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ORIGINAL RESEARCH

# The Gap Between Suspected Local Anesthetic Allergy and Formal Diagnostic Evaluation

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**Background:** Local anesthetics (LAs) are widely used, but true immune-mediated allergies are rare. Most adverse events are toxic or autonomic, yet patients are frequently mislabeled as allergic. This study aims to determine the prevalence of allergy evaluation and testing following suspected reactions to LAs.

**Methods:** A cross-sectional retrospective study was conducted with a total of 126 patients. The study collected medical records from tertiary care hospitals in Saudi Arabia from 2016 to 2022, analyzing patients with reported allergic reactions to LA. The analysis included demographics, occurrences, medical procedure type, and allergy testing history.

**Results:** Lidocaine was the most common agent, involved in over 90% of cases. Reactions primarily followed injections, with symptoms ranging from rash and itching to anaphylactic shock. Despite these events, only 10 patients (7.94%) were referred for further investigation. Allergy testing was performed in only three patients (2.38%). Among those tested, one was negative, while two tested positive (one for lidocaine and one for a lidocaine-bupivacaine combination).

**Conclusion:** The study highlights a low prevalence of follow-up allergy testing despite reported adverse reactions. Systematic testing is essential to confirm or rule out true LA allergies, ensuring patient safety and identifying viable anesthetic alternatives for future procedures.

**Keywords:** local anesthetics, adverse drug reaction, skin tests, methylprednisolone, anaphylaxis

## Introduction

Local anesthetics (LAs) have been routinely used since the late 19th century throughout different healthcare settings, especially in dentistry, surgery, dermatology, urology, orthopedics, and obstetric procedures to induce transient local or regional anesthesia.[1–3] LAs are made up of three structural components: an aromatic group, an intermediate chain, and an amine group. They are categorized based on their intermediate chain into esters (such as procaine, benzocaine, tetracaine) and amides (such as lidocaine, mepivacaine, articaine, and bupivacaine). LAs differ in their strength and duration of action. These agents may be administered via various routes either topically, or through subcutaneous, intravenous, perineural injections or neuraxial administration.[2–4] LAs are generally considered safe and adverse reactions are extremely rare. For example, when 70 million cartridges of lidocaine and prilocaine were administered during dental procedures in the United Kingdom, only 249 cases of adverse reaction were reported.[5] Most adverse reactions to LAs are not immune mediated and patients may be mislabeled as allergic although they experienced toxic or autonomic reactions. Toxic reactions may occur when a high dose of LA is administered and absorbed systemically or in cases of accidental vascular injection. Without recognition and proper treatment, toxic reactions can lead to cardiovascular collapse, coma, and death. Autonomic reactions generally involve vasovagal, or anxiety mediated reactions such as sweating, nausea, dizziness, and light tachycardia.[1,5] Although the incidence of reported allergic reactions to LAs is low, it can lead to moderate to severe and life-threatening events requiring immediate intervention. Both IgE-mediated (type I) and delayed (type IV) hypersensitivity reactions to LAs have been reported. The clinical identification and management of such

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reactions have been further refined by the World Allergy Organization (WAO) 2020 anaphylaxis guidance, which provides a standardized systemic allergic reaction grading system. This framework classifies reactions from Grade 1, which is the involvement of only one organ system (typically cutaneous) to Grade 5, which denotes fatal outcomes such as respiratory arrest and/or circulatory collapse. Notably, the WAO criteria specify that that only certain Grade 3 presentations and all Grade 4–5 events strictly meet the criteria for anaphylaxis. Understanding these distinctions is vital, as Type I IgE-mediated hypersensitivity typically requires prior sensitization; consequently, subsequent exposures to the same local anesthetic may trigger more rapid or severe mast cell degranulation and mediator release.[6]

Severe allergic reactions have been reported with both groups of LAs, however, ester LAs are considered more likely to produce such reactions. When ester LAs are metabolized in the body, para-aminobenzoic acid is produced, which is extremely antigenic.[7,8] True allergy to amides LA has been also reported with cross-reactivity within the group itself.[3,9–11] It is important to emphasize that most LA solutions contain 0.1% methylparaben as a preservative. Methylparaben is metabolized following administration to the very antigenic substance, para-aminobenzoic acid (PABA).[4,11] In addition, preservatives in LA solutions may cause both IgE-mediated (type I) and delayed (type IV) hypersensitivity reactions.[12,13] As a result, determining the source of allergic reactions through skin testing is critical to avoid serious complications, ruling out or confirming true LA allergy, and determining a safe alternative. To our knowledge, the prevalence of definitive allergy evaluation following suspected adverse allergic reactions to local anesthetic administration has not been previously quantified within our study region. Therefore, this study aims to determine the rate of subsequent allergy testing and comprehensive evaluation in these specific patient cases.

## Methods

Following the approval of the protocol of our study by the institutional review board and ethics committee (King Abdullah International Medical Research center, protocol# IRB/2131/23), medical records for patients with reported hypersensitivity or adverse allergic reactions to LA were collected from National Guard Health Affairs (NGHA) hospitals in the Western, Central and Eastern regions of Saudi Arabia. Medical chart review analysis was performed on all collected medical files of patients with suspected allergic reactions to LA over a 6-year period from 2016 to 2022. Information regarding demographics of the patients, the occurrence of an adverse allergic reaction following LA administration (including lidocaine, mepivacaine, articaine, bupivacaine, procaine, benzocaine, tetracaine, ropivacaine and L-bupivacaine), a description of the reaction including method of administration, its onset, type of undertaken medical procedure, and whether history of LA adverse reaction and skin testing was reported. Additionally, data on the patients' known medical history, specifically known food allergy and known drug allergies, was collected.

All collected quantitative data were analyzed using the SAS statistical software package (version 9.4). Descriptive statistics were used for summarization such as average and standard deviation, if following the normal distribution, otherwise median and (IQR) were used. Qualitative data, representing categorical variables, were concisely summarized using frequencies and corresponding percentages.

## Results

A cross-sectional retrospective study was conducted on a total of 126 patients with suspected hypersensitivity to local anesthetics (LAs). According to (Table 1), the age range of patients was between 4 to 98 years, with a median age of 40 years. The gender distribution demonstrated a female predominance, with 72 patients (57.14%) compared to 54 male patients (42.86%). Most patients in the study were of Saudi nationality (84.92%), consistent with the expected demographic catchment of the hospital setting.

The specific local anesthetic (LA) and LA-containing formulations suspected of triggering the adverse drug reactions are detailed in (Table 2). Lidocaine was the major implicated agent, collectively accounting for over 82% of all administered anesthetics. Plain lidocaine was the most frequently reported single agent, implicated in 78 cases (61.90%). Combinations involving lidocaine also played a significant role: the formulation of lidocaine with prilocaine was the second most frequent reported agent, accounting for 27 administrations (21.42%). Less common lidocaine-based triggers included lidocaine with epinephrine (4.76%), and rare single instances (0.79% each) involving lidocaine with hydrocortisone, lidocaine with methylprednisolone acetate, and lidocaine with morphine. The documented clinical setting

**Table 1** Demographics of the Population Included in the Analysis

| **Age** | **Median (IQR)** | **Min- Max** |
|---|---|---|
| | 40 (38) | 4-98 |
| **Gender** | **Frequency (%)** | |
| Male | 54 (42.86%) | |
| Female | 72 (57.14%) | |
| **Nationality** | **Frequency (%)** | |
| Saudi | 107 (84.92%) | |
| Non-Saudi | 19 (15.08%) | |

**Table 2** Used Local Anesthetic Prior to Adverse Allergic Reaction

| **Used Local Anesthetic** | **Frequency (%)** |
|---|---|
| Benzocaine | 2 (1.59%) |
| Bupivacaine MPF with epinephrine | 2 (1.59%) |
| Bupivacaine | 3 (2.38%) |
| Tetracaine | 1 (0.79%) |
| Lidocaine | 78 (61.9%) |
| Lidocaine with epinephrine | 6 (4.76%) |
| Lidocaine with hydrocortisone | 1 (0.79%) |
| Lidocaine with methylprednisoline acetate | 1 (0.79%) |
| Lidocaine with morphine | 1 (0.79%) |
| Lidocaine with prilocaine | 27 (21.42%) |
| Marcaine | 1 (0.79%) |
| Prilocaine | 1 (0.79%) |
| Lidocaine and sodium with ceftriaxone | 1 (0.79%) |
| Lidocaine with HCl | 1 (0.79%) |

and route through which the LA was administered prior to the reported adverse drug reaction (ADR) was analyzed as detailed in (Table 3). Data regarding the clinical setting in which the suspected drug hypersensitivity reaction (DHR) occurred was only available and documented in the medical records for a subset of the total patient population. Out of the 126 patients, information detailing the preceding procedure was explicitly captured for 22 reported events. The analysis of this sub-population indicated that dental procedures represented the most frequent trigger setting, accounting for 12 of the reported instances (57.14%). Surgical interventions were the second most common context, documenting 6 cases (28.58%). Less frequent procedural associations included intra-articular procedures (2 cases, 9.52%), and single instances each for biopsy and spinal anesthesia (1 case each, 4.76%). Injection was the overwhelmingly predominant method of LA application, accounting for 87.84% of all documented cases. The spectrum and frequency of clinical characteristics reported during the suspected adverse allergic reactions are summarized in (Table 4). Cutaneous findings were the most

**Table 3** Method of Local Anesthetics Administration and Types of Procedure

| Type of Procedure | Frequency (%) |
|---|---|
| Dental | 12 (57.14%) |
| Surgery | 6 (28.58%) |
| Biopsy | 1 (4.76%) |
| Spinal anesthesia | 1 (4.76%) |
| **Application Type** | **Frequency (%)** |
| Medicated plaster | 2 (2.70%) |
| Injection | 65 (87.84%) |
| Jell | 5 (6.76%) |
| Spray | 2 (2.70%) |

**Table 4** Reported Clinical Characteristics During the Adverse Allergic Reaction

| Clinical Characteristics | Frequency (%) |
|---|---|
| Headache | 2 (1.13%) |
| Fever | 1 (0.56%) |
| Fear, sweating, anxiety, nerviness | 2 (1.13%) |
| Anaphylactic shock | 11 (6.21%) |
| Nausea, vomitus, abnormal bowel movement, Abdominal pain, abdominal bleeding | 5 (2.82%) |
| Urticarial | 13 (7.34%) |
| Seizure | 2 (1.13%) |
| Angioedema, general Edema, swelling | 15 (8.47%) |
| Palpitations, arrhythmia, tachycardia, chest discomfort | 10 (5.65%) |
| Rash and redness | 66 (37.29%) |
| Dyspnea, bronchospasm, difficulty breathing, shortness of breath | 10 (5.65%) |
| Itch | 18 (10.17%) |
| Hypertension, hypotension, vasovagal attack | 7 (3.95%) |
| Generalized weakness, dizziness, fainting, syncope | 15 (8.47%) |

frequently documented category. Rash and redness emerged as the single most predominant finding, accounting for 66 instances (37.29% of all reported symptoms). Other significant skin-related symptoms included itch (10.17%, n=18) and urticarial lesions (7.34%, n=13). More severe manifestations, notably anaphylactic shock, were reported in 11 instances (6.21%). Signs of respiratory compromise (dyspnea, bronchospasm, difficulty breathing, shortness of breath) were documented in 10 cases (5.65%), mirroring the frequency of cardiovascular symptoms (palpitations, arrhythmia, tachycardia, chest discomfort, 5.65%, n=10).

The rate of patient referral to the Allergy/Immunology department following the reported adverse reaction incidence was extremely low. Out of the total cohort, only 10 patients (7.94%) were documented as being subsequently referred for further investigation. Allergy testing was performed later in three patients (2.38%). Of those tested, one patient (33.33%) had a negative reaction, while the other two patients (33.33% each) tested positive for lidocaine and lidocaine with bupivacaine, respectively (Table 5).

Three female patients (P1, P2, P3; mean age 27 ± 12.6 years) presenting with suspected immediate-type hypersensitivity reactions following exposure to LA agents were retrospectively evaluated. Patients 1 (13 years) and 2 (37 years) elicited positive reactions upon cutaneous testing, confirming LA hypersensitivity. Patient 1, exposed to lidocaine with procaine, developed generalized weakness and dizziness within 20 minutes of administration during an unreported procedure. Patient 2, with pre-existing Multiple Sclerosis (MS) and Sjögren's Syndrome, experienced hypotension and a vasovagal-like episode within 20 minutes of lidocaine administration during a dental procedure. In both cases, the clinical presentation and timing were consistent with an immediate reaction, which was subsequently substantiated by positive skin test results to the respective implicated agents. Patient 3 (31 years) demonstrated a severe, rapid-onset systemic reaction following an intra-articular injection of lidocaine combined with methylprednisolone acetate. The clinical course was characterized by profound cardiovascular and cutaneous involvement, commencing in less than five minutes post-injection, indicative of anaphylactic shock. A detailed allergy history revealed that the patient reported a delayed hypersensitivity event following hyaluronic acid (HA)-based cosmetic lip filler administration five years prior to the anaphylactic episode. Comprehensive allergy evaluation involving skin prick tests and intradermal tests with the suspected culprit (Lidocaine) with and without methylparaben as a preservative yielded uniformly negative results. Notably, six months later, the patient exhibited an allergic reaction characterized by generalized rash and itching following the oral consumption of the laxative (polyethylene glycol 3350 with electrolytes) (Table 6).

**Table 5** Referral to Allergy/Immunology Department and Subsequent Allergy Testing Results

| **Referral to Allergy/Immunology Department** | | **Frequency (%)** |
|---|---|---|
| Yes | | 10 (7.94%) |
| No | | 116 (92%) |
| **Results of Allergy Testing (n=3)** | | **Frequency (%)** |
| **1** | Positive allergy to lidocaine and bupavacaine | 1 (33.33%) |
| **2** | Positive to lidocaine | 1 (33.33%) |
| **3** | Negative | 1 (33.33%) |

**Table 6** Clinical Data of Three Patients with Allergy Testing

| Number | Age | Gender | Culprit Drug | Clinical Characteristics | Time | Comorbidity | Procedure | Food or Drug Allergy |
|---|---|---|---|---|---|---|---|---|
| **1** | 13 | F | Lidocaine with Procaine | Generalized weakness, dizziness | Within 20 minutes | None | Not Reported | No |
| **2** | 37 | F | Lidocaine | Hypotension, vasovagal attack | Within 20 minutes | MS and Sjogren | Dental | No |

(*Continued*)


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**Table 6** (Continued).

| Number | Age | Gender | Culprit Drug | Clinical Characteristics | Time | Comorbidity | Procedure | Food or Drug Allergy |
|---|---|---|---|---|---|---|---|---|
| **3** | 31 | F | Lidocaine with methylprednisolone acetate | Cutaneous, lower and upper airway symptoms and cardiovascular collapse/ hypotension | Less than 5 minutes | None | intra-articular injection | Yes (hyaluronic acid based cosmetic filler five years earlier, laxative polyethylene glycol 3350 six months later) |

## Discussion

Allergic responses to LAs are uncommon and when they occur, it can result in mild to severe, potentially fatal outcomes that need prompt medical attention. Although the majority of these reactions are not immune-mediated, few patients are referred to allergy clinics and undergo extensive evaluation to rule out a true immune-mediated reaction.[1,14]

The demographic profile of patients in our study who experienced suspected allergic reactions to LAs reveals notable patterns in age, gender, procedure type, and reaction severity. The median age was 40 years, with a wide interquartile range of 38 years and an age span from 4 to 98 years. This wide distribution underscores that hypersensitivity reactions to LAs can occur across all age groups, although middle-aged adults seem more represented in this cohort. Similar age trends have been observed in previous LA allergy-focused studies, suggesting increased exposure to invasive procedures and accumulated sensitization risk with age.[1,15–17] Gender distribution showed a slightly higher prevalence of reactions among females (57.14%) compared to males (42.86%). This finding is consistent with literature noting that hypersensitivity reactions are reported in females more frequently, possibly due to immunological and hormonal differences.[15,17–19]

Regarding the type of procedure, dental procedures were the most associated with reported allergic reactions (57.14%), followed by surgical procedures (28.58%). Dental treatments often involve repeated exposure to LAs, which may explain the higher frequency of reported reactions. These findings are important and support prior evidence that dental settings are a common source of reported anesthetic hypersensitivity.[1,16,20,21]

Additionally, lidocaine emerged as the most frequently administered local anesthetic in this study. This finding is consistent with current clinical practices, as lidocaine is widely preferred due to its rapid onset, intermediate duration, and relatively low risk of adverse effects.[1,15,20,22] The predominant use of injections as the administration mode for LAs, as observed in this study, is directly attributable to the nature of the procedures for which they were used. These procedures, including dental work, surgery, biopsies, spinal anesthesia, and intra-articular procedures, all necessitate the targeted, deep delivery of an anesthetic agent to achieve a sufficient and localized anesthetic effect.

While generally safe, some patients may experience adverse drug reactions. These reactions are a mix of allergic responses and systemic toxicities, and they can vary significantly in their presentation and severity.[4] Our findings indicate a range of symptoms, with dermatological issues being the most common. Specifically, rash and redness were the most frequent symptoms, affecting over a third of our cohort (37.29%). The predominance of cutaneous reactions in our dataset aligns with a significant body of literature that similarly identifies skin manifestations as the most common ADR to LAs. For instance, several studies reported a high incidence of skin manifestations such as rash, pruritus, urticaria and angioedema as the primary adverse reactions reported.[1,4,16,23] Skin manifestations might be the first signs of sensitization to an allergen or drug, acting as a warning signal that subsequent exposures may trigger significantly more severe, systemic, or even life-threatening reactions.[6] However, one study found that circulatory issues were the most common adverse reaction, with skin manifestations following as the second most prevalent symptoms.[15] These disparities in reported symptom profiles could be attributed to variations in patient demographics, the specific LA agents used, differences in dosage or differences in administration techniques.

According to our findings of 126 patients, only ten patients were referred to Allergy/Immunology clinic. Furthermore, definitive allergy testing was performed on only three of these patients following their reaction. Of those tested, all but one patient showed a positive reaction to both lidocaine and the lidocaine-bupivacaine combination. For the patient with the absence of a diagnostic cutaneous reaction to the LA indicates a probable non-IgE-mediated mechanism or the presence of a sensitivity to a non-LA component within the compounded formulation (eg., Methylprednisolone acetate, preservatives), necessitating an alternative diagnostic and management strategy. The case highlights a significant diagnostic challenge in LA hypersensitivity where a severe, immediate reaction is not mirrored by standard skin testing.

These findings, particularly the low incidence of confirmed allergy after testing, align with similar investigations in the field. For instance, one large-scale study involving 331 patients who underwent comprehensive skin testing identified a true allergic reaction in a very small fraction of only three patients (0.91%).[1] Another study focusing on patients evaluated in an anesthesia allergy clinic reported a similar trend; out of 109 patients who underwent testing for LAs, only six presented with a true type of allergy to the agents.[15] Collectively, the literature suggests that while reported LA reactions may be common, the rate of confirmed, true allergic reaction remains consistently low.

Interestingly, the patient with negative skin test results to lidocaine with and without methylparaben preservative, experienced an allergic reaction six months later following oral consumption of a laxative (polyethylene glycol 3350 with electrolytes). The occurrence of anaphylaxis subsequent to intra-articular steroid injection is extremely rare. When adverse reactions resembling allergies occur after administration of corticosteroid-lidocaine mixtures, the inherent anti-inflammatory nature of the steroid can lead physicians to presumptively identify lidocaine as the causative agent, often in the absence of corroborating skin test evidence. Existing case reports implicate polyethylene glycol 3350 (PEG 3350) used to suspend corticosteroid solutions, as a potential trigger for these reactions.[24,25] The patient described in our study presented with allergic reactions following the administration of methylprednisolone acetate injection and the laxative (polyethylene glycol 3350 with electrolytes), both formulations containing PEG 3350, strongly implicating PEG 3350 as the likely allergen. Recent studies have highlighted the potential for high molecular weight PEGs (also known as macrogols) to induce adverse immune responses.[25–27] Specifically, these PEGs have been implicated in cases of anaphylaxis associated with colonoscopy preparations.[28]

Reports from numerous patients indicate that prior skin contact, either through repeated exposure or localized reactions to topical items containing PEG, often precedes the development of systemic reactions to medications formulated with high molecular weight PEG, pointing towards a skin-based mechanism for initial sensitization.[29] Anaphylaxis upon initial exposure to PEG-containing formulations implies prior PEG sensitization. Notably, the patient in the present study reported a delayed hypersensitivity event following hyaluronic acid (HA)-based cosmetic lip filler administration several years prior to the anaphylactic episode. While HA, a polysaccharide, is generally considered non-immunogenic, many HA formulations include PEG 3350, and delayed hypersensitivity reactions to this excipient are relatively frequent, with reported incidences ranging from 4.2% to 6.7%. Maoz-Segal and colleagues observed a significant association between hypersensitivity reactions and prior use of hyaluronic acid as an injectable facial filler, potentially supporting the hypothesis that prior exposure to specific compounds can predispose individuals to subsequent hypersensitivity responses.[30,31]

This emphasizes the critical need for systematic evaluation and accurate diagnosis, such as thorough skin testing, to distinguish between true IgE-mediated allergies and non-allergic adverse events.[32] Moreover, the existing guidelines strongly support the necessity of LA testing for patients who report a history of LA hypersensitivity reactions. This recommendation is further reinforced by clinical data, such as the findings of Yilmaz et al, which advocate for testing in individuals with a past reaction and those presenting with multiple drug hypersensitivity reactions (DHR).[17] Mislabeling a patient as allergic without confirmation can lead to the avoidance of first-line anesthetics, potentially resulting in suboptimal care and increased procedural risks. Larger prospective studies are needed to further investigate the prevalence, mechanisms, and risk factors of LA hypersensitivity in our population.

## Conclusion

In conclusion, allergy testing protocols is crucial for the precise identification of the extremely rare instances of true LA-related allergy especially in individuals with a past reaction. The low referral rate for allergy testing underlines a potential

gap in the management of patients with suspected hypersensitivity to LAs. While LAs are generally safe, the persistent low rate of confirmed allergies, coupled with the potential for life-threatening reactions caused by excipients, demands a paradigm shift in the diagnostic approach. Clinicians must maintain a high index of suspicion for non-LA components in cases of suspected LA hypersensitivity. Labeling a patient as allergic to LAs without confirmation carries profound long-term implications since this class of medications is indispensable across a wide range of medical procedures and surgical interventions. This may lead to the selection of more invasive or higher-risk alternatives for routine procedures. Identifying the true sensitizing agent is essential for patient safety, preventing potentially catastrophic future exposures, and avoiding unnecessary labeling of patients with LA allergy, thereby preserving the use of this vital class of medications.

## Data Sharing Statement

The original contributions presented in the study are included in the article materials. Further inquiries can be directed to the corresponding author.

## Ethics Approval and Consent to Participate

This study complies with the ethical principles outlined in the Declaration of Helsinki. The ethical approval was obtained from the institutional review board at King Abdullah International Medical Research Centre (Saudi Arabia) with the reference number IRB/2131/23. Written informed consent to participate was not required for this study in accordance with national legislation and institutional requirements.

## Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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## Disclosure

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## References

1. Batinac T, Sotošek Tokmadžić V, Peharda V, Brajac I. Adverse reactions and alleged allergy to local anesthetics: analysis of 331 patients. *J Dermatol*. 2013;40(7):522–527. doi:10.1111/1346-8138.12168
2. Cherobin ACFP, Tavares GT. Safety of local anesthetics. *An Bras Dermatol*. 2020;95(1):82–90. doi:10.1016/j.abd.2019.09.025
3. Barradas Lopes J, Reis Ferreira A, Sousa MJ, Cadinha S. Anaphylactic shock to lidocaine: a rare case with evaluation of cross-reactivity between local anesthetics. *J Investig Allergol Clin Immunol*. 2021;31(5):449–450. doi:10.18176/JIACI.0658
4. Bahar E, Yoon H. Lidocaine: a local anesthetic, its adverse effects and management. *Medicina*. 2021;57(8). doi:10.3390/MEDICINA57080782
5. Thyssen JP, Menné T, Elberling J, Plaschke P, Johansen JD. Hypersensitivity to local anaesthetics – update and proposal of evaluation algorithm. *Contact Dermatitis*. 2008;59(2):69–78. doi:10.1111/J.1600-0536.2008.01366.X
6. Cardona V, Ansotegui IJ, Ebisawa M, et al. World allergy organization anaphylaxis guidance 2020. *World Allergy Organ J*. 2020;13(10):100472. doi:10.1016/J.WAOJOU.2020.100472
7. Bhole MV, Manson AL, Seneviratne SL, Misbah SA. IgE-mediated allergy to local anaesthetics: separating fact from perception: a UK perspective. *Br J Anaesth*. 2012;108(6):903–911. doi:10.1093/bja/aes162
8. Mertes PM, Tajima K, Regnier-Kimmoun MA, et al. Perioperative Anaphylaxis. *Med Clin North Am*. 2010;94(4):761–789. doi:10.1016/j.mcna.2010.04.002
9. Kamath A, Raghove V, Kalstein A, Yarmush J. Labor epidural in a patient who is allergic to lidocaine: a case series. *Local Regional Anesth*. 2021;14:21–23. doi:10.2147/LRA.S253087
10. Al-Dosary K, Al-Qahtani A, Alangari A. Anaphylaxis to lidocaine with tolerance to articaine in a 12 year old girl. *Saudi Pharm J SPJ off Publ Saudi Pharm Soc*. 2014;22(3):280–282. doi:10.1016/J.JSPS.2013.10.001

11. Fuzier R, Lapeyre-Mestre M, Mertes P-M, et al. Immediate- and delayed-type allergic reactions to amide local anesthetics: clinical features and skin testing. *Pharmacoepidemiol Drug Saf*. 2009;18(7):595–601. doi:10.1002/PDS.1758
12. Macy E, Schatz M, Zeiger RS. Methylparaben immediate hypersensitivity is a rare cause of false positive local anesthetic provocative dose testing. *J Allergy Clin Immunol*. 2002;109(1):149. doi:10.1016/S0091-6749(02)81574-3
13. Kajimoto Y, Rosenberg ME, Kyttä J, et al. Anaphylactoid skin reactions after intravenous regional anaesthesia using 0.5% prilocaine with or without preservative — a double-blind study. *Acta Anaesthesiol Scand*. 1995;39(6):782–784. doi:10.1111/J.1399-6576.1995.TB04170.X
14. Halling F, Neff A, Meisgeier A. True Allergies to Articaine: a 25-Year Analysis. *Dent J*. 2025;13(5):180. doi:10.3390/DJ13050180
15. Zuo J, Gong R, Liu X, Zhao J. Risk of true allergy to local anesthetics: 10-year experience from an anesthesia allergy clinic in China. *Ther Clin Risk Manag*. 2020;16:1297–1303. doi:10.2147/TCRM.S280259
16. Janas-Naze A, Osica P. The incidence of lidocaine allergy in dentists: an evaluation of 100 general dental practitioners. *Int J Occup Med Environ Health*. 2019;32(3):333–339. doi:10.13075/IJOMEH.1896.01235
17. Yilmaz I, Özdemir S, Aydin O, Çelik G. Local anesthetics allergy: who should be tested? *Eur Ann Allergy Clin Immunol*. 2017;50(2):66–71. doi:10.23822/EURANNACI.1764-1489.38
18. DeGroat W, Abdelhalim H, Patel K, Mendhe D, Zeeshan S, Ahmed Z. Discovering biomarkers associated and predicting cardiovascular disease with high accuracy using a novel nexus of machine learning techniques for precision medicine. *Sci Rep*. 2024;14(1):1–12. doi:10.1038/s41598-023-50600-8
19. Nowak-Wegrzyn A, Ellis A, Castells M. Sex and allergic diseases. *Ann Allergy Asthma Immunol*. 2019;122(2):134–135. doi:10.1016/j.anai.2018.12.010
20. Lisiecka MZ. Allergic reactions in dental practice: classification of medicines, mechanisms of action, and clinical manifestations. *Clin Rev Allergy Immunol*. 2025;68(1):1–13. doi:10.1007/s12016-025-09032-7
21. Yildiz E, Colkesen F, Aykan FS, et al. Allergic reactions to local anesthetics: should we test those with drug allergies and atopy history? *Ann Med Res*. 2022;29(6):1. doi:10.5455/annalsmedres.2021.12.642
22. Silva A, Mourão J, Vale N. A review of the lidocaine in the perioperative period. *J Pers Med*. 2023;13(12):1699. doi:10.3390/JPM13121699
23. Forkel S, Buhl T. Allergic contact dermatitis after injection of local anesthetic. *J Allergy Clin Immunol Pract*. 2020;8(6):2060–2061. doi:10.1016/j.jaip.2020.01.050
24. Borderé A, Stockman A, Boone B, et al. A case of anaphylaxis caused by macrogol 3350 after injection of a corticosteroid. *Contact Dermatitis*. 2012;67(6):376–378. doi:10.1111/J.1600-0536.2012.02104.X
25. Cox F, Khalib K, Conlon N. PEG that reaction: a case series of allergy to polyethylene glycol. *J Clin Pharmacol*. 2021;61(6):832–835. doi:10.1002/JCPH.1824
26. Wenande E, Garvey LH. Immediate-type hypersensitivity to polyethylene glycols: a review. *Clin Exp Allergy*. 2016;46(7):907–922. doi:10.1111/CEA.12760
27. Bianchi A, Bottau P, Calamelli E, et al. Hypersensitivity to polyethylene glycol in adults and children: an emerging challenge. *Acta Bio Medica Atenei Parm*. 2021;92(Suppl 7):e2021519. doi:10.23750/ABM.V92IS7.12384
28. Park GW, Park N, Kuk JC, Shin EJ, Lim DR. Anaphylactic shock induced by polyethylene glycol after bowel preparation for the colorectal cancer surgery: a case report. *World J Clin Cases*. 2023;11(23):5589–5594. doi:10.12998/WJCC.V11.I23.5589
29. Stone CA, Liu Y, Relling MV, et al. Immediate hypersensitivity to polyethylene glycols and polysorbates: more common than we have recognized. *J Allergy Clin Immunol Pract*. 2019;7(5):1533–1540.e8. doi:10.1016/j.jaip.2018.12.003
30. Özkaya E, Kılıç S. Polyethylene glycol as marker for nitrofurazone allergy: 20 years of experience from Turkey. *Contact Dermatitis*. 2018;78(3):211–215. doi:10.1111/COD.12931
31. Maoz-Segal R, Shavit R, Kidon MI, et al. Late hypersensitivity reactions to the BNT162b2 SARS-CoV-2 vaccine are linked to delayed skin sensitization and prior exposure to hyaluronic acid. *Life*. 2022;12(12):2021. doi:10.3390/LIFE12122021
32. AlGassim M, Alawami F, Bakhsh GH, et al. Towards standardized skin testing for drug-induced allergic reactions. *Saudi Pharm J SPJ*. 2025;33(4):26. doi:10.1007/S44446-025-00031-5