Guideline

Paediatric antibiotic allergy assessment, testing and de-labelling

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Applicable to	All CHQ Clinical Staff				
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Purpose

This guideline provides recommendations for the assessment, testing and de-labelling of paediatric antibiotic allergies.

Scope

This guideline provides information for Children's Health Queensland (CHQ) staff caring for paediatric patients with documented antibiotic allergy and provides a framework of assessment and oral challenge for de-labelling if possible.

Related documents

- CHQ-PROC-01017 Adverse Drug Reaction - Documentation and Reporting
  - CHQ Quick reference guide: ieMR: Allergies
- CHQ-PROC-34652 Communicating for Safety: Communication and Documentation of Critical Information
- CHQ-PROC-01036 Antimicrobial: Prescribing, Management and Stewardship
- CHQ-GDL-60011 Allergy and anaphylaxis - Emergency management in children

Guideline

Background

Beta-lactam allergy is reported in up to 10 % of the general population, however, over 90 % of patients reporting such an allergy tolerate penicillin without incident.

Common reasons for this include the previous reaction being attributed to penicillin when in fact it was more likely due to the infectious agent (i.e. a delayed viral exanthem) or a common side effect of the medication (i.e. nausea or diarrhoea). True penicillin induced anaphylaxis is exceedingly rare (0.015 % to 0.04 % of patients).

Patients labelled with an antibiotic allergy have longer hospital stays and increased exposure to suboptimal antibiotics. This use of suboptimal antibiotics leads to increase costs, contributes to antimicrobial resistance and increased side effects.

Due to the negative impact of an antibiotic allergy label on patient outcomes, evaluation of antibiotic allergy is considered an essential component of comprehensive antimicrobial stewardship programs.

Target population for penicillin allergy de-labelling

Inclusion criteria:

- *No increased risk for allergic reaction:* Patient is avoiding penicillin based on family history alone, or has tolerated penicillin since the concerning incident without reaction. Isolated gastrointestinal symptoms (nausea, vomiting, diarrhoea).
- *Low risk for allergic reaction:* Patients who have delayed onset (greater than 24 hours after the first dose) of isolated symptoms (such as hives/rash alone)

If a child has any of the following, do not undertake penicillin de-labelling at this time but consider doing during the admission as soon as these symptoms have resolved:

- Nil by mouth (unable to tolerate oral/enteral medication);
- Vomiting more than 1 time in last 24 hours;
- Concerning respiratory symptoms;
- Critically ill;
- Current rash
- If the patient has been on an antihistamine in preceding 48 hours, the oral challenge should be postponed

High risk antibiotics excluded from low risk oral drug provocation test (oral challenge) protocol:

- Cefaclor
- Trimethoprim/ sulfamethoxazole
- Macrolides (e.g. azithromycin, erythromycin, roxithromycin)
- Quinolones (e.g. Ciprofloxacin, moxifloxacin, norfloxacin)

Key steps to assess Paediatric antibiotic allergy

Step 1: Take a comprehensive antibiotic allergy history (Table 1)

Detailed history-taking is critical to the evaluation of possible antibiotic allergy, the level of patient risk, and for deciding whether skin testing or an oral challenge is indicated.

Individuals should be assessed and examined by a physician while they are experiencing a suspected reaction, if possible. Investigations will depend on the nature of the suspected reaction.

Questions to ask in an antibiotic allergy history:	
Severity and type of reaction	• Do you remember the details of the reaction? • How was the reaction managed? • Did it require treatment or hospitalisation?
Timing	• How long after taking the antibiotic did the reaction occur? • How many years ago did the reaction occur?
Antibiotic use since reaction	• Are there other antibiotics that have you taken without problems since the reaction?
Document responses in the patient's medical and pharmacy records in ieMR and iPharmacy.	

Table 1: Questions to ask in an antibiotic allergy history

Step 2: Utilize the Paediatric Antibiotic Allergy Assessment tool (PAT) (Figure 1) to define an allergy phenotype and assign risk:

The phenotypic outcomes of the Paediatric Antibiotic Allergy Assessment tool (PAT) are classified as follows:

- Severe immediate hypersensitivity (IgE-mediated),
- Non-severe immediate hypersensitivity (IgE-mediated),
- Severe delayed hypersensitivity (T-cell mediated),
- Non-severe delayed hypersensitivity (T-cell mediated),
- Potential immune-mediated (e.g., acute interstitial nephritis, DRESS, TEN, SJS), or
- Unlikely to be significant/non-immune-mediated (e.g., gastrointestinal upset and unknown history).

Step 3: Choose and action corresponding risk and management recommendation/s based on phenotype identified (Figure 2, Table 2 and Appendix C)

If more than 1 clinical manifestation is selected on PAT (Figure 1), default to the most likely or severe risk category.

Table 2: Risk assessment based on clinical history and assigned phenotype

Risk assessment based on clinical history and assigned phenotype If more than 1 clinical manifestation is selected on PAT (Figure 1), default to the most likely or severe risk category.		
Risk category	**Clinical History**	**Management recommendation**
No increased risk	Family history of penicillin allergy. Has tolerated same antibiotic since concerning incident without reaction. Isolated gastrointestinal symptoms (nausea, vomiting, diarrhoea)	Appropriate for direct de-labelling. Removal of allergy label without testing or consultation.
Low risk	Delayed onset (greater than 24 hours after first dose) onset of isolated, non-progressive symptoms (such as rash/hives alone) Or Unknown clinical history	In the appropriate setting, a supervised direct single dose oral challenge under observation, and if successful followed by a 3 day oral drug provocation test (daily dosing) may be performed by the Treating team. This is to ensure the immediate and delayed type hypersensitivity can be excluded. **See Appendix A for Protocol:** Single dose Oral challenge and 3 day drug provocation test (DPT) for Amoxicillin (Low risk only). For assistance, contact the AMS Pharmacist on 0436 815 492 (within working hours) or refer using "Consult to ID Pharmacist" in ieMR.
Moderate risk	• Symptoms concerning for anaphylaxis • Any symptoms requiring hospitalization • Immediate symptoms (less than 24 hours after first dose of antibiotic) • Progressive/worsening symptoms (within 60 minutes of dose) • Reaction to intravenous/intramuscular formulation (within 60 minutes of dose) • Primarily receiving enteral medicines via nasogastric tube (NG), gastric tube (GT), or jejunostomy tube (JT)	Appropriate for discussion with ID team (DECT 3068 4421) or referral to Allergy team (DECT 3068 4427) (within working hours). Investigations as per Appendix C and D. Patients classified as an "Immediate hypersensitivity" are appropriate for desensitization if the patient has a beta-lactam allergy history and required urgent penicillin-based therapy (discuss with ID Fellow/consultant (DECT 3068 4421) and Allergy team (DECT 3068 4427)).
High risk	Serious Cutaneous or Systemic Adverse Reactions concerning for but not limited to: • Stevens-Johnson Syndrome (SJS) or Toxic Epidermal Necrolysis (TEN) • Drug reaction with eosinophilia and systemic symptoms (DRESS) • Acute Interstitial Nephritis (AIN) • Serum Sickness	Appropriate for outpatient antibiotic allergy assessment – refer to Immunology/Allergy (drug allergy clinic) to Dr Peake (Director of Immunology). Investigation as per Appendix C and Appendix D.

Figure 1: Paediatric Antibiotic Allergy Assessment tool (PAT)

Figure 1: Paediatric Antibiotic Allergy Assessment tool (PAT)

Dermatological

Clinical Manifestation		Recommendations and resultant allergy type
A benign rash localised or widespread after 24 hours of starting treatment, with or without itchiness, the details of the timing of the rash after taking the dose are not specific, no severe features associated, and no hospitalisation due to the rash.	☐	Potentially delayed hypersensitivity (non-severe)
Immediate diffuse urticarial rash within 2 hours after taking any dose	☐	Immediate hypersensitivity (non-severe): Moderate risk
Angioedema (lips, facial, or tongue swelling")	☐	Immediate hypersensitivity (severe)
Swelling (outside of angioedema)	☐	Potential immediate hypersensitivity (severe)
Rash & Mucosal ulceration (mouth, eye or genital ulcer)	☐	Delayed hypersensitivity (severe): High Risk
Pustular, blistering or desquamation ("skin shedding") rash	☐	Delayed hypersensitivity (severe): high Risk

Respiratory or Systemic

Clinical Manifestation		Recommendations and resultant allergy type
Laryngeal Involvement ("throat tightness or hoarse voice")	☐	Immediate hypersensitivity (severe)
Respiratory compromise ("wheeze or shortness of breath") - required adrenaline or hospital presentation - not explained by the infection	☐	Immediate hypersensitivity (severe)
Fever, not explained by the infection or other cause	☐	Delayed Hypersensitivity (severe)
Anaphylaxis or unexplained hypotension or collapse	☐	Immediate Hypersensitivity (severe)

Haematological

Platelets < 150 x 10^9/L (without other clinical reason)	☐	Potential Immune mediated (severe)
Neutrophils < 1 x 10^9/L (without other clinical reason)	☐	Potential Immune mediated (severe)
Haemoglobin <100 g/L (without other clinical reason)	☐	Potential Immune mediated (severe)
Eosinophils (> 0.7 x 10^9/L) Assess for DRESS	☐	Delayed Hypersensitivity (severe, if DRESS)

Unknown Reaction

Clinical Manifestation		Recommendations and resultant allergy type
Family history of penicillin allergy	☐	No increased risk
Unknown Clinical history	☐	Unlikely significant reactions

Gastrointestinal or Neurological

Gastrointestinal symptoms ("nausea, vomiting, diarrhoea")	☐	Unlikely Immune mediated (non-severe, no increased risk)
Neurological or CNS manifestation ("headaches, agitation, sleepiness, confusion")	☐	Unlikely Immune mediated (non-severe, low risk)

Renal

Renal Impairment which does not meet criteria for renal failure (see below)	☐	Unlikely Immune mediated (non-severe, low risk)
Renal failure or severe renal Injury or transplantation or dialysis (Increase creatinine by 30 to 50% from baseline – within 48 hrs to 7 day period)	☐	Potential Immune mediated or Delayed hypersensitivity (severe reaction, if AIN)

Liver

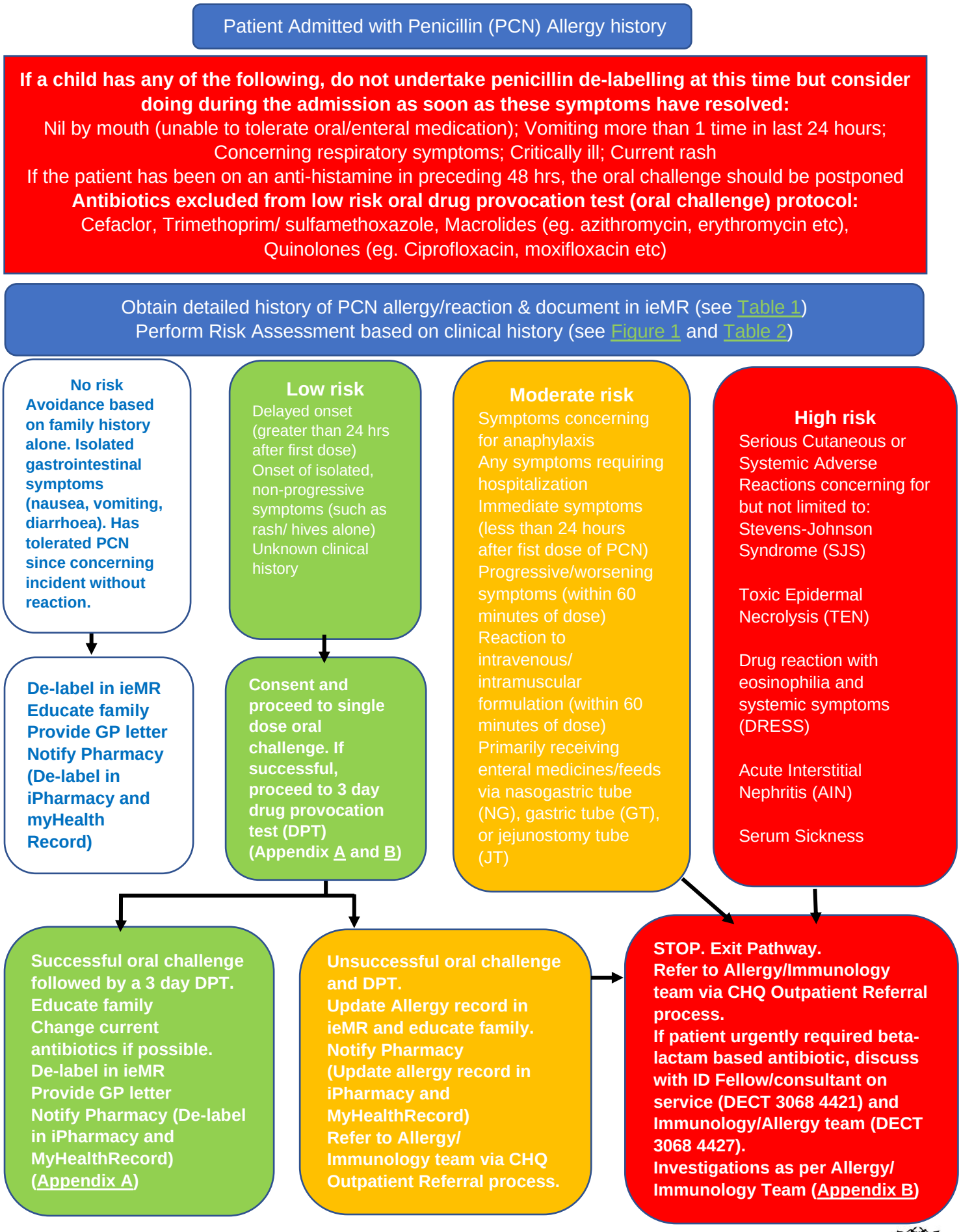
Hepatic derangement which does not meet criteria for liver failure or severe injury (see below)	☐	Unlikely Immune mediated (non-severe, low risk)
Liver failure/severe injury: • Elevated AST, ALT, bilirubin (total/conjugated), INR>1.5 or PT≥ 15 not corrected by vitamin K, clinical encephalopathy, • OR if PT≥20, INR≥2, decompensation or transplantation	☐	Potential Immune mediated (severe if DILI)

Risk category and management recommendation (for more detailed information refer to Table 2 and Appendix A)	
Appropriate for direct de-labelling- removal of allergy label without testing or consultation	
Appropriate for supervised direct oral challenge/ drug provocation test (DPT) by treating team	
Appropriate for discussion or referral to allergy team, if needed call DECT: 3068 4427 (within working hours)	
Appropriate for outpatient antibiotic allergy assessment – refer to Immunology/Allergy (drug allergy clinic)	

AIN, Acute Interstitial nephritis; CNS, Central nervous system; CrCl, Creatinine clearance; DILI, drug-induce liver injury; DRESS, Drug reaction with eosinophilia and system symptoms; PT, Prothrombin time

This tool has been modified for Paediatric use by the CHQ Immunology/Allergy service; CHQ IMPS Consultant and CHQ AMS Pharmacist; with permission from Dr Jason Trubiano (1)

Figure 2: Penicillin Allergy Delabelling Algorithm



Beta-lactam cross reactivity (Figure 3 and Appendix C) (4)

Immune-mediated penicillin hypersensitivity was historically thought to be due solely to the beta-lactam ring structure that is common to all beta-lactam antibiotics (penicillins, cephalosporins, carbapenems and monobactams).

However, recent evidence and clinical experience suggests that most reactions occur in response to antigenic molecules in the R1 side-chain that distinguishes individual penicillins and cephalosporins from one another.

Beta-lactams with the same or similar R1 side-chains are more likely to cross-react. Penicillins have one side-chain (R1), while cephalosporins have two side-chains (R1, R2). Similarity between the R1 side-chains can cause cross-reactivity (Figure 3).

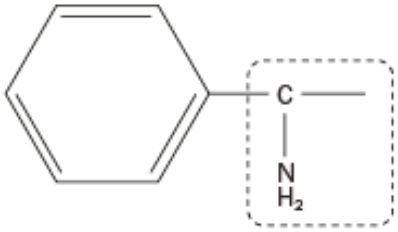
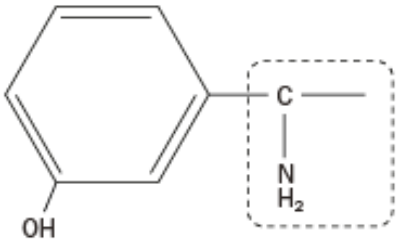
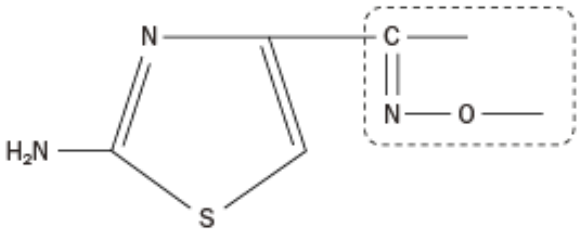
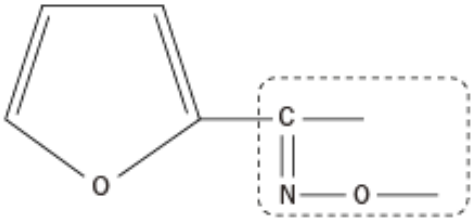
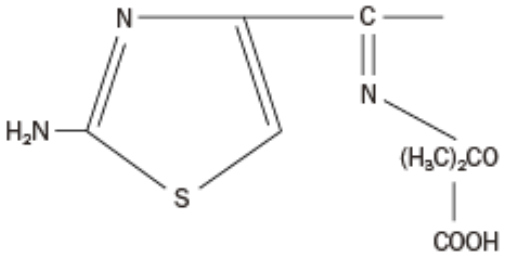
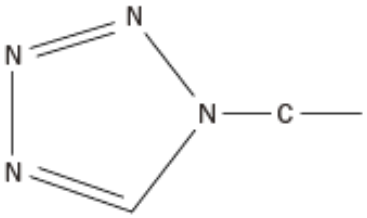
In settings where allergy testing is not available and a beta-lactam antibiotic is the preferred drug, antimicrobials to avoid based on potential cross-reactivity due to identical or similar R1 side-chains are:

- Amoxicillin or ampicillin allergy—avoid cefalexin and cefaclor (except in delayed non-severe hypersensitivity; see Appendix C for guidance)
- Ceftriaxone allergy—avoid cefotaxime, cefepime and cefuroxime
- Ceftazidime allergy—avoid aztreonam.

Special considerations:

- In patients with immediate severe penicillin hypersensitivity (e.g. anaphylaxis, angioedema)
  - Avoid penicillins and cephalosporins in most situations; however, in a critical situation when a beta lactam is the preferred drug.
  - Consider cephalosporin after undertaking a risk–benefit analysis and assessment of potential side-chain cross-reactivity (e.g. for sepsis, meningitis, endocarditis).
  - Seek advice from IMPS and/or Immunology team.
- In patients with delayed severe penicillin hypersensitivity (e.g. DRESS, SJS/TEN)
  - Do not use cross-reactivity to guide treatment and avoid all penicillins and cephalosporins.
  - See Appendix C and seek advice from IMPS and/or Immunology teams.

Figure 3: Beta-lactam structure and side-chain similarity (4)

Beta-lactam antibiotic	R1 side-chain [NB1]
ampicillin, cefaclor and cefalexin	
amoxicillin	
ceftriaxone, cefotaxime and cefepime	
cefuroxime	
aztreonam and ceftazidime	
cefazolin	

List of abbreviations

AIN	Acute Interstitial Nephritis
AMS	Antimicrobial stewardship
CHQ	Children's Health Queensland
DPT	Oral drug provocation test/challenge (Appendix A)
DRESS	Drug reaction with eosinophilia and systemic symptoms
GT	Gastrostomy tube
IDT	Intradermal testing
ieMR	Integrated electronic medical record
IMPS	Infection Management and Prevention service
JT	Jejunostomy tube
MDM	Minor determinant mix
NG	Nasogastric tube
PAT	Paediatric antibiotic allergy assessment tool (figure 1)
PPL	Diameter major determinant
QCH	Queensland Children's Hospital
QPIAS	Queensland Paediatric Immunology and Allergy Service
SJS	Steven Johnson's Syndrome
SPT	Skin prick testing
TEN	Toxic Epidermal Necrolysis

Acknowledgement

- Dr Jason Trubiano (Infectious Diseases Specialist, The Austin hospital, Victoria, Australia)
- Micha Devchand (Antimicrobial Stewardship Pharmacist, The Austin hospital, Victoria, Australia)

Consultation

Key stakeholders who reviewed this version are:

- Director – Infection Management and Prevention service, Immunology and Rheumatology
- Pharmacist Advanced- Antimicrobial Stewardship
- CHQ Medicines Advisory Committee (CHQMAC) – endorsed xx/12/2023

Key stakeholders who reviewed the previous version are:

- Director – Infection Management and Prevention service, Immunology and Rheumatology
- Director – General Paediatrics

- Director of Pharmacy
- Paediatric Oncology consultant
- Paediatric Emergency Medicine consultant
- General Practice Liaison
- Paediatric Infection Management Fellow (IMPS, QCH)
- Paediatric Medication Education Fellow
- Pharmacist consultant – Informatics
- Nursing educator – Haematology/Oncology
- Pharmacist Advanced - Antimicrobial Stewardship
- Paediatric Immunology and Allergy Specialists (QPIAS)
- Clinical Nurse Lead – Immunology and Allergy service (QPIAS)

References and suggested reading

1. Trubiano JA et al. Impact of an Integrated Antibiotic Allergy Testing Program on Antimicrobial Stewardship: A Multicentre Evaluation. Clin Infect Dis. 2017 Jul 1; 65(1): 166–174.
2. Bourke J, Pavlos R, James I, Phillips E. Improving the Effectiveness of Penicillin Allergy De-labelling. The journal of allergy and clinical immunology In practice 2015; 3(3): 365-34 e1.
3. Arnold A, Sommerfield A, Ramgolam A, Rueter K et al. The role of skin testing and extended antibiotic courses in assessment of children with penicillin allergy: An Australian experience. Journal of Paediatrics and Child Health; 2019; 55: 428–432
4. Therapeutic Guidelines: Antibiotic 2023 Therapeutic Guidelines Ltd. Melbourne

Guideline revision and approval history

Version No.	Modified by	Amendments authorised by	Approved by
1.0 12/11/2020	Infectious Diseases Consultant (IMPS) Immunology and allergy consultants Pharmacist Advanced – Antimicrobial Stewardship	Medicines Advisory Committee (CHQ)	Executive Director Clinical Services QCH
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Accreditation references	National Safety and Quality Health Service Standards (1-8): 3 Preventing and Controlling Healthcare-Associated Infection, 4 Medication Safety

Appendix A: Amoxicillin Drug provocation test (DPT) Protocol (4 days)

Patient name: _____ Date of birth_____ UR number _____

Inform Nursing Team Leader of plan for oral antibiotic challenge.
Provide Family Decision aid to parent/carer and consent for low risk oral challenge (Appendix B)

Before challenge:
Ensure that a single dose of intramuscular Adrenaline (Epinephrine) is charted in ieMR.
Prescribe a single dose of Adrenaline (Epinephrine) (1:1000; 1mg/mL formulation)

- Dose: 0.01 mg/kg/dose (maximum 0.5 mg/dose) INTRAMUSCULARLY in anterolateral middle third of thigh. Repeat doses can be given as required under Medical supervision.
- Indication: If required for anaphylaxis

Ensure that single dose of oral Amoxicillin is charted in ieMR Medication Administration record/ Power chart.

- Prescribe a single dose of Amoxicillin oral 10 mg/kg (maximum 250 mg)
- Indication: Oral amoxicillin challenge (under observation)

Clinical physical examination, including respiratory and skin assessment, to be performed by medical and nursing staff prior to commencement of challenge and documented.

- **At baseline:** Routine set of observations including pulse, oxygen saturation, temperature, blood pressure to be recorded in ieMR.
- **Throughout the oral challenge:** Perform a full set of observations every 30 minutes or if there is any suggestion of development of an allergic reaction. Skin and respiratory assessments should be performed every 15 minutes.
- Patient should be observed for minimum 60 minutes after the oral challenge is administered.
- Repeat a final set of observations at the end of 60 minutes observation period, including pulse, oxygen saturation, temperature, blood pressure and clinical examination (including skin examination and chest auscultation).

Observe for signs suggestive of allergic reaction:

Non serious reactions:	**Serious Reactions:**	
• Development of rash, hives, welts • Abdominal pain, vomiting	• Complaint of tingling or itching of the mouth • Difficulty breathing / noisy breathing • Tachycardia • Hypotension	• Swelling of tongue, swelling/tightness throat • Wheezing persistent cough • Difficult talking and or hoarse voice • Persistent dizziness or collapse • Pale, floppy

If patient complains of tingling or itching of the mouth, difficulty breathing / noisy breathing, hypotension, swelling of tongue, swelling/tightness throat, wheezing persistent cough, difficult talking and or hoarse voice, persistent dizziness or collapse, pale, floppy:

- Give Adrenaline (Epinephrine)
- MET must be called for at the same time.

If no reaction after 1 hour:

- Notify the Treating team (specify contact number _____) that oral challenge and observation is complete.
- Treating team to prescribe oral Amoxicillin for days 2 to 4 of oral challenge (either as inpatient order or on discharge/ outpatient prescription):
  - Prescribe Oral Amoxicillin 10 mg/kg (Maximum 250 mg) once daily for 3 more days

    Medication Instructions:
  - Amoxicillin 500 mg/ 5mL powder for suspension (100 mL bottle – reconstituted prior to discharge)
    - Give _____mL by metric measure once daily for 3 more days as per Doctor's instruction for oral amoxicillin challenge.

    OR
  - Amoxicillin 250 mg capsules (3)
    - Give ONE capsule once daily for 3 more days as per Doctor's instruction for oral amoxicillin challenge.
- Treating team should discuss result with parent/carer and give Family Decision Aid (Appendix B)
- Ensure that parent/carer has received the Oral amoxicillin supplies from Pharmacy before leaving the hospital.
- Treating team, Nursing staff and/or pharmacist provide counselling to parent/carer on discharge.
  - **If any reaction:** Cease antibiotic and present to the Emergency department - Treating Team to be notified immediately.

For QPIAS Drug Allergy clinic low risk oral challenges:

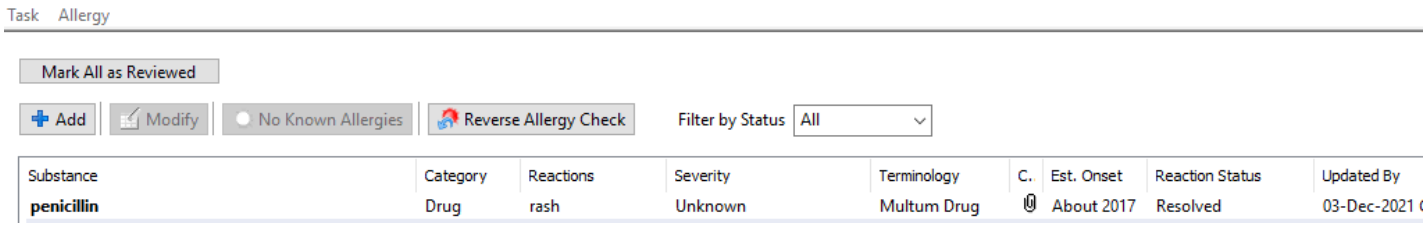
- Amoxicillin 250 mg capsules (3 per pack) and Amoxicillin 500mg/5mL 100mL powder for suspension pre-packs are available for use by QPIAS team in QCH Drug Allergy Outpatient clinic low risk oral amoxicillin allergy challenge as outlined above.
- These pre-packs are exclusively for dispensing by a QPIAS Medical Officer in line with the Poisons regulations from a written prescription.
- The Medical Officer to prescribe and then print oral amoxicillin challenge prescription from ieMR, sign and date both copies, then annotate prescription with "dispensed by _____(name, signature, date)" when medicines are supplied to parent/carer of patient.
- Original prescriptions to be returned to QCH Level 2 pharmacy at the end of each clinic for reconciliation and filing.

On day 5 (after completion of 4 day oral amoxicillin challenge):

Treating team to contact parent/carer to confirm outcome of the 4 day oral amoxicillin challenge.

If no reaction is experienced:

- Treating team to update allergy label in the patient's chart, with a notation of "patient had test dose of amoxicillin with no reaction on (date)"
- Utilise "resolve" allergy functionality in ieMR to ensure allergy label removed – the allergy will now appear with "resolved" in Reaction status column.



- Notify Pharmacy of the successful allergy de-labelling and request for iPharmacy allergy history to be updated by emailing Antibiotics_CHQ@health.qld.gov.au.
- Treating team should change antibiotic regimen if warranted
- Treating team to provide GP Letter detailing outcome of Amoxicillin Drug provocation test to family.

Allergy documentation in myHealthRecord:

Refer to: https://www.myhealthrecord.gov.au/for-you-your-family/howtos/add-or-update-personal-information

To add or modify an allergy or adverse reaction summary:

1. Log in to your My Health Record through myGov.
2. Select on the 'Documents' tab and select 'Key Information I've Added'.
3. Select 'Personal Health Summary'.
4. Select 'Add Allergy or Adverse Reaction'.
5. Enter the substance or agent and enter the reaction, then Select 'Save'.

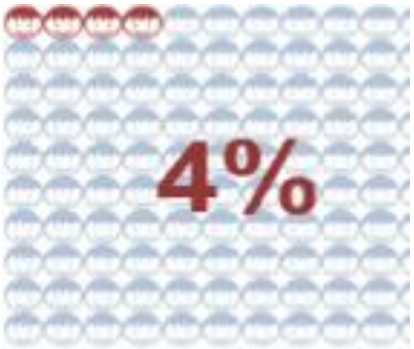
Appendix B: Family decision aid

Your doctor has determined your child is eligible to take amoxicillin to see if they are allergic to it during their visit today. Here is some important information to consider:

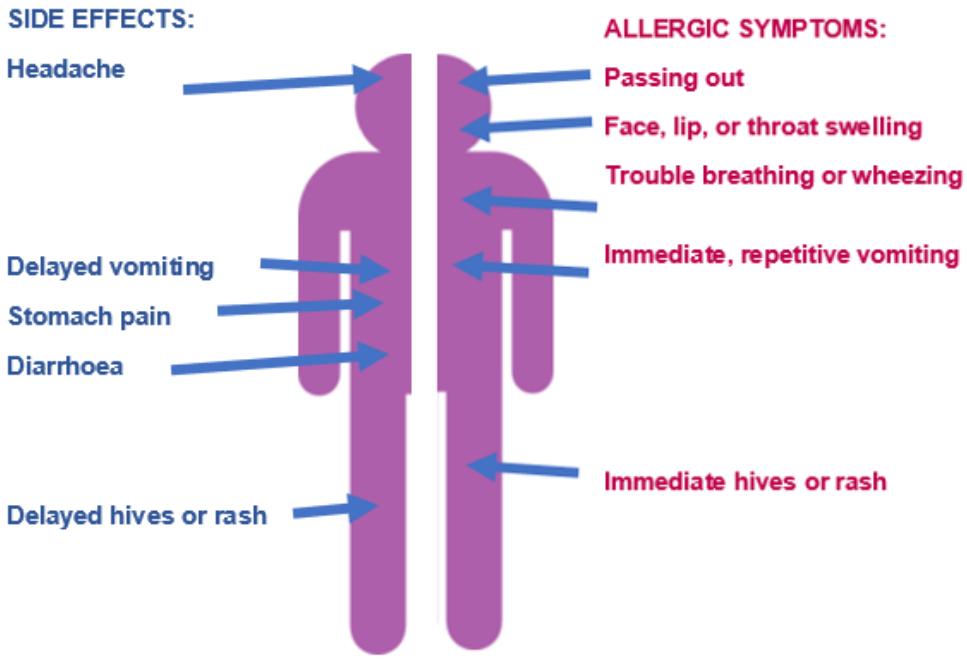
In 100 children who report a penicillin/ amoxicillin allergy:

One (1) will have an allergic reaction after taking a penicillin antibiotic.

Four (4) will have a rash that is not from an allergy and 96 will not have any reaction.



Your child's reaction was likely NOT an allergy.
It was probably a side effect or NOT due to the medicine.



What are the benefits of testing my child for an allergy to this medicine?

- Your child will be able to take penicillin/ amoxicillin to treat common infections
- This medicine costs less money
- This medicine treats lots of infections
- This medicine has less severe side effects
- This medicine allows more options for treating common infections

Acknowledgement: Children's Hospital Colorado Clinical Pathway – Penicillin allergy de-labelling

Appendix C: Suggested Management of Patients reporting Hypersensitivity to Penicillins…

Therapeutic Guidelines

Suggested management of patients reporting hypersensitivity to penicillins in whom a beta-lactam antibiotic is the preferred drug

Penicillin hypersensitivity reported by a patient in whom a beta-lactam antibiotic is the preferred drug

History of **immediate** (IgE-mediated) penicillin hypersensitivity (typically occurs within 1 to 2 hours of drug exposure)

Immediate severe penicillin hypersensitivity (eg extensive urticaria, compromised airway, angioedema, hypotension, collapse or anaphylaxis)

Avoid penicillins and cephalosporins [NB1].
Safe to administer a non–beta-lactam antibiotic or aztreonam.
Can consider a carbapenem [NB2].

If a penicillin is essential, perform desensitisation.
In a non-urgent situation, consider specific allergy testing and drug provocation under specialist supervision (where such testing is available).

Immediate nonsevere penicillin hypersensitivity (eg mild urticaria or immediate rash)

Avoid penicillins.
Safe to administer most cephalosporins. Avoid cefalexin and cefaclor in patients with amoxicillin or ampicillin allergy.
Safe to administer a carbapenem [NB2] or aztreonam.

If a penicillin is essential, perform desensitisation.
In a non-urgent situation, consider specific allergy testing and drug provocation under specialist supervision (where such testing is available).

History of **delayed** (T-cell mediated) penicillin hypersensitivity (typically occurs days after starting treatment, but can occur more rapidly on rechallenge)

Delayed severe penicillin hypersensitivity (eg severe cutaneous adverse reaction [NB3] or significant organ involvement such as acute interstitial nephritis)

Avoid penicillins and cephalosporins [NB4].
Safe to administer a non–beta-lactam antibiotic or aztreonam.
Can consider a carbapenem [NB2].

Avoid desensitisation in patients with a history of delayed severe hypersensitivity because further drug exposure can be fatal.

Delayed nonsevere penicillin hypersensitivity (usually a maculopapular rash or benign childhood rash; **not** a severe cutaneous adverse reaction [NB3] and no significant organ involvement)

Avoid penicillins. However, in a non-urgent situation and under specialist guidance, consider a single dose of a penicillin followed by a prolonged (5 to 7 day) provocation test.
Safe to administer a cephalosporin in patients with a history of a mild reaction or a reaction that occurred in the distant past [NB5].
Safe to administer a carbapenem or aztreonam.

History of **penicillin AND cephalosporin** immune-mediated hypersensitivity

Avoid all beta lactams, except for aztreonam [NB6].

Refer to specialised antibiotic allergy testing centre.

History of **non-immune-mediated adverse effect** (eg gastrointestinal intolerance)

Safe to administer any beta lactam.

Remove penicillin allergy from the patient's medical record or annotate the true nature of the reaction.

Penicillins include: phenoxymethylpenicillin, benzylpenicillin, amoxicillin, ampicillin, dicloxacillin, flucloxacillin, piperacillin

Cephalosporins include: cefalexin, cefuroxime, cefaclor, cefazolin, cefalotin, cefoxitin, ceftriaxone, cefotaxime, ceftazidime, cefepime

Carbapenems include: imipenem, meropenem, ertapenem

NB1: In a critical situation, a cephalosporin can be considered in this group after undertaking a risk–benefit analysis and assessment of potential side-chain cross-reactivity. Seek expert advice.

NB2: In patients with penicillin hypersensitivity, the rate of immune-mediated cross-reactivity with carbapenems is approximately 1%; therefore, carbapenems can be considered in supervised settings. However, in patients with a history of a severe cutaneous adverse reaction (eg drug rash with eosinophilia and systemic symptoms [DRESS], Stevens–Johnson syndrome / toxic epidermal necrolysis [SJS/TEN], acute generalised exanthematous pustulosis [AGEP]), consider a carbapenem only in a critical situation when there are limited treatment options.

NB3: For example DRESS, SJS/TEN, AGEP.

NB4: There is limited evidence on the safety of cephalosporins in patients with a history of penicillin-associated acute interstitial nephritis (AIN). In a critical situation, directed therapy with a cephalosporin can be considered.

NB5: In patients who have had a **recent** reaction, consider avoiding cephalosporins with the same or similar R1 side-chain as the implicated penicillin.

NB6: However, avoid aztreonam in patients hypersensitive to ceftazidime; these drugs have the same R1 side-chain, so there is a risk of cross-reactivity.

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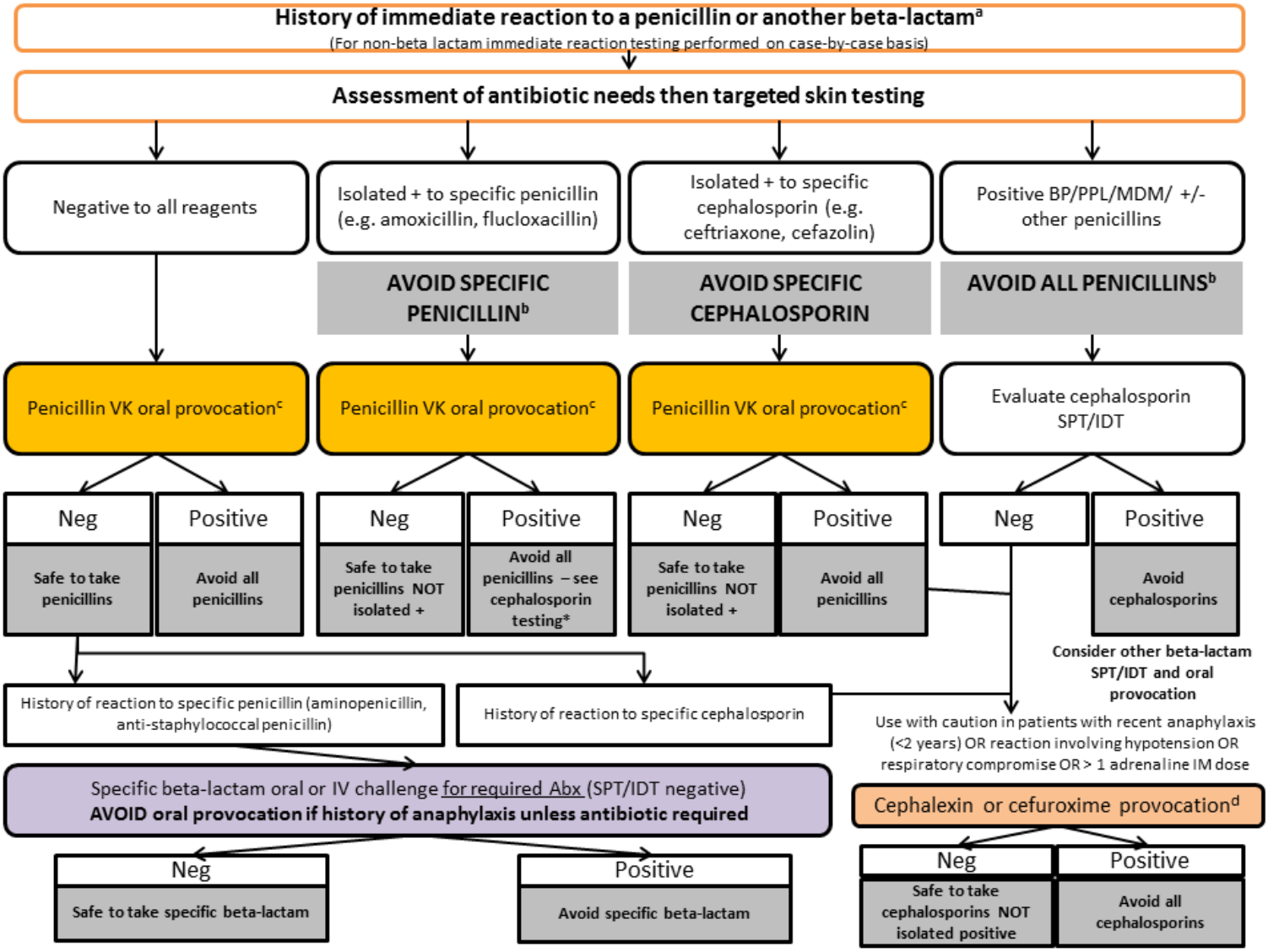
Appendix D: Antibiotic allergy testing algorithm

(For use by Immunology/Allergy Team only)

Antibiotic allergy testing for patients with a history of immediate of unknown hypersensitivity



Adapted from Trubiano et al and Bourke et al (with permission)[1, 2].

Abbreviations: SPT, skin prick testing; IDT, intradermal testing; BP, penicillin G; PPL, Diameter major determinant; MDM, minor determinant mix

Foot notes:

a If history "unknown" then patient should receive testing as per immediate hypersensitivity protocol, with the addition of a prolonged oral antibiotic challenge (4-day). Recent paediatric research has shown that there is very small chance (4.5%) that non reactors could develop a delayed rash within 4 days of antibiotic challenge but not anaphylaxis.

b Penicillin – penicillin V/G, amoxicillin, flucloxacillin, oxacillin, dicloxacillin, piperacillin-tazobactam

c If amoxicillin required acutely, 2-step should be performed (20% of dose initially and then remaining 80% of dose after 20 minutes).

Appendix D: Antibiotic allergy testing algorithm (continued)

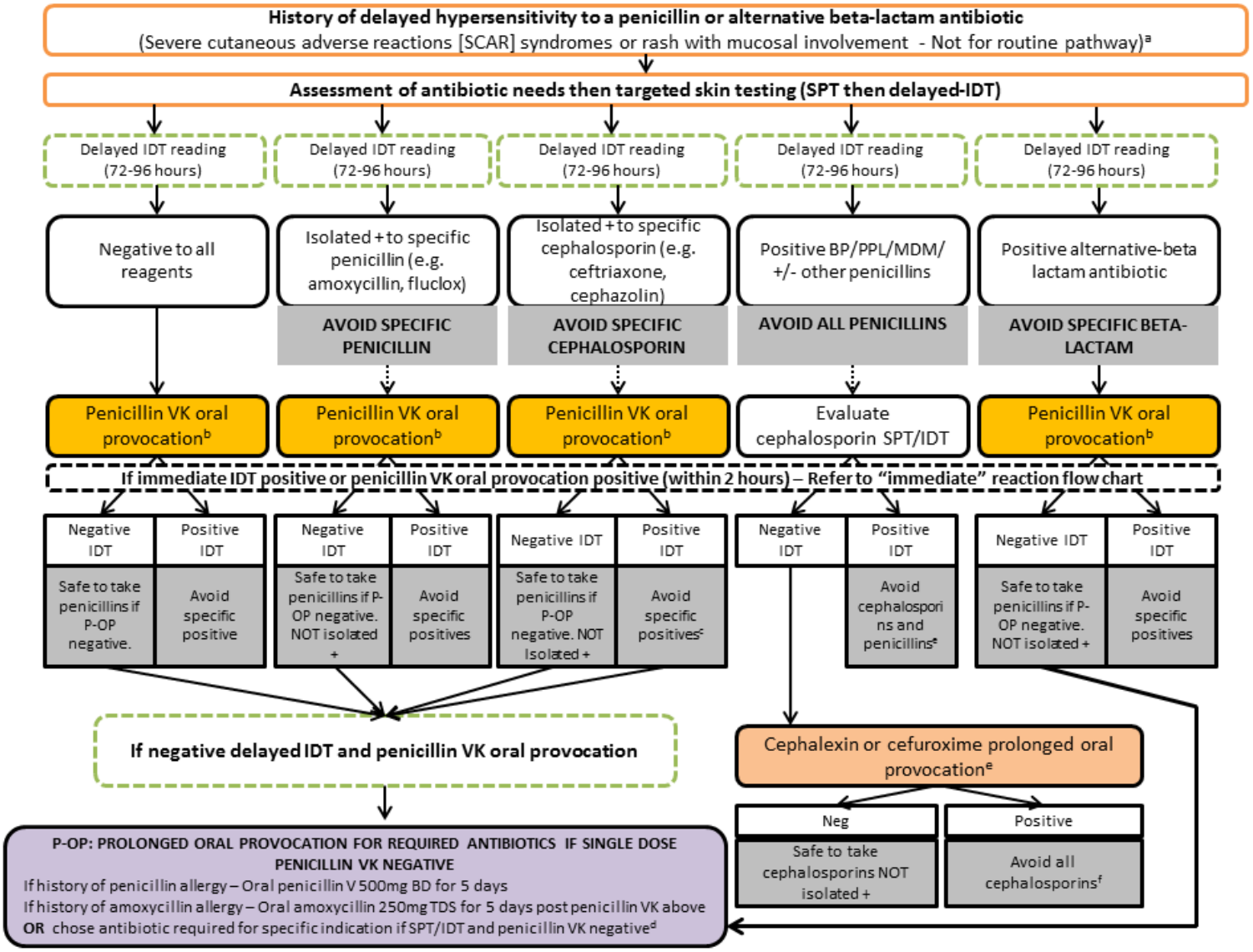
Foot notes (continued):
d If patient has a history of recurrent pulmonary infections then cefuroxime would be preferred oral provocation. If recurrent urinary tract infections then cefalexin challenge (if negative aminopenicillin SPT/IDT). If positive IDT to ceftriaxone or cefepime avoid cefuroxime challenge.

Note[1]: For oral provocation outside penicillin VK, consider 2-step oral provocation if challenging a patient with a history of anaphylaxis.

Note[2]: For patients with an unspecified penicillin allergy that occurred prior to the advent of amoxicillin release in Australia (1972), penicillin V challenge only performed. If penicillin allergy unspecified occurred post amoxicillin release, patient will undergo sequential penicillin V then amoxicillin challenge.

Appendix D: Antibiotic allergy testing algorithm (continued)

Antibiotic allergy testing algorithm (<u>For use by Immunology/Allergy Team only</u>) (continued):
Antibiotic allergy testing for patients with a history of delayed hypersensitivity



Adapted from Trubiano et al and Bourke et al (with permission)[1, 2].

Abbreviations: OP, oral challenge/provocation; P-OP, prolonged oral provocation; IDT, intradermal testing; SPT, skin prick testing; SCAR, severe cutaneous adverse drug reactions; BP, penicillin G; PPL, Diameter major determinant; MDM, minor determinant mixture.

Note[2,3]: If a patient has a history of a beta-lactam allergy and is known to tolerate alternative beta-lactams, prolonged oral provocations (4 days) can be performed following negative SPT/IDT outside of demonstrated schematic, tailored to known infection history and current/future antibiotic requirements. Recent paediatric research has shown that there is very small chance (4.5%) that non reactors could develop a delayed rash within 4 days of antibiotic challenge but not anaphylaxis.

Note[2]: In patients with more than 1 positive delayed IDT to a penicillin and cephalosporin that don't share identical/similar R1 side chain then recommended to avoid penicillins and cephalosporins.

Note[3]: In patients with positive delayed IDTs (>1) to beta-lactams that share the same R1 side chain (e.g. cefuroxime/ceftriaxone, cefepime/ceftriaxone, aztreonam/ceftazidime, cefalothin/penicillin G), oral challenges can be undertaken to beta-lactams that are dissimilar in R1 structure.

Foot notes:

[a] If history of drug reaction with eosinophilia and systemic symptoms (DRESS), fixed drug eruption (FDE) or acute generalised exanthematous pustulosis (AGEP) then delayed intradermal and oral provocations as required. If Steven Johnson syndrome (SJS) or toxic epidermal necrolysis (TEN) patch testing of implicated antimicrobials applied. Antibiotic provocations following testing in SCAR tailored to specific patient antibiotic requirements.

[b] If history of mild-moderate delayed hypersensitivity (not SCAR), single dose oral provocation may be performed directly post negative SPT/IDT, followed by 5-day provocation. If severe hypersensitivity or SCAR then only perform oral provocations post delayed IDT readings.

[c] If patient tolerates penicillins and aminopenicillins and isolated positive to a cephalosporin can consider further oral cephalosporin provocations with antibiotics that differ in R1/R2 side chains.

[d] Antibiotic oral duration for 4 days at lowest therapeutic dose. No intravenous or intramuscular challenges. In patients with a history of non-SCAR allergy to sulphonamide and trimethoprim-sulfamethoxazole (TMP-SMX) required, one single strength TMP-SMX challenge recommended, without prior skin testing. In patients with other non-beta lactam delayed allergy phenotypes a combination of delayed IDT, patch testing and oral provocations individualised for patient antibiotic requirements. For patients with positive isolated cephalosporin IDT or oral provocation, subsequent IDT/OC can be performed to cephalosporins with different R1/R2 side chains.

[e] Provide recommendations for antibiotic usage outside of penicillins and cephalosporins.

[f] Cefalexin

- Less than or equal to 12 kg: Give 125 mg orally twice daily for 4 days;
- More than or equal to 12 kg: Give 250 mg orally twice daily) for 4 days.
- If patient was positive to aminopenicillin on IDT or oral challenge then avoid challenge with amino-cephalosporin (e.g. cefalexin, cefaclor).