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ORIGINAL ARTICLE

Impact of antibiotic allergy labels on patient outcomes in a tertiary paediatric hospital

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Aims: Antibiotic allergies are reported in 5–15% of children. This study aimed to evaluate the impact of common β-lactam antibiotic allergy labels (AALs) on hospital treatment, focusing on length of stay and appropriateness of antibiotic prescribing.

Methods: This was a retrospective cohort study over 21 months at the Royal Children's Hospital Melbourne, Australia. A subset of children with the most common β-lactam allergies, and who required admission for intravenous antibiotics over a 12-month period, was analysed for appropriateness of prescribing. Non-allergic patients were matched to evaluate associations between AALs and hospital treatment.

Results: There were 98 912 children admitted over the study period, of whom 938 (1%) had at least one AAL on first admission. Of all encounters, 5145 (2.5%) were for children with AALs. The most common AALs were to amoxicillin and amoxicillin-clavulanic acid combinations (40.8%), cefalexin (14.4%) and trimethoprim-sulfamethoxazole (9.7%). For the subset, there were 66 admissions for children who required intravenous antibiotics. Documentation was adequate for 27% of AALs. Inappropriate prescribing occurred in almost half (47%). Hospital stay was longer for children with AALs (median 4.7 days; IQR 2.3–9.2) compared to non-allergic controls (median 3.9 days; IQR 1.9–6.8; $P = .02$). Children with AALs were more likely to receive restricted antibiotics (aOR 3.03; 95% CI, 1.45–6.30; $P = .003$).

Conclusion: This is the first study to demonstrate high rates of inappropriate prescribing in children with AALs. Children with AALs were significantly more likely to receive restricted antibiotics and had a longer length of stay compared with non-allergic controls.

KEYWORDS
antimicrobial allergy, antimicrobial stewardship, drug challenge

1 | INTRODUCTION

Antibiotic allergy labels (AALs) place a significant burden on the health system through higher medication costs,[1] increased length of stay and poorer treatment outcomes.[2,3] The prevalence of self-reported antimicrobial allergy is between 5 and 15% of all children and adults admitted to hospital or attending outpatient services.[4,5] β-lactam antibiotics are the most commonly implicated,[6–8] with up to 75% of patients labelled with these allergies before the age of 3 years.[9] Previous studies have shown that more than 90% of children with non-immediate reactions to amoxicillin do not have reproducible "allergic" reactions when re-challenged with the same drug.[10,11] Therefore, there is the potential for a large majority of these allergies to be effectively "de-labelled".[12,13]

Antibiotic allergy de-labelling is now recognised as a key component of antimicrobial stewardship programmes.[14] However, most institutions do not have automated processes by which patients can have their antibiotic allergy evaluated and, if possible, removed. In many instances, the reported allergy may only be noted when treatment for infection is urgently indicated and, therefore, there is no opportunity for formal assessment of the previous allergy.

Compounding these problems is the wide variability in knowledge of how to assess a child's drug allergy. Terms such as "allergy", "reaction" and "side effect" may be misunderstood by parents reporting their child's previous reactions, and clinicians' documentation of these is frequently inadequate.[15–17]

In this study, we aimed to evaluate the prevalence of antibiotic allergy in an Australian tertiary paediatric centre, focusing on accuracy of allergy documentation in the electronic medical record (EMR) and referral for drug allergy assessment. For a subset of patients with the most common β-lactam antibiotic allergies, the appropriateness of subsequent antibiotic prescribing and impact on hospital treatment—including length of stay and use of restricted antibiotics—was evaluated.

What is known about this subject

- The most common AALs in children are to penicillins, sulfas and cephalosporins.
- More than 90% of children with β-lactam AALs do not have reproducible reactions when re-challenged.
- Inadequate allergy documentation leads to higher rates of inappropriate prescribing in adults.

What this study adds

- AALs lead to higher rates of inappropriate antibiotic prescribing in children.
- Children with AALs are more likely to be prescribed restricted antibiotics and stay longer in hospital.
- Many children with β-lactam AALs are not assessed prior to admission for IV antibiotics.

2 | METHODS

This was a retrospective study of patients admitted between 30 April 2016 and 30 January 2018. Included children were aged between 0 to 18 years who had a pre-existing AAL, as defined by having a drug reaction documented within the allergy section of the EMR, and who presented to the Royal Children's Hospital Melbourne (RCH), Australia. The RCH is a tertiary paediatric hospital with 250 inpatient beds. The hospital's drug allergy service is the only public service for children in the state of Victoria. Referrals are generated from the hospital's Adverse Drug Reactions Committee, as well as from clinicians internally and externally.

The hospital's EMR was searched in April 2018. A report was generated detailing all patients with at least one AAL who had an encounter with the hospital (emergency, short stay, day unit or ward admission) since the introduction of EMR on 30 April 2016.

The study involved two parts: the first, a descriptive analysis of the burden of AAL on the hospital over a 21-month period; the second, a subset analysis of patients over a 12-month period (February 2017 to January 2018) who had a documented allergy to either amoxicillin, penicillin or cefalexin and who required treatment with intravenous (IV) antibiotics. This subset was chosen because allergies to these antibiotics are among the most common in children.[18]

Data were collected on patient demographics, antibiotic implicated in AAL, symptoms and severity of reaction and referral for drug allergy assessment.

For the subset analysis, additional data were collected to determine adequacy of allergy documentation, appropriateness of antibiotic prescribing and exposure to restricted antibiotics. Restricted antibiotics were defined as either a glycopeptide, third or fourth generation cephalosporin, fluoroquinolone or carbapenem.[19]

2.1 | Adequacy of documentation

Documentation of an allergic reaction was defined as adequate if it included information on the time to reaction onset after the first dose of the last course, clinical symptoms, and the severity of the reaction and/or treatment provided, thereby enabling clinicians to determine the safety of re-challenging the patient with the medication. We further classified each reaction as occurring either due to an adverse, but predictable, reaction to the drug or due to an immunologically mediated, or true allergic reaction. Finally, we cross-referenced every reaction documented in the allergy section of the EMR with the patients' clinical notes (either scanned paper notes or computer entries) to assess whether descriptions were accurate.

2.2 | Appropriateness of antibiotic prescribing

Appropriateness of the antibiotic prescribed was considered in two ways: (i) appropriate for the patient's documented antibiotic allergy as per existing guidelines[12,20]; and (ii) appropriate antibiotic type, route and duration for the infection being treated, as per the Australian Therapeutic Guidelines[21] and the methodology used in two previous studies on antibiotic prescribing undertaken at the same hospital.[22,23] Each decision was reviewed by an infectious diseases physician (A.G.).

Antibiotic decisions deemed inappropriate based on the patient's allergy were further subcategorised in the following ways: (i) prescribed an antibiotic from the same class to which the initial reaction occurred; (ii) prescribed an antibiotic from an alternate class despite an initial immediate reaction; (iii) antibiotic unnecessarily excluded based on available information.

Antibiotic decisions were deemed inappropriate for the infection being treated if any of the following were true: (i) failure to comply with antibiotic treatment guidelines; (ii) unnecessary treatment with an additional antibiotic; (iii) antibiotic prescribed by an inappropriate route, at an inappropriate dose or for an inappropriate duration. These were classified by an infectious diseases physician (A.G.).

2.3 | Impact on hospital treatment

As part of the subset analysis, non-allergic patients (those without an AAL to either amoxicillin, penicillin or cefalexin) were selected to evaluate the association between AAL and hospital treatment (i.e., length of stay and use of restricted antibiotics). For each hospitalised patient with an AAL who required IV antibiotics (excluding surgical prophylaxis), we matched between one and five non-allergic patients of similar age (within 1 year), hospitalised for IV antibiotics for the same diagnosis, under the same unit and within the same period (2016–2017). If more than five non-allergic controls were available, they were chosen randomly. Children with documented AALs for some hospitalisations were not eligible to be controls at previous hospitalisations. Difference in length of stay and use of restricted antibiotics were estimated using mixed model linear and logistic regressions, respectively, with child as random effect, adjusted for gender, age at admission and hospitalisation unit. A sensitivity analysis was performed using the data from the children's first admissions only. We did not include subsequent admissions in this analysis as repeat measurements from the same patient are likely to be more similar to each other than measurements from different patients, thus potentially over-influencing the results.

Proportions were compared using Fisher's exact test. Data were analysed using Stata v.13® (StataCorp, College Station, TX). All tests were two-sided. This study was approved by the RCH Human Research Ethics Committee (HREC 37302B).

3 | RESULTS

During the 21-month study period, there were 204 413 patient encounters for 98 912 children at RCH. There were 938 children (1.0%) who had at least one AAL recorded in the EMR at the start of their admission. These 938 children had 5145 encounters (median two encounters per child, range 1–88), accounting for 2.5% of all hospital encounters during the study period. The median age of these children at first admission during this period was 8.7 (range 3 months to 18 years) and 53.8% were male. These 938 children had 1049 documented antibiotic allergies (median one per child, range 1–6). The large majority of children (853/938 90.9%) had only one AAL. Only 47 (5.0%) children had been seen by the hospital's drug allergy service by the end of the study period.

Penicillins were the most commonly implicated antibiotic class in drug allergy among these 938 children (439, 46.6%), followed by cephalosporins (266, 28.3%), macrolides (112, 11.9%), sulphonamides (91, 9.7%), glycopeptides (68, 7.2%), fluoroquinolones (15, 1.6%) and aminoglycosides (14, 1.5%). The antibiotics most commonly implicated were amoxicillin or amoxicillin-clavulanic acid combinations (383, 40.8%), cefalexin (135, 14.4%), trimethoprim-sulfamethoxazole (91, 9.7%), cefaclor (79, 8.4%), erythromycin (71, 7.6%) and vancomycin (66, 7.0%).

Symptoms of the allergic reaction were documented in 912/1049 (86.9%) of all allergies with rash accounting for more than half (532/912, 58.3%), followed by gastrointestinal symptoms (99/912, 10.9%), urticaria (87/912, 9.5%), red man syndrome secondary to vancomycin (46/912, 5.0%), "swelling" (36/912, 3.9%), and anaphylaxis (31/912, 3.3%).

3.1 | Subset analysis (AALs to amoxicillin, penicillin and cefalexin)

Over a 12-month period there were 66 admissions for IV antibiotics for 45 children who had a label of either penicillin, amoxicillin or cefalexin allergy, or a combination of these. Of the 66 admissions, 48 (73%) were for children who reported an amoxicillin or amoxicillin-clavulanic acid allergy, 22 (33%) cefalexin and 3 (4.5%) penicillin allergy. The median number of admissions per child was one (range 1–6). Data were complete for the subset except for documentation of allergic reaction.

3.2 | Admission diagnosis, length of stay and use of restricted antibiotics ($n = 66$)

Admission diagnosis, antibiotic prescription and total length of stay for the 66 admissions are detailed in Table 1. The median age of the subset at their first hospital admission was 8.6 years (IQR 3.6–10.8 years, range 5 months to 17.7 years) and 56% were female. A total of 131 children of similar age (median 9.0 years, IQR 3.9–13.1) were selected as matched controls as outlined in the methods section.

Hospital stay was longer in the AAL patients (median 4.7 days; IQR 2.3–9.2) compared to the non-allergic patients (median 3.9 days; IQR 1.9–6.8; $P = .02$). Also, children with an AAL were more likely to be prescribed a restricted antibiotic (aOR 3.03; 95% CI, 1.45–6.30; $P = .003$) with restricted antibiotics used in 53.0% of hospital admissions for those with an AAL compared with 26.7% for non-allergic patients. A sensitivity analysis performed on first admissions only (for both allergic and non-allergic patients) found similar results.

3.3 | Accuracy and adequacy of antibiotic allergy documentation ($n = 73$)

The 45 children in this subset had 73 documented antibiotic allergies. All reported allergies had been diagnosed prior to admission, though

TABLE 1 Admission diagnosis and frequency of restricted antibiotic prescriptions for the subset of patients with an antibiotic allergy ($n = 66$). Non-allergic children who also required admission for IV antibiotics were matched for age (within 1 year), diagnosis and admitting unit

	Allergic patients			Non-allergic patients		
Diagnosis	Number of patient encounters	% use of restricted antibiotic	Median LOS among allergic patients (IQR)	Number of matched non-allergic patients	% use of restricted antibiotic	Median LOS (IQR, range)
Sepsis, unspecified	15	87%	5.5 (IQR 0.7–27.9)	23	57%	6.9 (IQR 4.3–10.3)
Pneumonia (including patients with cystic fibrosis)	13	38%	9.2 (IQR 6.6–16.2)	36	11%	3.3 (IQR 1.9–6.4)
Osteomyelitis unspecified	2	0%	18.2 (IQR 3.2–33.2)	3	0%	8.5 (IQR 6.0–39.2)
Cellulitis of lower limb	2	50%	2.6 (IQR 2.6–2.7)	9	44%	2.9 (IQR 1.3–4.4)
Crohn's disease	3	66%	5.8 (IQR 3.5–14.8)	8	25%	4.7 (IQR 3.6–7.5)
Urinary tract infection	3	33%	2.5 (IQR 1.0–2.8)	14	14%	1.8 (IQR 1.5–3.2)
Acute appendicitis with peritonitis	2	0%	5.3 (IQR 4.7–5.8)	10	0%	5.1 (IQR 3.7–6.9)
Cellulitis of face	3	33%	1.2 (IQR 0.3–2.9)	10	40%	2.4 (IQR 1.9–4.8)
Cellulitis of upper limb	2	0%	2.1 (IQR 1.2–3.0)	7	14%	2.0 (IQR 1.5–3.9)
Acute pharyngitis	1	100%	0.2	1	0%	0.7
Infection due to central vascular catheter	1	100%	5.5	1	100%	5.8
Mastoiditis	1	100%	2.3	4	100%	2.8 (IQR 1.8–5.5)
Pilonidal cyst with abscess	1	0%	1.5	5	0%	7.4 (IQR 1.7–12.7)
Surgical prophylaxis	17	18%	3.3 (IQR 2.1–4.3)	Matching not performed. Excluded from analysis as this group received prophylaxis rather than treatment of known infection.		
Total[a]	66	53.1%	4.7 (IQR 2.3 to 9.2)	131	26.7%	3.9 (1.9–6.8)

[a]Excluding surgical prophylaxis data. IQR: interquartile range; LOS: length of stay in days.

the age at which each child first had their "allergic" reaction was documented in only 27 cases (37%). The median age of the initial reaction was 4 years (range <1–16 years) and the median time that had lapsed between the initial reaction and the admission was 2 years (range <1–3 or more years).

Documentation was adequate in one-quarter of recorded allergies (20/73, 27.4%). Of the 53 that were documented inadequately, 30 (41.1%) included information about severity but no details on the timing of the reaction in relation to drug exposure, 8 (10.9%) described the timing but not the severity of the reaction, and 15 (20.5%) did not include either detail. Overall, information about the timing of the reaction was known in only 28/73 (38.5%) reactions—11 were immediate, occurring within 1 hour of exposure.

Of note, 12 of the 73 documented allergies (16.4%) were deemed by investigators to have experienced adverse or "on target" effects, rather than an immunologically mediated allergic response. These included 10 with gastrointestinal symptoms, one who had oral thrush and one where an AAL was given because the patient's infection appeared to worsen after antibiotics. In a further 8 (11.0%) records, the information included in the allergy section did not correlate with details in the clinical notes.

3.4 | Appropriateness of antibiotic prescribing per admission ($n = 66$)

Of the 66 admissions for IV antibiotics, 8 (12.1%) were inappropriately prescribed antibiotics based on their documented allergic reaction (Figure 1). Two were for children with a history of an immediate, severe β-lactam reaction (one had anaphylaxis and another angioedema). They were prescribed drugs from an alternate β-lactam class with the potential for cross-reactivity. The child with a history of angioedema had a similar allergic reaction to the antibiotics prescribed, the other had no repeat event.

The antibiotic prescribed was deemed inappropriate for the patients' infection in 28/66 (42.4%). Of these, 14 (21.2%) were for the right drug given for the wrong duration—all were children who received antibiotic prophylaxis for surgery, who were treated for >24 hours. A further 13 (19.7%) did not follow the institution's local antibiotic guidelines.

Adequacy of allergy labelling also impacted on antibiotic choice. Of the 66 admissions, only 19 started with a patient who had adequately documented information about their drug allergies. Inappropriate prescribing based on allergic reaction was more common in those admissions where the allergy documentation was inadequate;

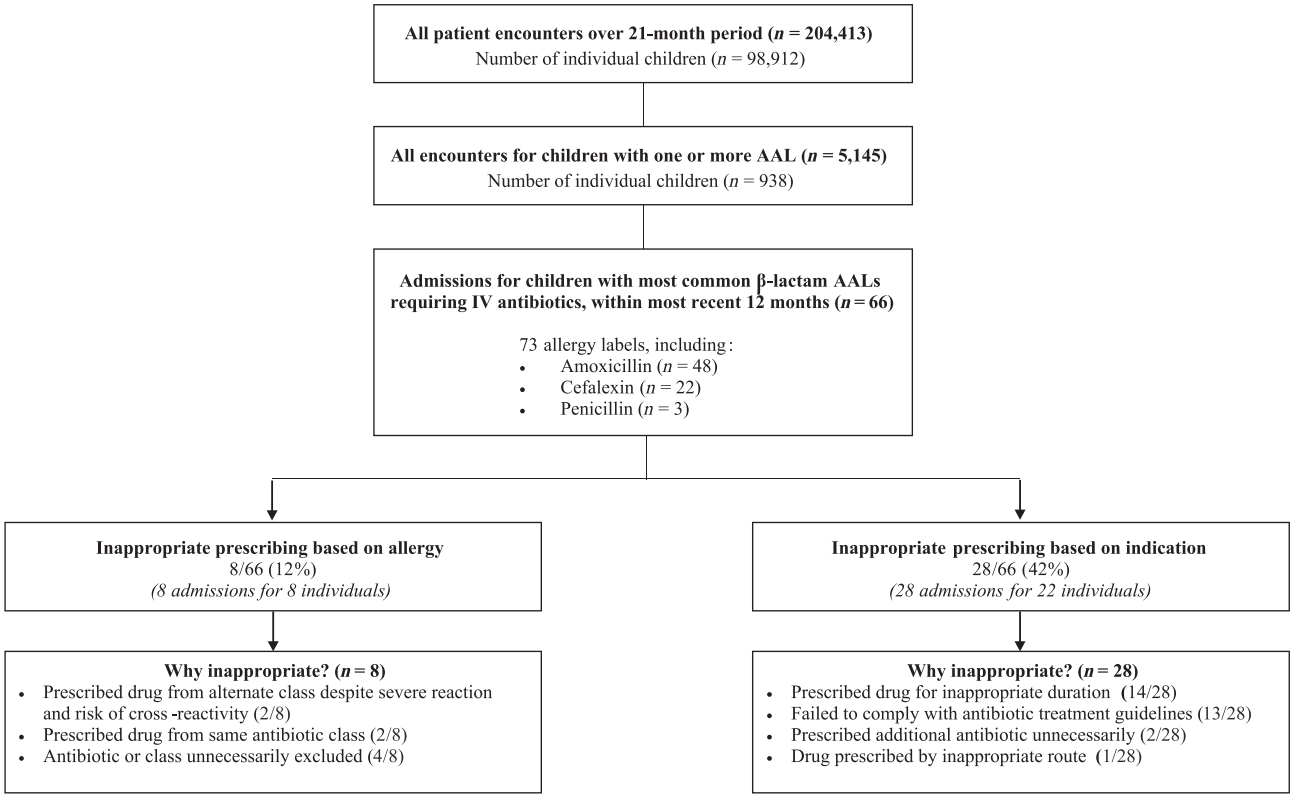


FIGURE 1 Study flowchart

TABLE 2 Impact of timing of antibiotic reaction on antibiotics prescribed

		Reason for inappropriate prescribing ($n = 31$)		
Timing of antibiotic reaction	**Appropriate prescribing ($n = 35$)**	**Allergic reaction only**	**Indication for treatment only**	**Both allergy and indication**
Immediate, ≤1 hour ($n = 10$)	3/10 (30%)	0/10 (0%)	5/10 (50%)	2/10 (20%)
Non-immediate, >1 hour ($n = 15$)	10/15 (66.7%)	0/15 (0%)	3/15 (20%)	2/15 (13.3%)
Timing unknown ($n = 41$)	22/41 (53.7%)	3/41 (7.3%)	15/41 (36.6%)	1/41 (2.4%)

however, this difference was not significant (7/47, 14.9% *vs* 1/19, 5.2%, $P = .4$). Overall, there were 5/66 (7.6%) admissions for five different children where the antibiotics prescribed were deemed inappropriate for both the allergic reaction and the infection type (see Table 2).

3.5 | Interactions with the drug allergy service

Of the 45 children included in this subset, only nine (20%) had undergone formal drug allergy assessment prior to their admission for IV antibiotics. Of these, three had reported anaphylaxis, and six had non-immediate reactions including non-specific rash alone (one), non-specific rash and angioedema (two), angioedema alone (one), a serum sickness-like reaction (SSLR) (one) and a drug reaction with eosinophilia and systemic symptoms (DRESS) syndrome (one).

Six had completed drug allergy testing (four graded oral challenge, one intradermal testing and one serology testing for specific IgE antibodies to the antibiotic) and only two were successfully "de-labelled" following a negative oral challenge. Notably, one of these "de-labelled" children—a 17-year-old girl with primary cilia dyskinesia who had a negative graded oral challenge to cephalexin—did not have their allergy label removed from the EMR prior to their next admission.

A subspecialist (clinical pharmacology, allergy & immunology or infectious diseases) was consulted in 9/66 (13.6%) admissions for these 45 children. Referral to a subspecialist was significantly associated with appropriate antibiotic prescribing [9/9 (100%) *vs* 26/57 (45.6%), $P = .002$].

4 | DISCUSSION

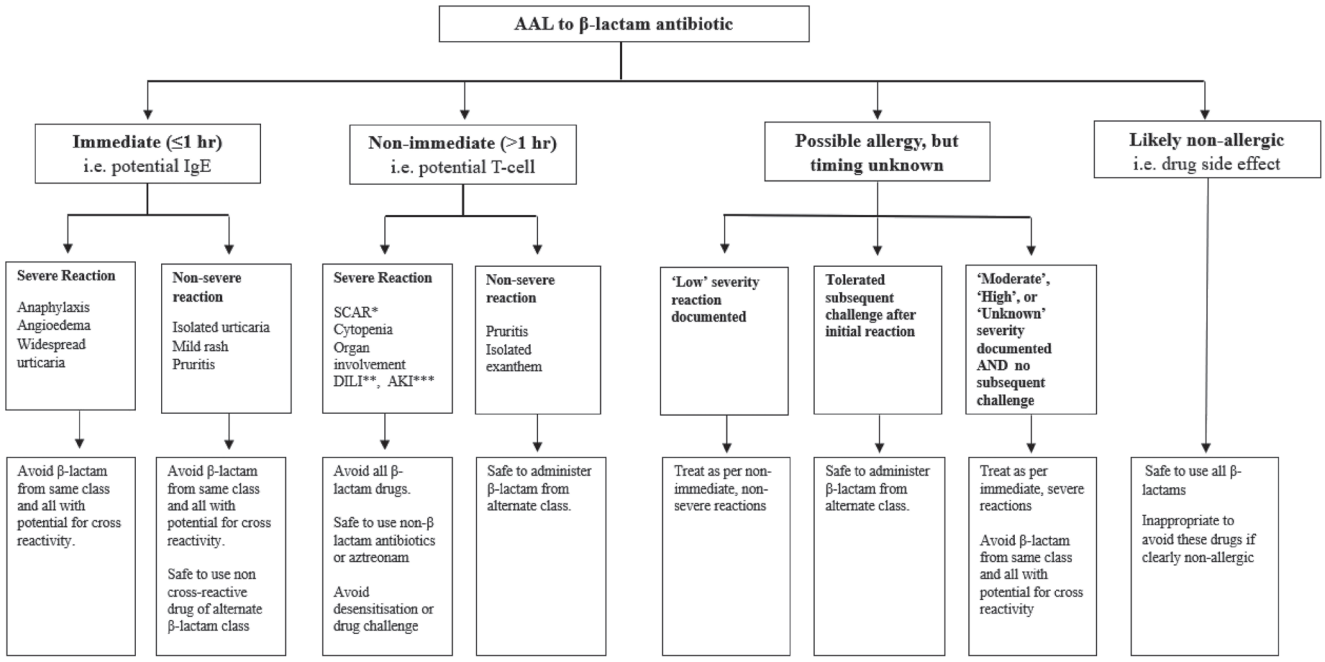
This study is the first to evaluate the impact of AALs on the appropriateness of antibiotic prescribing in children. We found that half of all children who had penicillin, amoxicillin or cefalexin allergy labels received inappropriate antibiotics. These children were significantly more likely to be prescribed restricted antibiotics and had a longer length of stay compared to non-allergic controls. This high rate of inappropriate prescribing exceeds that of a previous point-prevalence survey at the same hospital that showed 28% of prescriptions were inappropriate based on the infection being treated.[23] While numerous studies have reported high rates (29–33%) of antibiotic misuse in adults with AALs,[1–3,6,24] there has only been one cross-sectional study in 1672 children that found that both length of stay and use of alternate antibiotics was significantly greater in those with AALs.[4] Our study presents a more in-depth analysis of antibiotic use in children with AALs and found high rates of inappropriate prescribing both for the presumed allergy and the indication for treatment.

Our study shows that inadequate documentation of AALs is frequent. Clinicians may therefore be asked to make urgent decisions about antibiotic treatment without a full understanding of a child's risk of repeat reaction. These findings are consistent with studies in adults where only 21–36% of allergies were appropriately documented.[6,15–17,25] Consensus guidelines, including those published by the Australasian Society of Clinical Immunology and Allergy and a recent review by Blumenthal and colleagues, state that information about timing and severity are essential in determining appropriate management of AALs.[12,20,21] In our study, nearly three quarters of AALs lacked information on these key clinical features.

Limited clinician knowledge about antibiotic allergy[26] and a lack of clarity in EMR design[27,28]—where allergies and adverse reactions are often recorded in the same section—are key drivers of inadequate documentation. Several novel approaches, such as pharmacist-led patient review and revision of allergy labels[26,29,30] and EMR-embedded support tools prompting prescribers to update allergy details,[31] have been shown to improve the quality of allergy documentation.

Clinicians documenting antibiotic allergies in the EMR should be prompted to include the following information: drug name; symptoms and severity of reaction; timing of reaction; whether acute treatment and/or adrenaline was needed; and whether an antibiotic from the same class has since been tolerated.[16,28] Though such details may not always be known or accurately recalled at presentation, their consideration remains critical to ensuring a safe approach to antibiotic prescribing in children with AALs (outlined in Figure 2).

The approach to the management of β-lactam AALs in children has evolved in recent years. Up to 10% of children who take a β-lactam antibiotic will develop a rash,[32] but the large majority of these rashes are not allergic, with up to two-thirds of such children having a confirmed viral illness.[33–35] A review of five paediatric cohort and observational studies showed that for children with non-immediate amoxicillin reactions, the risk of a similar reaction when rechallenged was less than 10%.[10] Furthermore, a recent study of more than 800 children with both immediate and non-immediate



* SCAR = Severe Cutaneous Adverse Reaction – eg: Stevens-Johnson Syndrome, Toxic Epidermal Necrolysis, drug reaction with eosinophilia and systemic symptoms (DRESS)
** Dili = Drug Induced Liver Injury
*** AKI = Acute Kidney Injury

FIGURE 2 Algorithm for appropriate management of children with β-lactam AAL (adapted from Ref. [12])

reactions to amoxicillin found that 90% of children could be successfully de-labelled using a graded oral challenge without prior skin prick or intradermal testing.[11] Despite such evidence, our study found that only one in five children with AALs admitted for IV antibiotics had been seen by a drug allergy service, and just two (4.4%) had been de-labelled.

Approaches such as pharmacist-led assessment and rechallenge have shown great promise,[36] and would ideally be augmented with greater prescriber education on drug allergy.[37] A study of an automated notification system for patients with AAL that triggered an assessment by a pharmacist trained in allergy testing showed that 90% of patients could have their allergy de-labelled during their inpatient stay.[38] Although some centres report that limited access to drug allergy specialists is the primary reason for low rates of AAL de-labelling,[17] our study has shown that even where an established drug allergy service exists, referral for allergy evaluation is low.

A limitation of our study is that data were from a single centre. However, our centre is the primary referral centre for drug allergy for the state. Also, our reported prevalence of AALs was 1% of children who had encounters with the hospital. This is lower than the reported rate of 6% in another paediatric study.[5] This is likely due to differences in methodology in our study, where only those children with an allergy label at the commencement of the hospital encounter were included. Another potential reason could be that allergy labels documented in the paper record system were not transferred into the EMR after introduction. Another potential limitation is the lack of data on socioeconomic status. Though socioeconomic status has some impact on the rate of overall antibiotic prescription in children,[39] we did not find any studies describing a difference in length of stay for children needing treatment in hospital.

5 | CONCLUSION

This is the first study to demonstrate high rates of inappropriate prescribing in children with AAL, based both on an understanding of the presumed allergy and on the indication for treatment. Half of AALs had inadequate documentation and only one-quarter were referred for allergy evaluation and de-labelling. Integrated decision-support tools embedded within the EMR are needed to streamline AAL de-labelling and to preserve first-line antibiotics.

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COMPETING INTERESTS

The authors have no conflicts of interest relevant to this article to disclose.

CONTRIBUTORS

A.C.C. and A.G. analysed and interpreted the data and took primary roles in conceptualising and drafting the manuscript; L.F.P. oversaw the statistical analysis of the data; A.S. and D.S. designed and executed the acquisition of data via the electronic medical record; all other authors reviewed and revised the manuscript, approved the final manuscript as submitted, and agree to be accountable for all aspects of the work.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available on request from the corresponding author. The data are not publicly available due to both privacy and ethical restrictions.

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