# Hypochlorous acid

REJECTED

The Expert Committee, after evaluation, declines to list the medicine proposed in the application.
The Model List of Essential Medicines reports reasons that Committee Members have identified for denying listing.

**Section:** 15. Antiseptics and disinfectants > 15.1. Antiseptics

EMLc | ATC codes: V07AV

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| **Indication** | Disinfectant, not elsewhere classified — ICD11 code: XM7DD6 |
| **Medicine type** | Chemical agent |
| **List type** | Core (EML)<br>(EMLc) |
| **Formulations** | Local > Topical > Solution: |
| **EML status history** | Application rejected in 2017 (TRS 1006)<br>Application rejected in 2021 (TRS 1035) |
| **Sex** | All |
| **Age** | Also recommended for children |
| **Therapeutic alternatives** | The recommendation is for this specific medicine |
| **Patent information** | Patents have expired in most jurisdictions<br>Read more about patents. |
| **Wikipedia** | Hypochlorous acid |

## Expert Committee recommendation

The Expert Committee noted that recommendations for chlorine-based products, including hypochlorite formulations, are included in the 2020 WHO guidance on cleaning and disinfection of environmental surfaces in the context of COVID-19. Liquid, solid or powered hypochlorite-based formulations dissolve in water to create a dilute aqueous chlorine solution in which undissociated hypochlorous acid is the active antimicrobial compound. The EML and EMLc currently list chlorine-based compounds, with a square box, intended to indicate that various formulations can be acceptable alternatives for selection and use. However, the current listing does not specify the alternative formulations. In the review of square box listings on the Model Lists considered at the current meeting, an amendment to the square box listing of chlorine-based compounds in the disinfectant section of the EML and EMLc was proposed. The Committee recommended that the listing should be amended to specify the different recommended formulations to provide greater clarity and guidance for countries. This recommendation will result in liquid and solid formulations of chlorine-based compounds being specifically included as alternatives. Therefore, the Committee considered that a separate listing for the proposed formulation of hypochlorous acid solution was not necessary. As regards antiseptic use, the Committee noted that hypochlorous acid appears to be a safe and effective antiseptic with a broad activity against a wide range of pathogens and has an acceptable safety profile. Recent advances in manufacturing have improved standardization of the product. However, the evidence supporting these considerations is relatively limited and derived from small and heterogeneous studies. The Expert Committee noted that ongoing studies will have the potential to better clarify the advantages of hypochlorous acid and would inform a future consideration of this product for inclusion on the Model Lists. Therefore, the Expert Committee did not recommend hypochlorous acid for inclusion in the EML and EMLc for antisepsis and wound decontamination at this time, but advised that it would welcome a future application including data from ongoing studies and a more comprehensive review of the literature.

## Background

Hypochlorous acid solution and hydrogel were considered for inclusion on the Model Lists for use in wound management in 2017.

The Expert Committee did not recommend addition on the basis of inadequate evidence, noting that the quality of the evidence presented in the application for the solution formulation was uncertain, and that no evidence was presented for hydrogel (1). Antiseptics currently included on the Model Lists are chlorhexidine, ethanol and povidone iodine. Disinfectants currently included are alcohol-based hand rub, chlorine base compound, chloroxylenol and glutaral.

## Public health relevance

Disinfection The importance of environmental disinfection measures became more recognized in 2020 because of the coronavirus disease 2019 (COVID-19) pandemic. Regular decontamination of surfaces and air has become a necessary infection control measure. Antisepsis and wound care Infected wounds and the rise of antibiotic-resistant organisms are responsible for significant increases in morbidity, mortality and the cost of health care. Using topical antiseptics to treat superficial skin lesions with mild infections is advisable to avoid the use of antibiotics.

## Benefits

Disinfection An in vitro study showed antiprion activity of hypochlorous acid solution using intracerebral infectivity of treated prions of scrapie and with an in vitro fluorescent chemistry method showing efficacy against bovine spongiform encephalopathy, Creutzfeldt–Jakob disease and chronic wasting disease prions (2). Efficacy was shown to reach a log removal value of almost 6 after exposures of 60 minutes at room temperature. Log removal values of up to 3–4 were achieved with 5 minutes of contact with hypochlorous acid. Efficacy was also demonstrated against Bacillus spores. A retrospective, single-institution cohort study evaluated the efficacy of universal skin decolonization using mupirocin and hypochlorous acid solution to decrease health care-associated methicillin-resistant Staphylococcus aureus (MRSA) infections in patients admitted to a burn intensive care unit in a tertiary-care community hospital (3). Global MRSA infection rates per 1000 patient days were 7.23 before the intervention and 2.37 after the intervention (incidence rate ratio 0.35, 95% confidence interval (CI) 0.17 to 0.65). Patients in the burn intensive care unit who did not receive universal decolonization had a 3.05 times higher risk of acquiring an MRSA infection than those who did. No complications were noted from the use of hypochlorous acid solution for skin decolonization. An in vitro study to determine the efficacy of exposure to a pure hypochlorous acid solution for inactivation of high-risk human papillomavirus (HPV 16 and 18) found hypochlorous acid to be a highly effective disinfectant even with short contact times (4). All hypochlorous acid treatment times produced a > 99.99% reduction in infectivity of HPV16 and HPV18, comparable to the efficacy of 0.87% sodium hypochlorite. Antisepsis A randomized controlled trial in 111 participants on intraperitoneal dialysis evaluated the efficacy and safety of superoxidized solution versus povidone iodine following catheter placement in reducing the frequency of dialysis-associated infections (5). After 8 weeks of follow up, 24.5% of the povidone-iodine group had had catheter-related infections compared with 6.0% in the group treated with superoxidized solution ($P < 0.05$). In addition, the mean time for resolution of infection in the povidone-iodine group was 12 days compared with 4 days for the superoxidized solution group ($P < 0.05$). An in vivo and in vitro study assessed the effectiveness of a hypochlorous acid-based wound cleanser compared with other cleansers (povidone-iodine and chlorhexidine) in disrupting MRSA and Pseudomonas aeruginosa biofilms. The study also evaluated the bioburden reduction of venous stasis wounds with the different cleansers (6). All agents tested significantly neutralized MRSA and Pseudomonas aeruginosa biofilms compared with saline control. Undiluted hypochlorous acid was significantly less cytotoxic than 1% and 10% povidone-iodine and chlorhexidine wound solution. No significant difference was found in bacterial reduction in wounds after treatment with hypochlorous acid for any type of bacteria examined. In wounds treated with hypochlorous acid or chlorhexidine, similar percentage reductions were seen in bacterial colony-forming units from precleansing levels when plated on tryptic soy agar, MacConkey agar, streptococcal agar and mannitol salt agar. Plates treated with chlorhexidine tended to have higher bacterial reduction on non-selective and Gram-negative agars, whereas plates treated with hypochlorous acid tended to have higher bacterial reduction in streptococcal-selective agars. A randomized controlled trial of 80 participants with peritonitis compared peritoneal lavage with saline and peritoneal lavage with saline followed by superoxidized solution following surgery (7). Purulent discharge occurred in 20.0% of participants receiving superoxidized solution lavage versus 52.5% of participants receiving saline lavage ($P < 0.01$). The incidence of burst abdomen among the participants given superoxidized solution lavage was significantly lower than among the participants given saline lavage (12.5% versus 32.5%, $P < 0.05$). No difference in the incidence of superficial wound infection was observed between treatment groups. A randomized trial of 178 participants compared the effectiveness of irrigation with neutral pH superoxidized solution and povidone iodine in reducing the incidence of sternotomy wound infection following coronary artery bypass graft surgery (8). Wound infection with sternotomy was reported in 5.7% of participants in the superoxidized solution group and 15.6% of participants in the povidone-iodine group ($P = 0.03$). A randomized study of 100 participants undergoing exploratory laparotomy for peritonitis compared intraoperative peritoneal lavage with normal saline or normal saline followed by a superoxidized solution (9). Surgical site infection occurred in 14% of participants in the group treated with superoxidized solution compared with 40% of participants in the normal saline group (P = 0.003). The mean duration of hospital stay was similar between the two groups. Two participants in the superoxidized solution group died compared with eight participants in the saline group. Wound care A randomized trial of 60 participants evaluated the efficacy of hypochlorous acid versus povidone-iodine as a wound care agent in septic trauma wounds (10). Outcome measures for wound pain (no pain at day 14), odour (no odour at day 14), discharge (serous at day 14) and bacterial count (reduction in day 14 quantitative count) were significantly better in the hypochlorous acid group. At day 14, 90% of the participants treated with hypochlorous acid had wounds ready for surgical reconstruction, compared with 0% of the participants in the povidone-iodine group. A randomized trial of 60 participants compared the efficacy of dressings with superoxidized solution and povidone-iodine in the management of infected diabetic ulcers (11). The mean change in ulcer area was significantly greater in participants treated with superoxidized solution dressings compared with participants given povidone-iodine dressings (2215 mm2 versus 1641 mm2, P = 0.024). Similarly, the mean percentage reduction in ulcer area in participants receiving superoxidized solution dressings was significantly greater (58.90% versus 40.90%; P = 0.024). A randomized, prospective, multicentre, open-label pilot study tested the efficacy of topical superoxidized solution alone compared with normal saline irrigation plus oral levofloxacin, and superoxidized solution plus oral levofloxacin in 67 participants with mild diabetic foot infections (12). Based on the intention-to-treat population, the clinical success rate 14 days after completion of therapy (test of cure) for participants treated with superoxidized solution alone was 75.0%, compared with 72.0% for participants treated with superoxidized solution plus levofloxacin and 52.4% for participants treated with saline plus levofloxacin. Differences in clinical success rates were not statistically significant. A randomized case control trial of 100 patients with a variety of wounds compared the efficacy and outcomes of superoxidized solution-saturated dressings and povidone-iodine saturated dressings (13). The most common infecting organism isolated was Pseudomonas aeruginosa, followed by Staphylococcus aureus and Klebsiella spp. The decrease in surface area of wounds at the end of 1, 2, 3 and 4 weeks was significantly greater in the superoxidized solution group (P = 0.005, P = 0.002, P < 0.001 and P < 0.001, respectively). A randomized controlled trial examined the efficacy and safety of a superoxidized solution compared with povidone-iodine (as adjuncts to systemic antibiotics and debridement as needed) in the management of wide (> 5 cm) postsurgical lesions of the diabetic foot in 40 participants (14). Healing, as measured by complete re-epithelization, occurred in 90% of the participants treated with superoxidized solution compared with 55% of the povidone-iodine group (P < 0.01). Participants treated with superoxidized solution also had fewer episodes of reinfection (P < 0.01). A retrospective analysis of 897 patients with 1249 venous leg ulcers treated with hypochlorous acid solution found that all venous leg ulcers healed completely. Treatment involved cleaning and debriding foreign matter, debris and necrotic material by application of hypochlorous acid solution, with or without pressure and abrasion, using a sterile gauze soaked with hypochlorous acid. Sharp debridement was performed where required within 10 days of presentation. All ulcers were dressed and/or loosely packed with sterile gauze soaked with hypochlorous acid. Compressive bandaging was applied. Light abrasion using sterile gauze and flushing with hypochlorous acid solution was performed every few days. The longest healing times were observed in 10 patients for whom compression therapy was contraindicated. However, aggressive management adding hypochlorous acid resulted in complete wound closure within 180 days in these 10 patients (15). A randomized, single-blind trial studied the outcomes of standard care (without neutral pH superoxidized solution) and standard care plus neutral pH superoxidized solution in the treatment of 45 patients with diabetic foot ulcers (16). Odour reduction was reported in 100% of participants treated with superoxidized solution compared with 20% in the standard care group. Surrounding cellulitis diminished in 80.5% of participants treated with superoxidized solution versus 43.7% in the standard care group and advancement to granulating tissue stage occurred in 90.4% versus 62.5%. A hundred patients with diabetic foot ulcer wounds were randomized to treatment with either daily superoxidized solution or saline-soaked gauzes (17). Participants treated with hypochlorous acid had a significantly shorter period of hospitalization than saline-treated participants (68% versus 20% stayed in hospital for 1–7 days, P < 0.05) and a greater proportion experienced a downgrading of wound category (62% versus 15%, P < 0.05). Two hundred patients with different types of wounds were prospectively randomized to treatment with either superoxidized solution or povidone-iodine (using saturated gauzes), and antibiotics (18). After a mean follow-up of 21 days, the average reduction in the wound size of diabetic foot ulcer in the group treated with superoxidized solution was 70% compared with 50% in the povidone-iodine group. Earlier granulation and epithelization were also seen for wounds treated with superoxidized solution compared with those treated with povidone-iodine (100% versus 85% at day 18).

## Harms

Clinical adverse events from exposure to pure hypochlorous acid (present at a pH between 4.0 and 5.33) have not been recorded in the medical literature. Adverse events have been reported following exposure to relatively high pH (> 6.5), crude formulations containing mixed oxidants, including hypochlorite, which result from poorly controlled manufacturing processes. Eye and skin inflammation and respiratory irritation are common with hypochlorite (bleach), which can be present at levels of 30% or more in hypochlorous acid solutions made or adjusted to pH 7, or in swimming pools that are improperly managed, allowing the pH to rise into the alkaline range. A 2011 study evaluated the risk of biological toxicity in a mouse model when acid-electrolysed water was ingested as drinking water for 8 weeks. No abnormal findings were observed and the authors concluded this water would be safe if used as a mouthwash, even if ingested (19). Another study using an animal model looked at the potential toxicity associated with infusions of superoxidized solution into the intraperitoneal cavity of rats. No significant differences in blood biochemistry, renal function or liver function were found between rats infused with hypochlorous acid and control rats (20). A review of acid-electrolysed water versus normal saline as a peritoneal lavage to prevent postsurgical infections after perforated appendicitis in children found no evidence of toxicity associated with acid-electrolysed water (21). Environmental safety Hypochlorous acid is a highly reactive molecule and short-lived when exposed to pathogens or other biological matter. On exposure, pure hypochlorous acid degrades within minutes to form sodium chloride and water, becoming benign and non-reactive saltwater closely analogous to human tears (22). Because of that rapid reactivity, pure hypochlorous acid at a label concentration of 180 parts per million poses no risk of environmental contamination (except as a mild 0.9% salt solution) and does not require personal protective equipment. It can be stored without any hazardous materials protocol and can be disposed of with no risk of generating a toxic waste stream. In contrast, impure hypochlorous acid/hypochlorite solutions, such as hypochlorite (bleach), require personal protective equipment and hazardous material storage, and must be disposed of as both a toxic materials risk and an environmental hazard. These hazard considerations also apply to other classes of antisepsis and disinfection agents.

## Cost / cost effectiveness

The application states that modern manufacturing permits the generation of pure, stable hypochlorous acid in large volumes for roughly one eighth the cost of previous methods. Current pricing pf hypochlorous acid produced at scale can now be less than US$ 2 per wholesale litre at the manufacturing facility, with small regional variations.

## WHO guidelines

The WHO interim guidance document on cleaning and disinfecting surfaces in relation to COVID-19 specifies that “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” (23).

## Availability

Multiple branded aqueous hypochlorous acid formulations have been approved for topical use in wound management by the US Food and Drug Administration. The Food and Drug Administration has also approved hypochlorous acid for strong disinfection and sterilization of medical instruments (24). Multiple branded hypochlorous acid products are approved as COVID-19 disinfectants. A class III medical product approval for hypochlorous acid has been granted in the European Union, and the Japanese Ministry of Health has approved the use of hypochlorous acid for topical medical applications. The capacity to produce hypochlorous acid from small, local and networked manufacturing facilities is available. This eliminates the cost of transportation and allows remote locations to produce pure and stable hypochlorous acid that meets quality standards.

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