DRUG ALLERGY

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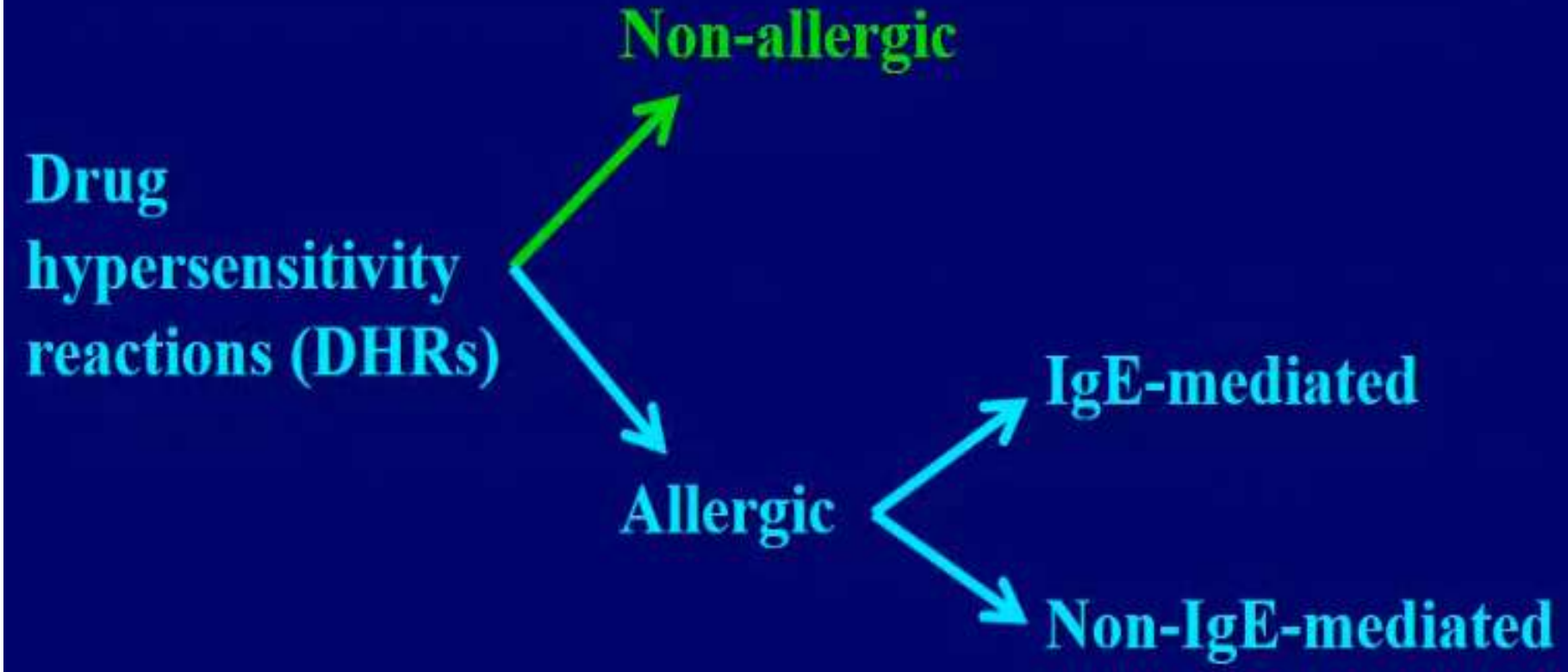
Drug hypersensitivity reactions

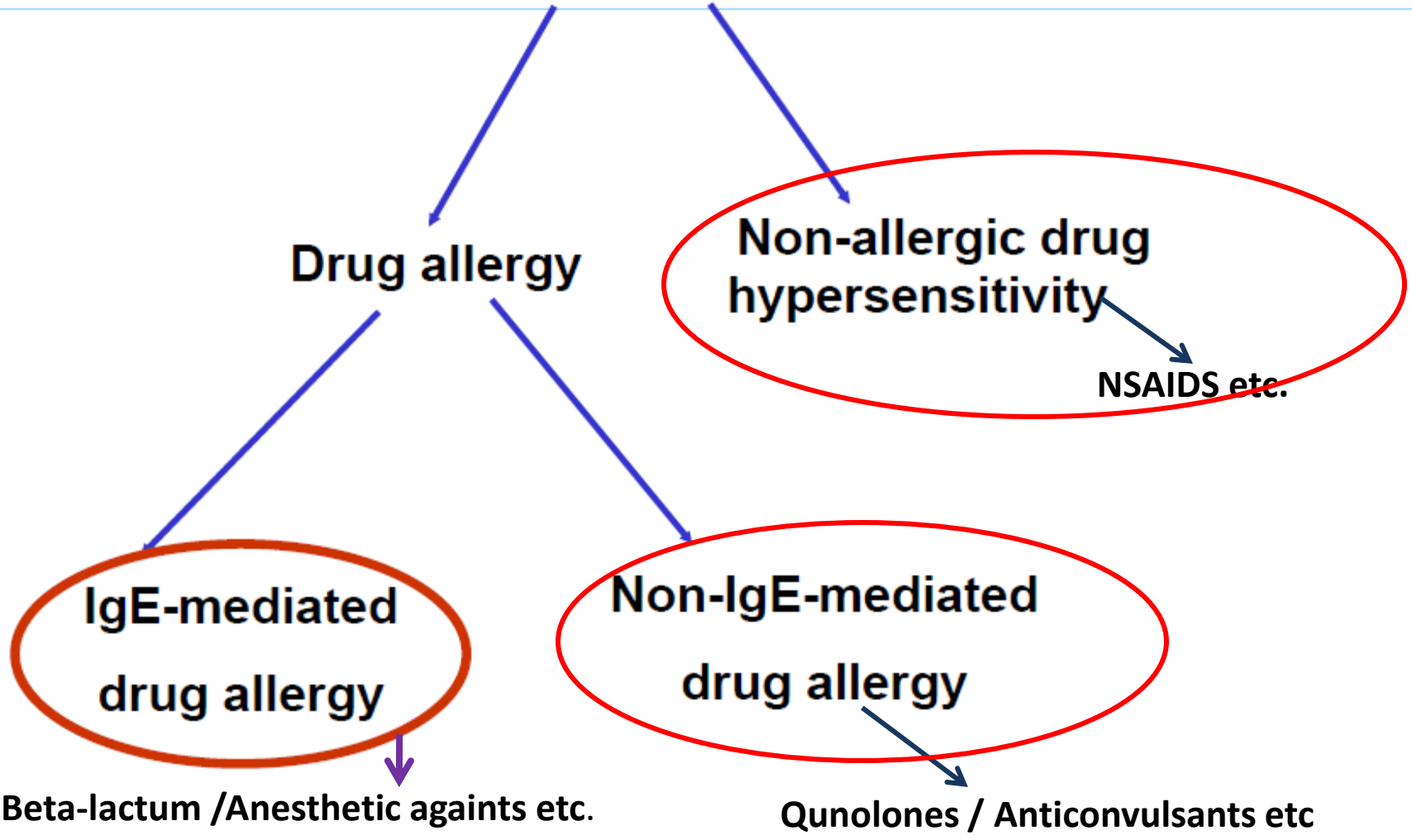
DHRs are adverse effects of drugs that clinically resemble allergic reactions

DHRs constitute 15% of all adverse drug reactions affecting more than 7% of the general population

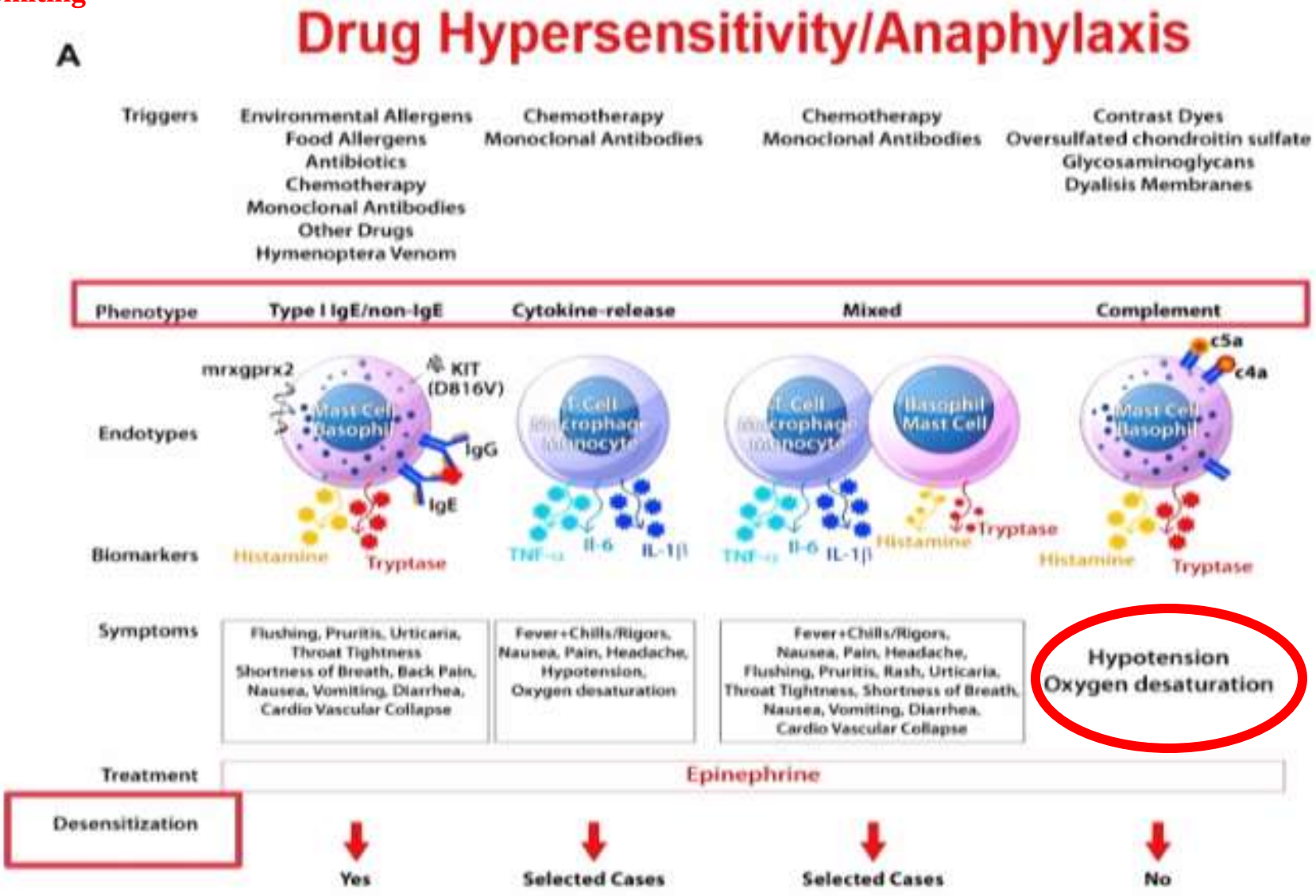
International consensus (ICON) on drug allergy



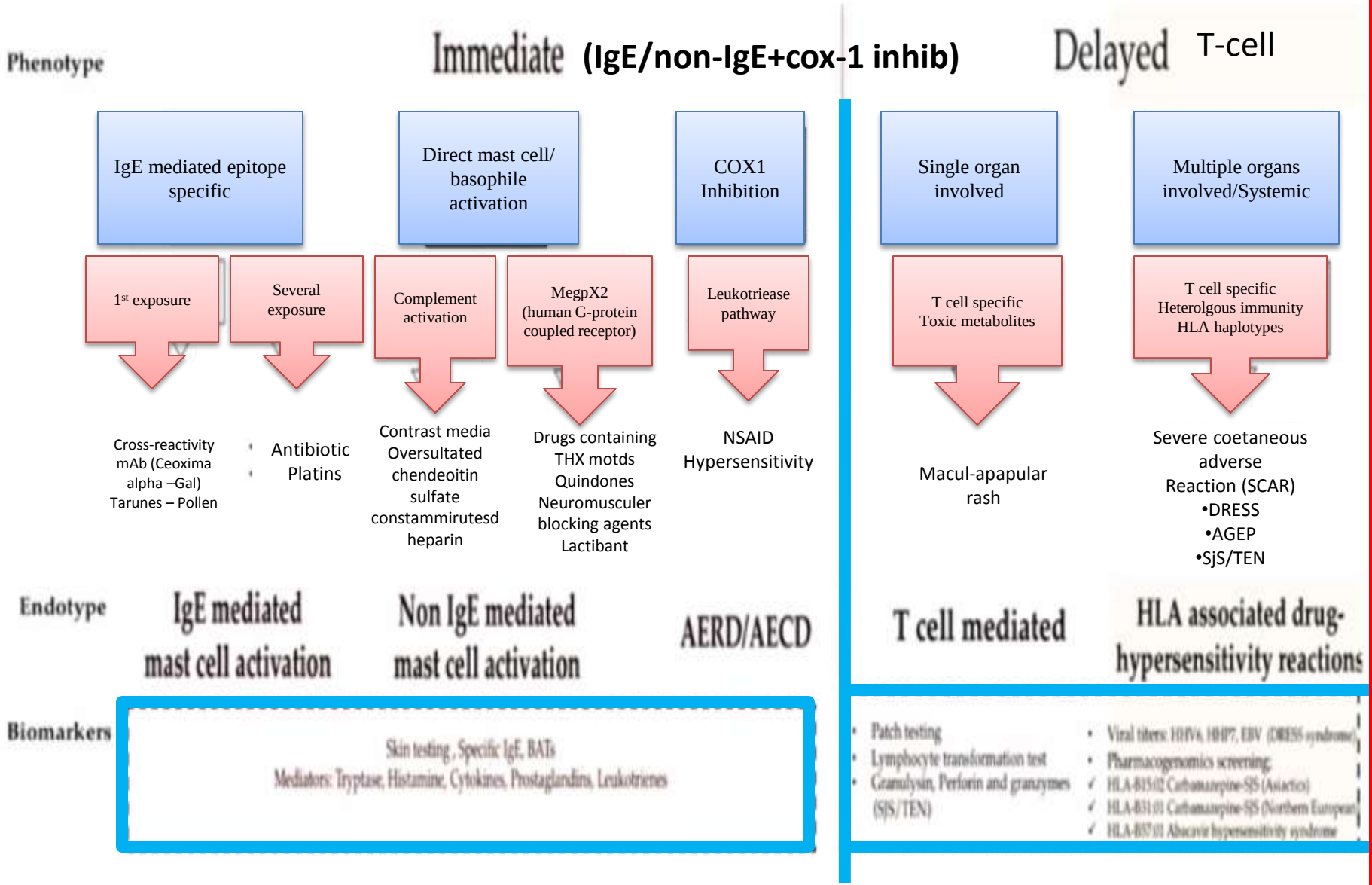
Drug hypersensitivity - nomenclature



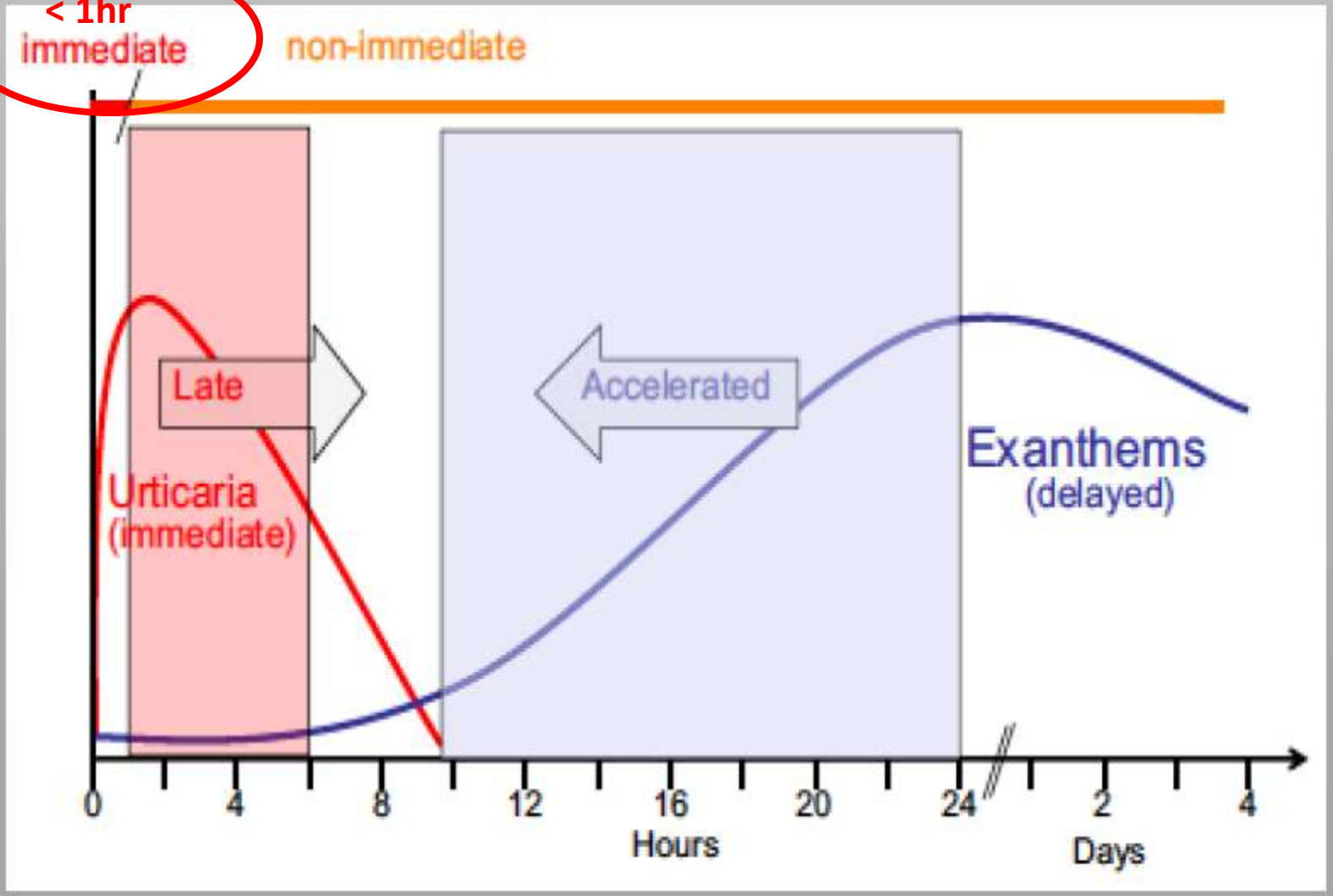
Flushing, Purities , Urticaria, Throat Tightness Shortness of Breath, Back Pain, Nausea Vomiting



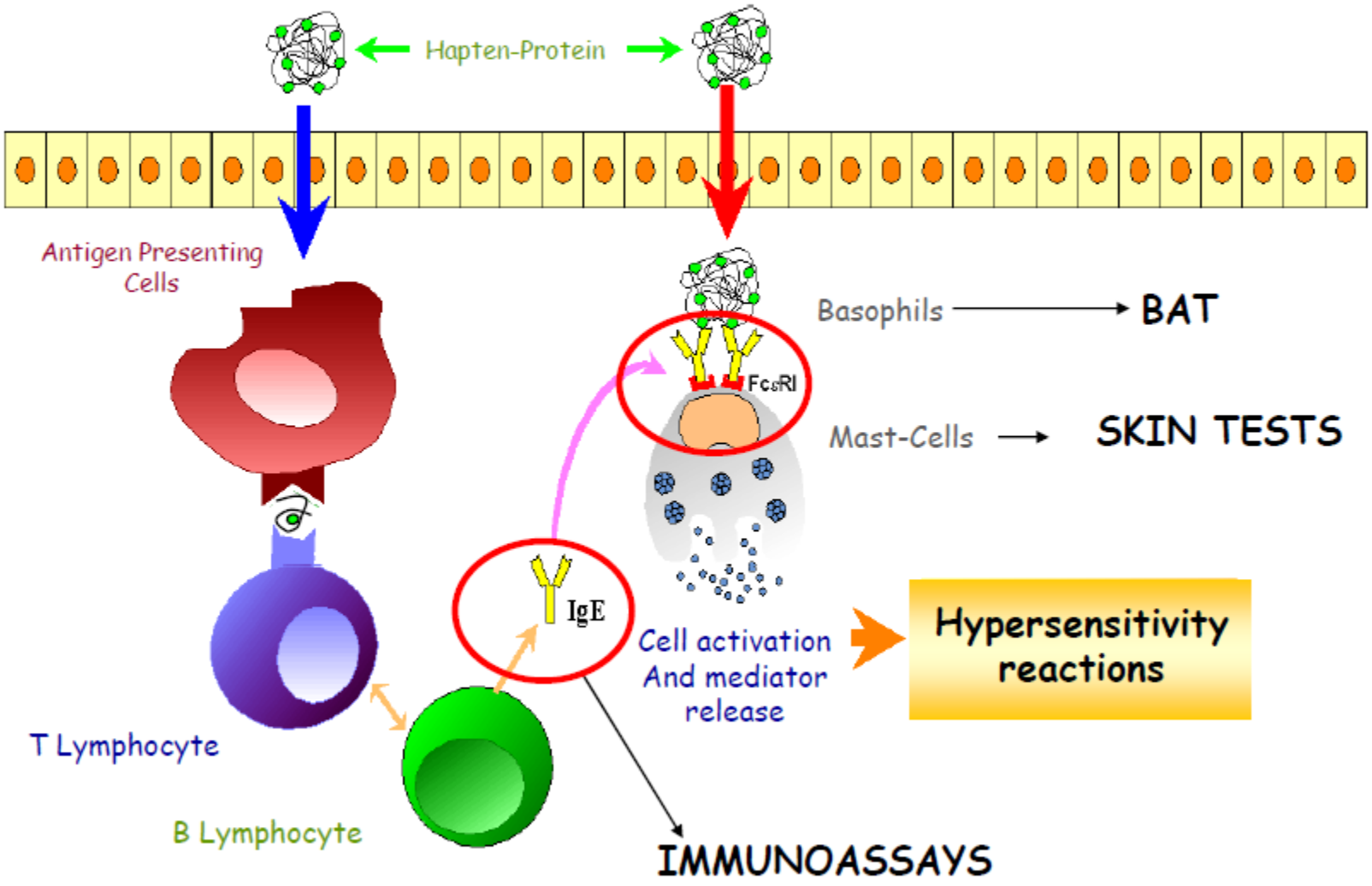
Phenotypes and endotypes in drug allergy



Time course of allergic reactions

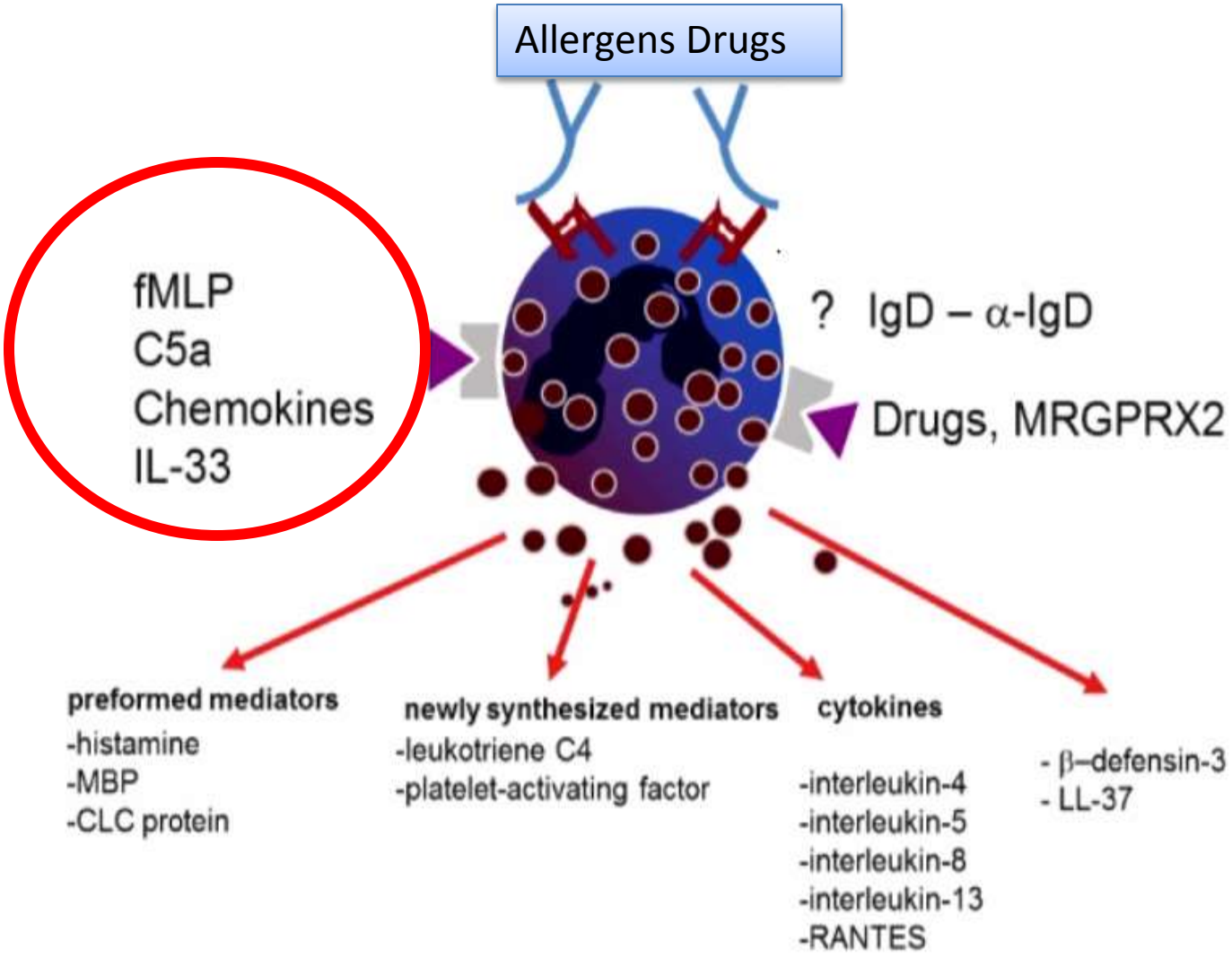


IMMEDIATE REACTIONS

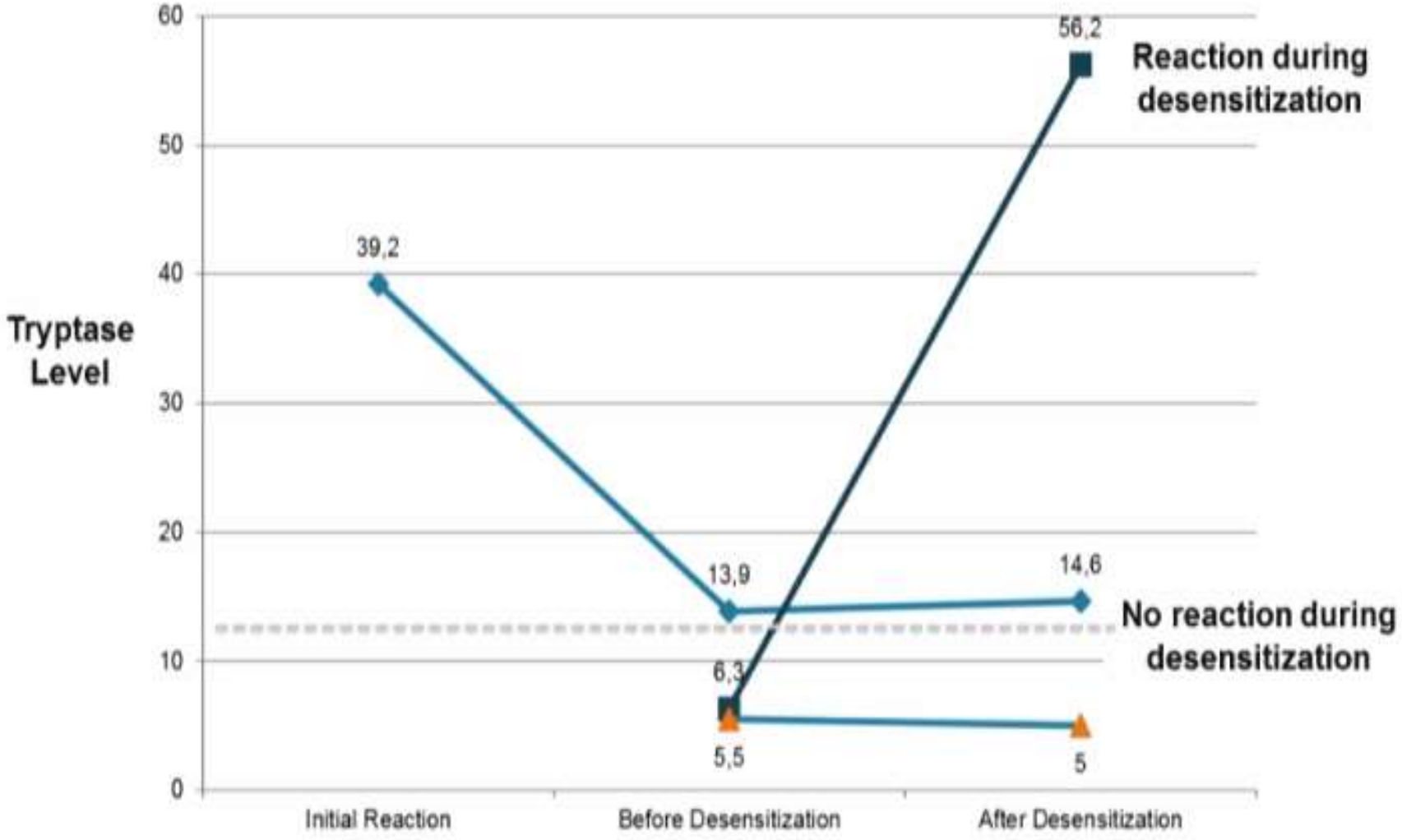


Immediate reaction

Activation of human basophils/mast cells



Tryptase: a marker of mast cell activation



DRUG ALLERGY

Immediate

Non- Immediate

Suspected IgE Mediated

In- vitro sIgE BAT

In vivo
Skin Prick/Intradermal Test

Suspected T Cell Mediated

In- vitro LTT

In vivo
Late Reading Intradermal Test/Patch Test

Drug Provocation Test

For High Risk Patients
Or
Severe Reaction
Or
For Drugs Where Skin Test Are Not Available
It Might Be Advisable To Perform In Vitro Tests Before In Vivo Test

In –vitro Serum specific IgE

- Most available commercial method is the fluoroimmunoassay (FEIA) ImmunoCAP (Thermo-Fisher, Uppsala, Sweden)

- Limi
- Low)
- Som
- Ben d sam

Pholcodine
Morphine
Chlorhexidine
Suxamethonium
Penicilloyl V
Penicilloyl G
Insulin porcine
Insulin human
Insulin bovine
Gelatin
Cefaclor
Ampicilloyl
Amoxicilloyl

ThermoFisher

In- vitro Basophile Activation Tests

- Based on flow cytometry and measuring activation markers (CD63 and CD203c)
  - For inject able drugs and mimics *in-vivo* response

Sensitivity

40 – 60 % depending on the drug

Specificity

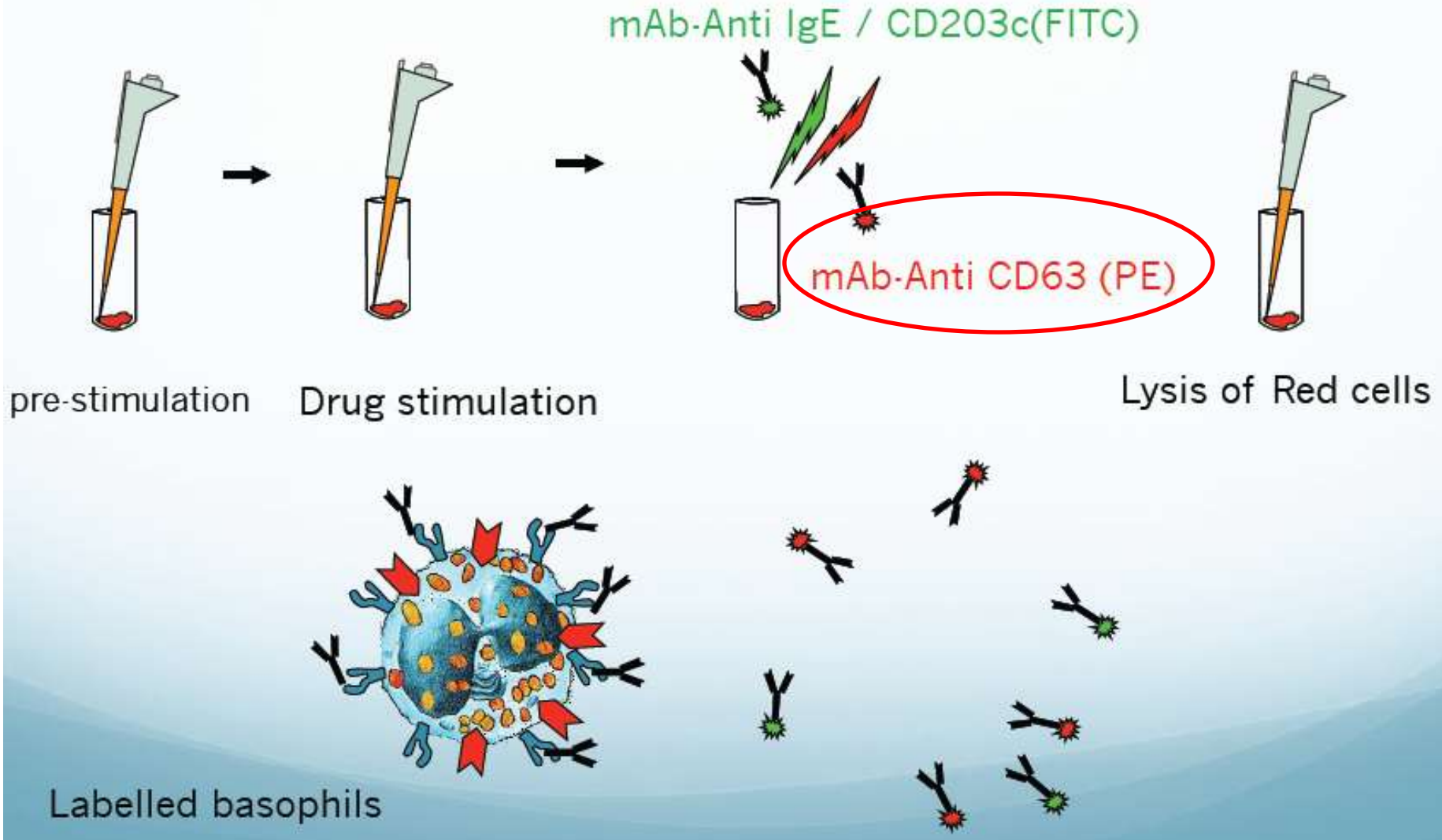
85 – 100%

Drug	Sensitivity
Penicillin	22-55%
Clavulanic acid	53%
Rocuronium	92%
NMBA	64-85%
Fluoroquinolones	36-71%

- At present no standardised approach and variations between laboratories

In- vitro Basophile Activation Tests

BAT protocol for flow cytometry



Non- immediate reaction

In vitro tests

A The Lymphocyte transformation test (LTT)
- absolutely safe
- useful for analysis of cross-reactivity

There is controversy over the specificity and sensitivity of LTT

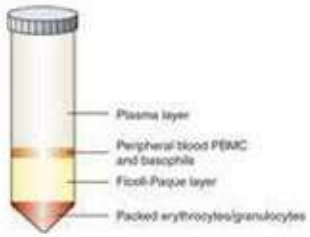
78% sensitivity and 85% specificity

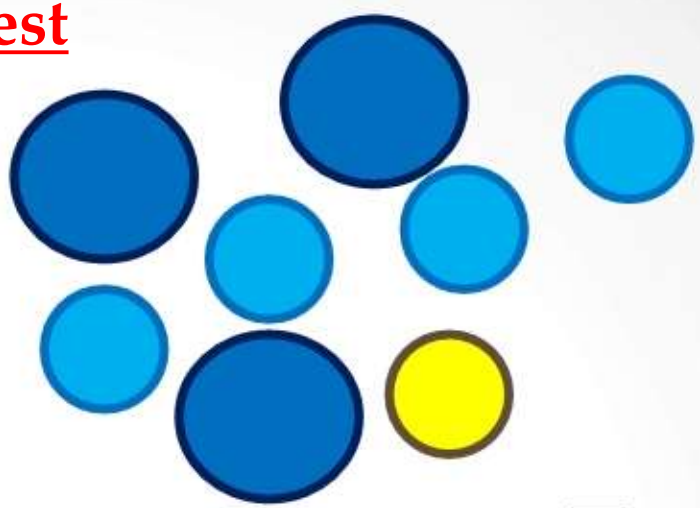
The result might depend on the drug and clinical entity

B (ELISpot) assay

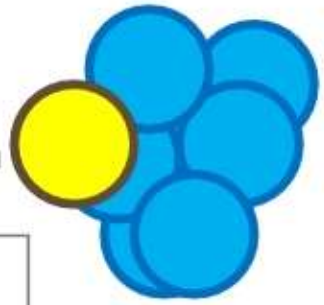
Bellon T et al, Curr Treat Options Allergy 2017.

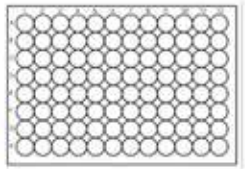
Lymphocyte Transformation Test



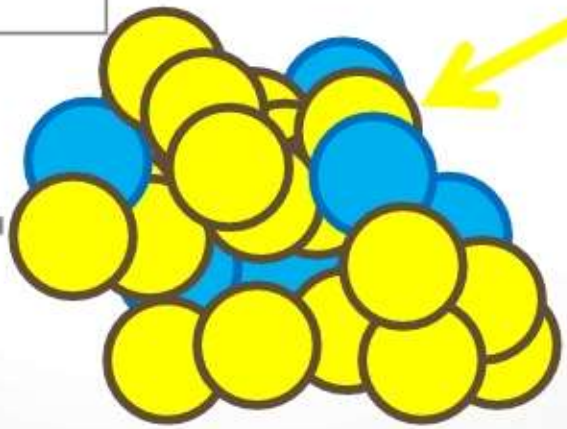


Activation of T-Cell conjugated with Drugs

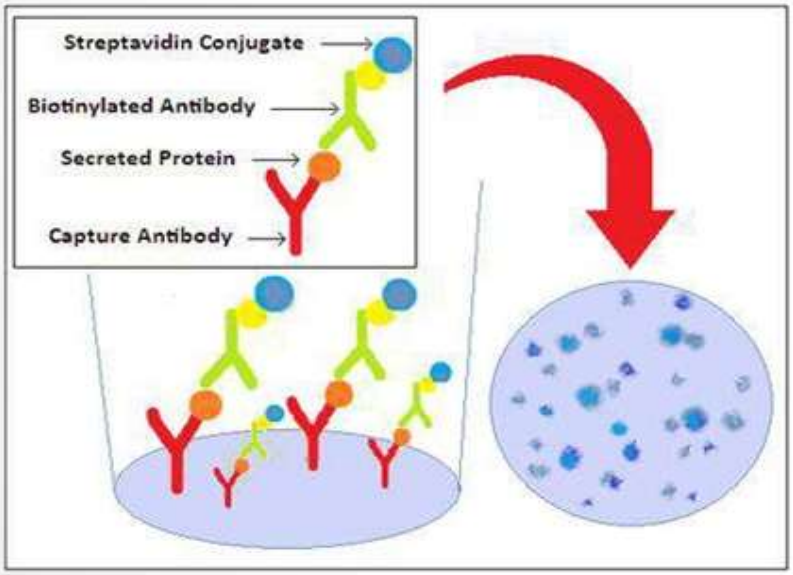




Radioactive THY



Enzyme-linked immunosorbent spot (ELISpot) assay



Determines the number of cells (even < 25 secreting cells per million) that produce and release target cytokines, such as IFN-γ, IL-5, or IL-13, and cytotoxic markers, such as **perforin, granzyme B, and granulysin**, after their activation by the **incriminated drug.**

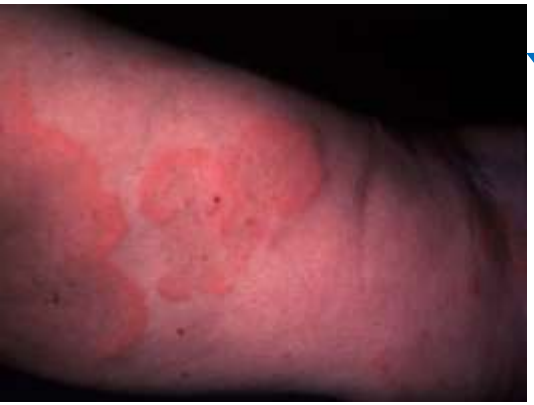
Skin test methods

	ENDA method*
Time interval	6 weeks – 6 months
Skin prick test	
Reading	20 min, (D1), D2, D3
Positivity criteria	after 15-20 min: wheal > 3 mm + erythema
	in late readings: infiltrate + erythema
Intradermal test	
Amount	0.02(-0.05) ml
Reading	20 min, (D1), D2, D3
Positivity criteria	after 15-20 min: initial wheal > +5mm
	in late readings: infiltrate + erythema
Patch test	
Reading	D2, D3, (D4)
Positivity criteria	EECDRG criteria

- Drug-free intervals
  - H1-antihistamines 5 days
  - ß-adrenergic drugs 5 days
  - Glucocorticosteroids

Long-term	oral, i.v.	3 weeks
Short-term, high dose	oral, i.v.	1 week
Short-term, <50 mg prednisolone	oral, i.v.	3 days
Topical	topical	> 2 weeks

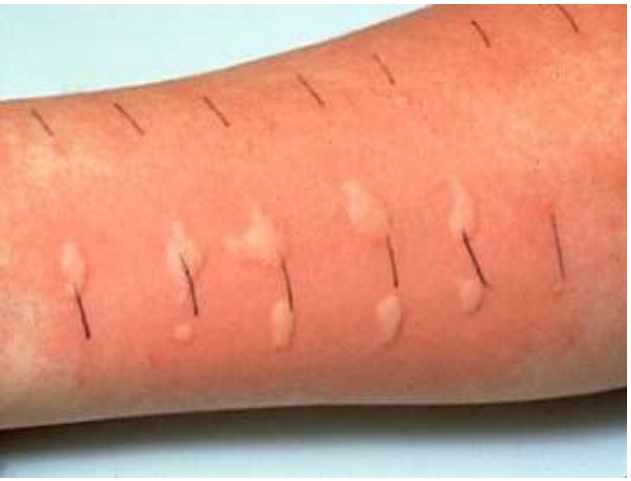
Drugs with well-standardized test protocols



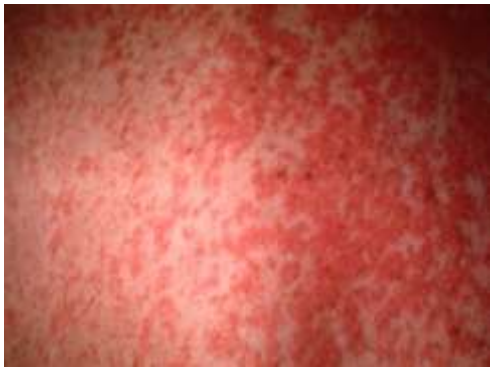
Drug-Induced Urticaria

IgE

IDST



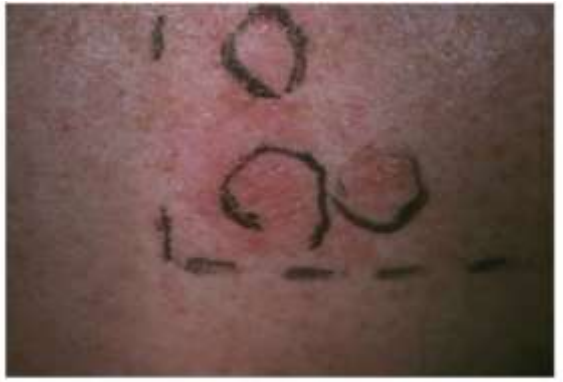
- *Imm diate type allergy:*
  - *Penicillins and cephalosporins*
  - *Neuromuscular blocking agents*
  - *Local anaesthetics*
  - *Iodinated contrast media*
  - *Chemotherapeutics (platinum salts)*
- *Contact allergy: Delayad Type Reaction*
  - *Many case reports*
  - *Several case series (iodinated contrast media, steroids, and others)*



Drug-Induced Maculopapular Eruption

Non-IgE

Patch Test



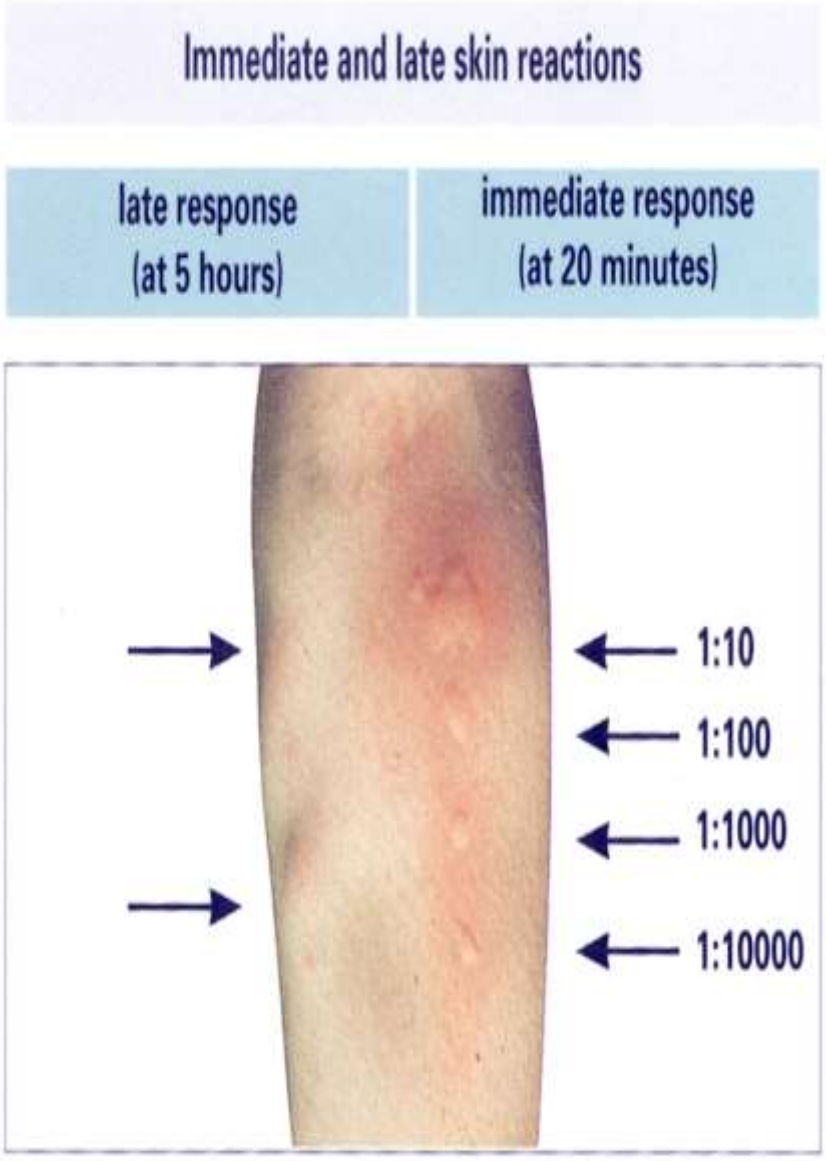
Patch Test

Diagnosing IgE mediated Drug Allergy-

- ✓ Mechanism depends on reaction investigated.
  - (types I & IV demonstrated)
- ✓ Sterile commercially available preparations.
- ✓ Serial dilutions (1:1,1000 – 1:1). eg cephalosporin
- ✓ 2-20 mg / ml
- ? 0.02-0.1 (0.05) ml papule.
- ✓ Back > forearm > arm.
- ✓ Immediate & delayed reading advised (20 min & 24 h).
- ✓ Beware of false positive reactions!
- ✓ Always >20 negative non-allergic controls.

Serial dilutions

Intradermal Test (IDST)



T-cell mediated severe coetaneous allergic reaction (SCAR)

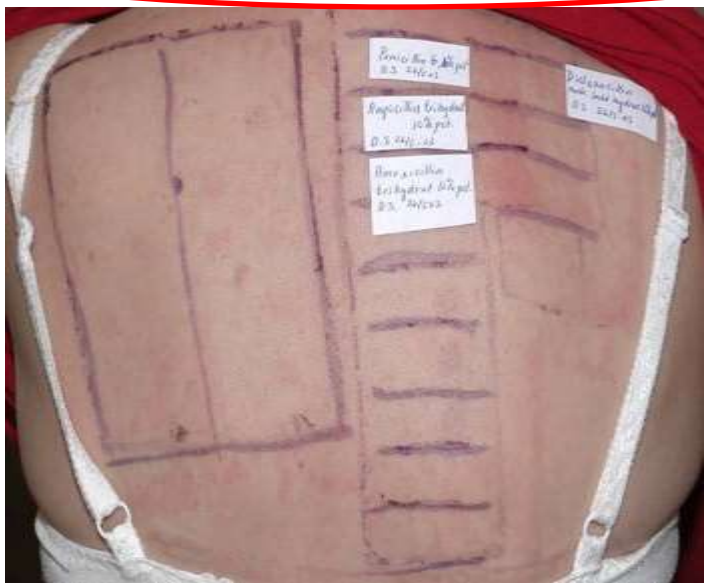
Usefulness-depends On Clinical Feature

	Patch test	Prick test	IDT
Maculopapular rash	useful	before IDT plus delayed reading	with immediate **and delayed** readings
Generalized eczema	useful	before IDT plus delayed reading	with immediate **and delayed** readings
Localized eczema caused by heparin	useful	no value but recommended	with immediate **and delayed** read-ings, frequently only positive >3 days
SDRIFE (Baboon)	useful	unknown value	unknown value
AGEP	useful	unknown value	unknown value
Fixed drug erupt.	useful in patch	unknown value	unknown value
DRESS	probably helpful	value?	unknown value
Vasculitis	no value	no value	no value, could be dangerous
TEN	can be done, rarely positive	no value	are rarely done, because could be dangerous
Photosensitivity	photopach test	no value	no value

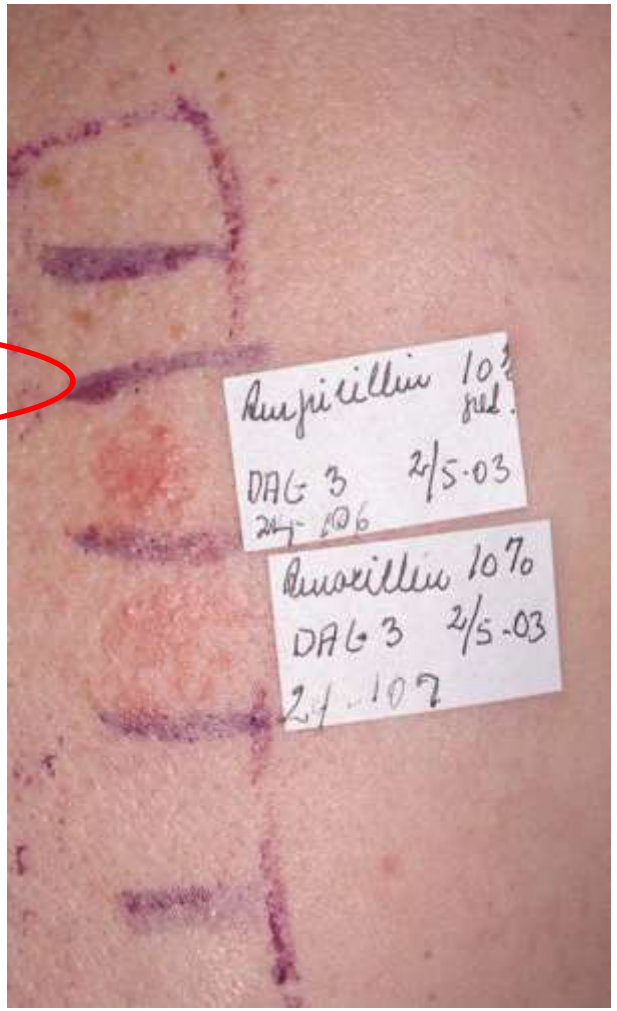
Diagnosing T-cell mediated Drug Allergy-

Delayed Reaction

- ✓*Controversial in systemic drug reactions.*
- ✓*Early reading advised (20 min).*
- ✓*Readings otherwise according to ICDRG.*
- ✓*Preparations commercially available for a number of drugs.*
- ✓*Commercially available drugs are tested in 30% pet./aq./eth.*



Patch test



Case 1 (suspected Penicillin Allergy)

- A 40 year old woman reports a lifelong history of **penicillin allergy.** She has no recollection what may have happened, but reports her mother always just told her she was allergic to penicillin.

- Is this an allergy? Would you skin test? What would you advise?

- The history in this case is not helpful. Yes, skin testing is recommended. If **skin test is negative**, should undergo **oral challenge**. If **skin test positive,** recommend **alternate** antibiotics in future or desensitization if penicillin is needed.

Case 1 (confirm PA)

- 47 year-old male with well-controlled moderate persistent asthma and AR who reports a **history of penicillin allergy** when he was 11 years old.
- Reaction: He was not sure why he was prescribed the penicillin. He recalls feeling that **his throat was closing and had shortness of breath** within 30 minutes after taking a dose. He doesn't recall hives or GI issues, but states that he was intubated in the ER. **(Anaphylaxis)**
- He has not had any penicillin/penicillin derivatives since that time.

Questions ?

- Are you concerned about a penicillin allergy?
  - Yes
- What are you going to tell him about taking penicillin?
  - Don't do it
- Can he lose his sensitivity to penicillin?
  - Yes
- Would you recommend a cephalosporin?
  - No. Recommend skin testing to PCN first. If negative OK to take cephalosporin. If positive would consider graded challenge or desensitization.

- What antibiotics would have the lowest risk of anaphylaxis for him?
  - Aztreonam and Non-beta-lactams.

Prevalence of antibiotic allergy

- Hypersensitivity reactions to antibiotics are commonly **reported** both in adults and children, with a prevalence of approximately **10%**

- In U.S., antibiotic-associated adverse events have been implicated in **19.3% of all emergency department visits** for drug-related adverse events

Legendre D. et al. Clin Infect Dis 2013:1-9
Romano A. and Caubet J. J Allergy Clin Immunol Pract 2014;2:3-12

Penicillin (PCN) "allergy" Leads to Use of alternative agents

The effect of using alternative agents to PCN:

- The use of broader-spectrum antibiotics, e.g., vancomycin and fluoroquinolones, leads to more **resistant organisms**
- **Increased cost** of alternative antibiotics
- Significant **comorbidities**
  - **Vancomycin-resistant enterococcus**
  - **Clostridium difficile-associated diarrhea**

Solensky R. et al. Ann Allergy Asthma Immunol 2010; 105:259-73
Picard M, et al. JACI Practice. 2013;252-257
Sade K, et al. Clin Exp Allergy. 2003; 33:501-506
Reddy V., et al. JACI. 2013;131:AB170

The dangers & Costs of being labeled

"Penicillin Allergic"

- Retrospective matched cohort study of 51, 582 "Penicillin Allergic" patients hospitalized in Kaiser Foundation South California Hospitals 2010-2012
- Longer hospital stays (.59 day/person)
- Treated with more fluoroquinolones, clindamycin, and vancomycin
- **23.4%** more C difficile
- **14%** more MRSA
- **30%** more vancomycin-resistant Enterococcus
- $20 Million increase cost/year for this group of patients

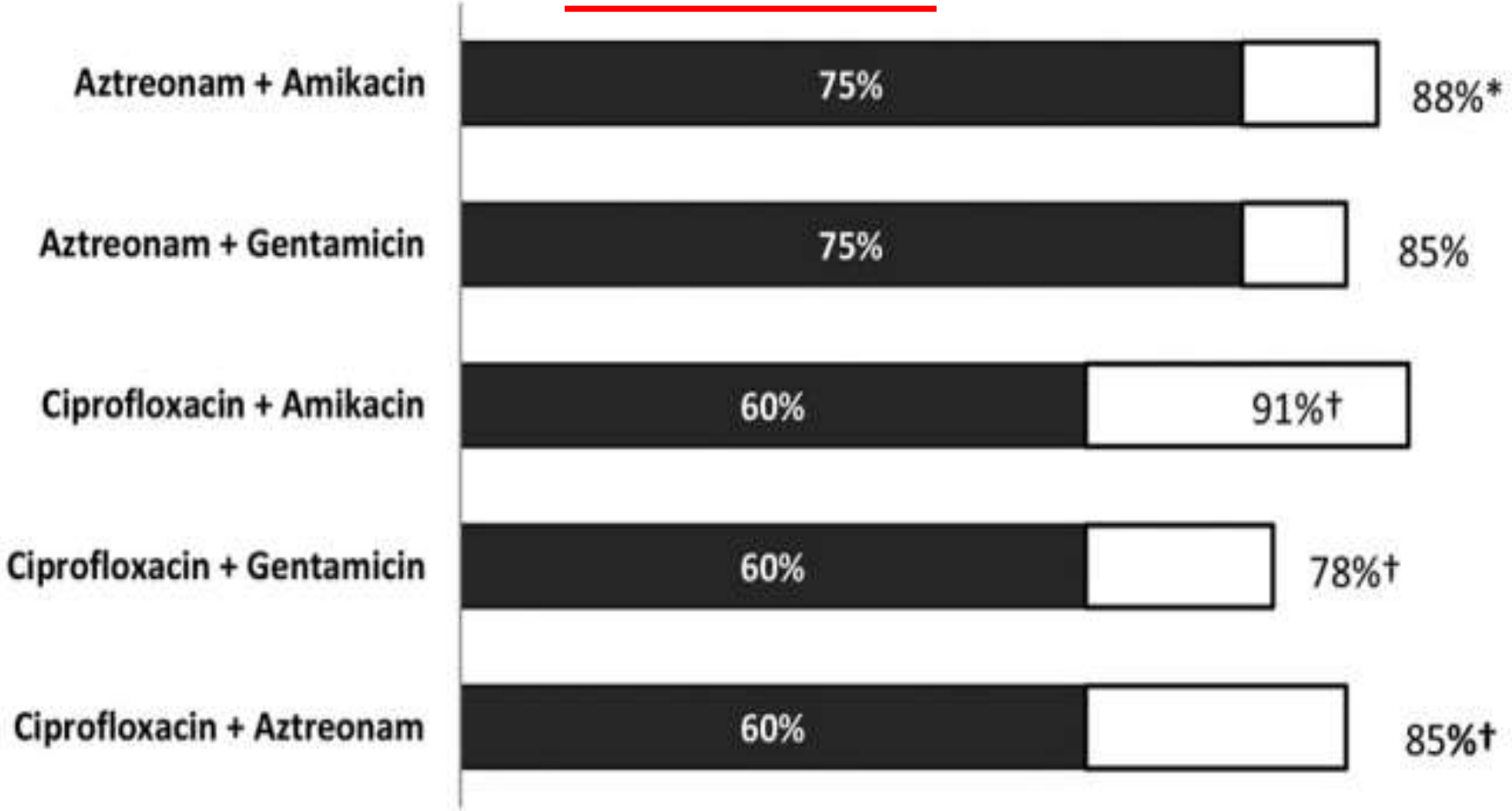
Macy E, Contreras R. JACI. 2014;133(3):790-6

Non- Beta-lactam antibiotics

- Quinolones
- Sulfonamides
- Macrolides
- Aminoglycosides
- Rifamycins
- Glycopeptides
- Clindamycin

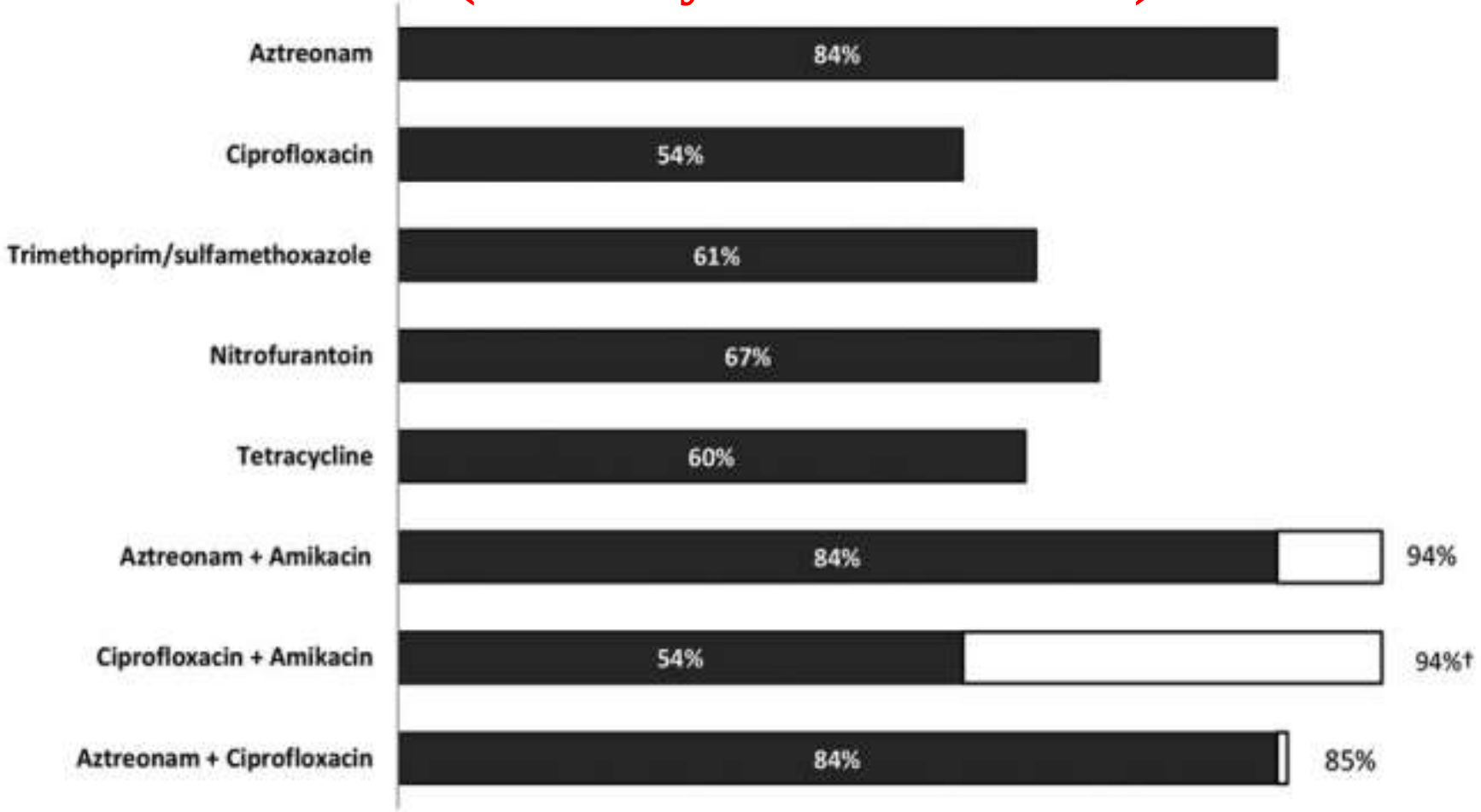
Romano A. and Caubet J. J Allergy Clin Immunol Pract 2014;2:3-12

All Infections



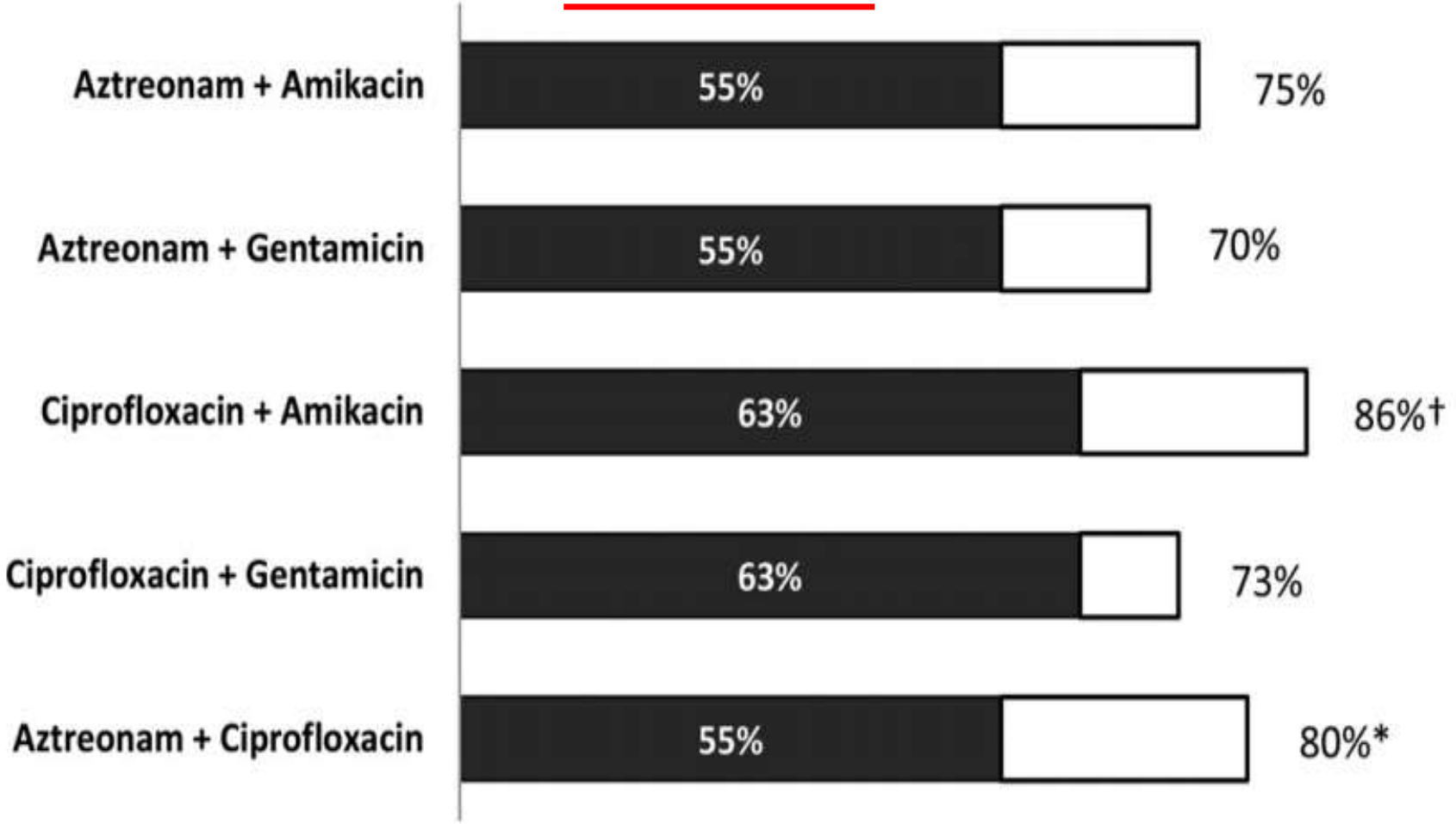
Adequacies of antibiotic combinations for all infections ($n = 116$). Black bars represent adequacies achieved by the first antibiotics. White bars represent additional adequacies gained by adding the second agents. *, $P < 0.05$ versus aztreonam alone; †, $P < 0.05$ versus ciprofloxacin alone.

UTI (Urinary Tract Infection)



Adequacies of antibiotics for urinary tract infections ($n = 67$). Black bars represent adequacies achieved by the first antibiotics. White bars represent additional adequacies gained by adding the second agents listed. †, $P < 0.05$ versus ciprofloxacin alone.

Pneumonia



Adequacies of antibiotics for pneumonia ($n = 40$). Black bars represent adequacies achieved by the first antibiotics. White bars represent additional adequacies gained by adding the second agents listed. *, $P < 0.05$ versus aztreonam alone; †, $P < 0.05$ versus ciprofloxacin alone.

Beta-lactam antibiotics

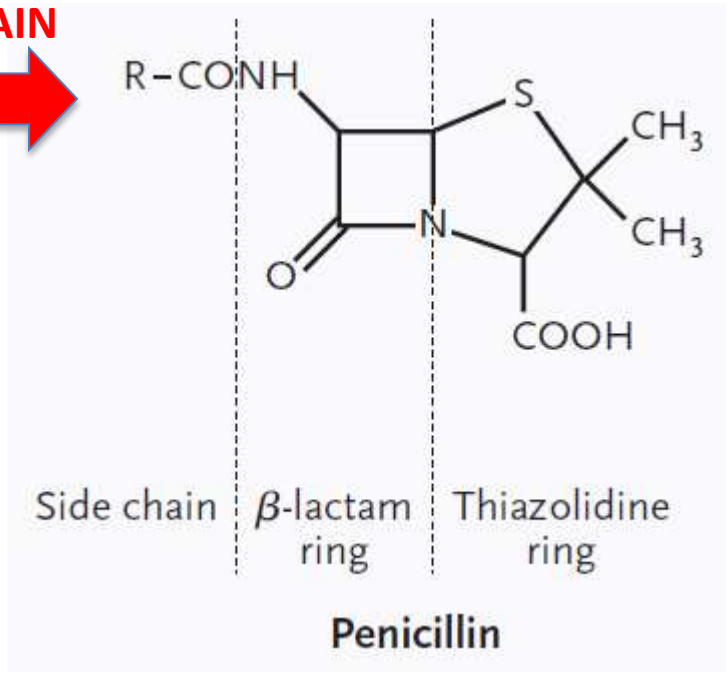
2 major classes

- Penicillins
- Cephalosporins

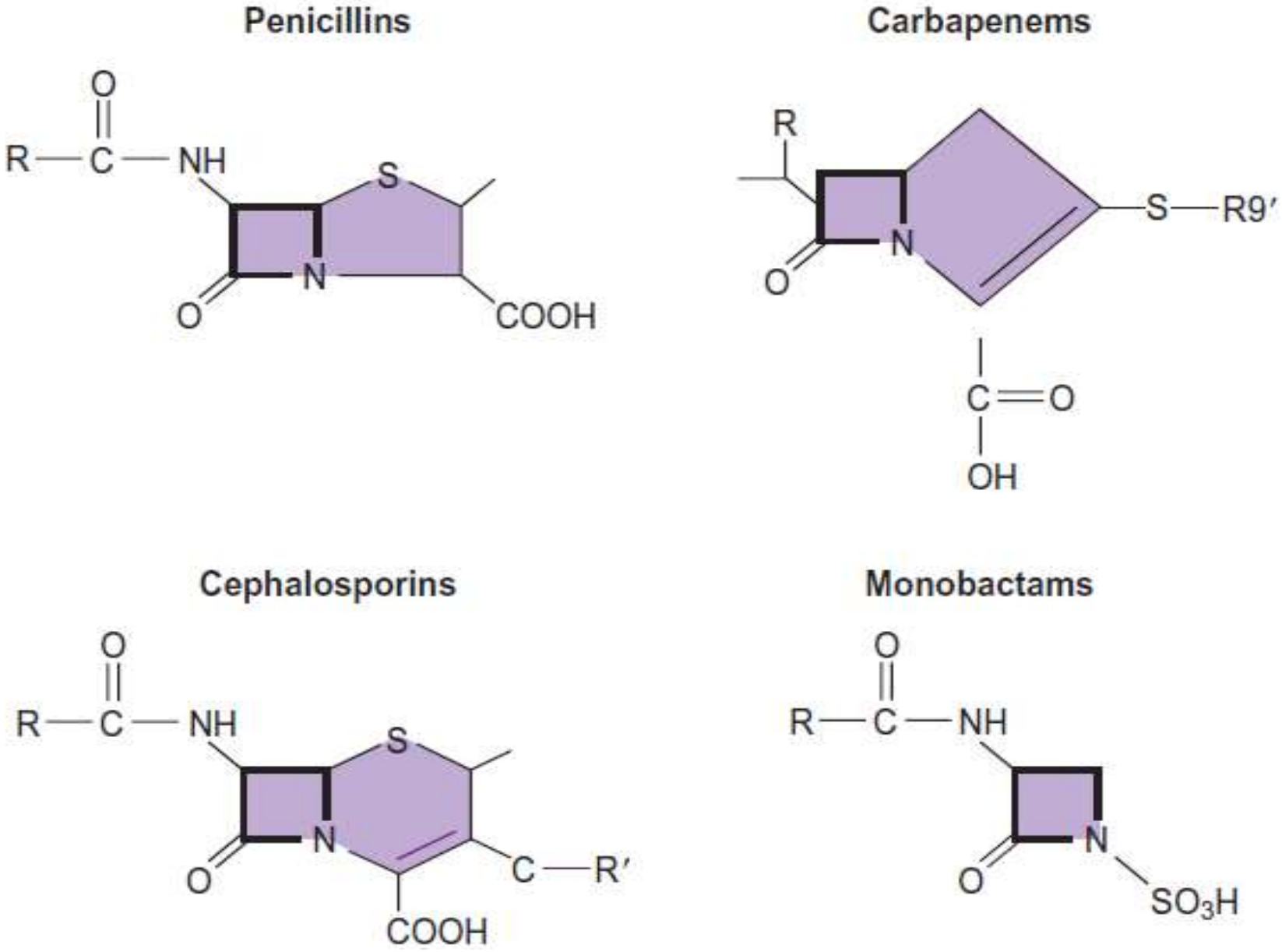
4 minor classes

- Carbapenems
- Monobactams
- Oxacephems
- Clavams

R- SIDE CHAIN



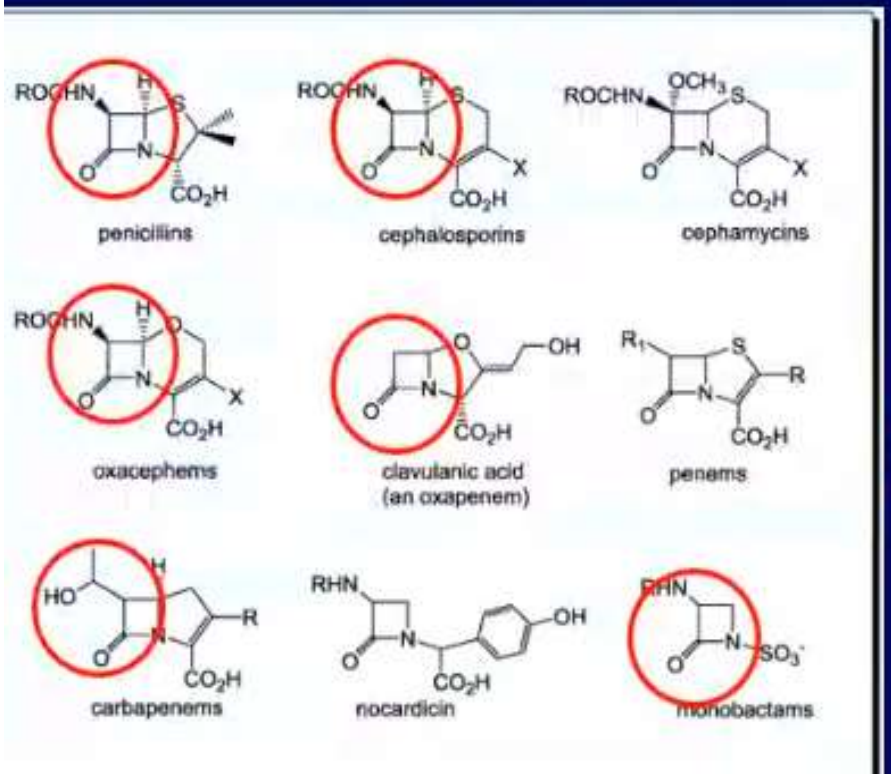
Romano A. and Caubet J. J Allergy Clin Immunol Pract 2014;2:3-12

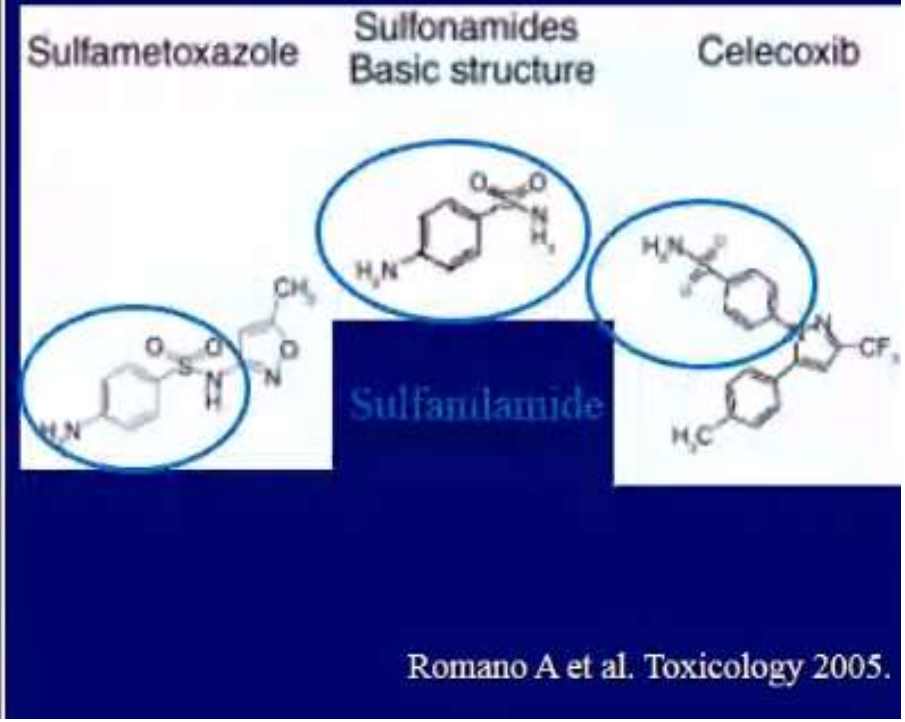


Celik G., Pichler W. and Adkinson F. Middleton's Allergy 8th edition,1274-95

Cross-reactivity among drugs mediated by immunologic mechanisms

- The presence of a common antigenic determinant in the cross-reacting drugs





Romano A et al. Toxicology 2005.

Definition

Cross-reactivity among drugs

Becomes clinically manifes when a drug not previously administered elicits hypersensitivity reactions because of a preexisting sensitisation to a structurally related compound or because of a common pharmacological characteristic

PCN Allergy and other Drugs

- **Monobactams (Aztreonam):** Does not cross react with penicillins or cephalosporins (except ceftazidime) and may be given without PCN skin testing.

- **Carbapenems**: PCN skin testing should be performed if possible, otherwise may receive via **graded challenge.**

Cross-reactivity between other BLs

- 0.9% rate of cross-reactivity to imipenem/cilastatin in 112 adults, with penicillin allergy

Romano A et al, N Engl J Med 2006.

- 0.9% rate of cross-reactivity to meropenem in 104 adults, with penicillin allergy

The ENDA position for the administration to penicillin-allergic patients of an alternative BL is that once an immediate penicillin allergy has been diagnosed, skin testing with the alternative BL (cephalosporin, carbapenem, aztreonam) is mandatory and, if negative, the relevant drug should be given in an appropriate setting at increasing doses

PCN Skin testing and Challenge

DRUG Testing– IMMEDIATE & DELAyed

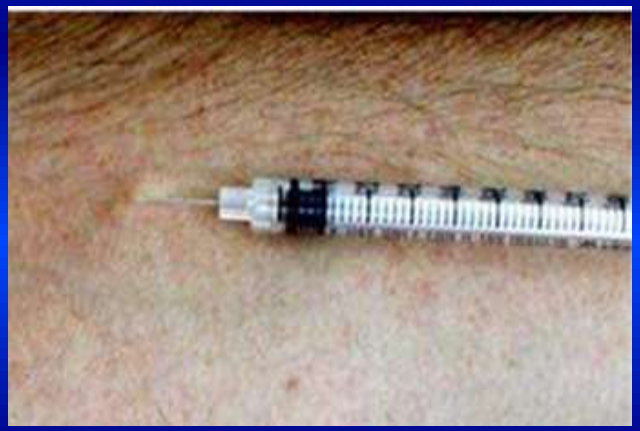
TABLE I. Diagnostic tests of hypersensitivity reactions to drugs

Type of reaction		Type of tests
Immediate	*In vitro*	Specific IgE assays (Not recommended)
		Flow cytometric BATs (Experimental)
Good option	*In vivo*	Skin tests Choice for PCN, ? cephalosporins
		Provocation tests
Nonimmediate	*In vitro*	LTTs or LATs (Experimental)
(Experimental)		ELISPOT assays for analysis of antigen-specific, cytokine-producing cells
	In vivo	Delayed-reading intradermal tests
		Patch tests
		Provocation tests

Skin Prick Testing

- Identify IgE mediated reaction (Sensitivity up to 70%)
- Maximal wheal after 15-20 mins
- Positive (histamine) and negative (saline) controls
- Wheal 3mm greater than negative control considered positive

Intradermal Testing



- 0.02mls giving 2mm BLEB
- Readings at 24, 48, and 72 hours Infiltrated erythema greater than 5mm in diameter considered positive

Contraindications for skin testing & Drug Challenge

- **Autoimmue Diseases**
  - Bullous pemphidoid, Pemphigus vulgaris, Linear IgA bullous disease, Drug-induced lupus
- Neutrophilic Dermatosis
  - Acute generalized exanthematous pustulosis (AGEP)
  - Sweets syndrome
- Severe Cutaneous Drug Reactions
  - SJS/TEN
  - DRESS
  - Exfoliative dermatitis

PCN Testing Protocol
2015 Drug & Anaphylaxis Committee

- Complete prick and ID testing (if prick is negative) with:
  - **Penicillin G 10,000 U/ml**
  - **PrePen** (benzylpenicilloyl polylysine) full strength
  - **Negative Control**: Sodium chloride solution without preservative
  - **Positive Control**:
    - Percutaneous: histamine base 6 mg/ml (histamine dihydrochloride 10 mg/ml)
    - Intradermal: histamine base 0.1 mg/ml (histamine phosphate 0.275 mg/ml)

Haptens and the highest concentrations recommended for prick and intradermal tests

HAPTEN	DOSE	UNIT
PPL	$5x10^{-5}$	mMol/l
MDM	$2x10^{-2}$	mMol/l
AMOXICILLIN	20	mg/ml
BENZYLPENICILLIN	10,000	IU/ml
CULPRIT DRUG		
• Cephalosporin	2	mg/ml
• Amoxicillin-clavulanic	20	mg/ml
• Ampicillin	20	mg/ml

M Blanca et al, Allergy 2009

Non-irritating concentrations of cephalosporins for skin testing

Table 18. Nonirritating Concentrations of 15 Antibiotics[428]

Antimicrobial drug	Full-strength concentration	Dilution from full strength	Nonirritating concentration
Azithromycin	100 mg/mL	10^{-4}	10 μg/mL
Cefotaxime	100 mg/mL	10^{-1}	10 mg/mL
Cefuroxime	100 mg/mL	10^{-1}	10 mg/mL
Cefazolin	330 mg/mL	10^{-1}	33 mg/mL
Ceftazidime	100 mg/mL	10^{-1}	10 mg/mL
Ceftriaxone	100 mg/mL	10^{-1}	10 mg/mL
Clindamycin	150 mg/mL	10^{-1}	15 mg/mL
Cotrimoxazole	80 mg/mL	10^{-2}	800 μg/mL
Erythromycin	50 mg/mL	10^{-3}	50 μg/mL
Gentamicin	40 mg/mL	10^{-1}	4 mg/mL
Levofloxacin	25 mg/mL	10^{-3}	25 μg/mL
Nafcillin	250 mg/mL	10^{-4}	25 μg/mL
Ticarcillin	200 mg/mL	10^{-1}	20 mg/mL
Tobramycin	80 mg/2 mL	10^{-1}	4 mg/mL
Vancomycin	50 mg/mL	10^{-4}	5 μg/mL

Solensky R. et al. Ann Allergy Asthma Immunol 2010; 105:259-73

PCN Testing Protocol
2015 Drug & Anaphylaxis Committee

- For ID testing administer 0.02-0.03 ml
- Read all prick/ID tests at 15 minutes
- Positive Prick & ID is ≥3 mm diameter with equivalent or greater erythema (flare) compared to the saline control
- Duplicate testing not recommended
- **Oral Challenge with Amoxicillin**
  - 1st dose (optional) **25 to 50 mg** Amoxicillin
  - 2nd dose (or only dose) **250 mg** Amoxicillin
- Observe for 30 and 60 minutes after 1st & 2nd dose, respectively

When PCN Testing is positive

- If a PCN skin test (major or minor determinant) is **positive,** there is approximately **50% chance of an immediate reaction to PCN**
- Many patients with a positive PCN skin test will have a negative challenge, indicating **sensitization** rather than true clinical allergy
- A **positive** in vitro specific IgE to PCN or major determinant or basophil activation tests indicates significant **risk for an immediate reaction**, but a **negative** test results **lacks** adequate sensitivity
- Patients with a both a **positive** history and skin test to PCN have a **2%** chance of being allergic to **cephalosporins**

Solensky R. et al. Ann Allergy Asthma Immunol 2010; 105:259-73

Testing for Amoxicillin/Ampicillin

2015 Drug & Anaphylaxis "Expert Opinion"

- **Amoxicillin and Ampicillin ARE different drugs** and there is the possibility of reacting to one and not the other
- **Ampicillin IV** is the only available commercial product in US that can be used for skin testing
- When the suspected or confirmed allergic reaction was to Amoxicillin or Ampicillin, and this drug will likely be needed in the future, consider skin testing with **Ampicillin**
- Test using **Ampicillin 20 mg/ml for Prick/ID testing**[1,2]
  - Note: Some US drug allergy experts recommend 2.5 mg/ml but no published studies could be located
- **When Augmentin is the allergic drug**, clavulanate (not commercially available) is not a required skin testing agent. However, consider using **Augmentin for oral challenge.**

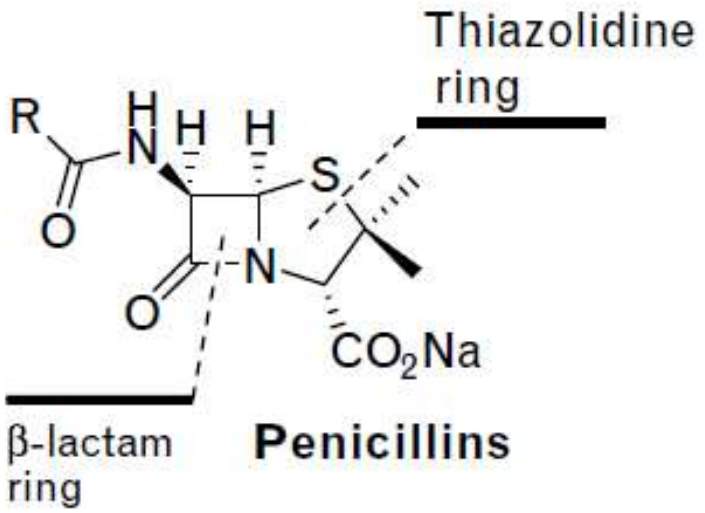
1.Blanca M. Allergy. 2009;64(2):183-93.
2.Padial A, Clinical and experimental allergy : journal of the British Society for Allergy and Clinical Immunology. 2008;38(5):822-8.

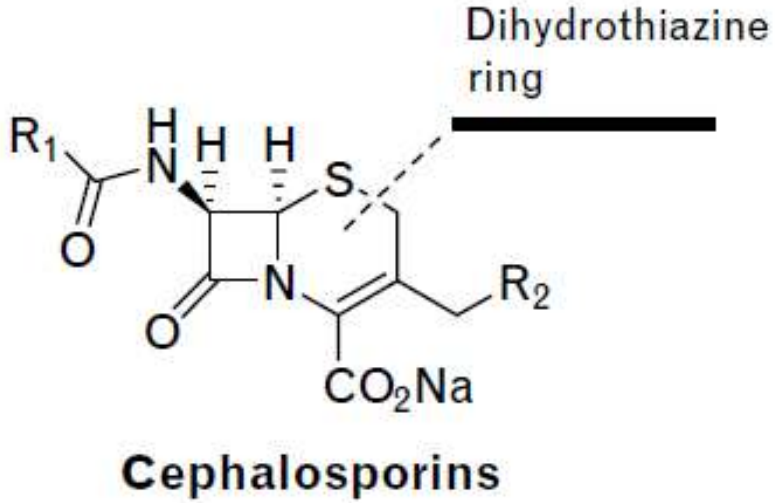
PCN skin testing

- **Negative predictive value approaches 100%**
- Positive predictive value between 40% and 100%
- If negative on prick testing patients should receive a penicillin challenge (Provocative Drug Testing)
  - If challenge not performed, patients and providers may still fear administration.

Solensky R. et al. Ann Allergy Asthma Immunol 2010; 105:259-73

CEPHALOSPORIN ALLERGY





Perez-Inestrosa E. et al. Curr Opin Allergy Clin Immunol 5:323–330

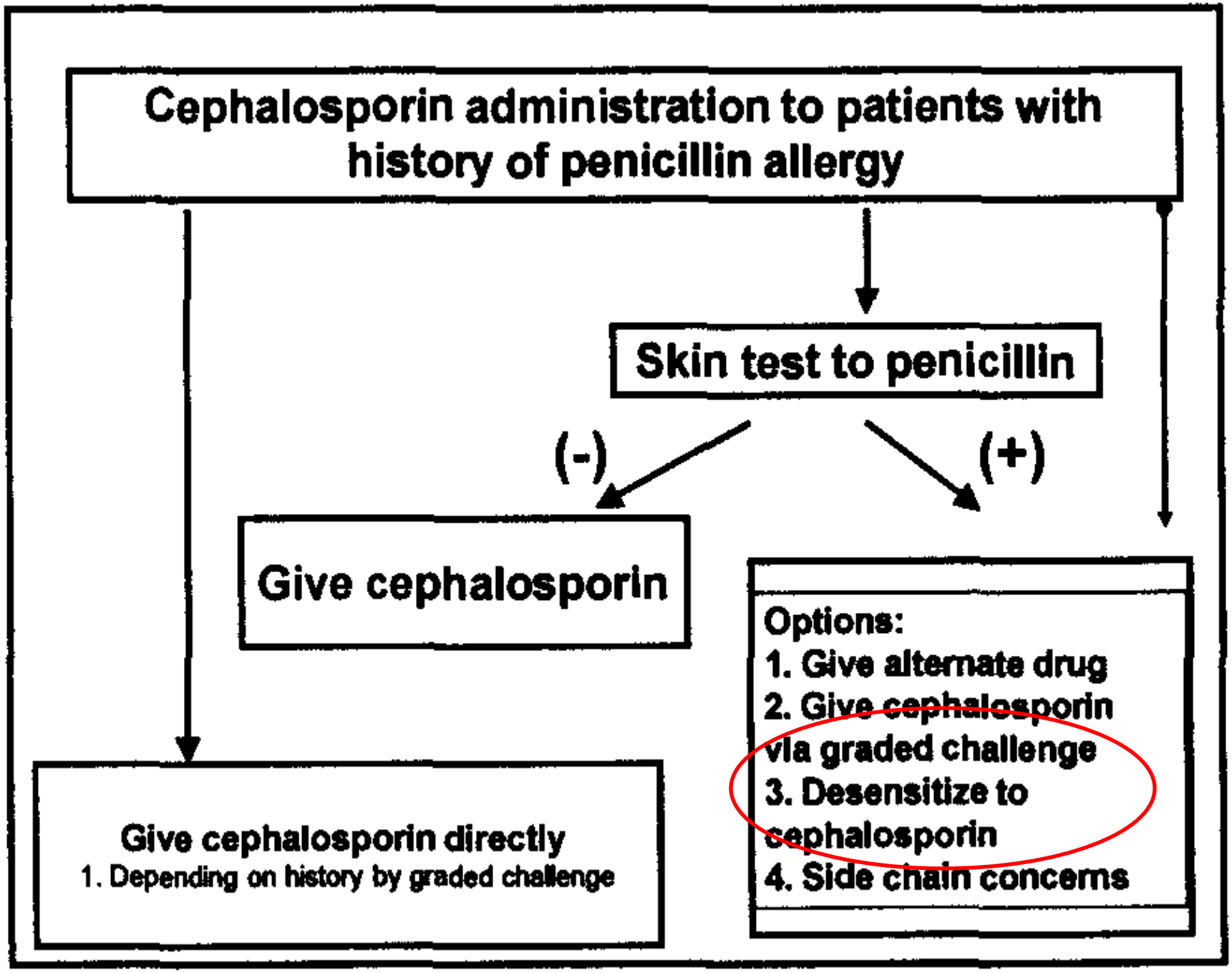
Cross-reactivity

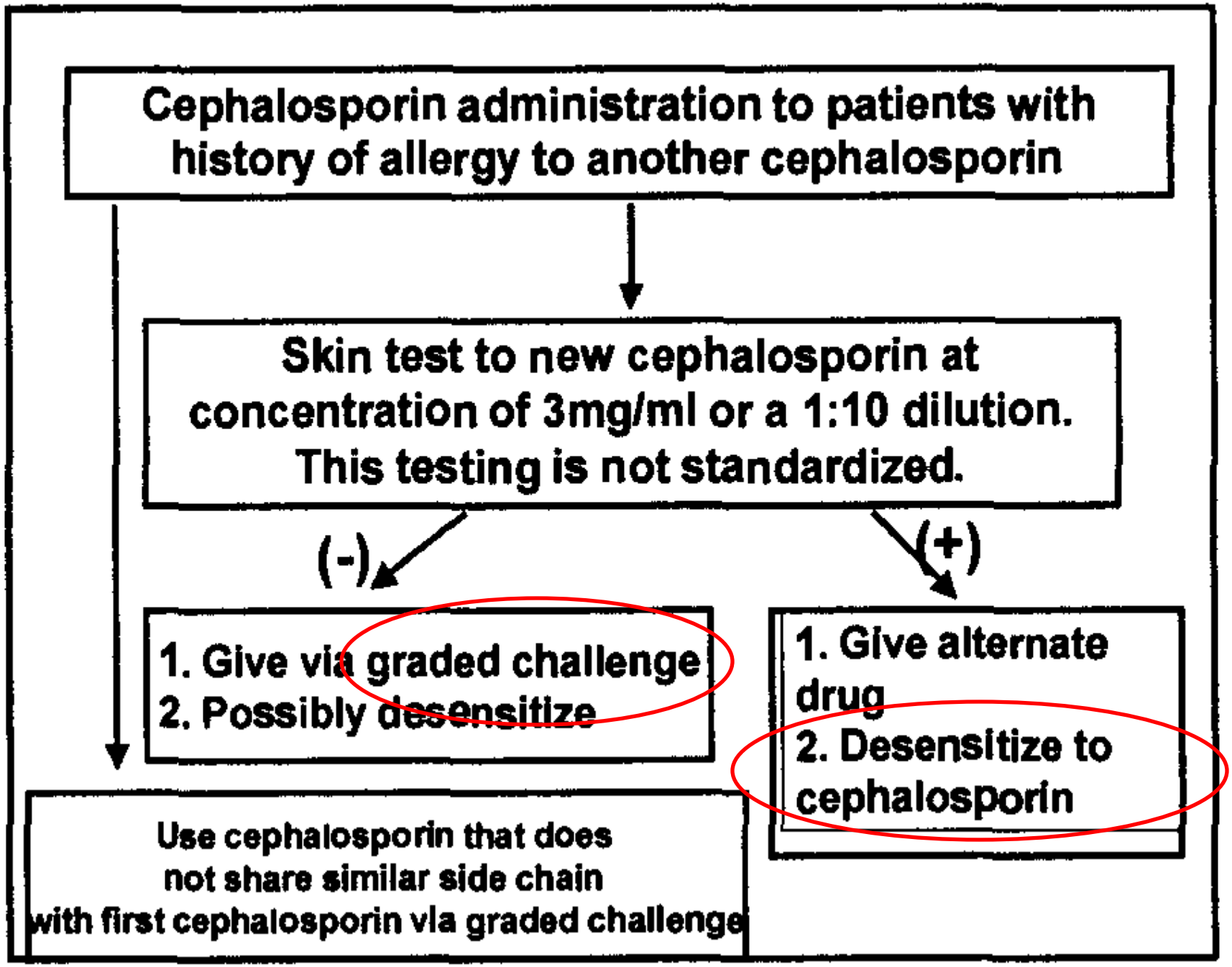
- 38% of subjects with a selective response to AX developed cross-reactivity with cefadroxil, which shares an identical side-chain at the R1 position with AX

Torres MJ et al, J Allergy Clin Immunol 2007.

- 12% of subjects with well-demonstrated IgE-mediated hypersensitivity to penicillins, developed cross-reactivity with cephalosporins with a similar side-chain

Romano A et al, Ann Intern Med 2004.


Cephalosporin administration to patients with history of penicillin allergy
Skin test to penicillin
(-)
(+)
Give cephalosporin
Options:
1. Give alternate drug
2. Give cephalosporin via graded challenge
3. Desensitize to cephalosporin
4. Side chain concerns
Give cephalosporin directly
1. Depending on history by graded challenge


Cephalosporin administration to patients with history of allergy to another cephalosporin
Skin test to new cephalosporin at concentration of 3mg/ml or a 1:10 dilution. This testing is not standardized.
(-)
(+)
1. Give via graded challenge
2. Possibly desensitize
1. Give alternate drug
2. Desensitize to cephalosporin
Use cephalosporin that does not share similar side chain with first cephalosporin via graded challenge

Cephalosporin administration With Cephalosporin Allergy History

- Complete cephalosporin **skin testing using a non-irritating concentration** of the selected cephalosporin taking into account if the specific cephalosporin responsible for the adverse reaction shares the same **R1 or R2 side chain** as the drug that that needs to be used

- Administer graded dose **challenge** with oral form of drug used for skin testing

Cross-reactivity between cephalosporins

- Must be considered in terms of the similar of the chemical structure of the R1 side-chain
  - ceftriaxone, cefotaxime, cefepim→ identical side-chain at the R1 position
  - cefuroxime, ceftazidime → similar R1side-chains

Romano A et al, J Allergy Clin Immunol 2000.
Antunez C et al, J Allergy Clin Immunol 2006.
Romano A et al, Clin Exp Allergy 2005.

- Must be considered in terms of different side-chains, probably because the specific antibodies are direct to the common chemical structure shared by all

Cephalosporin administration to patients with a hx of amoxicillin/ampicillin allergy

- Patients allergic to **amoxicillin** (or augmentin) should avoid cephalosporins with identical R-group side chains **(cefadroxil, cefprozil, cefatrizine)** or receive them via rapid induction of drug tolerance
- Patients allergic to **ampicillin** should avoid cephalosporins and carbacephems with identical R-group side chains **(cephalexin, cefaclor, cephradine, cephaloglycin, loracarbef)** or receive them via rapid induction of drug tolerance

Solensky R. et al. Ann Allergy Asthma Immunol 2010; 105:259-73

R-chains

Table 16. Groups of β-Lactam Antibiotics That Share Identical R_1-Group Side Chains[a]

Amoxicillin	Ampicillin	Ceftriaxone	Cefoxitin	Cefamandole	Ceftazidime
Cefadroxil	Cefaclor	Cefotaxime	Cephaloridine	Cefonicid	Aztreonam
Cefprozil	Cephalexin	Cefpodoxime	Cephalothin		
Cefatrizine	Cephradine	Cefditoren			
	Cephaloglycin	Ceftizoxime			
	Loracarbef	Cefmenoxime			

[a] Each column represents a group with identical R_1 side chains.

Table 17. Groups of β-Lactam Antibiotics That Share Identical R_2-Group Side Chains[a]

Cephalexin	Cefotaxime	Cefuroxime	Cefotetan	Cefaclor	Ceftibuten
Cefadroxil	Cephalothin	Cefoxitin	Cefamandole	Loracarbef	Ceftizoxime
Cephradine	Cephaloglycin		Cefmetazole		
	Cephapirin		Cefpiramide		

[a] Each column represents a group with identical R_2 side chains.

- With a reported cephalosporin allergy, testing and oral challenge should be with a cephalosporin that does not share the same R-chain

SKIN TEST WITH QUINOLONES

- The value of ST is uncertain (moderate/weak) and false-positive reactions may occur when the antibiotic is tested at high concentrations
- SPT and IDT with undiluted intravenous solutions is irritant (high/strong)
- Reports on the highest nonirritant dilutions vary greatly and sensitivity appears to be low (moderate/strong).
- Recommendations on concentrations are currently not possible

Quinolone	Test	Concentration (mg/ml)
Ofloxacin	Prick ID	2-400 0,5-400
Ciprofloxacin	Prick ID	0,02-2 0,000001-0,01
Levofloxacin	Prick ID	5 0,025-0,05
Moxifloxacin	Prick	1,6-400

- PATCH tests with different concentrations of crushed tablets in petrolatum, have been reported to be nonirritating (moderate/strong)

SKIN TEST WITH QUINOLONES

Commercial forms and doses of quinolones used in skin prick tests, intradermal tests, and DPTs

Variables	Commercial forms and doses of quinolones (mg)		Skin prick test (mg/mL)	İntradermal tests (mg/mL)	DPT (mg)
	Oral	IV			
CFX	250, 500, 700	200, 400	5.0	0.005-0.050	5-50-100-150-200
LFX	500	500	5.0	0.005-0.050	5-50-100-150-200
MFX	400	400	4.0	0.004-0.040	5-50-100-100-150
OFX	200, 400	-	4.0	NP	5-25-50-100-200
GFX	320	-	3.2	NP	4-20-40-80-180

IV, intravenous; DPT, drug provocation test; NP, not performed; CFX, ciprofloxacin; LFX, levofloxacin; MFX, moxifloxacin; OFX, ofloxacin; GFX, gemifloxacin.

SKIN TEST WITH QUINOLONES

IMMEDIATE REACTIONS

- Low reliable results. False positive results/Unspecific histamine release

Scherer K. Curr Allergy Astm Rep 2005
Venturini M. J investig Allergol Clin Immunol 2007

- Wheal area measured by digital image analysis and blood flow increase measured by laser Doppler flowmetry (LDF) **Ciprofloxacin: 0.0067 mg/ml**

Broz P. Clin Exp Allergy 2012

- SPT and IDT with **moxifloxacin** are unreliable methods for diagnosis

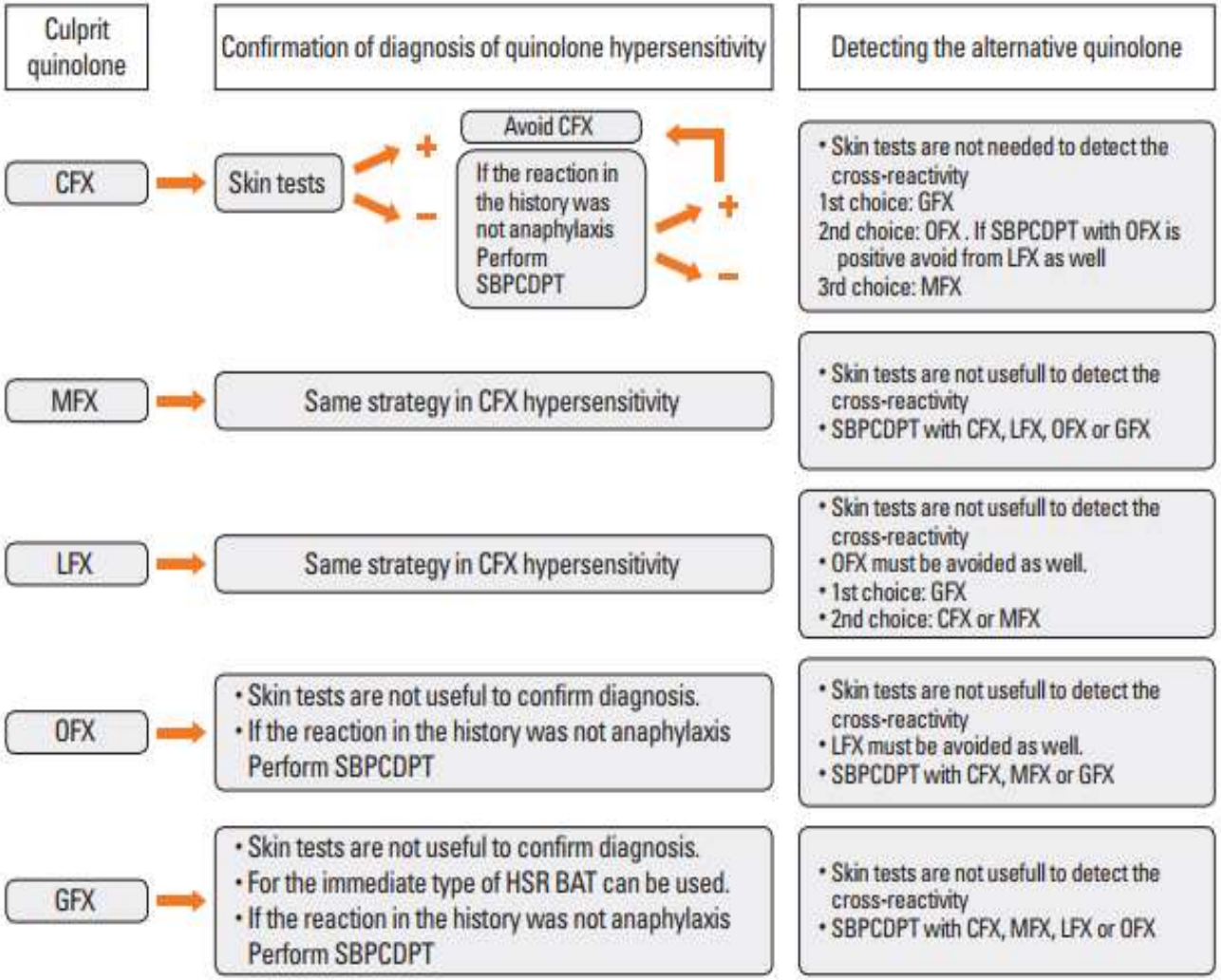
Bridsts CH. JACI in practice 2015

N= 48 patients with history of DHR to FQ

METHOD	SENSITIVITY	SPECIFICITY	PPV	NPV
Prick	20	97,7	50	91,3
Intradermal	75	29	12	90
BOTH	80	46,5	14,8	95,2

Perez E. Ann Allergy Asthma Immunol 2013

SKIN TEST WITH QUINOLONES



Suggestions which were extrapolated from the study for choosing alternative quinolone in a quinolone hypersensitive patient. CFX, ciprofloxacin; MFX, moxifloxacin; LFX, levofloxacin; OFX, ofloxacin; GFX, gemifloxacin; BAT, basophil activation test; SBPCDPT, single blind placebo controlled drug provocation test.

	Available agents	Prick-tests		Intradermal tests		
	maximal concentration and/or dilution	mg.mL^{-1}	Dilution	mg.mL^{-1}	Dilution	µg.mL^{-1}
Neuromuscular blocking Agents	atracurium	10	1/10	1	1/1000	10
	cis-atracurium	2	Undiluted	2	1/100	20
	mivacurium	2	1/10	0,2	1/1000	2
	pancuronium	2	Undiluted	2	1/10	200
	rocuronium	10	Undiluted	10	1/200	50
	suxamethonium	50	1/5	10	1/500	100
	vecuronium	4	Undiluted	4	1/10	400
	etomidate	2	Undiluted	2	1/10	200
Anesthetic Agents	midazolam	5	Undiluted	5	1/10	500
	propofol	10	Undiluted	10	1/10	1000
	thiopental	25	Undiluted	25	1/100	250
	ketamine	10	1/10	10	1/10	1000
Opoids Agents	alfentanil	0.5	Undiluted	0.5	1/10	50
	fentanyl	0.05	Undiluted	0.05	1/10	5
	morphine	10	1/10	1	1/1000	10
	remifentanil	0.05	Undiluted	0.05	1/10	5
	sufentanil	0.005	Undiluted	0.005	1/10	0.5
Local anesthetic Agents	bupivacain	2.5	Undiluted	2.5	1/10	250
	lidocain	10	Undiluted	10	1/10	1000
	mepivacain	10	Undiluted	10	1/10	1000
	ropivacain	2	Undiluted	2	1/10	200

Concentrations of anesthetic agents normally non-reactive in practice of skin tests.

Patient hidden Allergens

- 69 year old female with COPD
- Admitted to hospital with pneumonia Given IV amoxicillin and clarithromycin Within 15 mins developed hypotension (70/40mmHg), wheeze, and urticaria
- Tryptase level not taken
- Full recovery with adrenaline and steroids
- Treated with quinolone and labeled as “amoxicillin and clarithromycin allergy”
- SPT -ve to amoxicillin and clarithromycin
- DPT -ve to amoxicillin and clarithromycin
- Daughter reported that seemed to happen after the “bag of liquid put in”
- Strongly SPT positive to gelofusin
- Diagnosis: Colloid allergy. No restrictions on antibiotics.

”Hidden allergens”
(not given iv or po and therefore often overlooked..)

- **Latex** - Well known, probably on the decrease
- **Chlorhexidine**
- **Patent Blue -** Incidence 0.06-1.0% of sentinel node procedures, should always be tested if used prior to reaction (breast and plastic surgery). Hague RA et al Allergy 2010
- **Ethylene oxide**
- **Others -** Heparins, radiocontrast media, oxytocin**,** coating on catheters, bone cement, dressings, **macrogols (PEG), methylcelluloses** etc.

Non- Immediate Reaction

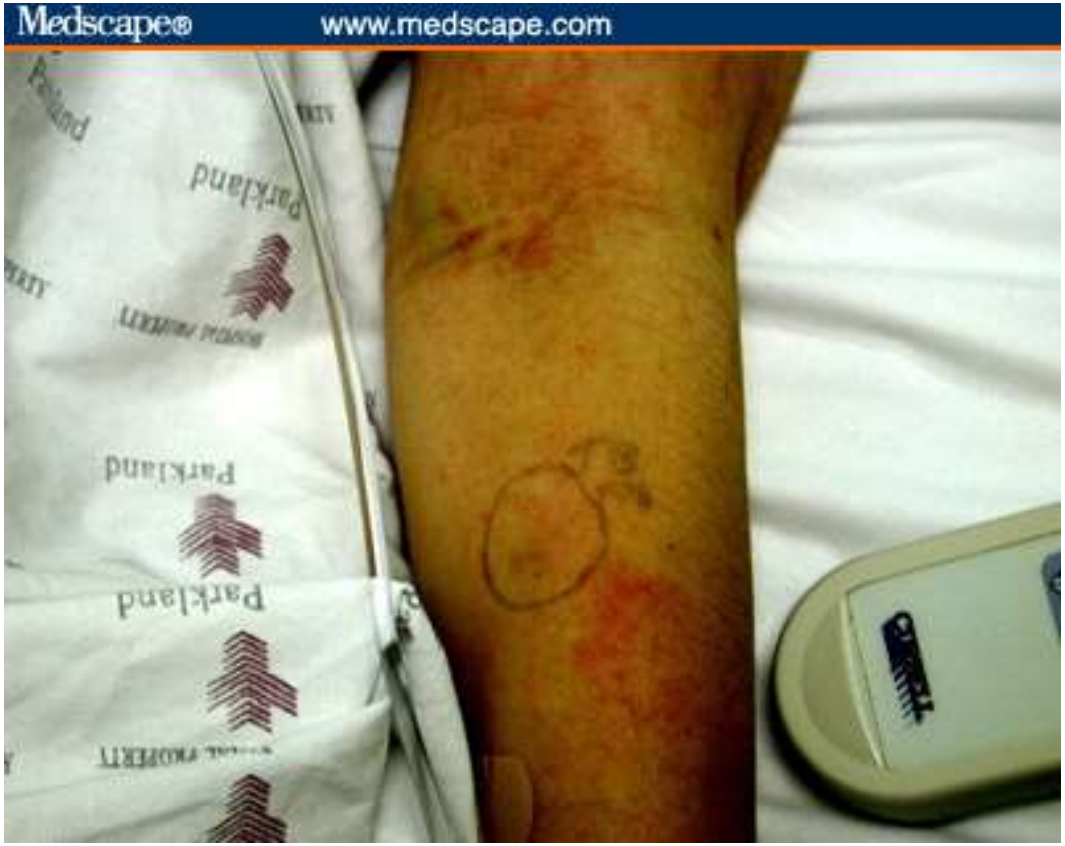
* Testing For Delayed Reactions (T-cell Mediated)

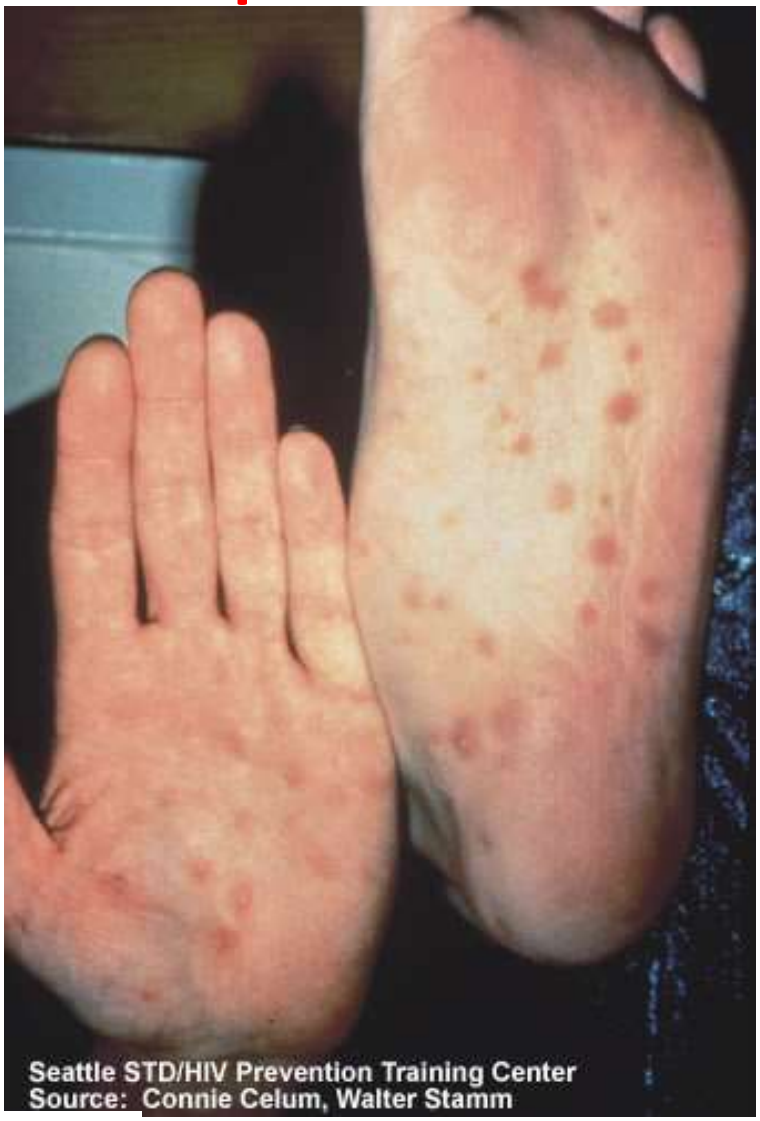
* Cross Reactivity Is Very Rare

Maculopapular Eruptions

- Most common drug allergic reaction
- Pathophysiology is mixed
  - **Often T-cell mediated**
- Onset variable, often within days or longer
- **Erythema, fine papules, pruritus**
- Usually begins on trunk, spreads to extremities, typically **symmetric**
- Often resolves with scaling/peeling
- Does not evolve into **anaphylaxis**

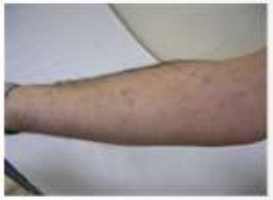
Maculo papular eruption

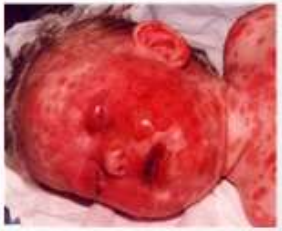


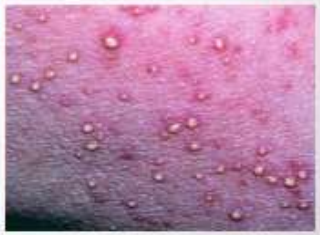


Individual T cell response and immune mediators involved determine the type of reaction

Category of Type IV reaction		Immune mediator	Cell type
Type IVa	TH1 cells: IFN-γ and TNF-α	T cells, macrophages	Contact dermatitis Tuberculin reaction
Type IVb	TH2 cells: IL-4, IL-5, IL-13	Eosinophils	Maculopapular rash
Type IVc	Cytotoxic T cells: Perforin, Granzyme B	T cells	Contact dermatitis Maculopapular rash Bullous eruptions (SJS, TEN)
Type IVd	T cells: GM-CSF CXCL8 IL-8	Neutrophils	**AGEP (Acute generalised exanthematous pustulosis)**



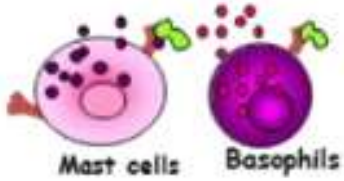




CLINICAL ENTITIES AND INVOLVED MECHANISMS

IMMEDIATE REACTIONS

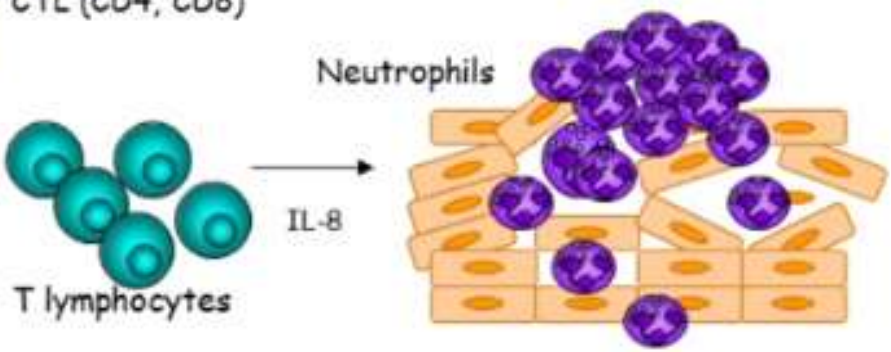
Urticaria/angioedema
Anaphylaxis



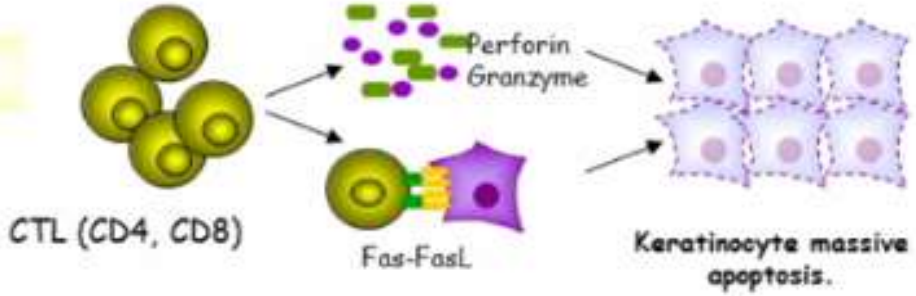
NON IMMEDIATE REACTIONS

Multiforme erythema
Exanthema
Urticaria
Fixed drug eruption
DRESS/DHIS

Acute generalized exanthematous pustulosis



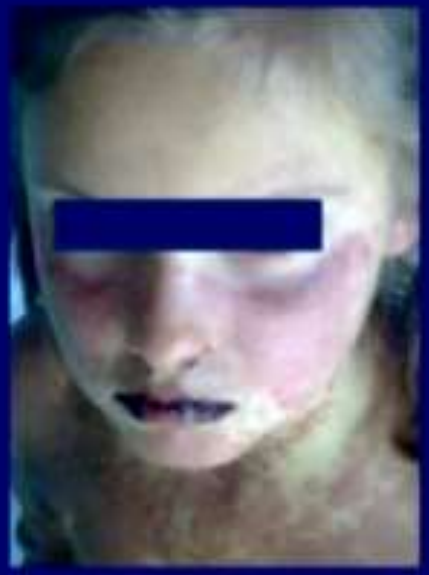
SJS/TEN



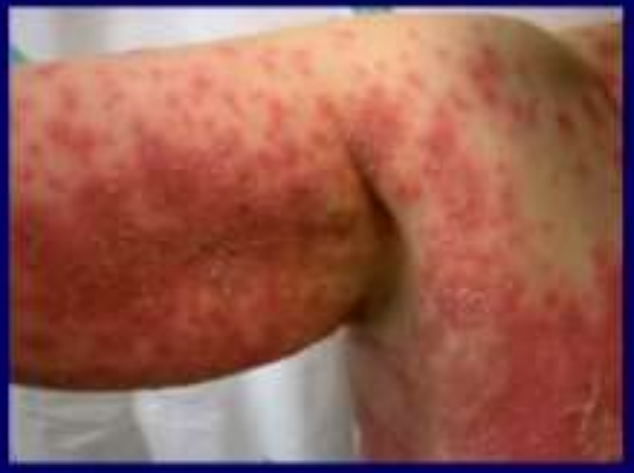
Severe cutaneous allergic reactions to drugs (SCARs)

- Acute generalized exanthematous pustulosis (AGEP)
- Drug reaction with eosinophilia and systemic syndrome (DRESS) / Drug induced hypersensitivity syndrome (DiHS)
- Stevens-Johnson syndrome (SJS)
- Toxic epidermal necrolysis (TEN)

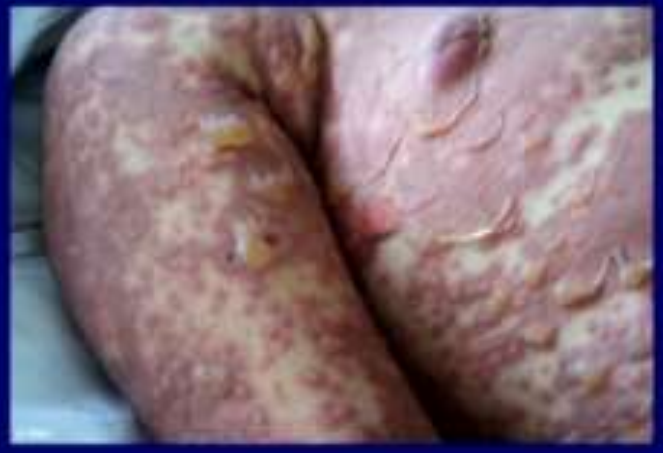
SCARs



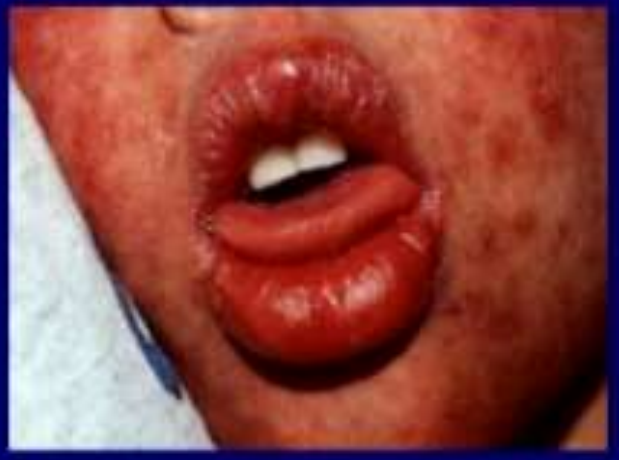
SJS



AGEP



TEN



DRESS

Assessment of SCARs

- A detailed clinical history of reactions
  - Clinical appearance of the eruption
  - How long the eruption has been present
  - Associated symptoms (eg, fever, lymphadenopathy.....)
  - The time elapsed between drug intake and SCARs onset
  - Was drug present in the body before the onset of SCARs? Factors considered:
    a) drug's half life
    b) patient's liver and kidney function

Bellon T et al, Curr Treat Options Allergy 2017.
Verma CR et al, AFMS 2013.

SJS / TEN in children

Severe mucocutaneous diseases characterized by subepidermal blisters and skin sloughing

- SJS - skin detechment affects less than 10% of body surfice area
- TEN- skin detechment affects more that 30% of body surfice area
- SJS/TEN overlap - skin detechment ranges between 10% and 30%

Bellon T et al, Curr Treat Options Allergy 2017.

SJS / TEN in children

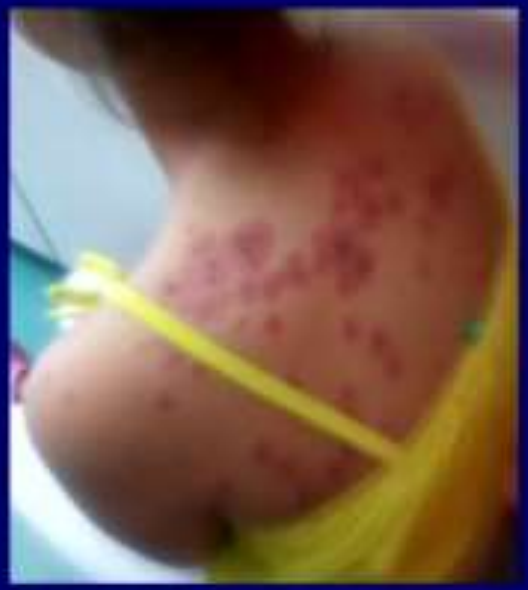
- Epidermal detechment with the appearance of burned skin

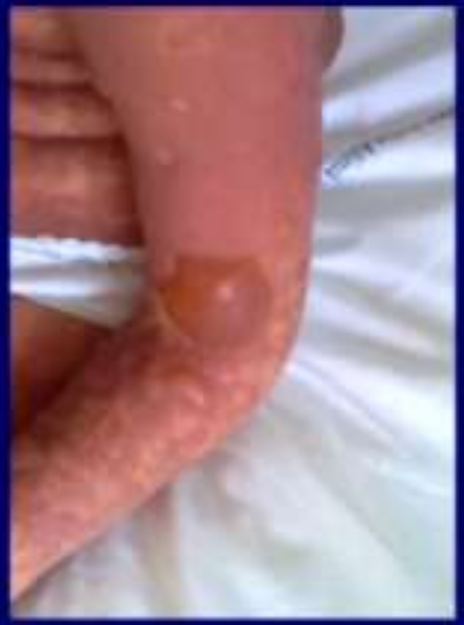
- Mucosal involvement: oral ulcers, hemorrhagic crusts on the lips, severe conjunctival affection
- Prodromal phase: fever, malaise, sore throat
- Cutaneous features: spots, atypical flat target lesions, positive Nikolsky sign

Bellon T et al, Curr Treat Options Allergy 2017.

SJS / TEN in children

- Internal organ involment
- Lymphopenia
- Electrolytic alterations (metabolic acidosis, low serum bicarbonate)



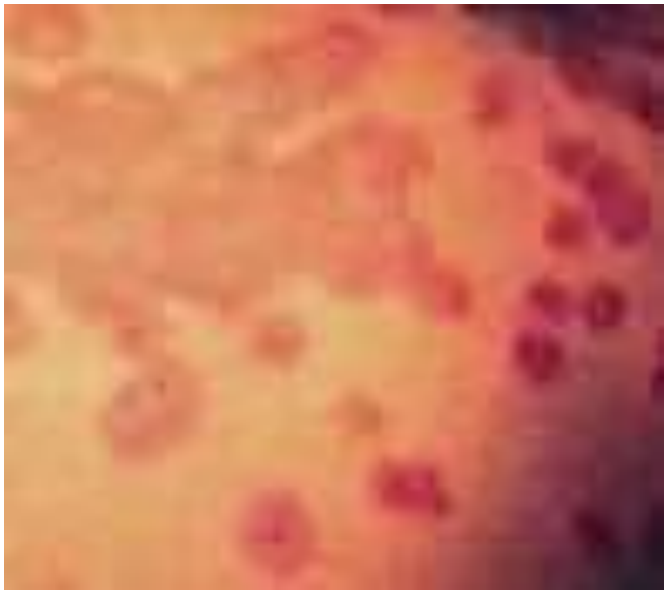


SJS / TEN in children

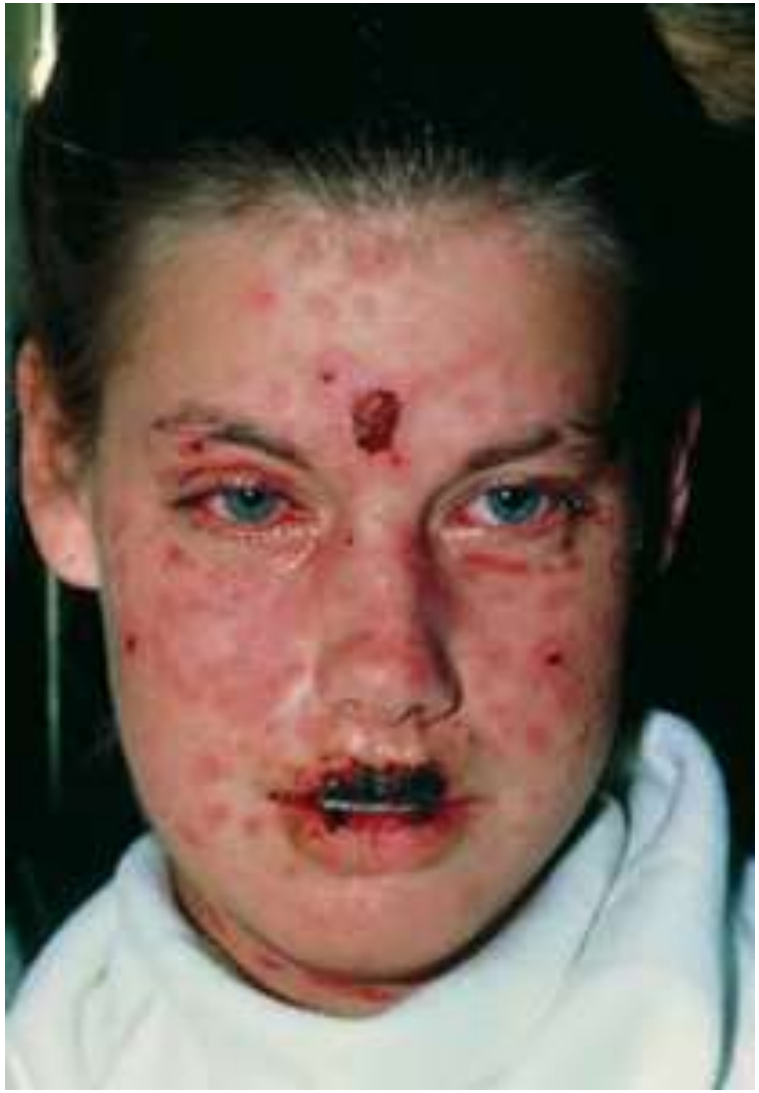
The most frequently involved drugs:

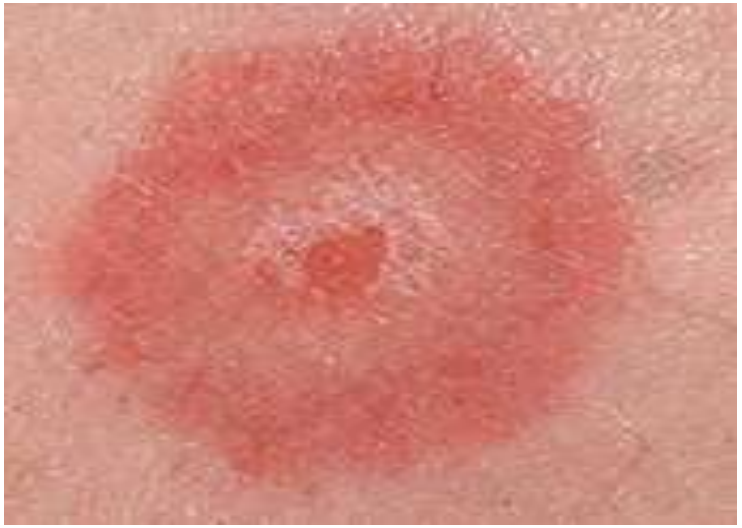
- Anticonvulsants
- Sulfonamides
- Antibiotics
- Nonsteroidal anti-inflammatory drugs
- Allopurinol
- .....

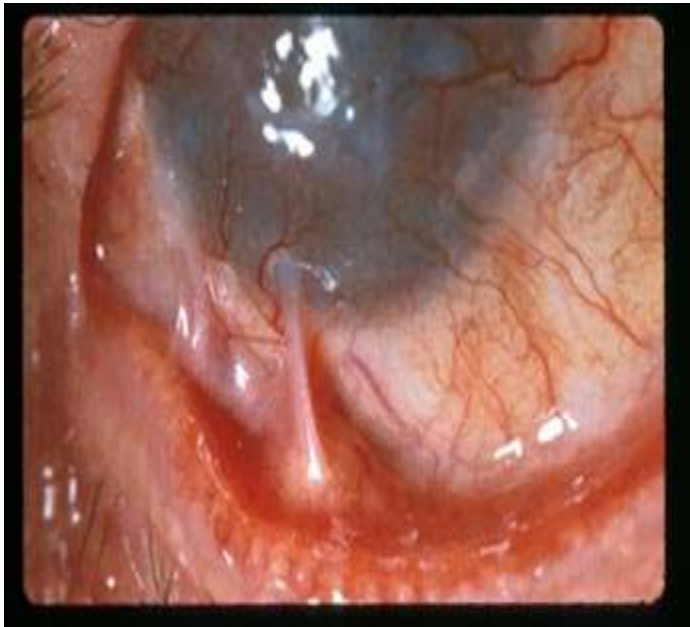
Erythema Exudativum Multiform



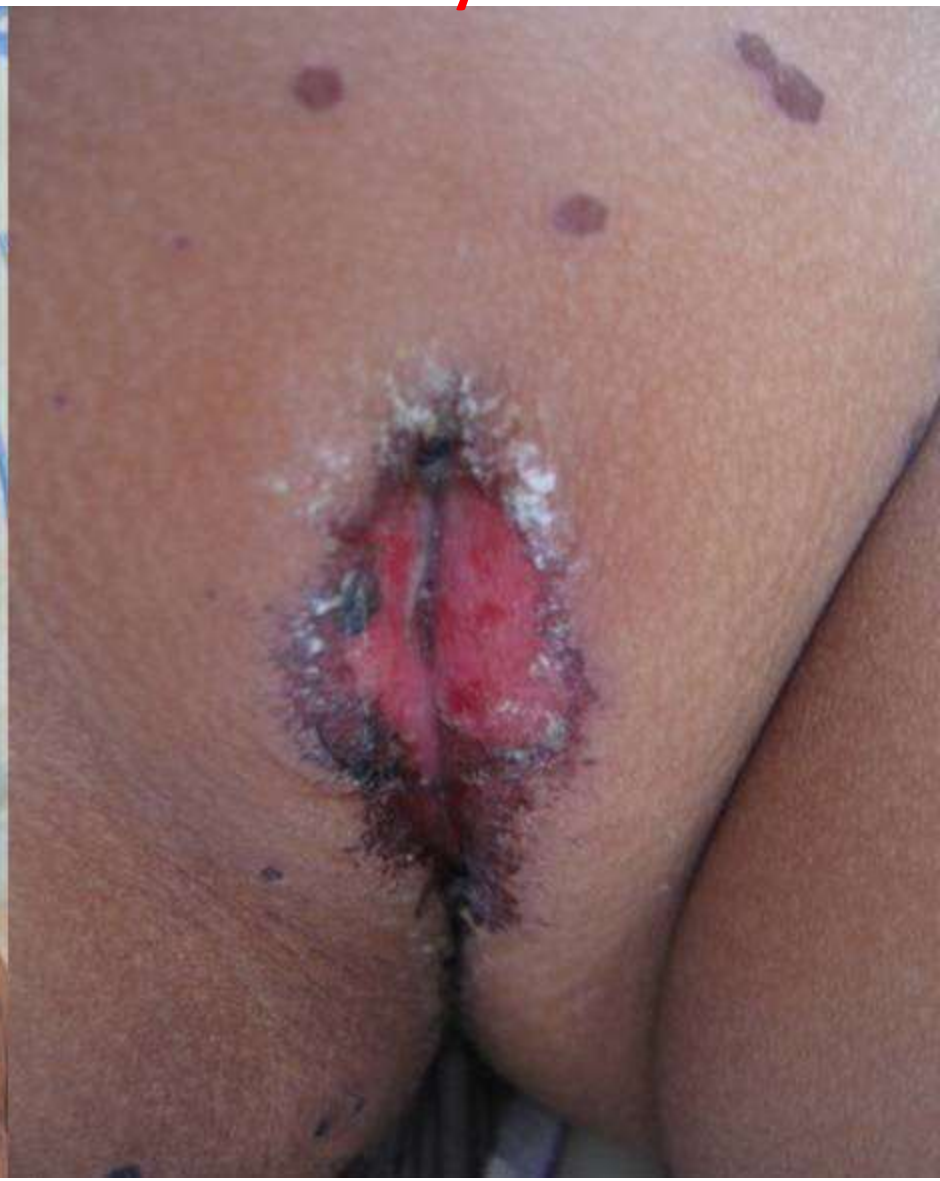
Steven Johnson Syndrome



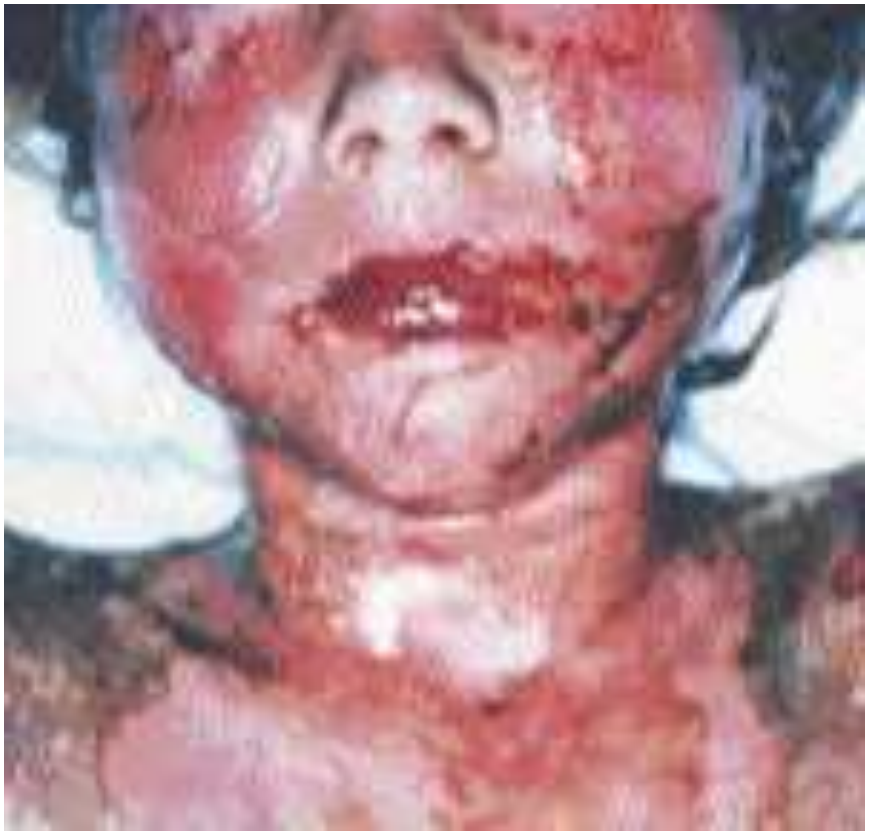


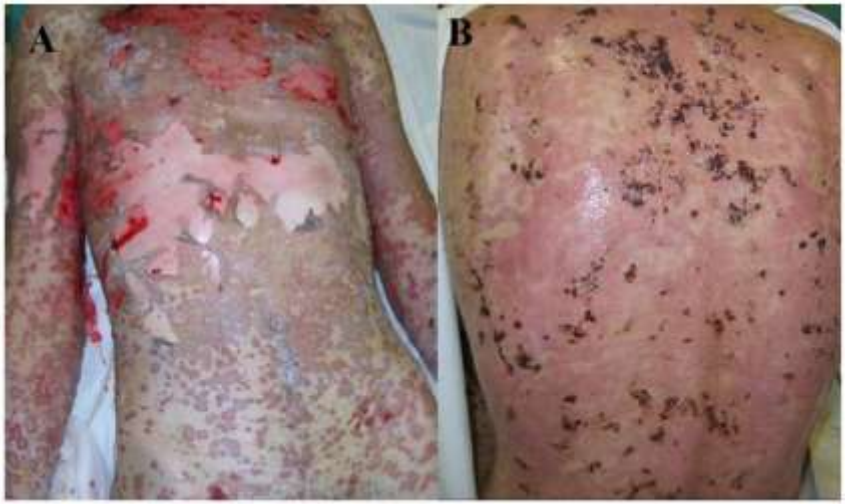


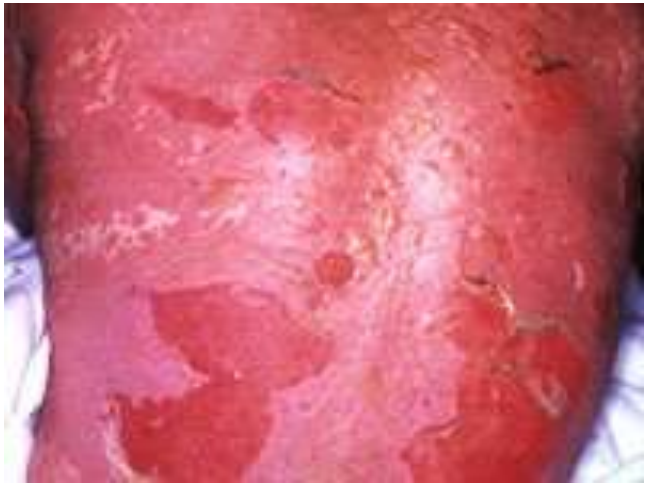
Steven Johnson Syndrome……

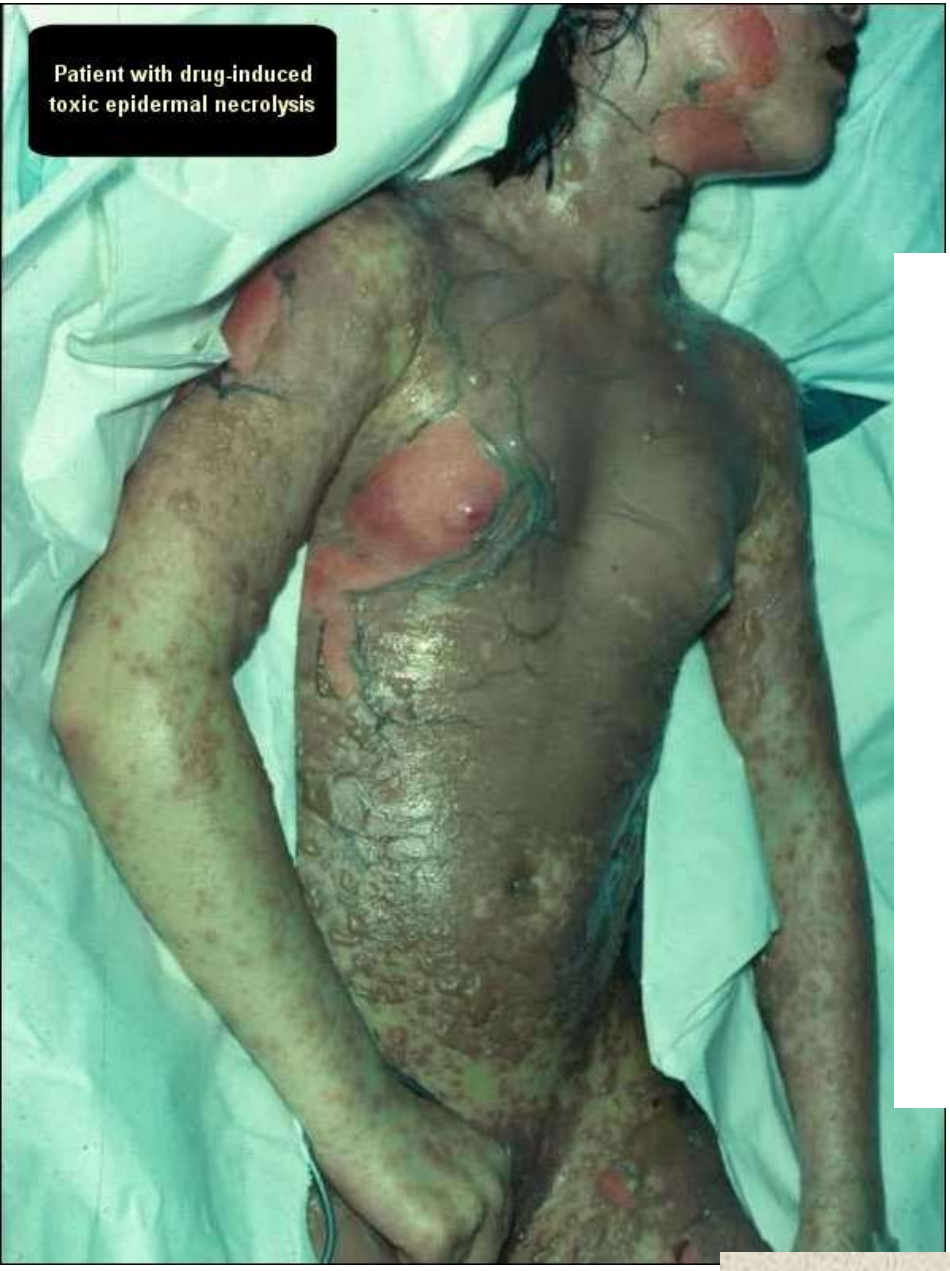


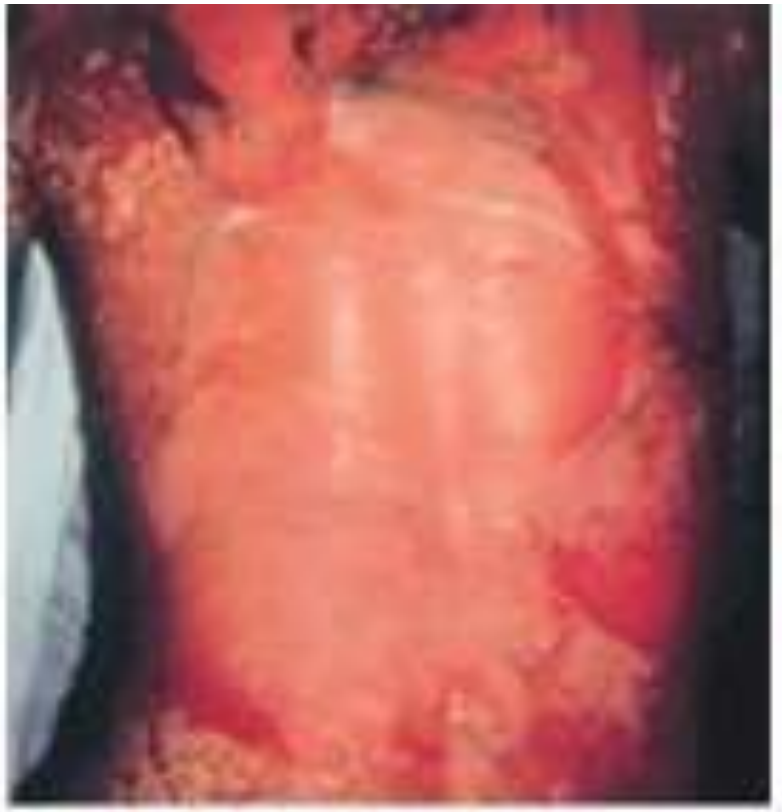
Toxic Epidermal Necrolysis



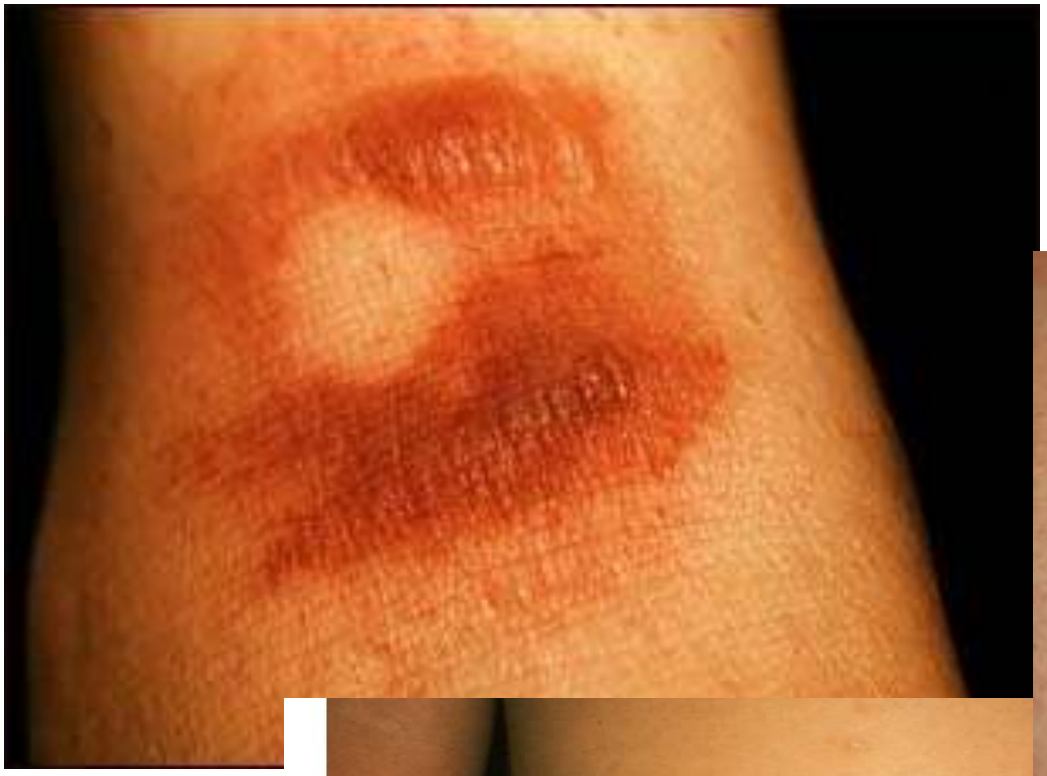


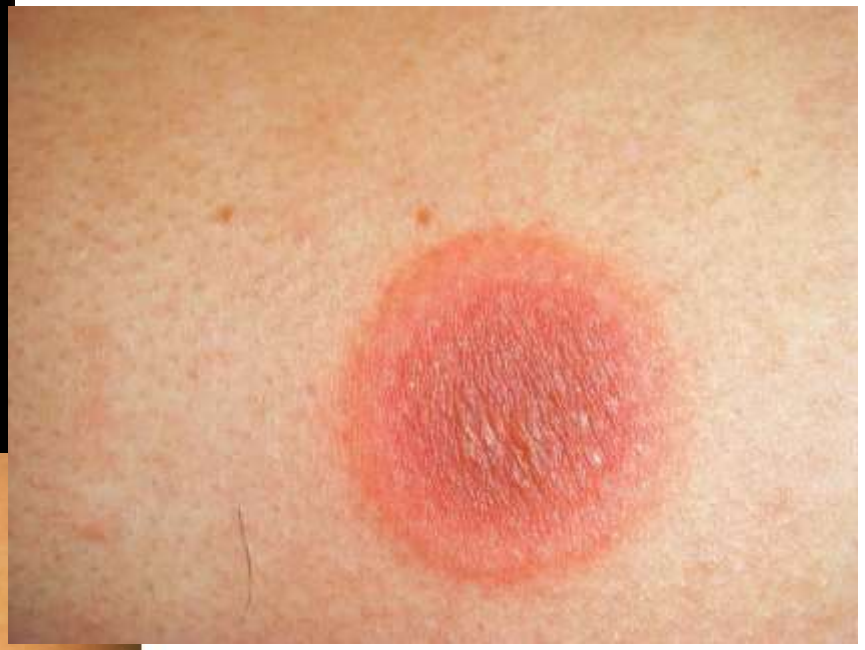


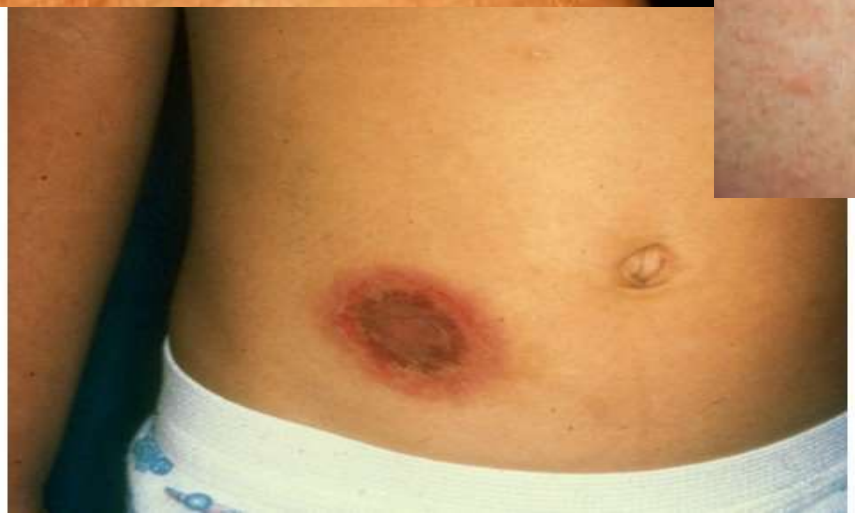

Patient with drug-induced
toxic epidermal necrolysis



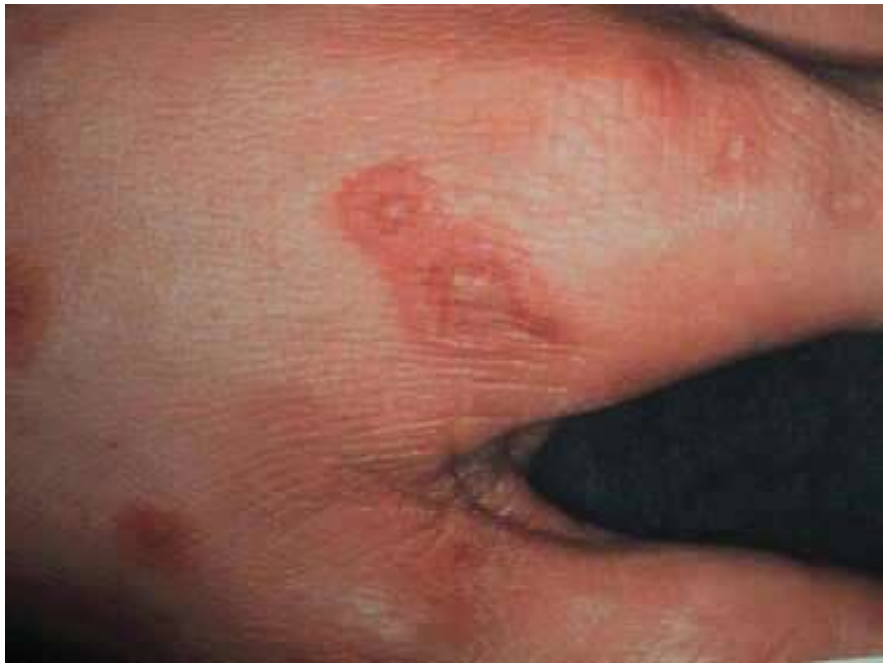
Fixed Drug Eruption

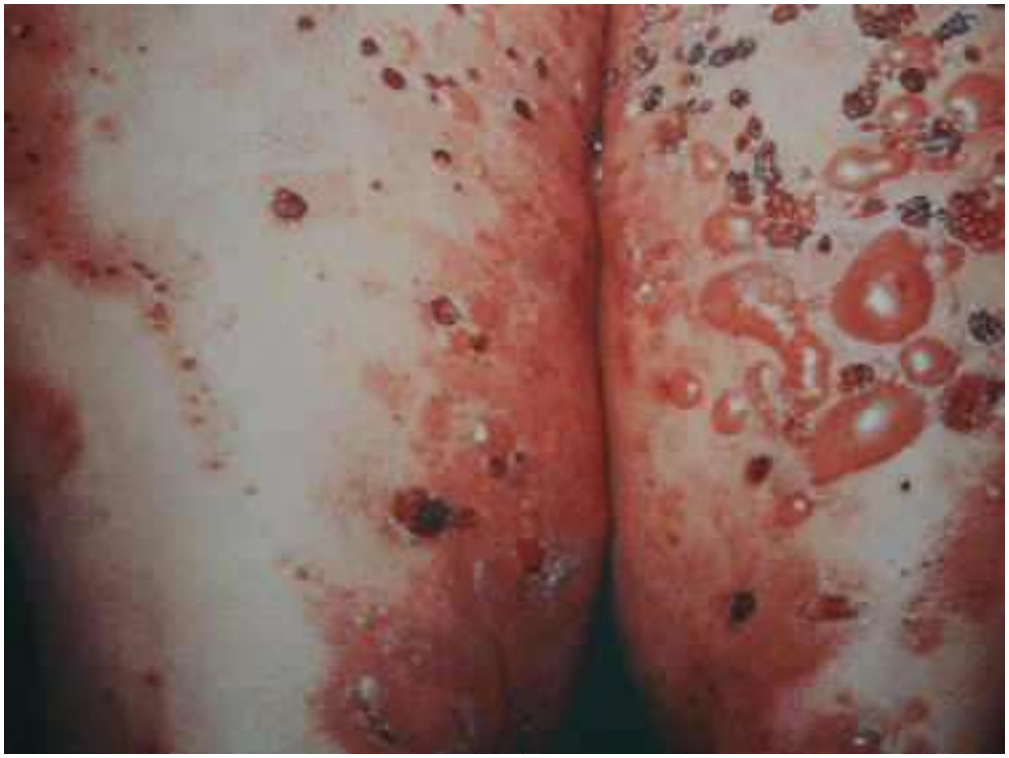




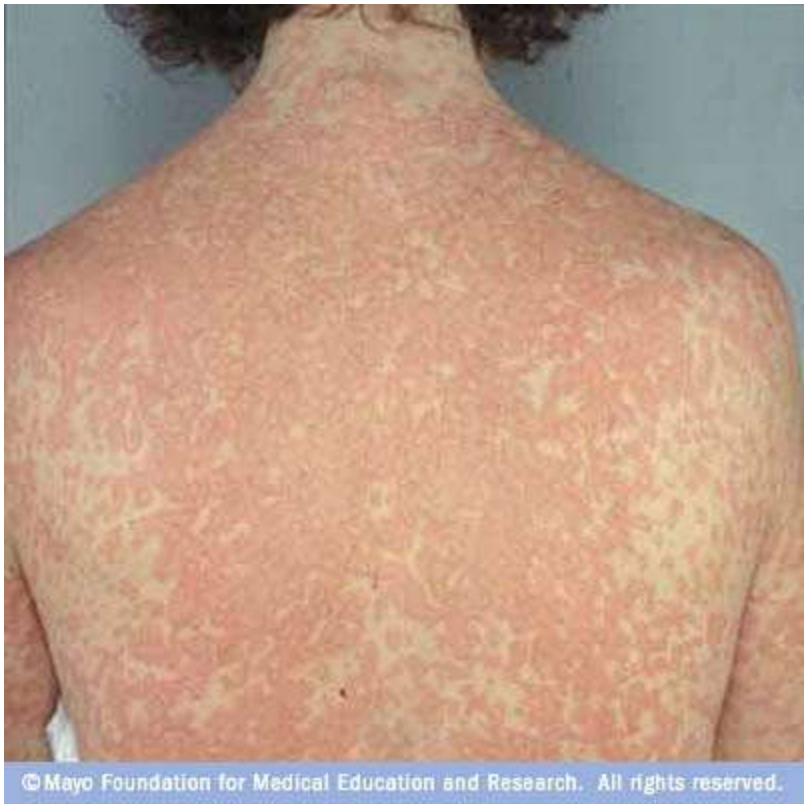


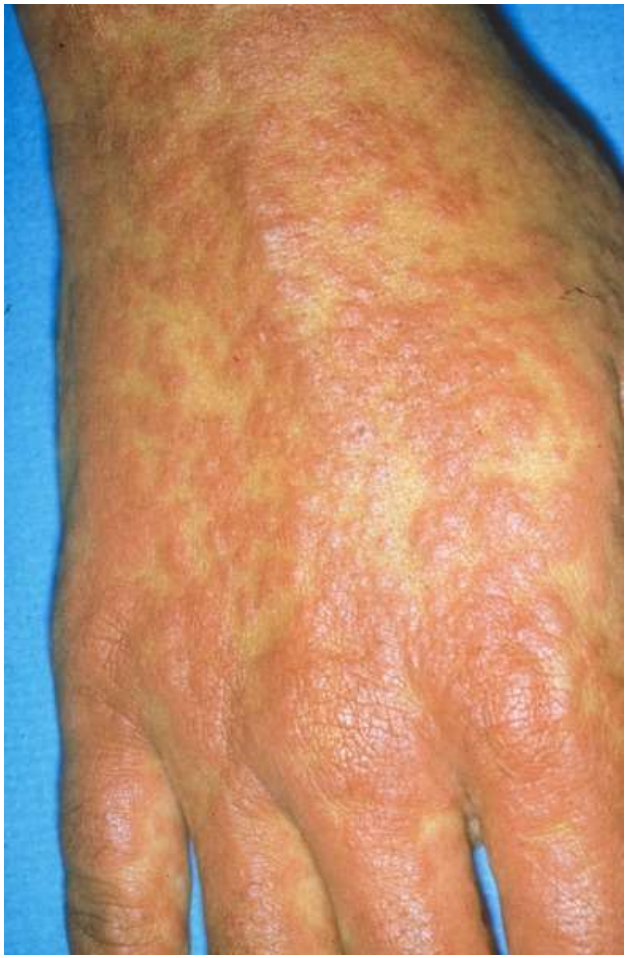
Vesico bullous Eruption





Morbiliform rash





Case report of positive DPT in a child with DRESS

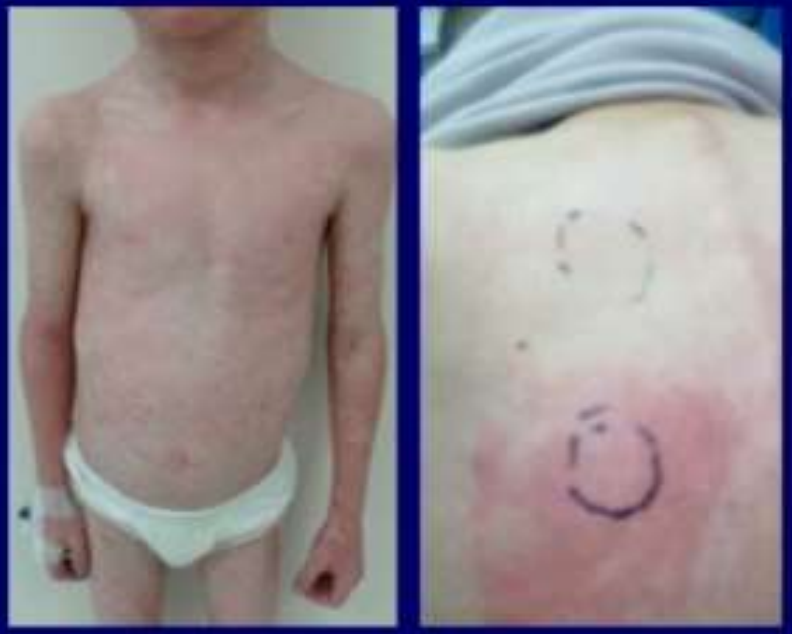
- A seven- year- old boy had developed DRESS after parenteral administration of meropenem and vancomycin given for abscesus cerebri
- Thirty-second day of therapy with meropenem and 29th day of therapy with vancomycin he developed generalized maculopapular rash with itching, without the involvement of mucosal surface
- Two days before appearing of rash he developed fever around 38 C

Case report of positive DPT in a child with DRESS

- Cervical lymphadenophaty and hepatomegaly were present
- Laboratory results :
  -leukocytosis with atypical lymphocytosis and eosinophilia
  -elevated transaminases both alanine and aspartate
  -gamma-glutamyl transferase (γGT)
  -proteinuria
  -protein-to-creatinine ratio (Prt/Cr9):↑
- Reactivation of EBV

Case report of positive DPT in a child with DRESS

- Patch tests with meropenem was only positive



DRESS / DIHS in children

The most frequently involved drugs:

- Aromatic anticonvulsants
- Sulfonamides
- Vancomycin
- Nonsteroidal anti-inflammatory drugs
- Allopurinol
- .....

Bellon T et al, Curr Treat Options Allergy 2017.

AGEP in children

- The presence of multiple pinhead-sized nonfollicular pustules on an erythematpus background, with predominant affectation of the head and folds
- Acute onset after drug ingestion
- High fever
- Peripheral blood neutrophilia
- Resolves spontaneously shortly after drug discontinuation

Bellon T et al, Curr Treat Options Allergy 2017.

AGEP

Diagnosis (scoring system- RegiSCAR group) :

3. Marked neutrophilic leukocytosis (>7000/μl)
4. Pustule smear and culture negative for bacteria
5. Rapid resolution of the rash after drug discontinuation

AGEP in children

The most frequently involved drugs:

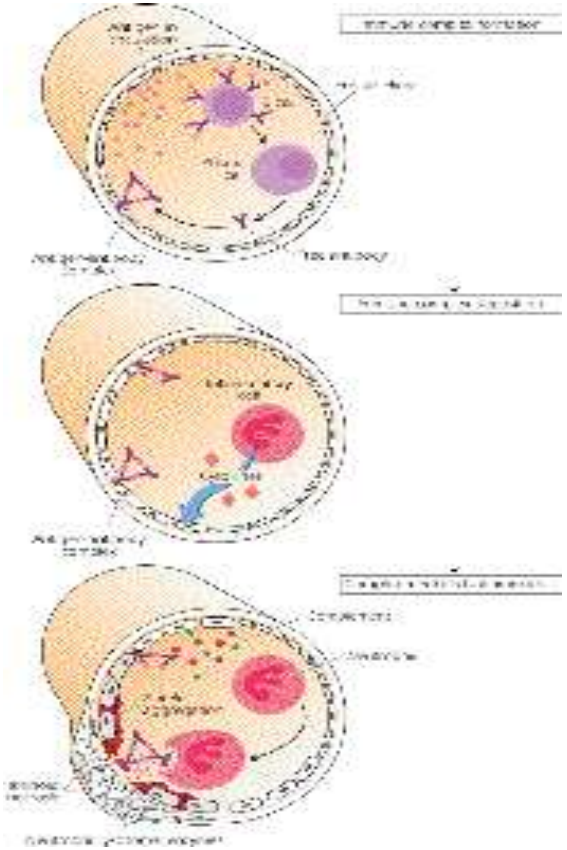
- Beta-lactams
- Macrolides
- Vancomycin
- Anti-infective sulfonamides
- Acetaminophen
- Carbamazepine
- .....

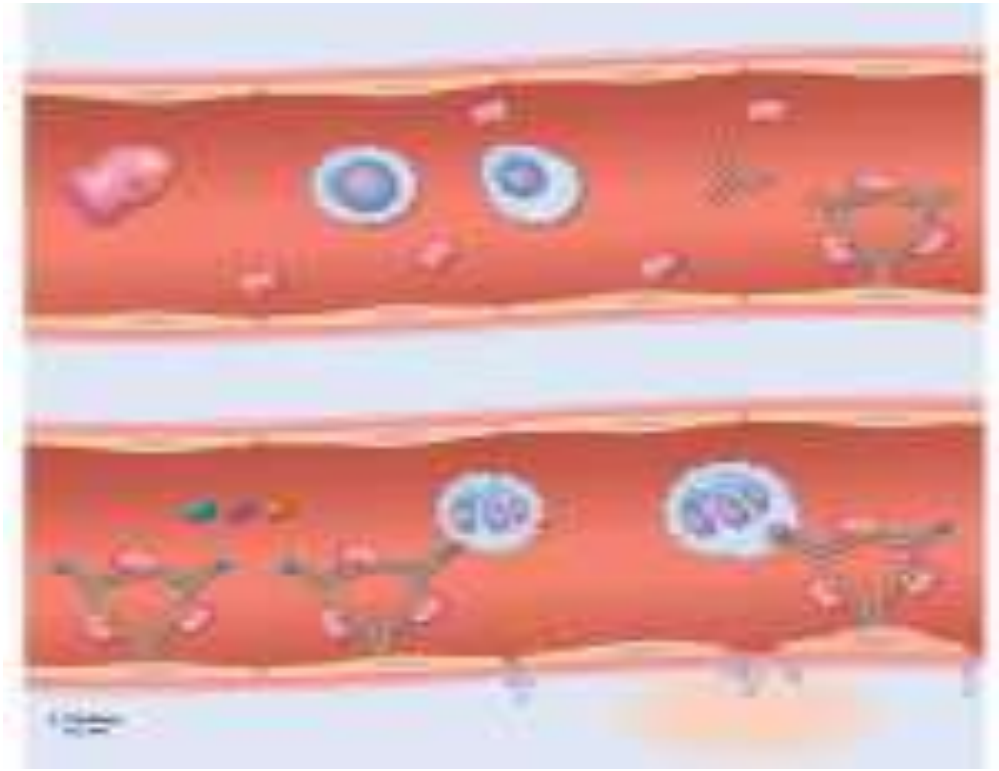
Bellon T et al, Curr Treat Options Allergy 2017.

Case C/O fevers, rashes, and arthritis.

- 20 yrs woman with cystic fibrosis is started on an extended course of **piperacillin/tazobactam**.
- 2 weeks into course she develops **fevers, rashes, and arthritis.** She is changed to cefepime with resolution of her symptoms.
- The next year she is treated with piperacillin and develops the same symptoms in 4 days before the antibiotic is changed.
- Is this an allergy? Would you skin test? What would you advise?
- Yes, but not IgE. (Coombs III – Immune complex). No skin testing. Avoid penicillins.

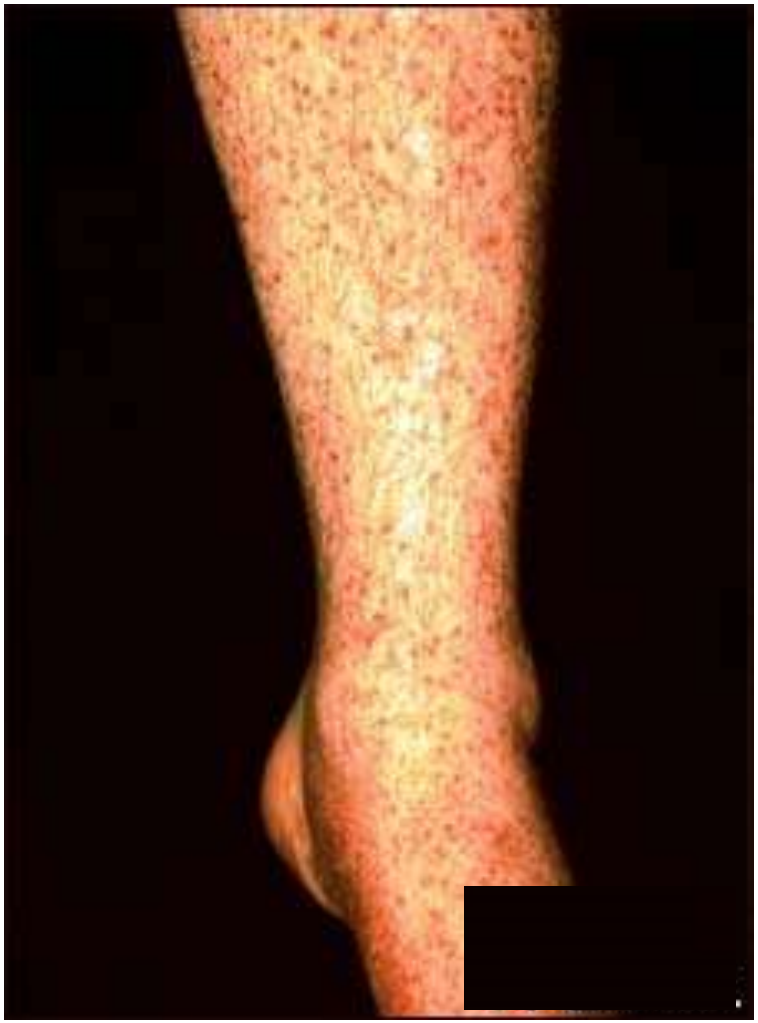
Serum Sickness Like Syndrome

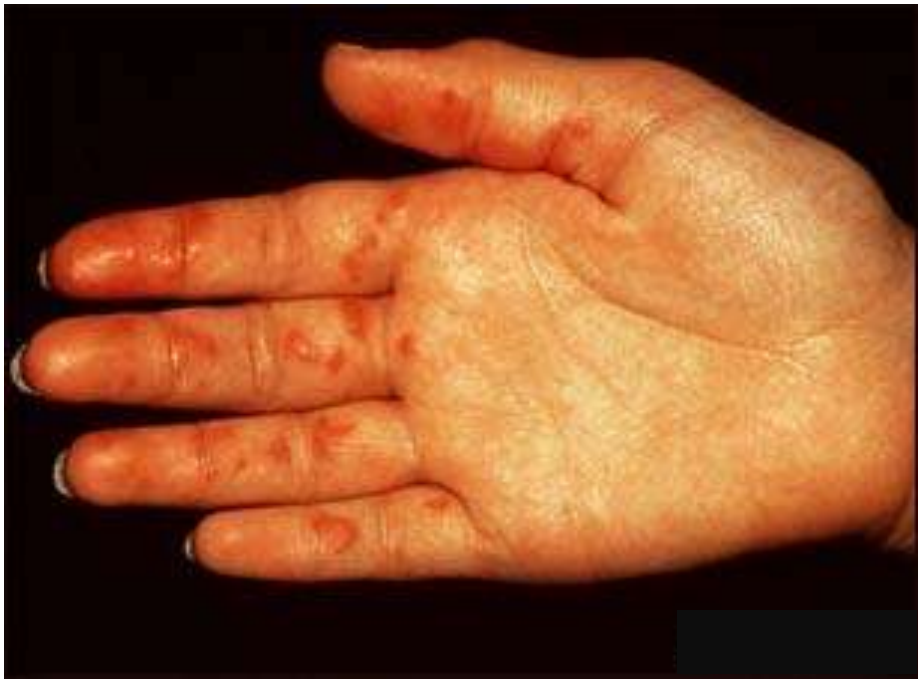




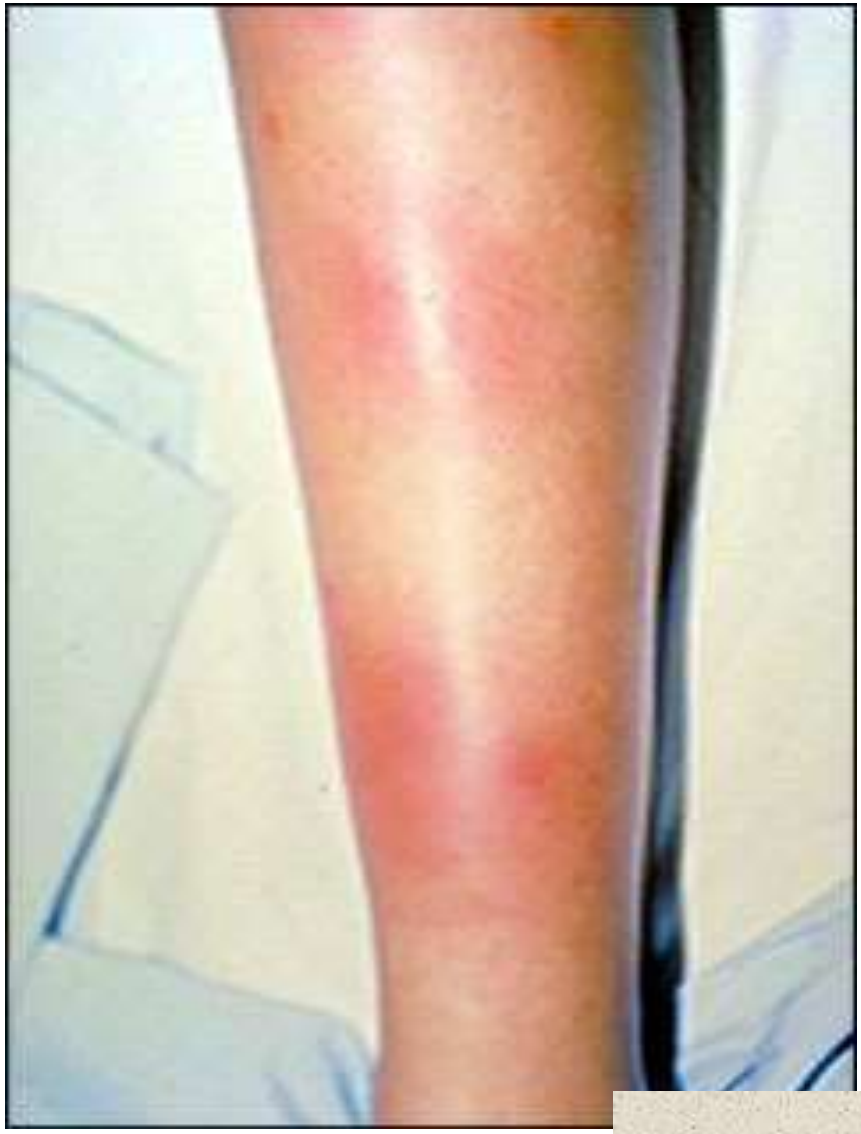
"It is a type of hypersensitivity, specifically immune complex (type 3) hypersensitivity. Serum sickness typically develops up to ten days after exposure to the antiserum, and symptoms are similar to an allergic reaction."

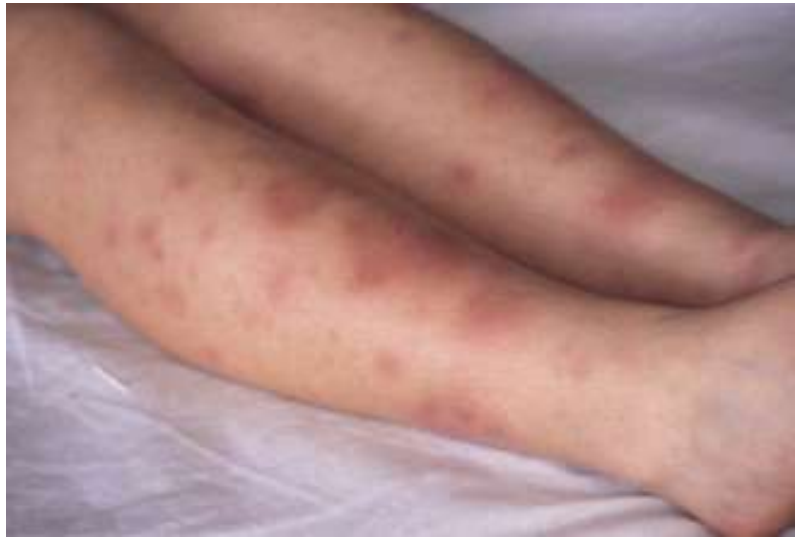
Vasculitis

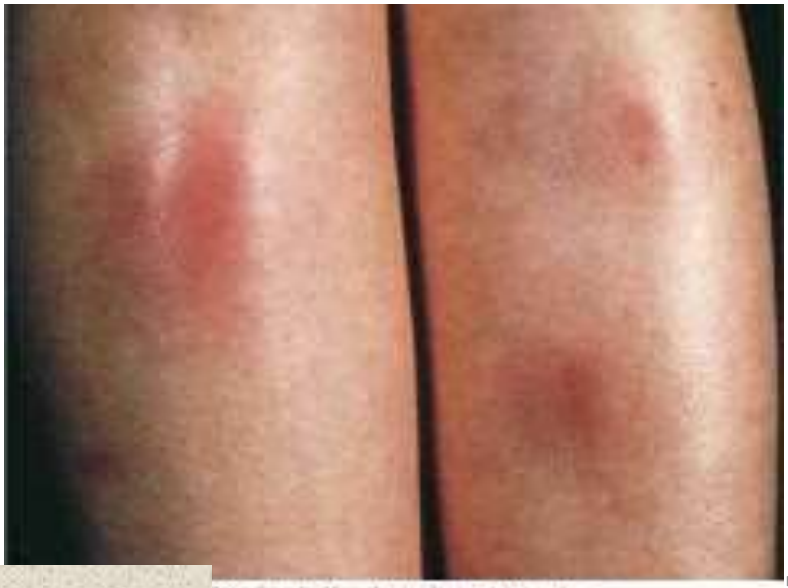




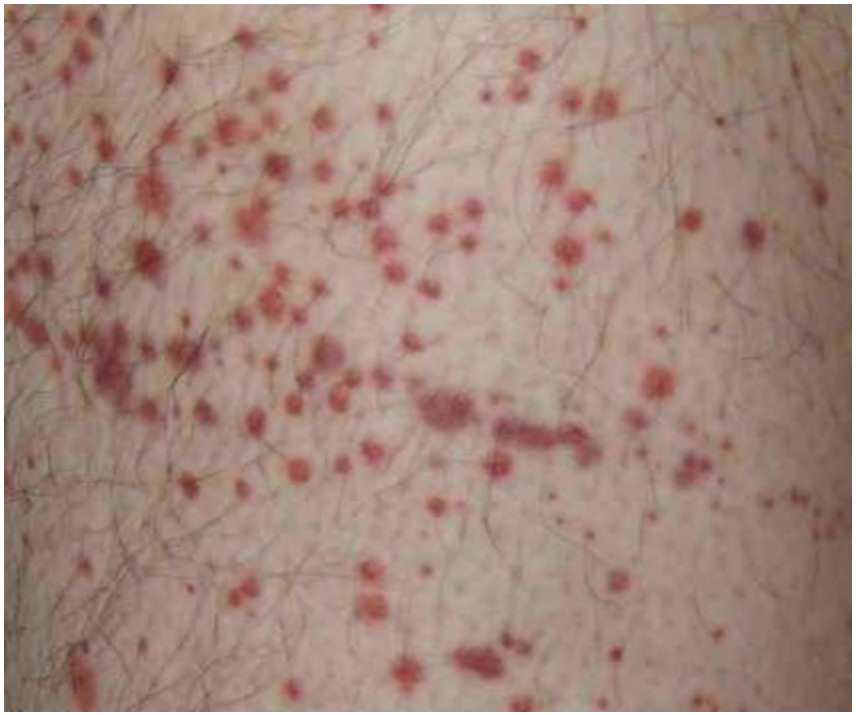
Erythema Nodosum

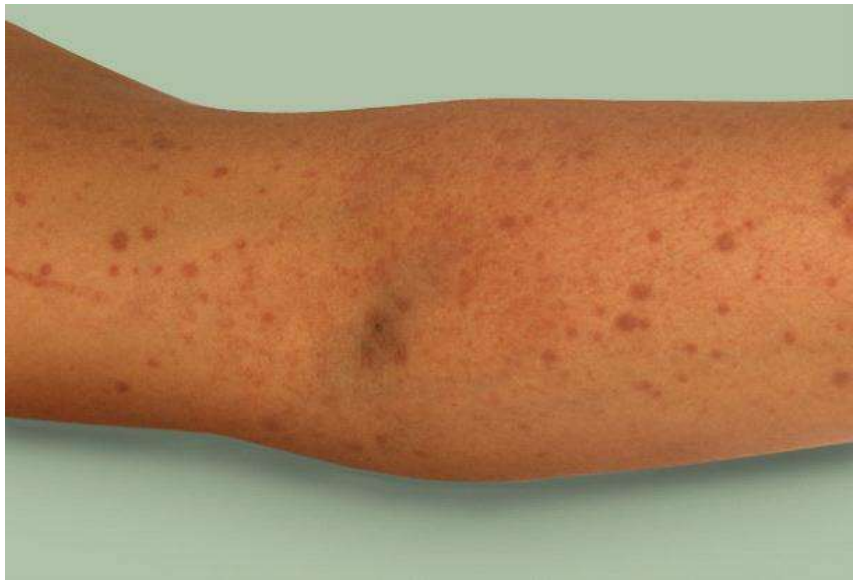






Purpura





NSAISs Hypersensitivity

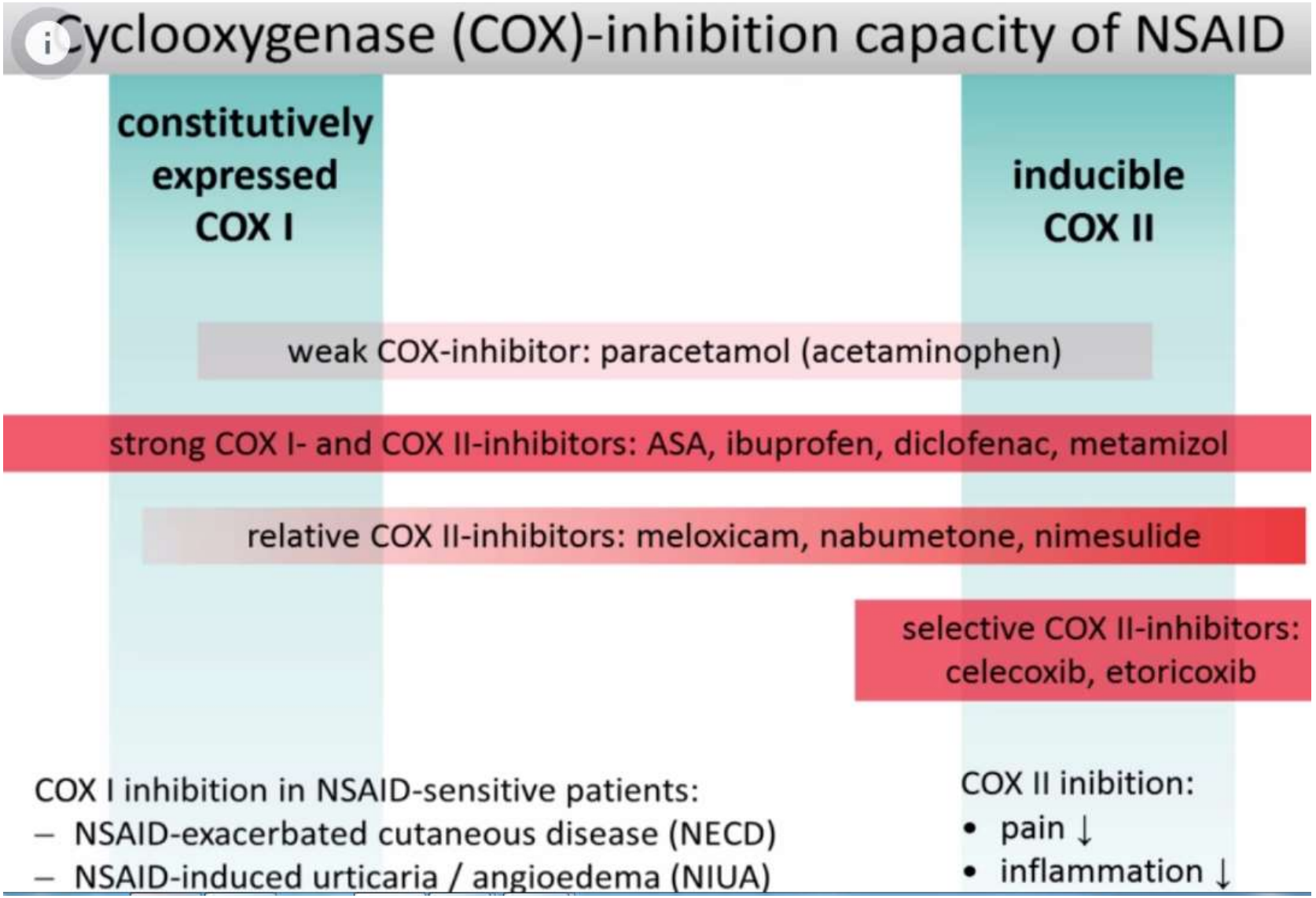
Cross-reactivity among drugs in non-allergic hypersensitivity reactions

Is explained by common pharmacological characteristics

- Cross-reactivity among anti-inflammatory agents has been attributed to their inhibitory effect on cyclooxygenase (COX)-1
- Cross-reactivity among muscle relaxants or contrast media attributed to their capability of releasing histamine through a non-immunologic mechanism

Romano A et al. Toxicology 2005

NSAISs Hypersensitivity



NSAISs Hypersensitivity

Acute

Delayed

Respiratory

Cuteneous / Anaphylaxis

Various organs

- NERD
- NECD
- NIUA
- SNIUAA
- SNIDHR

Non-immunologically Mediated(cross-reactive) Hypersensitivity reaction

Immunologically mediated (selective) hypersensitivity reaction)

Selection of suitable „NSAID reactors“

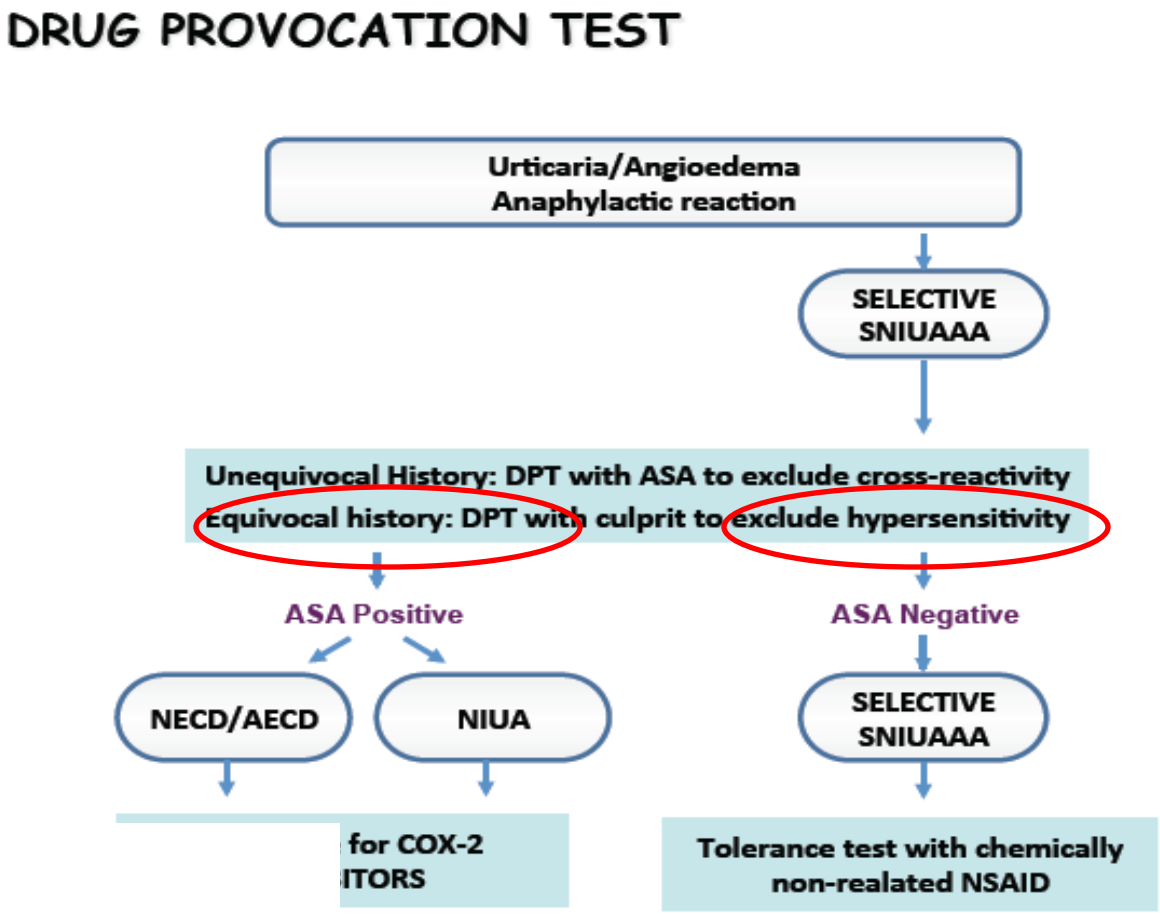
symptoms?

airway symptoms: nasal obstruction, rhinorrhea, throat tightness, bronchospasm	urticaria / angioedema		systemic anaphylaxis symptoms
chronic rhinosinusitis?, asthma?, spontaneous urticaria / angioedema?			
chronic rhinosinusitis with or without polyposis, asthma	spontaneous urticaria / angioedema	no	no
several similar episodes triggered by structurally different NSAID?			
yes	yes	yes	no
NSAID-exacerbated respiratory disease	NSAID-exacerbated cutaneous disease (NECD)	NSAID-induced urticaria / angioedema (NIUA)	single NSAID-induced anaphylaxis

CLASSIFICATION OF HYPERSENSITIVITY REACTIONS TO NSAIDs

Type of reaction	Clinical manifestation	Timing	Underlying disease	Cross reactivity	Putative mechanism	
NSAIDs exacerbated respiratory disease (NERD)	Rhinitis/asthma		Asthma/rhinosinusitis			Cox-1 inhibition
NSAIDs exacerbated cutaneous disease (NECD)	Urticaria/angioedema		Chronic urticaria	YES	Non-allergic	Cox-1 inhibition
NSAIDs – induced urticaria/angioedema (NIUA)	Urticaria/angioedema **Anaphylaxis**		No underlying chronic diseases			Unknown, probably COX-1 inhibition
Single NSAIDs – induced urti/angio/ anap (SNIUAA)	Urticaria/angioedema/anaphylaxis		No underlying chronic diseases	NO	Allergic	IgE-mediated
Single NSAIDs-induced delayed reactions (SNIDR)	various symptoms and organs involved	Delayed	No underlying chronic diseases			T cell-mediated

NSAISs Hypersensitivity



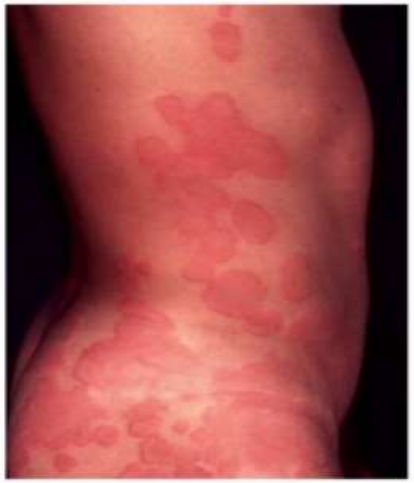
ENDA NSAID TF (Kowalsky M)

NSAISs Hypersensitivity

intake of cyclooxygenase (COX)-inhibiting NSAID such as acetylsalicylic acid (ASA), ibuprofen, diclofenac or metamizol

↓

acute urticaria episode within minutes to several hours



intensity of the urticaria episode depends on:

- COX I-inihibiting capacity of the NSAID
- NSAID dose
- activity of chronic urticaria

– NSAID-exacerbated cutaneous disease (NECD) or aspirin-exacerbated urticaria (AEU)
– NSAID-induced urticaria / angioedema (NIUA)

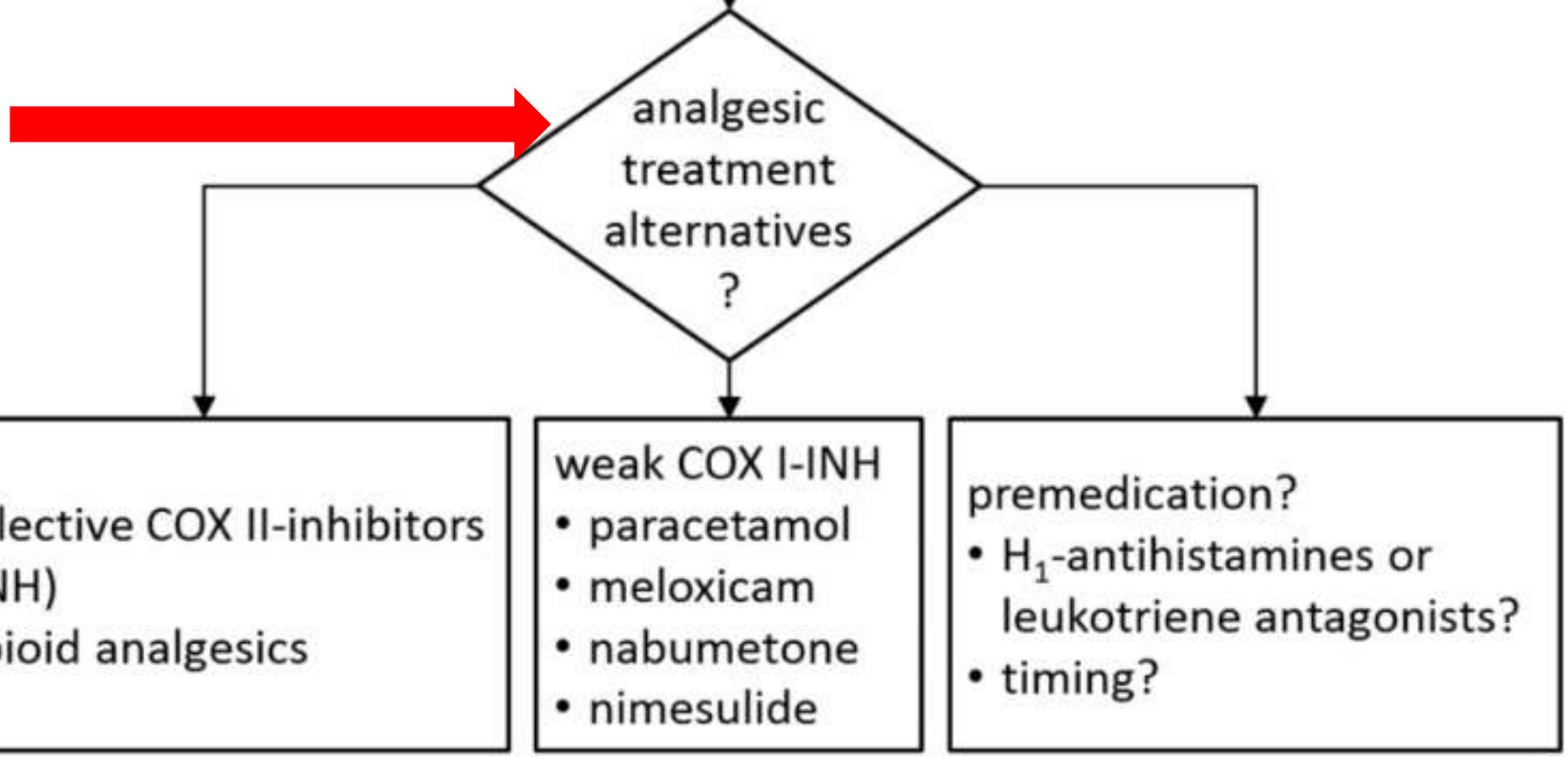
– NSAID-exacerbated cutaneous disease (NECD)
– NSAID-induced urticaria / angioedema (NIUA)

both can be treated successfully with H_1-antihistamines

↓

recurrent pain problems: back pain, arthralgia or headache

↓



NSAISs Hypersensitivity

DOSES RECOMENDED IN OPT

DRUGS	CUMMULATIVE DOSES (mg)
Etoricoxib	60 - 90
Celecoxib	100 - 200
Paracetamol	100 - 250 - 500 - 1000
Meloxicam	7,5 - 15
Nabumetone	500 - 1.000
Diclofenac	25 - 50
Metamizol	1° día: 50 - 100 - 250 2° dia: 575
Ibuprofen	1 día °: 50 - 100 - 200 - 400 2° día: 600
ASA	1 día °: 5 - 50 - 100 2° día: 250 - 500

ADULTS

CHILDREN

Drug	Doses used in DPT	Total cumulative dose (TCD)
Paracetamol	One dose	15 mg/kg/dose
Dipyrone	¼, ¼ and ½ of the TCD	20 mg/kg/dose
Ibuprofen	¼, ¼ and ½ of the TCD	10 mg/kg/dose
ASA	1st day: ¼, ¼ and ¼ of the TCD 2nd day: ½ and ½ of the TCD	20 mg/kg/dose

PT with ASA

25 mg/kg/24 hrs.

Temps	Flacon (mn/h) (n°)	Dose (ml)	Dose unitaire (mg)	Dose cumulée Observations (mg)
		0,05	1,25	1,25
		0,1	2,5	3,75
		0,25	6,25	10
		0,5	12,5	22,5
		1	25	47,5
		2	50	97,5
		4	100	197,5
		6	150	347,5
		8	200	547,5
		10	250	797,5
		12	300	1097,5
		14	350	1447,5

PT with Ibuprofen

20-30 mg/kg/24 hrs

Temps	Flacon (mn/h) (n°)	Dose (ml)	Dose unitaire (mg)	Dose cumulée Observations (mg)
		0,1	2	2
		0,25	5	7
		0,5	10	17
		1	20	37
		2	40	77
		3	60	137
		4	80	217
		6	120	337
		8	160	497
		10	200	697
		12	240	937
		14	280	1217

PT with paracetamol

25 mg/kg/24 hrs

Temps (mn/h)	Flacon (n°)	Dose (ml)	Dose unitaire (mg)	Dose cumulée (mg)	Observations
Flacon no 1 (10 mg/ml)					
	1	0,1	1	1	
	1	0,25	2,5	3,5	
	1	0,50	5	8,5	
	1	0,75	7,5	16	
	1	1	10	26	
	1	1,5	15	41	
	1	2	20	61	
	1	3	30	91	
	1	4,5	45	136	
Flacon no 2 (30 mg/ml)					
2		2	60	196	
2		3	90	286	
2		4	120	406	
2		5	150	556	
2		6	180	736	
2		7	210	946	

Ponvert &Scheimann. Arch Pediat 2007;14:507

ORAL DRUG PROVOCATION TEST

1. FEV1 decrease more than 20% from basal levels
2. Nasoocular symptoms
3. Skin symptoms

POSITIVE

4. Total cummulative doses with good tolerance

NEGATIVE

PREDICTIVE VALUE

- A positive oral provocation test (OPT) is confirmatory for suspected NSAIDs hypersensitivity.
- The test has been documented to have a very high (97,8 %) negative predictive value allowing for safe use of NSAIDs in most patients with equivocal history of hypersensitivity to NSAIDs.
- The positive predictive value of OPT is close to 100%.

Drug Desensitization: Induction Of Tolerance

Drug desensitization

- One form of induction of immune drug tolerance by which effector cells are rendered **less reactive** or **nonreactive to IgE-mediated** immune responses by rapid administration of incremental doses of an allergenic substance
- This can be used for **severe PCN allergy** when there are no alternative agents
- This is a hospital procedure usually conducted in the **ICU**

Solensky R. et al. Ann Allergy Asthma Immunol 2010; 105:259-73

Drug desensitization

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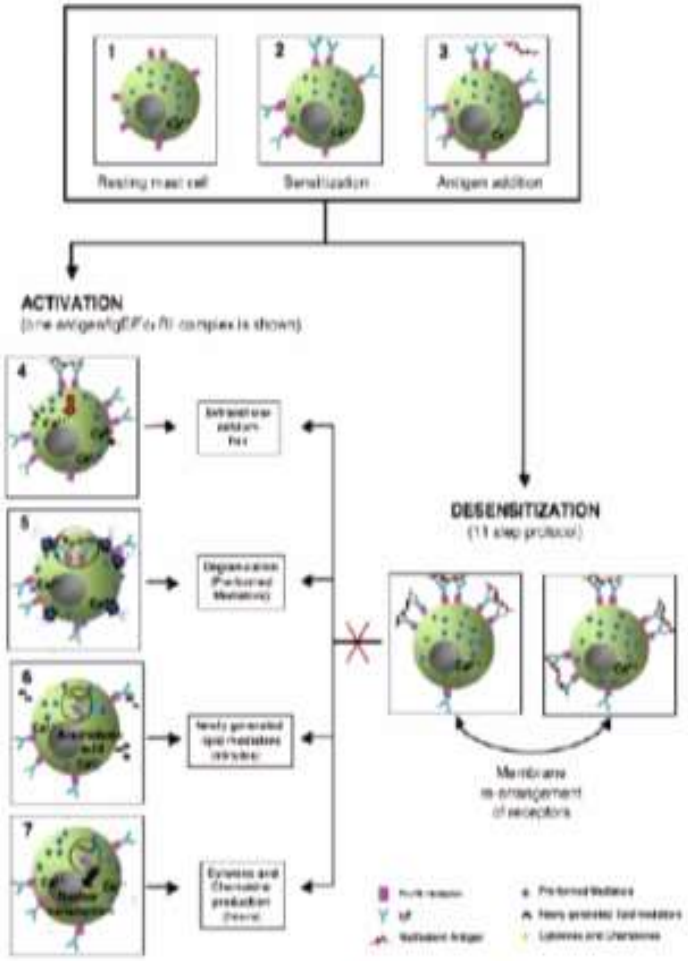
Solensky R. et al. Ann Allergy Asthma Immunol 2010; 105:259-73

Drugs with Successful Desensitization Protocols intravenous, oral, subcutaneous, intraperitoneal

- **Platins**: carboplatin, cisplatin , oxaliplatin
- **Taxenes**: paclitaxel, docetaxel, cabazitaxel, Abraxene
- **Monoclonals** :
- Rituximab, Trastuzumab, Cituximab, Tocilizumab, Bevacizumab, Ofatumumab, Alemtuzumab, Pertuzumab

  TNFa : ertanercept, adalimumab, infliximab
- **Antibiotics**: beta lactams, cephalosporins, sulfonamides, vancomycin
- **Enzymes** : laronidase
- **Iron** : sodium ferric gluconate
- **Aspirin**
- **Progesterone**

Principles of IgE Desensitization



Castells 2017

1. Occurs at the membrane level
2. Starting dose, the time between the doses, the increments (X2) are critical to support the inhibitory state
3. It is specific
4. Can be maintained

Lee et al 2004

Table 4.

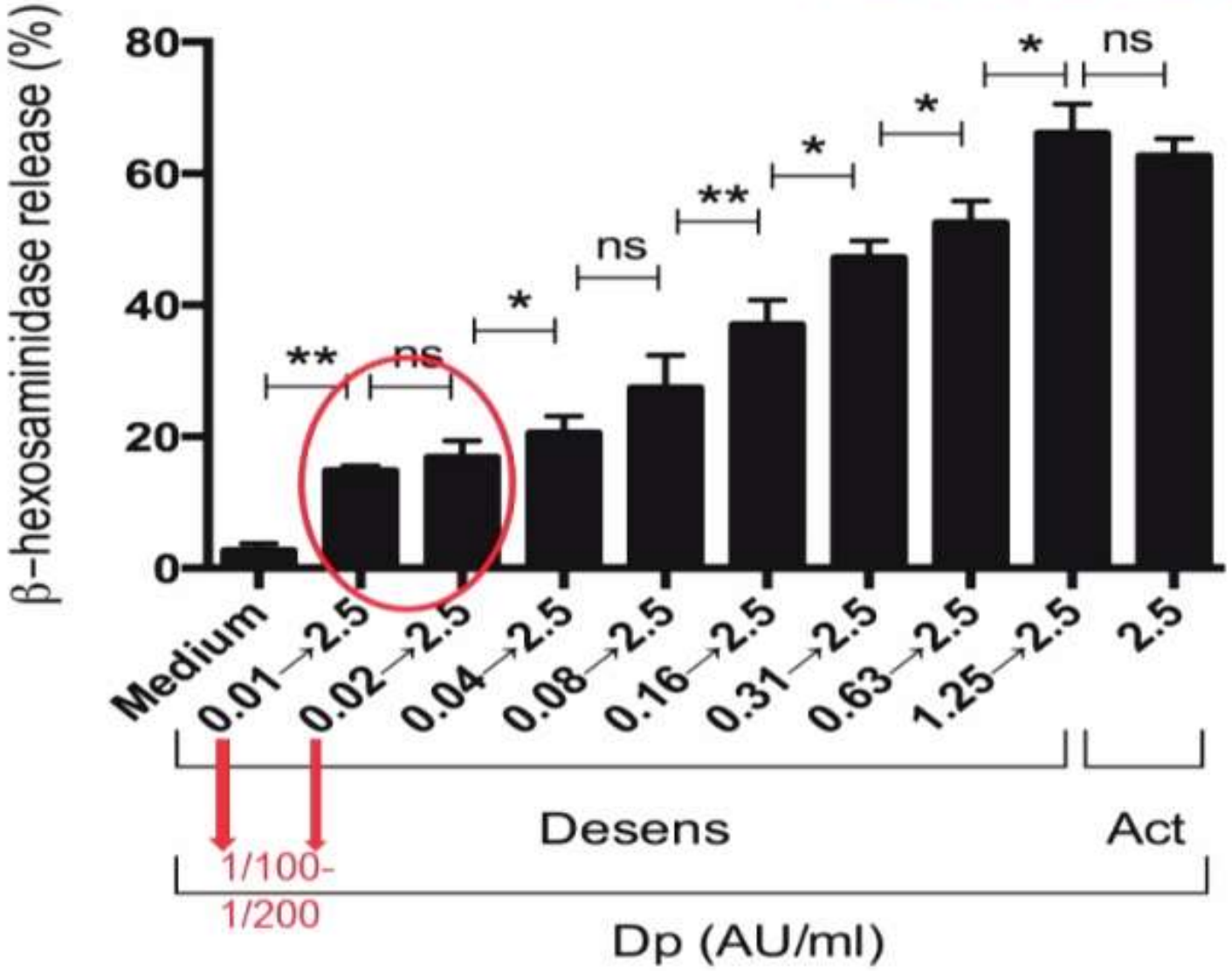
Effect of desensitization on skin test reactivity: wheal/flare (mm) response for Patient 10

	Controls		Carboplatin	
	Histamine (prick)	Diluent (intradermal)	10 mg/ml (intradermal)	Wheal ratio*
Before desensitization	positive (5/15)	negative (4/0)	positive (8/15)	1.6
After desensitization	positive (4/13)	negative (4/0)	negative (4/1)	1

* Wheal produced by carboplatin (intradermal) versus wheal produced by histamine (prick).

Influence of starting concentration/dose

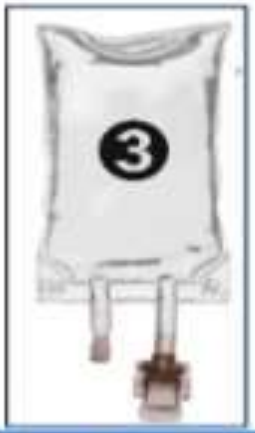
Picard el all submitted 2018



Desensitization Protocols BWH

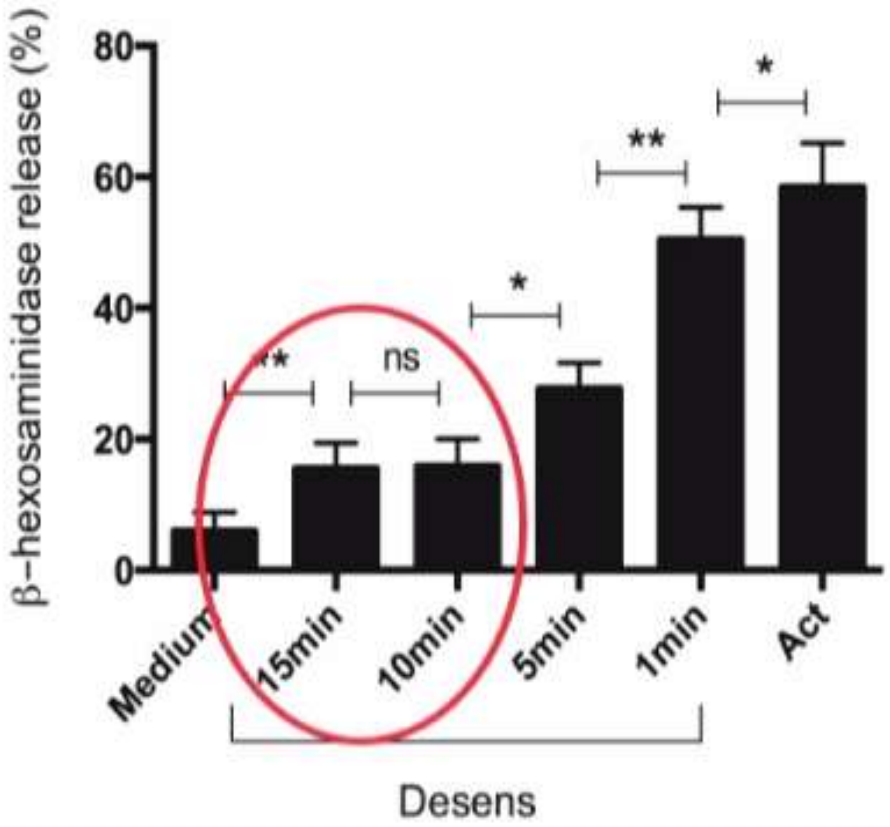
4-bag 16-step protocol (6.7h)

3-bag 12-step protocol (5.7h)

1/1000	1/100	1/10	Full dose
			
Rate (ml/h)	Rate (ml/h)	Rate (ml/h)	Rate (ml/h)
2.5 x 15min	2.5 x 15min	5 x 15min	10 x 15min
5 x 15min	5 x 15min	10 x 15min	20 x 15min
10 x 15min	10 x 15min	20 x 15min	40 x 15min
20 x 15min	20 x 15min	40 x 15min	80 x 2.9h

Influence of time interval between steps

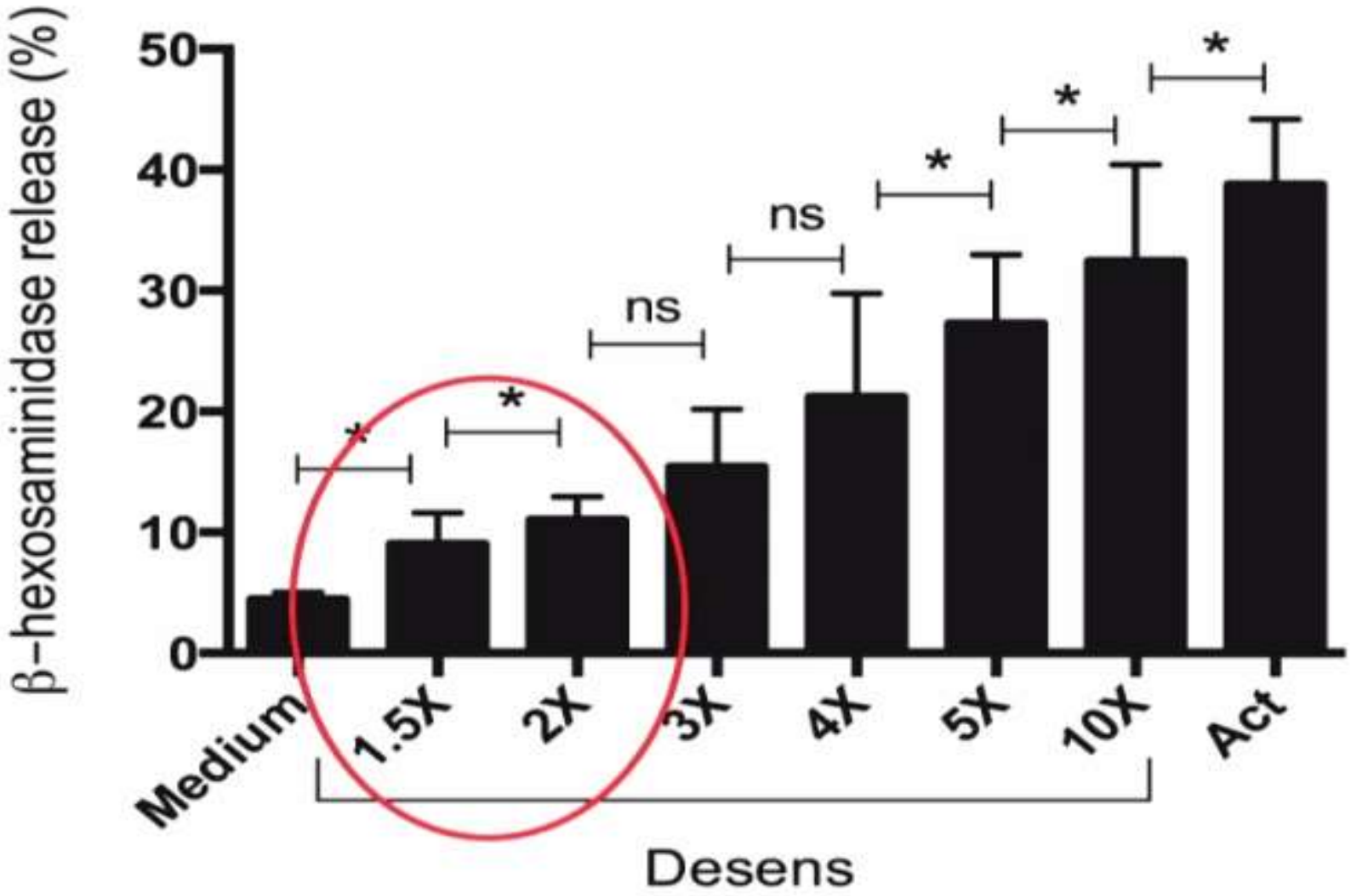
Picard el all submitted 2018



2X protocol
Starting at 0.02
AU/ml

Influence of fold-increase per step

Picard el all submitted 2018



Universal Desensitization Protocol

Castells et al 2008, Brennan et al 2009, Legere et al 2009, Slaone 2016

Full Dose	500.0	mg			total mg to be injected in each bottle
Solution 1	250	cc of	0.020	mg/ml	5.000
Solution 2	250	cc of	0.200	mg/ml	50.000
Solution 3	250	cc of	1.984	mg/ml	496.065
		note to pharmacy the total mg injected is more than the final dose because solutions 1 and 2 are not completely infused			

Step	Solution	Rate (cc/h)	Time (min)	Administered dose	Cumulative dose (mg)
1	1	2	15	0.0100	0.0100
2	1	5	15	0.0250	0.0350
3	1	10	15	0.0500	0.0850
4	1	20	15	0.1000	0.1850
5	2	5	15	0.2500	0.4350
6	2	10	15	0.5000	0.9350
7	2	20	15	1.0000	1.9350
8	2	40	15	2.0000	3.9350
9	3	10	15	4.9607	8.8957
10	3	20	15	9.9213	18.8170
11	3	40	15	19.8426	38.6596
12	3	75	186	461.3405	500.0000
	Total time =		351	minutes	

Beta-lactam Drug Desensitization

- Typical starting **dose is 1/10,000** of target therapeutic dose
- Can also use calculated dose from **skin test** as starting point
- Further dosage increases are typically **twice** the previous dose
- Administered at **15-20 minute** intervals under therapeutic dosage is achieved.

Outcomes and Safety of PCN de-sensitizations

- Most all patients can be desensitized
- About **1/3** of patients have mild cutaneous reactions during desensitization
- **Severe reactions** extremely rare
- **Delayed reactions < 10%**
- **Long-acting benzathine** PCN may be administered after desensitization safely at intervals of 1- weeks

Wendel GD et al. New Eng J Med 1985;312:1229-32.

DRUG ALLERGY

1. Antibiotics (Do Oral Provocation Test/ Injection)

A. Clarithromycin 10mg per kg (Maclar /Bioclar /Claribid)500mg X BD ./ Roxid / Rulide (Rexithromycine)150 mg X OD

B. Moxiflox (moxifloxacillin) 400 X OD / Levoflaxacine (Levoflox – 250mg / 500mg X OD.

C .Cefixime 200mg X OD./ Cefuroxime (cefoxim) 250 mg / cefoprox 200mg X OD.

F. Clindamycin (Dalacin – C) 300/600 mg X OD.

G. Lind (Linezolid) 600mg X OD.

E. Inj. Amikacin 500mg X BD.

H. Inj. Meropenom (carbapenan) .

2. Analgesics (Do Oral Provocation Test)

A. Nimesulide (Numulid)100 mg/ (NISE).

B. Tramadol (Tramazac/Domodal).

C. Paracetamol(Crocin).

D. Etoricoxib (Etov) 120 mg /(EBOE) 90 mg.

E. Meloxicam (Mel-OD)

For Emergency (Acute Urticaria & Angiodema) & During provocation tests of drugs

** (1st day 25% of therapeutic dose. / 2nd day 50% of therapeutic dose . / 3rd day 100% of therapeutic dose .)*

1. *ALLERGA 180mg stat.*
2. *MEDROL 16mg Stat.*
3. *Inj. EPIPEN AUTOINJEVTOR (Adrenaline 0.3-0.5 ml X SC /IM stat.)*

If History of Anaphylaxis to (Antibiotics/NSAIDS / Chemotherapy / Monoclonal antibodies)

During Desensitization of Drugs (Start With 1/1000 To 1/100 Dilution Of Drug)

A . Adrenaline : *I/V infusion During Desensitization (2mg / 100ml)*

@ 4 to 40 ml/ hr (Titrate as per monitoring of BP/HR (not more than 30% of Baseline) or s/s of Headache/ Palpitations & Chest Pain)

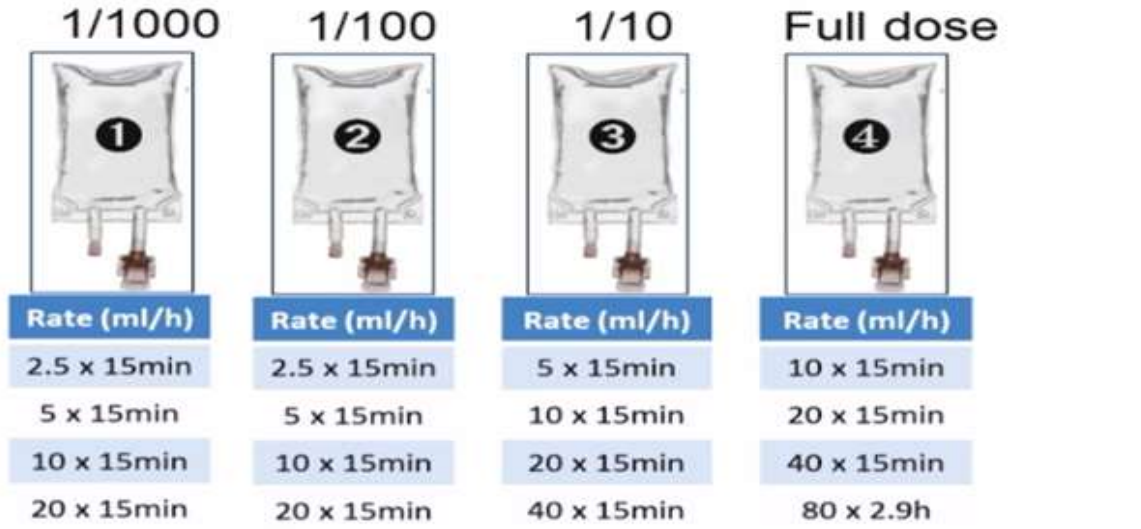
B. If Anaphylaxis (Occurs Allergy reaction)

1. *Stop CULPRIT Drug*
2. *Inj.I/V Solu- Medrol (1-4mg) 60-125 mg*
3. *Inj. I/V Avil X stat. or Inj Phenargan X stat*
4. *Increase I/V Adrenaline rate as per monitoring of BP/HR.*
5. *Restart the Drug after the control of symptoms*

Desensitization Protocols BWH

4-bag 16-step protocol (6.7h)

3-bag 12-step protocol (5.7h)



Provocation Tests

Table 2
Sequence of increasing doses during a drug provocation test

Drug	Drug Class	Doses (mg)[a]	Route	Daily Dose for Adults[b]
Amoxicillin	Penicillin	1, 5, 25, 100, 500, 1000	Oral	1000–2000 mg
Cefador	Cephalosporin	1, 5, 25, 125, 500	Oral	750 mg
Cefixime	Cephalosporin	1, 5, 25, 100, 225	Oral	400 mg
Ceftriaxone	Cephalosporin	1, 5, 25, 100, 500, 1000	Intravenous	1000–2000 mg
Azithromycin	Macrolide	1, 5, 25, 75, 125, 250	Oral	500 mg
Ciprofloxacin	Quinolone	1, 5, 25, 100, 500	Oral	500–1500 mg
Acetylsalicylic Acid	NSAID	1, 5, 20, 50, 100, 200, 500	Oral	500–3000 mg
Melaxicam	NSAID	1, 3, 7.5	Oral	7.5–15 mg
Prednisolone	Steroid	2, 10, 20, 40	Oral	20–80 mg
Omeprazole	PPI	1, 5, 10, 20	Oral	20–40 mg
Terazepam	Benzodiazepine	1, 2.5, 25, 50	Oral	50–100 mg
Any Vaccine	Vaccine	0.1, 0.5	Subcutaneous	0.5 (1.0) mL
Lidocaine	Local anesthetic	0.1, 1, 2	Subcutaneous	1–3 mL

Abbreviation: PPI, proton pump inhibitor.

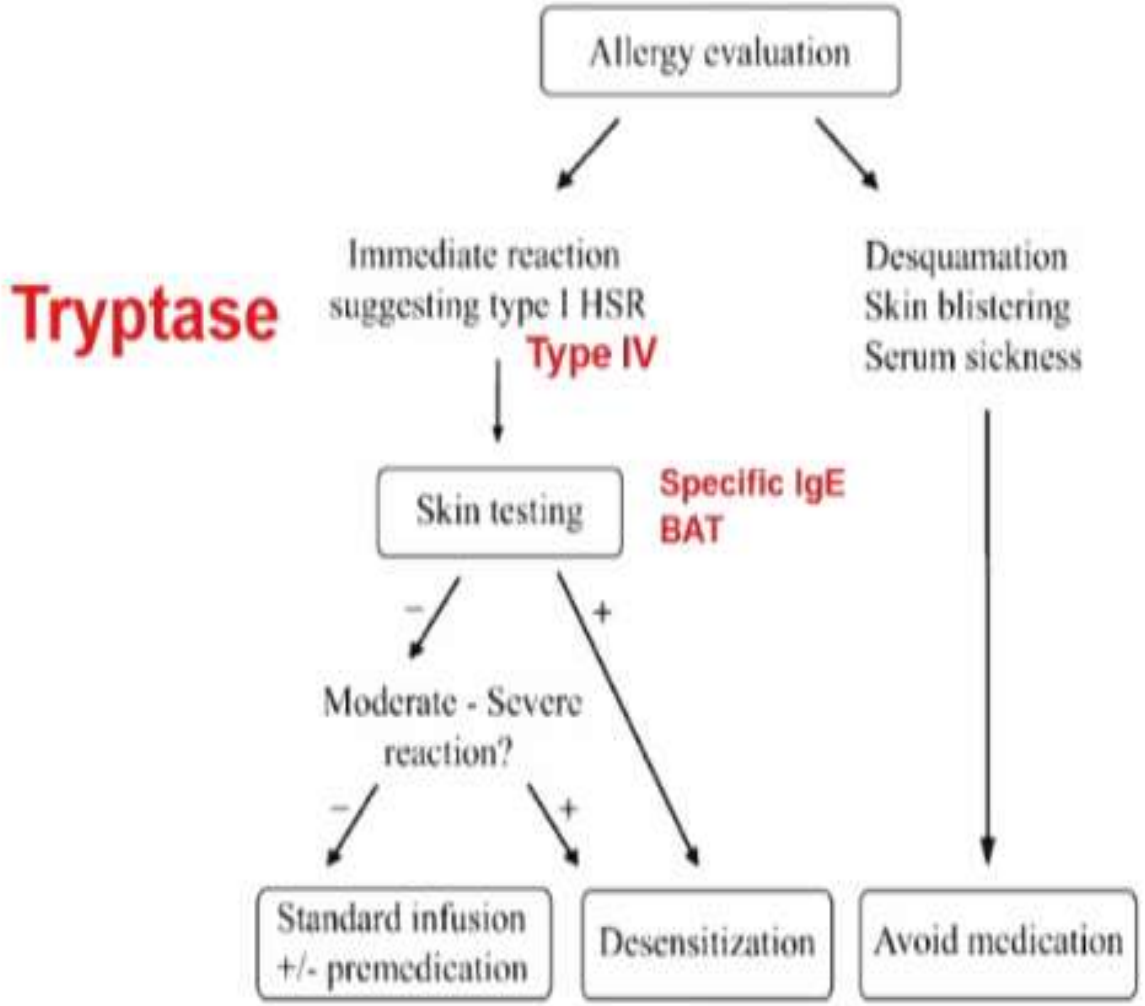
[a] Ten times less than the first dose for anaphylactic shock, individual approach.

[b] Recommendations may vary in different countries.

Ref. Roland solensky, MD & david a. khan , MD/ drug alllergy ;-an update practice parameter/annals of allergy, asthama & immunology /volume 105, oct2010

Recurrent Anaphylaxis due to Food & Drugs

multiple allergy syndrome



Hypersensitivity reactions to mAbs: 105 desensitizations in 23 patients, from evaluation to treatment. Brennan et al. J. Allergy Clin. Immunol. 2009; 124:1259-66

In summary
Stepwise approach to drug allergy

1	Confirm history is a drug allergic reaction
2	Classify drug allergic reaction
3	Determine likelihood of drug(s) in question to cause reaction
4	Determine elements that may influence drug allergy history
5	Evaluate if subsequent exposure to drug
6	What is likely future need of drug?

Khan DA. Drug Allergy. In Manual of Allergy & Immunology 5th Ed. 2012

Thanks

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