Supplemental Online Content

Copaescu AM, Vogrin S, James F, et al. Efficacy of a clinical decision rule to enable direct oral challenge in patients with low-risk penicillin allergy: the PALACE randomized clinical trial. *JAMA Intern Med*. Published online July 17, 2023. doi:10.1001/jamainternmed.2023.2986

This supplemental material has been provided by the authors to give readers additional information about their work.

eMethods

Recruiting centers and ethics

Vanderbilt University Institutional Review Board (IRB #202174), Tennessee, USA
Duke University Institutional Review Board (IRB #Pro00108461), North Carolina, USA
McGill University Health Centre Research Ethics Board in Canada (PALACE / 2022-7605), Quebec, Canada
Austin Health Human Research Ethics Committee (HREC/62425/Austin-2020), Victoria, Australia

The Trial Management Group (TMG) comprised the principal coordinating investigator, the trial statistician, the international trial coordinator and two research trial coordinators. The TMG supervised the day-to-day conduct of the clinical trial, including safety oversight activities, and acted on advice from other individuals or groups. The TMG was also responsible for communicating essential protocol modifications to relevant parties, such as the site investigators.

An independent data safety management board (DSMB) reviewed the study's progress and monitored adherence to the protocol, participant recruitment, outcomes, complications, and other issues related to participant safety. The DSMB comprised of two clinicians (infectious disease and internal medicine specialists) and one biostatistician unrelated to the study. They had scheduled meetings every two months and monitored the study's assumptions underlying sample size calculations. The DSMB could recommend whether the study should continue or be terminated and consider participant safety or other circumstances as grounds for early termination, including compelling internal or external evidence of treatment differences or the feasibility of addressing the study hypotheses (e.g. poor participant enrolment).

Eligibility criteria

Inclusion:

1. Adult patients (≥ 18 years) referred to the outpatient allergy clinic for a penicillin allergy history;
2. Willing and able to give consent

Exclusion:

1. Patient age is < 18 years;
2. Patients with a PEN-FAST score ≥3
3. Pregnancy
4. Any other illness that, in the investigator's judgement, will substantially increase the risk associated with the subject's participation in this study, including neurological or psychological conditions;
5. Patients with a history of type A adverse drug reaction, drug-associated anaphylaxis, idiopathic urticaria/anaphylaxis, mastocytosis, serum sickness, blistering skin eruption or acute interstitial nephritis;
6. Patients where the allergy history was not able to be confirmed with the patient;
7. Patients on concurrent antihistamine therapy;
8. Patients receiving more than stress dose steroids (i.e. > 50mg QID hydrocortisone [or steroid equivalent]).

Secondary outcomes

Feasibility outcome measures:

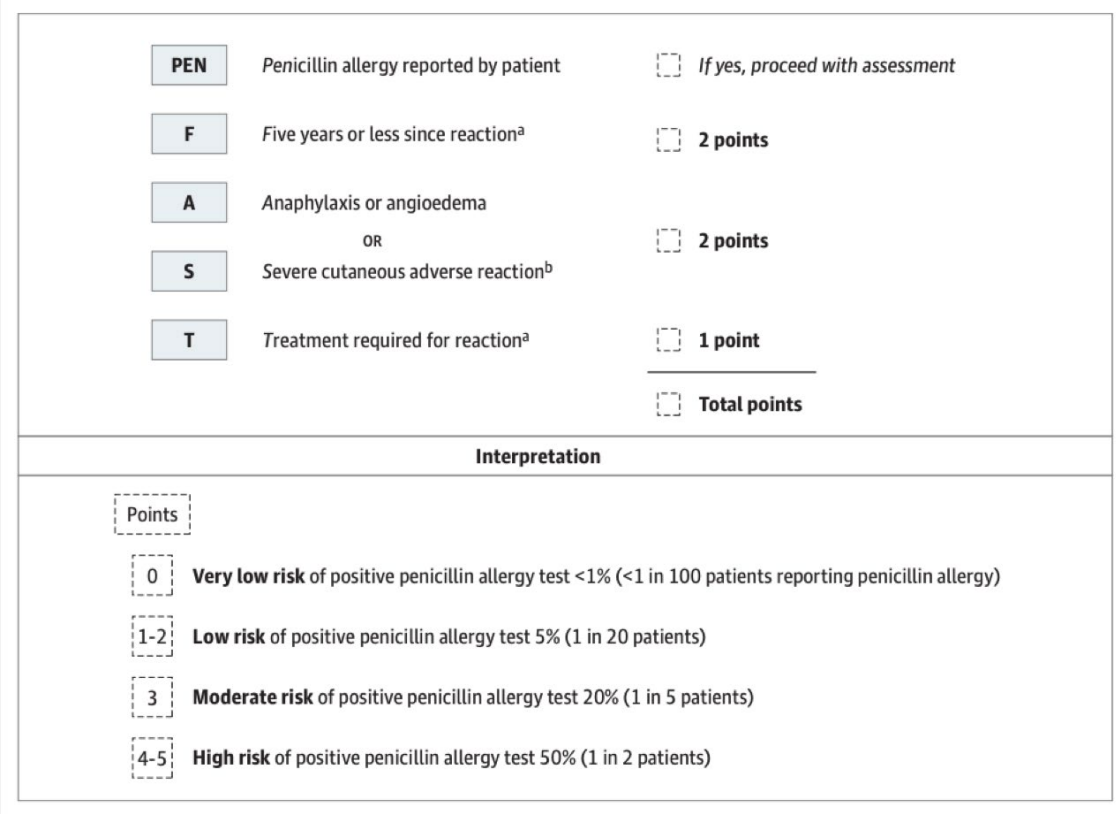
⇒ Proportion of patients referred to the outpatient allergy clinic that are eligible for intervention (i.e. randomisation) as per protocol (eligibility to screened ratio).
⇒ Feasibility of recruitment defined as the proportion of patients consenting to participate in the study per protocol from eligible patients (recruitment to eligibility ratio).
⇒ Feasibility of intervention delivery defined as the proportion of patients randomized to the intervention arm who had the intervention delivered as per protocol (intervention to recruitment ratio).

Safety outcome measures:

⇒ The proportion of patients with a penicillin allergy who experience an antibiotic-associated immune-mediated adverse event OR severe adverse drug reaction as per protocol definitions.
⇒ The proportion of patients with a penicillin allergy who experience an antibiotic associated, non-immune-mediated adverse event.
⇒ The proportion of patients who will respect the protocol (protocol compliance).

Exploratory efficacy outcomes:
⇒ Proportion of patients with a positive penicillin skin test.
⇒ Proportion of patients with non-immune-mediated positive oral provocation.
⇒ Proportion of patients with severe adverse reactions—anaphylaxis/ death.
⇒ Time from randomisation to delabeling.
⇒ Number of appointments required for penicillin allergy delabeling.
⇒ Assessment with the prequestionnaire and the 6-month follow-up questionnaire (outcomes not discussed in this report)

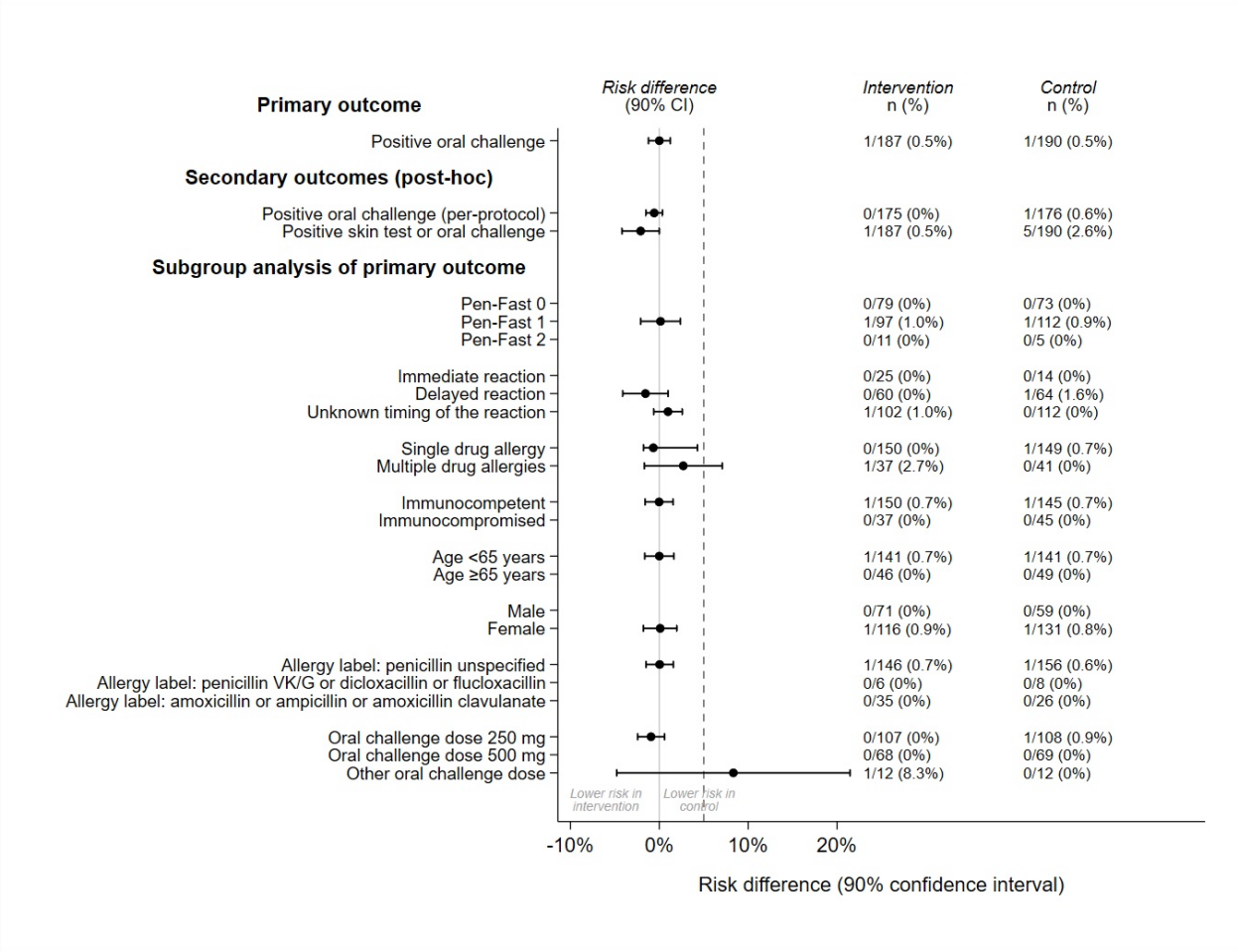
eFigure 1. The PEN-FAST clinical decision rule
Figure extracted for reference [13].



[a] Includes unknown

[b] Severe cutaneous adverse reactions include potential Stevens-Johnson syndrome, toxic epidermal necrolysis, drug reaction with eosinophilia and systemic symptoms, and acute generalized exanthematous pustulosis. Patients with a severe delayed rash with mucosal involvement should be considered to have a severe cutaneous adverse reaction. Acute interstitial nephritis, drug-induced liver injury, serum sickness and isolated drug fever were excluded phenotypes from the derivation and validation cohorts.

eFigure 2. Primary outcome, secondary outcomes and subgroup analysis of the primary outcome



Notes:

(1) The vertical grey lines represent no risk difference, while the dashed line represents the non-inferiority margin of 5%.

(2) A positive skin test and/or oral challenge occurred in 1/187 (0.5%) patients in the intervention group and 5/190 (2.6%) in the control group with a RD of -2.10 (90% CI, -4.20, 0.01) and a risk ratio of 0.20 (90% CI, 0.03, 1.22).

eTable 1. Skin testing drug allergy concentrations and type of penicillin and doses used in the trial

A. Drug allergy testing concentrations

Skin prick testing (read at 15 min)
Histamine 10 mg/ml
Sodium chloride 0.9%
Diater PPL (major determinant)*
Diater MDM (minor determinant)*
Benzylpenicilloyl polylysine 6.0 X 10-5 M (Pre-Pen®) †
Ampicillin 25 mg/ml
Penicillin G 10 000 U/ml
Intradermal testing (0.02 mL) (read at 15 min)
Sodium chloride 0.9%.
Diater PPL (major determinant) *
Diater MDM (minor determinant) *
Benzylpenicilloyl polylysine 6.0 X 10^{-5} M (Pre-Pen®) †
Ampicillin 25 mg/mL
Penicillin G 10 000 U/mL

MDM=minor determinant mixture. mg=milligram. ml=milliliter. PPL=penicilloyl-polylysine. U= unit.

*At the Australian sites, validated Diater reagents (DAP; Madrid, Spain) were used for the major (benzylpenicilloyl-poyl-L-lysine [PPL]) and minor determinant mixtures (MDM). Penicillin G and ampicillin were also used for all patients.

† At the North American sites, the major determinant benzylpenicilloyl polylysine 6.0 X 10^{-5} M (Pre-Pen®) was used. As the minor determinant was unavailable, penicillin G and ampicillin were used as surrogates for the Diater MDM.

Notes:

(1) The skin test reading was performed in two sequential steps: prick testing and, if negative, intradermal testing after 15 minutes.

(2) A positive skin test definition was a $\geq$ 3 mm wheal and $\geq$ 5 mm compared to the negative control (sodium chloride 0.9%).

B. Type of penicillin and doses used in the trial.

Antibiotic and dose	Intervention group (n= 187)	Control group (n = 190)
Amoxicillin 250 mg	91 (49%)	101 (53%)
Amoxicillin 500 mg	67 (36%)	68 (36%)
Amoxicillin 400 mg (2-step)	12 (6%)	11 (6%)
Penicillin VK 250 mg	15 (8%)	7 (5%)
Penicillin VK 500 mg	1 (1%)	0 (0%)
Penicillin VK 300 mg	0 (0%)	1 (1%)
Flucloxacillin 250 mg	1 (1%)	0 (0%)
No challenge	0 (0%)	2 (1%)

Data are n (%).

eTable 2. Characteristics of patients with positive primary outcomes

	Intervention group (n=1)	**Control group (n=1)**
Age group	30-40	30-40
Sex	Female	Female
Race	White	White
Other allergy reported	Yes (TMP-SMX, Cefdinir)	No
History of idiopathic urticaria/ angioedema	No	No
Reported penicillin allergy label	Penicillin unspecified	Penicillin unspecified
PEN-FAST score	1	1
Clinical phenotype	Unknown phenotype	Delayed phenotype
Childhood reaction	Yes	No
Time since reaction	>15 years ago	>15 years ago
Antibiotic used in oral challenge	Amoxicillin	Amoxicillin
Antibiotic dose in oral challenge	2-step challenge (80 mg + 320 mg)	250 mg
Description of the reaction	15 min: itching over neck/left upper back 30 min: objective erythematous macules confirmed by physician	53 min: itchiness on the abdomen 60 min: urticaria on the abdomen, back, shoulders and neck, ankles
Time following oral penicillin challenge (min)	20	50
Grade of the reaction	2	1
Treatment (single dose)	Diphenhydramine 25 mg PO	Loratadine 10 mg PO

min=minutes. TMP-SMX= trimethoprim-sulfamethoxazole.

eTable 3. Sensitivity analysis using exact methods for confidence intervals

	Intervention	Control	Risk difference (exact 90% CI), percentage points
Primary outcome			
Positive oral challenge	1/187 (0.5%)	1/190 (0.5%)	0.1 (-1.8, 1.9)
Secondary outcomes (post-hoc)			
Positive oral challenge (per protocol)	0/175 (0%)	1/176 (0.6%)	-0.4 (-2.6, 1.0)
Positive skin test or positive oral challenge	1/187 (0.5%)	5/190 (2.6%)	-2.1 (-4.8, 1.0)
Subgroup analysis of primary outcome			
Pen-fast score (post-hoc)			
0 (n=152)	0/79 (0%)	0/73 (0%)	0 (-4.0, 3.6)
1 (n=209)	1/97 (1.0%)	1/112 (0.9%)	0.1 (-3.1, 3.8)
2 (n=16)	0/11 (0%)	0/5 (0%)	0 (-45.0, 24.5)
Clinical immunophenotype			
Immediate reaction (n=39)	0/25 (0%)	0/14 (0%)	0 (-19.2, 11.2)
Delayed reaction (n=124)	0/60 (0%)	1/64 (1.6%)	-1.6 (-7.1, 3.0)
Unknown (n=214)	1/102 (1.0%)	0/112 (0%)	1.0 (-1.6, 4.5)
Number of reported drug allergies			
Single (n=299)	0/150 (0%)	1/149 (0.7%)	-0.7 (-3.1, 1.1)
Multiple (n=78)	1/37 (2.7%)	0/41 (0%)	2.7 (-4.0, 12.1)
Immunocompetency			
Immunocompetent (n=295)	1/150 (0.7%)	1/145 (0.7%)	-0.02 (-2.4, 2.2)
Immunocompromised (n=82)	0/37 (0%)	0/45 (0%)	0 (-6.4, 7.7)
Age			
<65 (n=282)	1/141 (0.7%)	1/141 (0.7%)	0 (-2.5, 2.5)
≥65 (n=95)	0/46 (0%)	0/49 (0%)	0 (-5.9, 6.2)
Sex			
Male (n=130)	0/71 (0%)	0/59 (0%)	0 (-4.9, 4.0)
Female (n=247)	1/116 (0.9%)	1/131 (0.8%)	0.10 (-2.6, 3.1)
Penicillin type			
Penicillin unspecified (n=302)	1/146 (0.7%)	1/156 (0.6%)	0.04 (-2.2, 2.4)
Penicillin VK/G or dicloxacillin or flucloxacillin (n=14)	0/6 (0%)	0/8 (0%)	0 (-31.1, 39.2)
Amoxicillin or ampicillin or amoxicillin clavulanate) (n=61)	0/35 (0%)	0/26 (0%)	0 (-10.9, 8.2)

Oral challenge dose				
	250 mg (n=215)	0/107 (0%)	1/108 (0.9%)	-0.9 (-4.3, 1.7)
	500 mg (n=137)	0/68 (0%)	0/69 (0%)	0 (-4.2, 4.2)
	Other* (n=24)	1/12 (8.3%)	0/12 (0%)	8.3 (-12.9, 33.8)

*Other: all but one were 400 mg (one was 300 mg)

eTable 4. Safety outcomes in the first 2 days and 5 days following oral penicillin challenge

	Intervention	Control	Risk difference (95% CI), percentage points	Risk ratio (95% CI)
Cumulative within 48 hours of challenge (2 days)				
All adverse events	18/187 (10%) (20 events)	17/190 (9%) (20 events)	0.68 (-5.18, 6.54)	1.08 (0.57, 2.02)
Immune mediated adverse event	8/187 (4%) (9 events)	6/190 (3%) (6 events)	1.12 (-2.70, 4.94)	1.35 (0.48, 3.83)
Antibiotic related immune mediated[a]	7/187 (4%) (8 events)	5/190 (3%) (5 events)	1.11 (-2.44, 4.66)	1.42 (0.46, 4.40)
Non-immune mediated adverse event	10/187 (5%) (11 events)	12/190 (6%) (14 events)	-0.97 (-5.70, 3.76)	0.85 (0.37, 1.91)
Cumulative within 120 hours of challenge (5 days)				
All adverse events	20/187 (11%) (22 events)	21/190 (11%) (24 events)	-0.36 (-6.64, 5.93)	0.97 (0.54, 1.73)
Immune mediated adverse event	9/187 (5%) (10 events)	10/190 (5%) (10 events)	-0.45 (-4.87, 3.96)	0.91 (0.38, 2.20)
Non-immune mediated adverse event	11/187 (6%) (12 events)	12/190 (6%) (14 events)	-0.43 (-5.26, 4.40)	0.93 (0.42, 2.06)
Other safety outcomes				
Serious adverse event at any time	0/187 (0%)	0/190 (0%)	N/A	N/A
Protocol compliance[b,c]	175/190 (92%)	176/192 (92%)	0.44 (-5.04, 5.91)	1.01 (0.95, 1.07)

[a] The antibiotic-related immune-mediated events are immune-mediated reactions that have a degree of causality: certain, probable/likely or possible

[b] Protocol compliance is defined as an absence of protocol violations (regardless of protocol deviations). The protocol violation occurred in a total of 31 patients: absence of performed intradermal testing in the control group and 2-step oral challenge (N=1), oral penicillin challenge was not performed following negative skin testing (N=2), oral penicillin challenge was performed after positive skin testing (N=2), patients meeting exclusion criteria and were subsequently excluded following randomization (N=3), 2-step oral challenge within the protocol dose range of 250-500 mg (N=23).

eTable 5. Safety outcome inclusions

A. Reported reactions classified as possibly immune-mediated

Immediate diffuse rash/urticaria
Delayed diffuse rash/urticaria (more than 1 hour) e.g. maculopapular rash; rash to torso and back
Localised reaction (examples of reactions: positive skin testing; immediate localized rash and redness on the chest (area of 6 cm), red macules on the legs; blister type rash <1 cm in size on chest; localised facial rash; localised rashes at left forearm (IDT site); localized oedema; localized macular eruption; 3-4 localized papules on left forearm where he had skin testing for aeroallergens; peri-orbital eczema; rash under arm that spread to arm lasting 2 days; swelling of the hands

B. Reported reactions classified as possibly non-immune-mediated

Nausea/Abdominal pain/vomiting/diarrhea
Headache
Isolated skin itchiness
Candida vulvovaginitis
Isolated chest tightness
Fatigue
Localized swelling sensation (absence of objective findings)
Mouth metallic taste
Nasal irritation / Sinus discomfort
Sensation of facial numbness / Tingling on the face and side of the tongue

eTable 6. Efficacy outcomes
A. Penicillin allergy delabel and the number of appointments required for delabeling

	Intervention	Control	Risk difference (95% CI), percentage points	Risk ratio (95% CI)
Delabeled *	186/187 (99.5%)	186/190 (97.9%)	1.57 (-0.72, 3.86)	1.02 (0.99, 1.04)
Number of appointments required				
1	184/186 (98.9%)	184/186 (98.9%)	Ref	Ref
2	2/186 (1.1%)	2/186 (1.1%)	0.00 (-2.10, 2.10)	1.00 (0.13, 7.02)

Data are n (%)

Notes:
* A patient from the intervention group was not delabeled because of a positive oral challenge (primary outcome). Four patients from the control group were not delabeled because one patient had a positive oral challenge (primary outcome); two patients had positive skin testing and no penicillin oral challenge was performed; and one patient had a delayed positive intradermal test to penicillin G and ampicillin and was re-labelled following a single dose negative oral challenge. This last patient had a confirmed delayed positive intra-dermal testing and safely tolerated a 5-day cephalexin challenge.

B. Time from randomization to delabeling

	Intervention (n=186)	Control (n=186)	Median difference (95%CI)
Time from randomisation to delabeling (hours)	1.80 (1.33, 3.72)	2.28 (1.72, 5.48)	- 0.45 (-0.65, -0.27)

Data are median (IQR).