Patient-related factors impact the implementation of inpatient antibiotic allergy delabeling

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Background: The clinical consequences of an antibiotic allergy label are detrimental, impacting health care delivery and patient outcomes. We assessed hospital inpatients with intent to offer free antibiotic allergy labeling (AAL) assessment within a randomized controlled trial.

Objective: We sought to determine the feasibility of establishing an adult antibiotic allergy delabeling service in a Western Australian tertiary public hospital.

Methods: Inpatients (N = 1503) with AAL were identified through medical records and screened for eligibility to participate in a randomized controlled trial. Those recruited were randomized to undergo assessment by skin testing ± oral challenge, or direct oral challenge. A control group received usual care.

Results: Of the 1503 inpatients with an AAL, 429 (28.5%) were eligible for AAL assessment. The primary excluding factor (1074 [71.5%]) was contraindicated medication use (387 [36.0%]), followed by cognitive impairment (298 [27.9%]). Thirty-nine patients were randomized, of which 20 received allergy testing and 19 usual care; all patients were followed up for 5 years. Older patients were less likely to be eligible (10-year increase: odds ratio, 0.82; 95% CI, 0.77-0.88; $P < .0001$), whereas surgical patients were more likely to be eligible than medical patients (odds ratio, 2.49; 95% CI, 1.97-3.16; $P < .0001$).

Conclusions: Antibiotic allergy delabeling in the acute care context is not straightforward. Competing clinical concerns and patient acceptance are some barriers to an inpatient service. Nor is it apparent that inpatient versus outpatient testing is cost saving although select patient groups may benefit. Testing younger people and those with predicted high antibiotic usage will derive maximal individual and health system benefits. (J Allergy Clin Immunol Global 2024;3:100326.)

Key words: *Antibiotic allergy, delabeling, adult inpatients, drug allergy*

Antibiotic allergy labeling (AAL) is a catch-all term used to describe antibiotic allergy documented in the patient's medical record.[1] Incorrect AAL affects patient care directly by limiting the choice of antibiotics for any given infection[2] and is associated with antibiotic resistance and increased health care use.[3,4] Unverified AAL has adverse implications for people with complex and chronic illnesses such as diabetes, HIV infection, and cancer.[5-7] If unaddressed, the consequences of acquiring a label in childhood span a lifetime.[8] A recent systematic review[3] describes 82.5% of studies conducted in the inpatient setting where the clinical and economic benefit of evaluating unverified AAL appeared undisputed. Many studies supporting inpatient delabeling arise from established antimicrobial stewardship initiatives, focus on penicillin allergy labels, and are nonrandomized.[9-13] In contrast, there are fewer studies conducted in pediatric or outpatient populations where primary or secondary care providers prescribe most antibiotics.[14-17] Therefore, the question as to whether an inpatient stay, *over other health settings*, is an optimal opportunity to "delabel" patients, who have carried an AAL lifelong, remains unanswered.

Our aim was to explore the practicality and benefit of establishing an adult specialist-led inpatient AAL delabeling service assessing patients with low- and higher-risk histories in a metropolitan hospital in Western Australia by implementing a randomized controlled trial (RCT). Intended outcome measures were rates of hospital readmission, and length of stay 6 months following antibiotic allergy testing to 1 year later, and economic viability. Here, we describe obstacles to recruitment we encountered, results of the RCT, and recommendations for inpatient delabeling in the context of tertiary care.

METHODS

The study was conducted at Sir Charles Gairdner Hospital, a 600-bed tertiary hospital in Western Australia, between July 2019 and October 2020. The study team consisted of a specialist immunologist/allergist, a junior doctor-in-training under supervision of the specialist, and an experienced allergy-trained

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Abbreviations used
AAL: Antibiotic allergy labeling
OPC: Oral provocation challenge
RCT: Randomized controlled trial
SPT: Skin prick testing
ST: Skin testing

clinical nurse. The nurse reviewed medical records hospital-wide to identify patients carrying AALs. These patients were then screened for eligibility to enroll in the RCT. Following written informed consent, patients meeting the inclusion criteria underwent a thorough clinical evaluation and were randomized to receive an antibiotic challenge, or usual care (controls). Randomized or borderline cases were discussed with the immunologist. The "challenge" patients gave a detailed allergy history (see Data S1 in this article's Online Repository at www.jaci-global.org) and underwent skin testing (ST) and/or an oral provocation challenge (OPC) with the culprit antibiotic. Patients from both groups were questioned about antibiotic use and health care access every 3 months for 12 months, and subsequently researchers conducted a 4-year review of patients' medical records. To enable an economic evaluation of the inpatient delabeling strategy considering costs associated with the development of a delabel plan during admission, a direct OPC, and/or ST before discharge, and potential adverse events, a sample size of 768 participants (n = 384 in each group) was calculated by the study statistician. The Sir Charles Gairdner Osborne Park Hospitals (SCGOPH) Human Research Ethics Committee approved the study (RGS 0844).

Inclusion and exclusion criteria

The inclusion criteria (Table I) comprised medically stable patients older than 16 years with a recorded AAL to any beta-lactam, sulphonamide, macrolide, quinolone, or tetracycline and who provided informed, written consent. Our exclusion criteria included a previous history of severe adverse reactions such as severe cutaneous adverse reaction, pregnancy, decompensated medical illness, an inability to provide written consent, and incorrect documentation of allergy (eg, no personal history, mild gastrointestinal symptoms, or family history). Patients on certain concomitant medications, considered at the time to interfere with testing or treatment of allergic reactions such as beta-blockers, antihistamines, steroids, or other immunosuppression, were also excluded.

Screening process

Researchers reviewed medical records and entered data to an electronic screening proforma (see Data S2 in this article's Online Repository at www.jaci-global.org) and evaluated the patient against the inclusion criteria. Patients with a family history of antibiotic allergy, or reporting only gastrointestinal side effects to the culprit antibiotic, were excluded from the RCT. Following prescreening, researchers offered the study information sheet and liaised with the admitting team before scheduling the allergy challenge. Informed consent, randomization, and testing usually took place the next day. The decision to carry out ST or proceed directly to a 2-stage oral challenge was based on our previously published risk framework and applied to all beta-lactam antibiotics (Fig 1).[18] Patients randomized to the control group received advice to maintain the unverified AAL until receiving specialist outpatient assessment at study completion.

Drug allergy assessment with ST and/or oral provocation testing

The nurse conducted the procedures, and 2-hour posttest observations. Skin prick testing (SPT) and intradermal testing for beta-lactam allergy included penicillin G, amoxicillin, ampicillin, major and minor determinant of penicillin (Diater kit; Diater Laboratorios, Madrid, Spain), and the culprit antibiotic including cephalosporins and carbapenems.[19] Histamine testing (by SPT only) served as a positive control for histamine responsiveness in all cases and normal saline as a negative control for SPT and intradermal testing. A positive response to SPT was a wheal reaction 3 mm greater compared with that with the negative saline control. A positive response to intradermal testing was a wheal increase by 3 mm, in addition to a flare reaction. Patients were assessed and triaged into low-risk and high-risk antibiotic allergy histories. A low-risk history of a benign rash (transient morbilliform or maculopapular rash that may be mildly pruritic[20]) without other systemic manifestations and occurring more than 1 year ago led to a 2-dose challenge with the culprit beta-lactam antibiotic (Fig 1). Amoxicillin was used where the description of the penicillin AAL was imprecise. Intravenous challenge to the culprit was not performed. Any other history was classified high-risk and ST was performed. For the assessment of non–beta-lactams, no ST was performed; being less validated for these antibiotics, 2-stage oral challenges were performed instead. The OPC was in 2 stages, 1/10 dose followed 30 minutes later by 9/10 of a single dose. Patients were contacted 48 to 72 hours following testing to query delayed adverse drug reaction. Challenge outcomes were recorded in the medical record, discharge summary, and a letter to the patient and their general practitioner. In the event of verified allergy, the patient was to be provided with a list of safe alternatives.

Data analysis and management

We used REDCap,[21] a secure, web-based software platform supporting automated randomization, direct data entry, and export to statistical packages. The R environment for statistical computing was used to summarize and analyze the data.[22] Counts and percentages were calculated for categorical variables and means and SDs for continuous variables. Univariate and multivariate logistic regressions were conducted to determine the impact of patient age, sex, and specialty on study eligibility (event = eligible) as well as being recruited into the RCT for those who were eligible (event = recruited). Odds ratios, 95% CI, and *P* values are provided.

RESULTS

Patient characteristics

In total, 1503 hospital-wide inpatients with a record of an antibiotic allergy were identified and screened for eligibility (Table II). The mean age was 67.4 ± 18.3 years (63.3% female). Most inpatients (63.3%) were admitted under a medical specialty, and 46.4% were prescribed antibiotics at the time of

TABLE I. Inclusion and exclusion criteria

Inclusion criteria	
Age	>16 y
Clinical record	AAL recorded in patient notes
History	Reported ADR to any beta-lactam, sulphonamide, macrolide, quinolone, or tetracycline
Medically well	"Reasonable" resolution of incident illness, determined by the admitting doctor
Written informed consent	Assent of young adults <18 y, written consent of parents
Exclusion criteria	
Clinical history	Clinically confirmed serious ADR
History of SCAR	SJS, TEN, DRESS, AGEP
Systemic illness	Hemolytic anemia, drug-induced liver injury
Pregnancy	Confirmation test necessary if unsure
Medically unwell	As determined by the admitting doctor
Cognitive impairment	Lack ability to give written informed consent
Concomitant medication	Beta-blockers, antihistamines, high-dose steroids, immunosuppressive treatment. Discretion with antipsychotic and other medication
No risk of allergy if tested	Incorrect labeling identified, eg, no personal allergy history on questioning, family history of antibiotic allergy, mild gastrointestinal symptoms

ADR, Adverse drug reaction; *AGEP*, acute generalized exanthematous pustulosis; *DRESS*, drug reaction with eosinophilia and systemic symptoms; *SCAR*, serious cutaneous adverse reaction; *SJS*, Steven-Johnson syndrome; *TEN*, toxic epidermal necrolysis.

screening. Most AALs were historical (74.7%), and 6.85% of inpatients were assigned microalerts indicative of an infection with an antibiotic-resistant pathogen, most commonly methicillin-resistant *Staphylococcus aureus* (5.79%). Often, key information concerning the index reaction was incomplete or imprecise. Of 1496 participants with a culprit antibiotic identified, 171 (11.4%) had both an antibiotic class and generic drug recorded, 750 (49.9%) had only a class, and 575 (38.3%) had only the generic drug recorded. Penicillin allergies were frequently reported (71.32%), followed by other antibiotics (16.98%), cephalosporins (12.83%), and sulphonamides (11.7%).

Results of screening, eligible versus ineligible patients. All case entries, including screening data, were retrospectively reviewed by a physician in consultation with the immunologist. Of the 1503 patients screened, 429 (28.5%) were eligible for recruitment into the RCT and 1074 (71.5%) were ineligible; of these, 737 (68.6%) had a single reason for ineligibility, and the remaining 337 (31.4%) more than 1. Cognitive impairment was common in 27.9%, and 14.7% of patients were too unwell for testing. Immunosuppressive therapies, affecting testing, such as high-dose corticosteroid (17.4%) or other immunosuppressants, were seen in 2.4%. Our study excluded a high number of patients on the basis of concomitant beta-blocker treatment (36.3%). Screening also detected that 32 (2.98%) patients were taking the antibiotic to which they were labeled as allergic, and another 133 (12.4%) could have been ruled out by history alone, for example, gastrointestinal side effects and family history of allergy (Table III). Of the eligible patients who did not participate, 95 had low-risk penicillin allergy histories and could have received a direct OPC. These patients were not part of the 4-year review.

Following multivariate regression, older patients were significantly less likely to be eligible (for a 10-year increase: odds ratio, 0.82; 95% CI, 0.77-0.88; $P < .0001$; Table IV) whereas patients admitted under a surgical specialty were more likely to be eligible than patients admitted under a medical specialty (odds ratio, 2.49; 95% CI, 1.97-3.16; $P < .0001$). A higher proportion of females were eligible than males (30% vs 26.1%); however, this difference did not reach statistical significance.

Eligible patients: Factors influencing study participation. Of the 429 patients who were eligible to be randomized, almost half were discharged before the consent and testing process could progress (45.6%), whereas 212 (54.4%) declined to participate. Of the people who declined, 206 gave a reason, which were categorized as (1) burdensome (n = 63 [30.6%]), for example, "too much going on," (2) fearful (n = 42 [20.4%]), for example, "I'm not putting myself through that again," (3) unimportant (n = 49 [23.8%]), for example, "too old," and (4) an activity that would jeopardise imminent discharge (n = 19 [9.22%]), for example, "Had enough of hospitals for now." The remaining 33 (16.0%) patients either declined to engage with the research nurse, did not believe they had an allergy and therefore the documentation was incorrect, or cited needle "phobia." However, practical everyday issues also fostered reluctance, for example, the lack of reading glasses or hearing aids.

Results of the randomized trial

A total of 39 of 1503 (2.6%) inpatients were randomized, 20 to receive an antibiotic allergy challenge and 19 to usual care; following randomization to the challenge group, 2 patients withdrew from the study, and the condition of 2 others deteriorated, preventing allergy testing at that time. Sixteen patients underwent allergy risk assessment after which 8 patients underwent oral challenge, and the others ST followed by an oral challenge. Allergy labels were removed from 16 patients (Table II, Fig 2). At the time of testing, 25 patients had more than 1 chronic condition (intervention = 14, controls =11) and 8 an active malignancy (intervention = 5, controls = 3).

Results of 12-month follow-up

Thirty-three patients completed the 12-month follow-up, of which 3 patients died. Eighteen intervention and 19 control patients were readmitted, totaling 34 and 58 admissions,

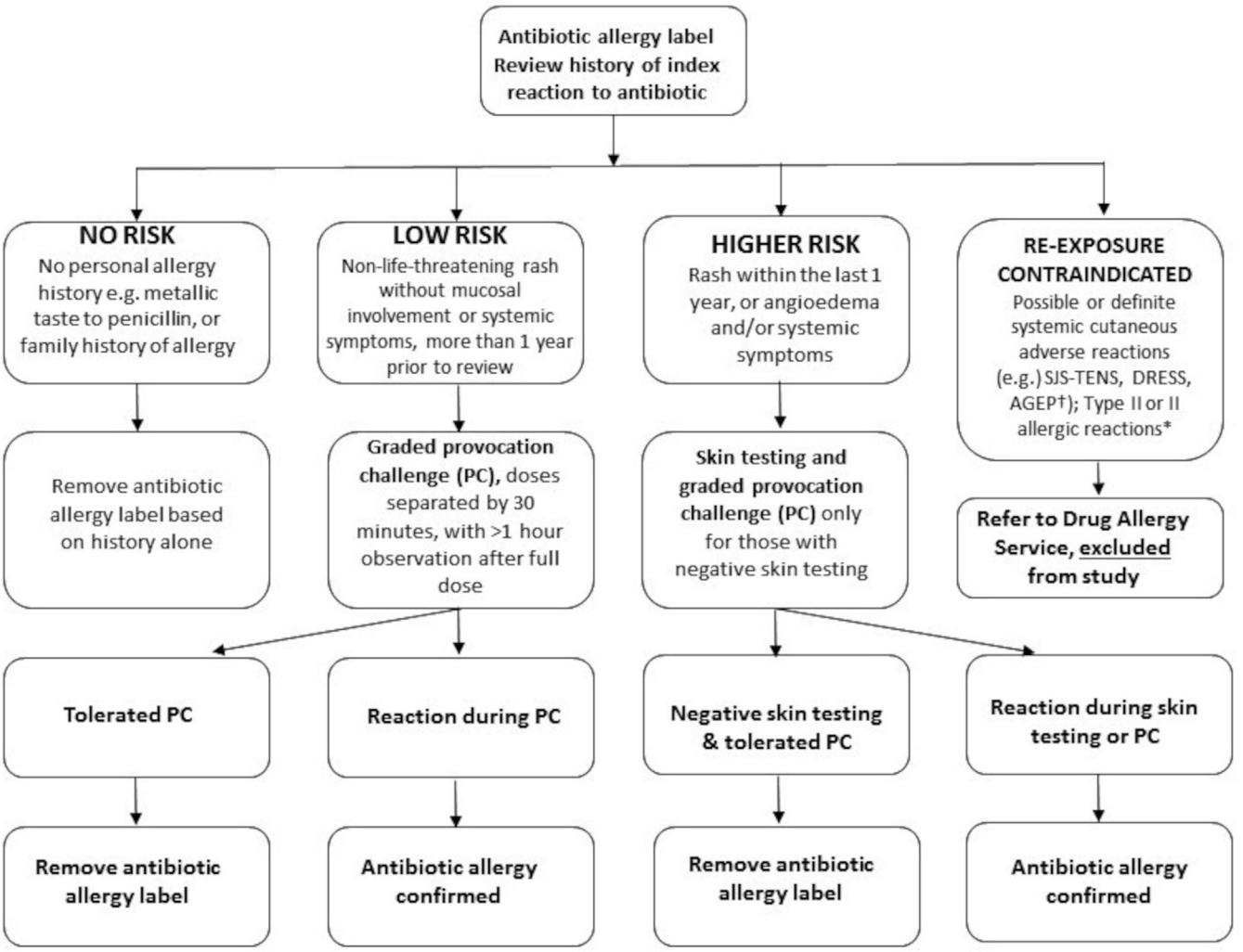

FIG 1. Antibiotic allergy delabeling strategy. *AGEP,* Acute generalized exanthematous pustulosis; *DRESS,* drug reaction with eosinophilia and systemic symptoms; *SJS/TENS,* Steven-Johnson syndrome/toxic epidermal necrolysis. *Serum sickness, acute interstitial nephritis, hemolytic anemia, and drug-induced liver injury.

respectively, not including the patient who underwent 23 sessions of chemotherapy. Primary care visits were common, often for repeat scripts. Antibiotic usage over the 12 months was reported (or obtained from hospital admission records) by 14 of 18 (78%) challenge patients and 13 of 19 (70%) control patients. Notably, 3 control patients received penicillin in the 12-month follow-up period despite carrying a penicillin label, but no adverse reactions were recorded. Three of the patients delabeled in the challenge arm received amoxicillin safely. One patient who had been delabeled after a successful challenge with amoxicillin presented 1 month later with a suspected drug reaction with eosinophilia and systemic symptoms (RegiSCAR score of 3) following exposure to oral phenoxymethylpenicillin. Subsequently, the patient was referred to the immunology outpatient clinic but failed to attend and was lost to follow-up.

Results of 4-year follow-up

A 4-year record review showed 18 of the patients randomized to receive an antibiotic challenge with the following clinical features: 3 (16%) had cultured multidrug-resistant bacteria, 2 (11%) had fungal growth, 7 (39%) had an active malignancy, 16 (89%) had significant comorbidities, 7 (39%) had been prescribed non–first-line antibiotics, 7 (39%) had been relabeled or had not had their records updated, and 4 (22%) had died. Of the 19 control patients, 7 (35%) had evidence of multidrug-resistant bacteria, 3 (15%) had fungal growth, 5 (25%) had an active malignancy, 18 (90%) had significant comorbidities, 8 (40%) had been prescribed non–first-line antibiotics, and 3 (15%) had died.

Cost analysis

Fig 3 illustrates the cost components of inpatient delabeling in Australia at the time of the study. Not including salaries, we calculated the cost of direct delabeling to be $131.85, a direct oral challenge to be $809.26, and ST followed by an oral challenge to be $1148.40 (Fig 3). If the cost of the DAP kit can be shared between 3 people, then cost of ST, followed by an oral challenge, decreases to $751.56 per person. At the time of the study, the average cost of a hospital bed stay (in Western Australia) was $56.58/h. Assuming the medical review and consent discussion had already taken place, testing and observation are estimated to add another

TABLE II. Summary of patient and allergy characteristics both overall and broken down by eligibility, whether they were recruited (if eligible) and the allocated intervention or control group for those recruited*

	Overall	Eligible	Ineligible	Eligible: Recruited	Eligible: Not recruited	Recruited: Intervention group	Recruited: Control group
	(N = 1503)	(N = 429)	(N = 1074)	(N = 39)	(N = 390)	(N = 20)	(N = 19)
Age (y), mean ± SD	67.4 ± 18.3	61.9 ± 18.4	69.6 ± 17.7	60.2 ± 16.2	62.1 ± 18.6	60.5 ± 29.6	59.9 ± 15.5
Sex							
Female	951 (63.3)	285 (30)	666 (70)	21 (7.4)	264 (92.6)	10 (47.6)	11 (52.4)
Male	552 (36.7)	144 (26.1)	408 (73.9)	18 (12.5)	126 (87.5)	10 (55.6)	8 (44.4)
Admitting team							
Medical/other	951 (63.3)	197 (20.7)	754 (79.3)	13 (6.6)	184 (93.4)	7 (53.9)	6 (46.2)
Surgical	552 (36.7)	232 (42)	320 (58)	26 (11.2)	206 (88.8)	13 (50)	13 (50)
Taking antibiotics at time of screening							
No	806 (53.6)	246 (30.5)	560 (69.5)	20 (8.1)	226 (91.9)	9 (45)	11 (55)
Yes	697 (46.4)	183 (26.3)	514 (73.7)	19 (10.4)	164 (89.6)	11 (57.9)	8 (42.1)
Antibiotic allergy alert class							
A clinical event during this admission	14 (0.9)	1 (7.1)	13 (92.9)	0 (—)	1 (100)	0 (—)	0 (—)
Historical— already documented in MR	1123 (74.7)	284 (25.3)	839 (74.7)	30 (10.6)	254 (89.4)	15 (50)	15 (50)
Patient report on admission	366 (24.4)	144 (39.3)	222 (60.7)	9 (6.3)	135 (93.8)	5 (55.6)	4 (44.4)
Allergy label attributed to drug class							
No	582 (38.7)	147 (25.3)	435 (74.7)	12 (8.2)	135 (91.8)	9 (75)	3 (25)
Yes	921 (61.3)	282 (30.6)	639 (69.4)	27 (9.6)	255 (90.4)	11 (40.7)	16 (59.3)
Generic antibiotic recorded							
No	757 (50.4)	240 (31.7)	517 (68.3)	23 (9.6)	217 (90.4)	10 (43.5)	13 (56.5)
Yes	746 (49.6)	189 (25.3)	557 (74.7)	16 (8.5)	173 (91.5)	10 (62.5)	6 (37.5)
Penicillins							
No	436 (29.01)	118 (27.51)	318 (29.61)	4 (10.26)	114 (29.23)	2 (10.53)	2 (10)
Yes	1067 (70.99)	311 (72.49)	756 (70.39)	35 (89.74)	276 (70.77)	17 (89.47)	18 (90)
Cephalosporins							
No	1311 (87.23)	384 (89.51)	927 (86.31)	34 (87.18)	350 (89.74)	16 (84.21)	18 (90)
Yes	192 (12.77)	45 (10.49)	147 (13.69)	5 (12.82)	40 (10.26)	3 (15.79)	2 (10)
Beta-lactams							
No	323 (21.49)	97 (22.61)	226 (21.04)	2 (5.13)	95 (24.36)	1 (5.26)	1 (5)
Yes	1180 (78.51)	332 (77.39)	848 (78.96)	37 (94.87)	295 (75.64)	18 (94.74)	19 (95)
Other							
No	1249 (83.1)	370 (86.25)	879 (81.84)	36 (92.31)	334 (85.64)	17 (89.47)	19 (95)
Yes	254 (16.9)	59 (13.75)	195 (18.16)	3 (7.69)	56 (14.36)	2 (10.53)	1 (5)
None recorded	1385 (92.2)	402 (29)	983 (71)	37 (9.2)	365 (90.8)	18 (48.7)	19 (51.4)
Yes	15 (1)	5 (33.3)	10 (66.7)	0 (—)	5 (100)	0 (—)	0 (—)
Yes, and micro alert in place	103 (6.9)	22 (21.4)	81 (78.6)	2 (9.1)	20 (90.9)	2 (100)	0 (0)
MRSA present							
No	1416 (94.2)	411 (29)	1005 (71)	39 (9.5)	372 (90.5)	20 (51.3)	19 (48.7)
Yes	87 (5.8)	18 (20.7)	69 (79.3)	0 (—)	18 (100)	0 (—)	0 (—)

MR, Medical record; *MRSA*, methicillin-resistant *Staphylococcus aureus*.
*Column percentages are provided for the overall summaries, whereas row percentages are provided for the other variables to allow appropriate comparisons.

$113 to the admission cost if discharge is delayed because of AAL assessment.

DISCUSSION

Our study identifies significant barriers to contesting unverified AALs outside of antimicrobial stewardship initiatives, including challenges such as chronic disease and cognitive dysfunction. We screened adult inpatients representative of a general hospital population where polypharmacy and comorbidity are prevalent.

This investigation was a specialist AAL evaluation study. Because the investigators were not the treating clinicians for the patients, it was not feasible to evaluate risks and benefits associated with beta-blockers in complex patients; hence, these patients were excluded. Current advice on beta-blockers lacks consensus. Barbaud et al[24] were unable to give a recommendation for or against pausing beta-blockers before oral challenges, Golden et al[25] suggest a risk-benefit shared decision-making approach, and the Scottish Antimicrobial Prescribing Group[26] suggests excluding patients on beta-blockers unless they are withheld for 24 hours. Australasian Society of Clinical Immunology and Allergy guidelines for ST consider beta-blockers to be relative contraindications.[27] Despite this, recent evidence indicates that beta-blockers might be safely administered during allergy immunotherapy,[28] suggesting that our exclusion criteria might have been overly cautious. In our study, although 387 (36%) of the excluded patients were on beta-blockers, nearly half (n = 182 [47%]) of them also had other factors, such as cognitive impairment or acute illness, making them unsuitable for inclusion. A total of 320 (29.8%) patients were excluded solely because of concomitant medication, with 205 (19.1%) being on beta-blockers. Other concomitant medications that served as the sole excluding factor included low-dose steroids (<10 mg

TABLE III. One or more factors affecting eligibility for 1074 patients

Ineligibility reason	N (%)
Concomitant medication	
Beta-adrenoceptor–blocking agents	387 (36.03)
High-dose steroids	151 (14.06)
Low-dose steroids	36 (3.35)
Immunosuppression nonsteroidal	26 (2.42)
Antihistamines	21 (1.96)
Other drug-related reasons	2 (0.19)
Cognitive impairment	300 (27.93)
Medically unwell	158 (14.71)
Systemic illness	45 (4.19)
Could have been directly delabeled	165 (15.36)
Current treatment with putative culprit antibiotic	32 (2.98)
History of SCAR	37 (3.45)
Already on beta-lactam antibiotic	1 (0.09)
Previously referred/assessed in allergy clinic	34 (3.17)
Language barrier	36 (3.35)
Legally blind/hearing loss	13 (1.21)
Social and lifestyle factors	7 (0.65)
Inappropriate allergy label	5 (0.47)
Antibiotic in allergy not part of delabeling service	4 (0.37)
Practical reasons	4 (0.37)
Medicare ineligible	4 (0.37)
Pregnant	3 (0.28)
Recruited in another study	1 (0.09)
Declined by medical team/staff	1 (0.09)

SCAR, Severe cutaneous adverse reaction.

prednisolone or equivalent; n = 8 [0.74%]), high-dose steroids (>10 mg prednisolone or equivalent; n = 70 [6.52%]), and antihistamines (n = 8 [0.74%]). This scenario highlights the need for further studies on acceptable concomitant medications during allergy testing and the difficulty of protocolising a one-size-fits-all delabeling service in an aging population with polypharmacy.[29]

Patient-related factors such as apprehension, perceived unimportance, and not wanting to add to their medical issues contributed to a high refusal rate to participate; in addition, hospital systems are primarily geared toward treating and resolving acute conditions and thereafter expediting discharge. Unsurprisingly, we found that younger and surgical patients were more likely to be eligible due to fewer medical comorbidities. Substandard allergy recording also persisted, leading to frequent relabeling among patients.

Comparatively, many studies describe inpatient penicillin allergy testing aimed at addressing low-risk labels and encourage nonspecialist involvement. Conversion rates from screening to consent in these studies varied significantly, ranging from 6% to 92%.[30-32] In the study with a 92% conversion rate from a sample of 112 adults, recruitment focused on 3 medical wards and did not encounter the same barriers as our study. The reasons for nonparticipation included medical instability (3.5%), patient refusal (2.8%), and no reason given (1.8%).[31] Interestingly, this study excluded only 9.8% of their sample because of a probable type 1 allergy history, with the remainder having a low-risk history, which is higher than in other literature. In contrast, the study with a 6% conversion rate was conducted in intensive care with COVID-positive patients and identified 285 patients with penicillin allergies. Of the 24 eligible patients, 19 consented to a challenge. Reasons for ineligibility included non–low-risk allergy histories or medical instability.[32] In neither of these studies did beta-blockers or cognitive impairment, our 2 highest reasons for ineligibility, feature as dominating factors.

The SPACE study illustrated that focusing recruitment in elective rather than acute settings improved their service's conversion rates—from 3% in acute settings to 17.9% in elective settings.[30] Highlighting the context-dependent nature of patient recruitment and testing, Chen et al[9] prioritized inpatients whose penicillin label impacted pharmacotherapy. Patients on beta-blockers were assessed individually, with testing approved verbally by duty allergists or treating physicians. Of 1203 screened patients, 252 (20.9%) were prioritized; 228 proceeded to testing, though discharge orders limited further evaluation for some of the 951 patients.[9]

Similarly, our findings show that approximately 46% of otherwise eligible patients were scheduled for discharge, and a similar proportion declined testing. This suggests that conducting testing as a clinical priority could potentially increase consent rates.

In a nonrandomized whole of hospital program involving a sample of 1225 patients with penicillin AAL, Chua et al[12] assigned 558 to either direct delabeling through history alone or an oral challenge; the remaining high-risk patients were referred to outpatient antibiotic allergy services. Notably, they were unable to get consent from 208 of 558 patients because of discharge orders or refusal to participate.[12] In concordance, we identified a large proportion of screened patients (69%) who would have required ST in the event they were otherwise eligible. We conclude that using specialist allergy services for inpatient delabeling of higher-risk patients is a costly venture compared with outpatient services. However, the potential savings from avoiding downstream health care costs, such as those from antibiotic-resistant infections and reduced hospital stays, could offset these expenses and make delabeling cost-effective, but only within a context of clinical need.[3]

Our study has limitations. First, our trial was designed for patients enrolled and randomized to receive antibiotic challenge or usual care to measure the study outcomes of antibiotic usage, hospital admission, and length of stay. We did not set out to report data from patients screened but not meeting inclusion criteria; therefore, we did not investigate patients with putative erroneous labels of negligible risk, and who could, potentially, have been directly delabeled. Nor did they receive the definitive communication required to thoroughly and effectively delabel them. Notably, and although this varies internationally, Australian guidelines do not currently recommend direct OPC for patients who could be delabeled solely on the basis of their medical history.[20] However, this position may require further discussion. Patients who have lived with an uncertain allergy label, sometimes for their entire lives, may need a challenge to verify they are not allergic. Importantly, if documentation is substandard, and patients cannot remember being tested, the likelihood of an AAL persisting is high, regardless of safe, accurate diagnostic testing to remove or confirm an AAL. Improved verbal and documentary communication can influence future antibiotic choices and reduce the risk of relabeling, as well as adverse downstream health and economic consequences.

Regarding the 39 RCT subjects, many already had poor health status, with 10% dying within the 12-month follow-up period. Even within this small group, we demonstrated high rates of antibiotic usage and readmissions that justify attempts to verify or refute these patients' AALs. Despite written

TABLE IV. Univariate and multivariate logistic regression model results from analyzing inpatient eligibility, and RCT recruitment status (the latter is limited to only eligible inpatients)

	Univariate		Multivariate	
	OR (95% CI)	*P* value	OR (95% CI)	*P* value
Eligible (model event) vs ineligible				
Age				
For a 10-y increase	0.80 (0.75- 0.85)	<.0001	0.82 (0.77- 0.88)	<.0001
Sex				
Female vs male	1.21 (0.96- 1.53)	.1085	1.21 (0.95- 1.55)	.1297
Admitting team				
Surgical vs medical/other	2.78 (2.20- 3.49)	<.0001	2.49 (1.97- 3.16)	<.0001
Recruited (model event) vs not recruited				
Age				
For a 10-y increase	0.95 (0.80- 1.13)	.5428	0.97 (0.81- 1.15)	.7007
Sex				
Female vs male	0.56 (0.29-1.08)	.0841	0.56 (0.29- 1.09)	.0863
Admitting team				
Surgical vs medical/other	1.79 (0.89- 3.58)	.1017	1.76 (0.87- 3.56)	.1137

OR, Odds ratio.

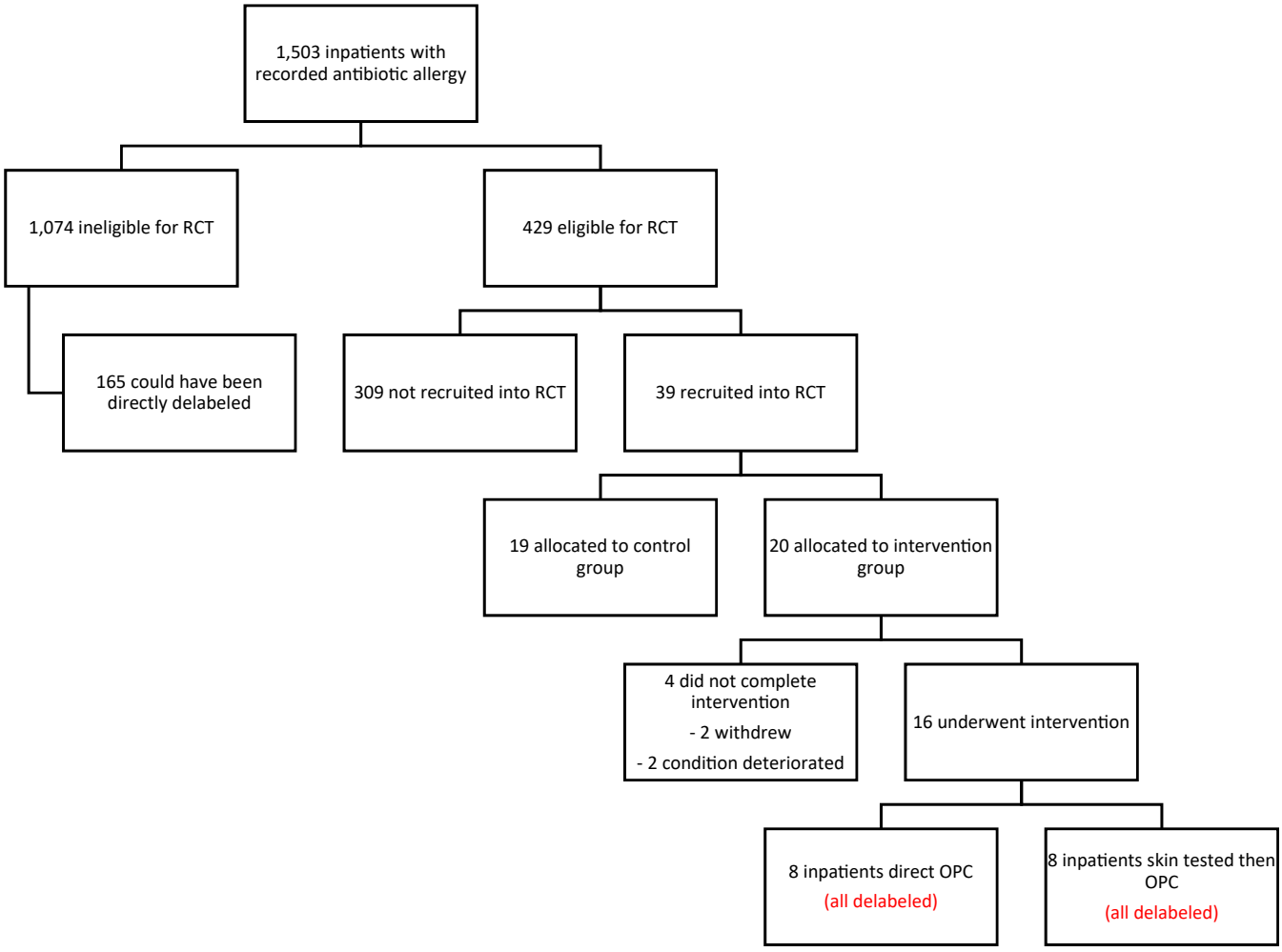

FIG 2. Flow chart showing screening for eligibility, recruitment, and outcomes of testing.

communication, relabeling persisted, highlighting the importance of improved communication with primary physicians, and patient education following discharge. Although not part of our protocol, there is emerging evidence of the advantages of an extended drug challenge over single-day challenge, particularly for identifying delayed reactions. This approach may have been beneficial in unmasking the reaction for the patient who developed drug reactions with eosinophilia and systemic

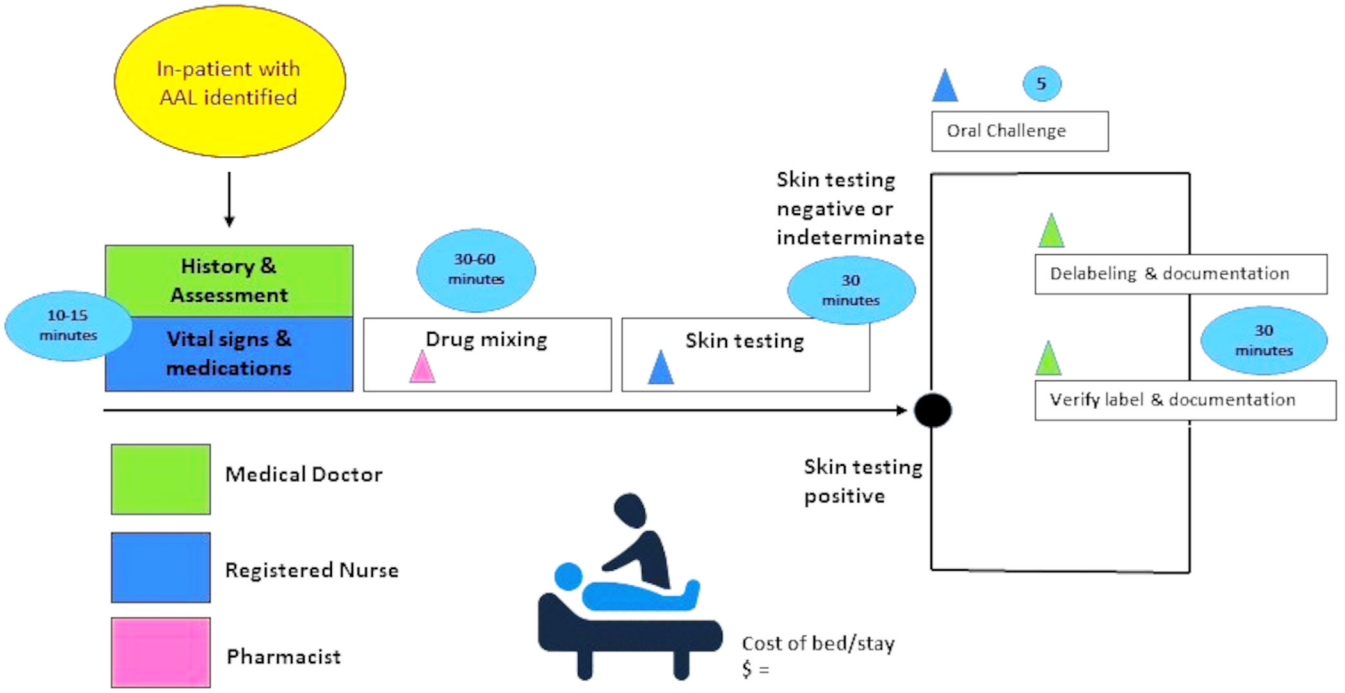

FIG 3. Inpatient allergy evaluation process map (figure derived from Blumenthal et al[23]). Identifies the components of inpatient drug allergy evaluation. The oval circles denote the time in minutes taken for each activity and colors indicate personnel type. The costs identified using this process represent the health sector perspective and not patient time/impost.

symptoms. However, ASCIA guidance at the time this study was conducted, and up to the present, does not explicitly recommend extended challenges. A meta-analysis by Barbaud et al[24] found that 28 additional extended-day challenges were needed to identify 1 additional mild reaction, and the findings did not conclusively support the use of an extended-day challenge over a single-day challenge.

Recommendations

We recommend verification of reported antibiotic allergy as contemporaneously as possible to the index reaction, and adherence to quality practices to prevent relabeling.[24,33] including documentation in medical records, communication with other health providers, and patient counseling. Thereafter, targeting, systematically, patients in the preoperative stages of elective surgical planning, and in the early "workup" stages of cancer or chronic disease management, the value of doing this has been demonstrated.[5,6,34-37] Reducing prevalent AAL requires a concerted multidisciplinary effort.[38] Commonly, medication discrepancies are found at the time of hospital admission or discharge. Nurses could, while completing admission documentation, ensure escalation of patient-reported antibiotic allergy for clinical action, working with pharmacists who are required to conduct medication reconciliations at the end of the next calendar day following the day of admission.[39,40] If the label is not evaluated at the current admission, then discharge documentation should communicate the patient's status with clear recommendations for clinical action. Importantly, documentation must be accurate and precise to prevent incorrect clinical information in perpetuity. Although studies point to the cost-effectiveness of adopting a systematic approach to tackling the high rate of AAL in hospitals and we acknowledge that delabeling patients at point of care appears expedient, we argue that earlier, multifaceted intervention is required. Although outpatient assessment of high-risk patients remains appropriate, evaluation of putative and low-risk penicillin allergies, including those in children, could be carried out in community settings by primary physicians. In effect this is where most antibiotics are prescribed, and where individual and societal benefits can accrue across the lifespan.[34,41]

Conclusion

This study highlights the complexity of antibiotic allergy delabeling in the acute care context, and provides recommendations to reduce the prevalence of spurious labels, and recurrence of relabeling.

DISCLOSURE STATEMENT

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Clinical implications: This article is a cautionary tale highlighting the barriers, health costs, and complexities associated with inpatient antibiotic allergy delabeling in the context of acute care medicine.

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