 88% removal efficiency in BOD5 removal, and the efficiency for MBR was 78%, while in case of COD removal, SBR showed 86% removal efficiency in comparison with 65% removal for MBR treatment (Khan et al., 2020a, b). Afzal Husain Khan et al. reported the results of a study on ibuprofen and ofloxacin drug removal using MBBR method. The removal efficacy of ibuprofen and ofloxacin was ˃ 90%. On the other hand, the optimal efficiency was occurred at hydraulic retention time (HRT) (16–20 h), mixed liquor suspended solids (MLSS) (2500–3500 mg/L), ozone consumption (OC) (7–9 L/h), time of ozone exposure (TOE) (4–10 min), and manganese oxide (MnO_2) concentration (MOC) (1.9–2.7 mg/L) (Husain Khan et al., 2020).

The primary goal of the study is to present a novel viewpoint on hospital wastewater formation, handling, and regulation during and after the COVID-19 pandemic. The paper explains the characteristics of hospital wastewater, the presence and concentrations of different discharged antibiotics in hospital wastewater, and the rules and guidelines that must be adhered to control hospital wastewater properly. The study's primary focus is then on several industrial-scale and pilot-scale methods of treatment to get rid of antibiotics in hospital wastewater. The present investigation also highlights numerous integrated technologies that combine biological methods of treatment with tertiary treatment approaches to completely eliminate the antibiotics that are discharged during the COVID-19 pandemic. The study reviews and provides the most recent information regarding the different components of hospital wastewater, the current treatment process, and the future perspectives. Therefore, it could be useful for investigators, environmental scientists, and researchers who work on waste management in hospitals.

COVID-19 pandemic

Use of antibiotics during the pandemic

According to Iran Food and Drug Administration (IFDA) (Administration, 2022), it was found that the azithromycin and ceftriaxone antibiotics are among the drugs that have been used for corona patients in Iran. The average azithromycin and ceftriaxone antibiotic consumption per month statistics before the Corona era in 2017–2018 and during the Corona era in 2019–2020, based on the inquiry made by Iran

Food and Drug Administration, is presented in the Table 1.

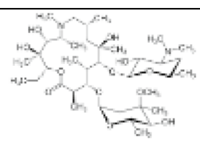
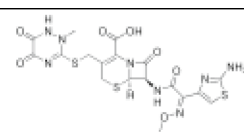
Azithromycin is an antibiotic from the macrolide group that is used to treat some bacterial infections such as middle ear infection, strep throat, pneumonia, traveler's diarrhea, and some other intestinal inflammations. This antibiotic is also prescribed for other cases such as sexually transmitted diseases such as chlamydia infection and gonorrhea. According to published studies, this antibiotic has been used along with other antibiotics in the treatment of corona patients. Some specifications of this antibiotic are presented in Table 2 (Arshad et al., 2020).

Ceftriaxone is one of the effective medicinal substances used in the treatment of infections caused by gram-negative and gram-positive bacteria, such as bacterial pneumonia, otitis media, urinary tract infections, bone and joint infections, and skin and soft tissue infections. One of the important uses of this substance is its use in the treatment of gonorrhea and salmonella. According to published studies, this antibiotic has also been used in the treatment of corona

Table 1 The average azithromycin and ceftriaxone antibiotic consumption per month statistics before the Corona era in 2017–2018 and during the Corona era in 2019–2020 (Diaconu et al., 2006, Medic et al., 2023)

Antibiotic generic name	Consumption 2017–2018	Consumption 2019–2020
Ceftriaxone (as sodium) injection, powder, for solution parenteral, 1 g	1,600,000	1,867,050
Ceftriaxone (as sodium) injection, powder, for solution parenteral, 250 mg	3,340	300,000
Ceftriaxone (as sodium) injection, powder, for solution parenteral, 500 mg	254,378	300,000
Azitromycin tablet oral, 250 mg	2,791,005	6,250,000
Azitromycin powder for oral suspension, 200 mg/5 ml, 30 ml	107,446	417,000
Azitromycin tablet oral, 500 mg	3,956,209	8,500,000
Azitromycin injection, powder, for solution parenteral, 500 mg	NA	500

Table 2 Specifications of azithromycin and ceftriaxone (Arshad et al., 2020)

Azithromycin		**Ceftriaxone**	
Chemical structure		**Chemical structure**	
Brand	Zithromax, Azithrocin	**Brand**	Rocephin, Arixon
Chemical formula	$C_{38}H_{72}N_2O_{12}$	**Chemical formula**	$C_{18}H_{18}N_8O_7S_3$
Molecular weight	748.984 g/mol	**Molecular weight**	554.58 g/mol
Metabolism	It is not metabolized and is excreted mainly in bile and through feces. Less than 10% of the drug is excreted through urine.	**Metabolism**	More than half of a drug dose is excreted unchanged through urine and the rest through feces.

disease (McCulloch et al., 2021). In Table 2, some specifications of this antibiotic are presented.

Therapeutic antibiotics

Antibiotics can be used to combat COVID-19, especially if microbial co-infections are anticipated or proven (Rawson et al., 2020a, b). Antibiotics should not be utilized to treat COVID-19 unless there are concurrent bacterial infections, according to the World Health Organization (WHO, 2020) (WHO). Nevertheless, mounting data indicates that a significant fraction of COVID-19 sufferers received unnecessary antibiotic treatment. Ninety percent of patients received empirical antibiotics although only 10% of secondary infections with bacteria being confirmed (Lai et al., 2020). Wei et al. (2020) (Wei et al., 2020) also reported that despite the lack of conclusive evidence of bacterial co-infection in these cases, antibiotics were begun at the admission time in 59% of COVID-19 patient populations. Furthermore, empiric prescriptions made up 98% of this list. Furthermore, while just 10% of individuals have bacterial or fungus coinfections, another relatively recent study of data from COVID-19 infections, largely from Asia, revealed that > 70% of individuals got antibiotic therapy (Rawson et al., 2020a, 2020b). The same research also discovered that broad-spectrum antimicrobial agents, which are used to fight a variety of germs, are being used. In acute care settings, the overuse of these antibiotics can promote antimicrobial resistance (AMR) (Hsu, 2020; Rawson et al., 2020a, b, Sodhi et al., 2023). Early surrounding potential COVID-19 therapies might increase the number of antibiotic prescriptions. In the US, shortages of the medication hydroxychloroquine and the antibiotic azithromycin have resulted from this (Reardon, 2020). There is a chance that many patients are taking antibiotics ineffectively trying to self-medicate in order to defend themselves against the illness. This might be fairly common in underdeveloped areas where getting antibiotics without a prescription. These medications are discharged in large amounts in bioactive shapes into the effluent water, where they may then penetrate biological ecosystems (Slater et al., 2011). Huge amounts of antimicrobials and the discharge of antibiotic-resistant organisms into sewage water might promote AMR and other unwanted environmental effects. Antimicrobials were the most often discovered substances, according to a recent analysis of pharmaceutical contaminants in aqueous systems throughout the world (Patel et al., 2019). It needs to be mentioned that wastewater, which is defined by exceptionally high microbial populations combined with sub-therapeutic drugs, is the main meeting place for AMR (Berendonk et al., 2015).

Antibiotic resistance hazard

One of the events that make it difficult to deal with diseases is antibiotic resistance, which may occur in all types of microorganisms, including bacteria, viruses, fungi, and protozoa. According to the existing guidelines, this problem should be solved by increasing the level of public awareness, reasonable antibacterial treatment, and improving living conditions. "The next pandemic might be worse than COVID-19 if it is not controlled" (Rizvi & Ahammad, 2022). Since the emergence of COVID-19, we are facing a sharp increase in antibacterial resistance, and it is expected that there will soon be a shortage of these drugs due to the increase in cases of resistance to antimicrobial drugs (Barocas et al., 2021). It is necessary to investigate the possible effects of antibiotic prescriptions connected to COVID-19 on the worldwide AMR problem and its associated toxicity on the environment. Figure 1 illustrates the pathway of the antimicrobial resistance during passing the pandemic.

To inform the community about the proper use and abuse of personal care products, there ought to be social education programs. New and flexible rules on water quality standards entry into the environment, focused on new and emerging pollutants like antibiotics, are urgently needed. To reduce the degree of pollution before it reaches the wastewater treatment processes, the effluent with an extremely high content of antimicrobials coming from medical institutions and pharmaceutical firms has to be controlled and pretreated. Before discharging the wastewaters into streams, wastewater treatment processes should be controlled using cutting-edge processes that completely remove any remaining antibiotics (Shi et al., 2018; Yi et al., 2017). The unexpected exposure to stress on front-line healthcare workers is having a major impact, causing over-prescriptions of antibacterial agents as global antimicrobial stewardship collapses, and if the global AMR sharp rise is not resolved right away, it is going to be unavoidable, and

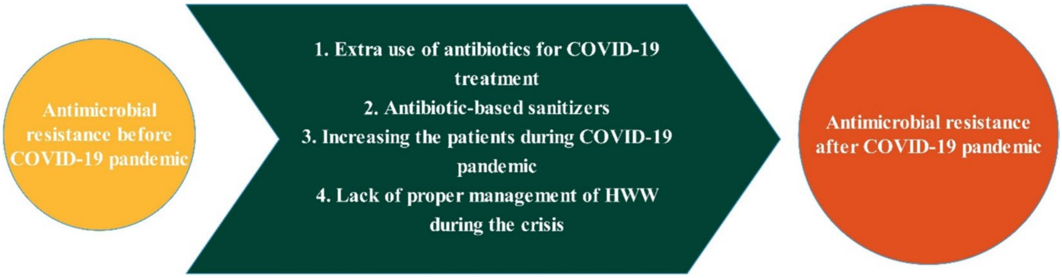


Fig. 1 The outcomes of the antimicrobial resistance during passing the COVID-19 pandemic

the globe cannot be spared from its effects (Allison et al., 2021).

Hospital wastewater

Hospital wastewater is one of the most dangerous wastewaters produced in hospital and human and animal treatment environments, whose entry into nature can bring many adverse effects (Ramírez-Coronel et al., 2023). In addition to creating a foul and bad smell in the environment, these wastes can cause problems such as genetic mutation in humans and also sexual changes in fish (Akter et al., 2012; Jirova et al., 2016). For this reason, hospital wastewater treatment has become very important in the treatment sector, and currently, there are many restrictions on the entry of these wastes into nature (Libralato et al., 2012).

Water consumption in hospital environments is very high, and in addition to a large part of the water that is used for washing surfaces and halls, laundry halls, restaurants, etc., a part is also used in sanitary services (Bloomfield et al., 2011). In response to the question of what hospital wastewater is, it can be said that it is all wastewater produced in hospitals and treatment units which are contaminated with pharmaceuticals and disinfectants, as well as chemical and radioactive substances (Khan et al., 2021a, b; Wang et al., 2020). None of the groups of hospital effluents, which contain infectious and medicinal substances, as well as urine and feces, will not have the possibility of directly entering the urban sewage as well as the nature (Akter, 2000; Oroei et al., 2014). Among the most important pollutants in these wastewaters, all kinds of hormonal drugs and antibiotics could be mentioned (Yu et al., 2022). In addition, there is a large amount of radioactive substances in the wastewater of these environments, which are often obtained from the radiotherapy treatment departments and carry many risks (Rathi, 2022).

In a general classification, the types of wastewater produced in hospital environments can be divided into the following groups based on the source of their production (Fig. 2 illustrates the summary of the explanations) (Sudarsan & Renganathan, 2011):

- Black water: This group of wastewaters is produced in the sanitary facilities of treatment units and is like urban sewage. To treat this group of wastes, the equipment in the sanitary waste treatment package is sufficient, and there is no need for multiple disinfection steps like other wastes of treatment units.
- Gray wastewater: It is the most dangerous type of wastewater in medical environments and contains a large amount of drugs, disinfectants, effluents containing radioactive substances, and antibiotics. It is necessary to use the hospital's wastewater treatment package for these effluents, and they should not enter the nature directly under any circumstances. Of course, despite the adverse effects of this group of wastewaters, in many countries, these wastewaters enter nature, the sea and rivers, and penetrate underground waters.
- Rainwater: It is the least dangerous type of wastewater in medical environments, which is obtained from the passage and accumulation of rainwater in the area and roof of the hospital. This group of wastewaters does not need to be treated and can be used to irrigate the green spaces of the hospital.

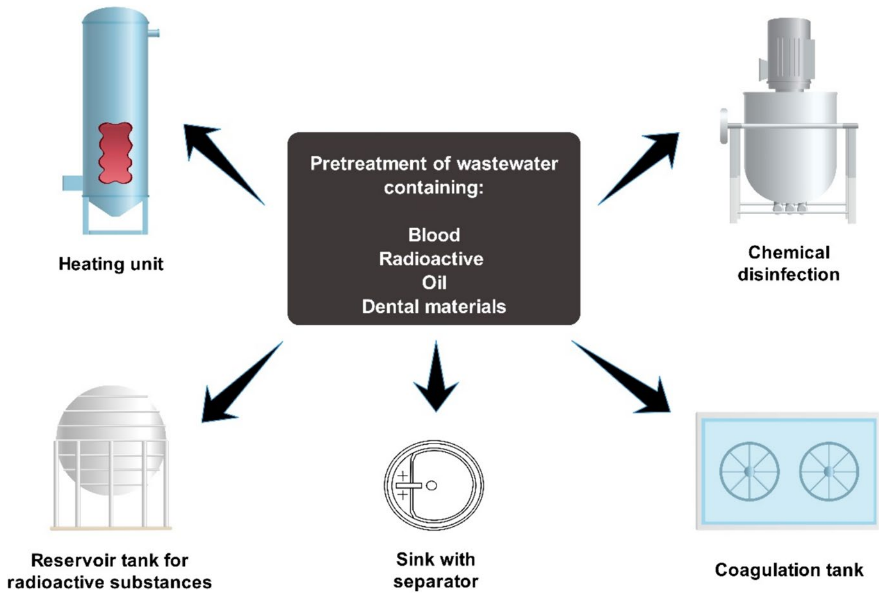


Fig. 2 Conventional methods for pretreatment of HWW

Regulations on hospital wastewater

Antibiotics are widely available on the market today, making it impossible to restrict their usage, endangering the entire ecosystem and all of its constituent parts. The system of regulation varies among nations based on a variety of criteria. The permitted limit of these new contaminants is quite small and up for debate when comparing to hospital effluent streams that include active pharmaceutical ingredients. Therefore, a distinct line between wastewater and hospital effluents must be drawn. The disposal requirements in different nations are split into two categories: municipal wastewater and industrial effluent. Analysis of the present hospital wastewater (HWW) issue reveals that aside from a few regulations, even Europe lags behind in terms of particular standards for managing such effluent (Emilia, Tamara and Carmen, Council & Directive, 1991). For populations larger than 2000, they typically take into account effluent collection and recycling, secondary treatment of all effluent and advance treatment for populations larger than 1000, pre-authorization of release from different companies, and tracking the effectiveness of current treatment systems (Grosso et al., 2010). Since there are no particular recommendations in the European Union, each of its countries has created its individual legislation, standards for evaluating HWW, and methods for disposing of it. HWW is regarded as municipal in Germany; hence, no previous authorization is required (Verlicchi, 2018). In other instances, if HWWs fulfill specific criteria for sewage, they are sent to a water treatment center without further thought (Carraro et al., 2016). In the particular instance of Italy, if a hospital has fewer than or equivalent to 50 beds, HWW is released as sewage without even being analyzed. This HWW is processed in typical treatment systems together with municipal wastewater (della Repubblica, 2012). Although its handling varies from region to region, it is generally regarded as residential effluent. In China, HWW is regarded as industrial wastes, and F-coliform is used as a sign for hospitals with 50 beds (Liu et al., 2010a, b). When the HWW issue in Vietnam is examined, it becomes clear that the country has particular legislation regulating the treatment and management of HWW (No. 55/2014/QH13) (2014). Based on the legislation, hospitals are required to gather and remove contaminants in accordance with set norms. However, legislation was created that takes into account the HWW collecting in waterways.

In Iran, for healthcare centers and hospitals that have limited management plans for their wastewater and do not have the ability to treat wastewater from their facilities, the following measures should be taken to reduce health risks (Education, 2020):

- Patients with intestinal infections should be kept in separate sections, and their wastes should be collected separately and then disinfected using strong chemicals. This action is especially important in connection with the cholera epidemic and COVID-19 pandemic.
- No type of chemical or medicinal substance should be emptied into the sewage collection networks.
- Sludge resulting from hospital wastewater treatment should be completely dewatered and dried by natural drying sludge beds and disinfected using chemicals (disinfection can be done with sodium hypochlorite, chlorine gas, and preferably with chlorine dioxide).
- Sludge from the hospital should never be used for agricultural purposes.
- Wastewater from the hospital should never be discharged into natural water sources that are used for irrigation of fields and vegetables, or as a source of water supply, or for recreational purposes.
- Hospitals and small health care centers that have limited management programs will probably discharge their wastewater into the environment. In these conditions, the acceptable solution is to use natural filtration through the permeable soil (absorbent well). But it should be noted that this work should be done outside the watershed of the underground aquifer used for water supply.

Antibiotics in hospital wastewater

Antibiotics have been widely used in recent decades. The increase in the percentage of antibiotic-resistant bacterial species can lead to problems in the selective treatment of bacterial infections (Van Hengel et al., 2020). The most important reason for the increase in the resistance of bacteria to antibiotics in Iran is due to the prescription and indiscriminate use of antibiotics. The occurrence of bacterial resistance in aquatic environments has been reported in many different studies (Sciortino et al., 2021, Wang et al., 2021). Therefore, many researchers consider water environments, especially sewage, as the main recipient of river bacteria, a favorable place for many bacteria to become resistant to various types of antibiotics (Khan et al., 2019a, b; Mousavi et al., 2021). In such an environment, the transfer of resistant genes takes place well between different bacterial species due to the high food load and microbial load. Today, the use of antibiotics with a wide range has led to the emergence of multiple resistances in these bacteria. *Klebsiella pneumoniae* bacteria is one of the most important pathogens of the respiratory tract and *Escherichia coli* bacteria as a non-pathogenic bacterium or a pathogenic bacterium in humans or other organisms can lead to various health problems (Pollock et al., 1982). The average amount of presence of antibiotics in HWW in middle- and low-income countries was lower than in high-income countries. The most frequently reported antibiotics in HWW were tetracycline, trimethoprim, erythromycin, sulfamethoxazole, and ciprofloxacin, with concentrations ranging from 0.1 to 382 g/L (Parida et al., 2022). Clinically important antibiotics such as vancomycin (with a prevalence of 12%) have been considered as the second most common cause of hospital infections including endocarditis since the early 1970s (Buelow et al., 2018). Therefore, it is necessary to carry out a careful epidemiological monitoring of these bacteria (Pollock et al., 1982) announced “global threat.” Unfortunately, the category of facing strains resistant to multiple drugs is more than an exception, and it has become a common process in the treatment of patients, especially hospitalized patients, and to the extent it has a significant effect on the results of treatment measures (Esplugas et al., 2007). One of the causes of increasing resistance to antibiotics is their excessive consumption by patients and even in livestock and poultry feeding. Studies have shown that other causes such as the presence of non-antibiotic compounds such as disinfectants and heavy metals in the environment can also lead to resistance, because the genetic indicators of resistance to heavy metals and antibiotics are often placed together on plasmids and transposons (Lee et al., 2017). For this reason, a contaminated effluent not only increases metal-resistant bacteria, but also increases antibiotic resistance (Freitas et al., 2015).

Environmental and health risks of HWW

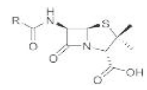
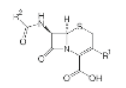
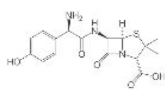
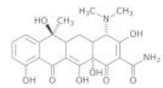
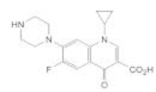
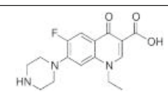
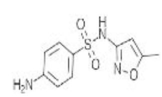
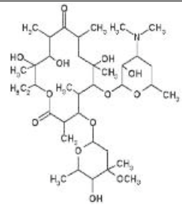
Wastewater from hospitals and healthcare centers is generally similar in quality to urban wastewater, but it may contain potentially toxic and infectious substances and compounds that endanger the health of the environment, healthcare workers, and the entire society. In developed countries and some developing countries, due to the fact that large amounts of water are consumed in hospitals, the produced wastewater is diluted and the effluent from hospitals and health centers is treated without additional pretreatment in urban wastewater treatment plants without causing specific health and environmental risk. Only under special conditions, such as the spread of acute diarrheal diseases or the situations such as COVID-19 pandemic, the wastes of patients should be specifically collected and disinfected (Siah et al., 2020). In countries where there is no sewage collection network, the discharge of sewage (hospitals and health care centers) in an untreated or incompletely treated form will cause unavoidable risks to the health of the society (Mesdaghinia et al., 2009, Al Aukidy et al., 2018). It should be noted that the toxic effects of chemicals in the wastewater of healthcare centers on bacteria and microorganisms active in the wastewater treatment process are among the other risks in the wastewater of these centers. The most important issue of concern in relation to hospital wastewater that contains intestinal pathogenic agents is bacteria, viruses, and parasitic agents; it is that these pathogens are easily transmitted through water. Contaminated wastewater produced from departments that treat intestinal patients are one of the most important issues and problems of environmental health during the epidemics and pandemics. Another issue that is raised is that some of the pathogenic agents present in hospital wastes have high drug resistance, for this reason, they are a serious threat to the health of society. In addition, some of the above microorganisms may transfer their drug resistance to other pathogenic agents, and for this reason, if infectious agents spread in the community, it will be difficult to treat them (Geddes-McAlister & Shapiro, 2019). Table 3 illustrates some of the most useful antibiotics, their application, and side effects. Partial amounts of chemicals enter the sewage collection networks due to disinfection and cleaning. However, if proper management is not applied, large amounts of chemicals may enter the sewage collection networks. Most of the partial amounts of pharmaceutical waste are emptied by different departments of the hospital and also by the pharmacy inside the sewage collection networks. If proper management is not applied, more amounts of pharmaceutical waste, including antibiotics and genotoxic drugs, may be discharged into sewage collection networks. On the other hand, some amounts of radioactive isotopes are discharged by oncology departments inside the sewage collection networks, which will not pose a threat to the health of the environment if proper management is applied.

Recent research has demonstrated the usefulness of several antibiotics from the cephalosporin family, such as ceftriaxone and cefixime (Cfx) (Li et al., 2012; Nadeem et al., 2020), and the macrolide family, such as azithromycin (Azr) in COVID-19 pandemic (Braz et al., 2020, Rushdi & Hameed, 2020) and in treating various malignant and viral infections. Due to the extensive usage of cephalosporin and macrolide antibiotics across the world, huge amounts of these medicinal items must be produced in order to keep up with demand. The effluent from hospitals and pharmaceutical manufacturers has increased water environmental contamination as a result of this extensive use. The renal tubules may become necrotic as a result of the high and inappropriate use of these antibiotics (Zhou et al., 2012). Azr is a semi-synthetic antibiotic that belongs to the macrolide class and is produced from erythromycin. Azr is very lipophilic, has a low oral bioavailability of 37% after consumption, and has a limited amount of antimicrobial water solubility (Hamzehloo & Karimi, 2016; Hernandez et al., 2019).

As mentioned before, the other antibiotic which is widely utilized during the COVID-19 pandemic is ceftriaxone. By attaching to proteins in the bacterial cell wall, ceftriaxone sodium produces its antibiotic properties (Kondaiah et al., 2017). Ceftriaxone is an antibiotic that is introduced to refined sugar and other food items in order to control the quality; therefore, its identification is crucial for protecting the environment, human health, and food industry quality. However, ceftriaxone does not quickly biodegrade; thus, removing it using conventional wastewater treatment methods may not be successful (Wang et al., 2018a, b). Thus, there is a considerable possibility that other forms of resistant bacteria may arise, which poses a serious threat to both the environment and public health (Liu et al., 2012, Kong et al., 2015; Moreira et al., 2016).

The insufficient removal of antibiotics from urban, agricultural, and industrial wastewater has resulted in the augmentation of different antibiotics in water resources. Consequently, prior to releasing polluted effluents into water sources, it is important to apply

Table 3 Physiochemical characteristics of some useful antibiotics and their application and side effects (Chaturvedi et al., 2021)

Antibiotic	Chemical formula	Structure	Clinical use	Side effects on human health
Penicillin G	$C_{16}H_{18}N_2O_4S$		Pneumonia, infections, meningitis, anthrax, gonorrhoea, and syphilis	Diarrhoea, Type-I hypersensitivity, nausea, type-III hypersensitivity (serum sickness), fever, rash, neurotoxicity, vomiting, seizures, angioedema
Cephalosporin	$C_{15}H_{21}N_3O_7S$		Pneumonia, gynaecological infections, urinary tract infections, bone and joint infections, and septicaemia	Perioperative anaphylaxis, positive coomb's test, maculopapular or morbilliform rash, serum sickness-type reaction, urticaria
Amoxicillin	$C_{16}H_{19}N_3O_5S$		Genitourinary tract infections, lower respiratory tract infection, tonsillitis, ear, nose, and throat infection, pharyngitis	Nausea, type- I, II, III, IV hypersensitivity reactions, diarrhoea, vomiting
Tetracycline	$C_{22}H_{24}N_2O_8$		Respiratory tract infection, urogenital, and gastrointestinal tract infection	Loss of appetite, sore throat, nausea, dizziness, headache, black hairy tongue, diarrhoea
Ciprofloxacin	$C_{17}H_{18}FN_3O_3$		Neonatal sepsis, urinary tract infection, cystic fibrosis, typhoid, and diarrhoea	Nausea, vomiting, tiredness, pale skin, abnormal liver, headache
Norfloxacin	$C_{16}H_{18}FN_3O_3$		Genitourinary tract infection	Muscle and joint pain, nausea, headache, rectal pain, dizziness, diarrhoea
Sulfamethoxazole	$C_{10}H_{11}N_3O_3S$		Respiratory tract and urinary tract infection, shigellosis	Insomnia, fatigue, nervousness, apathy, rash, pruritus, neuropathy, headache
Erythromycin	$C_{37}H_{67}NO_{13}$		Respiratory tract infection including bronchitis, pneumonia, pertussis, diphtheria	Nausea, vomiting, cramping, diarrhoea, upper abdominal pain, loss pf appetite

an appropriate and cost-effective strategy for completely removing antibiotics.

Treatment methods

In addition to the effects that hospital wastewater has on the environment, it will also cause many disturbances in the treatment plants. For example, one of the most important characteristics of wastewater treatment units for HWW is the presence of heavy metals in them. With the excessive increase of these metals, they will eventually cause problems for the microorganisms that are used in the biological treatment of wastewater and cause their growth inhibition (Lima e Silva et al., 2012, Alam et al., 2020). It should also be noted that the activated sludge method is widely used for the treatment of these wastewaters, and for this reason, a lot of aeration is necessary for this purpose. Frequent aeration causes a large amount of bacteria and viruses in the wastewater to penetrate outside in the form of bubbles and lead to the contamination of the employees and people present in the treatment plant. To deal with these risks, several standards for treatment environments are provided, and their implementation is necessary.

According to the standards provided by the World Health Organization, the effluents produced in hospital units, which include medicinal, infectious, antibiotics, and radioactive materials, should not enter nature directly (Khan et al., 2019a, b, Yan et al., 2020). For this reason, it is necessary to set up treatment units in hospitals in developed countries and some developing countries. In these units, it is necessary to go through various steps, which includes:

1. Hospital wastewater pretreatment

In order to reduce the negative effects of hospital wastewater and increase the treatment efficiency, as well as prevent damage to the treatment plant equipment, pretreatment of hospital wastewater is done. Different methods and techniques are used in pretreatment to reduce their effects, depending on what kind of polluting substances are present in them. For example, wastewaters containing radioactive materials are stored separately for a certain period of time, and their amount will decrease over time. In addition, in order to reduce the adverse effects of oil and colloidal particles suspended in wastewater, coagulant materials are used as well as various types of degreasing equipment (Azizkhani et al., 2021).

2. Hospital wastewater treatment

The most important and main steps for hospital wastewater treatment are done in this unit. In general, the packages considered for this purpose include several important parts, and they use equipment such as mechanical garbage collectors, pumping systems, clarifiers, aeration systems and equipment, chlorination equipment, and disinfection tanks. Overall, this equipment will perform three main steps, including physical and primary treatment, biological or secondary treatment, and finally tertiary treatment of wastewater.

Primary treatment of hospital effluents

Pretreatment of hospital wastewater is one of the most important steps in treating wastewater in medical environments, which is done in order to prevent damage to treatment plant equipment and to help improve the quality of its output (Gan et al., 2022). Sewage and effluents produced in hospital environments are one of the most dangerous types of wastewater due to the large volume of microorganisms, infectious particles, blood, and drug residues as well as detergents (Khan et al., 2021a, b). For this reason, according to the standards announced by the Environmental Protection Organization, all the wastewater produced in the hospital environment must be purified and reach the desired standards before entering the nature with the help of the sanitary wastewater treatment package. For this purpose, it is necessary to reduce the pollutants in them in different ways, including physical and chemical purification and biological treatments. Wastewater pretreatment is the first stage of treatment, which tries to help the next steps of treatment by collecting colloidal particles, oil and solid pieces in the wastewater, and reducing the radioactive effects of them. The measures taken in the pretreatment of hospital wastewater cannot prepare the effluents to the necessary standards for entering the nature. Rather, in this step, efforts are made to change the nature of the effluents in such a way that the purification equipment is not damaged in the next steps and does not cause the pipes and various parts of the devices to be blocked. In addition, the efficiency and effectiveness of the next steps in the chemical, physical, and biological treatment of wastewater should be improved.

Pretreatment of hospital wastewater containing blood

One of the most important compounds in hospital wastewater is blood, which in some cases is not an important issue and does not require pretreatment. On the other hand, sometimes, the amount of blood and clots created from them in the sewage may be enough to block the passage of the sewage in the purification devices. By measuring the amount of blood as well as the effects they may have on the next steps, they are taken into account in the pretreatment of hospital wastewater, and the effects of blood clots are reduced in different ways. Among the effective methods for this purpose, the wastewater containing blood is first heated with heating equipment and disposed of after disinfection (Nethercott & Holness, 1988; Wang et al., 2020). Disinfectants such as sodium hypochlorite are not used in the pretreatment of hospital wastewater where there is a lot of blood, because the effect of these substances to disinfect blood is low. In addition, sodium hypochlorite reacts with detergents and produces toxic and hazardous gases.

Pretreatment of radioactive wastewater

One of the most contaminant substances in hospital wastewater is the urine of patients in radiation therapy units, which should not enter the wastewater treatment package with other wastewaters (Carraro et al., 2017). As a stage of pretreatment of hospital wastewater, it could be mentioned the collection of urine and wastewater containing radioactive materials. Finally, these materials are kept separately for a certain period of time, and the radioactive level in them will decrease over time (Andres et al., 2011; Barbosa et al., 2022).

Pretreatment of wastewater containing hospital oil

Other pollutants found in hospital wastewater include fat and oil particles, which are added to sewage from different parts such as washing dishes in kitchens and halls, as well as oily particles in operating rooms. The entry of these particles into the equipment of the hospital's sewage treatment package will lead to their blocking and will cause failures (Khan et al., 2021a, b; Manouchehri & Kargari, 2017). For this reason, these particles are collected in different ways as a pretreatment step of hospital wastewater. The use of coagulants as well as mechanical equipment and degreasers can be useful for this purpose (Dehghani et al., 2014; Liu et al., 2010a, b).

Pretreatment of dental wastewater

The use of mercury-containing materials in dental units of hospitals and their entry into wastewater can be considered as one of the serious risks for the environment. For this reason, it is necessary to purify these materials in different ways before entering the purification equipment and to reduce their negative effects. For example, it is necessary to use an amalgam separator in sinks in dentistry, which are often installed next to the patient unit (Binner et al., 2022; Hylander et al., 2006). This equipment collects a large amount of polluting chemicals that are used to fill teeth, and after performing various pretreatment steps, mercury-free effluents will be able to enter the sewage system.

Disinfection in pretreatment of hospital wastewater

As mentioned, the presence of pathogenic bacteria and microorganisms that have a high spreading power is one of the most important threats to the health of nature. For example, during periods of time when infectious diseases such as cholera and corona virus, spread, feces, urine, and vomiting of patients are considered a serious risk. For this reason, it is necessary to disinfect in different ways. For example, the use of lime milk is effective in the pretreatment of these wastewaters. For this purpose, it is necessary to use lime in a ratio of one to two in the tanks and sewage wells, and it takes about 6 h to disinfect the feces and vomit of these patients. A one-to-one ratio of lime can also be effective for urine disinfection (Carraro et al., 2017, Khan et al., 2021a, b).

Overall, Fig. 2 illustrates the conventional methods for pretreatment of hospital wastewater.

In addition to the abovementioned methods, in order to collect larger particles and solids, equipment such as a mechanical garbage collector is used in the sewage inlet to the treatment site to prevent blockage of other equipment. Among the most important advantages of pretreatment of hospital and treatment unit wastewater, the following can be mentioned:

- Preventing the spread of infectious diseases by preventing bacteria, viruses, and dangerous microorganisms from entering other parts of the treatment plant
- Increasing the efficiency of other steps of wastewater treatment
- Preventing damage to treatment plant equipment and blocking pipes due to the accumulation of fat particles and the deposition of polluting substances, etc.

Secondary treatment of hospital effluents

Conventional ASPs

The activated sludge process (ASP) is a preferred technology in wastewater treatment due to its many advantages compared to other biotechnologies (Koh et al., 2009). ASPs have been used to deal with many different types of wastewater (Hamid & Eskicioglu, 2012). More than 90% of domestic wastewater treatment systems from urban areas used the ASP as the main process (Fernandes et al., 2013). The characteristic of the ASP is the conversion of organic matter in wastewater into carbon dioxide, bacterial cells, and water (Zhang & Chen, 2020). The bacterial cells are then separated as sludge for further processing steps. It can achieve very high treatment efficiencies with a wide variety of organic pollutants present in the wastewater (Peng et al., 2019). The ASP has shown many advantages, such as avoiding the generation of secondary pollutants and being a cost-effective technology. Many advanced technologies with ASPs are employed to treat wastewater, for instance, sequencing batch reactor (SBR), intermittent cycle extended aeration system (ICEAS), and UNITANK (Dan et al., 2021). The SBR works in batches with activated sludge based on a fill-and-draw principle. The SBR operation consists of five phases: fill, react, settle, decant, and idle, and at least two tanks are used in the SBR system due to intermittent influent (EPA, 1999). With advantages such as being widely applied to treat many different types of wastewater, used in different operating conditions (aerobic, anaerobic, and anoxic conditions), energy-saving, and low cost, SBRs were often seen as the basis for later modified systems (Marsili-Libelli et al., 2008). ICEAS, one of the modified systems from SBR, is an enhanced version that overcomes the shocks caused by unequal loads while operating the SBR using continuous flow in all phases of the processing cycle. This adjustment helps the ICEAS more effectively to remove nutrients present in wastewater (Zhang et al., 2012). Similar to ICEAS technology, UNITANK is considered modified from SBR (Feyaerts et al., 1997). Unlike SBR and ICEAS, the influent and effluent are maintained continuously during the operation of UNITANK. UNITANK combines traditional activated sludge treatment with SBR to treat biological wastewater into three units, A, B, and C (Brdjanovic et al., 2000). Furthermore, some of the modified systems from SBR have been commercialized and become popular in the market, such as the Culligan membrane bioreactor (MBR) system and LUCAS cyclic activated sludge system (LUCAS is the family name of wastewater technology developed by Waterleau, Belgium) (Kwon et al., 2008). With advantages such as space-saving, applicable to various types of wastewater, high treatment efficiency, and less sludge generation, these commercialization systems are increasingly becoming popular to use in wastewater treatment. However, their disadvantages such as high cost, complicated operation, and maintenance are the problems of concern. With the continuous improvement from traditional activated sludge technologies, besides removing common organic pollutants in wastewater, the ASP can also be applied to remove emerging organic contaminants in wastewater, such as micropollutants and nano/microplastics (Enfrin et al., 2019). The mechanisms and removal efficiency of emerging pollutants in wastewater using the ASP have been demonstrated in recent studies (Lakshminarasimman et al., 2021). This helps to confirm the wide applicability of the ASP in wastewater treatment.

HWW treatment with ASP is widely used in the world. In Greece, a HWW treatment system was designed and built by Kosma et al. (2010), which includes a sand filter, mixing tanks, disinfection, and aeration tanks. Disinfection was done by chlorine, and the removal of active medicinal compounds was done up to 45.51%. Diclofenac showed the most significant elimination among pharmaceutical compounds (Kosma et al., 2010). The combination of HDPE biofilm and ultrafiltration with ASP for wastewater treatment including PhAC was done by Mousaab et al. (2015). Removal of 100, 93, and 91% was shown for TSS, COD, and TN, respectively, in this system, and 78% purification was measured for PhAC. In this study, diclofenac, trimethoprim, and hydrochlorothiazide confirmed the low removals of 30%, 21%, and 11%, respectively. In addition, according to the observations of this study, there was a significant improvement in performance after using HDPE biofilm in the treatment system (Mousaab et al., 2015).

The performance of two conventional large-scale ASPs for HWW treatment in treatment plants in China was studied by Yuan et al. (2013). In the use of two ASPs, the percentage of PhAC removal was observed, and it was measured as 93–98% and 72–95% for compounds containing olanzapine and risperidone, respectively. Lorazepam, oxazepam, carbamazepine, clozapine, sulpiride, and quetiapine showed resistance to degradation due to their complex structure (Yuan et al., 2013). Additionally, compounds like lorazepam, oxazepam, zaleplon, and sulfide have been found to have poor PhAC removal in a single ASP. This is because the base compound conjugates in the effluent of the wastewater treatment process return to their original form following enzymatic changes in the treatment device (Yuan et al., 2013). Lien et al. (2016) studied the PhAC removal from HWW of Vietnam (Lien et al., 2016). For the purpose of the observation, two full-scale treatment systems were tested. The primary unit had a median PhAC removal of 66.3% and was constructed using mechanical and chemical treatment followed by a traditional ASP. Following the ASP, a sand filtration unit was used to build the second unit, which had an average PhAC elimination rate of 55.2% (Lien et al., 2016). Prado et al. (2011) investigated the treatment of HWW in Brazil by a large-scale ASP with extended aeration and chlorination (Prado et al., 2011). The combined device had an elimination potential of 75.3% for COD, 85.7% for BOD, and 84% for ammonia. Azar et al. in Iran (2010) used an ASP with aerobic and anaerobic steps to eliminate TSS, COD, BOD, nitrite, and nitrate to greater than 90% (Azar et al., 2010). Al Qarni et al. (2016) studied the performances of ASPs for the treatment of HWW (Al Qarni et al., 2016). Sand filtration and chlorination were used to observe the results of the ASPs, which were constructed from the most efficient aeration units. Eighty-three percent and 97%, respectively, of the binary treatment structures were removed by the illustrated PhACs. Despite the fact that more than 80% of the substance has been eliminated, negative elimination of nitrite and nitrate was found in both structures (Al Qarni et al., 2016). The reason for this behavior can be the absence of anaerobic denitrification and denitrification units (Jain et al., 2020; Khajouei et al., 2019, 2023). The percentage of PhACs eliminated by ASP-based technologies ranged from 40 to 99% (Majumder et al., 2021). Additionally, since chlorination was integrated into the ASP, PhAC removal has significantly improved. This is because chlorine in water releases a variety of radicals with high oxidizing potential, making it possible for the complex PhACs to be broken down. In all of the ASP-based studies, the average TSS removal was found to be greater than 90%. The traditional ASP can be an effective method for removing BOD, COD, and ammonia from hospital wastewater if it is properly modified or provided with essential pre-treatment, as shown by the observed elimination rates of around 80% and higher.

Constructed wetlands

Constructed wetlands (CWs) are engineered systems that have been designed and constructed to utilize the natural processes involving wetland vegetation, soils, and the associated microbial assemblages to assist in treating wastewaters. They are designed to take advantage of many of the same processes that occur in natural wetlands, but do so within a more controlled environment. CWs for wastewater treatment may be classified according to the life form of the dominating macrophyte, into systems with free-floating, floating leaved, rooted emergent, and submerged macrophytes (Brix & Schierup, 1989). Further division could be made according to the wetland hydrology (free water surface and subsurface systems), and subsurface flow CWs could be classified according to the flow direction (horizontal and vertical) (Vymazal & Kröpfelová, 2008a, b). A simple scheme for various types of constructed wetlands is shown in Fig. 3.

Various types of constructed wetlands differ in their main design characteristics as well as in the processes which are responsible for pollution removal.

A typical free water surface constructed wetland (FWS CW) with emergent macrophytes is a

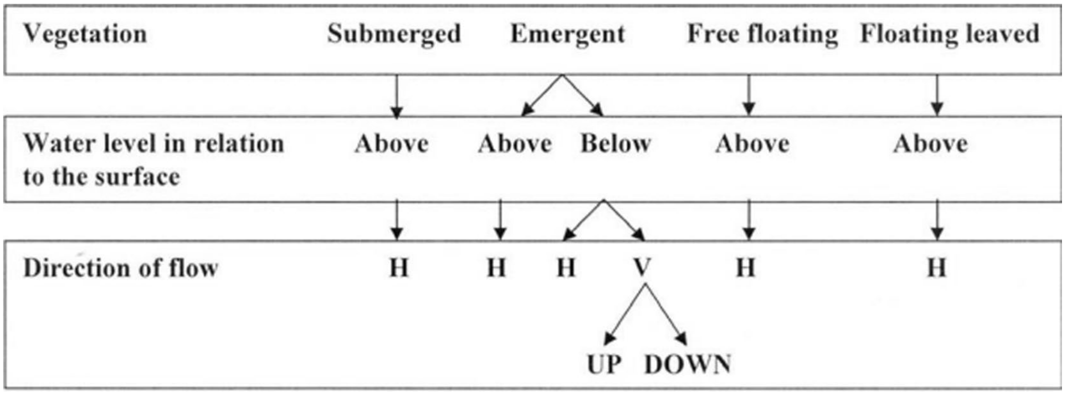


Fig. 3 The major characteristics of various types of constructed wetlands for wastewater treatment. *H* horizontal, *V* vertical (Vymazal, 2010)

shallow sealed basin or sequence of basins, containing 20–30 cm of rooting soil, with a water depth of 20–40 cm. Dense emergent vegetation covers a significant fraction of the surface, usually more than 50%. Besides planted macrophytes, naturally occurring species may be present (Kadlec, 1995). Plants are usually not harvested, and the litter provides organic carbon necessary for denitrification which may proceed in anaerobic pockets within the litter layer.

FWS CWs are efficient in removal of organics through microbial degradation and settling of colloidal particles. Suspended solids are effectively removed via settling and filtration through the dense vegetation. Nitrogen is removed primarily through nitrification (in water column) and subsequent denitrification (in the litter layer) and ammonia volatilization under higher pH values caused by algal photosynthesis. Phosphorus retention is usually low because of limited contact of water with soil particles which adsorb and/or precipitate phosphorus. Plant uptake represents only temporal storage because the nutrients are released to water after the plant decay (Kadlec, 2009).

Constructed wetlands with horizontal subsurface flow (HF CWs) consist of gravel or rock beds sealed by an impermeable layer and planted with wetland vegetation. The wastewater is fed at the inlet and flows through the porous medium under the surface of the bed in a more or less horizontal path until it reaches the outlet zone, where it is collected and discharged. In the filtration beds, pollution is removed by microbial degradation and chemical and physical processes in a network of aerobic, anoxic, anaerobic zones with aerobic zones being restricted to the areas adjacent to roots where oxygen leaks to the substrate (Vymazal, 2010). This type of constructed wetland was developed in the 1950s in Germany by Käthe Seidel who designed the HF CWs using coarse materials as the rooting medium. In the 1960s, Reinhold Kickuth suggested soil media with high clay content and called the system the "root zone method" (Kickuth, 1977). In the early 1980s, the HF CW technology was introduced to Denmark, and by 1987, nearly 100 soil-based systems were put in operation. Despite problems with surface flow soil-based systems exhibited high treatment effect for organics and suspended solids, reed bed area of 3–5 m^2 PE^{-1} (population equivalent) was used (Brix & Schierup, 1988). During the late 1980s, the HF CWs were also introduced to other countries, such as Austria and UK, and then in the 1990s, this system spread into most European countries and also to North America, Australia, Asia, and Africa (Vymazal & Kröpfelová, 2008a, b). In the late 1980s, soil material was replaced by coarse material, and at present, washed gravel or rock with grain size of about 10–20 mm is commonly used (Vymazal & Kröpfelová, 2008a, b). Organic compounds are effectively degraded mainly by microbial degradation under anoxic/anaerobic conditions as the concentration of dissolved oxygen in the filtration beds is very limited (Vymazal & Kröpfelová, 2008a, b). Suspended solids are retained predominantly by filtration and sedimentation, and the removal efficiency is usually very high (Vymazal & Kröpfelová, 2008a, b). The major removal mechanism for nitrogen in HF CWs is denitrification. Removal of ammonia is limited due to lack of oxygen in the filtration bed as a consequence of permanent waterlogged conditions (Vymazal, 2007). Phosphorus is removed primarily by ligand exchange reactions, where phosphate displaces water or hydroxyls from the surface of iron and aluminum hydrous oxides. Unless special materials are used, removal of P is usually low in HF CWs (Vymazal, 2007).

Vertical flow constructed wetlands (VF CWs) (Fig. 4) were originally introduced by Seidel to oxygenate anaerobic septic tank effluents (Seidel, 1965). However, the VF CWs did not spread as quickly as HF CWs probably because of the higher operation and maintenance requirements due to the necessity to pump the wastewater intermittently on the wetland surface. The water is fed in large batches, and then the water percolates down through the sand medium. The new batch is fed only after all the water percolates and the bed are free of water. This enables diffusion of oxygen from the air into the bed. As a result, VF CWs are far more aerobic than HF CWs and provide suitable conditions for nitrification. On the other hand, VF CWs do not provide any denitrification. VF CWs are also very effective in removing organics and suspended solids. Removal of phosphorus is low unless media with high sorption capacity are used. As compared to HF CWs, vertical flow systems require less land, usually 1–3 m^2 PE^{-1} (Brix & Arias, 2005). The early VF CWs were composed of several stages with beds in the first stage fed in rotation. At present, VF CWs are usually built with one bed, and the system is called "compact" VF CWs (Cooper, 1999). VF CWs are very often used to treat domestic and municipal wastewater and especially when discharge limits are set for ammonia–nitrogen. However, in the literature, numerous reports have been published on the use of VF CWS for various types of wastewater such as refinery effluent (Aslam et al., 2007), composting leachate (Lindenblatt & Horn, 2007), airport runoff (McGill et al., 2000), dairy (Vymazal, 2010), or cheese production effluent (Kern & Idler, 1999).

Due to their adaptability and durability in eliminating pollution, CWs are gaining popularity in the field of wastewater remediation. Some studies have demonstrated that CWs can degrade recalcitrant organic contaminants in addition to successfully removing organic compounds from wastewater (Auvinen et al., 2017; Casierra-Martinez et al., 2020). Auvinen et al. (2017) investigated how well a transportable pilot-scale constructed wetland with an aerated subsurface stream handled an effluent from a health facility in Belgium. For COD and ammonia nitrogen, respectively, high elimination efficiencies of 83% and 95.7% have been achieved. Atenolol, on the other hand, had a high elimination rate of 94.6%, while diclofenac, carbamazepine, and sulfamethoxazole had low elimination rates of 36%, 12%, and 50%, respectively, according to the unit (Auvinen et al., 2017). Another study looked into how well a full-scale, two-staged CW worked to treat HWW in Nepal. Interestingly, TSS, BOD, COD, ammonia nitrogen, and bacterial contamination were removed by the system (Shrestha et al., 2001). When compared to other methods of treatment, CWs performed better at removing organic

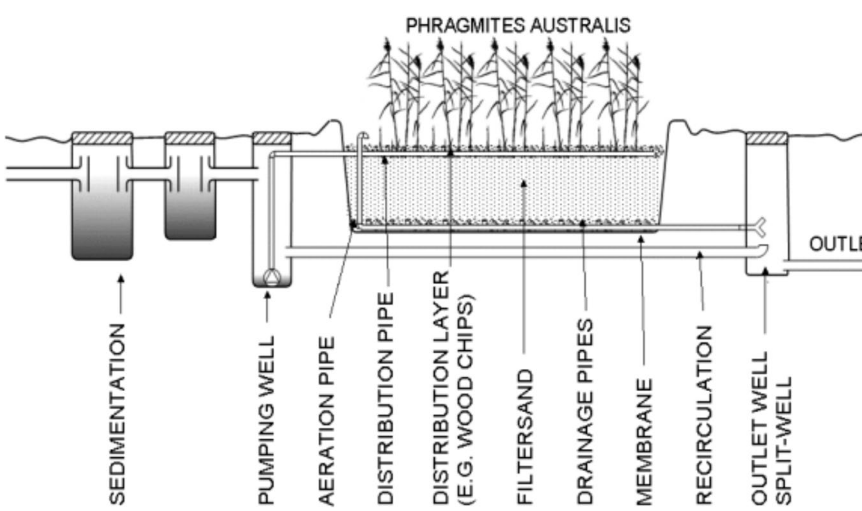


Fig. 4 Layout of a vertical-flow constructed wetland system for a single household. Raw sewage is pre-treated in a sedimentation tank. Settled sewage is pulse-loaded onto the surface of the bed by a level-controlled pump. Treated effluent is collected in a system of drainage pipes, and half of the effluent is recirculated back to the pumping well (or to the sedimentation tank) (Vymazal, 2010)

compounds, nutrients, and bacteria. This may be due to the effective nitrification–denitrification steps that occur in CWs and altered aeration regimes (Auvinen et al., 2017). CWs, on the other hand, have produced average results when treating PhACs and various micropollutants. Various factors, including daily fluctuations in influent composition, low dissolved oxygen (DO) concentration, and low hydraulic retention time (HRT), can account for this variation in the outcomes of PhAC elimination (Auvinen et al., 2017; Conkle et al., 2012). The cost-effective treatment of HWW may require the application of a longer HRT, adequate aeration, and the integration of CWs with other remediation strategies.

Membrane bioreactors

MBR combines membrane-based separation via microfiltration or ultrafiltration with biological treatment methods. Due to its effectiveness and low footprint in comparison to other treatment methods, such as CWs, this method is receiving a lot of attention right now (Chitnis et al., 2004, Cartagena et al., 2013, Alipourzadeh et al., 2016, Farsi et al., 2016, Prasertkulsak et al., 2016).

Over the past two decades, membrane bioreactors (MBRs) have been designed and operated for treatment of a variety of pollutants, such as particulates, carbonaceous substances, nutrients, and pathogenic microorganisms (Mir-Tutusaus et al., 2018). Compared with these pollutants, which can be removed easily by conventional methods, the removal of certain other pollutants, particularly the micropollutants (pharmaceuticals, personal care products, steroid hormones, surfactants, industrially generated chemicals, etc.), is often very different. Therefore, examination of the fate and removal of micropollutants during wastewater treatment is very much crucial for any of the treatment process to avoid their discharge into the environment (Luo et al., 2014). In this section, characterization and different removal processes utilizing MBRs with a focus on the fate and mechanism of micropollutant removal are discussed. Membrane bioreactor (MBR) systems seem to be promising under this scenario, due to their several advantages, including high performance efficiency compared to conventional activated sludge treatment plant (CASP), less space requirement, and environment friendliness. Therefore, it has been recognized as a key technology for water reuse and recycling in many developed and developing countries (Judd, 2010). MBR is a hybrid process integrating the membrane technique with biological treatment, which enables CASP to be operated as a single-step process by avoiding the need for a secondary clarifier. Figure 5 compares the conventional wastewater treatment process with that employing MBR technology. Also, various advantageous and limitations of MBR system for micropollutant removal are as follows (Goswami et al., 2018):

Advantages:

- Micropollutant removal can be achieved up to the discharge limits
- Low working space is required and lower foot print
- Utilized as a pre-treatment technique for RO and NF with excellent effluent quality
- Full retention of bacterial flocs with the membrane
- Membrane performed the biomass retention
- Performed at elevated solid retention time (SRT)
- Faster removal of persistent micropollutants
- High MLSS (10–15 g L^{-1}) and high SRT depict low sludge yield
- Low feed-to-microorganism ratio (F/M)

Limitations:

- Membrane fouling
- No significant removal of micropollutant when activated sludge process and MBR operate at comparable SRT. Enhanced removal efficiency could be achieved with integrated approach
- Requires high energy input to aerate MLSS and to reduce the membrane fouling
- Very less removal efficiency is achieved for some recalcitrant micropollutants, e.g., carbamazepine and diclofenac (5–10%)

In general, the MBR system is categorized into two kinds in accordance with the configuration: (1) submerged membrane bioreactor (SMBR) and (2) side-stream membrane bioreactor. Figure 5 shows a brief schematic of MBR system. Earlier, the side-stream MBR was developed where the membrane module is placed outside the bioreactor for the recirculation pump. Due to its high-energy consumption, in the 1980s, submerged-MBR systems were further developed where the membrane module was submerged

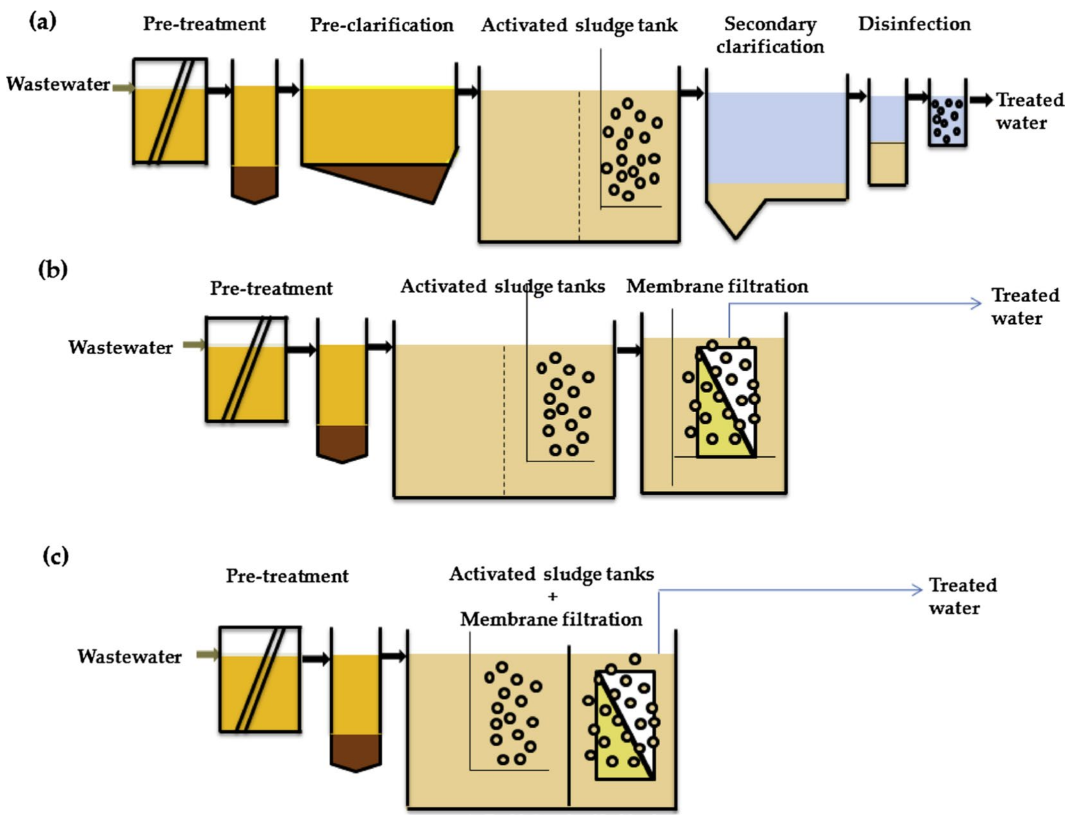


Fig. 5 Scheme of the **a** conventional wastewater treatment process, **b** side stream MBR, and **c** submerged MBR (Goswami et al., 2018)

within the bioreactor, thus permitting the effluent to pass through with sludge retention. In a SMBR, aeration maintains the activated sludge in suspended mode, limiting the membrane fouling. Figure 6 represents different types of membrane fouling mechanism within an MBR system.

According to Prasertkulsak et al. (2016), PhACs, including estradiol, ibuprofen, and trimethoprim, have been almost completely eliminated, but carbamazepine and diclofenac demonstrated very low removal efficiency in this method. They applied aeration at 340 L/min to the pilot-scale MBR unit and reported an average PhAC elimination of 75.13% after an HRT of 3 h (Prasertkulsak et al., 2016). Wen and others (2004) treated a clinic effluent in China with a submerged MBR, which eliminated BOD and ammonia by more than 90% (Wen et al., 2004). In another study, HWW was dealt with using a pilot-scale submerged MBR with hollow ultrafiltration fiber membranes. After a 14-h HRT, this system resulted in a 95% removal rate of TSS, BOD, and ammonia (Verlicchi et al., 2010a, b). Cartagena et al. (2013) used an MBR-based treatment to remove more than 98% of COD, 99% of ammonia, and 82% of total nitrogen (TN). However, the device was also able to eliminate between 78 and 82% of the PhACs (Cartagena et al., 2013). Kovalova et al. (2012) reported the use of a pilot-scale MBR setup with an oxic and an anoxic chamber to remediate a health center effluent in Switzerland (Fig. 7a) (Kovalova et al., 2012). After the MBR unit, a primary clarifier was used to handle the 1.2 m^3/day flow that was handled by the treatment unit. While the average amount of PhACs eliminated was around 90%, the average amount of iodinated X-ray comparison media was only 2%. Phenazonec and oseltamivirc had excessive negative removal rates of −158 and −42%, respectively (Kovalova et al., 2012). Kovalova et al. (2013) used powdered activated carbon to combine the MBR setup in situ with ozone treatment, UV treatment, and adsorption

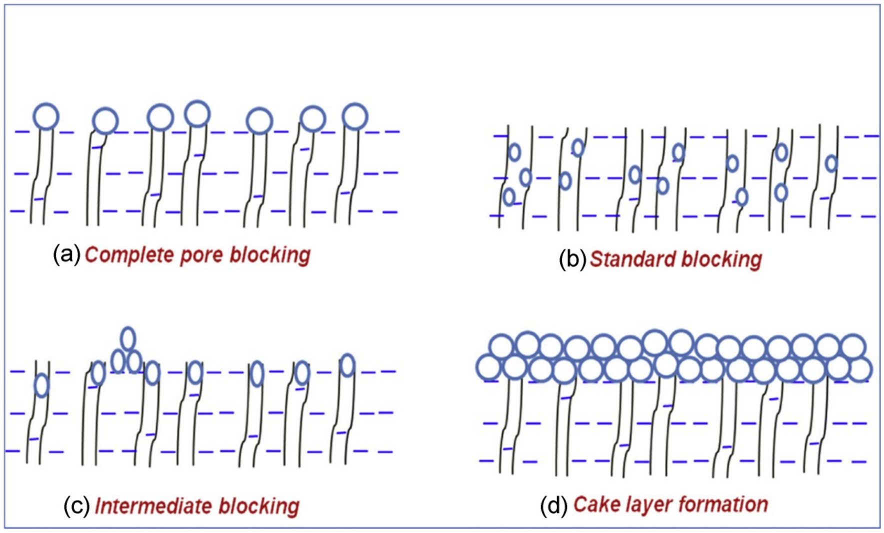


Fig. 6 Different types of Fouling mechanisms due to **a** complete pore blocking, **b** intermediate blocking, **c** standard blocking, and **d** cake layer formation

to be able to dispose of the media that contained X-rays (Fig. 7b) (Kovalova et al., 2013). The end level of PhACs and X-ray containing media stretched out to 99% and 51%, individually, while the emanating MBR was impacted by ozone cure utilizing 1.08 gO_3/g dissolved natural carbon (DOC). Also, the disposal level of X-ray containing media expanded to 62%, when the gushing from MBR treatment was supplanted by adsorption through powdered activated carbon (dose = 23 mg/L). While the MBR emanating became exposed to UV cure (2400 J/m^2), corruption of X-ray containing media duplicated to 66%, but the removal of PhACs dropped to 93% (Kovalova et al., 2013).

The other study found that using an MBR pilot unit resulted in a PhAC elimination rate of 34%. PhACs, such as oxcarbamazepine, paracetamol, sulfadiazine, and sulfamethoxazole, have, on the other hand, been almost entirely eliminated (Nielsen et al., 2013). In addition, the MBR effluent was subjected to adsorption with powdered activated carbon at a concentration of 450 mg/L to improve the system's overall performance. This increased the PhAC elimination rate to approximately 80 to 90% (Nielsen et al., 2013). Beier et al. claimed that an MBR was able to remove more than 95% of COD and ammonia after a retention time of 31.3 h (Beier et al., 2012). Beier et al. utilized an MBR-based treatment machine combined with reverse osmosis to remove PhACs from hospital effluent. PhACs were eliminated at a rate of more than 99% using this method (Beier et al., 2010). A blend of MBR and UV cure was utilized to treat clinical foundation emanating from Luxembourg. This pilot-scale treatment unit treated a flow rate of around 3.33 m^3/day (Köhler et al., 2012). A 10-kW UV medium-strain lamp was used to treat the wastewater, and hydrogen peroxide was also added to improve the device's overall performance. This method resulted in a COD removal percentage of 90% and TN removal percentage of 70%. In addition, a median percentage of 73% of PhACs was removed. Unfortunately, there was almost no elimination of some PhACs like erythromycin and ifosfamide (Köhler et al., 2012). BOD, COD, ammonia, and TSS could be efficiently eliminated from HWW by MBR-based pilots. Additionally, it was discovered that PhACs can be effectively eliminated by MBR systems. PhACs may have the potential to achieve a median removal rate of around 60% when utilized in the absence of any more advanced treatment. When the MBR effluent was subjected to UV treatment or adsorption, the overall performance of the MBRs also improved. However, when the MBR was used in conjunction with ozone treatment or reverse osmosis, the greatest amount of PhACs was found to be removed. MBR-based technology was found to be more effective than other treatment methods, with high removal rates of BOD, COD, TSS, ammonia, and PhAC. However, membrane clogging and fouling can occur with MBR-based technologies. In general, they require regular chemical cleaning and are expensive to maintain. The MBRs' overall performance suffers as a result

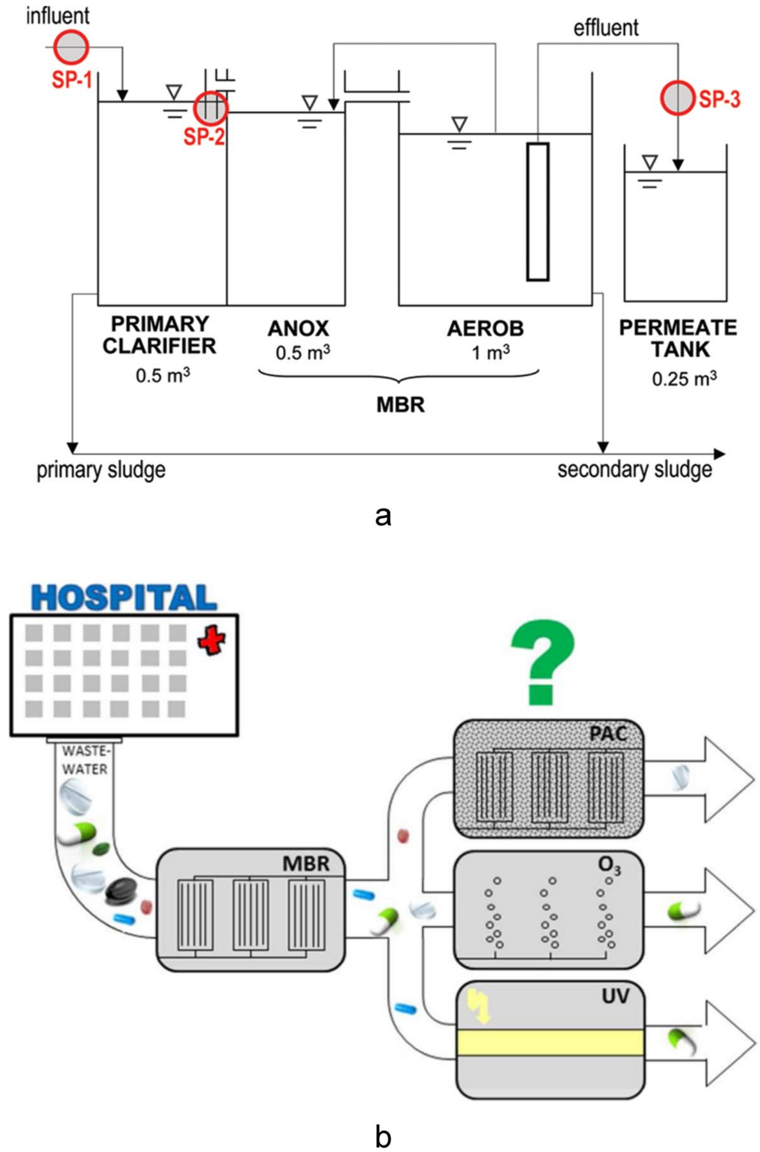


Fig. 7 **a** The MBR wastewater treatment unit (Kovalova et al., 2012) and **b** the schematic of hybrid MBR/PAC/O_3/UV unit (pharmaceuticals, metabolites, and industrial chemicals were passed through the MBR) (Kovalova et al., 2013)

of membrane fouling (Khajouei et al., 2018, 2017a, b; Majumder et al., 2021; Mutamim et al., 2012; Perreault et al., 2016; Zsirai et al., 2012). This drawback could be tackled via gas-scrubbing, aeration, or regular backwashing (King, 2007; Pang et al., 2017).

Moving bed biofilm reactors

Biofilm reactors mostly used for the removal of organic matter and nutrients (i.e., nitrogen and phosphorus), prior to occurrence of the development of moving bed biofilm reactors, were biological trickling filters, aerated submerged fixed film biofilm reactors, fluidized-bed reactors, and rotating biological contactors (Rittmann, 1982). These types of systems presented several flaws such as not having effective working volume in the case of trickling filters or be susceptible to mechanical failures (i.e., RBC). Moreover, aerated submerged fluidized-bed reactors showed frequent hydraulic instability and difficulties in having even biofilm distribution on support due to concentration gradients (Rusten et al., 2006). To overcome these limitations in the late 80 s and early 90 s, the moving bed biofilm reactor was developed in Norway (European Patent no. 0,575,314; US Patent no. 5,458,779). Its development originated from the Norwegian authorities for pollution control to address the needs of having small sewage treatment plants and easy to install and operate in small communities (i.e., 20–2000 people). However, the interest in upgrading existing treatment plants and enlarging volumetric capacity was the most predominant driver in the development of more reliable biofilm-based technologies. Biofilm technologies had to face strong diffusional limitations due to poor mass transfer which led to reduced reaction rate. It was in this context that the idea of having free-floating moving carriers had been generated and seen as a valuable alternative and solution to the other system flaws. The advantages of moving bed biofilm technology over the other biofilm-based technologies and conventional activated sludge systems are:

- Upgrading performance and volumetric treatment capability in existing wastewater treatment plant with minimal additional costs
- Sludge does not need recirculation because the biomass is retained as a biofilm on carriers
- Less clogging and no need to backwash when compared to fixed-film reactors
- Footprint is consistently reduced
- Biofilm is more resistant to variation in influent characteristics (e.g., shock loads, pH, temperature, and toxic compounds) (Dezotti et al., 2018)

Existing infrastructures can be equipped and adapted to host MBBR configurations with small modifications making it valuable to be used as an upgrade for conventional activated sludge (CAS) plants (Salvetti et al., 2006). Being a compact technology with small footprints and ease in operations makes it also an option for small decentralized wastewater treatment implementation. An overview of established and potential MBBR configurations is discussed in a separate section below. Moving bed biofilm reactors are applied in aerobic and anaerobic/anoxic systems depending on the process application. In the case of aerobic treatment (e.g., COD/BOD removal and nitrification), aeration is supplied at a greater level than the dissolved oxygen (DO) requirements for microbial activity. Air is supplied mainly with coarse aeration systems due to the mixing purpose and, therefore, contributing to increasing operational costs. Hence, mixing in aerated systems is done by agitation while in anaerobic/anoxic configuration, mechanical mixing and/or recirculation can be used (Odegaard, 1999). Mixing in MBBR systems is challenging, due to potential in biocarrier stagnancy and, particularly, in the early stage of biofilm development. Indeed, when biocarriers are uncolonized and biofilm is not yet established, they float due to their lower density compared to water. As microbial population starts to attach and develop on the biocarrier's protected surface area, they become heavier (e.g., greater density than water) and therefore mixing capabilities are improved. However, stagnant regions within the reactor may still exist due to poor air-flow patterns. Hence, mixing properties could be jeopardized even after long operation period from reactor startup, and aeration systems are of crucial importance to improve the performance of the MBBR process (Rusten et al., 2006).

Ooi et al. (2018) treated HWW at a Danish health center using a six-stage MBBR with a filling ratio of 50%. The results were promising, with ammonia nitrogen and TOC elimination rates of 91.3% and 88.4%, respectively. The machine eliminated emerging contaminants (ECs) by a mean of more than 80%, with high removal rates of more than 95% for atenolol, iohexol, and iopromide (Ooi et al., 2018, Parida et al., 2022). Casas et al. (2015) conducted a similar study that constructed a three-degree MBBR at Aarhus College Hospital in Denmark to treat the hospital's wastewater. Ammonia nitrogen was nearly completely eliminated from the effluent using this method, and COD and TOC were eliminated with efficiencies of 81.3 and 79.1%, respectively. Over 70% of common PhACs were removed by the system, with propranolol being eliminated at 95% (Casas et al., 2015). The aforementioned research demonstrated that the MBBR-based strategies were successful in preventing organics and vitamins from HWW. However, it could not be completely removed once it reached PhACs. This could be caused by the constant presence of such toxic organic contaminants, which can impede microorganism growth. The performance of MBBRs can be enhanced by combining them with advanced oxidation processes (AOPs), filtration, and adsorption-based techniques, allowing for the complete elimination of ECs (Shahavi et al., 2011; Mofidian et al., 2020, Parida et al., 2022).

Tertiary treatment of hospital effluents

Advanced oxidation processes

Hydroxyl and sulfate free radicals have higher reactivity than free electrons. This feature of them was used in 1900 for the first time (Grignard, 1900); the method and advanced test protocols of AOPs were introduced and used in various industries. Considering that in these processes conditions are provided for the removal of organic substances, it can be resulted that these substances cannot be removed by biological methods in the conditions in which it is used (Selakjani et al., 2021). For example, in pesticides and insecticides, there are very strong organic substances that are harmful and cannot be decomposed by aerobic and anaerobic organisms (Peyravi et al., 2017).

Despite the high efficiency of advanced processes, it is important to know that these methods are not cost-effective enough. For this reason, biological methods are used to remove organic matter as much as possible. Some organics can only be removed with AOPs and similar processes, such as dioxane, MTBE, NDMA, atrazine, diuron, diclofenac, carbamazepine, ibuprofen, hormones, geosmin, MiB.

The main feature of AOPS processes is the release of hydroxyl and sulfate free radicals to decompose strong organic materials. In order to release these radicals, there are various methods, the most common of which are described below.

Advanced oxidation with ozone O_3 (Machado et al., 2007) One of the practical methods for producing hydroxyl OH free radicals in advanced oxidation is the use of O_3 (ozone). After entering water or sewage and other fluids that you intend to treat, ozone reacts with water molecules. The relationship of the reactions that ozone performs to produce OH or hydroxyl radical is as follows:

$$O_3 + H_2O \rightarrow H_2O_2 + O_2 O_3 + H_2O \rightarrow 2OH^* + O_2$$

This method is easy and cheap, and the only negative point in it is the production of dangerous side compounds. For this reason, advanced oxidation using ozone method is less used in purification and more combined methods are used.

Oxidation by peroxon method (Kurt et al., 2017) In order to improve the ozone-based AOP method, a combination of H_2O_2 and O_3 can be used to generate OH hydroxyl radicals. By choosing the appropriate proportion of ozone and AOPs according to the type of effluents and environmental conditions and the amount of organic matter, ideal conditions for OH separation are provided. The reactions between H_2O_2 and O_3 in this method are as follows:

$$H_2O_2 \rightarrow HO_2 - + H \ + H_2O_2 \rightarrow HO_2 - + H^+$$

$$HO^{2-} + O_3 \rightarrow OH^* + O_2 - + O_2 HO^{2-} + O_3 \rightarrow OH^* + O^{2-} + O_2$$

Advanced oxidation with ozone and UV rays Considering that ozone alone does not have an ideal effect on the release of hydroxyl OH, for this reason, UV rays can be used along with it. After introducing the ozone in the water, they react together and produce H_2O_2, and the reactions are as follows:

$$O_3 + H_2O \ + h\nu \rightarrow H_2O_2 + O_2 O_3 + H_2O \ + h\nu \rightarrow H_2O_2 + O_2$$

AOPs with Fenton (Dolatabadi et al., 2020) Some metals, including Fe, can also be used to release hydroxyl radicals. Iron in contact with H_2O_2 is capable of producing OH* and is effective in the process of removing strong organic substances. The process of using iron and H_2O_2 to produce OH* is called Fenton. The following reactions show both the process of producing OH* with the help of iron and H_2O_2:

$$Fe^{2+} + H_2O_2 \rightarrow Fe^{3+} + OH^* + OH^- Fe^{2+} + H_2O_2 \rightarrow Fe^{3+} + OH^* + OH^-$$

$$Fe^{3+} + H_2O_2 \rightarrow Fe^{2+} + HO_2{}^* + H^+ Fe^{3+} + H_2O_2 \rightarrow Fe^{2+} + HO_2{}^* + H^+$$

Advanced oxidation with photo-Fenton (Segura et al., 2021) Photo-Fenton can be mentioned among other effective methods in the advanced oxidation process. In this method, in addition to iron salt and H_2O_2, ultraviolet rays are also used. For this reason, the OH production process is improved, and the purification efficiency increases with it. According to the type of organic substances and their amount, as well as the environmental conditions, any of the following systems can be used to produce hydroxyl:

- UV/H_2O_2/Fe (II)-oxalate
- UV/H_2O_2/Fe(II)
- UV/H_2O_2/Fe(III)

Oxidation by electro-Fenton method (Ahmadzadeh & Dolatabadi, 2018) The most advanced method in AOPs is to use electricity and Fenton together. In this method, dangerous substances and side compounds are not produced; more hydroxyl is produced; and for this reason, the purification process is carried out at a higher speed.

Types of advanced oxidation processes based on the type of radical In another category, AOP methods can be grouped based on the type of radicals they release, which are described as follows.

Advanced hydroxyl radical-based oxidation Hydroxyl radical OH* is one of the strongest oxidizing substances and reacts with a very high and constant speed. The presence of hydroxyl in water and wastewater causes the destruction of organic substances in several ways, which include:

- Radical addition
- Radical composition
- Electron transfer
- Hydrogen decomposition

Advanced sulfate radical-based oxidation (Giannakis et al., 2021) Sulfate radicals are other very strong compounds in oxidizing water that are used in the purification process. These compounds have high reactivity, and their lifespan is low.

Wastewater treatment with advanced oxidation process (Khan et al., 2020a, b) Regardless of the details of the production and release of hydroxyl and sulfate radicals, the general process of wastewater treatment with AOPs is as follows: Hydroxyl and sulfate radicals attack organic substances in wastewater and decompose them.

In the process of decomposition of organic materials, side compounds may be produced. These compounds are removed and destroyed by other methods, including biological processes. Advantages of AOPs processes could be (a) removal of strong and dangerous organic substances in a short period of time, (b) high speed in setting up conditions for purification with the help of AOPs due to no need for advanced equipment, and (c) being needless to extensive ponds to implement purification processes. On the other hand, disadvantages of AOPs processes are (a) the need to use different chemicals in the process of releasing hydroxyl and sulfate and being costly from an economic point of view, (b) the possibility of producing dangerous compounds in some conditions, and (c) reducing the oxidation rate due to the combination of several different methods.

Photocatalytic treatment

Utilizing low-bandgap substances (photocatalysts) that are excited by photons emanating from a specific light source is the basis of photocatalytic treatment. Electron–hole pairs are produced when the photons have an energy that is greater than the bandgap of the photocatalysts. The hydroxyl radicals produced by the reaction between the holes and the water molecules degrade the organic contaminants (Kanakaraju et al., 2018, Majumder et al., 2019, Majumder & Gupta, 2020, Gupta et al., 2021). Superoxide radicals, singlet oxygen, and holes are the other reactive species produced during photocatalysis. These species have the ability to redox and may actively participate in photocatalytic degradation (He et al., 2014, Majumder et al., 2019, Mirmousaei et al., 2019). Photocatalytic remediation has the potential to effectively reduce the concentration of PhACs by approximately 90%. In addition, photocatalysis has a significantly shorter reaction time than many biological strategies (Manouchehri & Kargari, 2017). The photocatalytic technique's overall performance is influenced by a number of variables, such as the catalyst's shape, the light source, the PhACs' physicochemical properties, and so on (Hernandez et al., 2019). For various PhACs, such as ciprofloxacin, erythromycin, trimethoprim, tetracycline, sulfamethoxazole, paracetamol, naproxen, atenolol, and metoprolol, researchers have noted high elimination rates of approximately 99%, 100%, 90%, 88%, 100%, 95%, 100%, 95%, and 90%, respectively (An et al., 2010, Xekoukoulotakis et al., 2011, Ambrosetti et al., 2015, Kanakaraju et al., 2015, Molinari et al., 2017, Rimoldi et al., 2017, Majumder et al., 2019, Majumder & Gupta, 2020, Gupta et al., 2021). It has also been demonstrated that photocatalytic methods can kill antibiotic-resistant bacteria (ARB). UV light effectively kills viruses, ARB, and the antibiotic-resistant gene (ARB) (Sharma et al., 2016). Tsai et al. (2010) investigated the removal of methicillin-resistant *S. aureus*, multidrug-resistant *Acinetobacter baumannii*, vancomycin-resistant *Enterococcus faecalis*, *S. aureus*, *A. baumannii*, *E. faecalis*, and *E. coli* using titanium dioxide–based photocatalyst (Tsai et al., 2010). The photocatalytic degradation ought to oxidize the microorganism, and the variety of bacteria was reduced by 1–3 log units (Tsai et al., 2010). Kangwansupamonkon et al. also successfully inactivated a variety of ARB and *E. coli* (2009), as well as (Xiong & Hu, 2013) the utilization of a distinct photocatalyst in the presence of ultraviolet (Xiong & Hu, 2013). Figure 8 shows a schematic of photocatalytic batch reactor framework in the presence of UV light. The ability of photocatalysts to simultaneously oxidize microorganisms and degrade PhACs makes the process a profitable option that could be scaled up for HWW control during and after the COVID-19 crisis (Demirel et al., 2018; Majumder et al., 2021).

UASB

Various advances and refinements of anaerobic reactors to accommodate changes in contact time and contact methods have led to the development of suspension growth networks, fixed growth systems, solid film systems, or a combination thereof. Anaerobic waste treatment systems have been in use since the late nineteenth century, but have been considered of limited effectiveness and too slow to meet the rapidly increasing demand for wastewater, especially in densely populated industrialized areas. One of the foremost curiously modern strategies is the up-flow anaerobic sludge blanket process (UASB) created by Lettinga and his colleagues in the Netherlands in the early 1970s. Key to this method was the disclosure that anaerobic sludge intrinsically shows great flocculation and sedimentation properties, given that the physical and chemical conditions of the sludge are favorable. Once these conditions are met, a long solids residence time (at high HRT loads) can be accomplished by isolating the gas from the sludge solids. UASB reactor is one of the high stack–capacity reactor types. It differs from other methods in its

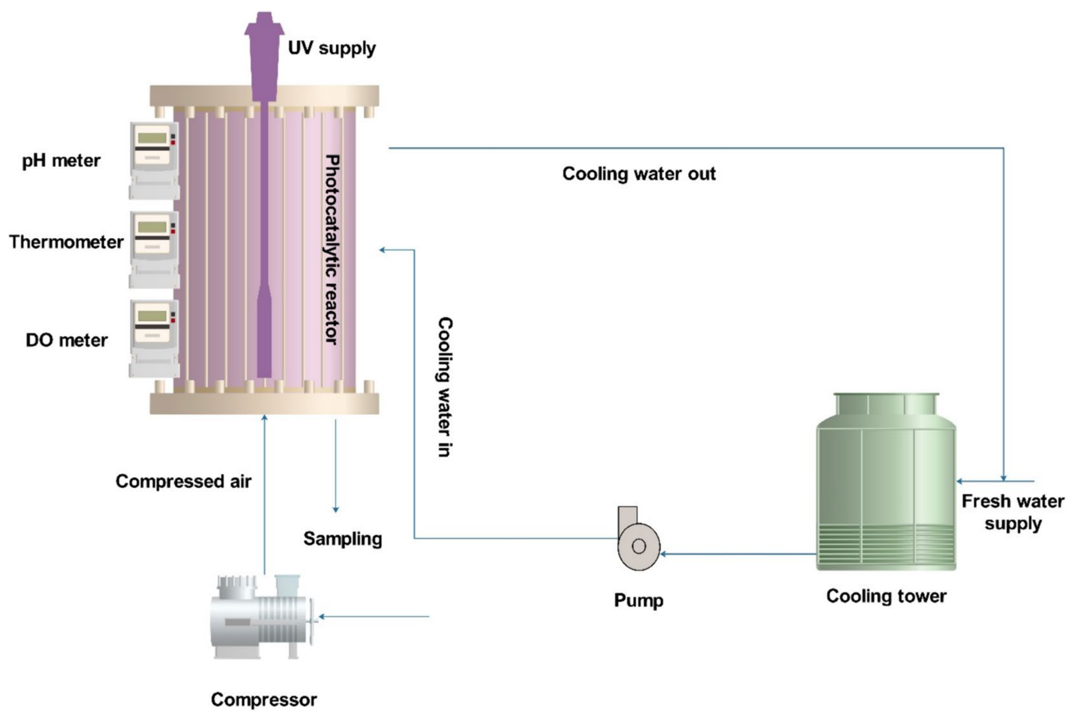


Fig. 8 The schematic of photocatalytic batch reactor system in presence of UV irradiation (Chong & Jin, 2012)

effortlessness of design. A UASB handle is a combination of physical and biological forms. The most highlight of physical forms is the division of solids and gasses from liquids, and the most inclusive of natural forms is the deterioration of degradable organic matter beneath anaerobic conditions. Unlike the anaerobic contact strategy, there is no need to introduce a sedimentation machine with a sludge return pump. There is no loss of reactor volume due to filters or support materials, as is the case with anaerobic filters and fixed film reactor sorts, and there is no requirement for quick recycling of wastewater and related pump power as in a fluidized bed reactor (Van Lier, 2008). Anaerobic sludge has innate substantial settling properties unless the slime is subjected to strong mechanical agitation. For this reason, mechanical blending is generally not utilized in UASB reactors (Englande et al., 2015). Due to the high organic loading factor, biogas generation ensures worthy contact between substrate and biomass. As far as the dynamic behavior of the aqueous phase, the UASB reactor approaches a fully mixed reactor (Bella & Rao, 2021; Nnaji, 2014). To achieve the necessary justified contact between sludge and wastewater, UASB systems rely on the agitation induced by natural gas output and the uniform feed inlet distribution at the bottom of the reactor (Bal & Dhagat, 2001).

As mentioned, one of the new biological treatment processes is the (UASB) process. One of the significant advances in anaerobic treatment technology is the UASB reactor, which was developed in the Netherlands in the late 1970s (Musee & Lorenzen, 2009). In this process, the wastewater enters from the end of the UASB reactor and flows upwards through the sludge coating unit (Loganath & Mazumder, 2018). The main components of the UASB reactor are the inlet wastewater distribution system, the gas phase separator from the solid, and the treated wastewater exit plan. The main feature of UASB systems, which allows it to use wastewater with a much higher COD load compared to other anaerobic processes, is the production of sludge in granular form. The advantages of this process include no need for aeration, very low sludge production, very low energy consumption and biogas production, and resistance to malnutrition (Tang et al., 2020). Wastewater pH parameters, oxidation–reduction potential (ORP), and food and microbial population, etc. affect the efficiency of the process.

Hou et al. reported an interesting hybrid system consists of UASB, anoxic–oxic tank (A/O), and AOPs in order to simultaneously remove 18 antibiotics and 10 antibiotic-resistant genes (ARGs) from a real pharmaceutical wastewater (Hou et al., 2019). The results indicated that the UASB provided the greatest contribution (85.8 ± 16.1%) for the removal of 18 antibiotics. The schematic of utilized system is presented in Fig. 9.

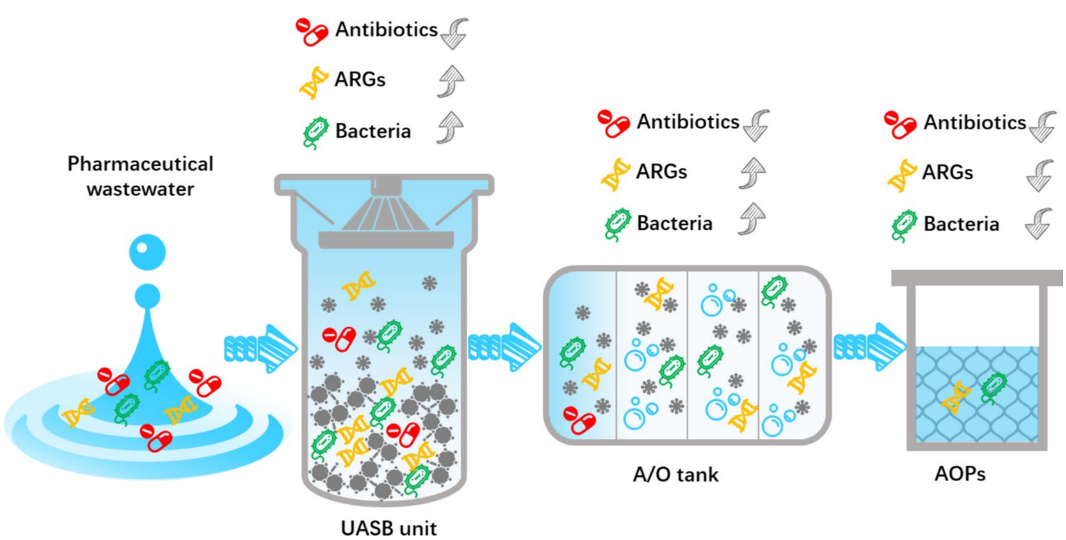


Fig. 9 Schematic for UASB combined by A/O tank and AOPs for antibiotics and ARG removal from pharmaceutical wastewater (Hou et al., 2019)

Hybrid technologies for antibiotic removal

Hybrid technology includes numerous combinations of various technologies in disposing of antibiotics from wastewater. In casting off tetracycline, some advanced methods include combining ultrafiltration, reverse osmosis, and powdered activated carbon (PAC) (Gadipelly et al., 2014, Khajouei et al., 2015, Khajouei et al., 2017a, b, Phoon et al., 2020). As a pre-treatment, nanofiltration was used to reduce fouling in reverse osmosis. The reduction coefficient and permeate flux of reverse osmosis will both rise as a result of the additional PAC. In this framework, antibiotic medication is proficient to be taken out up to 88% (Zhang et al., 2006). A study that looked at the combination of ozone, powdered activated carbon, or the membrane separation method with a membrane bioreactor (MBR) was conducted by Baumgarten et al. (Baumgarten et al., 2007). The other study combined the superior method of integrating activated sludge with microfiltration and reverse osmosis with the conventional approach. Activated sludge, microfiltration, and reverse osmosis each remove 87%, 43%, and 94% of 28 different antibiotics overall. Fenton and the algal action system were also used in a study on the elimination of amoxicillin and cefradine. After 48 h of algal remediation, amoxicillin was eliminated by this method up to 97.36%. However, only up to 22.52% of cefradine is eliminated in this instance, making it unsatisfactory (Li et al., 2015). Based on the findings of a study carried out by Du et al., utilizing UV-algae remediation can improve cefradine elimination (Du et al., 2015). Following the explained methods, a few AOPs methods may also produce traceable quantities of incomplete or undecomposed antibiotic compounds, as previously mentioned. Real-time detection at the wastewater's initial stage is essential in this scenario. The dealt-with antibiotic in wastewater may still be harmful to humans and the environment, so it must be carefully monitored before being released into the water source (Ait-Mouheb et al., 2020, Xu et al., 2020). As a result, membrane filtration must also be used to process this wastewater because it removes all harmful compounds. To put it another way, AOPs provide antibiotic pretreatment prior to membrane filtration treatment. This will unquestionably increase the membrane's resistance to fouling and extend its lifespan (Pouresmaeel et al., 2016, Oh et al., 2019). Although hybrid methods have demonstrated widespread improvement in the elimination of antibiotics, there are still numerous combinations that can be utilized. For the purpose of removing antibiotics from wastewater, current research focuses on simple and affordable methods. Nanomaterial-based technology has become increasingly popular in recent years for the removal of antibiotics from wastewater. Zhuang et al. (2019) used α-FeOOH loaded on rGO as hydrogels by combining it with α-FeOOH to form α-FeOOH/rGO hydrogels in a dual Fenton-like reaction to reduce antibiotics. The unique "π–π" interaction between TC and rGO helps antibiotics get rid of themselves because of the high surface area. They also found that the hydrogels could produce reactive oxygen species without H_2O_2. Nanocellulose from a waste straw has furthermore been utilized to push off TC by using the sonocatalyst method (Soltani et al., 2019). Within 45 min, the integration of ZnO into the nanocellulose resulted in an 87.6% TC elimination rate. When compared to digestion using a large bioreactor, this method has proven to be a more time-efficient option. Similarly, Afreen and colleagues (2020) dealt with TC and paracetamol using photocatalysis, a much "greener" method. As a nanophotocatalyst, rGO/CdS quantum dots were utilized (Afreen et al., 2020). Consequently, under visible light, the elimination performance of TC and paracetamol was found to be 84 and 90%, respectively. Despite the longer reaction time compared to the sonocatalyst technique, the use of a photocatalyst revealed greater energy savings.

Various tertiary treatment methods, including ultraviolet (UV) treatment, ozonation, catalytic wet air oxidation (CWAO), adsorption, nanofiltration (NF), reverse osmosis (RO), and others, have been used to remove ECs, antibiotics, and other microcontaminants from HWW (Souza et al., 2018, Davididou & Frontistis, 2021, Segura et al., 2021, Tufail et al., 2021, Yadav et al., 2021). Table 4 illustrates some of the most significant studies and their summary of results.

The current trend in research is toward a technology that is easier to use, cheaper, and better for the environment. The development of nanotechnology has made it easier for antibiotics to be eliminated (Mofidian et al., 2019). However, the task of recovering nanomaterials in subsequent processes remains a major concern, particularly in light of their environmental impacts.

Table 4 Recent studies on hybrid systems for removal of antibiotics and ECs

Order	Method	Results	Reference
1	Three-stage AOPs, together with CWAO, Fenton, and photo-Fenton	The AOPs affirmed exceptionally encouraging outcomes in eliminating the PhACs from HWW	Segura et al. (2021)
2	MBR technique with ozonation (effective concentration of 1.08 g O_3/g DOC) and UV remediation (effective flow rate of 7200 J/m^2)	Ozonation and UV treatment resulted in a median removal of ECs of 85.4% and 82.4%, respectively	Kovalova et al. (2013)
3	Ozonation and UV irradiation (operating at 96 W power with a UV-C source)	Got rid of almost whole ciprofloxacin, trimethoprim, atenolol, propranolol, and metoprolol. Additionally, surfactants were successfully eliminated, with an efficiency of over 94.9%	Souza et al. (2018)
4	UV and microalgae to the remediation of cefradine and amoxicillin under a mixture of UV-microalgae framework	The treatment was dominated by microalgae. In particular, *Scenedesmus obliquus* and UV-irradiation at 365 nm combined to remove cefradine and amoxicillin within 24 h with excellent efficiency (99.84%)	Yang et al. (2017)
5	Constructed wetlands (CWs) with air circulation and crossover plan in the evacuation of anti-microbials and anti-toxin safe qualities (ARGs) from anti-infection agents spiked homegrown sewage	The total aqueous removal efficiencies of antibiotics ranged from 87.4 to 95.3%, while those of ARGs ranged from 87.8 to 99.1%. The microbial degradation was primarily to blame for the CWs' massive antibiotic elimination	Chen et al. (2019)
6	Three distinct half and half frameworks coupling ultrafiltration (UF) with (i) UVC/H_2O_2, (ii) UVC/TiO_2, and (iii) UVC were assessed for the treatment of an optional profluent (SE) from a civil wastewater treatment plant and surface water (SW). A ceramic layer made of TiO_2 was used	111 L m^{-2} h^{-1} was the maximum pure water flux (PWF) Adsorption on the photocatalyst particles and additionally on the layer surface was viewed as a significant commitment for the expulsion of OTC and broken up natural carbon (DOC). In the photocatalytic membrane reactor (PMR) equipped with the UVC/TiO_2 system, the UF membrane significantly contributed to the rejection of pollutants and photocatalyst, whereas the membrane effect was negligible when the UVC/H_2O_2 process was used, with the highest H_2O_2 dose	Espíndola et al. (2019)
7	A hybrid microfiltration forward osmosis membrane bioreactor (MF-FOMBR)	Enrofloxacin, sulfamethazine, and cefalexin were the investigated antibiotics, followed by amoxicillin, lomefloxacin, and ampicillin. The influent concentration ranged from 4.1 to 716.9 ng/L. The system removed all antibiotics 58.9–100% overall	Qiu et al. (2021)
8	The apparent light-determined $WO_3/CdIn_2S_4$ hybrid photocatalysts with various WO_3 content	On tetracycline hydrochloride, the hybrid photocatalyst containing 70% $WO_3/CdIn_2S_4$ demonstrated the highest level of photodegradation activity	Pei et al. (2021)

Conclusions and future prospects

Antibiotics are largely manufactured by the pharmaceutical industry. Traditional wastewater treatment facilities struggle to manage antibiotic effluent from the pharmaceutical industry. Furthermore, while antibiotics can improve both public health and quality of life, both human and animal bodies do not entirely decompose them. Undegraded antibiotic residues may depart the body through feces and pollute wastewater. Researchers devised a variety of alternate strategies for removing antibiotics. The majority of techniques are often employed to remove antibiotics. Unfortunately, the disposal methods for antibiotics were either unclear or lacking. In order to avoid secondary pollutants, it is important to place greater focus on what happens to this antibiotic following treatment. It might be challenging to tell whether an antibiotic in effluent has been properly processed because the majority of antibiotic classes have no taste or color. Consequently, it is a reasonable idea to use modern removal systems to carry out actual detection and monitoring of removal of impurities. The majority of AOP treatments may also break down the chemical structure of pollutants. After the trial, though, a toxicity assessment is needed. Although these chemicals were occasionally eliminated, their toxicity persisted. Once they reach the water stream, these extremely hazardous effluents would affect the ecosystem and the environment. Adsorption and membrane filtration are two types of efficient technology that rapidly and effectively reduce contaminants from wastewater (Lashkenrai et al., 2019). Nevertheless, since this mechanism just changes from one stage to the other, secondary pollutants might be produced. The firm basis and knowledge of biological treatment, on the other hand, show that it can be a promising method for the removal of antibiotics from effluent. Regrettably, biological therapy only works on biodegradable antibiotics and is not cost-effective. Finally, several techniques for removing antibiotics from hospital effluent have been documented. It could be suggested that further study could concentrate on streamlining the removal procedure utilizing cutting-edge hybrid technologies to help improve the removal of antibiotics from wastewater. Aside from that, each antibiotic wastewater technology has advantages and disadvantages of its own. Consequently, the combination of UASB and AOPs is one of the most effective technologies which could tackle the issue of antibiotic contamination during and after COVID-19 crisis. Furthermore, the combination of an AOP system with membrane treatment is one of the optimum hybrid techniques, since membrane treatment can filter all the contaminants that an AOP technology is incapable of breakdown.

Nomenclatures Abbreviation AMR: Antimicrobial resistance; AOP$_s$: Advanced oxidation process; ASP: Activated sludge process; BOD: Biochemical oxygen demand; BOD/COD: Biodegradability index; CASP: Conventional activated sludge treatment plant; COD: Chemical oxygen demand; COVID-2019: Coronavirus disease 2019; CWs: Constructed wetlands; DO: Dissolved oxygen; DOC: Dissolved natural carbon; ECs: Emerging contaminants; FWSCWs: Free water surface constructed wetlands; HDPE: High density polyethylene; HF: Horizontal subsurface flow; HHW: Hospital wastewater; HRT: Hydraulic retention time; ICEAS: Intermittent cycle extended aeration system; IFDA: Iran food and drug administration; MBBR: Moving bed biofilm reactor; MBR: Membrane bioreactor; PAC: Powdered activated carbon; PE: Population equivalent; PEG: Polyethylene glycol; Phac$_s$: Pharmaceutically active compounds; RNA: Ribonucleic acid; RO: Reverse osmosis; SARS: Severe acute respiratory syndrome; SBR: Sequencing batch reactor; TC: Total carbon; TN: Total nitrogen; TOC: Total organic carbon; TOE: Time of ozone exposure; UASB: Up flow anaerobic sludge blanket; UV: Ultraviolet; WHO: World health organization

Author contribution All authors contributed to the study conception and design. Material preparation, data collection, and analysis were performed by Amirali Emadikhiav, Roya Mafigholami, Asghar Davood, Amirhossein Mahvi, and Lida Salimi. All authors have read, understood, and have complied as applicable with the statement on "Ethical responsibilities of authors" as found in the instructions for authors. The first draft of the manuscript was written by Amirali Emadikhiav, and all authors commented on previous versions of the manuscript. All authors read and approved the final manuscript.

Data availability The datasets generated during and/or analyzed during the current study are available from the corresponding author on reasonable request.

Declarations

Ethical approval We confirm that we have given due consideration to the protection of intellectual property associated with this work and that there are no impediments to publication, including the timing of publication, with respect to intellectual property. In so doing, we confirm that we have followed the regulations of our institutions concerning intellectual property.

Consent to participate Informed consent was obtained from all individual participants included in the study.

Consent for publication We, the undersigned, give my consent for the publication of identifiable details, which can include photographs and diagrams and details within the text to be published in the Silicon Journal.

Competing interests The authors declare no competing interests.

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