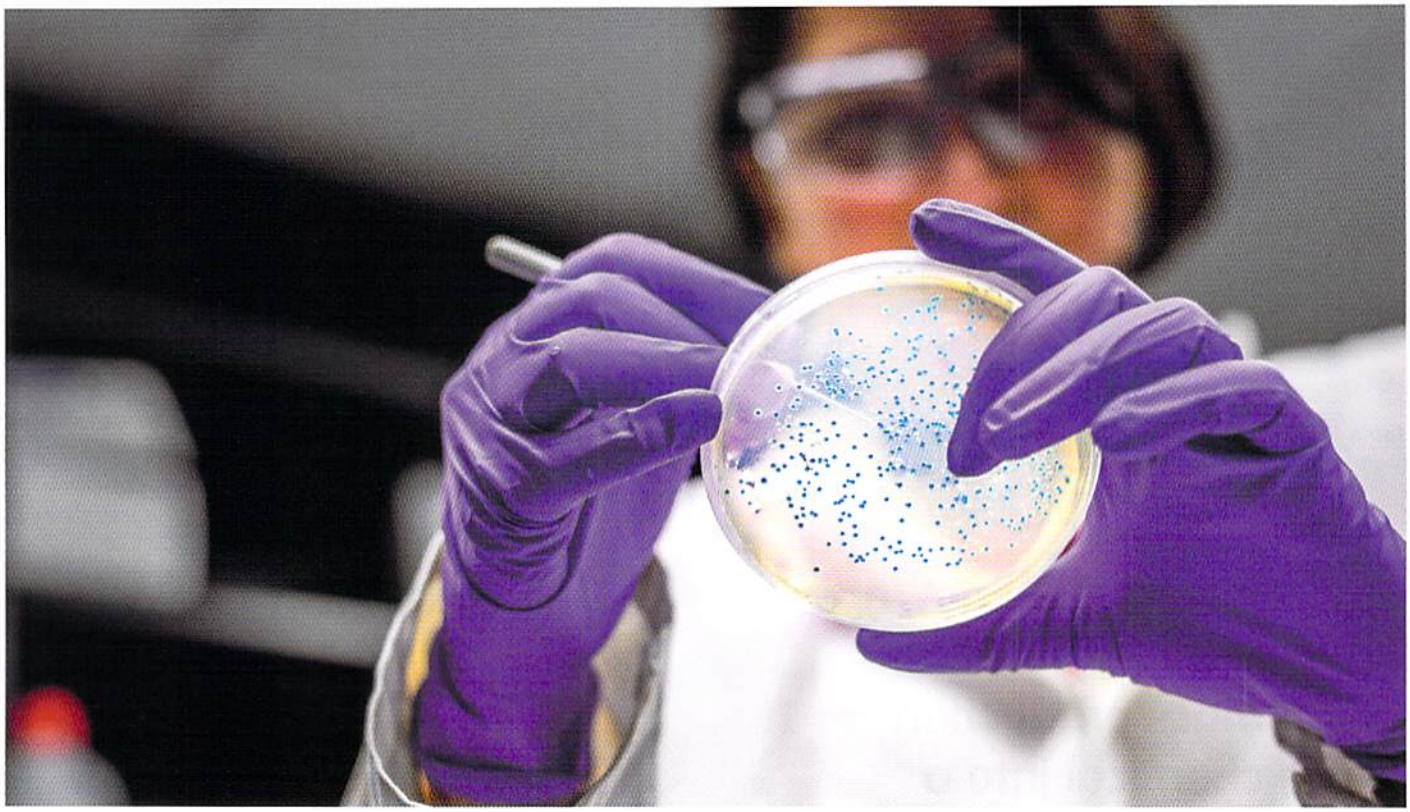

HYPOCHLOROUS ACID
A NEW SOLUTION IN PODIATRY?

Ivan Bristow looks at some of the research exploring the use of hypochlorous acid and discusses how it may have applications in clinical practice

The fight against microbes is a constant battle. Increasingly, with regular reports on microbial resistance and 'superbugs', new treatments are being sought to reduce infections and their associated morbidity.

In the last year or two, we have seen the introduction of hypochlorous solution into the UK podiatry market. Its potential benefits have been long known as a topical antiseptic, but only recently has it been manufactured into a stabilised, usable form suitable for regular clinical use.

A product that has a bacterial killing power 80 times greater than bleach[1,2] with limited toxic effects, and which does not delay wound healing sounds too good to be true.

IVAN BRISTOW
PHD

Above: HOCl has been shown to be effective against a number of micro-organisms.

HYPOCHLOROUS ACID (HOCL)

Hypochlorous acid (HOCl) (not to be confused with hydrochloric acid), is a naturally occurring weakly acidic molecule of chlorine in water used by the body as part of the innate immune system, particularly by neutrophils, eosinophils, macrophages and B cells.[2] During infection and inflammation, immune cells ingest and kill microbes. Consuming quantities of oxygen, they are able to produce superoxide species, which in turn dismutates into hydrogen peroxide which then converts to HOCl under the influence of the enzyme myeloperoxidase.[3] HOCl possesses strong antimicrobial properties being bactericidal, fungicidal, viricidal and sporicidal[4] through depletion of microbial energy stores (ATP),[5] oxidation of nucleotides and damage to microbial cell membranes,[6] whilst having little effect on mammalian cells,[2] probably as a result of its endogenous presence in the immune system. In addition, evidence suggests that bacterial toxins exposed to HOCl may undergo oxidative neutralisation.[7]

Despite the known advantages of HOCl, mass production of the chemical into a usable, stable form has been a challenge due to its chemistry. HOCl exists in an optimal pH of around 3.5–5.5. Below this level, chlorine gas is liberated. Above

Organism tested	Log reduction in culture	Exposure time To HOCl
Methicillin-resistant *Staph aureus* (MRSA)	>6.7 log10	30 seconds
Candida albicans	>5.2 log10	30 seconds
Escherichia coli	>6.7 log10	30 seconds
Pseudomonas aeruginosa	7.8 log10	30 seconds
Enterococcus faecalis	7.7 log10	30 seconds
HIV-1	>4.5log10	2 minutes
Mycobacterium	>5.0log10	1 minute

Table 1. Activity of HOCl against various strains of micro-organisms (from Selkon et al[4])

> **"Despite the known advantages of HOCl, mass production of the chemical into a usable, stable form has been a challenge due to its chemistry**

this level, HOCl is converted to the less effective hypochlorite (-OCl or bleach) with increased irritant properties and fewer antimicrobial effects. In the last few years chemical processes have been achieved to stabilise and purify the chemical, permitting wider clinical use with the introduction of HOCl-based products into the market.

ANTIMICROBIAL ACTIVITY

In 1999, Selkon et al[4] assessed the effectiveness of HOCl as a cleaning solution and evaluated its effectiveness against a range of micro-organisms including *Staphylococcus aureus* (summarised in Table 1 above).

Wang and colleagues[2] performed a test using HOCl against 16 common fungal and bacterial organisms including *Staph aureus, Candida albicans, Streptococcus pyogenes, pseudomonas, Escherichia coli* and MRSA. The work showed that, even in a low concentration, HOCl was able to kill 99.99% of all cultures within 2 minutes, apart from *Strep pyogenes* which required a longer exposure time to be destroyed (10 minutes). Similar results were reported in other studies highlighting broad-spectrum activity and rapid kill time for bacteria,[6, 8-10] viral pathogens,[11,12] fungi[13] and prions.[14] Further work using a branded hypochlorous solution (Clinisept+®) demonstrated that it was able to eliminate a range of common bacterial, viral and fungal isolates to 6 log10 reductions (99.9999%) in application times as low as 15 seconds (Data on file, Clinical Health Technologies Ltd, Leicestershire).

SKIN DISINFECTION

At a basic level, hypochlorous solution possesses all the properties of a surface disinfectant agent on the skin. Chlorhexidine gluconate is probably the most widely used antiseptic in podiatry in the UK today at a 0.5% concentration in a 70% alcohol vehicle. It is known to possess broad-spectrum activity, being most effective against gram-positive bacteria and weaker activity against gram-negative bacteria.[15] It is also active against yeasts, some dermatophytes and some lipophilic viruses,[16] with little action against acid-fast organisms and spores.[16] Cases of allergy and anaphylaxis to chlorhexidine have been reported in the literature.[17] Research has also highlighted how it may delay wound healing due to cytotoxicity[16] and emergence of resistant bacteria has been reported.[18]

Povidone-iodine comes in various formulations and has the trademark brown stain when applied to the skin. It has a broader spectrum of activity than chlorhexidine against a range of organisms[19] although its activity against some fungi and spores is limited.[20] True povidone-iodine allergy is rare although it may cause stinging and irritant dermatitis in some patients when used topically.[21] Comparison of the antimicrobial activity of HOCl with chlorhexidine gluconate and povidone-iodine has shown it to have a speed of action equal or superior to the two other chemicals against a range of organisms.[22]

Clinically, as a surface antiseptic, HOCl may offer advantages over chlorhexidine for patient skin preparation prior to treatment as it has a wide and rapid spectrum of activity and does not sting on application as it is water based. In addition, at its working pH of 5 it is compatible with the skin (pH 5.5), degrading to water to leave no toxic or irritant residue on the skin. In addition, HOCl is compatible with skin and mucous membranes so should not cause irritation to the operator if accidently sprayed into the eyes or face. HOCl appears to be well tolerated and safe, without any major adverse events reported.[23]

> **In podiatry, this has a great potential for use in treatment of foot wounds and ulcers, particularly because of its antimicrobial profile along with anti-biofilm activity**

ANTI-INFLAMMATORY ACTION OF HOCL

In addition to its antimicrobial properties, research has highlighted the effects of HOCl on moderating inflammation. Pelgrift & Friedman[24] summarised the main anti-inflammatory effects as follows:

1. HOCl adds one or more Cl groups to the NH2 group of histamine, thereby decreasing its potency.
2. Oxidation by HOCl of thiol or thioether groups directly decreases the activity of leukotrienes and interleukin-6 (IL-6).
3. Oxidation by HOCl of thiol or thioether groups directly increases the activity of transforming growth factor-beta (TGF-beta), which is anti-inflammatory.
4. Oxidation by HOCl causes increased synthesis of growth factors.
5. At high concentrations, HOCl decreases the activities of matrix metalloproteinase-7 (MMP-7) and collagenases.
6. HOCl oxidation can ultimately neutralise pro-inflammatory cytokines, including tumour necrosis factor-alpha (TNF-alpha), IL- 2, and IL-6.
7. HOCl chlorinates proteinaceous parts of antigens, which causes increased activity against gram-negative bacteria.

Anti-inflammatory effects can have positive benefits such as pain reduction and decreased healing times, and may be effective in the treatment of itch in conditions such as atopic dermatitis, as demonstrated in an animal model and in a paediatric population, performing equally as well as a potent topical steroid and other drugs.[25-27]

HOCL, BIOFILMS AND WOUND HEALING

Biofilms are collections of different types of organisms that may reside on a surface or on the bed of a wound, encased in a scaffold of glycoproteins which act as a protective shell, making their elimination difficult through normal immune processes or chemotherapy. Additionally, they can contribute to antibiotic resistance.[28] Hypochlorous acid has been shown to destroy biofilms,[29-31] control odour[32] and to be more effective for decreasing bacteria versus saline[33] or povidone-iodine[32] in wound irrigation. In a review of the use of HOCl,[34] led by Prof David Armstrong, the authors conclude that HOCl had comparable antimicrobial activity to other available agents but with much less cytotoxicity and more evidence on its safety and effectiveness. Strong evidence was found in favour of its use in diabetic foot wounds.

In podiatry, this has a great potential for use in treatment of foot wounds and ulcers, particularly because of its antimicrobial profile along with anti-biofilm activity. In addition, work has shown that, unlike other wound products, HOCl does not delay or inhibit the wound healing process,[30] ultimately improving healing rates and outcomes.[29]

SUMMARY

HOCl solution is a simple chemical with strong powers of oxidation and therefore antimicrobial activity across a very broad range of organisms, which emulates the body's own innate immune system. Modern manufacture processes have allowed for production of a pure form of the chemical stabilised for clinical use. Many of these properties make HOCl a valuable asset in podiatry as an antiseptic, anti-inflammatory and wound care agent, which does not delay wound healing and is entirely compatible with tissues, causing minimal irritancy or sensitivity. ■

DECLARATION OF INTEREST

The author declares he has undertaken work for Canonbury Limited who carry hypochlorous products in their catalogue.

REFERENCES

1. Hui YH, Sherkat F. *Handbook of Food Science, Technology and Engineering*, Vol 4. Boca Raton: CRC Press; 2006.
2. Wang L, Bassiri M, Najafi R, Najafi K, Yang J, et al. Hypochlorous acid as a potential wound care agent: part I. Stabilized hypochlorous acid: a component of the inorganic armamentarium of innate immunity. *Journal of Burns and Wounds* 2007; 6:e5.
3. Winterbourn CC, Kettle AJ, Hampton MB. Reactive oxygen species and neutrophil function. *Annu Rev Biochem* 2016; **85**(1):765-792.
4. Selkon JB, Babbt JR, Morris R. Evaluation of the antimicrobial activity of a new super-oxidized water, Sterilox®, for the disinfection of endoscopes. *J Hosp Infect* 1999; **41**(1):59-70.
5. Barrette WC, Jr., Hannum DM, Wheeler WD, Hurst JK. General mechanism for the bacterial toxicity of hypochlorous acid: abolition of ATP production. *Biochemistry* 1989; **28**(23): 9172-9178.
6. McKenna SM, Davies KJ. The inhibition of bacterial growth by hypochlorous acid. Possible role in the bactericidal activity of phagocytes. *The Biochemical Journal* 1988; **254**(3):685-692.
7. Mainnemare A, Megarbane B, Soueidan A, Daniel A, Chapple IL. Hypochlorous acid and taurine-N-monochloramine in periodontal diseases. *J Dent Res* 2004; **83**(11):823-831.
8. Ono T, Yamashita K, Murayama T, Sato T. Microbicidal effect of weak acid hypochlorous solution on various microorganisms. *Biocontrol Science* 2012; **17**(3):129-133.
9. Groitl B, Dahl JU, Schroeder JW, Jakob U. Pseudomonas aeruginosa defense systems against microbicidal oxidants. *Mol Microbiol* 2017; **106**(3):335-350.
10. Quan Y, Kim HY, Shin IS. Bactericidal activity of strong acidic hypochlorous water against *Escherichia coli* O157:H7 and Listeria monocytogenes in biofilms attached to stainless steel. *Food Science and Biotechnology* 2017; **26**(3):841-846.
11. Taharaguchi M, Takimoto K, Zamoto-Niikura A, Yamada YK. Effect of weak acid hypochlorous solution on selected viruses and bacteria of laboratory rodents. *Exp Anim* 2014; **63**(2):141-147.
12. Park GW, Boston DM, Kase JA, Sampson MN, Sobsey MD. Evaluation of liquid- and fog-based application of Sterilox hypochlorous acid solution for surface inactivation of human

norovirus. *Appl Environ Microbiol* 2007; 73(14):4463-4468.
13. Odorcic S, Haas W, Gilmore MS, Dohlman CH. Fungal infections after Boston Type 1 keratoprosthesis implantation: literature review and in vitro antifungal activity of hypochlorous acid. *Cornea* 2015; **34**(12):1599-1605.
14. Hughson AG, Race B, Kraus A, Sangare LR, Robins L, et al. Inactivation of prions and amyloid seeds with hypochlorous acid. *PLoS Pathog* 2016; 12(9):e1005914.
15. Hennessey TS: Some antibacterial properties of chlorhexidine. *J Periodontol Res* 1973; **12**(6):1-7.
16. Karpinski TM, Szkaradkiewicz AK: Chlorhexidine-pharmaco-biological activity and application. *Eur Rev Med Pharmacol Sci* 2015; **19**(7):1321-1326.
17. Sharp G, Green S, Rose M. Chlorhexidine-induced anaphylaxis in surgical patients: a review of the literature. *ANZ J Surg* 2016; **86**(4):237-243.
18. Kampf G. Acquired resistance to chlorhexidine – is it time to establish an 'antiseptic stewardship' initiative? *J Hosp Infect* 2016; **94**(3):213-227.
19. Reimer K, Wichelhaus TA, Schafer V, Rudolph P, Kramer A, et al. Antimicrobial effectiveness of povidone-iodine and consequences for new application areas. *Dermatology* 2002; **204** Suppl 1:114-120.
20. McDonnell G, Russell AD. Antiseptics and disinfectants: activity, action, and resistance. *Clin Microbiol Rev* 1999; **12**(1):147-179.
21. Wykoff CC, Flynn HW, Jr., Han DP. Allergy to povidone iodine and cephalosporins: the clinical dilemma in ophthalmic use. *Am J Ophthalmol* 2011; **151**(1):4-6.
22. Anagnostopoulos AG, Rong A, Miller D, Tran AQ, Head T, et al. 0.01% Hypochlorous acid as an alternative skin antiseptic: an in vitro comparison. *Dermatol Surg* 2018; **44**(12):1489-1493.
23. Del Rosso JQ, Bhatia N: Status report on topical hypochlorous acid: clinical relevance of specific formulations, potential modes of action, and study outcomes. *The Journal of Clinical and Aesthetic Dermatology* 2018; **11**(11):36-39.
24. Pelgrift RY, Friedman AJ: Topical hypochlorous acid (HOCl) as a potential treatment of pruritus. *Current Dermatology Reports* 2013; **2**(3):181-190.
25. Fukuyama T, Martel BC, Linder KE, Ehling S, Ganchingco JR, et al. Hypochlorous acid is antipruritic and anti-inflammatory in a mouse model of atopic dermatitis. *Clin Exp Allergy* 2018; **48**(1):78-88.
26. Fukuyama T, Ehling S, Wilzopolski J, Bäumer W. Comparison of topical tofacitinib and 0.1% hypochlorous acid in a murine atopic dermatitis model. *BMC Pharmacology and Toxicology* 2018; **19**(1):37.
27. Lebwohl MG, Del Rosso JQ, Abramovits W, Berman B, Cohen DE, et al. Pathways to managing atopic dermatitis: consensus from the experts. *The Journal of Clinical and Aesthetic Dermatology* 2013; **6**(7 Suppl):S2-S18.
28. Zhao G, Usui ML, Lippman SI, James GA, Stewart PS, et al. Biofilms and inflammation in chronic wounds. *Adv Wound Care* 2013; **2**(7):389-399.
29. Sakarya S, Gunay N, Karakulak M, Ozturk B, Ertugrul B. Hypochlorous acid: an ideal wound care agent with powerful microbicidal, antibiofilm, and wound healing potency. *Wounds: a Compendium of Clinical Research and Practice* 2014; **26**(12):342-350.
30. Robson MC, Payne WG, Ko F, Mentis M, Donati G, et al. Hypochlorous acid as a potential wound care agent: part ii. stabilized hypochlorous acid: its role in decreasing tissue bacterial bioburden and overcoming the inhibition of infection on wound healing. *Journal of Burns and Wounds* 2007; **6**:e6.
31. Kiamco MM, Zmuda HM, Mohamed A, Call DR, Raval YS, et al. Hypochlorous-acid-generating electrochemical scaffold for treatment of wound biofilms. Scientific Reports 2019; **9**(1):2683.
32. Ragab II, A K. The effectiveness of hypochlorous acid solution on healing ofinfected diabetic foot ulcers. *Journal of Education and Practice* 2017; **8**(8):58-71.
33. Hiebert JM, Robson MC. The immediate and delayed post-debridement effects on tissue bacterial wound counts of hypochlorous acid versus saline irrigation in chronic wounds. *Eplasty* 2016; **16**:e32.
34. Armstrong DG, Bohn G, Glat P, Kavros SJ, Kirsner R, et al. Expert recommendations for the use of hypochlorous solution: science and clinical application. *Ostomy Wound Manage* 2015; **61**(5):S2-s19.