Penicillin Allergy Assessment and Direct Oral Challenge

OFFICIAL

To provide a standardised approach for hospital clinicians on assessing penicillin allergies and undertaking direct oral penicillin challenges in hospitalised Victorians with a low-risk penicillin allergy.

Background

This procedure is designed to provide direction on the process of assessing and removing (i.e. delabelling) a patient-reported penicillin allergy. A patient-reported “penicillin” allergy is documented in 9-15% of hospitalised patients and is often referred to as a penicillin allergy “label”. (1)

Patients with a penicillin allergy label are more likely to have:

- Inferior prescribing and clinical outcomes,
- Increased hospital length of stay and costs,
- Increased mortality. (2)

Direct oral penicillin challenges (i.e. test dose) have been demonstrated to be safe and effective in patients who are identified as having a low-risk penicillin allergy. (3, 4)

Further information on the implementation of inpatient direct oral challenge program can be found in the Hannah et al. article “Adult penicillin allergy programmes in Australian hospitals: a practical guide from the National Antibiotic Allergy Network”. (4)

Definitions and Abbreviations:

- **Penicillin –** Phenoxymethylpenicillin, benzylpenicillin, benzathine penicillin, penicillin “unspecified”
- **Aminopenicillin** – Amoxicillin, ampicillin, amoxicillin-clavulanate
- **ADR** – Adverse Drug Reaction
- **MPE** – Maculopapular exanthema (rash without angioedema, urticaria, blistering, desquamation, internal organ involvement and/or mucosal involvement).
- **SCAR** – Severe cutaneous adverse reaction (e.g., Stevens-Johnson syndrome, toxic epidermal necrolysis, drug reaction with eosinophilia and systemic symptoms, acute generalised exanthematous pustulosis)
- **DILI** - Drug-Induced Liver Injury
- **Type A** – Non-immune mediated pharmacologically predictable side effect (e.g., headache, gastrointestinal upset)

- **Type B** – Immune mediated ADR (e.g., anaphylaxis, urticaria, angioedema, rash, SCAR, acute interstitial nephritis, drug induced liver injury)
- **Delabelling** – The removal of a patient's penicillin allergy label following medical reconciliation or testing (e.g. skin testing followed by oral challenge OR direct oral challenge without prior skin testing).

Penicillin Allergy Assessment

As per the National Safety and Quality Health Service (NSQHS) Standards Antimicrobial Stewardship Clinical Care Standard, "when an adverse reaction (including an allergy) to an antimicrobial is reported by a patient or recorded in their healthcare record, the active ingredient(s), date, nature and severity of the reaction are assessed and documented". (5)

To conduct a thorough penicillin allergy assessment the questions below may be asked:

- What is the name of the antibiotic you are allergic to?
- Please describe the details of the reaction
- How many years ago did the reaction occur?
- How long after having the first dose of the antibiotic did the reaction occur?
- How was the reaction managed?
  - Was an ambulance called or were you hospitalised as a result of the reaction?
- Which other antibiotics have you taken and tolerated since the reaction?

Oral Antibiotic Challenge - Inclusion & Exclusion criteria

Inclusion criteria for direct oral penicillin challenge:

- The patient is determined to have a low-risk penicillin allergy using either Appendix 1 or Appendix 2.
  - Appendix 1 (PEN-FAST): Low risk is less than 3 points
  - Appendix 2 (Antibiotic Allergy Assessment Tool, AAAT): Low risk is either a green or white coloured box
- Typical low risk penicillin allergy histories include:
  - Unknown reaction > 5 years ago or date cannot be recalled ("many years ago")
  - Type A adverse drug reactions (reaction documented is an expected side effect), where the patient does not accept direct removal of the allergy from the medical record
  - History of an unspecified childhood rash, localized injection site reaction only, or maculopapular exanthem (MPE) greater than 5 years prior.

Relative exclusion criteria for direct oral penicillin challenge:

- Haemodynamic instability (Medical Emergency Team (MET) review within the last 24 hours or in an Intensive Care Unit (ICU))
- Unable to tolerate medications orally or enterally

- Pregnancy (seek specialist advice)
- Allergy history unavailable from the patient due to cognitive impairment and no collateral history
- History of anaphylaxis to beta-lactam antibiotics
- History of Severe Cutaneous Adverse Reactions (SCAR) to beta-lactam antibiotics
- History of acute kidney injury or severe liver impairment associated with beta-lactam antibiotic therapy (Drug-Induced Liver Injury [DILI] defined as ≥ 5 ULN for ALT, or ≥ 2 ULN for ALP or ≥ 3 x ULN ALT with bilirubin ≥ 2 x ULN)
- Currently prescribed: prednisolone > 25 mg daily (or equivalent) or H1-antagonist antihistamines [relative contraindication – can be discussed on case-by-case basis]

Inpatient Direct Oral Challenge Procedure

Preparation

- Ensure the patient meets the criteria for direct penicillin oral challenge (see inclusion/exclusion advice above)
- Inpatient direct oral challenge to be performed only after consent by the treating team and the patient. The patient must be consented by a clinician with local governance approval
- Medical officer to be available to treat or advise on allergic reaction
- Adrenaline 1:1,000 (1mg/1mL) ampules available in the event of anaphylaxis (this does not need to be prescribed on the patient's medication chart)
- Antibiotic for direct oral challenge must be available
- Notify the ward nursing staff looking after the patient and the ward in-charge nurse about the direct oral challenge.

Direct oral challenge procedure

1. Drug order

Phenoxymethylpenicillin 250-500mg mg, flucloxacillin 250-500mg or amoxicillin 250-500 mg can be charted as a stat (once only) order by treating medical officer or approved prescriber.

Reported Allergy	Drug to be charted
Phenoxymethylpenicillin or benzylpenicillin	Phenoxymethylpenicillin
Amoxicillin or ampicillin	Amoxicillin
Flucloxacillin	Flucloxacillin
Amoxicillin-clavulanate	Direct oral challenge with amoxicillin first. If amoxicillin challenge is negative, proceed to amoxicillin-clavulanate challenge.
"Unknown penicillin"	Amoxicillin [default]

NOTE: If the reported reaction is a Type A penicillin drug reaction only with a clear patient history, and beta-lactam therapy is required, the penicillin allergy label can be removed, and administration of a full treatment dose of penicillin can proceed without test dose.

There is currently no clear guidance on the use of prolonged oral challenge (e.g. 3-5 days). These may be considered in patients with a clear history of delayed hypersensitivity.

2. Nursing requirements

a. Immediately prior to the direct oral challenge, perform baseline patient observations (Heart Rate, Blood Pressure, Oxygen Saturations & Respiratory Rate)

b. Administer orally either a single dose of phenoxymethylpenicillin 250mg-500mg or amoxicillin 250mg-500mg or flucloxacillin 250mg-500mg (as charted on the patient's medication chart)

c. Perform 30-minute observations for 60-minutes post direct oral challenge

3. Completion of direct oral challenge

- **If no evidence of reaction**, the medical team coordinating the direct oral challenge will:
  a. Discuss the outcome of the direct oral challenge with the patient.
  b. Remove penicillin allergy from the patient's medical record (and alert sheet where available) immediately post direct oral challenge.
  c. Send a letter to the patient, general practitioner and other treating clinicians to notify them of the removal of the allergy.
- **If a reaction from the direct oral challenge dose occurs**
  – The treating medical team must be notified immediately and the event documented in the patient's medical record.
  – For anaphylaxis: Follow your local hospital anaphylaxis protocol. For additional support see the Australasian Society of Clinical Immunology and Allergy (ASCIA) resources.
  – For mild dermatological reactions (e.g. maculopapular exanthem and localised itch): Administer loratadine 10mg or cetirizine 10mg orally as a single dose.
  – The detail of the reaction is to be documented/updated in the patient's medical record (and alert sheet where available) including date of reaction from direct oral challenge. The patient is NOT to have their penicillin allergy removed.

Appendix 1

PEN-FAST - Penicillin Allergy Clinical Decision Rule

A point-of-care risk assessment rule for patient-reported penicillin allergies. (6,7)

PEN	Penicillin Allergy reported by patient?		If yes, proceed with assessment
F	Five years or less since reaction *(If unknown, give zero points)*		☐ 2 points
A	Anaphylaxis or angioedema	**OR**	☐ 2 points
S	Severe cutaneous adverse reaction*		
T	Treatment required for reaction^		☐ 1 point
			Total Points =

^Includes unknown.

*Forms of severe delayed 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 mucosa involvement should be considered to have a severe cutaneous adverse reaction.

Interpretation

0 Points	Very low risk	Risk of positive penicillin allergy test is less than 1%
1 to 2 points	Low risk	Risk of positive penicillin allergy test is 5%
3 points	Moderate risk	Risk of positive penicillin allergy test is 20%
4 to 5 points	High risk	Risk of positive penicillin allergy test is 50%

- **VERY LOW RISK/LOW RISK** penicillin allergies can often be safely "delabelled" by a single oral test dose of penicillin, please refer to local hospital guidelines.
- **MODERATE** and **HIGH** risk allergies may require formal allergy testing, seek specialist advice.

Appendix 2

Antibiotic Allergy Assessment Tool

A point-of-care assessment tool for patient-reported penicillin allergies. (8)

Dermatological				Respiratory or Systemic			Unknown		
Skin manifestation			*Recommendation & Resultant allergy type*	**Clinical manifestation**		*Recommendation & Resultant allergy type*	**Clinical manifestation**		*Recommendation & Resultant allergy type*
Childhood exanthem (unspecified) *Mild rash with no severe features*		☐	Unlikely to be significant (non-severe)	**Laryngeal involvement** ("throat tightness" or "hoarse voice")	☐	Immediate hypersensitivity (severe)	**Unknown reaction** ≤ 5 years ago	☐	Unknown (non-severe)
Immediate diffuse rash ("itchy immediate rash") *<2 hours post dose*		☐	Immediate hypersensitivity (non-severe)				**Unknown reaction** > 5 years ago or **family history** of penicillin allergy only	☐	Unlikely to be significant (non-severe)
Diffuse rash or localized rash/swelling with no other symptoms *(non-immediate or unknown timing)*	> 5 years ago; or unknown	☐	Delayed hypersensitivity (non-severe)	**Respiratory compromise** ("shortness of breath")	☐	Immediate hypersensitivity (severe)	**Renal**		
	≤ 5 years ago	☐	Delayed hypersensitivity (non-severe)	**Fever** ("high temperature") *Not explained by infection*	☐	Delayed hypersensitivity (severe)	**Severe renal injury, failure or AIN** (>50% reduction in eGFR from baseline or absolute serum creatinine increase of ≥26.5µmol/L, or transplantation, or dialysis)	☐	Potential immune mediated (severe)
Angioedema ("lip, facial or tongue swelling")		☐	Immediate hypersensitivity (severe)	**Anaphylaxis or unexplained collapse**	☐	Immediate hypersensitivity (severe)	**Mild renal impairment** (Does not meet criteria in box above)	☐	Unlikely immune mediated (non-severe)
Generalized swelling (outside of angioedema)		☐	Immediate hypersensitivity (severe)	**Haematological**			**Liver**		
Urticaria ("wheals and hives") **Isolated childhood urticaria may be challenged on a case-by-case basis*		☐	Immediate hypersensitivity (non-severe)	**Low platelets** < 150 x10⁹/L or unknown	☐	Potential immune mediated (severe)	**Severe liver injury, failure or DILI** (≥5x upper limit of normal (ULN) for ALT or AST, or ≥3x ULN for ALT with ≥2x ULN for bilirubin, or ≥2x ULN for ALP, or transplant)	☐	Potential immune mediated (severe)
				Low neutrophils < 1x10⁹/L or unknown	☐	Potential immune mediated (severe)	**Mild hepatic enzyme derangement** (Does not meet criteria in box above)	☐	Unlikely immune mediated (non-severe)
Mucosal ulceration ("mouth, eye or genital ulcers")		☐	Delayed hypersensitivity (severe)	**Low haemoglobin** < 100 g/L or unknown	☐	Potential immune mediated (severe)	**Gastrointestinal, Neurological or Infusion-related**		
Pustular, blistering or desquamating rash ("skin shedding")		☐	Delayed hypersensitivity (severe)	**Eosinophilia** (>0.7 x 10⁹/L or unknown)	☐	Delayed hypersensitivity (severe)	**Gastrointestinal symptoms** ("nausea, vomiting, diarrhoea")	☐	Unlikely immune mediated (non-severe)
							Mild neurological manifestation ("headache, depression, mood disorder")	☐	Unlikely immune mediated (non-severe)
Appropriate for supervised direct oral rechallenge (or direct de-labelling) - Refer to ID, Pg 1547						☐ **Low risk**	**Severe neurological manifestation** ("seizures or psychosis")	☐	Unknown or unclear mechanism
Appropriate for supervised direct oral rechallenge – Refer to ID						☐ **Low risk**			
May be appropriate for referral for specialized skin testing - Refer to OP antibiotic allergy service						☐ **Moderate risk**	**Anaphylactoid/infusion reaction** (e.g. red man syndrome)	☐	Unknown or unclear mechanism
May be appropriate for referral for specialized skin testing - Refer to antibiotic allergy service						☐ **High risk**			

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