preventative antihistamine. There is no mention of previous episodes of cold-induced anaphylaxis. As ice cube testing, which is diagnostic for cold urticaria, was positive, and all other testing was negative in a patient with clinical anaphylaxis with a significant increase in tryptase, the authors concluded the cause to be cold-induced anaphylaxis triggered by intraoperative exposure to cool fluids.

Although we agree that this is an important differential diagnosis and congratulate the authors on drawing attention to this rare cause of intraoperative anaphylaxis, we have one concern regarding the investigation of the patient. Although the patient was thoroughly investigated with all intraoperative medications, in the paper, there was no mention of the investigation of possible hidden allergens such as chlorhexidine, latex, ethylene oxide, or excipients. Intraoperative exposure to these substances is almost inevitable and they are all known to cause intraoperative allergy.[2-4] In the Danish Anaesthesia Allergy Centre (DAAC), we test all patients for these potential hidden allergens routinely and we encourage others to do the same. Chlorhexidine deserves special attention because it is widely used in the health care setting, and in DAAC, chlorhexidine is the culprit drug in almost 10% of Danish patients investigated for intraoperative allergy.[5] The recent NAP6 project on perioperative anaphylaxis in the United Kingdom where all patients were also routinely tested with chlorhexidine found it to be the cause in 9% of cases.[6] In addition, recently, the American Food and Drug Administration issued a warning about the possibility of rare but serious allergic reactions caused by chlorhexidine.[7] Consequently, we believe that it is important to remember to test with chlorhexidine and other relevant hidden allergens[2] in patients with intraoperative allergy.

In conclusion, we appreciate the conclusions drawn in the study by Maciag et al and the focus on an important differential diagnosis in intraoperative anaphylaxis. However, we felt that it was appropriate to draw attention to the hidden allergens in intraoperative allergy and suggest excluding allergy to chlorhexidine, latex, and ethylene oxide and any relevant excipients to make the case for cold-induced anaphylaxis even stronger.

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Reply

To the Editor:

We would like to thank Opstrup and Garvey[1] for their commentary in "Intraoperative anaphylaxis: remember the hidden allergens." As they suggest, many agents employed during a procedure, from antiseptics to latex, can precipitate an intraoperative reaction in a susceptible individual.[1] These substances are rarely documented in operative notes by the surgeon, or in anesthesia records. We would like to highlight the importance of face-to-face multispecialty collaboration after an intraoperative reaction to prompt consideration of these possible culprits.

In our particular case, the patient did not previously experience cold-induced anaphylaxis outside of the setting of surgery. This may have been related to the lack of a more systemic exposure to cold before her procedure. In addition, many common anesthetic agents cause peripheral vasodilation and thus alter physiologic thermoregulation through a radiative loss of body heat. The physiologic effects of anesthesia likely lowered the threshold for her anaphylactic reaction to the cool fluids. It is likely that this systemic exposure, as well as large surface exposed to cold fluids, precipitated her reaction.

Opstrup and Garvey[1] suggest that latex exposure could have caused anaphylaxis. Uribe et al[2] report that in pediatric cases, latex is a primary cause of perioperative anaphylaxis, with an incidence of 1 of 10,159 anesthetic events. In pediatric patients with underlying atopy, approximately 4% are sensitized to latex.[3] Latex allergy is far more common in those who have had latex exposure intraoperatively in the first year of life.[4] In hopes of mitigating reactions as well as sensitization in employees as well as patients, all operative suites at Boston Children's Hospital are latex free. It is improbable that latex caused anaphylaxis in this case.

Chlorhexidine is a frequently employed antiseptic and is associated with a high rate of perioperative anaphylaxis.[5] In pediatric patients as well, chlorhexidine has been reported as a cause of anaphylaxis, but the frequency of this reaction is not known.[2] To mitigate infectious risk, our patient prepared for days preoperatively with chlorhexidine. Postprocedurally, she continues to use chlorhexidine regularly, and has not suffered a reaction. Consistent use before and after the procedure without reaction makes it improbable that chlorhexidine caused anaphylaxis in her case.

In their operative notes, surgeons diligently describe the technique employed during the procedure, but they rarely mention medications or topical products used. Similarly, the anesthesia record thoroughly recounts antibiotics, paralytics, and sedatives used, but does not reference other potentially allergenic substances used in the case. These "hidden allergens," as described by Opstrup and Garvey,[1] can indeed cause allergic reaction and even anaphylaxis. We appreciate the importance of this consideration. Furthermore, we would like to highlight the

importance of multispecialty team collaboration, involving allergy, surgery, as well as anesthesia after a case of intraoperative anaphylaxis. This can be instrumental in highlighting potentially missed culprits, as well as augment patient safety as a whole.

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Injured skin as risk factor for chlorhexidine anaphylaxis

To the Editor:

We have read with great interest the article on anaphylaxis elicited by invasive chlorhexidine (CHL) administration despite the apparent tolerance when applied topically on normal skin.[1] In our opinion and from a careful review of literature,[2] the integrity of the skin barrier is a key factor to avoid anaphylaxis induced by topical application of CHL.[2] A study evaluated the penetration of CHL gluconate 2% aqueous in human skin after 2 minutes, 30 minutes, and 24 hours following its application on intact cutis.[3] The authors demonstrated that CHL poorly permeated through excised full-thickness human skin, with high levels on the surface (100 micron) sections whereas the concentration of CHL within deeper layers (below 300 microns) fell to less than 0.002 μg/mg tissue.[3] Of course, absorption changes drastically when CHL is applied on damaged skin because cutaneous lesions greatly increase CHL penetration, enough to allow an allergic reaction in sensitized patients.

The first well-documented case of anaphylaxis following the topical use of CHL on disrupted skin dates back to1986.[4] Since then, many authors have reported that application of CHL on injured skin for burns,[5] minor abrasions,[6] or open minor wounds[7] increases the risk of eliciting a serious allergic reaction. Even subclinical thinness of the *stratum corneum* by repeated friction may be sufficient to facilitate CHL absorption on an apparently intact skin as occurred to a 33-year-old man after a horse ride.[8] In addition, CHL used in a disinfectant bath may be absorbed through the transcutaneous route of patients with skin diseases, leading to life-threatening consequences.[9] It is generally recognized that skin antisepsis does not sterilize the skin,[2] and CHL remains one of the most efficient topical disinfectants.[3] However, the report of Postlova et al is an important reminder that CHL is a hidden allergen in the perioperative setting that should always be included in subsequent allergy testing. CHL can induce an occult sensitization or it can cause minor symptoms, often underappreciated by patients and doctors,[4-6] before the sudden onset of a severe immediate hypersensitivity reaction. As a consequence, a preliminary screening allergic workup with CHL gluconate skin tests and specific IgE tests should be performed before any surgical session in patients at risk for anaphylaxis induced by CHL. This includes patients with a CHL-induced contact dermatitis, and patients with a history of any allergic reaction, however minor, in connection with exposure to CHL in any health care setting, including dental settings.[2]

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