Review Article

Clinical application of skin antisepsis using aqueous olanexidine: a scoping review

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Abstract

Surgical site infections (SSIs) and catheter-related bloodstream infections (CRBSIs) caused by bacteria from surfaces poorly disinfected with chlorhexidine gluconate (CHG) and povidone-iodine (PVP-I) are increasing. Olanexidine gluconate (OLG) was developed in 2015 in Japan to prevent SSI and CRBSI caused by bacteria resistant to CHG and PVP-I. This scoping review aimed to identify the knowledge gap between what is known and what is not known about the disinfection efficacy of OLG. We searched MEDLINE through PubMed, the Cochrane Central Register of Controlled Trials, the Cumulative Index to Nursing and Allied Health Literature (CINAHL), the International Clinical Trials Registry Platform search database, ClinicalTrials.gov, and the Web-based database of Japanese medical articles for works published to July 18, 2021. Manual reference searches were also carried out. A total of 131 studies were screened. Forty-seven studies were included in this review and classified into two major categories: studies on pharmacological effects and spectrum (n = 29) and studies on clinical and adverse effects (n = 18). Olanexidine gluconate showed bactericidal activity against methicillin-resistant Staphylococcus aureus and vancomycin-resistant enterococci, in addition to common Gram-positive and Gram-negative bacteria. In clinical settings, although there is limited evidence on SSI prevention, 1.5% OLG might be more effective than 10% PVP-I and 1% CHG in preventing SSI. However, the clinical usefulness of OLG is unclear due to the limited number of clinical studies. Also, clinical research is limited to studies targeting SSI prevention, and there are no clinical studies on CRBSI. Further clinical studies are needed on SSI and CRBSI prevention.

Key words: Catheter-related bloodstream infection, olanexidine, scoping review, skin antiseptic solution, surgical site infection

INTRODUCTION

MICROORGANISMS ON THE skin surface can cause various infections in hospital settings. Among such infections, surgical site infection (SSI) and catheter-related bloodstream infection (CRBSI) lead to higher mortality rates, longer hospital stays, and higher medical costs.1-4 Various disinfectants have been developed to prevent SSIs and CRBSIs. Regarding the balance between disinfection efficacy and adverse events, the guidelines of the Centers for Disease Control and Prevention and the National Institute for Health and Clinical Excellence recommend the use of alcohol-containing chlorhexidine gluconate (CHG).5,6 Chlorhexidine gluconate use is associated with a lower incidence of CRBSI, when compared to the use of povidone-iodine (PVP-I) or alcohol.7 Thus, CHG is recommended for CRBSI prevention.8-11 However, the occurrence of SSI and CRBSI caused by bacteria on surfaces that are poorly sterilized with CHG or PVP-I has been increasing in recent years.5,10-13 Specifically, Staphylococcus aureus and Enterococcus species are the most common causative bacteria of SSIs and CRBSIs.14,15 Clinical studies have shown that PVP-I is ineffective in disinfecting surfaces with enterococci, which include vancomycin-resistant enterococci (VRE).16,17 Furthermore, the studies have reported the inefficacy of CHG in disinfecting surfaces with methicillin-resistant S. aureus (MRSA) and VRE.18,19 To prevent SSIs and CRBSIs caused by bacteria resistant to CHG and PVP-I, olanexidine [1-(3,4-dichlorobenzyl)-5-
octylbiguanide] gluconate (OLG) was developed in Japan in 2015. In vitro, OLG has a broad-spectrum, disinfecting, and fast-acting activity against drug-resistant bacteria.\textsuperscript{20–25}

A randomized controlled trial (RCT) comparing the activity of OLG and PVP-I showed that OLG is superior to PVI in the prevention of SSIs.\textsuperscript{26} Although some of the disinfection effects of OLG have been clarified, some aspects of the clinical use of OLG need clarification: whether OLG is more effective than CHG for skin disinfection, which is recommended for CRBSI and SSI prevention; whether CHG is effective in preventing non-SSI infections; and whether OLG is more effective than other disinfectants against resistant bacteria in clinical settings.

Therefore, we undertook a scoping review to clarify what is currently known and what remains unclear about OLG’s disinfectant activity. Specifically, we focused on two points: OLG’s pharmacological effect, including its spectrum and associated adverse events; and its clinical effects, including prevention of SSI and CRBSI. The results were summarized separately for each of these points.

METHODS

THE PRESENT SCOPING review included all studies on OLG, regardless of their design. The studies included in vitro studies of animals and humans, case reports, observational studies, and RCTs. Conference abstracts with unavailable full texts were excluded, due to insufficient information for this review. We followed the Preferred Reporting Items for Systematic Reviews and Meta-Analyses extension for Scoping Reviews (PRISMA-ScR) Checklist.\textsuperscript{27} We searched MEDLINE through PubMed, the Cochrane Central Register of Controlled Trials (CENTRAL), the Cumulative Index to Nursing and Allied Health Literature (CINAHL), the International Clinical Trials Registry Platform (ICTRP) search database, ClinicalTrials.gov, and the Web-based database of Japanese medical articles (Ichu-shi) for articles published to July 18, 2021. Manual reference searches were also undertaken as appropriate. When searching MEDLINE/CENTRAL/CINAHL, we used the following search terms: “olanexidine”, “OPB-2045” (OPB; the development code of olanexidine), “olanedine”, and “olanexidine gluconate”. When searching Ichu-shi, the search terms used in the MEDLINE/CENTRAL/CINAHL search were translated into Japanese. There was no language restriction. The extracted studies were screened independently by two reviewers (ES and YS) to determine their eligibility for inclusion. Disagreements were discussed and resolved between the two reviewers. If the disagreement could not be resolved, the decision was left to a third reviewer (HY).

RESULTS

A TOTAL OF 131 studies (25 from PubMed, 13 from CENTRAL, 80 from Ichu-shi, six from CINAHL, two from the manual reference search, and five from ICTRP/ClinicalTrials.gov) were screened (Fig. 1, Table S1). Twenty-nine studies were excluded during the first screening (duplicates, 11; unavailable full text, 18). In the second screening that entailed a review of full texts, 50 studies were excluded: four in which OLG was not mentioned and 46 conference abstracts (Table S2). Finally, 47 studies were included in the review.

Forty-seven studies were classified into two major categories based on their focus areas: studies on pharmacological effects and spectrum (n = 29) and studies on clinical and adverse effects (n = 18). The studies on pharmacological effects and spectrum were animal or in vitro studies. The studies on clinical and adverse effects were human studies (Table 1).

In many studies, CHG and PVP-I used were formulated without alcohol. In studies in which CHG and PVP-I with alcohol were used, supplementary explanations were provided.

Pharmacology

Structural formula

Olanexidine gluconate is a biguanide antiseptic solution that was developed by Otsuka Pharmaceutical Factory, Inc. in 2015. To reduce skin irritation without decreasing its antimicrobial effect, the medicinal ingredient olanexidine (1-(3,4-dichlorobenzyl)-5-octylbiguanide [OPB-2045]) is converted to gluconate, and the solubilizer polyoxyethylene (20) polyoxypropylene (20) glycol (POEPOPG) is added to complete OPB.\textsuperscript{23} The chemical formula is 1-(3,4-dichlorobenzyl)-5-octylbiguanide mono-o-gluconate\textsuperscript{28} (Fig. 2).

Mechanism of action

There were four studies on bactericidal action\textsuperscript{23,28–30} and one on the inhibitory action of inflammatory chemokines.\textsuperscript{31}

Bactericidal action (in vitro/animal studies)

The mechanism underlying the bactericidal action of OLG differs between low and high concentrations, although the detailed mechanism has not been elucidated. At low concentrations (median effective dose [ED50], 8.4–25 μg/mL as the lower limit; no upper limit concentration), OLG has a higher affinity for bacterial surface proteins such as the lipoteichoic acid of Gram-positive bacteria and
lipopolysaccharide (LPS) of Gram-negative bacteria, compared to CHG with an ED50 of 27–610 µg/mL. Similarly, for phospholipids such as lysyl-phosphatidyiglycerol (L-PG) and phosphatidylethanolamine (PE), at a concentration higher than the minimal inhibitory concentration (0.63 µg/mL against Gram-positive bacteria and 4.0 µg/mL against Gram-negative bacteria), OLG had a stronger disruptive effect than CHG on membranes containing L-PG and PE. These actions cause irreversible leakage of intracellular components, which leads to a bactericidal effect. However, at high concentrations (>160 µg/mL), OLG showed a bactericidal effect by aggregating bacteria through a protein

Fig 1. Flowchart of study screening and inclusion in the present scoping review of studies regarding the clinical application of skin antisepsis using olanexidine. CINAHL, Cumulative Index to Nursing and Allied Health Literature; ICTRP, International Clinical Trials Registry Platform.
Table 1. Summary of included studies that reported the clinical use of olanexidine gluconate (OLG)

| No. | First author, year | Country | Design | Object | Intervention | Comparison | Outcomes | Main findings |
|-----|--------------------|---------|--------|--------|--------------|------------|----------|--------------|
| 1   | Seyama et al. 2019 | Japan   | In vitro | Microorganisms, containing clinical isolates | 1.5% OLG | None | Viable bacterial count (CFU/mL) after 1.5% OLG administration using time-kill assay |
|     |                    |         |         |        |              |            |          | - 1.5% OLG showed fast-acting fungicidal activity against all Gram-positive and Gram-negative bacteria tested, including multidrug-resistant strains, *Candida albicans*, *Microsporum canis*, and *Malassezia furfur* |
| 2   | Medical package insert | Japan | In vitro | Microorganisms, containing clinical isolates | 1.5% OLG | None | MBC or log reduction |
|     |                    |         |         |        |              |            |          | - Spectrum of 1.5% OLG against bacteria, viruses, and fungi is described based on the results of clinical trials undertaken by pharmaceutical companies |
| 3   | Imai et al. 2020   | Japan   | In vitro | Norovirus (all 11 genotypes of GI, GII, and GIV) | OLG-HR (1.5%), 1.5% OLG, 0.5% OLG, EtOH, 0.1% benzalkonium chloride, 0.5% CHG | Log10 reduction |
|     |                    |         |         |        |              |            |          | - Two types of disinfectants using OLG (hand sanitizer and surgical bandage), two types of ethanol solutions with different pH (approximately 3 and 7), and the base ingredient of OLG hand sanitizer were evaluated for their ability to kill 11 types of human noroviruses |
| 4   | Hagi et al. 2015   | Japan   | In vitro | Microorganisms, containing clinical isolates | 1.5% OLG | CHG (concentration unknown), PVP-I (concentration unknown) | MBC (µg/mL) |
|     |                    |         |         |        |              |            |          | - MBC of OLG was low for both Gram-positive cocci and Gram-positive rods, including multidrug-resistant bacteria. The bactericidal spectrum of OLG was comparable to that of CHG and PVP-I |
|     |                    |         |         |        |              |            |          | - OLG probably binds to the cell membrane, disrupts membrane integrity, and its bacteriostatic and bactericidal effects are caused by irreversible leakage of intracellular components |
| No. | First author, year | Country | Design | Object | Intervention | Comparison | Outcomes | Main findings |
|-----|-------------------|---------|--------|--------|-------------|------------|----------|---------------|
| 5   | Inoue et al. 2015 | Japan   | In vitro | Microorganisms, containing clinical isolates | 1.5% OLG | None | MBC (µg/mL) | • Bactericidal efficacy of OLG against MRSA and VRE was compared with CHG and PVP-I using MBC as an indicator, and the bactericidal efficacy was equal or better |
| 6   | Nishioka et al. 2018 | Japan | In vitro | Applied to the skin of the Yucatan micropig (culture collections) | 1.5% OLG | 0.5% CHG, 10% PVP-I, 1% CHG-AL | Log_{10} reduction at 30 s and 3 min | • OLG showed a fast-acting bactericidal activity that was similar to or stronger than that of CHG formulations up to a concentration of 1% and PVP-I with a short exposure time of 30 s, and substantivity until 12 h after rinsing, whereas the other antiseptics hardly showed any substantivity |
| 7   | Nakaminami et al. 2019 | Japan | In vitro | qacA/B-positive or negative MRSA | 1.5% OLG | None | MBC50 50% strain bactericidal and MBC90 90% strain bactericidal (µg/mL) | • Fast-acting bactericidal activity of OLG against qacA/B-positive MRSA is higher than that of CHG |
| 8   | Ni et al. 2019 | Japan | In vitro | Human oral keratinocytes with the addition of LPS from Porphyromonas gingivalis | 0.1% OLG | None | Degree of decrease in pro-inflammatory cytokines produced by human oral keratinocytes after application of 0.1% OLG | • Inflammatory cytokines, which cause chronic inflammatory reactions such as periodontitis, decreased after application of 0.1% OLG, suggesting that OLG could have anti-inflammatory effects |
| 9   | Imai et al. 2021 | Japan | In vitro | Influenza A (H1N1), human coronavirus OC43, feline infectious peritonitis virus, human herpesvirus, respiratory syncytial virus | OLG-HR (1.5%), 1.5% OLG, 0.5% OLG | ETOH, 0.1% benzalkonium chloride, 0.5% CHG | Mean log_{10} reduction | • OLG-containing disinfectants are as effective as ETOH in disinfecting some viruses |
| 10  | Nakata et al. 2017 | Japan | In vitro | Microorganisms from Male cynomolgus monkey’s skin | 1% OLG, 1.5% OLG, 2% OLG | 0.5% CHG, 10% PVP-I and normal saline (as a negative control) | Bacterial count after 10 min and 6 h, and the log_{10} reduction after | • Bactericidal effects of OLG were comparable to those of commercial antiseptics such as CHG and PVP-I in non-
Table 1. (Continued)

| No. | First author, year     | Country | Design       | Object                | Intervention                          | Comparison                          | Outcomes                              | Main findings                                                                 |
|-----|------------------------|---------|--------------|-----------------------|---------------------------------------|-------------------------------------|---------------------------------------|--------------------------------------------------------------------------------|
| 11  | Sakagami et al. 2000   | Japan   | In vitro     | Applied to normal skin without any treatment to simulate a standard presurgical application, and dirty skin with blood | OLG (concentration unknown)           | None                                | application of the antiseptic         | blood-contaminated conditions        |
|     |                        |         |              |                       |                                       |                                     | The bactericidal effect of the antiseptic on blood-contaminated skin | • Effect of OLG was hardly affected by blood, unlike commercial antiseptics |
|     |                        |         |              |                       |                                       |                                     | MIC and MBC of OLG                   | • OLG showed strong bactericidal activity against MRSA |
|     |                        |         |              |                       |                                       |                                     |                                       | • Marked decrease in MRSA cell numbers was recognized as the OLG concentration was increased |
| 12  | Umehara et al. 2000    | Japan   | In vitro     | Dog liver microsomes  | OLG (concentration unknown)           | None                                | Measurement of metabolites of OLG    |                                                                                     |
| 13  | Umehara et al. 2000    | Japan   | In vitro     | Rat and dog liver microsomes | OLG (concentration unknown)           | None                                | Measurement of metabolites of OLG    |                                                                                     |
| 14  | Sakagami et al. 2000   | Japan   | In vitro     | Pseudomonas aeruginosa | OLG (concentration unknown)           | None                                | MIC and MBC of OLG                   | • OLG was bactericidal by acting on the cell membrane and cell wall of Pseudomonas aeruginosa at MIC |
| 15  | Nakazawa et al. 2018   | Japan   | In vitro     | Staphylococcus aureus | 1.5% OLG 20% CHG                      | None                                | MIC                                   | • OLG has bactericidal effect against MRSA with qacA/B gene                          |
| 16  | Fujio et al. 2000      | Japan   | Animal study | Rats                  | OLG (concentration unknown)           | subcutaneous administration          | Reproductive and developmental adverse events | • No effect of the drug application on the estrus cycle of female rats, fertilization rate, nursery condition of mothers after birth, and all cycles up to fetal development |
| 17  | Kudo et al. 1998       | Japan   | Animal study | Rats                  | OLG (concentration unknown)           | subcutaneous administration          | Measurement of metabolites absorbed subcutaneously | • OLG remained in the skin and was poorly absorbed                                |
Table 1. (Continued)

| No. | First author, year | Country | Design | Object | Intervention | Objectives | Outcomes |
|-----|--------------------|---------|--------|--------|--------------|------------|----------|
| 18  | Kudo et al. 1998   | Japan   | Animal study | Rats | OLG (concentration unknown) subcutaneous administration | None | Measurement of metabolites absorbed subcutaneously |
|     |                    |         |        |        |              |            |          |
| 19  | Kudo et al. 1998   | Japan   | Animal study | Rats | OLG (concentration unknown) subcutaneous administration | None | Measurement of metabolites absorbed subcutaneously |
|     |                    |         |        |        |              |            |          |
| 20  |                    | Japan   | Animal study | Rats | OLG (concentration unknown) subcutaneous administration | None | Measurement of metabolites absorbed subcutaneously |
|     |                    |         |        |        |              |            |          |
| 21  |                    | Japan   | Animal study | Beagle dogs | OLG (concentration unknown) subcutaneous administration | None | Measurement of metabolites absorbed subcutaneously |
|     |                    |         |        |        |              |            |          |
| 22  |                    | Japan   | Animal study | Rats | OLG (concentration unknown) subcutaneous administration | None | Measurement of metabolites absorbed subcutaneously |
|     |                    |         |        |        |              |            |          |
| 23  |                    | Japan   | Animal study | Rats | OLG (concentration unknown) subcutaneous administration | None | Measurement of metabolites absorbed subcutaneously |
|     |                    |         |        |        |              |            |          |
| 24  | Takenaka et al. 1998 | Japan   | Animal study | Rabbits | OLG (concentration unknown) subcutaneous administration | None | Measurement of metabolites absorbed subcutaneously |
|     |                    |         |        |        |              |            |          |
| 25  | Takenaka et al. 1998 | Japan   | Animal study | Rats | OLG (concentration unknown) subcutaneous administration | None | Measurement of metabolites absorbed subcutaneously |
|     |                    |         |        |        |              |            |          |
| 26  | Takenaka et al. 1998 | Japan   | Animal study | Rats | OLG (concentration unknown) subcutaneous administration | None | Measurement of metabolites absorbed subcutaneously |
|     |                    |         |        |        |              |            |          |
| No. | First author, year | Country | Design | Object | Intervention | Comparison | Outcomes | Main findings |
|-----|-------------------|---------|--------|--------|--------------|------------|----------|--------------|
| 27  | Hosoya et al. 2016 | Japan   | Gray paper | None | None | None | None | None |
| 28  | Oie 2019          | Japan   | Gray paper | None | None | None | None | None |
| 29  | Taketomi 2015    | Japan   | Gray paper | None | None | None | None | None |

**Clinical effects**

| No. | First author, year | Country | Design | Object | Intervention | Comparison | Outcomes | Main findings |
|-----|-------------------|---------|--------|--------|--------------|------------|----------|--------------|
| 30  | Harhara et al. 2015 | Japan   | RCT | Adults | 1.5% OLG | Placebo 0.5% CHG | Bacteria count after 10 min of application | Rate of adverse events in 1.5% OLG, 0.5% CHG, and placebo |
| 31  | Obatake et al. 2020 | Japan   | Not mentioned | Children | OLG (concentration unknown) | None | Disinfection effect after 10 min of application | Rate of adverse events in 1.5% OLG and 10% PVP-I |
| 32  | Nagai et al. 2000 | Japan   | RCT | Adults | OLG (0.02%, 0.05%, 0.1%, 0.2%) CHG (0.05%, 0.5%) | Exponential reduction value of total viable bacteria before and after application | OLG was found to be more effective than CHG in reducing skin bacteria after 30 s and 3 min of application to normal skin |
| 33  | Kobayashi et al. 2000 | Japan   | Not mentioned | Adults | 0.05% OLG | None | Wound infection prevention and disinfection effects | Application of 0.05% OLG to wounded skin was found to be effective in preventing wound infection and disinfection |
| 34  | Matsumoto et al. 2018 | Japan   | Retrospective study | Adults | OLG (concentration unknown) | None | SSI incidence rate at 30 days postoperatively | OLG was effective in preventing surgical site infection |
| 35  | Harhara et al. 2020 | Japan   | Retrospective study | Adults | 1.5% OLG (applicator) | 10% PVP-I 1% CHG | All SSI incidence rates Adverse events | Incidence rate of SSI in gastrointestinal surgery was found to be lower in 1.5% OLG |
| 36  | Obara et al. 2020 | Japan   | RCT | Adults | 1.5% OLG | 10% PVP-I | 30-day postoperative SSI rate | Incidence rate of rash was found to be higher with OLG compared to PVP-I |

- Brief description of the bactericidal action of OLG and the results of clinical trials
- OLG has the advantages of less dripping and nonflammability. However, OLG is expensive
- OLG product features were described

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Table 1. (Continued)

| No. | First author, year | Country | Design | Object | Intervention | Comparison | Outcomes | Main findings |
|-----|-------------------|---------|--------|--------|--------------|------------|----------|---------------|
| 37  | Shiyanagi et al. 2019 | Japan | Retrospective study | Children | 1.5% OLG (applicator) | 10% PVP-I | All SSI incidence rates |
| 38  | Yamamoto et al. 2020 | Japan | RCT | Adults | Single application OLG applicator (concentration unknown) | Double applications OLG applicator (concentration unknown) | 30-day postoperative incisional SSI rate |
| 39  | Sugai, 1999 | Japan | Not mentioned | Adults | OLG (0.05%, 0.1%, 0.2%, 0.3%, 0.4%, 0.5%) | Placebo | Adverse events |
| 40  | Sugai, 1999 | Japan | Not mentioned | Adults | OLG (0.1%, 0.5%) | None | Adverse events |
| 41  | Sugai, 1999 | Japan | Not mentioned | Adults | 0.1% OLG, 0.5% OLG | None | Adverse events |
| 42  | Sugai, 1999 | Japan | Not mentioned | Adults | OLG (0.005%, 0.01%, 0.03%, 0.05%, 0.1%) | Placebo | Adverse events |
| 43  | Obara et al. 2020 | Japan | RCT | Adults | 1.5% OLG | Placebo, 0.5% OLG | Adverse events |
| 44  | Shiyanagi et al. 2019 | Japan | Retrospective study | Adults | 1.5% OLG | 10% PVP-I | Adverse events |
| 45  | Matsuoka et al. 2019 | Japan | Retrospective study | Adults | 1.5% OLG | PVP-I (concentration unknown) | Adverse events |
| 46  | Iijima et al. 2020 | Japan | Case report | 34 y.o. woman | OLG (concentration unknown) | None | Adverse events |
| 47  | Nagai et al. 2018 | Japan | Case report | 65 y.o. man, 66 y.o. woman | OLG (concentration unknown) | None | Adverse events |

Pharmacological effects:

- Incidence rate of SSI in clean surgery was found to be low for 1.5% OLG and 10% PVP-I.
- No difference in the incidence of SSI within 30 days postoperatively between single and double applications of OLG.
- Adverse events resulting from the application of OLG to healthy adults.
- Rate of adverse events in 1.5% OLG and 10% PVP-I.
- Incidence rate of chemical burn was found to be lower with 1.5% OLG compared to 10% PVP-I.
- Erythema and pruritus appeared on day 10 after OLG application.
- Erythema appeared after day 6 of OLG application.

Abbreviations: CFU, colony forming unit; CHG, chlorhexidine gluconate; CHG-AL, chlorhexidine gluconate alcohol; ETOH, ethanol; LPS, lipopolysaccharide; MBC, minimum bactericidal concentration; MIC, minimum inhibitory concentration; MRSA, methicillin-resistant Staphylococcus aureus; OLG-HR, OLG ethanol hand rub; PVP-I, povidone-iodine; RCT, randomized controlled trial; SSI, surgical site; VRE, vancomycin-resistant enterococci.
denaturation effect\textsuperscript{23,28} (with olanexidine at a concentration of 15 000 \( \mu \)g/mL), which means that it has both low and high concentration effects.

**Inhibitory action of inflammatory chemokines (in vitro)**

In addition to the bactericidal effects of OLG, it is reported that OLG has an inhibitory action on inflammatory chemokines. Nii et al.\textsuperscript{20} administered the LPS of *Porphyromonas gingivalis* to immortalized human oral keratinocytes, which are regarded as oral epithelial cells, and tested whether the inflammatory cytokines produced by human oral keratinocytes decreased after 0.1% OLG application. The levels of inflammatory cytokines such as interleukin-8, chemokine (C-C motif) ligand 20, and growth-regulated oncogene protein-\( \alpha \), which cause chronic inflammatory reactions such as periodontitis, decreased after 0.1% OLG application. This suggests that OLG could inhibit the inflammatory response.\textsuperscript{31}

**Spectrum (in vitro)**

Nine studies validated the spectrum: seven for bacteria and fungi\textsuperscript{20,22,25,28} and four for viruses.\textsuperscript{28,32,33} Several studies\textsuperscript{20,23,25,28} used the minimum bactericidal concentration (MBC) at which bacterial growth did not occur as an indicator of the bactericidal effect of skin disinfectants.

**Bacteria** Seyama et al. undertook a study\textsuperscript{21} to examine the bactericidal effect of 1.5% OLG on Gram-positive cocci, including MRSA and VRE, Gram-negative bacteria (*Burkholderia cepacia* and *Pseudomonas aeruginosa*), and fungi. The number of most Gram-positive cocci, including MRSA and VRE, reduced within 15 s after 1.5% OLG application (Table 2).

For MRSA, two studies showed that 1.5% OLG was more effective for disinfection than 0.5% CHG and 10% PVP-I (Table 3).\textsuperscript{22,25} In addition, two studies\textsuperscript{20,24} compared whether the MBC of OLG, CHG, and PVP-I changed in the presence or absence of *qacA/B*, which encodes a disinfectant efflux pump thought to be responsible for methicillin resistance. The researchers reported that only the MBC of OLG remained unchanged in the presence or absence of *qacA/B* (Table 3).

However, 1.5% OLG was more effective in disinfection against VRE than 0.5% CHG and 10% PVP-I.\textsuperscript{22,25} Inoue et al.\textsuperscript{25} also compared the MBC of OLG, CHG, and PVP-I against MRSA and VRE: the MBC of OLG against MRSA and VRE was equal to or lower than that of CHG or PVP-I (Table 3).

Regarding the bactericidal effect on resistant bacteria other than MRSA and VRE, such as methicillin-resistant *Staphylococcus epidermidis*, extended-spectrum \( \beta \)-lactamase-producing *Klebsiella pneumoniae*, and multidrug-resistant *P. aeruginosa*, 1.5% OLG killed these bacteria within 15 s after 1.5% OLG application\textsuperscript{21} (Table 3). However, *B. cepacia* was not eliminated more than 30 min after 1.5% OLG application,\textsuperscript{21,23} and the bactericidal effect of 1.5% OLG on *B. cepacia* was comparable to those of CHG and PVP-I (concentrations unknown) reported in a previous study.\textsuperscript{12} Furthermore, 1.5% OLG had a poor bactericidal effect on Mycobacterium, consistent with the previously reported bactericidal effect of CHG (concentration unknown).\textsuperscript{21,35}

**Fungi** Surfaces contaminated with *Candida albicans* and *Malassezia furfur* were disinfected within 30 s after 1.5% OLG application, whereas those contaminated with *Mycosporum canis* and *Trichophyton rubrum* were disinfected within 3 and 10 min, respectively, after 1.5% OLG application.\textsuperscript{21} However, *Aspergillus brasiliensis* was not eliminated even after 10 min of 1.5% OLG application (Table 2).

**Viruses** Influenza A virus, which has an envelope, was inactivated by 1.5% OPB for more than 1 min after application. However, feline calicivirus, which does not have an envelope, was not inactivated even 10 min after application.\textsuperscript{28}

In addition, Imai et al.\textsuperscript{33} reported on the efficacy of OLG hand rub against 11 genotypes of noroviruses, in which ethanol was added to OLG (concentration unknown) for hand disinfection. The OLG hand rub had the highest antiviral effect, when compared to other agents (ethanol [pH 7], ethanol-A [pH 3], and OLG), suggesting its potential for use as a hand sanitizer (Table 2). Imai et al.\textsuperscript{34} also reported on the potential usage of OLG formulations as environmental disinfectants for the control of infections by enveloped viruses (influenza A [H1N1], human coronavirus, feline infectious peritonitis virus, human herpesvirus, and respiratory syncytial virus).

**Immediate and sustained bactericidal action (in vitro/animal studies)**

Four studies were identified: three on the time-to-onset of bactericidal action\textsuperscript{20,22} and two on the duration of bactericidal action.\textsuperscript{22,36}
| First author, year | Microorganism                                                                 | Method                                                                 | Time and indicator                                                                 | Result                                                                 |
|--------------------|------------------------------------------------------------------------------|------------------------------------------------------------------------|---------------------------------------------------------------------------------|-----------------------------------------------------------------------|
| **Effective**      | **Bacteria**                                                                  |                                                                        |                                                                                 |                                                                       |
| Seyama et al. 2019 | Gram-positive bacterium                                                        | Evaluation of bactericidal effect by time kill assay (<10, detection limit) | Viable bacterial count (CFU/mL) at 0 s, 15 s, 30 s, and 1 min after 1.5% OLG administration | 15 s: <10 30 s: <10 1 min: <10                                      |
|                    | *Enterococcus faecalis*                                                        |                                                                        |                                                                                 |                                                                       |
|                    | Vancomycin-resistant enterococci                                              |                                                                        |                                                                                 |                                                                       |
|                    | *Staphylococcus aureus*                                                       |                                                                        |                                                                                 |                                                                       |
|                    | Methicillin-resistant                                                        |                                                                        |                                                                                 |                                                                       |
|                    | *Staphylococcus aureus*                                                       |                                                                        |                                                                                 |                                                                       |
|                    | epidermidis                                                                  |                                                                        |                                                                                 |                                                                       |
|                    | Methicillin-resistant                                                        |                                                                        |                                                                                 |                                                                       |
|                    | *Staphylococcus epidermidis*                                                  |                                                                        |                                                                                 |                                                                       |
|                    | Gram-negative bacterium                                                       |                                                                        |                                                                                 |                                                                       |
|                    | *Acinetobacter baumannii*                                                     |                                                                        |                                                                                 |                                                                       |
|                    | *Enterobacter cloacae*                                                        |                                                                        |                                                                                 |                                                                       |
|                    | Extended spectrum β-lactamase producing                                      |                                                                        |                                                                                 |                                                                       |
|                    | *Klebsiella pneumoniae*                                                       |                                                                        |                                                                                 |                                                                       |
|                    | *Escherichia coli*                                                            |                                                                        |                                                                                 |                                                                       |
|                    | *Pseudomonas aeruginosa*                                                      |                                                                        |                                                                                 |                                                                       |
|                    | Multidrug-resistant                                                          |                                                                        |                                                                                 |                                                                       |
|                    | *Pseudomonas aeruginosa*                                                      |                                                                        |                                                                                 |                                                                       |
|                    | *Serratia marcescens*                                                         |                                                                        |                                                                                 |                                                                       |
|                    | *Bacteroides fragilis*                                                        |                                                                        |                                                                                 |                                                                       |
| Seyama et al. 2019 | *Candida albicans*                                                            |                                                                        |                                                                                 |                                                                       |
|                    | *Malassezia furfur*                                                           |                                                                        |                                                                                 |                                                                       |
|                    | *Trichophyton rubrum*                                                         |                                                                        |                                                                                 |                                                                       |
|                    | *Microsporum canis*                                                           |                                                                        |                                                                                 |                                                                       |
| **Fungi**          |                                                                              |                                                                        |                                                                                 |                                                                       |
| Seyama et al. 2019 | *Candida albicans*                                                            |                                                                        |                                                                                 |                                                                       |
|                    | *Malassezia furfur*                                                           |                                                                        |                                                                                 |                                                                       |
|                    | *Trichophyton rubrum*                                                         |                                                                        |                                                                                 |                                                                       |
|                    | *Microsporum canis*                                                           |                                                                        |                                                                                 |                                                                       |
| **Virus**          |                                                                              |                                                                        |                                                                                 |                                                                       |
| Medical package    | Influenza A                                                                   | No detailed description                                                |                                                                                 |                                                                       |
| insert 2021        |                                                                              |                                                                        |                                                                                 |                                                                       |
| Imai et al. 2021   | Influenza A (H1N1)                                                            | Suspension test (comparison agents: OLG-HR [1.5%], 1.5% OLG, 0.5% OLG, ETOH, 0.1% benzalkonium chloride, 0.5% CHG) | Mean log$_{10}$ reduction ± 95% CI at 15 s, 30 s, 1 min | Inactivation in 1 min or more 1.5% OLG, OLG-HR, and ETOH completely inactivated at all time |
|                    |                                                                              |                                                                        |                                                                                 |                                                                       |
| Imai et al. 2020   | Norovirus (all 11 genotypes of GI, GII, and GIV)                              | Assay log$_{10}$ RNA copies by RT-qPCR (comparison agents: OLG-HR, ETOH [pH 7], ETOH-A [pH 3], OLG, base with OLG removed from OLG-HR) | Log$_{10}$ reduction at 30 s, 1 min | 30 s: log$_{10}$ reduction of OLG-HR is the highest 1 min: log$_{10}$ reduction of OLG-HR is the highest |
Table 2. (Continued)

| First author, year | Microorganism | Method | Time and indicator | Result |
|--------------------|---------------|--------|--------------------|--------|
| Imai et al. 2021   | Human coronavirus OC43 | Suspension test (comparison agents: OLG-HR [1.5%], 1.5% OLG, 0.5% OLG, EtOH, 0.1% benzalkonium chloride, 0.5% CHG) | Mean log_{10} reduction ± 95% CI at 15 s, 30 s, and 1 min | Viral titers after exposure to 0.5% OLG, 1.5% OLG, OLG-HR, and EtOH for 15 s were under the quantification limits. 1.5% OLG, OLG-HR, and EtOH completely inactivated at all time. Viral titers were under the quantification limits at all time. |
| Feline infectious peritonitis virus | | | | |
| Human herpesvirus | | | | |
| Respiratory syncytial virus | | | | |

**Not effective**

**Bacterium**

| Seyama et al. 2019 | Burkholderia cepacia | Evaluation of bactericidal effect by time kill assay (<10, detection limit) | Viable bacterial count (CFU/mL) at 0 s, 15 s, 30 s, and 1 min after 1.5% OLG administration | At all time points: not killed |
|--------------------|----------------------|------------------------------------------------|-------------------------------------------------|-----------------------------|
| Mycobacterium      | Mycobacterium kansasii | Evaluation of bactericidal effect by time kill assay (<10, detection limit) | Viable bacterial count (CFU/mL) at 0 s, 15 s, 30 s, 1 min, 60 min after 1.5% OLG administration | At all time points: not killed |
|                    | Mycobacterium intracellular | | | |
|                    | Mycobacterium fortuitum | | | |
|                    | Mycobacterium chelonae | | | |
|                    | Mycobacterium abscessus | | | |
|                    | Mycobacterium abscessus | | | |
|                    | Mycobacterium avium | | | |

**Fungi**

| Seyama et al. 2019 | Aspergillus brasiliensis | Evaluation of bactericidal effect by time kill assay (<10, detection limit) | Viable bacterial count (CFU/mL) at 0 s, 15 s, 30 s, and 10 min after 1.5% OLG administration | At all time points: not killed |
|--------------------|--------------------------|------------------------------------------------|-------------------------------------------------|-----------------------------|
| Medical package insert | | No detailed description | MBC (%) at 30 min | 30 min: not killed |
| Medical package insert | Microsporum canis | No detailed description | MBC (%) at 30 min | 30 min: not killed |

**Virus**

| Medical package insert | Feline calicivirus | No detailed description | Log_{10} reduction (only mentioned at 10 min) | 10 min: not killed |

**Note:** All studies are in vitro and animal studies.

**Abbreviations:** CFU, colony forming unit; CHG, chlorhexidine gluconate; CI, confidence interval; EtOH, ethanol; MBC, minimum bactericidal concentration; OLG-HR, olanexidine gluconate/ethanol hand rub; RT-qPCR, reverse transcription–quantitative polymerase chain reaction.
| First author, year | Microorganism | Object | Time and indicator | Concentration of OLG | Comparison (concentration) | Result |
|-------------------|---------------|--------|-------------------|----------------------|---------------------------|--------|
| Gram-positive bacterium | Methicillin-susceptible *Staphylococcus aureus* | Clinical isolates (30 strains) | MBC (μg/mL) at 30 s, 1 min, 3 min | Unknown | CHG (unknown) PVP-I (unknown) | 30 s: MBC of PVP-I was the lowest (OLG, >3,480; PVP-I, 1,560) <br> 1 min: MBC of PVP-I was the lowest (OLG, >1,740; PVP-I, 781) <br> 3 min: MBC of CHG was the lowest (OLG, 8,69; CHG, 156) |
| Hagi et al. 2015 | Methicillin-resistant *Staphylococcus aureus* | Culture collections (1 strain) | MBC (μg/mL) at 30 s, 1 min, 3 min | Unknown | CHG (unknown) PVP-I (unknown) | 30 s: MBC of OLG was equal to that of PVP-I and lower than that of CHG <br> 1 min: MBC of OLG was equal to that of PVP-I and lower than that of CHG <br> 3 min: MBC of CHG was the lowest |
| Inoue et al. 2015 |  | Clinical isolates (30 strains) | Log of the number of survived bacteria at 30 s, 3 min, and 10 min | 1.5% | 0.5% CHG 10% PVP-I | 1 min: Log of the number of survived bacteria of 1.5% OLG was equal to that of 10% PVP-I and lower than that of 0.5% CHG <br> 10 min: Log of the number of survived bacteria of 1.5% OLG was equal to that of 10% PVP-I and lower than that of 0.5% CHG |
| Nishioka et al. 2018 |  | Applied to the skin of mice (culture collections) | Log fot reduction at 30 s and 3 min | 1.5% | 0.5% CHG 10% PVP-I | 30 s: log reduction of 1.5% OLG was equal to that of 1% CHG AL and higher than those of 0.5% CHG and 10% PVP-I <br> 3 min: log reduction of 1.5% OLG was equal to that of 1% CHG AL and higher than those of 0.5% CHG and 10% PVP-I |
| First author, year | Microorganism | Object | Time and indicator | Concentration of OLG | Comparison (concentration) | Result |
|-------------------|---------------|--------|---------------------|----------------------|----------------------------|--------|
| Nakaminami et al. 2019 | Clinical isolates (19 qacA/B-positive strains and 10 qacA/B-negative strains) | MBC50 (50% strain bactericidal) and MBC90 (90% strain bactericidal) (µg/mL) at 2 min, 5 min and 30 min | Unknown | CHG (unknown) | PVP-I (unknown) | 2 min: MBC of OLG was equal to that of PVP-I and lower than that of CHG 5 min: MBC of OLG was equal to that of PVP-I and lower than that of CHG 30 min: MBC of OLG was equal to that of PVP-I and lower than that of CHG MBC of OLG was the same with or without qacA/B |
| Hagi et al. 2015 | Coagulase-negative Staphylococcus | Clinical isolates (20 strains) | MBC (µg/mL) at 30 s, 1 min, and 3 min | Unknown | CHG (unknown) | PVP-I (unknown) |
| Nishioka et al. 2018 | Staphylococcus epidermidis | Applied to the skin of the Yucatan micropig (culture collections) | Log₁₀ reduction at 30 s and 3 min | 1.5% | 0.5% CHG 10% PVP-I 1% CHG-AL |
| Inoue et al. 2015 | Enterococcus spp. | Culture collections (34 strains) | MBC (µg/mL) at 30 s, 1 min, and 3 min | Unknown | CHG (unknown) | PVP-I (unknown) |
| Hagi et al. 2015 | Enterococcus faecalis | Clinical isolates (30 strains) | MBC (µg/mL) at 30 s, 1 min, and 3 min | Unknown | CHG (unknown) | PVP-I (unknown) |
| Inoue et al. 2015 | Vancomycin-resistant | Culture collections (1 strain) | MBC (µg/mL) at 30 s, 1 min, and 3 min | Unknown | CHG (unknown) | PVP-I (unknown) |
| First author, year | Microorganism | Object | Time and indicator | Concentration of OLG | Comparison (concentration) | Result |
|-------------------|---------------|--------|-------------------|----------------------|--------------------------|--------|
| Nishioka et al. 2018 | *Enterococcus faecalis* | Applied to the skin of mice (culture collections) | Log of the number of survived bacteria at 30 s, 3 min, and 10 min | 1.5% | 0.5% CHG 10% PVP-I | 30 s: Log of the number of survived bacteria of 1.5% OLG was the lowest 3 min: Log of the number of survived bacteria of 1.5% OLG was the lowest 10 min: Log of the number of survived bacteria of 1.5% OLG was the lowest |
| Hagi et al. 2015 | Gram-positive bacilli | Culture collections (9 strains) | Log$_{10}$ reduction at 30 s and 3 min | 1.5% | 0.5% CHG 10% PVP-I 1% CHG-AL | 30 s: Log$_{10}$ reduction of 1.5% OLG was equal to that of 1% CHG-AL. Log$_{10}$ reduction of 1.5% OLG was higher than those of 0.5% CHG and 10% PVP-I 3 min: Log$_{10}$ reduction of 1.5% OLG was equal to those of 1% CHG-AL and 0.5% CHG. Log$_{10}$ reduction of 1.5% OLG was higher than that of 10% PVP-I |
| Hagi et al. 2015 | Gram-negative strains except *Burkholderia cepacia* | Culture collections (34 strains) | MBC (μg/mL) at 30 s, 1 min, and 3 min | Unknown | CHG (unknown) PVP-I (unknown) | 30 s: MBC of PVP-I was the lowest (OLG, 1,740; PVP-I, 781) 1 min: MBC of PVP-I was the lowest (OLG, 1,740; PVP-I, 781) 3 min: MBC of OLG was the lowest |
| | *Burkholderia cepacia* | Culture collections (2 strains) | MBC (μg/mL) at 30 s, 1 min, 3 min | Unknown | CHG (unknown) PVP-I (unknown) | 30 s: MBC of OLG was the lowest 1 min: MBC of OLG was the lowest 3 min: MBC of OLG was the lowest |
| | *Escherichia coli* | Clinical isolates (20 strains) | MBC (μg/mL) at 30 s, 1 min, 3 min | Unknown | CHG (unknown) PVP-I (unknown) | 30 s: MBC of OLG was the lowest 1 min: MBC of OLG was the lowest 3 min: MBC of OLG was the lowest |
| Microorganism       | Object                      | Time and indicator | Result                                                                 |
|---------------------|-----------------------------|--------------------|----------------------------------------------------------------------|
| *Klebsiella*        | *pneumoniae*                |                    | MBC (mg/mL) at 30 s, 1 min, 3 min                                      |
|                     | Clinical isolates (20 strains) |                    |                                                                      |
|                     | MBC: CHG (unknown) PVP-I (unknown) |                    |                                                                      |
|                     | 30 s: MBC of OLG was the lowest |                    |                                                                      |
|                     | 1 min: MBC of OLG was the lowest |                    |                                                                      |
|                     | 3 min: MBC of OLG was the lowest |                    |                                                                      |
|                     | PVP-I (unknown)              |                    |                                                                      |
| *Pseudomonas*       | *aeruginosa*                |                    | MBC (mg/mL) at 30 s, 1 min, 3 min                                      |
|                     | Clinical isolates (20 strains) |                    |                                                                      |
|                     | MBC: CHG (unknown) PVP-I (unknown) |                    |                                                                      |
|                     | 30 s: MBC of PVP-I was the lowest |                    |                                                                      |
|                     | 1 min: MBC of OLG was the lowest |                    |                                                                      |
|                     | 3 min: MBC of OLG was the lowest |                    |                                                                      |
|                     | OLG, 869; PVP-I, 781         |                    |                                                                      |
| *Serratia*          | *marcescens*                |                    | MBC (mg/mL) at 30 s, 1 min, 3 min                                      |
|                     | Clinical isolates (20 strains) |                    |                                                                      |
|                     | MBC: CHG (unknown) PVP-I (unknown) |                    |                                                                      |
|                     | 30 s: MBC of PVP-I was the lowest |                    |                                                                      |
|                     | 1 min: MBC of OLG was the lowest |                    |                                                                      |
|                     | 3 min: MBC of OLG was the lowest |                    |                                                                      |
|                     | OLG, 3,489; PVP-I, 391       |                    |                                                                      |
| *Acinetobacter*     | *baumannii*                 |                    | MBC (mg/mL) at 30 s, 1 min, 3 min                                      |
|                     | Clinical isolates (20 strains) |                    |                                                                      |
|                     | MBC: CHG (unknown) PVP-I (unknown) |                    |                                                                      |
|                     | 30 s: MBC of OLG was the lowest |                    |                                                                      |
|                     | 1 min: MBC of OLG was the lowest |                    |                                                                      |
|                     | 3 min: MBC of OLG was the lowest |                    |                                                                      |
|                     | OLG, 3,489; PVP-I, 391       |                    |                                                                      |
| *Staphylococcus*    | *epidermidis*               |                    | Log10 reduction at 30 s                                              |
|                     | Applied to the skin of the Yucatan micropig (culture collections) |                    |                                                                      |
|                     | 1.5% CHG                    |                    |                                                                      |
|                     | 10% PVP-I                   |                    |                                                                      |
|                     | 1% CHG-AL                   |                    |                                                                      |
|                     | 0.5% CHG                    |                    |                                                                      |

Note: All studies are in vitro and animal studies. Abbreviations: CFU, colony forming unit; MBC, minimum bactericidal concentration.
Immediate efficacy (in vitro/animal studies)

As mentioned in the section on spectrum, 1.5% OLG showed a disinfectant effect on a wide range of bacteria within 30 s (Tables 2 and 3). Furthermore, Nishioka et al. compared the bacterial counts of MRSA, S. epidermidis, VRE, Acinetobacter baumannii, Corynebacterium minutissimum, and Cutibacterium acnes, which were problematic in SSI, while comparing 1.5% OLG with 0.5% CHG and 10% PVP-I. Compared to 10% PVP-I and 0.5% CHG, 1.5% OPB showed an equivalent or greater reduction in bacterial counts 30 s after application.

Substantivity (animal studies)

Nishioka et al. discussed the amount of disinfectant left in the stratum corneum after 4, 8, and 12 h of rinsing immediately after application. The concentration of 1.5% OLG left was 2.8–4.2 times higher in the stratum corneum than that of 1.5% CHG at all incubation times. This indicated that the rate of washout for 1.5% OLG was lower than that for 1.5% CHG. The proportion of bacteria after 12 h of 1.5% OLG application was lower than that after 4 and 8 h, indicating that the bactericidal action time was approximately 12 h. Regarding the long action time of OLG, the reduced effectiveness of disinfectants was generally attributed to sweating and contamination with blood. Nakata et al. evaluated the effectiveness of reducing bacteria after 10 min and 6 h of application of 0.5% CHG, 10% PVP-I, and 1.5% OLG on blood-contaminated monkey skin. The decrease in bacterial count after 1.5% OLG application was higher than that after the application of 0.5% CHG or 10% PVP-I, indicating that the decrease in bactericidal action with blood contamination was smallest after 1.5% OLG application, compared to 0.5% CHG and 10% PVP-I.

Pharmacokinetics (animal studies)

Thirteen studies on pharmacokinetics were identified: three on dermal absorption, eight on metabolism and excretion, and five on biogenesis. Concerning dermal absorption, Kudo et al. reported two studies: one in which the radioactivity at the injection site was measured at 1, 8, and 24 h after dermal administration of biguanide 14C-labeled OLG (concentration unknown) in rats and another in which the dermal absorption of 0.1% OLG after the application was measured in intact and damaged rat skin. Olanexidine gluconate remained in the skin and was poorly absorbed in both studies. Regarding reproduction and development, Fujio et al. and Takenaka et al. carried out animal experiments on rats and rabbits. Parental animals treated subcutaneously with 0.04%–0.0004% OLG showed no effect of the drug application on the estrus cycle of female rats, fertilization rate, nursery condition of mothers after birth, and all cycles up to fetal development.

Clinical setting

Considering that the balance between the benefits and disadvantages is important for clinical adaptation, we provide a description of the efficacy and safety.

Efficacy

Normal skin

Three studies were undertaken on normal skin. Two of the studies were RCTs. Two studies included adults, and one study included children. One study compared 1.5% OLG, 0.5% CHG, and placebo. One study compared OLG with CHG; the concentration of OLG ranged from 0.02% to 0.2%, and that of CHG ranged from 0.05% to 0.5%. One study determined the efficacy of OLG (concentration unknown) without a comparator (Table 4).

In an RCT that assessed the efficacy of 1.5% OLG on normal skin, OLG showed a significant reduction in bacterial counts after 10 min of application on both the abdomen and groin, compared to placebo. Furthermore, 1.5% OLG was not inferior to 0.5% CHG. Obatake et al. collected samples from the skin (groin and umbilicus) both before and after disinfection with OLG (concentration unknown) and compared the presence or absence of bacteria. It was reported that OLG had a good bactericidal effect on both the groin and umbilical areas; however, specific data were unavailable. In a comparison of the number of viable bacteria before and after disinfection with various concentrations of OLG and CHG, both after 30 s and 3 min of disinfectant application, the exponential reduction in total viable bacterial counts was higher in the OLG groups than in the CHG groups at all concentrations.

Wounded skin

One study evaluated wounded skin. The study population consisted of 50 adult inpatients who underwent clean or semiclean surgical procedures (Table 4). The researchers applied 0.05% OLG to surgically sutured wounds on postoperative days 3, 7, and 14. No antiseptics were used for comparison. The efficacy rate determined by infection prevention and disinfection efficacy was 59.6% (95% confidence interval, 44.4–73.6). The efficacy was adjudged comprehensively based on progress after application and was not described in detail.
Prevention of SSI

Five studies evaluated the effect on SSI prevention.26,55–58 Two studies were RCTs, and three were retrospective observational studies. One study included children, and the remaining four studies included adults. One study compared OLG, PVP-I, and CHG,57 two studies compared OLG to PVP-I,26,56 and one study had no comparator.58 One study

Table 4. Effect of olanexidine gluconate (OLG) on normal skin and wounded skin

| First author, year | Design | Object | Intervention | Comparison | Efficacy |
|--------------------|--------|--------|--------------|------------|----------|
| Harihara et al. 201552 | RCT | Adults; region: abdomen, groin | 1.5% OLG | Placebo 119 cases | Item: bacteria count after 10 min of application Result: (OLG vs. placebo) 1.5% OLG < placebo (OLG vs. CHG) 1.5% OLG is noninferior to 0.5% CHG |
| Obatake et al. 202051 | Not mentioned | Children; region: umbilicus, groin | OLG (concentration unknown), 20 cases | None | Item: disinfection effect after 10 min of application Result: good bactericidal effect |
| Nagai et al. 200053 | RCT | Adults; region: back | OLG (concentration: 0.02%, 0.05%, 0.1%, and 0.2%) Total 30 cases | CHG (concentration: 0.05% and 0.5%) Total 30 cases | Item: exponential reduction value of total viable bacteria before and after application Result: 30 s after application CHG (0.05%, 0.5%) < OLG (0.05%, 0.1%, 0.2%) 3 min after application CHG (0.05%) < OLG (0.1%, 0.2%) |
| Kobayashi et al. 200054 | Not mentioned | Adults; sutured skin wound after surgical operation | 0.05% OLG | None | Item: wound infection prevention and disinfection effects Result: 59.6% |

Note: All studies are in vivo and human studies. Abbreviation: RCT, randomized controlled trial.
compared a single application of OLG to two applications of OLG55 (Table 5).

A retrospective study58 examined the effect of OLG (concentration unknown) on the prevention of SSI in 100 patients undergoing gastrointestinal surgery, breast malignancy surgery, and inguinal hernia repair. This study reported only one case (1%) of SSI within 30 days postoperatively in the OLG group. However, 84% of all patients in the study had a low-risk National Nosocomial Infections Surveillance SSI risk index.

Obara et al.26 undertook an RCT with a large sample size comparing 1.5% OLG with 10% PVP-I for disinfection during adult gastrointestinal surgery. A total of 587 patients were included; 294 and 293 patients in the 1.5% OLG and 10% PVI groups, respectively. The 30-day postoperative SSI rate was significantly lower in the 1.5% OLG group (7% in the 1.5% OLG group vs. 13% in the 10% PVP-I group; adjusted risk ratio, 0.48; 90% confidence interval, 0.03–0.74; p = 0.002). Similarly, in another retrospective study of adult gastrointestinal surgery patients,57 the overall SSI incidence rate was significantly lower in the 1.5% OLG group (7.2% in the 1.5% OLG group vs. 10.0% in the 10% PVP-I group). This study57 did not describe the detailed statistical methods and results. A retrospective study of clean

| Table 5. Effect of olanexidine gluconate (OLG) in the prevention of surgical site infection |
|----------------------------------------|---------------------------------|-----------------|-----------------|-----------------|
| First author, year | Design | Object | Intervention | Comparsion | Efficacy |
| Matsumoto et al. 201858 | Retrospective study | Adults; surgical type: gastrointestinal surgery breast malignancy inguinal hernia repair | OLG (concentration unknown), 100 cases | None | Item: SSI incidence rate at 30 days postoperatively Result: 1% (1 case/100 cases) |
| OLG vs. PVP-I, OLG vs. CHG | Retrospective study | Adults; surgical type: gastrointestinal surgery | 1.5% OLG (applicator), 2,077 cases | 10% PVP-I, 1,556 cases 1% CHG, 1,514 cases | Item: All SSI incidence rate Result: 1.5% OLG < 1% CHG < 10% PVP-I |
| Harihara et al. 202057 | RCT | Adults; surgical type: semiclean gastrointestinal surgery | 1.5% OLG, 299 cases | 10% PVP-I, 298 cases | Item: 30-day postoperative SSI rate Result: 1.5% OLG < 10% PVP-I |
| Obara et al. 202026 | Retrospective study | Children; surgical type: clean surgery (inguinal hernia, umbilical hernia, undescended testis, scrotal ema) | 1.5% OLG (applicator), 164 cases | 10% PVP-I, 130 cases | Item: all SSI incidence rate Result: no occurrence of either OLG or PVP-I |
| Shiyanagi et al. 201956 | RCT | Adults; surgical type: gastrointestinal surgery | Single application OLG applicator (concentration unknown), 198 cases | Double applications OLG applicator (concentration unknown), 202 cases | Item: 30-day postoperative incisional SSI rate Result: no significant difference |

Note: All studies are in vivo and human studies. Abbreviations: CHG, chlorhexidine gluconate; PVP-I, povidone-iodine; RCT, randomized controlled trial; SSI, surgical site infection.
pediatric surgeries\textsuperscript{56} found no difference between the 1.5% OLG group and the 10% PVP-I group because no postoperative SSI occurred in either group.

Regarding the comparison between 1.5% OLG and 1% CHG, a retrospective study of adult gastrointestinal surgery patients\textsuperscript{57} revealed that the overall SSI incidence rate was significantly lower in the 1.5% OLG group (7.2% in the 1.5% OLG group vs. 9.8% in the 1% CHG group). However, this study\textsuperscript{57} did not describe detailed statistical methods or results.

One RCT\textsuperscript{55} compared single and double application of OLG (concentration unknown) for disinfection during laparoscopic or robotic standby gastrointestinal surgery in adults. The incident rate of all SSIs within 30 days after surgery was not significantly different between the two groups, and single application was noninferior to double application (3.1% in the single application group vs. 2.0% in the double application group, \( p = 0.537 \)).

### Prevention of CRBSI

No relevant studies were identified.

### Safety

The overall incidence of adverse events in OLG was very low, ranging from 2% to 5.8%.\textsuperscript{26,52,56,57,59–61} Erythema, dermatitis, and pruritus each accounted for approximately 1.0%–1.9% of adverse events.\textsuperscript{26,52,59,61} The time of appearance of skin rash was approximately 3–17 days (median, 7 days) after application\textsuperscript{60} (Table 6). The severity of the disease ranged from mild to moderate, with some cases of spontaneous resolution and resolution after oral antihistamine or topical corticosteroid use.\textsuperscript{26}

In an RCT\textsuperscript{26} comparing 1.5% OLG and 10% PVP-I in adult gastrointestinal surgery, there was no significant difference in the rate of all adverse events between the two groups (2% in the 1.5% OLG group vs. 2% in the 10% PVP-I group, \( p = 1.00 \)). Although the results of the detailed statistical analysis were not described, another RCT\textsuperscript{52} also showed similar results (overall adverse event rate: 5.8% [3/52 cases] in the 1.5% OLG group vs. 7.4% [4/54 cases] in the 10% PVP-I group). In contrast, a retrospective study\textsuperscript{60} comparing the incidence of postoperative dermatitis between OLG (concentration unknown) and PVP-I (concentration unknown) revealed that OLG yielded a significantly higher incidence (3.7% in the OLG group vs. 0.7% in the PVP-I group, \( p < 0.0001 \)).

Only one study, a phase III trial,\textsuperscript{52} compared OLG with CHG in terms of adverse event rates. The subjects were adults with healthy skin (abdomen and groin), and there was no difference in the rates of skin eruption between 1.5% OLG and 0.5% CHG (1.3% [3/237 cases] in the 1.5% OLG group vs. 0.8% [2/236 cases] in the 0.5% CHG group). However, the results of detailed statistical analysis were not described in this study.\textsuperscript{52}

### Ongoing clinical studies

Five ongoing clinical studies were identified. All are being undertaken in Japan, and three are related to SSI prevention. One study was related to disinfection at the time of blood culture collection, and one study was related to CRBSI (Table S3).

### DISCUSSION

I

N THE PRESENT scoping review, we searched and summarized the evidence from existing studies on OLG. The retrieved published works were classified into 29 in vitro studies or animal studies and 18 clinical studies. In addition to common Gram-positive and Gram-negative bacteria, OLG showed bactericidal activity against MRSA and VRE. In clinical settings, although there is limited evidence on SSI prevention, 1.5% OLG might be more effective than 10% PVP-I and 1% CHG. However, its usefulness under other conditions is unclear.

In vitro studies have shown that the antimicrobial spectrum of OLG is broad and seems to be effective against resistant bacteria. However, its clinical usefulness remains unclear. Olanexidine gluconate showed a broad-spectrum bactericidal effect on both Gram-positive and Gram-negative bacteria\textsuperscript{21} (Table 1), and the bactericidal effects on resistant bacteria such as MRSA and VRE were characteristic\textsuperscript{21} (Table 2). In emergency and intensive care, infections such as CRBSI and SSI caused by resistant bacteria (such as MRSA and VRE) are becoming a problem.\textsuperscript{16–19} In addition, existing antiseptics such as PVP-I and CHG are considered ineffective against these resistant bacteria.\textsuperscript{16–19} Therefore, OLG could be a useful disinfectant in emergency and intensive care settings. However, clinical studies on OLG are limited, and its clinical usefulness remains unclear.

In clinical settings, the usefulness of OLG is limited to its potential effect on SSI prevention. Moreover, the superiority of OLG over standard skin antiseptics such as chlorhexidine alcohol (CHG-AL) is unclear. All studies on the usefulness of OLG in clinical settings are related to SSI. An RCT\textsuperscript{26} comparing 1.5% OLG with 10% PVP-I revealed that the overall SSI incidence rate was significantly lower in the OLG group. However, the comparator antiseptic used in this study was an aqueous formulation of PVP-I, which is a nonalcohol-based antiseptic and is already not
| First author, year | Design | Object | Intervention | Comparison | Adverse event |
|-------------------|--------|--------|--------------|------------|--------------|
| Sugai, 1999<sup>65</sup> | Not mentioned | Adults; region: forearm, back | OLG concentration: 0.05%, 0.1%, 0.2%, 0.3%, 0.4%, and 0.5%. Total 24 cases | Placebo 24 cases | Urticaria/light urticaria/phototoxic reaction: safety |
| Sugai, 1999<sup>66</sup> | Not mentioned | Adults; region: back | 0.1% OLG 9 cases 0.5% OLG 9 cases | None | Association unknown: transient elevation of white blood cells 1 case Serum/urine OLG unchanged Concentration: below the lower limit of detection Local and systemic subjective/objective symptoms: none Serum/urine OLG unchanged concentration: below the lower limit of detection |
| Sugai, 1999<sup>67</sup> | Not mentioned | Adults; region: forearm | 0.1% OLG 6 cases 0.5% OLG 6 cases Application times: twice a day for 5 days | None | Light Urticaria/phototoxic/contact sensitization/contact phototoxic/contact urticaria reaction: safety |
| Sugai, 1999<sup>68</sup> | Not mentioned | Adults; region: skin with artificially inflicted incisions | OLG concentration: 0.005%, 0.01%, 0.03%, 0.05%, and 0.1%. Total 25 cases | Placebo 25 cases | |
| Harihara et al. 2015<sup>52</sup> | RCT | Adults; region: abdomen, groin | 1.5% OLG 237 cases | Placebo 119 cases 0.5% CHG 236 cases | OLG erythema: 3 cases (1.3%) Placebo erythema: 1 case (0.8%) CHG erythema: 2 cases (0.8%) |
| Harihara et al. 2015<sup>52</sup> | RCT | Adults; surgical type: gastrointestinal surgery | 1.5% OLG 52 cases | 10% PVP-I 54 cases | OLG All: 3 cases (5.8%) erythema:1 case (1.9%) dermatitis:1 case (1.9%) pruritus:1 case (1.9%) PVP-I All: 4 cases (7.4%) erythema: 4 cases (7.4%) |
| Obara et al. 2020<sup>26</sup> | RCT | Adults; surgical type: semiclean gastrointestinal surgery | 1.5% OLG 299 cases | 10% PVP-I 298 cases | OLG All: 5 cases (2%) erythema:4 cases (1%) dermatitis:4 cases (1%) pruritus:2 cases (1%) PVP-I All: 5 cases (2%) |
recommended for use as a skin antiseptic in many countries.\textsuperscript{62} A study comparing 1.5% OLG with 1% CHG\textsuperscript{57} also revealed that the overall SSI incidence rate was significantly lower in the OLG group. However, the interpretation of the results is limited by the fact that this was a retrospective study, and the results of detailed statistical analyses were not described. Therefore, the clinical usefulness of OLG against CHG-AL is still unclear. In the future, more studies comparing OLG with standard skin disinfectants and more studies on OLG for infection prevention are needed.

We reviewed studies on the in vitro pharmacological effects, antimicrobial spectrum, pharmacokinetics, and in vivo efficacy and safety on normal skin, wounded skin, and infection prevention. In the clinical setting, there were only studies related to the prevention of SSI with OLG,\textsuperscript{26,56–58} and we did not identify any other studies on the prevention of infection, including CRBSI.

\begin{table}[h]
\centering
\caption{Continued}
\begin{tabular}{|l|l|l|l|l|l|}
\hline
First author, year & Design & Object & Intervention & Comparison & Adverse event \\
\hline
Shiyanagi et al. 2019\textsuperscript{56} & Retrospective study & Children & 1.5% OLG [applicator] 164 cases & 10% PVP-I 130 cases & erythema: 1 case (<1%) dermatitis: 2 cases (1%) pruritus: 2 cases (17%) Chemical burn incidence rate: OLG 0% vs. PVP-I 5% (p < 0.05) \\
\hline
Matsuoka et al. 2019\textsuperscript{60} & Retrospective study & Surgical type: not mentioned & OLG (concentration unknown) 626 cases & PVP-I (concentration unknown) 567 cases & Rash incidence rate: OLG 3.7% vs. PVP-I 0.7% (p < 0.0001) Onset: days 3–17 (median, day 7) \\
\hline
Harihara, 2020\textsuperscript{57} & Retrospective study & Adults & Surgical type: Gastrointestinal surgery & 1.5% OLG (applicator) 2,077 cases & 1% CHG 1,514 cases None Type: erythema, pruritus Onset: Day 10 PVP-I and CHG: not mentioned \\
\hline
Iijima et al. 2020\textsuperscript{59} & Case report & 34 y.o. woman & OLG (concentration unknown) & None & Type: erythema, pruritus Onset: day 10 \\
\hline
Nagai et al. 2018\textsuperscript{61} & Case report & 64 y.o. man; surgical type: thoracoscopic lobectomy & OLG (concentration unknown) & None & Type: erythema Onset: day 6 \\
\hline
Note: All studies are in vivo and human studies. 
Abbreviations: CHG, chlorhexidine gluconate; PVP-I, povidone-iodine; RCT, randomized controlled trial. 
\end{tabular}
\end{table}
related bloodstream infection is associated with high morbidity and mortality in critically ill patients\textsuperscript{1,3,4,63}, therefore, high-quality clinical studies focusing on CRBSI prevention are needed in the future. A large randomized controlled study comparing 1.5\% OLG and 1\% CHG-alcohol for the prevention of CRBSI during central venous catheter insertion is currently ongoing in Japan.\textsuperscript{64}

This review does have some limitations. The studies reviewed were all undertaken in Japan and, due to the novelty of the drug, the number of studies was limited.

**CONCLUSION**

Olanexidine gluconate is a novel disinfectant with a broad spectrum and bactericidal effect against organisms, including MRSA and VRE, that are resistant to existing disinfectants such as PVP-I and CHG. Olanexidine gluconate might be more effective than PVI and CHG for SSI prevention. However, the clinical usefulness of OLG is unclear due to the limited number of clinical studies. In addition, clinical research is limited to studies targeting SSI prevention, and there is no clinical study on CRBSI. Therefore, further clinical studies are needed not only on the prevention of SSI but also on the prevention of CRBSI.

**DISCLOSURE**

A PPROVAL OF THE research protocol: N/A.

Informed consent: N/A.

Registry and registration no. of the study/trial: N/A.

Animal studies: N/A.

Conflict of interest: None.

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**SUPPORTING INFORMATION**

Additional Supporting Information may be found in the online version of this article at the publisher’s web-site:

**Table S1.** Search strategy on the applications of olanexidine.

**Table S2.** List of excluded studies.

**Table S3.** Ongoing studies on olanexidine.