

ORIGINAL ARTICLE

Antibiotic allergy labels and optimal antimicrobial stewardship

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Key words

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Abstract

Background: Although common, antimicrobial allergy labels (AAL) rarely reflect immunologically-mediated hypersensitivity and can lead to poorer outcomes from alternative antimicrobial agents. Antimicrobial stewardship programs are ideally placed to assess AAL early as a means of improving antimicrobial use.

Aims: To quantify the prevalence of AAL in patients referred for antimicrobial stewardship review and assess their impact on antibiotic prescribing, patient mortality, hospital length of stay, readmission and rates of multidrug-resistant infections.

Methods: We conducted a retrospective analysis of adult patients referred for inpatient antimicrobial prospective audit and feedback rounds (PAFR) through an electronic referral system (*eReferrals*) over a 12-month period in 2015. Outcome data were collected for a period of 36 months following the initial review.

Results: Of the 639 patient records reviewed, 630 met inclusion criteria; 103 (16%) had an AAL, of which 82 (13%) had reported allergies to β -lactam antibiotics. Those with AAL were significantly less likely to be receiving guideline-recommended antimicrobial therapy (50% vs 64%, $P = 0.0311$); however, there were no significant difference in mortality, hospital length of stay, readmission or increased incidence of multidrug-resistant infections.

Conclusions: Our cohort demonstrated that AAL was associated with reduced adherence to antibiotic guidelines. The lack of association with adverse outcomes may reflect limitations within the study including retrospective cohort study numbers and observational nature, further skewed by high rates of poor documentation. A clear opportunity exists for antimicrobial stewardship programs to incorporate allergy assessment, de-labelling, challenge and referral into these rounds.

Introduction

The prevalence of documented antibiotic allergy in hospitalised patients ranges from 18% to 25%.^{1–3} Allergy is most commonly reported with the beta-lactam class of antibiotics, which comprises penicillins, cephalosporins, carbapenems and monobactams; accounting for approximately 50% of antimicrobial drug allergies.⁴ A significant proportion of these documented allergies are due to non-immune mediated (Type A) rather than true immune mediated (Type B) reactions.⁵ Although there is a wide variation in

the pathophysiology and severity of these reported allergies, the approach has traditionally been avoidance of implicated antimicrobial class, in favour of alternative second line agents.^{2,6} This has been shown to result in the use of suboptimal therapy leading to treatment failure, drug toxicity, increased hospital length of stay, and higher rates of hospital readmission in addition to increased risk of colonisation or infection from multidrug-resistant organisms including methicillin-resistant *Staphylococcus aureus* (MRSA), vancomycin resistant *Enterococcus* (VRE) and *Clostridioides difficile* infection.^{7–10}

Incorporating antibiotic allergy review into antimicrobial stewardship assessment has been suggested as

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effective in 'de-labelling' antibiotics with reported drug intolerances, and allowing for optimal directed antimicrobial utilisation.^{11,12} In patients unable to be de-labelled immediately, prospective audit and feedback rounds (PAFR) also provide opportunities for clinician education regarding the appropriate choice and duration of antibiotic treatment and true risk of cross-reactivity based on shared side chains.^{11,13} This study was designed to review the quality of documentation of antimicrobial allergy labels (AAL) in patients referred for PAFR, quantify the burden of incorporating AAL assessment during PAFR, and subsequently assess the impact of AAL labels on several clinical outcomes.

Methods

We performed a retrospective single-centre cohort study of adult patients referred to a 783-bed quaternary teaching hospital in Western Australia. The use of broad-spectrum antibiotics including carbapenems, fluoroquinolones, third and fourth generation cephalosporins, piperacillin/tazobactam and glycopeptides are restricted, in keeping with the hospital antimicrobial stewardship program. Hospital inpatients receiving these agents are identified by the clinical pharmacists or the responsible medical team through an electronic referral system (*eReferrals*); and referred for prospective audit and feedback rounds (PAFR) every weekday. These rounds incorporate chart and medical record review including available microbiological results by an Infectious Diseases physician and pharmacist, but do not include history or physical examination of the patient. Using this information, recommendations are made regarding dose, choice and duration of antimicrobial therapy during PAFR.¹⁴ A total of 639 patients were reviewed, chosen in order of unique patient medical record number from 1400 patients referred for PAFR in the inaugural year of hospital operation, between January 1st and December 31st 2015. Patients were excluded if they were younger than 16 years or if they were not prescribed antibiotics.

Data were collated from a prospectively maintained database of all patients identified for PAFR. The database included patient data from all inpatient wards except the intensive care unit and haematology ward, which have separate antimicrobial stewardship arrangements. The collected data included patient demographic information, history of diabetes mellitus, chronic liver or kidney disease, active malignancy, admitting specialty, prescribed antimicrobial and reported allergies. When an antibiotic allergy was reported, the characteristics of the index reaction were investigated by reviewing three areas of the patient documentation; the *eReferrals* database, the hospital electronic medical record (*eMR*) and

the National inpatient medication chart (NIMC). Allergies were categorised broadly into type A and type B reactions, as detailed in Table 2. Rash was further stratified by timing from drug exposure at 2week mark, in order to identify patients with delayed non-severe cutaneous reactions, where de-labelling would be difficult due to temporal gap between exposure and reaction. Severe cutaneous adverse reactions were not specifically reviewed. The *eMR* and NIMC were retrospectively reviewed 48 h after PAFR to assess whether advice regarding choice of antimicrobial was followed.

Outcome data assessed included prevalence of initial prescription of guideline-recommended versus alternative antimicrobial use, adherence to PAFR following assessment by the pharmacist from the *eMR* 48 h after the advice was provided, hospital length of stay, readmission at 4 and 26 weeks, inpatient mortality, and development of new *Clostridioides difficile* infection and MRSA colonisation over a period of 36 months following PAFR, obtained from the statewide public Laboratory Information System. Recommended antimicrobial therapy was defined based on recommendations from the Australian Therapeutic Guideline available during the study period (eTG:v15 2016).¹⁵ *C. difficile* infection was defined by molecular detection of *C. difficile* toxin in the presence of diarrhoea. MRSA colonisation was identified by molecular detection of MRSA DNA on screening swabs or following culture of clinical samples after PAFR. Patients known to be MRSA positive before PAFR were excluded from this analysis.

The study was approved by the quality improvement committee (Governance, Evidence, Knowledge Outcomes GEKO ref #22431) as a quality improvement project and was considered exempt from requiring formal ethics approval.

Statistical analysis

Counts and percentages are provided for categorical variables, means and standard deviations (SDs) are provided for normally distributed continuous variables, and medians and inter-quartile ranges (IQRs) are reported for non-normally distributed continuous variables. A multivariate binary logistic regression was performed to analyse the relationship between patient age, sex and specialty with any antimicrobial allergy label (AAL) (event = 'Labelled'). The impact of having an AAL, after adjusting for age, sex, immunocompromised status and specialty if significant, on being initially prescribed specific antibiotics, being initially prescribed guideline-recommended alternative antibiotics, incident MRSA colonisation or *C. difficile* infection, being readmitted in either 4 or 26 weeks, inpatient death and whether PAFR

Table 1 Baseline demographic information for cohort, by antibiotic allergy label (AAL) and subspecialty

Cohort demographics	Overall, N = 630 AAL, N = 103 No AAL, N = 527		
Age (years)			
Mean (SD)	63 (19.5)	66 (17)	62 (19.9)
Gender			
Female	280 (44%)	57 (20%)	223 (80%)
Male	350 (56%)	46 (13%)	304 (87%)
Immune status			
Immunocompromised	240 (38%)	49 (20%)	191 (80%)
Immunocompetent	390 (62%)	54 (14%)	336 (86%)
Subspecialty			
Medical specialties	148 (23%)	31 (21%)	117 (79%)
Surgical specialties	416 (66%)	63 (15%)	353 (85%)
Oncology	16 (3%)	0 (0%)	16 (100%)
Other	50 (8%)	9 (18%)	41 (82%)

advice was followed was assessed using binary logistic regressions (event = 'Yes' for all analyses). Additionally, the relationship between having an AAL, after adjusting for age, sex, immunocompromised status and specialty if significant, and (log-transformed) hospital length of stay was assessed using a linear regression. Significance for all analyses was considered at the 5% level; odds ratios (ORs), 95% confidence intervals (CIs) and *P*-values are provided for logistic regression results, whilst estimated mean differences (MDs), standard errors (SEs) and *P*-values are provided for the linear regression.

Results

Demographic and clinical characteristics

Records were reviewed for 639 patients; nine were excluded for not meeting the inclusion criteria (6 patients younger than 16 years and 3 patients were never prescribed antibiotics) leaving 630 adult patient records for analysis. The patient demographics from collected data are illustrated in Table 1. The mean age was 62.8 years (SD 19.5), 350 patients (56%) were male and 240 patients (38%) were immunocompromised. There were 416 surgical patients (66%), 164 patients (26%) were from medical wards, and 50 patients (8%) from other wards.

An AAL was present in 103 patients (16%), of which 19 patients (18%) reported two or more AAL. Of those with AAL, 71 patients (69%) reported allergy to penicillin, 15 patients (15%) to cephalosporin, one patient (1%) to carbapenem and 38 patients (37%) reported non- β -lactam allergies. The most commonly reported reaction to penicillin was early onset (within 2 weeks of exposure) rash (20%), followed by anaphylaxis (17%),

Table 2 Description of antibiotic allergy label, by broad antimicrobial class

Reaction type	β -Lactam, N = 87	Non- β -lactam, N = 38
Type A		
Chest pain	1 (1%)	0
Deranged liver function tests	1 (1%)	1 (3%)
Dizziness	3 (3%)	1 (3%)
Gastrointestinal upset	8 (9%)	2 (5%)
Renal impairment	0	1 (3%)
Shakes	1 (1%)	0
Thrush	1 (1%)	0
Type B		
Anaphylaxis	13 (15%)	2 (5%)
Angioedema	7 (8%)	1 (3%)
Rash < 2 weeks	21 (24%)	10 (26%)
Rash > 2 weeks	11 (13%)	4 (11%)
Rash (unspecified timing)	4 (5%)	1 (3%)
Documentation missing	16 (18%)	15 (39%)

late onset (greater than 2 weeks following exposure) rash (16%), and gastrointestinal upset (10%); 18% of reactions were not documented. Early onset rash was also commonly associated with cephalosporin allergies (40%) and in one carbapenem reaction. With regards to reported non- β -lactam adverse drug reactions, early onset rash was again the most commonly reported adverse effect (27%), followed by late onset rash (11%), anaphylaxis (5%) and gastrointestinal upset (5%); the reaction was non-specific in 3% and not documented in 38%. β -Lactam class and non- β -lactam reaction types are summarised in Table 2.

Patient characteristics and AAL

The mean age of patients with AAL was 66 years (SD 17) vs 62 years (SD 19.9) with no AAL. AAL were more likely to be reported in older patients (70+ years vs 16–40 years: OR = 2.68, 95% CI = 1.21–5.90; 41–60 years vs 16–40 years: OR = 1.92, 95% CI = 0.86–4.28; overall *P*-value = 0.0362), female patients (OR = 1.76, 95% CI = 1.14–2.71, *P* = 0.0103) and immunocompromised patients (OR = 1.62, 95% CI = 1.05–2.50, *P* = 0.0294). Specialty was not significantly related to having an allergy label.

Documentation quality

In the 103 patients with a reported antibiotic allergy, documentation of AAL was missing in the electronic medical record, *eReferrals* and NIMC in 28%, 40%, and 24% of patients respectively. Of the 87 documented β -lactam AAL, 31 (36%) were Type A reactions or had information missing; whilst 20 (53%) of the 38 reported

Table 3 Patient outcome statistics for the cohort, by AAL

Outcome	Overall	AAL	No AAL
Median hospital length of stay (IQR)	8 (9)	8 (7)	8 (10)
Readmission			
Within 4 weeks	138 (22%)	21 (20%)	117 (22%)
Within 26 weeks	293 (47%)	53 (52%)	240 (46%)
Death during admission	23 (4%)	2 (2%)	21 (4%)
MRSA colonisation			
Prior MRSA	40 (6%)	3 (3%)	37 (7%)
Incident MRSA	19 (3%)	4 (4%)	13 (2%)
<i>Clostridioides difficile</i> infection	15 (3%)	5 (5%)	8 (1.5%)
Incident MRSA or <i>Clostridioides difficile</i> infection		9 (9%)	23 (4.7%)
Guideline-recommended therapy initiated	390 (62%)	52 (50%)	338 (64%)
Penicillins	77%	34%	83%
Cephalosporins	14%	38%	11%
Quinolones	7%	20%	5%
Nitroimidazoles	10%	29%	7%
Lincosamides	3%	9%	3%
Vancomycin	7%	9%	7%
PAFR advice adhered	486 (84%)	77 (85%)	409 (84%)

AAL, antibiotic allergy label; CDI, *clostridioides difficile* infection; IQR, inter-quartile ranges; MRSA, methicillin-resistant *Staphylococcus aureus*; PAFR, prospective audit and feedback rounds.

non- β -lactam AAL were not documented appropriately or Type A reactions.

The impact of AAL on clinical outcomes including hospital length of stay, readmission, mortality, incident MRSA colonisation and *C. difficile* infection, adherence to PAFR and prescription of guideline-recommended antimicrobial therapy are summarised in Table 3.

AAL impact on outcome

There was no significant difference in hospital length of stay (AAL vs. no AAL: MD -0.05 , SE 0.09 , $P = 0.58$), 4-week or 6-month readmission (AAL vs no AAL: OR 0.83 , 95% CI 0.49 , 1.40 , $P = 0.48$; OR 1.12 , 95% CI 0.73 – 1.73 , $P = 0.61$ respectively) or inpatient death (AAL vs no AAL: OR = 0.41 , 95% CI 0.09 – 1.83 , $P = 0.24$) between patients with and without an AAL.

AAL impact on MRSA colonisation and *C. difficile* infection

After excluding those patients previously known to be colonised with MRSA prior to commencement of antimicrobial therapy, 9% of patients with AAL developed either MRSA or *C. difficile*, compared to only 4.7% of patients without AAL; however, this difference did not reach significance (OR = 2.01 , 95% CI = 0.90 – 4.48 , $P = 0.09$).

Impact of AAL on antimicrobial prescribing

Patients with an AAL were significantly less likely to be initially prescribed guideline-recommended therapy (OR 0.62 , 95% CI 0.40 – 0.96 , $P = 0.0311$). Patients with an AAL were less likely to be initially prescribed penicillin [OR 0.19 , 95% CI 0.12 – 0.29 , $P < 0.001$] and more likely to be prescribed cephalosporins [OR 3.58 , 95% CI 2.17 – 5.88 , $P < 0.001$], quinolones [OR 3.81 , 95% CI 1.98 – 7.32 , $P < 0.001$] and nitroimidazoles [OR 5.50 , 95% CI 3.03 – 10.0 , $P < 0.001$] than patients without an AAL.

AAL and stewardship prospective audit and feedback advice (PAFR)

Specific recommendations regarding the choice of antimicrobial made during PAFR was not recorded in 54 of the 630 patients, leaving 576 patients for analysis. There was no significant difference in adherence to PAFR with regards to antimicrobial therapy when comparing patients with and without an AAL ($P = 0.9454$).

Discussion

Antimicrobial stewardship programs are well established globally in order to maximise benefit of antibiotic utilisation, whilst minimising unwarranted drug adverse effects.¹⁶ PAFR are an important aspect of these programs, which allow chart assessment for rationalisation of antimicrobial therapy.¹⁷ A previous study examining our institution's electronic referral system had demonstrated steadily increased adherence to antimicrobial advice provided on PAFR over a 12-month period.¹⁴ To date, this is the first study specifically selecting patients referred for antimicrobial PAFR to identify and review patient AAL documentation and antimicrobial selection by the treating team, before and after PAFR.

Antimicrobials comprise of the most common reported drug allergies in hospitalised patients, surpassing opioids, anti-hypertensives, non-steroidal anti-inflammatory drugs, radiocontrast and anaesthetic agents.⁴ Our cohort study demonstrated 16% of inpatients had an AAL, similar to the rates of reported antibiotic allergy in previous studies (18%–25%) as well as the prevalence of antimicrobial allergy in hospitalised patients in Australia from the National Antimicrobial Prescribing Survey data.^{1–3} Our cohort reflected prior reviews with AAL more commonly reported in females, older patients and immunocompromised patients.⁴ In our study, almost 80% of AAL were to the β -lactam class. This is particularly important as β -lactams constitute first line antimicrobial therapy for the majority of infections.

The members of the PAFR team are uniquely placed to provide advice regarding antimicrobial selection, based on the clinical and laboratory data. AAL documentation, however, was missing commonly within the three assessed platforms of documentation in this cohort, with allergy information missing in 28% from the *eMR*, 24% from the NIMC and 40% from the *eReferrals* for PAFR. The nature of the allergy was also commonly unspecified, with no clarifying information in 16% of penicillin AAL, 20% of cephalosporin AAL and 38% of non- β -lactam AAL. Direct face-to-face interactions with the treating teams and clinical pharmacists managing the patient provide opportunities to improve allergy history taking and subsequent documentation.

In general, antimicrobial allergies may be divided into predictable dose-dependent side effects such as gastrointestinal upset (Type A) or immune-mediated drug reactions (Type B). Type A reactions are not true drug allergies, hence agents from the same antimicrobial class can usually safely be used subsequently without risk of clinical deterioration.^{5,18} The proportion of Type A AAL in our cohort (11% β -lactam and 8% non- β -lactam) represents an immediate opportunity to discuss de-labelling patients with the managing team during PAFR. Additionally, it is likely that a proportion of the unspecified AAL would also be Type A reactions on further investigation. AAL stemming from childhood often represent alternative diagnoses such as viral exanthem rather than true Type B immune mediated reactions,^{19,20} whilst IgE mediated reactivity often declines over time, with several previous studies demonstrating that 80% to 90% penicillin labels may be removed following formal skin prick testing or provocation challenge.^{11,18,21} Further, allergy cross-reactivity within β -lactam class of antimicrobials occurs less commonly than previously thought.²² A distant benign rash was reported in over a third of cohort patients, representing significant opportunity for assessment, supervised re-challenge and subsequent de-labelling in the majority of cases.^{23–25}

AAL in our cohort was associated with significantly lower use of penicillin (34% vs 83%), and increase in use of alternative agents; with 3-fold increase in the prescription of cephalosporins (38% vs 11%), lincosamides (9% vs 3%) and 4-fold increase in the prescription of quinolones (20% vs 5%) and nitroimidazoles (29% vs 7%). Utilising recommendations from the Australian Therapeutic Guidelines: Antibiotic (eTG v15 2016),¹⁵ the use of guideline-recommended therapy for the entire examined cohort was low (62%), with recommended therapy prescribed significantly less for patients with AAL (50%) than those without (64%). However, our data did not demonstrate any significant differences between the groups for hospital length of stay,

readmission at 4 or 26 weeks, inpatient mortality or development of incident MRSA or *C. difficile* infection. The presence of AAL did not affect adherence to PAFR.¹⁴

The presence of AAL often leads to patients receiving second line agents, which are often inferior and associated with higher rates of treatment failure or infection recrudescence,⁸ associated with poorer clinical outcomes including increased duration of hospital length of stay, higher rates of readmission and increased mortality.⁷ The association of AAL in our immunocompromised cohort is significant as AAL in oncology patients have been associated with increased antimicrobial use and duration, poorer adherence to prescribing guidelines as well as higher readmission rates,²⁶ indicating that these patients will particularly benefit from expert review and allergy assessment. Further, the use of generally broad-spectrum alternative agents in patients with AAL is associated with increased risk of healthcare associated *C. difficile* infection and the emergence of multidrug-resistant pathogens including MRSA and VRE colonisation or infection.¹⁰ There are likely several reasons for similar clinical outcomes between patients with and without AAL in our cohort, reflecting limitations of our study. The retrospective, observational design of the study limits result interpretation including causal relationships between AAL and subsequent outcomes. Our sample size of 630 patients, of which only 103 patients had any AAL may have been too small to demonstrate clinically significant outcomes. This was even more evident when examining the rates of incident *C. difficile* infection and MRSA colonisation; with small numbers in both of the cohort arms; further influenced by low initial population rates of *C. difficile* infection and MRSA prevalence.

Allergy history is the key in stratifying risk. Absent or non-specific documentation across the multimodal platforms during the study made interpretation of data difficult which in turn limits antimicrobial decision making by the treating team as well as during PAFR. There was no difference in adherence to advice provided on the PAFR regarding choice of antibiotic between patients with or without AAL. The high rate of adherence (85% and 84% respectively) reflects the high degree of acceptance overall for PAFR advice and the antimicrobial stewardship program in general at our institution.¹⁴

The patient cohort was derived from those initially identified by the clinical pharmacist or treating team who felt they would benefit from PAFR, therefore may not have been representative of the overall hospital population. There was overrepresentation of surgical patients in our cohort, reflecting the patient composition of our hospital but this may have influenced prescribing practices. Further, a significant proportion of these

patients would have received prior telephonic expert antimicrobial advice preceding PAFR; as further confounding factors, additionally reducing significance in findings between the cohort arms. Finally, outcomes for our cohort of patients were based on inpatient platforms of documentation unique to our hospital and so adverse events in the community or in a different health institution related to consequent prescription of alternative antimicrobial agents would not have been captured in this study.

Conclusion

This study utilised PAFR to investigate the documentation and impact of AAL within an inpatient cohort of patients in a quaternary hospital. Within this population, we noted that an AAL was reported frequently (16%), and most commonly associated with the β -lactam class of antibiotics; however, documentation quality was generally poor. AAL were associated with less appropriate use of antimicrobial agents, even when clear Type A

reactions were documented. Poorer clinical outcomes in patients with AAL were not demonstrated in our cohort; however, there were several limiting factors within our study; including small sample size and observational retrospective design, highlighted by high rates of poor AAL documentation. Type A and non-severe Type B reactions offer a clear opportunity for antimicrobial stewardship programs to improve antimicrobial use through direct de-labelling or re-challenge as a part of PAFR, in addition to targeting AAL documentation quality.^{23,27} These data have informed service planning in both the antimicrobial stewardship and Clinical Immunology departments in our institution. This is an evolving area of literature and future larger prospective trials may contribute further data to the link between AAL and adverse clinical outcomes.

Ethical approval

Exempt from formal ethics approval as approved by quality improvement committee.

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