ANESTHESIOLOGY

Immediate Hypersensitivity to Chlorhexidine: Experience from an Allergy Center in China

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EDITOR'S PERSPECTIVE

What We Already Know about This Topic

- Chlorhexidine, a topical antibacterial agent, is widely used perioperatively, and can cause allergic reactions including anaphylaxis. In some countries, it may not be frequently recognized as the culprit agent responsible for perioperative hypersensitivity.

What This Article Tells Us That Is New

- In a study from China, most allergic reactions to chlorhexidine were due to skin disinfectant for vascular cannulation and occurred repeatedly in most patients before it was recognized. This report further emphasizes the need for awareness of the potential allergenicity of chlorhexidine in a perioperative setting or after vascular cannulation.

ABSTRACT

Background: Chlorhexidine generally has a good safety profile. However, allergic reactions are reported with increasing frequency. In China, it is rarely reported, and its characteristics are unknown. The purpose of this study was to summarize the experience of a Chinese allergy center with chlorhexidine allergy.

Methods: The authors retrospectively reviewed all patients who underwent chlorhexidine allergy testing in the Allergy Center of West China Hospital, Sichuan University (Chengdu, China), in the period February 2018 to May 2022 (n = 43 patients) and included the patients diagnosed with chlorhexidine allergy for analysis.

Results: Ten patients who were diagnosed by skin prick and serum-specific immunoglobulin E tests were included. They experienced a total of 30 allergic reactions to chlorhexidine (mean ± SD, 3.0 ± 1.3). Five patients experienced six allergic reactions (6 of 30, 20%) during general or local anesthesia, and they may have been exposed to chlorhexidine *via* different routes. Only one allergic reaction (1 of 30, 3%) was recorded with exposure *via* a mouthwash. The other 23 allergic reactions (23 of 30, 77%) were caused *via* a skin disinfectant; the route of exposure was IV cannulation in 22 allergic reactions (22 of 23, 96%) and broken skin in one allergic reaction (1 of 23, 4%). The symptoms included a quick onset and great severity. Two patients (2 of 10, 20%) had been accidentally re-exposed to chlorhexidine after diagnosis.

Conclusions: This study conducted in China showed that the majority of reactions to chlorhexidine were attributed to skin disinfectants, and IV cannulation was the most common exposure route; in general, however, chlorhexidine allergy was easily overlooked. The potential allergenicity of chlorhexidine used for skin preparation before IV cannulation or should be considered in patients who develop allergic reactions perioperatively.

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Chlorhexidine is a topical antibacterial agent and cationic surfactant that can kill most Gram-positive and Gram-negative bacteria. It is widely used in different products, especially urethral gels, skin disinfectants, mouthwash, and central venous catheters.[1,2] Chlorhexidine generally has a good safety profile, but it can cause allergic reactions. Contact dermatitis caused by chlorhexidine was first reported in 1965[3]; subsequently, anaphylactic shock resulting from chlorhexidine was first reported in 1984.[4] The true prevalence of chlorhexidine allergy remains unknown. As use has become widespread, increasing numbers of cases have been reported in the literature.[1] Three studies from Denmark, the United Kingdom, and Belgium showed that chlorhexidine was the culprit in 9.6%, 9%, and 9% of patients with suspected perioperative anaphylaxis, respectively.[5–7]

Chlorhexidine is a "hidden" allergen that is easily overlooked, especially in the perioperative setting. In the Danish Anesthesia Allergy Center (Denmark), all referred patients are tested for chlorhexidine allergy as part of the investigation since 1999. Currently, the United Kingdom,

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Australia, New Zealand, and the European Academy of Allergology and Clinical Immunology (Florence, Italy) also recommend routine chlorhexidine allergy testing in patients with perioperative anaphylaxis.[8–10] However, only a few hospitals in China can perform allergy testing in patients with perioperative anaphylaxis. Recently, a study conducted from an anesthesia clinic in China suggested that neuromuscular blocking agents, sedatives, and opioids were the main causes of perioperative anaphylaxis, but chlorhexidine was not included in the detection.[11] Chlorhexidine can be allergenic, but it is not well understood by medical staff in some countries, such as China. In addition, skin disinfectant products containing chlorhexidine are more routinely used before IV cannulation in medical institutions in China, which may lead to distinct chlorhexidine allergy patterns. The purpose of this study was to summarize the experience of our Chinese allergy center with chlorhexidine allergy.

Materials and Methods

This retrospective single center study involved all patients who underwent chlorhexidine allergy testing in the Allergy Center of West China Hospital, Sichuan University (Chengdu, China), in the period February 2018 to May 2022. In our center, chlorhexidine allergy testing is routinely performed in all patients with perioperative allergic reactions and who suffered allergic reactions to more than two kinds of infusion drugs or even saline or glucose IV infusion. We obtained clinical written informed consent from all subjects before testing. This retrospective study was approved by the Biomedical Research Ethics Committee of West China Hospital of Sichuan University, China (approval No. 2022[1937]).

Age, sex, clinical setting, detailed symptoms, management, diagnosis, and accidental re-exposure thereafter were obtained for all patients. The severity of allergic reactions was classified according to the Ring and Messmer system (I, cutaneous signs: generalized erythema, urticaria, angioedema; II, measurable but not life-threatening symptoms: cutaneous signs, hypotension, tachycardia, respiratory disturbances; III, life-threatening symptoms: collapse, tachycardia or bradycardia, arrhythmias, bronchospasm; IV, cardiac and/or respiratory arrest).[12] The diagnostic procedure for chlorhexidine allergy is shown in figure 1.

Skin Prick Test

A skin prick test was carried out using chlorhexidine (2%, Fujian Weizhenyuan Pharmaceutical Technology Link Company, China) diluted to 5 mg/ml[13] with positive (histamine 10 mg/ml) and negative (diluent) controls (ALK-Abello, Denmark). A positive skin prick test reaction was defined as a wheal size of 3 mm greater than that of the negative control at 15 to 20 min. The coexistence of a flare and itch supported a positive result.[14]

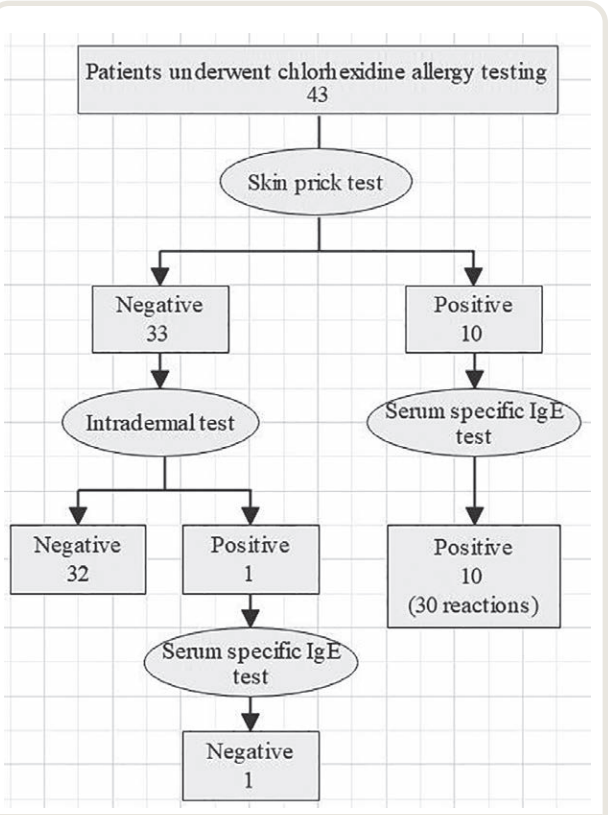

Fig. 1. Diagnostic procedure and clinical outcomes of chlorhexidine allergy.

Intradermal Test

If skin prick test was negative, an intradermal test was performed with 0.002 mg/ml[13] chlorhexidine. An increase in wheal size of more than 3 mm from the initial papule with flare at 15 to 20 min was considered a positive result.[14]

Serum Specific Immunoglobulin E Analysis

Chlorhexidine serum specific immunoglobulin E was measured by the UNICAP System (Thermo Fisher, Sweden) for patients whose skin prick test or intradermal test result was positive. A specific immunoglobulin E level 0.35 kUA/l or greater was deemed positive.

Patient Inclusion Criteria

No validated provocation model is available for chlorhexidine. We defined chlorhexidine allergy as one or more relevant clinical reactions to chlorhexidine in combination with two positive tests.[5] Finally, patients diagnosed with chlorhexidine allergy were included in our study.

Other Drug Allergy Tests

All other drugs, especially antibiotics and all the drugs used perioperatively, were also included in the allergy test

in accordance with the position paper.[10,12,15] In our cohort, for patients diagnosed with chlorhexidine allergy, povidone iodine skin test was performed to choose alternatives.

Patient Follow-up

In June 2022, all included patients were followed up by telephone and asked whether they had been accidentally re-exposed to chlorhexidine after the diagnosis.

Statistical Analysis

The data were processed with IBM SPSS Statistics 21.0 (USA), and descriptive statistics were reported. Mean ± SD or median and interquartile range were used to describe continuously scaled variables, and frequency counts (%) were used for categorical variables.

Results

Clinical Features

Forty-three patients investigated in our center in the period underwent chlorhexidine allergy testing; of these, 10 patients (median age, 40.5 yr [interquartile range, 19.0 to 57.0 yr]; 5 [50.0%] female) were positive based on allergy testing (fig. 1). The clinical data and drug allergy testing results are summarized in table 1. Only one patient (10%) had a history of allergic rhinitis, while the others had no atopic comorbidities. The mean time interval between the last allergic reaction and the evaluation was 4.5 months (interquartile range, 1.0 to 13.5 months).

Ten patients experienced a total of 30 allergic reactions to chlorhexidine (mean ± SD, 3.0 ± 1.3), and the details are summarized in table 2. Two patients experienced two allergic reactions, and three patients experienced four allergic reactions during general and local anesthesia, respectively. During these six allergic reactions (6 of 30, 20%), the patients may have been exposed to chlorhexidine *via* different routes, such as skin disinfectants, central venous catheters, urethral gels, or their combinations. Only one allergic reaction (1 of 30, 3%) occurred with exposure *via* a mouthwash. The other 23 allergic reactions (23 of 30, 77%) occurred *via* a skin disinfectant; the route of exposure was IV cannulation in 22 allergic reactions (22 of 23, 96%) and broken skin in one allergic reaction (1 of 23, 4%).

The symptoms included a rapid onset and ranged in severity from skin rash to anaphylactic shock, and in some cases cardiac arrest. The percentages of grade I, II, III, and IV reactions were 8 (27%), 11 (37%), 5 (17%), and 6 (20%), respectively. Grade II to IV reactions accounted for 73% (22 of 30) of all reactions. However, epinephrine was used in only 14% (3 of 22), and 50% (11 of 22) of these reactions were treated with dexamethasone (table 2).

Chlorhexidine Allergy Test Results

All included patients were diagnosed by skin prick and serum specific immunoglobulin E tests (fig. 1). The wheal diameters on skin prick test ranged from 6 mm to 14 mm (mean ± SD, 11.8 ± 2.7 mm); of these, the wheal diameters were larger than 10 mm in eight patients. The specific

Table 1. Clinical Data and the Drug Allergy Test Results

Patient No.	Sex (Female/Male)	Age, y	Total Reaction Times	Time Interval between Reaction and Assessment (mo)	Skin Prick Test (mm)	Serum Specific Immunoglobulin E (Value/Class)	Re-exposure	Atopy	Other Drug Allergy Tests and Results
1	Male	52	5	1	13	9.13/3	No	No	Propofol, midazolam, sufentanil, cisatracurium, latex, levofloxacin, and ambroxol (-)
2	Female	33	1	2	11	2.68/2	No	No	Not done (saline IV infusion)
3	Male	5	4	1	14	3.36/2	No	No	Not done (involved infused antibiotics could be orally tolerated in history)
4	Female	23	3	8	12	1.67/2	Yes	No	Clindamycin and lidocaine (-)
5	Female	48	4	6	14	19.9/4	No	No	Penicillin and cephalosporin (-)
6	Female	67	1	26	14	11.1/3	Yes	No	Cisatracurium, remifentanil, and propofol (-)
7	Male	7	2	12	14	13.6/3	No	Yes	Not done (saline IV infusion)
8	Female	57	3	1	12	14.9/3	No	No	Penicillin (-)
9	Male	57	4	18	8	0.76/2	No	No	Lidocaine (-), other involved drugs could be tolerated when using povidone iodine as an alternative after diagnosis
10	Male	25	3	3	6	43.5/4	No	No	Tetracaine hydrochloride jelly, lidocaine, ceftazidime (-)

IV, intravenous.

Table 2. Detailed Descriptions of the 30 Allergic Reactions to Chlorhexidine

Patient No.	Disease	Operation Stage	Medical Procedure	Culprit	Severity	Management
1	Kidney donation	Preoperative preparation	Ambroxol IV infusion	Skin disinfectant	II	Dexamethasone
		Preoperative preparation	Levofloxacin IV infusion	Skin disinfectant	II	Dexamethasone
		Preoperative preparation	Venipuncture	Skin disinfectant	II	Dexamethasone
		Preoperative preparation	Saline IV infusion	Skin disinfectant	III	Dexamethasone
		Anesthesia induction (general anesthesia)	Indwelling catheter	May be skin disinfectant, urethral gel	III	Epinephrine
2	Benign thyroid tumor	Preoperative preparation	Saline IV infusion	Skin disinfectant	II	Unknown
3	Pneumonia	—	Blood sampling	Skin disinfectant	I	Loratadine
		—	Antibiotic IV infusion (details unknown)	Skin disinfectant	I	Loratadine
		—	Amoxicillin–clavulanic acid IV infusion	Skin disinfectant	I	Loratadine
		—	Azithromycin IV infusion	Skin disinfectant	II	Loratadine
4	Foot fracture	Postoperation (Local anesthesia)	Clindamycin IV infusion	May be skin disinfectant	II	Dexamethasone and promethazine
	Dental caries	—	Mouthwash	Mouthwash	II	Unknown
	Erosions on the skin of the feet	—	Topical medications (ingredients unknown)	Skin disinfectant	II	Dexamethasone
5	Cholecystitis	Preoperative preparation	Blood sampling	Skin disinfectant	I	Unknown
		Preoperative preparation	Penicillin IV infusion (details unknown)	Skin disinfectant	I	Unknown
		Preoperative preparation	Penicillin IV infusion (details unknown)	Skin disinfectant	I	Unknown
		Preoperative preparation	Cephalosporin IV infusion (details unknown)	Skin disinfectant	IV	Unknown
6	Benign thyroid tumor	Postoperation (general anesthesia)	Glucose IV infusion	May be skin disinfectant	IV	Surgical exploration, epinephrine, and others
7	Virus infection	—	Saline IV infusion	Skin disinfectant	IV	Dexamethasone
		—	Saline IV infusion	Skin disinfectant	II	Dexamethasone
8	Benign bladder tumor	Preoperative preparation	Antibiotic IV infusion (details unknown)	Skin disinfectant	I	Unknown
		Preoperative preparation	Saline IV infusion	Skin disinfectant	II	Dexamethasone
		Preoperative preparation	Glucose IV infusion	Skin disinfectant	I	No treatment
9	Coronary heart disease	Postoperation (local anesthesia)	Coronary angiography	May be skin disinfectant, central venous catheter	IV	Temporary cardiac pacemaker, ventilator, norepinephrine, and others
		Preoperative preparation	Doxofylline IV infusion	Skin disinfectant	IV	Norepinephrine, endotracheal intubation, and others
		Preoperative preparation	Heparin sodium IV infusion	Skin disinfectant	III	Norepinephrine and others
		Preoperative preparation	Ambroxol IV infusion	Skin disinfectant	III	Dexamethasone
10	Ureteral calculi	Preoperative preparation	IV infusion (details unknown)	Skin disinfectant	IV	Epinephrine and dexamethasone
		Postoperation (local anesthesia)	Ureteral calculi removal and ureteral stenting	May be skin disinfectant, urethral gel	II	Loratadine
		Postoperation (local anesthesia)	Ureteral stenting removal	May be skin disinfectant, urethral gel	III	Dexamethasone

IV, intravenous.

immunoglobulin E values ranged from 0.76 kUA/l to 43.5 kUA/l (mean ± SD, 12.06 ± 12.77 kUA/l), which were graded as class II (0.71 to 3.5 kUA/l) in four patients, class III (3.51 to 17.5 kUA/l) in four patients, and class IV (17.6 to 50 kUA/l) in two patients (table 1).

Allergy Test Results for Other Drugs

The other drug allergy tests and their results are shown in table 1; all of the additional allergy tests were negative. All the patients in our cohort completed the povidone iodine allergy test, and the results were all negative. Thus, povidone iodine could have been used as an alternative disinfectant in these patients.

Accidental Re-exposure to Chlorhexidine

All patients diagnosed with chlorhexidine allergy were followed up by telephone, and none were lost to follow-up. The time between diagnosis and follow-up ranged from

1 month to 52 months (median time, 21.5 months [interquartile range, 6.7 to 32.2 months]). Two patients (2 of 10, 20%) had been accidentally re-exposed to chlorhexidine after diagnosis. Among them, patient number 4 experienced anaphylactic shock after accidental exposure to a mouthwash containing chlorhexidine during dental treatment, even though she told her dentist that she was allergic to chlorhexidine. Patient number 6 experienced anaphylaxis during acupuncture treatment due to the skin disinfectant used before the puncture.

Discussion

Our study showed that most of the allergic reactions to chlorhexidine were attributed to the skin disinfectants used before IV cannulation in China. Recently, a narrative review showed that topical chlorhexidine exposure before insertion of a peripheral venous cannula rarely caused systemic anaphylaxis.[16] In 2016, Sharp *et al.* reviewed the literature about chlorhexidine allergy and found that urethral gels and central venous catheters were the most common culprits (more than 80%) in 68 published case reports.[17] The reasons for the distinction were as follows.

First, skin disinfectants containing chlorhexidine used for skin preparation before IV cannulation are routinely used in medical institutions in China, which will increase the likelihood that more people will be exposed to chlorhexidine than with other methods, such as urethral gels and central venous catheters. In the long run, whether this will lead to more chlorhexidine sensitization and an increased incidence of allergies in China is a problem that needs attention. Although some studies have shown that chlorhexidine exerts a better effect than povidone iodine on infection related to intravascular catheters[18] or clean-contaminated surgery,[19] some experts have argued that chlorhexidine should not be used before short-term IV cannulation or for disinfecting needleless connector access points.[20] Based on our experience, we suggest reinforcing the awareness of the potential harm in the overzealous use of chlorhexidine in areas where there is little or no evidence that it reduces infection better than other, less allergenic antiseptics, especially used for IV cannulation.

Second, according to a previous study, the sensitization potential increases with increasing chlorhexidine concentrations.[21] In China, the Health Ministry has set a maximum concentration of 4.5% on skin,[22] which is much higher than in many other countries, such as the United Kingdom (2%)[23] and Japan (0.5%),[24] and may lead to more sensitization to chlorhexidine. Decreasing the recommended concentration might reduce the possibility of sensitization.

Third, although standard clinical practice requirements in China recommend that the antiseptic should be dry before IV cannulation, it is possible that it does not have an adequate time to dry; alternatively, cannulation has occurred through pooled chlorhexidine. When a patient is sensitized to chlorhexidine, even a small amount to the circulation can cause an allergic reaction.

Although increasing numbers of cases of chlorhexidine allergy have been reported in the literature[1] and numerous governmental warnings have been issued during recent decades to warn of the risk of this allergy,[24–26] chlorhexidine is not often recognized as a potential allergen by healthcare workers and is easily overlooked. In our study, two patients (numbers 3 and 5) developed local skin rashes after blood sampling, but this minor allergic symptom was often ignored by medical staff and patients, and the patients subsequently suffered a more severe allergic reaction. A previous study also suggested that mild allergic reactions to chlorhexidine can precede anaphylaxis.[27] Moreover, most patients in the current study experienced repeated allergic reactions (mean ± SD, 3.0 ± 1.3) and even several severe life-threatening reactions before being referred and diagnosed. During the process, the infusion drug was always blamed as the culprit, especially if it was an antibiotic, at which point it was changed to another infusion drug, and the patient experienced a reaction again. Therefore, chlorhexidine allergy should potentially be considered for patients who complain of allergic reactions after different drug infusions after its use as a disinfecting agent. It is often used as part of surgical preparation and in the perioperative setting. International guidelines on perioperative hypersensitivity investigations recommend testing chlorhexidine in all patients with suspected perioperative hypersensitivity.[8–10]

For chlorhexidine allergy testing, Opstrup *et al.* reported that both the estimated sensitivity and specificity were high for the skin prick test (sensitivity 95% and specificity 97%) and serum specific immunoglobulin E test (sensitivity 100% and specificity 97%). Moreover, when the skin prick test and serum specific immunoglobulin E test were combined, the highest sensitivity and specificity were observed compared to combinations of other tests (such as intradermal test and histamine release test).[5] In our study, all included patients were diagnosed by skin prick and serum specific immunoglobulin E tests, and the results were concordant with their clinical history. This further verified that the skin prick test and serum specific immunoglobulin E test both have a high sensitivity and specificity for chlorhexidine allergy diagnosis. However, to date, there have not been any commercially available chlorhexidine serum specific immunoglobulin E tests in China. If the clinical history indicates that the culprit is chlorhexidine, the skin prick test should be considered as an important screening and diagnostic method.

The chlorhexidine specific immunoglobulin E concentration is dynamic, increasing after exposure followed by a decline over time if further exposure is avoided.[28] In this study, specific immunoglobulin E was greater than 0.35 kUA/l in 22 of 23 patients at a median time of 10 weeks after the allergic reaction and declined to less than 0.35 kUA/l in 17 of 23 patients (most rapidly within 4 months) in the following months or years. Consequently, the optimal sampling time seems to be

more than 1 month and less than 4 months. In another study, specific immunoglobulin E was determined in the sera of 14 patients at an average of 29 months (range 1 to 61 months) after diagnosis, and only six patients were positive.[29] In our cohort, all levels were markedly elevated at a median time of 4.5 months, even at 26 months after the last allergic reaction. The high levels might be due to their repeated exposure and the relatively severe systemic symptoms.

For patients diagnosed with chlorhexidine allergy, re-exposure should be avoided. However, a study from the Danish Anesthesia Allergy Center showed that 35% of patients were accidentally re-exposed after diagnosis.[28] Another study from the United Kingdom showed that 1 patient was re-exposed to chlorhexidine and developed anaphylaxis in 18 patients diagnosed with chlorhexidine allergy.[6] In our study, two patients (20.0%) were also accidentally re-exposed. One reason for the difficulty in avoiding re-exposure is that chlorhexidine is widely used in the healthcare setting and may not be clearly labeled in products. Another reason is that the ingredients are not carefully checked by patients or healthcare workers. Therefore, avoiding re-exposure requires concerted efforts from multiple parties, including healthcare workers, patients, and manufacturers.

In cases of chlorhexidine allergy, tests against other allergens may also be positive, so when chlorhexidine is positive on testing, all other potentially relevant drug exposures should still be tested.[10,30] In our study, all other relevant exposures were tested, and any allergies to the associated agents were ruled out. Previous studies have shown that 25 to 35% of patients with chlorhexidine allergies were also positive for other potential culprits (such as latex, opiates, β-lactams, and neuromuscular blocking agents).[5,31,32] The reason for the difference may be attributed to the small sample size, and allergic reactions during the perioperative period were relatively rare in our study. More research on multiple sensitizations is needed.

There is an international consensus that timely administration of epinephrine is required for grade II to IV reactions.[33,34] In our study, although the majority of reactions were not life-threatening, a significant proportion were. Grade II to IV reactions accounted for 73% of the reactions. Only 14% of these reactions were treated with epinephrine, while 50% were treated with dexamethasone. Recently, Jiang *et al.* assessed the initial treatment for anaphylaxis in China by performing a systematic analysis of published case reports from 2014 to 2018 and found that only 14.2% of the patients were appropriately treated with epinephrine as the first-line intervention. These findings highlight the critical gap between clinical practice in China and the recommendations in international guidelines, and targeted training is urgently needed for healthcare providers in China.[35]

Limitations

Our study has some limitations. First, this was a single-center study with a small sample size and may not reflect the status of chlorhexidine allergy throughout China. Second, the retrospective nature of this study means that patient recall bias could not be avoided. Thus, further prospective, large-sample, multicenter clinical studies should be conducted in the future.

Conclusions

This study summarizes the characteristics of chlorhexidine allergy in an allergy center in China. The results showed that the majority of the reactions to chlorhexidine were attributed to skin disinfectants, and IV cannulation was the most common exposure route. Most patients were finally diagnosed after repeated allergic reactions, suggesting that chlorhexidine allergy was easily overlooked. Thus, we suggest increasing awareness of the potential allergenicity of chlorhexidine, especially after IV cannulation or during the perioperation. In addition, the skin prick test and serum specific immunoglobulin E test both had high sensitivity and specificity in diagnosing chlorhexidine allergy.

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Competing Interests

The authors declare no competing interests.

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