Proposal for the addition and inclusion of **hypochlorous acid** to the
2025 WHO Essential Medicines List
in the categories of disinfection, antisepsis, and wound care.

Hypochlorous Acid (HOCl)

for antisepsis, disinfection, and wound care in

Core Categories 15.1, 15.2, and 13

Submitted 29 October 2024

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1. Summary Statement of the Proposal

We request that Hypochlorous Acid (HOCl) be added to the core Essential Medicines List to address priority conditions in Categories 15.1 and 15.2 (Disinfectant and Antiseptic products), and Category 13 (Wound Care). There is nothing like its capabilities on the existing List.

In the aftermath of the coronavirus pandemic and the associated widespread use of environmental decontamination measures all over the world, it has become clear that HOCl is the most appropriate, most potent, cost-effective and safe solution for this purpose.*(1-7)* At the same time compelling evidence has emerged about previously unrecognized hazards arising from use of conventional disinfectants, adding emphasis to the need for the addition of HOCl to the EML.*(8-12)* Preparedness in the face of likely recurrences of pandemic virus infections means a need for more reliable interventions aimed at transmission pathways. The speed, power and efficacy of HOCl, including against all variants of coronaviruses,*(5, 7, 13)* extends even to highly-resistant human pathogens such as prions*(14)* and HPV-16.*(15)* These characteristics put HOCl in a unique category for infectious disease control.*(16-21)*

Manufacturing improvements for HOCl now enable reliable, consistent production of pure, stable solutions of HOCl in industrial quantities around the world, sufficient to meet global institutional needs. High purity HOCl products permit safe implementation of chemical disinfection without risks to patients, staff, surfaces, or equipment, and even allow unskilled operators to safely forego PPE use (which might be required for other reasons, but not due to danger from HOCl). These developments help healthcare providers battle pandemic agents while avoiding dependence upon conventional wide-spectrum antimicrobial agents now known to contribute to resistance traits and to harm patients and staff.*(9, 22)* HOCl also represents an especially appropriate resource in the face of natural disasters and the medical resources they require, not only for disinfection, but also for food safety, personal hygiene, and wound care.*(6, 13, 17)*

In the fields of Antisepsis (Core 15.2) and Wound Infection Control (Core 13), HOCl offers an unequaled combination of: 1) antimicrobial efficacy against the common bacteria and fungi that infect wounds,*(23-30)* and 2) a long-standing record of enhancing the rate of healing to reduce the burden of wound care costs.*(27-31)* These attributes are increasingly evident in the results of randomized clinical trials reported in peer-reviewed journals, *(32-43)* and from prospective studies on clinical outcomes following topical applications of HOCl.*(25, 44-46)* They open the possibility of reducing dependence on high-cost antibiotic uses for both acute and chronic wound management, and the selection for multi-drug resistance traits that accompanies such use. *(8, 47)*

Adding HOCl to the EML can have a significantly positive impact on health systems globally. The benefits of designating it as "essential" would reduce the costs of healthcare in developing nations. Tolerant of temperature extremes, and stable when packaged for up to several years, pure HOCl is ideally suited to tropical regions. The end products of its use are water and salt, so the compound poses no personal safety, toxicological hazard, or ecosystem risks either in handling or routine deployment.*(13, 48, 49)*

2. Consultation with WHO Technical Departments

This application is coming from the Health and Environment Advisor to the Sudanese National Academy of Sciences. We have a close relationship with multiple staff inside WHO Technical Departments and we have been conducting clinical research for four years on the use of HOCl in highly constrained environments, including war zones around Khartoum and refugee camps in northern Sudan. Some of our partners are WHO technical affiliates working with us, such as the late Dr. Omer Zayed (University of Khartoum) who have lost their lives during the civil war raging in Sudan. Others, including Dr. Mahdi Shamad (University of Bahri); Shames El Din A. Amara (Kordofan University) and Bakri Nour (Gezira University), have been members of our clinical teams testing HOCl with war wounds, chronic diabetic vascular infections, dermatological infections, and with infectious diseases including mycetoma, to great effect. The HOCl solution used in our studies was retail grade available on Amazon and approved by the Sudanese National Medicines & Poisons Board and all research efforts received ethical approval from the Ethical Committee, Federal Ministry of Health. Patients and physicians spoke extensively before the trials, and informed consent was established before inclusion in the studies.

Regrettably, the war disrupted our research, killed our people, destroyed our universities and we had to evacuate our homes that were then looted by the warring militias. Our own publications will not be found in the references as we are still trying to pull our work back together again after our diaspora. We are, though, consolidating our raw data, including photographs and planimetry, within the National Wound Center in Cardiff, Wales, and hope to publish our very positive and statistically powerful HOCl wound results in early 2025. Until then, please see the images within our case reports in the Appendix.

Further WHO EML Secretariat communication

Additional consultation with WHO is worth noting. A preliminary draft of this application was the subject of an Advisory Commentary by the EML Secretariat Office on 25 October 2024. In that Commentary staff at the Secretariat noted the amended inclusion of “aqueous chlorine formulations” in the EML eliminated the need for specifying Hypochlorous Acid (HOCl) as a disinfectant or sanitizer.

We respectfully disagree. Hypochlorite (NaOCl), often referred to as bleach, is an “aqueous chlorine formulation” and an unstable toxic industrial chemical that degrades in 90 days. HOCl is an “aqueous chlorine formulation” and a natural and organic product formed within the myeloperoxidase pathway in human neutrophils and benign to human tissues. It has been shown by certified laboratories to be stable in commercial formulations for years.

- **Hypochlorite** storage requires industrial toxin warnings and Personal Protective Equipment for use by healthcare providers. It is cytotoxic to wounds and requires hazardous material handling for disposal because it is an environmental toxin, particularly harmful to marine ecosystems.
- **HOCl** can be stored anywhere, is benign to human physiology, and degrades to dilute salt water within minutes after use.

- Despite its safety profile, **HOCl has been repeatedly found superior to hypochlorite as both a disinfectant and antiseptic.**

Citations for the statements of fact above are validated within the application below.

Medical product regulatory authorities in the EU, UK, Canada, Japan, Mexico, Australia, New Zealand and US, amongst others, all require registration of HOCl products for approval and clearance for sale as disinfectants. **In no instance** are HOCl products exempted from the relevant regulatory provisions on the grounds that their efficacy and safety performance is assumed by prior approval of aqueous chlorine formulations containing hypochlorite, chlorinated isocyanurates, chlorinated melamines, chlorine dioxide, chlorinated imidazolidines, organic and inorganic aqueous chloramines, or any other species of aqueous chlorine that may be present as products in the stream of commerce within their jurisdictions.

HOCl-specific regulatory requirements reflect recognition by these national health authorities that the composition of HOCl products and their efficacy, safety, stability and environmental toxicology profiles are distinct in every particular from those of commonplace aqueous chlorine formulations such as those listed above. This widely appreciated and soundly based distinction, detailed in the accumulated, abundant peer-reviewed scientific literature (samples of which are cited in our application below) make it clear that **HOCl product solutions should be identified specifically for inclusion in the EML**, as we are proposing in this petition.

Added emphasis for this position comes from emerging evidence in the aftermath of disinfection and sanitation measures applied on the unprecedented scale in the coronavirus pandemic, and from prior experiences in the West African Ebola epidemic that preceded it. There was extravagant deployment of conventional aqueous chlorine solutions that not only lacked speed and potency but also inflicted corrosive consequences on hospital equipment and instruments and exposed the hitherto unrealized damage to the respiratory systems of personnel occupationally exposed to these formulations.*(9-12)* It is precisely for these reasons that the case is made herein for the specific and by-name adoption of HOCl-based solutions for disinfection in Category 15.1 of the EML.

The EML Secretariat also references the response of the reviewers of a previously submitted proposal for inclusion of HOCl products for categories 15.2 and 13. It was determined at that time that there was insufficient support from rigorously conducted clinical evaluations to justify addition of HOCl, and that the evidence from the reported and numerous clinical experiences was not adequate for this purpose.

In the intervening years, and because of the expanded appreciation of the properties of HOCl, a stream of reports of Randomized Clinical Trials using HOCl products in the management of acute and chronic wounds has appeared, several of which are cited in the appropriate sections below. These and other reports submitted in support of product registrations to national regulatory agencies worldwide account for the growing trend of approvals for HOCl in the use patterns for which we are requesting inclusion in the EML. Health authorities have been persuaded of the legitimacy of the claims made for the superiority of HOCl products over existing standards of care when used as antiseptics and in wound cleansing and the promotion of healing.

Our request for re-consideration of the inclusion of HOCl in the EML is based on recent advances in scientific knowledge. RCTs have been published in the peer-reviewed literature during and after a pandemic that killed millions and during which HOCl became well-recognized by EU and US regulatory agencies as an exceptionally safe and thorough disinfectant against SARS-CoV-2.*(3, 5, 7, 13, 50)* The argument for HOCl-specific inclusion in the EML was strong before. Subsequent research has now made it compelling.

3. Other organizations consulting or supporting the submission

Médecins Sans Frontières (MSF) has written a letter specifically supporting this application, and their letter will be attached to this submission and included here in Appendix 1. The MSF International Medical Coordinator, Dr. Myriam Henkens, MD, MPH, signed that letter, and we understand she is an Advisor to the WHO Essential Medicines List Committee. Her letter says, in part:

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MSF supports the application for the inclusion of aqueous hypochlorous acid (HOCl) in the WHO Model List of Essential Medicines, in section 15.1 (Antiseptics) and 15.2 (Disinfectants), and section 13 (Dermatological Medicines).

Hypochlorous acid is a well-studied, non-toxic, non-corrosive, easy to use compound, and a more effective and a safer alternative to other chlorine generating disinfectant agents, such as sodium dichloroisocyanurate (NaDDC).

The European Chemical Agency (ECHA) lists hypochlorous acid as a biocide product type 1 (human hygiene), product type 2 (surface disinfection), product type 3 (veterinary hygiene), type 4 (food and feed area), and type 5 (drinking water).

Hypochlorous acid has been also approved by the US Food and Drug Administration (FDA) for disinfection of food-contact surfaces, for high level disinfection and sterilization of medical instruments, for topical applications, for use in drinking water, and as a no-rinse food sanitizer.

MSF would like to draw the attention of the Expert Committee to the following facts:

- *Hypochlorous acid is mainly registered in high regulated countries. Its inclusion in the WHO Model List of Essential Medicines will serve as a basis for National Essential Medicines lists and therefore will attract additional manufacturers, will facilitate importations, will alert manufacturers about the need for local registrations, will allow for competition between manufacturers in order to reduce price and improve accessibility, particularly in low-and middle-income countries, and will give a strong signal to manufacturers, generic producers, country programs, international donors, and health regulatory authorities.*

- *A stable, concentrated, long shelf-life (≥ 3 years), easy and ready-to-dilute product, must be available for settings where shipping is needed, especially in low- and middle-income countries, to reduce logistical constraints and increase availability and affordability.*

In light of these elements, MSF urges the Expert Committee on the Selection and Use of Essential Medicines to include hypochlorous acid in the WHO Model List of Essential Medicines.

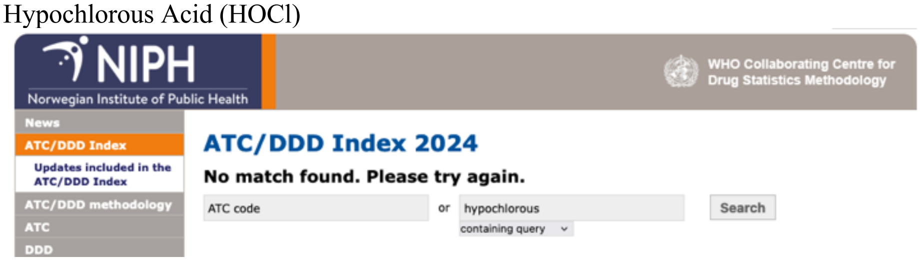
For Médecins Sans Frontières,
Myriam Henkens, MD, MPH

4. Key information summary for the proposed medicine

1. International Non-proprietary Name (INN)

- Hypochlorous Acid (HOCl)

2. Chemical Names (there is no ATC for hypochlorous acid)

- Hypochlorous Acid (HOCl)
- 

3. Registry Numbers and Identifiers

- CAS Registry Number: 7790-92-3
- IUPAC name: Hypochlorous acid
- FDA UNII: 712K4CDC10
- EC Number (European Community): 232-232-5
- EPA DSSTox Substance ID: DTXSID3036737
- Human Metabolome Database (HMDB) ID: HMDB0015036
- PubChem CID: 24341
- UNSPSC Code: 42312313 (Wound Cleaning Solutions)

4. Alternative Names in the historical and international medical literature

- Acidic Electrolyzed Water (AEW) (for HOCl produced by certain electrolytic methods)
- Electrolyzed Oxidizing Water
- Electrolyzed Water (used particularly when referring to HOCl generated via electrolysis)
- HClO (the preferred designation in UK and some other countries)
- Hypochlorous Solution (common in topical medical applications)
- Neutral pH Superoxidized Solution (used in some clinical applications)
- Oxidized Water (used for electrolyzed solutions of HOCl used in wound care)
- Oxidizing Water Solution (or variations like oxidized water solution)
- Slightly Acidic Electrolyzed Water
- Superoxidized Water
- Superoxidized Solution
- Superoxidized Saline
  - And there are others. They are all HOCl.

5. Pharmaceutical and Commercial Names (as will be seen in the Section 12 Reference publications)

- **Microcyn®** (a commercial stabilized HOCl solution for wound care)
- **Vashe®** (a branded HOCl solution for wound irrigation)
- **Avenova®** (HOCl used for ophthalmic and skin care)
- **Dermacyn®** (HOCl-based solution for treating wounds and infections)
- **NeutroPhase®** (HOCl antimicrobial wound care solution)
- **Puracyn®** (commercial HOCl solution for wound care)
- **Anolyte** (referring to the HOCl-containing solution in electrochemical generation)
- **PureCleanse, Biomiq, Toronto**
  - Health Canada licenses #108007, 108304, 111117, and 111115

6. Regulatory Classifications

- **US FDA**: Approved for disinfection of food-contact surfaces, high-level disinfection, sterilization, and wound care applications.
- **European Medicines Agency (EMA)**: Approved in some formulations as a Class III medical device for wound management.

7. Indications (NS with 40-550ppm HOCl, ideal 160-330ppm. No known difference with children under 18.)

- Dermatological disruption, for antisepsis and accelerated healing (human and animal), ICD-11
  - Laceration ND56.1
  - Abrasion ND56
  - Avulsion

- Shrapnel impact
- Surgical prep
- Surgical debridement
- Surgical irrigation
- Surgical incision care delivered post-op
- Mucositis (oral, from radiation or chemotherapy) DA01.11
- Cheilitis DA00.0
- Skin Ulceration
  - Diabetic
  - Vascular BD74.3
  - Decubitus EH90
  - Other
- Insect bite
- Cellulitis 1B70
- Burn (any depth) NE2Z
- Shingles amelioration (gel best) 1E91
- Contact dermatitis EK5Y
- Atopic dermatitis (subset) EA80
- Psoriasis EA90
- Rosacea ED90
- Mastitis (human and animal) GB21
- Tinea cruris 1F28.3
- Tinea pedis 1F28.2
- Bacterial infections (e.g. impetigo w *Staph. aureus*) 1B72
- Fungal infections (e.g. ringworm from *Trichophyton*) 1F28
- Viral infections, topical EA3Z
  - E.g. HPV, HSV and Zoster
- Gingivitis DA0B.Y

- Environmental sanitation
  - Area and surface disinfection,
    - 1 minute surface exposure
    - Area mist calculation available
    - Bacterial, fungal, viral, prion
- Oral infection risk reduction
  - Mucositis swish and swallow, 30 seconds, 5x/day beginning 1 day before radiation/CTX.
  - Gingivitis. S&S, 30 sec, BID
  - Halitosis, S&S, 30 sec, BID

5. Listing as an individual medicine

Base HOCl formulation in a <u>saline</u> solution (acceptable for disinfection, antisepsis, and wound care):

1. 150 parts per million or greater of hypochlorous acid (HOCl).
2. Isotonic solution of 0.9% saline (Normal Saline) preferred for clinical use.
3. pH less than 5.5, and greater than 99% pure HOCl
4. Oxidation-Reduction Potential (ORP) greater than 1000 mV.

Alternative HOCl formulation in a <u>non-salt</u> solution (also acceptable for disinfection, antisepsis, and wound care):

1. 150 parts per million or greater of hypochlorous acid (HOCl).
2. pH less than 5.5, and greater than 99% pure HOCl
3. Oxidation-Reduction Potential (ORP) greater than 1000 mV.
4. Salt-free water-based solution (rather than 0.9% saline) as an option for environmental use.

Aqueous solutions of HOCl approved for disinfection in the EU may contain up to 200 ppm of oxidative titratable chlorine (Cl). The Cl ppm content of approved disinfectant HOCl solutions in the US ranges from 180-460 ppm. Wound care solutions cleared for the US market by FDA range from 100-200 ppm Cl. A preparation of HOCl approved as a Class III medical product for wound care in the EU contains no more than 200 ppm Cl.

Potency, stability and safety of HOCl preparations depend on the purity of the solution,*(18, 51, 52)* and the avoidance of contaminating molecular species of aqueous chlorine (such as hypochlorite, chlorate, chlorite, perchlorates, and elemental chlorine.) Pure HOCl therefore provides a higher level of safety and a more consistent level of performance for users in all applications. Its production is achievable by improved process-controlled manufacturing advances introduced in the last several years.

Many HOCl products were made prior to the improved manufacturing processes now available, yet the historical medical literature clearly documents the many benefits derived from HOCl over the past 100 years even when sub-optimal manufacturing processes were used.*(22, 53)* Early attempts to make crude HOCl solutions by acidification of sodium hypochlorite, for example, generated hazardous amounts of chlorine gas.

However, the extensive literature on HOCl use since World War I attests to the advantages that emerge from its routine adoption, even in suboptimal, impure, short-lived unstable products, identified in the literature variously as electrolyzed water, superoxidized water, acid electrolyzed water, superoxidized saline, and many other variants apparent from Section 4.4 above and the Reference list below. HOCl production has now been optimized in multiple nations and the quality can be routinely superb, at a high volume of production, using modern manufacturing process controls.

Historically, laborious and carefully controlled HOCl manufacturing and testing methods brought with them cost implications that impeded the uptake and use of HOCl products. However, now that HOCl is available in well-characterized, reproducible, and economically attractive forms at industrial volumes, the superiority of its performance in disinfection, antisepsis and wound care argues for its deployment on a much wider scale. Recent analyses support the cost effectiveness of HOCl for these purposes, even in comparison to crude hypochlorite like Dakin's Solution that has been depended upon so widely for so long.*(54)* The 80-100x advantage in potency of HOCl over equivalent concentrations of hypochlorite bleach like Dakin's accounts in part for this outcome.

6. Information supporting the public health relevance

Hypochlorous acid (HOCl) for the purposes proposed in this application (EML Sections 15.1, 15.2 and 13) has been evaluated by regulatory agencies, healthcare institutions, professional organizations, independent laboratories, and academic institutions in more than 50 countries. More than 2,600 publications in peer-reviewed scientific journals address the potency and safety of HOCl as an antimicrobial agent for environmental disinfection and antisepsis. A further 3,000 journal articles report on the benefits HOCl provides to wound healing enhancement when applied topically, and the biochemical and physiological mechanisms involved in those processes. Representative examples of the published literature supporting these uses and benefits are included in the list of References in Section 12. These now include recent reports from the conduct of randomized controlled human clinical trials, and experimental animal models with proven relevance to human medical conditions. *(4, 32, 37, 38, 40, 55-64)*

HOCl solutions are already included in the WHO list of coronavirus-effective biocides, and in the US EPA 'N' list of disinfecting agents able to control emerging pathogens such as SARS-CoV-2, Mpox, and *Candida auris*.*(7)* HOCl solutions are registered for commercial use in many other countries worldwide, including within the EU, ASEAN, and MENA groups. A Class III medical product approval for HOCl has been granted in the EU, and the Japanese Ministry of Health has approved use of HOCl for topical medical applications. As of September 2024, at least eight branded aqueous HOCl formulations have been cleared by the US FDA for topical use in wound management over the last decade. In addition, the US FDA has approved HOCl for high level disinfection and sterilization of medical instruments, including those for use at critical (i.e., sterile) sites.*(65)*

An HOCl product is approved as a Class III medical product in the EU. Solutions of comparable composition are approved for topical uses within countries in Asia, Latin America, and the Middle East.

Product claims relating to details of composition and efficacy depend on the care with which solutions of HOCl are prepared. Electrolysis, as a method of production, optimizes the power and stability of the oxidative chlorine content. Some products, made with different processes, offer only very short shelf life and need to be used as soon as possible after production, preferably on-site. Pure homogeneous preparations (known to be made in at least Canada, Finland, India, Malaysia, Dubai, and the US as of September 2024) offer extended shelf life, optimal pH, and high Oxidation-Reduction Potential (ORP). These products ensure reliable potency in the inactivation of microbes, in addition to enhanced safety in the topical treatment of wounds. They maintain pH within the most desired range for stability and potency of HOCl, and they avoid the incorporation of extraneous chemical species, both inorganic and organic, that can contribute to rapid degradation. Careful selection of appropriate packaging materials also ensures stability and reliably long shelf life for the final product.

Consensus and guidance statements about HOCl for infection control and topical medical use have been issued in recent years by several governmental agencies responsible for healthcare product regulatory oversight, and by medical professional specialty organizations focused on advantageous technical innovations that better serve their physician's needs.*(23, 24, 26)* Some examples:

- **From the WHO Interim Guidance Document on "Cleaning and disinfection of environmental surfaces in the context of COVID-19", page 2:**
  "The use of chlorine-based products:
  Hypochlorite-based products include liquid (sodium hypochlorite), solid or powdered (calcium hypochlorite) formulations. These formulations dissolve in water to create a dilute aqueous chlorine solution in which undissociated hypochlorous acid (HOCl) is active as the antimicrobial compound."*(66)*

- **The Japanese National Institute of Technology and Evaluation determined that hypochlorous acid is effective at inactivating SARS-CoV-2 at virucidal levels:**
  "Based on these results, the Committee judged that HAW (hypochlorous acid water) of an ACC (active chlorine concentration) of 35 ppm or higher was effective, which showed a more than 99.9% reduction of viral titer in the evaluation study at NIID (the National Institute for Infectious Diseases) as well as a more than 99.99% reduction in the studies at OUAVM and QTEC (universities)." *(5)*

- **From the US FDA Analysis and Evaluation of Preventive Control Measures for the Control and Reduction/Elimination of Microbial Hazards, Chapter 5:**
  "Hypochlorous acid (HOCl) is the form of free available chlorine that has the highest bactericidal activity against a broad range of microorganisms."*(67)*

- **Also from the US FDA:**
  - Guidance on minimizing microbial food safety hazards using chlorine-based disinfectants
  - "For example, the antimicrobial activity of a chlorine-based disinfectant depends on the amount of hypochlorous acid (also called "free chlorine") present."

- **Consensus Guidelines within the Expert Recommendation on the use of Hypochlorous Acid (HOCl), published in "Wounds" (2016) included these statements:**
  - "Wound complications such as infection continue to inflict enormous financial and patient quality-of-life burdens. The traditional practice of using antiseptics and antibiotics to prevent and/or treat infections has been questioned with increasing concerns about the cytoxicity of antiseptics and proliferation of antibiotic-resistant bacteria.

- In the last 15 years, more advanced hypochlorous acid (HOCl) solutions, based on electrochemistry, have emerged as safe and viable wound-cleansing agents and infection treatment adjunct therapies."*(68)*

- **Bongiovanni et al. in 2016 in a comprehensive review of use of HOCl in treatment of more than 1,000 venous leg ulcers (VLU) concluded:**
  - "Perhaps the greatest advance in VLU care is the addition of HCA [hypochlorous acid, HOCl] to the treatment armamentarium. These aqueous solutions of hypochlorous acid, even in trace amounts, will kill most pathogens within 30 seconds of exposure. Additional actions of HCA include reduction of mast cell degranulation and active capillary dilation. The latter effect is of great importance in the diabetic VLU patient since one of the paradoxes in diabetes is the reduction of capillary perfusion via arteriovenous shunting at the microcirculatory level."*(27)*

- **Gold et al, in 2020 reporting on the conclusions of an expert panel on surgery and wound care, wrote as follows:**

  "HOCl can be indispensable in pre and peri-procedures as an antiseptic and anti-inflammatory agent, and in post-procedures, including post-sutures, as a wound healing agent.

  HOCl could become the first line pre and peri-procedure antiseptic for supporting wound healing and scar management."*(24)*

- **Del Rosso and Bhatia in 2020 published an updated status report on topical HOCl and concluded as follows:**

  "HOCl exhibits broad spectrum antimicrobial activity that is directly toxic to many bacteria and fungi.

  Hypochlorous acid exhibits anti-inflammatory and immunomodulatory properties based on multiple laboratory analyses. These properties appear to correlate with potential therapeutic benefits of topically applied HOCl for a variety of skin disorders."*(23)*

- **Block and Rowan in 2020 reviewed surgeons' needs for disinfection in the face of the coronavirus pandemic and concluded that:**

  "It [HOCl] comprises many of the desired effects of the ideal disinfectant: it is easy to use, is inexpensive, has a good safety profile, and can be used to disinfect large areas quickly and with a broad range of bactericidal and virucidal effects."*(26)*

- **Rasmussen and Williams (2017) writing on the usefulness of HOCl for the demands of healthcare after natural disasters, concluded:**

"HOCl offers a significant ability to protect humanitarian aid workers, the populations they serve and the communities that receive those displaced families. It can help control the next Ebola outbreak, or SARS epidemic. When used for area disinfection in tents, clinics, refugee camps, and hospitals, HOCl can significantly reduce pathogen bioloads. When used for traumatic injuries it can eliminate microbial wound biofilms while decontaminating tissue, potentially reducing the risk of sepsis while improving the rate of healing.*(17)*

The table below contains highlights from 25 publications (including **13 Randomized Controlled Trials**) summarized below the table and listed in the References, each of which independently document the safety and efficacy of HOCl (under various chemical names as discussed in Section 4.4 above) for each of the WHO EML categories proposed for HOCl inclusion:

	First author	**Study type**	**Key result**
1	Hughson	Bench research	HOCl inactivates prions at STP (unprecedented)
2	Rasmussen	Review	HOCl use in highly vulnerable populations
3	Gray	Cohort study	HOCl decolonization reduced Burn Unit MRSA
4	Williams	Review	HOCl against emerging and resistant pathogens
5	Robins	Bench research	HOCl evaluation for purity and stability
6	Meyers	Bench research	HOCl rapidly inactivates HPV 16 at STP
7	Mendez-Duran	RCT	HOCl reduces dialysis infections
8	Day	Clinical model	HOCl disrupts wound and ulcer biofilms
9	Khan	Clinical trial	HOCl effective in pre-op peritoneal lavage
10	Mohd	RCT	HOCl reduces sternotomy infections
11	Garg	RCT	HOCl effective in peritonitis lavage
12	Mekkawy	RCT	HOCl improves septic traumatic wounds
13	Prabhakar	RCT	HOCl better for infected diabetic ulcers
14	Landsman	RCT	HOCl best of 3 for diabetic foot infections
15	Pandey	RCT	HOCl better than Betadine for infected wounds
16	Piaggessi	RCT	HOCl better for post-surgical diabetic wounds
17	Bongiovanni	Clinical Review	HOCl better for venous leg ulcers
18	Suri	RCT	HOCl better for diabetic foot wounds

19	Martinez-DeJesus	RCT	HOCl safe and effective in severe wounds
20	Ricci	RCT	HOCl best for infected chronic wounds
21	Gold	Panel Review	HOCl best for wound care and scar management
22	Sakarva	Clinical model	HOCl for biofilm disruption and wound healing
23	Hadi	RCT	HOCl effective as adjunct wound therapy
24	Dalla-Paola	NR/OL Trial	HOCl better than Betadine for DM foot ulcers
25	Kapur	RCT	HOCl better than Betadine for all wounds

6a. EML Section 15.1 Disinfection

Paper: Hughson AG, Race B et. al. Inactivation of prions and amyloid seeds with hypochlorous acid. PLoS Pathogens 12(9): e1005914.doi:10.1371/journal.ppat.1005914

Objective: To test the anti-prion activity of a weakly acidic aqueous formulation of HOCl that poses no apparent hazard to either users or many surfaces.

Design: To test the effects of HOCl and other disinfectants on steel-bound prion seeding activity, wires coated with a 10−3 dilution of ScBH were immersed in HOCl, in 40% bleach, in 1 N NaOH, in 2% Environ LpHTM, or in saline for 1 h, rinsed, and added to RT-QuIC reactions.

Abstract: Anti-prion activity of HOCl was demonstrated using both intracerebral infectivity of treated prions of Scrapie, as well as with an *in vitro* fluorescent chemistry method showing HOCl efficacy versus BSE, CJD, CWD prions and amyloid prion-like proteins. Efficacy was shown to reach levels of almost 6 LRV after exposures of 60 minutes at room temperature, but significant reductions were achieved up to 3-4 LRV in only 5 minutes of contact with HOCl. High efficacy was also demonstrated against *Bacillus* spores. *(14)*

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Paper: Rasmussen ED and Williams JF, "Stabilized hypochlorous acid disinfection for highly vulnerable populations: HOCl wound disinfection and area decontamination," 2017 IEEE Global Humanitarian Technology Conference (GHTC), San Jose, CA, 2017, pp. 1-8, doi: 10.1109/GHTC.2017.8239259.

Objective: To assess the value proposition of HOCl in wound disinfection and area decontamination in conflict zones, natural disaster response, displacement camps, and slums.

Design: A literature review and description of the documented safety and efficacy profile of HOCl as determined by independent laboratories over more than 100 years of research.

Abstract: The US Food and Drug Administration regards HOCl as the most effective form of all chlorine-based antimicrobial compounds. Historically, conventional production pathways generate HOCl solutions that are flawed by their instability, and by their inclusion of heterogeneous mixtures of aqueous chlorine species and other oxidants. These detract from the intrinsic safety and efficacy of HOCl for a wide range of applications. Large scale manufacture of HOCl in a novel, stable form, uncontaminated with uncharacterized components or extraneous stabilizing additives, has now become possible through an innovative chemo-electrolytic process. It provides HOCl tolerant of elevated temperatures, with a practical storage shelf life of years, and disinfecting potency against viruses, bacteria, endospores, fungi, and even infectious proteins (prions). The high Oxidation/Reduction Potential (ORP) is sustained over years of storage, and the end products of its practical deployment are water and NaCl. Further evaluation is proposed for this form of HOCl for field hospitals, remote clinics, and disaster zones as a safe, effective, and affordable new disinfectant. HOCl offers a significant ability to protect humanitarian aid workers, the populations they serve, and the communities that receive those displaced families. When used for area disinfection in tents, clinics, refugee camps, and hospitals HOCl can significantly reduce pathogen bioloads, and when used for traumatic injuries it can eliminate microbial wound biofilms while decontaminating tissue, potentially reduce the risk of sepsis while improving the rate of healing. It is stable for months at temperatures above 150ºF, is unaffected by vibration or shock, and can be stored and used at ordinary temperatures without the need for personal protection.*(69)*

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Paper: Gray D et al., Universal decolonization with hypochlorous solution in a burn intensive care unit in a tertiary care community hospital. Am J Infect Cont. 2016

Objective: To evaluate the efficacy of universal decolonization to decrease health care–associated infections caused by MRSA in patients admitted to a burn intensive care unit (BICU) using mupirocin and hypochlorous solution for skin decolonization.

Design: A retrospective, single institution cohort study.

Results: Global MRSA infection rates per 1,000 patient days were 7.23 pre-intervention and 2.37 post-intervention, resulting in an incidence rate ratio of 0.328, favoring post-intervention (95% confidence interval, 0.167-0.646; P = .001).

BICU patients without universal decolonization had 3.05 times higher risk of acquiring an MRSA infection than those with universal decolonization. No complications were noted from use of hypochlorous acid solution for skin decolonization. *(25)*

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Paper: Williams JF, Rasmussen ED, and Robins L, Hypochlorous Acid: Harnessing an Innate Response
https://infectioncontrol.tips/2017/10/06/hypochlorous-innate-response/
Published online, October 6, 2017

Objective: We review here an emerging technology based on hypochlorous acid (HOCl), with emphasis on a novel, stable form, that inactivates viruses, bacteria, endospores, and fungi, is safe for human tissues, is environmentally benign requiring no toxic waste disposal or hazardous material management, and yet can degrade the infectivity of prions.

Design: Review of the HOCl literature associated with disinfection, with particular attention to human biocompatibility, immune-conservation, and the inactivation of a possible etiologic agent in Alzheimer's Disease.

Abstract: Human pathogens are becoming resistant to antibiotics developed over the past century, and common infections once routinely managed by conventional antibiotics can now become fatal even with best-practice therapy. One method for addressing that developing risk is to attack pathogens before they become life-threatening infections using area and wound decontamination and disinfection techniques. Current methods for disinfection, however, can contribute to the development of resistance, prove toxic to tissues, and damage the environment. We review here an emerging technology based on hypochlorous acid (HOCl), with emphasis on a novel pure and stable form that inactivates viruses, bacteria, endospores, and fungi, is safe for human tissues (including eye, lung, and skin), is environmentally benign requiring no toxic waste disposal or hazardous material management, and yet is capable of degrading the infectivity of prions at a Log Reduction Value (LRV) of >5, equating to roughly a 99.999% elimination. *(70)*

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Paper: Robins, L et. al. Purity and Stability of an Electrolytically-Generated Hypochlorous Acid Solution, Annual Meeting of the American Chemical Society, August 2017, Washington DC

Objective: To evaluate the decomposition kinetics of HOCl when generated electrolytically.

Design: We used Raman Spectroscopy, iodometric titrations, UV-visible spectrophotometry, and ORP measurements to characterize an electrolytically-generated, solution of pure HOCl (pH 4) made from only NaCl and water.

Abstract: This unbuffered solution was unexpectedly stable, even at elevated temperatures, sealed in a variety of vessels. There were no detectable changes in oxidative Cl levels (ppm), ORP (+mv), or pH in HOCl solutions maintained in glass containers at 52 °C for 38 days. After 30 days at 70 °C in glass, active Cl declined from 190 ppm to 151 ppm, but ORP remained constant, while pH rose to 4.3. No oxidative aqueous Cl species other than HOCl were detected in any stored samples. The results demonstrate that long-lived HOCl solutions can be prepared that undergo little or no change while in storage, even at high temperatures. The findings open up prospects for wider use

of HOCl in environmental disinfection, with avoidance of on-site production, or concerns about the efficacy of stored solutions. *(18)*

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Paper: Meyers, C et al, Efficacy Testing of HOCl as a Disinfectant for High-Risk HPV, The International Conference on Prevention & Infection Control (ICPIC) 2019 ICPIC Conference, Geneva, Switzerland, September 2019

Objective: Evaluation of HOCl against human papilloma virus (HPV16), a virus known to cause extensive morbidity as a sexually transmitted disease and implicated in causing two of the top ten fatal cancers globally, cervical and oropharyngeal.

Design: Infectious high-titer stocks of HPV16 and HPV18 were produced, titred, and infectivity-tested. Both suspension and carrier tests were performed with contact times spanning 15 seconds to 20 minutes. Following contact any remaining HOCl was neutralized. Residual HPV was isolated and measured by our published infectivity methods.

Results: All HOCl treatment contact times produced >99.99% reduction in infectivity of HPV16 and HPV18, comparable to the efficacy of concentrated (0.87%) sodium hypochlorite. HOCl is a highly effective disinfectant for HPV even at 15 seconds, the fastest process-measurable time. *(71)*

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6b. EML Section 15.2 Antisepsis

Paper: Méndez-Durán A. Efficacy and safety of the use of superoxidized solution in the prevention of dialysis-related infections. Dial Transpl. 2013: 34(4); 160-165.

Objective: To evaluate the efficacy and safety of super-oxidized solution in reducing the frequency of dialysis-associated infections.

Design: Randomized Controlled Trial in one hundred and eleven intraperitoneal dialysis patients treated with either povidone- iodine or super-oxidized solution following catheter placement.

Results: After 8 weeks follow-up, 24.5% of the povidone-iodine group had experienced catheter-related infections compared with 6% in the super-oxidized solution group ($p<0.05$). The mean time resolution of infection in the povidone-iodine group was 12 days compared with 4 days for the super-oxidized solution group ($p<0.05$). *(32)*

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Paper: Day, A., Alkhalil, A., Carney, B. C., Hoffman, H. N., Moffatt, L. T., & Shupp, J. W. (2017). Disruption of Biofilms and Neutralization of Bacteria Using Hypochlorous Acid Solution: An *In Vivo* and *In Vitro* Evaluation. Advances in skin & wound care, 30(12), 543-551. doi:10.1097/01.ASW.0000526607.80113.66

Objective: The aims of this study were to assess the effectiveness of a hypochlorous acid-based wound cleanser in disrupting methicillin-resistant *Staphylococcus aureus* and *Pseudomonas aeruginosa* biofilms relative to other cleansers using an *in vitro* collagen biofilm model and to evaluate cleansers' cytotoxicity.

Design: Plates coated with collagen films incubated with active bacteria cultures to yield biofilm mimics were treated with VWS, 1% and 10% povidone-iodine (PI), 0.05% chlorhexidine wound solution (CWS), or normal saline for 3 or 10 minutes. Biofilms were then analyzed for biomass density using a crystal violet assay, quantitative cultures, and fluorescent microscopy. Cytotoxicity was measured using neutral red uptake by primary human dermal fibroblasts. Pre- and post-cleansing exudates and swab samples obtained from venous stasis wounds of patients were processed and plated on a series of selective agar plates for bacteria typing and quantification.

Results: All agents tested significantly neutralized methicillin-resistant *S. aureus* and *P. aeruginosa* biofilms compared with saline control as assessed by crystal violet assay and fluorescent microscopy assays. Undiluted HOCl was significantly less cytotoxic compared with 1% PI, CWS, and 10% PI (in increasing order of cytotoxicity). There was no significant difference in bacterial reduction in wounds after treatment with HOCl for any type of bacteria examined using selective media. In wounds that were treated with HOCl, there was a similar percentage reduction in bacterial colony-forming units from pre-cleansing levels when plated on tryptic soy agar, MacConkey, streptococcal, and mannitol salt agar plates.

Conclusion: These findings support the use of HOCl in the treatment of wounds with biofilms and to reduce the bioburden of venous stasis ulcers. While HOCl-treated biofilms had higher biomass than saline-treated biofilms, most of the cellular component was not viable. Ultimately, HOCl had a similar effectiveness to CWS in eliminating bacteria but with lower cytotoxicity. *(44)*

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Paper: Khan S M et al. Evaluation of pre-operative peritoneal lavage by super-oxidized solution [HOCl] in peritonitis. Mid East J Int Med. 2009: 2(3); 15-35.

Objective: To assess the role of intraperitoneal lavage with super-oxidized solution in patient peritonitis.

Design: Eighty patients with peritonitis were randomly assigned to either 1hour gastric lavage with saline or super-oxidized solution following surgery.

Results: Purulent discharge occurred in 20% of patients receiving super-oxidized solution lavage versus 52.5% of patients receiving saline lavage (p<0.01). The incidence of burst abdomen among the super-oxidized solution lavage patients was significantly less than those receiving saline lavage (27.5% versus 47.5%, p<0.05). *(45)*

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Paper: Mohd A R R. Dermacyn® [a neutral pH superoxidized solution, HOCl] Irrigation in Reducing Infection of a Median Sternotomy Wound. Heart Surg Forum. 2010: 13(4); 228-232.

Objective: To compare effectiveness of a neutral pH superoxidized solution (HOCl) irrigation and povidone-iodine with respect to reducing the incidence of sternotomy wound infection following CABG.

Design: A prospective randomized trial of 178 post-CABG patients who were treated with either HOCl or povidone-iodine wound irrigation.

Results: The incidence of sternotomy wound infection was five (5.7%) of these cases were from the HOCl group, and 14 (15.6%) were from the povidone-iodine group (P = 0.033). No HOCl-related complication was identified. *(33)*

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Paper: Garg P K et al. Evaluation of intraoperative peritoneal lavage with super-oxidized solution and normal saline in acute peritonitis. Arch Int Surg. 2013: 3(1); 43-48.

Objective: To evaluate the role of intraperitoneal lavage with normal saline and normal saline followed by NEW in patients with acute peritonitis.

Design: One hundred patients were randomly allotted by slip method into two groups of 50 each. In the control group, after the definitive surgery for the pathology of peritonitis, the peritoneal cavity was lavaged with normal saline and closed after putting in drains. In the study group, after the definitive surgery the peritoneal cavity was lavaged with saline followed by 100 ml of super-oxidized solution and drains were closed for 1 h after abdominal closure. The patients were followed-up for morbidity and mortality.

Results: Surgical site infection occurred in 14% of super-oxidized solution lavage patients vs. 40% of saline lavage patients (p=0.0034). Eight (16%) patients in the control group died (saline lavage) compared to 2 (4%) patients in the study group (super-oxidized solution lavage). *(34)*

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6c. EML Section 13.0 Wound Care

Paper: Mekkawy M M and Kamal A. A Randomized Clinical Trial: The Efficacy of Hypochlorous Acid on Septic Traumatic Wound. J Ed Prac. 2014: 5(16); 89-100.

Objective: To evaluate the efficacy of hypochlorous acid as a wound care agent in a septic traumatic wound.

Design: A randomized clinical trial of sixty patients with septic trauma wounds at a single centre to treatment with either daily hypochlorous acid washes or daily povidone-iodine (P-I) washes.

Results: Wound pain (no pain at day 14, 100% hypochlorous acid versus 16.6% P-I, p=0.004), odour (no odour at day 14, 100% hypochlorous acid versus 13.3% P-I, p=0.001), no discharge (serous at day 14, 100% hypochlorous acid versus 10% P-I, p=0.004) and bacterial count (reduction in day 14 quantitative count, p=0.0001) were dramatically reduced by using hypochlorous acid compared to povidone-iodine. At day 14, 90% of the hypochlorous acid treated group had wounds ready for surgical reconstruction compared with 0% for the P-I group.

Hypochlorous acid was an effective, easy to perform, comfortable, inexpensive and safe in treatment for infected acute traumatic wounds and allows for earlier surgical closure and hospital discharge. Hypochlorous acid controls the tissue bacterial bioburden without inhibiting the wound healing process rapidly relieving pain with the area becoming well-prepared for skin flap or graft. *(56)*

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Paper: Prabhakar K B S et al., Comparison of Super-oxidized Solution [HOCl] versus Povidone Iodine in Management of Infected Diabetic Ulcers: Our Experience. Int Arch Integ Med. 2016: 3(5); 151-158.

Objective: To compare the efficacy of dressings with super-oxidized solution [HOCl] versus povidone iodine in the management of infected diabetic ulcers.

Design: This one-year randomized controlled trial was conducted on a total of 60 patients presenting with infected diabetic ulcers. Patients were divided into two groups of 30 each based on computer generated randomization that is, Group A (super-oxidized solution dressing) and Group B (topical povidone-iodine dressing). Wound was observed for decrease in size of the ulcer, granulation, tissue quality and discharge from the wound at the end of each week for two weeks.

Results: The mean percentage reduction in ulcer area among patients with group A (super-oxidized [HOCl] solution) was significantly better (58.90 ± 5.21 percent vs. 40.90 ± 8.76 percent; p=0.024). *(35)*

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Paper: Landsman A et al. An open-label, three-arm pilot study of the safety and efficacy of topical Microcyn Rx [HOCl] wound care versus oral levofloxacin versus combined therapy for mild diabetic foot infections. J Am Podiatr Med Assoc. 2011: 101(6); 484-496

Background: This randomized, prospective, multicenter, open-label study was designed to test whether a topical, electrolyzed, superoxidized solution (Microcyn Rx, HOCl) is a safe and effective treatment for mildly infected diabetic foot ulcers.

Methods: Sixty-seven patients with ulcers were randomized into three groups. Patients with wounds irrigated with HOCl alone were compared with patients treated with oral levofloxacin plus normal saline wound irrigation and with patients treated with oral levofloxacin plus [HOCl] wound irrigation. Patients were evaluated on day 3, at the end of treatment on day 10 (visit 3), and 14 days after completion of therapy for test of cure (visit 4).

Results: In the intention-to-treat sample at visit 3, the clinical success rate was higher in the [HOCl] alone group (75.0%) than in the saline plus levofloxacin group (57.1%) or in the [HOCl] plus levofloxacin group (64.0%). Results at visit 4 were similar. In the clinically evaluable population, the clinical success rate at visit 3 (end of treatment) for patients treated with [HOCl] alone was 77.8% versus 61.1% for the levofloxacin group. The clinical success rate at visit 4 (test of cure) for patients treated with [HOCl] alone was 93.3% versus 56.3% for levofloxacin plus saline-treated patients. This study was not statistically powered, but the high clinical success rate (93.3%) and the P value (P = .033) suggest that the difference is meaningfully positive for [HOCl]-treated patients. [HOCl] is safe and at least as effective as oral levofloxacin for mild diabetic foot infections. *(36)*

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Paper: Pandey P K et al. Outcomes of superoxide solution dressings in surgical wounds: a randomized case control trial. Int J Biol Med Res. 2011: 2(4); 965-968.

Objective: To evaluate the role of superoxide solution in wound healing. At the same time an effort was made to compare the efficacy and outcomes of superoxide solution dressings and those with povidone iodine solution.

Design: Randomized controlled trial of one hundred patients with a variety of wounds treatment with either superoxide solution-saturated dressings (Group A) or povidone-iodine saturated dressings (Group B).

Results: The incidence of infection in primarily sterile cases was 15% in group A and 36% in group B, respectively. The most common infecting organism isolated in the study was Pseudomonas aeruginosa followed by *Staphylococcus* aureus and *Klebsiella* spp. Decrease in surface area of wounds at the end of 1, 2, 3, and 4 weeks, which was statistically significant, was more in the superoxide solution group compared to the povidone-iodine group (p=0.005, 0.002, <0.001, and 0.001, respectively). This study revealed less induration in wound margins when superoxide solution was used. This finding appears to be consistent with the fact that this solution does not damage cellular elements or restrict microcirculation of wound. Thus, the solution ensures the wellbeing of surrounding healthy tissues.

In addition, this study also revealed the early reduction in discharge from wounds dressed with superoxide solution as compared to povidone-iodine solution. Granulation tissue formation was earlier in the superoxide solution group as compared to the povidone-iodine group and also covered a greater wound surface area as compared to povidone-iodine. *(37)*

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Paper: Piaggessi A et al. A randomized controlled trial to examine the efficacy and safety of a new super-oxidized solution for the management of wide postsurgical lesions of the diabetic foot. Int J Low Extrem Wounds. 2010:9(1); 10-15.

Objective: A study of the safety and efficacy of super-oxidized solution compared with standard treatment in the management of wide post drainage lesions of the infected diabetic foot ulcers.

Design: Non-randomized cohort study involving forty patients with >5 cm postsurgical wounds secondary to infected DFU treated with either super-oxidized solution or povidone-iodine as adjuncts to systemic antibiotics and debridement as needed. Patients were followed for 6 months.

Results: Healing as measured by complete re-epithelization at 6 months occurred in 90% of the super-oxidized solution-treated group compared with 55% of the povidone-iodine-treated the group ($p<0.01$). The super-oxidized solution-treated group also experienced significantly shorter period of antibiotic treatment (10.1 weeks vs. 15.8 ($p = 0.016$) and interventions (4 vs. 11, $p=0.022$). The super-oxidized solution-treated group also had fewer episodes of reinfection ($p<0.01$). *(38)*

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Paper: Bongiovanni C M. Effects of hypochlorous acid solutions on venous leg ulcers (VLU): experience with 1249 VLUs in 897 patients. J Am Coll Clin Wound Spec. 2016: 10.1016/j.jccw.2016.01.001

Objective: To assess the impact of comorbidities and identify factors that accelerate the healing rate of venous leg ulcers.

Design: An extensive, retrospective analysis of our experience in a diverse population.

Results: Initial treatment of all venous leg ulcers involved cleaning and debriding foreign matter, debris, and necrotic material via application of copious hypochlorous acid solutions, and under pressure if necessary. Where needed, this was accompanied by abrasion using sterile gauze soaked with hypochlorous acid solutions. In all cases requiring sharp debridement, this was performed in an appropriate surgical facility and within 10 days of presentation.

Following initial treatment, all ulcers were dressed and/or loosely packed with sterile gauze soaked with hypochlorous acid solutions. An appropriately compressive, multi-layered, overlying bandage system, utilizing short-stretch or non-stretch materials was constructed such that the greatest compression was at the ankle level. Light abrasion utilizing sterile cotton gauze soaked with hypochlorous acid solutions, followed immediately by flushing the wound with more of the solution effectively destroyed the extant biofilm in situ. With several repetitions over several days, it also prevented biofilm from re-establishing.

All 1249 venous leg ulcers reported in this data set were healed completely. The longest healing times were encountered by 10 patients for whom compression therapy was contraindicated: diabetic patients with severe arterial occlusive disease [ABI < 0.6]. Nonetheless, aggressive management with hypochlorous acid solutions resulted in complete wound closure within 180 days for this treatment refractory cohort. Perhaps the greatest advance in Venous Leg Ulcer (VLU) care is the addition of hypochlorous acid solutions to the treatment armamentarium. *(27)*

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Paper: Suri A P S. The effectiveness of stable pH-neutral super-oxidized solution [HOCl] for the treatment of diabetic foot wounds. Poster at the Diabetic Foot Global Conference, Los Angeles, 2008.

Objective: To evaluate the clinical efficacy and microbial load reduction of stable pH-neutral super-oxidized solution compared with saline in patients with diabetic foot wounds.

Design: A randomized trial of 100 patients with diabetic foot ulcers 2-15 cm in diameter treated with a once daily bath of either stable pH-neutral super-oxidized solution or saline for 16 weeks.

Results: The higher proportion of the stable pH-neutral super-oxidized solution treated group had a significant reduction in bioburden (76% vs 32%) and healed wounds (78% vs 40%). *(39)*

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Paper: Martinez-de Jesus F et al. Efficacy and safety of a neutral pH superoxidized solution in severe diabetic foot infections. Int Wound J. 2007;4(4):353-362

Objective: To assess the efficacy of neutral pH superoxidized solution for infection control, odour reduction and surrounding skin and tissue damage on infected diabetic foot ulcerations.

Design: A randomized, single-blind trial of forty-five patients with DFU treated with standard care with or without neutral pH superoxidized solution, which was applied as a foot soak followed by spray application. Standard care consisted of broad-spectrum IV antibiotics, surgical debridement, and glycaemic control.

Results: Odour reduction was achieved in all neutral pH superoxidized solution-treated patients compared to patients treated without neutral pH superoxidized solution (100% versus 25%; p<0.01) and surrounding cellulitis diminished in 17 patients (80.9% versus 43.7%; p<0.001). Nineteen patients in the neutral pH superoxidized solution group showed advancement to granulating tissue stage (90.4% versus 62.5%; p<0.05) with significantly less tissue toxicity (94% versus 31.2%; p<0.01). *(40)*

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Paper: Ricci E et al., Clinical results about an antimicrobial solution (Dermacyn® Wound Care) [HOCl] in the treatment of infected chronic wounds. Poster presented at: 17th Conference of the European Wound Management Association (EWMA); 2007 May 2-4; Glasgow, UK

Objective: To evaluate the clinical performance of the antiseptic solution Dermacyn [HOCl].

Design: Forty patients with infected wounds were randomly assigned twice daily dressings of either [HOCl] or povidone-iodine. All patients received standard antibiotic therapy.

Results: The [HOCl] group had fewer days on average with clinical signs of infection (7.9 vs 5.4), odour (19 vs 2) and hospitalized (12.3 vs 8.2). *(41)*

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Paper: Gold, M. H., Andriessen, A., Bhatia, A. C., Bitter, P., Chilukuri, S., Cohen, J. L., & Robb, C. W. (2020). Topical stabilized hypochlorous acid: The future gold standard for wound care and scar management in dermatologic and plastic surgery procedures. Journal of Cosmetic Dermatology, 19(2), 270-277. doi:10.1111/jocd.13280

Objective: This paper focuses on the use of topical stabilized HOCl in wound and scar management for pre-, peri-, and post-procedures—including its ability to reduce the occurrence of hypertrophic scars and keloids.

Design: A panel comprising clinicians with experience in cosmetic and surgical procedures met late 2018 to discuss literature search results and their own current clinical experience regarding topical stabilized HOCl. The panel of key opinion leaders in dermatology and plastic surgery defined key insights and consensus statements on the direction of use for the product.

Results: Topical stabilized HOCl provides an optimal wound healing environment and, when combined with silicone, may be ideal for reducing scarring. Additionally, in contrast to chlorhexidine, HOCl, used as an antiseptic skin preparation, raises no concerns of ocular- or ototoxicity.

Conclusion: For wound care and scar management, topical stabilized HOCl conveys powerful microbicidal and antibiofilm properties, in addition to potency as a topical wound healing agent. It may offer physicians an alternative to other less desirable wound care measures. *(24)*

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Paper: Sakarya, S., Gunay, N., Karakulak, M., Ozturk, B., & Ertugrul, B. (2014). Hypochlorous Acid: an ideal wound care agent with powerful microbicidal, antibiofilm, and wound healing potency. Wounds, 26(12), 342-350

Objective: The aim of this study was to investigate the effect of stabilized hypochlorous acid solution (HOCl) on killing rate, biofilm formation, antimicrobial activity within biofilm against frequently isolated microorganisms and migration rate of wounded fibroblasts and keratinocytes.

Design: Minimal bactericidal concentration of stabilized HOCl solution for all standard microorganisms was 1/64 dilution and for clinical isolates it ranged from 1/32 to 1/64 dilutions.

Results: All microorganisms were killed within the first minute and accurate killing time was 12 seconds. The effective dose for biofilm impairment for standard microorganisms and clinical isolates ranged from 1/32 to 1/16. Microbicidal effects within the biofilm and antibiofilm concentration was the same for each microorganism.

Conclusion: The stabilized HOCl solution had dose-dependent favorable effects on fibroblast and keratinocyte migration compared to povidone iodine and media alone. These features lead to a stabilized HOCl solution as an ideal wound care agent. *(19)*

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Paper: Hadi S F et al. Treating infected diabetic wounds with superoxidized water as antiseptic agent: a preliminary experience. JCPSP. 2007: 17(12); 740-743

Objective: To evaluate the effectiveness of superoxidized water in diabetic patients with different wounds.

Design: One hundred patients with diabetic foot ulcer (DFU) wounds randomized to treatment with either daily superoxidized water [HOCl] or saline soaked gauzes. All patients received IV antibiotic therapy and surgical debridement as necessary.

Results: Patients treated with superoxidized water [HOCl] had a significantly shorter period of hospitalization than saline-treated patients (1-7 days hospitalization of 68% vs. 20%, $p<0.05$) and a higher proportion experienced a down-grading of their DFU (IV to I, 62% versus 15%, $p<0.05$). *(42)*

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Paper: Dalla Paola L, Carone A, Ricci S, Russo A. Advances in treatment of diabetic foot ulcers. Avances en diabetología. 2010;26(5):296-305.

Objective: To evaluate the efficacy of a novel HOCl product compared with standard treatment (10% povidone-iodine) in the treatment of diabetic foot ulcers.

Design: An open-label, non-randomized trial involving two hundred and twenty consecutive patients with stage II/III infected diabetic foot ulcers (DFU) treated with either Dermacyn dressings or povidone-iodine dressings for 10 days plus oral or parenteral antibiotics as necessary. The mean follow-up time was 94.8 days.

Results: At the time of surgical closure, 75% of the Dermacyn [HOCl] group and 48% of the povidone-iodine group were microbiologically negative ($p<0.005$). *(46)*

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Paper: Kapur V and Mawaha A K. Evaluation of effect and comparison of superoxidized solution (Oxum) vs. povidone-iodine (Betadine). Ind J Surg. 2011: 73(1); 48-53.

Objective: To evaluate the effect of superoxidized solution vs povidone iodine (Betadine) on similar types of wounds.

Design: 200 patients having wounds (acute and chronic ulcers, diabetic foot ulcers, venous stasis ulcers, cellulitis, carbuncles, abscesses of different types, burns, traumatic wounds, post-surgical wounds, pressure sores, bed sores, anal fistulae, gangrenous wounds, and internal irrigation like peritoneal lavage in peritonitis) prospectively randomized to treatment with either NEW-saturated gauzes or povidone iodine-saturated gauzes. All patients received antibiotics.

Results: The mean follow-up of 21 days showed that the average reduction in Diabetic Foot Ulcer (DFU) wound size in the superoxidized solution-treated group was 70% compared to 50% in the povidone iodine-treated group. Pus discharge in patients with abscesses was reduced earlier in the superoxidized solution-treated group (100% vs. 90% at day 12 for superoxidized solution vs. povidone-iodine) and there was an earlier appearance of granulation and epithelization (100% versus 85% at day 18 for superoxidized solution versus povidone- iodine). Superoxidized solution was safe and efficient as a wound care product and superior to povidone-iodine. *(43)*

7. Treatment details

Hypochlorous acid solutions are routinely applied for environmental disinfection (EML 15.1) through use of conventional hand-held spray devices. Rigorous evaluations published in recent years have proven the usefulness of large-scale misting equipment and electrostatic sprayer devices for HOCl dispersion into enclosed spaces in institutions and healthcare facilities. *(5, 25, 72-74)*

For the purposes of antisepsis (EML 15.2) and wound decontamination (EML 13.0) HOCl solutions are applied topically. Whether initial debridement through primary wound irrigation as used in Canada and Ukraine, or soaking of primary dressings in HOCl, and then applying the saturated dressings to burns, superficial wounds, or packed into wound cavities – a technique used in many countries from Sudan to Japan to Myanmar. That quick, simple, and low-skill application is proving an effective measure in cleansing and removal of:

- explosion detritus,
- necrotic tissue in a decubitus or diabetic vascular ulcer,
- infectious biofilm on amputation stumps, or
- deep burns that would normally be subject to more aggressive physical debridement, further tissue damage, and further pain.

HOCl application and wound packing are often repeated one or more times a day in the early stages of wound management and are adjunctive to other procedures routinely aimed at soil, pathogen, and adherent biofilm removal.

Importantly, there are no reports of adverse reactions to topical applications by these methods based on the European Bioinformatics Institute of EMBL, the US CDC Toxic Substances and Disease Registry, nor at either the Development and Reproductive Toxicology Database, or the US EPA's Toxicology Database. This exemplary record supports use of HOCl as a safe and effective component of wound care for a wide range of dermal and oral lesions, including chronic non-healing wounds and radiation mucositis.

As is well-reported, other conventional antiseptics (povidone-iodine, Dakin's Solution, Normal Saline, chlorhexidine, alcohol, and others) are less effective than HOCl, are toxic to human tissue, generate resistant organisms, create a chemical disposal hazard, and cause pain for the patient. Dakin's Solution, for example, is dilute hypochlorite that damages recovering cells, especially human fibroblasts. A lead article by Kozol in April of 1988's *Archives of Surgery* recommended Dakin's never again be used for the care of open wounds after studies revealed its cytotoxicity. *(54)*

8. Review of evidence for benefits and harms

The safety of hypochlorous acid for human use has been evaluated thoroughly over the past century, with increasingly pure solutions proving to be increasingly safe for human contact. Hypochlorous acid is a natural compound produced by human neutrophils.*(75)* When pure, there are sound reasons to suppose HOCl might be safe for human use, and that physiological mechanisms would have evolved and likely be in place that maximize the benefits of its production and avoid any adverse consequences.*(76-78)* Rigorous studies have justified that supposition, though the terminology associated with the *in vitro* formation of hypochlorous acid for use in laboratory and clinical experiments over the past eight decades has been variable, as noted in Section 8f below on Product Chemistry.

Despite these shortcomings in the published literature, efficacy results for HOCl have been consistently convincing, and moreover the antimicrobial potency is only one part of the historical record. Equally compelling have been the outcomes of human safety evaluations and the absence of meaningful resistance of biological pathogens of any class. Some microbial organisms can respond to exposure to HOCl with a range of defensive tactics,*(79)* but the array of metabolic targets for HOCl interactions makes it difficult to conceive of any means whereby absolute insusceptibility, comparable to antibiotic resistance traits, could possibly arise since the physical chemistry of oxidation and reduction is unrelated to biological adaptation. For this reason, there are no published accounts of clinical resistance of pathogens over the 100 years or so of HOCl use.

As can be seen in Table 2 below, HOCl is not irritating. There are no clinical adverse events anywhere in the scientific literature from exposure to HOCl in its purest form (in the pH range of 4-5.5). Not surprisingly there are reports of incidents arising from exposure to crude formulations containing mixed-oxidants, including hypochlorite (bleach), generated from poorly controlled manufacturing processes. Similar problems may arise when modern HOCl formulations are deliberately pH-adjusted into the neutral or higher zone. Eye and skin inflammation and respiratory irritation are common with bleach, which can be present at levels of 30% or more in "HOCl" solutions promoted at a pH 7, or in swimming pools that are improperly managed, allowing pH to rise into the alkaline range.

Table 1: From Wang et. al.*(63)*

Table 5. *Safety studies with control vs stabilized HOCl in 4 different animal species*

Studies	Species	Site applied	NVC-101 (% w/v)	Results
Eye irritation	Rabbits	Eye, Q8 for 72 h	Saline 0.013 Betadine	No irritation No irritation Progressive irritation
Eye irritation	Rabbits	Eye, single instillation	Saline 0.01, 0.03, and 0.1	No irritation No irritation at any dose
Skin sensitization	Hartley-derived albino guinea pig	Skin	Saline 0.01, 0.03, and 0.1	No sensitization No irritation at any dose
28-Day toxicology	Rat	Full-thickness wound	Saline 0.01, 0.03, and 0.1	No systemic toxicity at any dose and histopathology consistent with wound healing
28-Day toxicology	Mini-pig	Full-thickness wound	Saline 0.01, 0.03, and 0.1	No systemic toxicity at any dose and histopathology consistent with wound healing

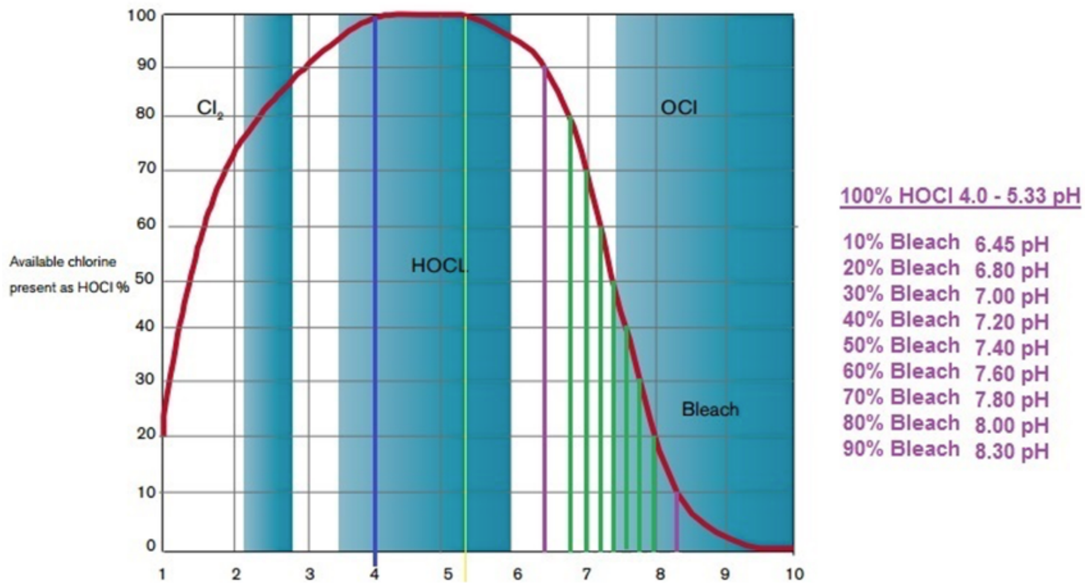

Figure 1: HOCl species concentration as a function of pH

The superior efficacy of HOCl over bleach and peroxide was highlighted above, and the significant toxicity inherent in the use of hypochlorite or peroxide when compared to HOCl is well known. The comparison is effectively summarized in the illustration of the respective therapeutic indices below in Table 3.

A Therapeutic Index, perhaps most familiar from cancer therapies, is a ratio between doing good and doing harm in the use of a biologically active substance. The data in Table 3 support the usefulness of HOCl in safely combatting infectious pathogens compared to hypochlorite or peroxide.

Table 2: Comparative safety vs. efficacy between hydrogen peroxide, bleach, and HOCl. Higher values are better.*(63)*

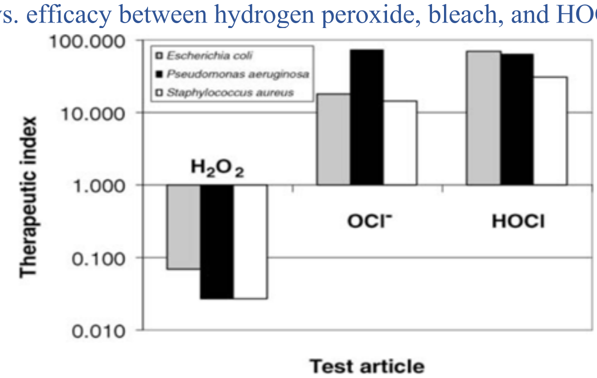

Figure 5. Relative therapeutic index of hypochlorous acid (HOCl; pH 4.0), hypochlorite (OCl^-; pH 10.5), and hydrogen peroxide (H_2O_2; pH 7.0). Therapeutic index is expressed as a ratio of the CT_{50} concentration (μg/mL) on L929 cells divided by the minimum bactericidal concentration (μg/mL) for *Staphylococcus aureus* 29213, *Pseudomonas aeruginosa* 27853 and *Escherichia coli* 2592. The higher the therapeutic index, the safer the test article will be.

8a. Clinical safety

A review by Thorn and colleagues in 2012 described both the exceptional antimicrobial efficacy of HOCl (particularly against *Cryptosporidium*) and its widely studied safety profile.*(21, 80)* They cite a large body of evidence available on safety, including single oral dose and 28-day repeated oral doses showing:

(1) no adverse effects in rats,

(2) studies showing no toxicity to mucous membranes, and

(3) accumulation-irritation tests and sensitization tests demonstrating biocompatibility at doses well above expected exposures.

In vitro mutagenicity studies, too, have shown no evidence of genotoxicity on either Ames or micronucleus tests. Another broad safety study showed HOCl did not degrade nucleic acids or induce oxidative damage in dermal fibroblasts. *(29)*

- A 2011 study by Morita, et. al. evaluated the risk of biological toxicity in a mouse model when HOCl was ingested as drinking water for eight weeks. Visual inspection, gastrointestinal histology, inflammatory markers, mucosal thickness, periodontal tissue, tooth enamel, and other metrics were evaluated. No changes from controls were seen. Their conclusion was that HOCl has no systemic effects and would be safe if used as a mouthwash, even if ingested. *(81)*

- In 2015 Kubota et.al. published a review of HOCl as a peritoneal lavage to prevent post-surgical infections after perforated appendicitis in children. The control lavage fluid was Normal Saline. There was no evidence of toxicity, and they found a statistically significant reduction in surgical site infections with HOCl. *(82)*

- A 2017 paper by Aras et. al. looked at the potential toxicity associated with infusions of HOCl into the intraperitoneal cavity of rats. Evaluations seven days after infusion showed no evidence of pathology, no evidence of toxicity, and no statistical difference in blood biochemistry, renal function, or liver function between HOCl-infused rats and two sets of Controls. *(83)*

- A 2019 review of the efficacy and safety profile of HOCl was published by Sipahi and colleagues. That review evaluated *in vitro* toxicology, cytotoxicity, skin irritation, and eye irritation, and found HOCl exposure caused no harm and was deemed safe for skin and eyes. The authors recommended expanded use in food decontamination and medical care. *(84)*

- Block and Rowan have published a 2020 review of hypochlorous acid with a focus on its use within dental offices. Their conclusion is that HOCl should be the dental disinfectant of choice. *(26)*

The most recent published account of the safety of HOCl included observations on controlled exposure of rats to aerosolized HOCl according to a US FDA-accepted protocol for evaluating potential respiratory tract toxicity. After breathing a dense fog of HOCl for four hours, subsequent observations over two weeks revealed no adverse effects on appearance or behavior of the rats and there were no detectable pathological changes at necropsy. *(85)*

Also included in that study were findings arising from the voluntary exposure of human volunteers who chose to inhale a dense fog of HOCl for two minutes a day as COVID-19 prophylaxis offered by the company that employed them. Volunteers described their experiences on a survey form. More than 450 voluntary exposures of two minutes or greater were documented, with a total inhalational exposure accumulation of more than 23 hours. Survey participant ages ranged from 18 to 77 and 84% were male. The results of the survey showed no remarkable adverse effects, with only 2.6% commenting on minor side effects such as "nose tingling", "runny nose", or "tickling feeling". None of these effects persisted beyond the short periods of inhalation exposure. *(85)*

8b. Environmental safety

HOCl is a highly reactive molecule, short-lived when exposed to pathogens or other bio-load under aqueous conditions.*(80)* Upon such exposure, the reactivity of pure HOCl leads rapidly to the formation of harmless chloride ions and water, becoming in effect a benign, dilute, and non-reactive saltwater solution. Halogenation of biomolecules in the very immediate environment occurs, along with oxidative changes in structures that contain susceptible moieties.*(76, 86)* At the concentrations employed in disinfectant formulations or topical preparations these alterations are trivial from an environmental safety viewpoint and are comparable to events that take place constantly in humans and almost all mammals, many lower vertebrates, many fish, some invertebrates, and even in some plants.

Consequently, use of pure HOCl at a concentration from roughly 100ppm up to about 550ppm delivers optimal efficacy for wound management and environmental disinfection, while posing no risk of environmental toxicity. For all the reasons related here and above regarding the safety and stability of HOCl, its use:

- Does not require Personal Protective Equipment (PPE), and
- Allows for extended room-temperature, tropical temperature, or refrigerated storage for years with no degradation in performance and without the need for hazardous materials handling or toxic material disposal protocols

In contrast, use of impure mixed-oxidant HOCl-hypochlorite solutions, like hypochlorite (bleach), requires PPE, must comply with hazardous material storage protocols, and the products must be disposed of as both toxic materials risks and as environmental hazards. Those same hazardous material considerations arise in the use of other classes of antisepsis and disinfection agents. See Figure 4 below.

8c. Disinfection

The global coronavirus pandemic led to a far greater appreciation of environmental disinfection measures. Regular decontamination of surfaces and of room air have become imperatives to assure the public that appropriate infection control measures are being taken for their safety and security. Along with heightened awareness of infectious disease hazards, there is now a well-founded cautiousness about the kind of rampant exposure to biocidal chemicals that came about during the pandemic. Most disinfectant formulations relied upon in the past (including examples already listed in EML 15.1) were historically expected to have intermittent use patterns and limited human exposure. Those disinfectants, when globally used against SARS-CoV-2 far in excess of any dispensing pattern previously considered or tested, proved dangerous to humans, livestock, pets, and plants, and the reported deaths were completely avoidable – as were the resulting societal objections and social unrest. As Choi and others have described below, commonly used concentrations of chlorine bleach, quats, and peroxide are not only more toxic than HOCl, but they are also considerably less effective*(9)*:

Table 3: Comparison of kill times for HOCl, bleach, and hydrogen peroxide. HOCl is superior.*(63)*

Table 3. *Comparative time kill studies of HOCl, NaOCl, and H_2O_2 against 3 test organisms at room temperature for a total of 90 min*

		Time kill (min)		
Pathogen	**ATCC**	**HOCl**	**OCl^-**	**H_2O_2**
Escherichia coli	25922	0	<5	>90
Pseudomonas aeruginosa	27853	<1	<20	<15
Staphylococcus aureus	29213	0	<10	>90

ATCC indicates American Type Culture Collection.

Figure 2: Comparison of kill times for HOCl, bleach, and hydrogen peroxide

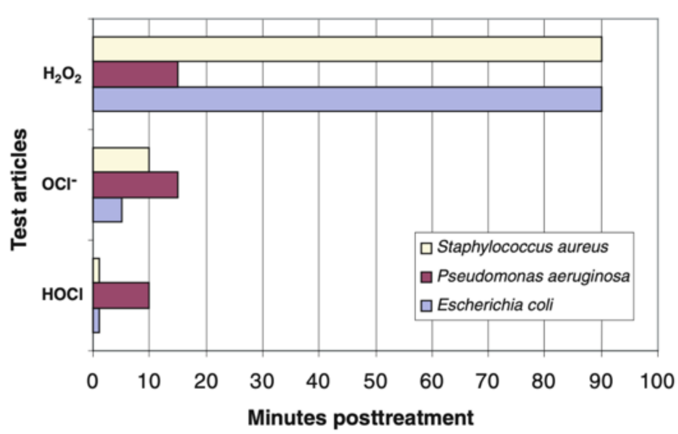

Figure 3. Comparative time kill studies of HOCl, NaOCl, and H_2O_2 against 3 test organisms—*Escherichia coli* 25922, *Pseudomonas aeruginosa* 27853, and *Staphylococcus aureus* 29213—at room temperature for total of 90 miniutes.

The options available for disinfection and antisepsis, particularly in the face of developing public health crises, have become narrowed by the previously unrecognized potential for harm in normal use:

1. By the toxicity in those exposed to conventional sanitizing formulations, especially occupationally,
2. By evidence of environmental degradation from commonplace products,
3. By their corrosiveness to equipment and surfaces,
4. By their encouragement of resistant traits,
5. By the persistence of toxic residues and the need for complex disposal procedures,
6. By heightened needs for personnel training and hazardous chemical protection,
7. By the compensation needed for those injured by dermal and respiratory exposure to conventional, approved, yet toxic disinfectants within the workplace that workers were ordered to use in ways never anticipated by their manufacturers.

None of those seven traits are found in HOCl, yet the killing power of HOCl against viruses, bacteria, and fungi is more strikingly thorough than the toxic disinfectants already on the EML. HOCl is more effective in killing a wider range of human and animal pathogens than conventional disinfectants yet HOCl is well-documented to have no toxicity to mammalian cells, and, within minutes after use, HOCl degrades to dilute salt water that can be mopped up when spilled and disposed of anywhere.

The emergence of antimicrobial resistance (AMR) to antibiotics on a truly dramatic scale is the subject of global conferences, United Nations research initiatives, and newspaper headlines. The loss of effective antibiotics is already severely limiting patient care options and causing excess mortality from unresponsive infections on every continent. AMR is made worse by the tendency for certain antiseptic formulations – like povidone-iodine – to promote genetic traits that confer resistance to antibiotics and other chemotherapeutics.*(8)*

In addition, several of the approved EML disinfectants and antiseptics are known to be extremely toxic at even very low levels of exposure. *(9, 12)*

For example, the US National Toxicology Program, NIOSH, and OSHA have all determined that the acceptable Occupational Exposure Level, or OEL, for quaternary ammonium compounds ("quats") and for bleach – both common in COVID-19 disinfection and conventional cleaning, was found to be zero.

Table 4: Comparison of toxicity across conventional disinfectants and antiseptics

Table 1. OELs for active ingredients of antimicrobial products under investigation by the National Toxicology Program (NTP 2019a).

Common name (chemical name)	CAS #	ACGIH (2019)	NIOSH (2020)	OSHA (2020)	OARS-WEEL (2020)
Alkyl dimethyl benzyl ammonium chloride (ADBAC QUAT)	68424-85-1	None	None	None	None
Bleach (sodium hypochlorite)	7681-52-9	None	None	None	None
Chlorinated isocyanurate (trichloro-s-triazinetrione)	87-90-1	None	None	None	None
Chlorine dioxide in solution (chlorine dioxide)	10049-04-4	TLV TWA (0.1 ppm) TLV STEL (0.3 ppm)	REL TWA (0.1 ppm)	PEL TWA (0.1 ppm) PEL STEL (0.3 ppm)	None
1-Decanaminium, *N*-decyl-*N*, *N*-dimethyl chloride (DDAC QUAT)	7173-51-5	None	None	None	None
Hydrogen peroxide (hydrogen peroxide)	7722-84-1	TLV TWA (1 ppm)	REL TWA (1 ppm)	PEL TWA (1 ppm)	None
OPP	90-43-7	None	None	None	None
PAA	79-21-0	TLV STEL (0.4 ppm)	None	None	None
PCMC	59-50-7	None	None	None	None
PHMB	32289-58-0	None	None	None	None

PHMB: poly(hexamethylene biguanide) hypochloride; PCMC: *p*-chloro-*m*-cresol; PAA: peracetic acid; OPP: ortho phenyl phenol; OEL: occupational exposure limit; ACGIH: American Conference of Governmental Industrial Hygienist; CAS #: chemical abstract number; NIOSH: National Institute for Occupational Safety and Health; OSHA: Occupational Safety and Health Administration; PEL: permissible exposure limit; REL: recommended exposure limit; STEL: short-term exposure limit (15 min); TLV: threshold limit value; TWA: time weighted average; OARS-WEEL: Occupational Alliance for Risk Science-Workplace Environmental Exposure Level.

Similarly, a conventional quat used in most countries of the world, **benzalkonium chloride**, was found to cause significant pulmonary damage at extremely low levels in a mammal exposure model. The safe level of exposure proved to be 0.000062 mg/m^3.*(9)* That level is incompatible with existing disinfection and antisepsis use patterns. The implication of these findings is that damage from quat exposure is routinely inflicted upon healthcare providers, patients, and the cleaning staff. Many post-COVID lawsuits for pulmonary damage to cleaning staff have been discussed in media, with some appearing in Workers Compensation hearings. *(10)*

Hypochlorous acid solutions, on the other hand, bring both safety and high-level potency to bear on this need. While proven safe to use by repeated evaluations across the mammalian spectrum, including humans, HOCl provides rapid inactivation across the spectrum of infectious pathogens (see Table 8 below).

Certain pathogens susceptible to pure HOCl, for example, are resistant to all other known disinfectants. *(14, 87, 88)* Unprecedented efficacy is matched by a safety profile that makes HOCl well suited to public health needs.

HOCl is now available in pure, homogeneous, and stable solutions that can be produced at industrial scale. The historical shortcomings of instability and cost have been overcome. Use of HOCl for the purposes identified in the EML 15.1 category will provide healthcare authorities with a superior tool for interventions aimed at environmental sanitation while avoiding the now well-established hazards of conventional chemical measures.

Table 5: HOCl comparison chart for safety and efficacy*(89)*

	HOCl	Alcohol	Bleach	Peroxide	Quaternary Ammonium	Chlorhexidine	Glutaraldehyde
Kills bacteria	✓	✓	✓	✓	✓	✓	✓
Inactivates viruses	✓	✓	✓	✓	✓	✗	✓
Kills spores	✓	✗	✓	✗	✓	✗	✓
Kills fungus	✓	✗	✓	✓	✓	✗	✓
Inactivates HPV	✓	✗	✓	✓	✗	✗	✗
Inactivates prions	✓	✗	✗	✗	✗	✗	✗
Remains stable for years	✓	✓	✗	✗	✓	✓	✓
Non-toxic	✓	✗	✗	✗	✗	✗	✗
Safe for skin	✓	✗	✗	✗	✗	✓	✗
Safe for eyes	✓	✗	✗	✗	✗	✗	✗
Safe for mucosa	✓	✗	✗	✗	✗	✗*	✗
Safe for inhalation	✓	✗	✗	✗	✗	✗	✗
Hypo-allergenic	✓	✗	✗	✗	✓	✗	✗
Safe for use (no PPE needed)	✓	✗	✗	✗	✗	✗	✗
Safe for food contact	✓	✗	✗	✗	✗	✗	✗
Rinse-free	✓	✓	✗	✗	✗	✗	✗
Environmentally friendly	✓	✗	✗	✓	✗	✗	✗
Biodegradable	✓	✓	✓	✓	✗	✗	✗
Not explosive	✓	✗	✗	✗	✓	✓	✓
Not flammable	✓	✗	✓	✗	✗	✓	✓
Does not stain or discolor	✓	✓	✗	✗	✓	✗	✓
No resistant organisms	✓	✗	✓	✓	✗	✓	✓
Odor control	✓	✗	✓	✓	✗	✗	✗
Biofilm slime disruption	✓	✗	✗	✓	✗	✗	✗

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The efficacy table below is assembled from independent laboratory reports that evaluated one such pure and stable HOCl product. The submissions are from US FDA-certified cGLP laboratories, academic laboratories, and national and reference laboratories in Canada, Australia, Peru, the United Arab Emirates, Europe, South America, and Asia. Similar kill rates and inactivation LRVs would be seen in any of the equivalent HOCl formulations and common manufacturing processes in India, Finland, South Korea, the US, Canada, Malaysia, and elsewhere.

Table 6: Independent laboratory evaluations of HOCl against a range of pathogenic organisms.*(89)*

Pathogen*	Elimination	Testing Date	Testing Laboratory
Acinetobacter baumannii	>99.999%	06-02-2016	NW Regional COE for Biodefense & Emerging Infectious Diseases Research at the University of Washington
Acinetobacter baumannii	>99.9999%	06-15-2016	Pacific Northwest Microbiology Services
Aspergillus brasiliensis	99.999%	07-07-2020	Laboratorio Baltic Control
Aspergillus niger	>99.9999%	08-03-2016	Pacific Northwest Microbiology Services
Aspergillus niger	>99.99%	11-20-2015	Pacific Northwest Microbiology Services
Aspergillus spp. (black mold spores)	>99.999%	02-01-2017	University of Costa Rica, Faculty of Microbiology
Bacillus cereus spores	99.999%	02-01-2017	University of Costa Rica, Faculty of Microbiology
Bacillus sp.	99%	05-11-2016	Scientific Clinical Labs, Dubai
Bacillus subtilis	>99.999%	11-20-2015	Pacific Northwest Microbiology Services
Bacillus subtilis	>99.9999%	08-03-2016	Pacific Northwest Microbiology Services
Candida albicans	>99.999%	11-20-2015	Pacific Northwest Microbiology Services
Candida albicans	>99.9999%	02-01-2017	University of Costa Rica, Faculty of Microbiology
Candida albicans	99.999%	07-07-2020	Laboratorio Baltic Control
Coronavirus (Human, OC43)	>99.999%	03-04-2016	School of Public Health, University of Washington
Ebolavirus	>99.99%	—	**See Below
Enterobacter cloacae	>99.9999%	06-15-2016	Pacific Northwest Microbiology Services
Enterococcus faecalis (VRE)	>99.9999%	11-20-2015	Pacific Northwest Microbiology Services
Enterococcus faecalis (VRE)	99.999%	07-07-2020	Laboratorio Baltic Control
Escherichia coli	>99%	03-02-2015	Cascade Analytical Inc.
Escherichia coli	>99.99999%	08-03-2016	Pacific Northwest Microbiology Services
Escherichia coli	99%	05-11-2016	Scientific Clinical Labs, Dubai
Escherichia coli	>99.9999%	2-15-2017	University of Costa Rica, Faculty of Microbiology
Escherichia coli	99.999%	07-07-2020	Laboratorio Baltic Control
Escherichia coli NDM-1	>99.99999%	06-15-2016	Pacific Northwest Microbiology Services
Escherichia coli 0157	>99.999%	11-20-2015	Pacific Northwest Microbiology Services
Feline calicivirus, (Human Norovirus)	>99.99%	04-06-2017	Microchem Laboratory
Human papillomavirus (HPV 16 & 18)	>99.999%	02-01-2016	Pennsylvania State University, Hershey Medical Center
Influenza H1N1 Swine	>99.99%	07-12-2017	Microchem Laboratory
Klebsiella pneumoniae	>99.99%	11-20-2015	Gibraltar Laboratories
Klebsiella pneumoniae	>99.99999%	11-20-2015	Pacific Northwest Microbiology Services
Klebsiella sp.	99%	05-11-2016	Scientific Clinical Labs, Dubai

Pathogen*	Elimination	Testing Date	Testing Laboratory
Listeria monocytogenes	>99%	03-02-2015	Cascade Analytical Inc.
Listeria monocytogenes	>99.9999%	02-25-2014	Gibraltar Laboratories
Methicillin-Resistant S. aureus (MRSA)	>99.999%	02-25-2014	Gibraltar Laboratories
Methicillin-Resistant S. aureus (MRSA)	>99.999%	06-02-2016	NW Regional COE for Biodefense & Emerging Infectious Diseases Research at the University of Washington
Mold (NOS)	>99%	04-15-2015	Cascade Analytical Inc.
Poliovirus	99.99%	06-02-2020	Cantacuzino Laborator Infectii Enterice Viral
Polymicrobial biofilm	99.96%	11-15-2016	Pacific Northwest Microbiology Services
Polymicrobial cafeteria table	99%	02-08-2016	P.A. Benjamin Manufacturing
Prions (vCJD, others)	>99.9999%	09-29-2016	Rocky Mountain Labs, The National Institutes of Health (NIH)
Proteus vulgaris	>99.99999%	06-15-2016	Pacific Northwest Microbiology Services
Pseudomonas aeruginosa	>99.999%	06-01-2017	Microchem Laboratory
Pseudomonas aeruginosa	>99.999%	11-20-2015	Pacific Northwest Microbiology Services
Pseudomonas aeruginosa	>99.9999%	2-15-2017	University of Costa Rica, Faculty of Microbiology
Pseudomonas aeruginosa	>99%	03-02-2015	Laboratorio Baltic Control
Salmonella (NOS)	99.999%	07-07-2020	Cascade Analytical Inc.
Salmonella choleraesuis	>99.99999%	11-20-2015	Pacific Northwest Microbiology Services
Salmonella enterica	>99.999%	11-20-2015	Gibraltar Laboratories
Salmonella enterica	99.999%	11-20-2015	Microchem Laboratories
Salmonella spp.	>99.9999%	2-15-2017	University of Costa Rica, Faculty of Microbiology
Salmonella typhi	>99.999%	01-29-2014	Gibraltar Laboratories
Severe Acute Respiratory Syndrome Coronavirus (SARS-CoV-2 / COVID-19)	99.96%	07-15-2020	Applied Biosafety Research Program, National Microbiology Laboratory, Public Health Agency of Canada
Severe Acute Respiratory Syndrome Coronavirus (SARS-CoV-2 / COVID-19)	99.98%	07-18-2020	Human Microbiology Institute
Shigella flexneri	>99.9999%	06-15-2016	Pacific Northwest Microbiology Services
Staphylococcus aureus	>99.999%	01-24-2014	Gibraltar Laboratories
Staphylococcus aureus	>99.9999%	06-01-2017	Microchem Laboratory
Staphylococcus aureus	>99.9999%	02-01-2017	University of Costa Rica, Faculty of Microbiology
Staphylococcus aureus	99%	05-11-2016	Laboratorio Baltic Control
Staphylococcus epidermidis	99.999%	07-07-2020	Scientific Clinical Labs, Dubai
Trichophyton interdigitale	99.999%	06-01-2017	Microchem Laboratory
Yersinia enterocolitica	99.999%	06-15-2016	Pacific Northwest Microbiology Services

8d. Antisepsis

Antimicrobial efficacy results for HOCl tested by the Cantacuzino Institute in Romania (Table 9) and the Functional Water Association of Japan (Tables 10 and 11) reinforce the scope and speed of microbial inactivation. They also emphasize the exceptionally high level of performance of HOCl against *Staphylococcus aureus* and *Pseudomonas aeruginosa*, both regularly implicated in both acute and chronic wound infections.

Table 7: Efficacy of HOCl manufactured by electrolysis. Independent evaluation by the Cantacuzino National Institute of Research and Development in Microbiology and Immunology - the EU's EUPEHM reference laboratory in Bucharest, Romania. Unpublished; Romanian Lab POC on request.

Summary	Tested	Briotech's		
European Union data	June 2020	Multi-Surface Sanitizer		
available on request				
Microbe	LRV	Percent Reduction	Exposure	Test Condition
Bacteria				
E. coli	5.13	99.9993%	30 seconds	Clean
Enterococcus	5.12	99.9992%	30 seconds	Clean
Pseudomonas	5.20	99.9994%	30 seconds	Clean
Staph aureus	5.25	99.9994%	30 seconds	Clean
Enterococcus	4.00	99.9900%	2 minutes	With bioload
Pseudomonas	4.15	99.9929%	2 minutes	With bioload
Staph aureus	4.23	99.9941%	2 minutes	With bioload
Fungus				
Aspergillus	2.94	99.8852%	2 minutes	Clean
Candida	4.23	99.9941%	30 seconds	Clean
Aspergillus	2.93	99.8825%	2 minutes	With bioload
Candida	4.23	99.9941%	2 minutes	With bioload
Virus				
Poliovirus	4.10	99.9921%	30 seconds	Clean

Table 8a: Efficacy of HOCl manufactured by electrolysis (independent evaluation in support of a Japanese regulatory application; original Japanese below with links)

microorganism virus		HOCl (40ppm)
Gram positive	Staphylococcus aureus	◎(10sec)
	MRSA	◎(10sec)
	Bacillus cereus	△(3～5min)
	Mycobacterium tuberculosis	△(2.5min)
	Others	△(1～2.5min)
Gram negative	Salmonella Enteritidis	◎(10sec)
	Vibrio parahaemolyticus	◎(10sec)
	Escherichia coli O157:H7	◎(10sec)
	Campylobacter jejuni	◎(10sec)
	緑膿菌 Pseudomonas aeruginosa	◎(10sec)
Virus	Norovirus	◎
	Influenzavirus	◎(10sec)
	Enterovirus	◎(10sec)
	Herpesvirus	◎(10sec)
Fungi	Candida albicans	◎(10sec)
	Aspergillus niger	△(5min)
	Penicillium cyclopium	△(5min)

◎＞○＞△＞▲＞×, where ◎= Complete kill

Table 8b: http://www.fwf.or.jp/kinousui.html

微生物･ウイルス		次亜塩素酸水（40ppm）
グラム陽性菌	黄色ブドウ球菌（*Staphylococcus aureus*）	◎（10秒）
	MRSA（メチシリン耐性ブドウ球菌）	◎（10秒）
	セレウス菌（*Bacillus cereus*）	△（3～5分）
	結核菌（*Mycobacterium tuberculosis*）	△（2.5分）
	その他の抗酸菌	△（1～2.5分）
グラム陰性菌	サルモネラ菌（*Salmonella* Enteritidis）	◎（10秒）
	腸炎ビブリオ菌（*Vibrio parahaemolyticus*）	◎（10秒）
	腸管出血性大腸菌（*Escherichia coli* O157:H7）	◎（10秒）
	カンピロバクター菌（*Campylobacter jejuni*）	◎（10秒）
	緑膿菌（*Pseudomonas aeruginosa*）	◎（10秒）
ウイルス	ノロウイルス（ネコカリシウイルス）	◎
	インフルエンザウイルス（2009年新型含む）	◎（10秒）
	エンテロウイルス	◎（10秒）
	ヘルペスウイルス	◎（10秒）
真菌	カンジダ（*Candida albicans*）	◎（10秒）
	黒カビ（アスペルギルス; *Aspergillus niger*）	△（5分）
	青カビ（ペニシリウム; *Penicillium cyclopium*）	△（5分）

殺菌効果または不活化効果：◎（即効）＞○＞△＞▲＞×（無効）

引用：　強電解水企業協議会編　「強酸性電解水使用マニュアル2002」
〃　「微酸性電解水使用マニュアル2002」
機能水研究振興財団発行　「次亜塩素酸水生成装置に関する指針 第2版–追補

Infected wounds and the rise of antibiotic-resistant organisms are responsible for significant increases in morbidity, mortality, and the costs of health care, especially in the aged.*(90)* HOCl is particularly suited to meet the pressing need for improved approaches to these growing problems worldwide. The urgency of this issue is emphasized by these recent public comments:

- November 23, 2020, Dr. Tedros Ghebreyesus commenting on a new international initiative to address the problem, said "Antimicrobial resistance is one of the greatest health challenges of our time, and we cannot leave it for our children to solve."*(91)*

- On the same occasion Dr. Monique Eloit, DG OIE, said "Antimicrobial resistance is a problem affecting animal and human health and the environment and we need to act today to protect the efficacy of antibiotics."*(92)*

Adoption of HOCl for the purposes of antisepsis (EML 15.2) can bring immediate and important benefits. Pure HOCl brings none of the cytotoxicity associated with hypochlorite bleach in earlier crude mixed-oxidant HOCl products.*(93, 94)* Nor does it cause the cytotoxic effects and discoloration associated with povidone-iodine antiseptic products.*(35, 95)*

Topical HOCl use also avoids entirely the selective pressures that can lead to resistance to silver and biguanide antiseptic formulations. It does not encourage antibiotic resistance traits in the way chlorhexidine has been shown to do.*(8)* Moreover, serious doubts have arisen recently about the basis for popular use of silver-based antiseptic products; Storm-Versloot et al published a Cochrane meta-analysis of topical antimicrobial agents that included silver sulfadiazine, and found that:

"There is insufficient evidence to establish whether silver-containing dressings or topical agents promote wound healing or prevent wound infection."(96)

8e. Wound care

In addition to the antiseptic contributions that HOCl can bring to wound management, there is abundant evidence that exogenous HOCl applied topically triggers a cascade of events leading to faster healing and faster restoration of normal tissue architecture with minimal scarring.*(24, 26, 27, 97)* These widely recognized effects on healing are now supported in compelling ways by the outcomes of randomized controlled human clinical trials, prospective clinical evaluations of HOCl in comparison to standards of care, and in laboratory animal models that have proven relevance to medical use patterns.*(98)* HOCl is, after all, a natural product of the human body, relied upon as the first line of chemical defense in response to injury and infection. Generated enzymatically on demand in phagocytes, endogenous HOCl brings about a rapid attack on infectious microorganisms of many types, including bacteria, yeasts, fungi, and viruses.*(21, 60, 72, 74, 80, 99-104)*

The end products of HOCl reactions with surrounding molecular substrates in tissues are responsible for the beneficial effects on physiological processes needed to enhance healing. These include:

- local coagulation to seal off the damaged tissues
- the proliferation and migration of new endothelial cells
- inhibition of harmful metalloproteases
- faster migration of dermal fibroblasts
- down-regulation of mast cell degranulation
- faster processing of microbial antigens in local lymph nodes
- Positive immunoregulatory alterations in IL-6

Plentiful biochemical evidence in support of these pathways appears in the peer-reviewed literature on wound healing and the pathophysiology of tissue repair. *(19, 23, 24, 27, 28, 44, 58, 97, 105-115)*

In contrast, certain currently used antiseptics, such as povidone iodine and chlorhexidine, have been shown to inhibit many of these healing processes, and are often applied to wounds in formulations that are seriously cytotoxic.*(35, 95)*

Beneficial enhancement of healing by exogenous HOCl has been described for both acute and chronic wound management. Documented HOCl treatment successes in the References below in Section 12 and in the photographic files of various HOCl manufacturers range from use on minor lacerations, fungal infections from compromised hygiene, road rash, and vascular ulcers, to serious traumatic injury like shrapnel, car crashes, urgent abdominal surgery, landmine amputations, gunshots, machete wounds, overpressure injuries from artillery, severe thermal and chemical burns, and surgical site infections. Examples are visible in the Case Studies found in Appendix 2.

As studied at the National Wound Center for the UK's NHS in Cardiff, Wales, topical HOCl significantly improves wound perfusion, measurable as $TcPO_2$ in tissues adjacent to ulcerous lesions, for example, and these improvements persist for up to 36 hours post treatment. Of the modified tissue constituents responsible for continued stimulation of wound healing after the short lived exogenous HOCl has all disappeared, N-chlorotaurine (NCT) is clearly the most important.*(76)* Its role has been thoroughly studied and reported in primary scientific journals.*(77, 78, 116)*

8f. Product chemistry

Modern manufacturing processes allow production of stable solutions with no detectable chlorine constituents other than HOCl. These differ markedly from former marketplace product offerings of 'mixed oxidants' that were nevertheless frequently described as HOCl. Those products often contained variable amounts of HOCl in the presence of other molecular species of chlorine in water and risked both alkaline cytotoxicity and the production of dangerous chlorine gas.

They also suffer from:

1) instability of the final product in storage
2) unreliable efficacy in all applications tried; and
3) significantly more toxicity to tissues and environmental surfaces; their higher pH leads to more hypochlorite, which make the solutions more damaging to healing tissues.

However, as previously stated, historically suboptimal preparations have still given rise to a substantial body of evidence in the biomedical literature that supports use of the much-safer modern HOCl in the ways here proposed.*(22, 53, 117)*

Pure solutions of HOCl for the purposes designated in this proposal for EML inclusion are optimally prepared to ensure stability over a narrow pH range (the green zone illustrated in the figure below). Within that zone the solution will show maximum potency, reliably displaying an efficacy approximately 100-fold higher than the equivalent amount of chlorine in the form of hypochlorite bleach (i.e., the red zone form). The degree of disinfecting power of such HOCl preparations is a function of the Oxidation-Reduction Potential (ORP) measured in millivolts (most effectively 1020 mV or higher). The capacity of that power is provided by the active chlorine content in ppm, with ranges in commercially available formulations described above.

It should also be apparent then, that any products designated as "neutral pH" contain a large fraction of toxic hypochlorite (see Figure 3 below) and will be far less valuable in the care of patients or the disinfecting of surfaces or spaces. They will inevitably, by the laws of chemistry, contain a much lower proportion of the optimally active HOCl needed for best performance. Post-production adjustments of final product pH to bring the solution to 'neutral' encourage the degradation of HOCl, which reaches its maximum concentration percentage at a pH of about 5. As reference, that optimal pH of 5 for HOCl is roughly the pH value of black coffee and of clean skin.

This EML application only considers HOCl solutions with pH values greater than 3.5 and less than 7.53, where the composition is predominantly HOCl

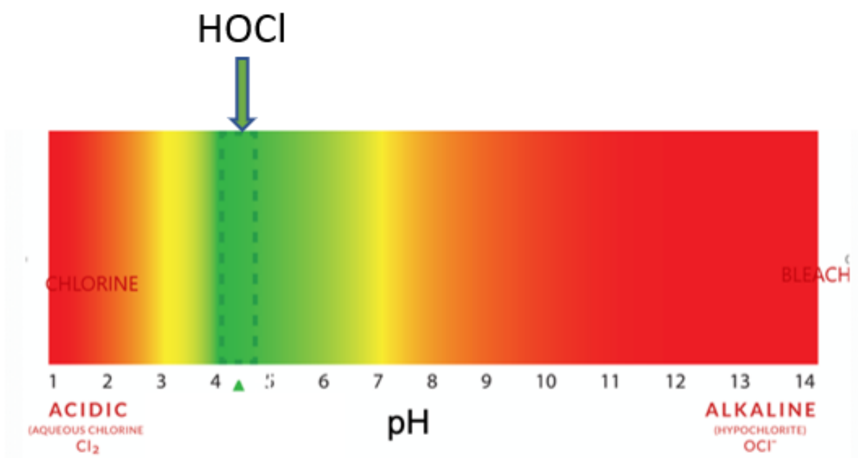

Figure 3: Chlorine species in water

Figure 3 above is a diagrammatic representation of the spectrum of chlorine species in water at various pH values. In the green zone HOCl predominates. In the region between the dashed lines, HOCl is the only molecular form of chlorine that can exist, ensuring homogeneity of products made to this pH specification.

Deterioration upon storage is also an inevitable consequence of impure mixed oxidant solutions. Pure HOCl products made at the proper pH with adequate process controls, however, will maintain their properties for months to years, depending on the storage container characteristics.*(17, 18)*

Raman spectroscopy is an analytical technology that can identify the unique energy resonance signature of every molecular species – a structural fingerprint, in a sense. In the figure below the singular peak for HOCl at wavenumber 732 is clearly evident over the background of water molecules.

HOCl in this form offers the most consistent and reliable utility for disinfection, antisepsis and wound care, and is routinely produced at the proper pH by multiple companies.

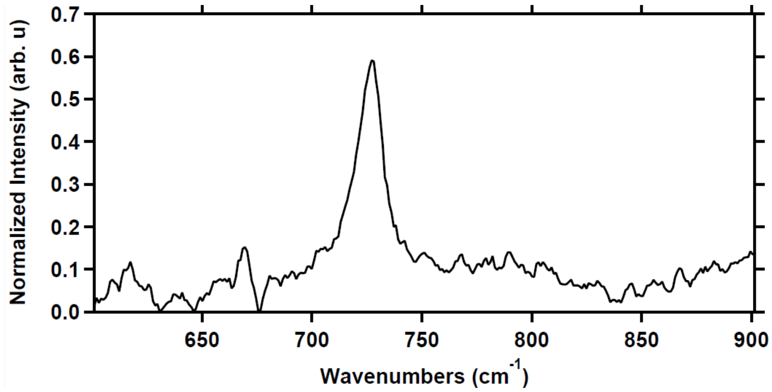

Figure 4: Raman spectrograph of pure HOCl detecting only hypochlorous acid at 732 and no other chlorine species [Courtesy Molecular Engineering Laboratory, School of Engineering, University of Washington, 2017]

9. Summary of recommendations in current clinical guidelines

Fazli et al published an RCT in 2024 that tested HOCl against chronic wounds. Clinical response was statistically more significant using HOCl-saturated dressings twice a day for 14 days using CONSORT guidelines. Wound area reduction was noted to be -2.99 square centimeters for daily dressings and -10.48 square centimeters on twice daily dressing applications, so they recommend twice a day dressing changes. *(60)*

Consensus Recommendations

Wound complications such as infection continue to inflict enormous financial and patient quality-of-life burdens. The traditional practice of using antiseptics and antibiotics to prevent and/or treat infections has been questioned with increasing concerns about the cytoxicity of antiseptics and proliferation of antibiotic-resistant bacteria. Solutions of sodium hypochlorite (NaOCl), commonly known as Dakin's solution, have been used in wound care for 100 years. In the last 15 years, more advanced hypochlorous acid (HOCl) solutions, most manufactured through electrochemistry, have emerged as safe and viable wound-cleansing agents and infection treatment adjunct therapies.

2015 Panel

After developing a literature-based summary of available evidence, a consensus panel of international wound care researchers and practitioners met in 2015 to review the evidence for:

1) the antimicrobial effectiveness of HOCl based on *in vitro* studies,
2) the safety of HOCl solutions, and
3) the effectiveness of HOCl in treating different types of infected wounds in various settings and to develop recommendations for its use and application to prevent wound infection and treat infected wounds in the context of accepted wound care algorithms. *(109)*

Findings: The antimicrobial activity of HOCl appears to be comparable to other antiseptics but without cytotoxicity and there is more clinical evidence about its safety and effectiveness.

Regarding the resolution of infection and improvement in wound healing by adjunct HOCl use, strong evidence was found for use in diabetic foot wounds; moderate evidence for use in septic surgical wounds; low evidence for venous leg ulcers, wounds of mixed etiology, or chronic wounds; and no evidence for burn wounds. The panel recommended HOCl should be used in addition to tissue management, infection, moisture imbalance, edge of the wound (the TIME algorithm) and aggressive debridement.

2024 Panel
In 2024 another international Expert Panel (France, Canada, and the US) reviewed the use of HOCl instillation for wound treatment in concert with negative pressure wound therapy. All 14 panel members (100%) considered HOCl safe when infused all the way to bone, and 100% also agreed that HOCl provides improved wound bed preparation than negative pressure used alone. 93% considered HOCl the primary option for instillation, and recommended early instillation. *(118)*

10. Summary of available data on comparative cost and effectiveness

HOCl was generated in crude unstable forms for use in management of trench warfare wounds during World War I by pH adjustment of cheap, readily available chlorine bleach solutions. For most of the 20th Century its availability for medical uses was limited by the uncontrollability of manufacturing methods and the short active life of the products made in this way. There was a resultant dependence upon on-site electrolytic generation, often at the bedside in the case of patient care, and prohibitive costs that precluded broad adoption for either disinfection or wound care.

Better manufacturing methods dating from the 1970s that could generate HOCl in a more pure form proved too expensive for widespread use, and there was no capability for large scale production. Past flaws have now been overcome through new production methods with process controls that enable fully scalable manufacturing systems. Some of those permit the generation of pure, stable HOCl in large volumes for a fraction of the cost of previous methods. **Current HOCl product pricing at scale can probably be achieved at less than one Euro per wholesale liter, with minor regional variations, based on water, salt and energy costs.** For historical comparison, a previous submission to the WHO EML for exclusive inclusion of a proprietary electrolytically generated HOCl formulation (Electrocyn, 2017) had specified the cost at more than US$11 (eleven dollars, about 10 Euros then) per liter wholesale, so **the bedside price of HOCl has dropped roughly 90% over the past seven years.**

11. Regulatory status, market availability, pharmacopeial standards

Australian Government, Department of Health, Therapeutic Goods Administration:

- HOCl approved for use against COVID-19:
    - http://search.tga.gov.au/s/search.html?collection=tga-artg&profile=record&meta_i=343431

The European Chemical Agency (ECHA) lists hypochlorous acid as a biocide product:

- Type 1 (human hygiene),
- Type 2 (surface disinfection),
- Type 3 (veterinary hygiene),
- Type 4 (food and feed area), and
- Type 5 (drinking water).

Health Canada:

- HOCl is approved as a COVID-19 disinfectant under DIN #024-957-16

US EPA:

- There are 17 approved HOCl products for COVID-19 disinfection in September 2024.
- HOCl is approved by the EPA for use in drinking water.
- HOCl is approved for use as a no-rinse food contact surface sanitizer.

US FDA:

- HOCl is cleared for use directly on meat, poultry, fish, and other seafood, fruits, and vegetables as a no-rinse sanitizer as a Food Contact Substance (FCS) under:
    - FCN 1811, 13 October 2017
    - 21 CFR 173.315
    - Decision #692
    - 21 CFR 178.1010
    - 21 CFR 7120.1
- HOCl may be applied to food-contact surfaces in public eating places, dairy processing equipment, food-processing equipment, and utensils.

US Department of Agriculture:

- HOCl is approved as an organic substance in the USDA's National Organic Program.

11a. Global and Local production

As a further advance over previous capabilities, the capacity to produce HOCl from small, localized manufacturing facilities is now routine. Adoption of this approach eliminates the cost of transporting an HOCl solution that is >99.5% water, and correspondingly heavy (at 1kg/liter).
As a result, the possibility has been created for even remote locations in Congo, Mali, Peru, Bangladesh, and Tuvalu to generate large quantities of pure and stable HOCl that meets the quality standards of a major production facility. These modular facilities are designed to produce between 5,000 and 40,000 liters a day and are not much larger than a UK refrigerator.

There are now multiple local manufacturing systems around the world creating a plentiful, affordable, high-quality HOCl supply, while generating local jobs that pay a living wage in the process. The result is the consistent availability of safe, stable, pure HOCl anywhere in the world.

11b. Charitable contributions

Arrangements have been made in recent years for at least three HOCl manufacturing companies to furnish donations of pure HOCl through a charitable arm. Additionally, a not-for-profit HOCl Foundation, engaging HOCl producers in multiple nations, has been established in the UK to further the use of HOCl throughout healthcare systems globally. The benefits of HOCl availability to healthcare services in developing countries are likely to be significant enough for governmental authorities to justify subsidized provision of HOCl to populations in need.

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12. References

The accumulated body of evidence, represented by the scope and rigor of the published literature citations included below, strongly supports the proposition that hypochlorous acid is safe for use on humans, and that significant environmental antimicrobial and wound management improvements would come about through the widespread use that would follow its inclusion into the WHO Essential Medicines List. We respectfully request hypochlorous acid (HOCl) be added to the World Health Organization's Essential Medicines List for 2025.

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Appendix 1: Letter of Support from MSF / Dr. Myriam Henkens

MEDECINS SANS FRONTIERES

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A.18 - Hypochlorous acid (HOCl)

MSF supports the application for the inclusion of aqueous hypochlorous acid (HOCl) in the WHO Model List of Essential Medicines, in section 15.1 (Antiseptics) and 15.2 (Disinfectants), and section 13 (Dermatological medicines).

Hypochlorous acid is a chlorine generating disinfectant. The active chlorine released by hypochlorous acid has a broad spectrum of bactericidal, virucidal, and fungicidal activity and is also a wound-cleansing agent, with antiseptic and healing properties, for the treatment of a variety of skin disorders.

Hypochlorous acid is a well-studied, non-toxic, non-corrosive, easy to use compound, and a more effective and a safer alternative to other chlorine generating disinfectant agents, such as sodium dichloroisocyanurate (NaDDC).

The European Chemical Agency (ECHA) lists hypochlorous acid as a biocide product type 1 (human hygiene), product type 2 (surface disinfection), product type 3 (veterinary hygiene), type 4 (food and feed area) and type 5 (drinking water).

Hypochlorous acid has been also approved by the US Food and Drug Administration (FDA) for disinfection of food-contact surfaces, for high level disinfection and sterilization of medical instruments, for topical applications, for use in drinking water and as a no-rinse food sanitizer.

In 2020, due to the need of specific guidance in the context of COVID-19 pandemic, hypochlorous acid has also been listed in the following documents:

- The WHO list of coronavirus-effective biocides (Cleaning and disinfection of environmental surfaces in the context of COVID-19, WHO, 2020).
- The United States Environmental Protection Agency (EPA) "N" list of Disinfectants for use against SARS-CoV-2.
- The Health Canada list of disinfectants with evidence for use against COVID-19.
- The Australian Register of Therapeutic Goods, as a hospital grade disinfectant effective against COVID-19.

MSF would like to draw the attention of the Expert Committee to the following facts:

- Hypochlorous acid is mainly registered in high regulated countries. Its inclusion in the WHO Model List of Essential Medicines will serve as a basis for National Essential Medicines lists and therefore will attract additional manufacturers, will facilitate importations, will alert manufacturers about the need for local registrations, will allow for competition between manufacturers in order to reduce price and improve accessibility, particularly in low-and middle-income countries, and will give a strong signal to manufacturers, generic producers, country programs, international donors, and health regulatory authorities.
- A stable, concentrated, long shelf-life ($\geq$ 3 years), easy and ready-to-dilute product, must be available for settings were shipping is needed, especially in low- and middle-income countries, in order to reduce logistical constraints and increase availability and affordability.

In light of these elements, MSF urges the 23rd Expert Committee on the Selection and Use of Essential Medicines to include hypochlorous acid in the WHO Model List of Essential Medicines.

For Médecins Sans Frontières

Myriam Henkens, MD, MPH
International Medical Coordinator

Appendix 2: HOCL Case Reports

Case 1- Topical HOCl was the only intervention.

65yo male
DM II
Presented to the ER
presumed septic shock
Blood cultures later grew
Klebsiella sp and
Pseudomonas sp.
Phlegmon in left inner thigh
unclear etiology
Initial excision 01 October 2020
This photograph 5 days after excision:
Iodophor gauze to wound edges.

Day 1 of Brio tid

65yo male
DM II
Presented in sepsis
Two weeks of topical BrioHOCl

Day 14 of Brio tid

65yo male
DM II
Left thigh phlegmon
Day 30 of BrioHOCl tid

Day 30 of Brio tid

Case 2- Topical HOCl was the only intervention.

Infected diabetic foot
Widespread necrosis
Topical BrioHOCl spray
First application 15 October 2020

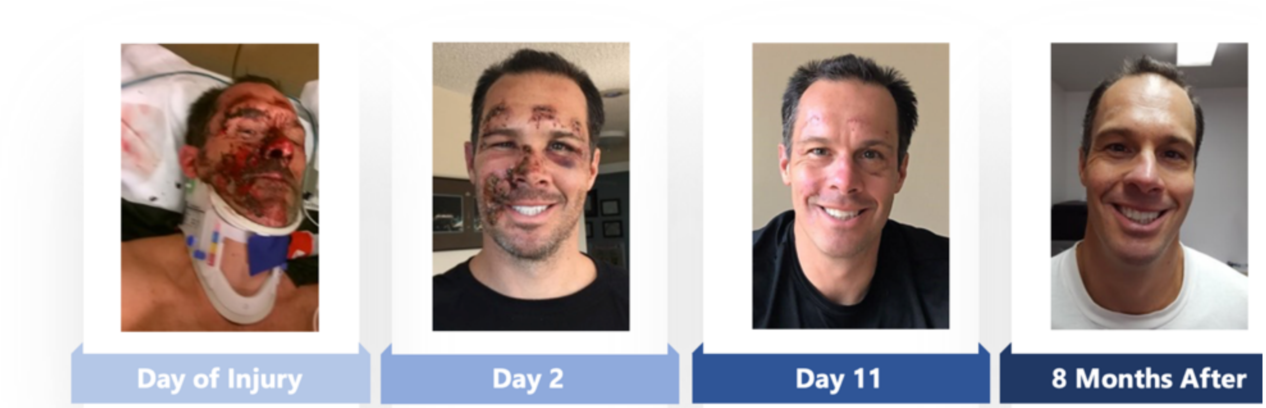
Day 1 of Brio tid

Infected diabetic foot
Widespread necrosis
Topical BrioHOCl spray

Day 27 of Brio tid

Case 3 - Topical HOCl was the only intervention after initial ER debridement.
(used with permission)

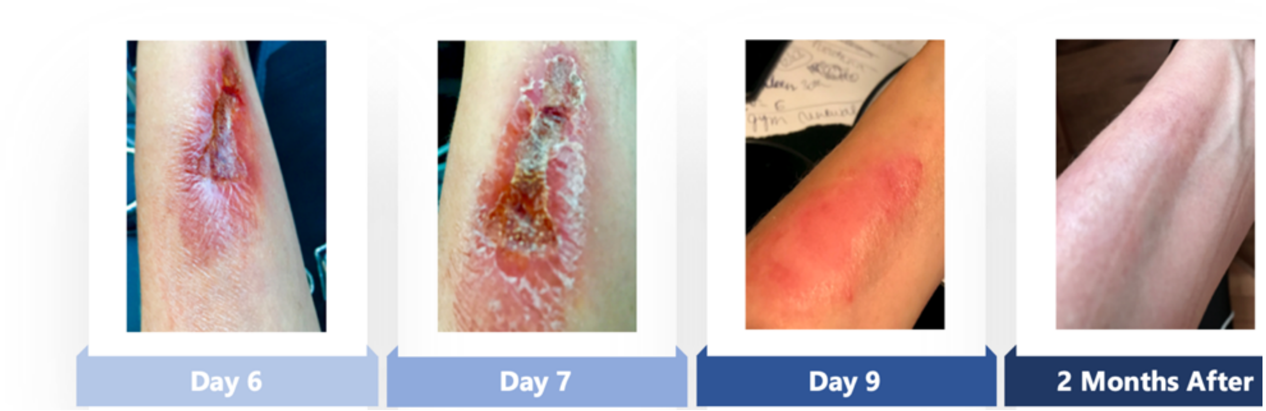
Traumatic Abrasion Wound Resolution
Age: 37 **Sex:** Male
Treatment: Sole use of BrioHOCl spray applied multiple times daily



Case 4 - Topical HOCl was the only intervention.
Deep Laceration Wound Resolution
Age: 52 **Sex:** Male
Treatment: BrioHOCl Topical Skin Spray and light dressing – 5 daily applications, no sutures

Case 5 - Topical HOCl was the only intervention.

Serious Full-Thickness Burn Resolution
Age: 50 **Sex:** Female
Treatment: BrioHOCl Topical Skin Spray using 4-5 daily applications



Case 6 - Topical HOCl was the only intervention.

(used with permission)

Chronic cystic acne since age 4

- at inception of Brio HOCl therapy - - one month later after TID application -

Case 7 - Topical HOCl was the only intervention.
(used with permission)

3yo boy fell into a cooking pot near the Ebola Clinic in Bukavu, DRC.

March 2019

3yo boy
Boiling water scald
Clinic presentation
NE of Kinshasa, DRC

BrioHOCl as sole therapy.

(Only care available – was not a study or a choice)

Used with permission.

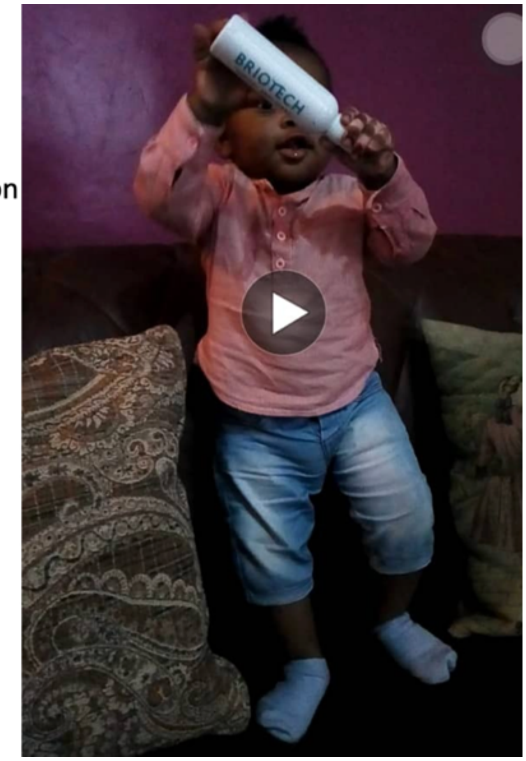
March 2019

3yo boy
Boiling water scald

96 hours after presentation.

BrioHOCl was only therapy.

Still from video
showing full function



Staff at the DRC Clinic in Bukavu, DRC expressing thanks for the HOCl burn care.

Case 8 - Topical HOCl was the only intervention.
(used with permission)

Early mycetoma ulcer infection in an 11yo girl in Sudan.
First image 04 March 2023.
Clinic Wad Medani, Sudan

Second image 18 March 2023
Clinic Wad Medani, Sudan