

Antibiotic Allergy Labels in Children Are Associated with Adverse Clinical Outcomes



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What is already known about this topic? There are clear data to demonstrate that adults carrying an antibiotic allergy label have poorer clinical outcomes; however, the impact of an antibiotic allergy label in childhood is not well understood.

What does this article add to our knowledge? Children with antibiotic allergy labels received more macrolide, quinolone, metronidazole, and lincosamide antibiotics than did patients without an antibiotic label. The impact of any antibiotic allergy label was to increase hospital length of stay.

How does this study impact current management guidelines? The data highlight that antibiotic allergy labels already have a significant impact on clinical care in childhood. Early intervention in the context of an antibiotic allergy label, for example, direct antibiotic challenges, may be feasible.

BACKGROUND: Self-reported antibiotic allergies are common among hospitalized adults and children. However, there is a paucity of studies investigating the impact of an antibiotic allergy label in childhood.

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OBJECTIVE: To investigate the impact of antibiotic allergy labeling on clinical outcomes in children.

METHODS: A retrospective study was conducted in a major pediatric tertiary hospital to capture inpatient admissions (N = 1672) in April 2014 and April 2015. Data, collected by chart review, included documented antibiotic allergy labels, antibiotic prescriptions, admitting specialty, hospital length of stay, and hospital readmissions.

RESULTS: Of the 1672 pediatric patients surveyed, 58.1% were male and 44.8% were prescribed antibiotics. Antibiotic allergy labels were recorded in 5.3% of patients; most were β -lactam allergy labels (85%), mostly to unspecified penicillins. There was an increasing incidence of antibiotic allergy label with age, which was statistically significant ($P < .001$); no sex effect was seen. Patients with antibiotic allergy labels received more macrolide ($P = .045$), quinolones ($P = .01$), lincosamide ($P < .001$), and metronidazole ($P = .009$) antibiotics than did patients without an antibiotic allergy label. After adjusting for patient age, sex, principal diagnosis, and admitting specialty, children with any antibiotic or β -lactam allergy label had longer hospital stays (odds ratio, 1.62; 95% CI, 1.05-2.50; $P = .03$) with a mean length of hospital stay of 3.8 days for those without a label and 5.2 days for those with a β -lactam allergy label.

CONCLUSIONS: This is the first study demonstrating the negative impact of antibiotic allergy labels on clinical outcomes in children, as evidenced by significant alternate antibiotic use and longer hospital stays. Crown

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Key words: Pediatric drug allergy; Antibiotic allergy labels; Antimicrobial prescribing; Adverse reactions/hypersensitivity

INTRODUCTION

Antibiotic allergy labeling is a substantial and growing public health concern.^{1,2} Self-reported antibiotic allergies among hospitalized adult patients range from 15% to 25%,³⁻⁵ but data in children are sparse. One study reported antibiotic allergy rates of 6.1% for patients aged 0 to 9 years, which rose to 10.2% for those aged 10 to 19 years.⁵ Many of the published studies investigating antibiotic allergy labeling relate to adults, with a paucity of data in the pediatric cohort.

The female sex and increasing age are associated with a significantly higher prevalence of reported antibiotic allergy in the adult Australian and international literature.⁵ In comparison, there are only limited pediatric data and no Australian pediatric data to describe the impact of age and sex on rates of antibiotic allergy.

Adult patients with an antibiotic allergy label are more likely to experience longer hospital stays,^{2,6,7} be readmitted, and receive second-line antibiotics such as vancomycin, quinolones, or macrolides.⁶⁻¹⁰ They are also more likely to develop clinical complications such as severe infections with vancomycin-resistant *Enterococcus*, methicillin-resistant *Staphylococcus aureus*, and *Clostridium difficile*.^{2-4,7,11,12} In addition to these adverse patient outcomes, there are significantly increased costs resulting from the use of alternative antimicrobials for β -lactam allergy-labeled patients.¹³⁻¹⁷ Currently, the impact of antibiotic allergy labels on clinical outcomes in hospitalized children is not known. Furthermore, the optimal timing of drug allergy assessment (to verify or remove antibiotic allergy labels) in childhood remains unclear.

The objective of this study was to examine whether parentally reported antibiotic allergy labeling in children has a significant impact on their clinical care. Outcome data for 1672 patient medical records were examined at an Australian tertiary pediatric center, of which 5.3% had at least 1 reported antibiotic allergy label.

METHODS

Study design and population

We conducted a retrospective single-center cross-sectional analysis of all pediatric inpatients (N = 1672) admitted in April 2014 and April 2015 to the state pediatric tertiary care teaching hospital in Perth, Western Australia. The audit captured data on all patients admitted to hospital wards including medical and surgical specialties, intensive care units, and psychiatry and rehabilitation wards. Admitting specialty units were categorized as general medical, general surgical, oncology (including hematology), and "other specialty" (all medical subspecialties and ophthalmology). Data collected included patient demographic characteristics, documented antibiotic allergy labels, principal diagnosis on admission, antibiotics prescribed (at the time of audit), admitting specialty unit, hospital length of stay, and readmissions within 4 weeks and 6 months of discharge, excluding hospital transfers, day procedures, and emergency department reviews.

Antibiotic allergy label is used to denote any antibiotic recorded in the "allergies and adverse drug reaction" section of the patient's medication chart. Data on antibiotic allergy label, the culprit medication, and alleged symptoms were collected by review of inpatient medical notes, medication charts, and allergy notification forms. Documented symptoms were classified as (1) anaphylaxis, (2) angioedema, (3) rash, (4) gastrointestinal upset, or (5) nonspecific symptoms (eg, headache). Groups 1 to 3 were considered to be

allergic symptoms (graded according to severity) and groups 4 and 5 were interpreted as nonallergic, nonimmunological adverse reactions.

Study groups were classified on the basis of the presence or absence of a documented antibiotic allergy label. We further classified patients with an antibiotic allergy label into " β -lactam" and "non- β -lactam" labels. We subclassified β -lactam labels as penicillin, cephalosporin, carbapenem, or monobactam labels.

Ethics approval

Our study was reviewed and approved through the Princess Margaret Hospital for Children Hospital Quality Improvement Committee (Governance Evidence Knowledge Outcomes, GEKO 8245).

Statistical methods

Baseline characteristics are expressed as counts and percentages for each categorical variable grouping for any antibiotic allergy label category (yes/no), any β -lactam allergy label category (yes/no), and overall. Associations between the 2 binary outcomes of any antibiotic allergy label and any β -lactam allergy label and the potential explanatory variables of sex, age group (0 to <5 years, 5 to <10 years, and >10 years), specialty (general medical, general surgical, oncology, and other), principal diagnosis (minor surgical, major surgical, minor medical, major medical, and oncology/hematology), whether the patient was currently on antibiotics at the time of audit (yes/no), whether the patient had a current infection at the time of audit (yes/no), and the interaction between age and sex were examined using binary logistic regression. Univariate and multivariate odds ratios (ORs) and 95% CIs along with *P* values for the final multivariate model are presented.

To examine the impact of having an antibiotic allergy label (ie, either any antibiotic allergy label or any β -lactam allergy label) on hospital-related outcomes, univariate and multivariate regression models were fitted. The length of stay was categorized into 4 groups (1 day, 2 days, 3 days, and >4 days) and ordinal logistic regression was used, whereas for the binary responses intensive care unit admission (yes/no), 4-week readmission (yes/no), 4-week readmission with infection (yes/no), 6-month readmission (yes/no), and number of antibiotics currently prescribed (dichotomized as 1 vs >2 antibiotics), binary logistic regression was used. For the latter responses, analysis was carried out on the subset of patients who were currently on antibiotics only. For each of these 6 responses, comparisons of either any antibiotic allergy label (yes/no) or any β -lactam allergy label (yes/no) were made in 2 separate models and results are presented univariately and multivariately after adjusting for patient age, sex, principal diagnosis, and medical specialty, through ORs and 95% CIs. In all hospital outcome multivariate models, either the "any antibiotic allergy label" or the "any β -lactam allergy label" variable was forced into the final model to enable comparisons; however, any other variable that was not statistically significant was removed from the final model.

For the subset of patients who were on antibiotics, chi-square tests (or Fisher exact tests) were used to examine associations between each of the 3 antibiotic allergy label groupings (any antibiotic allergy label, any β -lactam allergy label, and any penicillin allergy label) separately, and whether patients were receiving any specific antibiotic as well as antibiotics from any of the following broad antibiotic groupings: macrolides, quinolones, penicillins, cephalosporins, lincosamides, and nitroimidazoles. For each combination of antibiotic allergy label grouping and whether patients were receiving each specific antibiotic or broad antibiotic label grouping, counts

TABLE I. Counts and percentages of demographic variables categorized by any antibiotic or β -lactam allergy label

Variable	Any antibiotic allergy label		Any β -lactam allergy label		Overall (N = 1672)
	No (n = 1584)	Yes (n = 88)	No (n = 1597)	Yes (n = 75)	
Age group					
0-4.99 y	714 (96.8)	24 (3.3)	719 (97.4)	19 (2.6)	738 (44.1)
5-9.99 y	416 (95.6)	19 (4.4)	417 (95.9)	18 (4.1)	435 (26)
>10 y	454 (91)	45 (9)	461 (92.4)	38 (7.6)	499 (29.8)
Sex					
Female	657 (93.7)	44 (6.3)	664 (94.7)	37 (5.3)	701 (41.9)
Male	927 (95.5)	44 (4.5)	933 (96.1)	38 (3.9)	971 (58.1)
Specialty					
General medical	428 (96.4)	16 (3.6)	429 (96.6)	15 (3.4)	444 (26.6)
General surgical	836 (95.8)	37 (4.2)	843 (96.6)	30 (3.4)	873 (52.2)
Oncology	93 (90.3)	10 (9.7)	95 (92.2)	8 (7.8)	103 (6.2)
Other	227 (90.1)	25 (9.9)	230 (91.3)	22 (8.7)	252 (15.1)
Principal diagnosis					
Minor surgical	611 (94.7)	34 (5.3)	619 (96)	26 (4)	645 (38.6)
Major surgical	67 (98.5)	1 (1.5)	67 (98.5)	1 (1.5)	68 (4.1)
Minor medical	647 (95.4)	31 (4.6)	649 (95.7)	29 (4.3)	678 (40.6)
Major medical	165 (91.7)	15 (8.3)	166 (92.2)	14 (7.8)	180 (10.8)
Oncology/hematology	94 (93.1)	7 (6.9)	96 (95.1)	5 (5)	101 (6)
Current infection					
No	1087 (95)	57 (5)	1099 (96.1)	45 (3.9)	1144 (68.4)
Yes	497 (94.1)	31 (5.9)	498 (94.3)	30 (5.7)	528 (31.6)
Receiving antibiotics					
No	881 (95.5)	42 (4.6)	886 (96)	37 (4)	923 (55.2)
Yes	703 (93.9)	46 (6.1)	711 (94.9)	38 (5.1)	749 (44.8)

Values are n (%).

and percentages are presented along with risk ratios, 95% CIs, and *P* values.

A significance level of 5% was used throughout and all statistical analyses were carried out using the R environment for statistical computing (R Foundation for Statistical Computing, Vienna, Austria).¹⁸

RESULTS

Demographic and cohort characteristics

The study population included a total of 1735 inpatient visits to a pediatric tertiary care teaching hospital during the month of April in 2014 and 2015. Of these, 36 were repeat visits, which were removed, reducing the data set to 1699 unique patient visits. This number was further reduced to 1672 patients for analysis purposes after the removal of 26 patients who were admitted to the emergency ward and 1 patient who was admitted to the neonatal specialty. Table I presents the characteristics of all 1672 patients upon admission, categorized by antibiotic allergy label or β -lactam allergy label. Overall, 58% of patients were male and the mean age was 6.81 years (range, 0-18.7 years), with 44.1% of patients being younger than 5 years. The admitting specialty units were classified as 52.2% general surgical, 26.6% general medical, 6.2% oncology, and 15.1% other specialty. Principal diagnoses were classified as 38.6% minor surgical, 4.1% major surgical, 40.6% minor medical, 10.8% major medical, and 6% oncology/hematology. The mean length of hospital stay was 3.85 days (range, 1-147 days). Significantly

longer stays were seen for older patients (>10 vs 0-4.99 years: OR, 2.82, 95% CI, 1.67-4.78; >10 vs 5-9.99 years: OR, 2.12, 95% CI, 1.21-3.71).

Of the 749 patients who were prescribed antibiotics, 70.2% received intravenous antibiotics and 29.8% received oral antibiotics. The most commonly prescribed antibiotics were penicillins (63.6%), followed by cephalosporins (40.6%), aminoglycosides (11.6%), and sulfamethoxazole/trimethoprim (6.5%). In some instances, patients were prescribed more than 1 antibiotic and this explains why the values do not add up to 100%.

Antibiotic allergy labels

Antibiotic allergies were recorded in 88 cases (5.3% of cohort: 6.3% of female patients and 4.5% of male patients). Five (0.30%) patients reported more than 1 antibiotic allergy. β -Lactams were implicated in most of the cases (*n* = 75), of which penicillin was most commonly reported, followed by amoxicillin and cephalexin. For non- β -lactam labels, antibiotics from the macrolide group were the most commonly reported (*n* = 10). A little more than half (52.3%) of those with antibiotic allergy labels were receiving antibiotics during their hospital stay. Patients receiving antibiotics were more likely to have any antibiotic label (OR, 1.65; 95% CI, 1.06-2.58; *P* = .03), and patients with a current infection were more likely to have a β -lactam label (OR, 1.78; 95% CI, 1.08-2.93; *P* = .03; Table II).

Of those who had an antibiotic allergy label, 81.2% had reported rash, 13.6% anaphylaxis, 11.4% gastrointestinal upset,

TABLE II. Univariate and multivariate logistic regression results from modeling any antibiotic allergy label and any β -lactam allergy label (event = "Yes")

Variable	Any antibiotic allergy label						Any β -lactam allergy label					
	Univariate		Multivariate				Univariate		Multivariate			
	OR	95% CI	OR	95% CI	Pairwise P value	Overall P value	OR	95% CI	OR	95% CI	Pairwise P value	Overall P value
Sex, female vs male	1.41	0.92-2.17	Not significant				1.37	0.86-2.18	Not significant			
Age group												
5-9.99 y vs 0-4.99 y	1.36	0.74-2.51	1.33	0.71-2.50	.37	<.001	1.63	0.85-3.15	1.68	0.86-3.30	.13	<.001
>10 y vs 0-4.99 y	2.95	1.77-4.91	2.82	1.67-4.78	<.001		3.12	1.78-5.48	3.10	1.73-5.57	<.001	
>10 y vs 5-9.99 y	2.17	1.25-3.77	2.12	1.21-3.71	.009		1.91	1.07-3.40	1.85	1.03-3.31	.04	
Specialty												
General surgical vs general medical	1.18	0.65-2.15	0.91	0.49-1.70	.77	<.001	1.02	0.54-1.91	0.93	0.48-1.81	.84	.003
Oncology vs general medical	2.88	1.27-6.54	2.80	1.21-6.42	.02		2.41	0.99-5.84	2.74	1.09-6.91	.03	
Other vs general medical	2.95	1.54-5.63	2.36	1.21-4.62	.01		2.74	1.40-5.38	2.33	1.15-4.73	.02	
Oncology vs general surgical	2.43	1.17-5.05	3.05	1.44-6.46	.004		2.37	1.06-5.31	2.93	1.29-6.68	.01	
Other vs general surgical	2.49	1.47-4.22	2.59	1.50-4.48	<.001		2.69	1.52-4.75	2.49	1.40-4.44	.002	
Oncology vs other	0.98	0.45-2.11	1.18	0.54-2.59	.69		0.88	0.38-2.05	1.18	0.50-2.79	.71	
Principal diagnosis												
Major medical vs major surgical	6.09	0.79-47.03	Not significant				5.65	0.73-43.83	Not significant			
Minor medical vs major surgical	3.21	0.43-23.89					2.99	0.40-22.33				
Minor surgical vs major surgical	3.73	0.50-27.67					2.81	0.38-21.07				
Oncology/hematology vs major surgical	4.99	0.60-41.51					3.49	0.40-30.55				
Current infection												
Yes vs no	1.19	0.76-1.87	Not significant				1.47	0.92-2.36	1.78	1.08-2.93	.03	.03
On antibiotics												
Yes vs no	1.37	0.89-2.11	1.65	1.06-2.58	.03	.03	1.28	0.81-2.03	Not significant			
Sex and age group interaction	Not significant*		Not significant				Not significant*		Not significant			

*Performed in a model with effects of sex, age, and their interaction.

TABLE III. Counts and percentages (along with risk ratios, 95% CI, and *P* values) of patients taking specific antibiotics, categorized by whether they were also labeled with an antibiotic, β -lactam, or penicillin allergy label (limiting the data to only those patients who were on antibiotics; *n* = 749)

Antibiotic	Any antibiotic allergy label			Any β -lactam allergy label			Penicillin allergy label		
	No (n = 703)	Yes (n = 46)	<i>P</i> value	No (n = 711)	Yes (n = 38)	<i>P</i> value	No (n = 719)	Yes (n = 30)	<i>P</i> value
Receiving amoxicillin									
No	518 (73.68%)	43 (93.48%)		524 (73.7%)	37 (97.37%)		536 (74.03%)	25 (100%)	
Yes	185 (26.32%)	3 (6.52%)	.003	187 (26.3%)	1 (2.63%)	.001	188 (25.97%)	0 (0%)	.003
	RR = 0.25; 95% CI = 0.08-0.75			RR = 0.10; 95% CI = 0.01-0.69			Cannot calculate*		
Receiving azithromycin									
No	675 (96.02%)	41 (89.13%)		683 (96.06%)	33 (86.84%)		694 (95.86%)	22 (88%)	
Yes	28 (3.98%)	5 (10.87%)	.045†	28 (3.94%)	5 (13.16%)	.02†	30 (4.14%)	3 (12%)	.09†
	RR = 2.73; 95% CI = 1.11-6.74			RR = 3.34; 95% CI = 1.37-8.17			RR = 2.90; 95% CI = 0.95-8.86		
Receiving ceftriaxone									
No	636 (90.47%)	39 (84.78%)		644 (90.58%)	31 (81.58%)		657 (90.75%)	18 (72%)	
Yes	67 (9.53%)	7 (15.22%)	.20†	67 (9.42%)	7 (18.42%)	.09†	67 (9.25%)	7 (28%)	.008†
	RR = 1.60; 95% CI = 0.78-3.28			RR = 1.95; 95% CI = 0.96-3.96			RR = 3.03; 95% CI = 1.55-5.91		
Receiving ciprofloxacin									
No	694 (98.72%)	42 (91.3%)		701 (98.59%)	35 (92.11%)		712 (98.34%)	24 (96%)	
Yes	9 (1.28%)	4 (8.7%)	.006†	10 (1.41%)	3 (7.89%)	.02†	12 (1.66%)	1 (4%)	.36†
	RR = 6.79; 95% CI = 2.17-21.22			RR = 5.61; 95% CI = 1.61-19.56			RR = 2.41; 95% CI = 0.33-17.84		
Receiving clindamycin									
No	692 (98.44%)	39 (84.78%)		699 (98.31%)	32 (84.21%)		711 (98.2%)	20 (80%)	
Yes	11 (1.56%)	7 (15.22%)	<.001†	12 (1.69%)	6 (15.79%)	<.001†	13 (1.8%)	5 (20%)	<.001†
	RR = 9.73; 95% CI = 3.96-23.91			RR = 9.36; 95% CI = 3.71-23.57			RR = 11.14; 95% CI = 4.30-28.84		
Receiving metronidazole									
No	678 (96.44%)	40 (86.96%)		685 (96.34%)	33 (86.84%)		697 (96.27%)	21 (84%)	
Yes	25 (3.56%)	6 (13.04%)	.009†	26 (3.66%)	5 (13.16%)	.02†	27 (3.73%)	4 (16%)	.02†
	RR = 3.67; 95% CI = 1.58-8.49			RR = 3.60; 95% CI = 1.46-8.85			RR = 4.29; 95% CI = 1.62-11.33		
Receiving ofloxacin									
No	693 (98.58%)	42 (91.3%)		700 (98.45%)	35 (92.11%)		711 (98.2%)	24 (96%)	
Yes	10 (1.42%)	4 (8.7%)	.008†	11 (1.55%)	3 (7.89%)	.03†	13 (1.8%)	1 (4%)	.38†
	RR = 6.11; 95% CI = 1.99-18.75			RR = 5.10; 95% CI = 1.48-17.53			RR = 2.23; 95% CI = 0.30-16.37		

RR, Risk ratio.

*The RR cannot be calculated with an entry of 0.

†Fisher exact test performed.

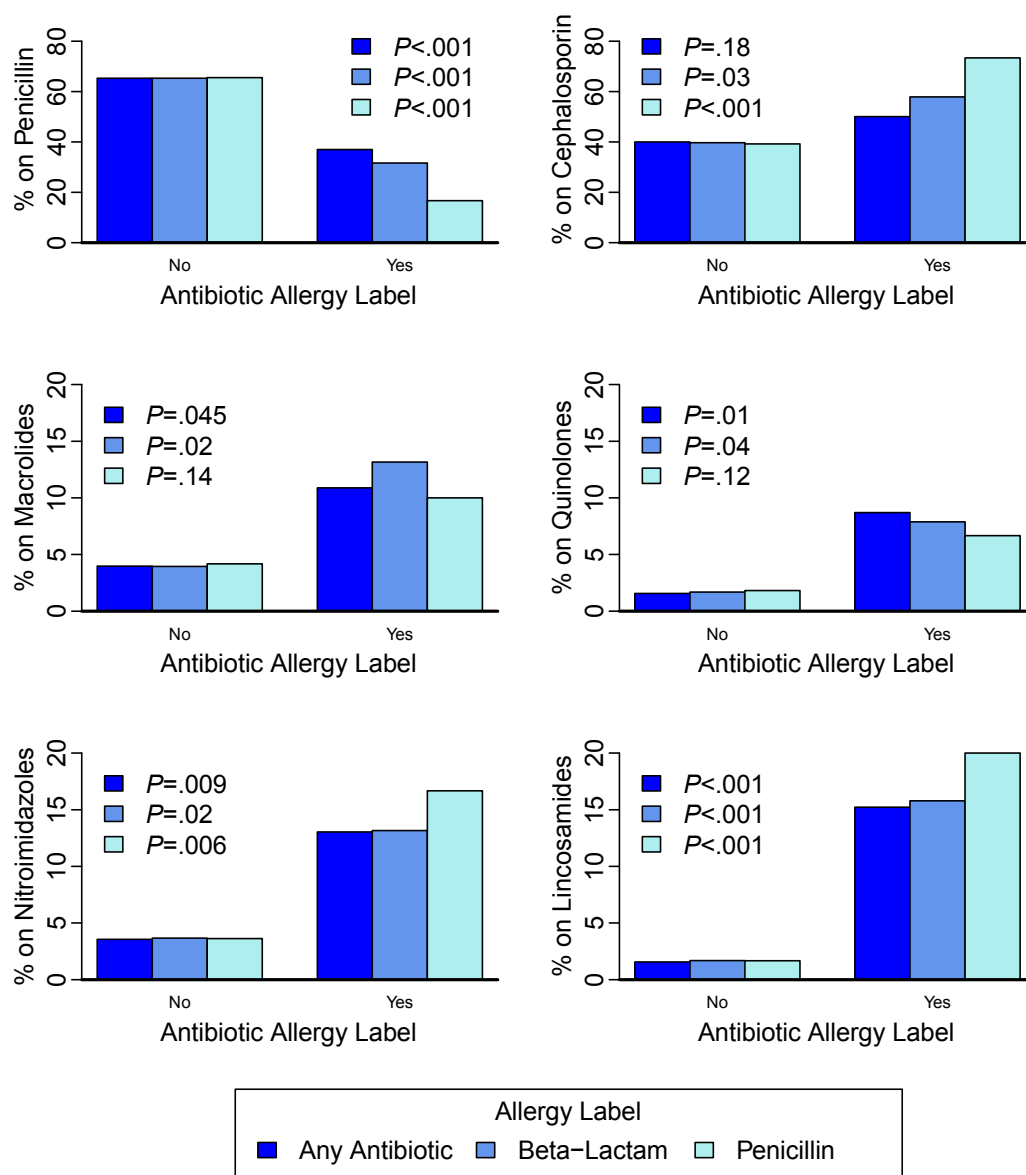


FIGURE 1. Bar plots of the proportion of patients taking different antibiotic groups categorized by antibiotic allergy label.

and less than 5% reported angioedema as the primary reaction to the culprit antibiotic. In 9 cases (0.54%), more than 1 symptom was reported. The nature of the reaction was not specified for 5 patients.

One patient was prescribed antibiotics that were contraindicated because of their reported allergy label in the absence of further testing. This patient had reported rash to amoxicillin and was prescribed Augmentin (amoxicillin/clavulanate potassium) in error but with no reaction.

The associations of age and sex with antibiotic allergy labels

With increasing age, individuals were more likely to have any antibiotic label (for >10 years vs 0-5 years: OR, 2.82; 95% CI, 1.67-4.78; $P < .001$) and, more specifically, a β -lactam allergy

label (for >10 years vs 0-5 years: OR, 3.10; 95% CI, 1.73-5.57; $P < .001$; Table II).

There was no difference in rates of antibiotic allergy labels when stratified by sex.

The association of admitting specialty with antibiotic allergy labels

When comparing specialties, patients in the oncology specialty and those admitted under other specialty were more likely to be labeled when compared with patients in general medical (OR, 2.80; 95% CI, 1.21-6.42; $P = .02$ and OR, 2.36; 95% CI, 1.21-6.42; $P = .01$, respectively) and in general surgical (OR, 3.05; 95% CI, 1.44-6.46; $P = .004$ and OR, 2.59; 95% CI, 1.50-4.48; $P < .001$, respectively; Table II).

TABLE IV. Univariate and multivariate logistic regression results from all analyses

Outcome	Comparison	Univariate			Multivariate*		
		OR	95% CI	P value	OR	95% CI	P value
Hospital length of stay	AAL vs NAAL	1.71	1.16-2.53	.007	1.59	1.03-2.28	.04
	BLAL vs NBLAL	1.90	1.24-2.89	.003	1.62	1.05-2.50	.03
ICU admission	AAL vs NAAL	1.83	0.55-6.11	.33	1.27	0.35-4.58	.72
	BLAL vs NBLAL	2.18	0.65-7.30	.21	1.47	0.41-5.36	.56
4-wk readmission	AAL vs NAAL	1.70	1.01-2.85	.045	1.42	0.76-2.66	.27
	BLAL vs NBLAL	1.55	0.88-2.74	.13	1.31	0.66-2.59	.44
4-wk readmission with infection	AAL vs NAAL	2.12	0.94-4.78	.07	1.63	0.68-3.94	.28
	BLAL vs NBLAL	2.12	0.89-5.06	.09	1.69	0.66-4.33	.28
6-mo readmission	AAL vs NAAL	1.60	1.02-2.50	.04	1.20	0.71-2.00	.50
	BLAL vs NBLAL	1.53	0.94-2.49	.09	1.16	0.67-2.02	.59
Number of antibiotics†	AAL vs NAAL	1.50	0.83-2.74	.18	1.47	0.75-2.87	.26
	BLAL vs NBLAL	1.80	0.94-3.46	.08	1.83	0.89-3.77	.10

AAL, Antibiotic allergy label; BLAL, β -lactam allergy label; ICU, intensive care unit; NAAL, no antibiotic allergy label; NBLAL, no β -lactam allergy label.

*Adjusting for patient age, sex, principal diagnosis, and specialty if statistically significant.

†Analyses carried out on the subset of patients who were currently on antibiotics ($n = 749$).

Association of antibiotic allergy labels with antibiotic prescriptions

The presence of an antibiotic allergy label (any allergy label, a β -lactam allergy label, or a penicillin allergy label) was significantly associated with prescription of alternative antibiotics (Figure 1; Table III). Among children currently receiving antibiotics ($n = 749$), those with antibiotic allergy labels received significantly more macrolides ($P = .045$), quinolones ($P = .01$), lincosamide ($P < .001$), and nitroimidazoles ($P = .009$) than those not labeled as allergic to antibiotics (Figure 1). Patients with β -lactam allergy labels were also significantly more likely to receive these alternative antibiotics (macrolides, quinolones, lincosamides, and nitroimidazoles) as well as cephalosporins ($P = .03$) (Figure 1). Table III presents prescriptions of individual antibiotics, categorized by patient allergy labels. There were significantly fewer prescriptions of amoxicillin ($P = .003$) and a higher use of clindamycin ($P < .001$), azithromycin ($P = .045$), ciprofloxacin ($P = .006$), metronidazole ($P = .009$), and ofloxacin ($P = .008$) among β -lactam allergy-labeled children (Table III).

Association of antibiotic allergy label with prolonged hospital length of stay

Table IV presents the results of the impact of an allergy label on hospital outcomes for any antibiotic allergy label and any β -lactam allergy label. After adjusting for patient age, sex, principal diagnosis, and admission specialty, any antibiotic allergy label was associated with increased hospital length of stay (OR, 1.59; 95% CI, 1.03-2.28; $P = .04$; 5 vs 3.8 days in hospital on average). Furthermore, when examining the impact of any β -lactam allergy label by multivariate analysis, a longer hospital stay was also observed (OR, 1.62; 95% CI, 1.05-2.50; $P = .03$; 5.2 days vs 3.8 days in hospital on average).

Nonsignificant association of antibiotic allergy label with readmission

The presence of an antibiotic allergy label was associated with higher 4-week and 6-month readmission rates by univariate analysis (OR, 1.70; 95% CI, 1.01-2.85; $P = .045$ and OR, 1.60; 95% CI, 1.02-2.50; $P = .04$, respectively). However, after

adjusting for patient age, sex, principal diagnosis, and admission specialty, this relationship was no longer significant.

DISCUSSION

To our knowledge, this is the first study in children analyzing the impact of an antibiotic allergy label on clinical outcomes. Antibiotic allergies were recorded for 5.3% of hospitalized children, which is similar to the 6.1% previously reported for 0- to 9-year-old patients⁵ and lower than the reported rate of 18% among hospitalized Australian adults.⁶

β -Lactams accounted for most (85%) of the antibiotic allergy labels among children as compared with 65% to 83%^{4,8} of labels reported in the adult literature. More than half (51%) of the antibiotic allergy-labeled patients in our study were receiving antibiotics during their hospital stays.

We observed an increased prevalence of antibiotic allergy labeling with age, which is in line with previous data.⁵ An American data linkage study analyzing adult and pediatric data found that increasing age was significantly associated with a higher prevalence of reported antibiotic allergy.⁵ It was also observed that female patients reported significantly higher rates of antibiotic allergy for all antibiotic classes in all age groups, apart from the first decade of life when significantly more boys than girls carry penicillin allergy labels. An effect of sex was not observed in our pediatric cohort, which may be due to the smaller sample size. This age and sex effect was also reported in Australian adults, with higher rates of antibiotic allergy labels among females and older patients.⁶ There may be higher rates of reporting antibiotic allergy in adult females because of higher overall rates of antibiotic utilization as well as other biological factors that may emerge in adulthood.

We found a significant impact of antibiotic allergy labels on prescribing practice. Children with antibiotic allergy labels received more macrolide, quinolone, lincosamide, and metronidazole antibiotics than did patients without an antibiotic label. This compares with published adult data where patients with a penicillin or a β -lactam allergy label more frequently receive macrolides,^{7,10,17} quinolones,^{6,10,17} lincosamides,^{6,7,17} metronidazole,⁶ aminoglycosides,⁶ tetracyclines,^{10,17} fusidic acid,⁶ and

daptomycin.⁶ Alternative antibiotic use in children and adults may be influenced by age-related indications for antibiotic use. Adults are also more likely to have multiple antibiotic allergy labels, resulting in fewer alternatives available to prescribers. Only 0.3% of children in our cohort reported more than 1 antibiotic allergy compared with 11% among Australian hospitalized adults.⁶ Other considerations could be the location where these studies were performed as well as the accessibility and cost of alternative antibiotics.

The use of broad-spectrum antibiotics for allergy-labeled children and adults with sometimes trivial infections is of concern, because these antibiotics should be reserved for serious infections. Reserve antimicrobials can be more expensive and can also increase the risk of multidrug resistance. Significantly higher rates of multidrug-resistant infections have been reported in adults with antibiotic allergy labels.^{2-4,14} A US study⁷ showed that penicillin allergy testing, to remove inappropriate allergy labels, was associated with greater use of narrow-spectrum antibiotics and significantly less health care utilization during the study follow-up of more than 3 years.

In addition to the impact on antibiotic prescribing, it is known that adults with an antibiotic allergy label experience poorer measurable clinical outcomes than do those without such a label^{2,11,12}; for example, having an antibiotic allergy label results in higher readmission rates^{6,8,12,17} and longer lengths of stay.^{2,11,12} Our pediatric cohort demonstrated an effect of an antibiotic allergy label on hospital length of stay. The reasons behind the observed longer length of stay are not entirely clear, but may be linked to the alternate antibiotic use in these children. Alternative antibiotics may be less effective, associated with more adverse reactions, and/or be more cumbersome to administer (eg, limited oral options or unsuitability for "hospital in the home" administration). We did not find evidence for an increased risk of readmission within 4 weeks for patients with an antibiotic allergy label. This may be due to differences in readmission rates between adult and pediatric patients. In our center, Australian adult patients had a 4-week readmission rate of 19.5% and a 6-month readmission rate of 38.9%,⁶ whereas the readmission rates in our pediatric cohort were 15.2% and 24.8%, respectively.

More than 80% of children report only mild to moderate and often non-IgE-mediated adverse reactions to antibiotics (commonly rashes),¹⁹ which can be safely assessed with an oral provocation challenge.¹⁹ In our cohort, 46 (52.3%) children with a penicillin or amoxicillin allergy reported mild to moderate reactions (rashes) and could potentially have been directly de-labeled after oral provocation challenge. This simple strategy could have mitigated the adverse clinical outcomes reported herewith. De-labeling strategies implemented in childhood together with drug stewardship could reduce the use of alternative antibiotics and the associated increase in bacterial resistance. Moreover, early de-labeling may be beneficial from a health economic point of view by reducing the prevalence and negative impact of allergy labels among children, the future adult population.

This study was performed in a single center by retrospective medical chart review; hence, further confirmation of the findings in other major pediatric centers is required. The retrospective nature of the study meant that accurate data collection was reliant on the record keeping of clinical staff at the time of admission. The study was strengthened through the use of multiple data sources (medication chart, medical record, and

allergy notification forms) for thorough data collection. Although the study was performed at a single center, this center is the sole tertiary pediatric hospital for the entire state of Western Australia.

CONCLUSIONS

This is the first study demonstrating the negative impact of antibiotic allergy labels on clinical outcomes in children, as evidenced by longer hospital stays and greater utilization of reserve antibiotics. Given the recent advances in the field of de-labeling in children, such as the selected use of direct amoxicillin challenges, early intervention in the context of an antibiotic allergy label could improve care and outcomes in children.

REFERENCES

- Macy E, Khan DA, Castells MC, Lang DM. Penicillin allergy testing: a key component of antibiotic stewardship. *Clin Infect Dis* 2017;64:531-2.
- 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;133:790-6.
- 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.
- Lee CE, Zembower TR, Fotis MA, Postelnick MJ, Greenberger PA, Peterson LR, et al. The incidence of antimicrobial allergies in hospitalized patients: implications regarding prescribing patterns and emerging bacterial resistance. *Arch Intern Med* 2000;160:2819-22.
- Macy E, Poon KYT. Self-reported antibiotic allergy incidence and prevalence: age and sex effects. *Am J Med* 2009;122:778.e1-7.
- Knezevic B, Sprigg D, Seet J, Trevenen M, Trubiano J, Smith W, et al. The revolving door: antibiotic allergy labelling in a tertiary care centre. *Intern Med J* 2016;46:1276-83.
- Macy E, Shu YH. The effect of penicillin allergy testing on future health care utilization: a matched cohort study. *J Allergy Clin Immunol Pract* 2017;5:705-10.
- Trubiano JA, Leung VK, Chu MY, Worth LJ, Slavin MA, Thursky KA. The impact of antimicrobial allergy labels on antimicrobial usage in cancer patients. *Antimicrob Resist Infect Control* 2015;4:23.
- Trubiano JA, Pai Mangalore R, Baey YW, Le D, Graudins LV, Charles PG, et al. Old but not forgotten: Antibiotic allergies in General Medicine (the AGM Study). *Med J Aust* 2016;204:273.
- Su T, Broekhuizen BDL, Verheij TJM, Rockmann H. The impact of penicillin allergy labels on antibiotic and health care use in primary care: a retrospective cohort study. *Clin Transl Allergy* 2017;7:18.
- Caubet JC, Kaiser L, Lemaitre B, Fellay B, Gervais A, Eigenmann PA. The role of penicillin in benign skin rashes in childhood: a prospective study based on drug rechallenge. *J Allergy Clin Immunol* 2011;127:218-22.
- Charneski L, Deshpande G, Smith SW. Impact of an antimicrobial allergy label in the medical record on clinical outcomes in hospitalized patients. *Pharmacotherapy* 2011;31:742-7.
- Sade K, Kivity S, Levy A, Fireman E. The effect of specific immunotherapy on T-cell receptor repertoire in patients with allergy to house-dust mite. *Allergy* 2003;58:430-4.
- Picard M, Begin P, Bouchard H, Cloutier J, Lacombe-Barrios J, Paradis J, et al. Treatment of patients with a history of penicillin allergy in a large tertiary-care academic hospital. *J Allergy Clin Immunol Pract* 2013;1:252-7.
- Borch JE, Andersen KE, Bindslev-Jensen C. The prevalence of suspected and challenge-verified penicillin allergy in a university hospital population. *Basic Clin Pharmacol Toxicol* 2006;98:357-62.
- Sade K, Holtzer I, Levo Y, Kivity S. The economic burden of antibiotic treatment of penicillin-allergic patients in internal medicine wards of a general tertiary care hospital. *Clin Exp Allergy* 2003;33:501-6.
- van Dijk SM, Gardarsdottir H, Wassenberg MW, Oosterheert JJ, de Groot MC, Rockmann H. The high impact of penicillin allergy registration in hospitalized patients. *J Allergy Clin Immunol Pract* 2016;4:926-31.
- R Core Team. A Language and Environment for Statistical Computing. Vienna, Austria: R Foundation for Statistical Computing; 2017.
- Mill C, Primeau MN, Medoff E, Lejtenyi C, O'Keefe A, Netchiporouk E, et al. Assessing the diagnostic properties of a graded oral provocation challenge for the diagnosis of immediate and nonimmediate reactions to amoxicillin in children. *JAMA Pediatr* 2016;170:e160033.