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CME Review

Who needs penicillin allergy testing?

Eric Macy, MD, MS*; David Vyles, DO, MS†

* Department of Allergy, Southern California Permanente Medical Group, San Diego Medical Center, San Diego, California
† Pediatric Emergency Medicine, Medical College of Wisconsin, Milwaukee, Wisconsin

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Key Messages

- All individuals with an unconfirmed penicillin allergy should have their penicillin allergy evaluated and, if appropriate, tested to confirm current hypersensitivity or tolerance.
- All individuals with a penicillin-associated history of anaphylaxis, rash, gastrointestinal symptoms, headaches, other low-risk symptoms, an unknown history, or a reported family history of penicillin allergy can undergo testing to confirm current tolerance and convince the patient that penicillins can safely be used.
- The reference standard test to confirm current penicillin class antibiotic hypersensitivity or tolerance is an oral challenge with a therapeutic dose, typically 250 mg for adults, and 1 hour of observation to confirm acute tolerance, followed by 5 days of at home follow-up to confirm the absence of clinically significant T-cell–mediated delayed-onset hypersensitivity.
- Low-risk individuals, with penicillin reaction histories that are unlikely to be IgE mediated, can safely go to a direct oral amoxicillin challenge with a therapeutic dose to confirm current tolerance.
- Puncture and intradermal skin testing using only penicilloyl-polylysine, with at least 5 mm of wheal and flare greater than wheal as the criteria for a positive test result, is now sufficient to rule out a high risk of having anaphylaxis during a confirmatory oral amoxicillin challenge.
- Individuals with positive skin test results should not undergo oral challenges and, like individuals with immediately positive oral challenge results, undergo oral penicillin desensitization if they have a documented infection for which a penicillin is the drug of choice.

Instructions

Credit can now be obtained, free for a limited time, by reading the review article and completing all activity components. Please note the instructions listed below:

- Review the target audience, learning objectives and all disclosures.
- Complete the pre-test.
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Reprints: Eric Macy, MD, MS, Department of Allergy, Southern California Permanente Medical Group, San Diego Medical Center, 7060 Clairemont Mesa Blvd, San Diego, CA 92111; E-mail: eric.m.macy@kp.org.

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Overall Purpose

Participants will be able to demonstrate increased knowledge of the clinical treatment of allergy/asthma/immunology and how new information can be applied to their own practices.

Learning Objectives

At the conclusion of this activity, participants should be able to:

- Recognize that all individuals with an unconfirmed penicillin allergy should have their penicillin allergy evaluated, and if appropriate tested to confirm current hypersensitivity or tolerance.
- Recognize that low-risk individuals, with penicillin reaction histories unlikely to be IgE-mediated, can safely go to a direct oral amoxicillin challenge with a therapeutic dose to confirm current tolerance.

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Target Audience

Physicians involved in providing patient care in the field of allergy/asthma/immunology.

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Authors

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CME Inquiries: Contact the American College of Allergy, Asthma & Immunology at education@acaai.org or 847-427-1200.

Introduction

Who needs penicillin allergy testing? It turns out just about everyone with an unconfirmed penicillin allergy in their health record needs to be tested. Physicians and health care professionals strive to "first, to do no harm." At first glance, continued avoidance of penicillin class antibiotics in individuals with a reported penicillin "allergy" noted in their electronic health record (EHR) would seem to be harmless. Obviously, if something happened in the past after taking a penicillin and someone thought it was serious enough to record it, reexposure to a penicillin could only be worse than continued avoidance. However, the opposite is often true. Penicillins often lead to improved outcomes as first-line agents for many infectious disease processes, including dental, skin, and bloodstream infections.[1-8] Choosing Wisely, an initiative of the American Board of Internal Medicine Foundation, recommends, "Don't overuse non −β-lactam antibiotics in patients with a history of penicillin allergy, without an appropriate evaluation."[9-12] However, many patients do not undergo evaluation for their penicillin allergy, and exactly what constitutes an appropriate evaluation has changed during the past decade. In addition, many physicians needlessly avoid cephalosporins in the setting of penicillin allergy, although this also causes more risk than benefit because of poor efficacy or increased adverse effects with alternate antimicrobial therapy and the lack of clinically significant immunologically mediated penicillin-cephalosporin cross-reactivity.[13] The use of quinolones, macrolides, clindamycin, and vancomycin is higher in individuals with unconfirmed penicillin allergies, and these antibiotics are associated with an increased risk of morbidity compared with narrow-spectrum penicillins.[5,14,15] Penicillin allergy testing is currently recognized as an important part of antibiotic stewardship.[16]

Reasons Why Penicillin Hypersensitivity Has Been Higher in the Past

In the past, early penicillin preparations were not very pure, and severe acute reactions were much more common. A recollection of the first successful use of penicillin in a nonmilitary patient in the United States was written by Tager in 1976: "We discussed what to do with the pungent, brown-red powder. We decided to dissolve it in saline and pass it through an E.K. Seitz [asbestos] filter pad to sterilize it."[17] Immunologically mediated sensitization to penicillins is most commonly seen with topical exposures, followed by parenteral exposures, and least likely with oral exposures. Suspected allergic reactions to penicillins were first reviewed in 1946.[18] There had been 47 cases reported in the medical literature by then. They were categorized into 4 classes: allergic hydrarthrosis, urticaria, simulating serum sickness, and anaphylactic shocklike syndrome. All these reactions followed intramuscular injections of penicillin. The frequency of these serious reactions to parenteral penicillin was believed to be between 0.56% and 5.7%, and the lower number was believed to be more likely.[18] It is now known that penicillins left in solution for longer periods, before parenteral administration, result in significantly higher rates of adverse reactions.[19]

Risks of Not Evaluating Individuals With a Penicillin Allergy

There are many risks that come with the avoidance of penicillin when it is reported as an allergy. These risks start with inferior clinical outcomes that can be quantitated. There are more surgical site infections when penicillins are not used when they are the prophylactic antibiotic of choice.[8,20] There are more deaths and inferior outcomes when penicillins are not used in the setting of methicillin-sensitive *Staphylococcus aureus* bacteremia.[3,4] Patients with penicillin allergy spend more time in the hospital, are exposed to significantly more antibiotics associated with *Clostridioides difficile* and vancomycin-resistant enterococci, and have increased hospital use.[15] In addition, many childhood illnesses, including otitis media, streptococcal pharyngitis, and community-acquired pneumonia, require a penicillin as the first-line agent, and the report of a penicillin allergy leads to avoidance and poorer clinical outcomes.[21]

An additional quantifiable risk associated with the report of an unconfirmed penicillin allergy is its economic effect. Patients with reported penicillin allergy spend a greater amount of time hospitalized compared with matched cohorts. These extra days are the main driver of increased overall health care expenditures, which are decreased after negative penicillin allergy test results.[22] We recently reported on 100 children 1 year after their conditions were delabeled as penicillin allergic. The cost savings of delabeling was $1,368.13, the cost avoidance was $1,812.00, and the total potential annual cost savings for a single pediatric emergency department (ED) population was $192,223.00.[23]

Risks Associated With Penicillin Reuse

Most symptoms reported as a penicillin allergy are adverse reactions inconsistent with clinically significant immunologically mediated hypersensitivity as noted in Table 1.[21,24] Every time a penicillin is used, even in individuals with no history of a penicillin allergy, there is a 1% to 2% per course chance of an adverse reaction occurring.[25] Unfortunately, many of these adverse reactions will be classified as a new penicillin allergy. The number of new penicillin allergy reports after each therapeutic penicillin exposure varies, depending on the time after the exposure when the audit for reported intolerance is made, the sex of the patient, and the underlying infection. The new penicillin allergy reporting rate within the year of exposure in unselected individuals without any history of penicillin allergy is 1.45% per course in females and 1.11% per course in males ($P < .001$).[26] In 304 individuals with negative penicillin allergy test results, of whom 139 (45.1%) were exposed to 337 therapeutic courses of penicillins during a 3.6-year follow-up period, there were 10 new penicillin allergies reported (3.0%).[22]

All penicillin allergy testing protocols need to be evaluated by following clinical outcomes during the several years after testing to determine whether patients are reexposed to penicillins when clinically indicated. In addition, the rate of recurrent penicillin-associated reactions and the morbidity associated with the use of non−penicillin class antibiotics should also be noted. The overall change in risk, after negative penicillin allergy test results, can be determined by

Table 1
Penicillin-Associated Adverse Reactions

Clinical presentations	Mechanism (s)	Frequency, %
Headaches, nausea, vomiting, yeast infections, benign rashes, other benign reactions or associations, fear because of family history or other benign reason, unknown	Underlying viral or bacterial infection, pharmacologic effect, adverse effect	93-96
Delayed-onset benign cutaneous reactions (maculopapular rashes)	T cells	3-5
Acute-onset benign cutaneous reactions (urticaria)	IgE	1-2
Acute-onset severe systemic reactions (anaphylaxis)	IgE	<0.1
Delayed-onset severe cutaneous or systemic reactions	T cells, IgG with or without complement	<0.01

following new antibiotic-associated reactions with all therapeutic antibiotic use in the future, along with health care use.[22]

Risk of Penicillin-Associated Anaphylaxis

When patients, or even many heath care professionals, see the word allergy linked to penicillin in the electronic health record, they often envision anaphylaxis with every subsequent penicillin exposure. However, penicillin-associated anaphylaxis is extremely rare. Many reactions coded for anaphylaxis are, in retrospect, not anaphylaxis for a variety of reasons. The code may have been used for another simultaneous exposure, such as a food or venom, unrelated to the penicillin. In addition, there may have been a penicillin-associated reaction, but the clinical course did not meet the case definition for anaphylaxis.

We recently audited penicillin-associated anaphylaxis at Kaiser Permanente Southern California (KPSC) (Eric Macy, unpublished data, June 25, 2018).[27] All penicillin use between January 1, 2009, and December 31, 2017, was identified along with all episodes of anaphylaxis coded the same day as a parenteral penicillin exposure or within 1 day of an oral penicillin exposure. Each case was then manually reviewed in detail to verify the episode was anaphylaxis and was penicillin associated. There were 6,144,422 unique health plan members (mean [SD] age, 34.25 [20.85] years and 52.16% females) who had at least one health care visit during the 8-year study interval. There were 2,115,406 individuals exposed to 4,558,196 courses of oral penicillins and 192,925 individuals exposed to 285,894 courses of parenteral penicillins. There were a total of 37,387,312 patient-years of follow-up. The most frequently used oral penicillins were amoxicillin (3,483,587 [76.42%]), amoxicillin-clavulanate (635,787 [13.95%]), and penicillin (362,565 [7.95%]). The most frequently used parenteral penicillins were piperacillin-tazobactam (117,450 [41.08%]), penicillin G (73,796 [25.81%]), and ampicillin (62,258 [21.78%]). There were 32,133 new penicillin allergy reports (0.66%) within 30 days of a course. Higher rates would be expected if all new penicillin allergy reports up to 1 year after the exposures were collected.[26]

There were 22 patients (1 in 207,191 [0.00048%]) with anaphylaxis associated with oral penicillin exposures. Of the 22 patients, 13 were females; the oral penicillin exposure was amoxicillin in 16 patients, amoxicillin-clavulanate in 4 patients, and dicloxacillin in 2 patients. There were 3 patients (1 in 95,298 [0.00105%]) with anaphylaxis associated with a parenteral penicillin exposure. Of the 3 patients, 1 was female, and the parenteral exposure was ampicillin-sulbactam in 1 patient and piperacillin-tazobactam in 2 patients. Parenteral exposures were more likely to result in anaphylaxis ($P < .001$).

Thus, if approximately 0.5% to 1% of all penicillin exposures result in a new allergy report, less than 1 in 1,000 penicillin allergies are from anaphylaxis. This finding highlights the extremely low current likelihood of anaphylaxis from penicillin exposure, either orally or parenterally. We also know that the risk of causing death with an oral amoxicillin exposure is extremely low because there was only 1 fatality noted after oral amoxicillin and 7 additional deaths associated with parenteral or unknown routes of amoxicillin exposure in more than 100,000,000 amoxicillin courses given in Great Britain during a 35-year period.[28]

Risk of Penicillin-Associated Severe Cutaneous Adverse Reactions

Penicillin-associated severe cutaneous adverse reactions are also extremely rare and much rarer than penicillin-associated anaphylaxis. In a nationwide study from Portugal, covering the years 2009 to 2014, a total of 132 individuals were hospitalized with any diagnosis of Stevens-Johnson syndrome (SJS) or toxic epidermal necrolysis (TEN),[29] corresponding to an annual incidence of 2.03 hospitalizations with SJS/TEN per million inhabitants. There were only 9 cases (6.8%) with any penicillin exposure in the 30 days before SJS/TEN diagnosis. The drug classes associated with a highest number of SJS/TEN episodes per million packages sold were antiviral drugs (8.7 per million packages sold), antineoplastic or immunosuppressive drugs (5.6 per million packages sold), uric acid metabolism drugs (5.0 per million packages sold), and anticonvulsants (1.2 per million packages sold).

There were only 2 cases of penicillin-associated severe cutaneous adverse reactions noted in 37,387,312 patient-years of follow-up in 6,144,422 unique KPSC members between January 1, 2009, and December 31, 2017, exposed to 4,844,090 total courses of penicillins, but both individuals also had co-trimoxazole exposure in the 45 days before diagnosis (Eric Macy, unpublished data, June 25, 2018).

Optimal Penicillin Allergy Testing Protocols Based on Reaction History

Currently available in vitro tests for penicillin specific IgE are not useful because their results do not correlate to oral challenge reactions in average penicillin allergic individuals.[30] They may have some utility when evaluating the rare individual with a recent history of penicillin-associated anaphylaxis.

Previously, the use of skin testing alone was the reference standard for penicillin allergy testing.[31] The need for oral challenges to confirm current penicillin tolerance has also been known for more than 16 years.[32,33] As previously noted, the rate of positive skin test results has been decreasing in the United States during the past 30 years.[34,35]

There is also an increasing realization that many penicillin skin test results are false positives. False-positive penicillin skin test results are more likely if a low threshold, such as a 3-mm wheal, is used to define a positive test result, if high concentrations (> 0.01 mol/L) of reagents other than penicilloyl-polylysine are used, or if reagents are improperly prepared or stored.[29,35-37] Females will have a 3-fold increased risk of having a positive skin test result if a 3-mm wheal is used as the criteria for a positive result, most of these apparently being false positives.[37,38] This sex difference disappeared in the study by Park et al[37] when the data were recalculated using 5 mm of wheal as the criteria for a positive result.

Penicillins can directly activate the RhoA/Rock signaling pathway, which affects endothelial hyperpermeability.[39] Tannert and coworkers[40] recently reported that histamine was only detected in a few positive intracutaneous penicillin skin test results by microdialysis.

More recently, skin testing followed by an oral amoxicillin challenge has been widely used.[41] The current reference standard test to confirm penicillin tolerance remains an oral challenge with a therapeutic dose, and skin testing is only performed to reduce the risk of serious oral challenge reactions in patients with high-risk histories.

Direct oral amoxicillin challenges are safe and effective in delabeling the conditions of patients who report penicillin allergy in large pediatric and adult studies. Since 2016 there have been 6 large studies, from the United States, Spain, Israel, and Canada, including children and adults, with both immediate and nonimmediate reaction histories, who have been evaluated for penicillin hypersensitivity using direct oral challenges (Table 2).[42-47] In a total of 3299 individuals with low-risk penicillin allergies evaluated with direct oral challenges, only 42 (1.3%; 95% CI, 0.9%-1.7%) had immediate-onset positive results and 130 (3.9%; 95% CI, 3.3%-4.7%) had delayed-onset positive results. Subjective reactions were more common than objective reactions.

At the KPSC in San Diego, California, from January 1, 2017, to March 30, 2018, during the time we used a direct 250-mg oral amoxicillin challenge on 519 children and adults with low-risk penicillin-associated reaction histories (Table 2), we used skin

Table 2
Direct Oral Amoxicillin Challenges

Reaction history	No. of patients	Age groups	Country	Challenge protocol (dose)	Immediate-onset positive result, N (%)	Delayed-onset positive result, N (%)	Skin testing results, No. (%)
Immediate or delayed onset	818	Children	Canada[42]	1 Day (up to 1.5 g)	17 (2.1)	31 (3.%)	17 (100) immediately positive underwent STs; 16 (94.1) tested negative
Immediate or delayed onset	328	Adults	United States[43]	1 Day (250 mg)	5 (1.5)	0 (0)	Not done (all subsequently tolerated intramuscular benzathine penicillin G)
Immediate or delayed onset	130	Children	Canada[44]	5 Day (45 mg/kg daily)	3 (2.3)	5 (3.8)	Not done
Immediate or delayed onset	155	Children And adults	United States[45]	1 Day (500 mg)	1 (0.6)	3 (1.9)	Not done
Immediate or delayed onset	732	Children	Spain[46]	NA	6 (0.8)	29 (4.0)	33 (94.3) with immediate or delayed positive results underwent STs and specific IgE testing; 30 (90.1) tested negative to both
Delayed onset	617	Children (n = 435) and adults (n = 207)	Israel[47]	1 Day (n = 126) and 5 day (n = 491) (therapeutic dose) (all underwent STs first and were challenged independent of ST result)	9 (1.5)	1 Day: 24 (19.0); 5 day: 30 (6.1)	Immediate positive results (1 ST positive, 7 ST negative, 1 ST indeterminate); 1-day delayed positive results (1 ST positive, 13 ST negative, 10 ST indeterminate); 5-day delayed positive results (0 ST positive, 20 ST negative, 10 ST indeterminate); negative results (19 ST positive, 301 ST negative, 141 ST indeterminate)
Immediate or delayed onset	519	Children and adults	United States (personal report)	1 Day (250 mg)	1 (0.2)	8 (1.6)	Not done
Total	3299	NA	NA	NA	42 (1.3; 95% CI, 0.9–1.7)	130 (3.9; 95% CI, 3.3–4.7)	NA

Abbreviation: CI, confidence interval; NA, not applicable; ST, skin test.

testing, only with commercially available penicilloyl-polylysine, first in an additional 291 adults and children with higher-risk histories. Only 5 (1.7%) had positive skin test results. An additional 5 (1.7%) had an short-term objective oral challenge reaction after negative skin testing results. There were no delayed-onset oral challenge reactions in the group who underwent skin tests first.

In patients who report penicillin-associated reaction histories considered to be low risk, a direct oral challenge currently appears to be the optimal strategy. A 2-dose challenge does not confer any significant safety advantage and takes longer but may be required for reimbursement in certain settings.[48]

Evaluation Locations

Individuals seen in all health care settings can be evaluated for current penicillin tolerance, including the hospital, intensive care units, EDs, and outpatient clinics and during preoperative evaluations. Recent studies have found that the ED is a safe and effective place to perform penicillin allergy delabeling. We tested 100 children in our ED who reported low-risk histories between April 1, 2015, and November 10, 2016, and no patients tested positive for penicillin allergy.[49] In addition, multiple adult studies have proven the utility of ED penicillin allergy testing, with most patients tolerating testing without any significant adverse reactions.[50,51] There may be an advantage to performing real-time penicillin allergy delabeling in patients who present to the ED because factors, such as cost, insurance, and time, may limit a patient's ability to go to an allergy clinic for testing. The ED is also an opportune place to perform direct oral amoxicillin challenges because of ED staff members know how to recognize and treat anaphylaxis if it were to occur.[52]

Current Penicillin Hypersensitivity Testing Recommendations

Our current penicillin hypersensitivity testing recommendations are outlined in Figure 1.

Higher-risk patients may benefit from puncture and intradermal skin testing with penicilloyl-polylysine, using a 5-mm wheal and flare greater than wheal as the criteria for a positive test result. If skin test results are negative, an oral challenge is still needed to confirm current tolerance.

Use of other noncommercially available skin test reagents for penicillin skin testing results in an increased number of false-positive results and no improvement in overall safety. Currently, recommendation of the routine use of native penicillin or minor determinants, such as penilloate or penicilloate, inhibits all testing because of the difficulty of obtaining these unstable reagents and properly preparing and storing them.[36] We have previously calculated that only using penicilloyl-polylysine, instead of what we have previously published as a complete panel of penicillin skin testing reagents, including native penicillin, penilloate, penicilloate, and amoxicillin, might result in one additional challenge reaction for every 3,375 individuals skin tested but with a marked increase in the number of false-positive skin test results.[11]

Resensitization Risk

Resensitization or new sensitization after a negative penicillin allergy test result is very rare.[53] Solensky and colleagues[54] noted no resensitization in a group of 40 individuals exposed to multiple courses of penicillins. New reactions will be reported after approximately 3% of all subsequent therapeutic penicillin exposures, but resensitization or new immunologically mediated sensitization will occur in less than 5% of these cases.[22,53]

Direct oral amoxicillin challenge can be safely performed in any patients with a history of any of the following penicillin-associated symptoms occurring more than 12 months ago:

- Any benign rash
- Gastrointestinal symptoms
- Headaches
- Other benign somatic symptoms
- Unknown history

Consider penicillin skin testing first if

- The penicillin-associated reaction occurred within the past 12 months
- The patient has any history of shortness of breath or anaphylaxis associated with penicillin
- The patient or treating physician is wary of a direct oral challenge

Proceed to amoxicillin challenge only if skin test result is negative

Figure 1. Recommendations for penicillin hypersensitivity testing.

Desensitization

Individuals with positive skin test results should not undergo oral challenges and, like individuals with immediately positive oral challenge results, should undergo oral penicillin desensitization if they have a documented infection for which a penicillin is the drug of choice.[55] Desensitizations can be safely performed in individuals with oral challenge–confirmed IgE-mediated penicillin allergy who need a penicillin class antibiotic for a future life-threatening infection. If a person has an acute oral challenge reaction to a therapeutic dose, when stabilized, he/she is essentially acutely desensitized, just as if he/she had undergone a 12-step desensitization procedure. If a penicillin class antibiotic is urgently needed, it can be administered immediately and continuously, just as in any desensitized patient. If more than 5 half-lives intervene between penicillin doses, they must again be desensitized. Oral penicillin desensitization should always be performed before any parenteral penicillin exposures.[56] Oral desensitizations can be performed via nasal gastric tube if needed.

Desensitization is not possible in individuals with T-cell–mediated delayed-onset hypersensitivity. It may be possible to treat through mild T-cell–mediated rashes.

Penicillin-Cephalosporin Cross-Reactivity

The existence of clinically significant immunologically mediated penicillin-cephalosporin cross-reactivity has been a theoretical concern since the 1960s because of similarities between β-lactam structures. We now know that clinically significant immunologically mediated penicillin-cephalosporin cross-reactivity, if it even exists at all, is extremely rare. This concern is now based mainly on immunochemistry or skin test data derived from individuals with β-lactam –associated IgE-mediated anaphylaxis and population-based clinical data showing an increased risk using β-lactams that share side chains are lacking.[13,57,58] It may still not unreasonable to avoid using a β-lactam with a shared side chain in an individual with proven IgE-mediated β-lactam–associated anaphylaxis, such as ceftriaxone in a person with cefepime anaphylaxis or cefotaxime in a person with cefuroxime anaphylaxis. However, in individuals with a history of only benign reactions, such avoidance is not necessary.[57] The risk of avoiding a needed β-lactam, when it is the drug of choice, generally outweighs the extremely low risk of immunologic cross-reactivity.[59] Concern that cephalosporin use in the setting of a penicillin allergy will result in an adverse legal outcome is generally unfounded.[60]

Conclusion

Most patients who report penicillin allergy can tolerate penicillins without having an adverse or hypersensitivity reaction. Unfortunately, most patients do not undergo penicillin allergy, which leads to use of alternative antibiotics that result in increased morbidity. This increased morbidity leads to a significant detrimental economic effect on health care. In patients with negative test results, most recurrent reactions are benign rashes. There is always a fear that an anaphylactic reaction would occur on reexposure to a penicillin; however, multiple studies have found that this is an extremely rare occurrence. Currently, an oral challenge with amoxicillin in patients with low-risk penicillin allergy histories seems to be the optimal method to confirm current tolerance. The ED is one of many appropriate locations for penicillin allergy delabeling.

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