Viewpoint

HOCl vs OCl−: clarification on chlorine-based disinfectants used within clinical settings

Felicity V Mehendale[1], Gillian Clayton[2], Kate M Homyer[3], Darren M Reynolds[4]

[1] Deanery of Molecular, Genetic and Population Health Sciences, University of Edinburgh, [2] HAS - Applied Sciences, University of the West of England, [3] NHS Lothian, [4] HAS Applied Sciences, University of the West of England

Keywords: disinfection, covid-19, chlorine, public health

https://doi.org/10.29392/001c.84488

Journal of Global Health Reports

Vol. 7, 2023

Disinfection is a mainstay of infection prevention, the importance of which was highlighted throughout the SARS-CoV-2 pandemic. There is frequent misuse of terminology surrounding chlorine solutions in the literature. This leads not only to confusion but has potentially dangerous outcomes, as inappropriate mixing of chlorine solutions with other disinfectants or cleaning solutions can lead to the release of chlorine gas. This article provides a resource for accurate terminology surrounding chlorine-based disinfection and clarifies some of the key inaccuracies, including the pH-dependent nature of chlorine species distribution of hypochlorous acid (HOCl) (neutral/acidic chlorine solution) and hypochlorite (OCl-) (alkaline chlorine solution). Misuse and misunderstanding of chlorine solutions and the terminology used can be harmful therefore this is an essential resource for those utilising chlorine as a disinfectant.

Household disinfection carries significant but often overlooked risks. Between January and March 2020, at the beginning of the SARS-CoV-2 pandemic, 45,550 calls were made to poison centres in the United States, representing a 15.5% rise on the mean of the previous two years throughout the same period.[1] Lack of clarity around the safe use of cleaning or disinfection solutions to deal with airborne viruses was highlighted by this, whereby 39% of US adults used high risk practices such as using bleach to wash food, or inhaling, ingesting or topically applying household cleaners/disinfectants.[2] Additionally, chlorine-based disinfection tunnels were set up in several countries despite limited evidence for the efficiency or efficacy of their ability to suppress airborne SARS-CoV-2. Potentially hazardous effects to humans through inhalation or dermal adsorption did not appear to be considered[3] and the chemicals used in these disinfection tunnels were not always clearly reported. Some disinfection tunnels used solutions containing hypochlorous acid (HOCl) whilst others used hypochlorite (OCl-)[4] commonly in the form of sodium hypochlorite [NaOCl], which is frequently referred to as bleach.[5] Furthermore, advertisements that market disinfectant solutions direct to consumers include trade names that do not clearly state chemical composition or active chlorine species (HOCl or OCl-) present in the solution, compounding confusion and potential hazards. This is further highlighted by the lack of clarity surrounding terminology and synonyms relating to chlorine-based disinfectants in the literature and frequent misuse or disuse of terminology.

Given the real risk to humans from using OCl- solutions instead of HOCl as an airborne disinfectant, the aims of this communication are three-fold. Firstly, to highlight the critical importance of pH in determining the ratio of OCl- and HOCl species present in chlorine-based disinfectant solutions. Secondly, to provide clarity on terminology surrounding chlorine-based disinfectants, in particular the difference between hypochlorite [OCl-] and hypochlorous acid [HOCl]. Finally, to summarise commonly used synonyms of chlorine solutions and their relevant uses, in particular the difference between clinical in vivo use and surface decontamination.

CLINICAL APPLICATIONS AND BACKGROUND

Chlorine-based disinfection has been used as part of clinical practice since Semmelweis highlighted the importance of handwashing in 1847.[6] Chlorine solutions continue to be used frequently in healthcare settings whether for surface or instrument disinfection[7] or as part of improving patient outcomes through wound care.[8,9] Hypochlorous acid (HOCl), an acidic chlorine disinfectant, has had notable uses in surface application in surgical centres, in treatment of blepharitis by application to skin and in hand sanitisation.[7] Hypochlorite (OCl-) (alkaline chlorine, or bleach) is used in surface disinfection but is irritant to skin, limiting clinical use.[5] Despite their similar names, there are critical differences between chlorine-based disinfectants and often it is not clearly reported which chlorine species is dominant as solutions are often broadly labelled as “chlorine solutions”. Similar sounding terms related to the predominant chlorine species (e.g. hypochlorous acid [HOCl] and hypochlorite [OCl-]), has led to inaccurate usage of terminology in publications, perpetuating a lack of clarity. The terms “chlorine” and “bleach” are often used as a catch all and are frequently interchanged with hypochlorous acid.[10] As noted in the introduction, this can lead to dangerous applications of chlorine-based disinfection for example use of hypochlorite (bleach) in disinfection tunnels.[4] Healthcare providers globally hold a responsibility to ensure safe and effective disinfection is carried out thereby protecting patients/members of the community, therefore an understanding of the properties of chemical disinfectants is of key importance.

Chlorine solutions, namely NaOCl, are used far and wide globally for water disinfection, disinfection of clinical material and were used throughout the Ebola outbreak in West Africa.[11] The use of sodium hypochlorite to sterilise equipment used in surgery has been documented in low- and middle-income countries [LMICs].[12] However, this is not a recommended sterilisation process by the World Health Organization,[13] yet the continued use of NaOCl to sterilise equipment in LMICs could be due to lack of access to reliable electricity which is required for WHO suggested sterilisation processes, such as autoclaves.[13] Utilising NaOCl solutions to 'sterilise' equipment that has not already had organic matter removed (e.g. blood and body fluids) can reduce activity or even inactivate the antimicrobial,[14] or result in the formation of hazardous disinfection by-products, including chloroform.[15]

THE IMPORTANCE OF PH AND SOLUTION GENERATION

The dominant species present in chlorine-based solutions, OCl- or HOCl, are dependent on a solution's pH (Figure 1) which results in differing modes-of-action, antimicrobial efficacy, and toxicity. Solutions where hypochlorite (OCl-) is the dominant chlorine species are commonly associated with sodium and calcium salts (e.g. NaOCl and Ca(OCl)2), and frequently termed as "bleach" products where the pH is >8 (see Figure 1). The antimicrobial effects of OCl- are well understood and it is widely used due to its stability within alkaline solutions, hence it is ubiquitous in domestic bleach and cleaning products. Domestic products contain between 3% and 8% sodium hypochlorite (NaOCl), as well as sodium hydroxide (NaOH) to slow decomposition. In industrial settings solutions can be far more concentrated (e.g. 40% NaOCl). All chlorine solutions are strong oxidizers and can cause corrosion to materials in concentrated forms (> 40% sodium hypochlorite by weight), hence many OCl- solutions have been identified as unsafe for clinical (patient) use as they can result skin burns, cause eye damage and be harmful when inhaled.[5] HOCl (pH 3.0 – 6.5, see Figure 1) is also a strong oxidizer, but it is a weak acid solution as does not dissociate in water and when prepared correctly can be used safely and with clinical efficacy on skin, wounds,[16] the oral cavity, in dentistry and on mucous membranes.[8,9]

The relationship between hypochlorite ions and hypochlorous acid is pH dependent (Figure 1).[17] Therefore, both OCl- and HOCl species can exist in varying degrees within the same disinfectant solution, especially in solutions that have a relatively neutral pH of 6 – 8.5. The

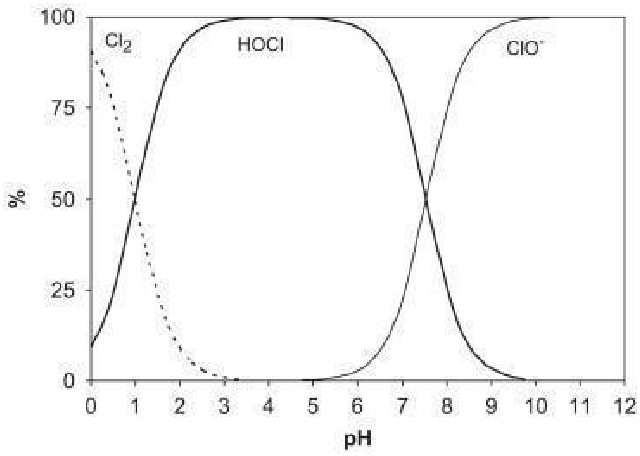

Figure 1. The effect of pH on distribution and type of chlorine species present in solutions at 25°C.

At a weakly acidic pH (3.0-6.5), HOCl is the dominant chlorine species, with minimal OCl- (expressed here as ClO-) and no free Chlorine gas. Cl2 is represented by a dashed line (- -), HOCl is represented by a bold solid line (-) and OCl-/ClO- is represented by a solid line (-) Taken) This figure has been reproduced from Deborde and Gunten (2008)[17] with permission from Elsevier under Licence Number 5384750686333.

method of manufacture (chemical or electrochemical) is also a key determining factor in the stability and composition of hypochlorite and hypochlorous acid solutions. For example, chemically produced solutions as a result of dissolution will result in a solution at a specific pH. However, electrochemical production of OCl- and/or HOCl solutions is dependent on the type of generator (e.g. with or without semipermeable membrane), the ratio of anolyte to catholyte, concentration of salt solution undergoing electrolysis and the current across the cell.[14,16]

At an acidic/slightly acidic pH, most of the aqueous chlorine species present in solution is in the form of HOCl, with minimal OCl- and no free dissolved chlorine (Cl2), (Figure 1). Dissolved chlorine (Cl2) is the dominant chlorine species in acidic solutions (pH < 3), whilst hypochlorite (OCl-, expressed in Figure 1 as ClO-) is dominant in alkaline solutions (pH > 8). Neutral solutions (pH 6.5 – 8) contain a mix of HOCl and OCl-. This highlights the need for a solid understanding of chlorine species and pH when utilising disinfecting solutions.

Hypochlorite (OCl-) is a potent germicide however there are several concerns regarding OCl- solutions including the rapid loss of efficacy due to decomposition,[18] the production of hazardous disinfection by-products[15] and tissue damage due to the alkaline pH.[5] In contrast, HOCl based disinfection solutions are weakly acidic with a pH range of between 3.0– 6.5.[17] HOCl is produced in vivo in small quantities as part of the human immune (antimicrobial) response by neutrophils, demonstrating increased biocompatibility when used in direct patient care.[9]

In an attempt to address limitations of OCl-, Smith[19] noted that HOCl can be ten times more efficacious than OCl- solutions (NaOCl and Ca(ClO)2) and so developed Edinburgh University Solution of lime (EUSOL), see Equation 1:

$$CaCl_2 + H_3BO_3 = BCaCl_2H_3O_5 \qquad (1)$$

EUSOL (BCaCl2H3O5) is produced from combining calcium chloride (CaCl2) and boric acid (H3BO3) which forms a combination of HOCl and OCl-, resulting in a powerful antimicrobial solution for use on wounds.[20] However, EUSOL had to be freshly and accurately made; and guidance on achieving and monitoring the optimum pH was limited. EUSOL is reported to have a pH of 7.5 - 8.5, therefore OCl- is the dominant chlorine species, rather than HOCl.[21]

Newer methods to form HOCl by electrolysis of NaCl (salt) solutions enable the production of a more stable solution at a neutral or slightly acidic pH (pH 3.0 – 6.5). The resultant electrolysed solutions are frequently referred to as electrolysed water [EW], electrolysed oxidising water [EOW] or electrochemically activated solution (ECAS). They contain HOCl and have a high positive oxidative reductive potential, both of which contribute to antimicrobial efficacy. SterilOx® (where HOCl is the dominant chlorine species) is commonly used in healthcare and clinical settings and is produced through the electrolysis of a weak saline solution.[22]

Both OCl- solutions and HOCl are known to kill bacteria and inactivate viruses, including coronaviruses.[23] In the USA the Food and Drug Association [FDA] oversees disinfectant validation whilst in the EU, European chemical disinfectant standards are described under the European Standards [EN] testing regimes. These standards dictate minimum levels of antimicrobial efficacy that must be achieved under standardised laboratory testing conditions depending on the intended use and application of the product. For example, requirements for medical uses differ from domestic or industrial uses and the efficacy of a chemical disinfectant against bacteria is not the same as its effectiveness against viruses, yeast, or fungi. The performance of any chemical disinfectant varies according to its intended application, either to disinfect a solution or surface in simulated organic conditions, or as a hand sanitiser. In addition to this, there is the need to understand the required disinfection concentrations of solutions for applications and the optimal contact time required for the disinfectant to achieve the minimum levels of antimicrobial activity as outlined in the standard tests. Misuse of disinfecting products has potential to result in harm to end users or patients.[1-3,5] When all of this is considered, this is a complex landscape for end-users to grapple with.

Further potential for lack of clarity between HOCl and OCl- is likely a result of how both chlorine species can exist within the same solution, as demonstrated in Figure 1. The ratio of the two is influenced by the method of solution preparation and the pH of the solution, as seen in Figure 1[17] and these parameters are often not specified in literature. Additionally, Figure 1 helps to explain the rationale behind warnings that bleach should not be mixed with other household cleaners, which often contain strong acids such as acetic acid (the active compound in vinegar) and phosphoric acid. When the pH of the resultant mixture is very acidic (pH < 3), free (toxic) chlorine gas is liberated potentially resulting in morbidity.[1] Similarly, mixing HOCl with a detergent, as in the case of some commercially available cleaners, leads to a reduction in antimicrobial efficacy as HOCl is converted into OCl-. All chlorine-based disinfectant solutions are heavily impacted by the presence of organic material, resulting in reduced antimicrobial efficacy[14] and so should be applied to physically clean surfaces.

TERMINOLOGY AND MISUSED SYNONYMS

Terms associated with chlorine-based chemical disinfectants can lead to confusion. Table 1 summarises chlorine-based disinfectants commonly used in healthcare and clinical settings. Bleach (sodium hypochlorite [NaOCl]) is undoubtedly the most well- known and widely used chlorine disinfectant and contains hypochlorite (OCl-) as the dominant chlorine species present in solution.[5] The disinfecting and deodorising abilities of hypochlorite solutions (OCl-) derived from sodium and calcium hypochlorite were discovered in the early 19th century by Antoine Germain Labarraque.[24] This work was instrumental in popularising the use of bleach (Labarraque's solution) and ultimately revolutionised medical practice, public health and sanitary conditions in hospitals, slaughterhouses and wider society. Labarraque solution was noted to be utilised on 'ulcers of the uterus' and advised those in contact with contagious diseases to 'breathe in' and 'moisten(ing) their hands with it.[24,] Hypochlorous acid [HOCl] was also discovered in the early 19th century by Antoine Jérôme Balard, yet it is not as well known, and so less widely used as a disinfectant. Sodium hypochlorite and hypochlorous acid are frequently interchanged and despite the differences are often referred to generally as chlorine solutions. Importantly, the dominant active species of HOCl and NaOCl occur at different pH's and exhibit different modes of action.[25] HOCl and OCl- solutions can be produced through several methods including the dissolution of chemically bound HOCl,[26] or electrochemically through the electrolysis of a weak saline such as NaCl.[14,16] Manufacturers of disinfection solutions often use associated trade names (e.g. Clorox, Sterilox) when detailing the use of integrated disinfectants. This lack of clarity amplifies already existing confusion amongst end-users.

There are many alternative names for OCl- solutions including Dakin's solution, which is a diluted sodium hypochlorite (bleach) solution developed as a topical antiseptic for the treatment of wound infections during the First World War.[27] It is caustic and even in low concentrations (>0.5% [v/v]) has been known to cause "Dakin Dermatitis".[27] Concerningly, hospital provided guidelines exist on how to make Dakin's solution at home using bleach and distilled water[28] and it is also commercially available without a prescription for use on wounds. The pH of Dakin's solution is reported to be between 7.5-8.5 which suggests that OCl- contributes at least 50% of the chlorine species (see Figure 1). Given the difficulty to test and control the pH and concentration of home-made solutions of liquid bleach; and the fact that Dakin's solution must not be used on mucous membranes or ingested,[5] it would seem prudent to exercise caution in advocating widespread use of Dakin's solution. While the hospital does appear to be publicising a helpful guide to save families money, the dangers around

Table 1. Commonly used disinfectants used in clinical and healthcare settings, with relevant chemical safety and toxicity according to PubChem (National Center for Biotechnology Iklkonformation, 2020). GHS = Globally Harmonised System

Chemical formula	Name / Synonyms	Uses	Chemical Safety	GHS Hazard statements
HOCl	Hypochlorous acid. [A]*Electrochemically activated solution (ECAS), Electrolysed oxidising water [EoW], superoxidised water, slightly acidic electrolysed water [SAEW].*	Antimicrobial agent (in vivo or surfaces). ECAS is a more effective disinfectant than hypochlorite and exerts microbicidal effect through chlorine species and the oxidative reductive potential of the solution.[14] Used on surfaces and in vivo on wounds and mucous membranes.[16]	None stated.	None stated.
OCl- ClO-	Hypochlorite anion that combines with cations to form salts.	Active chlorine species in sodium or calcium hypochlorite (see below).	None stated.	None stated.
NaOCl	Sodium hypochlorite, (liquid) bleach.	Antimicrobial agent (surfaces) Combined with a surfactant it is used as a surface cleaning agent, such as household bleach. NaOCl diluted in water (0.5% w/v) forms Dakin's solution, used as a topical wound treatment.	Corrosive and environmental hazard.	Very toxic to aquatic life. Anhydrous form unstable, can explode.
C3Cl2N3NaO3	Sodium dichloroisocyanurate (NaDCC); Sodium troclosene; Troclosene sodium (SDIC); Dichlorocyanuric acid - note this is not the same as the polychloro phenoxyphenol, Triclosan (TCS), ($C_{12}H_7Cl_3O_2$).	Antimicrobial agent. Tablets to make water potable.[26]	Irritant and environmental hazard.	Harmful if swallowed (Warning Acute toxicity, oral). May cause respiratory irritation (Warning Specific target organ toxicity, single exposure; Respiratory tract irritation).
Ca(OCl)2	Calcium hypochlorite. Chlorinated lime.	Antimicrobial and bleaching agent. Active ingredient in commercial bleaching powder. Used in swimming pools and for water treatment. Used by Semmelweis in 1847 to wash hands and prevent puerperal fever.	Oxidiser, corrosive irritant and environmental hazard.	Harmful if swallowed (Warning Acute toxicity, oral).
ClO2	Chlorine dioxide, Chlorine peroxide, chlorine oxide.	Tablets to make water potable. Used throughout paper manufacturing, and as a disinfectant in municipal water treatment and in oil field pollution clean-up sites.	Oxidiser, corrosive, acute toxic and environmental hazard.	Fatal if inhaled (Danger Acute toxicity, inhalation).
BCaCl2H3O5	EUSOL is produced through the dissolution of calcium hypochlorite with boric acid, see Equation 1.	Antimicrobial agent. Was used in vivo for wound disinfection.	None stated.	None stated.

Notes:
[A] Synonyms for HOCl produced through the electrolysis of a weak NaCl solution.

improper use of OCl- are not emphasised, which particularly when being applied to paediatric patients, is worrying.

Finally, a point of potential confusion is the occasional use of the term "hypochloric acid" when it appears that the authors are referring to HOCl.[29] "Hypochloric acid" is not a recognised synonym for HOCl and may be confused with hydrochloric acid (HCl). For clarity it is important to emphasise that HOCl (hypochlorous acid) is a disinfectant, whilst HCl (hydrochloric acid), is a strong corrosive acid and can cause acid burns if handled incorrectly and is not used within clinical care.[30]

CONCLUSIONS

Hypochlorite solutions (OCl-) and hypochlorous acid (HOCl) both have a place for effective disinfection. However, a clear understanding of the differences between these solutions and accurate use of terminology is essential to prevent harm from incorrect in-vivo use of hypochlorite (bleach), that should be used only for surface disinfection.

There is a need for greater clarity around the chemical composition (approximate ratio of HOCl to OCl-), concentration (mg/L or ppm), and crucially, pH of solutions to ensure solutions are used as intended. It is recommended that disinfectant solution pH is reported in any studies on chlorine-based disinfectants. Clarity around appropriate and safe storage of disinfecting solutions to prevent degradation is also essential (Box 1).

Box 1. Key Points

- When using chlorine solutions on wounds/membranes, be aware of the pH and potential risks.
- Do not combine chlorine solutions with detergents and highlight to users if you see this in practice.
- When publishing data on chlorine solutions be cautious with terminology.
- This paper provides guidance for clinicians requiring a safe tool to topically combat infections of human tissue, as part of a multifactorial approach.

Chemical terms that may appear superficially similar have been used loosely and interchangeably in literature, despite denoting disinfectants with very different properties, uses and safety profiles. Additionally, the range of synonyms, acronyms and brands can present challenges to accurate terminology use in clinical practice and in wider literature. As well as scientific inaccuracy, this confusion has potential as a public health concern, particularly in world events such as the SARS-CoV-2 pandemic when urgent and effective disinfectants are key to control. This paper outlines terms and acronyms used for different chlorine-based solutions, providing a resource to support safe and effective disinfection in healthcare and improving clarity for future publications that include chlorine-based disinfectants.

ACKNOWLEDGEMENTS

The authors would like to thank colleagues at the Usher Institute, University of Edinburgh and the Royal College of Surgeons of England for providing insight and consultation throughout. We are grateful to Marshall Dozier, the Academic Support Librarian at the University of Edinburgh, UK, for her assistance in developing the search strategies.

FUNDING

This manuscript was partially funded by the Engineering and Physical Sciences Research Council's [EPSRC] Redistributed in Healthcare Manufacturing Network [RiHN].

AUTHORSHIP CONTRIBUTIONS

FVM proposed the original concept for the article, wrote the initial draft and edited the final manuscript. GEC wrote the background, scientific and terminology sections, and edited the final manuscript. DMR contributed to the scientific sections and edited the final manuscript. KH assisted in writing and editing of the final manuscript.

DISCLOSURE OF INTEREST

The authors completed the ICMJE Disclosure of Interest Form (available upon request from the corresponding author) and disclose no relevant interests.

CORRESPONDENCE TO:

Kate Homyer
NHS Lothian
Scotland
kate.homyer@nhs.scot

Submitted: May 23, 2023 BST, Accepted: July 06, 2023 BST

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