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REVIEW

Chlorhexidine Allergy: Current Challenges and Future Prospects

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Abstract: Chlorhexidine is a synthetic bisbiguanide antiseptic and was introduced in healthcare use in 1954. Allergy to chlorhexidine has been increasingly reported particularly in the perioperative and medical procedural settings. The hypersensitivity reactions range from mild cutaneous reactions to anaphylaxis or death. There are many products and medical devices containing chlorhexidine that sometimes lack standardized labeling. With the various routes of chlorhexidine exposure, accidental or recurrent reactions in chlorhexidine-allergic patients have been reported. Therefore, we aim to review the most recent evidence in clinical manifestations, diagnostic methods, management, and preventive measures with a focus on the unique features of chlorhexidine allergy.

Keywords: chlorhexidine, allergy, antiseptics, anaphylaxis, hypersensitivity, perioperative

Introduction

Chlorhexidine is a synthetic bisbiguanide antiseptic with antibacterial, some antiviral, and antifungal activity.[1] It is a water-soluble powder substance[2] and is stable in a solution with a pH of 5–8.[2] Chlorhexidine is currently available in preparations of digluconate, acetate, and dihydrochloride salt forms.[1] Due to cationic charge property, chlorhexidine binds very well to anionic cutaneous protein, resulting in prolonged antiseptic effects.[1] The antibacterial activity of chlorhexidine is bacteriostatic at a lower concentration and becomes bacteriocidal at a higher concentration.[1] A previous meta-analysis reported the effectiveness of chlorhexidine was significantly greater than povidone-iodine in reducing surgical-site infection.[3] Chlorhexidine was introduced in healthcare use in 1954.[4] Due to good antiseptic properties and a favorable safety profile, chlorhexidine is now widely used and is contained in many healthcare products, including mouthwashes, oral paste, eye drops, lubricating gels for medical procedures, powder, dressings, scrubs, and central venous catheters. Furthermore, it is also increasingly used as a preservative in cosmetic and daily-used products, which probably causes sensitization.[5,6] Chlorhexidine containing products used in our hospital are shown in Table 1.

Epidemiology

In 1965, Birdwood reported a 72-year-old woman who presented with severe cutaneous lesions and thrombophlebitis 48 hrs after applying an antiseptic containing chlorhexidine on her forearms.[7] In 1984, the first case of chlorhexidine induced anaphylaxis in the perioperative setting was reported in a 9-year-old Japanese boy.[8] The true prevalence of chlorhexidine allergy is still unknown and is thought to be under-recognized. Chlorhexidine allergy has recently been increasingly reported

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Table 1 Chlorhexidine-Containing Products in a Tertiary-Care Hospital in Thailand

Product Categories	Chlorhexidine-Containing Products	Usage
Antiseptics	0.5% chlorhexidine in 70% alcohol in a bottle pump	Hand rub
	0.5% chlorhexidine tincture	Instrument disinfection
	0.5% chlorhexidine external solution	Instrument disinfection
	1% chlorhexidine in 61% alcohol	Hand wash
	2% chlorhexidine solution	Surgical skin preparation
	2% chlorhexidine in 70% alcohol	Surgical skin preparation
	4% chlorhexidine cleanser	Hand wash, surgical skin preparation
	4% chlorhexidine scrub	Surgical skin preparation
Ophthalmic agents	0.02% chlorhexidine eye drops	Ophthalmic antiseptics
Antiseptics used in the oral cavity	0.12% chlorhexidine mouth wash 2% chlorhexidine mouth care	Mouth care
Lubricant gel	2% lidocaine + 0.05% chlorhexidine	Local anesthesia and lubrication during catheterization, urological procedures, and symptomatic treatment of painful cystitis and urethritis

particularly in the perioperative and medical procedural settings.[9–12] The prevalence of perioperative allergic reactions was 9–10% in the United Kingdom, Denmark, and Belgium.[13–15] A recent survey from 13 centers reported 252 cases of anaphylaxis to chlorhexidine, and it was within the top four most commonly diagnosed causes of perioperative anaphylaxis along with neuromuscular blocking agents, antibiotics, and latex.[16] The prevalence of chlorhexidine contact allergy by performing a patch test was 0.47–1% of patients.[5,6] Despite the widespread use of chlorhexidine the healthcare settings, the prevalence of chlorhexidine-induced anaphylaxis in healthcare workers is still relatively low.[17,18] Nevertheless, the true prevalence in healthcare workers may be still underestimated.[2,4] As chlorhexidine allergy has been overlooked, authorities in several countries have already issued warnings for chlorhexidine-containing products and medical devices as shown in Table 2.

Clinical Features

Adverse reactions to chlorhexidine involve both immediate and non-immediate hypersensitivity, ranging from mild cutaneous reactions to anaphylaxis or death.[6,9,10] The delayed

Table 2 Warnings About Chlorhexidine Allergy from Different Authorities

Year	Sources of Chlorhexidine	Authority
2009	Lubricant gel	The Therapeutic Goods Administration, Department of Health in Australia[19]
2012	Central venous catheters	The Therapeutic Goods Administration, Department of Health in Australia[19]
2012	Products and devices	The Medicines and Healthcare Products Regulatory Agency in the UK[20]
2013	Products and devices	New Zealand Medicines and Medical Devices Safety Authority[21]
2016	Topical chlorhexidine	Health Canada[22]
2017	Skin antiseptics	The United States of America's Food and Drug Administration[23]

cutaneous rash, which is a T cell-mediated type IV hypersensitivity reaction, generally occurs in patients with a history of prolonged use of chlorhexidine-containing products or multiple exposure events of antiseptic use.[24] The most common delayed rash is contact dermatitis[24] while fixed drug eruption was reported in patients with allergy to chlorhexidine-mouth wash.[25,26] A study in 92 healthcare workers from Thailand found that 5% of participants had a cutaneous reaction to 2% and 4% chlorhexidine gluconate testing on the forearms.[27]

Immediate type I hypersensitivity reactions mediated by IgE were reported.[28] Clinical features range from localized urticarial angioedema to anaphylaxis and death.[17,29] Among patients with chlorhexidine-induced anaphylaxis reported in 36 articles, the most common chlorhexidine-containing product exposure was urinary catheter lubricant (44%), followed by chlorhexidine-coated central venous catheter (35%), and topical chlorhexidine solution (16%).[29] Reported mucosal routes involved in exposures resulting in chlorhexidine allergy included rectum, vagina, conjunctiva, oral mucosa, and periodontal pocket.[30,31] The reactions usually occur a few minutes after venipuncture and may be delayed to as much as 50 mins after mucosal or damaged-skin exposure.[32,33] In perioperative settings, anaphylaxis from chlorhexidine usually occurs from 15 to 45 mins after the beginning of anesthesia but it may occur at all times during surgery or even in the postoperative setting.[9,34] Severe anaphylaxis classified as grade 3–4 resulting in life-threatening condition was reported in 80% of patients.[10] Occupational airway allergy from chlorhexidine was also reported in three nurses confirmed by inhalation challenge.[2] Chlorhexidine could be easily overlooked as the

culprit agent and allergic reaction could be misattributed to other simultaneously administered agents, including anesthetic drugs and antibiotics. Some patients with anaphylaxis had a history of mild localized reactions for which investigations to identify the causative agents were not performed.[35] Some patients may concurrently have both immediate and delayed reactions.[6] The unique features of chlorhexidine allergy are summarized in Table 3.[14,36,37]

There are many routes of exposure to chlorhexidine such as skin, mucous membrane, and the parenteral route. Topical exposure in preoperative skin preparation or dressing wound can cause both immediate and non-immediate reactions.[38] Mucous membrane exposure through the transurethral, rectal, and vaginal routes could elicit the reactions in both delayed and immediate types, including anaphylaxis.[39] Exposures through the oral and ophthalmic routes generally present with mild immediate reactions, such as localized urticaria.[30] Allergy to chlorhexidine mouth wash was reported as contact dermatitis and fixed drug eruption confirmed by skin prick and intradermal tests.[40] Exposure by the parenteral route from the chlorhexidine-coated venous or arterial catheters, and epidural catheters can cause both immediate and delayed types, the clinical features of which may range from localized cutaneous lesions to anaphylaxis.[41] We reported a case of severe anaphylaxis after a pelvic examination, and this patient was allergic to both natural rubber latex and chlorhexidine confirmed by skin test and basophil activation test (BAT).[37]

Diagnosis

Further investigations for chlorhexidine allergy comprise in vivo and in vitro tests. The tests should be carried out in patients with a history suspicious of chlorhexidine allergy, in patients with allergic reactions in the healthcare setting where exposure to chlorhexidine cannot be excluded with certainty and in all patients with perioperative allergic reactions.[42]

Possible in vivo tests include skin prick test, intradermal test for immediate reactions, and patch tests for delayed reactions. For skin prick test, a concentration of 5 mg/mL of chlorhexidine digluconate was recommended by the Danish Anesthesia Allergy Center (DAAC) and European Network for Drug Allergy (ENDA) in 2013.[28,43] A wheal size of 3 mm or greater developing within 20–30 mins is considered a positive result.[36] In evaluating patients with perioperative allergic reactions, skin prick test yields a sensitivity of 95% and specificity of 97%.[13] To perform the intradermal test, a concentration of chlorhexidine of 0.002 mg/mL was recommended by DAAC and ENDA.[28,43] The correct technique is to inject 0.02 mL into the dermis to make a bleb of 3–5 mm, after which the wheal size is measured 20 mins later. A result is considered positive if the wheal size is 3 mm or greater compared to negative control.[43] Intradermal test yields a sensitivity of 68% and specificity of 100%.[13] Intradermal test is also potentially helpful for delayed hypersensitivity when used with delayed reading.[43] To perform the patch test for patients with delayed cutaneous reaction, a concentration of 1% chlorhexidine digluconate was recommended.[43]

Table 3 The Unique Features of Chlorhexidine Allergy[14,36,37]

• Often unrecognized and lack of clear labeling
• Reaction onset in the perioperative setting varies (rapid or delayed)
• Patients with anaphylaxis have a history of mild localized reaction to earlier exposure
• A skin test may have to be read 20–30 mins after SPT and IDT
• Single allergologic test may be insufficient to exclude allergy
• May be coincident with other drug allergies

Abbreviations: SPT, skin prick test; IDT, intradermal test.

Possible in vitro tests include specific IgE test, histamine release test (HRT), and BAT. Specific IgE generally increases in most patients at the time of the reaction. If negative, it should be repeated between 1–4 months after the event.[44] Since the specific IgE level can change over time, some previously sensitized patients with undetectable specific IgE may remain at risk of reactivity, and a rebound in specific IgE can be found on re-exposure.[44] The sensitivity and specificity on the cut-offs recommended by manufacturers range from 84–100% and 93–97%, respectively.[13,45] A previous study showed specific IgE should be evaluated with caution when total IgE was 500 kU/L or greater.[45] HRT and BAT are only available in some specialized centers and require a fresh blood sample. Both tests have a sensitivity of 50% and specificity of as much as 99%.[10,46] Therefore, these tests are generally used as additional tests to confirm the diagnosis after other tests have shown equivocal results.

According to DAAC, chlorhexidine allergy should be diagnosed based on a relevant clinical reaction in combination with two positive diagnostic tests.[13] If diagnostic tests are equivocal in highly suspicious cases, retests are recommended a few months later. Although a provocation test is the gold standard for diagnosis of drug allergy in both immediate and delayed types, it is contraindicated in patients with previous severe reactions or anaphylaxis. No standard protocol of the chlorhexidine challenge test is currently available.

Measures to Decrease the Prevalence of Chlorhexidine Allergy

Prevention of Sensitization

Populations that are repetitively exposed to chlorhexidine are at risk of sensitization. These include health care workers, patients with chronic leg ulcers or eczema, and those undergoing frequent surgical interventions.[12] It is still not clear whether type IV hypersensitivity could predispose an individual to type I hypersensitivity, but it has been shown that a substantial number of patients with type IV hypersensitivity have a positive skin prick test with chlorhexidine and therefore testing for type I hypersensitivity should be performed in all patients with a positive epicutaneous test with chlorhexidine.[6,47] Due to the widespread use of chlorhexidine as an antiseptic agent in health care settings, exposure to chlorhexidine is very common. The results from the 6th National Audit Project of the Royal College of Anesthetists showed the prevalence of exposure to chlorhexidine in perioperative settings by at least one route was as high as 73.5% of all cases.[14] Other sources of exposure may come from many daily-used products without standardized labeling in community settings. Although chlorhexidine belongs to the biguanides group, clinically relevant cases of cross-reactivity with other substances with similar chemical structures have not been reported yet.

Prevention of Re-Exposure in Patients with Proven Chlorhexidine Allergy

The frequency of exposure to chlorhexidine by at least one route is very high. Therefore, the possibility of accidental exposure remains challenging for these patients. The lack of standardized and clear chlorhexidine labeling is still problematic. Most of the patients with chlorhexidine-induced anaphylaxis have had previous mild reactions to chlorhexidine exposure, however mild reactions to chlorhexidine are also observed in many patients without chlorhexidine allergy.[48] The history of exposure could be retrospectively identified from these patients. Therefore, opportunities taken to investigate exposure history for early identification of chlorhexidine-allergic patients may prevent more severe reactions in the future. Appropriate diagnosis and management of these patients may lead to better outcomes, and future reactions may be prevented.[16] The management to avoid re-exposure in the patients with proven or suspected chlorhexidine allergy is summarized in Table 4.[14,42,49,50]

Table 4 Management for Patients with Suspected or Confirmed Chlorhexidine Allergy[14,42,49,50]

Management for patients with suspected chlorhexidine allergy
1. Confirm chlorhexidine allergy by careful history taking, reviewing of anesthesia records, and performing allergy tests
2. Assume to be chlorhexidine-allergic until proven otherwise and proceed to the same protocol to confirm chlorhexidine-allergic cases
3. In cases whom emergency surgery is required … • Avoid chlorhexidine during emergency procedures • Use all medications with caution as necessary • Have a high index of suspicion of diagnosing anaphylaxis • Since other culprits are still possible, a latex-free environment is recommended
Management in patients with confirmed chlorhexidine allergy
1. Provide a chlorhexidine allergy card or bracelet to chlorhexidine-allergic patients
2. Avoid chlorhexidine-containing drugs or medical devices, and use alternatives
3. All physicians, nurses, and healthcare workers who contact chlorhexidine-allergic patients should be aware of and re-check all drugs and medical devices before using them in these patients
4. A "chlorhexidine allergy" sign should be attached to the front door of the patient's room and on the chart of the patients, and a single chlorhexidine-free room is preferred
5. In the perioperative setting … • Surgical and anesthesia team should thoroughly review the patient's history and always ask about chlorhexidine allergy • List chlorhexidine-containing surgical devices • List alternative drugs or surgical devices that do not contain chlorhexidine • If a diagnosis of chlorhexidine allergy is suspected, allergy consultation should be promptly sought • Treat anaphylaxis promptly

A Low Concentration of Chlorhexidine Should Be Used in Healthcare Settings and Daily-Used Products

Although there is no firm conclusion on the mechanism of allergic sensitization to chlorhexidine, impairment of the skin barrier is thought to be the immunologic basis of allergic sensitization in other allergens, such as food, with suggested mechanistic links.[51,52] Previous data revealed higher concentrations of chlorhexidine, such as 2–4% weight by volume (w/v) had irritating effects on the skin, resulting in impairment of the skin barrier and potentially increasing the risk of

chlorhexidine sensitization. Therefore, there is an increased risk of allergic sensitization with higher concentrations of chlorhexidine. These findings were supported by two studies reporting the prevalence of chlorhexidine sensitization among healthcare workers. Different concentrations of chlorhexidine were used in these two centers, namely 0.5% and 4% (w/v). The center where 4% chlorhexidine was used had a higher prevalence of chlorhexidine sensitization.[4,18] However, no head-to-head controlled trial has been reported that the use of lower chlorhexidine concentrations can decrease the sensitization rate compared with higher concentrations. In contrast, the use of 2% (w/v) chlorhexidine concentration has no clear historical rationale. A comparative study demonstrated the effectiveness of different concentrations of topical chlorhexidine of 0.5%, 1%, and 2% (w/v) found no differences in antimicrobial efficacy.[53] Therefore, the use of the minimum effective concentration of chlorhexidine has been recommended.[16] Many countries have promoted the use of 0.5% (w/v) chlorhexidine due to concerns about chlorhexidine sensitization whereas the United Kingdom's national guidelines still recommend the use of 2% (w/v) chlorhexidine for single application products.[54]

Conclusions

Chlorhexidine allergy has been reported in many different medical specialties and settings. All patients with suspected perioperative or periprocedural hypersensitivity reactions should, therefore, be considered for chlorhexidine allergy testing and allergist consultation. Accidental reexposures causing severe allergic reactions have been reported, and some of them were preventable. Uniform labeling, registration of chlorhexidine-containing products, increased awareness among both patients and medical personnel could prevent chlorhexidine re-exposure.

Abbreviations

BAT, basophil activation test; DAAC, Danish Anesthesia Allergy Center; ENDA, European Network for Drug Allergy; HRT, histamine release test.

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Author Contributions

All authors contributed to data analysis, drafting or revising the article, gave final approval of the version to be published, and agree to be accountable for all aspects of the work.

Disclosure

The authors report no conflicts of interest in this work.

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