

Busting myths about antibiotic allergies

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NSW Antimicrobial Stewardship Forum

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Mark All as Reviewed

+ Add | Modify | No Known Allergies | Reverse Allergy Check | Display: All

D.	Substance	Category	Reactions	Seve...	I...	Type	C.	Reaction S...	Updated By	Source	Reviewed
✓	codeine	Drug	Mouth ulcer	Mod...		Sensi...	Active		05/09/2017 Kelsall, Sienna M...		17/01/201...
✓	contrast medi...	Drug	Mouth ulcer	Mod...		Allergy	Active		05/09/2017 Kelsall, Sienna M...		17/01/201...
✓	morphine	Drug	Mouth ulcer	Mod...		Sensi...	Active		05/09/2017 Kelsall, Sienna M...		17/01/201...
✓	Movicol	Drug	mouth ulcers	Mod...		Sensi...	Active		05/09/2017 Kelsall, Sienna M...		17/01/201...
✓	HMG-CoA red...	Drug	muscle cramps	Unkn...		Allergy	Active		10/09/2018 Richardson, Belin...	Exter...	17/01/201...
✓	penicillins	Drug	rash, anaphylaxis	Unkn...		Allergy	Active		09/10/2018 CORRIE, Dylan Ja...		17/01/201...
✓	NSAIDs	Drug	Renal papillary necrosis	Severe		Sensi...	Active		08/09/2018 Chan, Jenny Ms		17/01/201...
✓	ciPROFLOXacin	Drug	seizure	Severe		Sensi...	Active		08/09/2018 Chan, Jenny Ms		17/01/201...
✓	tRAMadol	Drug	Serotonin syndrome	Severe		Sensi...	Active		05/09/2017 Kelsall, Sienna M...		17/01/201...
✓	DULoxetine	Drug	Suicidal ideation	Unkn...		Allergy	Active		05/11/2017 Sparham, Emma ...		17/01/201...
✓	opioid agonist	Drug	ulceration of mouth	Unkn...		Allergy	Active		10/09/2018 Richardson, Belin...	Exter...	17/01/201...
✓	amiTRIPTYLine	Drug	Unknown	Unkn...		Allergy	Active		10/09/2018 Richardson, Belin...	Exter...	17/01/201...
✓	aspirin	Drug	Unknown	Unkn...		Allergy	Active		05/11/2017 Sparham, Emma ...		17/01/201...
✓	atorvastatin	Drug	Unknown	Unkn...		Allergy	Active		05/11/2017 Sparham, Emma ...		17/01/201...
✓	Contrast Dye	Drug	Unknown	Unkn...		Allergy	Active		05/11/2017 Sparham, Emma ...		17/01/201...
✓	diclofenac	Drug	Unknown	Unkn...		Allergy	Active		05/11/2017 Sparham, Emma ...		17/01/201...
✓	Eleva	Drug	Unknown	Unkn...		Allergy	Active		10/09/2018 Richardson, Belin...	Exter...	17/01/201...
✓	Epilim	Drug	Unknown	Unkn...		Allergy	Active		05/11/2017 Sparham, Emma ...		17/01/201...
✓	ERYthromycin	Drug	Unknown	Unkn...		Allergy	Active		05/09/2017 Kelsall, Sienna M...		17/01/201...
✓	esomeprazole	Drug	Unknown	Unkn...		Allergy	Active		05/11/2017 Sparham, Emma ...		17/01/201...
✓	gabapentin	Drug	Unknown	Unkn...		Allergy	Active		05/11/2017 Sparham, Emma ...		17/01/201...
✓	ibuprofen	Drug	Unknown	Unkn...		Allergy	Active		10/09/2018 Richardson, Belin...	Exter...	17/01/201...
✓	Indomethacin...	Drug	Unknown	Unkn...		Allergy	Active		10/09/2018 Richardson, Belin...	Exter...	17/01/201...
✓	Keflex	Drug	Unknown	Unkn...		Allergy	Active		05/11/2017 Sparham, Emma ...		17/01/201...
✓	laMICTAI	Drug	Unknown	Unkn...		Allergy	Active		05/11/2017 Sparham, Emma ...		17/01/201...
✓	Latex	Drug	Unknown	Unkn...		Allergy	Active		05/11/2017 Sparham, Emma ...		17/01/201...
✓	linEZOLID	Drug	Unknown	Unkn...		Allergy	Active		05/11/2017 Sparham, Emma ...		17/01/201...
✓	Macrochantin	Drug	Unknown	Unkn...		Allergy	Active		05/11/2017 Sparham, Emma ...		17/01/201...
✓	metocloprami...	Drug	Unknown	Unkn...		Allergy	Active		05/11/2017 Sparham, Emma ...		17/01/201...
✓	metronidazole	Drug	Unknown	Unkn...		Allergy	Active		05/11/2017 Sparham, Emma ...		17/01/201...
✓	paracetamol	Drug	Unknown	Unkn...		Allergy	Active		05/11/2017 Sparham, Emma ...		17/01/201...
✓	Peanuts	Drug	Unknown	Unkn...		Allergy	Active		10/09/2018 Richardson, Belin...	Exter...	17/01/201...
✓	pregabalin	Drug	Unknown	Unkn...		Allergy	Active		05/11/2017 Sparham, Emma ...		17/01/201...
✓	proMETHazine	Drug	Unknown	Unkn...		Allergy	Active		10/09/2018 Richardson, Belin...	Exter...	17/01/201...
✓	rosuvastatin	Drug	Unknown	Unkn...		Allergy	Active		10/09/2018 Richardson, Belin...	Exter...	17/01/201...
✓	topiramate	Drug	Unknown	Unkn...		Allergy	Active		05/11/2017 Sparham, Emma ...		17/01/201...
✓	trimETHOPRIM	Drug	Unknown	Unkn...		Allergy	Active		05/11/2017 Sparham, Emma ...		17/01/201...
✓	Vytorin	Drug	Unknown	Unkn...		Allergy	Active		10/09/2018 Richardson, Belin...	Exter...	17/01/201...
✓	ascorbic acid	Drug	Vomiting	Unkn...		Allergy	Active		10/09/2018 Richardson, Belin...	Exter...	17/01/201...

OK Cancel

Why is antibiotic allergy important to hospitals?

Burden



18%-24% report an antibiotic allergy
1-3,5

Severity



50% low risk –
Oral challenge target³



50% are high risk –
need specialist testing⁴

Impacts



25% EMR error rate & delays antibiotics^{3,4}



↑ restricted antibiotics¹



↑ readmit, LOS & death^{2,6-7}



↑ MRSA & *C. difficile*⁸



↑ ADRs, surgical time & hospital costs⁹⁻¹⁰

1. Trubiano *et al.* J Antimicrob Chemother 2016; 71(6): 1715
2. Trubiano *et al.* Antimicrob Resist Infect Control 2015; 4:23
3. Trubiano *et al.* Med J Aust 2016; 204 (&): 273
4. Conway *et al.* Clin Ther 2017; 39 (11): 2276
5. Trubiano *et al.* J Allergy Clin Immunol Pract. 2016; 4(6):1187-1193

6. Knezevic *et al.* Intern Med J 2016; 11: 1276
7. Blumenthal *et al.* J Gen Intern Med 2019 April 22
8. Blumenthal *et al.* BMJ 2018 Jun 27
9. MacFadden *et al.* Clin Infect Dis 2016; 63(7): 904
10. Mattingly *et al.* J Allergy Clin Immunol Pract 2018 6(5): 1649

10 Golden Rules of Penicillin Allergy

1. Penicillin allergy is rarely forever
2. Do not label penicillin allergic based upon family history
3. Do not label penicillin allergic if they report a known drug side effect
4. Do not label penicillin allergic if a rash to penicillin occurred during EBV
5. Penicillin allergy in the EMR should include type, timing, severity & tolerated antibiotics
6. Do not automatically label a penicillin allergic patient also allergic to cephalosporins
7. Do not label a patient allergic to a beta-lactam class - name the implicated drug
8. Penicillin allergy should always be investigated
9. A change in a patient's penicillin allergy "label" needs to be conveyed to all
10. Usual rules of penicillin cross-reactivity do not apply to SCAR

10 Golden Rules of Penicillin Allergy

1. **Penicillin allergy is rarely forever** [allergy is lost over time]
2. Do not label penicillin allergic based upon family history
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<https://antibioticallergy.org.au/resources#abd34176-6344-49ce-bbe7-9e36dc0da0a6>

Penicillin allergy is lost over time

Clinical Review & Education

JAMA Insights

Penicillin Allergy Is Not Necessarily Forever

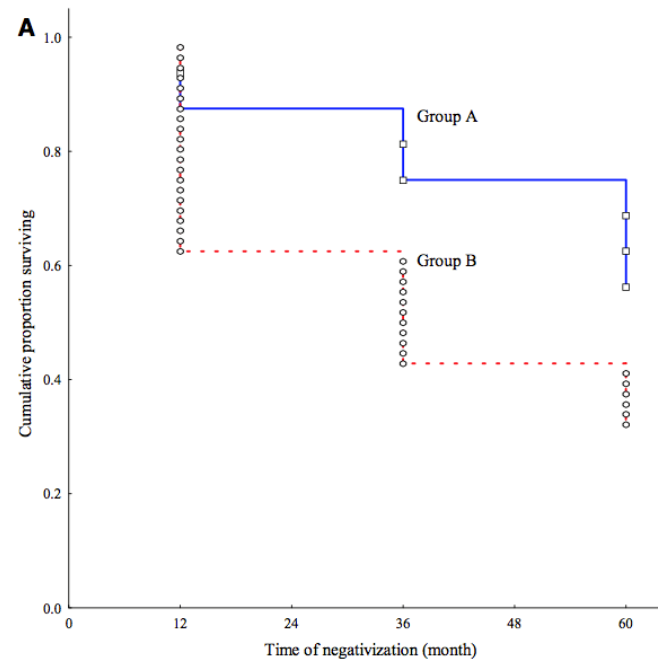
Jason A. Trubiano, MBBS; N. Franklin Adkinson, MD; Elizabeth Jane Phillips, MD

Many are labelled



Few have allergy!!

89.9% of 401 patients 'de-labeled'¹



Time to skin test conversion (pos → neg)

1. 50% at 5 years
2. 80% at 10 years

Cephalosporin decline is similar

10 Golden Rules of Penicillin Allergy

1. Penicillin allergy is rarely forever
- 2. Do not label penicillin allergic based upon family history ["false allergy"]**
- 3. Do not label penicillin allergic if they report a known drug side effect ["false allergy"]**
- 4. Do not label penicillin allergic if rash to penicillin occurred during EBV ["false allergy"]**
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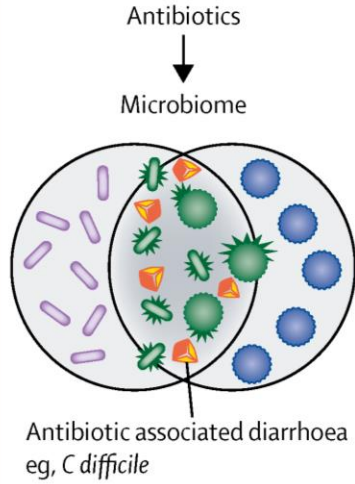
<https://antibioticallergy.org.au/resources#abd34176-6344-49ce-bbe7-9e36dc0da0a6>

Type A - "FALSE"

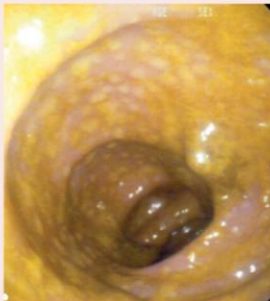
On-target ADRs

Predictable based on drug action*

ADR mechanisms



ADR phenotype/example



C difficile associated pseudomembranous colitis

Type B - "TRUE"

"False" allergy

Off-target ADRs

Non-immunologically-mediated HSRs

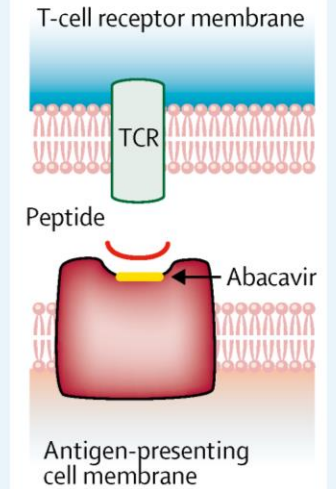
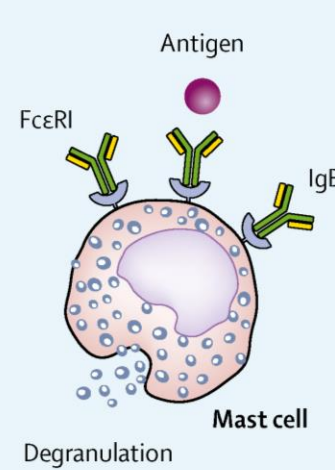
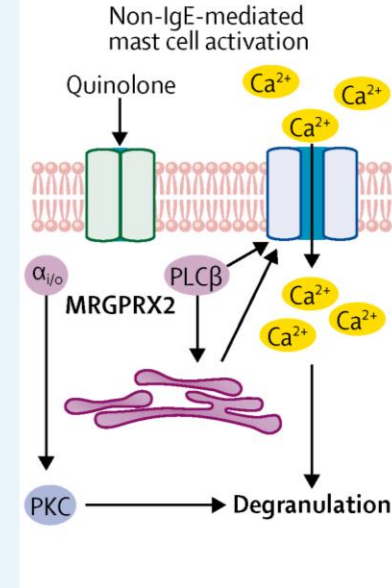
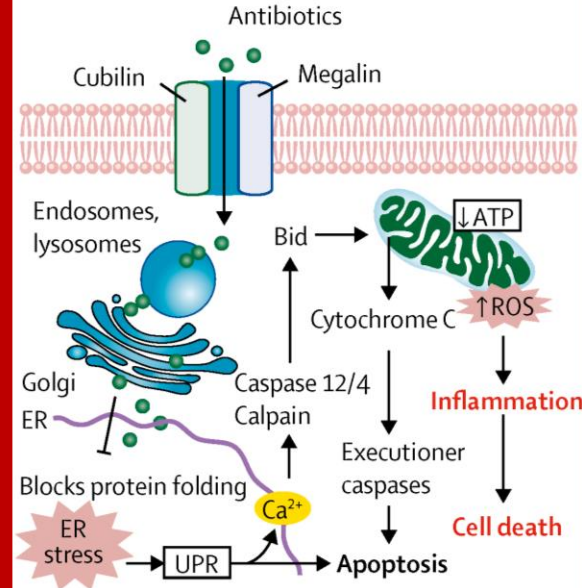
Cellular toxicity and disrupted physiology*
Non-immune cell receptor interaction*

Immune receptor interaction*

Immunologically-mediated HSRs

Antibody-mediated

Pure T-cell-mediated*



Aminoglycosides acute tubular necrosis



Fluoroquinolone urticaria



Penicillin angioedema



Abacavir hypersensitivity

AUS/NZ Pharmacist-led approaches to “false” allergy

Implementation of a pharmacist-led penicillin allergy de-labelling service in a public hospital

Tanya du Plessis^{1*}, Genevieve Walls¹, Anthony Jordan² and David J. Holland¹

¹Infection Services, Middlemore Hospital, Auckland, New Zealand; ²Department of Immunology, Auckland City Hospital, Auckland, New Zealand

Model: AMS Pharmacist allergy reconciliation

Stakeholders: Pharmacist review

Target: Penicillin allergy



Evaluation of a pharmacist-led penicillin allergy de-labelling ward round: a novel antimicrobial stewardship intervention

M. Devchand^{1-3*}, C. M. J. Kirkpatrick³, W. Stevenson¹, K. Garrett², D. Perera^{1,2}, S. Khumra¹⁻³, K. Urbancic ^{1,2,4}, M. L. Grayson^{1,5} and J. A. Trubiano ^{1,4,5}

¹Infectious Diseases Department and Centre for Antibiotic Allergy and Research, Austin Health, Heidelberg, Victoria, Australia; ²Pharmacy Department, Austin Health, Heidelberg, Victoria, Australia; ³Centre for Medicine Use and Safety, Faculty of Pharmacy and Pharmaceutical Sciences, Monash University, Parkville, Victoria, Australia; ⁴National Centre for Infections in Cancer, Peter MacCallum Cancer Centre, Victoria, Australia; ⁵Department of Medicine, Austin Health, University of Melbourne, Parkville, Victoria, Australia

Model: AMS lead antibiotic allergy ward round (weekly)

Stakeholders: AMS pharmacist/ID physician/Nurse

Target: Antibiotic allergy + antibiotic utilization



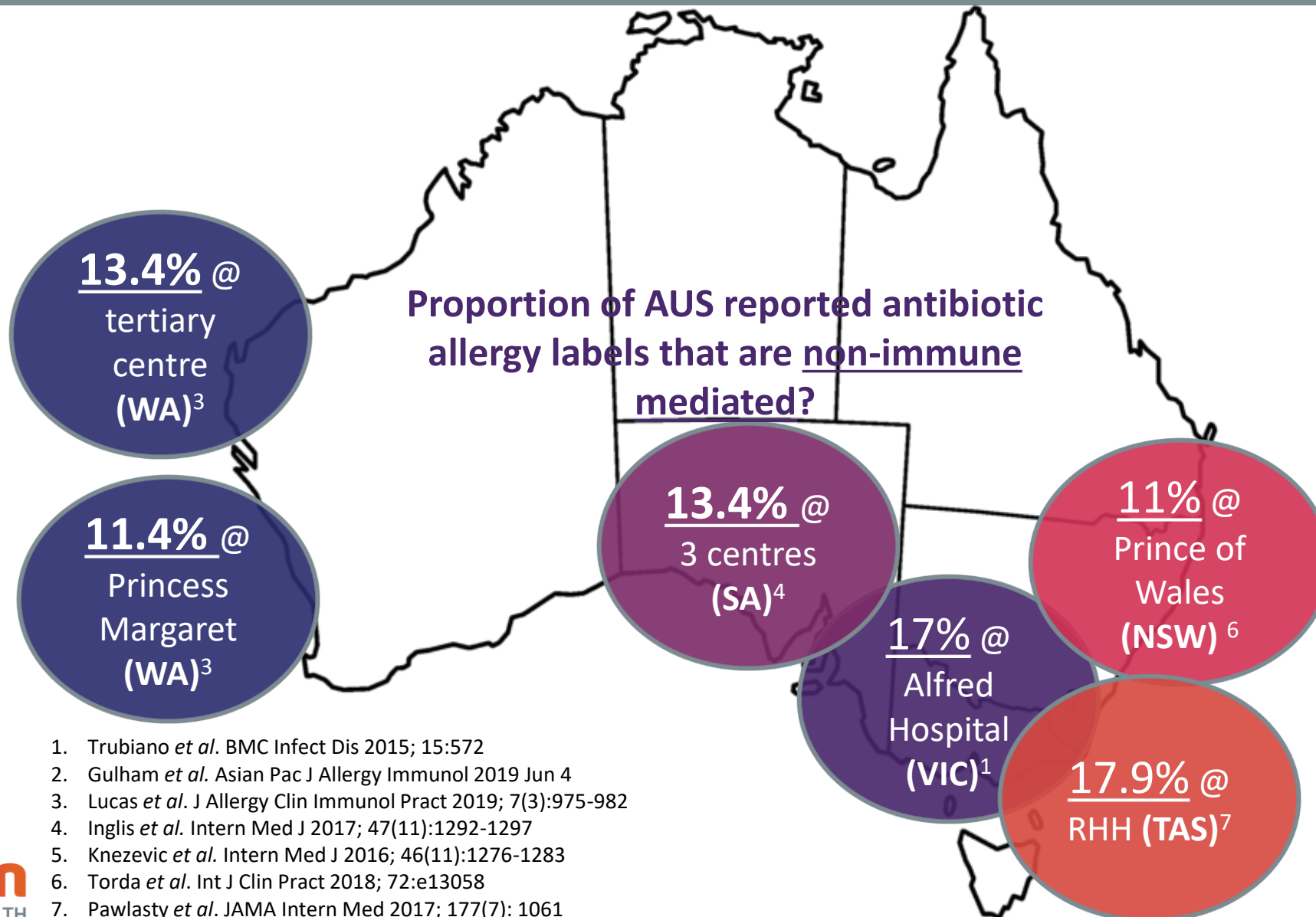
64% de-labelled via careful history and medical reconciliation

63.6% of Type A ADRs removed [Type A 20.8% all ADRs]

SPECIAL FEATURE

A practical guide for pharmacists to successfully implement penicillin allergy skin testing

How much "fake news" in Australia?



1. Trubiano *et al.* BMC Infect Dis 2015; 15:572
2. Gulham *et al.* Asian Pac J Allergy Immunol 2019 Jun 4
3. Lucas *et al.* J Allergy Clin Immunol Pract 2019; 7(3):975-982
4. Inglis *et al.* Intern Med J 2017; 47(11):1292-1297
5. Knezevic *et al.* Intern Med J 2016; 46(11):1276-1283
6. Torda *et al.* Int J Clin Pract 2018; 72:e13058
7. Pawlasty *et al.* JAMA Intern Med 2017; 177(7): 1061

Penicillin allergy & paed exanthems = false allergy

The role of penicillin in benign skin rashes in childhood: A prospective study based on drug rechallenge

Jean-Christoph Caubet, MD,^a Laurent Kaiser, MD,^b Barbara Lemaître, MS,^b Benoît Fellay, PhD,^c Alain Gervaix, MD,^a and Philippe A. Eigenmann, MD^a *Geneva and Fribourg, Switzerland*

- Only 6.5% reproducible on testing
- 65% of negative testing group had positive viral study

Amoxicillin-induced exanthema in patients with infectious mononucleosis: allergy or transient immunostimulation?

- Can occur also with CMV, HSV and HHV6 infections
- Most reactions are not present on representation
- Secondary to altered drug metabolism or immune mediated process

U. Jappe*

Cases of confirmed hypersensitivity reported, however RARE^{3,4}

1. Caubet *et al.* J Allergy Clin Immunol 2009; 127: 217
 2. Jappe *et al.* Allergy 2007; 62: 1474-5
 3. Dibek Misirlioglu *et al.* Int Arch Allergy Immunol 2018; 176(1):33-38

4. Ónodi-Nagy *et al.* Allergy Asthma Clin Immunol 2015; 11(1):1
 5. Chovel-Sella *et al.* Pediatrics; 131(5):e1424-7

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- 5. Penicillin allergy in the EMR should include type, timing, severity & tolerated antibiotics** [Assessment]
6. Do not automatically label a penicillin allergic patient also allergic to cephalosporins
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Assessment – The implications of guidelines

Contraindicated

At all times where reasonable evidence of penicillin allergy exists

Ampicillin
Amoxicillin
Amoxicillin/clavulanic acid (e.g. *Augmentin*®)
Benzathine penicillin
Benzylpenicillin (e.g. *penicillin G*)
Phenoxymethylpenicillin (e.g. *penicillin V*)
Dicloxacillin
Flucloxacillin
Piperacillin/tazobactam (e.g. *Tazocin*®)
Ticarcillin/clavulanic acid (e.g. *Timentin*®)

Caution

Avoid if severe penicillin allergy (e.g. anaphylaxis)
Use with caution if non-severe allergy (e.g. minor rash)
Seek specialist advice

Cefaclor
Cefepime
Cefotaxime
Cefoxitin
Ceftazidime
Ceftriaxone
Cefuroxime
Cephalexin
Cephazolin
Doripenem, ertapenem, imipenem, meropenem

- In **severe** penicillin allergy (e.g. anaphylaxis, bronchospasm, urticaria, angioedema), **avoid ALL** penicillins, cephalosporins and other beta-lactam antibiotics

Excessive caution due to an overestimation of SEVERITY and CROSS-REACTIVITY has been at the COST of a beta-lactam

Should guidelines avoid beta-lactams in PEN allergic?

Clinical Infectious Diseases

INVITED ARTICLE

CLINICAL PRACTICE: Ellie J.C. Goldstein, Section Editor



Is a Reported Penicillin Allergy Sufficient Grounds to Forgo the Multidimensional Antimicrobial Benefits of β -Lactam Antibiotics?

George Sakoulas,^{1,2} Matthew Geriak,¹ and Victor Nizet^{2,3}

¹Sharp Memorial Hospital, San Diego, and ²School of Medicine and ³Skaggs School of Pharmacy, University of California, San Diego, La Jolla

*** Antibiotic choice should be based upon an infection-specific risk/benefit analysis of β -lactam vs. non- β -lactam agent, with I.D., and possibly allergy, consultation**

Assessment – Correct Phenotyping

Determining penicillin allergy TYPE and SEVERITY is achieved by the approach outlined below

Approach to penicillin allergy

Questions to ask on history

Severity: Severe or non-severe

Do you remember the details of the reaction?
How was the reaction managed?
Did it require treatment or hospitalization?

Timing: Immediate or delayed

Immediate: Within hours of 1st or 2nd dose
vs. delayed: onset after days

How long after taking the antibiotic did the reaction occur?
How many years ago did the reaction occur?

Antibiotics tolerated

Penicillin tolerance pre allergy does not
confer tolerance post allergy

Are there other antibiotics, in particular penicillins,
you have taken without problem post the described
penicillin allergy?

If penicillin allergy still “unknown”...

Let time from reaction (e.g. childhood vs recent) and severity (e.g. no treatment or hospitalization) guide you



Assessment – Tools

A
Page 1

Toolkit A Penicillin Allergy History

Patient ID/ Sticker: _____

Date of reaction: _____
Route of last administration: Oral Intravenous

A
Page 2

Toolkit A (continued)

Patient ID/ Sticker: _____

Reaction details (check all that apply):

Intolerance histories

- Isolated GI upset (diarrhea, nausea, vomiting, abdominal pain) Chills (rigors)

Severity

Low-risk allergy histories

- Family history Itching (pruritus)
 Unknown, remote (> 10 yr ago) reaction Patient denies allergy but is on record

Moderate-high risk allergy histories (potential IgE reactions)

- Anaphylaxis Angioedema/swelling Bronchospasm (chest tightness)
 Cough Nasal symptoms Arrhythmia
 Throat tightness Hypotension Flushing/redness
 Shortness of breath Rash Syncope/pass out
 Wheezing
 Dizzy/lightheadedness
- Type of rash (if known): _____

HIGH RISK: Contraindicated penicillin skin testing/challenge (potential severe non-immediate reactions)

- Stevens-Johnson syndrome (rash with mucosal lesions) Serum sickness (rash with joint pain, fever, myalgia) Thrombocytopenia Fever
 Organ injury (liver, kidney) Erythema multiforme (rash with target lesions) Dystonia Anemia
 Acute generalized exanthematous (rash with pustules) Drug reaction eosinophilia and systemic symptoms (rash with eosinophilia and organ injury)

Timing/onset:

- Immediate (< 4 hrs)
 Intermediate (4-24 hrs)
 Delayed (> 24 hrs)
 Unknown

Treatment:

- None/penicillin continued Antihistamines
 Steroids (IV or PO) Epinephrine
 Penicillin discontinued IV Fluids
 Other: _____

Timing

How long ago was the reaction:

- < 6 mo 6 mo-1 yr 2-5 yrs 6-10 yrs > 10 yrs Unknown

Other beta-lactam use:

- Previous use of a penicillin or beta-lactam (prior to course that caused reaction)

If yes, please list drugs:

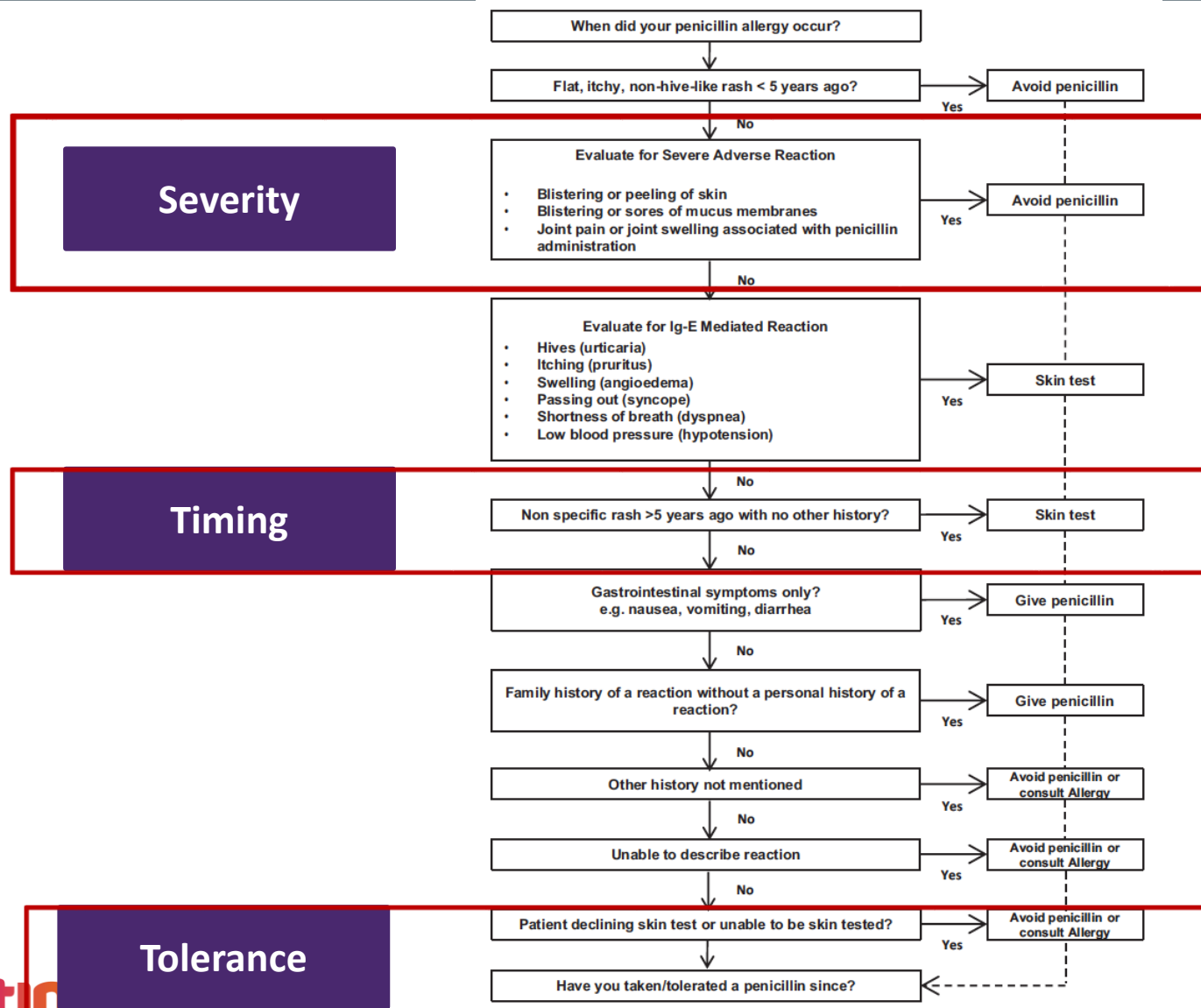
- Subsequent use of a penicillin or beta-lactam (after the course that caused a reaction)

Tolerance

Table 3. Risk Stratification for Penicillin Allergy Evaluation

	Low Risk	Medium Risk	High Risk
History^a	Isolated reactions that are unlikely allergic (eg, gastrointestinal symptoms, headaches) Pruritus without rash Remote (>10 y) unknown reactions without features of IgE ^b Family history of penicillin allergy	Urticaria or other pruritic rashes Reactions with features of IgE but not anaphylaxis ^b	Anaphylactic symptoms ^c Positive skin testing Recurrent reactions Reactions to multiple β-lactam antibiotics
Action	Prescribe amoxicillin course or perform a direct amoxicillin challenge under observation. ^d	Skin test followed by amoxicillin challenge under observation if the skin test is negative. ^e Consider allergy/immunology referral.	Allergy/immunology referral or desensitization.

Assessment – Tools



Predicting antibiotic allergy risk

Dermatological		Respiratory or Systemic		Unknown reaction	
Clinical manifestation	Recommendation & Resultant allergy type	Clinical manifestation	Recommendation & Resultant allergy type	Clinical manifestation	Recommendation & Resultant allergy type
Childhood exanthem (unspecified) <i>Details of rash timing unknown and no severe features or hospitalisation</i>	<input type="checkbox"/> Unlikely to be significant (non-severe)	Laryngeal involvement ("throat tightness" or "hoarse voice")	<input type="checkbox"/> Immediate hypersensitivity (severe)	Unknown reaction ≤ 10 years ago	<input type="checkbox"/> Unlikely significant (non-severe)
Immediate diffuse rash ("itchy immediate rash") <2 hours post dose	<input type="checkbox"/> Immediate hypersensitivity (non-severe)	Respiratory compromise ("wheeze or shortness of breath")	<input type="checkbox"/> Immediate hypersensitivity (severe)	Unknown reaction > 10 years ago or family history of penicillin allergy only	<input type="checkbox"/> Unlikely significant (non-severe, low risk)
Diffuse rash or localized rash with no other symptoms > 24 hours post starting antibiotic	≤ 10 years ago <input type="checkbox"/> Delayed hypersensitivity (non-severe)	Fever ("high temperature") - <i>Not explained by infection or other cause</i>	<input type="checkbox"/> Delayed hypersensitivity (severe)	Renal	
	> 10 years ago <input type="checkbox"/> Delayed hypersensitivity (non-severe, low risk)	Anaphylaxis or unexplained hypotension or collapse	<input type="checkbox"/> Immediate hypersensitivity (severe)	Severe renal injury or failure (>50% reduction in eGFR from baseline or absolute serum creatinine increase of ≥26.5µmol/L, or transplantation, or dialysis)	<input type="checkbox"/> Potential immune mediated (severe, if AIN)
Rash & mucosal ulceration ("mouth, eye or genital ulcers") <i>Be alert for history of SCAR</i>	<input type="checkbox"/> Delayed hypersensitivity (severe)	Haematological		Renal impairment (Does not meet criteria for renal failure or severe injury [see box above])	<input type="checkbox"/> Unlikely immune mediated (non-severe, low risk)
Pustular, blistering or desquamating ("skin shedding") rash <i>Be alert for history of SCAR</i>	<input type="checkbox"/> Delayed hypersensitivity (severe)	Platelets < 150 x10 ⁹ /L or unknown	<input type="checkbox"/> Potential immune mediated (severe)	Liver	
Angioedema ("lip, facial or tongue swelling")	<input type="checkbox"/> Immediate hypersensitivity (severe)	Neutrophils < 1x10 ⁹ /L or unknown	<input type="checkbox"/> Potential immune mediated (severe)	Severe liver injury or failure (≥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)	<input type="checkbox"/> Potential immune mediated (severe, if DILI)
Swelling (outside of angioedema)	<input type="checkbox"/> Immediate hypersensitivity (severe)	Haemoglobin < 100 g/L or unknown	<input type="checkbox"/> Potential immune mediated (severe)	Hepatic enzyme derangement (Does not meet criteria for liver failure or severe injury [see box above])	<input type="checkbox"/> Unlikely immune mediated (non-severe, low risk)
Urticaria ("wheals and hives")	<input type="checkbox"/> Immediate hypersensitivity (non-severe)	Eosinophilia (>0.7 x 10 ⁹ /L or unknown) <i>Examine history for DRESS</i>	<input type="checkbox"/> Delayed hypersensitivity (severe, if DRESS)	Neurological, gastrointestinal or other	
				Gastrointestinal symptoms ("nausea, vomiting, diarrhoea")	<input type="checkbox"/> Unlikely immune mediated (non-severe, low risk)
Appropriate for direct de-labelling - removal of allergy label without testing [oral rechallenge if required]				Severe neurological or CNS manifestation ("seizures or psychosis"),	<input type="checkbox"/> Unknown or unclear mechanism – Contact ID pharmacist for advice
Appropriate for supervised direct oral rechallenge ³				Other, <u>QR</u> ;	
May be appropriate for skin testing followed by oral rechallenge ³				Anaphylactoid/infusion reaction	
Appropriate for outpatient antibiotic allergy assessment +/- testing					

Low-risk

Moderate-risk

High-risk

Overall sensitivity 91.8%
(95% CI 88.9-94.0)

Now being implemented into
health services
internationally

1. Devchand *et al.* J Clin Immunol Pract 2019; 7(3):1063-1065.e5
2. Devchand *et al.* J Antimicrob Chemother 2019; 74 (6): 1725

How can I predict a “true” penicillin allergy?

Penicillin allergy history (n = 685)	Crude Odds Ratio [OR] (95% CI)		Adjusted Odds Ratio [OR] (95% CI)	
	Univariable	P-value	Multivariable*	P-value
Childhood	0.40 (0.21 – 0.77)	0.005	0.43 (0.22 – 0.84)	0.014
Anaphylaxis	3.67 (1.68 – 8.03)	0.001	3.53 (1.59 – 7.84)	0.002
Angioedema	3.51 (1.61 – 7.67)	0.001	3.60 (1.62 – 7.97)	0.002
Urticaria	1.00 (0.57 – 1.77)	0.99	-	-
Diffuse itchy rash	1.26 (0.77 – 2.06)	0.36	-	-
Diffuse non-itchy rash	0.65 (0.30 – 1.41)	0.27	-	-
Collapse (unspecified)	-	-	-	-
Swelling (unspecified)	0.71 (0.27 – 1.82)	0.47	-	-
Localised rash	0.69 (0.16 – 2.99)	0.619	-	-
Respiratory only	1.04 (0.31 – 3.58)	0.941	-	-

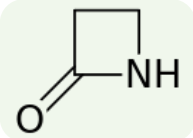
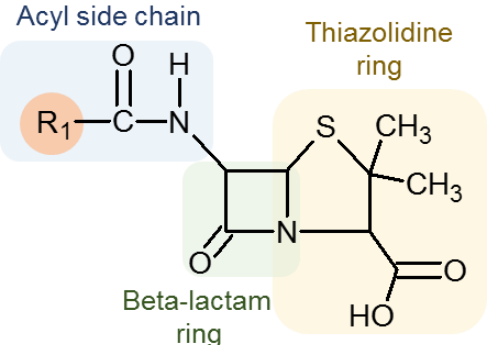
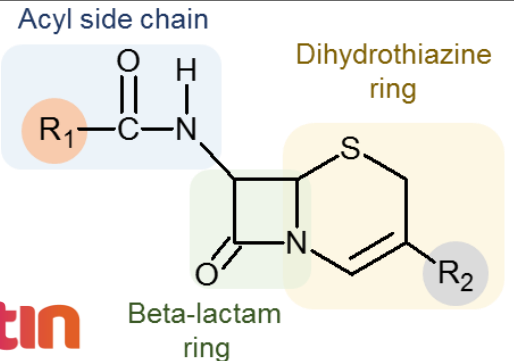
* Final multi-variable model with backward stepwise elimination

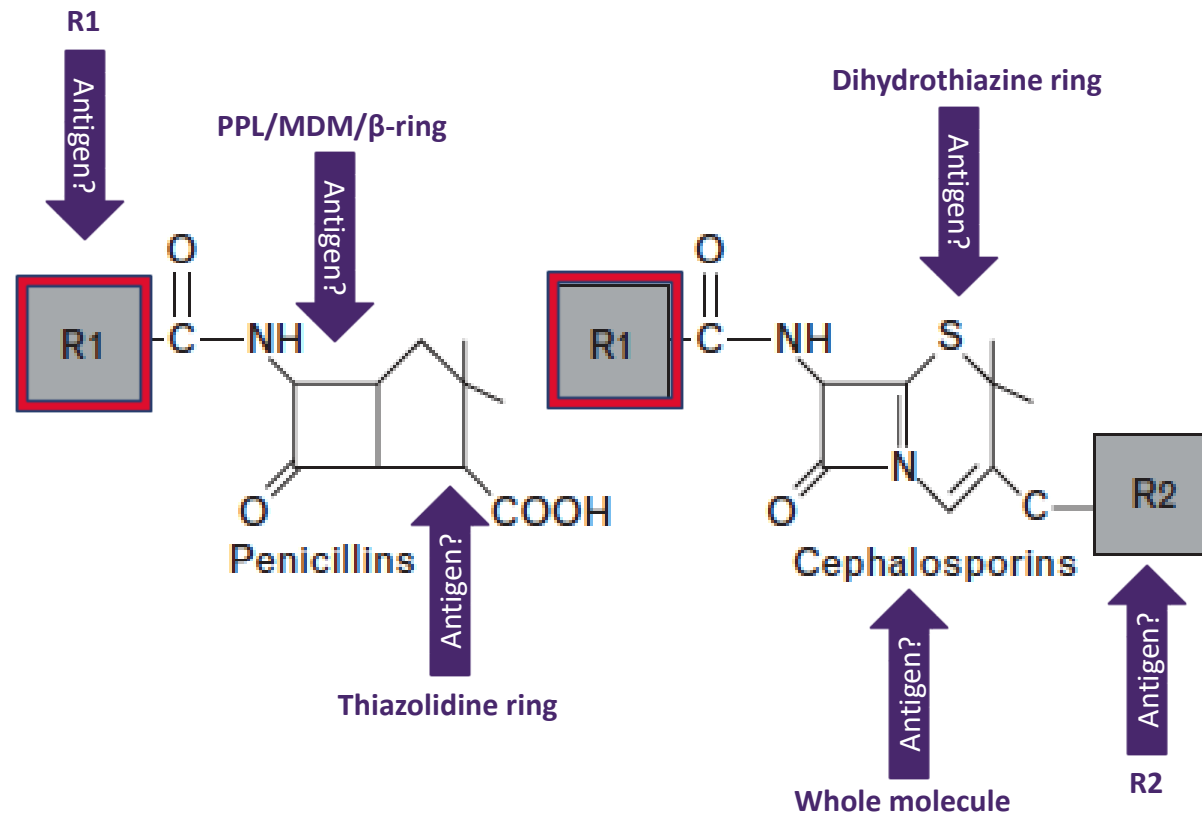
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[Cross-reactivity]
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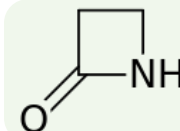
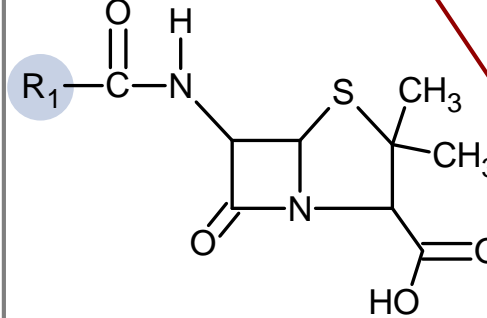
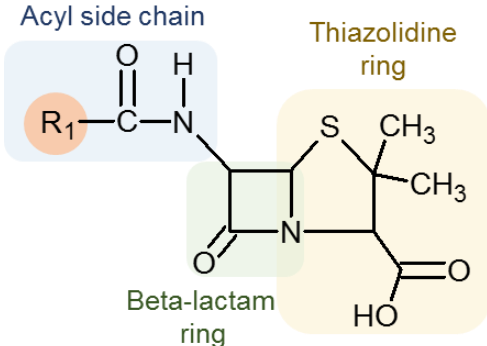
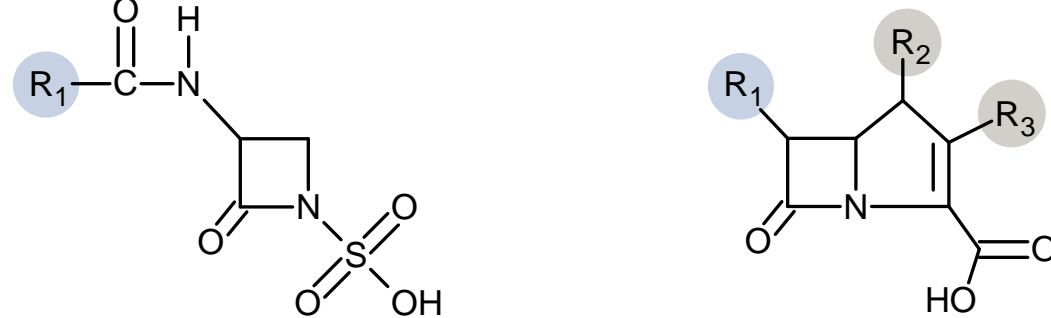
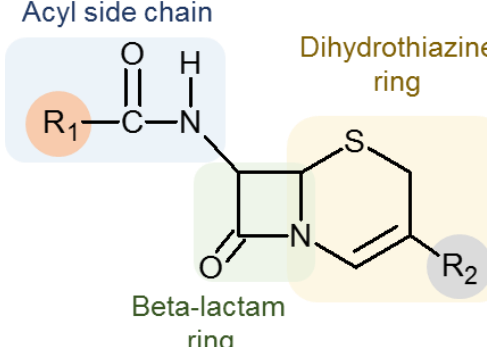
<https://antibioticallergy.org.au/resources#abd34176-6344-49ce-bbe7-9e36dc0da0a6>

Beta-lactam cross-reactivity – Mechanisms

Basic structures	
Beta-lactam ring	
	
Penicillin structure	
Acyl side chain	Thiazolidine ring
	
Cephalosporin structure	
Acyl side chain	Dihydrothiazine ring
	



Beta-lactam cross-reactivity - Rates

Basic structures	Beta-Lactam structures and rates of cross-reactivity
Beta-lactam ring	
	<p>Penicillins ↔ Cephalosporins (<math><2\%^*</math>)</p>
Penicillin structure	 <p>None</p>
<p>Acyl side chain</p> <p>Thiazolidine ring</p>  <p>Beta-lactam ring</p>	<p>Penicillins ↔ Carbapenems (<math>>1\%</math>)</p> <p>None</p>
Cephalosporin structure	<p>Monobactams[†] ↔ Carbapenems (None)</p> 
<p>Acyl side chain</p> <p>Dihydrothiazine ring</p>  <p>Beta-lactam ring</p>	<p>Blumenthal, Peters, Trubiano, Phillips. Lancet 2019; 393(10167):183-198</p>

Why such high earlier reports of cross-reactivity?

- **Earlier reports of 10% cross-reactivity limited by;** ¹⁻⁵
 - Contamination of early cephalosporin manufacturing by penicillins
 - Cross-reactivity studies included ALL reactions
 - Cross-reactivity between amoxicillin/ampicillin and cephalexin/ceclor 14.7-38%

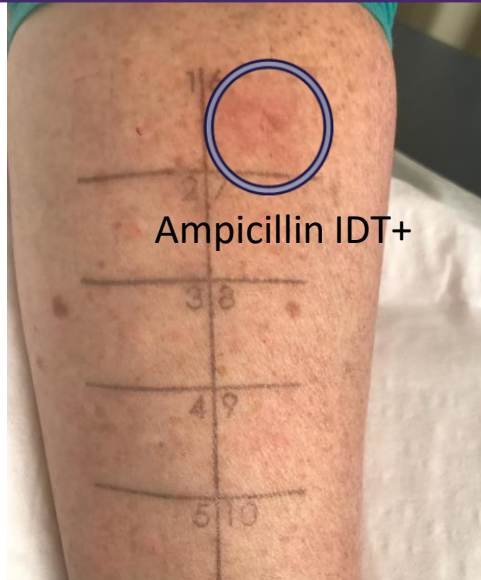
- Increased cross-reactivity with 1st gen cephalosporins (OR 4.8) but not with 2nd or 3rd
 - Modern studies of penicillin allergy pts (skin test variable) – **0.6-1.8% cross-reactivity**⁶⁻⁹
 - Recent meta-analysis (n = 21 studies) - **2.11% cross-reactivity**¹⁰
 - Austin/PMCC data – penicillin & cephalosporin skin test positive – **0.63% (4/630)**

1. Madaan *et al.* Immunol Allergy Clin North Am 2004; 24: 463
2. Pichichero *et al.* Otolaryngol Head Neck Surg 2007; 136:340
3. Romano *et al.* J Allergy Clin Immunol 2016; 138 (1): 179
4. Miranda *et al.* J Allergy Clin Immunol 1996; 98: 671

5. Zagursky *et al.* J Allergy Clin Immunol Pract 2018; 6:72
6. Beltran *et al.* J Pediatr Surg 2015; 50: 856
7. Macy *et al.* Perm J 2011; 15: 31
8. Macy *et al.* J Allergy Clin Immunol 2015; 135: 745
9. Romano *et al.* J Allergy Clin Immunol Pract 2018; 6(5):1662-1672

Penicillin-cephalosporin side-chain cross-reactivity

Ampicillin & Cephalexin shared R1



Ampicillin IDT+

Cephalexin urticaria with positive ampicillin IDT

	PENICILLIN G	PENICILLIN VK	AMPICILLIN	AMOXICILLIN	SEMI-SYNTHETIC ANTISTAPH PEN	PIPERACILLIN-TAZOBACTAM	CEFADROXIL	CEFAZOLIN	CEPHALEXIN	CEPROZIL	CEPHALOTHIN ^a	CEFOXITIN ^a	CEFOTETAN	CEFAMANDOLE	CEFUROXIME	CEFEPIME	CEFTRIAXONE	CEFOTAXIME	CEFTAZIDIME	CEFDINIR	CEFIXIME	CEFTAROLINE	CEFTIBIPROLE	CEFTOZOLANE-TAZOBACTAM	
PENICILLIN G	■	R1 *									◁	◁													
PENICILLIN VK	R1 *	■																							
AMPICILLIN			■	R1 *			R1 *	R1	R1 *	R1 *															
AMOXICILLIN			R1 *	■			R1	R1 *	R1 *	R1															
SEMI-SYNTHETIC ANTISTAPH PEN					■																				
PIPERACILLIN-TAZOBACTAM						■																			
CEPHALOSPORIN 1st GENERATION																									
CEFADROXIL			R1 *	R1			■	R1 *	R1 *	R1 *	R1														
CEPROZIL			R1 *	R1			R1	R1 *	R1 *	■															
CEFAZOLIN			R1	R1 *			R1 *	■	R1 *	R1 *															
CEPHALEXIN			R1	R1 *			R1 *	R1	■	R1 *															
CEPHALOTHIN	^										■	R1													R2

Amino-penicillin/cephalosporin cross-reactivity

Study - Region	N	Phenotype	Test + Amp/amox	Test + cephalosporin	Cross-reactivity
Audicana <i>et al.</i> (1994) – EU	16	Immediate	Yes - IDT	OC or IDT cephalixin	31.2%
Sastre <i>et al.</i> (1996) – EU	16	Immediate	Yes – IDT or OC	OC cephalixin	12%
Miranda <i>et al.</i> (1996) – EU	21	Immediate	Yes – IDT, OC or RAST	OC cefadroxil	38%
Atanaskovic-M <i>et al.</i> (2005) - EU	116	Immediate	Yes – IDT or OC	OC or IDT cephalixin	65.9%
Buonomo <i>et al.</i> (2014) – EU	26	Non-immediate	Yes - IDT	OC cephalixin	19%
Romano <i>et al.</i> (2016) – EU	214	Non-immediate	Yes – IDT	cephalixin	18.7%
Romano <i>et al.</i> (2018) – EU	252	Immediate	Yes – IDT	OC or IDT aminocephalosporin	36.1%
Phillips <i>et al.</i> (2001) – Canada	26	Delayed	Yes – IDT or PT	PT cephalixin (n = 5/16)	31.2%
Tritt <i>et al.</i> (2018) – USA	12	Immediate & delayed	Yes – IDT or OC	OC negative cephalixin	0%
Macy <i>et al.</i> (2018) – USA	34	Immediate & delayed	Yes – OC	OC cephalixin/cefactor (n = 13)	0%

Abbreviations: EU, Europe; USA, United States of America; AUS, Australia

AH/PMCC data: 6/15 (40%) of cephalixin anaphylaxis positive to amoxicillin/ampicillin

16.45% (95% CI: 11.07 – 23.75) cross-reactivity between amino-penicillins/cephalosporins¹

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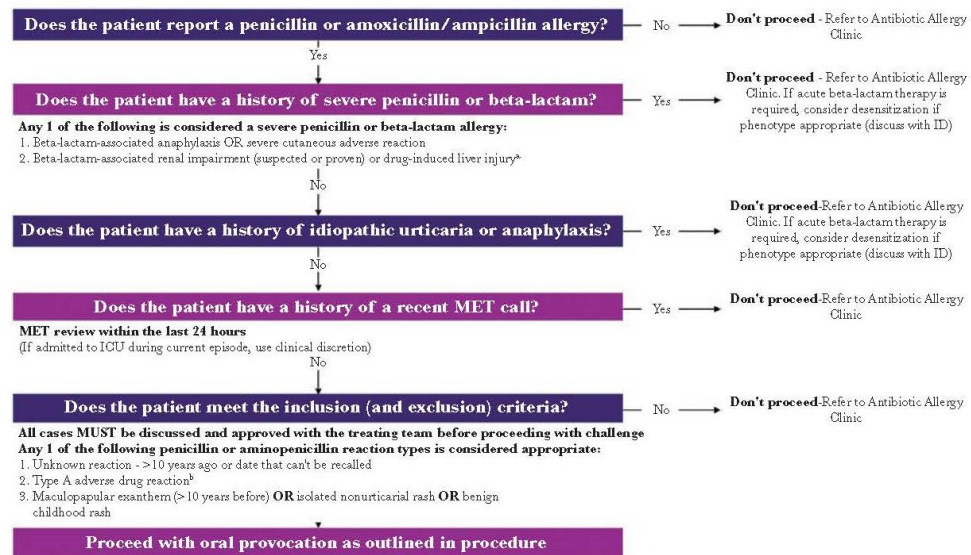
Low risk allergy - Evidence for direct oral challenge

Author	Year	N	Setting	Design	Patients	Phenotype	Procedure	Positive
Mustafa <i>et al.</i> (USA)	2019	159	Outpatient	RCT	> 5 years (median 37 yrs)	Rash or unknown <u>AND</u> > 10 years <u>AND</u> No emergency treatment	2-step amoxicillin	3.8%
Du Plessis <i>et al.</i> (NZ)	2019	34	Inpatient	Prospective cohort	16-70 years	Delayed onset rash > 5 years	5-step amoxicillin	9%
Trubiano <i>et al.</i> (AUS)	2018	48	Inpatient/ Outpatient	Prospective cohort	> 18 years	Rash > 10 years <u>OR</u> Unknown <u>OR</u> Childhood exanthema	1-step penicillin/amoxicillin	0%
Kuruvilla <i>et al.</i> (USA)	2018	20	Outpatient	Retrospective cohort	> 18 years	Benign rash > 12 months <u>OR</u> Benign somatic symptoms <u>OR</u> Unknown	Amoxicillin (unknown)	15%
Immatteo <i>et al.</i> (USA)	2018	155	Outpatient	Prospective cohort	> 7 years	“Non-life threatening” penicillin allergy <u>OR</u> Rash <u>OR</u> Unknown	2-step amoxicillin	2.6%
Macy <i>et al.</i> (USA)	2017	519	Outpatient	Retrospective cohort	Unspecified	“Low-risk” (unspecified)	Amoxicillin (unknown)	1.8%
Tucker <i>et al.</i> (USA)	2017	328	Outpatient	Retrospective cohort	> 18 years	All reactions excluding “severe cutaneous reactions”	Amoxicillin (unknown)	1.5%
Confino-Cohen <i>et al.</i> (Israel)	2017	617	Outpatient	Prospective cohort	Paediatrics (median 8 yrs)	Non-immediate hypersensitivity (except SCAR) <u>OR</u> Unknown reaction	2-3 step amoxicillin	5.3%
Vezir <i>et al.</i> (Europe)	2016	119	Outpatient	Retrospective cohort	Paediatrics (median 4 yrs)	Non-immediate cutaneous	5-step beta-lactams	3.4%
Mill <i>et al.</i> (Canada)	2016	818	Outpatient	Prospective cohort	Paediatrics (median 1.7 yrs)	All reactions (except SJS/TEN)	2-step amoxicillin	5.9%

Low risk allergy – Local approach

The Safety and Efficacy of an Oral Penicillin Challenge Program in Cancer Patients: A Multicenter Pilot Study

Jason A. Trubiano,^{1,2,3} Olivia Smibert,¹ Abby Douglas,¹
Misha Devchand,² Belinda Lambros,¹ Natasha E. Holmes,² Kyra Y. Chua,²
Elizabeth J. Phillips,⁴ and Monica A. Slavin¹



- Clinical protocol at Austin and Peter Mac
- Upscaling supported by Victoria DOH
- **Low risk criteria**
 - Unknown > 10 years
 - Type A ADR
 - MPE > 10yrs or benign childhood
- **Prospective inpatient cohort study (2018-19)**
 - 100 direct oral challenges (penicillin)
 - 100% rechallenge negative

Antibiotic allergy testing – Multidisciplinary service



Antibiotic Allergy Testing Program

Commenced May 2015
[prospective recruitment, $n = 1113$ to date]

**“De-label” in > 84%
of patients tested¹⁻³**

Infectious Diseases

AMS

Allergy

Pharmacy

**Short term AMS
impacts [90 day]**

**↑ 2.8 fold NS penicillins
↑ 12 fold appropriateness^{1,2}**

**Long-term allergy
impacts [365 day]**

**88% of penicillin AAL removed
95% willing to take de-labelled³**

**Long-term AMS
impacts [365 day]**

**↓ 2 fold restricted antibiotics
↑ 3 fold preferred antibiotics³**

1. Trubiano *et al.* Clin Infect Dis 2017; 65(1):166-174
2. Trubiano *et al.* J Antimicrob Chemother 2018; 73(11):3209-3211
3. Trubiano *et al.* ASID 2019 Oral Abstract #64

Antibiotic allergy testing – Patient perceptions

12-month follow up survey of “de-labelled” patients post allergy testing

95.2% willing to
use de-labelled
antibiotic

91.9% report the
correct allergy
history

96% of patients
utilization de-
labelled antibiotic
event-free

No evidence of Resensitization^{1,2}

1. Trubiano *et al.* ASID 2019 Oral Abstract #64
2. Solensky *et al.* Arch Intern Med 2002; 162 (7): 822
3. Dorman *et al.* J Allergy Clin Immunol Pract 2018; 6(1):196-200

Barriers to de-labelling

Original Article

Patient and Primary Care Physician Perceptions of Penicillin Allergy Testing and Subsequent Use of Penicillin-Containing Antibiotics: A Qualitative Study

Marta Wanat, PhD^a, Sibyl Anthierens, PhD^b, Christopher C. Butler, MD^a, Louise Savic, MD^c, Sinisa Savic, MD, PhD^d, Sue H. Pavitt, PhD^e, Jonathan A.T. Sandoe, PhD^{f,*}, and Sarah Tonkin-Crine, PhD^{a,g,*} *Oxford and Leeds, United Kingdom; and Antwerp, Belgium*

Patients unaware of the benefits and **Clinicians** reluctant to change patient records on clinical judgment alone

10 Golden Rules of Penicillin Allergy

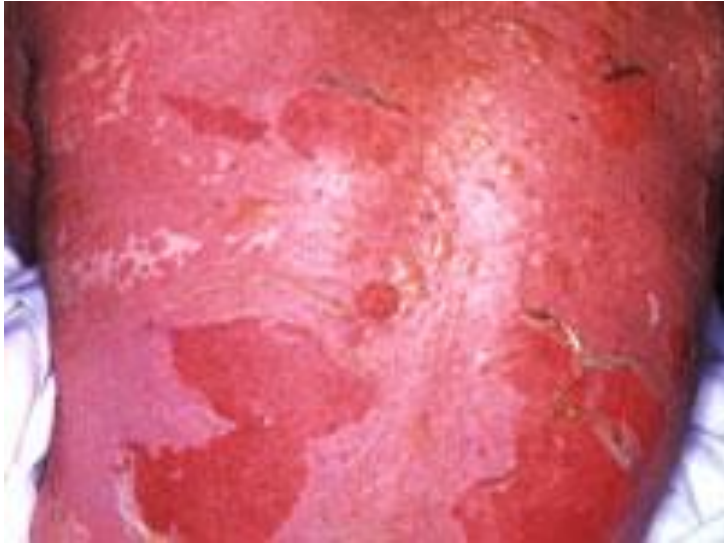
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Severe cutaneous adverse reactions –

20% inpatient mortality in SCAR (*severe delayed*) vs. **1%** in anaphylaxis (*severe immediate*)^{2,3}



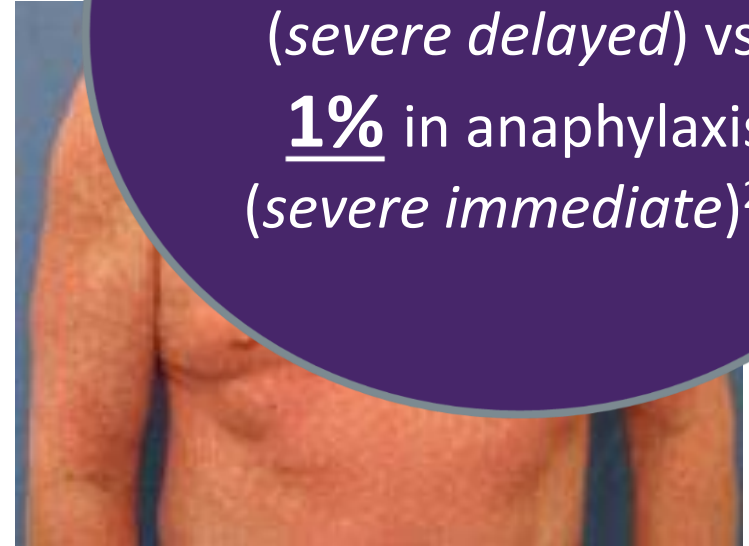
SJS/TEN

Stevens-Johnson Syndrome/Toxic Epidermal necrolysis



AGEP

Acute generalized exanthematous pustulosis



DRESS

Drug reaction with eosinophilia and systemic symptoms

1. Konvinse *et al.* Curr Opin Infect Dis 2016; 29(6): 561
2. Trubiano *et al.* J Allergy Clin Immunol Pract 2016; 4(6): 1187
3. Hall *et al.* ECCMID 2019 Poster Abstract #P2009

Cross-reactivity in severe delayed (i.e. SCAR)

1. Often multiple drugs implicated from the same class
2. Fear of disease reoccurrence influences clinical decisions
3. Data regarding cross-reactivity in SCAR (T-cell mediated) less well described
 - Avoid same class at a minimum = e.g. all penicillins OR all cephalosporins
4. Literature has noted difference patterns of cross-reactivity than IgE-mediated
 - “Penicillin ring” cross-reactivity

1. Watts *et al.* J Clin 2018; 6(5): 1766

2. Romano *et al.* J Allergy Clin Immunol 2016; 138 (1): 179

3. Buonomo *et al.* J Investig Allergol Clin Immunol 2014; 24(5):331-7

4. Romano *et al.* Allergy 2013; 68(12):1618-21

5. Schiavino *et al.* Allergy 2009; 64 (11): 1644

6. Tricka *et al.* J Antimicrob Chemother 2007; 60 (1): 107

What is the future of antibiotic allergy care?



Personalized antibiotic allergy care in Hospital AMS

On admission – Accurate assessment & record documentation

Low risk

Childhood, Type A, unknown, non-severe delayed[^]

ID/allergy Testing

AMS Prescribing

Oral challenge OR
direct de-label
[dependent on
phenotype]

Give preferred
antibiotic therapy

[^] *Non-severe delayed* - > 10 years post onset

Moderate risk

Non-severe immediate or delayed[‡]

ID/allergy Testing

AMS Prescribing

Skin testing OR
oral challenge
[risk assessment]

Give non-cross
reactive therapy

[‡] *Non-severe delayed* - < 10 years post onset

Severe risk

Severe delayed or immediate^{}*

ID/allergy Testing

AMS Prescribing

Specialist skin
testing or *in vitro*
diagnostics

Avoid class-related
[risk/benefit][†]

^{*}*Severity* - Severe delayed >>> severe immediate

[†]Consider non-cross reactive in severe immediate

Develop personalized antibiotic plan based on **allergy phenotype & infection**

Bust myths by obeying the Golden Rules...

1. Do not label a patient as penicillin allergic if they have not had a reaction to penicillin (e.g. family history only) [@PAallergy](#)
2. Do not label a patient as penicillin allergic if they report a known drug side effect (e.g. vomiting, diarrhoea) [@TrubianoJason](#)
3. Do not automatically label a patient that is penicillin allergic also allergic to cephalosporins [@TracyZembles](#) [@drdavidwig](#)
4. Do not label a patient allergic to a beta-lactam class (e.g. penicillins) - name the implicated drug (e.g. amoxicillin) [@ABsteward](#)
5. Do not label as penicillin allergic if a rash to penicillin or amoxicillin occurred during mononucleosis (i.e. EBV) [@TanyaLaidlawMD](#)
6. Penicillin allergy is rarely forever [@KimberlyBlumen1](#)
7. Penicillin allergy should always be investigated [@EricMacyMD](#)
8. Penicillin allergy in the EMR should include the allergy type, timing, severity and tolerated antibiotics [@julie_justo](#)
9. A change in a patient's penicillin allergy "label" needs to be conveyed to the patient, provider and referrer [@marylynnstaicu](#)
10. Usual rules of penicillin cross-reactivity do not apply to severe cutaneous adverse reactions (e.g. SJS, TEN, DRESS) [@peripatetical](#)

Thank you...

▪ Austin Health

- Drug and Antibiotic Allergy Services, Pharmacy and Respiratory departments
- Prof Lindsay Grayson
- Mrs Wendy Stevenson
- Mrs Rebecca Hall
- Ms Misha Devchand
- Dr Natasha Holmes
- Dr Kyra Chua
- Dr Ian Letson
- Dr Chris Fiddes



▪ Peter MacCallum Cancer Centre

- Infectious diseases and pharmacy departments
- Prof Monica Slavin
- Prof Karin Thursky
- Dr Abby Douglas
- Mrs Belinda Lambros
- Mrs Jacinta Lean



▪ Murdoch University & Vanderbilt University

- Prof. Elizabeth Phillips
- Prof. Simon Mallal
- Dr. Katherine Konvinse



▪ National Centre for Infections in Cancer



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- NHMRC Early Careers Fellowship
- University of Melbourne & Austin Medical Research Foundation (AMRF)
- National Centre for Infections in Cancer



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www.antibioticallergy.org.au