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Title:
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Date:
2022-01-01

Citation:
Rischin, K. J., Mostaghim, M., Rao, A., Smith, B., O'Brien, T. A., Trubiano, J. A., Frith, K. & McMullan, B. (2022). ESCAPE-Allergy: Evaluating screening for children and adolescents with penicillin allergy. Journal of Paediatrics and Child Health, 58 (1), pp.83-89. https://doi.org/10.1111/jpc.15657.

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Original Article

ESCAPE-Allergy: Evaluating Screening for Children and Adolescents with Penicillin Allergy

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Conflicts of interest:
The authors declare no conflicts of interest.

Ethics approval:
This project received approval from the Sydney Children's Hospital Network Human Research Ethics Committee (2019/ETH13213).

Acknowledgements:
We thank Dr Kylie-Ann Mallitt for advice on statistical analysis, the Infectious Diseases and Immunology teams, Heads of Department and survey respondents from Emergency, Emergency Department Staff, especially Ms Kylie Stark, Haematology/Oncology and Pharmacy respondents. We also thank the creators of the allergy assessment tool published by Devchand et al., which influenced the development of this project.

Abstract

Aim: Penicillin allergy labels are frequently encountered in children and are associated with significant harms. Most children are falsely labelled and can safely tolerate a penicillin but delabelling strategies are underutilised and paediatric-specific resources are lacking. The aim of this study was to evaluate an allergy assessment tool for children in hospital.

Methods: We evaluated a paediatric-adapted penicillin allergy assessment tool, using an online survey of clinicians in a tertiary paediatric hospital, with ten hypothetical potential penicillin allergy or adverse reaction cases (including non-allergy reactions). For each case, respondents were asked to use the tool to assign a reaction phenotype and recommend management. We determined the tool's sensitivity, specificity and acceptability to end-users.

Results: We evaluated 30 complete survey responses from senior and junior medical staff, nurses and pharmacists. The tool's overall sensitivity was 80.7% (95% CI 74.2 to 87.1%) for assigning the correct reaction phenotype and 85.3% (95% CI 79.4 to 91.3%) for appropriate management. The tool had high sensitivity for identifying immediate hypersensitivity reactions at 95.6% (95% CI 90.2 to 100%). Most respondents agreed or strongly agreed that they would use the tool in their practice (22/30, 73.3%).

Conclusions: This survey evaluated a paediatric-adapted penicillin allergy assessment tool in a tertiary paediatric hospital among multidisciplinary clinician groups. The tool performed well overall and had high safety in identifying immediate hypersensitivity reactions. Further research to support implementation of allergy assessment and delabelling programs among children is required.

Keywords:
Anti-Bacterial Agents / adverse effects*; Antimicrobial Stewardship*; Drug Hypersensitivity / diagnosis*; Children

What is known on this topic:

1. Penicillin allergy labels are frequently encountered in children and are associated with significant harms due to suboptimal alternative therapy
2. Most children with a penicillin allergy label can safely tolerate a penicillin
3. Penicillin allergy is poorly understood by most clinicians and delabelling strategies are underutilised

What this paper adds:

1. A paediatric penicillin allergy assessment tool may be used safely and effectively by clinicians to manage reported penicillin allergy
2. The tool is acceptable to clinicians and is likely to be useful in clinical practice
3. Implementation must occur in conjunction with education and training

Introduction

Penicillin allergies are frequently reported, with 11% of hospitalised adults carrying an allergy label.[1] Penicillin allergy in children is also prevalent and appears to increase with age.[2] One study found that the prevalence of reported penicillin allergies increased from 4.6% in 0-9 year-olds to 5.6% in 10-19 year-olds.[3] Despite a substantial proportion of the population labelled with a penicillin allergy, the vast majority are mislabelled and can be safely given penicillins.[4] Studies investigating children with a suspected ß-lactam allergy consistently find more than 84% are able to tolerate a penicillin on oral challenge.[5]

Penicillin allergy labels, irrespective of whether they are 'true' or 'false', are associated with significant potential harms for both the individual patient and the wider community. Patients with a penicillin allergy label are at an increased risk of treatment failure[6] and are more likely to acquire a resistant organism.[1] Penicillin allergy labels are also associated with increased inappropriate or broad-spectrum antimicrobial use which contributes to the rising prevalence of multidrug-resistant organisms.[2] Patients with a penicillin allergy label are also more likely to have a longer length of stay in hospital[2] and increased treatment costs.[7]

There is a clear need to assess children with a penicillin allergy label, as the majority can safely tolerate a penicillin. While formal allergy assessments are very effective, skin testing and possible subsequent oral challenge are time-consuming and costly, and are neither possible nor necessary for the majority of children with reported penicillin allergy. Those with a clear history of symptoms unlikely to be immunologically-mediated such as gastrointestinal discomfort or headache, can be delabelled without further investigation, though this is often not done.[8]

Lack of knowledge about antibiotic allergy and fear of the possibility of provoking a severe allergic reaction may prevent clinicians from delabelling children when this is appropriate.[9,10] This may be overcome by the availability of a validated tool to guide clinicians in the classification and management of children with penicillin allergy labels. While published and validated tools exist for adults,[11] no similar tools exist for children. The aims of this study were to adapt an adult penicillin allergy assessment tool for use in children, and to evaluate its accuracy for determining allergy phenotype and management, and its acceptability to end users.

Materials and Methods

Antibiotic Allergy Assessment Tool

This study was conducted at Sydney Children's Hospital, Randwick, NSW, a tertiary paediatric hospital caring for over 72,000 children per year. An antibiotic allergy assessment tool for children was created, based on a tool developed for adults by Devchand *et al.*[11] We consulted local paediatric immunologists, infectious diseases physicians, gastroenterologists and nephrologists to adapt the adult tool using paediatric parameters. The adult tool was modified to better reflect common and significant allergic or suspected allergic scenarios seen in children, including serum sickness-like reactions, and a family history of penicillin allergy only. Laboratory reference ranges were updated to age-appropriate values.

The tool was designed to be used by clinicians who frequently encounter children with a penicillin allergy label but may lack expertise in allergy phenotyping and management. Based upon patient or carer reported allergy symptoms, one of the following phenotypes is chosen: severe or non-severe immediate or delayed hypersensitivity, potential immune-mediated, unlikely to be significant or immune-mediated, unknown or unclear mechanism. Each phenotype is colour coded to one of the following management recommendations: appropriate for ward management with either direct delabelling (low risk; white) or supervised direct oral rechallenge (low risk; beige); requiring more formal assessment with skin testing followed by oral rechallenge (moderate or high risk; pink) or formal outpatient antibiotic allergy assessment (high risk; red) (Figure 1).

Survey

We developed a survey comprising ten hypothetical clinical case scenarios to evaluate the tool (Appendix A). The cases ranged in severity and complexity and were intended to mimic drug allergy histories encountered in clinical practice. For each case, respondents were asked to assign an allergy phenotype (immediate hypersensitivity, delayed hypersensitivity, unlikely hypersensitivity or unsure) and their recommended management.

Acceptability to end users was elicited by asking respondents about their agreement on a 5-point Likert scale (strongly disagree, disagree, neutral, agree, strongly agree) with the following three statements: 1) 'I found the tool easy to use'; 2) 'I found the tool easy to navigate'; 3) 'I would use the tool in my clinical practice'. Respondents could also provide written feedback. Finally, we asked respondents to specify their occupation and level of seniority. The tool and

survey were first piloted with junior paediatric immunology and infectious diseases medical staff, with minor modifications made for clarity before being sent to respondents.

We distributed a generic link to the survey via email to medical staff, nurses and pharmacists in selected departments where penicillin allergies are frequently encountered (pharmacy, emergency, haematology/oncology). No identifying information was collected from respondents. A reminder email was sent one week prior to the survey end date. After the survey was completed and no longer available, we emailed respondents an educational answer sheet.

Data analysis

Study data were collected and managed using REDCap.[12] Data analysis was performed using Stata, version 16.0 (StataCorp, USA).

The correct allergy phenotype and corresponding management for each case was determined by the investigators (KF & BM). Correct answers for appropriate management were dichotomised to align with a hospital allergy referral process: 'direct delabelling' and 'oral rechallenge' can both occur on the ward with guidance from the infectious diseases department and were considered the correct management for unlikely hypersensitivity reactions. 'Skin testing +/- oral rechallenge' and 'outpatient assessment' both require referral to the local immunology department for more specialised assessment and were considered the correct management for immediate and delayed hypersensitivity reactions. 'Unsure' responses were considered incorrect answers. Incomplete survey responses were excluded.

We defined sensitivity and specificity of the tool following the methodology of Devchand *et al.*[11] For example, the sensitivity and specificity for identifying immediate hypersensitivity reactions (represented by cases 1, 4 and 10) were calculated as:

$$Sensitivity = \frac{Total\ n.\ correct\ responses\ for\ cases\ 1,4\ \&\ 10\ (i.e. true\ positives)}{Total\ n.\ responses\ (cases\ 1,4\ \&\ 10)\ (i.e.\ true\ positives + false\ negatives)} \times 100$$

$$Specificity = \frac{Total\ n.\ responses\ for\ cases\ 2,3,5,6,7,8,9\ where\ immediate\ hypersensitivity\ was\ NOT\ chosen\ (i.e. true\ negatives)}{Total\ n. responses\ for\ cases\ 2,3,5,6,7,8,9\ (i.e.\ true\ negatives + false\ positives)} \times 100$$

We calculated overall responses and compared the proportion of correct responses by clinician type using a two-sample test of proportions. Differences were considered significant if $p<0.05$.

Acceptability of the tool was determined by calculating the proportion of respondents that either agreed or strongly agreed with each of the three acceptability statements and by analysis of further written feedback.

Results

Respondent characteristics

We emailed the survey to 175 potential participants and received 52 responses overall with 30 complete responses (600 total question responses, survey response rate 17.1%) (Figure 2). Respondents included 12 nurses (40.0%), seven pharmacists (23.3%) and 11 doctors (36.7%), most of which were senior clinicians (Table 1).

Tool performance: sensitivity and specificity

The proportion of correct responses varied by case for both phenotype and management (Table 2). The overall sensitivity of the antibiotic allergy assessment tool was 80.7% (95% confidence interval (CI) 74.2 to 87.1) for assigning the correct allergy phenotype and 85.3% (95% CI 79.4 to 91.3) for assigning the appropriate management (Table 3). The overall specificity of the assessment tool was 84.0% (95% CI 78.3 to 89.7) for assigning the correct allergy phenotype and 88.0% (95% CI 83.5% to 92.5%) for assigning the appropriate management.

The tool had the greatest sensitivity for identifying immediate hypersensitivity reactions (95.6%, 95% CI 90.2 to 100). Unlikely hypersensitivity reactions had the lowest sensitivity (74.2%, 95% CI 64.8 to 83.5). However, after excluding case 3, which was clinically complex and had the lowest proportion of correct responses for both phenotype (43.3%) and management (63.3%), the sensitivity for unlikely hypersensitivity reactions increased to 84.4% (95% CI 76.0 to 92.9). Specificity was high and similar across all phenotypes (90.6% to 92.9%). For correctly assigning the management of either ‘direct delabelling’ or ‘oral rechallenge’, the assessment tool demonstrated high sensitivity (80%, 95% CI 70.1 to 89.9) and specificity (90.6%, 95% CI 85.5 to 95.6). For correctly assigning the management of either ‘skin testing +/- oral rechallenge’ or ‘outpatient assessment’, the assessment tool also demonstrated high sensitivity (88.9%, 95% CI 82.7 to 95.1) and specificity (84.2%, 95% CI 75.5 to 92.8).

The tool performed similarly among doctors, nurses and pharmacists (Table 3). There were also no significant differences between groups in the proportion of correct responses for either phenotype or management.

Acceptability

Most respondents agreed or strongly agreed that they would use the tool in their practice (22/30, 73.3%), and found the tool was easy to use (17/30, 56.7%) and easy to navigate (20/30, 66.7%). Several respondents additionally commented the tool was “excellent”, “helpful” and “useful” but some respondents, particularly nurses, indicated that it was “busy” and that they would be “unlikely to use” the tool themselves compared to prescribers. Other respondents noted a need for concurrent education and queried whether this tool could be applied outside the hospital setting, for example in general practice.

Discussion

In this study we evaluated a novel paediatric-adapted penicillin allergy assessment tool, with good overall sensitivity and specificity for assigning the correct allergy phenotype and recommended management. The tool performed best at identifying moderate or high-risk children who are appropriate for either ‘skin testing +/- oral rechallenge’ or ‘outpatient assessment’. This suggests that implementation of our tool may result in an increase in appropriate referrals for formal evaluation and delabelling.

The tool also demonstrated good sensitivity for identifying low-risk children who are appropriate for either ‘direct delabelling’ or ‘oral rechallenge’. This is where the tool may have its biggest impact, as the majority of children with a penicillin allergy label report low-risk symptoms.[13] Currently, most children with a low-risk penicillin allergy label either do not have their allergies formally assessed and continue to carry their allergy label or are unnecessarily referred to outpatient allergy clinics which are usually oversubscribed. Providing clinicians with a clear framework to determine which children can be directly delabelled or undergo a direct oral challenge simplifies and facilitates delabelling. Oral challenge tests for low-risk children are safe and appropriate for delabelling.[14,15] They can be performed by non-allergy specialists in a variety of clinical settings.[16]

Although unlikely hypersensitivity reactions had the lowest overall sensitivity among allergy phenotypes in our evaluation, this significantly improved (from 43% to 84%) when case 3 was removed from the analysis. Case 3 involved a four-year-old boy who developed a delayed “red and itchy” rash 4-5 hours post-amoxicillin, given in the context of viral upper respiratory tract symptoms and was designed to reflect a likely viral exanthem. Most respondents incorrectly assigned either immediate or delayed hypersensitivity for this case. In retrospect, we concluded this scenario may have been particularly difficult or ambiguous and many of our respondents

appear to have cautiously assigned an allergic phenotype in response, rather than confidently exclude allergy. Although including this case resulted in lower sensitivity, the cautious response to a potentially ambiguous case demonstrated here is both useful information about further educational needs, and potentially a safety factor, during real-world implementation. This lower sensitivity for assigning delayed and unlikely hypersensitivity, compared with immediate hypersensitivity is supported by findings in other studies, which also report limited baseline understanding among most clinicians about antibiotic allergies and other types of reactions.[17,18] Implementation of allergy assessment tools such as this one require a concurrent educational initiative.

The tool's high specificity for all allergy phenotypes and management recommendations demonstrates that it appears safe to use. Our survey indicates respondents are unlikely to incorrectly assign a lower-risk management option for cases that are higher risk and require more intensive assessment and testing. However, as the potential dangers of misclassification can be dangerous (e.g., provoking a severe allergic reaction), our assessment tool should only be implemented with adequate ongoing education, audit and feedback and clinical supervision from appropriate clinicians, such as immunologists and infectious diseases physicians. There were no significant differences between occupations in the proportion of correct responses although we considered in our setting the tool would most commonly be used by prescribers. The written feedback from our validation echoed this with some nurses indicating that they would be more likely to defer to prescribers on the same team, rather than use the tool independently.

Our study has several limitations. The low overall response rate may limit the generalisability of our study findings. Low response rates are, however, common with this survey type and reflect competing priorities of busy clinicians.[19] We only distributed the survey to inpatient healthcare providers from select departments at a single tertiary paediatric hospital. Applicability to community settings, including general practice and community paediatrics, where clinicians also frequently encounter children with penicillin allergy labels is not yet known. We used ten hypothetical clinical vignettes as a proxy for real-life clinical practice, designed to represent a range of common paediatric allergy histories, including histories that were vague or incomplete. In reality, patients' allergy histories are not neatly synthesised into paragraphs and clinicians must be competent in gathering a sufficient allergy history themselves in order to use the assessment tool. A review of vignette methodologies concluded that vignette studies are a valid and reliable method to assess clinical decision-making.[20] However, further

research is needed to determine the validity of the assessment tool in clinical practice, where clinicians obtain the allergy history directly from the patient or carer. Another limitation of delabelling programs is potential refusal of acceptance by the patient or carer. A study following parents whose children had been formally delabelled after negative skin testing and oral challenge found that, of those who had received antibiotics in the past 2 years, 18% still refused penicillins due to fear of allergy.[21] This highlights a need for increased efforts towards education and communication about penicillin allergy and delabelling with both patients and clinicians alike.

Use of our paediatric assessment tool is likely to facilitate allergy delabelling during childhood, when the majority of allergy labels are acquired.[13] Stone *et al.* suggest that deferring antibiotic allergy testing to adulthood makes a false allergy label more difficult to remove, due to many more years of negative conditioning about penicillin avoidance.[22] Our preliminary findings suggest that this penicillin allergy assessment tool is now suitable for implementation. However, further studies evaluating its accuracy and safety in routine care are required prior to widespread use. This should be as part of a broader strategy, incorporating antibiotic allergy delabelling into existing antimicrobial stewardship programs.[23] After implementing an antibiotic allergy delabelling program, Trubiano *et al.* found that prescribing of narrow-spectrum penicillins was more likely and restricted antibiotics were less likely to be prescribed in adults.[24] It is likely that similar impacts of a delabelling program on antimicrobial stewardship would be seen for children, though more research is needed.

Conclusion

We developed and evaluated a paediatric penicillin allergy assessment tool in a hospital setting using hypothetical clinical cases and demonstrated good sensitivity and specificity. Implementation of our tool in routine care is likely to facilitate the delabelling of children who can safely tolerate a penicillin. Implementation should be in conjunction with existing antimicrobial stewardship programs and additional education to improve drug allergy knowledge.

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Tables

Table 1. Summary of respondent characteristics

Respondent characteristic (*n*=30)	Number (% of total)
Occupation	
Doctor	11 (36.7%)
Junior Medical Officer	2 (6.7%)
Senior Medical Officer	9 (30.0%)
Nurse	12 (40.0%)
<5 years' experience	2 (6.7%)
>5 years' experience	10 (33.3%)
Pharmacist	7 (23.3%)
<5 years' experience	1 (3.3%)
>5 years' experience	6 (20.0%)
Department	
Emergency	14 (46.7%)
Pharmacy	6 (20.0%)
Haematology/Oncology	10 (33.3%)

Table 2. Proportion of correct responses for each hypothetical case scenario

		Proportion of correct responses (%)	
		Phenotype	**Management**
Immediate hypersensitivity reactions (severe or non-severe)	Case 1	29/30 (96.7%)	29/30 (96.7%)
	Case 4	30/30 (100%)	29/30 (96.7%)
	Case 10	27/30 (90.0%)	26/30 (86.7%)
Delayed hypersensitivity reactions (severe or non-severe)	Case 2	27/30 (90.0%)	26/30 (86.7%)
	Case 7	18/30 (60.0%)	24/30 (80.0%)
	Case 8	22/30 (73.3%)	26/30 (86.7%)
Unlikely hypersensitivity reactions	Case 3	13/30 (43.3%)	19/30 (63.3%)
	Case 5	21/30 (70.0%)	26/30 (86.7%)
	Case 6	29/30 (96.7%)	26/30 (86.7%)
	Case 9	26/30 (86.7%)	25/30 (83.3%)

Table 3. The sensitivity[†] and specificity[‡] of the paediatric penicillin allergy assessment tool

	Phenotype				Management		
Validation	**Immediate hypersensitivity (cases 1, 4, and 10)**	**Delayed hypersensitivity (cases 2, 7, and 8)**	**Unlikely hypersensitivity (cases 3, 5, 6, and 9)**	**Overall**	**Direct delabelling or oral rechallenge[§] (cases 3, 5, 6, and 9)**	**Skin testing +/- oral rechallenge or outpatient assessment[¶] (cases 1, 2, 4, 7, 8, and 10)**	**Overall**
Overall ($n_{respondents}$ =30)							
Sensitivity % (95% CI)	95.6 (90.2-100)	74.4 (63.8-85.1)	74.2 (64.8-83.5)	80.7 (74.2-87.1)	80.0 (70.1-89.9)	88.9 (82.7-95.1)	85.3 (79.4-91.3)
Specificity % (95% CI)	92.4 (87.6-97.2)	92.9 (89.2-96.5)	90.6 (85.2-95.9)	84.0 (78.3-89.7)	90.6 (85.5-95.6)	84.2 (75.5-92.8)	88.0 (83.5-92.5)
Doctors ($n_{respondents}$ =11)							
Sensitivity % (95% CI)	90.9 (77.6-100)	72.7 (60.3-85.1)	84.1 (69.8-98.3)	82.7 (72.4-93.1)	90.9 (80.5-100)	83.3 (73.1-93.6)	86.4 (77.1-95.6)
Specificity % (95% CI)	96.1 (92.0-100)	96.1 (92.0-100)	84.9 (74.1-95.6)	85.5 (75.8-95.2)	83.3 (73.1-93.6)	93.2 (86.0-100)	87.3 (79.4-95.1)
Nurses ($n_{respondents}$ =12)							
Sensitivity % (95% CI)	100 (90.3-100)	77.8 (56.7-98.9)	72.9 (58.2-87.6)	82.5 (70.9-94.1)	75.0 (54.1-95.9)	91.7 (82.8-100)	85.0 (73.6-96.4)
Specificity % (95% CI)	92.9 (86.1-99.6)	90.5 (83.9-97.0)	94.4 (88.0-100)	85.0 (75.1-94.9)	94.4 (89.6-99.3)	79.2 (60.5-97.9)	88.3 (80.4-96.2)
Pharmacists ($n_{respondents}$ =7)							
Sensitivity % (95% CI)	95.2 (85.5-100)	71.4 (48.2-94.6)	60.7 (41.9-79.6)	74.3 (63.5-85.1)	71.4 (58.1-84.8)	92.9 (78.2-100)	84.3 (74.4-94.1)
Specificity % (95% CI)	85.7 (70.1-100)	91.8 (83.1-100)	92.9 (82.7-100)	80.0 (70.0-90.0)	95.2 (85.5-100)	78.6 (65.2-91.9)	88.6 (80.3-96.8)

[†]Sensitivity was regarded as how accurately the tool assigned the correct allergy phenotype or management (i.e. true positives).

[‡]Specificity was regarded as how accurately the tool did not assign the incorrect allergy phenotype or management (i.e. true negatives).

[§]Direct delabelling or oral rechallenge was considered the correct management for unlikely hypersensitivity cases.

[¶]Skin testing +/- oral rechallenge or outpatient assessment was considered the correct management for immediate and delayed hypersensitivity reactions.

Figure Legends

Figure 1. Paediatric Antibiotic Allergy Assessment Tool
Based on the patient's allergy history, users locate the reported allergy symptom on the tool. Allergy symptoms are categorised into systems (dermatological, haematological etc.). Each allergy symptom has a corresponding allergy phenotype (e.g. immediate hypersensitivity (severe)). If more than one allergy symptom or phenotype is present, users are directed to default to the most severe type. Each allergy phenotype is colour coded based on what further management is recommended (as per the bottom left of the tool). AIN, Acute interstitial nephritis; DILI, drug-induced liver injury; ULN, upper limit normal.

Figure 2. Study flow diagram

[†]As no identifying data was collected and the survey link was generic, this ensured exclusion of duplicate responses from participants who were interrupted at work while initially attempting the survey.

Original Article

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Conflicts of interest:
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This project received approval from the Sydney Children's Hospital Network Human Research Ethics Committee (2019/ETH13213).

Acknowledgements:
We thank Dr Kylie-Ann Mallitt for advice on statistical analysis, the Infectious Diseases and Immunology teams, Heads of Department and survey respondents from Emergency, Emergency Department Staff, especially Ms Kylie Stark, Haematology/Oncology and Pharmacy respondents. We also thank the creators of the allergy assessment tool published by Devchand et al., which influenced the development of this project.

Dermatological

Skin manifestation		Recommendation & Resultant allergy type	
Childhood exanthem (unspecified) *Mild rash with no severe features*		☐	Unlikely to be significant (non-severe)
Immediate diffuse rash ("immediate, often itchy rash") *Onset <2 hours post dose*		☐	Immediate hypersensitivity (non-severe)
Localised swelling *>4h post antibiotic or unknown timing*	with no other symptoms	☐	Delayed hypersensitivity (non-severe)
	With joint symptoms	☐	Delayed hypersensitivity (non-severe)
Angioedema ("lip or facial swelling")		☐	Immediate hypersensitivity (severe)
Generalized swelling (outside of angioedema)		☐	Immediate hypersensitivity (severe)
Urticaria ("wheals and hives") *Onset <4h post antibiotic or unknown timing*		☐	Immediate hypersensitivity (non-severe)
Mucosal ulceration ("mouth, eye or genital ulcers")		☐	Delayed hypersensitivity (severe)
Pustular, blistering or desquamating rash ("skin shedding")		☐	Delayed hypersensitivity (severe)

Respiratory or Systemic

Clinical manifestation	Recommendation & Resultant allergy type	
Upper airway ("throat tightness, tongue swelling or hoarse voice")	☐	Immediate hypersensitivity (severe)
Respiratory ("persistent cough, difficult/noisy breathing, wheeze")	☐	Immediate hypersensitivity (severe)
Cardiovascular ("persistent dizziness, hypotension or unexplained collapse")	☐	Immediate hypersensitivity (severe)
Fever ("high temperature") *Persistent and **not** explained by infection*	☐	Delayed hypersensitivity (severe)

Haematological

Low platelets < 150 x10^9/L or unknown	☐	Potential immune mediated (severe)
Low neutrophils < 1x10^9/L or unknown	☐	Potential immune mediated (severe)
Low haemoglobin < 100 g/L or unknown	☐	Potential immune mediated (severe)
Eosinophilia >0.7 x 10^9/L or unknown	☐	Delayed hypersensitivity (severe)

Other

Clinical manifestation		Recommendation & Resultant allergy type
Unknown reaction ≤ 10 years ago	☐	Unknown (non-severe)
Unknown reaction >10 years ago	☐	Unlikely to be significant (non-severe)
Family history only of penicillin allergy only	☐	Unlikely immune mediated (non-severe)

Renal

Severe renal injury, failure or AIN (Serum creatinine increase to >=1.5 baseline or increase of ≥26.5µmol/L, or transplantation, or dialysis)	☐	Potential immune mediated (severe)
Mild renal impairment (Does not meet criteria in box above)	☐	Unlikely immune mediated (non-severe)

Hepatic

Severe liver injury, failure or DILI (≥5x upper limit of normal (ULN) for ALT or AST, or ≥3x ULN for ALT with ≥2x ULN for bilirubin)	☐	Potential immune mediated (severe)
Mild liver enzyme derangement (Does not meet criteria in box above)	☐	Unlikely immune mediated (non-severe)

Gastrointestinal, Neurological or Infusion-related

Gastrointestinal symptoms ("nausea, vomiting, diarrhoea")	☐	Unlikely immune mediated (non-severe)
Mild neurological manifestation ("headache, depression, mood disorder")	☐	Unlikely immune mediated (non-severe)
Severe neurological manifestation ("seizures or psychosis")	☐	Potentially unknown or unclear mechanism – Contact ID for advice
Anaphylactoid/infusion reaction (e.g. red man syndrome)	☐	Potentially unknown or unclear mechanism – Contact ID for advice

Appropriate for direct de-labelling For advice call Infectious Diseases	☐ **Low risk**
Appropriate for supervised direct oral rechallenge For advice call Infectious Diseases	☐ **Low risk**
May be appropriate for skin testing followed by oral rechallenge Refer to Immunology	☐ **Moderate or high risk**
Appropriate for outpatient antibiotic allergy assessment +/- testing Refer to Immunology	☐ **High risk**