Antibiotic allergies in children

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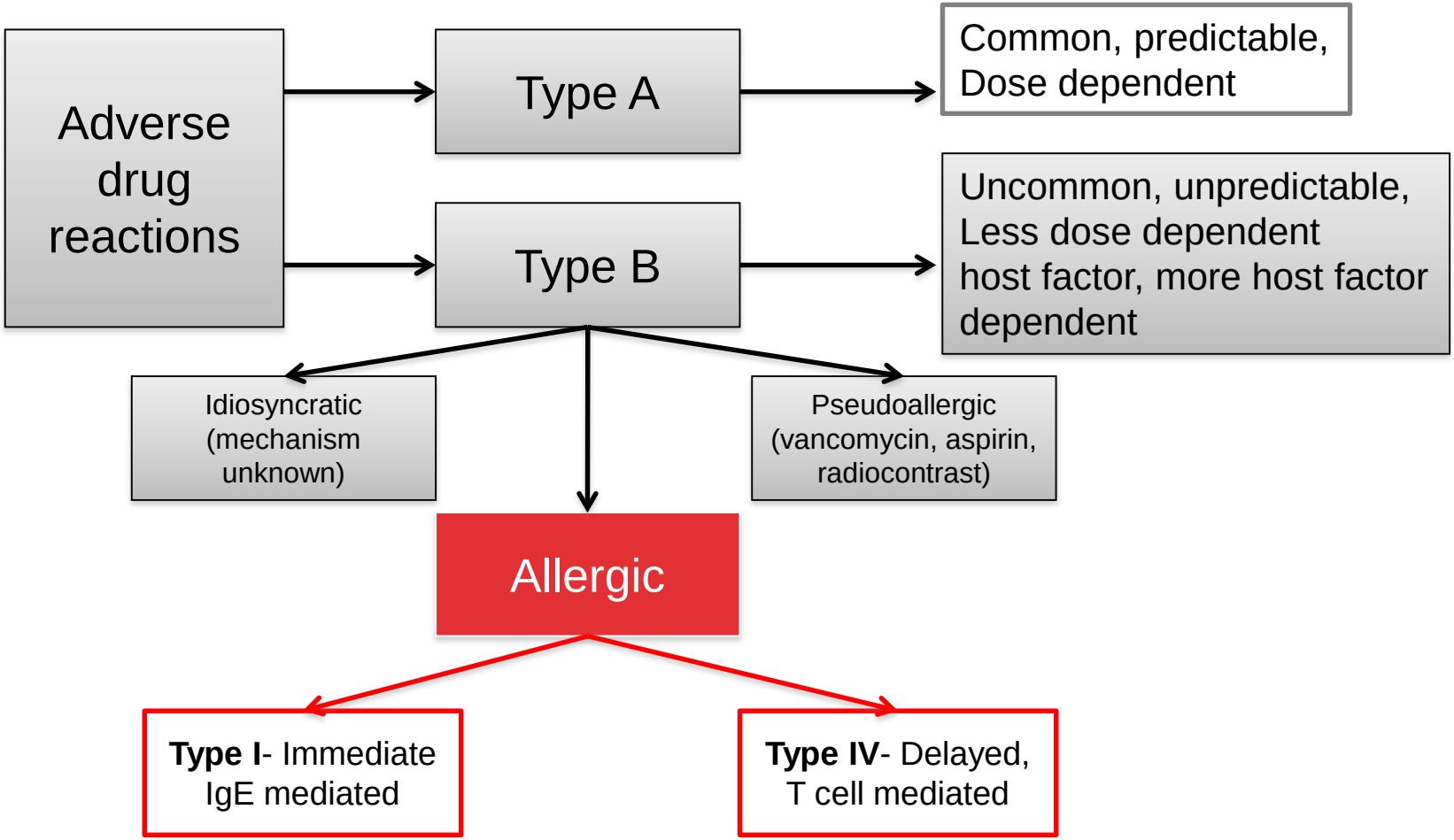
Adverse drug reactions (ADR)

- WHO definition of ADR: A response to a drug which is noxious and unintended, and which occurs at normal doses
- **ALLERGY**- a damaging reaction caused by an immunologic response

ADR classification



Type I reactions

1.Immediate DHRs

–**urticaria, angioedema**, rhinitis, conjunctivitis, bronchospasm, gastrointestinal symptoms (nausea, vomiting, diarrhea, abdominal pain), anaphylaxis, anaphylactic shock;

–they typically occur within 1–6 h after the last drug administration.

Type IV reactions

2. Non-immediate DHRs

–heterogenous clinical picture

- **delayed urticaria**, **maculopapular eruptions**, fixed drug eruptions, vasculitis, toxic epidermal necrolysis, and Stevens–Johnson syndrome, drug reaction with eosinophilia and systemic symptoms (DRESS), acute generalized exanthematous pustulosis and symmetrical drug-related intertriginous and flexural exanthemas; internal organs can be affected either alone or with cutaneous symptoms (DRESS, vasculitis) and include hepatitis, renal failure, pneumonitis, anemia, neutropenia, thrombocytopenia;

–Spectrum of disease with varying pathogenesis

–they may occur at any time as from 1 h after from the initial drug administration.

Antibiotic allergy label

- Patients frequently report antibiotic allergies (**antibiotic allergy label, AAL**) when presenting to hospitals

- But what does this mean?
- The patient (probably) had an adverse reaction to an antibiotic in the past, but commonly:
  - cannot recall to which antibiotic they reacted; e.g. a reaction to amoxicillin becomes penicillin allergy which may lead to the avoidance of all penicillin and cephalosporin (beta-lactam) antibiotics
  - is unsure of the type of the reaction
  - cannot recall how long ago the reaction occurred

→ **Penicillin allergy labels often lead to the avoidance of all beta-lactam antibiotics**

Terminology matters
What is de-labelling?

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Information
FOR HEALTH PROFESSIONALS

Drug (Medication) Allergy Terms

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De-labelling	• Drug allergy de-labelling is the process of removing a drug allergy diagnosis from the patient medical record, after assessment. • Assessment is achieved by allergy testing or subsequent safe exposure to the drug. • The patient should receive a written and dated confirmation if their drug allergy diagnosis 'label' is removed. • It is important that the updated drug allergy status is recorded in all medical records for each patient.

Self-reported antibiotic allergy in Australia is a growing problem

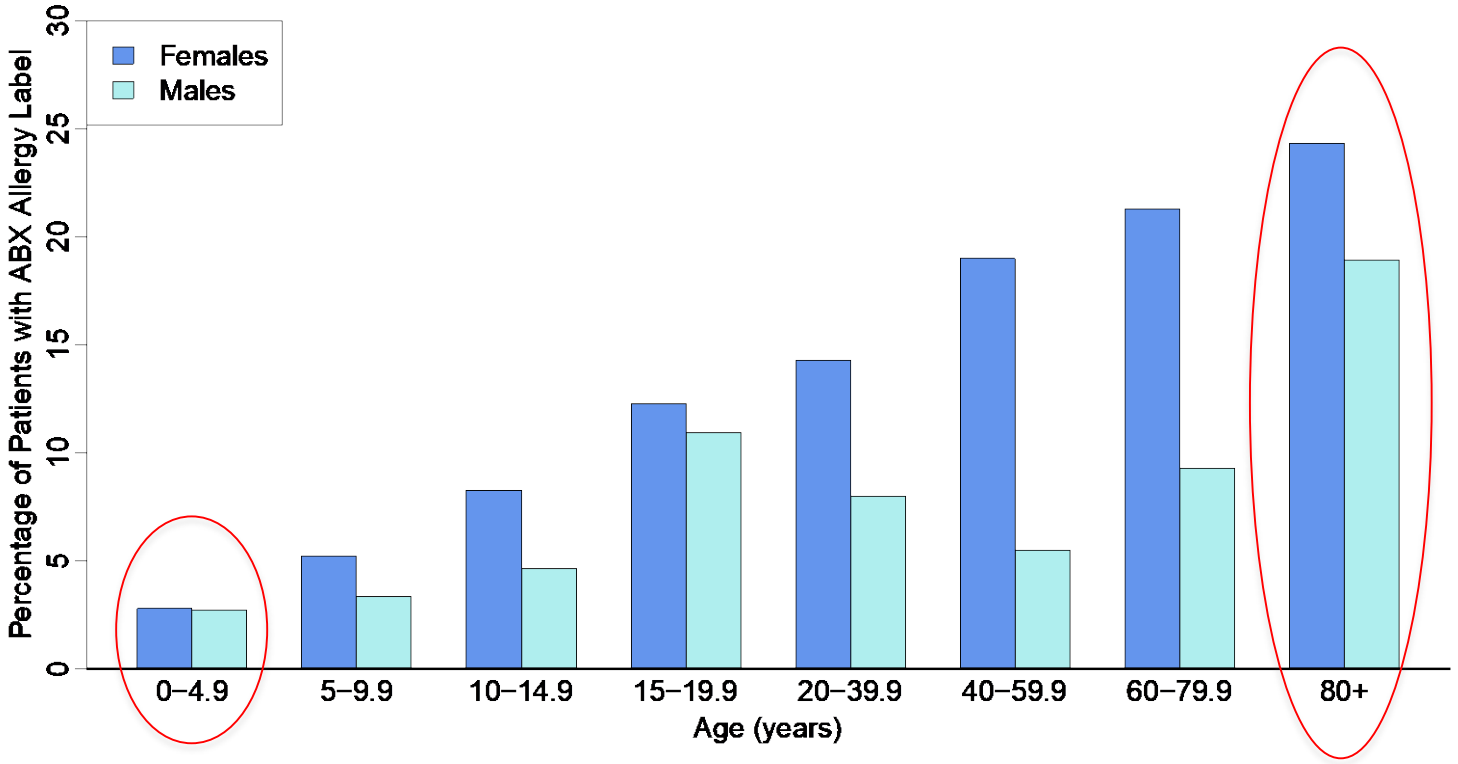
- The number of self-reported antibiotic allergy (AAL) in Australia is on average 18% in patients admitted to hospital (Trubiano JA et al. J Antimicrob Chemother. 2016 Jun; Knezevic B et al., IMJ 2016 Nov)

- The rate of patients with self-reported allergy in the primary care setting in Australia is not well known

- Self-reported antibiotic allergy in admittted elderly General Medicine patients is common: 21-24% (Trubiano JA et al. MJA 2016 April; Knezevic B et al., IMJ 2016); the rate is also higher in patients with chronic disease

- **The rate of self-reported antibiotic allergy in Australian children is 5.4% in children admitted to the sole WA tertiary paediatric care hospital (Lucas M., JACI in Practice 2018)**

Self-reported antibiotic allergy- age and gender



Lucas M, JACI In Practice 2018

Patient demographics self-reports antibiotic allergy (AAL)

Western Australian adult data:

- Females and older patients were significantly more likely to have an AAL (gender: OR=2.54, 95% CI=1.69-3.82, p<0.001) (for a one standard deviation (19.6 years) increase in age: OR=1.31, 95% CI=1.06-1.60, p=0.007).
- The same was also true for beta-lactam AALs alone (gender: OR=2.28, 95% CI=1.46-3.54, p<0.001) (for a one standard deviation increase in age: OR=1.33, 95% CI=1.07-1.67, p=0.011).

WA paediatric data:

- Older patients are significantly more likely to have an ABX allergy label than younger patients (For a 5 year increase in age: OR=1.64, 95% CI=1.06-2.54, p<0.0001).

What are the most common culprit antibiotics for children?

WA paediatric cohort study:

- Beta-lactam labels (85%), mostly penicillin, followed by amoxicillin and then cephalexin.

- Non-beta-lactam labels: Sulfamethoxazole/trimethoprim was the most common allergy

What impact does an Antibiotic Allergy Label (AAL) have in adults?

- AALs are associated with higher rates of inappropriate prescribing and increased use of broad-spectrum antimicrobials
  Multiple international studies; Australia: Trubiano JA et al.; J Antimicrob Chemother. 2016 Jun; Knezevic B et al.; IMJ 2016 Nov

- Increased use of β lactam alternative antibiotics (quinolones, clindamycin, macrolides) accounted for 55% of the increased risk of MRSA and 35% of the increased risk of C difficile.
  Blumenthal K; BMJ 2018

- Large American study reported increased lengths of stay, intensive care admission rates and higher mortality rates for patients with AALs
  Charneski L.; Pharmacotherapy 2011

- Patients with an AAL were significantly more likely to be readmitted within **four weeks** than NAAL patients (OR=2.16, 95% CI=1.34-3.46, p=0.001) and **six months** compared to NAAL patients (OR=1.55, 95% CI=1.06-2.27, p=0.025).
  Knezevic, IMJ 2016 Nov

What impact does an Antibiotic Allergy Label (AAL) have in kids?

- Children with antibiotic allergy labels received more macrolides (p=0.045), quinolones (p=0.01), lincosamide antibiotics (p<0.001) as well as more metronidazole (p=0.009) than patients without an antibiotic allergy label (Figure 2)

- After adjusting for patient age, sex and admitting specialty, children with any antibiotic or beta-lactam allergy label, had longer hospital lengths of stay (OR 1.74, 95% CI 1.13-2.67, p=0.01).

Lucas M, JACI In Practice 2018

AAL and Antimicrobial resistance (AMR)

- “Critical role of using the right antibiotic in the right way in every case”
- Preservation of all antibiotic choices whenever possible
- AAL are:
  - a barrier to Antimicrobial Stewardship
  - linked to increased antimicrobial resistance
  - lead to the use of alternative antibiotics (such as vancomycin, quinolones, aminoglycosides and aztreonam)
  - linked to increased infection with resistant pathogens (MRSA, VRE, C. diff)

Summary-Part 1

- There is a negative impact of antibiotic allergy labels on clinical outcomes in children including:
    1. Significant alternate antibiotic use
    2. Longer hospital lengths of stay

- Childhood de-labelling may reduce the use of alternative antibiotics and the associated increase in bacterial resistance to antibiotics

- 52.3% of children reported a mild or moderate reaction (mostly rashes) to a penicillin or amoxicillin which could be safely assessed with direct provocation testing

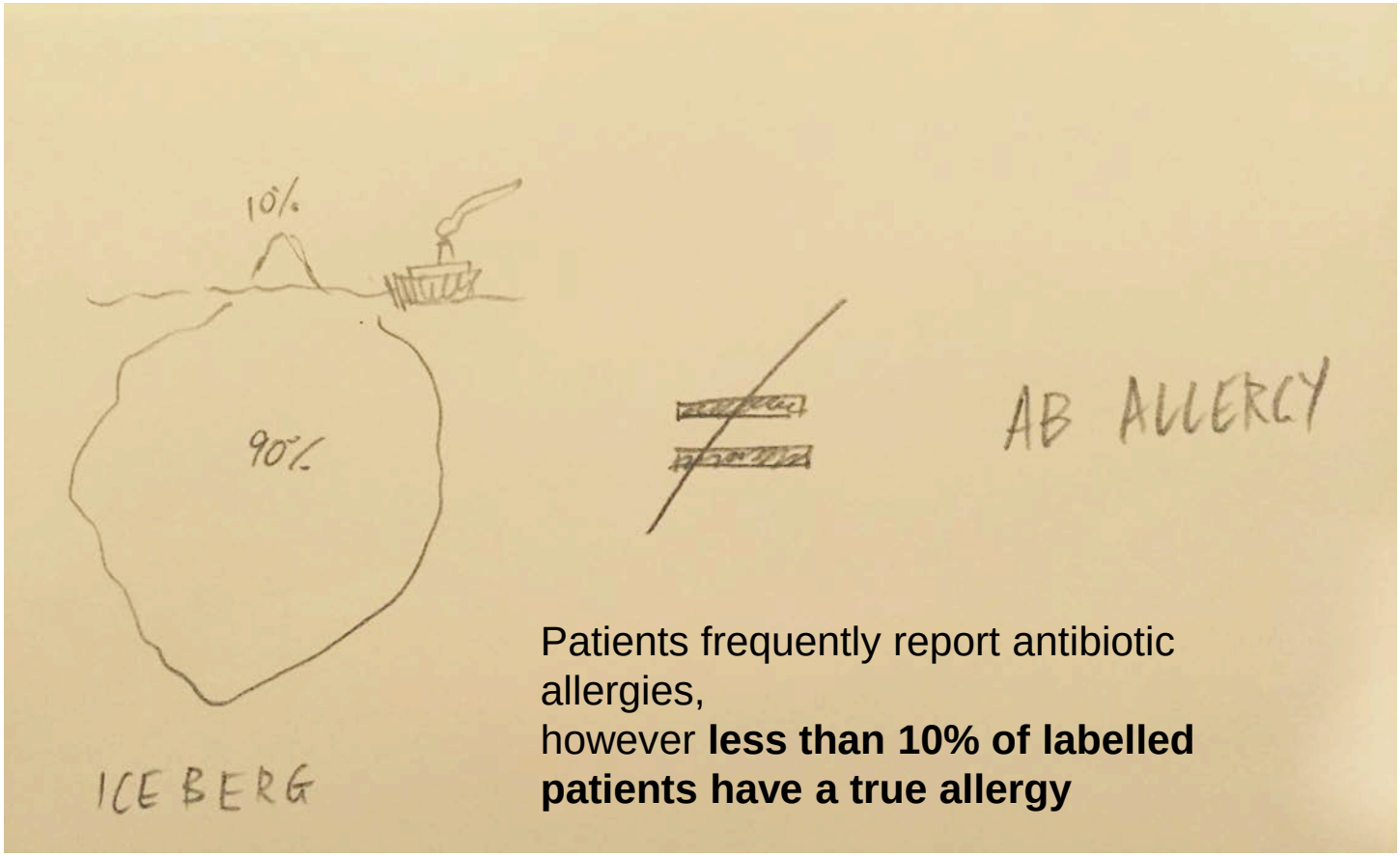
- Early de-labelling may be beneficial from a health economic point of view, by reducing the prevalence and negative impact of allergy labels among children, and the future adult population

Lucas M, JACI In Practice 2018

Summary-Part 2

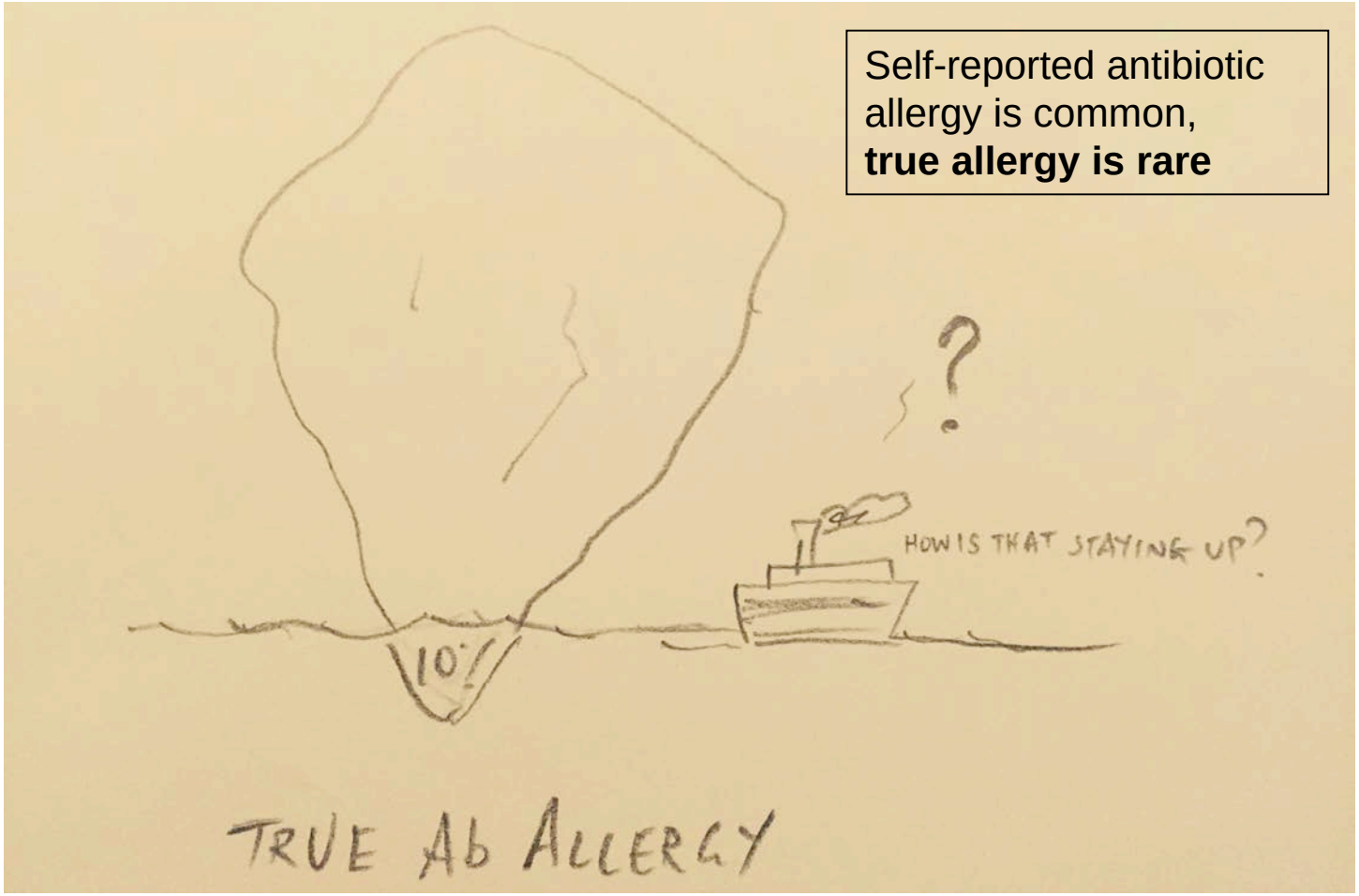
- The burden of self-reported antibiotic allergy (AAL) in Australia is high, however the rate of antibiotic allergy overall is low
- the highest prevalence of AAL (19–24%) is noted in the most vulnerable patients — those with chronic illness, cancer or alternative immunosuppression
- Over-labelling can set up a negative cycle of restricted access to antibiotics, poorer clinical outcomes, increased AMR and hospitalisation in children and adults
- Systematic drug allergy de-labelling, starting in childhood may mitigate these clinical and economic burdens

The truth
about self-reported antibiotic allergy:



Patients frequently report antibiotic allergies,
however **less than 10% of labelled patients have a true allergy**

So, it is a bit more like this…



Putting the genie back…
(the practical aspects of “de-labelling”)

How to evaluate? Clinical history

Critical information:

- Symptoms
- Chronology of symptoms (previous exposure, delay between the last dose and symptoms, effect of stopping treatment)
- Other medication taken (at the time and other drugs of the same class taken since)
- Medical background (previous allergies and medical conditions, past and present)

Can history be predictive of a positive challenge reaction?

- A history of a reaction within 5 minutes for immediate reactions and a history of prolonged resolution of a rash (> 2 weeks) is helpful (Mill C; JAMA Paeds 2016)

Standard diagnostic practice for antibiotic allergies

Immediate reaction

•2 or 3-tier testing with skin prick testing, intradermal testing
•If skin testing is negative: Oral provocation testing (single or graded)

Non-immediate reactions

•Patch testing and late reading of intra-dermal tests should be performed
•Extended challenges

→ In case the drug is not available in its adequate allergenic form →
Drug provocation is required

Extended drug challenges (lowest dose 2-5 days)

Single drug provocation tests-Which drug?

- Penicillin VK is best to assess for beta-lactam ring allergy which is extremely rare
- In children allergies against amoxicillin are common
- Amoxicillin allergies are mostly directed against its R1 side chain
- If a child reacts against amoxicillin, consider avoiding cephalexin, ceclor and ampicillin as well
  as they have a similar (not identical) R1 side chain
- Graded challenges are safer than one dose challenges
  (*Mill C, JAMA 2016*)

Skin testing and prolonged courses in children

- *Mill et al. (2016):* Graded penicillin challenges were safe for skin-related reactions to amoxicillin
- *Labrosse et al. (2018):* A 5-day challenge to amoxicillin in children with a non-severe allergy history is safe and effective to delab children and leads to higher penicillin use in future
- Other mixed pediatric and adult studies show similar results

2021 ASCIA Update

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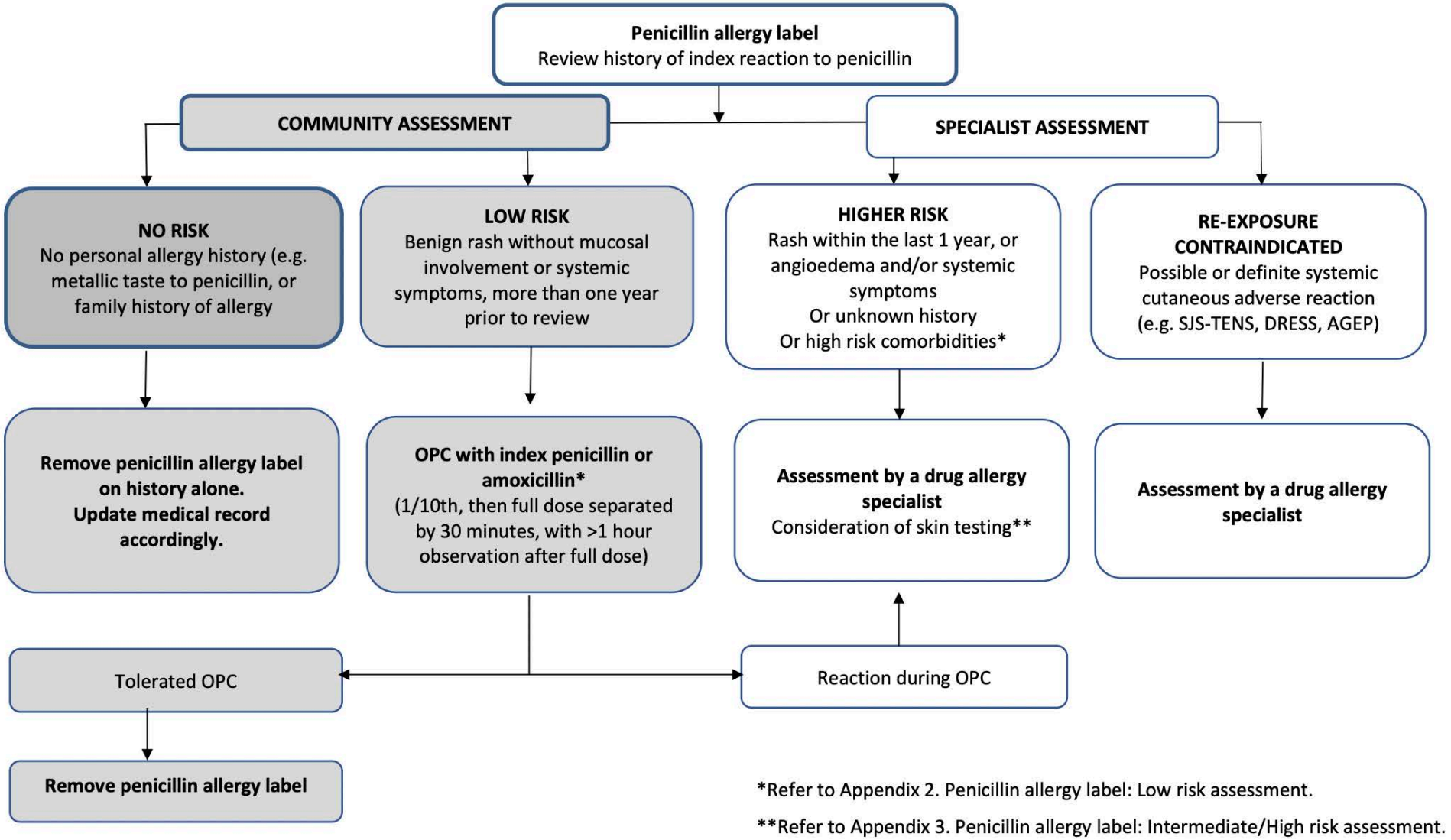
ASCIA Consensus Statement for the assessment of patients with suspected penicillin allergy

This document was initially developed by the ASCIA Drug Allergy Committee and revised at an expert panel* meeting in February 2020.

This document is to be used by medical practitioners as a guide to assess adult and paediatric patients that present with a suspected immediate allergy to penicillins, and to determine which patients require skin testing (ST) prior to provocation testing.

Appendix 1B. 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.

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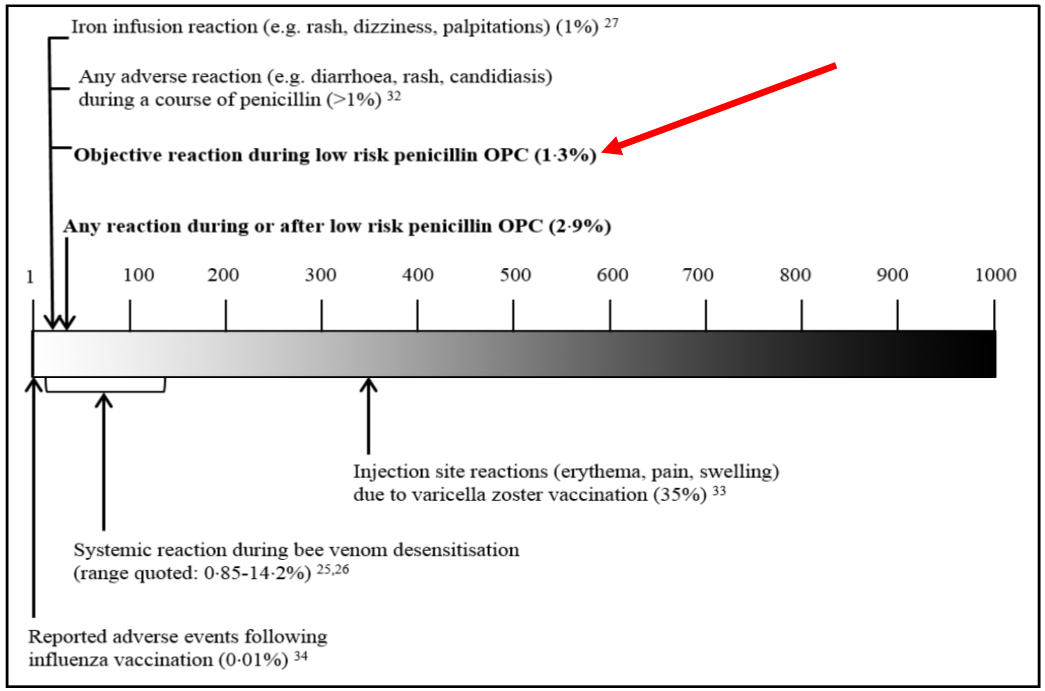
Benign rash	• In the context of drug allergy, a benign rash is a transient morbilliform or maculopapular rash that may be mildly pruritic and is not associated with other symptoms.
Beta-lactam antibiotics	• Beta-lactam antibiotics are antibiotics that contain a chemical structure called a beta-lactam ring. They include: - Penicillin derivatives (penams) - Cephalosporins (cephems) - Monobactams - Carbapenems - Carbacephems

Risk of adverse reactions

Figure 3. Risk of adverse reactions during primary care procedures, per 1000 individuals. (25-27, 32-34) The risk of an objective immediate reaction, or any reaction (including subjective symptoms) during a low risk direct one or two-dose penicillin OPC are provided based on our study cohort (bolded).



New ASCIA documents
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ACTION PLAN FOR
Drug (Medication) Allergy

Patient details

Name: _____

Date of birth: _____

SIGNS OF MILD TO MODERATE ALLERGIC REACTION

- Swelling of lips, face, eyes
- Hives or welts
- Sudden onset sneezing, rhinitis
- Tingling mouth
- Abdominal pain, vomiting

ACTION FOR MILD TO MODERATE ALLERGIC REACTION

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RECORD FOR Drug (Medication) Allergy

Patient Name: _____ **Date of birth:** _____

Patient Address: _____

DRUG ALLERGIES CONFIRMED BY SPECIALIST

Drug	Reaction Type	Date of Reaction (if known)*	Date Assessed and Recommendation after Assessment

DRUG ALLERGIES NOT ASSESSED (OR CURRENTLY BEING ASSESSED)

Drug	Reaction Type	Date of Reaction (if known)*	Recommendation before Finalised Assessment

Take home messages

- Direct provocation testing in children with a distant benign rash is safe

- There is a great need for collaborative approach/consensus opinion between specialties to provide evidence based, safe and cost-effective strategies to de-label patients

- Communicating updated allergy information and avoiding re-labelling is a major barrier to overcome

- We should also keep in mind that research into better in-vitro diagnostics may lead to a more straight-forward solution of the problem

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