



Update on penicillin allergy delabeling

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Purpose of review

To review phenotyping and risk classification of penicillin allergy and provide an update on penicillin allergy delabeling strategies for primary care.

Recent findings

Beta-lactams are considered the treatment of choice for a wide range of bacterial pathogens; however, many patients receive second-line agents due to being labeled as having an allergy to penicillin. This approach can lead to antibiotic resistance and inferior health outcomes. While 10% of the population is labeled as penicillin allergic, penicillin anaphylaxis occurs in less than 1% of patients. For patients with delayed benign skin rashes (e.g., urticaria or maculopapular exanthem >1 h after administration) attributable to beta-lactam administration occurring more than 12 months ago, direct oral challenge (rechallenge with antibiotic in the clinical setting) can be a safe and effective strategy, with immediate reactions occurring in less than 5% of such low-risk patients and delayed reactions appearing infrequently. In patients with penicillin-associated immediate urticaria, other IgE-mediated features, or anaphylaxis, further allergy evaluation and penicillin skin testing is warranted. Any severe idiosyncratic cutaneous adverse reaction is rare, but can be dangerous so prompt removal of the inciting agent is required.

Summary

Penicillin allergy delabeling is a high-value service that can be effectively delivered through a multidisciplinary collaborative approach.

Keywords

cost-effectiveness, delabeling, direct oral challenge, high-value care, IgE mediated, overdiagnosis, penicillin allergy, penicillin desensitization, severe cutaneous adverse reaction, skin testing

INTRODUCTION

It has been estimated that 10% of the US population and at least 5 million children carry a penicillin allergy label [1]. While 1–2% of all penicillin administrations will result in an adverse reaction – even in nonallergic individuals – the rate of true penicillin anaphylaxis is low [2[•],3[•],4[•]]. Macy and Vyles [2[•]] recently reported the rate of oral penicillin anaphylaxis in the Kaiser Permanente Southern California System was only 0.00048%. While true drug allergy may account for 20% of fatalities from anaphylaxis [5[•],6], fatalities attributed to oral amoxicillin are rare [5[•],7,8]. Among 100 million individuals exposed to oral amoxicillin in the United Kingdom between 1972 and 2007, only one death associated with anaphylaxis from oral amoxicillin was identified [3[•],9].

The majority of children who carry a penicillin allergy label have been overdiagnosed as a result of a viral exanthem occurring within the course of treatment [1]. However, less than 10% of patients with a penicillin allergy label will have a confirmed allergy by oral challenge [2[•],4[•],10]. With an abundance of caution and directed by *primum non nocere*,

traditional management of mild symptoms reported by patients when using penicillins often involves noting the patient to have a penicillin allergy [11]. However, it has become increasingly clear that unwarranted drug allergy labels cause more harm than good, and are poorly specific [12[•],13[•]]. Modern management of drug allergy has evolved to incorporate an active approach of penicillin allergy delabeling in recognition of the poor specificity of the ‘penicillin allergy’ label [2[•],3[•]]. With a heightened focus on antibiotic stewardship, healthcare

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KEY POINTS

- Penicillin allergy is commonly overdiagnosed and not assertively delabeled.
- Although 10% of the population may carry a penicillin allergy label, the prevalence of penicillin anaphylaxis is less than 1%.
- Penicillin hypersensitivity reactions may be IgE-mediated, benign T-cell mediated, or severe T-cell mediated.
- Clinical features can be used to classify reaction histories as low, medium, and high-risk, which can inform management steps including direct oral challenge, allergist referral for skin testing, avoidance, and/or desensitization.
- Penicillin anaphylaxis should be promptly managed with intramuscular epinephrine.

resources can be leveraged to decrease costs, decrease antibiotic resistance, and improve outcomes through penicillin allergy delabeling [1,3[¶]]. The cost-savings associated with penicillin delabeling in children is significant. From a national perspective, penicillin delabeling could result in cost-savings of \$68–143 million [1,14^{¶¶}]. Macy and Shu [15] found that, after delabeling, patients averaged fewer outpatient and emergency room visits and fewer hospitalizations than controls.

Beta-lactams are considered the treatment of choice for a wide range of bacterial pathogens including Group A and B *Streptococcus*, *Staphylococcus aureus*, *Neisseria gonorrhoeae* and *meningitidis*, *Treponema pallidum*, *Pasteurella multocida*, and others [3[¶]]. Unnecessary avoidance of these first-line agents leads to increased antibiotic resistance of potentially dangerous pathogens such as methicillin-resistant *S. aureus* and vancomycin-resistant *enterococcus*, as well as increasing the risk for *Clostridium difficile* and other hospital-acquired infections [3[¶]]. For example, in one recent study of 8385 patients undergoing 9004 surgical procedures, 11% of patients reported a penicillin allergy and 2.7% experienced a surgical site infection. Notably, patients who reported a penicillin allergy had significantly increased odds of a surgical site infection (adjusted odds ratio 1.51; 95% confidence interval 1.02–2.22) – a risk due to receipt of an alternative perioperative antibiotic [12[¶]].

TYPES OF ADVERSE DRUG REACTIONS

Adverse drug reactions (ADRS) are categorized as Type A or B. Type A reactions account for

approximately 80% of the total, are pharmacologic, dose-dependent, and resolve when the dose is reduced [1,16[¶],17]. Examples of symptoms commonly seen in Type A reactions include nausea, abdominal pain, vomiting, or diarrhea. In contrast, Type B reactions are idiosyncratic and unrelated to the pharmacologic properties of the agent. Drug hypersensitivity reactions are considered Type B reactions and can be evaluated in the classical Gell and Coombs types I, II, III, and IV paradigm of immune hypersensitivity (Table 1) [16[¶],18]. While the Gell and Coombs [17] classification is helpful, not all immunological reactions can be neatly classified into this system. Cutaneous reactions can be broadly described as IgE-mediated, benign T-cell mediated, and severe T-cell mediated (i.e., severe cutaneous adverse reaction or SCAR) [3[¶]]. IgE-mediated reactions have a rapid onset of minutes to hours and include pruritis, with lesions fading in less than 24 h [3[¶]]. Benign T-cell mediated reactions generally evolve over several days, are less pruritic, and are characterized by lesions that last longer than 24 h [3[¶]]. These rashes may be associated with fine desquamation and resolve over days to several weeks [3[¶]]. SCAR develops over days to weeks and may be associated with blistering, desquamation, mucosal and or organ involvement – usually severe enough to require hospitalisation [3[¶]].

Anaphylaxis may predominate as a drug safety concern [5^{¶¶}], but nonimmediate reactions can also cause significant morbidity and mortality. When recognized, anaphylaxis should be immediately treated with epinephrine administered intramuscularly into the anterolateral thigh (0.01 mg/kg to a maximum of 0.3 mg in children and 0.5 mg in adults

Table 1. Adverse drug reactions [16[¶],18]

Type A: Pharmacologic and dose dependent (e.g., nausea, abdominal pain, vomiting, or diarrhea)
Type B: Idiosyncratic and are not related to the pharmacologic properties of the agent. Drug hypersensitivity is considered a Type B reaction and these can be further categorized in the classical Gell and Coombs types classification
Type I: IgE mediated (e.g., anaphylaxis)
Type II: Antibody-mediated cytotoxic reactions (e.g., hemolytic anemia)
Type III: Immune complex-mediated reactions (e.g., serum sickness)
Type IV: Delayed hypersensitivity (e.g., contact dermatitis)

ADRS are categorized as Type A or B. Type A reactions account for approximately 80% of ADRS, are pharmacologic, dose-dependent, and resolve when the dose is reduced. Type B reactions are idiosyncratic and unrelated to the pharmacologic properties of the agent. Drug hypersensitivity reactions are considered Type B reactions and can be evaluated in the classical Gell and Coombs types I, II, III, and IV paradigm of immune hypersensitivity. ADRS, adverse drug reactions.

using the 1 mg/ml solution) [5¹¹,19,20¹¹]. SCAR to drugs are rare [2¹¹] and include Stevens–Johnson Syndrome/Toxic Epidermal Necrosis (TEN). Although beta-lactam agents may cause SCAR [3¹¹], a recent report by Macy and Vyles [2¹¹] reported only two cases of penicillin SCAR in 37 387 312 patient-years of follow-up in 6 144 422 unique Kaiser Permanente Southern California members exposed to 48 44 090 courses of penicillins. The drug rash/reaction with eosinophilia and systemic symptoms (DRESS) syndrome also represents a less common but equally important severe hypersensitivity reaction [21¹¹]. The DRESS syndrome is characterized by rash, elevated peripheral blood eosinophilia, and organ involvement frequently with liver and/or renal injury [21¹¹]. Symptoms may also include fever, lymphadenopathy, interstitial pneumonia, and myocarditis [22]. DRESS syndrome has been associated with reactivation of human herpes virus (HHV) 6, and other reactivated viruses including Epstein-Barr virus, cytomegalovirus, and HHV-7 [23,24]. HHV-6 reactivation has been associated with a more prolonged course of disease [23,25]. In a recent study that identified 69 patients with DRESS syndrome among 3 162 562 patients (prevalence 2.18 per 100 000), 42% of the 69 patients with DRESS syndrome had liver or renal injury with 16% having both [21¹¹]. In 74% of cases, antibiotics were the causative agents identified (i.e., 39% vancomycin, 23% beta-lactams, 4% fluoroquinolones, 4% tetracyclines, and 3% sulfonamides) while anticonvulsants were implicated in 23% of patients [21¹¹]. The median cost of inpatient treatment was \$17 101 per patient [21¹¹].

APPROACH TO PENICILLIN ALLERGY

Most children acquire a penicillin allergy label in early childhood. In a study of 605 patients presenting to a pediatric emergency department with parent-reported penicillin allergy (median age 6 years), 75% were diagnosed before their third birthday [26]. Notably, about three of every four children (76%) had low-risk symptoms, with rash and itching most commonly reported (93% and 41% of subjects, respectively) [26]. Symptom onset within 24 h of medication administration was reported in more than half (55%) of patients [26]. In this study, low-risk symptoms included either nonurticarial or urticarial rash, itching, vomiting, rhinorrhea, cough, headache, and dizziness [26]. It should be noted that some experts consider urticaria or other pruritic rash to shift assessment of risk from low-to-moderate. However, a large Canadian study noted that most urticaria was not reproducible upon drug provocation challenge, which would suggest that

isolated urticaria may be low-risk [3¹¹,10]. Family history has also been classified as a low-risk symptom, even though family history should not be considered a contraindication to penicillin and should never prompt adoption of a penicillin allergy label in a patient who has not received penicillin [26]. In contrast, higher-risk symptoms include facial swelling, difficulty breathing, lip swelling, wheezing, throat swelling, skin peeling, oral involvement, blisters, hemolytic anemia, nephritis, hepatitis, fever, joint pain, or hypotension (Table 2) [26]. Siew *et al.* [27¹¹] recently demonstrated that the absence of anaphylaxis, inability to recall the culprit antibiotic name, and reaction occurring more than

Table 2. Risk and penicillin allergy history [3¹¹,26]

Low or absent risk
Nonurticarial rash
Isolated vomiting
Rhinorrhea
Cough
Headache
Family history
Nonimmediate reactions
Remote unknown reactions without IgE-mediated features
Moderate risk
Urticaria or pruritic rash
Angioedema
Reactions with IgE-mediated features but not anaphylaxis
High risk
Anaphylaxis
Facial swelling
Difficulty breathing
Lip swelling
Wheezing
Throat swelling
Skin peeling
Oral involvement
Blisters
Hemolytic anemia
Hypotension
Arthritis
Hepatitis
Nephritis
Fever
Joint involvement
Eosinophilia
DRESS
SCAR

Examples of low/absent, moderate, and high-risk features penicillin ADRs. ADRS, adverse drug reactions; DRESS, drug rash/reaction with eosinophilia and systemic symptoms; SCAR, severe cutaneous adverse reaction.

1 year ago had nearly the same negative predictive value as skin testing (98.4 vs. 98.9% for type 1 beta lactam allergy). Not surprisingly, when children with low-risk symptoms are skin tested, the overwhelming majority have negative results [28]. In fact, Vyles *et al.* [28] reported that 100% of children with low-risk histories had negative skin tests to penicillin [95% confidence interval (CI), 96.4–100%].

Because the pretest probability of low-risk symptoms in children with a penicillin allergy label is less than 10% [10], it is not surprising that the negative predictive value of skin testing in this setting is exceedingly high. In the cohort reported by Vyles *et al.* [14²²] no child with negative skin test results developed immediate symptoms with penicillin re-introduction. One child (4%) developed a delayed rash 24 h after starting the medication, and no serious adverse reaction occurred [14²²].

Given the low rate of positive testing in patients with low-risk histories, Macy and Vyles [2²²] have suggested omitting penicillin skin testing and proceeding directly to supervised amoxicillin challenge in clinic in patients with low-risk histories (Table 3). Penicillin skin testing is suggested if a reaction occurred in the past 12 months, the patient had any history of shortness of breath or anaphylaxis associated with penicillin use, or the patient or

treating physician is wary of direct oral challenge [2²²]. In patients opting for skin testing, it has been recommended that oral challenge is subsequently pursued only if the skin test result is negative [2²²]. However, in low-risk patients the possibility of false-positive skin testing may be underappreciated [2²²,29].

With a low index of suspicion for IgE-mediated allergy, skin testing is a low-value service, in particular when an IgE-mediated reaction is unlikely to have explained the symptom. For example, Confino-Cohen evaluated adults and children with benign delayed penicillin rashes, identifying a positive skin test in 4.9% and equivocal skin testing in 3.2% of patients. When challenged, 96.7% of patients with positive skin testing and 99.5% of patients with equivocal skin testing had no immediate reaction to challenge, compared with 98.2% of patients with negative skin testing. Most patients tolerated the challenge procedure, with 6.1% developing mild delayed reactions regardless of skin testing results [29].

Proceeding directly to oral challenge in children with low-risk histories of both immediate and non-immediate reactions to amoxicillin appears safe. Mill *et al.* [10] evaluated 818 children (median age 1.7 years, interquartile range 1.0–3.9 years), reporting that 94.1% tolerated direct oral challenge without risk stratification by skin testing. Of note, patients with a history of anaphylaxis or SCAR were excluded from this study (representing high-risk criteria), and a single episode of vomiting was not considered a positive reaction. Only 2.1% of patients developed mild immediate reactions (limited to the oral mucosa or skin), with 3.8% of patients reporting nonimmediate reactions. History of a reaction within 5 minutes of exposure was associated with immediate reaction to a supervised challenge [10]. The supervised oral challenge had a specificity of 100% (95% CI, 90.9–100%), negative predictive value of 89.1% (95% CI, 77.1–95.5%), and positive predictive value of 100% (95% CI, 86.3–100%) [10]. Of the cohort of patients receiving subsequent full treatment courses, 89.1% reported ensuing tolerance with 10.9% developing nonimmediate cutaneous reactions [10]. Of note in the Mills study is that serum sickness-like reactions were not an exclusion to oral challenge. Serum sickness-like reactions may be encountered with some frequency in pediatric patients, but in contrast to true serum sickness, hepatic and renal involvement is rare (and serum sickness-like reactions do not represent a true type III Gell and Combs reaction) [10].

While graded oral provocative challenge is often performed, the incremental margin of safety of a two-step challenge compared with a single-dose

Table 3. Penicillin allergy delabeling in patients with a low-risk history [2²²]

Direct supervised oral amoxicillin challenge can be safely performed in a patient 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 symptoms
- Unknown history

Consider penicillin skin testing first (and proceed to amoxicillin challenge only if negative) if:

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

Patients with low-risk histories may undergo direct supervised challenge with a single dose of amoxicillin without skin testing. Some experts suggest patients with moderaterisk histories undergo skin testing and amoxicillin challenge if negative. The necessity of a 12-month interval before direct oral challenge has not been proven. Patients with high-risk histories may benefit from skin testing or desensitization, unless contraindicated (e.g., history of DRESS, SCAR, cytopenia, nephritis, hepatitis, etc). DRESS: drug rash/reaction with eosinophilia and systemic symptoms; SCAR: severe cutaneous adverse reaction.

challenge is likely small, as immediate reactions are typically mild [2²²,4²²,10]. A similar devolution of the utility of the graded challenge occurred with providing influenza vaccine to egg allergic individuals [30]. Compared with a one-step procedure, a two-step oral challenge may not be necessary [2²²,31,32²] but has been suggested by some experts [2²²,33²²]. Evidence also suggests an extended antibiotic challenge to evaluate for nonimmediate antibiotic reactions may be a low-value practice [34,35²²,36], with one recent study suggesting that 116 extended challenges would be required to identify a single patient with a mild maculopapular exanthem [35²²].

Further studies have corroborated the safety of direct oral challenge in low-risk patients. In one review describing 3299 individuals with low-risk histories, only 42 (1.3%, 95% CI 0.9–1.7%) had immediate positive results and 130 (3.9%, 95% CI, 3.3–4.7%) had delayed reactions [2²²]. In a recent randomized controlled trial of skin testing vs. direct oral challenge in low-risk patients, Mustafa *et al.* [37²²] reported direct challenge without skin testing was negative in 96.2% of low-risk patients. Direct oral amoxicillin challenge without skin testing was also recently investigated by Iammatteo *et al.* [4²²] in a prospective single-blind placebo controlled trial in 155 children and adults with non life-threatening penicillin reactions. The authors reported a 2.6% (95% CI 1.0–6.5%) rate of confirmed allergy with all reactive patients having mild allergic reactions [4²²]. Twenty percent of patients experienced investigator determined nonallergic reactions, with no difference between amoxicillin and placebo [4²²]. This rate of confirmed allergy was much lower than the penicillin allergy rate determined in historical controls diagnosed by a traditional approach of challenge only after negative skin testing (8.2%, 95% CI 5.0–13.4%) [4²²].

Historically there has been concern for cross-reactivity between penicillin and cephalosporins, to some degree confounded by penicillin contamination in first-generation cephalosporin preparations from the mid 1960s to early 1980s [38]. Earlier studies suggested rates of cross-reactivity could be as high as 10%. However, in actuality, rates are much lower [3²,39²]. New estimates suggest that true cross-reactivity between penicillins and cephalosporins occurs in no more than 2–5% of penicillin allergic patients, and this is primarily related to the first-generation and second-generation cephalosporins [3²,39²,40]. In addition to cross-reactivity related to the central beta-lactam ring, clinicians should also be aware of cross-reactivity due to R1 side chains [3²,41²²]. Although most reported cephalosporin allergic reactions are benign rashes, severe reactions

and anaphylaxis may occur [41²²]. The incidence of cephalosporin adverse drug reactions has been estimated at 0.64% (parental) and 0.8% (oral), and among inpatients cephalosporins are implicated in 4–7% of allergic drug reactions [41²²]. Population-based cephalosporin anaphylaxis rates are low. In a study of 622 456 patients exposed to 901 908 courses of oral cephalosporins and 326 867 patients exposed to 487 630 parenteral cephalosporins, anaphylaxis occurred after only five (0.00002%) oral exposures and eight (0.00016%) parenteral exposures [39²]. It has been estimated that about one new cephalosporin allergy will be noted for every 135 penicillin allergic patients given a cephalosporin without tolerance testing, with most of these reactions presenting as benign rashes [39²]. Although clinicians should be aware that a small risk of cephalosporin allergy exists in penicillin allergic patients, these risks are low and there is no evidence that has demonstrated the value of preemptively testing penicillin allergic patients before cephalosporin administration [39²]. A shared clinical decision-making approach has been recommended in managing patients with penicillin allergy who require a cephalosporin, with consideration of a test-dose in those with a convincing history of IgE-mediated penicillin allergy [39²]. There is a need to develop patient-decision aids to assist with patient-provider conversations about antibiotic allergies.

CONCLUSION

Management paradigms of penicillin allergy are rapidly evolving. Given the high rate of penicillin allergy labeling during childhood, collaborative approaches are needed to provide the optimal care [42,43,44²,45²]. For example, a recent evaluation of a multidisciplinary approach to inpatient penicillin delabeling reported an 11% prevalence of a penicillin allergy label in adult inpatients [44²]. Most patients (80%) could be delabeled, with 80% delabeled after pharmacist interview alone, 16% following uneventful oral challenge, and 4% delabeled after referral to an immunology clinic [44²]. At 1-year follow-up, 98% of patients who were delabeled had no adverse reaction to repeated administration of penicillin antibiotics [44²].

While dangerous penicillin allergies do occur, the majority of children who are considered penicillin allergic can have their care simplified through careful phenotyping and risk stratification [2²²,3²]. A partnership between primary care pediatric providers and pediatric allergy specialists is key to optimizing healthcare value. Appropriate penicillin allergy delabeling is important to ensure each patient receives the right care at the right time, every time.

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Conflicts of interest

M.S. has a brother who is CEO of Altrix Medical, developer of the EpiFind smart phone application to locate epinephrine autoinjectors by GPS technology; is a member of the Joint Task Force on Allergy Practice Parameters; and is a member of the Editorial Boards of the *Annals of Allergy, Asthma, and Immunology* and the *Journal of Food Allergy*. M.G. is supported by grant #5K08HS024599-02 from the Agency for Healthcare Quality and Research; is an expert panel and coordinating committee member of the NIAID-sponsored Guidelines for Peanut Allergy Prevention; has served as a consultant for the Canadian Transportation Agency, Thermo Fisher, Intrimmune, and Aimmune Therapeutics; is a member of physician/medical advisory boards for Aimmune Therapeutics, DBV Technologies, Nutricia, Kaleo Pharmaceutical, Nestle, and Monsanto; is a member of the scientific advisory council for the National Peanut Board; has received honorarium from Thermo Fisher, Before Brands, multiple state allergy societies, the ACAAI, the EAACI for lectures; is an associate editor for the *Annals of Allergy, Asthma, and Immunology*; and is a member of the Joint Taskforce on Allergy Practice Parameters. S.M. has a sister-in-law who is a senior research scientist at Tango Therapeutics.

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35. Van Gasse AL, Ebo DG, Chiriac AM, *et al.* The limited value of prolonged drug challenges in nonimmediate amoxicillin (clavulanic acid) hypersensitivity. *J Allergy Clin Immunol Pract* 2019; 7:2225–2229.e1.

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36. Shenoy ES, Blumenthal KG. Evaluation of patients with a history of penicillin allergy-reply. *JAMA* 2019; 321:2367.
37. Mustafa SS, Conn K, Ramsey A. Comparing direct challenge to penicillin skin testing for the outpatient evaluation of penicillin allergy: a randomized controlled trial. *J Allergy Clin Immunol Pract* 2019; 7:2163–2170.

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38. Kelkar PS, Li JT. Cephalosporin allergy. *N Engl J Med* 2001; 345:804–809.
39. Macy E, Blumenthal KG. Are cephalosporins safe for use in penicillin allergy without prior allergy evaluation? *J Allergy Clin Immunol Pract* 2018; 6:82–89.

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42. Gugkaeva Z, Crago JS, Yasnogorodsky M. Next step in antibiotic stewardship: pharmacist-provided penicillin allergy testing. *J Clin Pharm Ther* 2017; 42:509–512.
43. Wall GC, Peters L, Leaders CB, Wille JA. Pharmacist-managed service providing penicillin allergy skin tests. *Am J Health Syst Pharm* 2004; 61:1271–1275.
44. du Plessis T, Walls G, Jordan A, Holland DJ. Implementation of a pharmacist-led penicillin allergy de-labelling service in a public hospital. *J Antimicrob Chemother* 2019; 74:1438–1446.

The study found an 11% prevalence of a penicillin allergy label in adult inpatients. Most patients (80%) could be delabeled, with 80% delabeled after pharmacist interview alone, 16% following uneventful oral challenge, and 4% delabeled after referral to an immunology clinic. At 1-year follow-up, 98% of patients who were delabeled had no adverse reaction to repeated administration of penicillin antibiotics.

45. Devchand M, Kirkpatrick CMJ, Stevenson W, *et al.* Evaluation of a pharmacist-led penicillin allergy de-labelling ward round: a novel antimicrobial stewardship intervention. *J Antimicrob Chemother* 2019; 74:1725–1730.

A collaborative approach involving pharmacist-led penicillin allergy delabeling improved antibiotic stewardship.