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Review article

Post-treatment disinfection technologies for sustainable removal of antibiotic residues and antimicrobial resistance bacteria from hospital wastewater

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ABSTRACT

The World Health Organization (WHO) has identified antimicrobial resistance bacteria and its spread as one of the most serious threats to public health and the environment in the twenty-first century. Different treatment scenarios are found in several countries, each with their own regulations and selection criteria for the effluent quality and management practices of hospital wastewater. To prevent the spread of disease outbreaks and other environmental threats, the development of sustainable treatment techniques that remove all antibiotics and antimicrobial resistant bacteria and genes should be required. Although few research based articles published focusing this issues, explaining the drawbacks and effectiveness of post-treatment disinfection strategies for eliminating antibiotic residues and antimicrobial resistance from hospital wastewater is the reason of this review. The application of conventional activated sludge (CAS) in large scale hospital wastewater treatments poses high energy supply needs for aeration, capital and operational costs. Membrane bioreactors (MBR) have also progressively replaced the CAS treatment systems and achieved better treatment potential, but membrane fouling, energy cost for aeration, and membrane permeability loss restrict their performance at large scale operations. In addition, the membrane process alone doesn't completely remove/degrade these micropollutants; as a substitute, the pollutants are being concentrated in a smaller volume, which requires further post-treatment. Therefore, these drawbacks should be solved by developing advanced techniques to be integrated into any of these or other secondary wastewater treatment systems, aiming for the effective removal of these micropollutants. The purpose of this paper is to review the performances of post-treatment disinfection technologies in the removal of antibiotics, antimicrobial resistant bacteria and their gens from hospital wastewater. The performance of advanced disinfection technologies (such as granular and powered activated carbon adsorption, ozonation, UV, disinfections, phytoremediation), and other integrated post-treatment techniques are primarily reviewed. Besides, the ecotoxicology and public health risks of hospital wastewater, and the development, spreading and mechanisms of antimicrobial resistant and the protection of one health are also highlighted.

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1. Introduction

Hospital wastewater is spawned from several healthcare services, including examination and surgery rooms, medical laboratories, radiology rooms, nursery rooms, laundry rooms, kitchens, and toilets [1]. The estimated water demand in these activities is between 200 and 1200 L/bed/day in developed countries and a relatively lower quantity of 200–400 L/bed/day in developing countries [2,3] to produce 250–570 m^3/day of hospital wastewater [4]. This wastewater contains high concentrations of conventional pollutants such as COD, BOD, nutrients, total suspended solids (TSS), total dissolved solids (TDS), chlorides, total and fecal coliforms, and other microbial [5]. In addition to these pollutants, this wastewater contains various infectious and hazardous constituents [1], which occur at very low concentrations, in μg/L or ng/L) [5], which belong to emerging micropollutants [6].

In the twenty-first century, the World Health Organization (WHO) classified the spread and emergence of antimicrobial-resistance bacteria and their genes as one of the biggest threats to public health due to their potential for higher infectivity [7,8]. These classes of emerging micropollutants play a major role in spreading various infectious diseases and increase the potential epidemic risk and aggravation to global health [9]. Hence, these micropollutants enter and accumulate in the human body through different routes of exposure, such as food and drinking water, and then pose a potential health risk [5,6]. These contaminants are unregulated in the aquatic system during their use, fate, and consumption [5].

Antibiotics are classes of pharmaceutical active compounds (PhACs) that are of particular concern due to Ref. [10]: (i) their widespread presence in the environment, (ii) their low biodegradability by conventional treatment systems, and (iii) their associated risks such as mutagenicity, carcinogenicity, and endocrine disruption. Moreover, the incidence of antibiotics in the hospital wastewater also contributes to another potential anxiety by favoring the development and release of pathogens, antimicrobial-resistant bacteria and their genes, as well as other chemical contaminants. This is because, the misuse and overuse of antibiotics has led to the appearance of antimicrobial resistance bacteria, conceding the effectiveness of antimicrobial therapy (hence, the infectious microbes are resistant to the commonly prescribed antibiotic drugs). The WHO identified the global priority list of antimicrobial resistant bacteria, which includes VRE – vancomycin resistant *Enterococcus*), CRE – carbagepenem resistant *Enterobacteriaceae*), MDRA (multidrug resistant *Acinetobacter*), MRSA – methicillin resistant *Staphylococcus aureus*), and MDRP – multidrug resistant *Pseudomonas aeruginosa,* and an extended spectrum. There is no legislation or concentration limit for a specific or group of antibiotics for discharging treated hospital effluents into receiving water bodies under these conditions. This issue highlights the risk of antimicrobial resistance bacterial spreading in the hospital environment, particularly in developing countries [1].

Different treatment scenarios have been applied in several countries, each with their own legislation and selection criteria for hospital wastewater quality and its management practices [4]. For example, in many developing countries, hospital wastewater is discharged untreated into drainage systems, lakes, and rivers [11]. Moreover, some countries consider the hospital wastewater to be industrial and comply with certain characteristics that require certain pretreatment before being discharged into municipal wastewater treatments. According to another point of view, hospital wastewater are discharged into municipal wastewaters, where they mix and are eventually treated together in sewage treatment plants as “co-treatment”. This is an inadequate solution to remove the micropollutants due to the dilution effect. The existing conventional systems effectively remove conventional pollutants, which are not designed to treat emerging micropollutants. However, these systems contribute to the spread of antimicrobial resistance bacteria into the environment, which can be finally transferred to human, fish, and animal pathogens [1].

The development of sustainable techniques is required to guarantee safe hospital wastewater treatment and disposal practices to prevent the spread of disease outbreaks due to enteric pathogens and other micro-contaminants [4]. The application of conventional activated sludge (CAS) in large-scale wastewater treatments poses several disadvantages, including the high energy supply needed for aeration, capital and operational costs. Membrane bioreactors (MBR) are also progressively substituting for CAS treatment systems, although membrane fouling, energy cost for aeration, and membrane permeability loss restrict their performance at large scale operations [10]. In addition, the membrane process doesn’t remove/degrade the micropollutants, as a substitute, the pollutants are being concentrated in a smaller volume, which requires further post-treatment systems. Therefore, these drawbacks should be solved by developing advanced wastewater treatment techniques to be integrated into any secondary WWT systems, aiming for the effective removal of micropollutants from hospital wastewater and enhancing the reusability potential. The performance of post-treatment disinfection technologies for the removal of emerging micropollutants (antibiotics, antimicrobial resistant bacteria and their genes) from hospital wastewater is reviewed in this paper. Primarily, the performance of post-treatment disinfection technologies (such as adsorption via activated carbon, ozonation treatment, UV irradiation, disinfection) and other integrated techniques are reviewed. Besides, the ecotoxicology and public health risks of hospital wastewater, and the development, spreading and mechanisms of antimicrobial resistant and the protection of one health are also highlighted.

2. Occurrence of antibiotics and antimicrobial resistance bacteria in hospital wastewater

The antimicrobial resistance patterns have historically emerged following the discovery of very important and new antibiotics [12]. There are different antibiotics and antimicrobial resistance bacteria produced in hospitals. Humans and animals are the key sources of antibiotics and antimicrobial resistance bacteria that enter the aquatic environment. In human medicine, these groups of micropollutants are primarily excreted into wastewater as parent compounds and/or their metabolites in feces and urine. Methicillin-resistant *Stapylococcus aureus* (MRSA) is the most common antimicrobial resistance bacteria, and its impact on healthcare facilities has to be very significant [13]. Due to the spreading of high risk nosocomial infections, MRSA has been disseminated recently in the community [14], but it is less frequently found in the sewage system. When compared to gram-negative bacteria, gram-positive bacteria rapidly develop resistance to key antibiotics (e.g., methicillin and then penicillin) [12]. However, some Gram-positive

resistant bacteria, like *Vancomycin* resistant *Enterococci* (VRE) (which exist in the gastrointestinal tract), are frequently found in the wastewater and have been identified as a potential infectious risk for hospitals [13]. The most frequently detected antimicrobial resistance bacteria in sewage are VRE, *E. coli*, extended-spectrum beta-lactamase (ESBL)-producing bacteria, and intrinsically extremely resistant and environmentally adapted Gram-negative *P. aeruginosa* [14]. High concentrations of these antimicrobial resistance bacteria have also been found in hospital wastewater [12]. The carbapenamase-producing organisms (CPO) are resistant to the broad-spectrum penicillins and have been revealed to be spread within the hospitals, which is highly concerning [12]. According to monitoring studies [15–17], there are a considerable quantities of antibiotic residues occurred in areas that are close to intensive animal farming, hospital effluent, and soil and water. The key processes affecting the persistence and stability of antibiotic residues in the environment are their sorption to organic particles and their breakdown/degradation or transformation. The physical-chemical properties of the residue, the characteristics of the soil, and meteorological variables like temperature, rainfall, and humidity all play a role in the occurrence of these residues [15,17].

3. Antimicrobial resistant bacteria and protection of one health

The antimicrobial resistance bacteria is raising a global public health threat that kills at least 75,000 people per year and is interlinked with humans, animals, and various environmental health factors [18]. The antimicrobial resistance refers to the situation in which these bacteria alter their genetic codes, rendering medicines ineffective against these pathogens. Antimicrobial agents such as antibiotics, vaccines, therapeutic agents, antivirals, fungicides, and antiparasitics apply to control pathogenic microbes, protect humans, and lessen the risk of infectious diseases. Streptomycin-resistant cases were first reported in turkeys in 1951, and today, tetracyclines, sulfonamides, β-lactams, and penicillin-resistant patterns are on the rise [19]. Ampicillin and tetracycline resistance were detected in 198 samples collected from cattle in eastern Algeria, resulting in mostly common rod-shaped gram-negative bacteria, *E. coli* [20]. A common resistant bacteria, *Klebsiella pneumoniae*, isolated from environmental and clinical patient samples revealed *bla*CTX-M, *bla*SHV, and *bla*TEM (ESBL-producing genes) [21]. Antibiotic-resistant *E. coli bacteria were* also detected in animals, including raw meat, milk, and poultry. Multidrug-resistant (MDR) bacteria are becoming more common, with one study reporting over

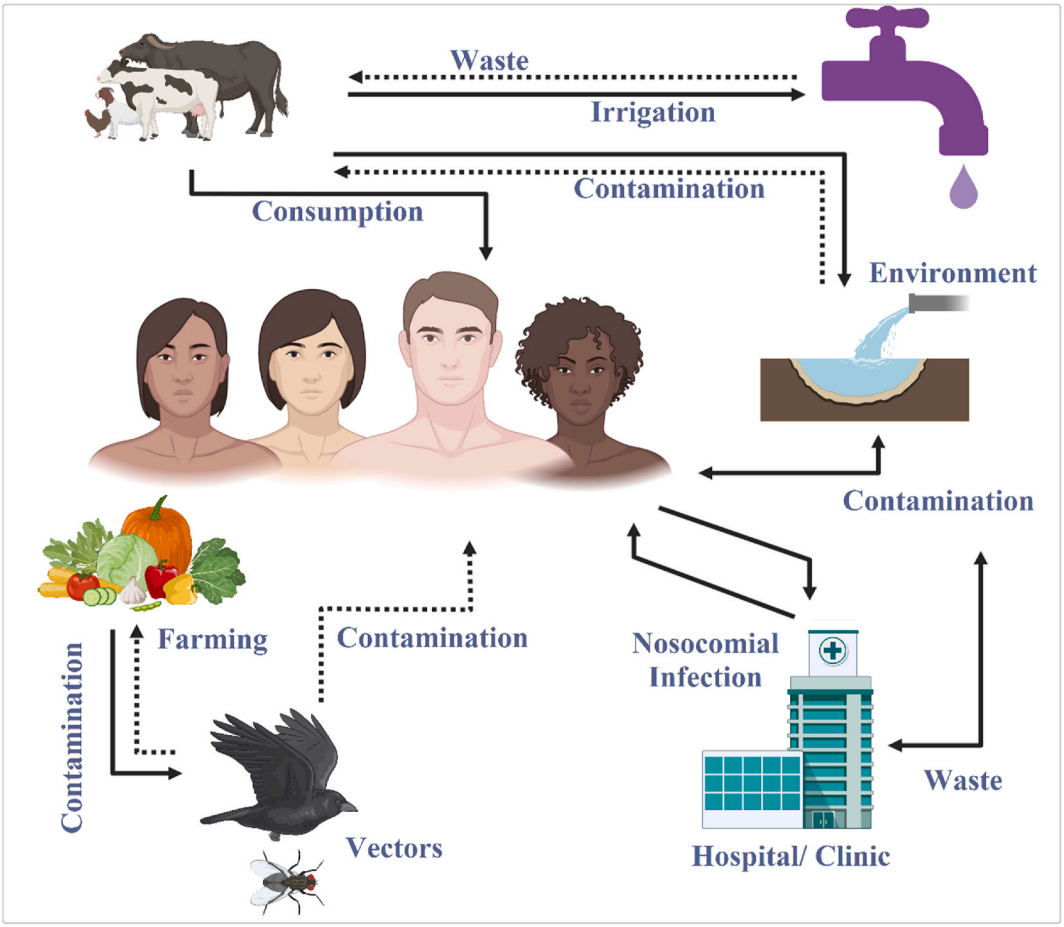

Fig. 1. Transmission of antimicrobial pathogens from one source to another in the context of One Health approach.

2 million patients infected, including 23,000 cases per year in the United States and 25,000 in Europe [22]. As a result of pneumococcal disease, which cannot be treated in approximately 195,763 patients due to antimicrobial resistance and results in 2925 child deaths per year, the antimicrobial resistance pattern in Ethiopia is found to be higher than in other countries. At least 52 outbreaks (4.2% CFR-case fatality rate) were investigated by the Centers for Disease Control due to antimicrobial resistance *Salmonella Spp.* In the years between 1971 and 1983 [23].

There are many factors involved in the rational use of antibiotics without proper knowledge, short courses, or excessive use: consumption of foods with antibiotics, lack of potable water, sanitation, poor hospital management, unhygienic conditions, availability of antibiotics, vaccines, and other drugs, and no strict legislation [24]. The persistence of MDR bacteria in the environment also allows resistant genes to spread to sensitive cells in human-animal-environment niches (Fig. 1), resulting in the development of superbugs [23]. There are many types of antimicrobials used against bacterial infections, along with other functional sectors like therapeutic, prophylactic, and development promoters. Antibiotics are used more in animals than in humans to increase production (meat, eggs, milk, and even early pregnancy outcomes). Broad-spectrum antibiotics are mostly used for patients and animals, like beta-lactams and quinolones (a few antibiotics are used in plants or crops, like tetracycline, triazoles, and streptomycin). An inefficient management system of antibiotics, infectious diseases, various animals, debris, or pollutants helps to migrate ABR bacteria [25].

Third-generation antibiotics such as cephalosporins and fluoroquinolones are now used in animals and plants to promote growth, and colistin, tetracyclines, and macrolides are used as growth promotion agents [25]. In the United States, antibiotic use in animals raised for food represents approximately 80% of the antibiotics used in the animal sector in the USA, and the FDA observed that a large portion of this (74% of it) was applied in feed for growth instead of against any disease. Long-term use of antibiotics in feed, such as colistin, tetracyclines, and macrolides, for growth promotion is very dangerous for humans. Some antibiotics are only recommended for humans, such as carbapenems, while others, such as flavophospholipol and ionophores, are only recommended for animals. Tetracycline and streptomycin are used for clinical purposes and treat infections caused by bacteria [18].

One Health collaborates with multiple sectors, including environmental health, animal health, and human health (Fig. 1), to achieve a healthy and safe lifestyle [26]. As antimicrobial resistance bacteria were identified from human, animal, and environmental sources, one health factor played a role in the origin, emergence, or re-emergence of novel pathogenic bacteria as well as the spread of antimicrobial resistance bacteria locally and globally [27]. This holistic system acts in agriculture, livestock, and human medicine to aid all of the sectors, including economists, consumers, and stakeholders, in providing sustainable solutions against antimicrobial resistance bacteria [28]. During the first introduction of the term “zoonosis” by Rudolf Virchow in the nineteenth century, another idea was coined and named “One Health” [28]. Then, Calvin Schwabe added one medicine concept and contributed to this multi-sectorial approach based on public health, epidemiology, and tropical medicine.

The national rules of the few developed countries have already altered their plans to focus on One Health clarifications, including proper guidelines suggested by the World Health Organization (WHO) and Food and Agriculture Organization (FAO). Surveillance measures worldwide (Global Antibiotic Resistance Partnership, GARP) play a very important role for antimicrobial resistance and the Global Antimicrobial Resistance Surveillance System (GLASS), which was started by the WHO for the same purposes. WHO and other international organizations (e.g., the Food and Agriculture Organization [FAO], OIE) have developed comprehensive action plans to address the antimicrobial resistance crisis [29]. Since 1990, WHO has pursued a variety of multi-sectorial initiatives in collaboration with experts, advisory groups, stakeholders, pharmaceutical regulatory authorities, veterinarians, and consumers. Another international organization, the OIE, developed guidelines for antimicrobial resistance monitoring, risk analysis, and use in veterinary medicine and aquaculture. Codex Alimentarius, which is also concerned with antimicrobial resistance, monitors international food guidelines, and the 29th meeting covered antimicrobial resistance risk assessment of foodborne antimicrobial resistance [30]. The European Center for Disease Control (ECDC) and the European Food Standards Agency (EFSA) publish an annual report on antimicrobial resistance. ESVAC (European Surveillance of Veterinary Antimicrobial Consumption) is an agency responsible for the European Union and the European Economic Area [31].

Veterinarians who prescribe antimicrobials and advise farmers on disease prevention obviously require a deeper understanding of the One Health dimensions of antimicrobial resistance. Veterinarians should possess the knowledge, attitudes, and behaviors that characterize good antimicrobial stewardship, thereby protecting the health and welfare of their patients, the economic interests of their clients, as well as the health of the wider community [32]. WGS (whole-genome sequencing), advanced bioinformatics, and metagenomics, as well as metadata analysis, can be used to analyze antimicrobial resistance bacteria responsible genes from animals, plants, humans, soil, and water. Phylogenetic analysis is more accurate and authentic in identifying the origin or source [33]. The high-throughput strategies, namely NGS (next-generation sequencing) and Rescon (resistance readiness condition), are using up-to-date techniques. Combating ABR is not easy, and bacteria change strategies as a weapon to persist in hosts.

4. Microbial mechanisms for development and spread of antimicrobial resistance in the environment

A bacterium is a versatile organism that can adapt to any environment, animal or human [34,35]. To survive in different conditions, bacteria follow diverse mechanisms and produce different substances or metabolites that help bacteria acquire antimicrobial resistance [36]. Few bacteria are naturally resistant to antimicrobial agents, with the majority earning resistance from various sources. The antimicrobial resistance bacteria transfer from hospitalized patients, nosocomial infections, hospital workers, dairy farms, poultry farms, physicians, doctors, nurses, and veterinarians who are used to close contact with antimicrobial resistant bacteria and are mostly prone to transferring antimicrobial resistance [37]. Bacteria with antimicrobial resistance genes have the capacity to survive in harsh environments and transfer easily from one host to another in various ecosystems (soil, water, air, even infected crops to other crops, disease animals to new animals) [38]. For example, it was found that at room temperature and normal humidity *Escherichia coli* can

survive a few hours to a day. In the suitable environment bacteria can multiply in each twelve min-12 h. In addition that, few bacteria can survive several months such spore producing bacteria, *Mycobacteria* and *M. tuberculosis, Clostridium difficile*. *Mycobacteria*, including *Mycobacterium tuberculosis*, and spore-forming bacteria, including *Clostridium difficile*, can also survive for months on surfaces. *Candida albicans* as the most important nosocomial fungal pathogen can survive up to four months on surfaces. Several bacteria such as *Escherichia coli, Pseudomonas putida, Serratia marcescens*, and *Alcaligenes faecalis* persistent rate in environment decrease 50% in the dry environment.

Chromosomal changes, also known as horizontal gene transfer, are one of the main causes of antimicrobial resistance, with transformation, transduction, and conjunction mainly responsible for this scenario [39]. Fig. 2 (A, B) shows the bacterial gene transformation methods and resistance mechanism. Transposons (transposable elements) help move antimicrobial resistance genes from one host to another into plasmids. These mobile DNA sequences are interlinked with bacterial chromosomal DNA or plasmids [40]. Carbapenemase, an important enzyme involved in antimicrobial resistance, was previously found in chromosome DNA; however, it has only recently been discovered on plasmids. *K. pneumoniae* is an important enteric bacteria that was first confirmed in the United States in the year 2000 after obtaining the carbapenemase gene (*bla*KPC). Transferring antibiotic resistance genes via plasmid is a common method for certain bacteria (*Acinetobacter* spp.) [41]. The three systems of gene transfer conjugation differ in gram-positive and gram-negative bacteria, where pills aid in amalgamation or genes with plasmid-resistant segments transfer to another bacteria [42]. Gram positive bacteria exchange from donor to recipient via mating. Rarely is a system of transduction discovered in which genes with resistant antimicrobial agents transfer using a bacterial virus known as a *bacteriophage* [43]. The last method of gene transfer is where resistant DNA is acquired and incorporated into other bacteria [44].

Antimicrobial susceptible microbes are destroyed during drug administration, whereas resistant microbes persist in the patient's

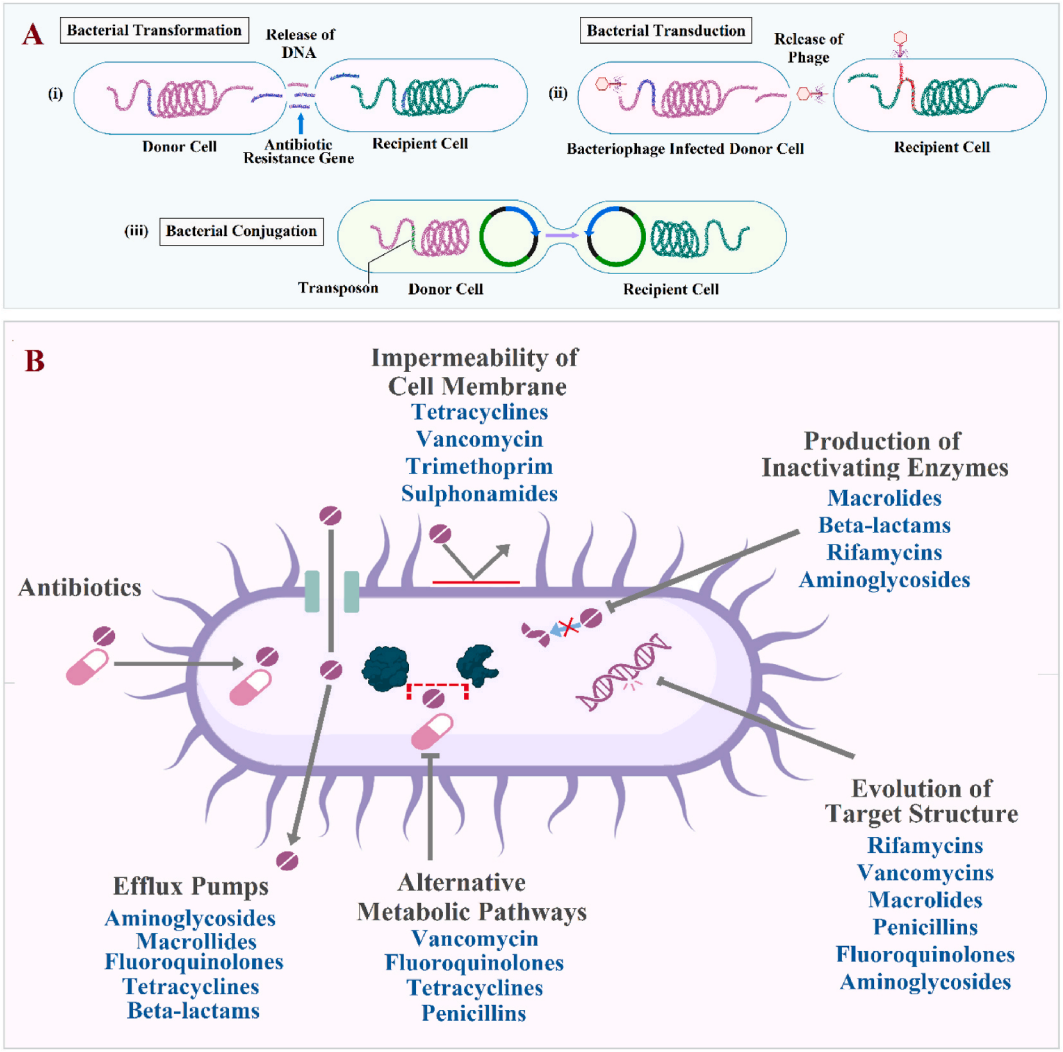

Fig. 2. Bacterial Gene transformation methods and resistance mechanism. A) Three methods of bacterial genetic material exchange - (I) Transformation (II) Transduction (III) Conjugation, B) Five mechanisms of antibiotic resistance of bacteria.

body and the normal flora is reduced [45]. It is also found that antimicrobial resistance genes are helpful to spread in the community, like the glycopeptide-dependent expression of the vancomycin-resistant *S. aureus* (VRSA), which transfers more than the intermediate susceptibility to vancomycin (VISA) [46]. Other factors, such as bacterial spores (*Clostridium difficile*), aid in colonization, environmental spread, and resistance to biocides [47]. Another important factor is biofilms, which assist microbes (Staphylococcus epidermidis, *Pseudomonas aeruginosa*, and *Legionella* species) to adhere to surfaces in hostile environments where antimicrobial agents cannot work properly [48]. Another bacteria, *S. aureus*, used clumping factor B and wall teichoic acid to colonize the nasopharynx by adhering epithelial cells in the nasal sites.

Antibiotic resistance genes also play a main role in antimicrobial resistance in different ways, such as by changing the targeted antibiotic sites [49]. Lactamases act on the lactam group to wipe out the capacity, so these genes encode enzymes. Because β-lactamases hydrolyze β-lactam rings, microbes develop resistance to carbapenems, penicillins, cephalosporins, and aztreonam. Another strategy is to pump out chemical agents before they adhere to the active site [50]. Alteration of the cell wall provides protection against antimicrobial agents for infection. Efflux pumps found in *P. aeruginosa* are active against multidrug resistance where genes are encoded in plasmids [51].

Genetic mutations in microbes are caused by stress conditions such as starvation, UV radiation, chemical exposure, amino acid substitutions, additions, or deletions, etc. Bacteria were found to have an average mutation rate of 10^6 to 10^9 mutations per cell multiplication [52]. In addition to that, microbes' cellular structure and various functions, such as those of gram negative bacteria, contain the LPS (Lipo-polysaccharide) coating, which works as a fence for a few groups of antimicrobial agents [53].

5. Ecological and public health concerns

The presence of antibiotics, antimicrobial resistance, and the resistant genes causes several disruptions in the ecosystem due to the long-term exposure of the environment to these micropollutants, even at very low concentrations. Besides, the efficiency of WWT plants is also disturbed by the existence of high strength micropollutants, which perhaps increases the public health risk [54]. The resistant pathogens may possibly enter human bodies through direct or indirect pathways, and their resistant genes are disseminated into the environment primarily through horizontal gene transfer mechanisms [55]. Antimicrobial resistance has a number of negative health consequences, including an increase in the length of epidemics, making cure more difficult, and an increase in fetal illness [7,8]. As suggested by Silva et al. [56], the WWT plants decrease the total load of bacterial strains, which may increase the antimicrobial resistance proportion in the outlet water (effluents). This should be considered to boost the existing WWT plants to disseminate the antimicrobial resistance removal. Consequently, the antimicrobial resistance results are associated with the risk of resistance to antimicrobials and yield therapeutic failures [54]. The environmental and human health impacts caused by antimicrobial resistance are not easy to quantify due to their occurrence at lower concentrations and their being difficult to detect in the aquatic environment. Antimicrobial resistance in the environment is caused by their release into wastewater as human and animal excretion, as well as from agricultural and industrial sources, into streams, and their egress into sewers. Their presence in the aquatic ecosystem has the potential to change the nature of the microbial ecosystem [54].

Now a days, the antimicrobial resistance bacteria, mainly the Gram-negative remains a serious clinical challenges [54,57]. Most of the antimicrobial resistance bacteria results in an "inferior response" to diagnosis because the selected treatment of these agents is not effective (the infecting pathogens are resistant) and results in the following conditions: (i) increases the number of surgeries and mortality rates due to the spreading of infections, and results in enhanced virulence, disease outbreak and transmission, and pathogenicity; (ii) leads to extended morbidity and increases the length of hospitalization, and (iii) increases the cost of healthcare for medications and upsurges secondary bacteraemia [54,58]. For example, in US hospitals, the morbidity from MRSA infections exceeds that from HIV/AIDS and tuberculosis together [57]. The presence of antimicrobials in unfavorable conditions causes bacterial adaptation, allowing for increased survival and, as a result, the formation of drug-resistant genes. There is a strong association between the use of antibiotics and the degree of their resistance within the environment and clinical field practice [54].

There are several antimicrobial resistance bacteria of major public health importance; among them are the foodborne pathogens such as *Clostridium perfringens, Salmonella* spp.*, Listeria* spp.*, Campylobacter* spp.*, Yersinia* spp., and a certain *E. coli* strain that usually originate from hospital wastewater [13]. There are also other pathogenic bacteria that were produced from hospital wastewater and have their own health significance, including *Mycobacterium tuberculosis, Staphylococcus aureus, Enterococcus* spp.*, Acinetobacter baumannii*, and *Pseudomonas aeruginosa* [54]. There are different antimicrobial resistance bacteria that are a major cause of nosocomial infections and increase patient-flow to hospitals, such as *Pseudomonas aeruginosa*, *Acinetobacter baumannii* [13,14]. *Enterococcus* spp., are among the usual gut flora that have lower colonization, virulence, and a nosocomial infection could occur in "immune-compromised patients" and in those with serious illness [59]. Besides, *Pseudomonas aeruginosa* is among the main pathogenic bacteria that challenge public health by causing nosocomial infections [59]. According to Hawkey [42], patients admitted to healthcare facilities and given a broad spectrum of antibiotics and clues to cause infection can develop gut colonization.

6. Potential limitation of conventional techniques

Hospital wastewater may contain high concentrations of micropollutants with greater diversities that contribute 4–50 times more than municipal wastewater (MWW) [60]. Conventionally, hospital wastewater treatments have been applied in a combination of primary, secondary, and tertiary processes, where different physicochemical and biological processes can be applied at each of the treatment stages. The primary treatment (i.e., sedimentation and filtration) is widely used in WWT plants to remove solid contents (sand, fats and oils, settleable solids). Although, the secondary treatment is applied to remove nutrients and organic matter via

anaerobic and anaerobic systems using several bioprocesses (using different bioreactor systems), the activated sludge system is mostly a common conventional approach [55]. Thus, the conventional activated sludge (CAS) system and membrane bioreactor (MBR) have been widely used along with the UWW in conventional wastewater treatment [11]. The currently adopted technologies could be designed for the removal of conventional pollutants produced from hospital effluents. However, these conventional techniques were unable to remove pathogens and other micropollutants, including antibiotics, antimicrobial resistance bacteria, and antimicrobial resistance genes, and their limited removal performances depended on the specific properties of the micropollutant, which varied from lower to higher removal efficiencies [11].

The main challenge with regard to hospital wastewater management in developed countries (like Europe) is the absence of specific directives/guidelines that work in all member states. On this aspect, every country puts in place its own regulations, evaluation criteria, and selection criteria before discharging into the sewage to be treated together with the municipal WWTPs or before discharging into the aquatic environment (like water bodies). Some other countries, like France and Spain, suggested the hospital wastewater be treated as industrial effluents that should comply with certain features before mixing with municipal WWTP, and often a pretreatment step is needed. Other countries, like Italy, also directly discharge the hospital wastewater into the sewage system and convey it to the existing municipal WWTP by complying with the specific characteristics to be recognized by the authorities of WWTPs; if not, it has to be subjected to pretreatment. In contrast, in developing countries, hospital wastewater is frequently discharged into municipal WWT systems and then to water bodies without treatment for both macropollutants and micropollutants in order to reduce ecotoxicity and public health concerns [61].

Typically, conventional treatment technologies are designed to remove nutrients from a domestic source [11,62]. However, the removal efficiency of micropollutants (including antibiotics, antimicrobial resistance bacteria, and antimicrobial resistance genes) originating from hospital wastewater is relatively poor (i.e., partially or not eliminated at all) [11]. A threat to environmental and human health could be found when the partially-treated effluents reach the aquatic environment [11,63]. This contributes to the spreading of resistant bacteria that can be ultimately transferred as pathogens to humans, animals, and fish [63,64] and develop nosocomial infections. This confirms the abundance of antimicrobial resistance bacteria in the surface water and contaminates the food chain as a result of conventional WWTPs' discharge into the aquatic ecosystem [60,63]. Therefore, there is a need to find alternative post-treatments or separate treatment techniques aiming at removing these micropollutants completely from hospital wastewater. Among the available miscellaneous WWT technologies, advanced oxidation processes (AOPs), activated carbon adsorption, and others have been developed and used to manage these micropollutants from hospital wastewater, while their removal effectiveness has targeted the individual pollutants but requires higher energy, financial, and spatial costs [11]. As a summary, there is no single treatment practice that is considered the only solution for hospital wastewater management, where miscellaneous technologies are required in combination and could be applied in any treatment step [11].

7. Performances of post-treatment technologies

This section describes the performance of various post-treatment techniques, which are primarily classified as tertiary processes for hospital wastewater management. As is known, the tertiary WWT systems can be applied at the last step, aiming to remove pathogens, remaining residual nutrients, and organic matter. In this regard, there are different disinfection technologies (post-treatment) that could be applied for the removal of antimicrobial resistance bacteria and their genes from hospital wastewater before discharging into the environment [55,65]. These post-treatment technologies could be applied at the source where the wastewater has to be produced (i.e., hospitals), either alone or in an integrated approach with another polishing treatment []. In hospital wastewater management, for the removal of micropollutants, pretreatment, biological treatments, advanced treatment, and then post–treatment are the most appropriate approaches. Therefore, this section focuses on the applications of advanced treatment technologies to be used as a post-treatment approach for the removal of antibiotics, antimicrobial resistance bacteria, and antimicrobial resistance genes from hospital wastewater. From the existing technologies, adsorption onto activated carbon (PAC or GAC), membrane separation, AOP (including ozonation, UV, chlorination, etc.), bioremediation via constructed wetlands (CW), and waste stabilization ponds (WSPs) may be recommended for the removal of several micropollutants from hospital wastewater, including antibiotics, antimicrobial resistance bacteria, and antimicrobial resistance genes.

7.1. Activated carbon adsorption

Adsorption is the most effective wastewater treatment approach that can be described as low-cost, high surface area, with the possibility to regenerate for reuse and a higher elimination potential [66] for a wide range of micropollutants [5]. Removal via adsorption can be performed through the following mechanisms [55,66]: (i) transport of solute/adsorbate into the surface of the bulk solid adsorbent, (ii) adsorbate transport or film diffusion, (iii) diffusion of pores, and (iv) adsorptive interaction by either physical or chemical-based mechanisms. In this technique, the removal efficiency can be influenced by the characteristics of the adsorbent (including surface polarity, porosity, physical shape, and specific surface area), the properties of the pollutants (i.e., hydrophobicity, size and shape, charge of the compound), and the effects of operating conditions (such as the bacterial load, pH, temperature, and presence of co-pollutants) [5,55,67]. The adsorption of antimicrobial resistance bacteria and antimicrobial resistance genes in activated carbon has been widely studied via powdered activated carbon (PAC) and granular activated carbon (GAC) [68]. When compared to the GAC, the PAC system's smaller particle size allows for higher adsorption kinetics and effective removal efficiency [10].

Different studies have been carried out using adsorption for the removal of antibiotics, antimicrobial resistance bacteria, and their

Table 1
Applications of different post-treatment techniques for removal of antibiotics from hospital and municipal wastewater.

Post-treatment	Type of antibiotics	Conditions	RE (%)	References
UV treatment	Ciprofloxacin	Applied fluence of 7200 J/m^2, 15.7 ± 8.0 ng/L influents	57 ± 3	[67]
		4800 ng/L of MBR outlet, 82 mg O_3/L, 10 min	86.46	[74]
	Sulfamethoxazole	UV_{254}: 10 min	51	[75]
		3.23 ± 4.70 ng/L influents, 7200 J/m^2 of fluence	85 ± 3	[67]
	Clarithromycin	1.28 ± 0.84 ng/L influents, 7200 J/m2 of fluence	14 ± 1	
	Metronidazole	1.86 ± 2.03 ng/L influents, 7200 J/m2 of fluence	22 ± 8	
	Erythromycin	up to 0.140 ng/L influents, 7200 J/m2 of fluence	10 ± 1	
	Norfloxacin	3.14 ± 1.82 ng/L influents, 7200 J/m2 of fluence	63 ± 2	[74]
	Trimethoprim	3.14 ± 1.82 ng/L influents, 7200 J/m2 of fluence	63 ± 2	[67]
MBR-PAC	Sulfamethoxazole	–	>99*	[69]
	Erythromycin	–	>99*	
PAC	Sulfamethoxazole	PAC dose: 43 ± 14 mg/L, 3.23 ± 4.70 ng/L influents	62 ± 11	[67]
	Trimethoprim	PAC dose: 43 ± 14 mg/L, 3.14 ± 1.82 ng/L influents	>99	
	Metronidazole	1.86 ± 2.03 ng/L influents, PAC dose: 43 ± 14 mg/L,	78 ± 5	
	Erythromycin	PAC dose: 43 ± 14 mg/L, up to 0.140 ng/L influents	>88	
	Norfloxacin	3.14 ± 1.82 ng/L influents, PAC dose: 43 ± 14 mg/L,	>99	
	Ciprofloxacin	PAC dose: 43 ± 14 mg/L, 15.7 ± 8.0 ng/L influents	>99	
	Clarithromycin	1.28 ± 0.84 ng/L influents, PAC dose: 43 ± 14 mg/L,	100	
WSP	Sulfamethoxazole	–	82–100	[76]
	Trimethoprim	–	44–100	[77]
MBR-GAC	Sulfamethoxazole	–	82*	[78]
Ozonation treatment	Trimethoprim	O_3 dose: 5 mg/L, time: 15 min.	>90	[79]
		3200 ng/L of MBR outlet, 82 mg O_3/L, 10 min	99.25	[74]
		3200 ng/L of MBR outlet, 156 mg O_3/L, 20 min	99.7	[74]
		235 ± 52 ng/L influents, O_3 dose: 2.3–9 mg/L	99 ± 2	[70]
		2.1 mg/L	>90	[80]
		O_3 dose: 1.08 ± 0.05 g O_3/g DOC, 3.14 ± 1.82 ng/L influents	>99	[67]
	Clarithromycin	O_3 dose: 1.08 ± 0.05 g O_3/g DOC, 1.28 ± 0.84 ng/L influents	100	
		2.1 mg/L	>90	[80]
		920 ng/L of MBR outlet, 82 mg O_3/L, 10 min	94.45	[74]
		920 ng/L of MBR outlet, 156 mg O_3/L, 20 min	98.7	[74]
		709 ± 418 ng/L influents, O_3 dose: 2.3–9 mg/L	93 ± 4	[70]
	Ofloxacin	234 ± 60 ng/L influents, O_3 dose: 2.3–9 mg/L	85 ± 20	[70]
		60 mg/L influent	100	[81]
	Metronidazole	O_3 dose: 1.08 ± 0.05 g O_3/g DOC, 1.86 ± 2.03 ng/L influents	49 ± 4	[67]
	Azithromycin	2272 ± 1472 ng/L influents, O_3 dose: 2.3–9 mg/L	74 ± 10	[70]
		1100 ng/L of MBR outlet, 82–156 mg O_3/L, 10–20 min	>99.54	[74]
	Clindamycin	65 ± 33 ng/L influents, O_3 dose: 2.3–9 mg/L	99 ± 1	[70]
		130 ng/L of MBR outlet, 82 mg O_3/L, 10 min	87.7	[74]
		130 ng/L of MBR outlet, 156 mg O_3/L, 20 min	96.2	
	Sulfapyridine	2.1 mg/L	>90	[80]
	Metronidazole	1168 ± 866 ng/L influents, O_3 dose: 2.3–9 mg/L	64 ± 12	[70]
	Erythromycin	O_3 dose: 1.08 ± 0.05 g O_3/g DOC up to 0.140 ng/L influents	>93	[67]
		540 ng/L of MBR outlet, 82–156 mg O_3/L, 10–20 min	>96.3	[74]
	Norfloxacin	O_3 dose: 1.08 ± 0.05 g O_3/g DOC, 3.14 ± 1.82 ng/L influents	>99	
		334 ± 167 ng/L influents, O_3 dose: 2.3–9 mg/L	75 ± 29	[70]
	Sulfamethoxazole	2.1 mg/L	>90	[80]
		680 ng/L of MBR outlet, 82 mg O_3/L, 10 min	25	[74]
		680 ng/L of MBR outlet, 156 mg O_3/L, 20 min	72.05	
		O_3 dose: 1.08 ± 0.05 g O_3/g DOC, 3.23 ± 4.70 ng/L influents	99	[67]
		340 ± 261 ng/L influents, O_3 dose: 2.3–9 mg/L	93 ± 7	[70]
	Ciprofloxacin	O_3 dose: 1.08 ± 0.05 g O_3/g DOC, 15.7 ± 8.0 ng/L influents	100	[67]
		2291 ± 600 ng/L influents, O_3 dose: 2.3–9 mg/L	53 ± 29	[70]
		4800 ng/L of MBR outlet, 156 mg O_3/L, 20 min	94.8	[74]
		2291 ± 600 ng/L influents, O_3 dose: 2.3–9 mg/L	53 ± 29	[70]
PAC-UF	Norfloxacin	334 ± 167 ng/L influents, PAC dose: 10–20 mg/L	82 ± 21	[70]
	Sulfamethoxazole	340 ± 261 ng/L influents, PAC dose: 10–20 mg/L	64 ± 25	
	Clarithromycin	709 ± 418 ng/L influents, PAC dose: 10–20 mg/L	92 ± 5	
	Ofloxacin	234 ± 60 ng/L influents, PAC dose: 10–20 mg/L	83 ± 24	
	Metronidazole	1168 ± 866 ng/L influents, PAC dose: 10–20 mg/L	79 ± 17	
	Azithromycin	2272 ± 1472 ng/L influents, PAC dose: 10–20 mg/L	76 ± 8	
	Clindamycin	65 ± 33 ng/L influents, PAC dose: 10–20 mg/L	82 ± 13	
	Trimethoprim	235 ± 52 ng/L influents, PAC dose: 10–20 mg/L	94 ± 4	
	Ciprofloxacin	2291 ± 600 ng/L influents, PAC dose: 10–20 mg/L	63 ± 32	
MBR-GAC	Erythromycin	–	>88	[67]
O_3/H_2O_2	Ciprofloxacin	4800 ng/L of MBR outlet, 130 mg O_3/L, 60 mg/L H_2O_2, 5 min	70.83	[74]
		4800 ng/L of MBR outlet, 450 mg O_3/L, 200 mg/L H_2O_2, 15 min	95.2	
	Sulfamethoxazole	O_3 dose: 5 mg/L, H_2O_2 dose: 3.5 mg/L	98	[82]

(*continued on next page*)

Table 1 (*continued*)

Post-treatment	Type of antibiotics	Conditions	RE (%)	References
	Azithromycin	1100 ng/L of MBR outlet, 130 mg O_3/L, 60 mg/L of H_2O_2, 5 min	96.63	[74]
		1100 ng/L of MBR outlet, 450 mg O_3/L, 200 mg/L of H_2O_2, 15min	>99.54	
	Clindamycin	1300 ng/L of MBR outlet, 130–450 mg O_3/L, 60–200 mg/L of H_2O_2, 5–15min	96.2	
	Erythromycin	540 ng/L of MBR outlet, 130–450 mg O_3/L, 60–200 mg/L of H_2O_2, 5–15min	>96.3	
	Clarithromycin	920 ng/L of MBR outlet, 130 mg O_3/L, 60 mg/L of H_2O_2, 5 min	96.7	
		920 ng/L of MBR outlet, 450 mg O_3/L, 200 mg/L of H_2O_2, 15 min	99.4	
	Trimethoprim	3200 ng/L of MBR outlet, 130 mg O_3/L, 60 mg/L of H_2O_2, 5 min	98.85	
		3200 ng/L of MBR outlet, 450 mg O_3/L, 200 mg/L of H_2O_2, 15 min	>99.85	
GAC	Trimethoprim	Full-scale, EBCT: 15 min.	90	[83]

Notice: WSP – waste stabilization pond, PAC – powdered activated carbon, EBCT – empty bed contact time, MBR – Membrane bioreactor, GAC – Granular Activated carbon, DOC – Dissolved organic carbon.

genes using PAC [67,69,70], GAC, or by integrating other techniques (see Tables 1 and 2). Kovalova et al. [67] studied a pilot-scale hospital wastewater treatment with the primary clarifiers, membrane bioreactor, and post-treatment approaches. In this study, about 86% of the pharmaceuticals and their metabolites (excluding the iodized contrast medium) were removed at a dose of 23 mg/L by the PAC system. The removal potential of a PAC system could be improved by integrating nanofiltration, where the micropollutants would be further retained in the membrane [71]. Li et al. [72] conducted a study on the adsorption of sulfamethoxazole using PAC in the membrane bioreactor in a series of treatment tests. The findings of this study revealed that adsorption to treatment sludge was negligible. The removal efficiency of sulfamethoxazole depends on its hydrophobicity (which results in a higher affinity towards PAC adsorption), loading rate, and PAC dosage. It achieved approximately 82 ± 11% removal rates when using 1 g/L of PAC dose. A pilot-scale study on 80% of the compounds revealed that adsorption onto GAC outperformed ozonation in terms of removal rate [73]. The removal performance of activated carbon adsorption (via GAC and PAC) to remove various antibiotics, antimicrobial resistance bacteria, and resistant genes is illustrated in Tables 1 and 2

Table 2
Inactivation performance of antimicrobial resistance bacteria (AMRB) and antimicrobial resistance genes (ARGs) from wastewater.

Technique	Type of AMRB and ARGs	Conditions	Max. Removal or reduction	References
Chlorination	Genes *tet*X, *tet*G, *int*l1, and 16 S rRNA	Cl_2 dose: 30 mg/L, time: 30 min	1.3 and 1.49 log	[84]
	Erythromycin and Sulfadia- zine resistance bacteria	Cl_2 dose: 60 mg/L, time: 1 min	Inactivation of bacteria	[85]
	AR *E. coli*	Cl_2 dose: 1 mg/L, time: over 2.5 min	Inactivation of bacteria	[86]
	(a, b, c, d, e, f and g) - resistance bacteria	Cl_2 dose: 15 mg/L, time: 1 min	Inactivation of bacteria	[85]
	E. coli DH5α, containing a multiresistance gene (pB10)	Cl_2 dose: 30 mg/L	2-log reduction* of AMRB and ARGs	[87]
	Plasmid-encoded ARGs (e.g. amp^R and kan^R)	At pH 7	4-log reduction of ARGs	[88]
UV treatment	Methicillin resistant *S. aureus* Vancomycin resistant *E. faecium* *E. coli SM-3-5* *P. aeruginosa 01*	UV req. from 10 to 20 mJ/cm^2	Reduction: 5 log	[89]
	Tetracycline resistant gene	UV req. 5 mJ/cm^2	Reduction: −1.9 log	[90]
	Erythromycin resistant gene	UV req. 5 mJ/cm^2	Reduction: −3.0 log	
	*tet*X and 16 S rRNA genes *sul*1, *tet*G, *intl1* genes	249.5 mJ/cm^2	−0.58 and 0.60 log −0.36 and 0.40 log	[84]
	Plasmid-encoded ARGs (e.g. amp^R and kan^R)	At pH 7	4-log reduction of ARGs	[88]
	Erythromycin resistant genes resistant genes Tetracycline	–	3.0 ± 0.1 log 1.9 ± 0.1 log	[90]
Fenton oxid. (Fe^{2+}/H_2O_2)	*int*l1, *sul*1, *tet*X, *tet*G, and 16 S rRNA genes	–	2.58–3.79 logs, and 2.26–3.35 logs	[91]
UV/H_2O_2 processes	*int*l1, *sul*1, *tet*X, *tet*G, and 16 S rRNA genes	–	2.8–3.5 logs, and 1.55–2.32 logs	[91]
	Plasmid-encoded ARGs (e.g. amp^R and kan^R)	At pH 7	4-log reduction of ARGs	[88]
Ozone-based treatment	–	Cl_2 dose: 30–33 mg/L, time: 1 min	2 log reduction	[87]
	*erm*B, *van*A*, *blaVIM***	–	2 orders of magnitude reduction in *erm*B	[92]
	VRE, CRE, MDRA, MRSA, MDRP and ESBL-E	Time: 10 min treatment	Complete inactivation***	[9]

Note: A - cephalexin, B - vancomycin, C - ciprofloxacin, D - chloramphenicol, E – gentamicin, F - rifampicin and G – tetracycline, AR – antibiotic resistant, * - achieved 90% removal rate, ** - Simultaneous increase in *van*A and *blaVIM*, VRE – vancomycin-resistant *Enterococcus,* CRE – carbapenem-resistant *Enterobacteriaceae*, MDRA – multidrug-resistant *Acinetobacter,* MRSA – methicillin-resistant *Staphylococcus aureus*, MDRP – multidrug-resistant *Pseudomonas aeruginosa,* and extended spectrum β-lactamase (ESBL) producing *Enterobacteriaceae* (ESBL-E), *** - achieved 99.9% removal rate.

7.2. Advanced oxidation processes (AOP)

The conventional oxidation methods using various oxidants such as Cl_2, H_2O_2, HClO, and $KMnO_4$ are not effective to remove micropollutants [10]. Against this, the advanced oxidation processes (AOP) perform with enhanced removal efficiency, mainly due to the formation of stronger oxidants, usually hydroxyl radicals (OH·). The formation of hydroxyl radicals takes place via direct photolysis of oxidants such as O_3, H_2O_2, or water through greater energy supplied by UV radiation, etc. Ozone, chlorination, and UV-based treatments are the most common AOP technologies used in pilot or full-scale hospital wastewater treatment around the world [93]. The potential benefit of using AOPs in hospital wastewater treatment is that they are environmentally friendly, as there is no pollution transfer and they do not produce large amounts of toxic sludge [10,94]. This section describes how various AOP techniques (ozonation, UV treatment, chlorination, and so on) perform in removing various antimicrobial resistance bacteria and antimicrobial resistance genes. The post-treatment applications for removing antibiotic residues and inactivation of antimicrobial resistance bacteria are presented in Tables 1 and 2

7.2.1. Ozonation treatment

Hospital wastewater treatment using ozone (O_3) oxidation has been widely studied in Europe, most recently in Germany and Switzerland [93,95]. This process is administered in/directly or indirectly through the oxidation of the micropollutants to hydroxyl radicals (OH·) in a non-selective way. O_3 reacts selectively with those micropollutants containing several functional groups (e.g., double bonds, C═C. –OH, $–CH_3$, $–OCH_3$ and certain anions (O, P, N and S) [10]. The main advantages of O_3 oxidation is that it leads to the transformation of pollutants into unknown products with unknown toxicity due to their presence at lower concentrations and insignificant antimicrobial and estrogenic activities when compared to the parent pollutant [94]. However, this technique is considered energy intensive, and the removal performance of HO· for micropollutants has been considerably influenced by the occurrence of inorganic anions and natural organic matter [10].

Different antimicrobial resistance bacteria and their genes were effectively removed from hospital and municipal wastewater treatment effluents (Table 2). A pilot-scale hospital wastewater treatment was demonstrated by Kovalova et al. [67] using various post-treatment techniques for the removal of active pharmaceutical micropollutants. This hospital wastewater effluent was first treated in the primary clarifier and membrane bioreactor systems. In this study, the ozonation, containing 1.08 g O_3/g DOC, achieved over 90% removal efficiency for the total load of pharmaceuticals produced from the hospital wastewater, except, the iodized contrast media (ICM). This study suggested that the majority of the analyzed hospital effluents can be effectively removed by ozonation.

The use of an integrated treatment system using O_3/H_2O_2 did not improve the removal rate compared to ozone treatment alone [67]. Azuma et al. [9] conducted a study to use various ozone-based treatments (O_3/UV and O_3/UV/H_2O_2) to inactivate the WHO list of priority antimicrobial resistance bacteria, such as vancomycin-resistant *Enterococcus*, carbapenem-resistant *Enterobacteriaceae*, multidrug-resistant *Acinetobacter*, methicillin-resistant *Staphylococcus aureus*, multidrug-resistant *Pseudomona*. This study found that the ozone-based advanced WWT deactivated more than 99.9% of the antimicrobial resistance bacteria and their genes. In practical applications, ozonation has performed efficiently for the reduction of sulfamethoxazole from wastewater [96]. In a study done by Lüddeke et al. [97], ozone has the capability to reduce the concentration level of the antimicrobial-resistant *enterococci, staphylococci, and E. coli* by 0.8–1.1 log-units when compared with the influent concentrations. The reduction mechanism was due to the oxidative damage to the plasmid DNA of the multidrug resistant bacteria by ozone, and the damage increased with the dose of the oxidant or ozone [93,95].

7.2.2. UV irradiation

Now a days, the UV/H_2O-based treatment is the most widespread used in full-scale hospital wastewater treatments. This technology was recently discovered as a membrane bioreactor (MBR) post-treatment at pilot-scale treatment of hospital wastewater [10]. Many WWT companies have adopted UV-light as the most applicable option over chemical disinfection options in order to balance environmental safety, public health implications, and the demand for an efficient disinfection strategy [98]. In comparison to O_3, H_2O_2 is more stable to store for an extended period of time prior to use, but it must be eliminated before discharging the H_2O_2-containing residuals. This technique is very effective in removing micropollutants from hospital wastewater, where its efficiency depends on several factors, such as the characteristics of the water matrix, which include alkalinity and turbidity [10].

Different results have been achieved in studies that were carried out using UV disinfection for hospital wastewater treatment. Kovalova et al. [67] investigated a study for the removal of a wide range of pharmaceuticals using post-treatment technologies in hospital wastewater, first treated using the primary clarifiers and MBR system. This study reported that the UV treatment having 2400 J/m^2 at 254 nm achieved lower removal efficiency (i.e., 33%) compared to the ozone and PAC-based treatments. The compound specific removal rate of this technique was found in Table 1. This study also suggested that the use of an integrated system using UV/TiO_2 did not improve the elimination rates. Besides, the extent of the removal rate of the selected pharmaceuticals and their metabolites was effectively associated with different physico-chemical characteristics and molecular structures of the compounds [67]. An increment in UV dose should be required to remove tetracycline resistance genes [99], but in a study by Auerbach et al. [100], the dose of UV investigated was unable to reduce the detectable tetracycline resistance gene types (*tet* gene). McKinney et al. [101] found only a slight reduction in ARGs from wastewater in another study. The UV-based disinfection was also carried out to achieve a total reduction of ciprofloxacin, sulfamethoxazole, and amoxicillin resistant *E. coli* with 1.25×10^4 μW/s.cm^2 at 60 min of irradiation [102]. In a study by Munir et al. [103], this technique was significantly unable to reduce sulfonamide and tetracycline-resistant *E. coli* bacteria. Guo et al. [90,104] found that a UV treatment with 5 mJ/cm^2 fluence increased the reduction potentials of erythromycin-resistant heterotrophic bacteria by 1.4 0.1 logs. In a similar study, total ARB counts were reduced to less than 1 CFU/mL

at an increased fluence of 20–50 mJ/cm^2.

7.2.3. Chlorination techniques

Disinfection is among the alternative techniques necessarily applied to control the health concerns of conventional pathogens in the treated effluents [98]. Because of their low cost and ease of use, as well as the potential concerns raised by the harmful by-products they produce, chlorine and/or chlorine-based compounds have gained widespread acceptance when compared to other available wastewater disinfectants. The disinfectants are quite effective at removing the enteric bacteria. However, it has to be achieved at a lower removal rate against bacteria, spores, viruses, and protozoan cysts [105]. Hence, an important proportion of such pathogens are carried out in the wastewater residues, develop resistance mechanisms, and continue to be present in the treated effluents [98,105]. Initially, the total bacterial load was decreased with chlorine-based treatments from wastewater. However, several studies have suggested that this technique may significantly increase the proportions of the antimicrobial resistance bacteria [93,102].

There have been limited reports on the removal of both antimicrobial resistance bacteria and antimicrobial resistance genes from wastewater using this technique [106–108]. A study conducted by Templeton et al. [106] revealed that the reduction of ampicillin-resistant *E. coli* has occurred due to the bacteria's lower tolerance to chlorine disinfection than "an antibiotics-sensitive one". Another study was conducted in the East Lansing WWTP in Michigan WWTP by Gao et al. [108], and the results revealed that higher concentrations of antimicrobial resistance bacteria and antimicrobial resistance genes were found in the treated effluent, but chlorine disinfection did not show an apparent reduction in the concentrations of sulfonamide and tetracycline resistance genes. An increase in the proportion of antimicrobial resistance bacteria has been observed after chlorination in the study of Huang et al. [107], which suggests that as a function of chlorine dosage, the response of chlorination on the disinfection of antimicrobial resistance bacteria has varied. The membrane bioreactor treated effluents were further polished with chlorine dioxide (ClO_2), which was found to be less effective in removing pharmaceuticals from hospital wastewater [74].

Disinfection methods reduced selected antimicrobial-resistant bacteria by up to 99% in various WWTPs [109], which appears to be sufficient for elimination into the environment [98]. According to the study conducted by Wiethan et al. [110], in three wastewater types (originating from several hospitals and the other two from communal sewage), approximately 95–99% removal efficiency was achieved for the non-resistant bacteria *E. coli, Enterococcus* spp., *and Pseudomonas* spp. In this study, about 93.5–100% removal rates for the resistant bacteria were reported, which showed no observed differences in removal rates between the two types of bacterial pathogens (i.e., resistant and non-resistant) [98]. The antimicrobial resistance bacteria removal rates vary with the effect of chlorination, which depends on the chlorine dosage and on the process conditions of chlorination [98,111].

7.3. Phytoremediation technologies

Phytoremediation is an emerging plant-assisted bioremediation technology in which green plants and their associated microorganisms are used to remove, stabilize, and transform pollutants from the contaminated environment [112]. The selected plants can either accumulate or detoxify the pollutants. Constructed wetlands (CWs) and waste stabilization ponds (WSPs) are the two well-known natural systems and the potential alternatives for hospital wastewater treatments, mainly in developing countries [61]. As a result, wetlands, aquatic plants, and algae use photosynthetic reactions to produce gases such as oxygen, which bacteria use to degrade organic matter. Compared to the existing conventional WWT systems, the CW and WSPs are typically well-established, low-cost, and have an efficient treatment potential for hospital wastewater [112]. This section illustrates the main appropriate phytoremediation techniques of CWs and WSPs for the removal of antibiotics and antimicrobial resistance bacteria and their genes from hospital wastewater.

7.3.1. Constructed wetlands

A constructed wetland (CW) is an engineered shallow pond or channel cultured with integrated interactions among plants, soil, sediments, water, microorganisms, gravel, aquatic animals, and environmental conditions that treat WW effluents [112,113]. This green approach occurs simultaneously through the infusion of photolysis, adsorption, volatilization, accumulation, plant uptake, microbial degradations, and plant-assisted exudation mechanisms [6,112,114]. Those processes have occurred alongside the CW and enhance the extensive removal efficiency of micro/pollutants and have been applied for decentralized WWT systems [6,115]. As illustrated by Beyene and Redaie [61], this system might be among the most viable alternatives for hospital wastewater treatment in developing countries. CWs are seen as a potential sustainable green solution for the micropollutants induced by hospital wastewater, including the removal of different antibiotics and antimicrobial resistance bacteria [6,114]. In practice, the CW has operated in horizontal flow (HCW) and vertical flow (VCW) configurations, where the VCW flow is more efficient for the treatment of hospital wastewater because of the advanced characteristics that it possesses: (i) ammonia nitrification and effective oxidation processes in the VCW flows, and (ii) the VCW requires a lower footprint than the counter HCW that uses 1–3 and 5 m^2 per population equivalent [6]. The removal efficiency of micropollutants is a function of design effects, environmental conditions, and operating conditions, but requires further understanding of the removal mechanisms and toxicity risks [114,116].

Different studies have investigated the use of CWs for the removal of antibiotics and antimicrobial resistance bacteria [112,114] for the treatment of hospital wastewater. Dires et al. [112] studied the hospital wastewater treatment for the removal of antimicrobial resistance bacteria in a pilot-scale HCW with subsurface flow. In this study, different investigations, such as indicator organism enumeration, bacteriological identifications, and susceptibility testing, were accomplished according to the standard procedures. The result revealed that the removal of total coliforms and fecal coliforms was 7.1 and 5.1 log10, respectively. Besides, the result of susceptibility testing of hospital wastewater reveals that the Salmonella isolates were established as 100% resistant to ampicillin, 75%

resistant to doxycycline, ceftazidime, erythromycin, cefoxitin, and chloramphenicol, and the antibacterial-resistant *E. coli* also showed 81.1% resistance to ampicillin and 72.7% resistance to amoxicillin-clavulanic acid and cotrimoxazole. In this study, higher removal rates (80–93.2%) of antimicrobial resistance bacteria were achieved in vegetated CW systems. The non-vegetated and vegetated wetlands also achieved very high removal efficiencies for *Staphylococcus* spp., fecal coliforms, and total coliforms, with 99.3%, 99.84%, and 99.98%, respectively. This suggests that the CW is promoted as an effective strategy for hospital wastewater treatment aiming at antimicrobial resistance bacteria removal, mostly suitable for developing countries [112]. Bôto et al. [114] also evaluated the potential of CWs in removing a wide range of antibiotics and antimicrobial resistance bacteria from wastewater using *Phragmites australis* wetland plants that could achieve a higher removal rate for a group of pharmaceuticals [117,118]. The results showed that more than 99% of the removal rates for oxytetracycline and enrofloxacin were achieved in this study, while the total bacterial load and antimicrobial resistance bacteria load were also removed with greater than 95% after three weeks of adaptation.

7.3.2. Waste stabilization ponds

Waste stabilization ponds (WSPs) are large artificial shallow basins where raw wastewater flows continuously and uses biological and physical processes to remove a wide range of pollutants from raw wastewater, including organic matter, pathogens, and other pollutants [65,119]. This technology is among the simplest techniques of WWT extensively employed globally, and specifically in developing countries where sufficient land is usually available and the climate conditions (i.e., sunlight and higher temperature) are highly favorable for the treatment processes [65]. In its operation, a retention time is attained after several hours/days, which enhances the performance of its treatment and yields well-treated effluent that can be safely discharged [65,119]. As a natural system, the WSP is successfully applied worldwide for domestic WWT in a series of anaerobic ponds (APs), facultative ponds (FPs), maturation ponds (MPs), and high-rate algal ponds working in parallel with two or more series ponds [61,65,119]. In this regard, Polprasert and Kittipongvises [119] reviewed the design criteria and factors influencing the removal rates of WSP during WWT in a previous study.

The WSPs system was used in several studies and achieved relatively higher removal efficiencies for some antibiotics, including trimethoprim [76,77] and sulfamethoxazole [76,77,120] from wastewater [76]. At pH levels greater than 9, a well-designed and operated WSP can achieve 99.9% removal efficiency for faecal coliforms and 100% removal rate for helminths [61,121]. Another investigation of WSPs (in a series of 2 FPs, 2 MPs, and 1 fish pond) had been carried out at Hawassa University Referral Hospital in Ethiopia for a total of 43 days of retention time for treating hospital wastewater [61]. The results revealed that above 99.4% of fecal and total coliform were removed, while the removal rate for pathogens was about 99.99%. This suggests that this system has been foreseen as an effective and feasible alternative to hospital wastewater treatment.

8. Conclusion

Hospital wastewater contains hazardous and very infectious pollutants, including antibiotics, antimicrobial-resistant bacteria, and resistant genes. The existing wastewater treatment plants were primarily designed to remove non-resistant pathogens before they reached the public by spreading through various exposure pathways. However, these technologies were not put in place to remove micropollutants, predominantly the antibiotics, antimicrobial resistance bacteria, and antimicrobial resistance genes. In this case, several resistant bacteria could be passed from hospital wastewater into urban sewage systems, affecting the ecosystem and public health. This paper reviews the performance of post-treatment techniques in removing antibiotics, antimicrobial resistance bacteria, and antimicrobial resistance genes from hospital wastewater. When compared to conventional methods, post-treatment techniques such as ozonation, PAC, GAC, UV, chlorination, and phytoremediation using CW and WSPs have the potential to remove a wide range of antibiotics, including antimicrobial resistance bacteria and antimicrobial resistance genes, from hospital wastewater. However, the removal rate of antibiotics was a function of the physico-chemical characteristics and structural elucidation of the specific compound. More systems integration research (phytoremediation technologies and improved oxidation processes) will be necessary to achieve an effective removal rate of micropollutants during the spiking conditions of actual hospital wastewater.

Author contribution statement

All authors listed have significantly contributed to the development and the writing of this article.

Data availability statement

No data was used for the research described in the article.

Declaration of interest's statement

The authors declare the following conflict of interests: I would like to publish my manuscript.

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