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ORIGINAL

Oral challenge vs routine care to assess low-risk penicillin allergy in critically ill hospital patients (ORACLE): a pilot safety and feasibility randomised controlled trial

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Abstract

Purpose: Critically ill patients are vulnerable to penicillin allergy labels that may be incorrect. The validity of skin testing in intensive care units (ICUs) is uncertain. Many penicillin allergy labels are low risk, and validated tools exist to identify those amenable to direct oral challenge. This pilot randomised controlled trial explored the feasibility, safety, and validity of direct enteral challenge for low-risk penicillin allergy labels in critical illness.

Methods: Consenting patients with a low-risk penicillin allergy label (PAL) (PEN-FAST risk assessment score < 3) in four ICUs (Melbourne, Australia) were randomised 1:1 to penicillin (250 mg amoxicillin or implicated penicillin) direct enteral challenge versus routine care (2-h post-randomisation observation for each arm). Repeat challenge was performed post -ICU in the intervention arm. Patients were reviewed at 24 h and 5 days after each challenge/observation.

Results: We screened 533 patients. 130 (24.4%) were eligible and 80/130 (61.5%) enrolled (age median 64.5 years (interquartile range, IQR 53.5, 74), PEN-FAST median 1 (IQR 0,1)), with 40 (50%) randomised to direct enteral challenge. A positive challenge rate of 2.5% was identified. No antibiotic-associated serious adverse events were identified. 32/40 (80%) received a repeat challenge (zero positive). Post-randomisation, 13 (32%) of the intervention arm and 4 (10%) of the control arm received penicillin (odds ratio, OR 4.33 [1.27, 14.78] $p = 0.019$).

Conclusion: These findings support the safety, validity, and feasibility of direct enteral challenge for critically ill patients with PEN-FAST assessed low-risk penicillin allergy. The absence of false negative results was confirmed by subsequent negative repeat challenges. A relatively low recruitment to screened ratio suggests that more inclusive eligibility criteria and integration of allergy assessment into routine ICU processes are needed to optimise allergy delabelling in critical illness.

Keywords: Allergy and immunology, Drug hypersensitivity, Antibiotics, Penicillins, Critical care, Direct oral challenge, Oral provocation

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Introduction

Penicillin allergy labels (patient reported penicillin allergies) are present in up to 15% of adult hospital patients [1, 2] and in 6.8% of critically ill patients in the intensive care unit (ICU) [3]. The prevalence of penicillin allergy labels (PALs) in the ICU and the frequent exposure to antimicrobials during critical illness (up to 80% of patients) make this patient cohort uniquely vulnerable to the negative health impacts of such allergy labels if they are incorrect [3, 4]. PALs in the ICU may be associated with increased infection recurrence, increased ICU length of stay, and increased rates of re-admission [4, 5]. They also lead to suboptimal antimicrobial prescribing, with lower rates of narrow-spectrum beta-lactams and increased use of vancomycin [3]. Despite this vulnerability, critically ill patients have been underrepresented in the antibiotic allergy assessment literature.

Traditional allergy assessment (skin testing followed by oral challenge) has been undertaken in the ICU setting. However it is time and resource intensive and there are increased rates of false negative or indeterminate (failed histamine positive control) skin test results [6–8]. This has led to interest in low-risk penicillin allergy assessment and direct oral challenge being performed in the ICU setting [9]. PEN-FAST (PENicillin allergy reported by the patient, Five years or less since the reaction, Anaphylaxis or Angioedema, Severe cutaneous adverse reaction, Treatment required for the reaction) is the only internationally validated PAL point-of-care risk assessment tool [10]. However the recent PALACE randomised controlled study only validated its use in the outpatient setting [11]. Further, whilst there is extensive evidence for direct oral challenge in the inpatient (non-critically ill) and outpatient settings [11, 12], there is limited evidence demonstrating its safety, validity, and efficacy in critical illness [13–16].

This study aims to explore the feasibility, safety, and validity of direct enteral challenge for low-risk penicillin allergy in critical illness following PEN-FAST risk assessment, through an open-label randomised controlled study design and to provide initial data on the impact of removing PALs ("delabelling") in ICU on subsequent antimicrobial prescribing.

The preliminary findings of the ORACLE study were presented at the annual meeting of the American Academy of Allergy, Asthma and Immunology 2024 [17].

Take-home message

This novel pilot randomised controlled trial supports the safety, validity, and feasibility of direct single-dose oral/enteral penicillin challenge for low-risk penicillin allergy in critical illness. However, further studies are needed to assess expanded eligibility criteria and the impact of direct enteral challenge in the intensive care unit on optimising penicillin utilisation.

Methods

Study design

The ORACLE study is a pilot, multicentre, parallel, 2-arm, open-label, randomised clinical trial. It was conducted in four teaching hospital ICUs in Melbourne, Australia (Austin Hospital, Monash Medical Centre, The Royal Melbourne Hospital/Peter MacCallum Cancer Centre, Alfred Hospital). The rationale and design of the ORACLE study have been previously published [18]. The study was designed and overseen by a Trial Management Group (electronic supplementary material, ESM, 1). Study administration, data management, and statistical analyses were performed at Austin Health (Melbourne, Victoria, Australia). All deaths and complications were reviewed by intensive care clinicians as part of standard quality processes in each participating intensive care unit. Serious adverse events were independently reviewed by two antibiotic allergy clinicians and two critical care clinicians.

The trial protocol [18] (ESM 2) was approved by the Austin Health Human Research Ethics Committee (HREC/59438/Austin-2020) and subsequently by the independent institutional review boards at each site. Written informed consent was provided by participants or their designated medical treatment decision maker in keeping with clinical circumstances and local ethics committee requirements.

Participants

Patients admitted to the ICU, labelled with a penicillin allergy, with a calculated PEN-FAST score of less than 3 (ESM 3) and expected to remain in ICU for $\geq$ 24 h post-assessment, were eligible for enrolment. PEN-FAST was utilised as previously published and validated [10, 11]. Allergy phenotyping to enable PEN-FAST utilisation was performed using the antibiotic allergy assessment tool (AAAT) [19]. Key exclusion criteria included age less than 18 years, need for high dose vasoactive infusion ($\geq$ 0.1 µg/kg/min norepinephrine (base) or any dose adrenaline within 4 h prior to randomisation), high ventilatory support requirement (any of: (i) ventilation mode other than spontaneous, (ii) peak end expiratory pressure > 5 cmH_2O, (iii) FiO_2 > 40%) and receipt of more than stress-dose steroid therapy (> 200 mg total daily dose of hydrocortisone or equivalent). Patients who could not receive oral/enteral medications were excluded. Patients with allergy histories of severe non-cutaneous reactions such as severe delayed organ, neurological, or

haematological reactions were also excluded. The full inclusion and exclusion criteria are provided in the protocol [18] and in ESM 2. Site investigators confirmed eligibility prior to participant randomisation.

Randomisation and masking

Participants were randomised in a 1:1 ratio to either the intervention group (direct enteral penicillin challenge) or the control group (routine care). Randomisation was performed via sealed sequentially numbered envelopes (at a single study site, Austin Hospital) and a centralised web-based REDCap [20] (Austin Health) at all other sites, by permuted block design (block sizes ranging from 2 to 6), stratified by hospital site. Group allocation was concealed until randomisation. Blinding post-randomisation was not possible. The sequence was computer generated by the trial statistician (SV). Trial investigators enrolled the participants and performed randomisation.

Procedures

Open-label administration of 250 mg enteral (oral/nasogastric/percutaneous endoscopic gastrostomy tube (PEG)) penicillin (either amoxicillin or implicated penicillin) was performed by bedside nursing staff. Participants were directly observed (monitoring for adverse events and measurement of vital signs at baseline and at 30-min intervals) for 2-h post-challenge. Patients in the control arms were directly observed for 2-h post-randomisation. Safety evaluation and the outcome of enteral challenges was undertaken by site investigators.

Patients in the intervention arm received a repeat penicillin challenge once they met all the following criteria: (a) at least 48 h since the first challenge, (b) resolution of critical illness (discharged from ICU or remaining in ICU due solely to bed access restrictions), (c) negative initial penicillin challenge.

Site investigators reviewed all participants at 24 h and 5 days post each period of direct observation to assess for any delayed adverse events and assess post-testing antibiotic utilisation.

Outcomes

The primary outcome measures were the proportion of eligible patients that consented to enrol in the study (a ratio of $\geq 50\%$ was used as the primary determinant of feasibility) and the proportion of patients who experienced an antibiotic-associated immune-mediated or serious adverse event (a proportion of $< 5\%$ was used to determine safety). Exploratory outcomes included subsequent antibiotic utilisation, length of stay and mortality (Table 3).

Statistical analysis

Given Australian national penicillin allergy prevalence data (9%) [1] and local ICU observational data [3], 200 patients would be expected to be eligible in a 12-month study period. Assuming 50% recruitment and 85% completion, a pool of 85 eligible participants in 1 year was projected. As such, a total of 80 enrolments and 1:1 randomisation (40 in each arm) was planned.

Statistical analysis was performed on an intention-to-treat basis. Descriptive statistics are presented as median (interquartile range, IQR) and frequency (percentage). Feasibility and safety outcomes are reported as percentages with 95% exact confidence intervals (CIs). *P* values of less than 0.05 were considered statistically significant. Exploratory outcomes were analysed using logistic regression (antibiotic utilisation, mortality) and negative binomial regression (length of stay). All outcomes are reported with 95% CI. To aid clinical interpretation, exploratory results are also expressed as risk ratios with exact 95% CI (binary outcomes) and median differences with 95% bootstrapped intervals (continuous outcomes) (post hoc). Stata 18 was used for statistical analysis (StataCorp LCC, TX).

Results

Study population

Between March 20, 2021, and November 1, 2023, 533 patients were screened, with 80 patients enrolled from four ICUs (Fig. 1). The characteristics of the participants are presented in Table 1. The median age of participants was 64.5 years (IQR 53.5, 74) with 40 (50%) female participants. Median Charlson comorbidity index was 4 (IQR 2, 6) and median ICU admission Sequential Organ Failure Assessment (SOFA) and acute physiology and chronic health evaluation (APACHE) II scores were 4 (IQR 2, 6) and 11 (IQR 6.5, 14) respectively. At the time of randomisation, two (5%) patients in the intervention arm and one (2.5%) patient in the control arm were mechanically ventilated.

Reported penicillin allergies included penicillin unspecified ($n = 60$), amoxicillin ($n = 10$), penicillin ($n = 5$), flucloxacillin ($n = 4$), and amoxicillin clavulanate ($n = 1$). PEN-FAST scores were 0 ($n = 34$ (42%)), 1 ($n = 35$ (44%)), and 2 ($n = 11$ (14%)). In 31/80 (39%), the reaction had occurred > 10 years prior to screening and 51/80 (64%) participants described an unknown latency between antibiotic exposure and reaction. The most common allergy phenotype was a mild rash (57 of 88 (65%) reported symptoms) and 47/80 (59%) participant's reactions resolved without treatment. Allergy phenotypic distributions, as characterised by the

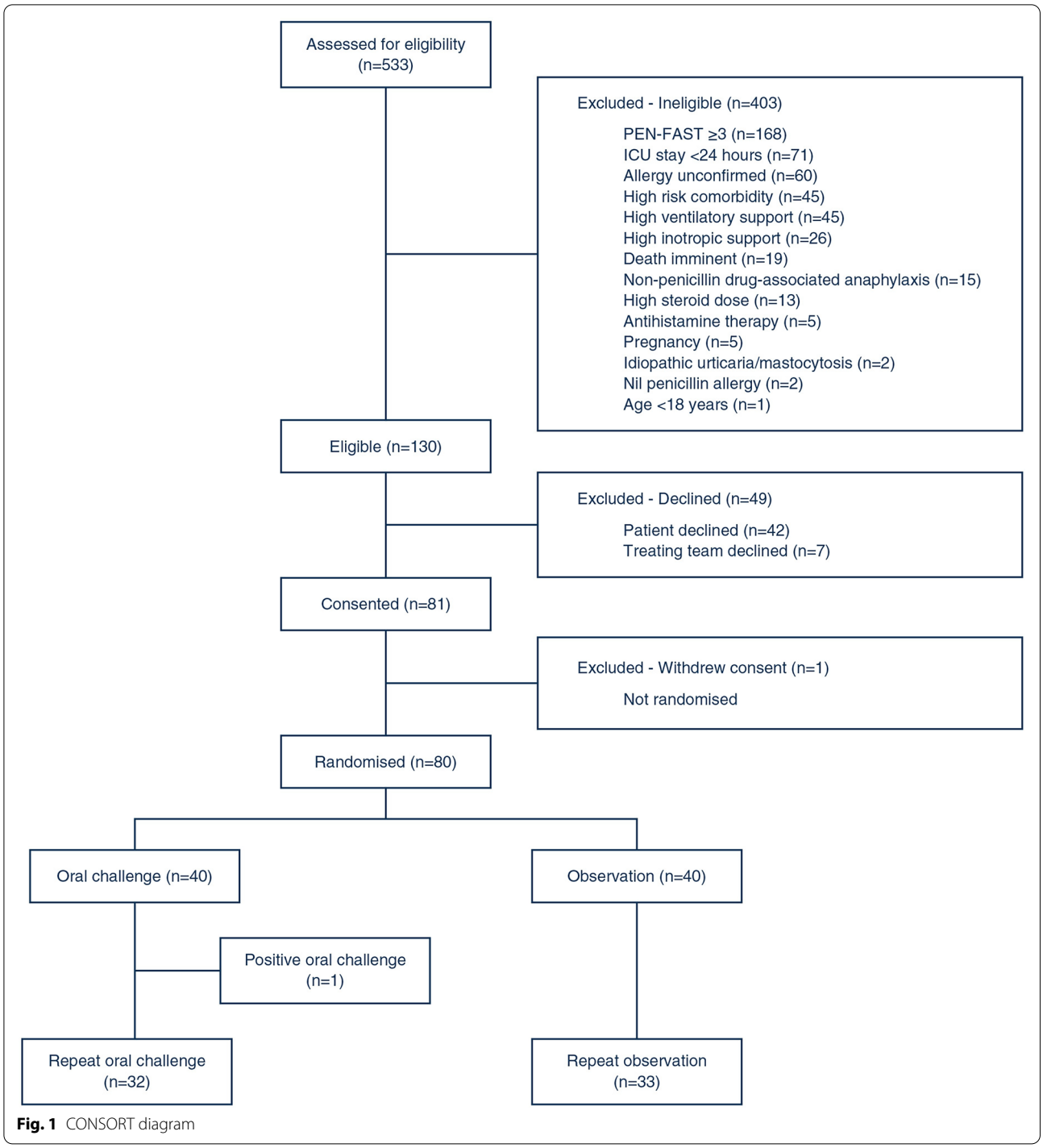

Fig. 1 CONSORT diagram

Antibiotic Allergy Assessment Tool [19], are listed in ESM 4.

Primary outcomes

Feasibility

The study demonstrated feasibility with 80 of 130 (62%, 95% CI [53, 70]) eligible patients being enrolled (recruitment to eligibility ratio). Moreover, 130 of 533 (24%, 95% CI [21, 28]) screened patients met all eligibility criteria

Table 1 Participant characteristics

	Intervention	Control
Number, *n* (%)	40 (100)	40 (100)
Age in years, median (IQR)	62.5 (52.5, 73.5)	67 (54.5, 75.5)
Female, *n* (%)	23 (57)	17 (42)
Ethnicity/race		
Caucasian, *n* (%)	32 (80)	38 (95)
Aboriginal and/or Torres Strait Islander, *n* (%)	2 (5)	0
East Asian, *n* (%)	1 (2)	0
Other, *n* (%)	5	2
Charlson comorbidity index, median (IQR)	3 (2, 5.5)	4 (2, 6)
Obesity (BMI > 30 kg/m^2), *n* (%)	11 (30)	17 (46)
Immunosuppressive therapy, *n* (%)	3 (8)	3 (8)
Non-antibiotic allergy, *n* (%)	14 (35)	9 (22)
Infective diagnosis—hospital admission, *n* (%)	17 (42)	13 (32)
Sepsis—hospital admission, *n* (%)	9 (22)	10 (25)
SOFA score, median (IQR)	3 (2, 5)	4 (2.5, 6.5)
APACHE II score, median (IQR)	10 (6.5, 13.5)	11.5 (7, 15)
Pre-randomisation antibiotic use, *n* (%)		
Any antibiotic	33 (82)	37 (92)
Penicillin (any)	4 (10)	3 (8)
Penicillin (narrow spectrum)[a]	0	1 (2)
Penicillin/beta-lactamase inhibitor[b]	4 (10)	2 (5)
Cephalosporin (1st/2nd generation)[c]	11 (28)	19 (48)
Cephalosporin (3rd/4th generation)[d]	17 (42)	18 (45)
Carbapenem	5 (12)	6 (15)
Glycopeptide	6 (15)	8 (20)
Fluoroquinolone	5 (12)	2 (5)
Restricted antimicrobial[e]	24 (60)	25 (62)

APACHE Acute Physiology and Chronic Health Evaluation, *BMI* body mass index, *IQR* interquartile range, *SOFA* Sequential Organ Failure Assessment

[a] Narrow-spectrum penicillin: penicillin G, penicillin VK, amoxicillin, ampicillin, flucloxacillin

[b] Penicillin/beta-lactamase inhibitor: amoxicillin/clavulanate, piperacillin/tazobactam

[c] Cefazolin, cefuroxime, cephalexin

[d] Ceftriaxone, cefepime, ceftazidime

[e] Restricted antimicrobial: third-/fourth-generation cephalosporin, fluoroquinolone, glycopeptide

(eligibility to screened ratio). All participants randomised (80/80, 100%, 95% CI [96, 100]) underwent initial enteral challenge/observation as per protocol (intervention to recruitment ratio). 32/40 (80%) in the intervention arm received a repeat challenge, whilst 33/40 (83%) in the control arm completed a repeat observation period as per protocol. In addition, 2/40 (5%) participants in the control arm had their penicillin allergy label removed following a negative penicillin challenge. This challenge occurred following routine inpatient allergy assessment during the study period (independent of the study) and was prompted by clinical need. Overall protocol compliance was 80% (95% CI [70, 88]).

Safety

Intervention enteral challenge ($n=40$) was undertaken with 250 mg of either amoxicillin ($n=26$ (65%)), penicillin V potassium (penicillin VK) ($n=11$ (28%)), or flucloxacillin ($n=3$ (8%)). The enteral challenge was delivered orally in 36/40 (90%) patients, via nasogastric tube in 2/40 (5%) and via PEG in 2/40 (5%).

The study demonstrated safety, with no immune-mediated or severe adverse events identified during the 2-h observation period following enteral challenge, and only one (2.5%, 95% CI [< 0.1, 13.2]) antibiotic-associated immune-mediated adverse event identified (positive challenge). The positive enteral challenge was identified at 24-h review (pruritic macular rash on trunk without severe features), which occurred 15 h after amoxicillin oral challenge and resolved within 1 h following administration of an oral antihistamine. This occurred on a background of reported mild childhood rash without severe features, which had occurred following exposure to oral amoxicillin.

Initially, 31/32 (97%, 95% CI [84, 100]) of the repeat challenges were reported as negative. One repeat challenge was initially suspected to be positive (mild pruritic, erythematous, maculopapular truncal rash), 24 h after commencing amoxicillin/clavulanate therapy. This occurred 5 days after the initial oral amoxicillin challenge and a subsequent 5 days of therapeutic benzylpenicillin (with a history of distant lightheadedness and peri-oral tingling to an unspecified penicillin). The rash resolved spontaneously. Subsequent specialist allergy testing including skin prick and intra-dermal testing with delayed reads and phenoxymethylpenicillin and amoxicillin extended oral challenges were negative and the penicillin allergy label was removed.

Overall, 4/80 (5%, 95% CI [1, 12]) participant deaths were reported during the study period. Three deaths that occurred in the intervention arm (severe aspiration pneumonia complicated by respiratory failure; septic shock following perforated ischaemic bowel; cardiac arrest in the setting of pneumonia) were temporally distant from the enteral challenge (2, 19, and 74 days, respectively) and were deemed unrelated by two independent allergy specialists and two critical care specialists. The death in the control arm (respiratory failure secondary to aspiration pneumonia and pulmonary embolism) occurred more than 30 days after randomisation, in a participant who had not received any penicillins during the study period. No other serious adverse events were identified.

The initial and repeat enteral challenges and outcomes are further characterised in Table 2 and adverse events in ESM 5.

Exploratory outcomes

Antibiotic utilisation

Use of any antibiotic was identified in 33 (82%) of the intervention arm patients and 37 (92%) of the control arm prior to randomisation and in 25 (62%) patients in each arm after randomisation. Pre-randomisation, 4/40 (10%) of the intervention arm and 3/40 (7.5%) of the

Table 2 Recruitment and oral challenge outcomes

Feasibility	Number	% (95% CI)
Eligibility to screened ratio	130/533	24% (21, 28)
Recruitment to eligibility ratio[a]	80/130	62% (53, 70)
Intervention to recruitment ratio	80/80	100% (96, 100)
Oral challenge	**Number (%)**	
First oral challenge		
Total	40 (100%)	
Route of administration		
Oral	36 (90%)	
Nasogastric	2 (5%)	
PEG	2 (5%)	
Agent		
Amoxicillin	26 (65%)	
Phenoxymethylpenicillin	11 (28%)	
Flucloxacillin	3 (8%)	
Oral challenge outcome		
Negative	39 (98%)	
Positive	1 (2%)	
Allergy label removed	39 (98%)	
2nd oral challenge		
Total	32/40 (80%)	
Agent		
Amoxicillin	18 (56.3%)	
Phenoxymethylpenicillin	6 (18.8%)	
Amoxicillin–clavulanate	4 (12.5%)	
Flucloxacillin	3 (9.4%)	
Benzylpenicillin[b]	1 (3%)	
Reason second oral challenge withheld		
Discharged from hospital	4 (10%)	
Participant refused re-challenge	2 (5%)	
Critical illness unresolved	1 (2.5%)	
Positive first oral challenge	1 (2.5%)	
Second oral challenge outcome		
Negative	32/32 (96.9%)[c]	

Positive challenge description—mild macular erythematous pruritic rash on the left flank and epigastrium. Onset 15 h after amoxicillin oral challenge. Nil severe features. Treated with oral antihistamine. Resolution within 4 h (background of childhood rash (unspecified) without severe features, following oral amoxicillin. PENFAST = 1)

CI confidence interval, *ICU* intensive care unit, *IQR* interquartile range, *IRR* incidence rate ratio, *OR* odds ratio, *PEG* percutaneous endoscopic gastrostomy

[a] A recruitment to eligibility ratio of ≥ 50% was identified as the a priori determiner of feasibility

[b] Participant transitioned to benzylpenicillin therapy post-first oral challenge with phenoxymethylpenicillin. Second challenge completed with benzylpenicillin

[c] One possible antibiotic-associated mild rash following repeat oral challenge was subsequently determined to be unrelated to penicillin use, following skin testing and extended oral challenges with both phenoxymethylpenicillin and amoxicillin (ESM, Table 4)

control arm had received an alternate penicillin antibiotic (not implicated in their penicillin allergy label).

In-hospital use of any penicillin after randomisation was noted in 13 (32%) of the intervention arm and 4 (10%) of the control arm, (odds ratio (OR) 4.33, 95% CI [1.27, 14.78] $p=0.019$). Post-randomisation use of a narrow-spectrum penicillin was noted in 3 (8%) of the intervention arm vs. 1 (2%) of the control arm (OR 3.16, 95% CI [0.31, 31.78] $p=0.328$).

Post-randomisation use of restricted antimicrobials (3rd-/4th-generation cephalosporins, fluoroquinolones, glycopeptides) was noted in 15 (38%) of the intervention arm and 18 (45%) of the control arm (OR 0.73, 95% CI [0.30, 1.79] $p=0.496$). In-hospital antibiotic use is further characterised in Table 3, along with the length of stay and mortality data.

Discussion

In this pilot, multicentre, open-label, randomised controlled study of direct oral challenge for PEN-FAST-assessed low-risk penicillin allergy in critically ill adults, a programme of allergy assessment and direct oral challenge was found to be both feasible and safe. This finding supports the existing observational literature which has demonstrated low rates of positive direct oral challenge in patients with critical illness (0.5%) [14] and is consistent with test positivity rates seen in the non-ICU setting (1.7%) [12]. Importantly, no severe antibiotic allergy-associated adverse events were identified and no resensitisation events.

The enrolment of 62% of eligible participants, whilst similar to non-ICU settings [12], was lower than that noted in prior observational ICU studies (79.0–89.4%) [13–15]. However, these prior studies reported allergy assessment as being consented to as part of routine care rather than as a research intervention. The eligibility to

Table 3 Exploratory Outcomes

Exploratory outcomes					
	Intervention	Control	Intervention vs control		
			OR (95% CI)	*p* value	RR (95% CI)*
Post-randomisation antibiotic use, *n* (%)					
Any antibiotic	25 (62)	25 (62)	1 (0.4, 2.47)	>0.99	1 (0.71, 1.4)
Penicillin (any)	13 (32)	4 (10)	4.33 (1.27, 14.78)	0.019	3.25 (1.16, 9.12)
Penicillin (narrow spectrum)[a]	3 (8)	1 (2)	3.16 (0.31, 31.78)	0.33	3 (0.33, 27.63)
Penicillin/beta-lactamase inhibitor[b,f]	12 (30)	4 (10)	3.86 (1.12, 13.26)	0.032	3 (1.06, 8.52)
Cephalosporin (1st/2nd generation)[c,f]	7 (18)	13 (32)	0.44 (0.15, 1.26)	0.126	0.54 (0.24, 1.21)
Cephalosporin (3rd/4th generation)[d,f]	8 (20)	15 (38)	0.42 (0.15, 1.14)	0.088	0.53 (0.26, 1.12)
Carbapenem[f]	2 (5)	1 (2)	2.05 (0.18, 23.59)	0.56	2 (0.19, 21.18)
Glycopeptide	3 (8)	7 (18)	0.38 (0.09, 1.6)	0.188	0.43 (0.12, 1.54)
Fluoroquinolone[f]	4 (10)	1 (2)	4.33 (0.46, 40.61)	0.199	4 (0.47, 23.24)
Restricted antimicrobial[e]	15 (38)	18 (45)	0.73 (0.3, 1.79)	0.50	0.83 (0.49, 1.41)
Mortality, *n* (%)					
In-hospital	2 (5)	1 (2.5)	2.05 (0.18, 23.59)	0.56	2 (0.18, 21.18)
30 days	0	0	n/a		
Length of stay (days), median (IQR)[g]			**IRR (95% CI)**	***p* value**	**Median difference (95% CI)[f]**
ICU	3 (2, 5)	3 (2, 5)	1.25 (0.83, 1.87)	0.29	3 (−2, 8)
Hospital	11 (7, 21.5)	16 (8, 27.5)	0.86 (0.59, 1.26)	0.44	0 (−1, 1)

CI confidence interval, *ICU* intensive care unit, *IQR* interquartile range, *IRR* incidence rate ratio, *OR* odds ratio, *PEG* percutaneous endoscopic gastrostomy, *RR* relative risk

[a] Narrow-spectrum penicillin: penicillin G, penicillin VK, amoxicillin, ampicillin, flucloxacillin

[b] Penicillin/beta-lactamase inhibitor: amoxicillin/clavulanate, piperacillin/tazobactam

[c] Cefazolin, cefuroxime, cephalexin

[d] Ceftriaxone, cefepime, ceftazidime

[e] Restricted antimicrobial: third-/fourth-generation cephalosporin, fluoroquinolone, glycopeptide

[f] Post hoc analysis

[g] Length of stay recorded as number of nights spent in hospital/ICU (integer values only)

screened ratio 130/533 (24%) was lower than had been anticipated prior to commencing the study. Subsequent data has demonstrated consistent ratios (8.4–31.5%) when applying similar eligibility criteria [13–15]. However, given the clinical need for optimised antimicrobials in critical illness, expanded eligibility criteria could improve access to timely allergy delabelling in the ICU. The most common single-cause exclusions included a PEN-FAST score ≥ 3 ($n=141$) and ICU stay <24 h ($n=61$). A further 45 patients were excluded due to high ventilatory support needs alone and 26 for high-dose vasoactive support. Removing the need for 24 h of post-challenge ICU care, expanding ventilatory and vasoactive therapy eligibility criteria, and integrating allergy assessment into routine ICU care may improve the timeliness of oral challenge and increase access to delabelling.

Previous direct oral challenge programmes in critical illness have applied institutional allergy risk assessment tools to determine which patients are eligible for oral challenge. The PEN-FAST clinical decision rule is an internationally validated tool for identifying low-risk penicillin allergy [10] and has recently been used to safely facilitate direct oral challenge in an international multicentre randomised controlled trial in the outpatient setting [11]. In addition, this study utilised the previously published AAAT to help obtain the clinical history required for PEN-FAST completion [19]. Notably, this study included a higher proportion of oral challenges in participants with a PEN-FAST score of 2 (12%) compared to the non-ICU setting (6%) [11]; importantly, none of these participants demonstrated a positive oral challenge. This study supports the ongoing expansion of the application of PEN-FAST beyond the outpatient or ambulatory setting.

Whilst prior studies have reported the frequency of post-delabelling penicillin use and episodes of re-application of allergy labels, none have explored this through routine re-challenge after resolution of critical illness. This is particularly important given the concerns regarding the reliability of allergy skin testing in critical illness and thus the question of potentially false negative oral challenges in ICU. We aimed to address this question, delivering a repeat oral challenge in 32/39 (82%) after a negative initial challenge. All 32 repeat oral challenges were found to be negative (following subsequent formal allergy assessment of one episode of mild rash post-repeat challenge). This is consistent with the low rates of positive re-challenge reported in the literature (1%) [14] and further supports the validity of oral penicillin challenge in critical illness.

Exposure to therapeutic penicillins in 13/40 (32%) participants post-challenge is consistent with observational data (up to 31.5%) [13, 15] Although the impact of oral challenge in ICU on subsequent antibiotic prescribing was an exploratory outcome, we noted a statistically significant increase in the inpatient use of penicillins in the intervention arm compared to the control group.

Pilot studies have some inherent limitations, including that the modest number of participants limits the ability to detect differences in rare outcomes. This, coupled with the study being performed across a single city, may limit the generalisability of results. We also acknowledge the relatively low ICU-admission mortality risk of participants, with median SOFA and APACHE II scores of 4 and 11, respectively, and the low number of patients receiving mechanical ventilation at the time of randomisation. Whilst a small number of patients in each arm received pre-randomisation penicillin antibiotics, none had received the penicillin implicated in their penicillin allergy label.

The performance of this study in a high-income setting with relatively low rates of multi-resistant bacterial infections may limit the generalisability of these findings. Furthermore, whilst the prevalence of penicillin allergy labels may be lower in some low/middle-income settings, point-of-care delabelling could still play an important role in settings with limited ambulatory allergy clinic access [21].

Whilst this randomised controlled pilot study adds support to the feasibility, safety, and validity of direct oral challenge for low-risk PALs in critical illness, further international implementation trials are needed to fully describe the impact and sustainability of ICU PAL assessment and direct oral challenge on subsequent penicillin use, and to optimise access to allergy testing in this most vulnerable cohort through expanded eligibility criteria.

Supplementary Information
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Data availability
The data that support the findings of this study are not openly available due to the reason of sensitivity and are available from the corresponding author upon reasonable request. Data are located in controlled access data storage at Austin Health.

Declarations

Conflicts of interest
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