Beta-Lactam Allergy

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Objectives

By the end of this session participants will be able to:

- Define Type 1-IV hypersensitivity reactions
- Describe approach to a patient with label of penicillin/cephalosporin allergy
- Compare and contrast cross-reactivity of beta-lactam antibiotics
- Discuss beta-lactam allergy management at NSHA

Cases

- 56 year-old male admitted to MTU with cellulitis
  - Label of penicillin allergy
  - Team starts him on vancomycin

- 76 year-old female seen in pre-op clinic prior to TKR
  - Label of penicillin allergy
  - Anesthesia wonders if they can use cefazolin intra-operatively

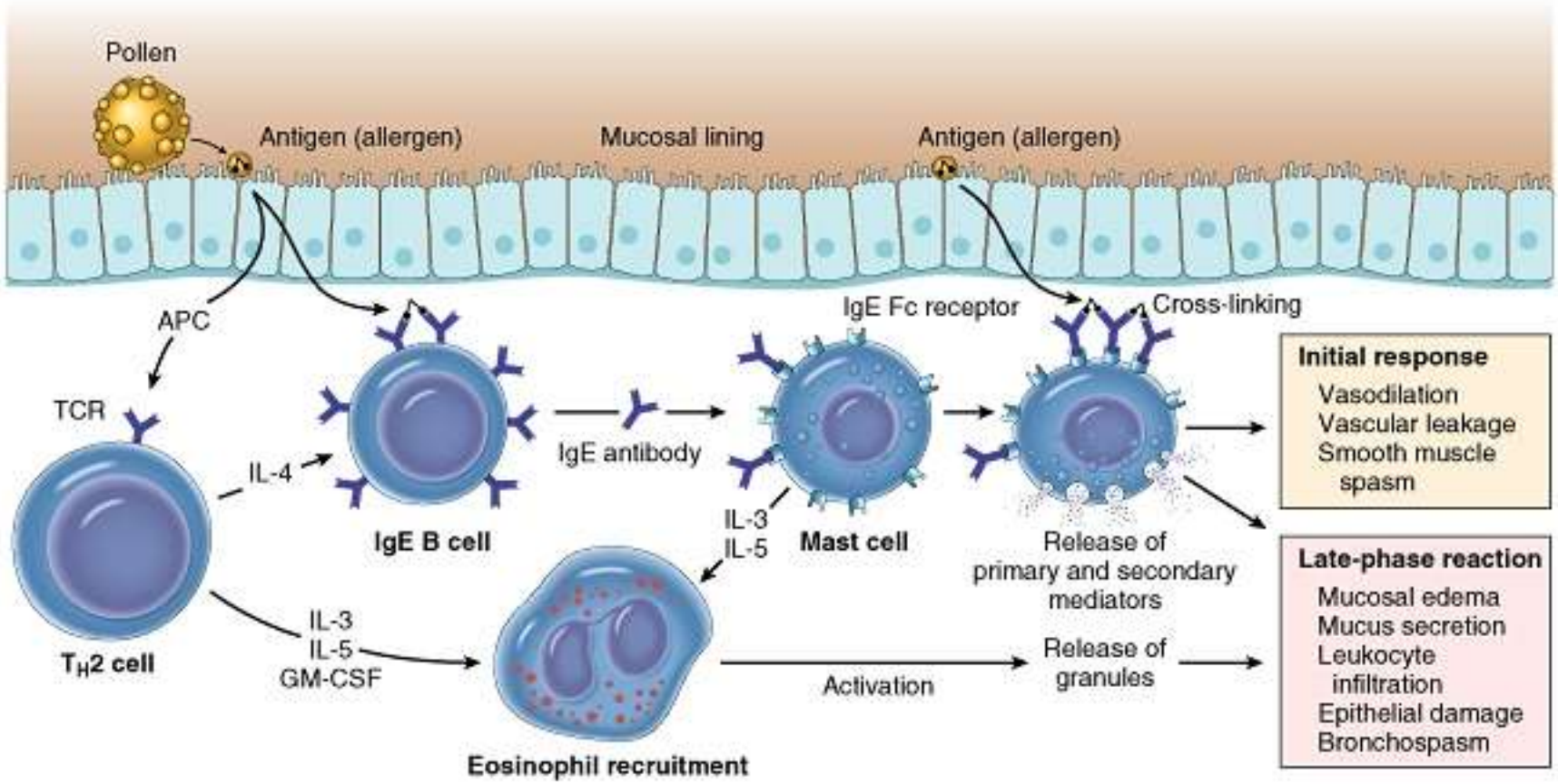
Cases

- 28 year-old male with label of penicillin allergy
  - No Hx of reaction
  - Sister had a rash with penicillin as a baby

Table 1. Modified Gell and Coombs Classification System for Allergic Drug Reactions (From Janeway C, Travers C, Walport M, Shlomchik M, Immunology: The Immune System in Health and Disease. 5th ed. New York: Garland; 2001)

Extended Gell and Coombs classification	Type of Immune Response	Pathologic Characteristics	Clinical Symptoms	Cell Type
Type I	IgE	Mast-cell degranulation	Urticaria, anaphylaxis	B cells/Ig
Type II	IgG	FcR-dependent cell destruction	Blood cell dyscrasia	B cells/Ig
Type III	IgG and complement	Immune complex deposition	Vasculitis	B cells/Ig
Type IVa	Th1 (IFN-γ)	Monocyte activation	Eczema	T cells
Type IVb	Th2 (IL-5 and IL-4)	Eosinophilic inflammation	Maculopapular exanthema, bullous exanthema	T cells
Type IVc	Cytotoxic T lymphocytes	CD4- or CD8-mediated killing or cells	Maculopapular exanthema, eczema, bullous exanthema, pustular exanthema	T cells
Type IVd	T cells	Neutrophil recruitment and activation	Pustular exanthema	T cells

Type 1 Hypersensitivity



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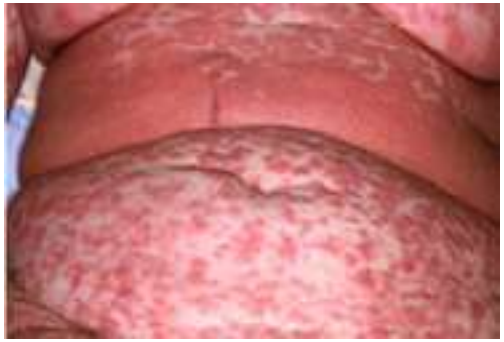
IgE-mediated Hypersensitivity

Non-IgE mediated Reactions



←DRESS syndrome

Morbilliform eruption→

Bullous pemphigoid ↑

←SJS/TEN

Fixed drug eruption ↓

AGEP ↓

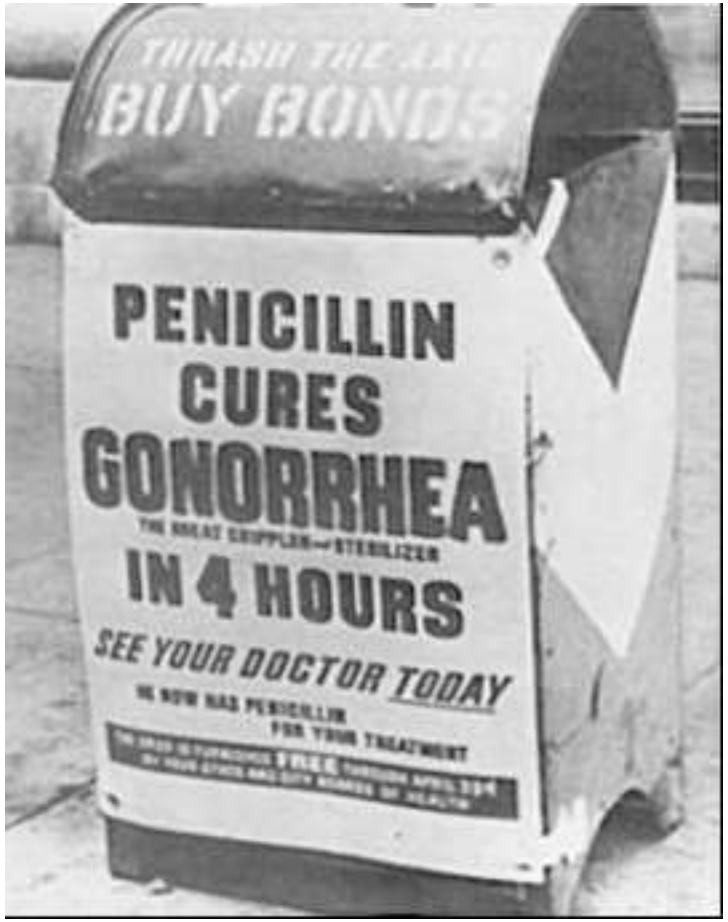
Worrisome non-IgE mediated adverse drug reactions

- Stevens-Johnson syndrome
- Serum sickness
- Vasculitis
- Hemolytic anemias
- Allergic interstitial nephritis
- DRESS (DIHS)

Risk Factors for Drug Allergy

- High dose
- IV administration
- LMW agents
- Frequent, repeated courses
- Female
- Young or old

Drug Allergy: An Updated Practice Parameter.
Annals of Allergy, Asthma & Immunol. 2010;105



PENICILLIN ALLERGY

Epidemiology

- The frequency of all adverse reactions to penicillin in the general population ranges from 0.7% to 10%[1].
- Anaphylactic reactions occur in about 0.004% to 0.015% of penicillin courses and are most commonly seen in adults between the ages of 20 and 49 years[1].
- The mean antibiotic costs for patients allergic to penicillin are 63% higher than those who are not allergic to penicillin[2].

1.Salkind A et al. JAMA 2001
2.Sade K et al. Clin Exp Allergy 2003

Epidemiology

- After an allergic reaction to penicillin, penicillin-specific immunoglobulin decrease by 10% per year, to approximately 30% after 10 years[1].
- More than 80% of patients self-reporting a penicillin allergy have negative skin testing[2].

1.Greenberger PA. Patterson's Allergic Diseases 6th edition 2002
2.Fiszenson-Albala F et al. Br J Dermatol 2003

Beta-lactams

- Physicians often avoid all beta-lactams when patient labeled pen allergic
- Non beta-lactams may be:
  - less effective
  - more toxic
  - broader spectrum
  - more expensive
  - more likely to lead to infection or colonization with resistant organisms

Teirico, Terry et al. Beta-lactam allergy and cross-reactivity. Journal of Pharmacy Practice. 2014(27): 330-41

Lee, C.L., Zembower, T.R., Fotis M.A., Postelnick, M.J.; Greenberger, P.A., *et al.* The Incidene of Antimicrobial Allergies in Hospitalized Patients. Arch Intern Med 2000; 160:2819-2822

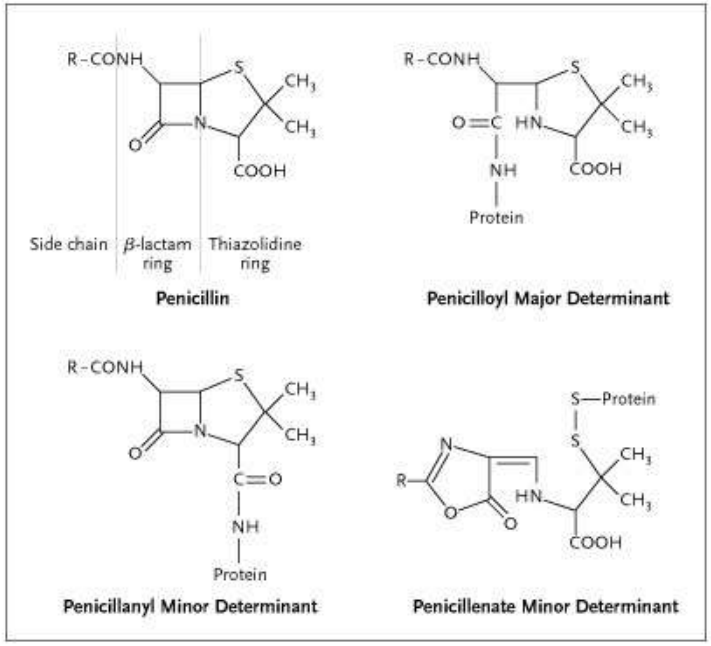
The label

- Increases the likelihood of prolonged hospital stay
- Increases the risk of infections
  - *Clostridium difficile*, VRE, MRSA

Macy E. and Contreras R. Health care use and serious infection prevalence associated with penicillin"allergy" in hospitalized patients: A cohort study. J Allergy Clin Immunol 2014;133:790-796

Diagnosis of Penicillin allergy

- History
- Physical examination
- *Skin testing*
  - *Major and minor determinants*
- *Immunologic testing*
  - *ImmunoCAP*
- Oral challenge



Penicillin allergy history

- What age was the patient when the drug was taken?
- Does the patient recall the reaction?
- Why were they on penicillin?
- With which dose did the reaction occur?
- Symptoms of reaction?
- Route of administration?
- What other medications were they on at the time?
- What happened when the penicillin was discontinued?
- Have other antibiotics been tried since then?
  - Reactions with those?

- The positive predictive value for the clinical history of penicillin allergy is 14% (95% CI, 12%-18%)[1]

1. JAMA 2001

Penicillin skin testing

- Epicutaneous, then intradermal (if epicutaneous testing negative)
- Both major and minor determinants
  - PrePen
  - PenG
- Ampicillin/amoxicillin testing (some centres)
- Test is positive in 90% of patients with IgE-mediated hypersensitivity

Penicillin skin testing

Source, year	Sample size (n), % Pen allergic	Sensitivity	Specificity	LR+ (95% CI)	LR- (95% CI)
Adkinson et al, 1971	218, 11.9	0.61	0.74	2.4 (1.6-3.5)	0.5 (0.3-0.85)
Green et al, 1977	2947, 8.1	0.79	0.45	1.4 (1.4-1.5)	0.5 (0.39-0.57)
Sogn et al, 1992	1298, 12.6	0.85	0.50	1.7 (1.6-1.9)	0.3 (0.21-0.44)
Gadde et al, 1993	5063, 2.5	0.43	0.85	2.9 (2.4-3.7)	0.7 (0.57-0.77)
Summary				1.9 (1.5-2.5)	0.5 (0.4-0.6)

Salkind A. et al., The Rational Clinical Exam. JAMA 2001

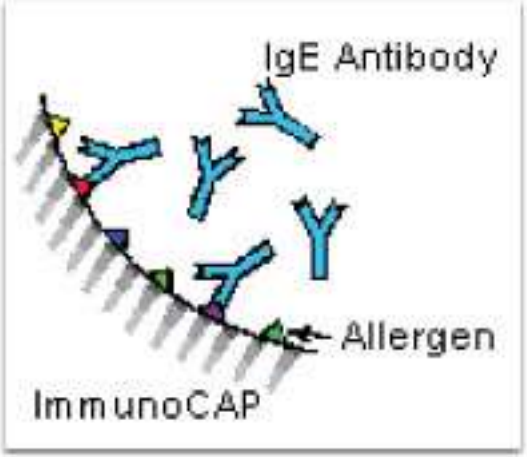
Penicillin skin testing

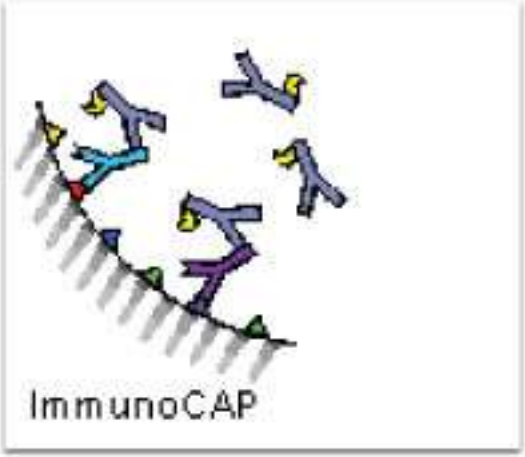
- 98% of patients with a negative skin test will tolerate penicillin with no adverse reaction.
- Positive PEN skin test indicates the presence of IgE but only 50 -70% of these patients will actually have an allergic reaction when challenged
- Patients with a positive skin test who need penicillin should undergo desensitization.

Weiss et al, Immediate hypersensitivity reactions to penicillin and related antibiotics, Clin Allergy, 1988

Immunologic testing

- ImmunoCAP testing
  - Allergen specific IgE antibody assay
  - ImmunoCAP: cellulose sponge matrix in the form of a small cap as an allergosorbent on which allergen is covalently coupled
- Only detect antibody to the major determinant; therefore, less sensitive than skin testing





Pivotal Article

Assessing the Diagnostic Properties of a Graded Oral Provocation Challenge for the Diagnosis of Immediate and Nonimmediate Reactions to Amoxicillin in Children

Christopher Mill, MPH; Marie-Noël Primeau, MD; Elaine Medoff, MD; Christine Lejtenyi, MD; Andrew O'Keefe, MD; Elena Netchiporouk, MD; Alizee Dery, BSc; Moshe Ben-Shoshan, MD, MSc

JAMA Pediatr. 2016;170(6):e160033. doi:10.1001/jamapediatrics.2016.0033

From: **Assessing the Diagnostic Properties of a Graded Oral Provocation Challenge for the Diagnosis of Immediate and Nonimmediate Reactions to Amoxicillin in Children**

JAMA Pediatr. 2016;170(6):e160033. doi:10.1001/jamapediatrics.2016.0033

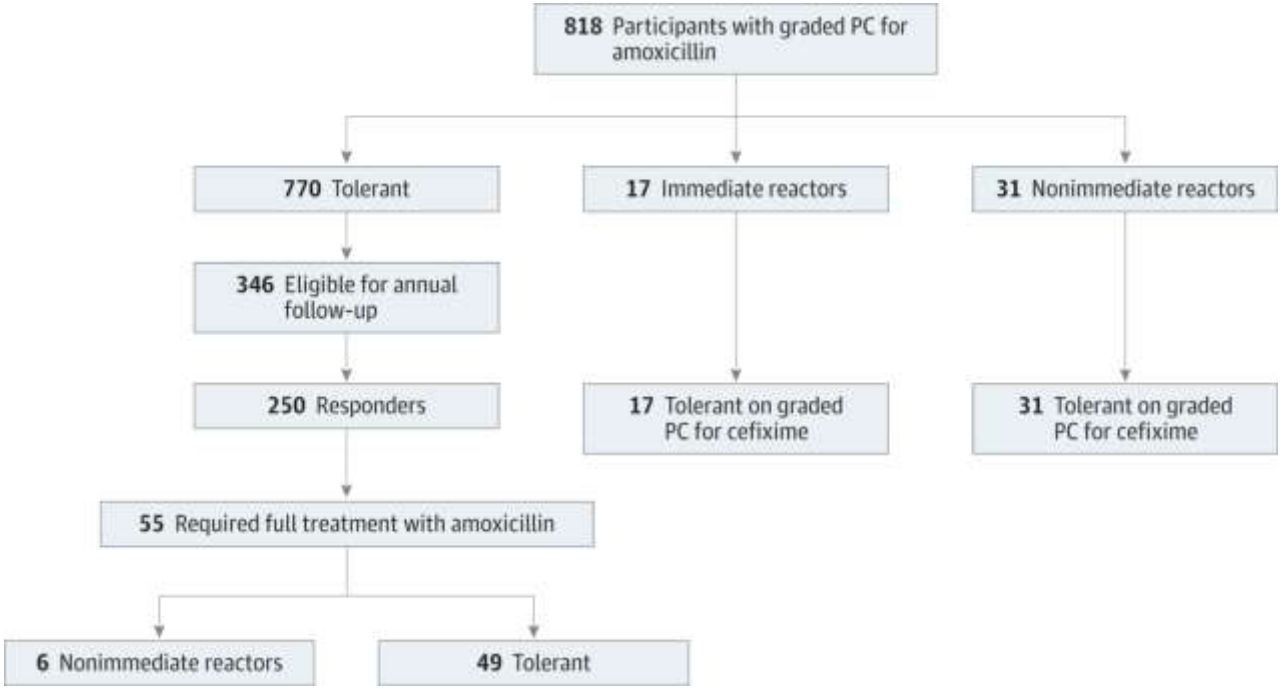


Figure Legend:

Flow Diagram of 818 Patients With a Graded Oral Provocation Challenge (PC) for AmoxicillinAmong 818 patients, 94.1% were tolerant to the graded PC for amoxicillin, 2.1% reacted immediately (within 1 hour), and 3.8% had nonimmediate reactions. Of those tolerating the PC for amoxicillin and requiring subsequent full treatment with amoxicillin, 89.1% tolerated the full treatment.

Date of download: 6/18/2017

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Cross reaction: cephalosporin

- Cephalosporins can cause allergic-type skin reactions in 1-3% of those exposed
- Anaphylaxis to cephalosporins is rare (0.0001- 0.1%)
- Share a beta-lactam ring with penicillin, but side chains differ dramatically
- Haptenic determinants are likely many and unknown, therefore no standardized skin testing exists

Yates, Beta-lactam antibiotic allergies, Amer Journ Med, 2007

Cephalosporin cross-reactivity

Reference	Cephalosporin Reaction Rate	
	+ Hx Penicillin Allergy	- Hx Penicillin Allergy
Dash CH (1975)*	7.7%	0.8%
Petz LD (1978)*	8.1%	1.5%
Goodman EJ (2001)	0.24%	0.03%
Dalat SB (2004)	0.17%	0.06%

* Cephaloridine and cefamandole most commonly implicated

Cross reaction: cephalosporins

- Combining data from 11 studies, 6 of 135 (4%) patients with positive penicillin testing had reactions to cephalosporins
- 2 of 351(0.6%) with negative penicillin testing had reactions to cephalosporins
- Reviewing 12 fatal anaphylaxis in the UK, 6 were with first dose cephalosporin, of which 3 were known allergic to penicillin
- Penicillin allergic patients have a 3-fold higher rate of allergic reactions to any drug, even structurally unrelated drugs

- *Kelkar et al, cephalosporin allergy, NEJM, 2001*

CROSS-REACTIVITY

- Between penicillins and cephalosporins
  - Due to similarities of side chains (**NOT due to beta-lactam ring)**
    - cephalosporins with similar 7-position side chains should be used with caution
    - cephalosporins with different side chains **are not more likely** to produce allergic reactions
    - **ceFAZolin, ceFIXime and ceftAZIDime have unique side chains and** should not cross react (and therefore are not included in the table below)

- Among cephalosporins: **RARE**
  - Most side chains are different, may cross-react if in same group (see table below)
  - **ceFAZolin, ceFIXime and ceftAZIDime have unique side chains and** should not cross react with other cephalosporin's including cephalexin(and therefore are not included in the table below)

- Penicillins and carbapenems(meropenem, ertapenem)
  - ~1% cross reactivity

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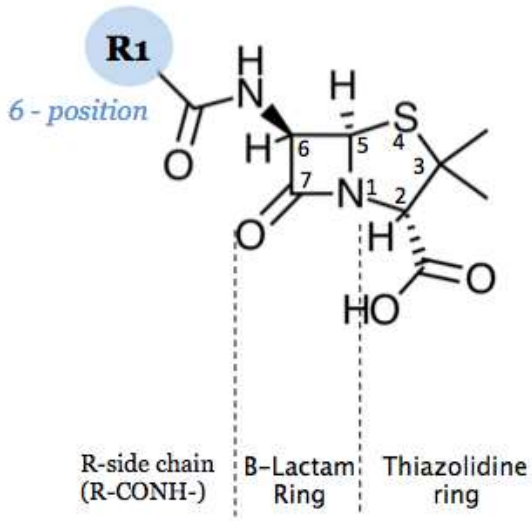
Side Chains

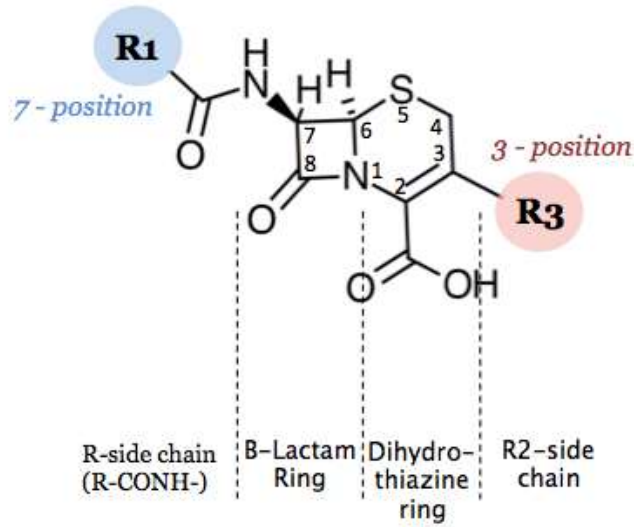
CROSS REACTIVITY BETA-LACTAMS

7-position Side Chains Cross reactions possible **within** groups		
A	B	C
Penicillin cefOXItin	Amoxicillin Ampicillin cephalexin cefADROxil cefPROZil cefaCLOR	cefoTAXime cefTRIAXone Cefepime

3-Position Side chains Cross reactions possible **within** groups	
A	B
cephALEXin cefADROxil	cefUROXime cefOXItin



Penicillins



Cephalosporins

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Beta-lactam cross-allergy

		penicillin	amoxicillin	ampicillin	cloxacillin	piperacillin	ticarcillin	cefadroxil	ceFAZolin	cephalexin	cephalothin	cefaclor	cefprozil	cefuroxime	cefOXitin	cefixime	cefotaxime	cefTAZidime	cefTRIAXone	cefepime	meropenem	imipenem	ertapenem	aztreonam
PENICILLINS	penicillin		*	*	*	*	*				*				*									
	amoxicillin	*		*	*	*	*	*		*		*	*											
	ampicillin	*	*		*	*	*	*		*		*	*											
	cloxacillin	*	*	*		*	*																	
	piperacillin	*	*	*	*		*																	
	ticarcillin	*	*	*	*	*																		
1ST GENERATION CEPHALOSPORION	cefadroxil		*	*						*		*	*											
	ceFAZolin																							
	cephalexin		*	*				*				*	*											
	cephalothin	*													*		*							
2ND GENERATION CEPHALOSPORIN	cefaclor		*	*				*		*			*											
	cefprozil		*	*				*		*		*												
	cefuroxime														*									
	cefOXitin	*									*			*										
3RD GENERATION CEPHALOSPORIN	cefixime																							
	cefotaxime										*								*	*				
	cefTAZidime																							*
	cefTRIAXone																*			*				
4TH GEN CEPH	cefepime																*		*					
CARBAPENEMS	meropenem																					*	*	
	imipenem																				*		*	
	ertapenem																				*	*		
Monobactam	aztreonam																	*						

What do we actually do?

- Cutaneous only
  - Amoxicillin challenge
- Severe, systemic reaction
  - Skin testing, challenge if skin tests negative
- Approximately 2-4 amoxil challenges/day in office
- Drug allergy clinic 1 day/month
- Urgent referrals pre-op/ID clinic

Possible Approaches to Beta-lactam allergy management

Beta-lactam Allergy Skin Testing (BLAST)

- Abstract presented at AMMI
- Point of care skin testing for beta-lactams done by pharmacy/physician team, trained by allergists
- Study included 827 patients with reported beta-lactam allergy
  - For 67% beta-lactam would be preferred therapy
- Without testing 50% would get beta-lactam
- With BLAST 81% got beta-lactams
- Days of FQ's and carbapenems significantly decreased

Beta-lactam Allergy Skin Testing (BLAST) at the Point-of-care for Patients with Infectious Diseases: A Pragmatic Multicentre Evaluation

JA LEIS[1,4,5], L Palmay[1], G Ho[2], S Raybardhan[3], S Gill2, T Kan[3], J Campbell[1], S Walker[1], JB McCready[2,4], P Das[3,4], B Minnema[3,4], JE Powis[2,4], H Ferguson[1], B Wong[3], E Weber[1]

Beta-lactam Testing

Table 1 Nonirritating test concentrations for betalactam antibiotics

DRUG	SPT	IDT	PT
Penicilloyl-poly-L-lysine	5×10^{-5} mM	5×10^{-5} mM	NA
Minor determinant mixture	2×10^{-2} mM	2×10^{-2} mM	NA
Benzylpenicillin	10.000 UI	10.000 UI	5%
Amoxicillin	20 mg/ml	20 mg/ml	5%
Ampicillin	20 mg/ml	20 mg/ml	5%
Cephalosporins	2 mg/ml	2 mg/ml	5%

For this and all following tables: SPT, skin prick test; IDT, intradermal test; PT, patch test.

IWK Health Centre

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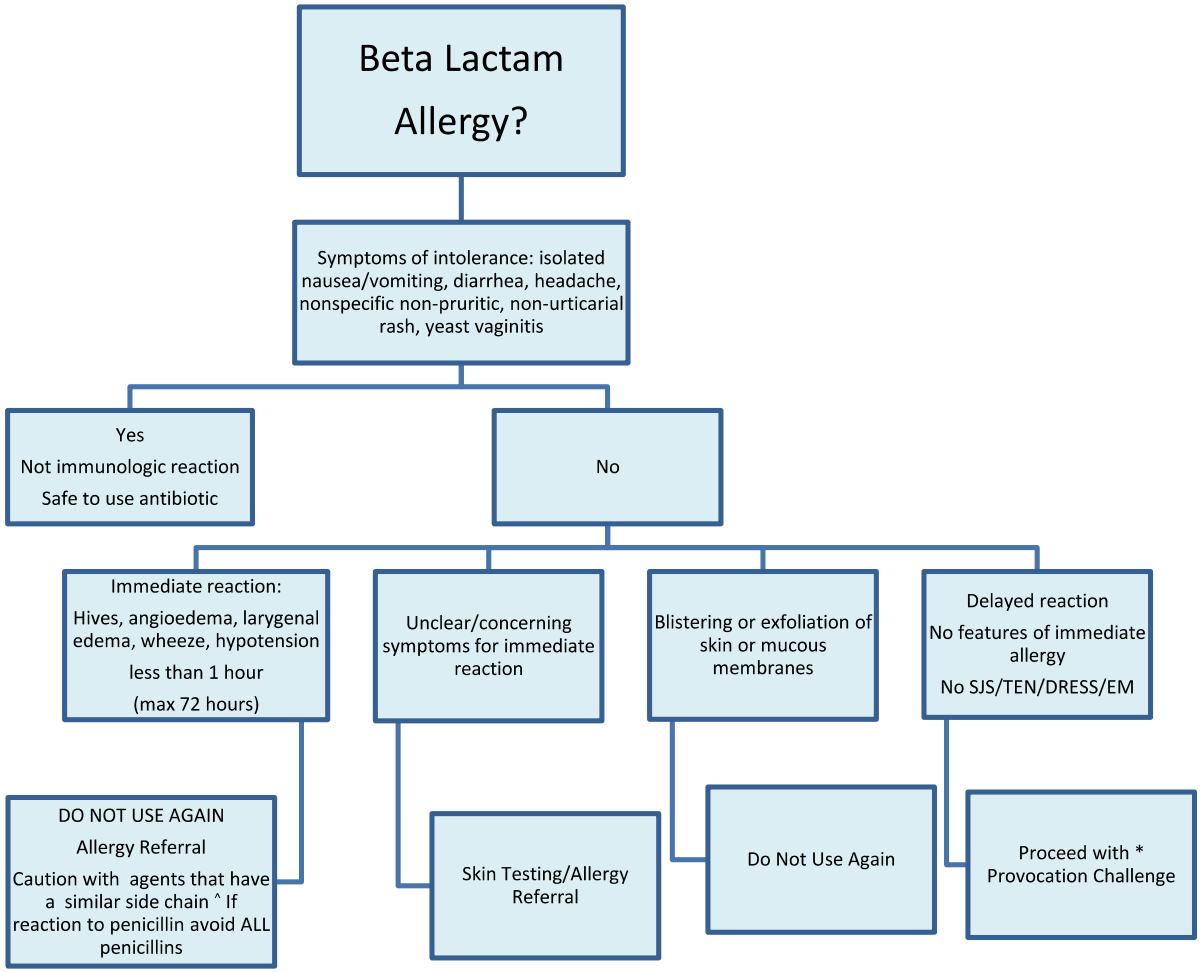
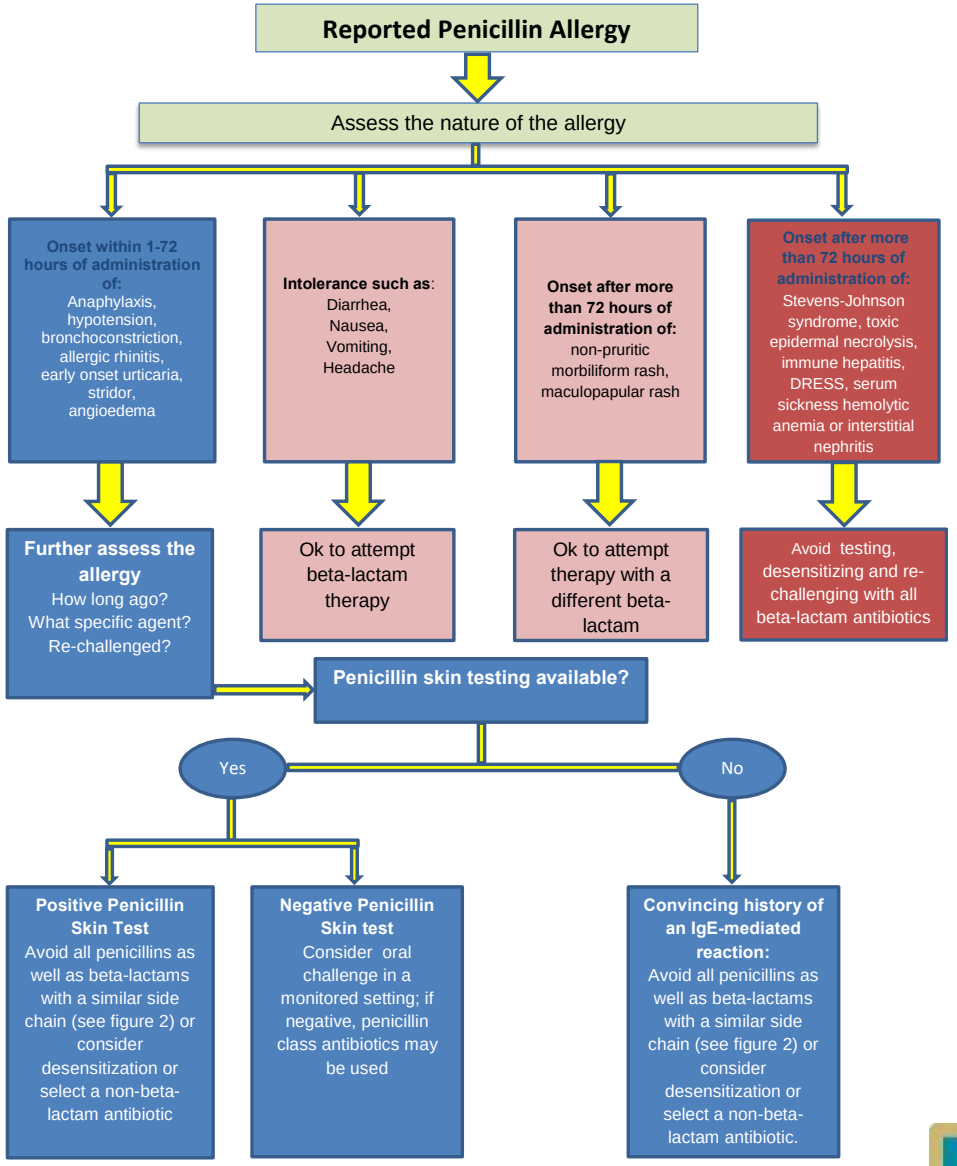


*10% of therapeutic dose, then 20 minutes later 90 % of therapeutic dose. Observation should occur for one hour after receiving the last dose



NB Comité de gérance des antimicrobiens
Anti-Infective Stewardship Committee
Optimal antimicrobial care for our patients and our future
Thérapie antimicrobienne optimale pour nos patients et notre avenir

Possible approach?

Ann Allergy Asthma Immunol. 2015 October ; 115(4): 294–300.e2. doi:10.1016/j.anai.2015.05.011.

Impact of a clinical guideline for prescribing antibiotics to inpatients reporting penicillin or cephalosporin allergy

Kimberly G. Blumenthal, M.D.[1,2,3], **Erica S. Shenoy, M.D., Ph.D.**[2,3,4,5], **Christy A. Varughese, Pharm. D.**[4,7], **Shelley Hurwitz, Ph.D.**[3,6], **David C. Hooper, M.D.**[3,4,5], and **Aleena Banerji, M.D.**[1,3]

Methods

- Guideline developed by AI, ID and Pharmacy
- Assisted providers to take drug allergy history
- Standardized test dose procedure
- Prior to guideline AI always consulted for such cases

Education

- Presented to 15 diff groups (general inpatient providers)
- Laminated cards with figures from guideline distributed
- Trained AI and ID fellows, peds residents, medicine residents (and repeated prn)

3-Step Guideline for Clinicians:

Step 1. Obtain and document an accurate history of the adverse reaction from the patient.

Ask about:

1. Timing of adverse reaction after taking antibiotic: minutes to hours or days later? Was this a first dose reaction?
2. How many years ago was the reaction?
3. How was the reaction treated: was there a need for urgent care or epinephrine administered?
4. Has the patient tolerated similar medications, such as ampicillin, amoxicillin or cephalexin with a history of penicillin allergy?
5. Symptoms of adverse reaction:

5. Symptoms of adverse reaction:

1.5.1 Raised, erythematous, pruritic rash with each lesion typically lasting less than 24hrs? (hives/urticaria)

1.5.2 Swelling of the tongue, mouth, lips, or eyes (angioedema)

1.5.3 Respiratory or hemodynamic changes (anaphylaxis)

1.5.4 Lesions or ulcers involving the mouth, lips, or eyes; skin desquamation (Stevens Johnson Syndrome (SJS), Toxic Epidermal Necrolysis (TEN), and other severe type IV reactions)

1.5.5 Organ involvement such as kidneys or liver (Acute Interstitial Nephritis (AIN). Drug Rash Eosinophilia and Systemic Symptoms (DRESS) syndrome, and other severe type IV reactions)

1.5.6 Joint pains (serum-sickness like reaction)

1.5.7 Rashes that were not hives, were mild, or delayed in onset (mild type IV reaction or maculopapular rash)

1.5.8 Nausea, vomiting, diarrhea, minor laboratory abnormalities or local injection reactions are ***minor adverse effects***, and should not preclude consideration of penicillin/cephalosporin use with appropriate monitoring.

1.5.9 Severe cytopenias or other significant laboratory abnormalities (i.e., nephrotoxicity) are ***major adverse effects that may preclude use***.

1.5.10 This pathway does not address antibiotic prescription for patients who have experienced adverse reactions.

Step 2. Document details of the reaction in the electronic medical record allergy section.

Step 3. Follow the pathway for patient with PCN Allergy (Figure 1) or Cephalosporin Allergy (Figure 2). If the pathway suggests a Test Dose Procedure, follow directions on Test Dose Procedure sheet. Page Allergy Fellow on Call with patient's name/Medical Record Number if you have questions related to pathway.

Type II-IV HSR

Serum sickness

Stevens-Johnson Syndrome

Toxic Epidermal Necrolysis

Acute Interstitial Nephritis (AIN)

Drug Rash Eosinophilia Systemic Symptoms (DRESS) Syndrome

Hemolytic anemia

↓

Avoid using PCN or cephalosporin; use alternative agents by microbial coverage§

If there is a strong clinical indication for use of a PCN or cephalosporin, please involve the Allergy and Infectious Disease services.

Type I (IgE-mediated) HSR

Anaphylaxis

Angioedema

Wheezing

Laryngeal edema

Hypotension

Hives/urticaria

OR

Unknown reaction WITHOUT mucosal involvement, skin desquamation or organ involvement

↓

OK to:

Use 3rd/4th generation cephalosporins or carbapenems* by **Test Dose Procedure**

OR

Use alternative agent by microbial coverage§

OR

Aztreonam*

If ID consult determines that PCN or a 1st/2nd generation cephalosporin is the preferred therapy, or that one of the alternative agents is substandard, consult Allergy

Mild reaction

Minor rash (not hives)

Maculopapular rash (mild Type IV HSR)

EMR lists allergy, but patient denies

↓

OK to:

Use full dose 3rd/4th generation cephalosporin

OR

Use penicillin or 1st/2nd generation cephalosporin by **Test Dose Procedure**

OR

Use carbapenem*

Test Dose Procedure

Place the following orders in POE prior to Test Dose Procedure:

1. If possible, hold the following medications the day of the Test Dose Procedure:
    a. Beta blockers: inhibit the action of epinephrine.
    b. ACE inhibitors: increase the risk of an allergic reaction.
2. RN to record vital signs (blood pressure, heart rate, and respiratory rate) prior to administering the drug (time 0) and every 30 minutes form the start of the procedure to the end of the procedure (time 120 minutes).
3. Write for the following PRN medications to be at the patient's bedside:
    a. Epinephrine 1:1000 for intramuscular administration (0.3 mg)
    b. Benadryl 50 mg for IV/PO administration
4. Order: Medication Order:
    a. Calculate and order 1/10 of the intended treatment dose for an IV medication or ¼ of a pill for an oral medication. Indicated in the instructions for this order that this dose is for step 1 of the Test Dose Procedure per the **MGH Penicillin and Cephalosporin Hypersensitivity Pathway.**
    b. One dose of the full treatment dose. Indicate in the instructions for this order that this dose is for step 2 of the Test Dose Procedure per the **MGH Penicillin and Cephalosporin Hypersensitivity Pathway.**

Test Dose Procedure:

- Step #1: The RN administers test dose as per orders above. RN records vital signs just prior to administration of test dose. At 30 minutes later, the RN checks vital signs and makes sure that the patient has not developed any rash or other symptoms. RN repeats vital signs and evaluation at 60 minutes (from initial test dose). If the patient remains asymptomatic and vital signs remain normal the RN may proceed to step #2.
- Step #2: The RN administers the full intended treatment dose of the medication. At 30 minutes later, the RN checks vital signs and makes sure that the patient has not developed any rash or other symptoms. RN repeats vital signs and evaluation at 60 minutes (from full treatment dose). If the patient remains asymptomatic and vital signs remain normal, then the patient will have successfully completed the test dose procedure without any reaction and can subsequently receive the medication as scheduled by the team.

➢ If a reaction occurs as a consequence of this procedure, please page the allergy fellow on call (p13042) and complete an Incident Report.

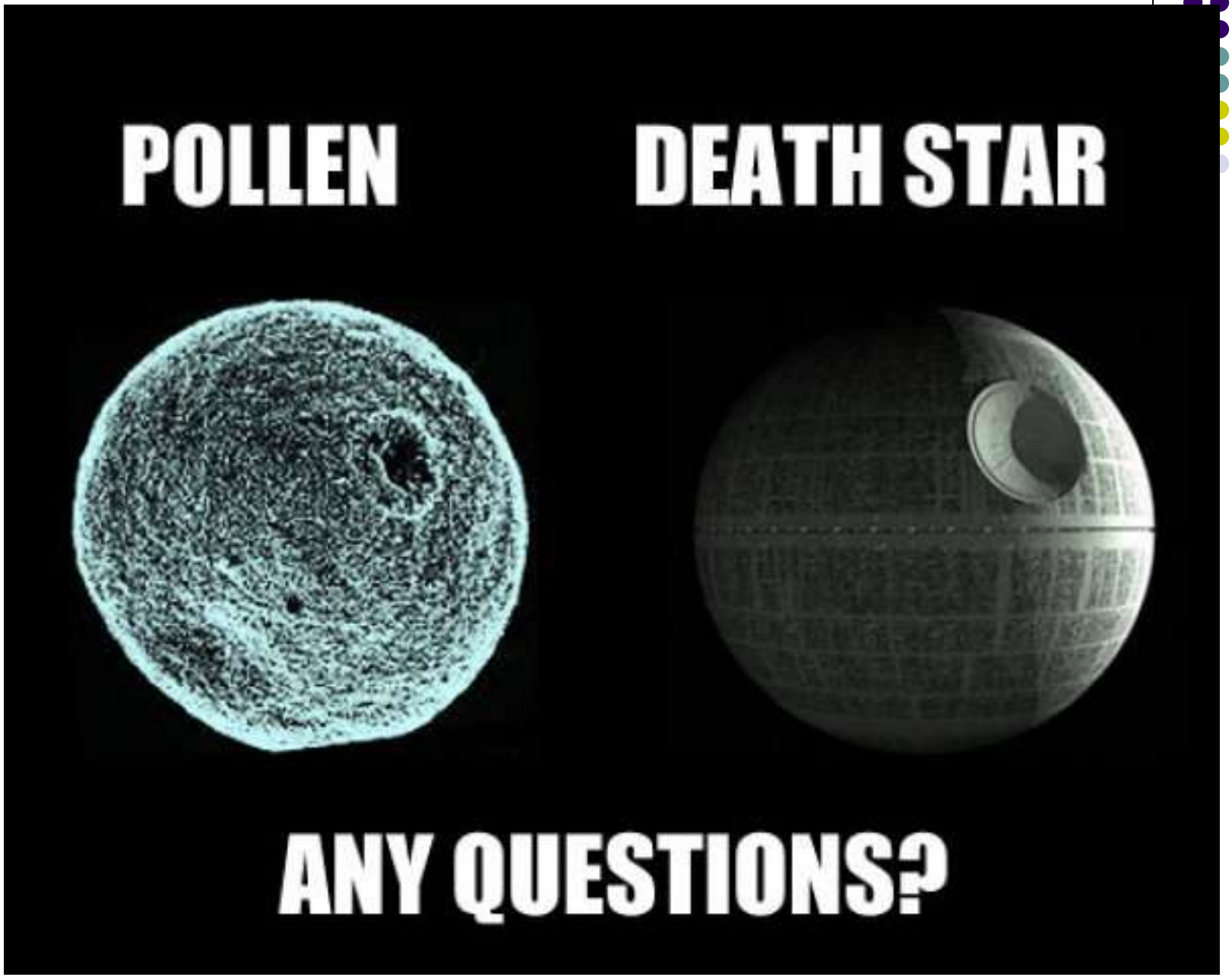
➢ Please document any appropriate changes in allergy status once Test Dose Procedure is completed.

	Pre-guideline	Post-guideline	P Value
ADRs N (%)	3 (6)%	7 (4%)	0.44

Figure 2. Impact of the clinical guideline on test dose usage and adverse drug reactions to β-lactam antibiotics

Adoption of the clinical guideline was associated with a significant increase in test doses ($p<0.001$) without a significant change in the rate of adverse drug reactions ($p=0.44$).


LET'S
DISCUSS


POLLEN
DEATH STAR
ANY QUESTIONS?