ASCIA Consensus Statement for the assessment of patients with suspected penicillin allergy

This document has been developed by the ASCIA Drug Allergy Committee and revised by an expert panel in February 2020, to assist registered medical practitioners with an interest and experience in the management of immediate drug allergy to penicillin antibiotics, and to determine which patients require skin testing (ST) prior to provocation testing.

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Background

Allergy to penicillins is commonly reported in the community and in hospitalised patients, however, the majority will be able to tolerate penicillins after appropriate assessment. Dismissing a penicillin allergy (also known as “de-labelling”) after adequate assessment prevents the unnecessary restriction of antibiotic options in patients who are not truly allergic and improves antimicrobial stewardship. Penicillin allergy de-labelling has been shown to reduce patient morbidity and mortality, microbial resistance to antibiotics and the economic costs associated with prolonged hospital stays (Solenksy, 2014). On the other hand, verifying true penicillin allergy in patients enables appropriate documentation, precautionary measures and increases the safe use of antibiotics.

Penicillins and cephalosporins are the two major classes of beta-lactam (BL) antibiotics, whereas carbapenems, monobactams and clavams are the three minor classes. All contain a shared beta-lactam ring (see Appendices 2 and 3). In penicillin allergies, the majority of subjects who have allergic reactions have Immunoglobulin E (IgE) that recognises the side chains (for example the amino group of amino-penicillins) that are attached to the BL ring, whilst people with penicillin allergic IgE directed against the beta-lactam ring are rare.

IgE mediated immediate reactions manifest with one or more of the following; urticaria, angioedema, rhinitis, conjunctivitis, bronchospasm, significant gastrointestinal symptoms (nausea, vomiting, diarrhea, abdominal pain), anaphylaxis and anaphylactic shock. This typically occurs within one and up to six hours after the last drug administration. These reactions commonly cause a rise in serum mast cell tryptase.

Penicillin allergy testing should always be performed in a setting where skills and equipment to treat anaphylaxis are available.

The management algorithms provided here are based on a review of the current literature (Bourke, Pavlos, James, & Phillips, 2015; Brockow, et al., 2013; Castells, Khan, & Phillips, 2019; Caubet et al., 2011, Testi et al., 2010; Torres et al., 2001; Torres et al., 2003;) and expert consensus.

If allergy to a particular antibiotic is considered highly likely (in the absence of testing) or is confirmed by testing and in a situation where the antibiotic is strongly indicated to treat an episode of infection, desensitisation may allow temporary tolerance of the antibiotic. This requires an appropriate validated desensitisation protocol, administered in a hospital setting with input and supervision from a clinical immunology/drug allergy specialist.

It is possible that a person may develop an allergy to penicillin at any time after negative testing. The patient should be advised that a negative penicillin allergy test is not conclusive for life, and they may develop a new penicillin allergy.

The pre-clinic questionnaire is an editable template provided to facilitate assessment and the triage of patients referred to a drug allergy clinic. It is available at:

www.allergy.org.au/members/ascia-drug-allergy-pre-clinic-information-template

Penicillin Serum Specific IgE testing

Specific IgE (sIgE) testing has limited diagnostic utility. It may only be useful in patients with a very recent IgE mediated reaction.

If penicillin sIgE tests are performed within three months of a systemic reaction, 30-50% are positive (Blanca et al., 2001). Sensitivity is much lower when reactions are in the more distant past, and specificity is also lower when the pre-test probability of penicillin allergy is relatively low, therefore sIgE testing is not useful for screening in a low-risk population.

Notably a **negative sIgE result does not exclude penicillin allergy** and it will be necessary to proceed with further testing (Parameters JTFOP, American Academy of Allergy AAI, Joint Council of Allergy AAI, 2010).

Mast cell tryptase

Acute elevation of mast cell serum tryptase indicates degranulation of mast cells, which can be due to an IgE mediated reaction, for example anaphylaxis due to penicillins. It should be measured within one to four hours after a suspected reaction as the level will gradually decrease to normal levels after six to 24 hours. Therefore, serum mast cell tryptase taken in a timely manner can be helpful in the diagnostic assessment of contemporaneous adverse drug reactions (ADRs) to drugs. A significant increase in mast cell tryptase during the reaction can be calculated using the formula; [1.2 x baseline tryptase + 2mcg/mL] (Baretto et al., 2017). A significant increase may be present even below the upper normal value of 11.4 mcg/mL.

Scope of Document

The following issues are beyond the scope of this document:

- Severe cutaneous adverse reactions (SCAR) is not addressed in this document.
- Minimal reference to cephalosporins has been included. Management and diagnosis of cephalosporin allergy is addressed in a separate document.

Prioritisations

Penicillin allergy testing should be prioritised in the following patient groups:

- Patients who have frequent infections with requirement for antibiotics several times per year.
- Patients who have infections for which penicillins are the most appropriate antibiotic.
- Patients who are allergic or intolerant to other antibiotics in addition to penicillins in whom the choice is narrowing.
- Patients with primary or secondary (acquired) immunodeficiency, patients on significant immunosuppressive therapy, patients with bronchiectasis or other risk factors for infections requiring frequent antibiotic use.
- Patients who are undergoing splenectomy or asplenia.

Skin Testing Protocol

General remarks for low and high pre-test probability

- ASCIA information regarding the technical aspects of skin testing is available from the ASCIA website: www.allergy.org.au/health-professionals/papers/skin-prick-testing
- Solutions used for skin prick testing (SPT) and intradermal testing (IDT) should not exceed non-irritant concentrations (see Table 1) (Brockow et al., 2013).
- Histamine is to be used as a positive control for skin prick testing, and morphine for IDT. Relevant negative test controls must be included.
- We recommend the testing panel should include as a minimum benzylpenicillin BP, amoxicillin (AMX), and the culprit penicillin, if available. The Diater® PPL **(**benzylpenicilloyl-polylysine) and Diater® MDM (minor determinant mixture) should also be included in the testing panel if they can be sourced. The panel can be further supplemented with ampicillin (AMP), augmentin, flucloxacillin (FLX)**,** and Diater Clavulanate acid.
- If the culprit penicillin is not available in parenteral formulation, IDT should not be performed. There is currently no scientific evidence supporting the use of solutions of oral preparations for IDT or SPT.
- Dilution of drugs for SPT is unnecessary as the risk of anaphylaxis from SPT is very low (Mirakian et al., 2015).
- IDT however can precipitate anaphylaxis (Torres et al., 2001). Therefore, in those with high pre-test probability of IgE-mediated penicillin allergy, commencing IDT at 1:10 or 1:100 dilution is recommended**.**
- If you choose to include cephalosporins in your testing panel, beware of cross reactivity between cephalexin, cefaclor and AMP due to an identical R_1 side chains.
- Furthermore, AMX has a similar but not identical R_1 side chain to ampicillin, cephalexin and cefaclor. The rate of clinically relevant cross-reactivity is currently unknown and testing of the patient by drug challenge to determine tolerance is recommended (Romano & Caubet, 2014; Parameters JTFOP, American Academy of Allergy AAI, Joint Council of Allergy AAI, 2010).
- To assess non-immediate penicillin hypersensitivity the IDT protocol may be used with delayed readings at 48-72 hours.
- Testing is more likely to be positive if performed within 6-12 months of the reaction (Patriarca, Schiavino, Nucera, & Milani, 1996).

Table 1: Non-irritating test concentrations for penicillin (Brockow et al., 2013; Torres et al., 2003)

Drug	SPT	IDT
Diater PPL®	Neat	Neat
Diater MDM®	Neat	Neat
Benzylpenicillin (Penicillin G)	10,000 UI (6mg/mL)	10,000 UI (6mg/mL)
Amoxycillin	20mg/mL	20mg/mL
Ampicillin	20mg/mL	20mg/mL
Diater Clavulanate®	Neat	5mg/mL, 20mg/mL
Flucloxacillin*	2mg/mL	2mg/mL

High Pre-test Probability

True IgE-mediated penicillin allergy holds the risk for anaphylaxis or death. Testing algorithms may need to be individualised. Patients with high risk penicillin allergy (refer to Appendix 1) should be referred to a specialised drug allergy centre for further testing.

In people with high pre-test probability of IgE-mediated penicillin allergy, the aim is to either confirm the culprit penicillin allergy and/or find an alternative penicillin antibiotic.

- Use of SPT, IDT and DPT must be assessed against the clinical need to confirm a diagnosis of antibiotic allergy, the risk of a reaction and effect on clinical management.
- The choice of ideal alternative antibiotics is driven by many factors including clinical need, pharmacological and antimicrobial properties of penicillin and potential cross-reactivity between antibiotics, in multidisciplinary consultation with infectious disease and treating team.
- In the case of a severe reaction to penicillin, it may be prudent to initially perform IDT with lower concentrations of the reagents. Generally, reagents are diluted by 1:10, 1:100 or 1:1000 (Torres et al., 2003). IDT is performed with gradually increasing concentrations until there is the appearance of a positive skin response or until the maximum concentration is reached.

Drug Provocation Testing

If DPT is to be performed, then a graded challenge is recommended with the choice of penicillin dependent on the clinical indications for testing.

Graded challenges can be performed as a three-dose challenge (1/100, 1/10, full dose) or two-dose challenge (1/10, full dose). In children, the daily treatment dose should not be exceeded. The recommended time interval between doses is a minimum of 30 minutes (up to 90 minutes) and patient should be observed for two hours after the last dose. Refer to Appendix 3.

When the culprit penicillin is unknown (e.g. distant reaction), use AMX for the challenge. DPT with Phenoxymethylpenicillin (penicillin VK) alone does not rule out AMX allergy and vice versa. However, DPT with AMX can assess both IgE directed against beta-lactam ring and the R_1 AMX side chain. It is reasonable to perform DPT with AMX, particularly since AMX is the more commonly used antibiotic in the community, except where penicillin VK is the known offending drug.

Performing DPT with the culprit drug should be considered if the culprit drug is known and would be the most effective way of excluding penicillin allergy. Challenge protocol:

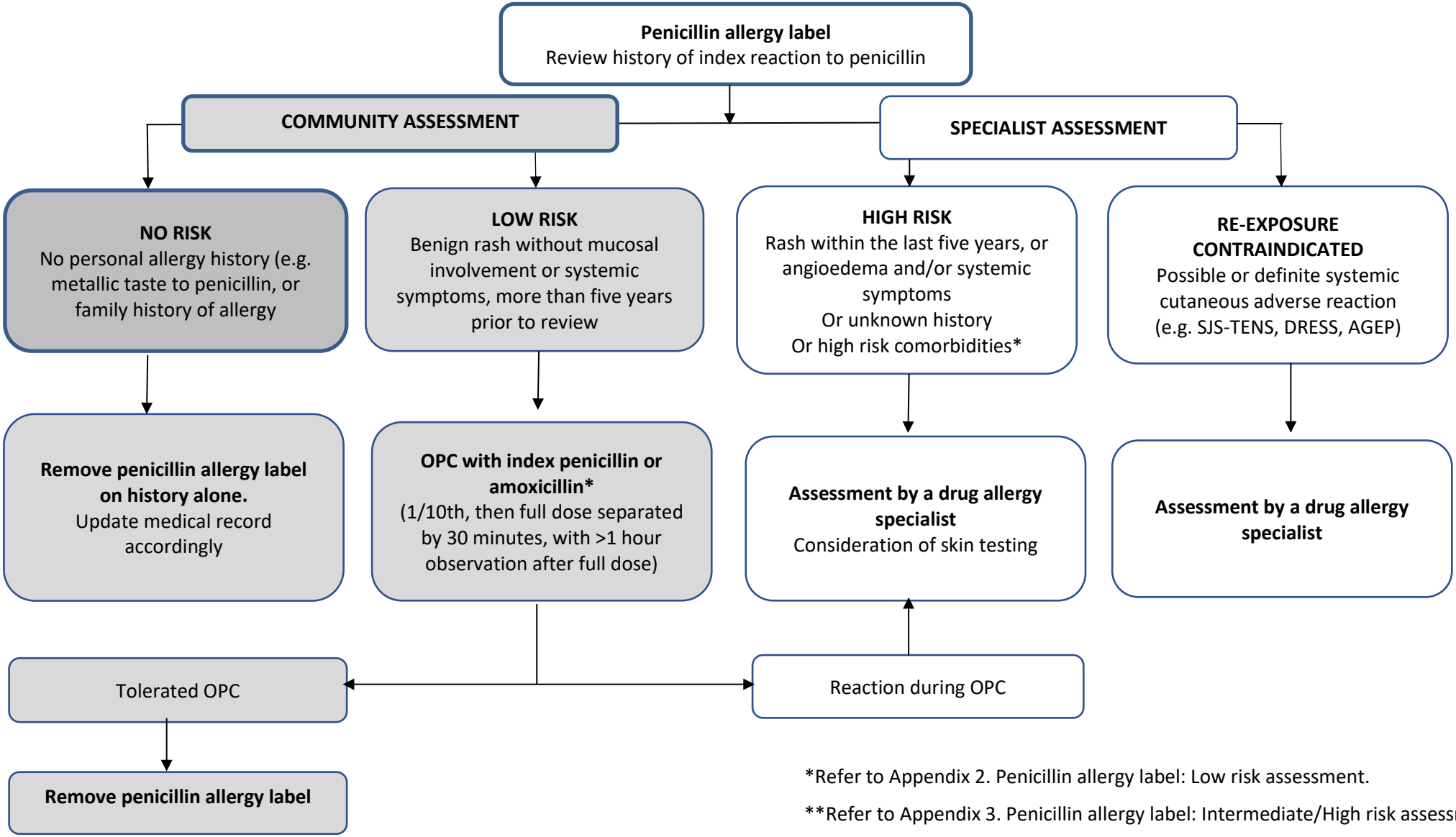
- IV graded challenges can be performed as a three-dose challenge (1/100, 1/10, full dose) of full treatment dose or two-dose challenge (1/10, full dose).
- Low risk patients can be oral tested as a one or two dose challenge.
- In children, the daily treatment dose should not be exceeded.
- The recommended time interval between doses is a minimum of 30 minutes, and the patient should be observed for a minimum of one hour after the last dose.
- A longer treatment course (three to seven days) of penicillin-based antibiotic may be required to adequately exclude delayed-type penicillin hypersensitivity (Hjortlund, Mortz, Skov, & Bindslev-Jensen, 2013; Mirakian et al., 2015; Sagar, & Katelaris, 2013).

In order to administer a fractionated dose (1:10, 1:100) a liquid (suspension) form of amoxicillin or phenoxymethyl penicillin is commonly used. The standard preparation is 100mL at a concentration of 250mg/5mL and daily dosing should be age appropriate. Fractionated doses are 0.1mL, 1.0mL, and 10mL. After the first set of provocation doses (11mL or 11.1mL), it is convenient to provide the patient with the remainder of the bottle which is sufficient for at least three days. Refer to Appendix 1.

In the context of drug allergy, a benign rash is a transient morbilliform or maculopapular rash that may be mildly pruritic and is not associated with other symptoms. Features indicating a more serious reaction include immediate onset urticaria, erythroderma, and constitutional symptoms such as fever, sore throat, malaise, arthralgia, lymphadenopathy, cough with facial or mucous membrane involvement, skin tenderness or blistering such as purpura or desquamation.

The ASCIA Action Plan for Drug (Medication) Allergy, and ASCIA Record for Drug (Medication) Allergy are available on the ASCIA website at www.allergy.org.au/hp/drug-allergy/ascia-action-plan-drug-medication-allergy

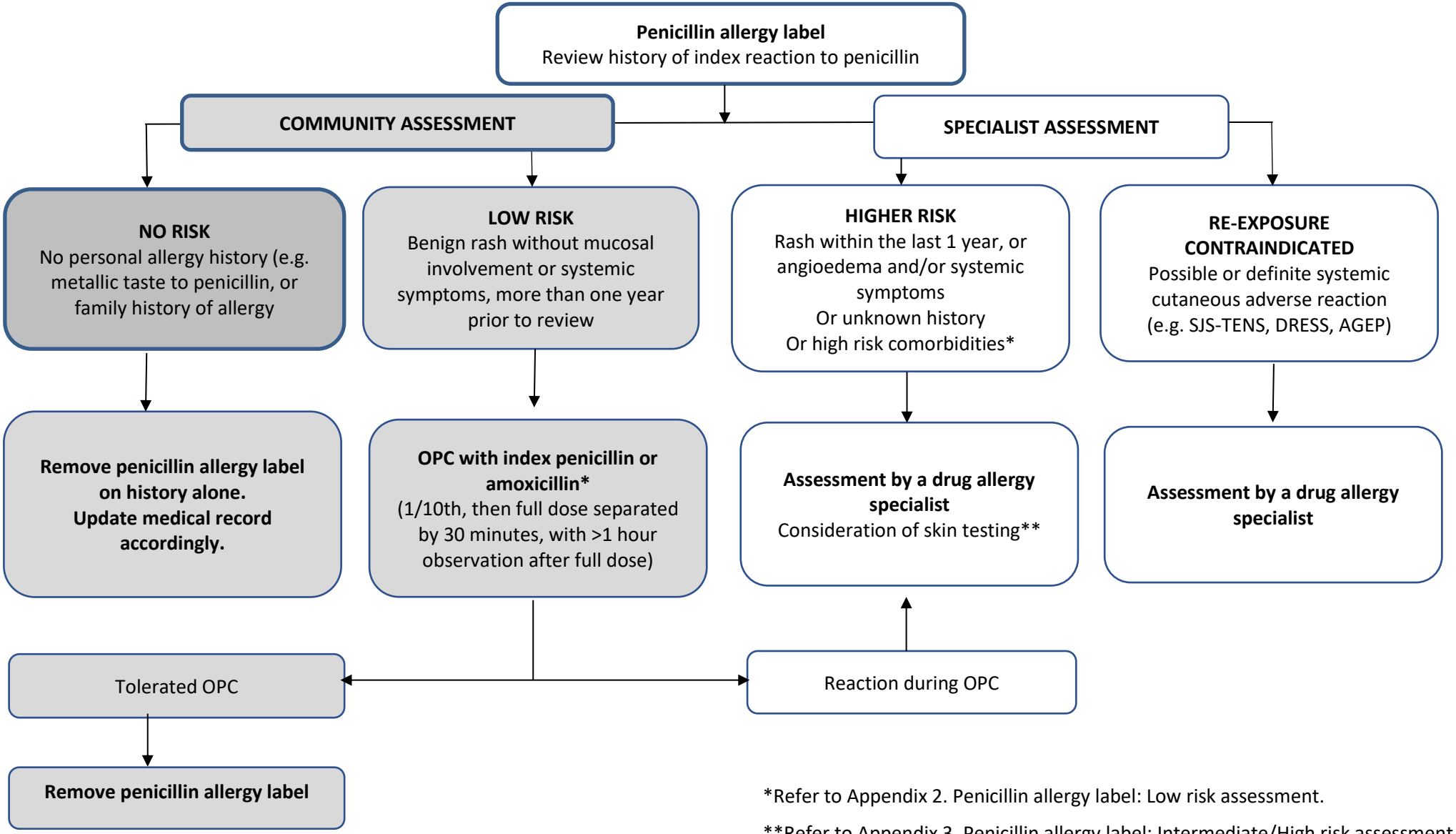
Appendix 1. Penicillin allergy label: Risk stratification plan for adults



*Refer to Appendix 2. Penicillin allergy label: Low risk assessment.

**Refer to Appendix 3. Penicillin allergy label: Intermediate/High risk assessment.

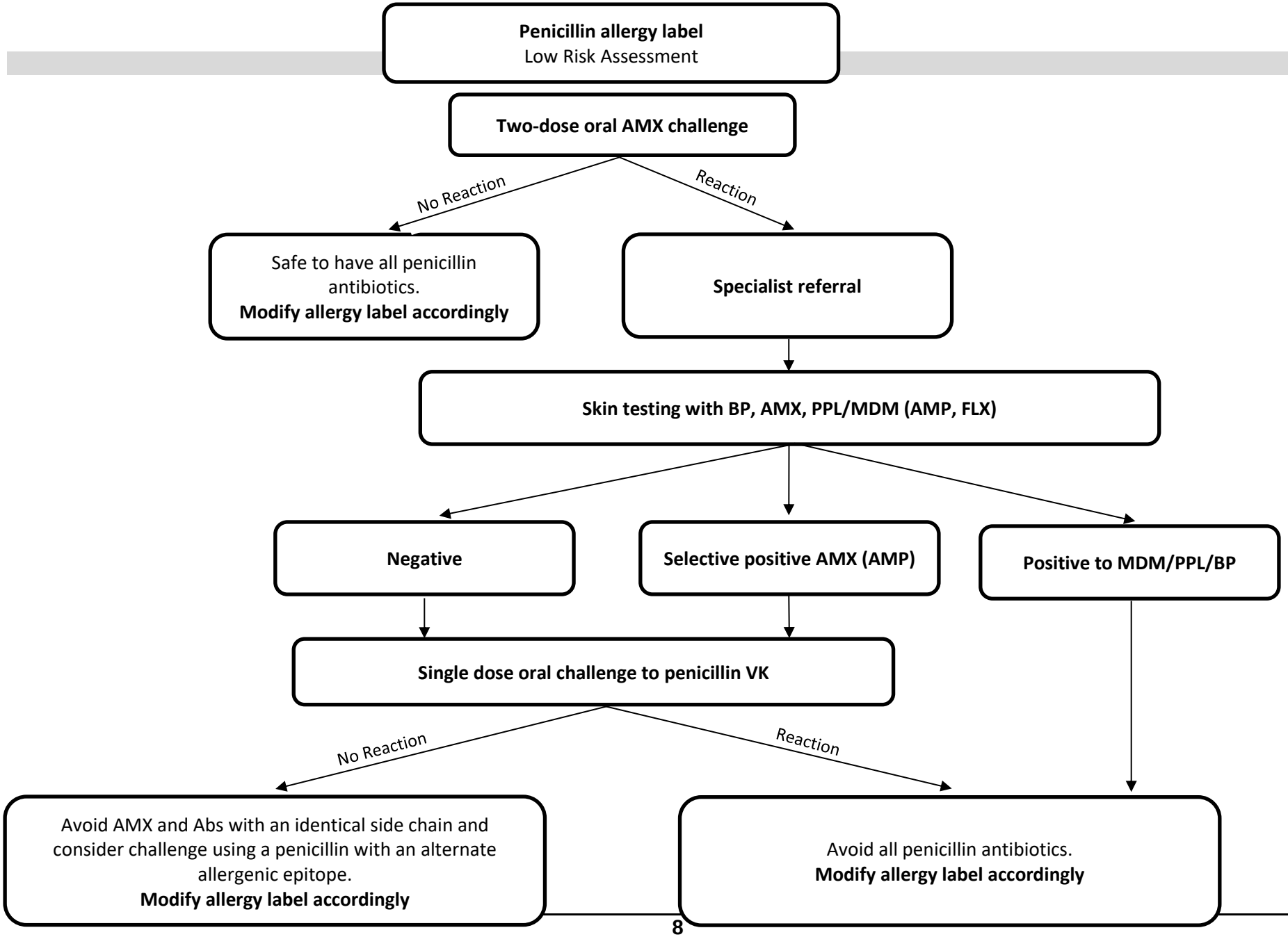
Appendix 2. Penicillin allergy label: Risk stratification plan for children 16 years old and under



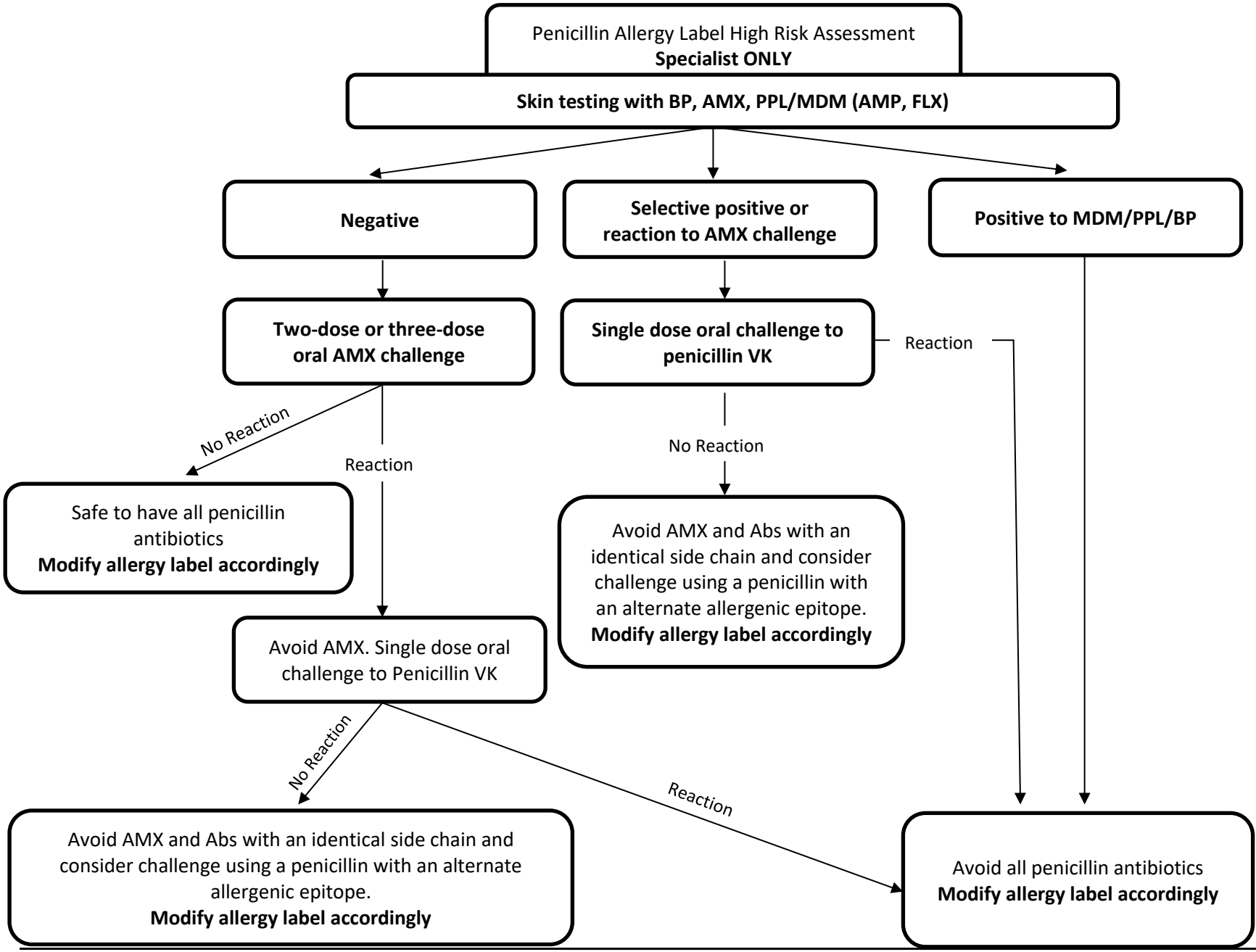
*Refer to Appendix 2. Penicillin allergy label: Low risk assessment.

**Refer to Appendix 3. Penicillin allergy label: Intermediate/High risk assessment.

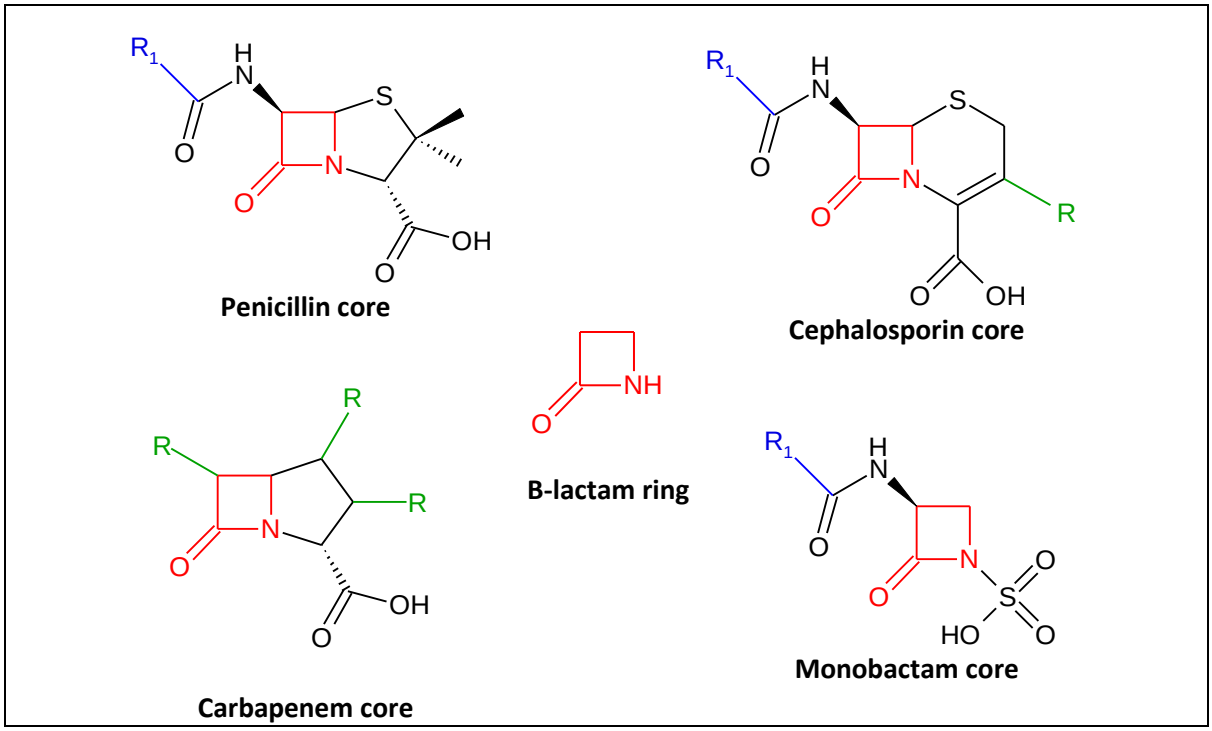
Appendix 3: Penicillin allergy label low risk assessment



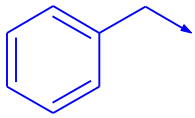
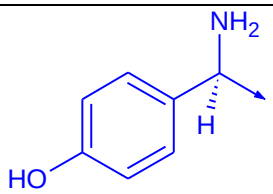
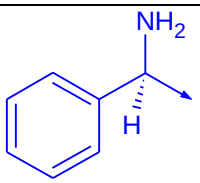
Appendix 4: Penicillin allergy label high risk assessment



Appendix 5: Core structures



Appendix 6: Penicillins with a R_1 side chain

Penicillins with a R_1 side chain similar or identical to other β-lactam antibiotics		
 **Penicillin G (benylpenicillin)**	 **Amoxicillin**	 **Ampicillin**
Cefalotin* **Cefoxitin***	Cefaclor* Cephalexin*	**Cefaclor** **Cephalexin**

*similar side chains; **bold** – identical side chains

Penicillins with a unique R_1 side chain	B-lactam antibiotics with R_1 side chain not identical/similar to a penicillin or without a R_1 side chain	
Penicillin V **(phenoxymethylpenicillin)** **Dicloxacillin** **Flucloxacillin** **Piperacillin (tazocin®)** **Ticarcillin (timentin®)**	**Cephalosporins** Cefepime Cefotaxime Cephazolin Ceftaroline Ceftazidime Ceftriaxone Cefuroxime	**Carbapenems** Ertapenem Imipenem Meropenem **Monobactams** Aztreonam

Note: Only β-lactam antibiotics registered in Australia and New Zealand as at 20/12/2015 according to TGA www.tga.gov.au and Medsafe www.medsafe.govt.nz (respectively) are presented.

References

Baretto, R. L., Beck, S., Heslegrave, J., Melchior, C., Mohamed, O., Ekbote, A., Huissoon, A. P., & Krishna, M. T. (2017). Validation of international consensus equation for acute serum total tryptase in mast cell activation: A perioperative perspective. *Allergy*, 72(12), 2031-2034. DOI: 10.1111/all.13226 https://www.ncbi.nlm.nih.gov/pubmed/28609557

Blanca, M., Mayorga, C., Torres, M. J., Reche, M., Moya, M. C., Rodriguez, J. L., Romano, A., Juarez, C.(2001). Clinical evaluation of Pharmacia CAP System RAST FEIA amoxicilloyl and benzylpenicilloyl in patients with penicillin allergy. *Allergy*, 56(9), 862-870. DOI: 10.1034/j.1398-9995.2001.00995.x https://www.ncbi.nlm.nih.gov/pubmed/11551251

Bourke, J., Pavlos, R., James, I., Phillips, E. (2015). Improving the Effectiveness of Penicillin Allergy De-labelling. *J Allergy Clin Immunol Pract*, 3(3), 365-374. DOI: 10.1016/j.jaip.2014.11.002 https://www.ncbi.nlm.nih.gov/pubmed/25609352

Brockow, K., Garvey, L. H., Aberer, W., Atanaskovic-Markovic, M., Barbaud, A., Bilo, M.B... Terreehorst, I. (2013). Skin test concentrations for systemically administered drugs -- an ENDA/EAACI Drug Allergy Interest Group position paper. *Allergy*; 68(6), 702-12. DOI: 10.1111/all.12142 https://www.ncbi.nlm.nih.gov/pubmed/23617635

Castells, M., Khan, D. A., & Phillips, E. J. (2019). Penicillin Allergy. *N Engl J Med*, 381(24), 2338-2351. DOI: 10.1056/NEJMra1807761 https://www.nejm.org/doi/full/10.1056/NEJMra1807761?url_ver=Z39.88-2003&rfr_id=ori%3Arid%3Acrossref.org&rfr_dat=cr_pub%3Dpubmed

Caubet, J. C., Kaiser, L., Lemaitre, B., Fellay, B., Gervaix, A., Eigenmann, P. A. (2011). The role of penicillin in benign skin rashes in childhood: a prospective study based on drug rechallenge. *J Allergy Clin Immunol*; 127(1), 218-222. DOI: 10.1016/j.jaci.2010.08.025 https://www.ncbi.nlm.nih.gov/pubmed/21035175

Hjortlund, J., Mortz, C. G., Skov, P. S., & Bindslev-Jensen, C. (2013). Diagnosis of penicillin allergy revisited: the value of case history, skin testing, specific IgE and prolonged challenge. *Allergy*, 68(8), 1057–1064. DOI: 10.1111/all.12195 https://www.ncbi.nlm.nih.gov/pubmed/23889703

Mirakian, R, Leech SC, Krishna MT, Richter AG, Huber PAJ, Farooque S, Khan N, Pirmohamed M, Clark AT, & Nasser SM. (2015). Management of allergy to penicillins and other beta-lactams. *Clin Exp Allergy*, 45(2), 300–327. DOI: 10.1111/cea.12468. https://www.ncbi.nlm.nih.gov/pubmed/25623506

Parameters JTFOP, American Academy of Allergy AAI, Joint Council of Allergy AAI (2010). Drug Allergy: An Updated Practice Parameter. *Ann Allergy Asthma Immunol*;105 (4), 259–73 https://www.aaaai.org/Aaaai/media/MediaLibrary/PDF%20Documents/Practice%20and%20Parameters/drug-allergy-updated-practice-param.pdf

Patriarca, G., Schiavino, D., Nucera, E., & Milani, A. (1996). Positive allergological tests may turn negative with no further exposure to the specific allergen: a long-term, prospective, follow-up study in patients allergic to penicillin. *J Investig Allergol Clin Immunol*, 6(3), 162-165. PMID: 8807506 https://www.ncbi.nlm.nih.gov/pubmed/8807506

Romano, A., & Caubet, J. C. (2014). Antibiotic allergies in children and adults: from clinical symptoms to skin testing diagnosis. *J Allergy Clin Immunol Pract,* 2 (1), 3-12. DOI: 10.1016/j.jaip.2013.11.006 https://www.ncbi.nlm.nih.gov/pubmed/24565763

Sagar, P. S. & Katelaris, C. H. (2013). Utility of penicillin allergy testing in patients presenting with a history of penicillin allergy. *Asia Pacific Allergy*, 3(2), 115-119. DOI: org/10.5415/apallergy.2013.3.2.115 https://apallergy.org/DOIx.php?id=10.5415/apallergy.2013.3.2.115

Solensky, R. (2014). Penicillin allergy as a public health measure. *Journal of Allergy and Clinical Immunology*, 133(3), 797–798. https://www.jacionline.org/article/S0091-6749(13)01646-1/fulltext

Testi, S., Severino, M., Iorno, M. L., Capretti, S., Ermini, G., Macchia, D., Campi, P. (2010). Nonirritating concentration for skin testing with cephalosporins. *J Investig Allergol Clin Immunol*; 20(2), 171-172. PMID: 20461975 https://www.ncbi.nlm.nih.gov/pubmed/20461975

Torres, M. J., Blanca, M., Fernandez, J., Romano, A., Weck, A., Aberer, W…Demoly, P. (2003). Diagnosis of immediate allergic reactions to beta-lactam antibiotics. *Allergy*; 58(10), 961-972. DOI: 10.1034/j.1398-9995.2003.00280.x https://www.ncbi.nlm.nih.gov/pubmed/14510712

Torres, M. J., Romano, A., Mayorga, C., Moya, M. C., Guzman, A. E., Reche, M., Juarez, C., Blanca, M. (2001). Diagnostic evaluation of a large group of patients with immediate allergy to penicillins: the role of skin testing. *Allergy*; 56(9), 850-856. DOI: 10.1034/j.1398-9995.2001.00089.x https://www.ncbi.nlm.nih.gov/pubmed/11551249

Trubiano, J. A., Vogrin, S., Chua, K. Y. L., Bourke, J., Yun, J., Douglas, A…Phillips, E. J. (2020). Development and Validation of a Penicillin Allergy Clinical Decision Rule. JAMA Intern Med., 180(5), 1-9. DOI: 10.1001/jamainternmed.2020.0403 https://pubmed.ncbi.nlm.nih.gov/32176248/