

Journal Pre-proof

Direct drug provocation testing may be safe for de-labelling the majority of inpatients with a penicillin allergy label and is associated with improved health and economic outcomes

Jamma Li, MBBS, Aryan Shahabi-Sirjani, B Pharm, Nikhita Ange, MBBS, Melanie Figtree, MBBS, Philip Hoyle, MBBS, Suran L. Fernando, MBBS PhD

PII: S1081-1206(19)30581-2

DOI: <https://doi.org/10.1016/j.anai.2019.08.005>

Reference: ANAI 2982

To appear in: *Annals of Allergy, Asthma and Immunology*

Received Date: 6 May 2019

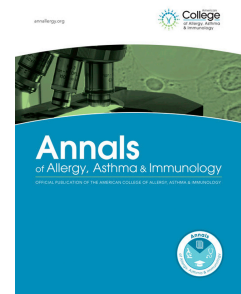
Revised Date: 15 July 2019

Accepted Date: 7 August 2019

Please cite this article as: Li J, Shahabi-Sirjani A, Ange N, Figtree M, Hoyle P, Fernando SL, Direct drug provocation testing may be safe for de-labelling the majority of inpatients with a penicillin allergy label and is associated with improved health and economic outcomes, *Annals of Allergy, Asthma and Immunology* (2019), doi: <https://doi.org/10.1016/j.anai.2019.08.005>.

This is a PDF file of an article that has undergone enhancements after acceptance, such as the addition of a cover page and metadata, and formatting for readability, but it is not yet the definitive version of record. This version will undergo additional copyediting, typesetting and review before it is published in its final form, but we are providing this version to give early visibility of the article. Please note that, during the production process, errors may be discovered which could affect the content, and all legal disclaimers that apply to the journal pertain.

© 2019 American College of Allergy, Asthma & Immunology. Published by Elsevier Inc. All rights reserved.



Direct drug provocation testing may be safe for de-labelling the majority of inpatients with a penicillin allergy label and is associated with improved health and economic outcomes

Jamma Li, MBBS

1 Department of Clinical Immunology and Allergy, Royal North Shore Hospital, Sydney, Australia

2 New South Wales Health Pathology, Sydney, Australia

3 University of Sydney, Sydney, Australia

Jamma.li@health.nsw.gov.au

Ph +612 99264108

Fax +612 94631058

Aryan Shahabi-Sirjani, B Pharm

4 Department of Pharmacy, Northern Sydney Local Health District, Sydney, Australia

Nikhita Ange, MBBS

1 Department of Clinical Immunology and Allergy, Royal North Shore Hospital, Sydney, Australia

Melanie Figtree, MBBS

5 Department of Infectious Diseases, Royal North Shore Hospital, Sydney, Australia

2 New South Wales Health Pathology, Sydney, Australia

Philip Hoyle, MBBS

6 Executive Unit, Northern Sydney Local Health District, Sydney, Australia

Suran L Fernando, MBBS PhD

1 Department of Clinical Immunology and Allergy, Royal North Shore Hospital, Sydney, Australia

2 New South Wales Health Pathology, Sydney, Australia

3 University of Sydney, Sydney, Australia

Conflicts of Interest: none

Funding sources: none

Keywords: penicillin allergy, drug allergy, skin testing, drug provocation testing, drug hypersensitivity, Type B adverse reactions

Abbreviations: penicillin skin testing (PST), drug provocation testing (DPT)

Word Count: 3758

Figures: 2

Tables: 4

INTRODUCTION

It is well established that there are significant benefits of prescribing beta-lactam antibiotics for susceptible infections. Prescription of non-beta-lactam antibiotics in inpatients with penicillin allergy labels is associated with increased hospital days (1), increased cost of admission (1, 2), increased readmissions (3), increased intensive care unit admissions, increased multi-resistant organisms (MROs) (1), and increased mortality (4).

The prevalence of penicillin allergy labels in the adult inpatient population has been reported as high as 15% (1, 5, 6). Further, amongst patients who truly have IgE-mediated allergy to penicillins, less than 50% of patients retain their allergy after 5 years, and less than 20% of patients retain their allergy after 10 years (7).

However, assessing a label of penicillin allergy requires specialized knowledge. Adverse reactions to penicillins comprise Type A or Type B reactions (8). Type A accounts for approximately 80% of reactions, and are pharmacological and dose-dependent, resolving when the dose is reduced (8). Common Type A reactions to penicillins include nausea, abdominal pain, vomiting or diarrhea. Type B reactions, however, are idiosyncratic, not related to drug pharmacology, and resolve only when the drug is discontinued (8). Type B reactions include immunoglobulin-E (IgE)-mediated drug allergy (Gell and Coombs Type 1 hypersensitivity reaction) and maculopapular drug eruptions (Gell and Coombs Type 4 hypersensitivity reaction), in addition to hemolytic anemia (Gell and Coombs Type 2 hypersensitivity reaction), serum sickness (Gell and Coombs Type 3 hypersensitivity reaction) and severe cutaneous adverse reactions including Stevens-Johnson syndrome/toxic

epidermal necrolysis, drug reaction with eosinophilia and systemic symptoms and acute generalized exanthematous pustulosis (Gell and Coombs Type 4 hypersensitivity reaction).

Obtaining an allergy history, and direct removal of penicillin allergy labels for Type A reactions has been shown to be safely performed by a specialist antimicrobial stewardship pharmacist (9, 10). However, Type B reactions are more complex and generally require input from an allergist/immunologist. ~~Patients with Type 2, 3 or severe Type 4 hypersensitivity reactions have penicillin allergy labels confirmed and do not precede to~~ PST and/or DPT are not appropriate methods of evaluation for Type 2, 3 or severe Type 4 hypersensitivity reactions due to persistence of the reaction and risk of recurrence of a severe reaction on testing (11). The traditional approach for Type 1 and mild Type 4 hypersensitivity reactions have been to perform penicillin skin testing (PST) prior to drug provocation testing (DPT). Recent literature has explored the feasibility of more resource-efficient strategies which center upon reducing PST.

An increasing body of literature suggests the safety and feasibility of DPT without PST for evaluation of both Type 1 and 4 hypersensitivity reactions to penicillins in the pediatric population (12-14). The low positive predictive value of PST leads to inappropriate penicillin allergy labels, particularly in children (13). In adults, Chiriac et al. reviewed the literature and showed that 100% of patients with anaphylaxis to a beta-lactam had positive PST at the time of the index reaction (15). The authors raised the question of whether PST should be monitored and patients proceed to DPT once PST becomes negative, but noted the lack of evidence base. Overall, however, the positive predictive value of PST in adults is low, estimated at less than 50%, even when skin testing is correctly performed using major and all minor determinants (16, 17), although negative predictive value is high at 97-99%. Specialist

training is required to correctly perform skin testing, and periodic proficiency evaluation is recommended (11). In many centers, there is no access to suitable personnel for PST (18).

There is emerging literature studying the safety and expanding use of DPT without PST for evaluation of penicillin allergy labels in the adult population. Blumenthal et al. recommended that low risk patients, that is, patients reporting non-urticarial minor rash, maculopapular eruption, or where an allergy is recorded in hospital records but denied by the patient, proceed to incremental challenge (19). DPT has been safely used in patients with a history, over 12 months ago, of rash or pruritus or an unknown reaction to penicillins (20-23).

Recently, this was expanded to a mixed pediatric and adult population, who did not have life-threatening reactions to penicillins with no specified timeframe. Safety was established as only 4 out of 155 patients experienced an allergic reaction, all of which were mild (24).

We studied the safety of penicillin allergy evaluation with DPT for adult patients with Type B reactions. We assessed, as secondary outcomes, the impact of removal of penicillin allergy labels on length of stay, total cost of admission, cost of antimicrobial treatment, and inpatient readmission within 6 months. We also followed up each patient's penicillin allergy status in the electronic medical record (eMR) as well as in the medical records of their primary care physician.

METHODS

Trial design and setting

We conducted a prospective clinical case series with retrospective controls used for secondary outcomes between April 1, 2017 and April 30, 2018 at a single-center tertiary hospital in Sydney, Australia. The study was reviewed and approved by the Northern Sydney

Local Health District's (NSLHD) Human Research Ethics Committee (LNR/16/HAWKE/452). No funding was obtained to support this study.

Inclusion and exclusion criteria

Inpatients over 16 years of age, with a label of Type B penicillin allergy, and requiring a penicillin-containing antibiotic for treatment were eligible for inclusion. Pregnant patients and patients with haemodynamic instability were excluded from the study on the basis of risk of the intervention.

Intervention

Suitable patients were flagged by inpatient treating teams and the antimicrobial stewardship service. The intervention comprised evaluation of penicillin allergy labels, conducted by an allergy/immunology registrar under the guidance of an allergist/immunologist, and an allergy/immunology nurse.

Allergy histories were ascertained from patient history in conjunction with the Electronic Medical Record (EMR). Patients with Type A adverse reactions received direct DPT. Patients with Type B reactions comprising Type 2, 3 or severe Type 4 hypersensitivity reactions had their allergy label confirmed on clinical history and did not proceed to further testing. Patients with all other Type B adverse reactions except anaphylaxis within 10 years all received DPT to amoxicillin, however, we performed PST to collect data but would proceed to DPT regardless of the result. Patients with anaphylaxis within 10 years of review would receive PST, then DPT if PST was negative.

PST was performed using benzylpenicillin, amoxicillin, Diater PPL® (benzylpenicilloyl-polysine) and Diater MDM® (minor determinant mixture) (Diater Laboratories, Madrid, Spain). Intradermal testing was performed using all four reagents each at two serial concentrations (Table 1) in the presence of satisfactory negative saline and positive histamine controls (ABK-Abello, Hørsholm, Denmark).

DPT to amoxicillin was administered by a 3 step protocol in a hospital ward bed with 1:1 support from an allergy/immunology nurse or registrar. The target single dose was 500mg, or as adjusted for renal failure. Initially 1% of target amoxicillin dose (as 250mg/5mL suspension) was administered followed by 30 minutes of observation, followed by subsequent administration of 10% of target dose and 30 minutes of observation. Finally the full target dose was administered followed by two hours of observation.

Patients then received a full 3 day course of amoxicillin. DPT was complete after three days or stopped in the event of reaction. Amoxicillin was continued past 3 days if warranted for medical treatment. If an antibiotic other than amoxicillin was required for inpatient medical treatment, then the 3 day amoxicillin challenge was completed later in the admission prior to discharge.

Primary outcomes

We assessed the safety of our protocol by determining the number of patients who had life-threatening, and non-life threatening Type B adverse drug reactions to DPT. Life-threatening reactions are anaphylaxis requiring intubation and/or epinephrine, or Type 2, Type 3 or severe Type 4 hypersensitivity reactions (24).

Secondary outcomes

Retrospective matching to control patients to assess secondary outcomes

The closest control subject was identified for each patient included in the intervention arm. All control subjects were inpatients at the same tertiary hospital in Sydney, Australia between April 1, 2017 and April 30, 2018, with a label of penicillin-allergy, and admitted for infection affecting the same body system. Subjects meeting these two criteria were then matched as closely as possible for age (within 10% of that of the intervention subject), date of admission (admitted within 4 weeks of the date of admission of the intervention subject), gender, and accommodation status (home, rehabilitation, low level nursing care, high level nursing care, other hospital) by an antimicrobial stewardship pharmacist.

The following data was collected for all intervention and control subjects: demographics, date of admission and discharge, clinical history, cost of antimicrobial therapy, cost of stay, length of stay, admission to intensive care unit, readmissions within a 6 month period, and colonisation by MROs.

Total hospital costs for each subject were obtained from the Finance Manager, NSLHD, which are official figures reported to NSW Health. These figures encompass all costs associated with the admission except for pharmaceuticals. Costs of antibiotics administered during the admission were obtained from the hospital's Department of Pharmacy.

Statistical analysis

All statistical analyses were conducted with SPSS Version 24 (IBM, Armonk, New York, United States). Means and standard deviations were calculated on continuous variables.

150 Statistical significance was assessed on categorical variables by using χ^2 and t tests for
151 continuous variables. $P < 0.05$ was considered statistically significant.

152

RESULTS

Seventy-one patients were enrolled sequentially in the prospective intervention arm for evaluation of penicillin allergy labels (Figure 1, Table 2). One patient did not have a penicillin-sensitive infection and was excluded from all analyses. There were no patients referred who were pregnant or hemodynamically unstable. All 70 patients reported a reaction that was over 12 months old.

Primary outcome

Seven patients were not included in the primary outcome as allergy history suggested a Type A reaction or a reaction unrelated to penicillins; nausea (4 patients), pain (2 patients), weakness (1 patient).

Of the remaining 63 patients, 30 patients reported a benign rash, and 12 reported an unknown reaction. Twenty-one patients reported reactions that could be consistent with an IgE-mediated etiology, comprising anaphylaxis (2 patients), urticaria with or without angioedema (9 patients), symptoms of upper airway edema without need for intubation (6 patients), and angioedema with no airway features (4 patients).

Therefore 63 patients had previously experienced Type B or unknown adverse drug reactions (Figure 1, Table 2). No patients had a history of anaphylaxis requiring intubation or epinephrine within the last 10 years. No patients had a history of reaction to suggest Type 2, 3 or severe Type 4 hypersensitivity reaction. A total of 7 patients did not complete DPT as the treating team used a beta-lactam antibiotic other than amoxicillin and the patients did not complete DPT prior to discharge.

Fifty-four of 56 (96%) remaining patients completed a 3 day DPT to amoxicillin with no adverse reaction. Two patients were confirmed to have penicillin allergy, both reported a history of benign rash. Both received the first dose of amoxicillin with no adverse reaction. The first patient, a 64-year-old male was subsequently switched to flucloxacillin, and developed symmetrical drug-related intertriginous and flexural exanthema (SDRIFE) on the third day of flucloxacillin treatment for cellulitis. The rash resolved with cessation of flucloxacillin and no specific medical treatment. The second patient, a 61-year-old female, developed a maculopapular rash on the fourth day of amoxicillin for a urinary tract infection. The rash resolved with cessation of the drug, and symptomatic treatment with antihistamines and low dose prednisone.

Secondary outcomes (Table 4)

Number of positive penicillin skin tests

Of 63 patients with a reported history of Type B adverse reaction to penicillins, there was only one positive PST, and to amoxicillin only, in one patient who had not been exposed to amoxicillin. This patient required penicillin VK for treatment, and so completed 3 day amoxicillin DPT in the outpatient clinic.

Length of stay

The total length of stay for 70 patients in the intervention arm was 900 days, against 1276 days for the control arm ($P < 0.05$). Assuming a conservative estimate of 1 inpatient de-labelling per weekday, this projects to a reduction of 1395 hospital days per year and a reduction in the average length of stay by 6 days.

Cost of hospital admission

The total cost saving for 70 patients in the intervention arm was \$469,290 based on the length of stay ($P<0.05$). The tertiary hospital in which the study was performed currently admits 7000 patients with a penicillin allergy of which 45% require penicillin therapy during their admission. Assuming a conservative estimate of one inpatient de-labelling per weekday, this projects to a cost saving of \$1,743,077 per year.

Cost of antimicrobial therapy

The total cost saving for antimicrobials alone in the intervention arm was \$20,856 ($P<0.05$).

Readmission rate

There were 30 readmissions within 6 months in the intervention arm, and 43 in the control arm. The number of readmissions requiring penicillin within 6 months of discharge was significantly lower in the intervention arm compared to the control arm ($P<0.05$).

ICU admission

There was no significant difference between the number of patients requiring intensive care unit admissions in the intervention and control arms ($P=0.45$).

Multi-resistant organisms

Three new MRO were acquired by patients in the intervention arm during the study period. Two were infections, and 1 colonisation alone. Five new MRO were acquired in the control arm during the study period, 4 infections and 1 colonisation. There was no significant difference in MRO acquisition ($P=0.50$).

Recording of allergy label

228 Sixty-one of 63 patients (97%) with a history of Type A or B adverse reactions who
229 completed assessment of their penicillin allergy label had their electronic medical records
230 updated. Allergy information was updated in the hospital discharge summary for 50 patients
231 (79%). Telephone follow-up to the treating local medical officer revealed that only 21
232 patients (33%) had accurate penicillin allergy information documented in the clinic's medical
233 record.

DISCUSSION

Evaluation of penicillin-allergy labels and prescription of beta-lactam antibiotics for non-allergic patients is associated with improved clinical outcomes and economic benefits. The majority of reported adverse drug reactions to penicillin are Type A, estimated at 80% (8), and these penicillin-allergy labels can be removed following interview. Recent publications have shown that this can be effectively done with a specialist antimicrobial stewardship pharmacist with adequate training in allergy history (9, 10). More problematic is the evaluation of penicillin-allergy labels where the reported adverse reaction is Type B. Traditionally, PST is used prior to DPT. However, PST is not available at many centers, leading to delay in penicillin-allergy label evaluation. Where it is available, PST incurs labor and reagent costs, and requires training and proficiency assessment. Further, a recent survey by the European Academy of Allergy and Clinical Immunology (EAACI) showed significant heterogeneity in PST practice amongst its members. We estimate the cost of PST reagents at AUD650 (approximately per week assuming one inpatient evaluation per day).

In our study, we sought to evaluate the safety and feasibility of DPT without PST in adult inpatients, many with multiple comorbidities and reported clinical history that could be compatible with IgE-mediated reactions. Because the demographic and clinical history of our cohort was different to many published cohorts, we wished to We collected PST data for all patients with Type B reactions as our cohort was different to many published cohorts, however, we proceeded to DPT regardless of the result except for patients with anaphylaxis within 10 years of review, however, there were no patients in that category.

Consistent with published literature, the incidence of positive PST was low. In our study, only 1 of 71 patients had a positive PST, and went on to tolerate a 3 day course of amoxicillin.

Literature suggests safety of DPT without PST for a history of pruritus and benign rash greater than 12 months prior to review for children with a 1-5% incidence of mild adverse reaction (12-14). Recently a few studies have examined the safety and feasibility of DPT without PST in adults (20, 22, 24). In Tucker et al, DPT without PST was safe for 328 healthy Marine recruits aged between 18 and 25 with a label of penicillin allergy with only 5 mild adverse reactions noted, all cutaneous (20). The only exclusion criteria were serious cutaneous reactions (excluding urticaria/angioedema), hepatitis, hemolytic anemia, or nephritis. In Iammatteo et al., DPT was safe in a mixed pediatric and adult population where the only exclusion criteria were anaphylaxis requiring intubation or epinephrine, and Type 2, 3 or severe Type 4 drug hypersensitivity reactions (24). Only four of the 155 (2.5%) enrolled patients experienced adverse reactions, all mild in symptomatology. Only five patients assessed had a history of life-threatening reaction and required PST prior to DPT. These studies suggest that DPT without PST may be safe in patients with a history of non-life-threatening reactions to penicillins. Our study expands the data in this area, and we also experienced a similar rate of adverse reactions, which were all mild (3%).

In our study of 71 sequential patients with Type B or unknown reactions, no patients had Type 2, 3 or severe Type 4 hypersensitivity reactions. We had two patients with a history of anaphylaxis but beyond 10 years of time of review. Our cohort comprised only of adults who were all inpatients, many with significant comorbidities and life-threatening infection that required treatment, unlike the cohort of Tucker et al where patients were healthy and had no

history of anaphylaxis to penicillins (16). We enrolled 71 patients sequentially, and performed PST for all 63 patients with Type B reactions. There was only one positive PST to amoxicillin alone, in a patient who reported a penicillin VK reaction. This patient tolerated 3 days of penicillin VK treatment and subsequently de-labelled to amoxicillin in an outpatient setting. All 21 patients with possible histories of IgE-mediated reactions had negative PST. Apart from 4 patients who did not complete DPT prior to discharge, all remaining 17 patients completed the 3 day DPT with no adverse reaction. Our study supports the findings of Iammatteo et al., that evaluation of penicillin allergy labels in adults, inclusive of labels compatible with IgE mediated allergy, may be safe and feasible without PST (24).

The procedure of penicillin allergy evaluation is labor-intensive, and requires specialist attendance for approximately 3.25 hours, in our experience, it requires up to 15 minutes to obtain a drug history, and 3 hours to supervise the completion of DPT. A cost saving of a half-hour per patient could be achieved if we adopted the 2-step protocol used in Iammatteo et al. (24). However, traditionally the 3-step protocol has been used in our institution. It may also be possible to coordinate testing so that two patients may undergo DPT at the same time, but this can be difficult in an inpatient setting.

~~We think therefore inpatient penicillin allergy label evaluation is most efficiently conducted by an allergy/immunology nurse or trainee with remote support from an allergist/immunologist.~~ We suggest further study of a resource-efficient model (Figure 2) where DPT without PST is used for all patients unless exclusion criteria of a history of anaphylaxis requiring epinephrine or intubation (15), IgE-mediated reaction within 12 months of review, or a history of Type 2, 3, or severe Type 4 Gells and Coomb hypersensitivity reactions are met (Figure 2). In our study, personnel comprised an

allergy/immunology nurse or trainee with remote support from an allergist/immunologist. Patients meeting exclusion criteria are infrequent. In the uncommon occurrence where a referred patient requires PST before DPT, specialized allergy/immunology personnel can immediately proceed to PST, and then DPT if appropriate. For Type 2, 3, or severe Type 4 hypersensitivity reactions, penicillin allergy labels can be confirmed. Further study will help to clarify safety and feasibility, and whether exclusion criteria could be further narrowed.

In relation to secondary outcomes, a total cost saving of \$1,743,077 per year is projected, applying a conservative estimate of 1 penicillin allergy label assessment per weekday. Additional fiscal benefit will be derived through significantly reduced readmissions, reduced length of stay and antibiotic costs in future admissions, and reduced absences from work from appropriate prescribing in the community.

The total length of stay was reduced by 6 days per patient per admission. This may be because beta-lactams are superior in treatment of beta-lactam sensitive infections, literature shows this for *Staphylococcus aureus* (25) and gram-negative bacilli infections (26). We did not find any significant difference between new colonization or infection by MROs between the intervention and control groups. This may be because our cohort size is small.

Our study reinforces the principle that penicillin allergy label evaluation should be a mandatory part of Antimicrobial Stewardship given the removal of penicillin allergy label in over 95% of patients with a diagnosis of penicillin allergy in which penicillin antibiotics are still the primary antibiotics of choice to eradicate infection. This intervention reduces length of stay and reduces hospital expenditure.

Retrospective audit of allergy documentation on EMR shows that a significant percentage of patients did not have their allergy status updated. This is crucial as the readmission rate of patients de-labelled of their penicillin allergy label is significantly lower as a result of better clearance of infection and recrudescence infection. Telephone follow-up revealed that the majority of patients (67%) did not have their allergy status updated in the records kept by their local medical officer. Our findings are not isolated, one group found that 36% of patients de-labelled of penicillin allergy had penicillin allergy documented at a subsequent admission (27). Better communication to patients and primary care physicians is required to maximize clinical and financial benefits to the community. A strategy therefore needs to be put in place to ensure improved documentation, particularly at the community level. One publication suggested a four-step intervention could be effective in improving allergy documentation following de-labelling (27). This intervention comprised counselling by a pharmacist during the admission, a post-discharge phone call, a printed wallet card for the patient with the test date and result, and implementation of an eMR alert for re-documentation of penicillin allergy. Finally, patients who do not logistically complete an inpatient amoxicillin 3-day challenge must follow up in outpatient clinics to complete DPT before the penicillin allergy label can be removed.

The limitations of our study are the relatively small sample size. We relied on contact by inpatient teams and antimicrobial stewardship for patient enrolment. This data would be improved if we were able to recruit all patients in the Emergency Department prior to commencement of antibiotics as soon as they were admitted. This was not possible as personnel were only on site from 8:30am to 5pm, and have other responsibilities within our department. Further, a randomized control trial would have reduced selection bias as controls were retrospectively matched, although performed independently by a pharmacist.

357

358 We need to further study whether DPT without PST is a safe, feasible and resource-efficient
359 method of de-labelling inpatients with a history of IgE-mediated penicillin allergy as well as
360 benign rash or unknown reactions. Our rigorously matched control data reveals confirms that
361 it reduces length of stay, and reduces hospital expenditure on bed and second-line antibiotics.
362 It also significantly reduces readmission rates. ~~However, more study is needed before we can~~
363 ~~demonstrate that DPT without PST is safe and feasible in adults.~~ At the hospital level,
364 penicillin allergy label evaluation should be integrated into antimicrobial stewardship, and
365 the results of evaluation entered correctly into eMR. A greater challenge is to ensure that
366 changes to the penicillin allergy label are communicated to local medical officers, and
367 updated in these primary care records.

Acknowledgments

We are grateful for the Immunology nursing staff, Ms Jane Dorahy and Ms Anne Whitfeld for their supervision of the oral challenges. We would like to thank the Department of Pharmacy and the Department of Infectious Diseases for referrals and promotion of the study. We acknowledge Division of Medicine Executive (Dr Terry Finnegan, Ms Amanda Harriss, Ms Tracey Gray), Director of Acute Clinical Care Network, Northern Sydney Local Health District (Dr Peter Roberts) and Ms Jocelyn Purisima, administrative assistant for their support of the study.

REFERENCES

1. 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.
2. Li M, Krishna M, Razaq S, Pillay D. A real-time prospective evaluation of clinical pharmaco-economic impact of diagnostic label of “penicillin allergy” in a UK teaching hospital. *J Clin Pathol.* 2014;67:1088-92.
3. Knezevic B, Sprigg D, Seet J, et al. The revolving door: antibiotic allergy labelling in a tertiary care centre. *Intern J Med.* 2016;46:1276-83.
4. Charneski L, Deshpande G, Smith S. Impact of an antimicrobial allergy label in the medical record on clinical outcomes in hospitalized patients. *Pharmacotherapy.* 2011;31:742-7.
5. Unger N, Gauthier T, Cheung L. Penicillin skin testing: potential implications for antimicrobial stewardship. *Pharmacotherapy.* 2013;33:856-67.
6. Trubiano J, Cairns K, Evans J, et al. The prevalence and impact of antimicrobial allergies and adverse drug reactions at an Australian tertiary centre. *BMC Infect Dis.* 2015;15:572-7.
7. Joint Task Force on Practice Parameters representing the American Academy of Allergy AaIA CoA, Asthma and Immunology; Joint Council of Allergy, Asthma and Immunology. Drug allergy: an updated practice parameter. *Ann Allergy Asthma Immunol.* 2010;105:259-73.
8. Pirmohamed M, Breckenridge A, Kitteringham N, Park B. Adverse drug reactions. *BMJ.* 1998;316:1295.
9. Devchand M, Kirkpatrick C, Stevenson W, Garrett K, Perera D, Khumra S, et al. Evaluation of a pharmacist-led penicillin allergy de-labelling ward round: a novel antimicrobial stewardship intervention. *J Antimicrob Chemother.* 2019.
10. du Plessis T, Walls G, Jordan A, Holland D. Implementation of a pharmacist-led penicillin allergy de-labelling service in a public hospital. *J Antimicrob Chemother.* 2019.
11. Shenoy E, Macy E, Rowe T, Blumenthal K. Evaluation and Management of Penicillin Allergy. *JAMA.* 2019;321:188-99.
12. Caubet J, Kaiser L, Lemaitre B, Fellay B, Gervaix A, Eigenmann P. The role of penicillin benign skin rashes in childhood: a prospective study based on drug rechallenge. *J Allergy Clin Immunol.* 2011;127:218-22.
13. Mill C, Primeau M, Medoff E, et al. Assessing the diagnostic properties of a graded oral provocation challenge for the diagnosis of immediate and non immediate reactions to amoxicillin in children. *JAMA Paediatr.* 2016;170:e160033.
14. Abrams E, Atkinson A, Wong T, Ben-Shoshan M. The Importance of Delabeling Beta-lactam Allergy in Children. *J Paediatr.* 2019;204(291-7.e1).
15. Chiriac A, Vasconcelos M, Izquierdo L, Ferrando L, Nahas O, Demoly P. To challenge or not to challenge: Literature data on the positive predictive value of skin tests to beta-lactams. *J Allergy Clin Immunol Pract.* 2019.
16. Barlam T, Cosgrove S, Abbo L, et al. Implementing an Antibiotic Stewardship Program: Guidelines by the Infectious Diseases Society of America and the Society for Healthcare Epidemiology of America. *Clin Infect Dis.* 2016;62:e51-e77.
17. Tannert L, Mortz C, Skov P, Bindslev-Jensen C. Positive skin test or specific ige to penicillin does not reliably predict penicillin allergy. *J Allergy Clin Immunol Pract.* 2017;5:676-83.

18. Chen J, Khan D. Evaluation of Penicillin Allergy in the Hospitalized Patient: Opportunities for Antimicrobial Stewardship. *Curr Allergy Asthma Rep.* 2017;17:40.
19. Blumenthal K, Shenoy E, Wolfson A, Berkowitz D, Carballo V, Balekian D, et al. Addressing Inpatient Beta-Lactam Allergies: A Multi-Hospital Implementation. *J Allergy Clin Immunol Pract.* 2017;5:616-25.e7.
20. Tucker M, Lomas C, Ramchandrar N, Waldram J. Amoxicillin challenge without penicillin skin testing in evaluation of penicillin allergy in a cohort of Marine recruits. *J Allergy Clin Immunol Pract.* 2017;5:813-5.
21. Kuruvilla M, Thomas J. Direct oral amoxicillin challenge without antecedent penicillin skin testing in low-risk patients. *Ann Allergy Asthma Immunol.* 2018;121:627-8.
22. Kuruvilla M, Shih J, Patel K, Scanlon N. Direct oral amoxicillin challenge without preliminary skin testing in adult patients. *Allergy Asthma Proc.* 2019;40:57-61.
23. Sacco K, Cochran B, Epps K, Parkulo M, Gonzalez-Estrada A. Inpatient beta-lactam test-dose protocol and antimicrobial stewardship in patients with a history of penicillin allergy. *Ann Allergy Asthma Immunol.* 2019;122:184-8.
24. Iammatteo M, Alvarez Arango S, Ferastraoaru D, Akbar N, Lee A, Cohen H, et al. Safety and Outcomes of Oral Graded Challenges to Amoxicillin without Prior Skin Testing. *J Allergy Clin Immunol Pract.* 2019;7:236-43.
25. McDanel J, Perencevich E, Diekema D, Herwaldt L, Smith T, Chrischilles E, et al. Comparative effectiveness of beta-lactams versus vancomycin for treatment of methicillin-susceptible *Staphylococcus aureus* bloodstream infections among 122 hospitals. *Clin Infect Dis.* 2015;61:361-7.
26. Jeffres M, Narayanan P, Shuster J, Schramm G. Consequences of avoiding beta lactams in patients with beta-lactam allergies. *J Allergy Clin Immunol.* 2016;137:1148-53.
27. Rimawi R, Cook P, Gooch M, Kabchi B, Ashraf M, Rimawi B, et al. The impact of penicillin skin testing on clinical practice and antimicrobial stewardship. *J Hosp Med.* 2013;8:341-5.

Figure Legend

Figure 1. A flow diagrammatic representation of the procedures and outcomes of 71 recruited patients in the study

Figure 2. Proposed algorithm for penicillin allergy label assessment for further study

Journal Pre-proof

Table 1. Penicillin skin testing concentrations. Adapted from Australasian Society of Clinical Immunology and Allergy Consensus Statement for the assessment of patients with immediate (IgE mediated) penicillin allergy

Skin testing reagent	Intradermal concentrations applied
Benzylpenicillin (6mg/cc)	1:100 dilution (0.06mg/cc)
	1:10 (0.6mg/cc)
Amoxicillin (20mg/cc)	1:100 dilution (0.2mg/cc)
	1:10 (2mg/cc)
Diater PPL ® (0.04 mg benzylpenicilloyl poly-L-lysine + 20 mg mannitol in 1mL PBS)	1:10 dilution
	Neat
Diater MDM ® (0.5 mg each of benzylpenicillin, benzylpenilloate and benzylpenicilloate + 20 mg mannitol in 1mL PBS)	1:100 dilution
	1:10 dilution

IgE, immunoglobulin-E
PPL, benzylpenicilloyl-polysine
MDM, minor determinant mixture
PBS, phosphate buffered solution

Table 2. Patient Characteristics. Control subjects were retrospectively matched.

	Intervention Patients*
Number	70
Median age (years)	70.38
Female (%)	36 (51.4)
Infection type	
Intra-abdominal	16
Genitourinary	16
Lower respiratory tract	13
Skin and soft tissue	10
Osseous	7
Meningoencephalitis	2
Sepsis	1
Cardiovascular	1
Febrile neutropenia	4
Accommodation status	
Home	63
Nursing home	5
Rehabilitation	1
Another acute hospital	1

* Received penicillin allergy label evaluation

Table 3. Characteristics of reaction to penicillin-containing antibiotic

Type of reaction	Number of patients	Reaction over 12 months	Reaction within 12 months	Passed amoxicillin challenge	Did not complete DPT
<i>Type B</i>					
Maculopapular or benign rash	30	30		25	3 (2 received pen VK only, 1 received IV only)
Unknown	12	12		12	0
Urticaria with/without angioedema	9	9		7	2 (received IV only)
Angioedema with no airway features	4	4		2	2 (1 received pen VK only, 1 received IV only)
Symptoms of upper airway involvement, no intubation required	6	6		6	0
Anaphylaxis	2	2		2	0
<i>Type A</i>					
Nausea, and/or vomiting	3	3		3	
Pain	2	2		2	
Tremor	1	1		1	
Lethargy	1	1		1	

DPT, drug provocation testing

Pen VK, penicillin VK

IV, intravenous beta-lactam antibiotic

Table 4. Summary of Secondary Outcomes

Secondary Outcome	Intervention arm	Control arm	P value
Length of stay (days)	900	1276	P<0.05
Cost of hospital admission (AUD)	1,624,150	2,100,150	P<0.05
Cost of antimicrobial therapy (AUD)	10900	31783	P<0.05
Readmission rate	30	43	P<0.05
ICU admissions	12	8	P=0.45
Newly acquired multiresistant organisms	3	5	P=0.50
Recording of new allergy label in electronic medical record (%)	97	n/a	n/a
Recording of new allergy label in records of local medical officer (%)	33	n/a	n/a

n/a, not applicable

Table 1. Penicillin skin testing concentrations. Adapted from Australasian Society of Clinical Immunology and Allergy Consensus Statement for the assessment of patients with immediate (IgE mediated) penicillin allergy

Skin testing reagent	Intradermal concentrations applied
Benzylpenicillin (6mg/cc)	1:100 dilution (0.06mg/cc)
	1:10 (0.6mg/cc)
Amoxicillin (20mg/cc)	1:100 dilution (0.2mg/cc)
	1:10 (2mg/cc)
Diater PPL ® (0.04 mg benzylpenicilloyl poly-L-lysine + 20 mg mannitol in 1mL PBS)	1:10 dilution
	Neat
Diater MDM ® (0.5 mg each of benzylpenicillin, benzylpenilloate and benzylpenicilloate + 20 mg mannitol in 1mL PBS)	1:100 dilution
	1:10 dilution

IgE, immunoglobulin-E
PPL, benzylpenicilloyl-polysine
MDM, minor determinant mixture
PBS, phosphate buffered solution

Table 2. Patient Characteristics. Control subjects were retrospectively matched.

	Intervention Patients*
Number	70
Median age (years)	70.38
Female (%)	36 (51.4)
Infection type	
Intra-abdominal	16
Genitourinary	16
Lower respiratory tract	13
Skin and soft tissue	10
Osseous	7
Meningoencephalitis	2
Sepsis	1
Cardiovascular	1
Febrile neutropenia	4
Accommodation status	
Home	63
Nursing home	5
Rehabilitation	1
Another acute hospital	1

* Received penicillin allergy label evaluation

Table 3. Characteristics of reaction to penicillin-containing antibiotic

Type of reaction	Number of patients	Reaction over 12 months	Reaction within 12 months	Passed amoxicillin challenge	Did not complete DPT
<i>Type B</i>					
Maculopapular or benign rash	30	30		25	3 (2 received pen VK only, 1 received IV only)
Unknown	12	12		12	0
Urticaria with/without angioedema	9	9		7	2 (received IV only)
Angioedema with no airway features	4	4		2	2 (1 received pen VK only, 1 received IV only)
Symptoms of upper airway involvement, no intubation required	6	6		6	0
Anaphylaxis	2	2		2	0
<i>Type A</i>					
Nausea, and/or vomiting	3	3		3	
Pain	2	2		2	
Tremor	1	1		1	
Lethargy	1	1		1	

DPT, drug provocation testing

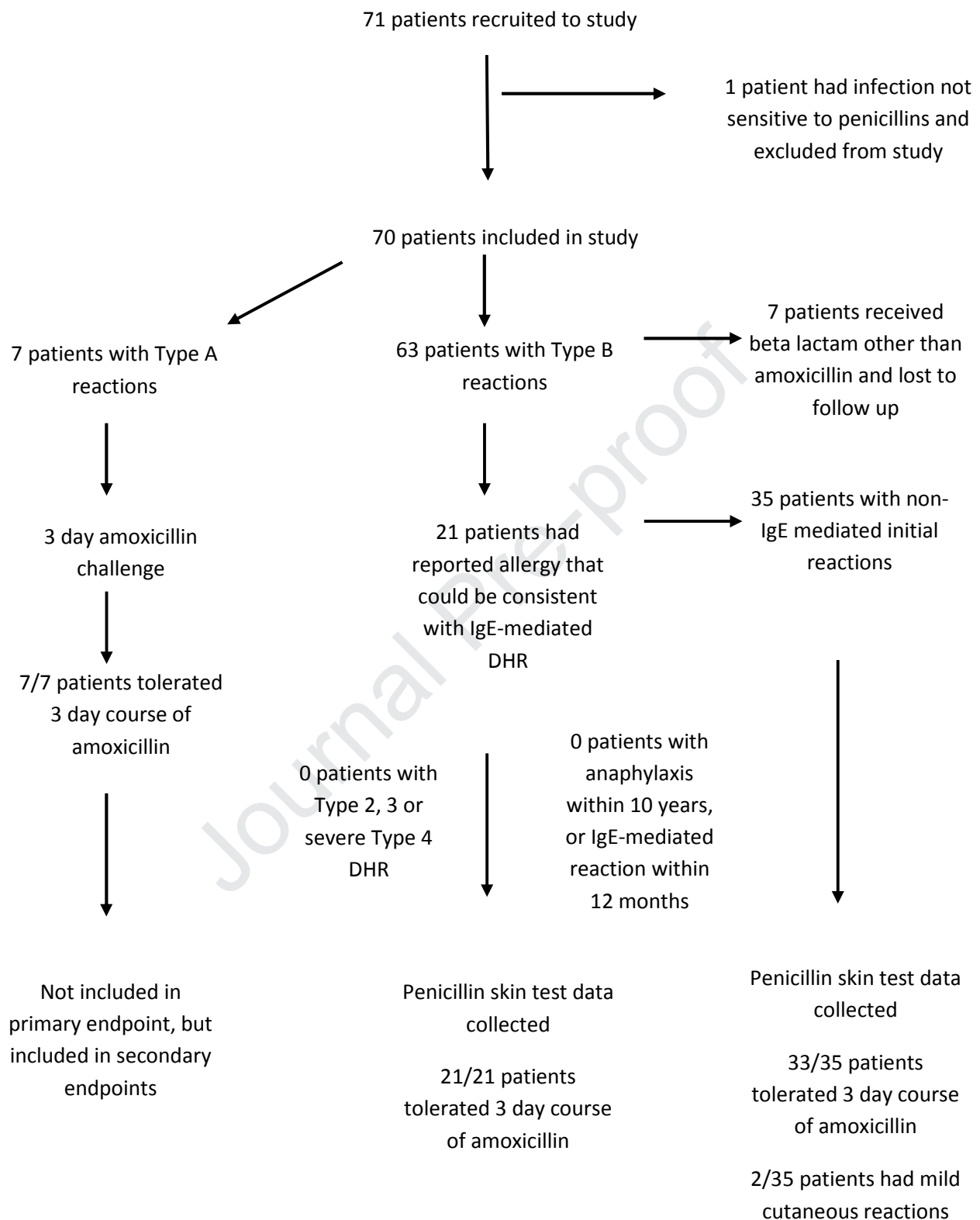
Pen VK, penicillin VK

IV, intravenous beta-lactam antibiotic

Table 4. Summary of Secondary Outcomes

Secondary Outcome	Intervention arm	Control arm	P value
Length of stay (days)	900	1276	P<0.05
Cost of hospital admission (AUD)	1,624,150	2,100,150	P<0.05
Cost of antimicrobial therapy (AUD)	10900	31783	P<0.05
Readmission rate	30	43	P<0.05
ICU admissions	12	8	P=0.45
Newly acquired multiresistant organisms	3	5	P=0.50
Recording of new allergy label in electronic medical record (%)	97	n/a	n/a
Recording of new allergy label in records of local medical officer (%)	33	n/a	n/a

n/a, not applicable



DHR, drug hypersensitivity reaction

