

IgE-mediated anaphylaxis from chlorhexidine: diagnostic possibilities

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Case Report

We report on 4 allergic reactions during perioperative skin disinfection and urethral catheterization (Table 1). Analyses were carried out between 6 and 16 weeks after the acute event and included quantification of total IgE and chlorhexidine-specific IgE (sIgE) (Immuno-CAP, Phadia AB, Uppsala, Sweden). Prick tests were performed with 2% chlorhexidine digluconate in 70% alcohol (start dilution: 10^{-2} up of commercial stock solution).

Flow cytometric analysis of activated basophils (BAT) was performed as described elsewhere (1), and implied a negative and positive control (anti-IgE), and 2% chlorhexidine digluconate in 70% alcohol (serial dilution 2, 0.2, and 0.02 $\mu\text{g/mL}$).

Table 1 summarizes sIgE and prick test results of patients and chlorhexidine-tolerant controls. Fig. 1 shows the percentages of chlorhexidine-activated basophils in patients and 8 chlorhexidine-tolerant individuals.

Chlorhexidine, a cationic bisguanide antiseptic and disinfectant, is used as the (di)acetate or (di)gluconate salt. Chlorhexidine salts can trigger irritant dermatitis, allergic contact dermatitis (2, 3), and combined urticaria/anaphylaxis and allergic contact dermatitis (2).

Table 1. Characteristics of patients^a

N	Sex/age	Signs	Cause	IgE ^b	Prick test ^c
1	M/68	B, H, VF	Skin disinfection	3.5	5/10
2	M/54	B, H, S	Skin disinfection	0.55	7/25
3	M/87	P, U, A, B, H	Urethral gel	10.9	5/9
4	M/22	U, S	Skin disinfection	1.68	10/35

^aM, male; F, female; B, bronchospasm; H, hypotension; VF, ventricular fibrillation; S, shock; P, pruritus; U, urticaria; A, angio-edema. All 30 control individuals had a negative prick test (up to native solution) and sIgE for chlorhexidine.

^bChlorhexidine-specific IgE ≥ 0.35 kUa/L is considered positive.

^cPrick test. Ten-fold dilution of the stock solution of 2% chlorhexidine digluconate in 70% alcohol. A reaction $\geq 3/3$ mm is considered positive.

Life-threatening anaphylaxis is generally associated with mucosal or parenteral exposure. As already addressed in this journal (3), life-threatening anaphylaxis from cutaneous application remains anecdotal and probably underestimated.

Most authors apply skin testing to confirm diagnosis of chlorhexidine anaphylaxis. However, data on the irritative potential of these skin tests are scarce. Our findings support prick test to constitute a reliable diagnostic instrument. In patients, diagnosis of chlorhexidine anaphylaxis was established with prick test applying a 10-fold dilution of the stock solution. All 30 control individuals had negative prick test with the undiluted antiseptic. However, in some cases, skin tests to chlorhexidine were deemed unethical (4). Therefore, a reliable *in vitro* technique to diagnose chlorhexidine anaphylaxis would be more than welcome.

IgE-sensitized basophils, upon encounter with allergen that cross-links membrane-bound IgE, up-regulate the expression of certain membrane markers which can be detected by flow cytometry (5). It appears the BAT can contribute to the diagnosis of chlorhexidine anaphylaxis

(Fig. 1). All patients demonstrated a consistent chlorhexidine-induced basophilic CD63 expression. In control individuals, basophilic CD63 expression remained merely unchanged ($\leq 5\%$).

Chlorhexidine sIgE antibodies have been demonstrated in patients showing immediate chlorhexidine-induced hypersensitivity reactions (4–7). However, a commercial assay (ImmunoCAP[®]) has become available only recently. From our data it emerges that this assay constitutes a reliable tool to diagnose chlorhexidine anaphylaxis. All patients, but none of the control individuals, had an sIgE result exceeding the recommended threshold of 0.35 kUa/L.

In conclusion, prick test, chlorhexidine sIgE, and the BAT constitute reliable instruments to document chlorhexidine anaphylaxis. The sIgE assay is technically easier and, once fully validated, might become more readily available than the BAT. Alternatively, the BAT might be useful in patients with equivocal skin test and/or sIgE results and prove effective in the establishment of safe alternative antiseptics, which is not possible with an sIgE method at this moment.

References

1. Ebo D G, Hagendorens M M, Bridts C H, Schuerwegh A J, De Clerck L S, Stevens W J. Flow cytometric analysis of in vitro activated basophils, specific IgE and skin tests in the diagnosis of pollen-associated food allergy. *Cytometry B Clin Cytom* 2005; 64: 28–33.
2. Ebo D G, Stevens W J, Bridts C H, Matthieu L. Contact allergic dermatitis and life-threatening anaphylaxis to chlorhexidine. *J Allergy Clin Immunol* 1998; 101: 128–129.
3. Krautheim A B, Jermann T H, Bircher A J. Chlorhexidine anaphylaxis: case report and review of the literature. *Contact Dermatitis* 2004; 50: 113–116.
4. Pham N H, Weiner J M, Reisner G S, Baldo B A. Anaphylaxis to chlorhexidine. Case report. Implication of immunoglobulin E antibodies and identification of an allergenic determinant. *Clin Exp Allergy* 2000; 30: 1001–1007.
5. Ebo D G, Hagendorens M M, Bridts C H, De Clerck L S, Stevens W J. In vitro allergy diagnosis: should we follow the flow? *Clin Exp Allergy* 2004; 34: 332–339.
6. Ohtoshi T, Yamauchi N, Tadokoro K, Miyachi S, Suzuki S, Miyamoto T et al. IgE antibody-mediated shock reaction caused by topical application of chlorhexidine. *Clin Allergy* 1986; 16: 155–161.
7. Layton G T, Stanworth D R, Amos H E. The incidence of IgE and IgG antibodies to chlorhexidine. *Clin Exp Allergy* 1989; 19: 307–314.

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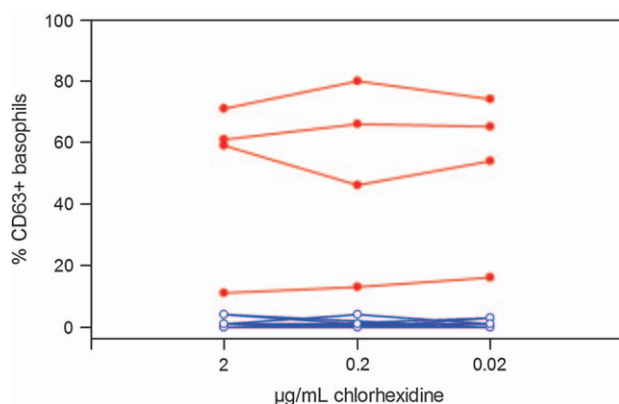


Fig. 1. Chlorhexidine-induced CD63 up-regulation in chlorhexidine-allergic patients ($n = 4$, closed circles) and chlorhexidine-tolerant individuals ($n = 8$, open circles). Results are expressed as percentages of CD63 positive basophils relative to spontaneous CD63 expression.