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.1 Hypersensitivity reactions to CHX are increasingly reported and include allergic contact dermatitis, photosensitivity, fixed drug eruptions, asthma, and life-threatening anaphylaxis.2-4 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 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. IgE were increased (487 kU/L). Serum tryptase was 116 μg/L, in accordance with intraoperative anaphylaxis. The patient required treatment with adrenaline, corticosteroids, and antihistamines. After 6 weeks, PT and IDT for suxamethonium, atracurium, esmeron, propofol, and fentanyl were negative, and sIgE were negative for quaternary ammonium and suxamethonium, but increased for CHX (5.94 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. Serum tryptase was 43 μg/L after 1 hour and normal 24 hours later.

PT and IDT were negative for lidocaine, rocuronium, propofol, and fentanyl. PT was negative for latex, CHX and Instillagel. sIgE were negative for ethylene oxide and increased for latex (nHevb 1.04 kU/L, rHevb8 1.59 kU/L); negative rHevb1, rHevb3, rHevb5, rHevb6.01, rHevb6.02) and CHX (3.25 kU/L). sIgE were slightly increased (104 kU/L). Lidocaine 2% provocation test was tolerated. Allergy to CHX was noted in the medical chart.

Fourteen months later surgery was reattempted. Latex was avoided, but Instillagel for urethral catheterization (latex-free catheter) and Bichsel gel for tracheal tube insertion (latex-free tube) were used, both containing CHX. After 20 minutes, the patient developed an anaphylactic shock (blood pressure 59/32). PT and IDT were negative for lidocaine, rocuronium, atracurium, esmeron, propofol, and fentanyl. PT was negative for latex, but increased for CHX (5.94 kU/L).

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,5 but male patients seem to develop CHX anaphylaxis more frequently than females.1,2,5

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.
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. 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.

Although high sIgE levels might affect measurement of sIgE against CHX, the sensitivity and specificity of sIgE are 100% and 97%, respectively. All 3 cases had positive sIgE against CHX, confirming their high specificity.

There is no current evidence that CHX allergy may resolve with time, as in cases 1 and 2. sIgE levels to CHX are known to rapidly decline over time, 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.

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 dilution if PTs are negative.

FIGURE 1. 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.

REFERENCES