

Original article

Sublingual rush immunotherapy with latex extract in children

Immunothérapie accélérée par voie sublinguale avec des extraits de latex chez l'enfant

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Abstract

Latex allergy prevalence has increased notably in the last two decades. Latex ubiquity and its cross-reactivity with fruits make complete avoidance difficult to attain and studies have questioned long-term avoidance efficacy. Subcutaneous and sublingual routes of specific immunotherapy (SIT) to latex have been tested in double blind placebo controlled studies, with significant improvement in patients' tolerance to latex. We present our experience with a sublingual desensitization protocol in three latex allergic children. The build-up phase consisted of rush, with daily admission for 4 consecutive days, followed by a maintenance period at home. Only local reactions, with good response to antihistamines were observed during rush and no reactions have been reported with maintenance dose during 6, 5 and 2 months, respectively. The first patient has accomplished 6 months maintenance treatment. Allergological re-evaluation has shown a decrease in skin reactivity and serum specific IgEs to latex and cross-reactive fruits. Comparison of the results of specific IgEs measurement to a panel of latex recombinant allergens before rush and 6 months later clearly showed a decrease in Hev b 5 and Hev b 6.01, with no other detectable new sensitizations. Immunoblot was also performed before rush and 6 months later and shows a decrease in sensitization without appearance of new bands. Future enlargement of our series and prospective follow-up will help to clarify the real clinical efficacy of sublingual SIT. As this is a safe and easy to use protocol, it seems to be specially appropriate for children.

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Résumé

La prévalence de l'allergie au latex a notablement augmenté au cours des deux dernières décades. En raison de son caractère d'allergène ubiquitaire et de ses réactions croisées avec les fruits, le latex est difficile à éviter complètement et des études ont mis en doute l'efficacité à long terme de son éviction. L'évaluation de l'immunothérapie spécifique au latex par voie sous-cutanée et sublinguale, au cours d'études en double insu vs placebo, témoigne d'une amélioration significative de la tolérance des patients vis-à-vis du latex. Nous présentons notre expérience d'un protocole de désensibilisation par voie sublinguale chez trois enfants allergiques au latex. La phase d'attaque a consisté en une administration d'allergènes par voie sublinguale pendant quatre jours consécutifs en hospitalisation, suivie d'une période d'entretien à domicile. Il ne fut observé que des réactions locales pendant la phase accélérée, répondant favorablement aux antihistaminiques. Aucune

Abbreviations: DBPC, double blinded placebo controlled; MD, maintenance dose; MWD, mean wheal diameter; NRL, natural rubber latex; PRP, pathogenesis-related proteins; SIT, specific immunotherapy; sIgE, specific IgE; SPT, skin prick tests.

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réaction ne fut enregistrée pendant la phase d'entretien respectivement pendant six, cinq et deux mois. Le premier patient a effectué six mois de traitement d'entretien. La réévaluation allergologique a montré une diminution de sa réactivité cutanée au latex, et une baisse des IgE sériques spécifiques dirigées contre le latex et les fruits responsables de réactions croisées. La comparaison des résultats des IgE sériques spécifiques vis-à-vis d'un panel d'allergènes recombinants du latex, avant l'immunothérapie et six mois plus tard, a montré une diminution de Hev b 5 et Hev b 6.01, sans autre nouvelle sensibilisation détectable. Les immunoblots, également réalisés avant l'immunothérapie accélérée et six mois plus tard, montrèrent une diminution de la sensibilisation sans apparition de nouvelles bandes. Notre série doit être complétée et un suivi prospectif nous aidera à préciser l'efficacité clinique de cette immunothérapie sublinguale. Dans la mesure où ce protocole est sûr et facile à réaliser, il apparaît particulièrement adapté à l'enfant.

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Mots clés : Latex ; Immunothérapie spécifique ; Immunothérapie par voie sublinguale ; Enfants

1. Introduction

Latex allergy is an important medical, occupational, medico-legal and financial problem. Epidemiological studies demonstrate that 1% of general population and at least 20% of healthcare workers are sensitized to natural rubber latex (NRL). Latex is a major cause of intraoperative anaphylaxis, causing up to 19% of such reactions [1–3].

Predisposing factors to latex allergy include atopy and frequent exposure to latex products. Healthcare and rubber industry workers and individuals who have undergone multiple surgical procedures, especially children with spina bifida and/or urogenital anomalies, are the main risk groups for NRL allergy [1,2,4–8]. The relation with atopy may be reciprocal. Children with latex allergy present a significantly higher incidence of sensitization to inhaled and food allergens, atopic dermatitis, rhinitis and conjunctivitis when compared to children without latex allergy [5–8].

The nature of latex is complex. Thirteen latex allergens have been recognized by the International Union of Immunological Societies (*Hevea brasiliensis* proteins – Hev b 1–13), including latex proteins from the rubber tree that remain in manufactured products and smaller molecules resulting from latex purification and manufacturing process [1,9,10]. Hev b 2, Hev b 5, Hev b 6, Hev b 13, and Hev b 4 are the major allergens in latex-sensitized adults. Latex elongation factor Hev b 1 and Hev b 3 are the most relevant allergens in patients with spina bifida [3].

Latex proteins have strong cross-reactivity with several proteins from vegetable grains and fruits, namely banana, avocado, sweet chestnut, mango, kiwi and peach. Pathogenesis-related proteins (PRP) belonging to different groups have been identified as major allergens in fruits cross-reacting with latex. Class I chitinases, identified as major allergens in avocado, chestnut and banana cross-react with Hev b 6 and 11. Inhibition studies have also demonstrated that Hev b 2 and Hev b 12 cross-react with other types of PRP explaining latex-fruit syndrome clinical manifestations [4,10,12].

Latex avoidance is the primary treatment for allergic patients. Several guidelines for perioperative procedures are recommended for patient's allergic/sensitized to latex. However, latex is ubiquitous in medical and nonmedical devices

of daily use, making latex-free environment almost unattainable, particularly when considering pediatric population.

An increasing number of studies describe the efficacy of specific immunotherapy (SIT). Different protocols and routes of administration have been used with diverse efficacy and tolerance, mostly in adult patients. We report our initial experience with a sublingual rush protocol in three children allergic to latex.

2. Material and methods

We studied three patients referred to our Pediatric Immunology Unit with immediate clinical manifestations after exposure to latex containing products. Their clinical history is summarized in Table 1.

2.1. Allergological evaluation before immunotherapy

Allergological evaluation was performed in all patients before immunotherapy, including:

a) Skin prick tests (SPT), to:

- a battery of standardized common aeroallergens (*Stallergenes*[®], France);
- two different NRL extracts (500 mg/ml of total protein *Alk-Abelló*[®] S.A., Spain and *Stallergenes*[®], France);
- extracts of fruits frequently implied in latex-fruit syndrome (avocado, banana, chestnut, mango, kiwi and peach) and other fruits/vegetables, according to the individual clinical history (*Stallergenes*[®], France);
- prick-to-prick method with fresh fruits was programmed for evaluating patients with positive clinical history to a specific fruit/vegetable and negative SPT to the standardized extract.

Prick tests were performed with *Stallerpoints*[®] (*Stallergenes*[®], France) on the volar surface of forearm, using histamine hydrochloride (10 mg/ml) and saline solution, as positive and negative controls. Reactions were scored 20 min after puncture and a wheal diameter larger than 3 mm was considered as a positive response.

b) Total IgE and specific IgEs (sIgE):

Laboratory evaluation included serum measurement of total IgE (UniCAP, fluorescent enzyme immunoassay (FEIA);

Table 1
Clinical characteristics of the patients

	Patient 1	Patient 2	Patient 3
Age (year)/gender	12/male	12/male	11/male
Duration of symptoms (year)	6	1	2
Symptoms	Angioedema and upper respiratory difficulty (balloons and latex gloves exposure)	Angioedema and Conjunctivitis (contact with balloons)	Angioedema and urticaria (contact with balloons, latex pens and cirurgical proceedings)
Intolerance to foods cross-reacting with latex	Banana (lips pruritus and angioedema)	None	Kiwi, spinach (abdominal cramp and vomiting)
Other allergies	Atopic eczema/rhinoconjunctivitis	Rhinitis/asthma	None
Past history	One surgery	Three surgeries (first year)	Spina bifida and obtuse feet four surgeries
Family history of atopy	Rhinitis	Rhinitis	Rhinitis and asthma

Pharmacia Diagnostics[®], Sweden) and sIgE (UniCAP - FEIA; *Pharmacia Diagnostics*[®], Sweden) to latex, avocado, banana, chestnut, mango, kiwi and peach. Specific IgEs to other fruits/vegetables were evaluated when mentioned in clinical history even with negative SPT. The results were expressed in KU/L and classes.

In face of the clinical severity of the reactions in these patients, it was decided not to perform provocation tests before desensitization. In all patients, the clinical history clearly suggested latex allergy and sensitization was confirmed by SPT and measurement of sIgE.

2.2. Sublingual rush

SLIT-Latex[®] (ALK-Abello[®] S.A.; Spain), a commercially available NRL extract for sublingual administration was used in this protocol. Methods of production of this extract, including neutralization, semipurification, concentration and biological standardization have been described in [13].

Treatment included five vials containing five different dilutions of NRL extract with glycerolsaline phenol solution (0.4%) as a preservative and human serum albumin (0.04%) in all vials, except for the most concentrated one. All parents gave fully informed written consent before rush.

Desensitization procedure started with a 4 days rush build-up phase, until reaching the maintenance dose (MD). During rush, patients were admitted daily and all doses were administered in a hospital setting with permanent access to completely latex-free resuscitation equipment.

Protein concentration of each vial and the standard treatment schedule, as suggested by the manufacturer, are detailed in Table 2.

Patients were instructed to keep the allergen solution in the mouth for at least 3 min and then to spit the liquid (sublingual-spit technique). During the first 3 days, doses were administered at 15 min intervals. In the fourth day 25 drops of the highest concentration were administered as a single dose. Patients were kept under medical surveillance for 3 h after the administration of the last dose, with monitoring of vital signs.

Adverse reactions were classified as local or systemic, according to the European Academy of Allergy and Clinical

Immunology [14]. Local reactions to sublingual SIT have not been officially classified up to now. Symptoms affecting the tongue, lips, and/or mouth as well as itching and reddening of the eyes and gastrointestinal complaints were classified as local reactions.

An individual schedule adjustment was considered in face of adverse reactions.

2.3. Maintenance phase

After the build-up phase, patients were instructed to pursue at home with a MD of five drops (100 µg NRL) three times a week or two drops (40 µg NRL) daily of the vial 5 solution. MD was also adjusted individually in case of adverse reactions during the build-up phase. In order to guarantee the safety of our protocol at home, it was established that the last dose during the rush period should be at least equivalent to 1 week's full dose during maintenance phase.

Patients were asked to contact the medical team in case of adverse reactions and instructed on their immediate treatment at home or in the hospital, if serious reactions occurred.

2.4. Immunotherapy follow-up

Clinical and allergological re-evaluation was programmed for 6 months after rush including:

Table 2
Concentration of vials and build-up treatment schedule (SLIT Latex[®], ALK Abello[®], S.A.)

Day	Vial	Vial concentration (mg/mL of NRL proteins)	Number of drops
1	0	5×10^{-8}	1
			10
	1	5×10^{-5}	1
2	2	5×10^{-2}	1
			10
	3	5	1
3	4	500	10
			1
			2
			3
			4
4	4	500	10
			25

- SPT, total IgE and sIgEs to NRL and fruits with cross-reactivity, as previously performed before rush.
- Glove-use and rubbing challenge tests.
- Serum sIgE to a panel of latex recombinant allergens (UniCAP - FEIA; *Pharmacia Diagnostics*[®], Sweden) and Immunoblot to latex (Alablot - DPC[®], Germany), using blood samples collected before rush (T0) and 6 months later (T1), in order to allow a more correct interpretation of the results.

3. Results

3.1. Allergological evaluation

Results of in vivo and in vitro allergological evaluation before rush are summarized in Table 3.

SPT with latex extracts were positive in all subjects. Patient 1 was the only one sensitized to aeroallergens (gramineae). SPT with fruit extracts were positive to banana, avocado, chestnut and kiwi in Patient 1 and to peanut in Patient 3.

Both total IgE and latex sIgE were quite variable. Latex sIgE was positive in all patients, ranging from 7.2 KU/L (Patient 2) to 81.2 KU/L (Patient 3). Specific IgEs were positive to avocado and mango in Patient 1, being negative to all the other tested fruits in the three patients.

3.2. Sublingual rush

Patient 2 completed rush without any adverse reactions.

Patient 1 had daily adverse reactions, motivating successive adaptations to the standard rush schedule. All reactions were local (lip pruritus; epigastric pain/nausea; ocular pruritus, reddening of the eyes and perioral urticariform lesions) and started during the first hour after the last daily dose. Treatment with oral or intravenous antihistamines was sufficient to clinical resolution. Vital signs were always stable during reactions both in Patients 1 and 3.

Fifteen minutes after the fourth day's dose, Patient 3 complained of oropharyngeal discomfort, with no dyspnea or dysphonia, which was promptly treated with oral hydroxyzine and subsided in 1 h. The day after, 15 drops were administered as a single dose with no reaction.

3.3. Maintenance phase

MD was established as 100 µg NRL (five drops of vial 5), three times a week for Patients 2 and 3, undergoing their fifth and second month of treatment, respectively.

Table 3
Allergological evaluation of the patients

	Patient 1	Patient 2	Patient 3
Total IgE (KU/L)	199.0	37.4	171.0
SPT to latex (MWD – mm)	12.5 Histamine 4.5	11 Histamine 4	7 Histamine 4,5
sIgE to latex (KU/L)	80.2 (class 5)	7.2 (class 3)	81.2 (class 5)
Positive SPT to fruits (MWD – mm)	chestnut 6.5; avocado 5.0; banana 3.5; kiwi 3.5	none	peanut 11
Positive sIgE to fruits (KU/L)	Mango 0.95 (class 2) avocado 0.49 (class 1)	none	none

Table 4
SPT and sIgEs before rush (T0) and 6 months later (T1) in Patient 1

	T0			T1		
	SPT (MWD – mm)	sIgEs KU/L	Class	SPT (MWD – mm)	sIgEs KU/L	Class
Histamine	4.5			6		
Latex	12.5	80.2	5	5.5	24.9	4
Avocado	5	0.49	1	< 3	0.58	1
Mango	< 3	0.95	2	< 3	< 0.35	0
Banana	3.5	< 0.35	0	< 3	< 0.35	0
Kiwi	3.5	< 0.35	0	< 3	< 0.35	0
Chestnut	6.5	< 0.35	0	8.5	< 0.35	0
Peach	< 3	< 0.35	0	< 3	< 0.35	0

In Patient 1, owing to difficulty in dose progression, it was not possible to achieve the standard MD and we decided to establish MD as 20 µg NRL (one drop of vial 5) every day.

There have been no adverse reactions.

3.4. Immunotherapy follow-up

Patient 1 has recently completed 6 months of maintenance treatment. Maintaining strict avoidance of NRL products, banana and other fruits he is sensitized to, he reports no further clinical manifestations. SPT to latex and fruits 6 months after rush revealed significant decrease in wheal diameter for latex, banana, avocado and mango with concomitant decrease both in serum sIgE to latex and mango (Table 4) and total IgE (103 KU/L). There was a slight increase in sIgE to avocado (within the same class) and sIgEs to banana, kiwi, peach and chestnut persisted undetectable.

Evaluation of sIgEs to a panel of latex recombinant allergens showed pronounced sensitization to Hev b 5 and Hev b 6.01 major allergens in T0, both decreasing in T1. Serum sIgE to Hev b 6.02 mildly increased from T0 to T1. Serum sIgEs to all other recombinant allergens were not measurable in either T0 or T1 (Table 5).

Immunoblotting study showed a decrease in all detected bands from T0 to T1 maintaining a similar sensitization profile (Fig. 1).

4. Discussion

Avoidance has been pointed as the cornerstone of primary, secondary and tertiary latex allergy prevention and treatment. Alternative materials to latex in gloves, condoms and

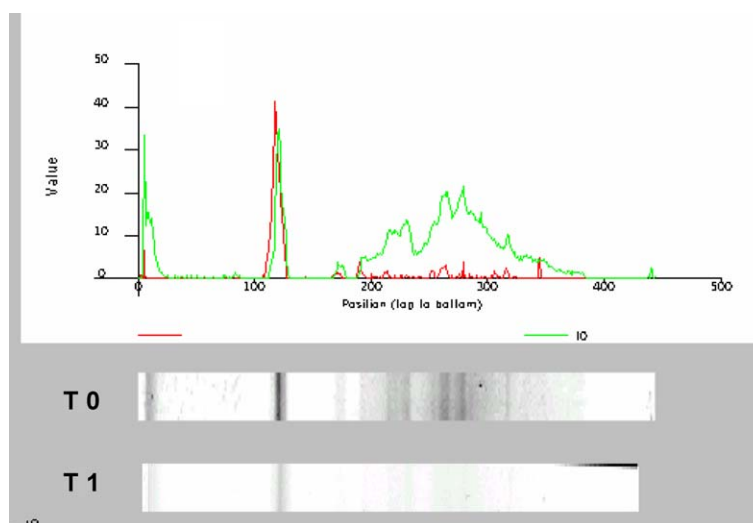


Fig. 1. Immunoblot to latex in T0 and T1 in Patient 1.

Table 5
Specific IgEs to recombinant allergens before rush (T0) and 6 months later (T1) in Patient 1

Recombinant allergen	T0		T1	
	SIgEs		sIgEs	
	KU/L	Class	KU/L	Class
RK 215 (Hev b 1)	< 0.35	0	< 0.35	0
RK 216 (Hev b 2)	< 0.35	0	< 0.35	0
RK 217 (Hev b 3)	< 0.35	0	< 0.35	0
RK 218 (Hev b 5)	52.1	5	14.8	3
RK 219 (Hev b 6.01)	17.5	3	11.1	3
RK 220 (Hev b 6.02)	2.21	2	12.0	3
RK 221 (Hev b 8)	< 0.35	0	< 0.35	0
RK 222 (Hev b 9)	< 0.35	0	< 0.35	0
RK 224 (Hev b 11)	< 0.35	0	< 0.35	0

many other medical and nonmedical devices have been developed. When considering such an ubiquitous material as latex, complete avoidance is extremely difficult to achieve, particularly in children and patients with latex–fruit/vegetables syndrome. Highly sensitized patients may have severe reactions to unexpected contact with latex. Some authors suggest that the severity of these reactions may increase after a long-time avoidance [15]. Avoidance efficacy has also been questioned in many prospective studies showing increasing sensitization in some patients, and in some cases leading to clinical manifestations in previously asymptomatic latex-sensitized patients [16–19]. In latex-sensitized healthcare workers evolution to occupational asthma has been described, even with minimal environmental exposure [20].

Double blind placebo controlled (DBPC) studies support the efficacy of SIT, mainly in respiratory allergy, using different protocols and administration routes.

One report is available in the literature describing an original desensitization exposure protocol involving five patients [21]. All the other papers describe subcutaneous or sublingual SIT protocols. Latex SIT was first reported by Toci et al. [22] in 1998, describing an oral desensitization protocol involving three healthcare workers with occupational rhinitis

and/or asthma. The protocol was considered to be efficient, as assessed by SPT and good tolerance to work re-incorporation.

Leynadier et al. [23] described the first DBPC subcutaneous latex SIT study. This protocol involved 20 patients, including one patient with a previous anaphylactic shock, and included a 2 days rush followed by a maintenance therapy period of 1 year. Although the treatment proved to be effective, it was poorly tolerated, with almost half the patients receiving active treatment for local reactions and four out of nine suffered moderate-to-severe systemic reactions requiring medical treatment.

Pereira et al. [24] described a subcutaneous protocol involving four patients with good efficacy and acceptable tolerance, reporting only one systemic reaction.

Recently, Sastre et al. [25] have described a DBPC study with a subcutaneous cluster schedule with a higher MD than that used by Pereira et al. This group reports frequent systemic reactions, although with less severe clinical manifestations and no cases of anaphylaxis were reported.

The first description of sublingual SIT to latex reported the case of a 23 year-old medical student with contact urticaria, asthma and rhinitis when exposed to latex gloves [26]. The protocol was successful and encouraged the use of this route.

Two different groups have later reported their experience on sublingual latex desensitization in larger series of adult patients [27,28]. Both protocols start with a 4 days rush, with different dose progression, reaching in the last day 500 µg NRL in a single administration, reporting good response to treatment and good tolerance with mild local reactions [28] and low rate of systemic reactions [27].

In our Unit, we have recently started latex desensitization in three children. Latex-fruit/vegetables syndrome was diagnosed in two patients and gramineae sensitization in one, suggesting different profiles of latex sensitization.

The protocol we used demonstrated to be well tolerated and safe, as only mild local reactions, with quick resolution

after antihistamine treatment, were observed during the rush and no adverse reactions have been reported during the maintenance phase.

Some authors suggest a relation between sIgE serum level and type and severity of allergic reactions to latex [1]. In our patients we did not observe a relation between latex sIgE and individual tolerance. Patient 1 had similar sIgE to Patient 3 and was much more difficult to manage during rush phase, presenting with daily adverse reactions.

Cisteró Bahima et al. [27] evaluated the clinical efficacy of a sublingual desensitization protocol 10 weeks after rush, with glove-use and rubbing tests, demonstrating significant improvement of symptom scores after challenge. No change was detected in SPT and no laboratory evaluation was performed. Patriarca et al. [28] showed that after 3 months maintenance treatment, sublingual, cutaneous and mucous challenges were negative in all patients with previously positive challenges. In this study, serum latex sIgE decreased in seven out of 12 patients.

Based in our experience with other allergens desensitization protocols we believe that a longer maintenance period should be considered in order to ensure long-time tolerance, even if earlier evaluations suggest tolerance improvement.

Our first re-evaluation was programmed to 6 months after rush, which at the moment has only been accomplished by Patient 1. The decrease in both skin reactivity and sIgEs to latex and cross-reactive fruits suggest an improvement in the patient's tolerance, although we are aware that these changes do not necessarily correlate with clinical effectiveness. As only half of standard MD had been used in Patient 1, MD was increased to the standard 40 µg NRL/day.

Some studies demonstrated that patients with concomitant pollen and fruit sensitization submitted to pollen SIT may concomitantly improve their respiratory symptoms and tolerance to fruits [29]. Latex SIT protocols may have a similar effect. We do not know if this is the case with our patient, who has strict indication to avoid latex, banana and all the fruits he is sensitized to, and until now did not have any unexpected contact with these.

As different sensitization profiles have been described in latex allergy, major criticism concerning SIT has pointed the possibility of sensitization to new latex allergens when using a universal extract for all patients. Inclusion of the most relevant allergens in each individual extract would improve the efficacy of the immunotherapy and decrease the incidence of adverse reactions [2].

In Patient 1, sIgEs to latex recombinant allergens, revealed sensitization to Hev b 5, Hev b 6.01 and Hev b 6.02, both in T0 and T1. All values decreased in T1 except for Hev b 6.02, strongly suggesting SIT efficacy. All negative sIgEs to other recombinant allergens in T0 remained undetectable in T1.

Although there is an increasing tendency to identify and characterize latex allergens on the basis of their recombinant forms, not all such recombinant proteins have been fully validated against their native counterparts as regards to clinical significance [5]. Recombinant Hev b 5 has been validated

and is one of the most relevant latex major allergen, described in 92% of patients [30]. This was also the higher sensitization in our Patient 1.

Immunoblotting study at T0 and T1 clearly shows the decrease in sensitization induced by SIT. Both the inexistence of new bands in immunoblot and the persistence of the same sensitization profile as detected by the recombinant allergens panel argue against the induction of new sensitizations. Prospective evaluation of our patients and the extension of our series possibly will help to clarify this question.

5. Conclusion

Our initial experience with rush sublingual immunotherapy with latex extract in children has been quite positive considering both the efficacy and safety of this protocol. Known advantages of sublingual desensitization include the possibility of auto-desensitization at home during the maintenance phase, mild side effects and rapid induction of tolerance. On the other side, the rush protocol requires a short day admission for 4 days, and the maintenance efficacy depends on adequate compliance by the patient.

Long-term studies of the clinical efficacy of this treatment are not yet available, but our results suggest that sublingual route may be an excellent alternative, at least in mild to moderate forms of childhood latex allergy. Our promising preliminary results require future studies involving larger series of patients.

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