

Educational & Teaching Material

Case Report



Chlorhexidine: a hidden life-threatening allergen

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Conflict of Interest

The authors have no financial conflicts of interest.

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ABSTRACT

Chlorhexidine is a commonly used antiseptic and disinfectant in the health-care setting. Anaphylaxis to chlorhexidine is a rare but potentially life-threatening complication. Epidemiologic data suggest that the cases of chlorhexidine allergy appears to be increasing. In this article we report a life-threatening anaphylactic shock with cardiorespiratory arrest, during urethral catheterization due to chlorhexidine. The authors also performed a literature review of PubMed library of anaphylactic cases reports due to this antiseptic between 2014 and 2018, demonstrating the increase in the number of cases occurring worldwide and the importance of detailed anamnesis and appropriate diagnostic workup of allergic reactions to disinfectants.

Keywords: Allergy; Anaphylaxis; Chlorhexidine

INTRODUCTION

Chlorhexidine is an antiseptic and disinfectant used against a broad of bacteria, viruses and fungi [1]. Since its introduction in 1954, it is used in the hospital settings for medical and surgical products and widely in over-the-counter products [1, 2]. Many health professionals are unaware of its presence in different products, so it is often a 'hidden' allergen.

The most common allergic reactions described to chlorhexidine are delayed reactions (type IV hypersensitivity), T cell mediated, and occur after exposure to the antiseptic for topical use. Contact dermatitis is the most frequent manifestation [2-4]. Immediate reactions (type I hypersensitivity), have also been reported, but much less frequently, and symptoms can range from urticaria to anaphylaxis with a risk of cardiorespiratory arrest and death [2-4].

It has not been described cross reactivity between chlorhexidine and other antiseptic agents [1].

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CASE REPORT

A 75-year-old male with hypertension receiving beta-blocker and bladder cancer underwent transurethral tumor resection in 2014. Surveillance postsurgical cystoscopy under local anesthesia was performed every 6 months. During the 2nd procedure he developed generalized cutaneous pruritus with no other symptoms with spontaneous resolution after one hour. This reaction was interpreted as allergy to cefoxitin and it was recommended to avoid 2nd generation cephalosporins.

Twenty minutes after the 4th cystoscopy, he developed generalized urticaria, oropharyngeal tightening, dyspnea, hypotension (75/40 mmHg) and loss of consciousness with cardiorespiratory arrest. Cardiopulmonary resuscitation was initiated immediately with endovenous administration of adrenaline (1 mg), clemastine (2 mg) and hydrocortisone (200 mg) and orotracheal intubation with invasive ventilation. The patient recovered over the next 2 hours and was extubated on the same day.

The patient was referred to the immunoallergology outpatient clinic and a complete workup was performed. Local disinfection and anesthesia were performed with iodopovidone (Betadine, manufacturer, city, country) and lidocaine + chlorhexidine gel (Optilube, manufacturer, city, country). Prophylactic antibiotic therapy was performed only in 2nd procedure (cefoxitin) and ortho-phthalaldehyde (Cidex, manufacturer, city, country) was not used as cystoscope disinfectant.

The allergologic investigation revealed negative skin prick test (SPT) to iodopovidone and latex, and negative cutaneous tests (standard concentration [5]) to PPL, MDM, amoxicillin, penicillin, cefoxitin). Specific IgE (sIgE) available (latex, penicillin, amoxicillin) were negative. Provocation tests to lidocaine and cefoxitin were negative.

SPT to chlorhexidine (2%) was strongly positive (11 mm × 10 mm wheal), with a positive sIgE - 4 kU/L (normal value: <0.35 kU/L). **Table 1** summarizes the allergologic workup.

Table 1. Allergologic workup carried out in our immunoallergology outpatient clinic

Reagent	Skin prick test	Intradermal test (standard ENDA concentration) [5]	Specific IgE (RV <0.35 kU/L)	Challenge
Antiseptic agents				
Iodopovidone	Negative	Not advised	Not available	Tolerated
Chlorhexidine	Positive	Not advised	4 kU/L	Contraindicated
Local anesthetics				
Lidocaine	Negative	Not advised	Not available	Negative (SC)
Antibiotics				
PPL and MDM	Negatives	Negative	-	-
Amoxicillin	Negative	Negative	Negative	Not performed
Penicillin	Negative	Negative	Negative	Not performed
Cefaclor	Negative	Negative	Negative	Not performed
Cefoxitin	Negative	Negative	Not available	Negative (IV)
Cefazolin	Negative	Negative	Not available	Not performed
Cefuroxime	Negative	Negative	Not available	Not performed
Other				
Latex	Negative	-	Negative	Tolerated

ENDA, European Network for Drug Allergy; RV, reference value; SC, subcutaneous; PPL, **abc**; MDM, **abc**; IV, intravenous.

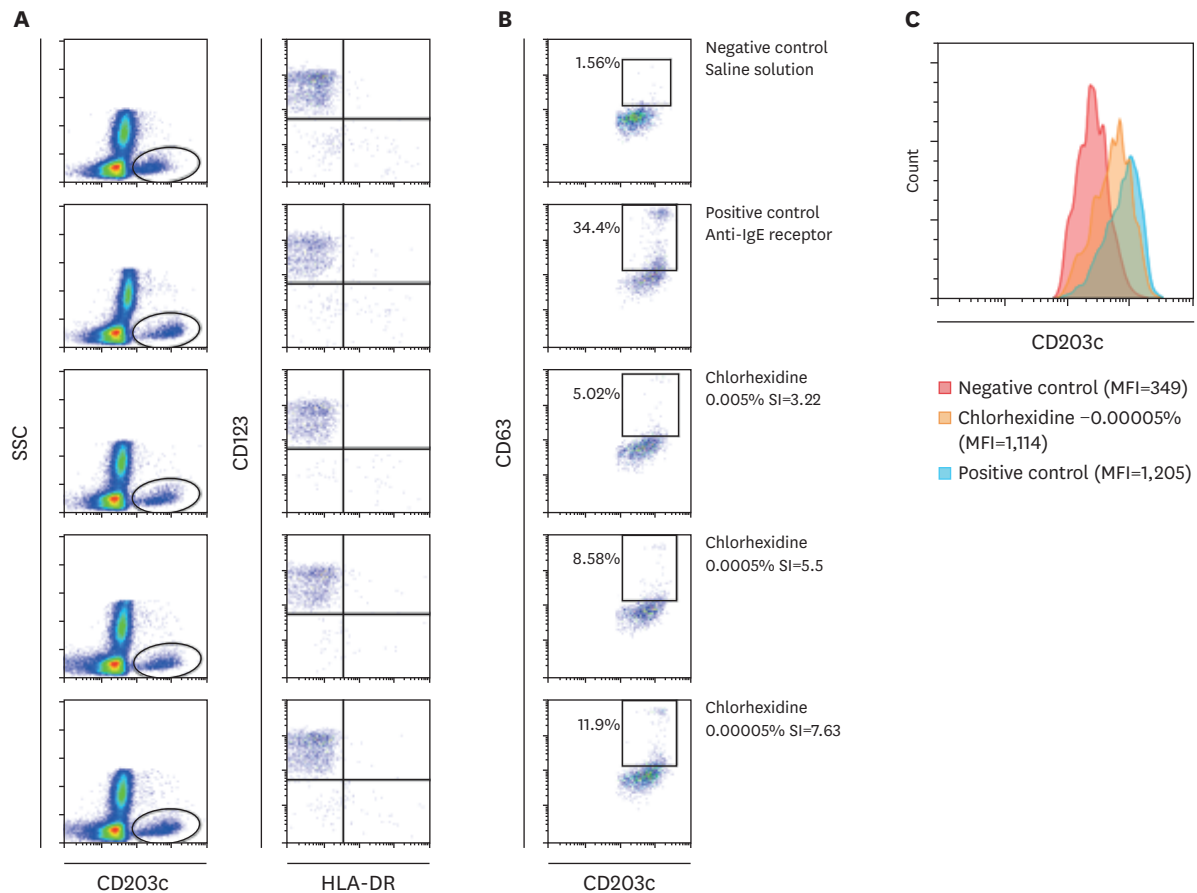


Fig. 1. Basophil activation test performed in whole blood. (A) Identification of basophil population in the lymphocyte-monocyte gate a SSC/CD203c+. (B) Flow cytometry dot plots of CD63 expression (%) on CD123+/HLA-DR-/CD203c+ cells. (C) Histogram showing the mean fluorescence intensity (MFI) median of CD203c expression. SI, stimulation index (ratio of stimulated/unstimulated basophils).

We also performed a basophil activation test (BAT) using chlorhexidine digluconate 20% (1062 mg/mL) at 0.05%, 0.005%, 0.005%, and 0.00005% [6]. The basophil population was identified as HLA-DR-CD123+ CD203c+ cells and activation by CD63 expression. BAT was positive at 0.005%, 0.0005%, and 0.00005% with activation of 5.02%, 8.58%, and 11.9% and stimulation index of 3.22, 5.5, and 7.63 respectively (**Fig. 1**).

The diagnosis of severe allergic reaction to chlorhexidine was confirmed. The patient was advised to avoid products containing chlorhexidine. Subsequent cystoscopy was uneventful using lidocaine gel as local anesthetic and iodopovidone as disinfectant. Moreover, he was informed to be aware of chlorhexidine as a component of over the counter products and the need to avoid them.

DISCUSSION

The first case of anaphylaxis to chlorhexidine has been reported in 1984 in Japan [1, 3]. Although rare, the number of clinical case reports of anaphylaxis (type I hypersensitivity) to this antiseptic is increasing. Odedra et al. [1] published that from 1994 to 2013, 65 case reports of chlorhexidine-related anaphylaxis were diagnosed. The majority was

among surgical patients (urology and cardiothoracic) [6]. From 1984 to 2014, 36 cases of perioperative anaphylaxis to chlorhexidine were published [2].

Most reactions have been reported after application of chlorhexidine to damaged skin surfaces (wounds, burns, surgical incision); and to mucous membranes (urethra, eyes, nose) or after insertion of medical devices (central venous catheters, CVC) impregnated with chlorhexidine [4].

The prevalence of perioperative anaphylaxis range from 0.05%–2% and is increasing [2]. True incidence attributed to chlorhexidine is unknown, with several authors suggesting that is rare, but some studies referring incidences ranging from 5.5% to 8.8% [2]. Sharp et al. (Australia, 2016) [2] in a review to chlorhexidine-induced anaphylaxis in surgical patient (total of 68 anaphylactic reactions) showed that most frequent cases occur due to the presence of chlorhexidine in urinary catheter lubricant (n = 30 [44.12%]), CVC (n=24 [35.29%]) and topical solutions (n=11 [16.18%]).

It appears to occur more frequently in men with mean age of 58 years, previously reporting a mild cutaneous reaction on chlorhexidine exposure [1].

Patients rarely have history of atopic disease. The clinical presentation is variable. In most cases patients developed erythematous rash/urticarial at the time of reaction and hypotension, with some presenting cardiorespiratory arrest [1, 2]. Bronchospasm is rarely reported [1, 2]. Our patient was older than the mean presented, however the reaction occurred during a cystoscopy. This procedure and the severity of the symptoms were similar to the most commonly described.

To our knowledge, in the last five years (2014–2018), a total of 24 cases of chlorhexidine-related anaphylaxis were published (Table 2). The male gender is the most affected (83%).

Table 2. Published cases of chlorhexidine-induced anaphylaxis between 2014–2018

Study	Country	No. of cases	Sex	Age (yr)	SPT	slgE (<0.35 kU/L)	BAT
Nakonechna et al., 2014 [7]	United Kingdom	6	M	50	NR	30	NR
			M	78	NR	2.3	NR
			M	72	Pos	4.4	NR
			M	73	Pos	3.3	NR
			M	73	Pos	11.8	NR
Weng et al., 2014 [8]	China	2	M	48	Pos	NR	NR
			F	34	Pos	NR	NR
Buerji et al., 2014 [9]	Switzerland	1	M	45	Pos	6.1	NR
Odedra et al., 2015 [1]	United Kingdom	1	M	62	Pos	NR	NR
Rutkowski et al., 2015 [10]	United Kingdom	1	M	73	Pos	13.1	NR
Hong et al., 2015 [11]	Singapore	1	M	66	Pos	NR	NR
Stewart et al., 2015 [12]	Australia	1	M	60	Pos	Pos	NR
Chen et al., 2016 [13]	United Kingdom	1	-	-	Pos	NR	NR
Wang et al., 2016 [14]	Thailand	1	M	54	NR	7.21	NR
Teixeira de Abreu et al., 2017 [15]	Brazil	1	F	25	Pos	NR	NR
Lasa et al., 2017 [16]	Spain	2	M	3	Pos	2.31	Pos
			M	12	Pos	24.5	Pos
Totty et al., 2017 [17]	United Kingdom	1	M	70	Pos	NR	NR
Kow et al., 2017 [18]	Malaysia	1	M	20	Pos	0.77	NR
Postolova et al., 2017 [19]	United States	2	M	60	Pos	0.25 (RV=0.1)	NR
			F	29	Pos	NR	NR
Toletone et al., 2018 [3]	Italy	1	M	63	Pos	0.04	Pos
Gu et al., 2018 [20]	China	1	M	57	Neg*	NR	NR

SPT, skin prick test; BAT, basophil activation test; NR, not reported; Pos, positive; RV, reference value; Neg, *abc*.

*The diagnosis was confirmed after the 2nd provocation test.

Mean age was 51 ± 15 years (range, 3–78 years) in agreement with what has already been described. The majority of the diagnosis was established through SPT. Twenty-one patients performed SPT, 20 were positive. The diagnosis in patient with negative SPT was determined by positive provocation test. Fifteen patients performed sIgE and were all positive (mean, 7.12 kU/L; range, 0.04–30 kU/L). Only 3 performed BAT and were positive.

Our review showed that immediate type I allergic reactions to chlorhexidine are increasing, with a mean of 4.8 cases/yr described over the last 5 years, comparing with the 3.25 cases/yr referred in Odedra et al. [1] review over 20 years. This allows us to admit that true incidence of chlorhexidine anaphylaxis is likely to be underestimated in view of its large use as a disinfectant. Undervaluation of previous chlorhexidine reactions increases the risk of a possibly fatal outcome for the patient after re-exposure in future medical-surgical procedures.

A prompt referral to a specialist consultation and detailed allergy study is crucial. Detailed history and diagnostic testing allow to confirm the diagnosis of chlorhexidine allergy.

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