

Anaphylaxis to invasive chlorhexidine administration despite tolerance of topical chlorhexidine use



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Clinical Implications

- Patients without previous hypersensitivity reactions to topical chlorhexidine can have anaphylaxis upon invasive exposure such as incision sites and impregnated catheters. Skin test reactions to chlorhexidine can be delayed and should be read 30 minutes after application.

TO THE EDITOR:

Perioperative anaphylaxis is a potentially life-threatening hypersensitivity reaction (HSR) caused by drugs used during anesthesia or surgery. Early symptoms of anaphylaxis including pruritus and dyspnea are unattainable in anesthetized patients. Diagnosis is thereby delayed until hypotension and inability to ventilate the patient are present, likely contributing to the 3% to 9% mortality rate.¹ The incidence of perioperative anaphylaxis differs regionally, ranging between 1 in 5,000 to 1 in 20,000 anesthetic procedures.² Because numerous medications are rapidly administered, a causative agent is identified in less than 60% of cases, with neuromuscular-blocking agents (NMBAs) and antibiotics being the most commonly implicated.^{2,3}

Chlorhexidine, a preferred antiseptic in both household and hospital products, is an underrecognized cause of immediate HSRs. Previously used mostly in topical preparations, chlorhexidine is now frequently impregnated in catheters and implantable devices to mitigate infections. The ubiquitous use of chlorhexidine has been implicated in the increasing rates of sensitization and subsequent severe reactions.⁴ As of 2015, 68 distinct perioperative anaphylactic reactions to chlorhexidine were reported in the literature and most were preceded by minor HSRs such as rash.⁵ In addition, there is limited information on delayed skin prick test (SPT) positivity with chlorhexidine and the dangers of false-negative results with subsequent intradermal test (IDT).^{4,6} We report 2 cases of chlorhexidine-induced perioperative anaphylaxis after invasive exposure, who were completely asymptomatic with topical use and demonstrated delayed SPT positivity 30 minutes after application.

CASE 1

A 60-year-old nonatopic man with coronary artery disease presented after perioperative anaphylaxis during anesthesia for attempted coronary artery bypass graft surgery. In the decade before this event, he underwent multiple surgeries and procedures; intraoperative medications included fentanyl, midazolam, NMBAs, and skin cleansing with chlorhexidine. The day before the coronary artery bypass graft, he cleansed his skin and rinsed

his mouth with chlorhexidine solution. Anesthesia included induction with midazolam, fentanyl, and rocuronium, followed by central venous catheter (CVC) (Arrowgard Blue+) placement. Minutes later, his blood pressure and end-tidal CO₂ dropped (70/40 mm Hg and 21 mm Hg, respectively), requiring continuous intravenous epinephrine for stabilization (Figure 1, A). Line placement and vascular integrity were confirmed by transesophageal echocardiography. Given continued dependence on vasopressor support, surgery was aborted and the patient was admitted to the intensive care unit. Tryptase level measured before intensive care unit transfer was 60 ng/mL. He presented to allergy clinic 2 weeks later. Labs showed a baseline tryptase level of 7.3 ng/mL and negative latex sIgE, and plans were made for follow-up skin testing. Weeks later he was emergently taken back for surgery due to unstable angina; we advised avoidance of rocuronium as the most suspicious agent. Despite NMBA avoidance, the patient had recurrent anaphylaxis about 10 minutes after induction (and same brand CVC placement). Surgery was again aborted and the patient returned to our clinic 4 weeks after the incident.

Skin testing to agents used during both procedures and potential alternatives including fentanyl, remifentanyl, midazolam, lidocaine, and chlorhexidine digluconate was performed according to previously published nonirritating skin prick testing (SPT) and intradermal testing (IDT) concentrations (Figure 2, A; see Table E1 in this article's Online Repository at www.jaci-inpractice.org) as available at various clinics in our institution.^{7,8} Chlorhexidine digluconate SPT result was negative at 15 minutes (histamine: wheal [W], 5 mm, flare [F], 7 mm; saline: negative) but turned positive at 30 minutes (1.2 mg/mL; W, 7 mm, F, 20 mm; Figure 2, A). A lower SPT concentration was used on the basis of availability at our institution. The IDT result was negative at 1:100 dilution of the highest nonirritating concentration but positive at 1:10 dilution (0.0002 µg/mL; W, 12 mm, F, 25 mm; Figure 2, A) at 30 minutes. Chlorhexidine IgE level by immunocap (Phadia/ThermoFisher Laboratories) was elevated at 0.25 kU/L (reference range, <0.1 kU/L). In collaboration with the anesthesiologist, we identified that the CVCs in both cases were chlorhexidine impregnated. He subsequently underwent successful surgery with avoidance of chlorhexidine products.

CASE 2

A 29-year-old nonatopic woman was undergoing elective knee surgery. The preceding evening, she bathed with chlorhexidine solution. On the day of the surgery, she was sedated with intravenous fentanyl and midazolam and her skin was prepped with chlorhexidine for peripheral nerve block placement. Forty minutes later she was induced with propofol and given preoperative dexamethasone, lidocaine, and cefazolin. Soon after she became acutely hypotensive (50/30 mm Hg) with weak peripheral pulses and diminished end-tidal CO₂. She received phenylephrine, epinephrine, ephedrine, hydrocortisone, and crystalloid (Figure 1, B). She remained hypotensive, requiring pressor support for an hour. Her tryptase level was 26 ng/mL. Hives, airway swelling, bronchospasm, and stridor were not noted. Three weeks later, she was evaluated in our clinic with

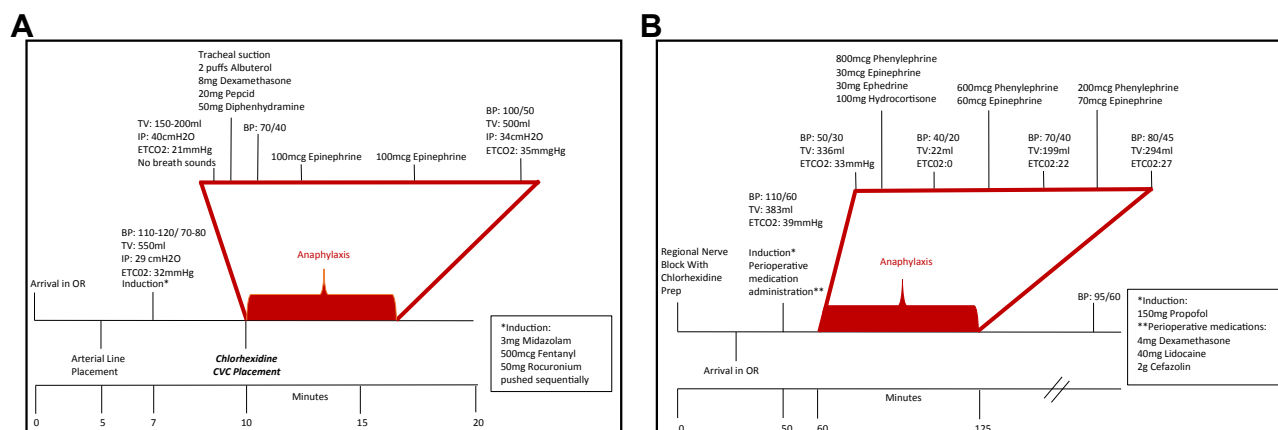


FIGURE 1. Timeline of chlorhexidine-induced perioperative anaphylaxis events. **A**, Case 1: Anaphylaxis following insertion of chlorhexidine-impregnated CVC. **B**, Case 2: Anaphylaxis following skin incision over chlorhexidine-prepped nerve block site. *BP*, Blood pressure; *ETCO2*, end-tidal carbon dioxide; *IP*, peak inspiratory pressure; *OR*, operating room; *TV*, tidal volume. All medications given intravenously.

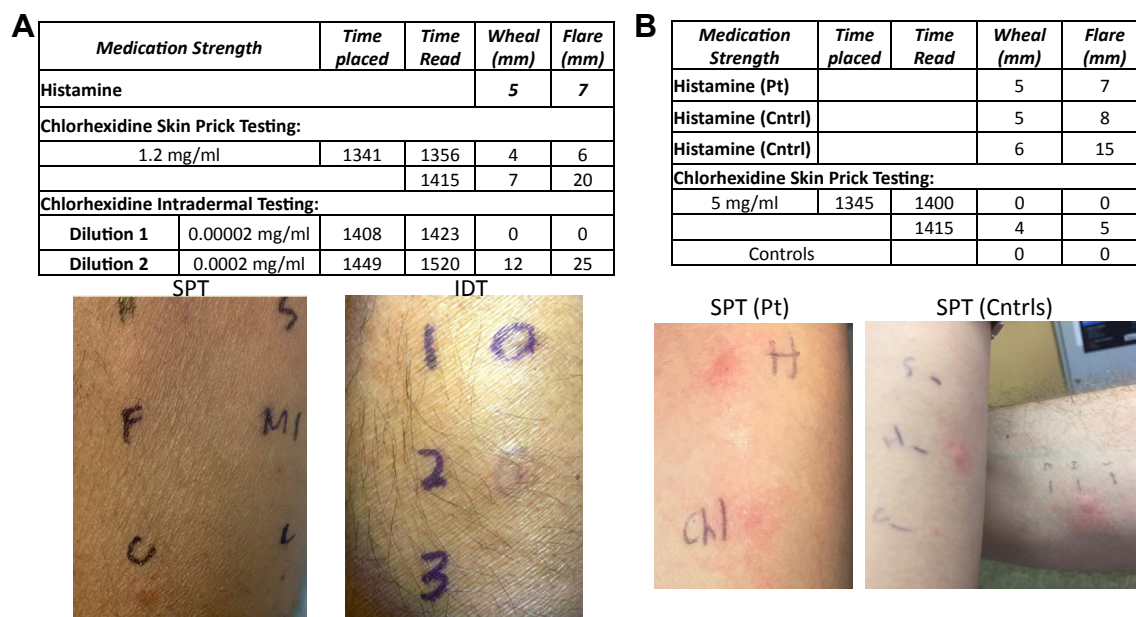


FIGURE 2. Positive chlorhexidine SPT result at 30 minutes. **A**, Case 1: IDT dilution 2 was positive so 3 not done. **B**, Case 2: Negative chlorhexidine SPT result at 30 minutes in clinic providers (Cntrls). Saline and chlorhexidine SPT results were negative at 15 minutes in both cases (not pictured). *C/Chl*, Chlorhexidine; *Cntrl*, control; *F/Fen*, fentanyl; *H*, histamine; *L*, lidocaine; *ME*, mepivacaine; *MI*, midazolam; *Pt*, patient; *R*, remifentanyl; *S*, saline.

skin testing to propofol, chlorhexidine, midazolam, fentanyl, penicillin, and cefazolin (see Table E2 in this article's Online Repository at www.jaci-inpractice.org). Lidocaine and dexamethasone were not tested because they were considered less likely to be culprit drugs. Chlorhexidine digluconate SPT result was negative at 15 minutes but turned positive at 30 minutes (5 mg/mL; W, 4 mm, F, 5 mm; histamine: W, 5 mm, F, 7 mm; saline: negative; Figure 2, B). The SPT result of 2 clinic providers as controls was negative to chlorhexidine digluconate (histamine: W, 5 mm, F, 8 mm; W, 6 mm, F, 15 mm; saline: negative; Figure 2, B). The patient's remaining SPT result was negative

and she tolerated oral challenge to cephalexin. She had a successful surgery during which propofol, midazolam, fentanyl, and cefazolin were again used but chlorhexidine was avoided.

DISCUSSION

In most reported cases of chlorhexidine-associated anaphylaxis, patients demonstrated prior mild HSRs to topical chlorhexidine.^{4,5} We present 2 cases of anaphylaxis after invasive chlorhexidine administration in individuals who tolerated topical chlorhexidine exposures without any symptoms. The patient in

case 1 continued to be asymptomatic with topical chlorhexidine administration between his 2 anaphylactic episodes. Our cases emphasize that when evaluating perioperative anaphylaxis, allergists need to be aware that vascular devices are frequently impregnated with chlorhexidine and even skin penetration of chlorhexidine at incision sites can elicit systemic reactions.

Delayed positivity of chlorhexidine skin testing is a poorly reported peculiarity, which could potentially result in serious adverse reactions. Similar to only 2 reports in the literature,^{4,6} our SPT and IDT results turned positive 30 minutes after application in both cases. Although only a lower concentration was available for SPT in case 1, we do not think this explains delayed positivity given that IDT in case 1 and SPT in case 2 also had delayed positivity despite using published concentrations. In highly sensitized patients, proceeding to IDT if the SPT result is negative after 20 minutes could lead to systemic reactions. The interpretation of the SPT result should always be done at 30 minutes to avoid false-negative readings and possibly hazardous IDT.

Once considered a rare cause of perioperative anaphylaxis, reports of serious adverse reactions to chlorhexidine have increased over the last several years, prompting a drug safety communication from the Food and Drug Administration.⁹ Our cases emphasize the need to be vigilant of chlorhexidine HSRs and 2 unique aspects of these reactions: first, the risk of anaphylaxis with invasive exposure despite tolerance of topical administration, and second, the delayed reactivity of individuals on skin testing.

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TABLE E1. Case 1—Skin prick and intradermal testing concentrations and results

Skin prick testing					
Drug	Strength	Time placed	Time read	W (mm)	F (mm)
Histamine	—	1341	1356	5	7
Saline	—	1341	1356	0	0
Fentanyl	0.05 mg/mL	1341	1356	0	0
Midazolam	5 .0 mg/mL	1341	1356	0	0
Chlorhexidine	1.2 mg/mL	1341	1356	4	6
			1415	7	20
Lidocaine	10 mg/mL	1341	1356	0	0
Mepivacaine	10 mg/mL	1341	1356	0	0
Remifentanyl	0.05 mg/mL	1341	1356	0	0
Intradermal skin testing					
Drug	Strength	Time placed	Time read	W (mm)	F (mm)
Saline	—	1401	1416	0	0
Fentanyl	0.00005 mg/mL	1408	1423	0	0
Fentanyl	0.0005 mg/mL	1435	1450	0	0
Fentanyl	0.005 mg/mL	1450	1505	0	0
Midazolam	0.005 mg/mL	1408	1423	0	0
Midazolam	0.05 mg/mL	1435	1450	0	0
Midazolam	0.5 mg/mL	1450	1505	0	0
Chlorhexidine	0.00002 mg/mL	1408	1423	0	0
Chlorhexidine	0.0002 mg/mL	1449	1520	12	25
Chlorhexidine	0.002 mg/mL	—	—	—	—
Lidocaine	0.01 mg/mL	1408	1423	0	0
Lidocaine	0.1 mg/mL	1435	1450	0	0
Lidocaine	1.0 mg/mL	1450	1505	0	0
Mepivacaine	0.01 mg/mL	1408	1423	0	0
Mepivacaine	0.1 mg/mL	1435	1450	0	0
Mepivacaine	1.0 mg/mL	1450	1505	0	0
Remifentanyl	0.00005 mg/mL	1408	1423	0	0
Remifentanyl	0.0005 mg/mL	1435	1450	0	0
Remifentanyl	0.005 mg/mL	1450	1505	0	0

TABLE E2. Case 2—Skin prick and intradermal testing concentrations and results

Skin prick testing					
Drug	Strength	Time placed	Time read	W (mm)	F (mm)
Histamine	—	1345	1400	5	7
Saline	—	1345	1400	0	0
Propofol	10 mg/mL	1345	1400	0	0
Fentanyl	0.05 mg/mL	1345	1400	0	0
Midazolam	5 .0 mg/mL	1345	1400	0	0
Chlorhexidine	5 mg/mL	1345	1400	0	0
			1415	4	5
Benzylpenicillin	10,000 U/mL	1341	1356	0	0
Penicillin G	10,000 U/ml	1341	1356	0	0
Cefazolin	330 mg/mL	1341	1356	0	0
Intradermal skin testing					
Drug	Strength	Time placed	Time read	W (mm)	F (mm)
Chlorhexidine	Not done	—	—	—	—
Saline	—	1400	1415	0	0
Propofol	0.1 mg/mL	1400	1415	0	0
Propofol	1 mg/mL	1425	1440	0	0
Fentanyl	0.0005 mg/mL	1400	1415	0	0
Fentanyl	0.005 mg/mL	1425	1440	0	0
Midazolam	0.05 mg/mL	1400	1415	0	0
Midazolam	0.5 mg/mL	1425	1440	0	0
Benzylpenicillin	10,000 U/mL	1400	1415	0	0
Benzylpenicillin	10,000 U/mL	1400	1415	0	0
Penicillin G	10,000 U/mL	1400	1415	0	0
Cefazolin	3 mg/mL	1400	1415	0	0
Cefazolin	33 mg/mL	1425	1440	0	0

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