

# How antibiotic allergy labels may be harming our most vulnerable patients

Antibiotic allergy testing programs will ensure that vulnerable patients receive appropriate antibiotic therapy

**A**ntibiotic allergy labels are accumulated by various mechanisms and are often incorrectly self-reported or recorded. Incorrect antibiotic allergy labels frequently persist in community and hospital medical records throughout patients' health care journeys, either with the phenotype unverified by clinicians or recorded as unknown.<sup>1,2</sup> Among a cohort of older Australian general medical inpatients, we identified that 25% had a mismatch between their reported and recorded antibiotic allergy.<sup>3</sup> Further, as an additional source of incorrect antibiotic allergy labels, patients with a true immunological basis for antibiotic allergy, such as immediate (IgE-mediated) reactions, may lose reactivity over time.<sup>4</sup> Incorrect antibiotic allergy labels often prevent the use of appropriate narrow spectrum penicillin and targeted antibiotic therapies in both community and hospital practice, frequently among the patients most in need.<sup>4,5</sup>

Using National Antimicrobial Prescribing Survey data, we found antibiotic allergy label prevalences among hospitalised Australians of 18% overall and 9% for penicillin alone, with the highest prevalence (19–24%) noted in the most vulnerable patients — those with chronic illness, cancer or alternative immunosuppression.<sup>1</sup> This burden was similar to that reported in other Australian centres<sup>2</sup> and to contemporary estimates from the United States health care system.<sup>3</sup> In Australia, as many as one in four inpatients with cancer have an antibiotic allergy label,<sup>1,4</sup> and their risk of being prescribed an inappropriate antibiotic is almost 50% higher than for patients without an antibiotic allergy label (odds ratio [OR], 1.47; 95% CI, 1.05–2.08;  $P = 0.032$ ).<sup>1</sup> Between 2010 and 2012, 23% of patients with cancer and a concomitant infection at the Peter MacCallum Cancer Centre in Melbourne had an antibiotic allergy label on file.<sup>4</sup> On multivariate logistic regression, the label was associated with significantly more antibiotic treatments per admission (3 *v* 2;  $P = 0.01$ ) and more readmissions with an infective diagnosis (53% *v* 28%;  $P < 0.001$ ).<sup>4</sup> The deleterious effects of a  $\beta$ -lactam allergy were also demonstrated in a prospective study of 507 inpatients with infectious diseases in Canada, where multivariate analysis identified that  $\beta$ -lactam allergy was associated with an increased risk of adverse events (adjusted OR, 3.1; 95% CI, 1.28–7.89) and a composite endpoint of readmission, *Clostridium difficile* infection, drug reaction or acute kidney injury (adjusted OR, 3.18; 95% CI, 1.28–7.89).<sup>5</sup> These impacts are concerning given that almost 20% of antibiotic allergy labels arise from drug side effects,<sup>6</sup> and most childhood antibiotic allergy labels likely reflect a viral aetiology rather than true immune-mediated antibiotic hypersensitivity.<sup>7</sup> Caubet and colleagues<sup>7</sup> detected respiratory viruses by polymerase chain reaction of throat swab samples or serological testing in 66% of oral challenge-negative



children at the time of reported allergy, while Vezir and colleagues<sup>8</sup> found that over 96% of children with a non-immediate allergy did not have their allergy reproduced on antibiotic re-challenge. In a seminal article, Bourke and colleagues<sup>9</sup> found that 90% of all penicillin allergy labels can be removed by formal penicillin skin testing and subsequent oral provocation.

When prescribing in a setting of self-reported penicillin allergy, clinicians are more likely to be risk averse and avoid penicillin and, to a lesser extent, all  $\beta$ -lactam therapies.<sup>10</sup> Antibiotic allergy testing, although effective, is not widely available,<sup>10</sup> requiring specialised services and use of penicillin reagents not commonly present at the frontline of medical care. The resultant unnecessary use of broad spectrum second or third choice antibiotics contributes to the development of multidrug-resistant infections and *C. difficile* acquisition.<sup>11</sup> Avoiding alternative targeted  $\beta$ -lactams (eg, cephalosporins) in patients with a remote history of mild penicillin allergy is generally unnecessary, as overall cephalosporin cross-reactivity is less than 2% for third generation cephalosporins, 1% for carbapenems and zero for monobactams.<sup>12–15</sup> Cross-reactivity is often predicted by conserved R1 side chains of  $\beta$ -lactams, especially among aminopenicillins (eg, amoxicillin, ampicillin) and aminocephalosporins (eg, cephalexin, cefaclor).<sup>13</sup> In the setting of such low rates of penicillin cross-reactivity, even patients with true immune-mediated penicillin allergy need not, under appropriate specialist advice, avoid all alternative  $\beta$ -lactam therapies.

It is reasonable to suggest that antibiotic prescribing in patients with reported antibiotic allergies would be improved through the incorporation of antibiotic allergy programs in antimicrobial stewardship (AMS) services.<sup>16</sup> Comprehensive AMS programs which aim to guide appropriate selection, dosing, route and duration of antimicrobial therapy have been shown to decrease antimicrobial use by 22–36%, with annual savings of US\$200 000–\$900 000 in larger US academic hospitals.<sup>17</sup> AMS programs have been shown in systematic and

Jason A Trubiano<sup>1,2,3</sup>

M Lindsay Grayson<sup>1,3</sup>

Karin A Thursky<sup>2,4</sup>

Elizabeth J Phillips<sup>5</sup>

Monica A Slavin<sup>2,4</sup>

<sup>1</sup> Austin Health, Melbourne, VIC.

<sup>2</sup> Peter MacCallum Cancer Centre and National Centre for Infections in Cancer, Melbourne, VIC.

<sup>3</sup> University of Melbourne, Melbourne, VIC.

<sup>4</sup> Royal Melbourne Hospital, Melbourne, VIC.

<sup>5</sup> Institute for Immunology and Infectious Diseases, Murdoch University, Perth, WA.

Jason.Trubiano@austin.org.au

Cochrane reviews to increase guideline-concordant antibiotic therapies and reduce restricted antibiotic usage.<sup>18</sup> Infectious Diseases Society of America guidelines recommend that such AMS programs incorporate penicillin allergy assessment.<sup>19</sup> While the cost-effectiveness of an antibiotic allergy testing program needs to be examined in an Australian context, international assessments have shown that such a program can reduce antibiotic costs per patient.<sup>20</sup> Centralised antibiotic allergy testing targeted to our vulnerable patients, particularly people with cancer and those who are immunocompromised, may be a more pragmatic approach and an appropriate starting point for antibiotic allergy AMS programs. Antibiotic allergy testing may be associated with serious adverse events and should be performed in specialised centres, especially for patients with histories of severe or life-threatening adverse reactions. However, in many vulnerable patients, low risk antibiotic allergies can be clarified by history alone. Improving clinician understanding of cross-reactivity is likely to increase  $\beta$ -lactam uptake in patients with penicillin allergy, as may a refined AMS program focus.

In an effort to reduce inappropriate hospital antibiotic prescription by frequent antibiotic prescribers, we developed a centralised multidisciplinary antibiotic allergy testing program integrated within our AMS program at Austin Hospital and the Peter MacCallum Cancer Centre. After introducing the program, we found that 83% of patients could have an antibiotic allergy label removed.<sup>21</sup> This finding has particular significance as 48% of patients were immunocompromised, with conditions and treatments including haematological and oncological malignancy, autoimmune disease, solid organ or stem cell transplants, and steroid usage of more than 15 mg daily for 1 month.<sup>21</sup> After testing in this cohort, guideline-preferred antibiotic prescribing significantly improved (95% [3 months after implementation] *v* 62% [3 months before implementation]), as did antibiotic appropriateness (adjusted OR, 12.27; 95% CI, 5.00–30.09).<sup>21</sup> In another recent Australian study using allergy testing in an emergency department, 81% of patients had their penicillin allergy label removed following penicillin skin testing and oral provocation.<sup>22</sup>

Ideally, all patients with a history of immune-mediated allergy should be referred for specialist assessment and/or skin testing followed by oral provocation, which for immediate penicillin allergy is particularly safe and carries a 99.2% negative predictive value.<sup>9</sup> However, considering the large population burden of antibiotic allergy in Australian health care, specialist review

remains impractical. Vulnerable patients and those with severe, high risk or complex allergy histories should therefore be the target of specialised centralised testing programs. Other practical programmatic approaches that avoid skin testing and should be explored include direct oral penicillin challenge, which has recently been shown to be effective in carefully selected patients with low risk allergies.<sup>8,23</sup>

Validation of antibiotic allergy labels will clearly improve appropriateness of antibiotic use, although antibiotic allergy testing, while proposed as a way for AMS to reclaim antibiotics,<sup>16</sup> may not be viable in broad application. However, even simple measures such as educating clinicians about antibiotic cross-reactivity, pursuing a viral aetiology instead of antibiotic prescription for childhood exanthems, forensically evaluating purported allergy in the electronic medical record, and deleting labels that are drug side effects (eg, gastrointestinal intolerance) are likely to significantly aid de-labelling efforts. Raising the profile of antibiotic allergy in Australian health care and identifying vulnerable patients who would benefit from targeted antibiotic allergy testing are also likely to have a significant impact on antibiotic prescribing practices. Frequent users of antimicrobials, especially those with an immune-mediated antibiotic allergy, should be the primary targets for testing services. The establishment of multidisciplinary specialised antibiotic allergy testing referral centres involving allergists, infectious diseases physicians, AMS programs and pharmacists<sup>21</sup> enables centralised testing with minimisation of program costs and provision of specialised interpretation. Centralised antibiotic allergy testing programs integrated within AMS programs providing supervised skin-testing services — combined with widespread education regarding low rates of  $\beta$ -lactam cross-reactivity, development of programmatic oral re-challenges of low risk patients, and direct de-labelling of patients with antibiotic-related side effects — would underpin a collective effort to deliver the most appropriate antibiotic therapy for all patients, particularly those who are most vulnerable.

**Acknowledgements:** We thank Megan Crane for her significant contribution to the manuscript preparation and Michael Sutherland for establishing the Austin Health multidisciplinary antibiotic allergy testing service.

**Competing interests:** No relevant disclosures.

**Provenance:** Not commissioned; externally peer reviewed. ■

© 2018 AMPCo Pty Ltd. Produced with Elsevier B.V. All rights reserved.

References are available online at [www.mja.com.au](http://www.mja.com.au).

- 1 Trubiano JA, Chen C, Cheng AC, et al. Antimicrobial allergy 'labels' drive inappropriate antimicrobial prescribing: lessons for stewardship. *J Antimicrob Chemother* 2016; 71: 1715-1722.
- 2 Knezevic B, Sprigg D, Seet J, et al. The revolving door: antibiotic allergy labelling in a tertiary care centre. *Intern Med J* 2016; 46: 1276-1283.
- 3 Zhou L, Dhopeswarkar N, Blumenthal KG, et al. Drug allergies documented in electronic health records of a large healthcare system. *Allergy* 2016; 71: 1305-1313.
- 4 Trubiano JA, Leung VK, Chu MY, et al. The impact of antimicrobial allergy labels on antimicrobial usage in cancer patients. *Antimicrob Resist Infect Control* 2015; 4: 23.
- 5 MacFadden DR, LaDelfa A, Leen J, et al. Impact of reported beta-lactam allergy on inpatient outcomes: a multicenter prospective cohort study. *Clin Infect Dis* 2016; 63: 904-910.
- 6 Trubiano JA, Pai Mangalore R, Baey YW, et al. Old but not forgotten: Antibiotic allergies in General Medicine (the AGM Study). *Med J Aust* 2016; 204: 273. <https://www.mja.com.au/journal/2016/204/7/old-not-forgotten-antibiotic-allergies-general-medicine-agm-study>
- 7 Caubet JC, Frossard C, Fellay B, Eigenmann PA. Skin tests and in vitro allergy tests have a poor diagnostic value for benign skin rashes due to beta-lactams in children. *Pediatr Allergy Immunol* 2015; 26: 80-82.
- 8 Vezir E, Dibek Misirlioglu E, 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.
- 9 Bourke J, Pavlos R, James I, Phillips E. Improving the effectiveness of penicillin allergy de-labeling. *J Allergy Clin Immunol Pract* 2015; 3: 365-334 e361.
- 10 Trubiano JA, Worth LJ, Urbancic K, et al. Return to sender: the need to re-address patient antibiotic allergy labels in Australia and New Zealand. *Intern Med J* 2016; 46: 1311-1317.
- 11 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.
- 12 Campagna JD, Bond MC, Schabelman E, Hayes BD. The use of cephalosporins in penicillin-allergic patients: a literature review. *J Emerg Med* 2012; 42: 612-620.
- 13 Romano A, Gaeta F, Arribas Poves MF, Valluzzi RL. Cross-reactivity among beta-lactams. *Curr Allergy Asthma Rep* 2016; 16: 24.
- 14 Kula B, Djordjevic G, Robinson JL. A systematic review: can one prescribe carbapenems to patients with IgE-mediated allergy to penicillins or cephalosporins? *Clin Infect Dis* 2014; 59: 1113-1122.
- 15 Patriarca G, Schiavino D, Lombardo C, et al. Tolerability of aztreonam in patients with IgE-mediated hypersensitivity to beta-lactams. *Int J Immunopathol Pharmacol* 2008; 21: 375-379.
- 16 Ressler RA, Gada SM, Banks TA. Antimicrobial stewardship and the allergist: reclaiming our antibiotic armamentarium. *Clin Infect Dis* 2016; 62: 400-401.
- 17 Dellit TH, Owens RC, McGowan JE Jr, et al. Infectious Diseases Society of America and the Society for Healthcare Epidemiology of America guidelines for developing an institutional program to enhance antimicrobial stewardship. *Clin Infect Dis* 2007; 44: 159-177.
- 18 Schuts EC, Hulscher M, Mouton JW, et al. Current evidence on hospital antimicrobial stewardship objectives: a systematic review and meta-analysis. *Lancet Infect Dis* 2016; 16: 847-856.
- 19 Barlam TF, Cosgrove SE, Abbo LM, 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.
- 20 King EA, Challa S, Curtin P, Bielory L. Penicillin skin testing in hospitalized patients with beta-lactam allergies: effect on antibiotic selection and cost. *Ann Allergy Asthma Immunol* 2016; 117: 67-71.
- 21 Trubiano JA, Thursky KA, Stewardson AJ, et al. Impact of an integrated antibiotic allergy testing program on antimicrobial stewardship: a multicenter evaluation. *Clin Infect Dis* 2017; 65: 166-174.
- 22 Marwood J, Aguirrebarrena G, Kerr S, et al. De-labelling self-reported penicillin allergy within the emergency department through the use of skin tests and oral drug provocation testing. *Emerg Med Australas* 2017; 29: 509-515.
- 23 Confino-Cohen R, Rosman Y, Meir-Shafir K, et al. Oral challenge without skin testing safely excludes clinically significant delayed-onset penicillin hypersensitivity. *J Allergy Clin Immunol Pract* 2017; 5: 669-675. ■