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Should testing be initiated prior to amoxicillin challenge in children?

Short Title: Testing in children with amoxicillin allergy

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Abstract

Amoxicillin is the most common antibiotic prescribed in children with increasing use over time. While up to 10% of children are labeled as amoxicillin allergic, most children can tolerate amoxicillin after allergy evaluation. It is well documented that the label of amoxicillin allergy in children is associated with adverse health outcomes such as antibiotic resistant infections. However, it remains controversial how best to assess children for amoxicillin allergy. While in general it is recommended that skin testing be done prior to drug provocation test in the evaluation of amoxicillin allergy, there is increasing evidence

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that drug provocation testing could be done in lower risk children without skin testing prior.

The goal of this article as a narrative review is to review the strengths and limitations of skin testing prior to drug provocation test in children who have a history of either immediate, or non-immediate, reactions to amoxicillin.

The necessity of ruling out amoxicillin allergy in children

Amoxicillin is the most common antibiotic prescribed internationally in children.¹ Its use is increasing over time and surpassing other beta-lactam antibiotics such as penicillin.¹ The European Surveillance of Antimicrobial Consumption project identified beta-lactam antibiotics as the most commonly prescribed antibiotic class in all 25 European countries, ranging from 31% to 63% of all outpatient antibiotic use, with amoxicillin as the most common beta-lactam antibiotic prescribed.² It is first-line antibiotic therapy for many common childhood infections including acute otitis media, streptococcal pharyngitis, and acute bacterial sinusitis.³

Up to 10% of children in North America and Europe are labeled as amoxicillin allergic.^{4,5} However, approximately 90-99% of children labeled as allergic can tolerate amoxicillin after allergy evaluation.^{4,6,7} This may be largely explained by the common occurrence of viral-induced delayed exanthems and viral urticaria in children, which are often mislabeled as allergic reactions to amoxicillin.⁸ In addition, predictable side effects of amoxicillin, such as gastrointestinal upset, are often labeled as allergic reactions. A study of 818 children with a suspected allergy to amoxicillin found that 94.1% tolerated an oral amoxicillin provocation challenge, thereby ruling out an amoxicillin IgE-mediated allergy.⁹

Even if the child is truly allergic, the natural history of amoxicillin allergy is a very high rate of resolution over time,^{10,11} which may be even higher for amoxicillin than for other beta-lactam antibiotics.¹²

In addition, it has been noted that de-labeling amoxicillin allergy is an important public health goal.¹³ The label of amoxicillin allergy is associated with a multitude of adverse health outcomes. The most pertinent of these may be the prescription of alternative, broader-spectrum antibiotics in its place, increasing the risk of antibiotic-resistant infection, as documented in cross-national studies.¹⁴ While the data is mostly in adult populations, it has been noted that a history of beta-lactam allergy is associated with increased risk of methicillin resistant staphylococcus aureus, vancomycin resistant enterococcus, and clostridium difficile infections.¹⁵ The Centers for Disease Control and Prevention found that in each year in the United States, at least 2 million people become infected with antibiotic resistant bacteria and at least 23,000 people die each year as a direct result of these infections.¹⁶

The use of broader spectrum antibiotics also increases the likelihood of adverse events, including increased duration of hospitalization¹⁷ and higher health care costs.¹⁸ An inpatient evaluation of 252 subjects with beta-lactam antibiotic allergy on their charts found that evaluation (and de-labeling in 90.5% of these patients) prevented 504 inpatient days and 648 outpatient days on alternative antibiotics.¹⁹ In a recent matched cohort study it was demonstrated that penicillin allergy testing reduced health care utilization, outpatient visits, emergency department visits and hospital days.²⁰ It was estimated that evaluation of beta-lactam allergy through skin tests in 146 inpatients (and de-labeling in 145/146 patients) resulted in an annual health care savings (antibiotic alteration and associated drug-costs) of \$82,000.²¹

There have been a number of international initiatives to de-label patients with amoxicillin allergy including through the American Academy of Allergy, Asthma and Immunology²² and the North American Choosing Wisely initiatives.²³ There has also been a surge of studies aiming to de-label beta-lactam allergy, including perioperative programs,^{24,25} pharmacy-led programs,^{26,27} inpatient programs,^{28,29} and Emergency-Department-led programs,³⁰ which have demonstrated resounding success at de-labeling this allergy and improving antibiotic stewardship in both inpatient and outpatient settings.³¹

While there is near universal consensus on the importance, and benefit, of de-labeling amoxicillin allergy in children, there is lack of consensus on the best means of accomplishing this goal. In particular, it remains controversial whether skin testing is required as an initial step prior to a drug provocation test (DPT). The goal of this article is to review the evidence for, and against, skin testing prior to a DPT in the evaluation of amoxicillin allergy, in both immediate and non-immediate reactions in children. This article, in contrast to previous articles on the use of testing in beta-lactam allergy, will focus specifically on amoxicillin instead of more broadly at the beta-lactam class of antibiotics, as it is the most common beta-lactam prescribed in children. In addition, as 5-10% of children with exposure to amoxicillin will develop an exanthem,³² it is the beta-lactam most commonly implicated as a cause of drug allergy in the pediatric population.^{7,10}

Whether to test with a history of an immediate reaction to amoxicillin

Clinical evaluation of immediate reactions to amoxicillin

Clinically, reactions to amoxicillin are often defined as either immediate or non-immediate based on the time interval between administration of amoxicillin and onset of a clinical reaction,^{33,34} although other classification schemes exist with no international

consensus on the preferred terminology. In addition, clinical challenges exist as it is often difficult to determine an exact timeline of reactivity. For the purpose of this review we will use immediate and non-immediate as terminology.

According to most classification systems, immediate reactions occur within one hour after amoxicillin administration and are usually immunoglobulin (Ig)-E mediated.^{9,35–38}

Clinical manifestations include cutaneous symptoms (urticaria, angioedema, erythema), respiratory symptoms (cough, wheeze, shortness of breath), gastrointestinal symptoms (profuse emesis or diarrhea) or a combination of the above clinical manifestations (anaphylaxis).¹¹

Prior to any testing, evaluation of a potential amoxicillin reaction involves taking a detailed clinical history, establishing the symptoms and timing of the reaction in relation to the first dose of amoxicillin, previous and subsequent exposure to amoxicillin, other medications in use at the time, and a screen for reaction risk factors (such as prolonged duration of use, repetitive exposure, and underlying conditions such as cystic fibrosis).³²

Testing for immediate reactions to amoxicillin

If history is consistent with a possible immediate reaction to amoxicillin, multiple guidelines including the American Academy of Allergy, Asthma and Immunology (AAAAI) and the British Society for Allergy and Clinical Immunology (BSACI) recommend skin testing (both epicutaneous and intradermal) as first-line followed by DPT if negative.^{10,32} However, recent guidance endorsed by the AAAAI, Infectious Diseases Society of America (IDSA), and the Society for Healthcare Epidemiology of America (SHEA) notes that in lower-risk individuals DPT could be done without pre-emptive skin testing.³⁹ In general, skin testing is recommended with the major (penicilloylpolylysine;PPL) and minor (penicillin G, penicilloate

and/or penicilloate) determinants as well as ampicillin or amoxicillin.³⁵ There is no commercially available standardized kit that covers all major and minor penicillin determinants although such a kit is currently being tested.⁴⁰

It is worthwhile noting that while history is important, studies suggest that patients' self-reported history has low accuracy for diagnosis of true beta-lactam allergy. For example a recent study of 605 children presenting to the Emergency Room with parent-reported penicillin/amoxicillin allergy found that 76% (95%CI: 72.3-79.7%) of symptoms reported were inconsistent with true drug allergy.⁴¹ As a result, as clinicians we rely on available testing such as skin testing and DPT. To assess the validity of the skin tests prior to DPT it is crucial to discuss the major traits of the confirmatory tests i.e.: sensitivity, specificity, positive and negative predictive values (PPV and NPV). Of note for any diagnostic test, the NPV value will rise as the prevalence of the disease falls.

Two recent pediatric studies by Mill et al and by Ibanez all in North America and in Europe respectively reveal low sensitivity (less than 20%) of skin testing in the assessment of immediate reactions to amoxicillin in children (Table 1).^{9,42} The low sensitivity demonstrates the poor ability of the test to detect true allergy (low true positive test rates among all those who have amoxicillin allergy according to drug challenge) and argues against the use of skin testing prior to DPT. However, there is a low pre-test probability as most children will not have a positive skin test to begin with. It is also possible that the low sensitivity demonstrated by Mill et al may be due to the fact that tests were limited to penicilloyl polylysine (PPL; Pre-Pen, the only skin test reagent ever submitted for Food and Drug Administration (FDA) approval) and penicillin G and did not include amoxicillin or ampicillin (although the negative predictive value of amoxicillin testing is unknown). However, the findings of the Ibanez study reveal that all skin tests for amoxicillin were negative in those

with an immediate reaction to amoxicillin and hence the addition of this test is unlikely to skew the sensitivity estimate substantially.

In addition, there is a low pre-test probability as most children will not have a positive skin test to begin with. More recently it was reported that some of the reactions defined as immediate are actually due to direct mast cell activation through binding of certain antibiotics (antifungal agents, aminoglycosides, and sulfonamides) that have large amounts of tertiary amine and secondary amine groups with easily protonated nitrogen atoms. These antibiotics will cause mast cell degranulation through binding to the human G-protein-coupled receptor (MrgprX2). These reactions are often referred to as pseudo-allergic reactions.⁴³ It was reported that direct pharmacologic interaction between antibiotics including beta lactams and immune receptors/ HLA even in the absence of a hapten can directly stimulate an immune response.⁴⁴ These mechanisms may account for the poor properties of skin tests to detect individuals that will react upon challenge.

An argument in favour of skin testing is its documented high negative predictive value in ruling out beta-lactam allergy in multiple large studies. For example, a prospective multicenter study of penicillin skin testing by Solensky et al using the penicillin kit (containing the major allergenic determinant, a minor determinant mixture and amoxicillin) determined a negative predictive value in 455 adult patients of 97.9% (95%CI: 95.8-99.1%; $P < .0001$).⁴⁰ A prospective study of 500 adults with a history of penicillin allergy evaluated with skin testing to PPL and penicillin G by Macy et al found a low rate of reactivity among those with negative skin testing (0.8%; 95%CI: 0.32-2.03%).⁴⁵ In the Solensky et al study 13.8% of patients had a positive skin test result while in the Macy et al study only 0.8% had a positive skin test result, and DPT results were similar. It is possible some of the positive skin test results in the Solensky et al study were false positives.

However, studies in support of a high NPV with skin testing are predominantly adult studies and have looked at penicillin allergy more broadly instead of amoxicillin allergy more specifically. Immediate reactions to amoxicillin can be directed at the R-group side chain (which would cause negative tests to the major and minor penicillin determinants and positive tests to non-irritating concentration of amoxicillin or ampicillin). The NPV of non-irritating concentrations of amoxicillin/ampicillin is unknown, and there is no consensus regarding the appropriate concentration of these reagents that should be used for testing.³⁵ Given the low prevalence of amoxicillin allergy, if we consider the prevalence to be the probability that a person has the disease before we do the test, a low prevalence simply means that the person we are testing is unlikely to have the disease and therefore, based on this fact alone, a negative test result is likely to be correct.⁴⁶

In addition, the positive predictive value (PPV) of skin testing is poor. For example, a study of 783 children aged 1-14 with symptoms of a reaction to beta-lactam antibiotics (with amoxicillin the most commonly implicated beta-lactam) found the PPV of skin testing in those with a history of an immediate reaction to be only 22.22%, while the PPV of DPT was 55.56%.⁴⁷ Further a more recent pediatric challenging all 732 children (mean age= 6 years) that had skin tests (and specific IgE levels), it was reported that 80% had a false positive skin test and that the positive predictive value (the % of true allergy among those with positive skin test) was only 23%.⁴² The latter again argues against the use of the skin test prior to DPT in the pediatric population. Finally, although a recent systematic review argues that skin tests may have high PPV this study has some major limitations.⁴⁸ The authors indicate they did not include studies reporting low predictive values given their methodologies. In the majority of studies that were assessed the majority of patients with positive skin tests were not included. In one study almost half of the patients challenged did

not have skin tests⁴⁹ while in the second large study included in this review 7 were challenged but mostly with negative skin tests and among 11 with positive tests, 9 were not challenged.⁵⁰ In addition, authors indicate that “Of note systemic reactions occurred also in controls as well as patients with negative skin tests” however, the latter were removed from the analysis. The authors grouped cases with amoxicillin and ceftriaxone together. This strategy is likely to result in selection and/ misclassification bias as these antibiotics have non related side chains and are administered through different routes (oral vs intravenously), the PPV are likely different for these two groups.⁵¹ Finally the review focused on adults rather than children and included cases with non immediate reactions as well as desquamative rashes in which skin tests have a controversial role.⁵² Given the limitations described above, the conclusion does not seem to be supported by the data reviewed and we believe that a more accurate estimate is reported by Ibanez et al.⁴²

Skin testing to beta-lactams is safe in children. Studies have shown predominantly mild to moderate reactions to skin testing in children, although systemic reactions including anaphylaxis have been reported in the adult population.⁵³ A prospective study of 1865 children with suspected beta-lactam allergy found mild to moderate reactions to skin testing in only 0.6% of children,⁵ which is in keeping with other studies noting the safety of this procedure in children.⁵⁴ However, it is an ‘unpleasant’ test in children, and can be ‘not possible to undertake’ in younger children.¹⁰ The reagents are costly, can be difficult to obtain, and have short half-lives once diluted to skin testing concentrations.⁵⁵

In addition, DPT without skin testing has also been shown to be safe in the pediatric population. In the study by Mill et al of 818 children with suspected amoxicillin allergy who were evaluated by graded DPT without pre-emptive skin testing, only 2.1% of patients had an immediate reaction, all of which were mild (urticaria) and resolved within a few hours.⁹ The Ibanez study had revealed similar rates of reactions that were all mild and limited to the skin.⁴² Of note, in the Ibanez et al study severe anaphylaxis (involving hypoxia, hypotension or neurologic compromise) was an exclusion criteria. A prospective study of 155 patients (≥ 7 years of age) with a suspected reaction to penicillins echoed these findings, noting graded DPT to be safe and effective in diagnosing beta-lactam allergy without skin testing (only 2.6% had immediate reactions, of whom all the reactions were mild and self-limiting).⁵⁶

A severe reaction to a DPT would be uncommon as, severe reactions to beta-lactams are more commonly described to intramuscular or intravenous forms of beta-lactams (such as intramuscular penicillin G), and even then are rarely noted in the pediatric population.⁵⁷ Recent studies suggest that the risk of fatality with oral amoxicillin use is extremely rare. The Medicines and Healthcare products Regulatory Agency (MHRA) in the UK MHRA's database that collects data on adverse events to antibiotics reports only one case of fatal anaphylaxis in association with oral amoxicillin between 1972 and 2007 (1 per 100,000,000).⁵⁸ This was in a female adult patient prescribed 250 mg orally four times daily for an unknown indication. The MHRA are not aware of any fatal cases reported with oral dose of amoxicillin in children.⁵⁸

There are some categories of children in whom skin testing may be prudent prior to DPT. These include children with comorbidities which place them at increased risk of anaphylaxis, or could increase anaphylaxis severity, including asthma (especially if severe and/or uncontrolled) and mastocytosis.⁵⁹ Testing prior to DPT may be prudent in children at higher risk, such as children with a history of a life-threatening anaphylactic reaction to amoxicillin (such as angioedema including laryngeal edema, syncope, hypotension or bronchospasm), even if delayed, although this is rare. Testing may also be beneficial if there is hesitancy of parents to proceed with DPT in the absence of skin testing, or in other situations that could increase risk (such as if there is not a tertiary care center in close proximity or if the child has reacted to multiple different beta-lactams). Risk stratification studies have been done showing good success in the evaluation of patients with a label of penicillin allergy (with higher risk having skin testing first, and lower risk proceeding to DPT), although protocols vary between studies.^{60,61}

In general however, given the low rate of true allergy in the pediatric population, the predominantly mild reactions noted on DPT, and the low PPV of skin testing, we believe that DPT without pre-emptive skin testing may be acceptable in the pediatric population with a history of an immediate reaction to amoxicillin, as long as that reaction was limited to the skin (ie the children were lower risk).

To test with a history of a mild non-immediate reaction to amoxicillin

Clinical evaluation of non-immediate reactions to amoxicillin

Non-immediate, or delayed, reactions occur more than an hour after amoxicillin administration, although these reactions typically occur several days after commencing amoxicillin.³² It is thought that these reactions are caused by a delayed T-cell dependent

mechanism.³² A common presentation of a mild non-immediate reaction to amoxicillin is an isolated cutaneous reaction such as a maculopapular exanthem or delayed urticaria/angioedema. Non-immediate cutaneous reactions occur in about 5% of children prescribed amoxicillin.³⁵

Testing for non-immediate reactions to amoxicillin

Guidance is more ambivalent around the role of skin testing prior to DPT in children with a history of non-immediate reactions to amoxicillin. The BSACI has recommended that in children with non-immediate reactions a DPT could be considered without pre-emptive skin testing, although recommended testing sequence is not specified for this scenario in the AAAAI guideline.^{10,35} A recent report from the AAAAI/World Allergy Organization 2018 symposium penicillin and cephalosporin allergy testing working group echoed the findings of the BSACI, reporting that DPT without skin testing could be done in children with non-immediate reactions to amoxicillin.⁶²

Guidance is more supportive of DPT without skin testing in this population as non-immediate exanthems while on amoxicillin in children are rarely reproducible, with less than 7% of children reacting with future courses of amoxicillin.⁵² Reactions, when they occur, tend to be milder than the initial reaction and to our knowledge no severe life-threatening reaction has been recorded in a child with a non-immediate reaction to amoxicillin on re-exposure.

The pathophysiology of these reactions, when present, is not IgE-mediated and hence skin testing would, by definition, be less accurate in diagnosing them. A retrospective review of 80 pediatric patients evaluated for potential beta-lactam allergy noted limited utility to skin testing in the evaluation of low-risk, low-pretest probability patients (such as

those with delayed exanthems).⁶³ A retrospective review of 352 children with a history of a non-immediate reaction to amoxicillin found the sensitivity and specificity of skin testing in diagnosing these reactions to be 8% and 99.7% respectively.⁶⁴ Similarly a sensitivity of less than 9% was reported for intra dermal skin test in a small, pediatric sample.⁶⁵ Analysis by Caubet et al of 14 children with a positive DPT to beta-lactams (of whom 12 had reacted to amoxicillin or amoxicillin-clavulanic acid) and 82 children with negative DPT as controls found that skin testing was positive in only 50% of children with a positive DPT (sensitivity of 50%; specificity 91.5%).⁶⁶ In addition, the DPT has been found to be a safe and effective way of diagnosing non-immediate reactions to amoxicillin in children. A study of children with a non-immediate reaction to aminopenicillin found that among those with a confirmed non-immediate reaction, only 1/20 had a positive skin testing and the remainder (19/20) required a DPT to confirm the diagnosis.⁶⁷ Mill et al's study of 818 children suspected of amoxicillin allergy (in whom the majority had a history of non-immediate reactivity) found the graded DPT to have a specificity of 100.0% (95%CI: 90.9-100.0%), a NPV of 89.1% (95%CI: 77.1-95.5%) and a PPV of 100.0% (95%CI: 86.3-100.0%).⁹ In addition the DPT was safe with both immediate (2.1%) and nonimmediate (3.8%) reactions being mild and self-limiting. As concluded by Caubet et al in their study, DPT without previous skin testing is 'an easy and safe approach that should be considered in every patient developing a benign rash during a beta-lactam treatment.' Attesting for the safety of these reactions are reports suggesting that continuous treatment with the culprit antibiotic despite mild cutaneous reactions is safe.^{68,69}

To test with a history of a severe non-immediate reaction to amoxicillin

Severe non-immediate reactions to amoxicillin include a fixed drug eruption, acute generalized exanthematous pustulosis (AGEP), drug reaction with eosinophilia and systemic symptoms (DRESS), toxic epidermal necrolysis (TEN) and Stevens-Johnson syndrome (SJS).^{32,70,71} The onset of these reactions in general are days to weeks after amoxicillin exposure. Guidelines recommend that for severe non-immediate reactions DPT is contraindicated and avoidance of amoxicillin would be recommended.^{10,35} Intradermal testing may have some role and is being done in Europe and some areas of the United States in particular for the diagnosis of AGEP and DRESS.⁷²

One possible exception to this recommendation may be children with a history of SSLR to amoxicillin (fever, rash, arthralgias/myalgias; in contrast to true serum sickness hepatic and renal involvement is very rare). Mill et al's study found DPT to be safe in children with a history of SSLRs, a finding supported by other longitudinal studies of beta-lactam allergy in children.^{5,9,73} Further studies are required to confirm the safety of this approach prior to a change in guidance.

In addition, patch testing may also have a role in a few of the severe non-immediate reactions including AGEP and DRESS.⁷²

Moving forward

Some controversies remain. It remains unclear whether DPT should be done as single-dose, graded single dose, or five-day DPT. It is recommended the DPT always be done when the child is well to avoid confusing an allergic exanthem with a viral exanthem. The BSACI guideline recommends a 5-day DPT with a full therapeutic dose of amoxicillin as mean time to exanthem after starting amoxicillin is about 4 days.¹⁰ However, Mill et al's study

found a high specificity and PPV with a single graded DPT (10% of therapeutic dose followed by 90% of therapeutic dose 20 minutes later).⁹ In this study the median time between DPT and development of delayed reaction was 12 hours, with 29.0% of children reacting more than 24 hours after the DPT, suggesting that a one-day DPT could detect reactions developing days after treatment. Moreover, in some cases the diagnosis of antibiotic allergy in the context of infection could be challenging as an interaction between a viral infection and antibiotic is suggested to play a role in the development of drug allergy.⁷⁴ Hence, these cases are unlikely to be captured even with long DPT when the child is well.

Finally, ensuring comfort with the use of amoxicillin after de-labeling is of paramount importance, as studies have documented ongoing hesitancy by physicians and patients to use beta-lactam antibiotics if there is a history of a reaction, even if allergy evaluation is negative.^{75,76} Moving forward, however it occurs, de-labeling of amoxicillin allergy remains a pressing public health goal.

Conclusion

Multiple international guidelines recommend skin testing prior to DPT in children with suspected immediate reaction to amoxicillin. Skin testing is safe, and has a high NPV in studies (although largely adult based and not focused specifically on amoxicillin). However, the PPV of skin testing is poor, it is often poorly tolerated in young children, and the rate of true allergy is exceedingly low. As a result, we believe that DPT without skin testing should be considered in children with a history of immediate/non-immediate reactions limited to the skin and not involving vesicular lesions or desquamation. DPT is the gold standard in diagnosing drug allergy, both immediate and nonimmediate, and there remains a 2-5%

baseline risk of any child at any time having a rash with amoxicillin despite previous tolerance.

Given that most reported reactions in children are cutaneous we are confident that this shift of paradigm in the diagnosis strategy will be cost effective. There may be circumstances (such as proximity to a tertiary care facility or parental acceptance) that impact decision making.

The value of such an approach in adults as well as other populations at increased risk (e.g. patients with chronic diseases such as cystic fibrosis) should be assessed in large scale future studies.

Table 1: Strengths and limitations of skin testing prior to DPT

Immediate reaction -Pros	-Recommended by multiple international guidelines -High negative predictive value of skin testing (although studies are predominantly adult studies) -Skin testing is safe
Immediate reaction – Cons	-Low sensitivity of skin testing -Low positive predictive value of skin testing -Skin testing reagents are costly, can be difficult to obtain, and have short half-lives once diluted
Nonimmediate reaction – Pros	-High specificity of skin testing
Nonimmediate reaction - cons	-Guidelines are more ambivalent about the role of skin testing in non-immediate reactions -Low sensitivity of skin testing

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