





Perspective

Killing Two Crises with One Spark: Cold Plasma for Antimicrobial Resistance Mitigation and Wastewater Reuse

José Gonçalves ^{1,*}, João Pequeno ¹, Israel Diaz ², Davor Kržišnik ³, Jure Žigon ³ and Tom Koritnik ⁴

¹ MARE—Marine and Environmental Sciences Centre, ARNET—Aquatic Research Network Associate Laboratory, NOVA School of Science and Technology, NOVA University Lisbon, 2829-516 Caparica, Portugal; j.pequeno@fct.unl.pt

² Institute of Sustainable Processes, University of Valladolid, 47002 Valladolid, Spain; israel.diaz@uva.es

³ Department of Wood Sciences and Technology, Biotechnical Faculty, University of Ljubljana, 1000 Ljubljana, Slovenia; davor.krzisnik@bf.uni-lj.si (D.K.); jure.zigon@bf.uni-lj.si (J.Ž.)

⁴ Department for Public Health Microbiology, National Laboratory of Health, Environment and Food, 1000 Ljubljana, Slovenia; tom.koritnik@nlzoh.si

* Correspondence: jose.goncalves@fct.unl.pt

Abstract: Global water scarcity and antimicrobial resistance (AMR) represent two escalating crises that urgently demand integrated and effective solutions. While wastewater reuse is increasingly promoted as a strategy to alleviate water scarcity, conventional treatment processes often fail to eliminate persistent contaminants and antibiotic-resistant microorganisms. Cold plasma (CP), a non-thermal advanced oxidation process, has demonstrated the strong potential to simultaneously inactivate pathogens and degrade micropollutants. CP generates a diverse mix of reactive oxygen and nitrogen species (ROS and RNS), as well as UV photons and charged particles, capable of breaking down complex contaminants and inducing irreversible damage to microbial cells. Laboratory studies have reported bacterial log reductions ranging from 1 to >8–9 log₁₀, with Gram-negative species such as *E. coli* and *Pseudomonas aeruginosa* showing higher susceptibility than Gram-positive bacteria. The inactivation of endospores and mixed-species biofilms has also been achieved under optimized CP conditions. Viral inactivation studies, including MS2 bacteriophage and norovirus surrogates, have demonstrated reductions >99.99%, with exposure times as short as 0.12 s. CP has further shown the capacity to degrade antibiotic residues such as ciprofloxacin and sulfamethoxazole by >90% and to reduce ARGs (e.g., bla, sul, and tet) in hospital wastewater. This perspective critically examines the mechanisms and current applications of CP in wastewater treatment, identifies the operational and scalability challenges, and outlines a research agenda for integrating CP into future water reuse frameworks targeting AMR mitigation and sustainable water management.

Keywords: cold plasma; wastewater; wastewater treatment; antimicrobial resistance; water reclamation; water reuse; bacterial inactivation; viral inactivation



Academic Editor: Andreas Angelakis

Received: 7 March 2025

Revised: 11 April 2025

Accepted: 13 April 2025

Published: 18 April 2025

Citation: Gonçalves, J.; Pequeno, J.; Diaz, I.; Kržišnik, D.; Žigon, J.; Koritnik, T. Killing Two Crises with One Spark: Cold Plasma for Antimicrobial Resistance Mitigation and Wastewater Reuse. *Water* **2025**, *17*, 1218. <https://doi.org/10.3390/w17081218>

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1. Introduction: Global Water Challenges and the Need for Innovation

Water scarcity is a growing concern worldwide, occurring when water demand exceeds supply due to factors such as climate change, population growth, and pollution [1]. This scarcity triggers severe impacts, including diminished agricultural productivity [2,3], the higher incidence of waterborne diseases [4–6], potential conflicts over limited resources [7,8], and substantial economic losses [9]. Southern Europe is notably vulnerable, with recent severe droughts [10,11]. An 11% reduction in water resources is projected by 2060 for the Mediterranean region of Europe (Portugal, Spain, France, Italy, Greece,

Malta, and Cyprus) [12,13]. The water report of the United Nations from 2018 predicts that, by the year 2050, water scarcity will create problems for nearly 6 billion people (approximately 78% of the global population) [14]. These trends underscore an urgent need for advanced water treatment, recycling, and reuse strategies. More broadly, they call for a holistic rethinking of the water supply that includes unconventional sources and resilient infrastructure systems [15].

Wastewater treatment is key to bridge the supply–demand gap for water reuse [16]. The level of untreated wastewater discharged to water bodies is highly variable. In low-income countries, only 8% of wastewater undergoes any form of treatment, and less than 25% is safely treated, highlighting significant disparities in global wastewater management [17–20]. Modern wastewater treatment plants (WWTPs) employ multi-stage processes, as illustrated in Figure 1, to progressively remove contaminants [21]. This figure provides an overview of the common steps in WWTPs, from preliminary screening and sedimentation to advanced quaternary treatments, highlighting the progression and integration of techniques that are essential for effective water treatment. The preliminary stage involves the removal of large debris and coarse materials through screening and grit removal. The primary stage focuses on sedimentation, allowing suspended solids to settle and form sludge, which can be further processed. In the secondary stage, biological processes break down organic matter using microbial activity, significantly reducing the biochemical oxygen demand (BOD) and suspended solids [22,23]. Tertiary treatment targets the removal of remaining inorganic compounds, nutrients, and pathogens through advanced filtration, chemical treatment, and disinfection methods [24]. Finally, quaternary treatment, the most advanced stage, employs complex technologies like reverse osmosis, advanced oxidation/reduction processes (AOPs, ARPs, and AORPs), and adsorption, targeting trace pollutants and ensuring high water quality for reuse or environmental discharge [25–27].

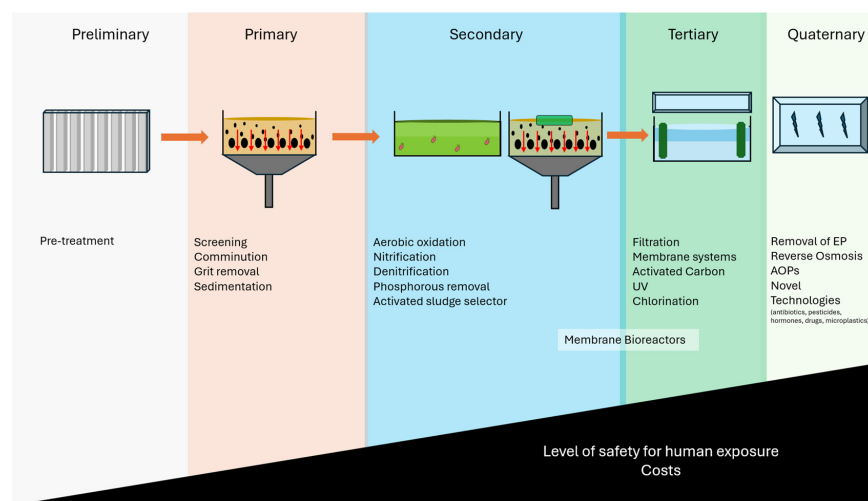


Figure 1. Main steps currently used in WWTPs for wastewater treatment. The figure includes the primary methods employed at each stage, illustrating the corresponding levels of water safety and the progressively increasing costs associated with each step.

In recent decades, WWTP technologies have improved the efficiency and broadened the removal of contaminants [28]. Novel threats were recognized by the EU in the Pathway to a Healthy Planet for All EU Action Plan: ‘Towards Zero Pollution for Air, Water and Soil’ [29], where the European Union recognized the importance of combating antimicrobial resistance (AMR). In the Proposal for a Directive of the European Parliament and of the Council concerning urban wastewater treatment (recast), the monitoring of AMR and micropollutants was suggested. In addition, a quaternary treatment became compulsory

for WWTPs exceeding 150,000 p.e. (10,000 when water is discharged to sensitive water bodies) so to remove at least 80% of the micropollutant concentration.

Conventional biological treatments alone are often insufficient for the removal of many pharmaceuticals and other contaminants of emerging concern (CECs), which require more advanced or high-energy oxidation processes for effective degradation [30]. Studies show that conventional activated sludge and membrane bioreactors effectively remove hydrophobic contaminants, but many hydrophilic compounds persist with <20% removal [31]. Specialized methods, like adsorption on activated carbon [32], and various AOPs (ozonation, UV/H₂O₂, UV/chlorine, photocatalysis, Fenton processes, persulfate activation, etc.) have been developed to tackle these pollutants [33]. The efficacy of each method depends on specific target compounds, often requiring hybrid or sequential processes for broad-spectrum removal [31].

Among the newest AOP innovations, cold plasma (CP) has emerged as a promising solution for simultaneous disinfection and pollutant degradation. CP-based processes generate a cocktail of highly reactive species capable of destroying microorganisms and oxidizing organic contaminants. This dual action suggests that CP could address the following two crises at once: mitigating AMR by inactivating resistant bacteria and degrading pollutants, thus giving hope for water reuse. In this perspective article, we evaluate cold plasma technology for wastewater treatment, examining its fundamental mechanisms with a focus on its efficacy against bacteria and viruses. We discuss the operational and scalability challenges to assess whether CP can “kill two crises with one spark”. This perspective aims to contribute a forward-looking vision for the field by identifying critical knowledge gaps and technological challenges that must be addressed to enable the real-world application of cold plasma in wastewater treatment. The novelty of this work lies in its integrative approach, emphasizing CP’s dual role in antimicrobial resistance mitigation and safe water reuse, while outlining a targeted research agenda. By connecting plasma science with environmental microbiology and public health, we aim to guide future interdisciplinary efforts towards sustainable and effective water treatment solutions.

2. Fundamentals of Cold Plasma Technology

The term “plasma” was first introduced by Irving Langmuir in 1928 [34]. Plasma is often termed the fourth state of matter, distinct from solids, liquids, and gases [35]. It can either occur in a ground state or in its excited state, and it is a fully or partially ionized gas that contains neutrals, ions, free radicals, and electrons that can be generated by several electrical discharges [36,37]. Depending on the temperature, plasmas are categorized as thermal plasmas or non-thermal plasmas (alternatively CP). CP operates at or near ambient temperature, making it suitable for treating heat-sensitive materials, including living tissues and organic compounds. CP’s unique composition of reactive oxygen species (ROS) and reactive nitrogen species (RNS), along with UV photons and charged particles, underpins its potent antimicrobial and oxidative capabilities [38,39]. It has been studied for applications ranging from food preservation and surface decontamination to medical sterilization owing to its efficacy against bacteria, fungi, spores, and viruses [39,40].

There are several methods to generate cold plasma, each yielding plasmas with different characteristics. The most common discharge configurations are illustrated in Figure 2, including dielectric barrier discharges, plasma jets, glow discharges, and corona-based plasmas. Dielectric barrier discharge (DBD) devices apply a high voltage across two electrodes separated by a dielectric barrier, preventing a continuous arc and enabling a stable diffuse plasma. DBDs efficiently produce ROS/RNS and are relatively easy to scale for treating liquids or surfaces at atmospheric pressure. This makes DBDs highly suitable for water treatment, as they can be engineered to treat flowing water films or droplets with

modest energy input, effectively degrading organic pollutants and inactivating microorganisms [40–43]. Atmospheric pressure plasma jets (APPJs) generate plasma plumes in open air or chambers using noble gases (e.g., He and Ar). They direct reactive species onto targets and have been used for localized disinfection and pollutant degradation on surfaces or in small water volumes. Glow discharge plasmas are traditionally formed in low-pressure gas by DC or RF voltage, producing a stable, uniform plasma. Recent adaptations allow for glow discharges at atmospheric pressure for water treatment, combining the uniformity of low-pressure plasmas with the practicality of ambient operation [41–43]. Corona discharges occur when a strong electric field around a sharp electrode ionizes the surrounding gas, creating plasma regions without a full arc. Corona systems efficiently generate ozone and other radicals, and have been used for air treatment and water pollutant oxidation. A related variant is the pulsed corona discharge, which uses high-voltage pulses to enhance the plasma chemical output and energy efficiency. Pulsed corona plasmas have shown the effective breakdown of organic pollutants and microbial inactivation in water [40,44].

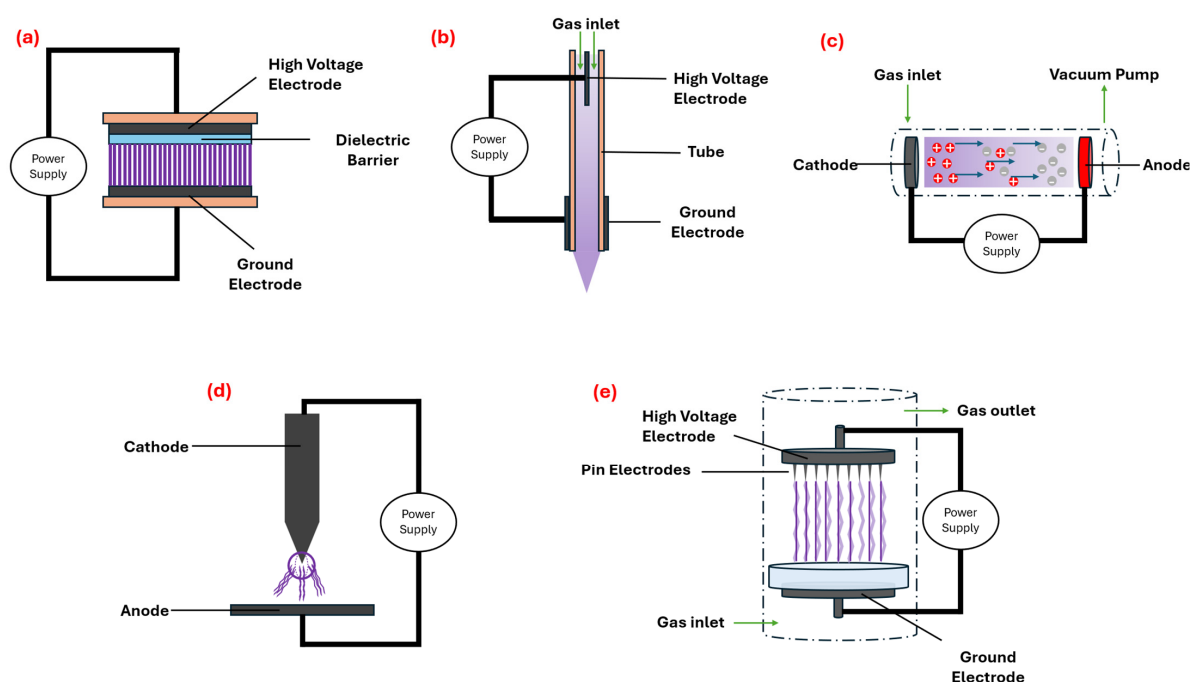


Figure 2. Schematic representation of the most common methods for generating cold plasma (CP): (a) dielectric barrier discharge (DBD), (b) atmospheric plasma jet (APPJ), (c) glow discharge, (d) corona discharge, and (e) pulsed corona discharge.

Each plasma type has pros and cons, but DBD plasmas have gained prominence for water applications due to their operational simplicity, ability to function at atmospheric pressure, and scalability [40,45]. For example, planar DBD reactors can be placed in contact with flowing water films or used to generate plasma-activated water (PAW) rich in ROS/RNS. DBD designs have demonstrated high microbial inactivation rates and pollutant degradation with a relatively low energy per volume treated [40,46–48]. Key reactive species produced by CP in contact with water include hydroxyl radicals ($\bullet\text{OH}$), superoxide ($\text{O}_2-\bullet$), ozone (O_3), hydrogen peroxide (H_2O_2), nitric oxide ($\text{NO}\bullet$), and nitrogen dioxide ($\text{NO}_2\bullet$) [40,46–48]. In addition to water treatment, cold plasma has recently shown potential in activating catalytic materials for enhanced chemical conversions, such as methane oxidation and selective conversion to low-carbon alcohols [49,50]

These species initiate a cascade of oxidation, reduction, and UV emission processes that can attack a broad range of chemical bonds and microbial structures. However, harnessing this potential in real wastewater systems requires understanding how plasma

generation parameters and water parameters influence the reactive species profile generated by cold plasma. The presence of natural scavengers (e.g., bicarbonates, chloride, and nitrate) or high organic matter can rapidly quench key oxidants, such as hydroxyl radicals, thereby reducing the treatment efficiency and increasing the energy demand for pollutant degradation. Factors such as the working gas composition (air, oxygen, argon, etc.), discharge power and frequency, electrode configuration, treatment time, and the conductivity and organic content of the water all affect the treatment outcomes [48]. Environmental factors such as the hydrostatic pressure or redox interactions can modulate microbial activity and contaminant transformation, highlighting the need to consider local water matrix characteristics when designing CP treatments [51]. For instance, adding oxygen or certain gas mixtures can increase the ROS yield and UV emissions, thereby enhancing spore inactivation [52]. Humidity and liquid conductivity can influence the discharge mode and efficiency [53]. Studies also show that hydrostatic pressure can shape microbial degradation dynamics in aquatic systems, a factor that may be relevant when designing CP-based treatments for complex matrices [54].

A growing number of studies have demonstrated the potential of cold plasma technologies to remove diverse contaminants from different wastewater matrices. Table 1 summarizes key examples from the literature, including applications targeting pathogens, pharmaceuticals, resistance genes, phenol, dyes, and heavy metals. For each case, we report the type of wastewater, plasma configuration, treatment conditions, and observed removal efficiencies, along with comparisons to conventional or advanced technologies. Despite promising results, systematic data on energy consumption and long-term performance remain scarce, underscoring the need for further quantitative evaluation and techno-economic assessments.

Table 1. Summary of cold plasma (CP) applications in wastewater treatment reported in the literature, including the types of contaminants targeted, treatment conditions, removal efficiency, and comparisons with other technologies.

Target Contaminant(s)	Wastewater Type	CP Type and Conditions	Removal Efficiency	Comparison to Other Technologies	References
<i>E. coli</i> (Gram– bacterium)	Synthetic/municipal	Air plasma jet; ~15 min	>7 log ₁₀ reduction	Comparable to UV; no DBPs; fast	[45]
<i>S. aureus</i> (Gram+ bacterium)	Synthetic/municipal	~3–4 log ₁₀ ; higher resistance than Gram–	~3–4 log ₁₀ reduction	Less efficient than on Gram–; combo recommended	[6,8]
<i>Bacillus spores</i>	Synthetic/lab	Radio-frequency plasma jet; 5–10 min; with O ₂ /N ₂	~4 log ₁₀ spores; enhanced by UV/ROS	UV/Cl ₂ less effective; CP good without heat	[9,50]
Viruses (e.g., MS2, PMMoV)	Synthetic/real effluent	Atmospheric plasma jet or submerged DBD; 0.12 s–5 min	>95–99.99% virus inactivation	CP inactivates viruses faster; works on surfaces	[55,56]
Antibiotics (e.g., ciprofloxacin)	Hospital wastewater	DBD; 30 kV; 15 min	100% ciprofloxacin; >72% other antibiotics	Better than biological; no added chemicals	[26]
ARGs (tetA, tetR, aphA)	Synthetic saline water	Glow discharge; 15–30 min	~5.8 log gene reduction	Unlike UV/Cl ₂ , CP degrades DNA	[34]
Phenol	Phenol-spiked water	DBD; 100 W; +Fe ²⁺ (Fenton); 10–12 min	86.8% with Fe ²⁺ ; 33% COD	Plasma–Fenton better than standalone	[57]
Mixed wastewater (slaughterhouse)	Slaughterhouse wastewater	Glow discharge; continuous flow; 5 L/min	COD 78–93%; TN 51–92%; TP 35–83%	Outperformed biological + chemical combo	[36]
Mixed dyes (textile)	Synthetic textile wastewater	Underwater plasma; pulsed high voltage	100% mixed dye; enhanced on mixtures	Synergistic degradation in dye mixtures	[52]
Heavy metals (Fe, Cu, Zn)	Industrial wastewater	AC diaphragm underwater plasma	>90% removal of Fe, Cu, Zn	No chemicals needed; better than factory system	[58]

3. Bacterial Inactivation Using Cold Plasma Based Technologies

Studies have demonstrated that CP can effectively inactivate bacteria in water [41,54,59–61]. Most of these studies have been at the laboratory scale, examining different plasma setups and bacterial targets under controlled conditions [62–64]. Collectively, they reveal key insights into how bacteria respond to plasma-induced stress and which factors influence the inactivation efficacy.

CP's reactive species primarily inflict oxidative damage on cells. ROS such as hydroxyl radicals and ozone degrade cell envelope components (lipids and peptidoglycan), causing the loss of membrane integrity, while RNS and ROS together can cause protein denaturation and DNA breaks, leading to cell death. CP also generates UV radiation (especially with certain gas mixtures) and acidifies liquids by forming nitric and nitrous acids; these effects further contribute to microbial inactivation [46,55,65]. For example, *Listeria monocytogenes* mutants lacking the stress-response regulator SigB were significantly more sensitive to CP, confirming that oxidative stress responses are pivotal for bacterial survival under plasma treatment. These mutants showed the initial induction of stress and biofilm-related genes after mild plasma exposure, but longer treatment (3 min) overwhelmed their defenses, ultimately inactivating the bacteria. This demonstrates that, while bacteria can mount short-term defenses, sufficiently intense or prolonged CP treatment can lead to irreversible damage [66].

Reported bacterial reductions by CP range from $\sim 1 \log_{10}$ to $>8\text{--}9 \log_{10}$, depending on the strain and treatment parameters [56,67–71]. Notably, Gram-negative bacteria (e.g., *E. coli* and *Pseudomonas aeruginosa*) are generally more susceptible to CP than Gram-positive bacteria (e.g., *Staphylococcus* and *Enterococcus*). Due to the thinner peptidoglycan layer and less cross-linked cell wall of Gram-negative bacteria, they may be more easily penetrated by ROS, whereas the thick peptidoglycan of Gram-positive bacteria provides some protection [67,70]. Plasma-induced damage in Gram-positive bacteria tends to involve a direct effect on the peptidoglycan and membrane lipid peroxidation, leading to the leakage of cellular contents and DNA damage. The cell wall thickness correlates inversely with the inactivation rate in some cases. One study found that species with thinner walls had higher log reductions for a given treatment time. However, the cell envelope architecture is not the sole determinant—*E. cloacae* (Gram-negative bacteria with a relatively thick cell wall) was more susceptible to CP than *P. aeruginosa*, indicating that other factors, like the outer membrane composition and detoxifying enzymes, also play important roles [70].

Bacterial communities often exist as biofilms or clumped cells on surfaces, which are more resilient to disinfection than free-floating (planktonic) ones. Many studies focus on planktonic cultures [67,72,73], but these may underestimate the challenge of biofilm-associated bacteria. Biofilms delay the diffusion of reactive species and can harbor more persistent cells. Mixed-species biofilms exhibit higher tolerance to AOP treatments; for example, a co-culture biofilm of *P. aeruginosa* and *S. Typhimurium* showed only a $\sim 2.6 \log_{10}$ reduction in *P. aeruginosa* with CP versus a $\sim 3.6 \log_{10}$ with *P. aeruginosa* alone [70]. This suggests inter-species protective effects and the need for higher plasma doses or combined strategies to achieve thorough biofilm disinfection. Nevertheless, CP has shown the ability to disrupt biofilm matrices and kill embedded cells in other settings (e.g., on medical device surfaces and food processing equipment) [74–77].

Another challenge when dealing with bacterial inactivation is that certain bacteria (e.g., *Bacillus* and *Clostridium* spp.) can form endospores [78], which are extremely resistant dormant forms. Spores are notorious for surviving traditional disinfection; thus, their inactivation is a stringent test for any novel technique. CP has demonstrated significant sporicidal effects under the right conditions. Spores' resistance stems from their robust coats and metabolic dormancy, but plasma's multi-pronged attack (ROS, RNS, UV, and

charged particles) can overcome these defenses [79,80]. Short-lived radicals (like $\bullet\text{OH}$) are thought to be the most effective in spore killing, causing critical damage to spore coats, while longer-lived species play a secondary role [81,82]. The gas composition is crucial. Adding small percentages of O_2 and N_2 to an argon plasma dramatically increased the spore kill due to a surge in the UV-C photon emission from the plasma [52]. For example, an Ar plasma with $\sim 0.1\%$ O_2 and 0.2% N_2 yielded the highest UV output and spore inactivation in one study [52]. Other work showed that adding helium to O_2 plasma improved the CP killing of *Candida* fungal spores [83]. Besides the gas mixture, parameters such as the input voltage, exposure time, and humidity also affect the sporicidal efficacy [57,84]. Spores often require substantially longer treatments than vegetative cells for equivalent log reductions, but the characteristics of the spore itself (the coat thickness, DNA-protective proteins, etc.) influence the efficiency [58,85,86]. Studies indicate that the initial spore concentration, organic load in the water, and even the temperature can modulate the CP effectiveness [85].

4. Viral Inactivation Using Cold Plasma-Based Technologies

Viruses are abundant in wastewater and environmental waters and many pose serious public health risks (e.g., enteric viruses like norovirus and rotavirus) [87–90]. Outbreaks of emerging viruses (SARS-CoV-2, influenza, flaviviruses, etc.) have highlighted the need for robust disinfection methods [89,91]. Cold plasma has garnered attention as a tool for viral inactivation in contexts ranging from surface disinfection (e.g., food packaging) to air sterilization and water treatment [68,92–95].

Early CP virus studies often used bacteriophages as surrogates for human viruses to gauge the efficacy, and these studies showed rapid and substantial viral inactivation. For instance, using an atmospheric CP jet, researchers achieved the almost complete inactivation of MS2 bacteriophages in aerosols with exposure times as short as 0.12 s [52,83]. Similarly, the CP treatment of liquids spiked with bacteriophages yielded near-total inactivation within a few minutes [57,84]. The CP mechanism against viruses can differ by virus type. Enveloped viruses (like influenza or coronaviruses) are often more easily inactivated than non-enveloped viruses because ROS/RNS can disrupt the envelope and surface proteins. However, non-enveloped viruses (like norovirus or poliovirus) can be quite resilient. CP has been tested on a variety of surrogates and actual pathogens. *Enteric viruses* (e.g., norovirus, adenovirus) showed significant titer reductions after CP treatment on surfaces (stainless steel, glass, and foods) and in liquids [58,85,96]. Notably, surrogate viruses (e.g., bacteriophages) are sometimes inactivated more readily than the actual enteric viruses, indicating that the results must be interpreted with caution [85]. For respiratory viruses, CP has proven effective as well. One study found that a nitrogen-based plasma efficiently inactivated respiratory syncytial virus (RSV), likely by the oxidative modification of viral surface proteins [97]. Plasma-based air sanitizers have achieved up to 98.6% inactivation of aerosolized porcine reproductive and respiratory virus (PRRSv) in farm settings [98], suggesting a role for HVAC-integrated plasma in controlling airborne pathogens. An often-overlooked aspect of water reuse is the transmission of plant pathogens. Irrigation with reclaimed wastewater can introduce plant viruses to crops, risking agricultural losses. Tobacco mosaic virus (TMV), a notoriously resistant plant virus, was significantly inactivated by CP; plasma exposure damaged TMV's coat proteins and RNA, thereby reducing the infectivity [95]. Other plant viruses in irrigation water have also been effectively inactivated by cold plasma [99].

While the full mechanisms are still under investigation, it is generally thought that ROS/RNS degrade viruses by oxidizing capsid or envelope proteins and damaging nucleic acids. For example, ozone and other radicals generated by CP can degrade viral capsids, as observed in studies of poliovirus surrogates [100]. Interestingly, different viruses may be

neutralized by different primary agents. Plasma-generated hydrogen peroxide was found to be a key agent in influenza A and RSV inactivation, whereas singlet oxygen played a larger role for certain plant viruses [93,99].

5. Challenges for Cold Plasma Implementation

A holistic benefit of CP is its ability to target antimicrobial resistance (AMR) genes, antibiotic residues, and other contaminants concurrently with pathogens. Wastewater often contains antibiotics and other pharmaceuticals that drive AMR in the environment, and conventional treatment may not fully eliminate these. CP, however, can degrade many organic micropollutants, such as antibiotic compounds, endocrine disruptors, and dyes [46]. For instance, in a study treating actual hospital wastewater, a cold plasma system successfully removed several antibiotic residues from the solution [47]. The oxidative species in CP can break down complex organic molecules. Antibiotics like ciprofloxacin and sulfamethoxazole have been shown to undergo oxidative degradation under plasma, with the by-products eventually mineralizing or transforming into less potent compounds [36]. This means that CP could simultaneously inactivate bacteria (including drug-resistant strains) and destroy the trace antibiotics that contribute to its resistance. Despite the known advantages, several practical challenges and knowledge gaps need to be addressed. CP technology shows great promise for sustainable water and wastewater treatment, but translating laboratory successes into full-scale operation requires a careful evaluation of the scalability, operational challenges, energy use, and by-product management.

Most CP studies to date are limited to bench-scale setups treating small volumes (milliliters to liters) under controlled conditions [53,62,101]. Scaling up the technology for large water volumes per day in a municipal plant is non-trivial. One fundamental issue is the plasma–liquid contact area. To efficiently treat large volumes, reactors must maximize the interface where plasma species dissolve into water. Scaling up is not simply a matter of increasing the volume; it often requires incorporating multiple discharge units or enlarging the plasma zone to treat thin films or sprays of water. For example, a prototype thin-film plasma reactor was developed as a tertiary treatment for industrial wastewater, demonstrating that expanding the plasma–liquid interface can enhance the treatment efficacy at larger scales [102]. However, maintaining uniform treatment in large reactors is challenging—ensuring every portion of the water receives sufficient plasma exposure may require flow management or staged treatment. Additionally, the complexity of real wastewater (solids, foams, and variable chemistry) may affect the plasma stability; designing reactors that handle these without fouling or electrical faults is an engineering hurdle.

Operating CP systems continuously in a WWTP environment also poses several challenges. Electrodes and dielectric materials in reactors can degrade over time due to erosion, scaling from water hardness, or the deposition of organic matter. Choosing robust materials (e.g., high-grade ceramics for DBD dielectrics and corrosion-resistant electrode coatings) and developing self-cleaning designs will be important for long-term reliability. Moreover, plasma generation in liquid environments can be sensitive to the water conductivity and composition [62]. High conductivity (from salts in wastewater) can dampen plasma formation or cause unwanted arcing, so often the plasma is generated in a gas phase rather than directly within the bulk liquid [48]. This indirect approach works but it introduces additional parameters that must be optimized for each water matrix. Another operational factor is controlling the discharge power to balance efficacy with avoiding excessive heating or arc formation. *Pulsed power* plasma systems are being explored to fine-tune the energy input and maximize the reactive species yield while minimizing unwanted heating [44]. For instance, nanosecond-pulsed discharges can produce high peak electric fields for reactivity but with a low average power, thereby improving the

efficiency. Lastly, the energy efficiency of the CP treatment is a critical determinant of the practicality. While CP is often described as relatively low energy compared to some AOPs, it still requires electricity to generate high voltages. The question is: how much energy per volume of water is needed to achieve disinfection and pollutant removal targets? Reported energy consumptions are on the order of a few kWh per cubic meter of water for significant contaminant removal, but the values vary widely with the reactor design [36]. One review noted that plasma-based advanced oxidation can consume less energy than ozonation for certain pollutants but might be higher than UV disinfection for equivalent log reductions [46]. In general, traditional chlorination and UV treatments have lower operational costs and energy use than current CP systems. However, CP technology is still maturing; optimizing the power delivery and reactor geometry could substantially improve the energy efficiency. Integration with renewable energy sources (e.g., solar or wind) at treatment facilities could also mitigate the operational costs and reduce the carbon footprint of plasma systems. Another consideration is that CP, by potentially replacing multiple steps (e.g., chemical disinfection and separate AOPs for micropollutants), might justify a higher energy input if it simplifies the overall process train. Economic feasibility studies are needed to compare life cycle costs, including the plasma reactor capital and energy costs versus savings from reduced chemical usage and improved water reuse outcomes.

Encouragingly, small-scale implementations (e.g., on-site plasma units for hospital wastewater) have demonstrated the feasibility of CP technologies [47]. However, detailed assessments of energy costs—such as the electric energy per order (EE/O) for the removal of antibiotics and pathogens—are still lacking in the literature. Future research should address these gaps to guide a scale up and technology comparison with existing advanced treatment methods. These values are essential to benchmark CP against other advanced treatment technologies, like UV/H₂O₂, ozonation, or electrochemical AOPs. Future research should prioritize systematic energy performance assessments under real wastewater conditions to clarify the scalability potential.

All oxidation-based treatments risk generating by-products from the partial breakdown of contaminants or from reactions with water constituents. A benefit of cold plasma is that it does not introduce external chemicals, so it avoids the disinfection by-products (e.g., trihalomethanes) common in chlorine treatment [103]. However, a study has noted that the plasma treatment of phenolic compounds can result in short-chain carboxylic acids before full mineralization [104]. Ensuring that CP either mineralizes pollutants fully to CO₂, water, and inorganic salts, or pairing CP with a downstream biofilter to polish residual organics will be important for safe reuse. Hybrid systems that combine oxidative and biological treatments are essential [105].

6. Conclusions

Cold plasma technology stands out as a promising and versatile tool to address the following two interconnected global challenges: antimicrobial resistance and water scarcity. Its ability to generate reactive species at ambient conditions enables the simultaneous inactivation of a wide range of microorganisms—including drug-resistant bacteria, spores, and viruses—and the degradation of persistent organic micropollutants, such as antibiotics and resistance genes. These characteristics make it a strong candidate for integration into advanced wastewater treatment and reuse strategies. Nonetheless, key challenges must be overcome before widespread implementation is possible. These include improving the energy efficiency, scaling up reactor designs while maintaining treatment uniformity, and ensuring that the formation and fate of by-products are fully understood and controlled. Most studies to date remain at the laboratory scale, and further work is needed to validate the performance under real wastewater conditions.

To guide future efforts, this perspective outlines the need for (i) optimized reactor designs tailored to diverse water matrices, (ii) integration with complementary treatment processes or renewable energy sources, and (iii) comprehensive assessments of the cost, sustainability, and safety. By bridging microbiology, plasma science, and environmental engineering, this emerging approach has the potential to evolve from experimental systems into a transformative solution for safer water reuse and resistance mitigation, which are key priorities in building resilient and sustainable water systems.

Author Contributions: J.G.: Conceptualization, Writing—original draft, Writing—review and editing, and Funding acquisition. J.P.: Writing—original draft and Writing—review and editing. I.D.: Writing—original draft and Writing—review and editing. D.K.: Writing—review and editing. J.Ž.: Writing—review and editing. T.K.: Writing—original draft and Writing—review and editing. All authors have read and agreed to the published version of the manuscript.

Funding: This work received support by the Marie Skłodowska-Curie Actions Postdoctoral Fellowship (project PLASMARISE—101151154). This work was also funded by national funds through FCT—Fundação para a Ciência e a Tecnologia, I.P., within the framework of the UID/04292/MARE—Centro de Ciências do Mar e do Ambiente and the project LA/P/0069/2020 (<https://doi.org/10.54499/LA/P/0069/2020>) granted to the Associate Laboratory ARNET—Aquatic Research Network.

Data Availability Statement: Data is contained within the article.

Conflicts of Interest: The authors declare no conflicts of interest.

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