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Empowering community physicians to remove erroneous labels of childhood penicillin allergy

With adequate training and use of clinical guidelines, nonallergist health care providers can help reduce the consequences of unverified beta-lactam allergy and improve the capacity for allergy evaluation by safely implementing direct oral provocation testing in children at low risk of true allergy.

ABSTRACT: Childhood beta-lactam allergy is frequently reported, but most of the children in these cases can safely tolerate the antibiotics without adverse reaction. This discrepancy may be due to the attribution of viral exanthems and drug-virus interactions to beta-lactam hypersensitivity without reliable evaluation. Erroneous beta-lactam allergy labels confer substantial public health consequences, including longer hospital admissions, higher rates of antimicrobial resistance, and higher health care costs. These preventable outcomes, stemming from the unnecessary withholding of first-line antimicrobial therapy for several common infections, have prompted several large-scale initiatives that promote the widespread evaluation of beta-lactam allergy. Recent studies have generated a shift in the routine evaluation of beta-lactam allergy in a large proportion of children in favor of direct oral challenges that forgo traditional antecedent skin tests. A Canadian Paediatric Society statement from January 2020 recommends using a clinical algorithm to administer a test dose of amoxicillin to children deemed to be at low risk of true allergy, such that family physicians and general pediatricians may safely and reliably evaluate unverified beta-lactam allergy—as long as they are equipped to carefully select patients, interpret clinical findings, and manage adverse reactions, including anaphylaxis. The involvement of nonallergist physicians can dramatically expand the capacity for evaluating childhood beta-lactam allergy, a responsibility that has been shouldered exclusively by pediatric allergists, and subsequently permit the use of first-line antimicrobial therapy in a large group of patients.

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Beta-lactams, particularly penicillins and their derivatives, are among the most commonly prescribed medications for children globally,[1,2] with common indications for the ambulatory, inpatient, and perioperative settings. They are the antibiotics of choice for the treatment of many infectious illnesses due to their low toxicity, targeted spectra of activity, excellent distribution throughout the body, and low cost.[3,4] Acute otitis media, the most common cause of childhood visits to a physician, remains the most frequent indication for beta-lactam prescribing in children.[5] Beta-lactam allergy is commonly misdiagnosed in children, as over 90% of children with this label are able to tolerate the antibiotics upon evaluation.[6-8] Unverified beta-lactam allergy presents a major set of challenges related to patient safety, antimicrobial resistance, and health care costs. We discuss the consequences of unverified beta-lactam allergy, highlight the importance of beta-lactam allergy de-labeling, and make suggestions for confronting this issue.

Erroneous beta-lactam allergy labels in childhood

Drug allergy, a reproducible, immune-mediated response to a pharmaceutical in a sensitized person,[9] represents a minority of adverse drug reactions to beta-lactams.[10] Adverse drug reactions to beta-lactams are common in children, with maculopapular exanthems occurring in 5% to 10% of children prescribed amoxicillin or ampicillin.[9]

Pediatric beta-lactam allergy labels are frequently acquired due to rashes that are reported by parents.[10] Viruses are the most common cause of childhood maculopapular or urticarial eruptions **[Figure 1]**.[2] A Swiss study involving 88 children with nonimmediate cutaneous eruptions after beta-lactam exposure revealed,

after a complete evaluation, that only 7% were allergic to the antibiotics.[2] A drug-viral interaction can result in a cutaneous reaction that is misattributed to drug allergy,[10] an example being aminopenicillin-induced exanthema in children with Epstein-Barr virus infection.[2] Other signs and symptoms of illness, such as cough and tachypnea, or coincidental events unrelated to illness, such as headache, can also be mislabeled as an allergic reaction.[11] Predictable side effects of beta-lactams, such as gastrointestinal upset, may be misattributed to drug allergy **[Table 1]**.[11]

Despite the unverified status of most beta-lactam allergy labels, this diagnosis often persists into adulthood because many clinicians—fearing a severe allergic reaction—elect to use alternative antibiotics, often without referral for evaluation.[2] Individuals frequently outgrow true penicillin allergy through the loss of IgE-mediated sensitivity over time,[12,13] which highlights the importance of reassessment.

Consequences of erroneous beta-lactam allergy labeling

Mislabeling of beta-lactam allergy is associated with significant public health concerns, including health consequences to patients, antimicrobial resistance, and higher health costs.[3,9,14,15] Direct consequences to patients include the needless reliance on second-line, more toxic, broader spectrum antibiotics such as fluoroquinolones, clindamycin, and vancomycin;[14] higher rates of multiple and parenteral antimicrobial therapy;[14] and increased hospitalization.[14] A cohort study involving 51 582 participants revealed that patients with unverified penicillin allergy had nearly 10% longer stays in hospital and were 14.1% to 30.1% more likely to suffer from *Clostridium difficile*, methicillin-resistant *Staphylococcus aureus*, and vancomycin-resistant *Enterococcus* infections versus matched controls.[14] Alternative antibiotics tend to be more costly than penicillin derivatives[3,16] and place patients at risk of adverse events.[17]

More widespread and routine evaluation of unverified beta-lactam allergy has become a major public health goal and is recognized as an essential component of antimicrobial stewardship,[18] which is reflected in recent Canadian Paediatric Society statements,[19,20] in American

FIGURE 1. Viral exanthem in a child. Source: DermNet NZ (Creative Commons Licence: https://creativecommons.org/licenses/by-nc-nd/3.0/nz/legalcode).[40]

TABLE 1. Classification of drug allergy as it pertains to beta-lactams.

Gell-Coombs classification	Timing of onset	Clinical presentation	Comments
Type I (IgE-mediated)	Immediate: < 1 hour	Urticaria, angioedema, respiratory distress, hypotension, anaphylaxis	Penicillin is the most common cause of medication-induced anaphylaxis;[30] however, the incidence of anaphylaxis to beta-lactams is reported to be < 1%.[35]
Type II (cytotoxic)	Nonimmediate: 10 hours to weeks	Anemia, thrombocytopenia	
Type III (immune-complex mediated)	Nonimmediate: 1–3 weeks	Serum sickness, tissue injury	Beta-lactam antibiotics, particularly cefaclor, have been implicated in serum sickness-like reactions,[36] which present with fever, rash, and urticaria; however, unlike serum sickness, they do not involve immune complexes, vasculitis, or renal lesions.[37]
Type IV (cell-mediated)	Nonimmediate: 2–14 days	Mild cutaneous: Maculopapular exanthema Severe/systemic: Stevens-Johnson syndrome, toxic epidermal necrolysis, drug rash with eosinophilia and systemic symptoms (DRESS) syndrome, acute generalized exanthematous pustulosis	Nonimmediate reactions are the most common reactions to beta-lactams in children. They occur in 5%–10% of patients taking beta-lactams,[9] and typically present as mild, self-limited maculopapular or urticarial exanthemas;[31] however, most of these reactions are attributed to an infectious cause, while the remainder are thought to be cell-mediated.[9]

and Canadian Choosing Wisely initiatives,[21,22] and most notably in the Obama administration's National Action Plan for Combating Antibiotic-Resistance Bacteria.[23]

Economic projections have produced compelling data on the increased costs associated with erroneous beta-lactam allergy. In reviewing inpatient charts, an antimicrobial stewardship program at a US tertiary hospital estimated an annual savings of US$82 000 from the de-labeling of unverified penicillin allergy in just 145 patients, accounted for by obviating several unnecessary measures, including intravenous therapy where oral beta-lactams were deemed superior, PICC line insertion/removal, routine drug-level testing, laboratory costs, and pharmaceutical drug calibration costs.[15] Further, a case-control study of 118 randomly selected inpatients with unverified penicillin allergy, and the same number of matched controls, revealed a 63% greater mean cost of treatment in the penicillin-allergic group.[3]

Evaluation of beta-lactam allergy in children

The conventional evaluation of penicillin allergy incorporates clinical history with confirmatory testing, including skin testing and oral provocation challenge in skin test-negative individuals.[12] Traditionally, diagnostic pathways for children have been extrapolated from adult guidelines, under the assumption that general principles are applicable across age groups.[24] However, growing evidence over the past decade has influenced a shift in routine practice, which supports the use of direct—that is, without antecedent skin testing—oral challenges to beta-lactams in children with mild index reactions to the antibiotics.[2,6,7,25-29]

Skin testing

Despite longstanding use of tests adjunctive to oral challenges in the evaluation of adult penicillin allergy, the diagnostic utility of such tests is not well established in the pediatric population.[2,27] A recent systematic review revealed a lack of rigorous evidence to support the use of specific IgE determination, intradermal testing, or skin prick testing for evaluating pediatric beta-lactam allergy.[27] In comparing clinical pathways against oral testing, Caubet and colleagues demonstrated the limited sensitivity of specific IgE (0%), intradermal testing (67%), and patch testing (0%) in 88 children with histories of mild cutaneous reactions to beta-lactams.[2] International guidelines recommend skin testing as first-line investigations for penicillin allergy[9,13] by virtue of its low risk[11] and negative predictive value of nearly 100% with standardized reagents in adults;[30] however, recent studies suggest a substantial false-negative rate in the pediatric population. A Canadian study revealed that 94% of children with observed immediate reactions to an oral amoxicillin challenge had negative intradermal testing.[7] The positive predictive value of skin testing in the evaluation of pediatric beta-lactam allergy is reported as 36%,[2] indicating a tendency to "overcall" beta-lactam allergy when a positive skin test is deemed sufficient for diagnosis. Aside from bearing diagnostic ambiguity, skin testing is time- and resource-consuming, causes discomfort, and is exclusively performed by allergists, who have limited capacity for the increasing demand for beta-lactam allergy evaluation.

Beta-lactam allergy is commonly misdiagnosed in children, as over 90% of children with this label are able to tolerate the antibiotics upon evaluation.

Oral provocation testing

Oral provocation testing, the accepted gold standard for evaluation of suspected beta-lactam allergy,[1,7,20] is relied upon for the confirmation or exclusion of allergy in carefully selected individuals.[7] However, there is no international consensus on how direct oral challenges are best conducted. Investigations have employed a variety of methods ranging from single dose[2] to graded dosing regimens[7,25,28,29,31] in a single day[8] or with an extended course.[25,29,31] Amoxicillin is the recommended beta-lactam for oral challenge[14,20] because it contains the immunologically relevant penicillin core structure.[14] Individuals with histories consistent with anaphylaxis or severe delayed reactions are considered to be at high risk of true allergy and are not suitable candidates for direct oral provocation testing.[9,20] Given the limited role of adjunctive testing in pediatrics, direct oral provocation testing appears to be more reliable[20,27] in evaluating nonserious pediatric beta-lactam allergy than conventional clinical pathways, with recent evidence demonstrating a specificity of 100.0%, negative predictive value of 89.1%, and positive predictive value of 100.0%.[7]

In recent studies, the safety of direct oral provocation testing for beta-lactams has been demonstrated in children identified as low risk of true allergy.[6,7,25,27-29] A Montreal prospective study involving 818 children with suspected amoxicillin-induced rash with low-risk features employed a direct, graded two-step direct amoxicillin challenge, which revealed tolerance in 94% of participants.[7] Of the remaining 6% of participants, 17 children experienced mild immediate reactions (urticaria), while 31 children developed mild nonimmediate reactions.[7] A Winnipeg chart review of 306 predominantly pediatric patients with suspected beta-lactam allergy demonstrated tolerance to the culprit beta-lactam in 96% of patients via direct oral challenge in low-risk patients or by oral challenge following negative intradermal testing in those patients with vague histories or those suggestive of an IgE-mediated reaction.[6] Of those patients who had positive oral testing, one experienced a possible Type I reaction (acute onset abdominal pain and emesis), while the remainder experienced nonimmediate maculopapular exanthema. A prospective study that used a graded five-step method of direct oral testing with the culprit beta-lactam in 119 children with a history of nonimmediate mild cutaneous reactions, followed by a 5-day, twice-daily extended course demonstrated tolerance in 97% of children, and only mild cutaneous symptoms in the remaining children.[25]

Direct oral challenges can safely[27] preclude diagnostically unhelpful, uncomfortable, time-consuming, and costly skin testing practices in low-risk children. In light of growing evidence that supports direct oral challenges

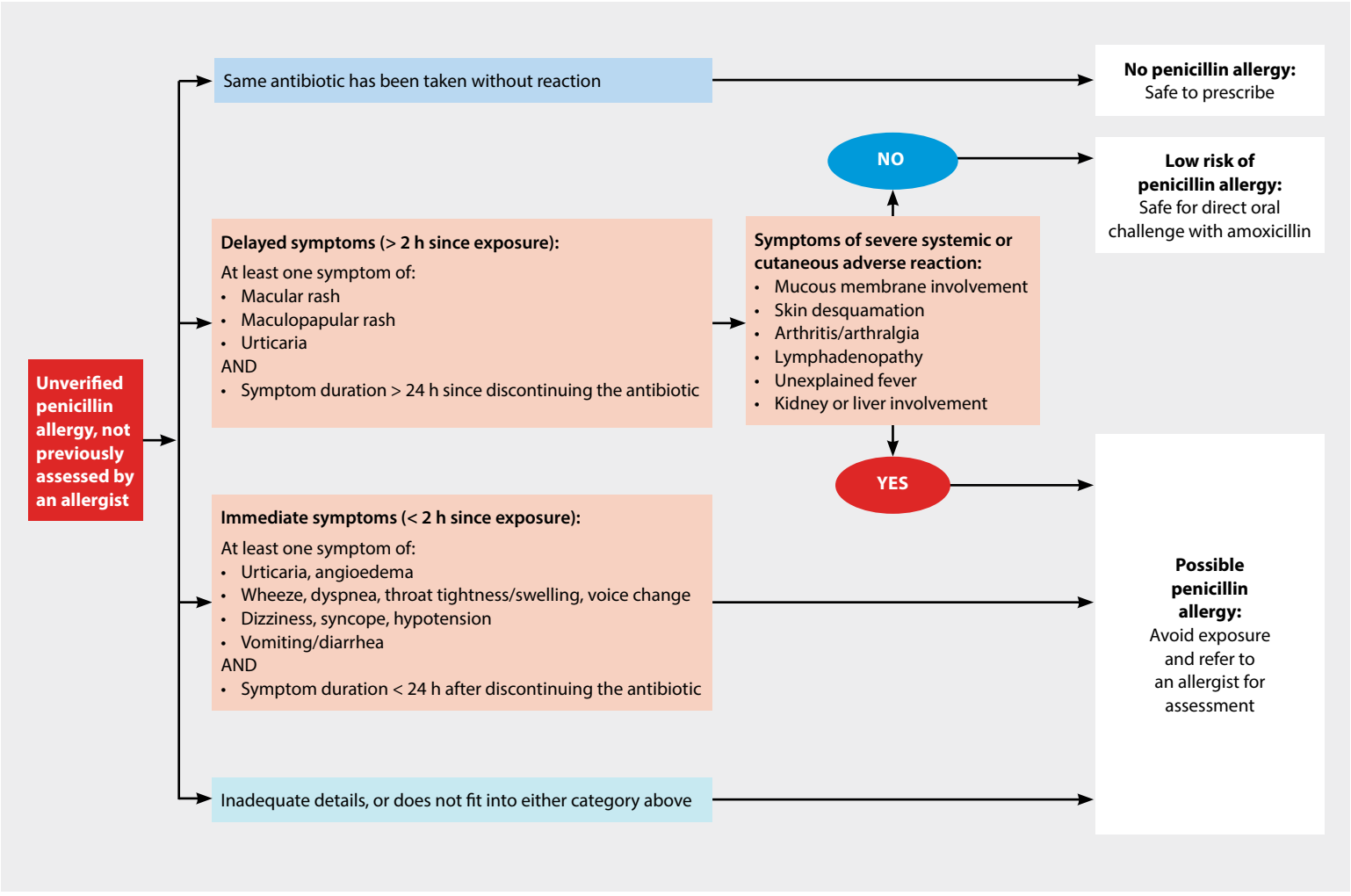

FIGURE 2. Algorithm for identifying pediatric patients at low risk of true penicillin allergy on the basis of history taking (adapted from Wong et al.[20]).

in this group, recent clinical guidelines have recommended direct oral testing in children with histories of mild nonimmediate reactions to beta-lactams.[20,24]

A new CPS Practice Point recommends an approach to the evaluation of suspected beta-lactam allergy in children, and provides guidance on patient selection (with reference to a succinct algorithm **[Figure 2]**), test dosing with amoxicillin, and in-office monitoring.[20] Although the risk of anaphylaxis is remote for carefully selected children, practitioners who perform direct oral challenges must be prepared to manage these life-threatening events. Proximity to a hospital is necessary to optimize successful outcomes in anaphylaxis. Stepwise recommendations for the evaluation of childhood beta-lactam allergy with direct oral challenges, including recommendations for in-office anaphylaxis preparedness, are outlined in **Table 2**.

Future directions

Pediatric allergists have limited capacity to meet the increasing demand for evaluating beta-lactam allergy. Given the high level of safety of direct oral provocation testing in children who are at low risk of true allergy, the burden of evaluating beta-lactam allergy in this group can be eased by the involvement of nonallergist physicians, such as general pediatricians and family physicians. In adhering to the recommendations outlined in the CPS Practice Point,[20] primary care providers can safely and reliably challenge a well-defined group of children to oral amoxicillin in the community, without referral to an allergist. That being said, given the remote but nevertheless important risk of anaphylaxis, it is critical for these physicians to possess the knowledge, training, and experience to select suitable patients, interpret clinical features associated with allergen exposure, and manage severe reactions should they arise in the office setting.[11] Regarding inpatients, one US hospital implemented a novel clinical guideline with associated educational sessions for various inpatient providers, including internal medicine specialists, surgical specialists, nurse practitioners, and physician assistants to aid in the prescription of antibiotics to inpatients with reported beta-lactam allergies.[32] The clinical pathway implemented direct two-step oral test doses for low-risk patients—a procedure that was previously ordered exclusively by

TABLE 2. Steps for evaluating suspected pediatric beta-lactam allergy in the community.

1. Prepare the clinic for anaphylaxis management.	Anaphylaxis protocol: • Clinic staff should be familiar with a printed, highly visible anaphylaxis protocol that has been tailored specifically for the office via input from multidisciplinary team members.[38] • The protocol should include medication dosages, flow sheets for managing respiratory distress and hypotension, and contact information for allied health services (e.g., ambulance, local emergency department).[38]
	In-office anaphylaxis simulation scenarios: • Regular rehearsal of the anaphylaxis protocol is strongly recommended in international guidelines.[39] • Roles for providing treatment, calling emergency services, and conducting treatment logging should be established. • Medical professionals who will be providing treatment should be able to quickly locate and assemble the necessary supplies (e.g., epinephrine, oxygen).
	Ensure certifications for medical professionals are up to date (e.g., Advanced Cardiovascular Life Support, Pediatric Advanced Life Support).
	Assemble an easily accessible, regularly maintained anaphylaxis cart. Essential components: • Injectable aqueous epinephrine (1:1000 solution) with needles and syringes, or epinephrine autoinjector (preferred) Consider including: • Personal protective equipment • Stethoscope • Blood pressure cuffs (pediatric and adult sizes) • Pulse oximeter • Oral second-generation antihistamine • Salbutamol metred-dose inhaler with spacer • Airway adjuncts (e.g., oral or laryngeal mask airway) • Oxygen and equipment for administration • One-way valve face mask with oxygen inlet port • Intravenous fluids and equipment for administration • Automatic electric defibrillator
2. Carefully select patients for direct oral challenge.	Figure 2 provides an algorithm for identifying pediatric patients who are at low risk of true penicillin allergy and are safe for direct oral challenge with amoxicillin.
3. Conduct direct oral challenge.	Low-risk individuals can safely undergo a single test dose of amoxicillin (15 mg/kg, max 500 mg), followed by a 1-hour observation period in the clinic to confirm tolerance.[20] Signs of immediate hypersensitivity should prompt urgent assessment and consideration for initiating the anaphylaxis protocol.
4. Document the outcome.	Medical records (e.g., community, pharmacy, and hospital records) should be updated.

allergists—which resulted in nearly a sevenfold increase in beta-lactam challenges, and thereby improved antimicrobial management with no increase in the rate of adverse drug reactions or consultation with allergy subspecialists.[32] The implementation of antimicrobial stewardship programs across Canadian centres that similarly empower nonallergist physicians to order test doses would improve rates of de-labeling among inpatients, and thereby improve patient safety, mitigate antimicrobial resistance, and reduce health care costs. Although the existing limited evidence of the safety and effectiveness of nonallergist-implemented direct oral challenges in children appears encouraging, further research is required.

Education for health care providers, patients, and families is critical in mitigating the ongoing misdiagnosis of beta-lactam allergy. Understanding drug hypersensitivity and how it differs from nonimmunological adverse drug reactions, how to interpret and accurately document index events, and how to properly obtain a drug allergy history will reduce erroneous allergy labels and prompt appropriate referrals.[10] Counseling for patients and their families on the implications of drug allergy test results, along with appropriate discharge paperwork and dissemination of results (e.g., pharmacy, primary care provider), are necessary components of the de-labeling process.[33] A Montreal study revealed that 18% of parents refused penicillins for their children despite negative skin testing and drug challenge within the past 4 years.[34] In following up with 88 families with children who had tolerated oral challenges to beta-lactams 1 year previously, Vyles and colleagues found that 52% of children retained a beta-lactam allergy label on their primary care provider's electronic medical record, while 28% of parents reported being less than "comfortable" with their children receiving beta-lactam antibiotics, mostly for fear of an allergic reaction.[33] De-labeling strategies must aim to provide succinct, clear messages to patients and their families to avoid erroneous re-labeling of drug allergy.

Summary

Unverified beta-lactam allergy in children is a major public health issue, conferring direct patient harm, administrative burdens for hospitals, and health care overspending as the result of the needless withholding of first-line treatment for a large group of patients. This has led to initiatives to encourage the widespread evaluation of patients with unverified beta-lactam allergy. Direct oral challenges are safe in a well-defined group of children comprising most cases of unverified beta-lactam allergy, which obviates the requirement for time- and resource-consuming—not to mention painful—antecedent skin testing in this group. With adequate training and use of clinical guidelines, nonallergist health care providers can safely implement direct oral challenges in low-risk patients and thereby improve capacity for beta-lactam allergy evaluation. This will permit the use of first-line antimicrobial therapy in a large group of patients, and subsequently improve patient safety, reduce contributions to antimicrobial resistance, and improve health care costs. ■

Competing interests
None declared.

References

1. Abrams EM, Atkinson AR, Wong T, Ben-Shoshan, M. The importance of delabeling β-lactam allergy in children. J Pediatr 2019;204:291-297.
2. Caubet J-C, Kaiser L, Lemaître B, et al. The role of penicillin in benign skin rashes in childhood: A prospective study based on drug rechallenge. J Allergy Clin Immunol 2011;127:218-222.
3. Sade K, Holtzer I, Levo Y, Kivity, S. The economic burden of antibiotic treatment of penicillin-allergic patients in internal medicine wards of a general tertiary care hospital. Clin Exp Allergy 2003;33:501-506.
4. Wright AJ. The penicillins. Mayo Clin Proc 1999;74: 290-307.
5. Vergison A, Dagan R, Arguedas A, et al. Otitis media and its consequences: Beyond the earache. Lancet Infect Dis 2010;10:195-203.
6. Abrams EM, Wakeman A, Gerstner TV, et al. Prevalence of beta-lactam allergy: A retrospective chart review of drug allergy assessment in a predominantly pediatric population. Allergy Asthma Clin Immunol 2016;12:4-9. https://doi.org/10.1186/s13223-016-0165-6
7. Mill C, Primeau M-N, Medoff E, et al. Assessing the diagnostic properties of a graded oral provocation challenge for the diagnosis of immediate and non-immediate reactions to amoxicillin in children. JAMA Pediatr 2016;170:e160033.
8. Vyles D, Adams J, Chiu, A, et al. Allergy testing in children with low-risk penicillin allergy symptoms. Pediatrics 2017;140;e20170471.
9. Joint Task Force on Practice Parameters; American Academy of Allergy, Asthma and Immunology; American College of Allergy, Asthma and Immunology; Joint Council of Allergy, Asthma and Immunology. Drug allergy: An updated practice parameter. Ann Allergy Asthma Immunol 2010;105:259-273.
10. Norton AE, Konvinse K, Phillips EJ, Broyles, AD. Antibiotic allergy in pediatrics. Pediatrics 2018;141:e20172497.
11. Lang DM, Castells MC, Khan DA, et al. Penicillin Allergy in Antibiotic Resistance Workgroup. Penicillin allergy testing should be performed routinely in patients with self-reported penicillin allergy. J Allergy Clin Immunol Pract 2017;5:333-334.
12. Solensky R. Allergy to β-lactam antibiotics. J Allergy Clin Immunol 2012;130:1442-2.e5. https://doi.org/10.1016/j.jaci.2012.08.021
13. Khan DA, Solensky R. Drug allergy. J Allergy Clin Immunol 2010;125:126-137.
14. Macy E, Contreras R. Health care use and serious infection prevalence associated with penicillin "allergy" in hospitalized patients: A cohort study. J Allergy Clin Immunol 2014;133:790-796.
15. Rimawi RH, Cook PP, Gooch M, et al. The impact of penicillin skin testing on clinical practice and antimicrobial stewardship. J Hosp Med 2013;8:341-345.
16. Solensky R. Penicillin allergy as a public health measure. J Allergy Clin Immunol 2014;133:797-798.
17. Xie H, Chen H, Hu Y, et al. Clindamycin-induced acute kidney injury: Large biopsy case series. Am J Nephrol 2013;38:179-183.
18. Iammatteo M, Alvarez Arango S, Ferastraoaru D, et al. Safety and outcomes of oral graded challenges to amoxicillin without prior skin testing. J Allergy Clin Immunol Pract 2019;7:236-243.
19. Le Saux N. Position statement: Antimicrobial stewardship in daily practice: Managing an important resource. Canadian Paediatric Society; 2020. www.cps.ca/documents/position/antimicrobial-stewardship.
20. Wong T, Atkinson A, t'Jong G, et al. Practice point: Beta-lactam allergy in the paediatric population. Canadian Paediatric Society; 2020. www.cps.ca/documents/position/beta-lactam-allergy.

Primary care providers can safely and reliably challenge a well-defined group of children to oral amoxicillin in the community, without referral to an allergist.

21. Choosing Wisely Canada. Infectious disease. Five things physicians and patients should question in infectious disease. Accessed 1 June 2020. https://choosingwisely canada.org/infectious-disease.
22. Choosing Wisely. American Academy of Allergy, Asthma & Immunology: Ten things physicians and patients should question. Accessed 1 June 2020. www.choosingwisely.org/societies/american-academy-of-allergy-asthma-immunology.
23. White House Office of the Press Secretary. National Action Plan for combating antibiotic-resistant bacteria. March 2015. Accessed 1 June 2020. www.cdc.gov/drugresistance/pdf/national_action_plan_for_combating_antibotic-resistant_bacteria.pdf.
24. Gomes ER, Brockow K, Kuyucu S, et al. Drug hypersensitivity in children: Report from the pediatric task force of the EAACI Drug Allergy Interest Group. Allergy 2016;71:149-161.
25. Vezir E, Misirlioglu ED, Civelek E, et al. Direct oral provocation tests in non-immediate mild cutaneous reactions related to beta-lactam antibiotics. Pediatr Allergy Immunol 2016;27:50-54.
26. Arnold A, Sommerfield A, Ramgolam A, et al. The role of skin testing and extended antibiotic courses in assessment of children with penicillin allergy: An Australian experience. J Paediatr Child Health 2019;55:428-432.
27. Marrs T, Fox AT, Lack G, du Toit G. The diagnosis and management of antibiotic allergy in children: Systematic review to inform a contemporary approach. Arch Dis Child 2015;100:583-588.
28. Mattheij M, de Vries E. A suspicion of antibiotic allergy in children is often incorrect. J Allergy Clin Immunol 2012;129:583.
29. Chambel M, Martins P, Silva I, et al. Drug provocation tests to betalactam antibiotics: Experience in a paediatric setting. Allergol Immunopathol 2010;38:300-306.
30. Lieberman P, Nicklas RA, Oppenheimer J, et al. The diagnosis and management of anaphylaxis practice parameter: 2010 update. J Allergy Clin Immunol 2010; 126:477-480.
31. Mori F, Cianferoni A, Barni S, et al. Amoxicillin allergy in children: Five-day drug provocation test in the diagnosis of nonimmediate reactions. J Allergy Clin Immunol Pract 2015;3:375-380.
32. Blumenthal KG, Shenoy ES, Varughese CA, et al. Impact of a clinical guideline for prescribing antibiotics to inpatients reporting penicillin or cephalosporin allergy. Ann Allergy Asthma Immunol 2015;115:294-300.e2.
33. Vyles D, Chiu A, Routes J, et al. Antibiotic use after removal of penicillin allergy label. Pediatrics 2018; 141:e20173466.
34. Picard M, Paradis L, Nguyen M, et al. Outpatient penicillin use after negative skin testing and drug challenge in a pediatric population. Allergy Asthma Proc 2012;33:160-164.
35. Kaufman DW, Kelly, JP. Risk of anaphylaxis in a hospital population in relation to the use of various drugs: An international study. Pharmacoepidemiol Drug Saf 2003;12:195-202.
36. Heckbert SR, Stryker WS, Coltin KL, et al. Serum sickness in children after antibiotic exposure: Estimates of occurrence and morbidity in a health maintenance organization population. Am J Epidemiol 1990;132:336-342.
37. Knowles SR, Uetrecht J, Shear NH. Idiosyncratic drug reactions: The reactive metabolite syndromes. Lancet 2000;356:1587-1591.
38. Wallace DV. Anaphylaxis in the allergist's office: Preparing your office and staff for medical emergencies. Allergy Asthma Proc 2013;34:120-131. https://doi.org/10.1016/j.jaci.2009.10.028
39. Simons FER, Ardusso LRF, Bilò MB, et al. World allergy organization guidelines for the assessment and management of anaphylaxis. World Allergy Organ J 2011;4:13-37.
40. DermNet NZ. Exanthems. Accessed 26 July 2020. https://dermnetnz.org/topics/exanthems.