Drug Allergy

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Drug Allergy or Drug Reaction?

10 y boy with otitis media need to start of co-amoxiclav in PMH have HX of Penicillin reaction in 4 years ago.

Is this a problem?
Questions?
Medications hx?
Plan?

What about diarrhea in day 3 of co-amoxiclave ?

Morbilliform Rash in day 3 upper trunk?

Epidemiology

- Adverse drug events (ADEs) occur about 4 per 100 admissions and cost about $7,000 per event.
- Serious ADEs cause between 75,000 and 106,000 deaths per year.
- 51% of all serious ADEs are reported after FDA approval.

An adverse drug reaction (ADR) is defined as a harmful or unintended reaction to a drug that occurs at doses used for prevention, diagnosis, or treatment

A Drug allergy is an immunologically-mediated type B ADR that not only affects patient quality of life, but may also lead to delayed treatment, use of suboptimal alternate medications, unnecessary investigations, and increased morbidity and mortality.

Table 1 Classification of ADRs [1, 5, 6]

ADR type	Characteristics	Examples
A	• Common • Predictable—may occur in anyone • Dose dependent • Related to known pharmacologic actions of drug	• Drug overdose • Secondary drug effects • Side effects • Drug interactions
B	• 20–25% of ADRs • Unpredictable • Not necessarily dose dependent • Unrelated to known pharmacologic actions of drug	• Drug allergy: immunologically mediated, 5–10% of ADRs • *Non-IgE-mediated reactions (previously called pseudoallergic or anaphylactoid)*: a reaction with the same clinical manifestations as an allergic reaction, but that lacks immunological specificity • *Drug intolerance*: an undesirable pharmacologic effect that occurs at low and sometimes sub-therapeutic doses of the drug that are not caused by underlying abnormalities of metabolism or drug excretion • *Drug idiosyncrasy*: an abnormal/unexpected effect, usually caused by underlying abnormalities of metabolism, excretion, or bioavailability

Classification of ADRs

- Type A: common, predictable, dose-dependent
  - Overdose (e.g. hepatic necrosis from acetaminophen)
  - Side effects (e.g. tremor from albuterol)
  - Secondary effects (e.g. *C.difficile* infection from clindamycin)
  - Drug-drug interactions (e.g. macrolide causing supratherapeutic INR in patient on Varfarin)

Classification

- Type B: uncommon and unpredictable
  - Intolerance (e.g. tinnitus with aspirin)
  - Idiosyncratic (e.g. hemolysis in G6PD deficiency)
  - Pseudoallergic (e.g. vancomycin causing red man syndrome)
  - Hypersensitivity reactions: **HSRs**

Classification of HSRs

Gell & Coombs

- Type I: IgE-mediated (e.g. PCN anaphylaxis)
- Type 2: Antibody mediated (e.g. PCN-induced hemolytic anemia)
- Type 3: Immune complex (e.g. amoxicillin serum sickness)
- Type 4: Cell mediated (e.g. amoxicillin maculopapular rash)

High molecular weight therapeutic agents such as monoclonal antibodies (mAbs) recognized as foreign by the immune system, resulting in primarily type I, cytokine release type or type III (immune-complex-mediated) reactions.

Mixed reactions with both type I and cytokine release phenotypes may occur in the context of allergy to chemotherapeutic agents.

Unlike immune-mediated drug reactions, nonallergic reactions (previously called pseudoallergic or anaphylactoid reactions) are not associated with the production of antibodies or sensitized T cells but are often clinically indistinguishable from immune-mediated drug HSRs.

During these reactions, the drug has the ability, via its chemistry or pharmacology, to directly stimulate the release or activation of inflammatory mediators, such as histamine, from mast cells and basophils. Non-steroidal anti-inflammatory drugs (NSAIDs), opioids, radiocontrast media, and ACE inhibitors are common causes of these non-allergic reactions

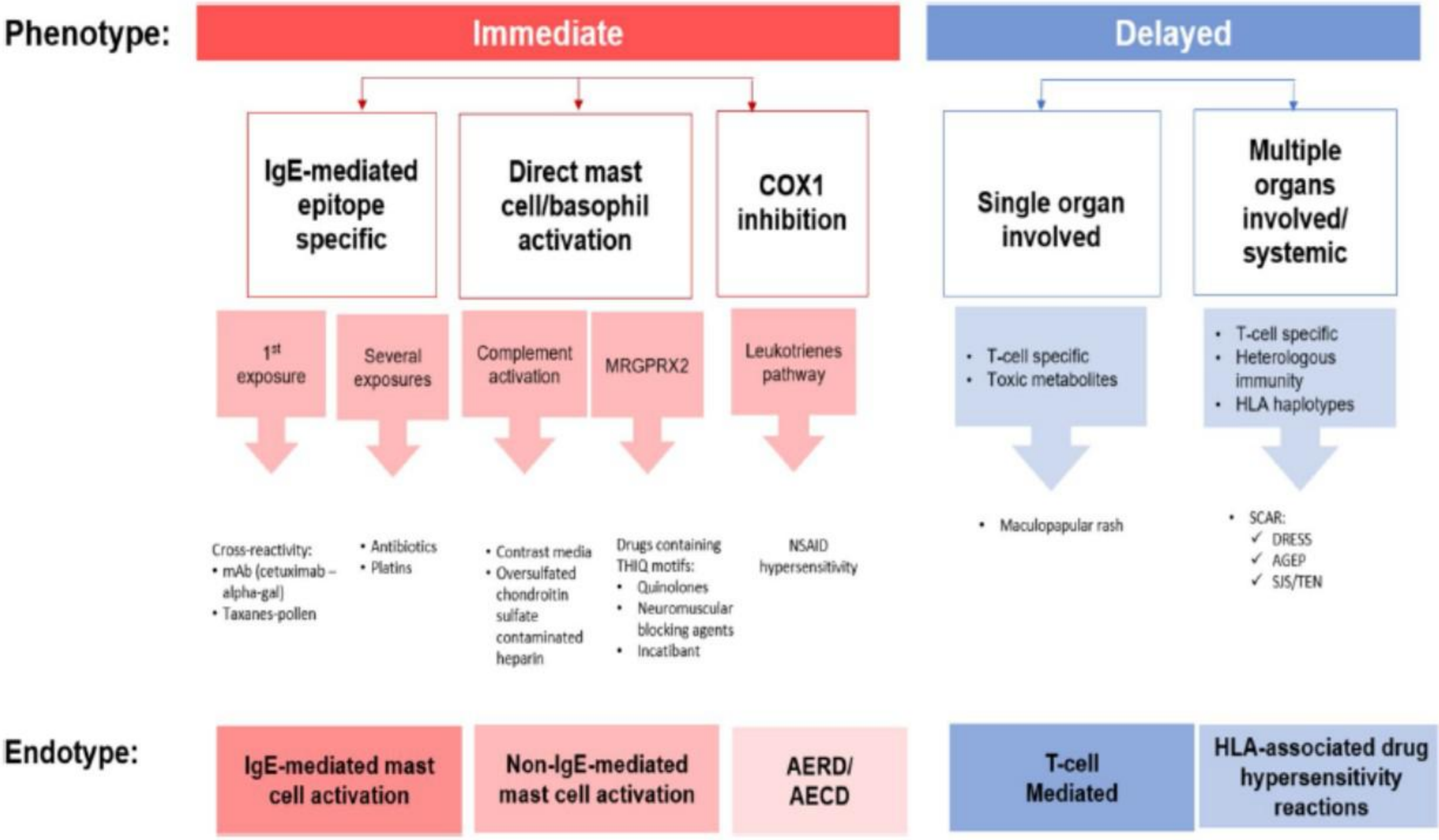

Phenotype:
Immediate
Delayed
IgE-mediated epitope specific
Direct mast cell/basophil activation
COX1 inhibition
Single organ involved
Multiple organs involved/ systemic
1st exposure
Several exposures
Complement activation
MRGPRX2
Leukotrienes pathway
• T-cell specific
• Toxic metabolites
• T-cell specific
• Heterologous immunity
• HLA haplotypes
Cross-reactivity:
• mAb (cetuximab – alpha-gal)
• Taxanes-pollen
• Antibiotics
• Platins
• Contrast media
• Oversulfated chondroitin sulfate contaminated heparin
Drugs containing THIQ motifs:
• Quinolones
• Neuromuscular blocking agents
• Icatibant
NSAID hypersensitivity
• Maculopapular rash
• SCAR:
✓ DRESS
✓ AGEP
✓ SJS/TEN
Endotype:
IgE-mediated mast cell activation
Non-IgE-mediated mast cell activation
AERD/ AECD
T-cell Mediated
HLA-associated drug hypersensitivity reactions

Table 3 Risk factors for the development of drug allergy [27]

Patient-related factors:

- Age: young/middle-aged adults > infants/elderly
- Gender: Women > men
- Genetic polymorphisms
  - HLA (a gene product of the MHC)
  - Drug metabolism
- Viral infections: HIV, EBV, herpes viruses
- Previous reaction to the drug

Drug-related factors:

- High molecular weight compounds and hapten-forming drugs are more immunogenic
- Route: topical > IV/intramuscular > oral
  - IV administration → more severe reactions
- Dose: frequent/prolonged > single dose

7 years girl with redness and flashing post Vancomycin started last day

Dx and plan?
What about next time if needed?

Is it possible that a drug that is used multiple times before with no reaction; cause allergic reactions?

Antihistamines or Corticosteroid also can have Allergic reactions?

Brand is important?

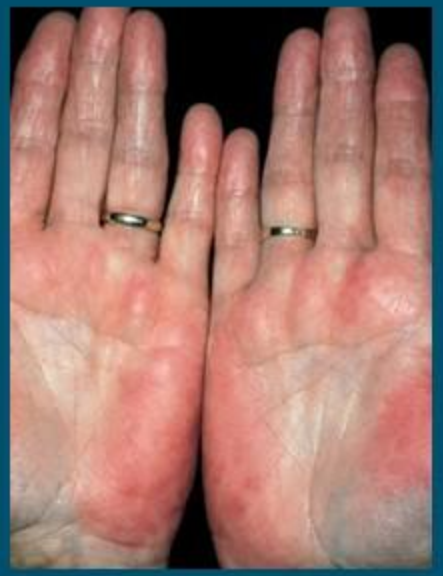
Type I, IgE-mediated

- Usually within two hours after drug exposure
- Can recur/worsen with repeat exposure
- Skin testing may be helpful (not in definite anaphylaxy)
- If convincing history, or skin test positive, patients should avoid and may be candidates for desensitization if it is necessary
  - Desensitization induces a state of temporary tolerance through gradual introduction of the drug

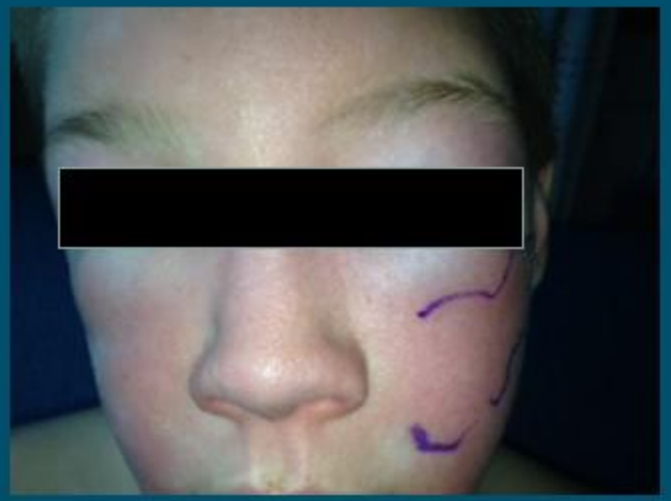
Symptoms and Signs

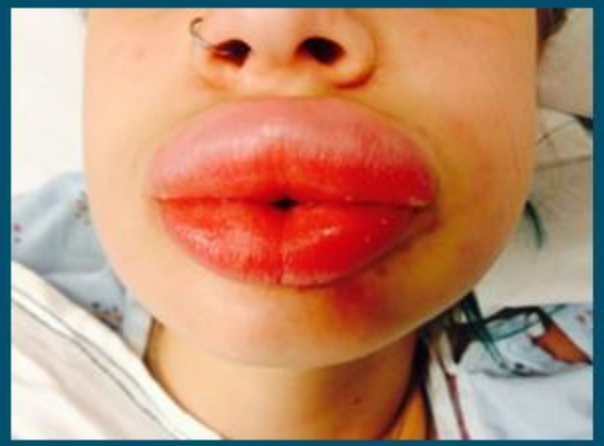
- Cutaneous and mucosal: urticaria, angioedema, pruritus, rhinitis, conjunctivitis
- Gastrointestinal: nausea, throat tightness, difficulty swallowing, vomiting, diarrhea
- Respiratory: cough, dyspnea, wheezing, stridor, hypoxia
- Cardiovascular: hypotension, tachycardia
- Neurologic: confusion, loss of consciousness

Common IgE Exam Findings

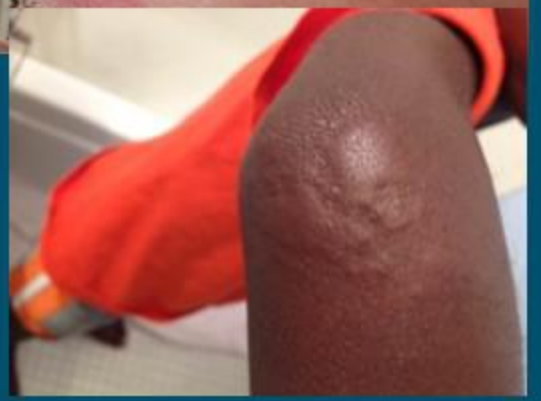


Palmar erythema
and pruritus





Angioedema,
often asymmetric



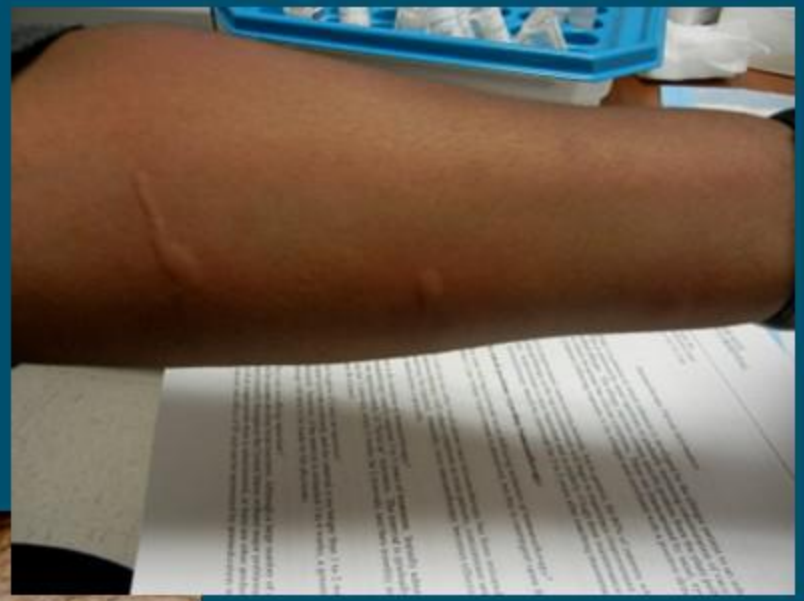
Urticaria, erythematous,
raised pruritic lesions,
with each lesion lasting
hours (but <24 hrs)

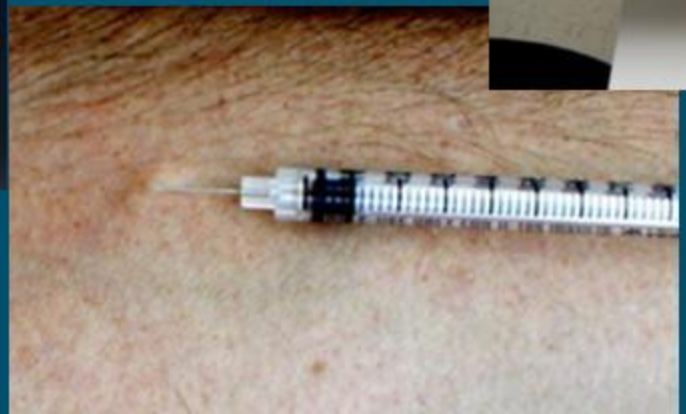
Evaluation: Skin Testing

- Useful for reactions with possible IgE mechanism
- All patients with an “unknown” reaction may be considered for skin testing to rule out IgE
- No role for skin testing in patients with history of Stevens-Johnson syndrome/toxic epidermal necrolysis, DRESS syndrome, acute interstitial nephritis, exfoliative dermatitis, hemolytic anemia
- No role for Patch test

Evaluation: Skin testing

- Skin testing is performed in steps: skin prick (epicutaneous) and intradermal testing using increasing concentrations





Skin Testing: Caveats

- Skin testing for drug allergy is only validated for penicillin allergy where antigenic determinants have been identified
- All other drug testing can be performed using an established non-irritating concentration with drug challenge being an important part of the evaluation

Drug Challenges

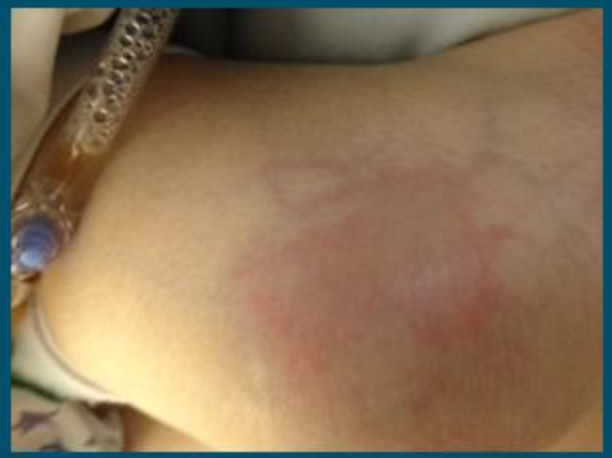
- Referred to as graded challenge or test dose
- Gold Standard and Final action in tests
- Indicated for low risk patients unlikely to be allergic
- Completing a challenge or test dose without an adverse reaction shows there is no immediate (IgE-mediated) drug allergy

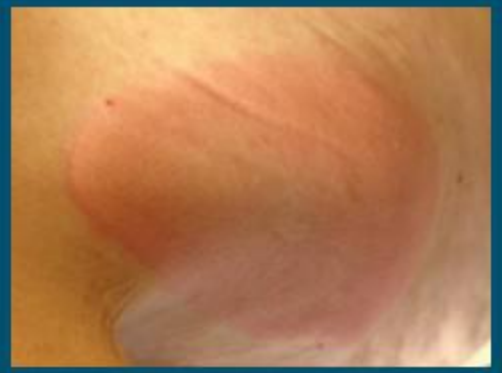
Desensitization

- For reactions that are clinically consistent with IgE mediated hypersensitivity reactions
- Indicated when there is no acceptable treatment alternative
  - must be performed under the supervision of a trained allergist
- Induces a state of *temporary* tolerance though once drug is cleared from system, state of tolerance is lost

Non-Immediate Hypersensitivity

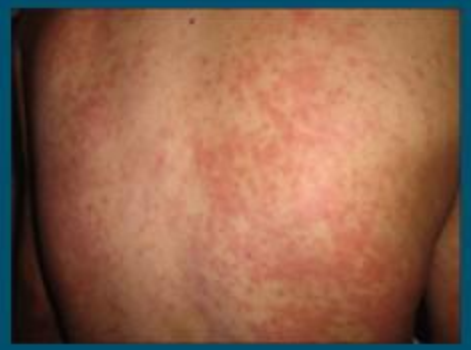
- Type II: Hemolytic anemia, neutropenia, thrombocytopenia
- Type III: Serum sickness: fever, rash (MC urticaria), joint pains, high inflammatory markers, low complement

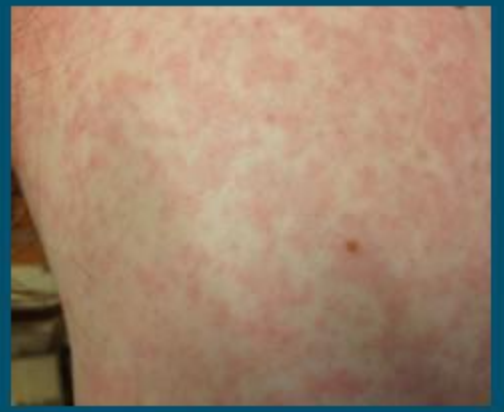




Non-Immediate Hypersensitivity

- Type IV: Morbilliform (maculopapular) rash
  - Onset days into therapy
  - May have peripheral blood eosinophilia
  - Usually benign and self limited
  - Can “treat through” with monitoring
  - May not recur on subsequent exposures
  - Cross reactivity is of less concern





Non-Immediate Hypersensitivity

- Organ specific reactions
  - Immune-mediated nephrtitis (includes Acute interstitial
  - nephritis, eg nafcillin/NSAIDs, ciprofloxacin)
  - Immune-mediated hepatitis

- Severe Cutaneous Adverse Reactions (SCARs)
  - Drug Rash Eosinophilia and Systemic Symptoms
  - Stevens-Johnson Syndrome/ Toxic Epidermal Necrolysis
  - Erythema Multiforme

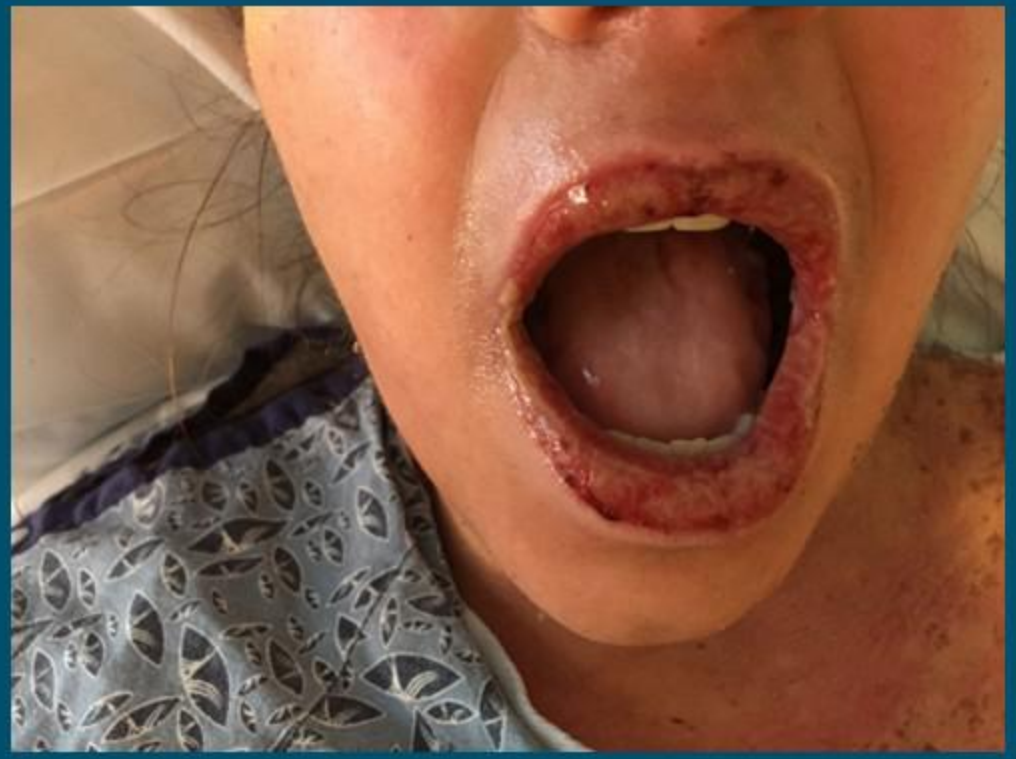
Non-Immediate Hypersensitivity

- DRESS syndrome
  - High mortality (5-40%)
  - Clinical criteria, AEC > 1500/mL, rash, and systemic involvement (fever, LAD, hepatitis, nephritis)
  - Anticonsulvants, antimicrobials, sulfasalazine, NSAIDs, ACE inhibitors, Beta blockers, dapsone, allopurinol, azathioprine, diltiazem, methimazole, dobutamine

Non-Immediate Hypersensitivity

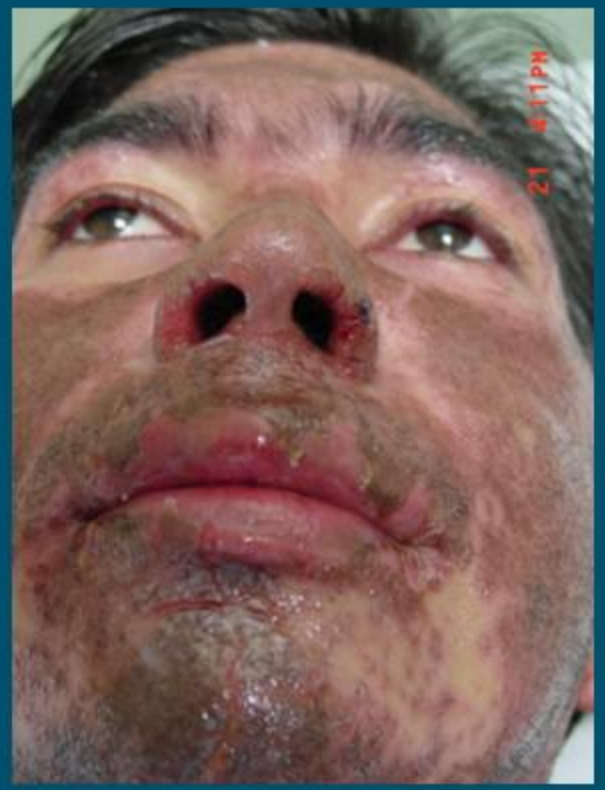
- Stevens-Johnson syndrome/toxic epidermal necrolysis
  - Mucous membrane involvement
  - Mortality 5-40%
  - Causative agents: allopurinol, antiepileptics, NSAIDs, sulfa-containing antibiotics, and nevirapine

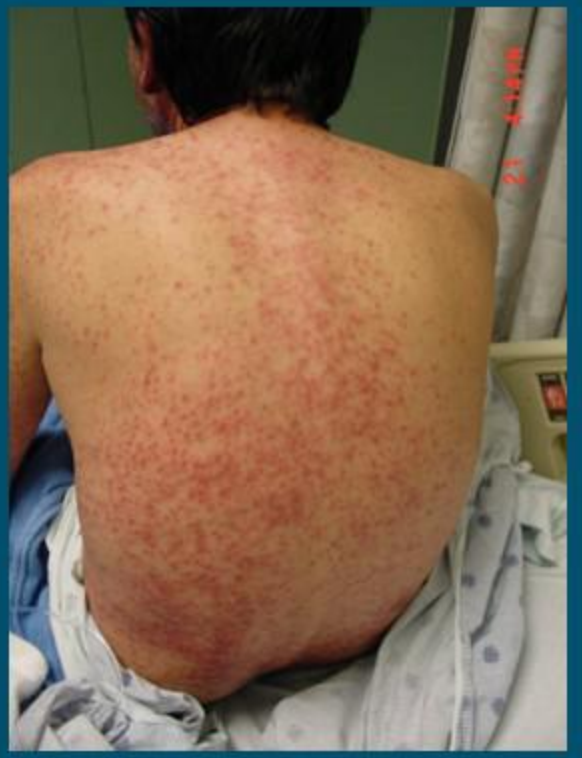
Stevens Johnson Syndrome from Sulfamethoxazole in an Healthy Patient



Photos courtesy of Dr. Kimberly Blumenthal 08/07/2017

Stevens Johnson Syndrome from Sulfamethoxazole in an AIDS Patient





Photos courtesy of Dr. David Khan 7/28/15

American Academy of Allergy Asthma & Immunology

Management of common drug allergies

The most effective strategy for the management of moderate to sever drug allergy is avoidance or discontinuation of the offending drug

When available, alternative medications with unrelated chemical structures with no cross-reactivity should be substituted.

Desensitization In cases where there is a definite medical need for a particular drug (with no acceptable alternative) and the clinical history is indicative of an IgE-mediated reaction

In non-IgE desensitization not allowed

Additional therapy for drug HSRs is largely supportive and symptomatic. For example, topical corticosteroids and oral antihistamines may improve cutaneous symptoms.

Systemic corticosteroids and/or immunomodulators may also be used to treat severe systemic reactions

Idiosyncrasy and Intolerance (Double I) No use medication again

Psudoallergic can use again

Type 1 (specillay sever form)-2-3 Gell&Coombs contraindicate use again

Penicillin Allergy

Antibiotic Stewardship

- > 90% of patients with PCN allergy label are NOT allergic
- Tools to assess PCN allergy status are highly accurate and cost-effective
- Outpatient prescription costs were estimated from $14 to $193/patient higher for PCN allergic patients.
- Total inpatient costs were less for patients without PCN allergy with average savings from $1145 to $4254/patient.

Epidemiology

- In patients with confirmed PCN allergy, allergy wanes with time.
- Up to 30% of patients with an IgE-mediated hypersensitivity to penicillins and/or cephalosporins may lose sensitivity and become ST negative within 1 year and more than 60% within 5 years.

Questions:

1- is penicillin test required in first time of injection?

2- 8 y girl need penicillin 6.3.3 for Pharyngitis in PMH 2 years ago have flashing and vomiting in 1 hour after same injection. What to do? Test?

3- Penicillin injection in 10 y boy with PMH of pruritus 1 hour after penicillin 2 years ago but unclear HX of any skin lesion and no problem with co-amoxiclave. Test?

How is penicillin test?

The positive predictive value of penicillin skin testing is approximately 50 percent

The negative predictive value is very high (97 to 99 percent)

Skin testing with a simple solution of penicillin that normally administered is not adequate to identify allergy in most patients

Anyone who is allergic to one of the penicillins should be presumed to be allergic to all penicillins and should avoid the entire group, unless they have been specifically evaluated for this problem.

Table 6 PEN-FAST penicillin allergy risk score

PEN — Penicillin allergy reported by patient *(if yes, proceed with assessment)*

F — Five years or less since reaction —2 points

A — Anaphylaxis or angioedema OR

S — Severe cutaneous adverse reaction —2 points

T — Treatment required for reaction —1 point

Interpretation:

0: Very low risk of positive penicillin allergy test < 1% (< 1 in 100 patients reporting penicillin allergy)
1–2: Low risk of positive penicillin allergy test ~ 5% (1 in 20 patients)
3: Moderate risk of positive penicillin allergy test ~ 20% (1 in 5 patients)
4–5: High risk of positive penicillin allergy test ~ 50% (1 in 2 patients)

More use in adult. PEN-FAST was recently successfully adapted for sulfonamide antibiotic allergy (SULF-FAST).
FASTS can identify individuals at low-risk for a true (IgE-mediated) allergy who could proceed to an oral challenge as a delabelling strategys

Evaluation: Skin Testing

- Useful for reactions with suspected IgE-mediated mechanism
- All patients with an “unknown” reaction may be considered for skin testing to rule out IgE-mediated mechanism
- No clear role for skin testing in patients with history of non-IgE mediated reactions (ie. Stevens-Johnson syndrome/toxic epidermal necrolysis, DRESS syndrome, acute interstitial nephritis, exfoliative dermatitis, hemolytic anemia)

"major determinant“
It is the major metabolite of penicillin and
is commercially available:
Pre-Pen = benzylpenicilloyl-polylysine = PPL = penicilloyl-polylisine

"minor determinant“
mixture of minor metabolites of penicillin consisting of penicillin G
potassium+benzylpenicilloate sodium+ benzylpenicilloyl-N-propylamine

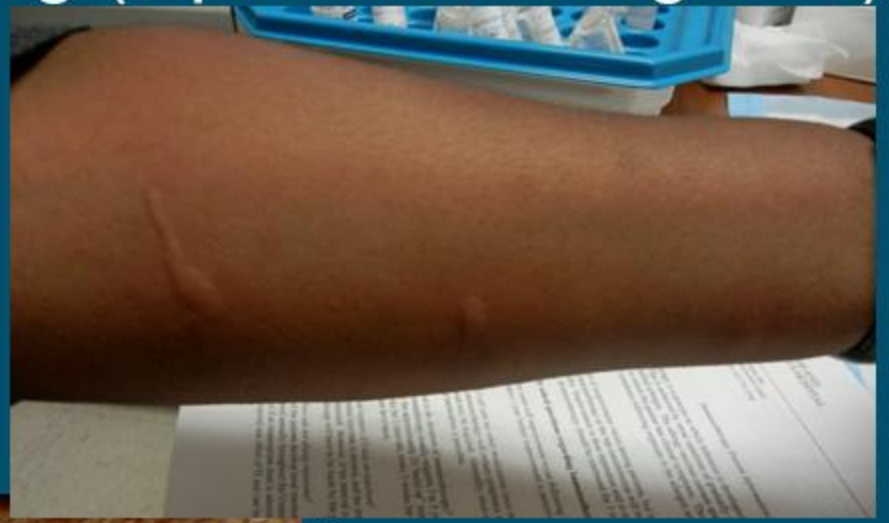
mixture is not yet commercially available, and penicillin G alone is only a slightly
less satisfactory reagent
Benzylpenicillin=BP= penicillin G= penilloate and penicilloate

No: Penicillin 6.3.3 –Penicillin V
Now in IRAN: Ampicillin???

Evaluation: Skin Testing

- Skin testing is performed in steps: starting with skin prick (epicutaneous) testing then moving on to intradermal testing (if pricks are negative)


1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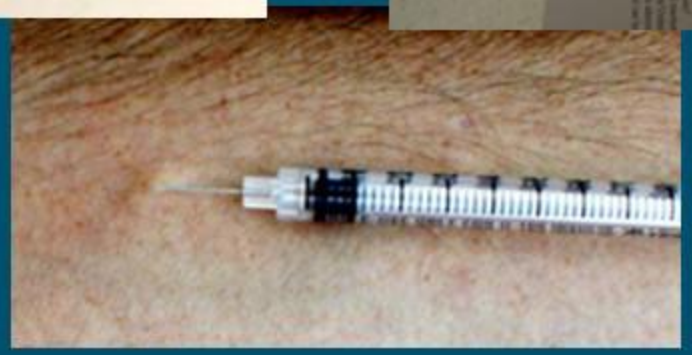
3

Oral Challenge :
Amoxicillin

	Prick Test		Intradermal Test	
	Time of Administration	Reaction/ Result	**Time of Administration**	Reaction/ Result
Histamine Control				
Negative Control				
PRE-PEN				
PENICILLIN G				
B(1,000 U/ml)				
A(10,000 U/ml)				

Oral Challenge with: Amoxicillin
Observe for 2 hours for any signs of reaction

Drug Challenges

- Referred to as graded or test dose challenge
  - PCN is administered under supervision by MDs trained to recognize and treat anaphylaxis
  - Small test dose(s) administered with observation period before being given a larger portion of the dose. Usual minimum of 2 hours observation.
- Indicated for low risk patients unlikely to be allergic
- Completing a challenge or test dose without an adverse reaction shows there is no immediate (IgE-mediated) drug allergy → De-labeling

EAACI/ENDA guidelines:

DPT is the gold standard to establish a definitive diagnosis in patients with convincing histories of drug hypersensitivity but negative diagnostic tests.

Challenge protocole:
1-one-hundredth (or lower if the reaction was of rapid onset and/or severe) of the therapeutic dose,
2- if negative, one-tenth of the therapeutic dose is given half an hour to 1 hour later, (1/4 in PO first and full dose next)
3-followed by the full dose after a further half an hour to 1 hour.

prohibited in cases of severe and serious reactions, such as SJS, TEN,AGEP, and DRESS

In penicillin-allergic patients, it may be advisable to avoid first-generation cephalosporins unless skin testing and challenge to an appropriate cephalosporin is negative.

In cephalosporin-allergic subjects, there is limited cross-reactivity on immunological testing between second- and third-generation cephalosporins and penicillins, especially amino-penicillins

In children with non-severe, skin-limited symptoms during cephalosporin treatment, a direct oral challenge is a safe and appropriate diagnostic strategy

8 Years boy with SJS admitted. Lesion start 3 days after use of co-amoxiclave and Brufen Syr.

Co-amoxiclave and amoxicillin used before but brufen was first time.

Which drug is suspected? What is plan for future?

In Multi drug allergy

1- D/C of unnecessary drugs

2- in sever cases D/C all medications

3- more suspected is new medication in second medication that was tolerated before

4- After 1-2 months drug test will be done start by less suspected. In this case ASA test maybe. Prefer not to use brufen again.

17 year boy need clarithromycin but have HX of suspected anaphylaxy to Penicillin in 8 years ago; Rash 1 day after Co-amoxiclave in 2 years ago; Also reaction to lidocaine in dentist office 30 min after injection.

Can he use Clarithromycin safely?

Take Home Points

History is main important factor.

Anaphylaxy means no use the same structural medication again or even test.

Mild Ige or non-Ige reaction can use medication again.
Sever Non-Ige reaction means no use same structural again or even test. Also no use again in Idiosyncrasy and intolerance

Skin Prick test and Desensitization is in only Ige mediated reaction

Patch test and laboratory does not work at all.

Drug challenge is gold standard. Use in mild to Moderate Ige (even non-Ige) previous reactions.

Premedication is only in Ige or anaphylactoid reactions.

Just in mild reactions challenge can be done at home or office.

راهنمای کاربردی ارزیابی و مدیریت

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دکتر حسین اسماعیل‌زاده

بسان رود که در نشیب دره سر به سنگ می زند

رونده باش

امید هیچ معجزه ای ز مرده نیست

زنده باش


There is always A way...