Published in final edited form as:

J Allergy Clin Immunol Pract. 2019 March ; 7(3): 1063–1065.e5. doi:10.1016/j.jaip.2018.07.048.

Pathways to Improved Antibiotic Allergy and Antimicrobial Stewardship Practice - The Validation of a Beta-Lactam Antibiotic Allergy Assessment Tool

Misha Devchand, BPharm^{1,2}, Karen Urbancic, BPharm^{1,2}, Sharmila Khumra, BPharm^{1,2}, Abby Douglas, MBBS³, Olivia Smibert, MBBS³, Emma Cohen, RN PhD⁴, Michael Sutherland, MBBS PhD⁵, Elizabeth J Phillips, MD^{6,7}, and Jason A Trubiano, MBBS PhD^{2,3,8,9}

¹Department of Pharmacy, Austin Health, Melbourne, Australia

²Department of Infectious Diseases, Austin Health, Melbourne, Australia

³Department of Infectious Diseases, Peter MacCallum Cancer Centre, Melbourne, Australia

⁴Department of Cancer Services, Austin Health, Melbourne, Australia

⁵Department of Respiratory and Allergy, Alfred Health, Melbourne, Australia

⁶Institute of Immunology and Infectious Diseases, Murdoch University, Murdoch, Australia

⁷Department of Infectious Diseases, Vanderbilt University Medical Centre, Nashville, United States

⁸Department of Medicine (Austin Health), University of Melbourne, Melbourne, Australia

⁹National Centre for Infections in Cancer, Department of Oncology Sir Peter MacCallum Cancer Centre, University of Melbourne, Melbourne, Australia

Summary:

The validation of a beta-lactam antibiotic allergy assessment allows non-allergists to effectively phenotype patient-reported antibiotic allergies and direct them to appropriate ‘de-labeling’ strategies.

To the editor,

While patient-reported antibiotic allergies (so-called antibiotic allergy labels [AALs]) are encountered in up to 1 in 4 hospitalized patients they are frequently “unknown” and not

Contact details: Dr Jason Trubiano BBSiomedSci MBBS (hons) FRACP PhD, Director of Antimicrobial Stewardship and Antibiotic Allergy Services Austin Health - 145 Studley, Road, Heidelberg, VIC, Australia 3084, jason.trubiano@austin.org.au, Ph: +61394966676; Fax: +6139496677.

Transparency, declarations and conflicts of interest: Nothing to declare for all authors

Publisher's Disclaimer: This is a PDF file of an unedited manuscript that has been accepted for publication. As a service to our customers we are providing this early version of the manuscript. The manuscript will undergo copyediting, typesetting, and review of the resulting proof before it is published in its final citable form. Please note that during the production process errors may be discovered which could affect the content, and all legal disclaimers that apply to the journal pertain.

clarified by clinicians.¹ The high prevalence of potentially misleading AALs is further confounded by poor clinician understanding of beta-lactam prescribing in penicillin allergy and underutilization of appropriate “delabelling” strategies.^{2,3}

Antibiotic allergy assessment tools have been used previously to aid phenotyping,⁴ and screening algorithms employed to guide appropriate antibiotic allergy prescribing⁵. The assessment of penicillin allergy is a recommended component of antimicrobial stewardship (AMS), considering the established links between AALs and inferior patient outcomes.^{6–8} What remains absent is a validated point-of-care tool that can be used by a spectrum of healthcare workers to accurately assess and record AALs and enable referral to specialized testing services. Therefore, we validated a beta-lactam antibiotic allergy assessment tool (AAAT) to aid non-allergists in the phenotyping and management of patients with reported beta-lactam AALs.

The AAAT was developed at Austin Health (Melbourne, Australia), a tertiary referral hospital with specialist antibiotic allergy services. The tool was primarily designed for use by healthcare providers who frequently encounter AALs when reviewing adult inpatients with infective episodes that require antibiotics. The AAAT utilizes patient-reported symptoms and signs associated with an index beta-lactam AAL (Figure 1), to assign an accurate (i) phenotype and (ii) management recommendation. The phenotypic outcomes of the AAAT were classified as;

- (i) Severe immediate hypersensitivity (IgE-mediated),
- (ii) Non-severe immediate hypersensitivity (IgE-mediated),
- (iii) Severe delayed hypersensitivity (T-cell-mediated),
- (iv) Non-severe delayed hypersensitivity (T-cell-mediated),
- (v) Potential immune mediated (e.g. acute interstitial nephritis), or
- (vi) Unlikely to be significant/non-immune mediated (e.g. gastrointestinal upset, unknown history).

Each phenotype was allocated a corresponding management recommendation of either;

- (i) Direct de-labelling with removal from medical record,
- (ii) Oral rechallenge (provocation),
- (iii) Antibiotic allergy skin testing followed by oral rechallenge, or
- (iv) Outpatient antibiotic allergy assessment - potentially including skin testing and oral rechallenge, only after detailed specialist consultation

The tool underwent an internal review for content and usability, utilizing hypothetical case scenarios representing immune and non-immune phenotypes. This initial review was performed by specialists in antibiotic allergy care, including adverse drug reaction (ADR) committee pharmacists, allergists and infectious diseases physician specializing in antibiotic allergy. Following modifications to the AAAT post internal review, the primary validation involved a range of healthcare workers utilizing the AAAT, using real-patient case studies

from the Austin Health Antibiotic Allergy Database. The cases formed the reference gold standard as all ‘phenotypes’ were confirmed by *in vivo* methods (skin prick testing and/or oral challenge) and such ‘management’ followed either a local or international guideline.^{9,10} A secondary validation was undertaken in a group of specialist hematology/oncology nurses. All real-patient case studies were de-identified and had their phenotypes confirmed by specialist review, including skin testing and/or oral rechallenge, as per published national and international guidelines.^{9,10} The real-patient cases studies were prepared by study investigators (JAT, MD), reviewed by additional investigators (SK, KU, AD, EP and OS) and were forwarded to respondents who were able to answer questions anonymously (**Supplementary materials**). This project received approval from the Austin Health Ethics Committee (CD 17/005).

In the primary validation, eight antibiotic allergy case studies (immune-mediated [5] and non-immune-mediated [3]) were evaluated by forty participants (317 total responses). The respondents included 19 junior doctors (48%), 11 pharmacists (28%), 8 (20%) senior doctors (infectious diseases doctors [consultants and fellows]) and 2 (5%) specialist nurses. The secondary validation utilized the same case studies in a group of 11 specialist hematology/oncology nurses. In the primary validation, the AAAT demonstrated an overall sensitivity of 91.8% (95% CI 88.9–94.0) for assigning the correct phenotype and 85.2% (95% CI 80.8–88.7) for the appropriate management. The performance of the AAAT was improved for senior doctors (sensitivity; 93.8% [95% CI 84.8–98.3], specificity; 85.9% [95% CI 75.0–93.4] and pharmacists (sensitivity; 92.9% [95% CI 85.4–97.4], specificity; 96.5% [95% CI 90.0–99.3]). In the primary validation, sensitivity and specificity varied for phenotype. (Table 1) The overall sensitivity in secondary validation by hematology/oncology nurses was 97.8% (95% CI 92.0–99.7) for phenotype and 96.6% (95% CI 92.0–99.72) for management.

Regarding management recommendations the AAAT demonstrated a sensitivity and specificity highest for *direct de-labelling* (non-significant/non-immune phenotypes). (Table 1) Regarding potentially hazardous recommendations, defined as a less restrictive management recommendation (e.g. oral rechallenge in case of severe immune-mediated reaction), the highest number was seen in the *skin testing +/- oral rechallenge* recommendations where 5 of 15 incorrect responses were considered potentially hazardous. For the *outpatient assessment* recommendation, 4 of 16 incorrect responses were potentially hazardous, whilst 0 were identified from the 9-incorrectly given responses for the *direct de-labelling* option. All potentially hazardous recommendations were made by junior medical staff respondents.

When examining the proportion of correct responses per group there was no significant difference between senior and junior doctors overall for phenotyping (137/152 vs. 60/64, $p = 0.60$) or management recommendations (116/152 vs. 55/64, $p = 0.14$). When comparing pharmacists to doctors there was no difference for phenotyping (79/85 vs. 197/216, $p = 0.82$), but there was for management (82/85 vs. 171/216, $p = 0.0001$). Nurses (hematology/oncology, specialist nurses) performed better than doctors overall for phenotyping (101/104 vs. 197/216, $p = 0.059$) and management (100/104 vs. 171/216, $p = 0.0001$).

The beta-lactam AAAT proved useful to a range of non-allergist healthcare workers that frequently encounter AALs, in the identification of antibiotic allergy phenotypes and designating appropriate management. The study was limited by the validation in a retrospective cohort of patient-cases and small number of respondents. However, our tool demonstrated good overall sensitivity and performed best for assigning the correct phenotype and management in non-significant beta-lactam allergy phenotypes, which would aid direct oral rechallenge protocols, an approach increasingly performed as part of AMS programs.¹¹ Good sensitivity was also noted for immediate hypersensitivities, where skin prick and intradermal penicillin testing is increasingly being performed by trained non-allergists.³ We propose that the AAAT could be integrated into the workflow of healthcare workers that frequently encounter AALs (e.g. infectious diseases physicians, hematology/oncology nurses and AMS pharmacists) enabling patient referral to supervised testing programs, to reduce the significant public health issue of beta-lactam allergy.⁸

The lower sensitivity for severe delayed hypersensitivity phenotyping, by junior medical staff, highlights the need for greater education, as this group are at risk of re-prescribing implicated antibiotics in severe hypersensitivity without formal assessment. Also there remains a risk of misclassification with any clinical assessment tool, and site-specific validation, auditing and clinical oversight must remain *in situ*. However, considering the primary targets of this tool would be AMS pharmacists and infectious diseases physicians, the AAAT is likely to aid effective beta-lactam allergy assessment, appropriate allergy de-labelling of spurious beta-lactam allergy and referral to specialist-run antibiotic allergy services. Importantly, the tool performed particularly well in the hands of hematology nurses, working in units where the AAL burden is known to be greatest,¹² which could significantly benefit “de-labelling” programs that improve prescribing in vulnerable patients.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgements:

Ms Claire Keith (Austin Health), Mrs Wendy Stevenson (Austin Health), Mrs Linda Graudins (Alfred Health) and Dr Ar Kar Aung (Alfred Health) for initial components on assessment tool design.

Funding: JAT is supported by an NHMRC Early Careers FellowshipEJP is funded by the 1P50GM115305–01 (NIH) and NHMRC

References

1. Trubiano JA, Cairns KA, Evans JA, Ding A, Nguyen T, Dooley MJ, et al. The prevalence and impact of antimicrobial allergies and adverse drug reactions at an Australian tertiary centre. *BMC Infect Dis* 2015; 15:572. [PubMed: 26675619]
2. Trubiano JA, Beekmann SE, Worth LJ, Polgreen PM, Thursky KA, Slavin MA, et al. Improving Antimicrobial Stewardship by Antibiotic Allergy Delabeling: Evaluation of Knowledge, Attitude, and Practices Throughout the Emerging Infections Network. *Open Forum Infect Dis* 2016; 3:ofw153. [PubMed: 27800527]
3. Trubiano JA, Thursky KA, Stewardson AJ, Urbancic K, Worth LJ, Jackson C, et al. Impact of an Integrated Antibiotic Allergy Testing Program on Antimicrobial Stewardship: A Multicenter Evaluation. *Clin Infect Dis* 2017; 65:166–74. [PubMed: 28520865]

4. Miller LE, Knoderer CA, Cox EG, Kleiman MB. Assessment of the validity of reported antibiotic allergic reactions in pediatric patients. *Pharmacotherapy* 2011; 31:736–41. [PubMed: 21923599]
5. Ramsey A, Staicu ML. Use of a Penicillin Allergy Screening Algorithm and Penicillin Skin Testing for Transitioning Hospitalized Patients to First-Line Antibiotic Therapy. *J Allergy Clin Immunol Pract* 2017.
6. MacFadden DR, LaDelfa A, Leen J, Gold WL, Daneman N, Weber E, et al. Impact of Reported Beta-Lactam Allergy on Inpatient Outcomes: A Multicenter Prospective Cohort Study. *Clin Infect Dis* 2016; 63:904–10. [PubMed: 27402820]
7. Trubiano JA, Chen C, Cheng AC, Grayson ML, Slavin MA, Thursky KA, et al. Antimicrobial allergy 'labels' drive inappropriate antimicrobial prescribing: lessons for stewardship. *J Antimicrob Chemother* 2016; 71:1715–22. [PubMed: 26895771]
8. Barlam TF, Cosgrove SE, Abbo LM, MacDougall C, Schuetz AN, Septimus EJ, et al. Implementing an Antibiotic Stewardship Program: Guidelines by the Infectious Diseases Society of America and the Society for Healthcare Epidemiology of America. *Clin Infect Dis* 2016; 62:e51–77. [PubMed: 27080992]
9. Joint Task Force on Practice P, American Academy of Allergy A, Immunology, American College of Allergy A, Immunology, Joint Council of Allergy A, et al. Drug allergy: an updated practice parameter. *Ann Allergy Asthma Immunol* 2010; 105:259–73. [PubMed: 20934625]
10. Barbaud A Skin testing in delayed reactions to drugs. *Immunol Allergy Clin North Am* 2009; 29:517–35. [PubMed: 19563995]
11. Tucker MH, Lomas CM, Ramchandrar N, Waldram JD. Amoxicillin challenge without penicillin skin testing in evaluation of penicillin allergy in a cohort of Marine recruits. *J Allergy Clin Immunol Pract* 2017; 5:813–5. [PubMed: 28341170]
12. Huang KG, Cluzet V, Hamilton K, Fadugba O. The Impact of Reported Beta-Lactam Allergy in Hospitalized Patients with Hematologic Malignancies Requiring Antibiotics. *Clin Infect Dis* 2018.

Dermatological			Respiratory or Systemic			Unknown reaction		
Clinical manifestation		Recommendation & Resultant allergy type	Clinical manifestation	Recommendation & Resultant allergy type		Clinical manifestation	Recommendation & Resultant allergy type	
Childhood exanthem (unspecified) <i>Details of rash timing unknown and no severe features or hospitalisation</i>		☐ Unlikely to be significant (non-severe)	Laryngeal involvement ("throat tightness" or "hoarse voice")	☐	Immediate hypersensitivity (severe)	Unknown reaction ≤ 10 years ago	☐	Unlikely significant (non-severe)
Immediate diffuse rash ("itchy immediate rash") <i><2 hours post dose</i>		☐ Immediate hypersensitivity (non-severe)				Unknown reaction > 10 years ago or family history of penicillin allergy only	☐	Unlikely significant (non-severe, low risk)
Diffuse rash or localized rash with no other symptoms <i>> 24 hours post starting antibiotic</i>	≤ 10 years ago	☐ Delayed hypersensitivity (non-severe)	Respiratory compromise ("wheeze or shortness of breath")	☐	Immediate hypersensitivity (severe)	Renal		
	> 10 years ago	☐ Delayed hypersensitivity (non-severe, low risk)	Fever ("high temperature") - <i>Not explained by infection or other cause</i>	☐	Delayed hypersensitivity (severe)			
Rash & mucosal ulceration ("mouth, eye or genital ulcers") <i>Be alert for history of SCAR</i>		☐ Delayed hypersensitivity (severe)	Anaphylaxis or unexplained hypotension or collapse	☐	Immediate hypersensitivity (severe)	Renal failure or severe injury (>50% reduction in eGFR from patient's baseline or absolute serum creatinine increase of ≥26.5 μmol/L, or transplantation, or dialysis)	☐	Potential immune mediated (severe, if AIN)
			Haematological			Liver		
Pustular, blistering or desquamating ("skin shedding") rash <i>Be alert for history of SCAR</i>		☐ Delayed hypersensitivity (severe)	Platelets < 150 x 10 ⁹ /L or unknown	☐	Potential immune mediated (severe)	Liver failure or severe liver injury (≥5x upper limit of normal (ULN) for ALT or AST, or ≥3x ULN for ALT with ≥2x ULN for bilirubin, or ≥2x ULN for ALP, or decompensation, or transplantation)	☐	Potential immune mediated (severe, if DILI)
Angioedema ("lip, facial or tongue swelling")		☐ Immediate hypersensitivity (severe)	Neutrophils < 1x10 ⁹ /L or unknown	☐	Potential immune mediated (severe)	Hepatic enzyme derangement (Does not meet criteria for liver failure or severe injury [see box above])	☐	Unlikely immune mediated (non-severe, low risk)
Swelling (outside of angioedema)		☐ Potential immediate hypersensitivity (severe)	Haemoglobin < 100 g/L or unknown	☐	Potential immune mediated (severe)	Neurological or gastrointestinal		
Urticaria ("wheals and hives")		☐ Immediate hypersensitivity (non-severe)	Eosinophilia (>0.7 x 10 ⁹ /L or unknown) <i>Examine history for DRESS</i>	☐	Delayed hypersensitivity (severe, if DRESS)			
Appropriate for direct de-labelling - removal of allergy label without testing oral rechallenge if required						Neurological or CNS manifestation ("headache, optic neuritis, confusion, depression, mood disorder, low mood, psychosis")	☐	Unlikely immune mediated (non-severe, low risk)
Appropriate for supervised direct oral rechallenge ^a								
Appropriate for skin testing followed by oral rechallenge ^b								
Appropriate for outpatient antibiotic allergy assessment +/- testing								

Figure 1: Beta-lactam antibiotic allergy assessment tool

Note: Patients classified as an "immediate hypersensitivity" are appropriate for desensitization if the patient has a beta-lactam allergy history and requires urgent penicillin based therapy

Abbreviations: SCAR, severe cutaneous adverse drug reactions, DRESS, drug reaction with eosinophilia and systemic symptoms, AIN, acute interstitial nephritis, DILI, drug-induced liver injury, ULN, upper limit normal

^a In the appropriate setting a direct oral rechallenge may be performed under specialist guidance

^b Skin testing followed by oral rechallenge can be performed in the outpatient or inpatient setting. Those patients with features of severe life threatening allergy are those marked for "outpatient assessment" rather than inpatient setting to ensure a (i) detailed collateral history is obtained, (ii) presence of specialist allergy oversight and (iii) resolution of acute illness. If the aforementioned can be achieved in the acute setting then testing may proceed with caution.

Table 1:

The sensitivity and specificity of the beta-lactam antibiotic allergy assessment tool

	Phenotype			Management		
	Immediate hypersensitivity (cases 3,5,7)	Delayed Hypersensitivity (cases 4,8)	Non-significant (cases 1,2,6)	Direct de-labelling or oral rechallenge ^a (cases 1,2,6)	Skin prick testing +/- OC ^b (cases 7,8)	Outpatient assessment ^c (cases 3,4,5)
Primary validation - Doctors, pharmacists, specialist nurses (n _{respondents} = 40)						
Sensitivity % (95% CI)	97.5 (91.3–99.7)	84.8 ^d (76.0–91.9)	96.7 (91.7–99.1)	92.5 (86.2–96.5)	79.2 (68.5–87.6)	87.5 (80.2–92.8)
Specificity % (95% CI)	97.9 (94.9–99.5)	97.5 (94.4–99.2)	97.9 (94.9–99.5)	94.4 (90.2–97.2)	93.8 (89.9–96.46)	93.4 (89.0–96.4)
Secondary validation - Hematology/oncology nurses (n _{respondants} =11)						
Sensitivity % (95% CI)	96.9 (84.2–99.2)	95.5 (77.1–99.9)	98.2 (90.3–99.5)	100 (89.42–100)	95.5 (77.2–99.8)	93.9 (79.9–99.2)
Specificity % (95% CI)	100 (93.5–100)	98.2 (90.3–99.5)	98.2 (90.3–99.9)	96.4 (87.5–99.6)	98.5 (91.8–99.6)	100 (91.9–100)

Abbreviations: OC, oral rechallenge; CI, confidence interval

^a**Direct de-labelling or oral rechallenge** were considered the corrected management options for cases designated as unlikely significant or delayed (non-severe, low risk) hypersensitivity only.

^b**Skin prick testing +/- OC** were considered the correct management option for cases designated as immediate hypersensitivity (not anaphylaxis) or delayed hypersensitivity (non-severe) only

^c**Outpatient assessment** was considered the correct management option for cases designated as delayed hypersensitivity (severe) anaphylaxis or severe potential immune mediated adverse drug reactions only.

^dLowest sensitivity noted for severe delayed hypersensitivities – 77.5% (95% CI 61.6–89.2), whilst retaining 152 high specificity 99.6% (95% CI 97.7–99.99)