Pitfalls and peculiarities in chlorhexidine allergy

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Chlorhexidine (CHX) is a synthetic biguanide available in different forms (diacetate, dihydrochloride, and digluconate) and used as an antiseptic. In the past few years, there has been a substantial increase in the number of CHX-containing products used in health care. Hypersensitivity reactions to CHX are increasingly reported and include allergic contact dermatitis, photosensitivity, fixed drug eruptions, asthma, and life-threatening anaphylaxis. Here, we report 3 cases of anaphylaxis due to CHX with a particular course, highlighting possible pitfalls and peculiarities in CHX allergy.

CASE 1
A 38-year-old nonatopic female patient had a vulvovaginal disinfection for intrauterine device insertion. The gynecologist wore latex gloves and used CHX. Ten minutes after the insertion, the patient developed severe anaphylaxis with dyspnea, urticaria, and hypotension. The device was rapidly removed, and the patient was treated with corticosteroids, antihistamines, and adrenaline.

Allergy workup with prick test (PT) and measurement of specific IgE (sIgE) was negative for latex. Basal serum tryptase was within the normal range. PT (dilution 1:10) and intradermal test (IDT) (dilution 1:10,000,000) with CHX 0.5% were negative after 10 minutes. Subsequently, PT and IDT were performed at higher concentrations (1:1 and 1:10,000 dilution, respectively). After 25 minutes, IDT became positive (Figure 1) and the patient developed generalized itching and dizziness. She was treated with antihistamines leading to full recovery. sIgE against CHX (6.03 kU/L) and total IgE (tIgE) (114 kU/L) were increased. After 17 months, PT was negative (dilution 1:10), but sIgE were still increased (0.87 kU/L).

CASE 2
A 22-year-old atopic male patient of African origin was scheduled for an abdominal biopsy of a pancreatic mass. Lidocaine, propofol, rocuronium, and fentanyl were used for anesthesia. Urethral catheterization was performed with latex gloves and Instillagel (containing CHX). Urticaria and hypotension (blood pressure 51/38) developed after 20 minutes, requiring treatment with adrenaline, antihistamines, and corticosteroids.

CASE 3
A 38-year-old male atopic patient required surgery for a minor injury at the elbow. The surgeon used latex gloves and injected lidocaine for local anesthesia. At the end of the procedure, the patient developed urticaria, rhinitis, and laryngeal edema, requiring treatment with corticosteroids, antihistaminics, and nebulized adrenaline.

Allergological workup showed a basal serum tryptase within the normal range and increased sIgE against latex (2.43 kU/L). The patient was suspected having latex allergy and was addressed to our clinic. PT (1:1 dilution) and IDR (1:100,000 dilution) for CHX were positive. Of note, this reaction appeared after 25 minutes. tIgE were increased (487 kU/L). sIgE against ethylene oxide and rHevb1, rHevb3, rHevb5, rHevb6.01, rHevb6.02, rHevb8 were negative. sIgE against cross-reactive carbohydrate determinants (CCD) (1.64 kU/L) and CHX (10.1 kU/L) were increased. Provocation test ruled out lidocaine and latex allergy. Subsequent search of the medical charts confirmed that disinfection during surgery was performed with Merfen, containing CHX.

DISCUSSION
This case series highlights known and novel features of CHX allergy. Two of the reported cases were male and atopic. Atopy was not reported to be a risk factor so far, but male patients seem to develop CHX anaphylaxis more frequently than females.

Case 3 developed an anaphylactic reaction after wound disinfection. The first allergist did not test CHX and only further workup allowed identifying CHX hypersensitivity. This case shows that CHX can elicit anaphylactic reactions not only during general anesthesia or mucosal contact, but also after minor surgery. Moreover, it highlights that CHX is still a neglected allergen. Also, case 2 was accidentally re-exposed to CHX. This case indicates that CHX avoidance should be better trained.
and 97%, respectively.\(^5\) All 3 cases had positive sIgE against CHX,\(^6\) the sensitivity and specificity of sIgE are 100% and 97%, respectively.\(^5\) PT with CHX was negative in case 2, highlighting suboptimal sensitivity of skin tests in particular when reading is performed too rapidly. The latter was seen in cases 1 and 3, who showed positive IDT only after a prolonged time interval. In case 1, IDT (dilution 1:10,000,000) was initially considered negative and was subsequently performed at a higher concentration, eliciting a systemic reaction, IDT with different dilutions than those shown in the figure have not been performed.

PT and IDT for CHX hypersensitivity are cheap and rapidly performed. Sensitivity and specificity of PT are 95% and 97%, of IDT 68% and 100%, respectively.\(^5\) PT with CHX was negative in case 2, highlighting suboptimal sensitivity of skin tests in particular when reading is performed too rapidly. The latter was seen in cases 1 and 3, who showed positive IDT only after a prolonged time interval. In case 1, IDT (dilution 1:10,000,000) was initially considered negative and was subsequently performed at a higher concentration, eliciting a systemic reaction. Compared with data in the literature,\(^5\) IDT in our patients induced a much larger wheal and erythema, whereas sIgE were slightly above the average levels. These cases suggest that the CHX skin test should be performed starting with low concentrations, and reading should be performed after a prolonged interval, when histamine control starts to abate. Although high tIgE levels might affect measurement of sIgE against CHX,\(^6\) the sensitivity and specificity of sIgE are 100% and 97%, respectively.\(^5\) All 3 cases had positive sIgE against CHX, confirming their high specificity.

There is no current evidence that CHX allergy may resolve with time,\(^1\) as in cases 1 and 2. sIgE levels to CHX are known to rapidly decline over time,\(^2,7\) as seen in case 1. Nevertheless, re-exposure to CHX can lead to a rise of CHX sIgE in sensitized patients, as seen in case 2.

Interestingly, 2 of the reported cases had sIgE against latex, although both had negative PT to latex. Case 2 showed positive sIgE against rHevb8, and case 3 against CCD. In both cases, latex was not considered to be the causative allergen. This highlights the low specificity of sIgE against latex, as shown in previous studies.\(^8\)

In summary, possible peculiarities are as follows:

- CHX can elicit anaphylaxis after minor wound disinfection or mucosal contact.
- CHX skin tests may have to be read 25 minutes after prick testing and IDT.
- sIgE against CHX have a high sensitivity and specificity for CHX allergy.

Possible pitfalls are as follows:

- CHX is contained in many medical products and is still a neglected potential allergen.
- CHX skin test should be performed initially at low concentration to avoid a systemic reaction. We recommend starting skin tests using CHX gluconate 0.5% in aqueous solution, diluted 1:10 in NaCl 0.9% for PT. If negative, we recommend prick testing with undiluted CHX before proceeding to IDT. IDT should be performed starting with a 1:10,000,000 in NaCl 0.9% dilution if PTs are negative.

![Prick test and intradermal test (IDT) to chlorhexidine in case 1 becoming positive only after 25 minutes. In the prick test, the ink circle marks the size of the wheal. In IDT, the inner circle surrounds the papule at the time of the injection; the outer circle the wheal after 30 minutes. Because the patient developed a systemic reaction, IDT with different dilutions than those shown in the figure have not been performed.](image)

**REFERENCES**