CASE REPORT

Nagoya J. Med. Sci. **88**. 149–156, 2026
doi:10.18999/nagjms.88.1.149

Recurrent allergic reactions to unrecognized chlorhexidine exposure leading to pulseless electrical activity: a case report

Akari Kawaguchi[1], Yasuhiro Amano[2], Takahiro Ando[2], Tasuku Fujii[2] and Takahiro Tamura[2]

[1]*Department of Anesthesiology, Aichi Children's Health and Medical Center, Obu, Japan*
[2]*Department of Anesthesiology, Nagoya University Graduate of School of Medicine, Nagoya, Japan*

ABSTRACT

Chlorhexidine applied to the skin during catheter insertion can cause allergic reactions; however, its potential to cause perioperative anaphylaxis is often overlooked. Herein, we report a case of recurrent allergic reactions to unrecognized chlorhexidine exposure, leading to pulseless electrical activity. A 66-year-old man exhibited an allergic reaction during anesthesia induction for Y-graft replacement for an abdominal aortic aneurysm, and the planned surgery was aborted. Skin tests for anesthetics were negative. Two months later, he experienced itching after epidural catheter insertion but did not report it. During a second anesthesia induction, the patient experienced another allergic reaction of unknown etiology. Although hemodynamics stabilized after vasopressor administration, insertion of a central venous catheter 1 hour later to prevent further hypotension triggered pulseless electrical activity. Chlorhexidine was used as a skin disinfectant during catheter insertion before all four reactions and was confirmed to have caused the anaphylaxes using diagnostic tests. Chlorhexidine should be considered a potential cause of perioperative anaphylaxis.

Keywords: anaphylaxis, chlorhexidine, alcohol allergy, catheter insertion, pulseless electrical activity

BACKGROUND

Determining the cause of perioperative anaphylaxis is challenging. Although diagnostic tests, including skin tests, are useful for identifying causative agents, suspected allergens must first be considered for such tests. Unlike intravenous drugs, chlorhexidine can enter the bloodstream through several routes, including catheter insertion after skin preparation. In 2017, the US Food and Drug Administration (FDA) issued a Drug Safety Communication warning of rare but serious allergic reactions to chlorhexidine gluconate when used as a skin antiseptic.[1] However, its potential as an anaphylactic agent is often overlooked. Herein, we describe a case of recurrent allergic reactions to chlorhexidine—which was initially overlooked as a causative allergen—resulting in pulseless electrical activity.

Received: May 22, 2025; Accepted: July 3, 2025
Corresponding Author: Yasuhiro Amano, MD, PhD
Department of Anesthesiology, Nagoya University Graduate School of Medicine,
65 Tsurumai-cho, Showa-ku, Nagoya 466-8550, Japan
Tel: +81-52-744-2340, E-mail: amano.yasuhiro.f1@f.mail.nagoya-u.ac.jp

CASE PRESENTATION

A 66-year-old man (height 176 cm; weight 86 kg) underwent a Y-graft replacement for an abdominal aortic aneurysm. His medical history included hypertension, dyslipidemia, and acute myocardial infarction. Seven years prior, he had undergone stent placement in segments 6 (#6) and 7 (#7). Preoperative cardiac angiography showed 75% stenosis in #6 and #7 and 90% stenosis in segments 9 and 10; the fractional flow reserve of the left anterior descending artery was 0.85. Accordingly, surgery was planned. He had previously developed a rash following the use of alcohol wipes and was considered to have an alcohol allergy. Therefore, chlorhexidine wipes were used instead. For arterial catheter insertion, topical lidocaine was applied before general anesthesia induction with propofol, fentanyl, remifentanil, and rocuronium, following which endotracheal intubation was conducted. Following the procedure, blood pressure and heart rate transiently increased, and then the blood pressure dropped to 49 mmHg. Hence, ephedrine (20 mg) and phenylephrine (0.1 mg) were administered (Figure 1), which stabilized the patient's blood pressure, and 1 g of cefazolin administration was initiated. Subsequently, localized rash and urticaria were noted, and drug allergy was suspected. Thus, surgery was aborted, cefazolin was discontinued, and the patient was extubated in the operating room. Skin tests were performed after 4 weeks. Propofol, fentanyl, remifentanil, and rocuronium yielded negative results in the skin prick test (SPT) and intradermal test (IDT). The serum tryptase levels (positive threshold,

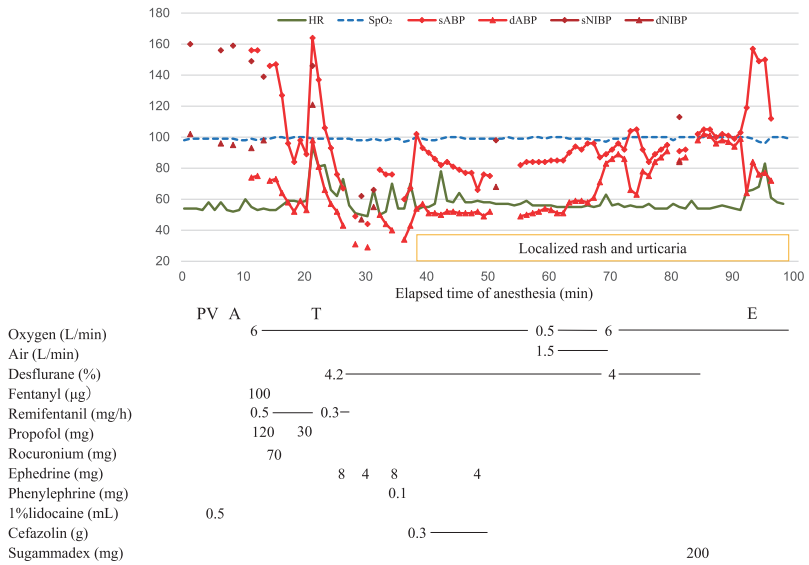

Fig. 1 Anesthetic chart for the first general anesthesia

HR: heart rate
SpO_2: peripheral oxygen saturation
sABP: systolic aortic blood pressure
dABP: diastolic aortic blood pressure
sNIBP: systolic non-invasive blood pressure
dNIBP: diastolic non-invasive blood pressure
PV: peripheral venous catheter insertion
A: arterial catheter insertion
T: intubation
E: extubation

 doi:10.18999/nagjms.88.1.149

3.2 μg/L) were 1.3 and <1 μg/L at 1 and 24 hours after symptom onset, respectively.[2] Due to the possibility of false-negative results in the skin tests, we decided to avoid the four drugs tested. However, fentanyl and remifentanil have no alternatives, and anaphylaxis induced by these agents is extremely rare.[3] Moreover, propofol could be replaced with thiamylal, and abdominal muscle relaxation was considered achievable with epidural anesthesia. After an initial diagnosis of an unknown drug allergy, the procedure was planned to be performed under combined general and epidural anesthesia 2 months after onset, avoiding the use of rocuronium and propofol.

An epidural catheter was inserted between the 11th and 12th thoracic vertebrae before the day of the surgery. For the test dose, 5 mL of 1% lidocaine was administered epidurally, and loss of cold sensation was confirmed. Although the patient noticed itching around the epidural catheter insertion site and swelling in his arm after the procedure, he did not report it to the healthcare provider. Arterial catheter insertion was performed with topical lidocaine applied before general anesthesia induction with thiamylal, fentanyl, and remifentanil. Endotracheal intubation was uneventful and performed after the administration of a 4% lidocaine spray. However, following the procedure, his blood pressure dropped to 45 mmHg, and ephedrine (24 mg) was administered to achieve hemodynamic stability (Figure 2). Subsequently, localized rash and urticaria were noted, and a drug allergy was suspected. Therefore, we discontinued remifentanil administration. Although the patient's hemodynamics were stable for 1 hour, we decided to insert a central venous catheter to prevent further hypotension. For this, the patient's neck was disinfected with 1% chlorhexidine gluconate, and a triple-lumen catheter was inserted into the right internal jugular vein. Three minutes later, the patient's blood pressure suddenly decreased to 44 mmHg. Despite repeated administration of ephedrine, phenylephrine, and noradrenaline, the patient developed pulseless electrical activity. Cardiopulmonary resuscitation was immediately initiated, and 0.6 mg of adrenaline was administered. Subsequently, generalized rash and urticaria were noted, and chlorhexidine anaphylaxis was suspected. The surgery was aborted again, and the patient was extubated on the day of the reaction with no sequelae. Four days later, an SPT was performed, which revealed that the positive control and 5 mg/mL chlorhexidine showed a positive response for wheal (6 and 9 mm, respectively).[4] Additionally, we performed a basophil activation test for chlorhexidine using previously described methods.[5] The basophil activation test was performed using a flow cytometer (Navios EX; Beckman Coulter, Brea, CA, USA) and an allergenicity kit (Beckman Coulter, Brea, CA, USA). Chlorhexidine showed a positive response (67.4% basophil activation at 5 μg/mL dilution). Blood tests showed positivity for chlorhexidine-specific immunoglobulin E (7.06 kUA/L). Additionally, plasma histamine and tryptase levels (positive thresholds 1.5 and 3.2 μg/L, respectively) were significantly elevated to 3.48 and 4.2 μg/L, respectively, 30 minutes after symptom onset compared with the levels of 0.65 and <1 μg/L, respectively, measured 24 hours post-onset.[2,6] Based on these findings, chlorhexidine anaphylaxis was confirmed. The Table shows the clinical characteristics of the four allergic reactions. In the first and third allergic reactions, chlorhexidine may have entered the bloodstream via peripheral catheter insertion or intravenous tube injection ports. The patient presented with grade 2 reactions, including hypotension, localized rash, and urticaria.[7,8] At both instances, the Hypersensitivity Clinical Scoring Scheme (HCSS) scores were 13 points.[9] The second allergic reaction was considered to have been caused by chlorhexidine exposure during skin preparation before epidural catheter insertion. The patient presented with a grade 1 reaction, namely localized urticaria. In the fourth allergic reaction, chlorhexidine may have reached the bloodstream due to skin preparation before central venous catheter insertion. The patient presented with generalized rash and urticaria and developed severe grade 4 anaphylactic shock leading to pulseless electrical activity, with a HCSS score of 22 points. Herein, the symptoms, severity, and HCSS scores of the allergic reactions varied across the four events, which might have been

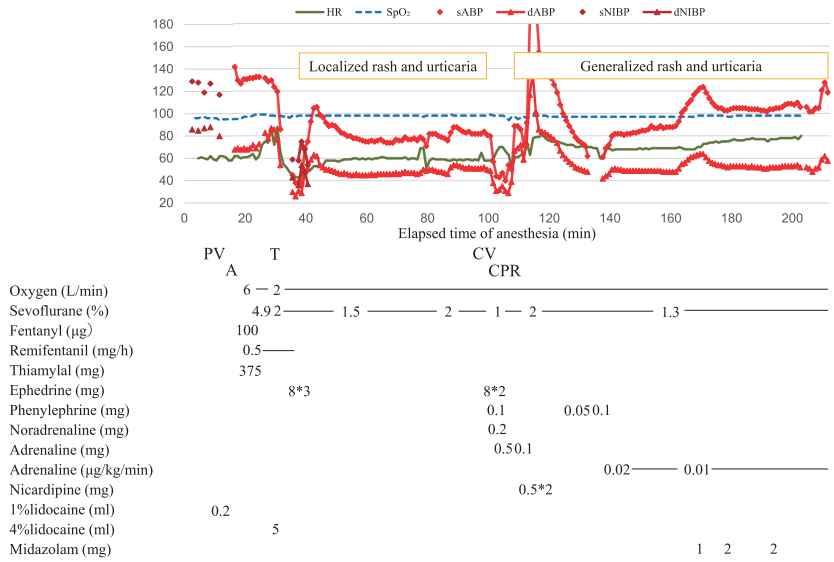

Fig. 2 Anesthetic chart for the second general anesthesia

HR: heart rate
SpO_2: peripheral oxygen saturation
sABP: systolic aortic blood pressure
dABP: diastolic aortic blood pressure
sNIBP: systolic non-invasive blood pressure
dNIBP: diastolic non-invasive blood pressure
PV: peripheral venous catheter insertion
A: arterial catheter insertion
T: intubation
CV: central venous catheter insertion
CPR: cardiopulmonary resuscitation

Table Clinical characteristics of the observed chlorhexidine allergic reactions

Procedure	Clinical features	Possible route of exposure to chlorhexidine	Grade	Clinical score
Induction of the first general anesthesia	Hypotension, localized rash, and urticaria	Skin preparation before PV and arterial catheter insertion Injection port of IV tubing	2	13
Epidural catheter insertion before the second general anesthesia	Localized urticaria	Skin preparation before epidural catheter insertion	1	NA
Induction of the second general anesthesia	Hypotension, localized rash, and urticaria	Skin preparation before PV and arterial catheter insertion Injection port of IV tubing	2	13
CVC insertion during the second general anesthesia	PEA, generalized rash, and urticaria	Skin preparation before CVC insertion	4	22

CVC: central venous catheter
IV: intravenous
NA: not available
PEA: pulseless electrical activity
PV: peripheral venous catheter

due to the amount of chlorhexidine that entered the bloodstream (Table). After 6 days, all skin disinfections and intravenous tubing injection ports were performed with povidone-iodine, and the surgery was successfully performed.

DISCUSSION

Herein, we report a case of recurrent allergic reaction to chlorhexidine—which was initially overlooked as a causative allergen—eventually leading to pulseless electrical activity. Chlorhexidine-induced allergic reactions commonly occur due to chlorhexidine exposure to mucosal membranes and the use of chlorhexidine-containing catheters.[10] The use of chlorhexidine-impregnated catheters and their application to mucous membranes are prohibited in Japan[11]; thus, we mistakenly assumed that chlorhexidine could not have caused the anaphylaxis as it is usually applied only on the skin. We finally suspected chlorhexidine as the cause because during the hour leading up to the pulseless electrical activity, there were no other potential antigens identified besides chlorhexidine. Had the second allergic reaction following the epidural anesthesia been reported by the patient to the healthcare provider, it might have been possible to identify chlorhexidine as the causative agent, given that allergic reactions to local anesthetics are extremely rare[4] and chlorhexidine would have been considered as a possible causative agent. Chlorhexidine has multiple routes of exposure, and the severity of allergic reactions can vary significantly.[12,13] Chlorhexidine is considered to undergo minimal systemic absorption in the epidural space; however, caution is required as a few cases of anaphylaxis due to chlorhexidine exposure during skin preparation before epidural anesthesia have been reported.[14,15] Following our experience with this patient who developed pulseless electrical activity, we considered chlorhexidine as a possible causative agent in cases of all suspected perioperative allergy.

In current guidelines, the management of perioperative anaphylaxis includes the discontinuation of possible causative drugs.[16] Accordingly, in case of a chlorhexidine allergy, discontinuation of chlorhexidine is necessary; however, attention must also be paid to residual chlorhexidine on the skin. While chlorhexidine applied to the skin does not typically penetrate in the short term, it can permeate the skin and enter the bloodstream after prolonged exposure, such as over 24 hours.[17] Therefore, it is important to thoroughly wipe off any chlorhexidine applied to the skin after diagnosis of possible chlorhexidine allergy. In addition, chlorhexidine-free alternatives should be used for routine dressings at central venous catheter insertion sites. Furthermore, it is essential to carefully communicate with medical staff—not only in the operating room but also in the intensive care unit and general wards—to ensure the complete avoidance of chlorhexidine-containing products.

In Japan, alcohol or chlorhexidine wipes are widely used for skin preparation before peripheral line cannulation or the disinfection of injection ports for intravenous tubing. In routine practice, patients who develop redness, rash, or urticaria after being rubbed with alcohol wipes are considered to have an alcohol allergy, and for them, chlorhexidine wipes are used instead. In such cases, skin reactions include subjective irritation, contact urticaria, or allergic contact dermatitis.[18] Alcohol can be metabolized into acetaldehyde in the skin[19]; however, if aldehyde dehydrogenase (ALDH2), the enzyme that metabolizes acetaldehyde to acetate, has low activity, acetaldehyde can accumulate and potentially cause contact urticaria.[20] In Japan, 43.6% of people are estimated to have inactive genotypes of ALDH2.[21] Patients with low ALDH2 activity may not necessarily develop alcohol allergies; additionally, the epidemiology of these allergies remains unclear. However, healthcare providers are likely to encounter some patients with suspected alcohol allergies. Even when performing routine general anesthesia without central venous catheter

insertion, anesthesiologists should be aware that patients with alcohol allergies are at a greater risk of chlorhexidine exposure, which may cause anaphylaxis.

In cases of perioperative anaphylaxis, all drugs administered before its onset should be considered for diagnostic tests, including chlorhexidine.[16] Usually, drugs administered before the onset of anaphylaxis are reviewed by consulting the anesthesia record. However, agents such as povidone-iodine and latex, in addition to chlorhexidine, are often not documented in the anesthesia record. Our experience demonstrates that these potential agents should be included in the records as suspected agents. Both SPT and IDT have high sensitivity and specificity for diagnosing chlorhexidine allergy and are supplementary to each other.[12,22] Since our patient yielded clearly positive SPT results, we did not perform IDT, considering the high risk of recurrence of chlorhexidine anaphylaxis.[4] When performing IDT, chlorhexidine should be diluted as recommended because its high concentrations can cause skin irritation.[23] Recently, the use of a dilute solvent has been discussed.[24] Additional tests, such as the specific immunoglobulin E and basophil activation tests, can be used as well. Herein, the patient yielded three positive results in the diagnostic tests and underwent a third general anesthesia with the same anesthetic as the first general anesthesia, confirming the diagnosis of chlorhexidine anaphylaxis.

This report did not assess the safe alternatives of antibacterial agents other than povidone-iodine. Recently, olanexidine, a biguanide antibacterial agent, was made available in Japan, which shares structural similarity with chlorhexidine. Although there are no reports of olanexidine anaphylaxis, a theoretical risk of olanexidine anaphylaxis remains. We would like to perform further tests if the patient wishes to test for cross-reactivity with other biguanides.

In conclusion, chlorhexidine should be considered a potential cause of perioperative anaphylaxis, especially in patients with alcohol allergies.

DECLARATIONS

Ethical approval and consent to participate

This case was included in two prospective observational studies on perioperative anaphylaxis approved by Institutional Review Board of Nagoya University Hospital (approval numbers, 2019–0023, 2020–0020).

Consent for publication

Written informed consent was obtained from the patient for the publication of this case report and accompanying images.

Authors' contributions

AK and YA wrote the original manuscript. AK and TA performed the anesthetic management of the patient. TF and TT helped revise the manuscript. All the authors have read and approved the final version of this manuscript.

Competing interests

The authors declare that they have no competing interests.

Funding

Not applicable.

Availability of data and material

Data relevant to this case report are not publicly available because of concerns regarding patient privacy but are available from the corresponding author upon reasonable request.

Acknowledgment

We thank Natsumi Kameyama for performing basophil activation tests.

REFERENCES

1 U.S. Food and Drug Administration. FDA Drug Safety Communication: FDA warns about rare but serious allergic reactions with the skin antiseptic chlorhexidine gluconate. Published 2017. Accessed May 15, 2025. https://www.fda.gov/drugs/drug-safety-and-availability/fda-drug-safety-communication-fda-warns-about-rare-serious-allergic-reactions-skin-antiseptic

2 Valent P, Akin C, Arock M, et al. Definitions, criteria and global classification of mast cell disorders with special reference to mast cell activation syndromes: a consensus proposal. *Int Arch Allergy Immunol.* 2012;157(3):215–225. doi:10.1159/000328760

3 Mertes PM, Ebo DG, Garcez T, et al. Comparative epidemiology of suspected perioperative hypersensitivity reactions. *Br J Anaesth.* 2019;123(1):e16–e28. doi:10.1016/j.bja.2019.01.027

4 Garvey LH, Ebo DG, Mertes PM, et al. An EAACI position paper on the investigation of perioperative immediate hypersensitivity reactions. *Allergy.* 2019;74(10):1872–1884. doi:10.1111/all.13820

5 Horiuchi T, Yokohama A, Orihara M, et al. Usefulness of Basophil Activation Tests for Diagnosis of Sugammadex-Induced Anaphylaxis. *Anesth Analg.* 2018;126(5):1509–1516. doi:10.1213/ANE.0000000000002879

6 Horiuchi T, Takazawa T, Haraguchi T, Orihara M, Nagumo K, Saito S. Investigating the optimal diagnostic value of histamine for diagnosing perioperative hypersensitivity: a prospective, observational study. *J Anesth.* 2023;37(4):645–649. doi:10.1007/s00540-023-03199-z

7 Ring J, Messmer K. Incidence and severity of anaphylactoid reactions to colloid volume substitutes. *Lancet.* 1977;1(8009):466–469. doi:10.1016/s0140-6736(77)91953-5

8 Mertes PM, Malinovsky JM, Jouffroy L, et al. Reducing the risk of anaphylaxis during anesthesia: 2011 updated guidelines for clinical practice. *J Investig Allergol Clin Immunol.* 2011;21(6):442–453.

9 Hopkins PM, Cooke PJ, Clarke RC, et al. Consensus clinical scoring for suspected perioperative immediate hypersensitivity reactions. *Br J Anaesth.* 2019;123(1):e29–e37. doi:10.1016/j.bja.2019.02.029

10 Sharp G, Green S, Rose M. Chlorhexidine-induced anaphylaxis in surgical patients: a review of the literature. *ANZ J Surg.* 2016;86(4):237–243. doi:10.1111/ans.13269

11 Okano M, Nomura M, Hata S, et al. Anaphylactic symptoms due to chlorhexidine gluconate. *Arch Dermatol.* 1989;125(1):50–52. doi:10.1001/archderm.1989.01670130052005

12 Rose MA, Garcez T, Savic S, Garvey LH. Chlorhexidine allergy in the perioperative setting: a narrative review. *Br J Anaesth.* 2019;123(1):e95–e103. doi:10.1016/j.bja.2019.01.033

13 Amano Y, Matsuura A, Tamura T, et al. Life-threatening chlorhexidine anaphylaxis caused by skin preparation before chlorhexidine-free central venous catheter insertion: a case report and literature review. *J Anesth.* 2023;37(3):474–481. doi:10.1007/s00540-023-03189-1

14 Weng M, Zhu M, Chen W, Miao C. Life-threatening anaphylactic shock due to chlorhexidine on the central venous catheter: a case series. *Int J Clin Exp Med.* 2014;7(12):5930–5936.

15 Harukuni I, Ishizawa Y, Nishikawa T, Takeshima R, Dohi S, Naito H. Anaphylactic shock with ventricular fibrillation induced by chlorhexidine. Article in Japanese. *Jpn J Anesthesiol.* 1992;41(3):455–459.

16 Takazawa T, Yamaura K, Hara T, et al. Practical guidelines for the response to perioperative anaphylaxis. *J Anesth.* 2021;35(6):778–793. doi:10.1007/s00540-021-03005-8

17 Karpanen TJ, Worthington T, Conway BR, Hilton AC, Elliott TS, Lambert PA. Penetration of chlorhexidine into human skin. *Antimicrob Agents Chemother.* 2008;52(10):3633–3636. doi:10.1128/AAC.00637-08

18 Ophaswongse S, Maibach HI. Alcohol dermatitis: allergic contact dermatitis and contact urticaria syndrome. A review. *Contact Dermatitis.* 1994;30(1):1–6. doi:10.1111/j.1600-0536.1994.tb00719.x

19 Cheung C, Smith CK, Hoog JO, Hotchkiss SA. Expression and localization of human alcohol and aldehyde dehydrogenase enzymes in skin. *Biochem Biophys Res Commun.* 1999;261(1):100–107. doi:10.1006/bbrc.1999.0943

20 Chularojanamontri L, Tuchinda P, Pongparit K, Pinkaew S, Nuchkull P, Kulthanan K. Contact urticaria caused by alcohol: Clinical characteristics and cross-reactions. *Ann Allergy Asthma Immunol.* 2016;117(6):721–723.

e1. doi:10.1016/j.anai.2016.09.434
21 Harada S. Genetic polymorphism of alcohol metabolizing enzymes and its implication to human ecology. *J Anthropol Soc Nippon.* 1991;99(2):123–139. doi:10.1537/ase1911.99.123
22 Opstrup MS, Malling HJ, Krøigaard M, et al. Standardized testing with chlorhexidine in perioperative allergy--a large single-centre evaluation. *Allergy.* 2014;69(10):1390–1396. doi:10.1111/all.12466
23 Garvey LH, Krøigaard M, Poulsen LK, et al. IgE-mediated allergy to chlorhexidine. *J Allergy Clin Immunol.* 2007;120(2):409–415. doi:10.1016/j.jaci.2007.04.029
24 Shah D, Cojuc-Konigsberg G, Brown SD, et al. Stability of diluted chlorhexidine for skin testing in drug allergy evaluations. *J Allergy Clin Immunol Glob.* 2024;4(1):100372. doi:10.1016/j.jacig.2024.100372