

Suspected allergy to local anaesthetics: follow-up in 135 cases

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Background: Local anaesthetics (LA) are generally considered safe with respect to allergy. However, various clinical reactions steadily occur. Even though most reactions are manifestations of reflexes to perceptive stimuli, uncertainty often remains regarding a possible allergic mechanism. This uncertainty later leads to an avoidance of local anaesthesia and unnecessarily painful interventions, resource-consuming general anaesthesia or even the risk of re-exposure to other yet unidentified allergens. In the present study, follow-up procedures at an allergy clinic were analysed to examine the frequency of identified causative agents and pathogenetic mechanisms and evaluate the strength of the diagnostic conclusions.

Method: The medical records of 135 cases with alleged allergic reactions to LA were reviewed. Diagnoses were based on case histories, skin tests, subcutaneous challenge tests and *in vitro* IgE analyses.

Results: Two events (1.5%) were diagnosed as hypersensitivity to LA, articaine–adrenaline and tetracaine–adrena-

line, respectively. Ten reactions (7%) were diagnosed as IgE-mediated allergy to other substances including chlorhexidine, latex, triamcinolone and possibly hexaminolevulinate. As challenge testing was not consistently performed with the culprit LA compound, follow-ups were short of definitely refuting hypersensitivity in 61% of the cases. The reported clinical manifestations were in general diagnostically unspecific, but itch and generalised urticaria were most frequent in test-positive cases.

Conclusion: Reactions during local anaesthesia are rarely found to be an IgE-mediated LA allergy. Whenever the clinical picture is compatible with allergy, other allergens should also be tested.

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LOCAL anaesthetics (LA) are infrequent causes of allergic reactions. Still, when adverse reactions do occur, there seems to be a tendency to overestimate allergy as the mechanism. Studies report a fraction of allergy to LAs in populations of suspected reactions with frequencies that vary from 0 to ~30%.^{1–7} For safety reasons, it might seem best to liberally use the term allergy after such adverse reactions, as possible life-threatening reactions by re-exposure might be avoided. As a consequence, however, without a proper follow-up examination, patients will be left subject to unnecessarily painful procedures or costly and time-consuming general anaesthesias. Furthermore, wrongfully maintain-

ing LA as the suspected adverse agent may divert attention from the actual allergens to which the patient may be re-exposed. Many allergy clinics regularly see patients referred on the suspicion of LA allergy. Given that most patients actually tolerate LAs, the challenge is how to cost beneficially organise the follow-up. With the intentions of optimising the diagnostic protocol at an outpatient allergy clinic, the medical records of previously examined cases were studied. The aims of the study were to evaluate the frequency of identified causative agents, the disclosure of pathogenetic mechanisms and the strength of the diagnostic conclusions.

Material and methods

From 1995 to 2006, 135 outpatients with suspected allergy towards LAs were examined at the Section

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for Clinical Allergology, Department of Occupational Medicine, Haukeland University Hospital, Bergen, Norway. The patients were referred from general practitioners, hospital specialists and dentists for evaluation after adverse reactions suspected to be allergic. The follow-up examinations were conducted by five different physicians who were either allergologists or anaesthetists supervised by a senior allergologist. The specific medical records obtained at the outpatient follow-ups, in paper or electronic format, were analysed retrospectively. The study was approved by the Regional Committee for Medical Research Ethics in Western Norway, the Norwegian Social Science Data Services and the Directorate for Health and Social Affairs as a clinical quality control study.

Clinical history

The 30 signs and symptoms most frequently reported or those typical for an immunoglobulin E (IgE)-mediated mechanism were used as variables in a database. The manifestations deemed as particularly relevant to allergy were: skin rash (localised or generalised, non-specified or urticaria), oedema (localised or generalised), itch, hypotension, tachycardia and bronchospasm. Manifestations included because of frequent occurrence in case histories were: loss of consciousness, feeling ill, faint, nauseous or dizzy, feeling of narrow throat, convulsions, muscle cramps, tremors, feeling warmth, diaphoresis, visual obscuration, bradycardia, palpitations, tachypnoea, dyspnoea, anxiety, peripheral and perioral paraesthesias. Other data extracted were patient age and sex, date of reaction, the LA associated with the reaction, type of anaesthetic procedure, time from administration of LA to reaction, date of follow-up, diagnostic tests used and conclusions at follow-up. When the dates of reactions were reported as approximate intervals (e.g. 'in 1980'), the median dates of the intervals (e.g. '1 July 1980') were used for further calculations. All 135 medical records were entered into the database.

Diagnostic methods

The number of diagnostic tests performed in each case varied over the 12 years covered by this study, the variation caused by changes in staff and diagnostic strategy. The test methods were, however, standardised as described in the following sections. Before skin testing and subcutaneous challenge, patients who had a history of systemic manifesta-

tions, received a peripheral intravenous cannula and were monitored with a three-lead electrocardiogram. A nurse and a doctor attended the patients during testing. Tests were also performed with other substances such as latex, chlorhexidine and concomitant medication if deemed relevant based on the referral information.

Regarding patients who developed clinical reactions during the testing procedure, the most frequently or the most clinically significant recorded manifestations were entered into the database, i.e., bradycardia, convulsions, feeling dizzy, faint, ill or nauseous, hypotension, loss of consciousness, pallor, palpitations, paraesthesias and tachycardia.

Skin tests

Skin tests were performed by trained allergy nurses and followed the guidelines of the European Academy of Allergy and Clinical Immunology.^{8,9}

Skin prick tests (SPTs) were performed in duplicate on the anterior side of the patients' lower arms and evaluated against a positive (Histamine chloride 10 mg/ml, ALK Abelló, Hørsholm, Denmark) and negative control (ALK Abelló). LAs and other drugs were tested at vial concentrations. Latex was tested at 100 histamine-equivalent prick (ALK Abelló). The reactions were read at 15 min, and positive tests required a mean wheal diameter of at least 3 mm more than that of the negative control.

Intradermal tests (IDT) were performed when SPTs were negative with LAs, chlorhexidine and glucocorticoids. Injections were administered on the anterior side of the patients' lower arms with approximately 0.03 ml of fluid aiming at yielding an initial mean intradermal wheal diameter of 4 mm. Dilutions varied from 1:1000 to undiluted drugs with LAs and glucocorticoids. Chlorhexidine was tested at 0.001–0.01 mg/ml. The reactions were read at 15 min and considered positive if the mean wheal diameters were at least doubled.

The epicutaneous tests (EPT) were performed with Finn ChamberTM panels. The chemicals were partly commercially accessible: prilocaine, tetracaine, lidocaine, chlorhexidine, parabens and thiuram mix. Bupivacaine, carbocaine, oxybuprocaine and latex were also included in the standard test panel. Betamethasone and benzalkonium chloride were also included in individual cases if indicated by the case history. The test was evaluated as 0 (no reaction), 1 (erythema and infiltration in the entire test area), 2 (small vesicles in addition to erythema and infiltration) or 3 (bullous reaction). Results were read at 76 h.

In cases of delayed reactions, where EPTs were not performed, patients were requested to report eventual delayed responses to IDTs and subcutaneous challenge tests (SCCTs) the day after the testing procedure.

SCCTs

SCCTs were performed by a subcutaneous injection of titrated amounts of LA from 0.1 ml at 1:10 of the vial concentration (or lower) to 1.0 ml (or larger) of the vial concentration in at least three-step procedure. The injections were administered in the lateral aspects of the patients upper arms, and aspiration was performed before deposition of the fluid volume in order to avoid intravascular administration. The patients were observed for local or generalised reactions for 15 min and after the last injection for at least 30 min before leaving the clinic. If suggested by the history, more prolonged observation periods were individually determined.

IgE

Serum IgE antibodies towards latex and chlorhexidine were analysed by ImmunoCAP™ (Phadia, Uppsala, Sweden), the cut-off for the positive test being 0.35 kU_A/l.

Histamine release tests (HRTs)

HRTs were performed in washed blood cells using a glass fibre micro titre plate-based test.¹⁰ Heparinised blood was washed once in Pipes buffer, pre-incubated for 15 min at 37 °C and then 25 µL was applied into micro titre plate wells. Twenty-five microlitres of drug solution was added and incubated at 37 °C for 1 h before the wells were washed. Glass fibre-bound histamine was resolubilised,

complexed with o-phthalaldehyd and quantified fluorometrically. The amount of histamine released was assayed in duplicate 2.5-fold dilution series. A negative control was included.

Basophile CD63 up-regulation assayed by flow cytometry (CD-Sens)

CD-Sens was applied only in a single case. The method is therefore not described here.

Results

Clinical history

The mean age of the patient population was 36 years (range 2–76 years) at the time of the reaction, and the median time interval from reaction to follow-up was 21 months (range 1 month–44 years). In 12 cases, the time of reaction was not recorded. The female: male ratio was 4:1. Anaesthetic procedures, associated with the reactions that led to referral, are displayed in Table 1. LAs administered before the reactions were lidocaine (65%), bupivacaine (9%), mepivacaine (8%), tetracaine, articaine and prilocaine (≤ 2% each), and in 17% of the reactions, the LA was unknown to the investigator. Time intervals from LA exposure to the associated clinical manifestations were ≤ 30 min in 69%, between 30 min and 48 h in 20% and not recorded in 11% of the cases.

The manifestations most frequently reported from the reactions that led to referral were loss of consciousness (31%), feeling ill (23%), feeling faint (20%) and generalised unspecified rash (15%). Other manifestations, commonly associated with IgE-mediated allergy, were somewhat less frequently reported: documented hypotension (13%), itch

Table 1

Anaesthetic procedures, number of hypersensitivities, reaction types and causal agents.

Type of procedure	No. of cases (%)	No. with hypersensitivity (% of category)	Reaction types in positive cases	Causal agents in positive cases
Dental anaesthesia	61 (45%)	3 (5%)	Generalised urticaria Anaphylaxis	Articaine–adrenaline Chlorhexidine
Infiltration for minor surgery	31 (23%)	2 (6%)	Dyspnoea Generalised urticaria Anaphylaxis	Latex Chlorhexidine Latex
Adjuvant to steroid injection	12 (9%)	1 (8%)	Anaphylaxis	Triamcinolone
Mucosal topical anaesthesia	9 (7%)	2 (22%)	Anaphylaxis Delayed rash, fever	Chlorhexidine Tetracaine–adrenaline
Epidural anaesthesia	8 (6%)	1 (13%)	Anaphylaxis	Latex
Spinal anaesthesia	5 (4%)	3 (60%)	Anaphylaxis Anaphylaxis Anaphylaxis	Chlorhexidine Chlorhexidine Chlorhexidine
Miscellaneous	9 (7%)	0	Anaphylaxis None	Hexaminolevulinate None

Table 2

Reported clinical manifestations in suspected allergic reactions to local anaesthetics.

Clinical manifestation	Positive test results*	Negative test results*	
	Any time interval <i>n</i> = 11	Time interval ≤ 30 min <i>n</i> = 87	Time interval > 30 min <i>n</i> = 22
Local swelling	1 (9%)	12 (14%)	3 (14%)
Local rash	1 (9%)	7 (8%)	7 (32%)
Generalised unspecified rash	3 (27%)	9 (10%)	7 (32%)
Generalised urticaria	4 (36%)	5 (6%)	3 (14%)
Itch	7 (63%)	3 (3%)	4 (18%)
Hypotension	5 (46%)	11 (13%)	0
Palpitations	0	16 (18%)	0
Dyspnoea	3 (27%)	14 (16%)	3 (14%)
Feeling of narrow throat	0	13 (15%)	1 (5%)
Loss of consciousness	3 (27%)	29 (33%)	3 (14%)
Convulsions	0	9 (10%)	1 (5%)
Diaphoresis	0	16 (18%)	2 (9%)
Feeling ill	2 (18%)	24 (28%)	3 (14%)
Feeling faint	1 (9%)	24 (28%)	1 (5%)
Nausea	0	15 (17%)	2 (9%)
Visual obscuration	1 (9%)	10 (12%)	1 (5%)
Peripheral/oral paresthesias	1 (9%)	10 (12%)	2 (9%)

Cases grouped with respect to diagnostic test results and to time interval from local anaesthesia to reaction.

*Diagnostic tests: Skin prick tests, intradermal tests, subcutaneous challenge tests, serum IgE antibody analyses and histamine release tests. Case considered positive if one or more test(s) were positive with relevant allergen.

Bold indicates manifestation present in >30% of cases.

Table 3

Performance of the diagnostic tests in identifying the causative agent and IgE-mediated mechanism in 135 patients with suspected allergic reactions to local anaesthetics.

Case	Allergen	Test positive	Test negative
1	Chlorhexidine	SPT; HRT; SAB	None
2	Chlorhexidine	IDT; HRT	SPT
3	Chlorhexidine	IDT; HRT	SPT
4	Chlorhexidine	IDT; HRT	SPT
5	Chlorhexidine	IDT	SPT
6	Latex	SPT; SAB; HRT	None
7	Latex	SPT; SAB	None
8	Latex	SPT; SAB	None
9	Triamcinolon	SPT	HRT
10	Hexaminolevulinate	SPT	CD-Sens

SPT, skin prick test; HRT, histamine release test; IDT, intradermal test; SAB, serum IgE-antibody assay; CD-Sens, basophile CD63 up regulation assayed by flow cytometry.

(11%), generalised urticaria (10%), tachycardia (7%) and bronchospasm (1.5%). The distribution of manifestations in three sub-populations is shown in Table 2. There was a considerable overlap in manifestations between the test-positive and negative groups even though itch, urticaria and documented hypotension were reported most frequently in cases with positive tests.

Diagnostic tests

The number of different diagnostic tests performed in each case varied. EPT were performed with LA

in 6%, SPT with LA in 98%, SPT with latex in 70%, SPT with chlorhexidine in 55%, IDT with LA in 83% and SCCT with LA in 87% of the cases. Two patients (1.5%) were given the diagnosis of LA hypersensitivity, none of whom had clinical anaphylaxis or positive skin tests, with details provided in separate sections below.

Ten patients (7%) were diagnosed with IgE-mediated allergy, all of whom reacted to agents other than LAs (Table 3). Seven of these developed hypotension, loss of consciousness or dyspnoea in addition to skin reactions indicating anaphylaxis (Table 1). All 10 had negative SCCTs with LAs, although three cases had either an unknown culprit LA or were not tested with relevant additives. In the remaining 123 cases (91%), no hypersensitivity was demonstrated. However, allergic reactions to LA or additives could not be definitely excluded as challenge testing with the culprit LA for various reasons was not performed in 83 cases. SCCT results are shown in Table 4. A number of examinations were performed with a certain degree of urgency before delivery or planned surgery, and provision of an alternative LA was then the primary objective. An LA safe to use on future occasions was identified, by challenge testing or by the case histories revealing tolerance, in all except one case.

None of the patients demonstrated positive EPT, but only two of the 27 patients with a late onset of

Table 4

Strategic application and performance of subcutaneous challenge tests (SCCT) in 118 (87%) cases of suspected allergic reactions to local anaesthetics (LA).

Test status	Number
SCCT positive to culprit LA	1 (0.8%)
SCCT negative to culprit LA with relevant additives	51 (43%)
SCCT incomplete with respect to culprit LA	66 (56%)
Unknown culprit LA	19 (16%)
Test performed with alternative LA	9 (8%)
Test performed with culprit LA but without relevant additives	29 (25%)
Status on test with relevant additives not documented	9 (8%)

Table 5

Testing procedure for suspected allergic reactions during local anaesthesia.

SPTs	Positive and negative control Culprit LA compound*† at vial concentration, additives included
IDTs	Other relevant agents (e.g. latex, chlorhexidine) Negative control (saline 9 mg/ml) Culprit LA compound† at 1 : 100 dilution Other relevant agents at recommended test concentrations‡
SCCTs	Negative control§ (saline 9 mg/ml) 0.1 ml Culprit LA at 1 : 10 dilution, 0.1 ml Culprit LA at vial concentration, 0.1 ml Culprit LA at vial concentration, 1.0 ml

*If culprit LA is not known, tests may be performed with most common LA, i.e. lidocaine compound.

†LA compound containing vasoconstrictor not suitable for skin testing, LA and additives tested separately.

‡Recommendations in published guidelines when available.

§May be used as single blinded control if agreed by the patient. SPT, skin prick test; IDT, intradermal test; SCCT, subcutaneous challenge test.

reaction (>30 min) had EPT performed. None of them did, however, report delayed responses to skin tests or SCCTs. In five of the 10 patients where an IgE-mediated mechanism was identified, the reactions occurred with a considerable delay from the start of anaesthesia. In four reactions occurring from 40 to 90 min after the start of anaesthesia, tests were positive with chlorhexidine. This agent is typically introduced at a later stage of procedures, yielding a time relation between exposure and reaction quite plausible for an IgE-mediated mechanism. In the case of a possible reaction to hexaminolevulinate, this agent was instilled to the patient's bladder nearly 5 h before the reaction. However, the reaction occurred shortly after transurethral cystoscopy and prostate surgery, which may have caused a delayed systemic exposure to the agent.

Two patients with hypersensitivity reactions to LA compounds

Case no. 1. A 37-year-old woman with allergic rhinitis and allergic contact dermatitis to nickel was anaesthetised with tetracaine–adrenaline topically before nasal endoscopy. Five hours later, she developed nasal congestion, rhinorrhoea, facial rash and fever with a temperature of 39 °C. The ENT specialist performed a local re-challenge with tetracaine–adrenaline a week later, with the reaction reoccurring after 6 h. A SPT with tetracaine yielded a 35 mm flare but no wheal. IDTs and SCCTs with lidocaine were negative. EPTs were not performed, but this was diagnosed as a certain case of a delayed hypersensitivity reaction towards tetracaine–adrenaline.

Case no. 2. A 25-year-old female was anaesthetised with articaine–adrenaline for dental treatment. After 20–30 min, her legs started to itch. The itch soon became generalised, and she developed a generalised rash. She felt faint and was treated with intravenous hydrocortisone and antihistamines at a medical emergency clinic before the reaction resided. SPT and IDT were negative with articaine–adrenaline, lidocaine and sodium-metabisulphite. Open SCCT with articaine–adrenaline was titrated from 1 : 10 of vial concentration, 0.1 ml, and 35 min after receiving 1.0 ml at a vial concentration (40 mg/ml), she developed a scarce but generalised itching urticaria located on her face, back and thighs. This was diagnosed as a certain hypersensitivity reaction towards articaine–adrenaline. The itching urticaria could point towards mast cell involvement, but an IgE-mediated mechanism was not verified.

Systemic reactions during testing

Twenty-eight patients (21%) were recorded to have developed clinical reactions during the skin and challenge test procedures. None of these had positive skin tests or manifestations compatible with allergy during SCCTs. The most common manifestations were feeling ill (10%), bradycardia (7%), tachycardia (7%), feeling faint (5%), diaphoresis (5%), hypotension (4%), peripheral paraesthesias (4%) and pallor (4%). Loss of consciousness was observed in two cases (1.5%). These reactions were generally self-limiting, the patient being brought in the supine position and occasionally treated with atropine 0.5–1 mg intravenously.

Discussion

This study describes a population of 135 patients examined for suspected allergic reactions to LAs. Even though the frequency of detected hypersensitivity (1.5%) was similar to that found by others, the number of allergic reactions towards other allergens (7%) suggests that reactions during local anaesthesia should be investigated with several possible causes in mind. In the cases where the diagnostic results suggested a causative agent, hypersensitivity reactions were five times more frequently caused by substances such as chlorhexidine and latex than by the LAs or their additives. Only reactions caused by substances other than LAs were diagnosed as anaphylactic and IgE mediated. In accordance with the World Health Organisation causality assessment of adverse drug reactions,¹¹ the two reactions caused by LAs could be designated certain due to the positive rechallenges in addition to the requirements of a plausible time relation and a lack of alternative explaining factors. However, in these cases, the pathogenetic mechanisms could not be identified. As a considerable portion of the examinations (61%) did not include challenge with the culprit LA compound, the frequency of hypersensitivity reactions to LAs, including their additives, could thus have been underestimated in the total study population. As in most reports, the major cause of unwanted general reactions during exposure to LAs were considered to be central nervous reflex reactions elicited by perceptive stimuli.

The results were in part difficult to interpret due to the heterogeneity of the data and the retrospective approach of the study. In a few cases, the delay from reaction to testing was very long. Even though allergy to anaesthetic drugs has been shown to last for up to 27 years,¹² testing when delayed for several years, as in the present study, appears more to be a demonstration of tolerance rather than an investigation of the mechanism of the primary reaction. The variable amount of tests performed in each case limits the analyses of the entire population. On the other hand, panel testing with substances that are not, by case history, linked to particular reactions could produce some contextually false-positive results. In the present study, limited referral information about possible concomitant medication at the time of reaction may also have led to insufficient testing and false-negative diagnostic conclusions.

The reported clinical manifestations could be used neither to differentiate between possible hy-

persensitivity and non-hypersensitivity reactions nor between allergic and non-allergic mechanisms. When symptoms and signs typical for IgE-mediated allergy, such as itch, urticaria, bronchospasm and sustained hypotension, were reported, they indicated that the examinations would result in diagnosing IgE-mediated reactions to allergens other than LAs or additives, and underlines that all relevant exposures during the anaesthetic and interventional procedures should be tested. Differential diagnosis based on the reaction characteristics alone is furthermore made difficult not the least as referrals for the follow-up were accompanied by a very limited description and documentation of the reactions. In addition, the patients often had a blurred memory of the incident that may have involved lowered blood pressure and altered perception. A better description of the reactions would be advantageous but does not seem very realistic to achieve. Most physicians and dentists witness these reactions quite infrequently and normally do not incorporate routines and equipment for monitoring patients during procedures performed under local anaesthesia.

SCCT with LA is a well-recognised method for demonstrating tolerance, and, as the prevalence of hypersensitivity reactions to LA is low, the tests usually turn out negative. Some authors have argued that SCCT should be performed with LAs without additives.^{13–15} In the present material, however, tests without additives contributed to SCCTs not being used to their full potential. Unnecessary uncertainty remains if SCCTs are performed with an alternative LA or the suspected LA without relevant additives. When the culprit LA is unknown, however, there is of course only the option to demonstrate tolerance to a commonly available LA. The guidelines on provocation testing for drug hypersensitivity by the European Network for Drug Allergy and the EAACI interest group on drug hypersensitivity state that the proof of tolerance to a drug should be addressed with the commercial preparation.¹⁶ They also recommend that single components are tested separately. However, this may relate to diagnostic accuracy and not to matters of test safety. In cases of suspected LA allergy, where the probability of a true allergy is generally low, it is believed that single-component tests may be reserved for situations where commercial compounds turn out to be positive. The number of steps in the diagnostic procedure, number of substances, dilutions and volumes should be as few as possible with respect to time and economy without being unsafe with respect to a risk of serious allergic reactions. At present, we follow a strategy as

shown in Table 5, based on our own results and procedures recommended by other authors.^{2-4,14}

The diagnostic procedures used in the present material did not detect any cases of delayed-type hypersensitivity. Through scarce use of EPTs and no readings of tests later than 72 h, cases of delayed hypersensitivity to LAs may have been lost. Allergic mechanisms were detected in a few cases of seemingly delayed onsets but they were shown to be caused by immediate-type reactions to allergens introduced later in the event than the LA. A diagnostic procedure for suspected LA allergy should consistently include EPTs for investigation of delayed reactions.¹⁷

Psychogenic reactions during testing were common, especially where the case history included a transient systemic reaction. We believe that the test procedures can be used to demystify symptoms, and this may actually have been of some cognitive benefit for several patients. By gradually increasing the test invasiveness, progressing from SPTs through IDTs to SCCT, both the patient and the staff had sufficient time to observe and register eventual non-allergic manifestations. A special chair, able to bring the patient in the supine position, was often useful. Intravenous atropine was occasionally used to alleviate bradycardia associated with hypotension. Patients who had unspecific reactions during testing often reported no memory of anxiety or nervousness before the reactions at their dentist or doctor. They still accepted the explanation that perceptive stimuli by reflex mechanisms may have lowered their blood pressure or carbon dioxide level. When communicating with the patients about negative test results, emphasis was placed on the opportunity regained to use LA in the future.

Conclusion

The present study supports previous observations that only a small fraction of cases examined for suspected allergy to LAs are actual cases of LA hypersensitivity, but it also observed that a notable number of such patients actually suffered reactions towards other allergens. Whenever the clinical picture is in keeping with an immediate-onset allergic reaction, the role of other possible allergens such as latex and chlorhexidine should be evaluated.

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