

# Self-reported antibiotic allergy What next?

Michaela Lucas

Clinical Immunologist/Immunopathologist  
MBBS, MD/Dr.med, FRACP, FRCPA

# Introduction

- Patients frequently report antibiotic allergies, however less than 10% of labelled patients have a true allergy
- Penicillin allergy labels often lead to the avoidance of all beta-lactam antibiotics
- There are significant gaps in knowledge in regards to antibiotic allergies, even in Specialties such as Immunology, Infectious Diseases, Physicians etc.
- The frequency of cross-reactivity reactions between  $\beta$ -lactams is relatively low and often overestimated, while allergies to specific drugs are very common
- E.g. cephalosporin and penicillin cross-reactivity in contemporary studies suggest the true rate of cross reactivity to be <2% and potentially lower for third and later generation cephalosporins

# Self-reported antibiotic allergy in Australia is a growing problem

- The number of self-reported antibiotic allergy (AAL) in Australia is app. 18% in patients admitted to hospital (Trubiano JA et al. J Antimicrob Chemother. 2016 Jun; Knezevic et al., unpublished data)
- The rate of patients with self-reported allergy in the primary care setting in Australia is not known
- Self-reported antibiotic allergy in Gen. Medicine patients is common: 21-24% (Trubiano et al. MJA 2016 April; Knezevic et al., unpublished data)
- The rate of self-reported allergy in Australian children is also not well studied; it is 5.5% in children admitted to the sole WA tertiary paediatric care hospital; antibiotic allergy is self-reported in 1% of children presenting to the Emergency department of the same hospital (Arnold, Rueter et al.; unpublished data)

# Self-reported antibiotic allergy increases with age

Patient Age	Any Antibiotic Allergy		Any Beta-Lactam Allergy		Total Number of Patients
	Count	%	Count	%	Count
0-4.99 years	10	2.51	8	2.01	399
5-9.99 years	12	4.69	11	4.3	256
10-19.99 years	11	5.85	10	5.32	188
20-39.99 years	13	14.13	10	10.87	92
40-49.99 years	10	11.76	9	10.59	85
50-59.99 years	14	13.59	12	11.65	103
60-69.99 years	23	19.01	20	16.53	121
70-79.99 years	27	20.77	18	13.85	130
80+ years	35	23.65	32	21.62	148

Lucas M, unpublished data

**Note:**  
The median age of the recent AGM study published in the MJA by Trubiano et al. was 82 years (interquartile range 74-87 years)

# Patient demographics self-reports antibiotic allergy (AAL)

- WA 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,  $p=0.011$ ).
- Patient admitting team (by individual specialties), audit year and prescription of antibiotics at the time of audit were not significantly associated with presence of AALs or, more specifically, beta-lactam AALs.

# What are the most common culprit antibiotics?

## **AGM study/Victoria:**

- 34% Penicillins; 13% sulfonamide; 11% cephalosporins

## **WA cohort study:**

- Beta-lactam labels (83%), mostly “penicillin group” (n=87; 71% of “allergic” cohort; 13% of whole cohort).

- beta-lactam group: “penicillin (not otherwise specified)” (n=76; 75%), “cephalexin” (n=7), “amoxicillin” (n=5), “amoxicillin/clavulanic acid” (n=3), “piperacillin/tazobactam” (n=2) and “cephazolin” (n=2).

- Non-beta-lactam labels: Sulfamethoxazole/trimethoprim (n=11), macrolide (n=7) and glycopeptide (vancomycin) (n=7) groups.

- In the AAL group, 108 (89%) patients had a single allergy, 10 (8%) had two documented AAL, and 4 (3%) had three or more labels.

# What impact does it have?

- AALs are common and 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)
- One small Australian study reported that patients with penicillin allergy labels, hospitalized with community acquired pneumonia, had longer lengths of stay (Irawati L et al.; J Res Pharm Pract. 2006).
- Significant extra costs of using alternative antimicrobials for beta-lactam allergy labelled patients (Sade K.; Clin Exp Allergy 2003; Picard M.; JACI IP 2013)
- Large American study reported increased lengths of stay, intensive care admission rates and higher mortality rates for patients with AALs (Charneski L.; Pharmacotherapy 2011)

# What impact does it have?

## **WA Cohort, label of antibiotic allergy (AAL):**

- 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,  $p=0.001$ )
- Patients with an AAL also had significantly more readmissions within six months compared to NAAL patients (OR=1.55, 95% CI=1.06-2.27,  $p=0.025$ ).



# What impact does it have?

## WA Cohort, label of Beta-lactam allergy:

Significantly more readmissions:

**4 weeks (p=0.0054, OR=2.05, 95% CI=1.24-3.38)**

- 83% had significant infections
- 10% readmitted with same serious infection

**6 months (OR=1.56, 95% CI=1.04-2.34)**

- 30% had 2+ admissions (19% for non-labelled patients)
- In our study there were no significant differences in antibiotic costs, hospital length of stay, and intensive care admissions. This may be due to the smaller sample size and the broad inclusion of all patients rather than higher risk patient groups.

# Conclusions-Part 1

- Antibiotic allergy labels are common, however the rate of antibiotic allergy overall is low
- Over-labelling can set up a negative cycle of restricted access to antibiotics, poorer clinical outcomes and increased hospitalisation
- Systematic drug allergy delabelling may mitigate these clinical and economic burdens

What next?

The practical aspects of de-labelling

# Who should we de-label?

- The elderly?

Note: that the mean age of the recent MJA study was 82 years

- Children?
- Those in need of recurrent antibiotics? (e.g. those seen by anti-microbial stewardship programs)
- Those with more than one allergy?
  
- Everybody?

# How should we de-label?

## Recommended algorithm for assessment

Suspicion of DHR



Evaluation of clinical history



Possible DHR



Skin test available?

**Yes**→results→positive→proven drug allergy

**Yes**→results→negative→drug provocation available→results

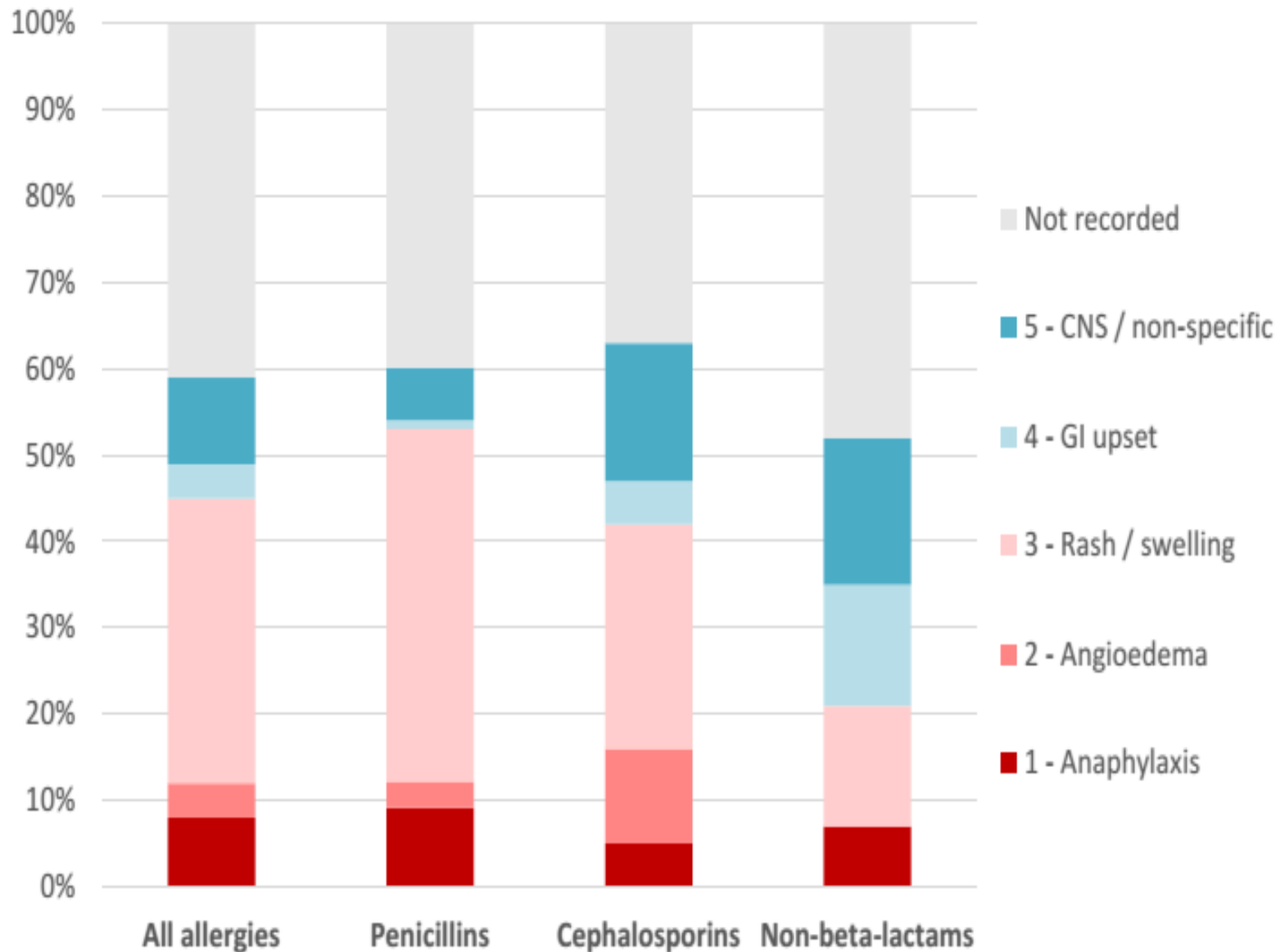
**Yes**→results→negative→no drug provocation available→therapeutical approach (no other alternative; desensitisation, premedication etc)



drug provocation available→results

drug provocation not available→therapeutical approach (no other alternative)

# WA Cohort: Poor Documentation of allergies



# Issues with testing strategies (Lacombe-Barrios J.; JACI 2016)

- Prospective study of 97 consecutive patients evaluated for a history of  $\beta$ -lactam allergy (March-October 2014). Patients were classified as immediate reactors (<1 hour) or nonimmediate reactors (>1 hour).
- Of the 97 patients included, 23 were confirmed as allergic (23.7%). The median time between the last reaction and the study was **9.5 months**, and the culprit drugs were AX-CLV in 15 cases, AX in 3, CEP in 2, BP in 1, and an undetermined BL in 2
- Twenty-two patients experienced an immediate reaction presenting mainly as anaphylaxis (59.1%) or urticaria (36.4%).

# Issues with testing strategies (Lacombe-Barrios J.; JACI 2016)

- Skin testing with all the reagents used in this study only confirmed the diagnosis in 47.8% of cases; **in the remaining 52.2%, the basophil activation test, ImmunoCAP, or drug provocation testing was necessary**
- Skin testing to the culprit drugs (Amoxicillin, AMX-Clavulanic acid, Cephalosporins) and major and minor determinants of Penicillin was most useful
- Skin testing with Benzylpenicillin (BP) was positive in 2 patients, both of whom tolerated administration of BP and PV in the drug provocation test
- The false-positive rate should be highlighted, since the results could lead to avoidance of penicillin, with the subsequent costs and potential side effects that result from the use of other non- $\beta$ -lactam antibiotics



# Issues with antibiotic allergy testing in Australia

- Long delays before testing occurs
- Limited availability of specialists performing testing
- Most patients have a very distant history and cannot remember details
- Sensitivity of our current testing strategies decrease significantly over time (to the fact that they may not be useful at all)
- We therefore need to have separate approaches for patients with well documented recent history (e.g. anaphylaxis with General Anaesthesia) and those with self-reported allergy and distant reactions

# How should we de-label in Australia?

- Is skin testing everybody feasible? Or should we challenge everybody (judgement call based on history)?
- **Case example:** 78 year old man; history of Penicillin allergy(rash) as a child, not sure what else happened, has been avoiding Penicillin since childhood
- Other medical history: Obesity, hypertension, Type II Diabetes, previous NSTEMI, on beta-blocker and Ace-I; needs antibiotics for a foot infection with cellulitis
- Would you directly challenge this patient in your rooms?

# Who should de-label in Australia? Scandinavian cohort study

**Borch JE et al., Basic Clin Pharmacol Toxicol. 2006 April**

- 3642 patients, 96 fulfilled the inclusion criteria giving a point-prevalence of alleged penicillin allergy (5% in a hospital in-patient population; mean age 61 years).
- Mean time elapsed since the alleged first reaction to penicillin was 20 years.
- 25% did not recall the time of their reaction
- 82.2% did not remember the name of the penicillin they reacted to
  
- During the 5–12 months interval between inclusion and planned investigations 24 (25%) died, 59 (61.4%) refrained from participation, and only 13 (13.5%) patients completed the investigations.**

# Is de-labelling effective? Will it change behaviour?

- Willingness to challenge: yes; 54% in the AGM study (Trubiano JA; MJA 2016)
- Uptake of active testing not yet clear (sobering Scandinavian data)
- Change use of antibiotics after testing, encouraging results: Of 182 patients, 137 (75.3%) were following the allergy label modifications at the time of follow-up. (Bourke J; JACI IP 2015 June)

# Summary

- The burden of self-reported antibiotic allergy in Australia is high
- The solution to this problem is not elusive but requires a collaborative approach/consensus opinion between specialties to provide evidence based, safe and cost-effective strategies to de-label patients
- We should also keep in mind that research into better in-vitro diagnostics may lead to a more straightforward solution of the problem

# Thank you!



"Mr. Osborne, may I be excused? My brain is full!"

## Acknowledgements

Brittany Knezevic  
Dustin Sprigg  
Michelle Trevenen  
Annabelle Arnold  
Jason Seet

Staff from the  
Immunology Department  
Pharmacy Department  
Emergency Department  
at the QE2 Medical Centre in WA

Members of the  
ASCIA Drug Allergy Working Party