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Review

Traditional and Emerging Water Disinfection Technologies Challenging the Control of Antibiotic-Resistant Bacteria and Antibiotic Resistance Genes

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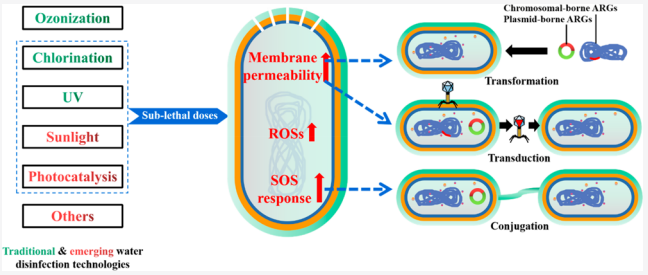
ABSTRACT: The emergence of antibiotic-resistant bacteria (ARB) and antibiotic resistance genes (ARGs) in the environment has created obstacles when treating infectious diseases with antibiotics. Wastewater treatment plants (WWTPs) serve as reservoirs for ARB and ARGs and can disseminate them into the environment. It is important to understand and address these risks. Generally, professional disinfection processes have been used in WWTPs to disinfect the target water body, with the goal of eliminating pathogenic microorganisms in the water. However, ARGs are not generally considered, and antibiotic resistance has spread and developed through horizontal gene transfer (HGT). This Review provides a detailed overview of the application progress of different traditional and new disinfection technologies in removing ARB and ARGs, mainly focusing on the bacterial inactivation mechanisms of chlorination, ozonation, ultraviolet (UV) (including UVA, UVB, and UVC), sunlight, sunlight-dissolved organic matter (DOM), and photocatalysis (PC)/photoelectrocatalysis (PEC). In addition, this Review also focuses on the disinfection technology involved in the transfer of ARGs and clarifies the underlying transfer mechanisms in water environments. Furthermore, by linking the mechanisms of bacterial inactivation, the Review describes how SOS response and cell membrane permeability may be the key step in the conjugation, transformation, and transduction of ARGs. Finally, given the applications and current problems associated with traditional water disinfection technologies and light-based disinfection technologies in removing and controlling ARB and ARGs, this Review describes the current challenges and opportunities to facilitate the development of future disinfection technologies. The Review also highlights future research directions related to ARG transmission control.



KEYWORDS: *Antibiotic-resistant bacteria, Antibiotic resistance genes, Disinfection processes, Light-based disinfection technologies, Gene transfer mechanisms*

1. INTRODUCTION

The 2019 coronavirus outbreak has reminded people that microbes can have serious impacts.[1] Unlike viruses, bacteria do not need to be attached onto host cells and can multiply using only the micronutrients in a water environment. Because of their ubiquitous nature, people have developed antibiotics that specifically fight against pathogenic bacteria to protect themselves from infection.[2,3] However, an excessive dependence on antibiotics in the medical, agricultural farming, industrial, and aquaculture domains has led to large amounts of antibiotics being discharged in wastewater, directly into the water environment or through wastewater treatment plants (WWTPs). A study showed that the mean concentration of clarithromycin in medical wastewater reached 2.8 μg/L, while it is rare in other types of wastewater.[4] The study also showed that the mean concentrations of oxytetracycline, sulfamethoxazole, tetracycline, and trimethoprim in industrial wastewater are as high as 23 119.0, 18 416.8, 453.5, and 3078.7 μg/L, respectively.[4] Another study reported that sulfonamides, macrolides, tetracyclines, and quinolones are the dominant antibiotics observed in surface water and are mainly attributed to aquaculture and the emission of domestic sewage. Quinolones are the dominant antibiotics observed in coastal water and are mainly attributed to aquaculture.[5] This has led to the gradual increase in the presence of local antibiotic-resistant bacteria (ARB) and antibiotic resistance genes (ARGs).[6−8] Some pathogenic bacteria, including pathogenic *Escherichia coli*, *Salmonella*, *Vibrio cholerae*, *Mycobacterium tuberculosis*, and staphylococci, have acquired or have improved their antibiotic resistance, leading to failures in the efficacy of routinely used

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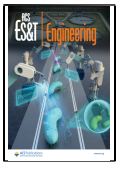

antibiotics.[9−13] This has decreased the probability of a cure when people are infected by antibiotic-resistance pathogens, and may even lead to death.[14,15] According to reports, more than 2.8 million ARB infections occur in the USA each year, resulting in 35 000 deaths.[16] Before 2016, 700 000 people died of antibiotic resistance each year, and it is estimated that by 2050, antibiotic resistance will cause 10 million deaths each year.[17] The fight against antibiotic resistance cannot be stopped.

Under normal circumstances, ARB replicate ARGs into their offspring through vertical gene transfer (VGT); this proliferation maintains the genetic stability of the population.[18] However, in many cases, bacteria also exchange genes through horizontal gene transfer (HGT) to promote gene diversity.[19−21] However, this gene exchange gives ARGs an opportunity to spread and further develop in the environment.[22,23] Antibiotic-sensitive bacteria can obtain ARGs through HGT to form new ARB, while ARB obtain ARGs through HGT to form multi-drug-resistant bacteria (MDRB), including *Enterococcus faecalis*, *Staphylococcus aureus*, *Klebsiella pneumoniae*, *Acinetobacter baumannii*, *Pseudomonas aeruginosa*, and *Enterobacter*.[24] This creates significant obstacles when treating pathogenic bacterial infections.[25,26]

Bacterial HGT includes three pathways: conjugation, transformation, and transduction.[25] Conjugation refers to the process by which two bacteria form a connection "bridge" through physical contact. Moveable genetic elements, such as plasmids, integrons, or transposons, are then transferred from the donor cell to the recipient cell.[27] Minimum inhibitory concentrations of chlorhexidine (24.4 μg/L), triclosan (0.1 mg/L), gentamicin (0.1 mg/L), and sulfamethoxazole (1 mg/L) were used to significantly increase the frequency of conjugative transfer of *E. coli*.[22] Transformation refers to the process by which a competent bacterial cell absorbs extracellular DNA and recombines the introduced genes into its own genome.[28] Lu et al. used triclosan at environmentally detected concentrations (0.2−20 μg/L) to significantly enhance the transformation of plasmid-borne ARGs into *E. coli* DH5α for up to 1.4-fold.[29] Transduction occurs when, after the donor bacteria are infected by a phage, the bacterial DNA is accidentally packed in the progeny phage capsid. When the phage containing the donor bacterial DNA infects the recipient bacterial cell, it binds and injects the foreign DNA. Transduction occurs if the donor bacterial DNA is recombined with the genome of the recipient bacteria.[30] Han et al. used nano-TiO_2 to promote the horizontal transfer of ARGs to *E. coli* through transduction by constructed phage gM13.[31] These three pathways can all lead to the transfer and spread of ARGs in the environment, especially in water.

WWTPs and waterworks use special processes to disinfect target water, with the goal of eliminating pathogenic microorganisms.[32,33] Current disinfection technologies used in WWTPs mainly include chlorination, ozonation, light-based disinfection, peroxyacetic acid, ferrate, and other disinfection technologies.[34−37] These disinfection technologies apply different disinfection principles to inactivate pathogenic microorganisms.[35,38] Wastewater is often polluted with ARB, so these disinfection technologies indiscriminately inactivate all microorganisms. However, in some cases, ARB are more resistant to the damage from disinfection compared to antibiotic-sensitive bacteria.[39] As a result, many ARB and antibiotic-sensitive bacteria are present in WWTPs, and a large number of HGT likely occurs between them.[40] Cheng et al. used chlorination with sub-inhibitory concentration (<8 mg/L) to effectively reduce the relative abundance of ARGs, but increase the diversity of the main bacterial genera carrying ARGs, which may be attributed to the spread of antibiotic resistance through horizontal transfer throughout the bacterial genus.[41] In addition, another study showed that exposure to medical wastewater will benefit the growth of recipient *E. coli*, thereby increasing the relative abundance of transconjugants.[42] This leads to the question: in the process of water disinfection, do these disinfection technologies accelerate or inhibit the HGT process of these ARGs?

Many studies have posited that disinfection processes may affect the transfer of ARGs during implementation, and early reported experiments have supported this hypothesis.[43,44] However, few comprehensive overviews have addressed this topic. Therefore, this Review provides a series of evidence to summarize the impact of different disinfection technologies on ARG transfers, including chlorination, ozonation, and light-based disinfection. The goal is to provide new insights into the control of the spread of antibiotic resistance in WWTPs, to better develop and improve disinfection technologies. Furthermore, the Review discusses development opportunities and challenges, based on our early knowledge about ARG transfers and disinfection technologies.

2. ADVANCES IN WATER DISINFECTION TECHNOLOGIES IN REMOVING ARB AND ARGs

Antibiotics are continuously discharged into the environment due to their excessive use in medical and health settings, animal breeding, and agriculture.[45] The increase in the concentration of antibiotics in the water environment can further select or induce an increase in ARB and ARGs.[46] In particular, WWTPs are sewage storage systems that collect ARB and ARGs from a wide range of different sources, including municipal, medical, and slaughter wastewater. The most common ARGs-related antibiotics in WWTPs include aminoglycoside, β-lactam, macrolides, quinolone, sulfonamides, tetracyclines, and trimethoprim.[47] *Proteobacteria*, *Firmicutes*, and *Bacteroidetes* harbor the highest number of identified ARB in wastewater.[48] Researchers have developed several traditional and emerging wastewater disinfection technologies to inactivate pathogenic microorganisms in wastewater (Figure 1).[49−52] These technologies can be divided into light-based disinfection and non-light-based disinfection, and some have received extensive research attention. The role of traditional WWTPs is generally to effectively remove impurities in sewage, including organic matters, nitrogen, phosphorus, and metals. A key question is, can these high tolerance ARB and their extracellular products ARGs be effectively removed in these processes?

2.1. Traditional Water Disinfection Technologies.

Chlorination remains one of the most used traditional water disinfection technologies, however, it is known to produce disinfection byproducts (DBPs).[53,54] Chlorination may cause different responses to ARB and ARGs, depending on the type, dose, reaction time, and the nature of the ARB.[55] The bacterial inactivation mechanism of chlorination mainly involves using chlorinating agent oxidation to kill the target microorganisms. This leads to further hydrolysis, followed by the mechanical destruction of the cell wall and changes in permeability (Figure 2).[56] After the cell wall is damaged, chlorination can destroy the cell membrane by acting on peptidoglycan components; the chlorine further enters the cytoplasm and act on targets in

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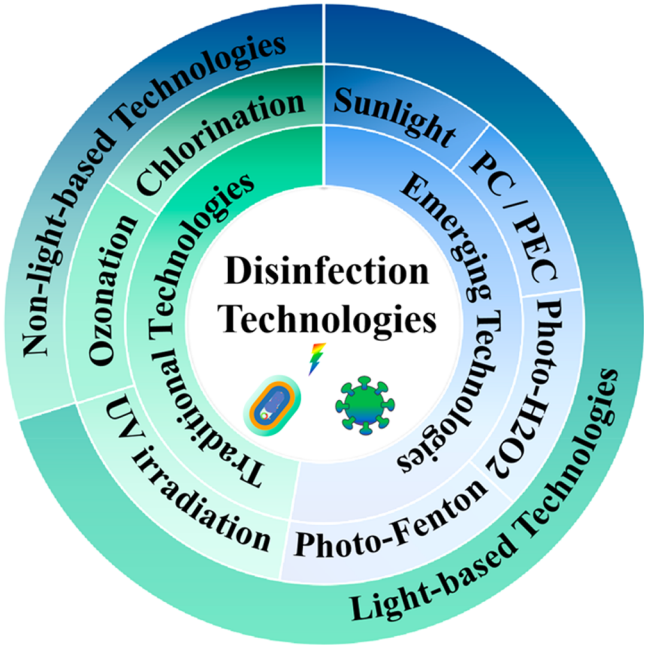

Figure 1. Traditional and emerging wastewater disinfection technologies, which can be divided into light-based technologies and non-light-based technologies. Abbreviations: UV, ultraviolet; PC, photocatalysis; PEC, photoelectrocatalysis.

the cytoplasm (DNA, glutathione, and enzymes) (Figure 2).[57] This means that the intracellular ARG (iARG) is acted upon after the chlorine penetrates the cell membrane, thereby causing damage. In addition, the damage of the cell membrane and cell wall leads to the intracellular biological macromolecules (protein, DNA, and RNA) leaking outside of the cell; these substances are further damaged by the chlorinating agent outside the cell.[58]

One study found that the permeability of the cell membrane was damaged at low doses of chlorine (<5 mg/L NaOCl); slight damage to DNA was also observed at high doses of chlorine (>5 mg/L NaOCl).[59] After 30 min exposure to 5 mg/L chlorine, the repair function (RecA mRNA) needed to correct DNA damage was completely inhibited in the bacteria.[59] When iARG is released outside the bacterial cell, it becomes free DNA independent of bacteria, also known as extracellular ARG (eARG). Therefore, chlorination damages eARG earlier than iARG.

In another study, Zheng et al. explored the effects of chlorination and other disinfection methods on ARGs in secondary wastewater discharged from municipal WWTPs. They found that in the 0−5 mg/L available chlorine concentrations, with a contact time of 30 min, as the chloride concentration increased, ARGs including *tetA*, *tetM*, *tetO*, *tetQ*, *tetW*, *sulI*, and *sulII* decreased linearly (R^2 = 0.77−0.99).[60] When the chlorine concentration was 2 mg/L, tetracycline-resistant bacteria and sulfamethoxazole-resistant bacteria decreased by 0.24 and 0.26 log, respectively. When the chlorine concentration was 32 mg/L, the culturable bacteria removal efficiency of the two ARB reached 100%, reflecting a reduction of 3.36 and 4.30 log, respectively.[60] Miranda et al. reported that using 1 mg/L of NaOCl for chlorination disinfection reduced the MDRB, showing multiple resistances to ciprofloxacin, ampicillin, and tetracycline in surface water by 6 log (an initial concentration of 7 log) after 2.5 min contact time.[61] Under the identical chlorination conditions, the MDRB with multiple resistances to ciprofloxacin, ampicillin, and tetracycline in municipal sewage reduced by 5 log (an initial concentration of 6 log) after 15 min contact time.[62] The difference between the results may be due to the respective aqueous matrices studied; a typical feature of urban wastewater is that the concentration of oxidant consumption compounds (oxidant demand) is significantly higher, such as inorganic nitrogen compounds. Therefore, as the contact time increases, chlorine is consumed, so it can no longer available for bacterial inactivation.[63]

Chlorination is not a universal disinfection technology, and the recent emergence of chlorine-resistant bacteria has led to negative evaluations.[64] Douterelo et al. used the whole metagenome to sequence the microorganisms in the distribution system of chlorinated drinking water. They

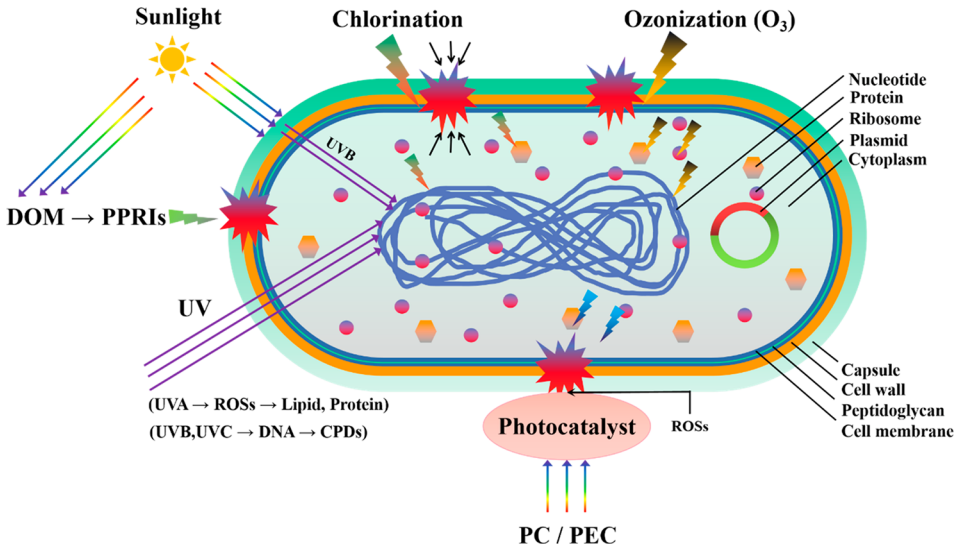

Figure 2. Bacterial inactivation mechanism of traditional water disinfection technologies (chlorination and ozonation) and light-based disinfection technologies (UV, sunlight, sunlight-DOM, and PC/PEC). Abbreviations: DOM, dissolved organic matter; PPRIs, photo-produced reactive intermediates; CPDs, cyclobutane pyrimidine dimers.

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Table 1. Research on ARGs Removal by Chlorination or Ozonation

disinfectant	concentration	contact time	target microorganisms	target genes	ARGs removal	ref
			Chlorination			
NaClO	0−32 mg/L	30 min	bacteria in wastewater	*tetA*, *tetM*, *tetO*, *tetQ*, *tetW*, *sulI*, and *sulII*	+	60
	1 mg/L	2.5 min	*E. coli* in surface water	ciprofloxacin, ampicillin, and tetracycline resistance genes	+	61
	1 mg/L	15 min	*E. coli* in urban wastewater	ciprofloxacin, ampicillin, and tetracycline resistance genes	+	62
	4 mg/L	30 min	bacteria in wastewater	119 ARGs	+	66
	4 mg/L	30 min	bacteria in wastewater	*dfrA1*, *tetPB-03*, *tetPA*, *ampC-04*, *tetA-02*, and *erm(36)*	−	66
ClO_2	8−9 mg/L	30 min	bacteria in wastewater	*ermB*, *tetA*, *tetB*, *tetC*, *sul1*, *sul2*, *sul3*, *ampC*, *aph(2′)-Id*, *katG*, *vanA*, and *qnrA*	−	67
			Ozonation			
O_3	7−10 mg/L	10 min	*E. coli*	amoxicillin, streptomycin, sulfamethoxazole, and tetracycline resistance genes	+	78
	50 g/Nm^3	30 min	bacteria in wastewater	*sul1*, bla_{TEM}, *qnrS*, and *vanA*	+	79
	1 mg/L	5 min	*E. coli*	*tet(A)*, *ampC*, *ermB*, and *vanA*	+	80
	25 mg/L	15−140 min	bacteria in wastewater	quinolone, mupirocin, polymyxin, aminoglycoside, glycopeptide, *β*-lactam, and trimethoprim resistance genes	+	81
	91 mg/L	1 d	bacteria in wastewater	*tetA*, *tetG*, *qnrA*, *qnrS*, and bla_{NDM-1}	+	82
O_3 + Cl_2	2−3 mg/L, 2−3 mg/L	10−15 min, 30−60 h	bacteria in wastewater	ARGs within the resistance-nodulation-cell division and ATP-binding cassette antibiotic efflux families	−	85

found that relevant defense systems against oxidative stress and antibiotics appeared to be upregulated (including the OxyR system, SoxRS system, several genes regulated by RpoS, *β*-lactamase, and efflux pump related genes).[65] Another study found that the relative abundance of most ARGs (119 species) decreased after chlorination. In other word, chlorination cannot co-select ARGs.[66] Interestingly, the study by Cheng et al. showed that sub-inhibitory concentration (<8 mg/L) chlorination caused an increase of ARB in sewage, but it was effective in reducing the relative abundance of ARGs.[41] This indicates that chlorination may stimulate the spread of antibiotic resistance across bacterial genera through HGT. In contrast, Liu et al. reported that chlorine dioxide (ClO_2) preferentially increased the abundances of eARGs (*ermB*, *tetA*, *tetB*, *tetC*, *sul1*, *sul2*, *sul3*, *ampC*, *aph(2′)-Id*, *katG*, and *vanA*) up to 3.8-fold and the abundances of iARGs up to 7.8-fold.[67] Additionally, Xu et al. reported that chlorination enhanced the relative abundance of ARGs from 6.4- to 109.2-fold in tap water compared to the final water.[68] Therefore, there is a certain risk in the chlorination treatment of ARGs in sewage.

Besides chlorination, ozonation is another common sewage disinfection technology.[69−71] Ozone (O_3) is a powerful oxidant that acts against a variety of microorganisms. It does, however, produce DBPs during water disinfection.[72,73] The inactivation mechanism of ozonation for bacteria mainly involves O_3 attacking the cell wall and causing its cleavage. This leads to the oxidative denaturation of nucleic acids and the breaking of the carbon and nitrogen bonds of proteins, leading to depolymerization (Figure 2).[74] O_3 is highly reactive to amino acids and unsaturated carbon−carbon bonds contained in proteins, peptidoglycans, and lipids in cell walls and membranes.[57] Therefore, after the cell wall and cell membrane are damaged, O_3 may further attack iARG.[57] The eARG is also more susceptible to O_3 oxidation attack compared to iARG.

The effect of ozonation disinfection is affected by the physical characteristics of the target microorganism, contact time, and O_3 concentration.[75] Different bacteria show distinct sensitivities to ozonation; these specifically relate to the guanine-cytosine content of the target organism's genome.[76] ARGs with lower guanine-cytosine content may be more easily damaged by O_3. However, due to the hydrogen bonds between DNA double-strands, the reactivity of O_3 to double-stranded DNA is not as high as expected.[77] This leaves questions about how efficiently ozonation removes ARGs.

Pak et al. evaluated how efficiently O_3 removed ARB and antibiotic-resistance plasmids and explored optimal disinfection conditions.[78] When the O_3 concentration was 7 mg/L, the removal efficiency of MDRB (with amoxicillin, streptomycin, sulfamethoxazole, and tetracycline resistance) was 122.73 mg min/L, and the removal efficiency of plasmids was 127.15 mg min/L.[78] Sousa et al. used 50 g/Nm^3 of O_3 to disinfect wastewater for 30 min; the resulting removal efficiency of ARGs, including *sul1*, bla_{TEM}, *qnrS*, and *vanA*, all exceeded 95%.[79] Another study reported that using 1 mg/L O_3 resulted in a 5 log reduction (an initial concentration of 7 log) of tetracycline and *β*-lactam antibiotic-resistance *E. coli*, and also reduced vancomycin and teicoplanin-resistant *Enterococcus faecalis*. Other ARGs, including *tet(A)*, *ampC*, *ermB*, and *vanA*, were reduced by at least 4.3 log (more than 99.995%).[80] Xia et al. used 25 mg/L O_3 to disinfect wastewater in a bioreactor and observed that the levels of multidrug, quinolone, mupirocin, polymyxin, aminoglycoside, glycopeptide, *β*-lactam, and trimethoprim resistance genes were reduced by more than 70%.[81] A more recent study used an O_3 concentration as high as 91 mg/L to disinfect wastewater from a high-speed railway train; five ARGs (*tetA*, *tetG*, *qnrA*, *qnrS*, bla_{NDM-1}) were reduced by 1.67−2.49 log (an initial concentration of 4.35−7.78 log), and antibiotic-resistant enterococci was reduced by 3.16 log CFU/mL (an initial

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concentration of 6 log).[82] Another study summarized recent progresses on ozone application for enhanced wastewater treatment for chemical and biological contaminants, including DBP issues, elimination/disinfection efficiencies as a function of ozone doses or DOC normalized ozone dose.[83] The study found that disruption of iARGs was observed at specific ozone doses feasible for full-scale application, but may be interfered by flocs. However, ozone doses are relevant for micropollutant abatement do not eliminate iARG of wastewater community.[83] In general, O_3 has a good performance in removing ARB and ARGs, but the removal efficiency of ARGs is relatively low. Therefore, to completely eliminate antibiotic resistance in wastewater, a higher dose of O_3 may be required.

He et al. investigated the degradation and deactivation of fluoroquinolones, chloramphenicol, doxorubicin, and aclaflavin resistance genes during exposure to free chlorine, monochloramine (NH_2Cl), ClO_2, O_3, ultraviolet (UV) light and hydroxyl radicals ($^{\bullet}OH$).[84] The results found that degradation rate constants were as follows, in decreasing order: $^{\bullet}OH$ > O_3 > free available chlorine > ClO_2 > NH_2Cl > UV. The iARG degradation/deactivation was consistently behind cell inactivation.[84] The results above show that ozonation is associated with powerful treatment performance, because its main substances include O_3. However, another study applied a metagenomic assembly analysis to show that using a O_3/chlorine coupled disinfection method significantly increased the relative abundance of ARB-carrying ARGs and movable genetic elements, providing a different perspective.[85] Although ozonation is widely used to remove ARB, it may increase the relative abundance of ARGs under certain conditions, creating a prerequisite for the spread of antibiotic resistance.

To summarize this section, chlorination and ozonation are the most traditional water disinfection technologies, and their status in the water disinfection industry is demonstrated by their wide range of applications and the longevity of their use. These two disinfection technologies use chemicals as disinfectants, which produce DBPs under certain circumstances. These DBPs generated by the water system pose a threat to biological health.[86] In addition, some ARGs may be enriched under certain circumstances, due to the characteristics of target microorganisms (such as chlorine-resistant bacteria), disinfectant dosage, contact time, and other factors. In order to understand how to choose the disinfectant, dosage, and contact time, some disinfection studies using chlorination or ozonation are summarized in Table 1. It can be used as a reference when using these disinfection techniques to reduce the risk of ARGs. Therefore, these two traditional water disinfection technologies still require technical improvements and optimization to maximize reductions or eliminate the generation of DBPs. Chlorination and ozonation did not show absolute advantages in the removal of ARB and ARGs. In particular, a higher dose of O_3 was required to completely eliminate ARGs, while chlorination might not necessarily reduce the relative abundance of ARGs. Therefore, both disinfection techniques need to be used with caution.

2.2. Traditional and Emerging Light-Based Water Disinfection Technologies. In contrast to chlorination and ozonation, light-based disinfection technologies usually use the physical element of light as the main starting factor of the system.[87−89] In addition to UV, there are many light-based disinfection technologies, including photocatalysis (PC) or photoelectrocatalysis (PEC), photo-Fenton, and the coupling of light and other disinfection technologies.[90−94] However, due to economic and practical constraints, UV remains the current primary light-based disinfection technology used in WWTPs.

UV inactivates bacteria by easily penetrating the transparent structure of cell membrane and cytoplasm, and then being absorbed by bases, such as pyrimidine and purine in nucleic acid.[57] UV is divided into three parts based on different wavelength ranges: UVA (320−400 nm), UVB (280−320 nm), and UVC (200−280 nm). The main mechanism by which UV damages bacteria depends on the specific UV wavelength; the degree of DNA damage may vary with a specific absorption wavelength.[95]

The photosensitivity of UVA may generate several reactive oxygen species (ROSs), including singlet oxygen ($^1O_2$), superoxide free radicals ($O_2^{\bullet-}$), and $^{\bullet}OH$. These ROSs further lead to oxidative changes in lipids and proteins, which subsequently damage bacteria (Figure 2).[96−98] In contrast to UVA, the antibacterial effect of UVB is mainly caused by an endogenous mechanism: the DNA absorbs photons with a shorter wavelength.[99] After the DNA absorbs the UVB, the light products of DNA are mainly cyclobutane pyrimidine dimers (CPDs) and 6-4 pyrimidine−pyrimidinone. These are the main substances involved in the antibacterial process (Figure 2).[100] The mechanism by which UVC inactivates bacteria is mainly based on the specific destruction of DNA and other biological components (such as proteins, lipids, and membranes) (Figure 2).[101] Due to its short wavelength, UVC can promote the formation of CPDs in bacterial DNA, thereby inhibiting the physiological activities of bacteria (Figure 2).[55]

UVA has a low disinfection efficiency, making it rare for researchers to apply UVA alone to remove ARB and/or ARGs from water bodies. A few researchers have applied UVA to inactivate antibiotic-sensitive bacteria, however, the bacteria could still be recovered after the inactivation.[102] Pezzoni et al. used 20 W/m^2 UVA to inactivate tetracycline-resistant *katA*-deficient *Pseudomonas aeruginosa* in the form of planktonic bacteria and biofilm. They observed a reduction of more than 3 log (an initial concentration of 6 log) for both bacterial forms.[103] In addition, the extracellular catalase (KatA) in the biofilm matrix attenuated the killing effect of UVA on tetracycline-resistant *P. aeruginosa*, confirming that ROSs were the main bactericidal substance associated with UVA.[103] Similarly, Argyraki et al. explored the bactericidal effect of UVB on *P. aeruginosa* biofilms,[104] as biofilm is a dormant form of bacteria that can tolerate antibiotics.[105] The results showed that UVB at a dose of 10 000 J/m^2 reduced *P. aeruginosa* non-mature biofilm by more than 4.8 log (growth 24 h). UVB at a dose of 20 000 J/m^2 inactivated 3.9 log of mature biofilm (growth 72 h).[104] In another study, UVB radiation was identified as a key factor in sunlight that hindered the cultivability, resistance, and regrowth of ARB.[106] Although a few researchers have paid attention to the inactivation of bacteria by UVA and UVB, related examples of their application in WWTPs are rare, reflecting their limitations.

Compared with UVA and UVB, UVC is more widely used for water disinfection due to its higher disinfection efficiency. For example, UVC irradiation of 600 J/m^2 reduced tetracycline and β-lactam antibiotic-resistance *E. coli* and vancomycin and teicoplanin-resistant *Enterococcus faecalis* by 4.8−5.5 log (an initial concentration of 7 log); however, there was a negligible reduction in ARGs (*tet(A)*, *ampC*, *ermB*, and *vanA*) (0−1.0 log) (an initial concentration of 7 log).[80] Shen et al. used 0.38 mJ/cm^2 UVC to disinfect tetracycline-resistant *Bacillus cereus* and *Bacillus pumilus*. They observed at least 5.7 log inactivation

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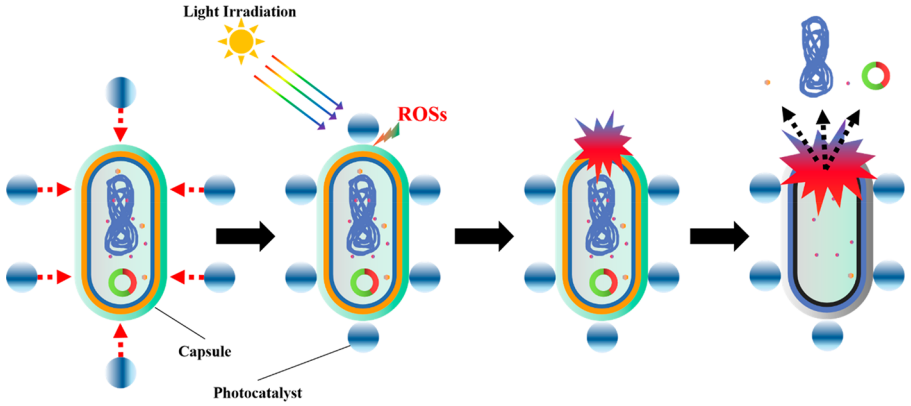

Figure 3. Whole process of bacterial inactivation under photocatalytic disinfection.

(an initial concentration of 6 log) and inhibited ARG expression.[107] However, the recovery rates of the two ARB were very high within 24 h after the end of the irradiation, even when a irradiation dose of up to 46.08 mJ/cm^2 was used.[107] In addition, Tavares et al. were able to isolate 25 CTX-M-producing *E. coli* strains from wastewater after UVC treatment; they identified the presence of nine kinds of ARGs (*sul1*, *sul2*, *sul3*, *tet (A)*, *tet (B)*, $bla_{OXA\text{-}1\text{-}like}$, *aacA4*, *aacA4-cr*, and *qnrS1*).[108] The recovery of ARB after water disinfection demonstrates low disinfection ability of UV. Therefore, to completely inactivate bacteria, it is necessary to improve the original technology or use it in conjunction with other technologies.

Sunlight contains a broad spectrum of UV and has considerable economic benefits; as such, it is also used to inactivate microbes in water.[109−111] The mechanism by which sunlight inactivates bacteria is mainly explained by the fact that most UVB in sunlight can penetrate bacteria and reach their cytoplasm, damaging the membrane-binding proteins, cytoplasmic proteins, and genomic DNA.[112] Zhang et al. found that the inactivation of tetracycline-resistant *E. coli* under simulated sunlight (SS) was caused by membrane damage from direct light irradiation and the generated ROSs.[113] ARB is more resistant to inactivation by sunlight compared to antibiotic-sensitive bacteria.[114] While ARB can be inactivated by sunlight, the ARGs inside the bacterial cells can be transferred to other bacteria.[115] Dissolved organic matter (DOM) in sewage can absorb visible light (VL), UVA, and UVB in sunlight and produce photo-produced reactive intermediates (PPRIs) (excited triplet state (3 DOM*), $^1O_2$, and $^{\bullet}OH$), which damage membrane-bound proteins, cytoplasmic proteins, and the genomic DNA of bacteria.[112,113] Zhang et al. added Suwannee River fulvic acid (SRFA), a representative DOM, under sunlight and observed that it promotes the inactivation of tetracycline resistant *E. coli* and further inhibits the expression of tetracycline resistance genes, which is attributed to the production of PPRIs.[113] Another previous study focused on the killing effect of different light sources on different ARB.[44] ARB and antibiotic-sensitive bacteria concentrations were reduced by 99.9% under 4 μW/cm^2 UVC (UV_{254nm}) irradiation within 120 min, while SS irradiation achieved a less than 10% decrease. Further, none of the tested bacterial strains were easily inactivated by VL irradiation.[44] Therefore, SS shows a higher ARB bactericidal efficiency than VL but is less efficient than UVC. In summary, sunlight disinfection seems to show good application prospects, because it is economical and sustainable, showing a certain degree of disinfection efficiency. But compared with UV, its disinfection efficiency is very limited. In addition, light-DOM has good prospects, because it can not only use sunlight to degrade DOM in water, but also can be used for disinfection.

PC is an advanced oxidation processes based on semiconductors. The most widely used photocatalyst is TiO_2.[116] In order to allow it to absorb visible light, a large number of modification studies have been carried out, including ion doping, noble metal deposition, dye sensitization, and coupling with other substances.[117−120] Simultaneously, many researchers are dedicated to the development of non-TiO_2 photocatalysts, including complex metal oxides, sulfides, nitrides, and nitrogen oxides.[121−124] PC has recently emerged as a "green" water disinfection technology with several advantages.[116,125−127] One of the advantages is that it can directly use sunlight to achieve various chemical reactions, which can show a more excellent bacterial inactivation effect than sunlight disinfection.[90] In addition, UV-driven PCs show better disinfection performance than UV alone.[116] Previous studies have found that the mechanism involved in the photocatalytic inactivation of bacteria is mainly the adsorption of photocatalyst particles to the bacterial surface by the capsular extracellular polymer materials.[128] Then, under the action of light, ROSs generated on the surface of photocatalyst can destroy the cell membrane of the bacteria, causing the leakage of cytoplasmic components and the death of the bacteria (Figure 2).[128] The procedure involved in the bacterial cell membrane damage (Figure 3) has been observed and confirmed using scanning electron microscope images by Li et al.[129] Zhou et al. explained that the mechanism of photocatalytic inactivation of eARG mainly involves the photocatalyst adsorbing ARGs through intermolecular forces to form a synergistic interface. This leads to the further photocatalytic oxidation inactivation of bacteria.[130] A recent article reported that using UVC-driven PC can effectively inactivate ampicillin-, kanamycin-, and tetracycline-resistant multi-drug-resistant *E. coli* (>6.5 log) (an initial concentration of 8 log) within 80 min, and can effectively remove *aphA* (kanamycin resistance gene) and *tetA* (tetracycline resistance gene) (>3.0 log) (an initial concentration of 8 log) within 80 min.[92]

PEC is an improved advanced oxidation processes based on PC; it applies a potential bias to timely remove the photogenerated electrons, suppressing the recombination of photoelectrons with photoholes.[131,132] This leads to a longer

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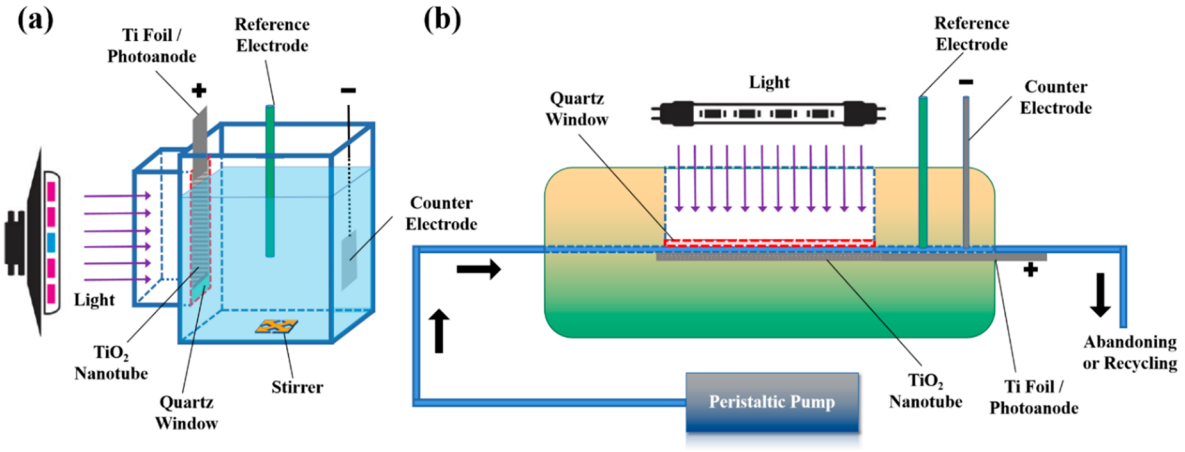

Figure 4. PC/PEC reactors using a sheet photocatalyst with TiO_2 nanotube arrays: (A) large-volume reactor and (b) microfluidic thin-layer cell reactor.

lifetime of the charge and therefore improves the photocatalytic activity.[131,132] Simultaneously, the oxidation of water through the anode surface and the possible direct electron transfer reaction will inevitably increase the oxidation rate of pollutants.[133] In addition, since the catalyst is immobilized on the conductive substrate in the PEC, there is no challenge of catalyst recovery after treatment in the photocatalytic device.[133] As such, PEC can effectively degrade organic pollutants and inactivate biohazards like bacteria and viruses.[133−135]

Previous studies also found that the mechanism by which PEC inactivates bacteria can be mainly attributed to bacterial attacks by photoholes and other photogenerated ROSs. Stable H_2O_2 molecules can generate a sharp increase of intracellular ROSs and the overload of antioxidant systems (such as superoxide dismutase (SOD) and catalase), which leads to oxidative damage to the bacteria.[136,137] The attack of ROSs damages the cell wall, cell membrane, and certain proteins, and the biological macromolecules in the cytoplasm and cytoplasm leak, as shown in Figure 3.[136] Similarly, a study applying antioxidant single-gene knockout mutants confirmed the important roles of catalase and SOD in bacteria.[138] In addition, the destruction of the bacterial energy metabolism system caused by membrane protein damage may be the initial lethal step in bacterial inactivation by PEC.[139] In a previous study, PEC was used to inactivate *E. coli* resistant to β-lactams and aminoglycosides; the complete inactivation of ARB (8 log) and complete damage to ARGs bla_{TEM-1} and *aac(3)-II* were achieved within 10 and 16 h, respectively.[140]

Regardless of whether the method is PC or PEC, a specific photocatalyst is needed.[141,142] However, powder-type photocatalysts are difficult to recycle, and the high cost of photocatalysts is a major obstacle, making PC/PEC difficult for wastewater treatment. A previous study prepared TiO_2 into nanotube arrays, so they could be fixed on Ti foil.[143] TiO_2 nanotube arrays can be used in large-volume reactors (Figure 4a) and can also be applied to reactors in the form of a microfluidic thin-layer cell (Figure 4b).[138,144] This fixed type of catalyst can be reused, addressing the problem of the photocatalyst being difficult to reuse. Many other light-based disinfection technologies have also been recently derived; however, the fixation and cost of current catalysts or auxiliary agents remain a major challenge. As such, these technologies will be difficult to apply to real sewage disinfection in the near future. However, many advanced oxidation processes, such as photo-H_2O_2, photo-Fenton, and other photo-coupling disinfection technologies, have been reported being used to inactivate ARB and ARGs.[145−149]

This paper has provided a detailed review of the mechanism by which different forms of light inactivate bacteria and remove ARB and ARGs. These types of light include UV, sunlight, light-DOM, PC/PEC, and other light-based technologies. UV is widely used in WWTPs for water disinfection because it does not produce as many harmful DBPs compared with traditional non-light-based water disinfection technologies (chlorination and ozonation). However, there remains a widely criticized bacteria recovery problem after water disinfection; this problem occurs with UVA, UVB, and UVC. Therefore, future research on sewage disinfection technology should focus on controlling the disinfection of bacteria, so that the bacteria are no longer regenerated or are completely inactivated. Light-DOM seems to be a promising disinfection technology because it not only consumes DOM in wastewater, but also inactivates bacteria. PC/PEC and other light-based disinfection technologies developed during recent decades require additional auxiliary agents and may increase costs, due to the fixation or recycling of photocatalysts and auxiliary agents or by applying potential bias. Therefore, optimizing these emerging disinfection technologies and reducing the required economic investment are key problems to address to increase their practical application for water disinfection in WWTPs.

3. HORIZONTAL TRANSFER OF ARGs DURING VARIOUS DISINFECTION TECHNOLOGIES

WWTPs are the central hub of antibiotic resistance in cities, because they continuously receive and spread ARB and ARGs from human sewage.[150−152] ARB and ARGs have been widely detected in wastewater samples from WWTPs, and the antibiotic resistance ratio of natural surface water is lower compared to that in wastewater. This demonstrates the antibiotic resistance storage effect of sewage.[153] It is well known that WWTPs contain high levels ARGs; however, no special processes have been established to remove ARGs in WWTPs equipped with a disinfection process to inactivate bacteria. The disinfection process can kill microorganisms in the water and significantly reduce their levels to achieve water

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standard thresholds. However, these disinfection processes are less efficient in removing ARGs than in inactivating ARB.[154,155] Disinfection processes can directly lead to the inactivation or lysis of ARB; however, they cannot completely inactivate the iARGs. As such, iARGs flow into the effluent water, and the indigenous bacteria living downstream become antibiotic resistant by transforming or transducing these ARGs (Figure 5).[57,156] In addition, ARB recovery after disinfection creates a good precondition for the conjugative transfer of ARGs between bacteria. This highlights the need to assess the impact of different disinfection technologies on the horizontal transfer of ARGs.

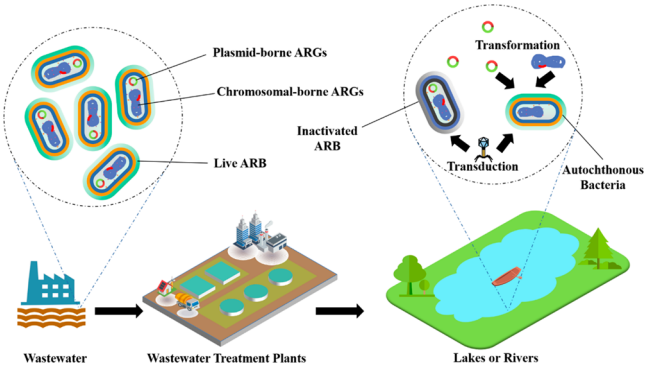

Figure 5. Fate of the ARGs after ARB are inactivated or lysed by water disinfection technologies.

3.1. Chlorination- and Ozonation-Mediated Horizontal Transfer Mechanism of ARGs. Chlorination and ozonation are the most traditional water disinfection technologies used in WWTPs, due to their economic benefits, easy operation, and mature technology.[155,157] However, these two disinfection technologies may produce DBPs and affect the horizontal transfer of ARGs between bacteria in sewage (Table 2). Conjugation occurs when genes are exchanged between bacteria in the form of contact; the ARGs of the donor bacteria are transferred to the recipient bacteria through pilus.[158,159] Guo et al. used sub-inhibitory chlorine doses (40 mg Cl min/L) to increase the frequency of ARGs conjugate transfer by 2−5 times; high inhibitory chlorine doses (80 mg Cl min/L) significantly inhibited conjugation.[160] This may be because the sub-inhibitory chlorine dose increases cell membrane permeability and induces the synthesis of conjugative pilus on the surface of the donor cells. This facilitates conjugative transfer.[160]

Zhang et al. later found that both free chlorine and chloramine at sub-inhibitory concentrations (0.1−1 mg/L Cl_2) promoted the conjugative transfer of ARGs within and between genera; the conjugation within *E. coli* increased by 3.4−6.4 and 1.9−7.5 times, respectively. The intergenus conjugation of *E. coli* to *Salmonella typhimurium* increased by 1.4−2.3 times.[161] In contrast, exposure to a free chlorine or chloramine concentration higher than the minimum inhibitory concentration significantly inhibits conjugation.[161] The mechanism involved may be as follows: free chlorine/chloramine can generate free radicals in water, promoting intracellular ROS production. Intracellular ROSs are highly active molecules that interfere with the normal function of bacteria during aerobic respiration.[162] The study used 2′,7′-dichlorofluorescein diacetate to measure intracellular ROSs and found that compared with the control sample, the free radical levels in the donor and recipient bacteria increased significantly with the increase in the concentration of free chlorine.[161] Moderately elevated levels (1.5−5 times) of ROSs may only damage the cell membrane and increase its permeability, promoting the conjugation of antibiotic resistance plasmids.[161,163]

In addition, the following genes may experience significant differences in expression after the treatment by sub-inhibitory disinfection: DNA damage and repair genes involved in the SOS response (*recA*, *polB*, *uvrD*, *umuD*, *ssb*, *ada*); an important regulatory gene for general stress response (*rpoS*); outer membrane protein gene (*omp*); and conjugation related genes. These final genes include global regulator genes (*korA*, *korB*, *trbA*); mating pair formation system genes (*trbBp*, *traF*); and plasmid DNA transfer and replication system genes (*trfAp*, *traJ*).[161] This result may be attributed to the bacteria being attacked by the generated ROSs in water disinfection systems, as the SOS response in bacteria has been shown to promote conjugative transfer.[164] Similarly, a recent study reported that sub-inhibitive chlorine doses (0.5 mg/L) can increase the efficiency of conjugative transfer. This may significantly increase the mRNA expression levels of the type IV secretion system (T4SS) proteins vir4D, vir5B, and vir10B.[165] Therefore, sub-inhibitory chlorination disinfection is likely to affect the conjugation of ARGs, by promoting the production of

Table 2. Influence of Chlorination and Ozonation on the ARGs Transfer

disinfectant	concentration	target genes	transfer forms	impact	ref
		Chlorination			
NaClO	40 mg Cl min/L	tetracycline resistance gene	conjugation	+	160
	>80 mg Cl min/L	tetracycline resistance gene	conjugation	−	160
	0.5 min/L	ampicillin and gentamicin resistance genes	conjugation	+	165
	0.3−0.5 mg/L Cl_2	*aphA*, *tetA*, *tetR*, *bla*	conjugation	−	176
		kanamycin, ampicillin, and tetracycline resistance genes	transformation	+	167
free chlorine	0.1−1 mg/L Cl_2	ampicillin, chloromycetin, and tetracycline resistance genes	conjugation	+	161
	10 mg/L	ampicillin, chloromycetin, and tetracycline resistance genes	conjugation	−	161
chloramine	0.1−1 mg/L Cl_2	ampicillin, chloromycetin, and tetracycline resistance genes	conjugation	+	161
	10 mg/L	ampicillin, chloromycetin, and tetracycline resistance genes	conjugation	−	161
		Ozonation			
O_3	3−75 mg/L	Tn5393c, Tn1721-like, *sul1*	conjugation	−	78
	50 mg/L	*ermF*, *mefA/E*, *tetO*, ISCR1	HGT	+	194

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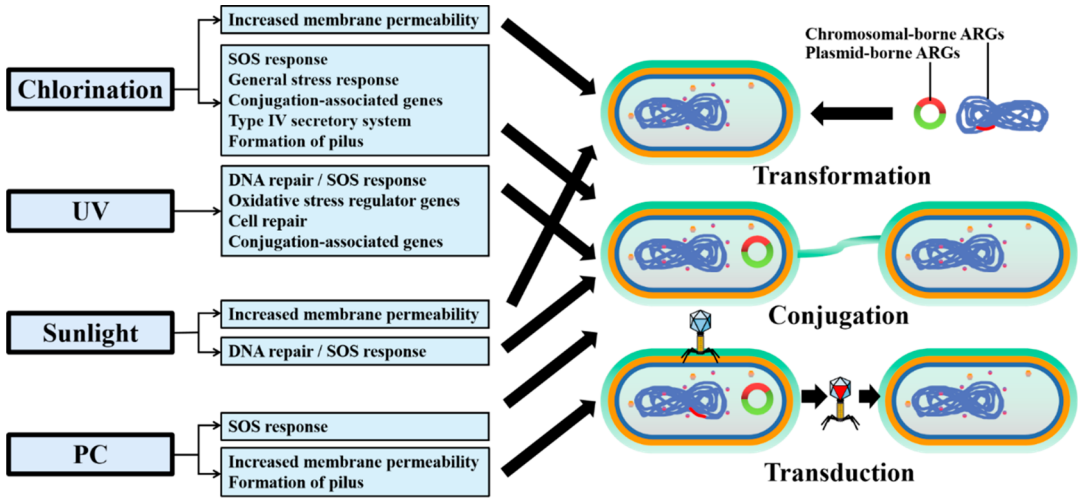

Figure 6. ARGs transfer mechanism during different disinfection processes: chlorination, UV, sunlight, and PC.

Table 3. Influence of Light-Based Disinfection Technologies on ARGs Transfer

light and additives	intensity	target genes	transfer forms	impact	ref
		UV			
UVC	0−2.88 × 10^4 mW/cm^2	*bla_{CTX}, mcr-1*	conjugation	+	44
	10 μW/cm^2	IncJ conjugative transposon-like elements R391, R392, R705, R706, R997, pMERPH	conjugation	+	174
	>10 mJ/cm^2	tetracycline resistance gene	conjugation	−	160
	>5 mJ/cm^2	*aphA, tetA, tetR, bla*	conjugation	−	176
	0−180 mJ/cm^2	*amp*	transformation	−	177
	10 mJ/cm^2	*tetA, tetC, tetM, tetW, tet X, sul1*	conjugation	−	178
	1 mJ/cm^2	kanamycin, tetracycline, and ampicillin resistance genes	conjugation	−	195
	31.5 mJ/cm^2	*rbcL-Prrn-aadA*	transformation	−	179
		Sunlight			
simulated sunlight	60 mW/cm^2	*bla_{CTX}, mcr-1*	conjugation	+	44
	153 mJ/cm^2	*rbcL-Prrn-aadA*	transformation	+	179
		upregulation of genes related to horizontal transfer	HGT	+	114
		PC			
UVA + TiO_2	80 W/m^2	chloramphenicol resistance gene	conjugation	+	185
	150 μW/cm^2	ampicillin and kanamycin resistance genes	transduction	+	190
UVC + TiO_2-modified PVDF membrane	12 μW/cm^2	*floR, tetC, tetW, tetQ, sul1, sul2, intI1, intI2, intI3*	transformation	−	189
SS + TiO_2/Ag/graphene oxide		rifampicin, kanamycin, tetracycline, and ampicillin resistance genes	conjugation	+	43
UVC + persulfate	400 μW/cm^2	*sul1, sul2, ermB, qnrS, tetO, intI1, intI2*	transformation	−	196
		Light-Coupling			
UVC + chlorination	UVC ≥ 4 mJ/cm^2, Cl ≥ 1 mg/L	ampicillin and gentamicin resistance genes	conjugation	−	165
UVC + H_2O_2	UVC 0−180 mJ/cm^2, H_2O_2 10 mg/L	*amp*	transformation	−	177, 193
UV + high temperature	0.5 kJ/m^2	*stx*, kanamycin resistance gene	conjugation	+	191

intracellular ROSs. This in turn affects the SOS response, general stress response, membrane permeability, expression of conjugation-related genes, and the formation of T4SS and pilus (Figure 6). Pak et al. also evaluated the effect of ozonation on the conjugation efficiency of ARGs, observing significant inhibition.[78] This may be because O_3, together with the produced $^{\bullet}OH$, attacked the bacteria and penetrated the cell membrane. This caused oxidative damage to plasmids and inhibited the expression of the conjugative function (Figure 6).

Transformation is another transfer pathway of ARGs; it occurs when external DNA is absorbed by competent cells with greater cell membrane permeability.[29,166] Jin et al. found that chlorination promoted the release of ARGs and transferable RP4 plasmids from ARB and cultivable chlorine-damaging bacteria. These can be transformed into viable cells at a frequency of up to 550 times.[167] Another study demonstrated that disinfection using chlorination can increase the abundance of both iARGs and eARGs, increasing the risk of spreading resistance by transforming ARGs in the water environment.[67]

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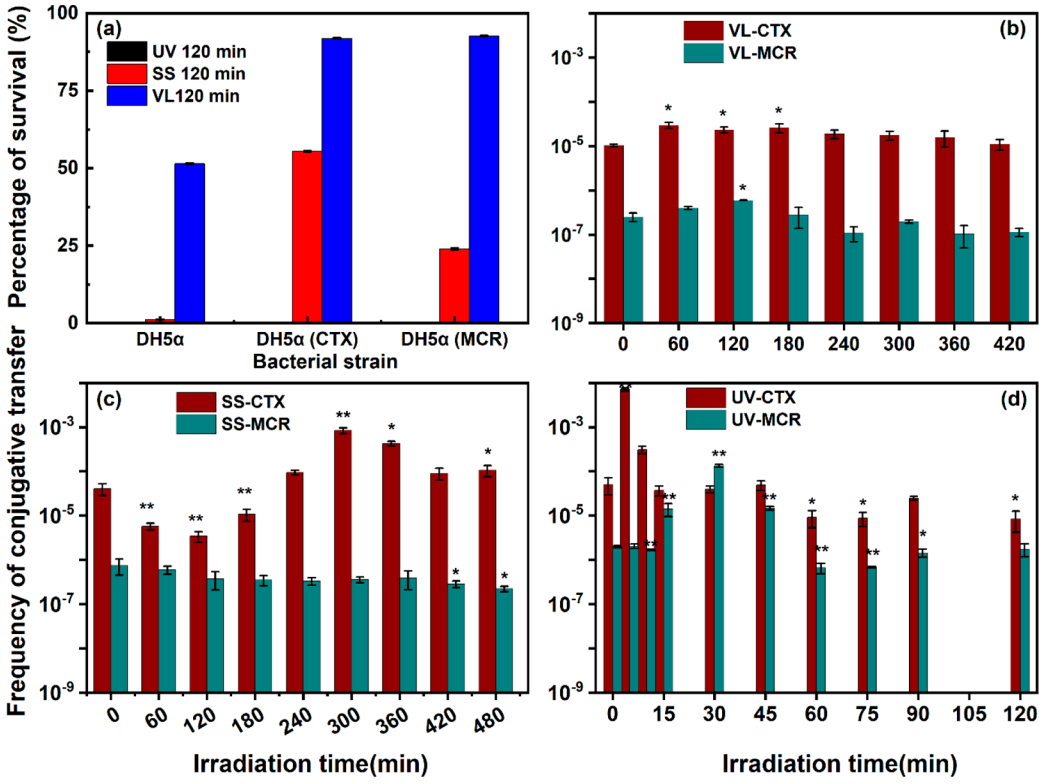

Figure 7. Effects of different light on bactericidal efficiencies and conjugation. (a) Effect of three light processes on the survival of *E. coli* DH5a (MCR), *E. coli* DH5a (CTX), and *E. coli* DH5a at 120 min. Effects of (b) visible light, (c) simulated sunlight, and (d) UV on the frequency of conjugation. Adapted with permission from ref 44.

The transformation of ARGs that are not inactivated due to the incomplete disinfection in the water environment may become the main pathway for transfers to a new host. The mechanism by which chlorination disinfection promotes ARG transformation may be that a sub-inhibitive dose of chlorine promotes the production of intracellular ROSs. This in turn attacks the cell membrane components and causes damage. Subsequently, the membrane permeability increases, improving the chance of eARG transformation (Figure 6).

Transduction is another form of gene transfer, mediated by a phage as a transfer tool. This can transfer the iARG of the donor bacteria to the recipient bacteria.[168,169] Currently, little evidence indicates that chlorination or ozonation can affect the transduction of ARGs. This may be because phages are also affected by chlorination and ozonation, which complicates the research on the transduction of ARGs.

In summary, chlorination and ozonation are widely used in WWTPs. However, they may further exacerbate the spread of antibiotic resistance. The evidence indicates that chlorination is more likely to promote conjugation between bacteria; ARG transfers then follow. ARGs may be released from the inactivated ARB; they are then absorbed by other bacteria through transformation to form new ARB or even MDRB. Therefore, WWTPs that use chlorination or ozonation for water disinfection should further improve the types or dosages of disinfection technologies; They should choose the right dose to remove ARB and reduce the abundance of ARGs, rather than promote the spread of antibiotic resistance.

3.2. Light-Based Disinfection-Mediated Horizontal Transfer Mechanism of ARGs. The disinfection of wastewater from WWTPs faces obstacles in limiting the spread of ARGs. Ideally, disinfection technologies should destroy ARGs to prevent horizontal transfers to downstream bacteria. Light-based disinfection technologies have recently received attention in removing ARB and are often used to remove ARGs.[170−172] Given the widespread use of light-based disinfection in WWTPs, Table 3 lists relevant reports about the impact of these technologies on the HGT process.

The most used light-based disinfection technology in WWTPs is UV; however, it has limited potential to damage ARGs in wastewater. Commonly used UV doses do not completely eliminate ARGs in wastewater, and it is impractical for water companies to reduce ARGs by 3−4 log.[173] In addition, the use of ineffective doses may also affect the HGT of ARGs. McGrath et al. reported that UVC increased the frequency of conjugative transfer of the original Inc.J-like conjugated transposon.[174] Another study reported that UVC induction promoted HGT in *Hyperthermophilic archaea*.[175] A previous study explored the effects of different lights on the conjugation of ARGs; the results found that UVC has the greatest promotion effect on the transfer frequency, followed by SS. Conjugation is not affected by VL (Figure 7).[44] Under VL irradiation, no bacterial inactivation occurred within the 480 min exposure period (Figure 7a), and the overall trend did not show a significant increase in the efficiency of conjugate transfer (Figure 7b). In contrast, SS irradiation slightly increased the efficiency of conjugate transfer after 180 min (2−10 times) (Figure 7c). The efficiency of conjugate transfer was greatly accelerated (up to 100 times) in the presence of UVC irradiation (Figure 7d).[44]

This research demonstrates that ineffective disinfection dosages and technologies fail to eliminate ARGs in the water environment and may accelerate their spread in the water systems. During the UVC and SS disinfection, the following

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genes were up-regulated to different degrees: oxidative stress regulation related genes (*oxyR*, *rpoS*, *soxR*, *soxS*, *marA*, *ompR*, *osmC*, *osmY*), cell repair related genes (*basS*, *cusC*, *mdtB*, *motA*, *yiaD*), DNA repair related genes (*mukB*, *radA*, *recF*, *recJ*, *recA*, *rpoD*, *rpoH*, *ruvB*, *lexA*, *rcsC*), and conjugation related genes (*tesB*, *ftsY*, *gspE*).[44] Similarly, oxidative stress occurs slowly during SS irradiation, and there is significant oxidative stress under UVC irradiation. In contrast, VL irradiation does not induce oxidative stress and gene expression.[44]

Therefore, the mechanism by which UV disinfection accelerates the conjugation of ARGs may be as follows: the UV leads to the rapid production of intracellular ROSs, and UV simultaneously causes damage to DNA. This facilitates a cascade of bacterial responses, including DNA repair, cell repair, oxidative stress regulation, and up-regulation of conjugation-related gene expression. This, in turn, accelerates conjugation (Figure 6). A previous study clarified that the up-regulation of the DNA repair related system (SOS response) may promote the HGT process. The above research indicates that UV disinfection promotes the spread of ARGs in water environments. However, this may not be true in all cases, as some studies have advanced different views. For example, a suitable dose of UV may inhibit HGT and reduce transfer efficiency.[160,176−178] One study showed that when the UV exposure dose increased from 5 to 20, 50, and 100 mJ/cm^2, the transfer frequency decreased from 2.75×10^{-3} to 2.44×10^{-5}, 1.77×10^{-6}, and 2.44×10^{-8}, respectively.[176] Another study focusing on the natural transformation activity of ARGs showed that the UV energy flux required for every log10 reduction in transformation activity during UVC treatment was approximately 37 mJ/cm^2.[177] Another study using a real wastewater sample showed that after UVC irradiation of 10 mJ/cm^2, the average detection frequency of the ARGs *tet* and *sul* on the plasmid decreased by 15% and 6% respectively, affecting the subsequent HGT.[178] While UV disinfection cannot completely eliminate ARGs in water, it significantly impacts their further spread.

Unlike UV disinfection, few studies have reported the horizontal transfer of ARGs, although water disinfection by sunlight can lead to this.[44,114,179] One study exploring the effect of sunlight on the horizontal transfer of ARGs (bla_{CTX}, *mcr-1*) found that under SS irradiation, the conjugate transfer frequency increased by 2−10 times (Figure 7c).[44] Augsburger et al. evaluated the effects of both SS and UVC on the absorption of eARGs by *Acinetobacter baylyi* through gene transformation. They observed that SS, and not UVC, stimulated eARG absorption and integration in the natural water environment.[179] Another study did not experiment with conjugate transfer, but found that *E. coli* showed up-regulation of genes related to HGT when irradiated by SS.[114] Few studies have reported on sunlight inhibiting the transfer of ARGs, due to the low disinfection efficiency of sunlight when compared with UV. This aligns with the general rule that low-dose UV promotes HGT. Combined with the bacterial inactivation mechanism, the result that sunlight promotes HGT may be explained by the fact that just a little UVB in sunlight penetrates the bacteria, damaging cell membrane components and genomic DNA, and changing the permeability. This leads to the upregulation of DNA repair systems (such as SOS response), promoting transformation and conjugation.

Traditional disinfection technologies have the disadvantage of not completely eliminating ARGs. As such, other light-based disinfection technologies, including PC/PEC, photo-Fenton, and photo-coupled disinfection have recently attracted research attention.[130,180,181] Although these emerging technologies seem more destructive, they do not necessarily prevent the spread of ARGs in the water environment. PC and its derivative technologies are considered to be promising disinfection technologies. Adhikari et al. reported an efficient bacterial disinfection approach based on an integrated system containing nanoporous titanium dioxide and ruthenium oxide.[182] Jiang et al. studied the photoelectrocatalytic removal of ARB and ARGs in water systems for the first time.[140] PC appears to have good application prospects for removing ARGs; however, other studies have found that PC may promote the occurrence and maintenance of antibiotic resistance.[183,184] Dunlop et al. first reported the potential of PC to induce the horizontal transfer of ARGs. They found that the sublethal stress induced by TiO_2 under UVA irradiation increased the conjugative transfer of ARGs between *E. coli*.[185] Guo et al. also found that a new nanocomposite photocatalyst synthesized from Ag, TiO_2, and graphene oxide showed excellent bactericidal activity under the action of SS. However, it also promoted the conjugation of ARGs.[43] Finally, another study recently reported that PC technology can facilitate the conjugative transfer of ARGs in bacteria at the interface of natural sphalerite under the irradiation of different lights.[186] Therefore, as one of the emerging disinfection technologies, PC should be used with caution.

The nature of the photocatalyst may also affect HGT performance. Recent studies found that natural sphalerite nanoparticles in the environment can accelerate the plasmid-mediated HGT process, and natural sphalerite has been shown to have a series of photocatalytic properties.[187,188] This occurs when the capsular extracellular polymer material adsorbs the photocatalyst particles on the bacterial surface and then generates ROSs on the photocatalyst surface. When there is direct contact with the bacteria under the action of light, the extracellular ROSs further attack the bacteria, causing the bacteria to produce a cascade of responses including an SOS response.[184] The SOS response will subsequently accelerate conjugation, prompting the transfer of ARGs from the donor bacteria to the recipient bacteria. However, Ren et al. prepared a photocatalytic reactive ultrafiltration membrane to effectively degrade ARGs and integrons (*intI1*, *intI2*, *intI3*), finding that the conjugation of ARGs may also be effectively controlled by photocatalytic reactions.[189] Obviously, this may be caused by the performance of different photocatalytic reactions or the difference in killing ability to bacteria.

Few researchers have addressed the effect of disinfection on phage-mediated gene transduction. This may be attributed to the fact that disinfection may also affect the activity of the phage. However, a recent study reported low-dose UVC excited TiO_2 effectively increasing the transduction efficiency of the filamentous bacteriophage gM13 to its host *E. coli*.[190] The extracellular ROSs produced by PC can increase the permeability of the bacterial membrane, promoting phage infection.[190] At the same time, in the presence of TiO_2, intracellular ROSs can induce the synthesis of pili. This increases phage recognition and invasion sites and facilitates transduction.[31,190] In addition, the synergistic effect of high temperature and UV accelerated the transfer of *stx* and kanamycin resistance genes to non-pathogenic *E. coli* in feedlots by enhancing phage-mediated transduction.[191]

These results indicate that disinfection processes may also promote the transduction of ARGs. To achieve a higher ARB

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and ARGs removal efficiency, researchers generally couple different disinfection technologies, with the goal of achieving better results compared to using one approach alone. Wang et al. studied the synergistic effect of UVC and chlorination and found that, although low doses of chlorine alone can stimulate conjugation, the synergistic effect showed greater potential for simultaneously removing ARB and ARGs as well as inhibiting conjugation.[165] Similarly, Zhang et al. explored the removal of ARGs and control of HGT risk by UV, chlorination, and UV/chlorination treatments and found that UVC/Cl_2 shows more advantages in simultaneous removal of ARB and ARGs as well as inhibiting HGT.[192] The mechanism involved in UV/chlorination may be that the generated free radicals (main contributing substances are $Cl^{\bullet}$, $ClO^{\bullet}$, and $Cl_2^{\bullet-}$) through the cell membrane with increased permeability to destroy genomic DNA and inhibit transfer function.[192] Furthermore, two other studies reported the coupling of UVC with H_2O_2 to effectively inhibit the transformation of ARGs.[177,193] Therefore, these coupling technologies seem to be able to remove ARGs and inhibit HGT well and have good application prospects.

A synthesis of the evidence discussed above concludes that regardless of whether conventional UV, sunlight disinfection, or more advanced PC/PEC is used, there are no guarantees for completely removing ARGs and inhibiting the progress of HGT. This may be due to sublethal disinfection, which promotes conjugation, transformation, or transduction through a series of effects on bacteria, enabling the transfer of ARGs. Therefore, identifying suitable technologies and economical doses to find the best bacterial inactivation and HGT inhibition effects is a key step for applying these disinfection technologies in actual WWTPs. In addition, coupling traditional water disinfection technologies may more effectively inactivate ARB and inhibit the spread of ARGs, while being less expensive disinfection options for WWTPs.

4. CONCLUSIONS AND OUTLOOK

The goal of disinfection is to remove microorganisms in sewage, especially pathogens that pose risks to human health. However, the emergence of ARB and ARGs has created significant challenges for disinfection technologies, because incomplete disinfection may lead to the further spread and development of antibiotic resistance. This Review summarized progress in traditional water disinfection and light-based disinfection with respect to removing ARB and ARGs. The Review focused on the bacterial inactivation mechanisms of chlorination, ozonation, UV (including UVA, UVB, and UVC), sunlight, sunlight-DOM, and PC/PEC. Chlorination and ozonation mainly apply oxidants to destroy the cell wall and cell membrane, damaging the intracellular nucleic acid and other substances. UV and sunlight mainly attack the bacterial DNA that absorbs light in the UV band, forming CPDs and other substances. The mechanism driving PC/PEC inactivation is that a capsular extracellular polymer adsorbs the photocatalyst particles to the bacterial surface, generating ROSs on the surface under the stimulation of light. This leads to the attack of the cell membrane and the leakage of cytoplasmic components.

In addition, this Review highlighted the impact of disinfection technologies on the transfer of ARGs and clarified the important mechanisms. Sub-lethal doses of chlorination, UV, sunlight, and PC may facilitate the production of intracellular ROSs and increase the expression of genes related to DNA repair (SOS response). This may promote the conjugation of ARGs. The SOS response is the key to conjugation and may regulate the expression of conjugation-related genes and the synthesis of T4SS and pilus. Bacterial cell membrane permeability is key to ARG transformation and transduction. Disinfection technologies cause damage by attacking cell membrane components, increasing permeability, and increasing the chance that eARGs will transform and enable phage infection. However, even with this explanation of these important mechanisms, there are many scientific challenges and practical difficulties in applying these disinfection technologies to remove ARB and ARGs and to control the horizontal transfer of ARGs. These challenges are as follows.

First, due to advantages in economic efficiency and simple operation, traditional water disinfection technologies (chlorination and ozonation) have been widely used for a long time. These disinfection technologies focus on completely inactivating microorganisms in the target sewage, but do not consider whether ARGs are also completely inactivated. This creates ideal conditions for the spread and development of antibiotic resistance. Therefore, we should consider increasing disinfectant doses to simultaneously inactivate ARGs in the target wastewater. However, the substances that these disinfection technologies work on may produce DBPs, which are a major threat to human health. Therefore, identifying the minimum dosage of disinfectant that can inactivate ARB and ARGs in target wastewater should be explored to prevent increased DBP production.

Second, UV and sunlight are widely used as water disinfection technologies in WWTPs because they do not produce more harmful DBPs, compared with chlorination or ozonation. However, the inability to recover bacteria after disinfection has been widely criticized (whether it is UVA, UVB, UVC, or sunlight). Therefore, controlling disinfection processes so that bacteria are completely inactivated or no longer recovered should be a future research focus with respect to sewage disinfection technologies. Photo-Fenton, PC/PEC, and other light-based disinfection technologies have performed well in effectively mineralizing ARB and ARGs. However, these approaches may be expensive, due to the fixation or recycling of photocatalysts and auxiliary agents. Therefore, optimizing these emerging disinfection technologies and reducing the economic investment is key for applying them in WWTPs.

Third, although the initial goal of disinfection technology in WWTPs is to eliminate microorganisms in the target sewage, more recently, attention has also been paid to removing ARGs. However, few researchers are focusing on the possible influence of the horizontal transfer of ARGs in the disinfection processes. The evidence in this Review demonstrates that ineffective disinfection doses or technologies will not completely inactivate ARGs. Instead, they may accelerate their transfer and spread in water environment. Therefore, an in-depth understanding of different disinfection technologies affecting the transfer of ARGs in wastewater, and clarifying the underlying mechanism, is key to controlling the spread of antibiotic resistance. This should be a focus for sewage treatment researchers.

Finally, traditional water disinfection technologies have been used in the sewage treatment industry for a long time, and the technologies are mature. This Review has shown that the coupling of traditional disinfection technologies, especially the coupling of light-based disinfection technologies, demonstrate excellent performance in effectively removing ARGs and

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controlling their horizontal transfer. Therefore, coupling traditional disinfection technologies, and exploring more coupling forms, are promising directions for controlling the removal and spread of ARGs in sewage. This should be another key focus area in disinfection technology research.

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Notes

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