EXPERT RECOMMENDATIONS
FOR THE USE OF
HYPOCHLOROUS SOLUTION:
SCIENCE AND CLINICAL APPLICATION

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SCIENCE AND CLINICAL APPLICATION

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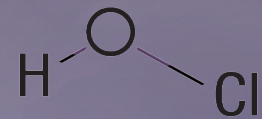
ABSTRACT

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 cytoxitity 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, based on electrochemistry, have emerged as safe and viable wound-cleansing agents and infection treatment adjunct therapies.

After developing a literature-based summary of available evidence, a consensus panel of wound care researchers and practitioners met 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 acid 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. Each participant gave a short presentation; this was followed by a moderated roundtable discussion with consensus-making regarding conclusions. Based on *in vitro* studies, the antimicrobial activity of HOCl appears to be comparable to other antiseptics but without cytotoxicity; there is more clinical evidence about its safety and effectiveness. With regard to 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. The panel also recommended intralesional use of HOCl or other methods that ensure the wound is covered with the solution for 15 minutes after debridement. More controlled clinical studies are needed to determine the safety and efficacy of HOCl in wound types with limited outcomes data and to evaluate outcomes of various application methods.

KEYWORDS: hypochlorous acid, review, anti–infective agents, wound, cleansing

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KEYPOINTS:

- Following a review of commonly used antiseptics and available preclinical and clinical evidence, a panel of wound care experts met to discuss the results and develop recommendations.

- The overall safety and effectiveness profile of electrochemistry-based hypochlorous acid solutions (HOCl) is promising, especially for the management of infected foot wounds in persons with diabetes mellitus.

- Controlled clinical studies to compare the safety and efficacy of HOCl to other treatment modalities and in other types of wounds are warranted.

Managing infection always has been part of wound care clinical practice guidelines[1] because infection episodes not only halt the wound-healing process, but also can lead to complications, including hospitalization, loss of tissue, and amputation of feet or legs.

Hypochlorous acid (HOCl) was introduced in World War I as a means of treating wound infection, but its use was eclipsed by the widespread introduction of antibiotics. However, in recent years as antibiotic resistance and questions about the cytotoxicity of antiseptics have impacted wound care practice, interest has increased regarding more advanced HOCl solutions introduced into the marketplace.

A literature review was conducted to ascertain 1) the technology behind advanced HOCl solutions, 2) their effectiveness as antimicrobial agents from both a biochemical and clinical point of view, and 3) clinical outcomes and associated evidence levels of studies that have used such solutions to treat or prevent wound infection.

A consensus panel comprising professionals in the fields of wound care and burns (wound care researchers and practitioners, podiatrists and surgeons) met on January 10, 2015 in Miami, FL to discuss the findings of their research and evaluate 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 acid 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. The meeting was sponsored by Innovacyn (Rialto, CA). Each panel member presented research on a preassigned topic, followed by a round-table discussion with consensus guided by a moderator. After all presentations had been made, further moderated discussion took place to achieve consensus in regard to all the aforementioned goals. In regard to clinical outcomes, the level of evidence supporting the efficacy or effectiveness of HOCl acid solutions was defined as follows: 1) strong: at least 1 well-conducted randomized controlled trial supported by poorly conducted randomized controlled trials and/or cohort studies; 2) moderate: 2 or more poorly conducted randomized controlled trials or well-conducted cohort studies; 3) low: only comparative non-cohort, cross-sectional, case control, case series or similar design studies.
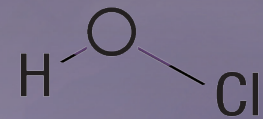
LITERATURE REVIEW

Methods. A literature search was undertaken to locate clinical studies that involved HOCl treatment of any type of wound. The search was conducted using PubMed, the Cochrane database, and Google of publications from 1950 to mid-January 2015, with a restriction to English but no restriction in regard to type of publication. Search terms included *chronic wound, acute wound, diabetic ulcer, venous leg ulcer, pressure ulcer, surgical wound, traumatic wound, mixed wound, burn,* or *sepsis* with each of the following terms: *hypochlorous, HOCl, hypochlorite, antiseptic, cleanser, cleansing,* and brand names of specific HOCl solutions. Abstracts were reviewed for relevancy and full text of articles was obtained; letters and other cited documents also were obtained if they comprised comments on relevant clinical studies. Studies were included in the review if they involved any type of wound or burn and any kind of HOCl solution or Dakin's solution was used as an adjunct treatment.

HYPOCHLOROUS ACID BACTERICIDAL ACTION.

The role of hypochlorous acid in the inflammatory response. The acute inflammatory response to injury or pathogens, typically lasting 1–2 days but as long as 2 weeks,[2] is characterized by an influx of immune cells that destroy and remove bacteria, cellular debris, and necrotic tissue.[3] Innate immune cells can sense pathogens both chemotactically and by direct physical contact, ultimately resulting in phagocytosis, although recent evidence suggests this is a combinatorial process by which neutrophils recognize the pathogen.[4] Once phagocytosis is accomplished (see **Figure 1**), the nicotinamide adenine dinucleotide phosphate oxidase complex located in the cell membrane is activated, generating superoxide (O_2^-), which can be converted to hydrogen peroxide (H_2O_2) via the action of superoxide dismutase. Using physiological concentrations of chloride and hydrogen peroxide, myeloperoxidase — a heme protein principally secreted by neutrophils but also by monocytes and some populations of macrophages — then produces hypochlorous acid (HOCl) in a reaction often termed the oxidative or respiratory burst of activated neutrophils[5,6]: $H_2O_2 + Cl^- + H^+ \rightarrow HOCl + H_2O$.

HOCl is a weak acid formed by the dissolution of chlorine in water. Its conjugate base (OCl^-) is the active ingredient in bleach and the chemical species responsible for the microbiocidal properties of chlorinated water.[5] However, in mammalian systems it is also responsible for destroying many pathogens. Because HOCl has a pKa of 7.5,[7] it is present physiologically as an equal mixture of hypochlorite (OCl^-) and the protonated or active form (HOCl). (The pKa is the equilibrium constant for a chemical reaction called *dissociation* in the context of acid-base reactions; the larger the Ka value, the more molecules dissociate in solution producing a stronger acid.) The chlorine atom in HOCl is in a formal oxidation state of +1 and may act as a 1-electron or 2-electron oxidizing agent

although reduction potentials favor the latter.[8] As an oxidant, HOCl is extremely powerful, capable of oxidizing thiol groups (SH) and thioethers (R–S–R', where R is an alkyl group, such as methionine), and halogenating amine groups to form monochloramines and dichloramines, which are oxidizing agents in their own right, thus extending the reactivity of HOCl.[9] Within the cell, it has been suggested HOCl covalently modifies key amino acid residues belonging to MMP-7, in essence activating it at relatively low concentrations.[6] However, higher HOCl-to-protein ratios eventually inactivate MMP-7, apparently via the oxidation of nonactive site residues,[10] which suggests a key role for the oxidant in controlling MMP-7 activity based on local concentrations and other factors.

The antipathogenic response of HOCl. With regard to HOCl's bactericidal activity, early work involving Escherichia coli cultures suggested HOCl exerts a rapid and selective inhibition on RNA synthesis as well as DNA synthesis, and that it may disrupt membrane/DNA interactions needed for replication, alter the DNA template itself, inactivate enzymes of the replication system, or even inhibit synthesis of critical proteins required for DNA replication and/or cell division.[11] More recent *in vitro* investigations have emphasized bactericidal actions based on inducing, unfolding, and aggregating microbial proteins[12] through high reaction rates with free cysteines and amino acid side chains.[13] Winter et al[13] also speculate these high reaction rates enable HOCl to oxidize residues that are buried or only transiently accessible for oxidative modifications, which is particularly relevant to microbial thermolabile proteins in that sufficiently rapid bimolecular oxidation reactions can compete with the refolding reaction of partially unfolded conformations, thus causing protein unfolding and aggregation.[13] A key cell culture study
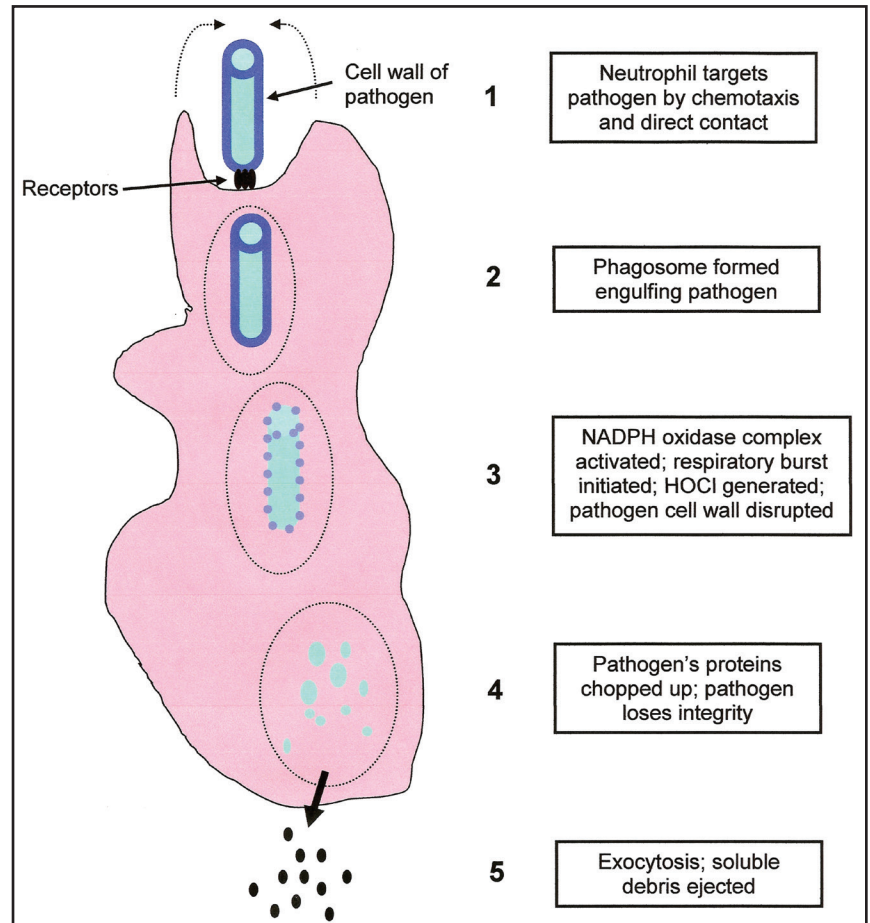

Figure 1. Phagocytosis of pathogen by neutrophil and subsequent digestion.

conducted by Rosen et al[14] using *E coli* confirmed HOCl targets methionine residues in proteins of phagocytosed bacteria for oxidation and that formation of oxidized methionine was strongly associated with bacterial killing. Moreover, based on additional results, the authors hypothesized that HOCl can impair the function of the essential secYEG translocon by 1) depletion of energy sources, 2) oxidation of vulnerable amino acids, or 3) cross-linking secYEG to peptide chains in process of translocation, thereby jamming the channel. (Protein transport via the Sec translocon represents an evolutionary conserved mechanism for delivering cytosolically-synthesized proteins to extra-cytosolic compartments; in bacteria, it is located in the cytoplasmic membrane.[15]) The efficiency of HOCl

in attacking bacterial microorganisms by destroying the functionality of their membrane-bound components is likely enhanced by its relatively small molecular size and lack of electrical charge, which would not cause it to be repelled against the negatively charged surface of bacterial cell membranes.

A powerful oxidant such as HOCl also can cause unwanted host protein damage, although this is mitigated by scavenger molecules, such as taurine and nitrites,[16] and hypochlorite-induced modifications of human α2-macroglobulin, which prevents the extracellular accumulation of misfolded and potentially pathogenic proteins, particularly during innate immune system activity.[12] Myeloperoxidase also produces hypothiocyanous acid, which has the potential to

modulate both the extent and nature of oxidative damage in vivo.[17]

In vitro studies demonstrate HOCl is effective against all human bacterial, viral, and fungal pathogens. For example, a freshly generated HOCl solution provided a >5 $\log_{10}$ reduction in *Mycobacterium tuberculosis* within 1 minute of exposure.[18] Exposure of other bacterial pathogens (in the absence of interfering organic material) generally exceeded a log10 reduction of 6 within a few minutes, with *E coli* 0157 clinical isolate taking the longest (see **Table 1**). Likewise, the minimum bactericidal concentration of HOCl solutions stabilized at different pH values for various microorganisms demonstrate that with the exception of Aspergillus niger, they are consistently in the range of 0.17–5.5 (see **Table 2**).[19,20]

Perhaps the most remarkable property of HOCl is its ability to destroy biofilms. Many wound care clinicians and burn specialists have come to realize the simple concept of wound colonization, critical colonization, and infection dependent on classification by number of colony forming units of bacterial species per weight or volume of tissue is naïve in practice.[21] Rather, as exemplified by one cross-sectional study, nearly two thirds of chronic acquire overgrowths charac-

terized as biofilms over time.[22] Biofilms differ from planktonic microbial colonies in terms of structure, gene expression, antibiotic resistance, and host interaction largely because 5% to 30% of the biofilm is composed of extracellular polymeric substances, such as glycoproteins.[23] Moreover, biofilms can contain anaerobes, which often are missed by classical culture techniques and grow by contiguous spreading or shedding of planktonic bacteria, seeding onto surrounding surfaces, and resulting in infection dissemination. Biofilms are also notorious for their persistence, being resistant to the host immune system, systemic antibiotics, and topical antimicrobials.[24] Although it was thought that inability to penetrate the extracellular material barriers was the reason for failure of antibiotics to clear biofilms, *in vitro* evidence is increasing to suggest antibiotics are able to slowly diffuse through the biofilm matrix.[24] Thus, mechanisms such as alteration of activity status (dormancy) and triggering of mutations and gene expression by environmental stress, bacterial density, nutrition supply, and oxidative stress may be responsible for antibiotic resistance.[23] Although aggressive debridement, enzymes targeting the polymeric matrix, lactoferrin administration, and ultrasound

and other physical disruption strategies all have been posited as methods to break up biofilms, evidence is lacking regarding their efficacy.[25]

Sakarya et al[19] noted a pH-stabilized HOCl solution was able to reduce the amount of biofilms grown *in vitro* and the quantity of microorganisms within the biofilms in a dose-dependent manner depending on the species involved; effective HOCl concentrations were between 5.5 and 11 µg/µL. Likewise, Sauer et al[26] demonstrated relatively low concentrations of neutral pH solutions of HOCL were able to reduce the viability of *Pseudomonas aeruginosa* biofilms grown in continuous flow tube reactors by about 3 logs within 30 minutes. Biofilm disaggregation was cited as one mechanism responsible for the killing efficiency of the bacteria. Even more impressive results were observed by Robson[27] in biofilm tube experiments with *Staphylococcus aureus* in which bacterial counts were reduced by >5 logs after a 1 minute exposure to HOCl and 6 logs after 10 minutes. About 70% of the biofilm polysaccharide and >90% of the biofilm protein also were removed after a 10-minute exposure. However, clinical studies characterizing the presence of biofilms in chronic wounds followed by their eradication with HOCl are lacking.

Evolution of HOCl and other antiseptics. In the modern era, several antiseptics came into use in connection with surgery and cleansing of wounds to help prevent infection. Chlorhexidine, invented in 1946, came into clinical practice in 1954 and is still used today in some hospitals as surgical scrub and in wound irrigation even though reviews of the evidence provide insufficient data for safety and efficacy assessment.[28,29] An ancient remedy for the treatment of wounds, honey received renewed attention with demonstrations of its antibacterial properties against many species

Table 1. In vitro data for bactericidal actions of hypochlorous acid[1]		
Organism	**Maximum mean $\log_{10}$ reduction**	**Time (minutes)**
Escherichia coli NCTC 9001	→ 6.7	0.5
E coli NCTC 12900	7.0	0.5
E coli 0157 clinical isolate	→ 6.8	4
MRSA[2] clinical isolate	→ 6.7	0.5
Candida albicans isolate	→ 5.2	0.5
Bacillus subtilis spores	7.5	0.5
Enterococcus faecalis	7.7	0.5
Pseudomonas aeruginosa	7.8	0.5
[1]Ratio of 10:1 freshly prepared hypochlorous acid: organism. Data from Selkon et al[18] [2]Methicillin-resistant *Staphylococcus aureus*.		
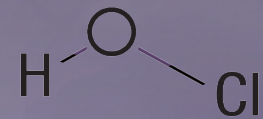
Table 2. In vitro minimum bactericidal concentration (MBC) for HOCl solutions.[1]				
Organism	ATCC[2]	HOCl pH	Temperature	MBC (µg/µL)
Aspergillus niger	16404	3.75	Room	86.6
Candida albicans	10231	3.75	Room	0.17
C albicans	90028	7.1	37°C	2.75
C albicans	CI 4	7.1	37°C	2.75
C albicans	CI 5	7.1	37°C	2.75
C albicans	CI 11	7.1	37°C	5.5
Corynebacterium amycolatum	49368	3.75	Room	0.17
E aerogenes	51697	3.75	Room	0.68
E coli	25922	3.75	Room	0.70
Haemophilus influenzae	49144	3.75	Room	0.34
Klebsiella pneumoniae	10031	3.75	Room	0.70
Micrococcus luteus	7468	3.75	Room	2.77
Proteus mirabilis	14153	3.75	Room	0.34
Pseudomonas aeruginosa	15692	7.1	37°C	2.75
P aeruginosa	27853	3.75	Room	0.35
P aeruginosa	CI 1	7.1	37°C	2.75
P aeruginosa	CI 47	7.1	37°C	2.75
P aeruginosa	CI 1112	7.1	37°C	2.75
Serratia marcescens	14756	3.75	Room	0.17
S aureus	29213	3.75	Room	0.17
S aureus	35556	7.1	37°C	2.75
S aureus	CI 3	7.1	37°C	2.75
S aureus	CI 12	7.1	37°C	5.5
S aureus	CI 23	7.1	37°C	2.75
S aureus	CI 64	7.1	37°C	2.75
S aureus	CI 263	7.1	37°C	5.5
S epidermidis	12228	3.75	Room	0.34
S haemolyticus	29970	3.75	Room	0.34
S hominis	27844	3.75	Room	1.4
S saprophyticus	35552	3.75	Room	0.35
S pyogenes	49399	3.75	Room	0.17
MRSA[3]	33591	3.75	Room	0.68
VREF[4]	51559	3.75	Room	2.73

[1]Stabilized at different pH values for various microorganisms and tested for 1 hour. Data taken from Sakarya et al[19] and Wang et al.[20]
[2]ATCC: American Type Culture Collection; [3]methicillin-resistant *S aureus*; [4]vancomycin-resistant *E faecium*.

including methicillin-resistant *S aureus* (MRSA) and vancomycin-resistant *Enterococci* (VRE).[29,30] Although many controlled trials have been conducted using honey, a recent Cochrane review[31] concluded while honey dressings might be superior to some conventional dressing materials, the reproducibility and applicability of the evidence remains uncertain. Honey significantly improved time to heal infected postoperative surgical wounds and Stage I and Stage II pressure injuries but showed no statistically significant difference in wound healing for venous leg ulcers or diabetic foot ulcers.[31] A meta-analysis of 7 burn wound studies in which burns were positive for culture but rendered sterile after 7 days of honey treatment also showed a statistically significant result in favor of honey, although very high statistical heterogeneity was also present.[31]

According to authors of a literature review, a 3% hydrogen peroxide solution also has been used as a wound cleansing agent for many decades; although no definitive wound healing impairment has been found, there is good evidence for its bactericidal activity.[32] An equally old remedy — iodine in solution form — has been used to treat wounds for more than 150 years but has been supplanted by the more modern iodophores povidone-iodine and cadexomer-iodine.[32] Today, povidone-iodine is used extensively in preoperative surgery, and both iodophores are used in the cleansing of wounds. Conflicting evidence has been found regarding safety and efficacy of povidone iodine, although some reviews have separated out animal and human studies, noting it is the animal studies that suggest cytotoxicity issues and that the bulk of human studies support reduced bacterial load, decreased infection rates, improved healing rates in one instance, and no cytotoxicity.[33] In contrast, cadexomer-iodine studies are more consistent,

supporting its antimicrobial effect and improvement in patient quality-of-life issues, as well as lack of toxicity.[33]
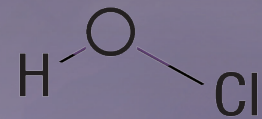
Dakin's solution, used today as a wound cleanser in strengths of 0.0125% to 0.5%, is a diluted version of household bleach, which is a 5% solution of sodium hypochlorite. Dakin's solution for wound sterilization was developed by Henry Dakin, PhD, during World War I but incorporated as part of new aseptic techniques developed by Alexis Carrel, MD, not far from the war's front lines.[34] While Dakin worked on new methods for quantifying measurement of germicidal action, Carrel created novel approaches to quantify wound healing, principles that are still in use today, and a method of instilling Dakin's solution after meticulous wound cleaning and debridement. With the advent of penicillin during World War II and the ushering in of the modern antibiotic era, the continuous instillation techniques based on the short-acting antimicrobial properties of Dakin's solution pioneered by Carrel fell into disuse.[34] One might question, given that current recommendations are to use Dakin's solution once or twice a day, why Dakin's recommendation of using continuous instillation, which was based on the short half-life of HOCl,[35] became ignored. The answer probably relates to the absence of controlled trials using the infusion process. Nevertheless, not all wound care researchers have ignored Dakin's findings; case studies describing applications of intermittent infusion with negative pressure wound therapy (NPWT) are now being published.[36,37]

Harms versus benefits. For many decades, the possibility that antiseptics could interfere with wound healing was not well studied. Today, with more research published on *in vitro* cytotoxicity of antiseptics, the concept antiseptics can do more harm than good is not just theoretical.[38] In the levels of evidence

hierarchy, systematic reviews based on human studies rank far above animal or *in vitro* studies but when human studies are absent, interpretation becomes more difficult in extrapolating data to humans; this is the problem in regard to antiseptic cytotoxicity.

Hydrogen peroxide. Human studies evaluating topical application of hydrogen peroxide to wounds are very much lacking, and inference with regard to wound healing impairment has come from *in vitro* and *in vivo* animal investigations. For example, a cell proliferation study conducted by Thomas et al[38] found hydrogen peroxide reduced both migration and proliferation of fibroblasts in a dose-dependent manner. A recent investigation employing C57BL/6 mice also confirmed several other animal studies demonstrating impaired wound healing with hydrogen peroxide concentrations far below those used in topical human applications, although evidence suggests impaired wound healing is not due to oxidation, which is surprising.[39] Coupled with the unproven antimicrobial efficacy of hydrogen peroxide, such data suggest this antiseptic should not to be used in wound care at all. Nevertheless, translating results of *in vitro* and animal studies to human clinical results can be problematic.[40] As an illustration, in a randomized controlled trial[41] conducted on patients with approximately 28% total body surface area burns and chronic colonized burn wounds, a 2% hydrogen peroxide-soaked gauze was found to cause mean graft take to increase from 65.6% to 82.9%. This statistically significant result seems unexpected in light of the aforementioned animal and culture studies.

Iodine formulations. Angel et al's[42] review of human studies using povidone-iodine reported the majority show its positive effect in reducing infection rates or bacterial load; however, evidence is lacking with regard to

wound healing (positive or negative). A more recent but less thorough review published by Wilkins and Unverdorben[43] generally agrees with Angel et al's[42] conclusions but suggests wound healing impairment might be due to the presence of detergent in commercially available preparations.

In contrast, both animal and human studies consistently demonstrate cadexomer-iodine is an effective antimicrobial agent that improves wound healing.[42] Although Vermeulen et al's[44] systematic review only examined RCTs, it included all kinds of iodine preparations and noted iodine preparations were not generally beneficial for acute wounds. For chronic ulcers, about half of the trials reviewed (n=12) demonstrated positive wound healing attributes, and favorable wound healing outcomes were noted for pressure ulcers. In treatment of burn wounds, all trials showed significantly faster wound healing times for iodine preparations compared to control treatments. Perhaps the most important conclusion from all the research work on the subject is that benefits and harms differ substantially according to the method by which iodine is introduced into the wound.

Although effective antimicrobials against common contaminants *in vitro*, most of the remaining cleansers or antiseptics commonly used in burns, wound care, and surgery (eg, acetic acid, alcohol, and chlorhexidin[43]) do not improve wound healing and may impair wound-healing processes at certain concentrations.

Most *in vitro* cytotoxicity studies of Dakin's solution have found if the sodium hypochlorite concentration is kept to 0.025% or less, effects on cultured cells are minimal or nonexistent (chemotaxis may be an exception).[45-48] These same concentrations are bactericidal. Like cytotoxicity, effective bacteriostatic and bacteriocidal concentrations in wounds in vivo and in

clinical wounds can be up to 1,000 times the dose required for these effects in the culture dish.[49]

Manufacturing HOCl solutions. The manufacture of bleach is an old process dating back to the late 19th century. Today, manufacture of sodium hypochlorite solution (bleach) is based on a continuous process in which dilute sodium hydroxide is mixed with chlorine gas under controlled temperature and pH; Dakin's solution is a diluted form of sodium hypochlorite. The major difference between Dakin's solution and a solution of HOCl is the former is stabilized with sodium carbonate or hydroxide at a pH of 9 to 10 so the major anion is hypochlorite (OCl–); whereas, HOCl solutions tend to be stabilized at a much lower pH resulting in a higher proportion of the protonated anion, HOCl. However, more advanced HOCl solutions have come to market in the last 15 years; these are manufactured by a variety of approaches, which can be divided into nonelectrochemical and electrochemical.

Nonelectrochemical. A formulation of pure HOCl (NVC-101, NovaBay Pharmaceuticals, Emeryville, CA) is manufactured by acidification of reagent grade sodium hypochlorite (NaOCl) with dilute HCl solution in the presence of ~150 mM NaCl so pH ranges from 3.5 to 4.5 (see **Table 3**).[20]

Electrochemical. Sakarya et al[19] described a HOCL formulation, but poorly: "Hypochlorous acid is generated from sodium hypochlorite and hydrogen peroxide reverse reaction." The standard reaction equation between hypochlorite and hydrogen is $NaOCl + H_2O_2 \rightarrow O_2 + NaCl + H_2O$ in which the oxygen is initially produced in singlet form.[50] This highly exothermic reaction under normal conditions is not reversible. Enzymes such as myoperoxidase in a neutrophil can reverse the reaction to produce HOCl because they lower the activation ener-

gy substantially. However, this also may be accomplished by electrolyzing a dilute sodium chloride solution. A review of the electrochemical reactions can enhance understanding of this concept.

The basic electrochemical set-up to generate electrochemically activated solutions (ECAS, as known as "super-oxidized water") consists of 2 separate cells containing an anode and cathode, respectively, separated by an ion-permeable diaphragm or membrane (see **Figure 2**).[51] Depending on the cell designs, the nature membrane connecting the cells, the type of electrodes employed, the strength of the solutions, and exact composition, a variety of basic reactions will occur (shown in **Figure 2** and in this case, many more [types of] reactions). The final reaction sequences produce HOCl at the anode or both anode and cathode cells depending on the nature of the permeability of the membrane connecting the cells. Hydroxide ions, produced at the cathode (with hydrogen gas as a byproduct), react with the released chlorine to produce the desired product along with the oxygen byproduct. The electrodes are usually titanium-coated with a porous metal oxide catalyst for better stability, corrosion resistance, selectivity, and electrochemical reactivity characteristics.[51] The electrochemical process is pH-dependent and temperature-dependent; the cell operating characteristics and solution species will generate many other reactive chemicals in small quantities. The pH levels of the ECAS and available free chlorine differ widely, with ranges of 2.3–10 and 7–180 ppm, respectively.[52]

Many ECAS are available commercially in bottles, but some solutions can only be generated *in situ* from provided electrolysis equipment. For example, the Japanese-manufactured "Oxylyzer" (Miura-Denshi, Akita, Japan) was used by Nakae and Inaba[53] to generate an ECAS containing 0.287–1.148 mEq/L

Table 3. Commercially available formulations of hypochlorous acid available on the market.		
Name	**Manufacturer**	**Manufacturing Method**
NVC-101 (NeutroPhase)	NovaBay Pharmaceuticals, Emeryville, CA	Chemical
No name	NPS Biocidal, Istanbul, Turkey	Electrolysis
No name	Miura-Denshi, Akita, Japan (equipment only)	Electrolysis
Aquaox Hypochlorous Acid Solutions	Aquaox, Fontana, CA	Electrolysis
Sterilox	Sterilox Technologies, International, Stafford, UK	7.1
(now Puricore)	Electrolysis	7.1
Vashe Wound Therapy/Solution	PuriCore, Malvern, PA.	Electrolysis
Microcyn Microcyn-60 Oxum	51697	3.75
Dermacyn Wound Care	Oculus Innovative Sciences, Petaluma, CA	Electrolysis
Puracyn Plus	Innovacyn, Rialto, CA	Electrolysis

of effective chlorine concentration from just tap water and added sodium chloride (see **Table 3**). The authors note little hydrogen gas is produced and dissolved oxygen levels varied widely. Likewise, the solution reported by Sakarya et al[19] does not yet seem to be available commercially. Some ECAS are also available as packaged units, or users can buy electrolysis units themselves from the manufacturer and produce the solution on site on demand (eg, Vashe Wound Therapy/ Solution, PuriCore, Malvern, PA). ECAS also vary considerably in pH ranges, although oxidation-reduction potential (ORP) is at least 800 mV (the solution produced by Miura-Denshi claims to be >1,000 mV). HOCl concentrations also differ substantially; the values of some of these parameters may have implications for efficacy in pathogen killing, wound-healing improvements, cytotoxicity, and genotoxicity.[51]

## USE OF HYPOCHLOROUS ACID IN WOUNDS AND BURNS

In reviewing the literature with regard to wounds and burns and the potential effect of ECAS, it is important to be aware of the level of evidence associated with each study. The level of evidence used here reflects the following: level I (well-conducted RCTs); level II: poorly conducted RCTs; level III: prospective/ retrospective cohort studies; level IV: case-control or cross-sectional studies; level V: case series/non-comparative studies; level VI: expert opinion.[54]

Diabetic foot ulcers (DFUs). Landsman et al[55] conducted a RCT in which participants were randomized to: Microcyn Rx (Oculus Innovative Sciences, Petaluma, CA) alone, the same ECAS and levofloxacin (750 mg daily), or saline and levofloxacin for 10 days, with daily treatment (see **Table 4**). The main outcome was overall clinical success rate (cure or improvement) based on clinical signs and symptoms of the infection at visits 3 and 4. Although none of the primary results were statistically significant, the ECAS–treated group consistently (but not significantly) performed better than the other 2 groups regardless of time in the trial. No adverse events related to the ECAS occurred. Although the results suggest the ECAS could be of benefit in resolving infection, the underpowered nature of the study precluded more definitive conclusions.

Paola et al's[56] prospective, comparative cohort study involved consecutive participants (UT grade 2b or 3b DFU), who received either 10% povidone-iodine or Dermacyn (Oculus Innovative Sciences) daily as a dressing (the solution was impregnated into a gauze, which was placed over the wound and changed daily) along with standard care (debridement, systemic antibiotics, and revascularization if the wound was ischemic) (see **Table 4**). When assessed before surgery (conservative, minor amputation, or major amputation; actual time to surgery varied), a statistically significant higher proportion of patients had no bacterial strains present as determined by culture in the ECAS group compared to the povidone-iodine group (*P* < .001; see **Table 4**). Relative reduction in the number of *S aureus,* MRSA, and *P aeruginosa* cultures between the 2 treatments also heavily favored the ECAS group. Higher proportions of participants in the povidone-iodine group also had major or minor amputations although the result was not statistically tested. Median healing time after surgery was significantly faster in the ECAS group compared to the povidone-iodine group (see **Table 4**). Finally, while 16.7% of the povidone-iodine group had skin rashes or allergic reactions, no patients in the ECAS group had local adverse events. In summary, the group of patients in this study had a high percentage of serious comorbidities such as neuropathy and peripheral vascular disease, and severe wounds, yet microbiological and clinical outcomes were
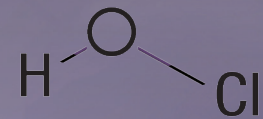
considerably better — and statistically significant — in the group treated with the ECAS compared to povidone-iodine.

Another smaller RCT examined whether patients with Tampico Hospital Diabetic Foot grades B or C56 randomized to Microcyn-60 (Oculus Innovative Sciences) plus standard care had better outcomes in terms of odor, infection control, and safety compared to patients receiving conventional disinfectants and/ or standard of care.[57] (Tampico Hospital Diabetic Foot grades B or C correspond roughly to 3b and 4b UT grades, although the Tampico grades may be slightly more severe.) Standard care included appropriate debridement, offloading, glycemic control, and aggressive antibiotic administration (eg, parenteral route). ECAS administration was achieved by initially immersing the foot in the solution for 15–20 minutes before appropriate debridement, followed by repeated immersion weekly or biweekly and then wound cleansing with the ECAS spray and gauze removal with the same spray; saline was substituted for the ECAS in the control group. Immersions were discontinued upon clinical improvements or the first sign of maceration, while sprays were continued until resolution of infection or end of the study at 20 weeks. Patients and wound covariates were well balanced at baseline. Fetid odor control, cellulitis reduction (erythema area reduction >50%), and improvements of skin around the diabetic foot ulcer (absence of periulcer skin conditions and presence of healthy tissue) were all significantly reduced in the ECAS group compared to the control group (see **Table 4**). These results support the addition of an ECAS as part of a comprehensive regimen to help control odor, infection, and erythema reduction.

Another recently published RCT[58] involved patients undergoing diabetic foot surgery for infection. Inclusion criteria included surgical lesions from drainage or minor amputation with the lesion being a grade 2b/3b UT wider than 5 cm^2 left open to heal by secondary intention; exclusion criteria stipulated wounds with transcutaneous oxygen measurement (TCOM) ≤50 mmHg, bilateral lesions, prior history of lesions with duration >6 months, immunosuppression, creatinine >2 mg/dL, life expectancy <1 year, and intolerance to povidone-iodine. Standard care included appropriate antibiotic therapy, prompt and aggressive debridement, and metabolic control. Patients were randomized to either daily wound instillation of an ECAS injected into moist gauze over the wound or povidone-iodine diluted 50% with saline. At 6 months, a statistically significantly higher proportion of wounds had healed in the ECAS group compared to the povidone-iodine
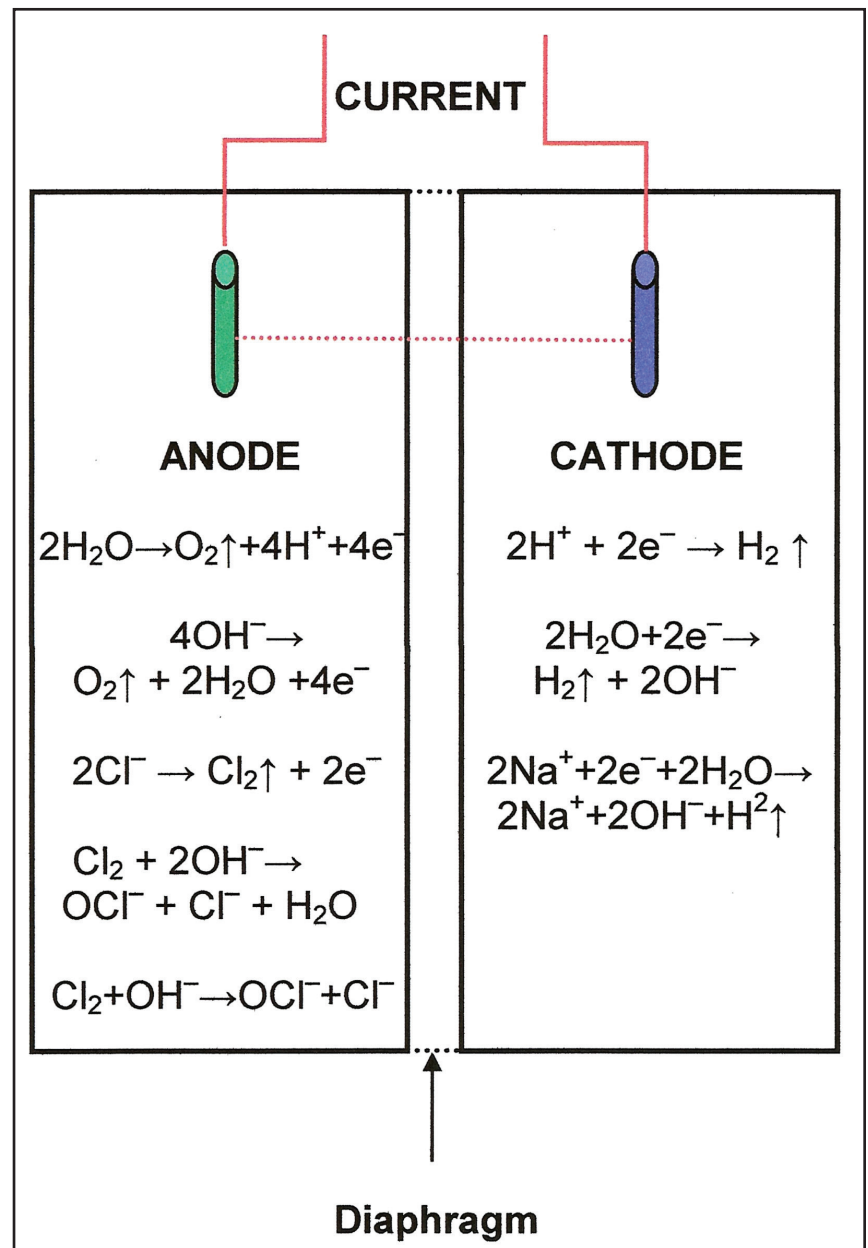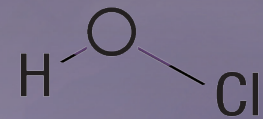

Figure 2. Diagram of generic electrolysis apparatus for the production of hypochlorous acid including anode, cathode, and ion-permeable exchange diaphragm or membrane.

Table 4. Details of wound and burn studies in which electrochemically activated solutions (ECAS) containing					
Design	Evidence level[a]	N	Etiology	ECAS	Treatment
RCT	II	G1: 21 G2: 21 G3: 25	DFU infected	Microcyn Rx	G1: ECAS G2: Saline + ABX G3: ECAS + ABX
Prospective cohort	III	G1: 108 G2: 110	DFU infected	Dermacyn	G1: 10% PI G2: ECAS
RCT	I	G1: 16 G2: 21	DFU infected	Microcyn-60	G1: Conventional antiseptics G2: ECAS
RCT	I	G1: 20 G2: 20	Post-surgical diabetic wounds	Dermacyn	G1: PI G2: ECAS
RCT	II	G1: 50 G2: 50	Diabetic wounds, infected	Microcyn	G1: Saline G2: ECAS
Case series	V	14	Post-operative diabetic foot osteomyelitis	Dermacyn	ECAS
Case series	V	20	DFU infected	Oxum	ECAS
Single case design	IV	G1: 10 G2: 30	Non-healing VLUs	Sterilox	G1: SOC G2: ECAS
Case series	V	31	Non-healing VLUs or mixed arterial/venous ulcers	Vashe Wound Therapy	ECAS
Case series	V	30	VLU infected	Oxum	ECAS
RCT	II	G1: 95 G2: 95	Sternotomy wounds	Dermacyn	G1: PI G2: ECAS
Prospective cohort	III	G1: 25 G2: 25	Post-cesarean wounds	Oxum	G1: PI G2: ECAS
Prospective cohort	III	G1: 15 G1: 15	Chronic wounds	Oxum	G1: PI G2: ECAS
Retrospective cohort	III	G1: 100 G2: 100	Mixed wounds	Oxum	G1: PI G2: ECAS
RCT	II	G1: 30 G2: 30	Septic traumatic wounds	HOCl	G1: PI G2: HOCl

[a]Carter[54]; [b]Not tested by the study authors—value reported here is that obtained by review authors. ABX: antibiotics; DFU: diabetic statistically significant; PI: povidone-iodine; PP: per protocol; RCT: randomized controlled trial; SOC: standard of care; VLU: venous

hypochlorous acid were used		
Main Outcomes	**Comments**	**Reference**
Clinical success rate at 2 weeks: G1: 75%; G2: 52%; G3: 72%; (NSS); Clinical success rate per pathogen: G1: 80%; G2: 64%; G3: 58% (NSS)	Underpowered; no statistically significant results; prespecified statistical analysis not conducted	Landsman et al[55]
Proportion of patients with negative culture at time of surgery: G1: 68.5%; G2: 88.2%; (P <.001); Time to heal (post-surgery, median, days): G1: 55; G2: 43; (P <.0001)	Severe wounds; no adjustment of results using regression	Paola et al[56]
Fetid odor reduction: G1: 25%; G2: 100%; (P =.001); Cellulitis reduction: G1: 44%; G2: 81%; P =.01; Periwound skin improvement: G1: 31%; G2: 90%; P =.001	No adjustment of results using regression or FWER adjustment	Martínez-De Jesús et al[57]
Proportion healed at 6 months: G1: 55%; G2: 90%; P =.002; Time to heal (weeks, within 6 months): G1: 16.5; G2: 10.5; (p=.007); Reduction in bacterial count (at 1 month): G1: 11%; G2: 88%; P <.05	No adjustment of results using regression or FWER adjustment	Piaggesi et al[58]
Wound downgrading (at 1 week): G1: 15%; G2: 62%; (P < .05); Hospital stay (≤ 1 weeks): G1: 20%; G2: 62%; (P < .05)	Many trial details missing	Hadi et al[59]
Amputation (minor): 1/14 (7%); Time to heal (median, weeks): 6.8		Aragón-Sánchez et al[60]
Infection (day 5): 1/20 (5%)		Chittoria et al[61]
Wound healing (at 12 & 20 weeks): G1: (90%; NA; G2: 25%; 45%		Selkon et al[62]
Wound healing (at 90 days): 79%; Odor (3 months): 0%; Pain: (3 months): 0%		Niezgoda et al[66]
Change from baseline to 4 weeks (p for all analyses: P <.05): Reduction in wound area: 72%; Reduction in periwound edema: 64%; Reduction in erythema: 65%; Increase in fibrin: 43%; Increase in granulation: 66%		Dharap et al[67]
Incidence of infection by 6 weeks: G1: 14/90 (16%); G2: 5/88 (6%); P =.033; PP analysis	No ITT analysis	Mohd et al[68]
Day 10: Odor: G1: 4%; G2: 0%	Application method not specified	Anand[69]
Reduction in wound area (Day 14): G1: 37%; G2: 56%; P =.0045 Reduction in microbial count (day 14): G1: 84%; G2: 93%; NSS	Application method not specified; standards of care not reported	Abhyankar et al[70]
Wound size reduction; periwound and other healing parameters	Variety of application methods; sizes of subgroups not reported; no data for entire groups	Kapur & Marwaha[71]
At 2 weeks: Ready for surgery: G1: 0%; G2: 90%; P <.00001[b]; Serous exudate: G1: 10%; G2: 100%; P =.004; Low exudate: G1: 30%; G2: 100%; P =.005; No wound odor: G1: 13%; G2: 100%; P =.001; No wound pain: G1: 17%; G2: 100%; P =.004; Reduction in bacterial load:	Blinding and allocation concealment unclear; baseline characteristics minimal	Mekkawy & Kamal[73]
foot ulcer; ECAS: electrochemically activated solution; FWER: familywise error rate; G: group; NA: not applicable; NSS: not leg ulcer		

group (*P* = 0.002) with a significantly longer time to heal (*P* = 0.007) based on Kaplan-Meier analysis (see **Table 4**). In addition, after 1 month of treatment, a significantly higher reduction was noted in bacterial count in the ECAS-treated group versus the control group (see **Table 4**). Again, the results suggest better management of infection when ECAS is incorporated into standard care.

Another RCT conducted in Pakistan[59] involved treatment of patients with diabetic wounds randomized to either an ECAS or saline as an adjunct therapy in addition to standard care (debridement, surgical drainage, systemic antibiotics). Statistically significant differences were found in favor of the ECAS in regard to "downgrading" of the wound category [from IV to I; category IV means wounds with necrotic tissue or frank pus; category I means wounds with healthy epithelialization), duration of hospital stay, and wound healing time (see **Table 4**)].

Two case series have been published. The first[60] included consecutive patients in whom postsurgical management of diabetic foot osteomyelitis had become an issue because clean bone margins could not be ensured (ie, eradication of infection). The surgical wounds of these patients were treated with an ECAS during surgery followed by daily irrigation. Treatment success was defined as healing of the surgical wound and associated index ulcer without any complications (reinfection or amputation) (see **Table 4**).

The second case series[61] involved patients with DFUs infected by *S aureus* (6); *E coli* (4); *Enterococci* (3); *Pseudomonas* (3); *P mirabilis* (2); and *Streptococci* (2). Irrigation was accomplished with Oxum (Oculus Innovative Sciences) solution on a daily basis plus a dressing of gauze impregnated with the solution. Of the 20 wounds, 11 ultimately received a skin graft and 1 wound a flap; all 20 wounds healed (see **Table 4**).

The level of evidence showed the addition of ECAS to standard care can reduce wound infection, improve wound healing, and reduce periwound issues, as well as other patient-centered outcomes is at least moderate overall and may be high for some specific issues.

VENOUS LEG ULCERS (VLUS)

A single case design study in which patients acted as their own controls and 2 published case series have reported on the effectiveness of ECAS as an adjunct therapy in the treatment of VLUs. The first, conducted by Selkon et al,[62] was a follow-up to favorable smaller case studies planned to be before-and-after design in which participants had 3 weeks of standard compression bandaging. Participants who did not achieve a 44% reduction in wound area[63,64] after this time were offered an HOCl wash for 20 minutes in a forced circulation leg hydrobath twice a week for 3 weeks and weekly for a further 9 weeks in addition to standard care. Of the 10 patients who met the reduction in wound area criterion, 9 achieved complete wound closure within 12 weeks (see **Table 4**). Of the 20 who had the additional ECAS therapy, 5 had complete wound closure within 12 weeks, a further 4 within another 8 weeks. An additional 5 participants had a substantial reduction in wound area within 12 weeks (60% to 88%); of the 20 patients who had initial pain (3–5 on a modified McGill pain questionnaire[65]), pain was reduced in 14 to 0–1 on the same scale. One patient developed eczema after 4 weeks treatment that later resolved. Based on the work published by Phillips et al[63] and Margolis et al[64] in which 22% of patients are likely to experience healing if they failed the 44% area reduction test at 3 weeks, the results in the Selkon et al[62] study suggest the odds of healing were doubled by adding the ECAS treatment.

In a case series,[66] patients received an ECAS as an adjunctive treatment in addition to appropriate debridement, vascular assessment, and compression bandaging (see **Table 4**). The ECAS was administered by applying gauze soaked with the solution over the wound for 15–20 minutes followed by a gentle scrub with the gauze, providing additional sharp debridement if the scrub did not remove all slough and necrotic tissue, and a final rinse with the ECAS. The patients were relatively old (mean: 74.5 years) and had wounds of long duration (mean: 29 months), and nearly two thirds of the VLUs were infected. After 90 days, 79% of wounds had closed. In addition, two thirds of subjects had rated their wounds as having a moderate odor (4.6 on a 1–10 scale), which was reduced to 0 by the end of the study (3 months) in all cases. Likewise, moderate pain was completely reduced to no pain.

Finally, a case series published by Dharap et al[67] examined the effect of the addition of an ECAS (post-debridement rinsing followed by gauze dressing impregnated with the same ECAS) in addition to standard compression bandaging. The VLUs could be infected but could not be ischemic nor deeper than subcutaneous level of exposure. The mean reduction in wound area after 4 weeks was statistically significant (*P* <0.05). Significant reductions in levels of periwound edema (*P* <0.05) and erythema (*P* <0.05) and increases in granulation and fibrin were observed over the same timeframe. Of the 30 patients, 80% had pain at baseline (VAS pain values not reported) but none had pain at the end of the study (pain was evaluated in 25 patients), and reports of irritation decreased from 83% to 25% in all patients during the same time period. Additionally, 30% of patients had no microbial load after 4 weeks, but this was not further defined by the authors and no bacterial counts were provided.
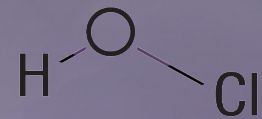
The level of evidence (IV) that ECAS can improve wound healing is relatively low, although other lower evidence studies demonstrate such solutions may improve odor and pain control. However, higher evidence-level controlled trials are still needed to establish the effect of ECAS therapy with regard to infection moderation, wound healing, and other patient-centered outcomes.

SURGICAL WOUNDS

Two comparative studies examined the effectiveness of ECAS as an adjunct therapy to standard care in the management of surgical wounds. In an RCT, Mohd et al[68] investigated whether an ECAS would reduce the postoperative infection rate compared to povidone-iodine when used as an irrigation agent for 15 minutes before insertion of sternal wires and closure in patients undergoing coronary bypass grafting (CABG). Patients were followed for 6 weeks. Of the 88 patients in the ECAS group, 5 (6%) developed a postoperative infection compared to 14 out of 90 (16%) in the povidone–iodine group (specific criteria for infection; bacterial counts not reported). Moreover, of the 5 participants with infected wounds in the ECAS group, all were superficial infections; whereas, in the povidone-iodine group, of the 14 infected wounds 4 (29%) had deep sternal infections that led to sternal dehiscence (see **Table 4**).

In a prospective cohort study, Anand[69] reported on a cohort of 50 patients who had undergone a cesarean section (CS) in which the surgical wound was managed either by ECAS dressings twice a day for 10 days or povidone iodine (application method not specified). Evaluation was based on wound healing and other parameters and patient clinical symptoms at day 5 and 10. Although the proportion of wounds healed at day 10 was slightly higher in the ECAS group compared to the povidone-iodine group (96% ver-

sus 88%) and the proportion of patients rated by the surgeon as *excellent* or *good* based on global efficacy was also higher in the ECAS group compared to the povidone-iodine group (76% versus 60%), neither of these findings were statistically significant (see **Table 4**).

In summary, some evidence indicates the use of ECAS may lower infection rates in surgical wounds, but no evidence shows it improves wound healing. More well powered controlled trials are required to establish whether ECAS can improve wound healing.

CHRONIC OR MIXED WOUNDS (WOUNDS WITH AN ISCHEMIC COMPONENT)

Abhyankar et al[70] performed a small prospective cohort study of persons with chronic wounds to determine whether an ECAS treatment (details not specified) over a period of 14 days could improve wound healing compared to povidone-iodine. Wound area reduction was significantly higher in the ECAS group than the povidone-iodine group ($P = 0.045$; see **Table 4**). Other wound parameters between the 2 groups were similar after 2 weeks. However, local adverse events, such as pain, irritation, redness, and edema in the povidone-iodine group outnumbered those in the ECAS group by approximately 5:1.

Kapur and Marwaha[71] recently reported the results of a retrospective cohort study conducted to evaluate the effect of an ECAS in regard to reduction in infection and inflammation and improvements in wound healing involving DFUs, VLUs, traumatic wounds, surgical wounds pressure ulcers (PUs), wounds with carbuncles, cellulitis, and abscesses; burns; fistula *in ano*; and gangrenous wounds. All wounds were treated with an ECAS or povidone-iodine in addition to standard care for the wound etiology via washing or irrigation techniques, immersion, or

impregnation of dressings. ECAS-treated wounds showed increased benefit over the 3-week study period compared to povidone iodine-treated wounds in terms of wound area reduction, reduction of periwound problems, pus discharge, granulation, and epithelialization, but no statistical analysis was presented (see **Table 4**). Moreover, due to the lack of information presented, it is hard to assess the results (for example, the results were clinically and statistically significant for all types of wounds).[72]

Studies including many mixed wound etiologies are harder to assess in terms of efficacy or effectiveness of endpoints for a variety of reasons — most importantly, because sample sizes for subgroups are likely to be small and thus most statistical analysis will be underpowered. It is understandable some researchers may want to perform such studies when reimbursement in their country does not permit complete wound etiology differentiation, but nevertheless from an evidence-based medicine point of view such studies do not always add credible evidence. In this instance, the evidence presented should be regarded as low.

SEPTIC TRAUMATIC WOUNDS

Mekkawy and Kamal's[73] RCT focused on acute, septic traumatic wounds. Participants received HOCl (created from 0.5% NaCl and 51.5% HCl, ratio 9:1) or povidone-iodine (control) in addition to standard care. Sponge-soaked saline was used to clean the wound followed by irrigation for 3–5 minutes of the intervention or control solution. At 2 weeks, 27 of 30 (90%) of the HOCl–treated wounds but none of the povidone-iodine-treated wounds were ready for a flap or graft; by contrast, the majority (93%) of the control group members were not ready until more than 4 weeks. This result was not tested statistically but inferred to be very significant ($P < 0.00001$). The type

of exudate differed enormously at day 14, with all wounds treated with HOCl having only serous exudate while only 3 out of 30 control wounds (10%) had serous exudate and 90% had serosanguinous, sanguinous, or purulent exudate. Exudate volume was low for all HOCl wounds and 30% for control wounds. After 2 weeks, all wounds in the HOCl group and 13% of the control wounds had no odor, and no pain was reported by HOCl patients after 2 weeks, while 17% of control participants could report no pain. Finally, although it appears the control group had far higher bacterial loads with regard to the 5 strains of bacteria tested in the HOCl group, the reduction in bacterial load was superior in the HOCl group compared to the control $P = 0.0001$). Although this RCT was graded level II, this trial clearly demonstrated an advantage of using HOCl over povidone-iodine in terms of microbial wound management, exudate control, pain management, and preparation of patients for reconstructive surgery, even though the trial results were not adjusted for other factors that might have partially confounded the results.

Burn wounds. No controlled trials investigating the use of HOCl in burns have been reported in the literature. That does not mean that such trials have not been conducted; rather that they have not been published. For example, in a press release, Oculus reported in 2008 that an RCT involving 162 burn patients had been completed in China.

PANEL RECOMMENDATIONS FOR THE USE OF HOCL

Panel Recommendation 1: Cleanse the wound (if needed) with HOCl, followed by debridement, if needed. Follow a standard algorithm to prepare the wound bed, such as TIME.

Preparing the wound bed is part of the many algorithms developed for the treatment of wounds. In 2003, one such algorithm — the tissue management, infection, moisture imbalance, edge of the wound (TIME) — was created from a meeting of wound care experts.[74]

However, wound care researchers have been concerned that practitioners have not been debriding wounds as frequently as they should be, and thus they modified TIME to DIME in which the D emphasized debridement.[75] A recent, large retrospective study (N = 312,744 wounds)[76] confirmed more frequent debridement results in faster healing of all types of wounds.

Several different debridement techniques are available, including surgical, sharp, autolytic, enzymatic, larval, and mechanical. Sharp debridement is generally preferred for most chronic wounds because it is fast and helps convert a chronic wound to an acute wound, removing devitalized tissue and senescent cells.[74] Although considered conservative under some circumstances, sharp debridement requires considerable expertise on the part of the practitioner, and the skill set needed includes knowledge of anatomy, identification of viable or nonviable tissue, and the ability and resources to manage complications, such as bleeding, as well as patient consent before starting the procedure.[77] Surgical debridement is usually performed when there are large areas to be debrided and significant infection risk, and often takes place in the OR with or without general anesthesia.
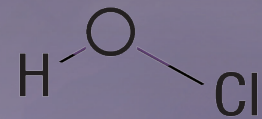
Cleansing is basically removal of loose debris and wound surface pathogens but *wound cleansing is not debridement*. This is an important distinction. Moreover, all wounds do not need to be cleansed, especially clean, granulating wounds.[78] Thus, the usual care flow would be to cleanse the wound if needed with HOCl then debride if needed.

According to clinical practice guidelines, the approach to burn wounds vis-à-vis debridement and cleansing is similar to chronic wounds but also depends on the degree of the burn and whether blisters should be deroofed, which is also a function of area.[79,80]

Panel Recommendation 2: Treat infected wounds with HOCl by integrating into best practices according to wound etiology.

Infection management in acute and chronic wounds has been complicated for decades by appropriate culture sampling techniques, when to sample (ie, under what conditions), when to culture as opposed to determining infection by clinical symptoms, and the fact culture results will not necessarily be representative of the microbiological organisms causing an infection.[81] The standard approach to treating wound infection is antibiotics, orally or intravenously for more serious infections, but overusage of antibiotics has led to increasing bacterial resistance at a time when few new antibiotics are coming on to the market.[82] Although better stewardship can mitigate the problem, in the field of wound care, some researchers have suggested local targeted therapy with highly concentrated antibiotics is a better approach.[83] This may certainly have some benefits, but it is too soon to know if this approach will be adopted instead of systemic antibiotic administration. Moreover, it is not known if systemic levels of the antibiotic could cause problems later. It also has been argued that if microbiological screening was much faster, broader, and more accurate (eg, developing personalized topical therapeutics based on the results of molecular diagnostics), wounds would heal a lot faster.[84,85] In this context, although the use of HOCl will not obviate the need for antibiotics, it may augment treatment and speed wound healing without itself being the cause per se of further antibiotic resistance nor introducing undesirable side effects. That said, in general, the use of HOCl should be integrated with best

practice guidelines for management of infection by wound etiology, which are summarized next.

DFUs. For DFUs, the Infectious Diseases Society of America (IDSA) recommends: clinically uninfected wounds not be treated with antibiotic therapy; prescribing antibiotic therapy for all infected wounds, but caution that this is often insufficient unless combined with appropriate wound care; clinicians select an empiric antibiotic regimen on the basis of the severity of the infection and the likely etiologic agent(s); definitive therapy be based on the results of an appropriately obtained culture and sensitivity testing of a wound specimen as well as the patient's clinical response to the empiric regimen; basing the route of therapy largely on infection severity (parenteral therapy for all severe, and some moderate, DFUs, at least initially, with a switch to oral agents when the patient is systemically well and culture results are available; clinicians can probably use highly bioavailable oral antibiotics alone in most mild, and in many moderate, infections and topical therapy for selected mild superficial infections; continuing antibiotic therapy until, but not beyond, resolution of findings of infection, but not through complete healing of the wound; and an initial antibiotic course for a soft tissue infection of about 1–2 weeks for mild infections and 2–3 weeks for moderate to severe infections.[86]

VLUs. For infected venous leg ulcers, the Society for Vascular Surgery and the American Venous Forum recommend: antibiotics not be used to treat colonization or biofilm without clinical evidence of infection; VLUs with >1 x 106 CFU/g of tissue and clinical evidence of infection be treated with antimicrobial therapy, but the bioburden threshold for antibiotics should be lower for virulent or difficult-to-eradicate bacteria; a combination of mechanical disruption and antibiotic therapy is most likely to be successful in eradicating infection; VLUs with clinical evidence of infection should be treated with systemic antibiotics guided by sensitivities performed on wound culture; oral antibiotics are preferred initially, and the duration of antibiotic therapy should be limited to 2 weeks unless persistent evidence of wound infection is present; and use of topical antimicrobials should be avoided.[87]

PU. The National Pressure Advisory Panel (NPUAP), European Pressure Advisory Panel (EPUAP), and Pan Pacific Pressure Injury Alliance recommend: bacterial load and biofilm in the PU be reduced per the cleansing and debridement guidelines section; the use of tissue appropriate strength, nontoxic topical antiseptics be considered for a limited time period to control bacterial bioburden; the use of topical antiseptics in conjunction with maintenance debridement be considered to control and eradicate suspected biofilm in wounds with delayed healing; the use of silver sulfadiazine in heavily contaminated or infected PUs be considered until definitive debridement is accomplished; the use of medical–grade honey should be considered in heavily contaminated or infected PUs until definitive debridement is accomplished; the use of topical antibiotics should be limited on infected PUs, except in special situations where the benefit to the patient outweighs the risk of antibiotic side effects and resistance; systemic antibiotics for individuals be used with clinical evidence of systemic infection, such as positive blood cultures, cellulitis, fasciitis, osteomyelitis, systemic inflammatory response syndrome (SIRS), or sepsis.[88]

Surgical wounds. The IDSA recommends: Suture removal plus incision and drainage should be performed for surgical site infections; adjunctive systemic antimicrobial therapy is not routinely indicated, but in conjunction with incision and drainage may be beneficial for surgical site infections associated with a significant systemic response, such as erythema and induration

extending >5 cm from the wound edge, temperature >38.5°C, heart rate >110 beats/minute, or white blood cell (WBC) count >12 000/μL; a brief course of systemic antimicrobial therapy is indicated in patients with surgical site infections following clean operations on the trunk, head and neck, or extremities that also have systemic signs of infection; a first-generation cephalosporin or an antistaphylococcal penicillin for methicillin-sensitive *S aureus* (MSSA), or vancomycin, linezolid, daptomycin, telavancin, or ceftaroline where risk factors for MRSA are high (nasal colonization, prior MRSA infection, recent hospitalization, recent antibiotics), is recommended; agents active against Gram-negative bacteria and anaerobes, such as a cephalosporin or fluoroquinolone in combination with metronidazole, are recommended for infections following operations on the axilla, gastrointestinal tract, perineum, or female genital tract.[89]

Burn injuries. The American Burns Association Guidelines do not specifically discuss infection. Other clinical practice guidelines for burn injuries indicate: prophylactic antibiotics are not routinely given to burn patients because they do not reduce the risk of infection; antibiotics are only given to patients with known infections and are prescribed to sensitivities; in the initial postburn stage, the patient may experience febrile periods. These do not necessarily indicate infection, although they should be monitored. Febrile episodes often are related to the release of large amounts of pyrogens resulting from the initial injury.[79] In commenting upon recent developments, however, Dries[90] notes: As in general critical care practice, sepsis is a condition warranting empiric antibiotics and a search for infection during that short course of

empiric therapy; the burn literature supports discontinuation of antibiotics where microbiologic thresholds are not met.

Panel Recommendation 3: For infected wounds, treat with HOCl for 15 minutes either intralesionally or by ensuring the wound is covered with the solution.

As yet, there are no credible clinical trial data from which to base decisions regarding how to introduce HOCl into the wound. Thus, there are several possibilities based on clinical trial practice:

- Wound irrigation after any debridement (suggested time: 15 minutes):
  o Use a syringe with low pressure
  o Enclose the wound partially and instill using a catheter
  o Inject intralesionally, with or without the use of ultrasound
- Instillation in combination with another therapy, such as NPWT
- Impregnate into primary dressing and secure to the wound; change dressings every day.

Best practice recommendation based on the roundtable discussion by the panel is to use HOCl either intralesionally or by ensuring the wound is covered with the solution for 15 minutes after any debridement. There is no necessity to "rinse" off the solution with water or saline after this time.

INDICATIONS FOR USE OF ECAS OF HOCL

All ECAS solutions have been cleared under 501(k) by the US Food and Drug Administration (FDA) for the following indications when used by a health care professional:

- DFUs
- VLUs
- PUs
- Postsurgical wounds
- First-degree and second-degree burns
- Grafted and donor sites (not all solutions)

Preparations available over-the-counter (OTC) are indicated for minor abrasions, lacerations, minor irritations, and intact skin only.

THE FUTURE OF HOCL

Although the evidence for use of HOCl is sufficient for DFUs and septic surgical wounds, it is low or absent for some wound-related conditions (eg, burns). Appropriately powered controlled trials as well as cohort studies are needed to confirm the efficacy or effectiveness of HOCl in relation to infection prevention and treatment and improvement in wound healing, including periwound parameters and patient-centered outcomes, particularly for pressure ulcers, VLUs, and burn wounds. Trials also will need to be conducted in various settings, particularly long-term care facilities, where resources are often very limited in regard to infection control.

LIMITATIONS

Because the review of clinical studies using HOCl may have missed some studies, the level of evidence associated with different wound types may change. Given the lack of trials testing the method of HOCl application in wounds, it is also possible the recommendations may change in the future to better reflect best practice.

CONCLUSION

Technologically advanced (ie, electrochemically adjusted) HOCl solutions have been tested in the prevention and treatment of infection in a number of different wound types. Based on *in vitro* studies, antimicrobial activity appears to be comparable to other antiseptics. However, contrary to the use of some antiseptics, these solutions do not impair wound healing but rather can improve wound healing in addition to resolving infection. The level of evidence for these

outcomes in humans varies according to type of wound treated, but it is sufficient for DFUs and septic surgical wounds. Further research is needed to determine the efficacy of these solutions in pressure ulcers, VLUs, and burns, as well as to determine the best method for application.

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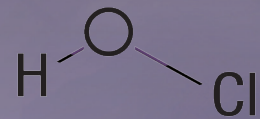
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