

Antibiotic Allergy

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It ain't what you don't know
that gets you into trouble. It's
what you know for sure that
just ain't so.

?Mark Twain - 1899

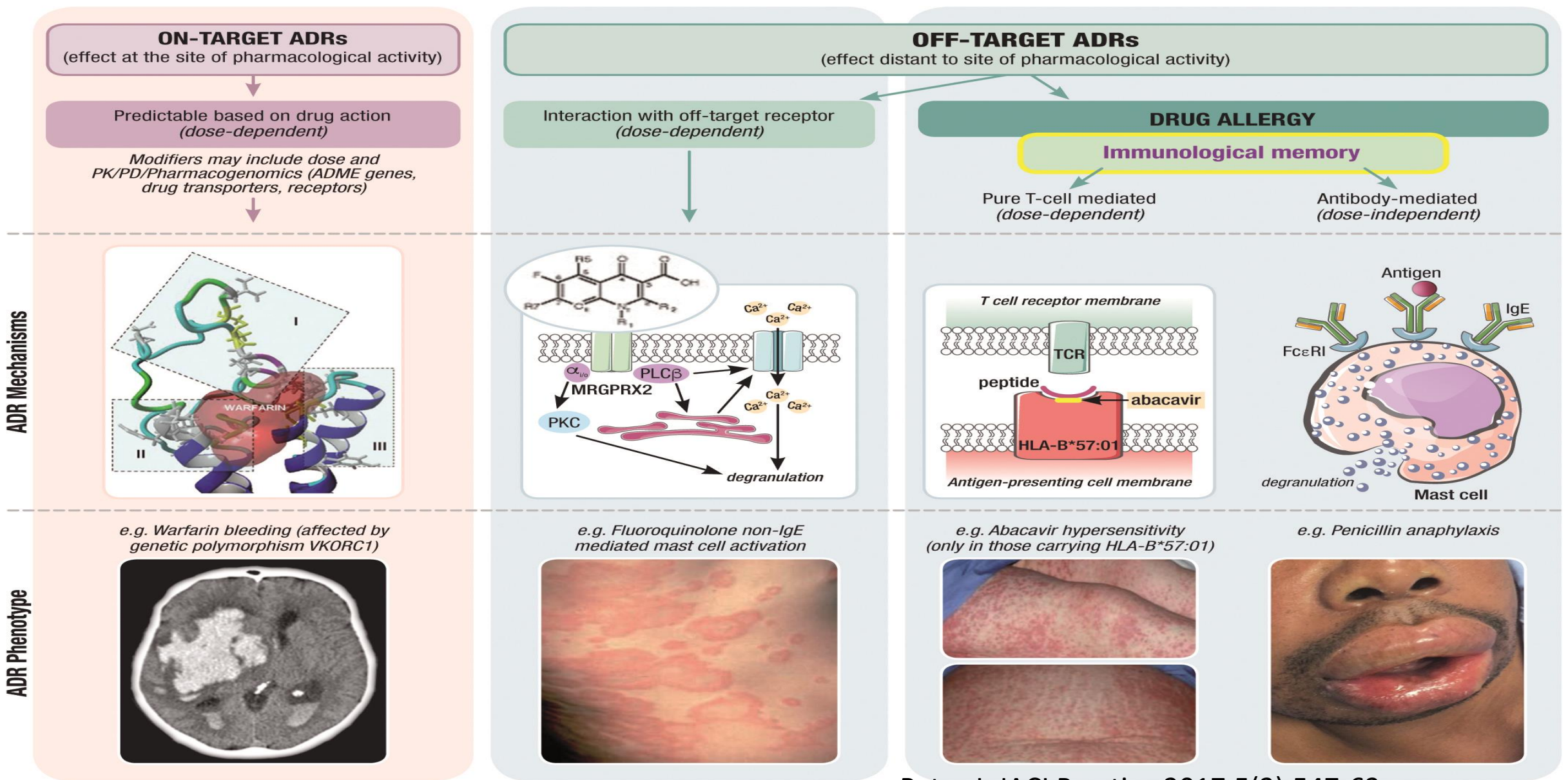
Overview

- Side effects versus “drug allergy”
- Approach to the patient labeled as penicillin allergic
- Penicillin cephalosporin cross-reactivity
- Definitions, recognition and approaches to immediate antibiotic reactions
- Definitions, recognition and approaches to delayed antibiotic reactions

The Threat of Adverse Drug Reactions

- 4-6 most common cause of death
- >\$3 billion to health care system annually
- Unpredictable
- Otherwise healthy individuals
- Uncommon effects of common drugs
- Cause long-term disability
- Life-threatening
- Constrict future treatment choices
- No single constituency – “Relevant to all but owned by none”

Only a Portion of "Off-Target" ADRs are Drug Allergy



Over-labelled



Most tolerate the drug!

IgE – not permanent

Under-recognized



Require permanent avoidance of the drug but often underlabeled!!!

HLA-restricted = permanent

Many are "labeled" few have disease but the disease when true can be life threatening....

Adverse and Allergic Drug Reactions:

Penicillins (anaphylaxis)

Cipro (anaphylaxis)

amoxicillin (anaphylaxis)

Clindamycin (anaphylaxis)

vancomycin (anaphylaxis)

azithromycin (anaphylaxis)

gentamicin (Rash, Itching)

lidocaine (rash)

- A 34 year old HIV+ man on screening is found to have an RPR 1:128 without any other history. You are planning treatment for latent syphilis however he was 4 years old he was given penicillin for an ear infection and he thinks developed a rash and his mother told him never to take it again. Since then he thinks he may have taken clarithromycin once for a URTI and has no knowledge of exposure to cephalosporins.

Which of the following is true:

1. He is of significant risk for anaphylaxis to penicillins.
2. His risk of having any reaction associated with penicillin is approximately 20-30%.
3. Penicillin is not the treatment of choice for syphilis so this is not relevant here.
4. He is at high risk of having a reaction to a cephalosporin because of the cross-reactivity.
5. When patients like this undergo formal skin testing and oral challenge >90% of them will tolerate penicillin.

“My Mother Told me I am Allergic to Penicillin”



“Mothers are all slightly insane”

JD Salinger, *The Catcher in the Rye*

Penicillin Allergy – The Label Starts in Childhood

- Many patients labeled in an EMR have been told they were penicillin allergic as a child
- Label becomes lifelong (in one study 75% labeled by age 3*)
- Most were never allergic
 - Drug viral interaction
 - Side effect
- Even in patients with allergy that is proven by recognized testing methods as a child 10% per year will lose reactivity to penicillin and this number is higher for aminopenicillins and cephalosporins
- Reconciliation of the EMR is important

*Vyles D et al Acad Pediatr 2017;3:251-55

Penicillin Allergy Is Not Necessarily Forever

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

- Majority not truly allergic to begin with
- IgE mediated reactions are not life long
 - 10% of patients per year lose reactivity to penicillin
 - 80% over five years to amoxicillin and other aminopenicillins
 - Probably a higher percentage for cephalosporins
- Many T-cell mediated HLA restricted reactions appears to be life long
 - Assume this for DRESS and SJS/TEN
- Testing can help differentiate these reactions
 - Skin/prick/oral challenge – immediate
 - Delayed intradermal/patch/ex vivo - delayed

Why Bother?

Individual Health

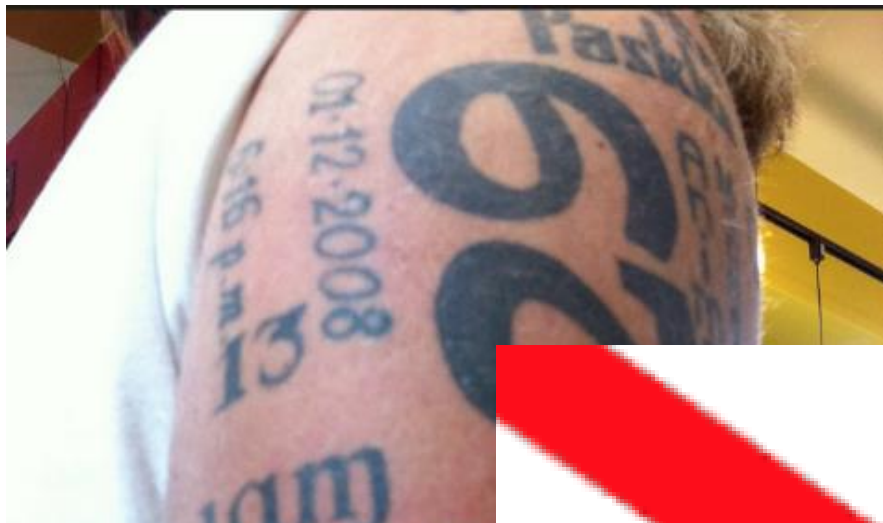
- Most are not allergic
- Second and third line drugs are less effective and often have more toxicities
- Easier to appropriately label patients when they are well rather than sick (when they actually need antibiotics)
- Constricted choices from over-labeling (domino effect)

Public Health/Stewardship

- Facilitate antibiotic appropriateness on a population level
- Antibiotic resistance
- Clostridium difficile
- Cost (both of the drugs and treating the adverse drug reactions)

Penicillin Allergy Testing

What can be done to appropriately label patients



Adverse a
Allergic to
Glutensdf



S:
OX

Definitions

❖ Immediate reaction

- Within 1 hour of dosing
- Highest risk to be IgE (wheezing, hives, angioedema, hypotension, collapse)
- Non-IgE mediated mast cell activation (pseudoallergic or anaphylactoid)
 - most common with vancomycin or fluoroquinolones.

❖ Delayed reaction

- > 1 hour of dosing
- Likely to be non-IgE mediated
- Can include urticarial rashes or non-specific exanthems

Testing Management Strategies for Immediate Reactions

- **Desensitization**

- Useful in skin test positive patients or in acute setting where other approaches not possible
- Rapid desensitization includes several increasing doses over <5 hours
- Mechanism of action still unclear (IgG blocking antibodies, STAT regulation)
- **DO NOT DE-LABEL** (most patients who make it through desensitization without symptoms are not truly allergic!!)

- **Skin testing**

- Immediate - Prick and intradermal (0.02 ml) read at 15 minutes for immediate reactions (IgE) – significantly less than 100% negative predictive value therefore NOT standalone tests

- **Oral challenge**

- Single low dose oral challenge (graded in high risk patients) will rule out an IgE mediated reaction

- **Blood tests**

- Evidence based low and lack sensitivity and specificity

Penicillin Skin Testing



- Prick & intradermal (0.02 ml)
- Penicillin skin testing with validated major and minor determinants has negative predictive value of 97-99%
- Additional 1-3% picked up on oral challenge with penicillin VK
- In combination with oral challenge takes about 3-4 hours
- Approximately 10% per year will lose skin test reactivity (unstable phenotype)
- Percent skin test positive higher when reaction within last year
- <5% of more remote reactions skin test positive

Clinical Experience With Penicillin Skin Testing in a Large Inner-City STD Clinic

Jyothi Gadda, MD; Michael Spence, MD, MPH; Barbara Wheeler, RN; R. Franklin Adkinson, Jr, MD

JAMA 1993; 270:2456-63

How to improve effectiveness of antibiotic allergy label removal

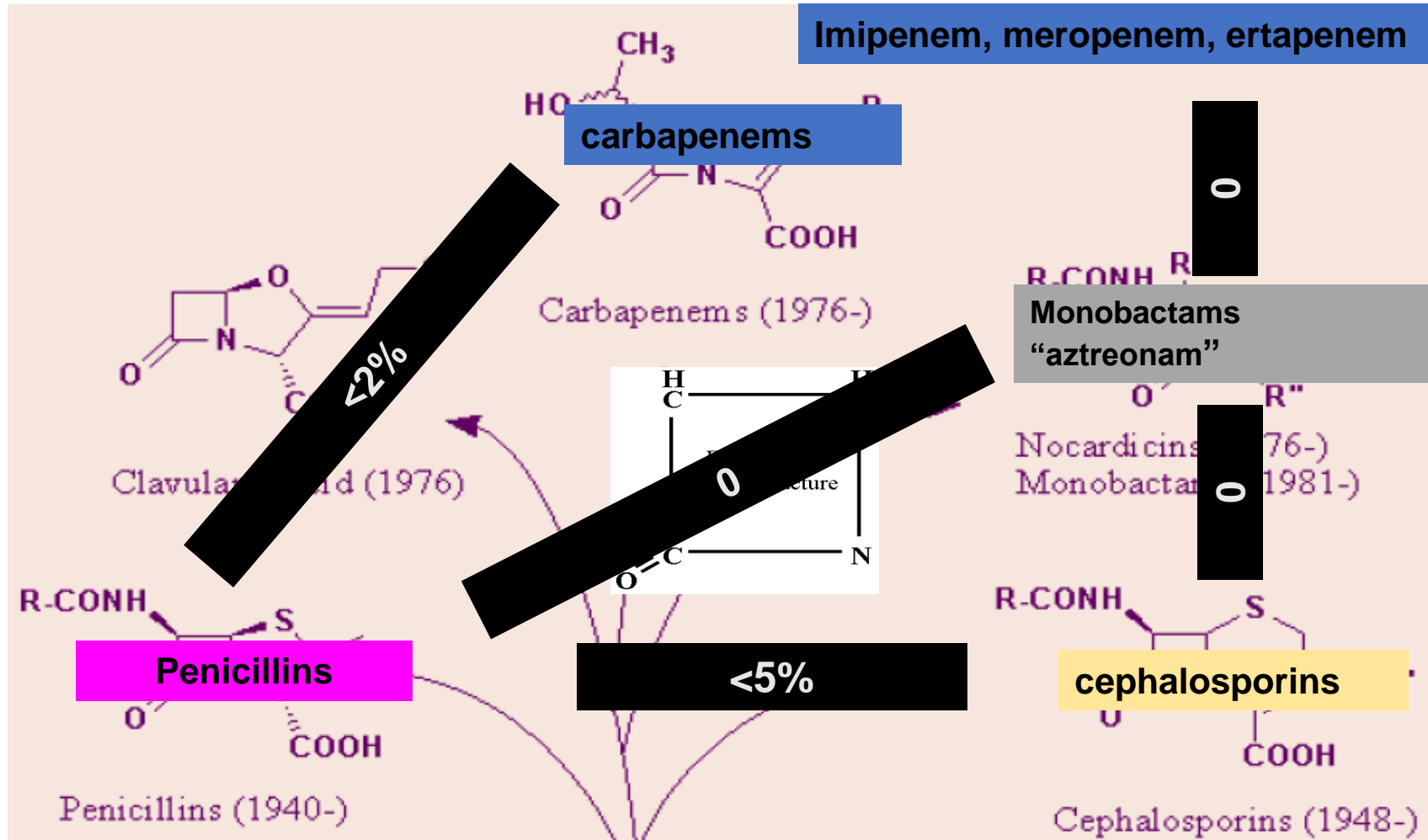
- Allergy label removal particularly for IgE mediated reactions after skin testing and oral challenge is safe and efficacious for allergy removal.
- For T-cell mediated reactions (mild to moderate rash history) need multiple dose challenge to rule out
- Communication very important to entire healthcare team
- Follow-up with patient for reinforcement

Key Points: Penicillin Allergy Testing

- Penicillin skin testing with major determinant, benzyl penicillin and ampicillin + oral challenge key strategy for removing risk of immediate reaction to penicillins
- Effectiveness of penicillin allergy label removal can be improved with communication to patient and providers
- Re-sensitization (with oral antibiotics) is very uncommon (<1%)
- Desensitization does not de-label and should ideally be reserved for emergencies where other testing strategies unavailable and when skin test is positive

Penicillin and Cephalosporin Cross-reactivity

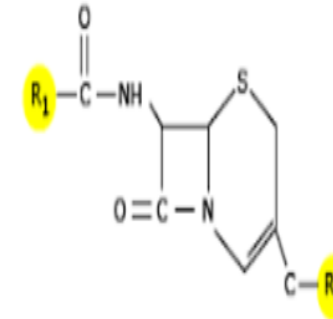
Beta-lactam allergies



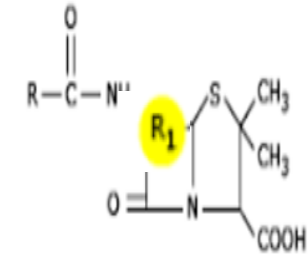
MOST CEPHALOSPORIN CROSS-REACTIVITY AT THE LEVEL OF THE R1 SIDE-CHAIN

Trubiano et al. JACI In Practice 2017; epublished August 23

	PENICILLIN G	PENICILLIN VK	AMPICILLIN	AMOXICILLIN	SEMI-SYNTHETIC ANTI-STAPH PEN	PIPERACILLIN-TAZOBACTAM	CEFADROXIL	CEFACLOR	CEFAZOLIN	CEPHALEXIN	CEFPROZIL	CEPHALOTHIN*	CEFOXITIN*	CEFOTETAN	CEFAMANDOLE	CEFUROXIME	CEFEPIME	CEFTRIAXONE	CEFOTAXIME	CEFTAZIDIME	CEFDINIR	CEFIXIME	CEFTAROLINE	CEFTIBIPROLE	CEFTOZOLANE-TAZOBACTAM	
PENICILLIN G	R1	R1																								
PENICILLIN VK	R1	R1																								
AMPICILLIN			R1	R1			R1	R1	R1	R1																
AMOXICILLIN			R1	R1			R1	R1	R1	R1																
SEMI-SYNTHETIC ANTI-STAPH PENICILLINS					R1																					
PIPERACILLIN-TAZOBACTAM						R1																				
CEPHALOSPORIN 1st GENERATION																										
CEFADROXIL			R1	R1			R1	R1	R1	R1																
CEFPROZIL			R1	R1			R1	R1	R1	R1																
CEFACLOR			R1	R1			R1	R1	R1	R1																
CEPHALEXIN			R1	R1			R1	R1	R1	R1																
CEPHALOTHIN												R1										R2				
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CEFOTETAN														R2												
CEFAMANDOLE														R2												
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CEPHALOSPORIN 3rd/4th/5th GENERATION																										
CEFEPIME																	R1	R1								
CEFTRIAXONE																	R1	R1								
CEFOTAXIME																	R1	R1								
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CEFTIBIPROLE																							R1	R1		
CEFTOZOLANE-TAZOBACTAM																							R1	R1		
MONOBACTAM																										
AZTREONAM																									R1	



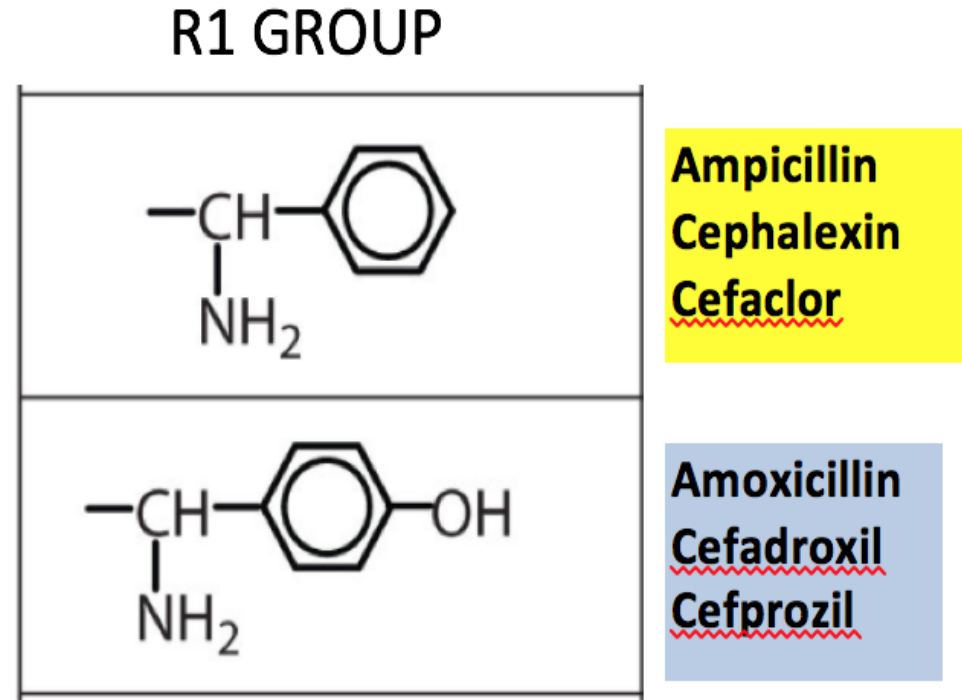
Cephalosporins



Penicillins

Most Common Cross-reactivity Patterns

- Aminopenicillins
(amoxicillin, ampicillin)
- Aminocephalosporins
(cefalexin, cefadroxil,
cefprozil, cefaclor)



Key Points: Cephalosporin cross-reactivity

- ❖ **Penicillin-cephalosporin cross-reactivity is low** overestimated in previous literature (<5% versus 15-25%)
- ❖ Key cross reactivity patterns exist (aminopenicillins and aminocephalosporins)
 - R1 shared ampicillin/amoxicillin = cefadroxil/cephalexin/cefaclor/cefprozil
 - R1 shared ceftriaxone/cefepime/cefotaxime/cefepodoxime
- ❖ Cefazolin important cause of peri-operative anaphylaxis and unique R1-R2 side chains (often selective allergy)

Delayed Reactions

- A 60 year old woman who presented with a 2 month history of fevers and malaise and a heart murmur is found to have continuous bacteremia with penicillin and cephalosporin sensitive Viridians group Streptococci and a 5 mm vegetation on her aortic valve. She is clinically stable and commences ceftriaxone 2 gm IV daily. 8 days into therapy she develops a generalized pruritic mild to moderate rash but feels otherwise well.

Which of the following are true about this woman's delayed rash temporally associated with ceftriaxone:

1. Anti-histamines and topical steroids can be used to help treat through the rash which could be expected to abate within 4-7 days.
2. The presence of mucosal involvement, increasing severity of rash and any perturbation in organ function are warning signs that this could be a severe cutaneous ADR and that the drug needs to be stopped.
3. This woman is unlikely to develop a rash with penicillins.
4. Cross-reactivity between cephalosporins when it occurs is thought to commonly occur on the basis of the R1 side chain.
5. All of the above.

Clinical Approach to Delayed Reactions

- **MUST STOP**

- Mucous Membrane +
- Severe Rash +
- Internal Organ Involvement+



-Drug Reaction with Eosinophilia and Systemic symptoms (DRESS)
(vancomycin, minocycline, Trimethoprim-sulfamethoxazole)

-Stevens-Johnson-Syndrome Toxic Epidermal Necrolysis (SJS/TEN) (Bactrim)

-Acute Generalized exanthematous pustulosis (aminopenicillins, clindamycin)

-Drug-induced liver disease (minocycline, amoxicillin-clavulanate, TMP-SMX, anti-tuberculous drugs)

- **CONSIDER STOPPING**

- Patient tolerance issues

- **TREAT THROUGH OR STOP/DESENSITIZE**

- Mild rash without fever or internal organ



Maculopapular



Urticarial

Severe Skin Involvement:Life-threatening

Stevens-Johnson Syndrome/Toxic Epidermal Necrolysis



-prick/intradermal testing will not pick these up

-desensitization or reintroduction of any structurally related drugs contraindicated

Management/Testing Strategies for Delayed reactions

- Patch testing
 - Drug applied in vehicle (e.g. petrolatum) to skin for 48 hours
 - Potentially useful for some delayed reactions
- Delayed intradermal (0.02 to 0.04 ml sterile solution and read at 24 hours)
- Multiple dose oral challenge
 - Contraindicated in severe delayed reactions (severe skin, mucosal or organ involvement).
- Blood tests
 - Research (flow cytometry, ELISpot)
 - HLA typing and other genetic testing (abacavir, carbamazepine, dapsone, allopurinol)
- Desensitization
 - More like graded reintroduction (over several hours to weeks)
 - Contraindicated for severe reactions such as DRESS/SJS/TEN

- A 52 year old Chinese woman with recent single dermatomal shingles has developed had developed post-herpetic neuralgia and was prescribed carbamazepine by her PCP 2 weeks ago. She is now presenting with fever and malaise and sore mouth. She is seen in the emergency department and prescribed amoxicillin for presumed Strep throat and ibuprofen for fever and sent home. 12 hours later she returns and has develops atypical target lesions on her trunk and 24 hours later widespread blistering lesions and eye soreness. She has tolerated both ibuprofen and amoxicillin in the past without event. She is diagnosed as having Stevens-Johnson-Syndrome/Toxic epidermal necrolysis (SJS/TEN) overlap syndrome (20% total BSA involved).

Which of the following is most likely:

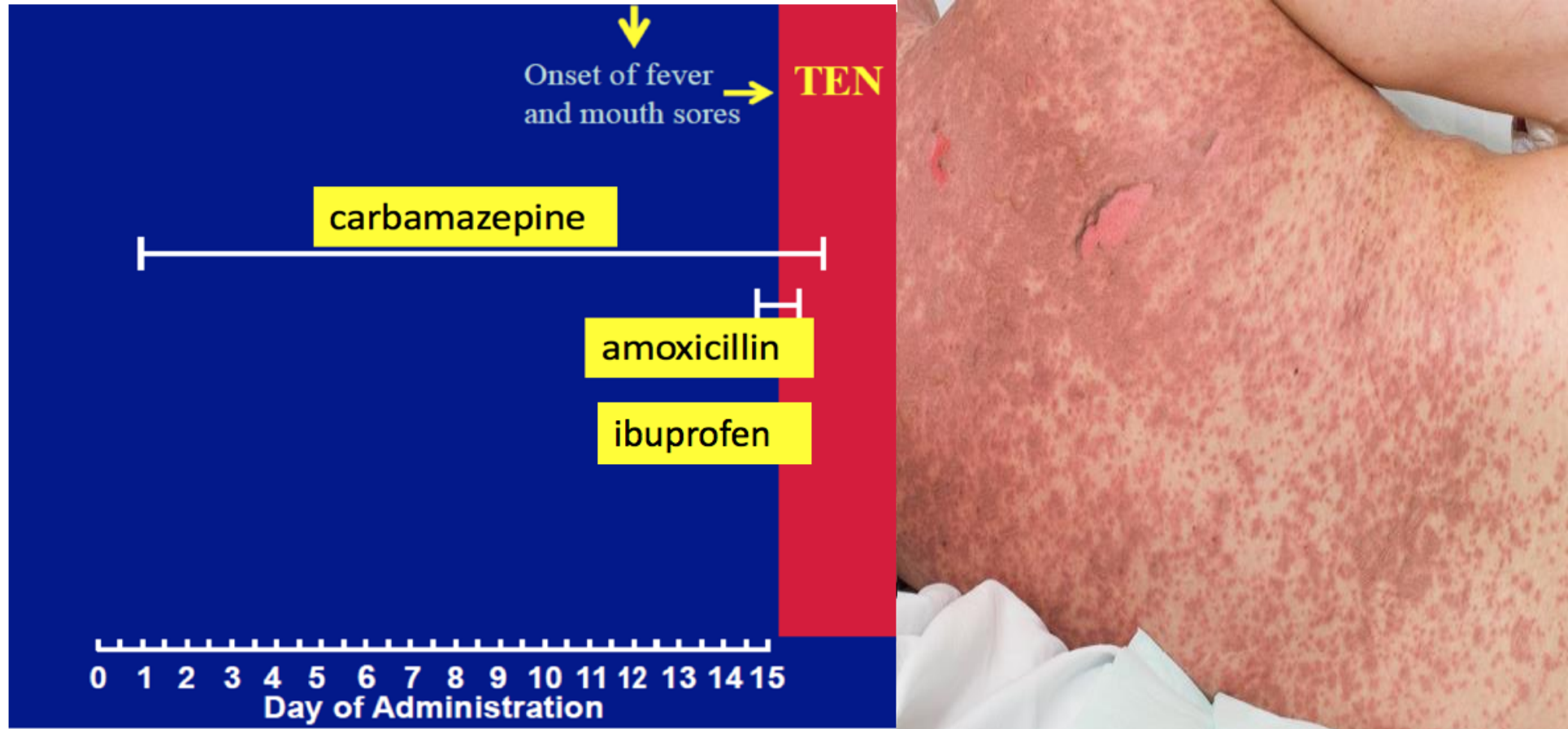
1. Amoxicillin is most likely the cause because antibiotics are the most common cause of SJS/TEN.
2. Ibuprofen is most likely the cause since NSAIDs have been frequently associated with SJS/TEN
3. Carbamazepine is the most likely cause of SJS/TEN because the time course fits, it is a prevalent cause and is it associated with a gene that is carried in 10-20% of Southeast Asians.
4. This is most likely a late complication of shingles and she should have a full work-up to make sure she does not have an underlying immunocompromising state.

Time Windows for Antibiotic Reactions

TYPE OF REACTION	TIME FROM MEDICATION ONSET
Maculopapular eruption (benign exanthem)	4-12 days
DRESS	2-5 weeks (out to 8 weeks)
SJS/TEN	4-28 days
Acute Generalized Exanthematous Pustulosis	Hours to 2 days (for aminopenicillins)
Drug-induced liver disease	5-90 days (peak > 4 weeks)
Drug-induced interstitial nephritis	2-3 weeks or later
Vasculitis or drug-induced lupus etc	months

Timeline & History for Delayed Rashes is Critical

- 52 year old woman presenting with toxic epidermal necrolysis



Beware of protopathic effect

Key points: Delayed Reactions

- Clinical findings and timing of reaction is critical
- Recognizing when rash is mild and benign and drug can be continued
- Recognizing when drug must be stopped
- Testing procedures evolving but not widely available and many are research
- Desensitization in select cases but as per immediate reactions is not permanent (If greater than 3 half lives of drug have evolved then risk of "rechallenge" reaction")

Conclusions

- The label of penicillin allergy common starts in childhood but can be removed in >95% of individuals by adulthood
- Cross-reactivity between different classes of beta-lactam antibiotics increasingly recognized as being low and often the highest risk is with drugs with a shared side-chain
- Desensitization can be applied for IgE mediated reactions or low risk delayed reaction
- For mild rashes continued dosing can occur
- Recognition of the timing of the reaction is crucial to determining the most likely causal drug(s)

Questions?