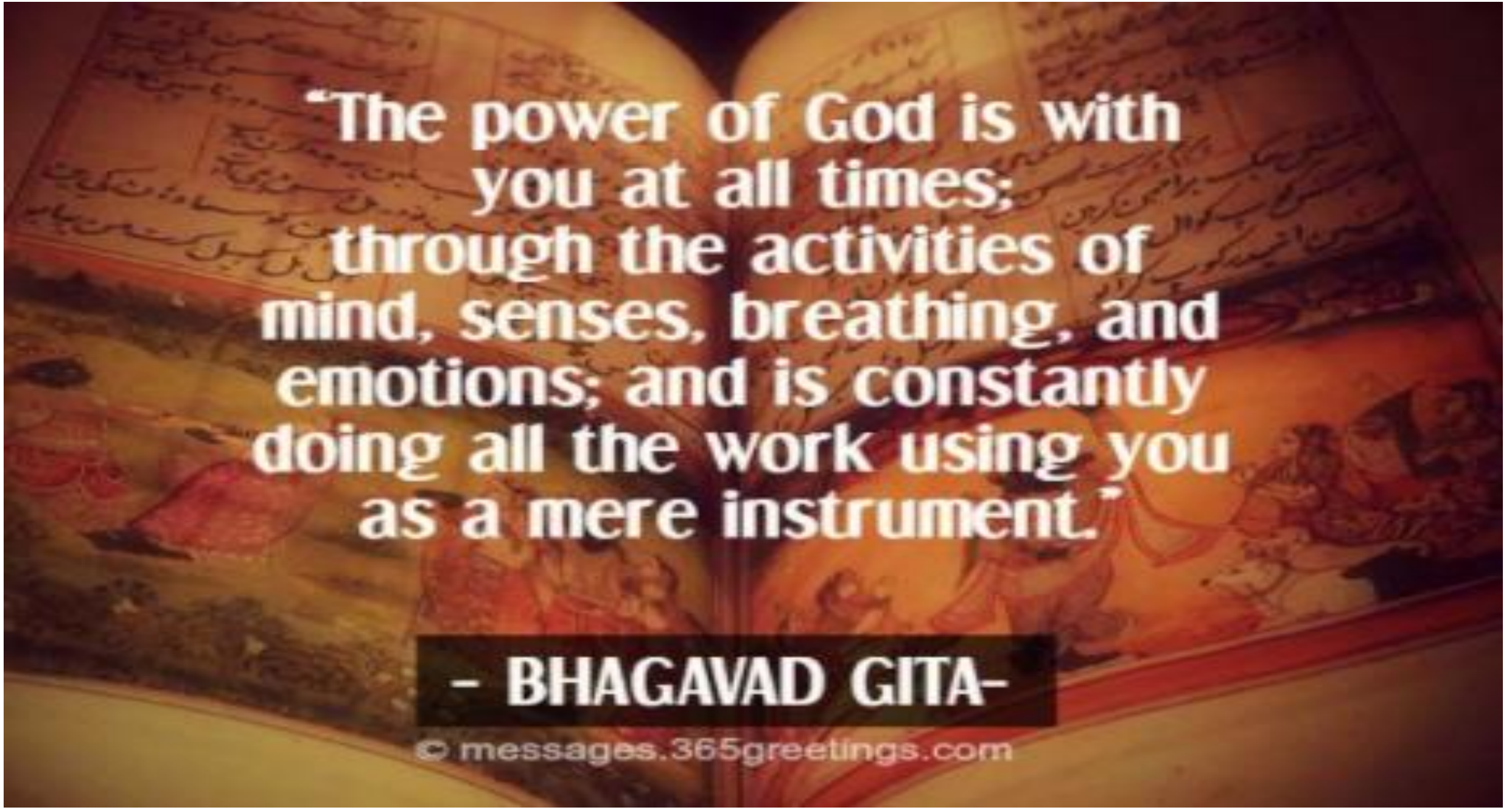
"The power of God is with
you at all times;
through the activities of
mind, senses, breathing, and
emotions; and is constantly
doing all the work using you
as a mere instrument."
- BHAGAVAD GITA-
© messages.365greetings.com


# DRUG ALLERGY

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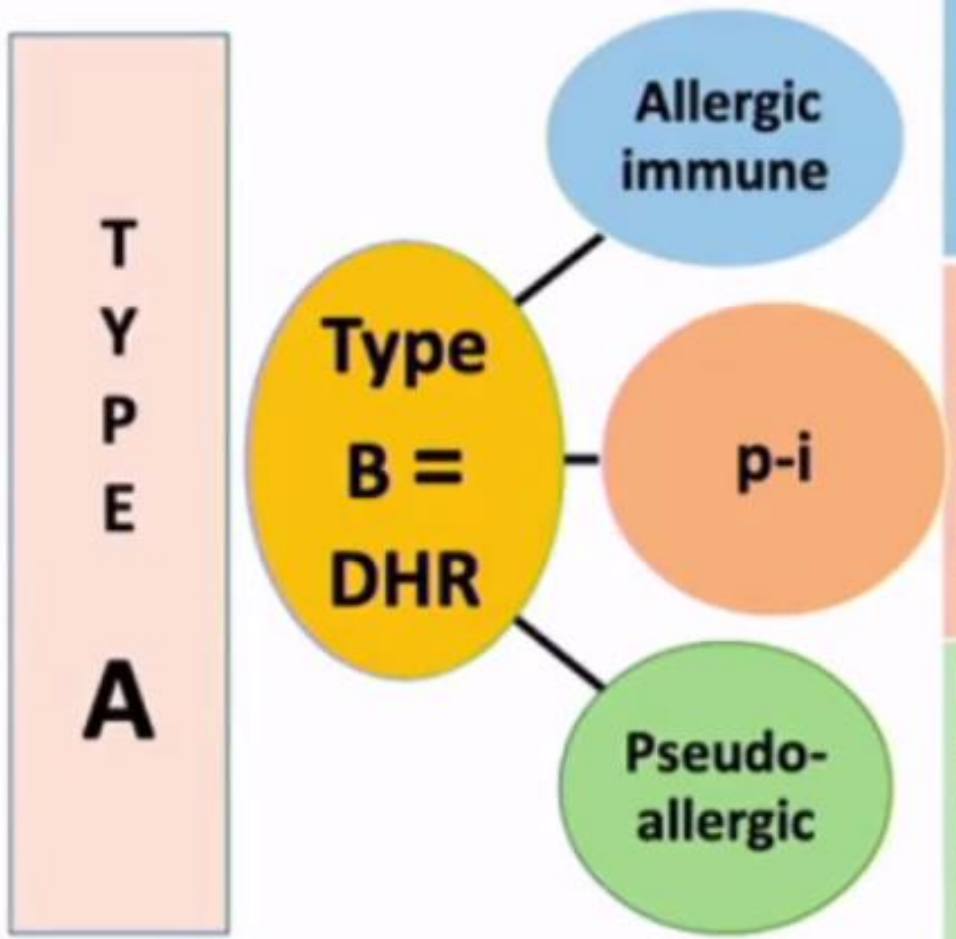
# Drug hypersensitivity reactions

DHRs are adverse effects of drugs that clinically resemble allergic reactions

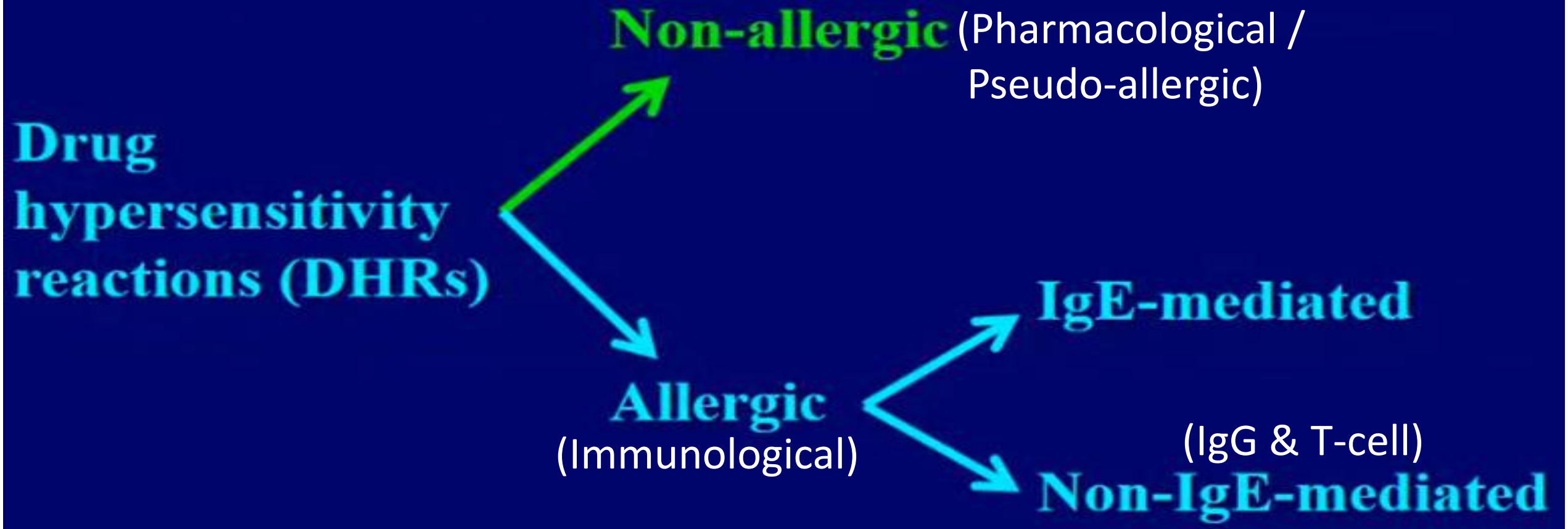
DHRs constitute 15% of all adverse drug reactions affecting more than 7% of the general population

# Dissection of drug hypersensitivity reactions based on the mode of action of drugs

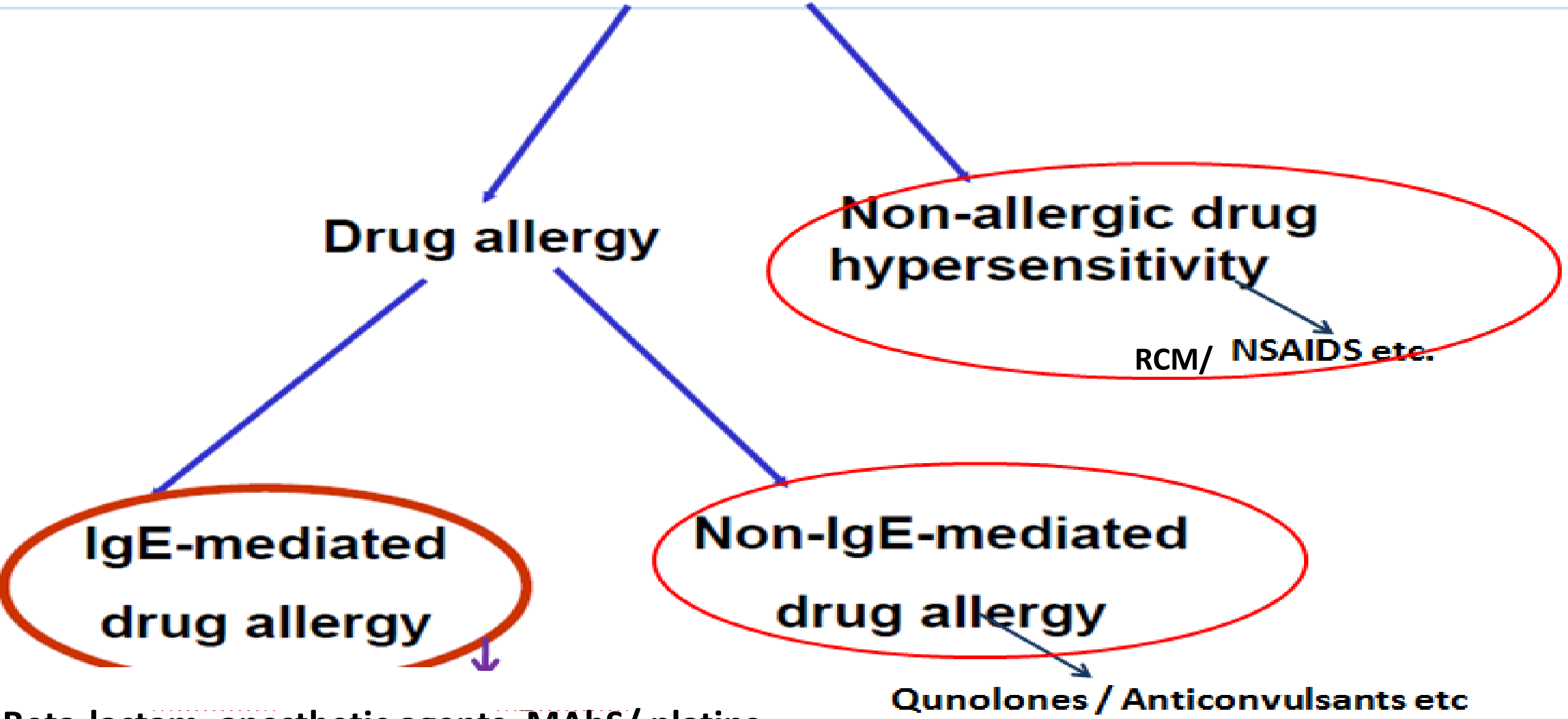



| | | |
|---|---|---|
| Allergic immune | Formation of a new antigen; Classical allergic form of DHR | **IgE:** *Anaphylaxis, urticaria*<br>**T cells:** MPE<br>**IgG:** haemolytic anaemia, immun-complex disease |
| p-i | Drugs bind directly to immune receptors (HLA, TCR) | **Only T cells:** MPE, DRESS, SJS/TEN, AGEP, hepatitis |
| Pseudo-allergic | Drugs bind directly to receptors and enzymes of effector cells, no real allergy | **MRPGPRX2**/ Mast cells *Anaphylaxis/urticaria*<br>**Cyclooxygenase**↓/Leukotriens ↑ *Bronchospasm, asthma, urticaria*<br>***Bradykinin***↑*: angioedema* |

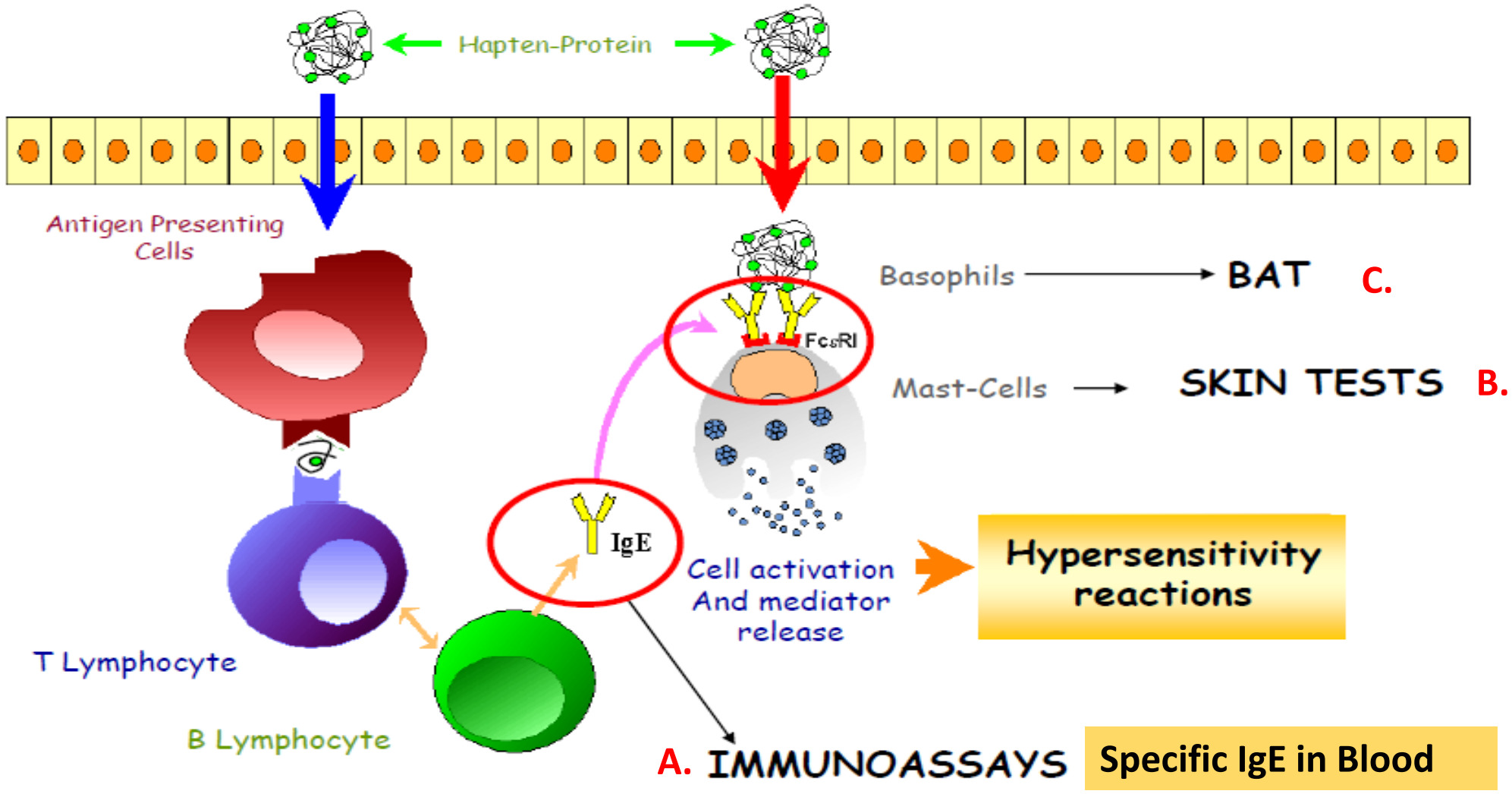
# International consensus (ICON) on drug allergy



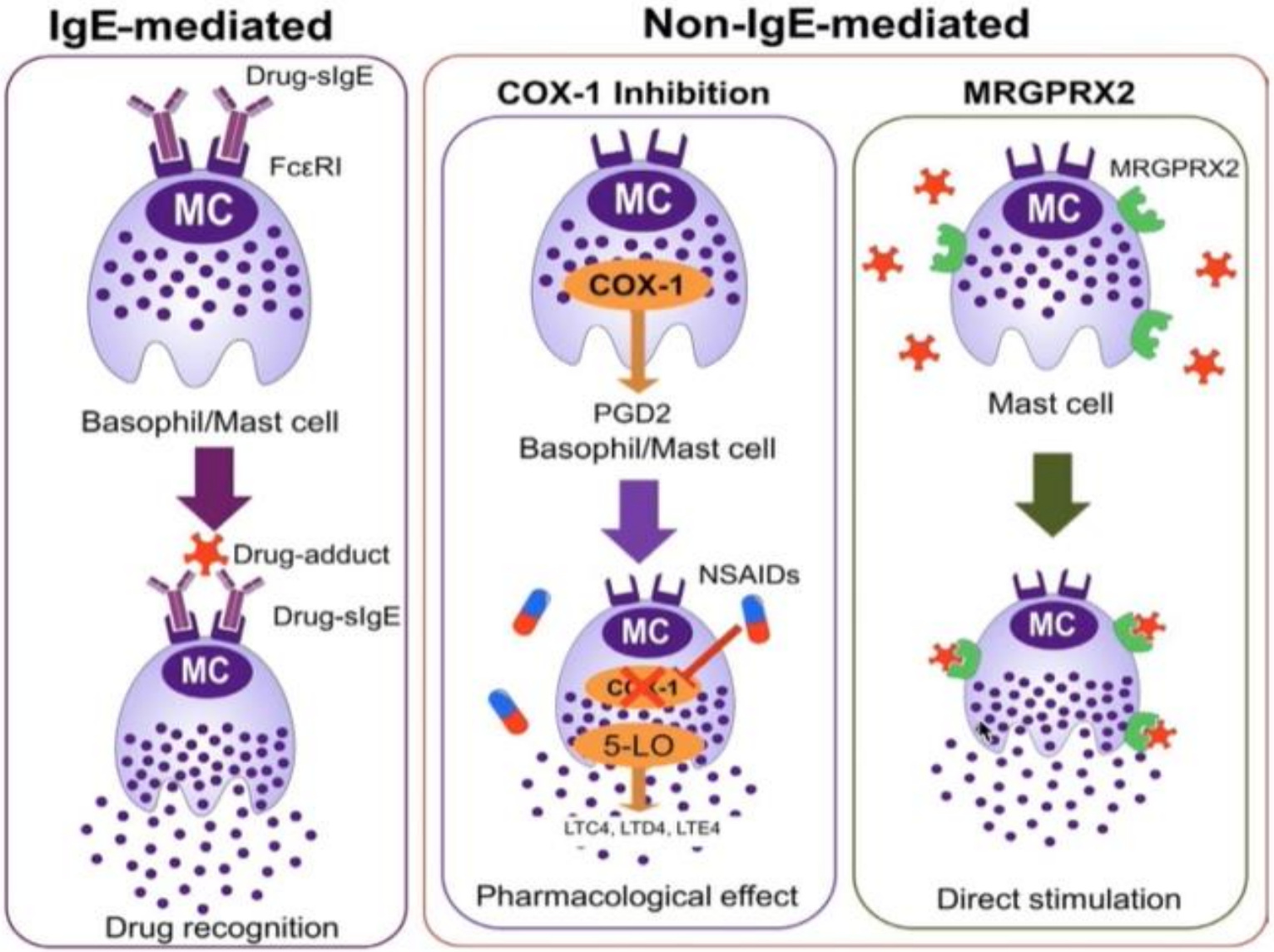
# Drug hypersensitivity - nomenclature



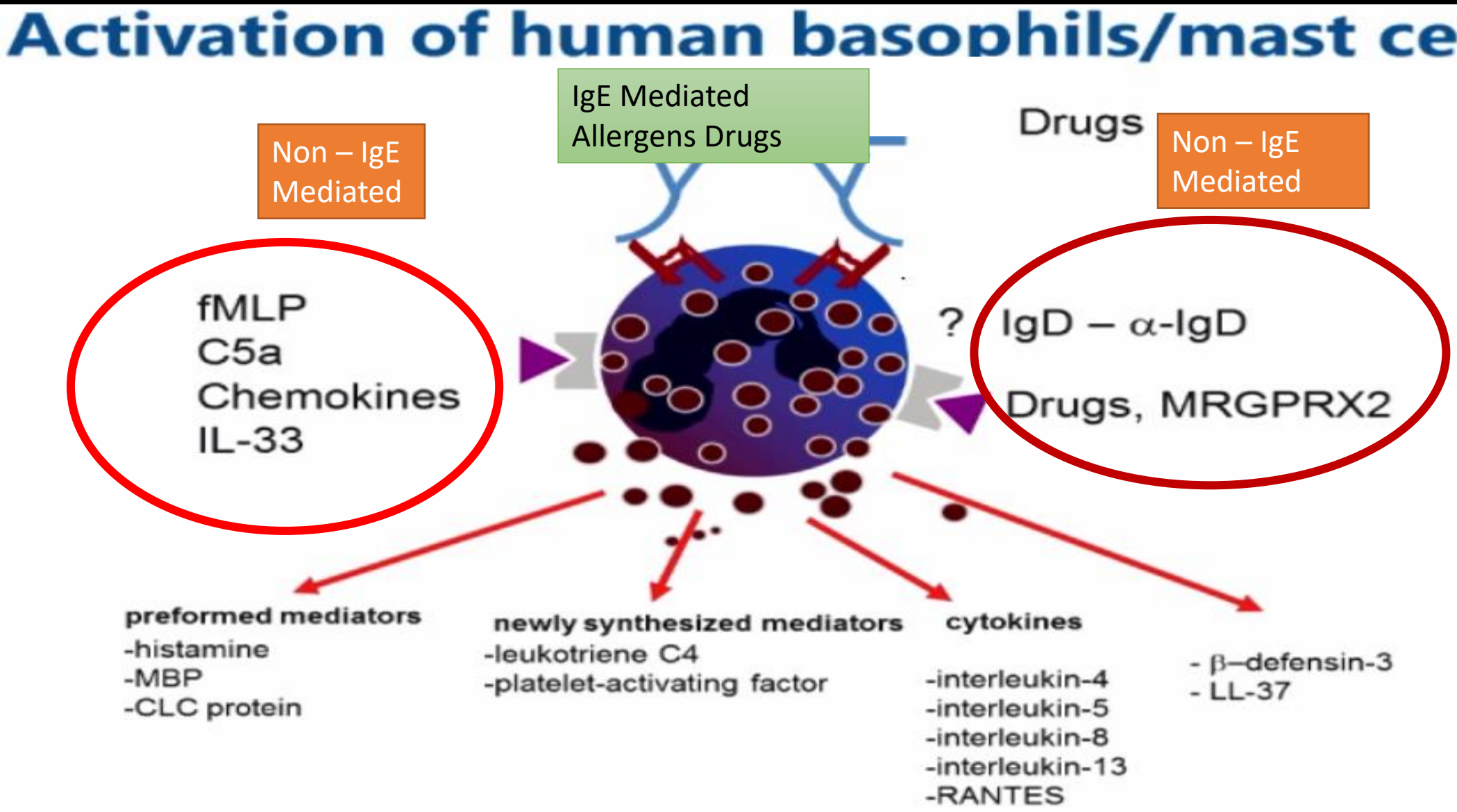
# IgE - mediated IMMEDIATE REACTIONS



# Immediate-onset DHR Mechanisms



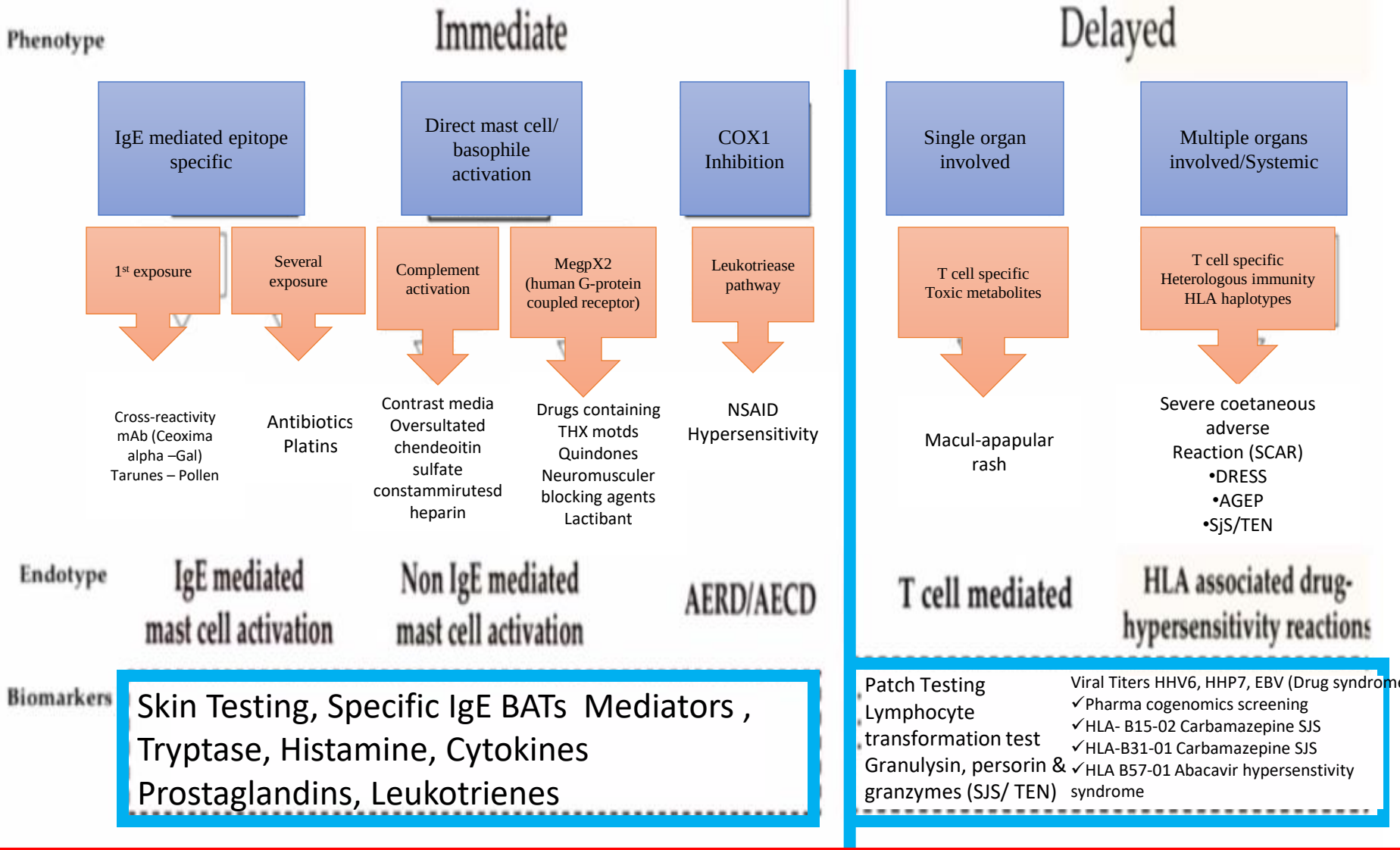
# Immediate reaction



# Phenotypes and endotypes in drug allergy

## (IgE/non-IgE+cox-1 inhib)

## T-cell & HLA marker

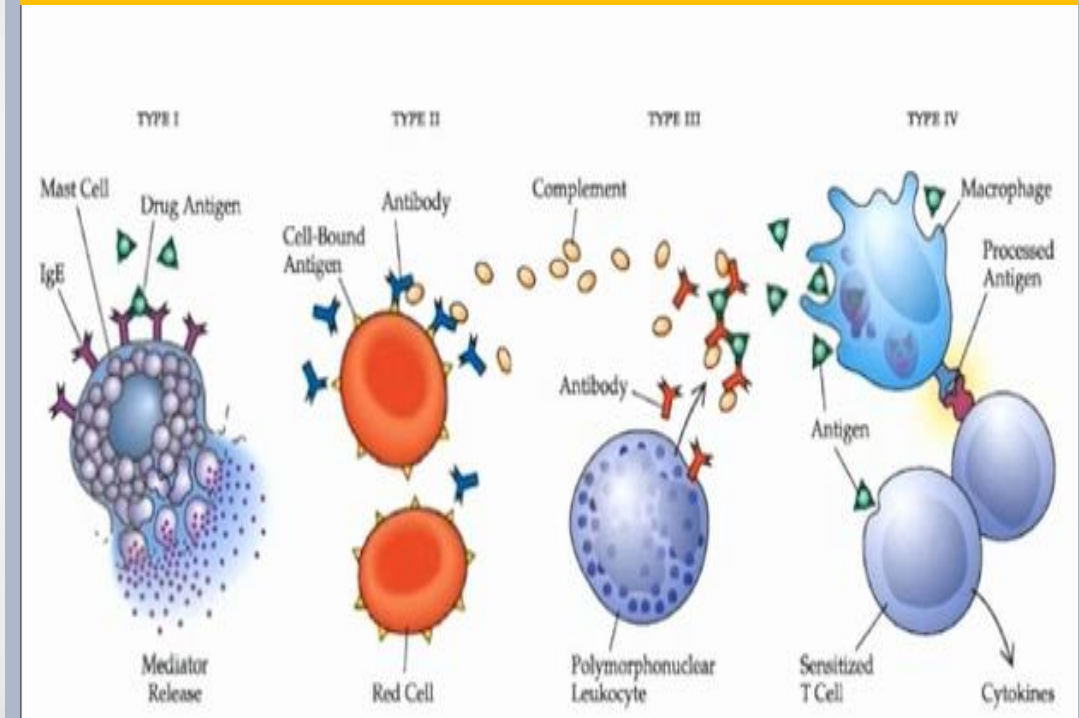


# Gell & Coomb's Classification

| | Type I | Type II | | Type III | Type IV | | |
|---|---|---|---|---|---|---|---|
| Immune reactant | IgE | IgG | | IgG | $T_H1$ cells | $T_H2$ cells | CTL |
| Antigen | Soluble antigen | Cell- or matrix-associated antigen | Cell-surface receptor | Soluble antigen | Soluble antigen | Soluble antigen | Cell-associated antigen |
| Effector mechanism | Mast-cell activation | Complement, $FcR^+$ cells (phagocytes, NK cells) | Antibody alters signaling | Complement, Phagocytes | Macrophage activation | IgE production, Eosinophil activation, Mastocytosis | Cytotoxicity |
| | Ag | platelets + complement | | immune complex, blood vessel, + complement | IFN-γ, $T_H1$, chemokines, cytokines, cytotoxins | IL-4, IL-5, $T_H2$, eotaxin, cytotoxins, inflammatory mediators | CTL |
| Example of hypersensitivity reaction | Allergic rhinitis, asthma, systemic anaphylaxis | Some drug allergies (eg, penicillin) | Chronic urticaria (antibody against FCεR1α) | Serum sickness, Arthus reaction | Contact dermatitis, tuberculin reaction | Chronic asthma, chronic allergic rhinitis | Contact dermatitis |

Figure 12-2 Immunobiology, 6/e. (© Garland Science 2005)

IgE IgG Immune complex T cell [I-IV]

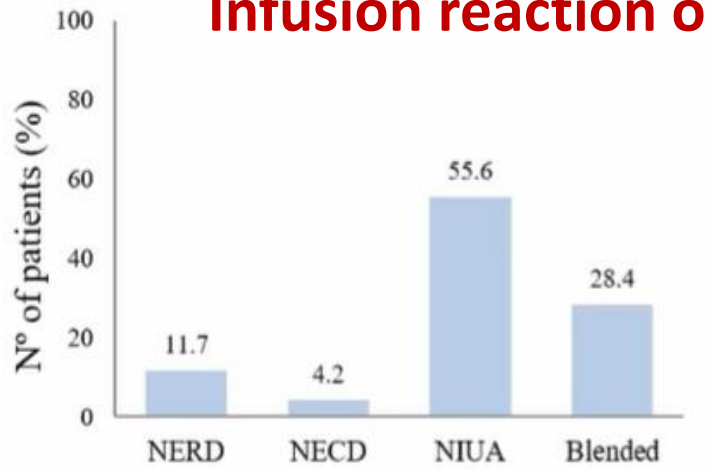



TYPE 1 TYPE II TYPE III TYPE IV

**Infusion reaction or cytokine storm due Cytotoxic T Cells ag Mabs ?**

# One classification does not fit all

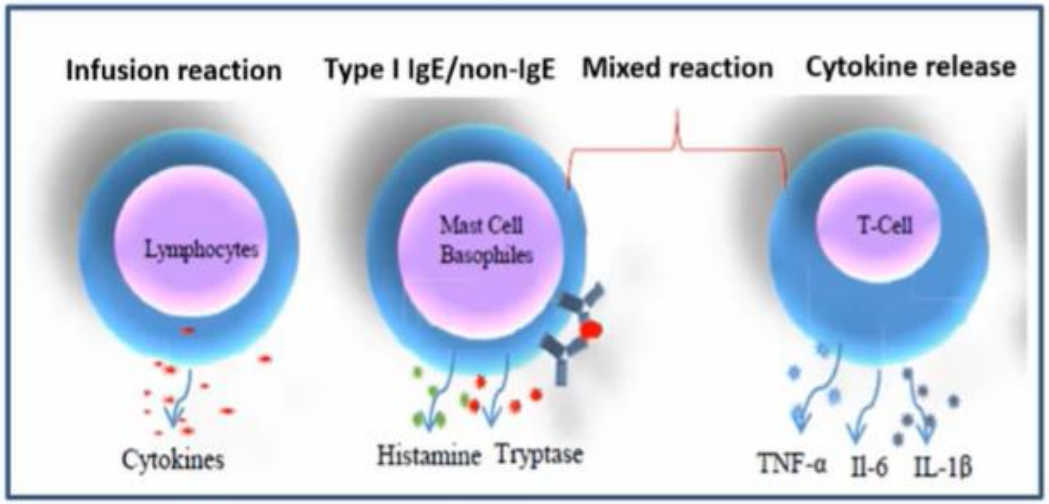
## Infusion reaction or cytokine storm due Cytotoxic T Cells ag Mabs ?



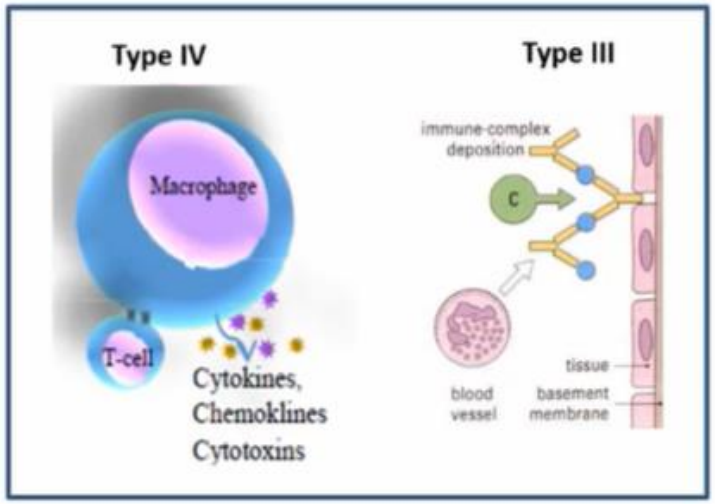

**Blended reactions** are characterised by mixed patterns of clinical entities affecting at least two organs

Doña I. Scientific Reports 2018

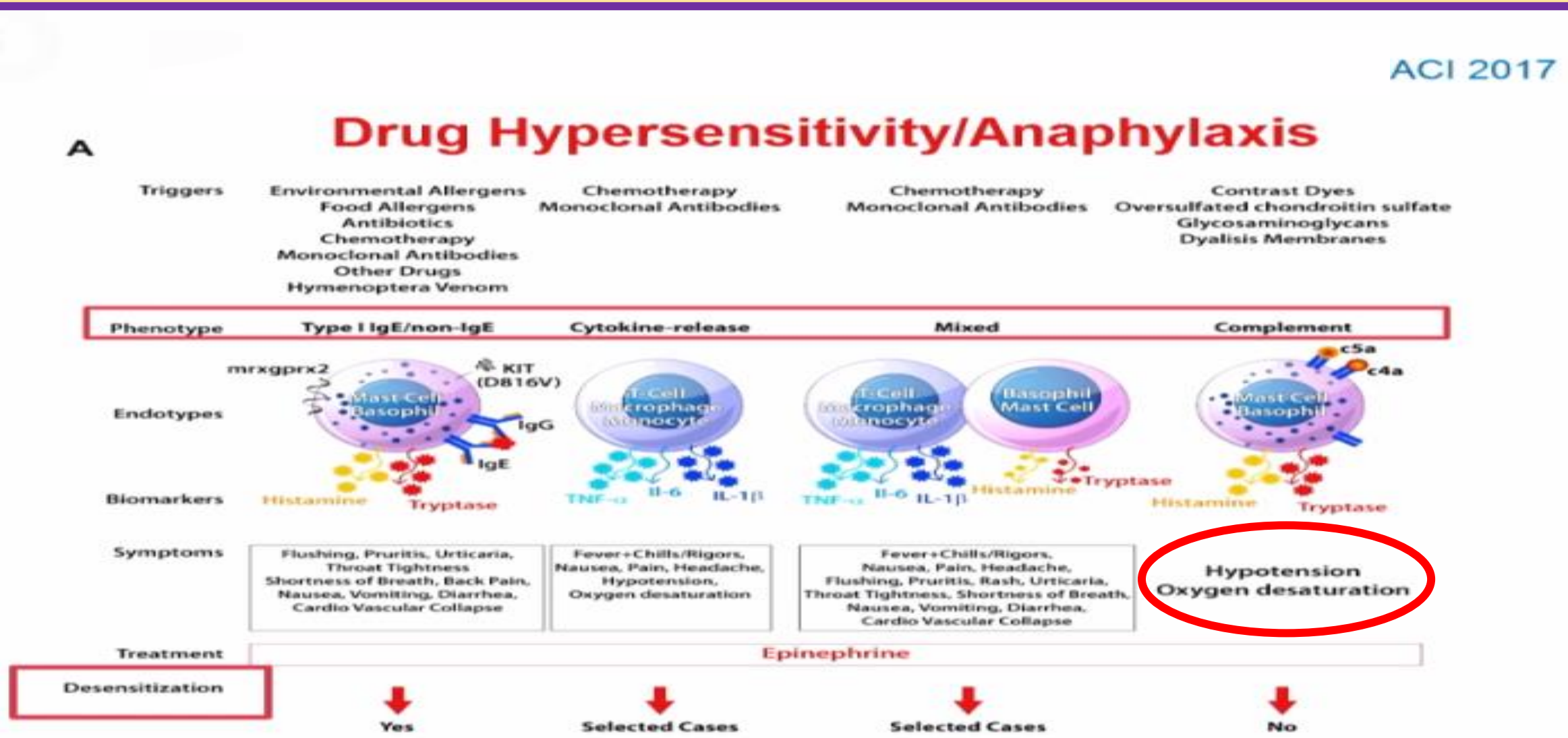
### Immediate (<1h)




### Non-immediate (>1h)

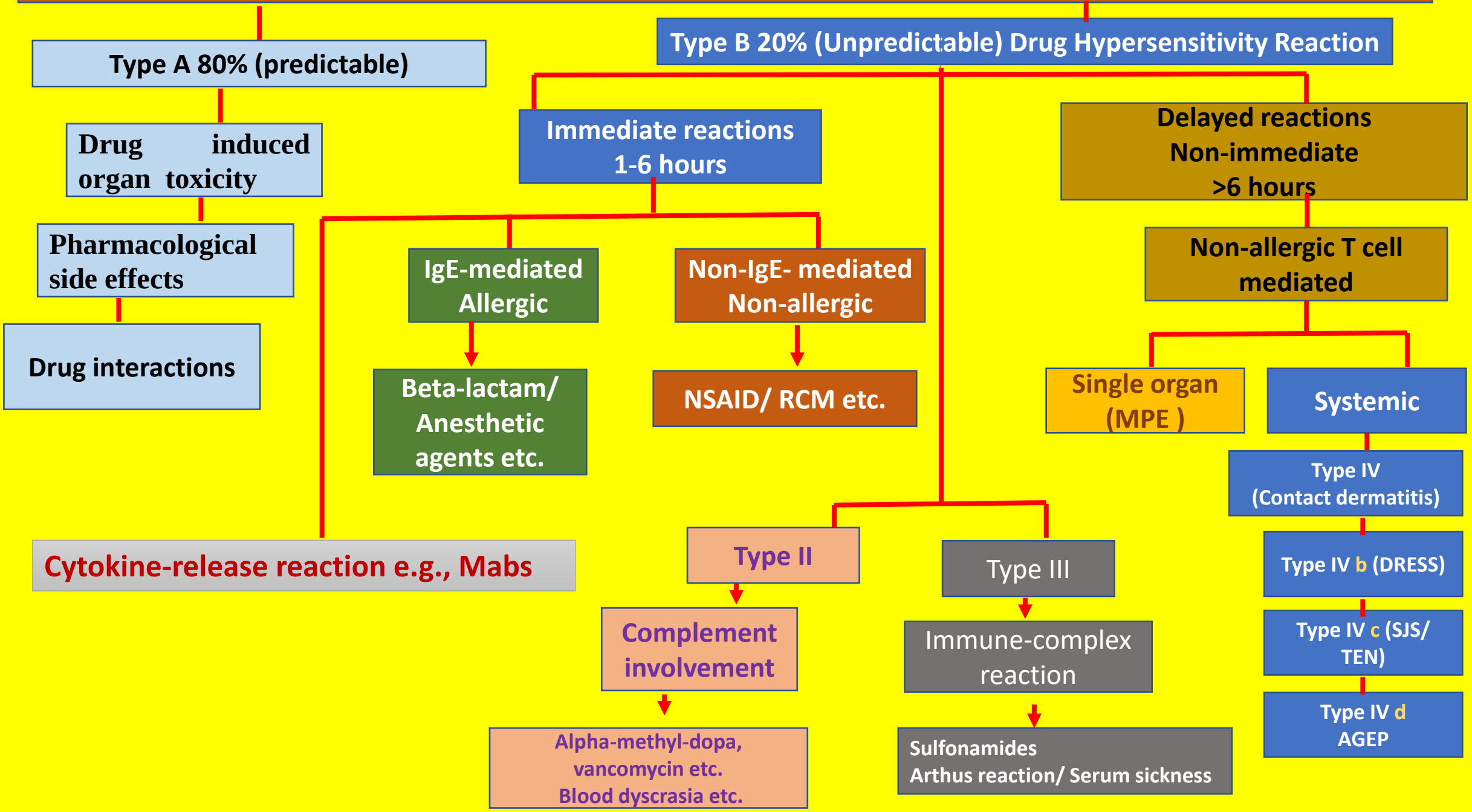


**Flushing, Puritus , Urticaria, Throat tightness, Shortness of Breath, Back Pain, Nausea & Vomiting** → MAST CELLS ⇄ T -CELLS → FEVER , CHILLS & PAINS (CYTOKINE-STROM)

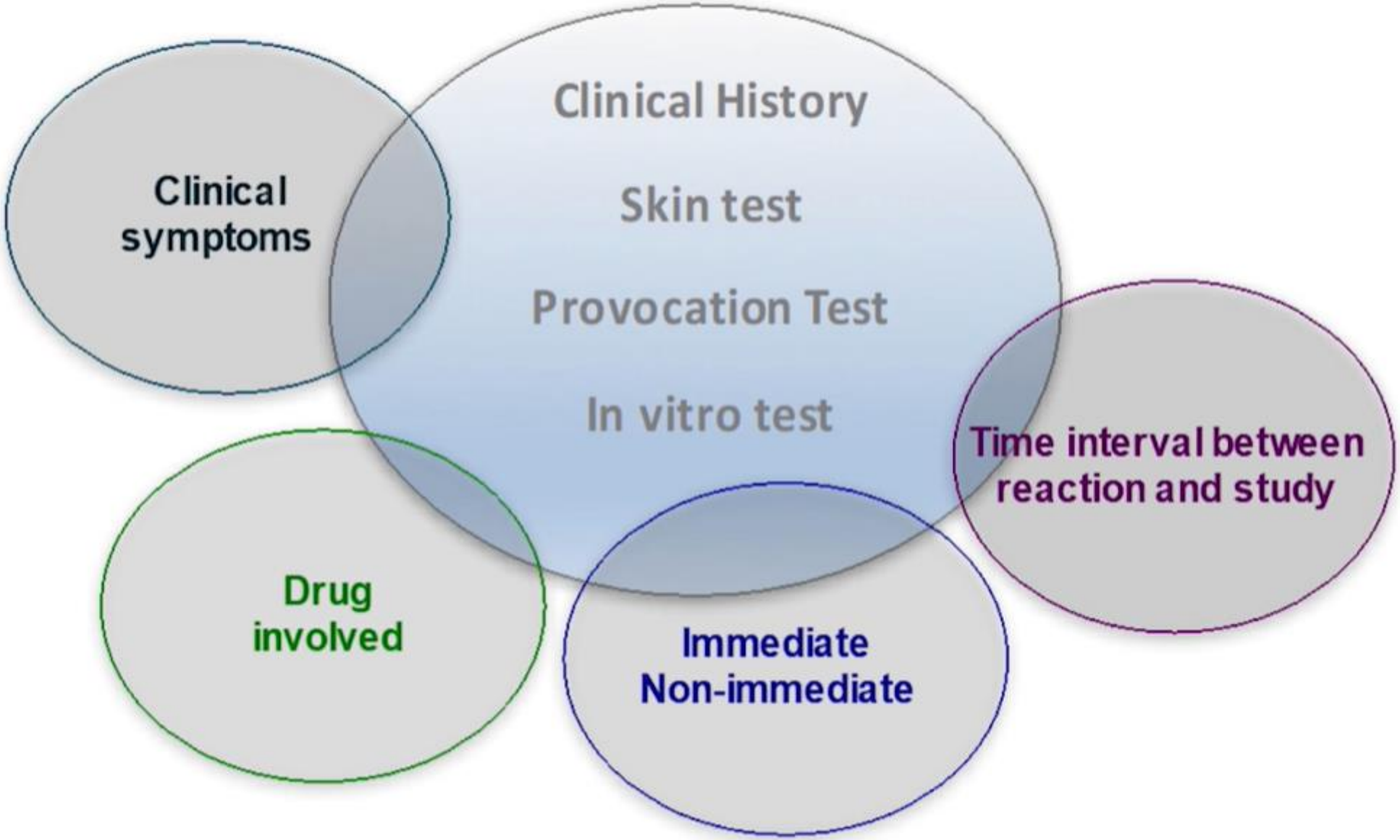



**Mast Cell Degranulation & cytokine strom due Cytotoxic T Cells ag Mabs ?**

# ADVERSE DRUG REACTIONS



# Drug allergy diagnosis



# Which ones do you choose as allergological work-up?

## IgE and non IgE-ALLERGIC

A.
- Clinical history
- Skin prick test
- Intradermal test
- Patch test
- OPT with the culprit drug

Past h/o anaphylaxis

B.
- Clinical history
- Skin prick test
- Intradermal test
- Patch test
- In VITRO TEST
- OPT with the culprit drug

Present h/o anaphylaxis

Systemic Cutaneous Adverse Reaction (SCAR)/IgG/IgM/Immune-complex

C.
- Clinical history
- OPT with alternative drug

## PSEUDO-ALLERGIC-NSAIDs

Single organ involvement

D.
- Clinical history
- OPT with the culprit drug

## MPE-Beta lactam

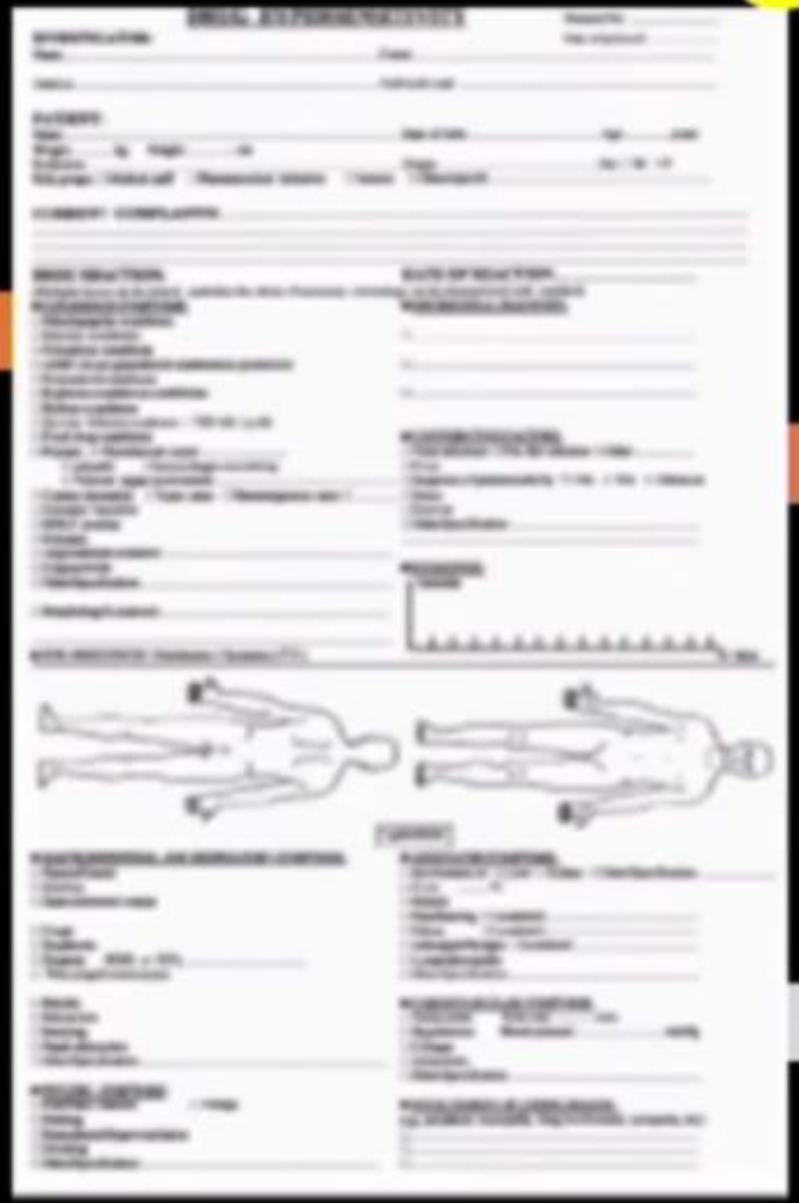
## CLINICAL HISTORY

## *IN VIVO* TESTS


## *IN VITRO* TESTS

## DPT

# Allergy Work-up

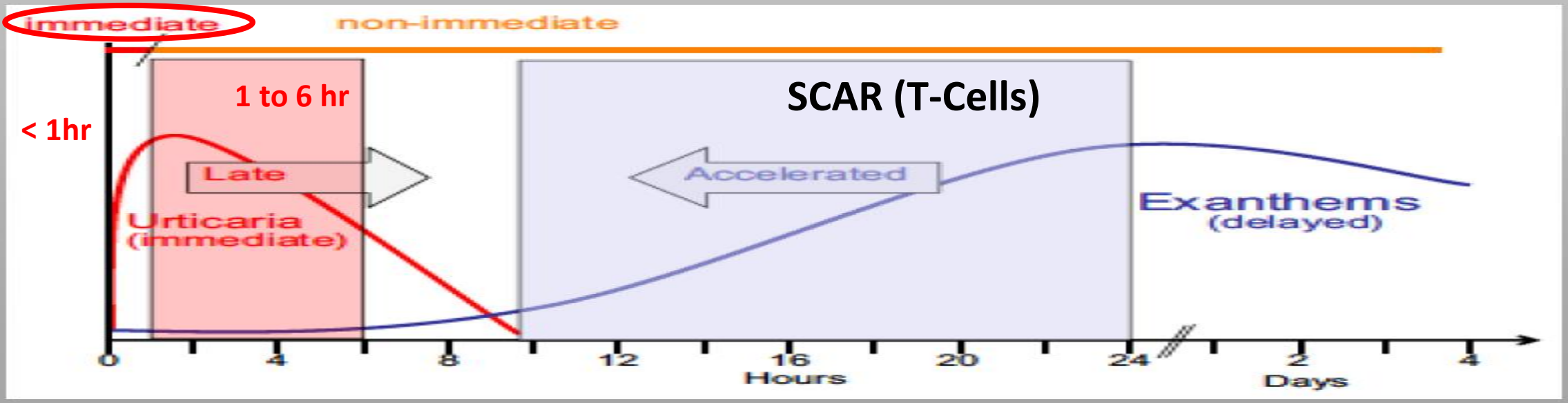


***IN VIVO* TESTS**


***IN VITRO* TESTS**

**DPT**

# Time course of allergic reactions




## Clinical Phenotypes In Drug Allergy

### Immediate-onset drug allergy

1–6 h of exposure to a drug, and present with cutaneous (e.g., flushing, pruritus, urticaria, angioedema), respiratory, and/or gastrointestinal symptoms, and anaphylaxis

→ Anaphylaxis and anaphylactic shock

### Delayed-onset drug allergy

- Reaction usually occurs than 1 hour, mostly 24 hours or even weeks, after drug intake
- Heterogeneous clinical manifestations:
  - (1) isolated, single-organ involvement
  - (2) systemic, multi-organ involvement.
- Cutaneous reactions are the most common with numerous clinical phenotypes (MPE,FDE, urticaria, angioedema)

→ SCARs which include Steven Johnson Syndrome and Toxic Epidermal Necrolysis

| | Immediate | Non-immediate | Non-immediate suspected serious |
|---|---|---|---|
| | **Time-scale from first administration** | | |
| | < 1 hour | > 1 hour | **> 6 hour to days** |
| Possible associated symptoms & signs | Urticaria, angio-oedema, airway & systemic compromise | Maculopapular exanthema | Lymph node, joint, mucous membrane involvement, bullae, cytopenia, hepatitis, nephrititis & vasculitis |
| Specific syndromes include | * IgE-mediated anaphylaxis | * Fixed drug eruption, non-bullous | # Drug Rash with Eosinophilia and Systemic Symptoms |
| | * Non-IgE-mediated anaphylactoid reactions | * Erythema multiforme | * Acute Generalised Exanthematous Pustolosis |
| | | | * Serum Sickness Syndrome |
| | | | * Drug-induced dermatoses (eg lupus spectrum) |
| | | | # Stevens Johnson Syndrome & # Toxic Epidermal Necrolysis |

# ALLERGY WORK-UP

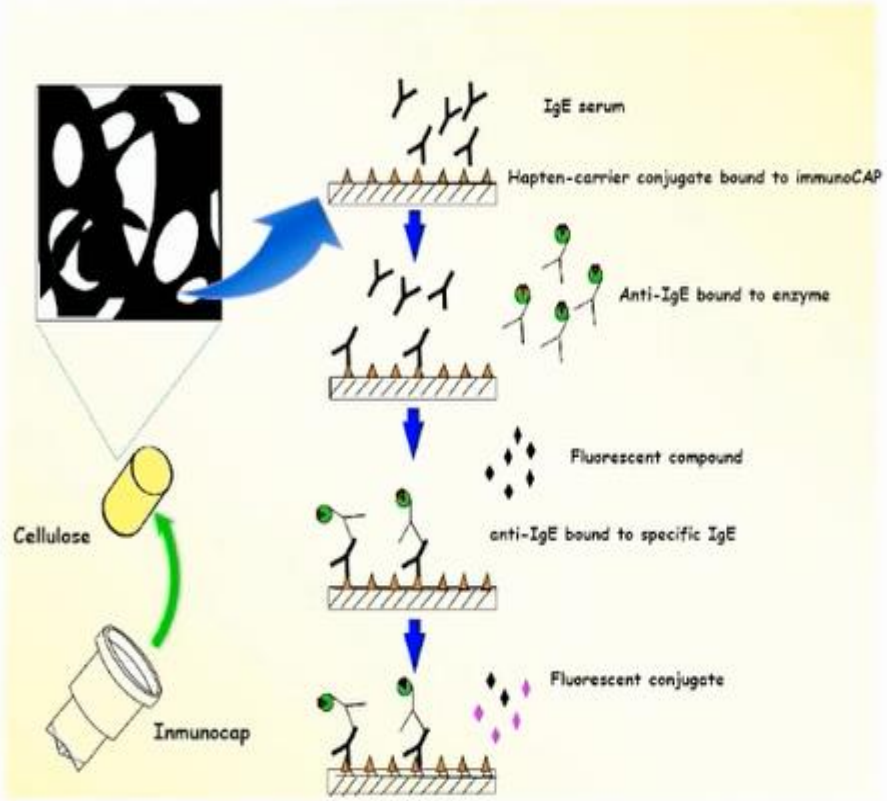
DIAGNOSTIC

| | Immediate testing 15 min to 1 hr | 4-6 weeks after |
|---|---|---|
| (Histamine) |  | |
| Tryptase |  | |
| sIgE |  |  |
| Skin tests | |  |

± Drug provocation tests as needed

- **Serum tryptase**
  - At time of reaction (15 min-3 hrs after reaction)
  - Baseline level (minimum 24 hrs after reaction)
  - New algorithm: Reaction tryptase > Baseline tryptase x 1.2 + 2
- **In vitro tests**
  - Allergen specific IgE
  - Basophil histamine release/(BAT)
- **In vivo tests**
  - Skin prick test
  - Intradermal test
  - Drug provocation (iv, sc, po)

# In vitro tests to evaluate IgE mediated reactions



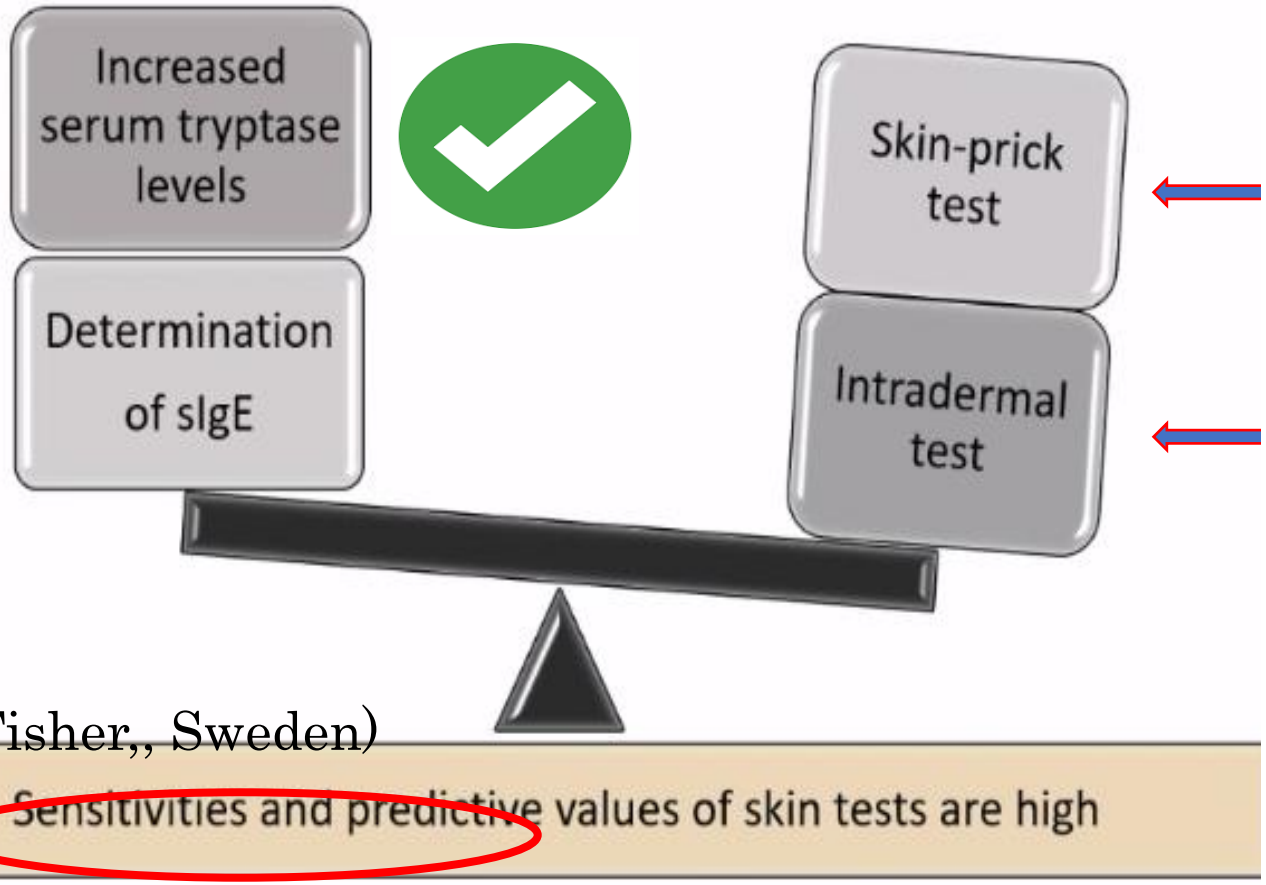

## ImmunoCAP

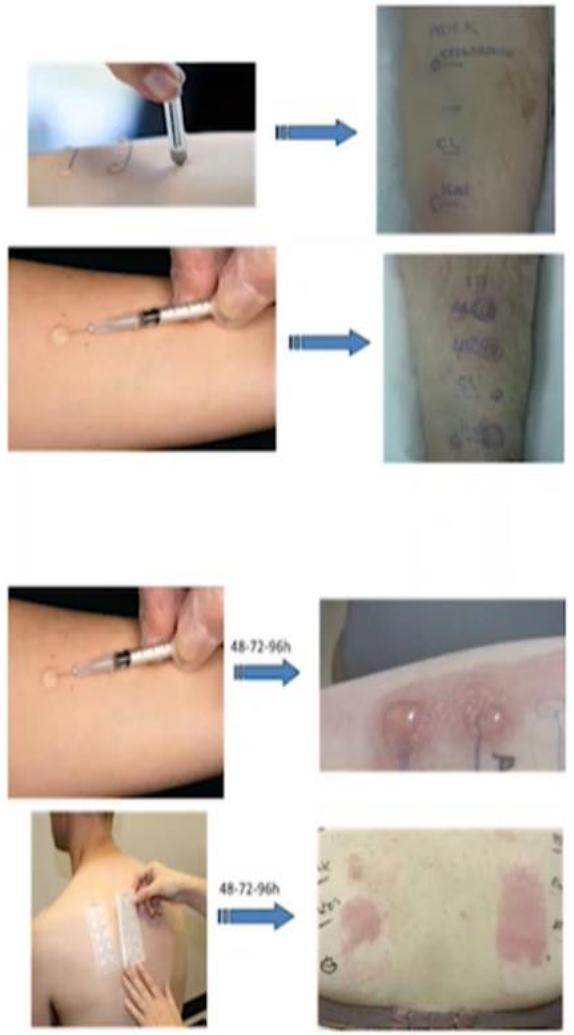
| | Penicillin sIgE (PG and/or AX sIgE) | | | |
|---|---|---|---|---|
| **Cut-off** | Sens (SPAIN) | Sens (ITALY) | p | Specif |
| **sIgE ≥0.1 kUA/L** | 39.57% (N=139) | 52.40% (N=250) | 0.019 | 68.75% (N = 32) |
| **sIgE ≥0.35 kUA/L** | 15.83% (N=139) | 32.40% (N=250) | 0.000 | 93.75% (N = 32) |
| **sIgE/tIgE ≥0.002** | 13.67% (N=139) | 35.66% (N=244) | 0.000 | 81.25% (N = 32) |

# Diagnostic tests for general anesthetic agent hypersensitivity

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

ImmunoCAP (Thermo- Fisher,, Sweden)




Turkish National Society of Allergy and Clinical İmmunology, drug hypersensitivity guideline, 2014.
Drug Allergy: An Updated Practice Parameter: American Academy of Allergy, Asthma and Immunology, the American College of Allergy, Asthma and Immunology, and the Joint Council of Allergy, Asthma and Immunology.

# Tryptase measurement

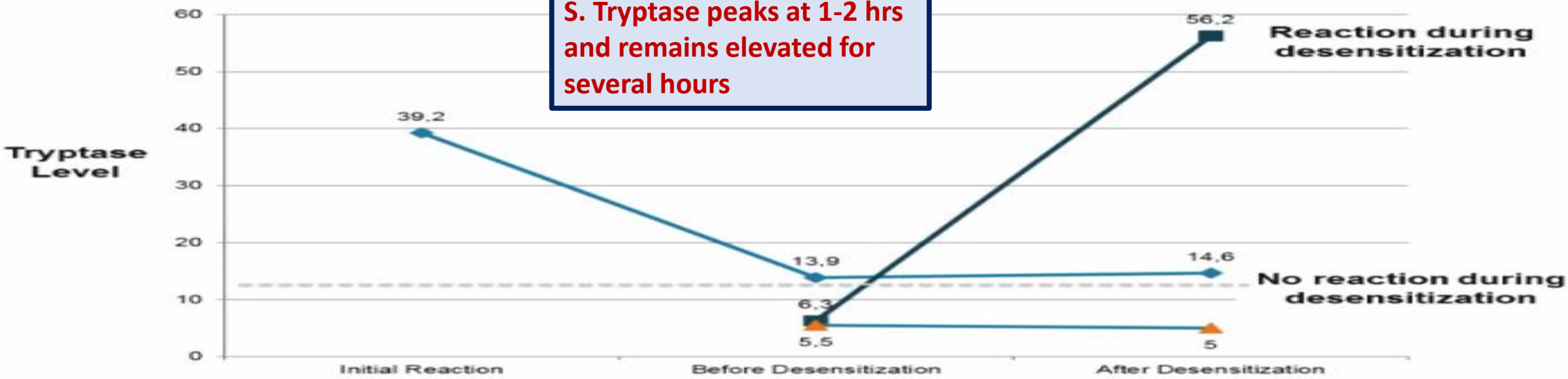
## Thresholds for « increase »

>25 microg/L- Diagnostic of IgE mediated reaction

- ☑ < 11.4 microg/L (commercial kit) :95% of healthy individuals are below
- ☑ > 25 microg/L (SFAR / SFA) : 95% specificity for IgE-mediated reactions
- ☑ > 1.2 x basal tryptase level + 2 microg/L

## Tryptase: a marker of mast cell activation

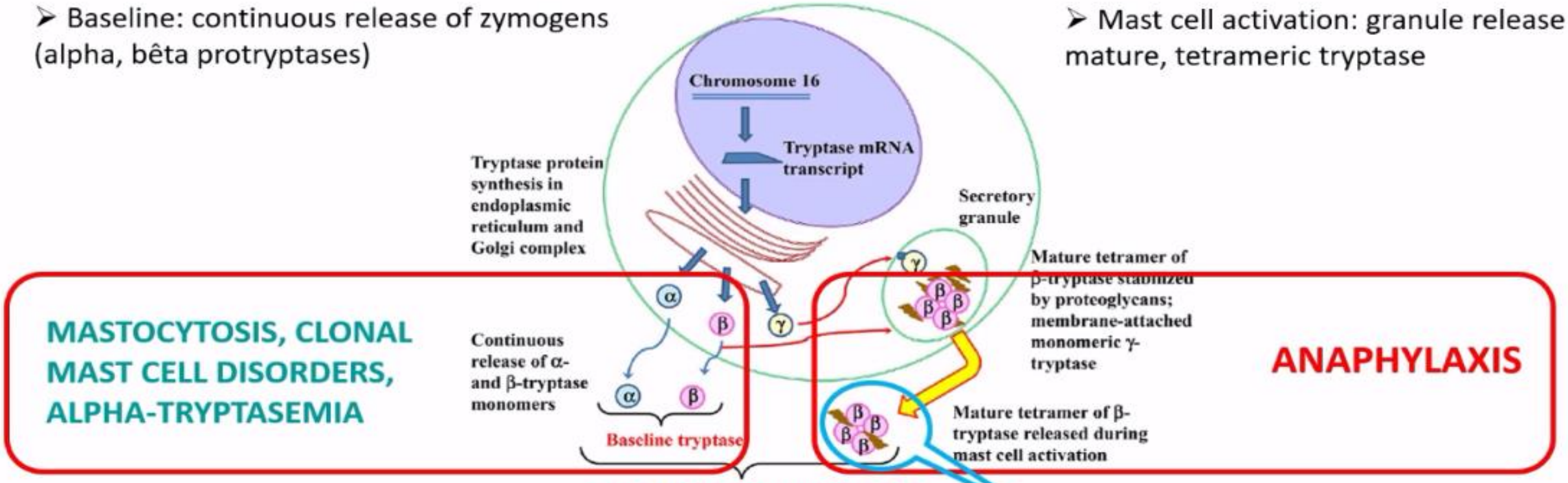
S. Tryptase peaks at 1-2 hrs and remains elevated for several hours



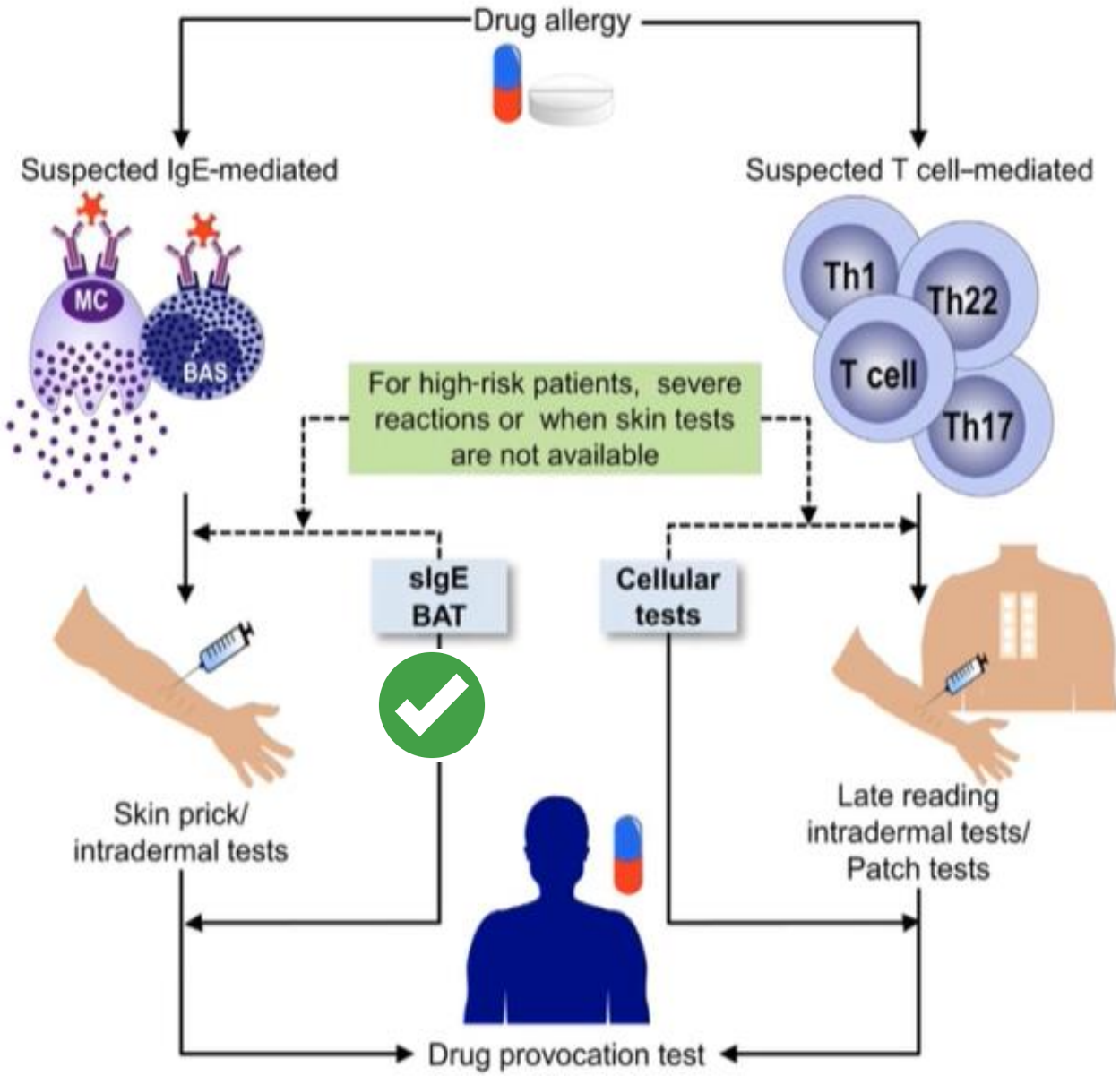
# *Tryptase determination as a complementary criterion for the diagnosis of perioperative anaphylaxis*

➢ Baseline: continuous release of zymogens (alpha, bêta protryptases)

➢ Mast cell activation: granule release of mature, tetrameric tryptase



# Placing in vitro tests in the diagnosis



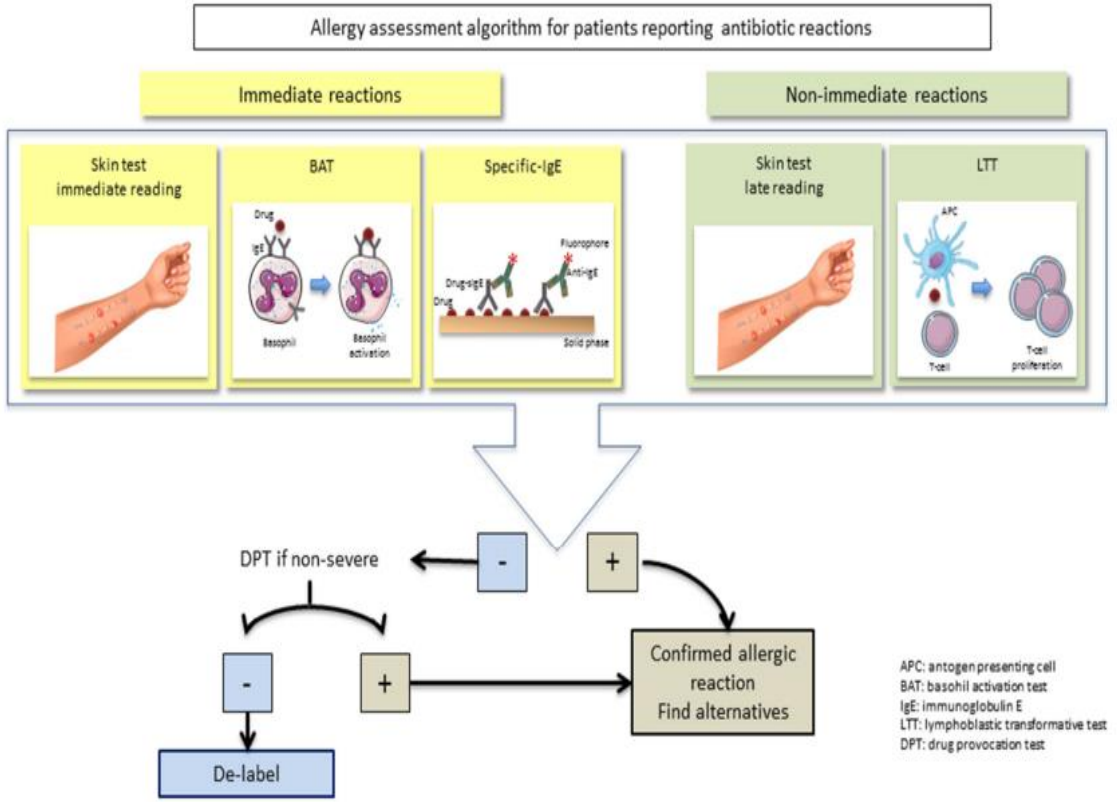
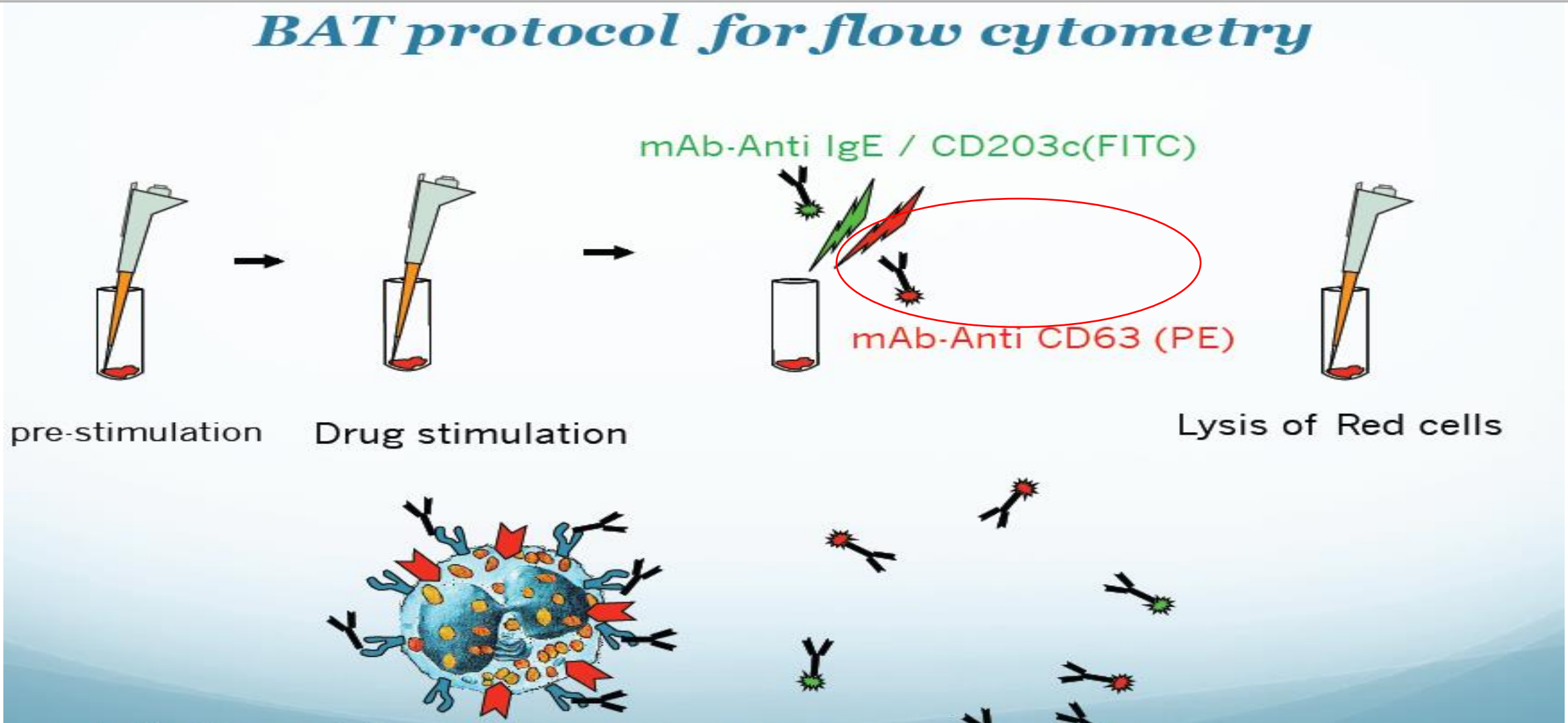




**Figure 2.** Algorithm for evaluating suspicion of allergic reactions to antibiotics.

## Diagnostic Biomarkers in IgE mediated reactions Low sensitivity but high specificity

# In- vitro Basophile Activation Tests



# Diagnostic Biomarkers in IgE mediated reactions Low sensitivity but high specificity

## 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

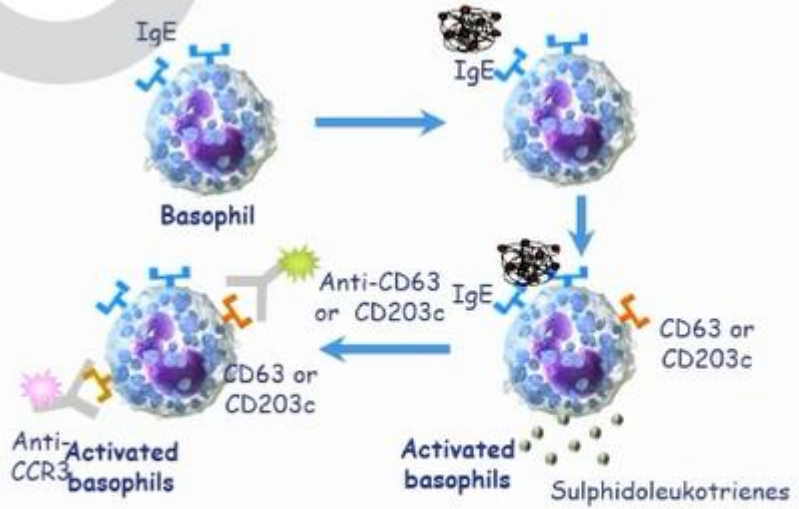
Sensitivity
40 – 60 % depending on the drug

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 tests to evaluate IgE mediated reactions




## Basophil activation test

**Sensitivity [51.7%] & NPV 50.0%]- Poor**
**Specificity [89.2%] & PPV [90.5%]- Good**

| Paper | Patients | Drugs | Diagnosis | Sens | Spec | NPV | PPV |
|---|---|---|---|---|---|---|---|
| Sanz 2002 | 58 Pat<br>30 Cont | PG, AX, AMP, CEFU, CEFAZ | ST | 50 | 93.3 | 49.1 | 93.5 |
| Torres 2004 | 70 Pat<br>40 Cont | PG, AX, AMP, CEFs | ST, DPT | 48.6 | 93 | 50.8 | 92.4 |
| Abuaf 2008 | 27 Pat<br>14 Cont | AX, AMP, CEFU | ST | 63 | 79 | 52.5 | 85.2 |
| De Weck 2009 | 178 Pat<br>81 Cont | BP, AX, AMP, CEFs | ST, DPT | 48.3 | 88.9 | 43.8 | 90.5 |
| Torres 2010 | 55 Pat<br>30 Cont | PG, AX, AX-CLV, CLV | ST | 52.7 | 90 | 50.9 | 90.6 |
| Eberlein 2010 | 24 Pat<br>15 Cont | PG, PV, AMP, AX, CEFU | ST | 55 | 80 | 52.6 | 81.5 |
| Sanchez-Morillas 2010 | 9 Pat<br>5 Cont | CLV | ST, DPT | 44.4 | 100 | 49.9 | 100 |
| | | | **MEAN VALUES** | **51.7** | **89.2** | **50.0** | **90.5** |

# Diagnostic Biomarkers in IgE mediated reactions Low sensitivity but high specificity

## ImmunoCAP

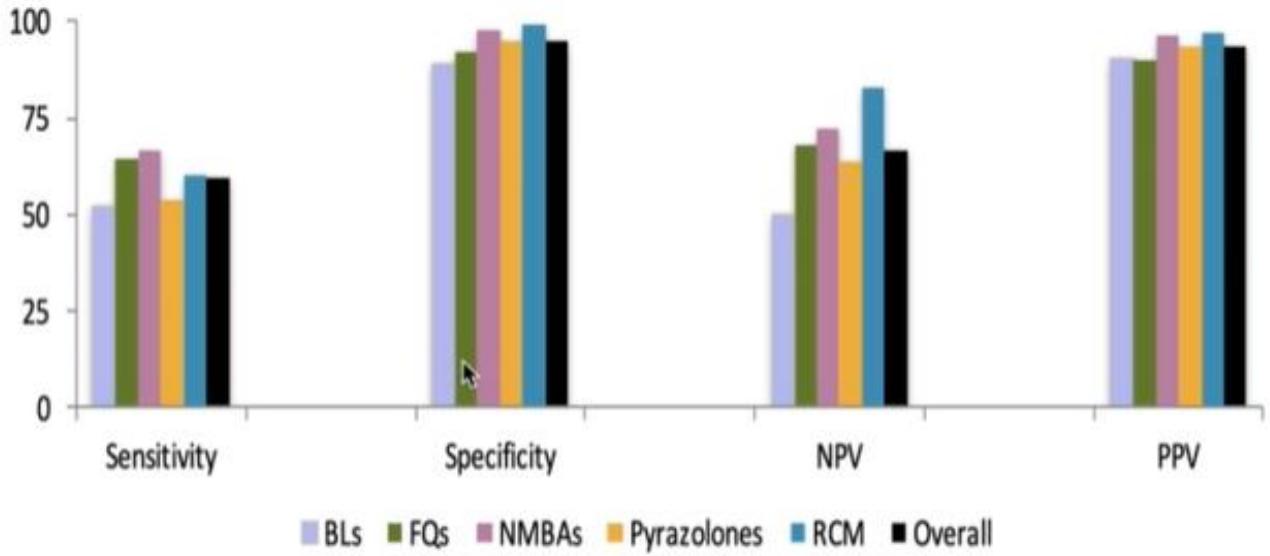
| | Blanca M Allergy 2001 | Sanz ML CEA 2002 |
|---|---|---|
| **Sensitivity** | 54% | 38% |
| **Specificity** | 95% | 87% |

- Cut off point 0.35 kUA/l or 0.1 kUA/l??
- False positive with penicillin V
- It is recommended for diagnosing BLs, NMBAs, chlorhexidine, and cetuximab DHR.

Vultaggio A, Clin Exp Allergy 2009

Johansson SGO. J Allergy Clin Immunol 2013

## Basophil Activation Test




BAT is not useful for cross-intolerant reactions to NSAIDs

Hoffmann HJ et al. Allergy 2015

Ariza A. Cytometry Part A 2014

# How to perform skin tests

Standard procedures, trained staff, and 4-6 weeks after the reaction

**Immediate reactions:** Within 1 hour

SPT is the initial screening due to its simplicity, rapidity, low cost, and high specificity

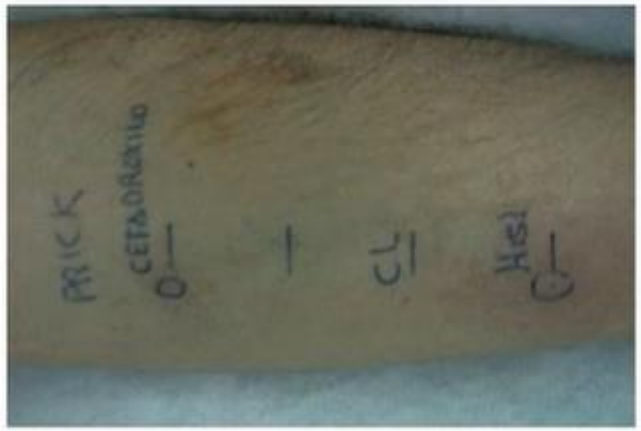
IDT are undertaken when SPT are negative, and compared to SPT, they provide an enhanced sensitivity. They should be performed with the intravenously injectable form of the drug whenever possible

**Nonimmediate reactions:** > 6 hours

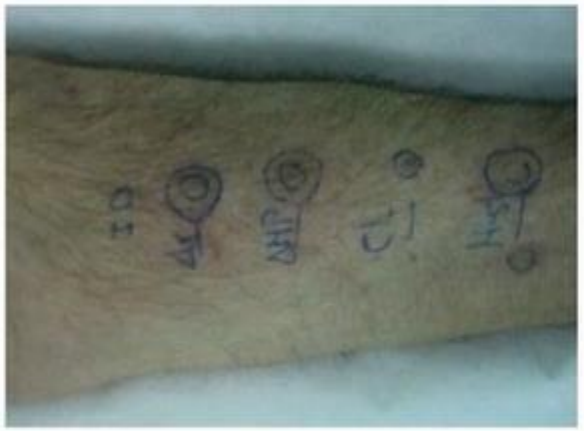
PT and/or late-reading IDT should be performed

Demoly P et al. Allergy 2014

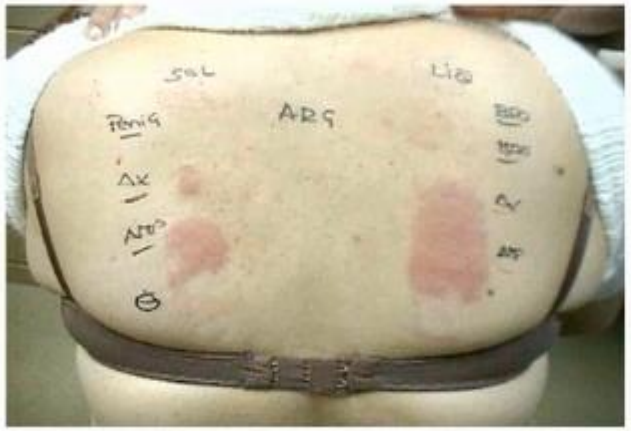
Prick test




Intradermal tets



PT/ Late reading IDST



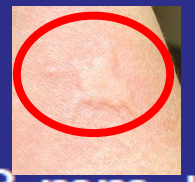
# Skin test methods

- 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 |

| | 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: Oedema + erythema |
| **Intradermal test** | |
| Amount | 0.02(-0.05) ml |
| Reading | 20 min, (D1), D2, D3 |
| Positivity criteria | after 15-20 min: initial+5mm > +3 mm |
| | in late readings: Oedema + erythema |
| **Patch test** | |
| Reading | D2, D3, (D4) |
| Positivity criteria | EECDRG criteria |

Wheal



oedema + erythema

*K Brockow et al, Allergy 2002

# Allergy work-up

- **Skin tests** (prick and intradermal):
  - BP-OL, MD, penicillin G
  - Ampicillin, amoxicillin
  - Cephalexin, cefaclor, cefazolin, cefadroxil, cefamandole, cefuroxime, ceftazidime, ceftriaxone, cefotaxime, ceftibuten, cefepime
- **Specific IgE assays:**
  Penicilloyl G, penicilloyl V, ampicilloyl, amoxicilloyl, cefaclor
- **Challenges:**
  Cefaclor, cefuroxime axetil, ceftriaxone, cefazolin, ceftibuten

# Haptens and the highest concentrations recommended for prick and intradermal tests

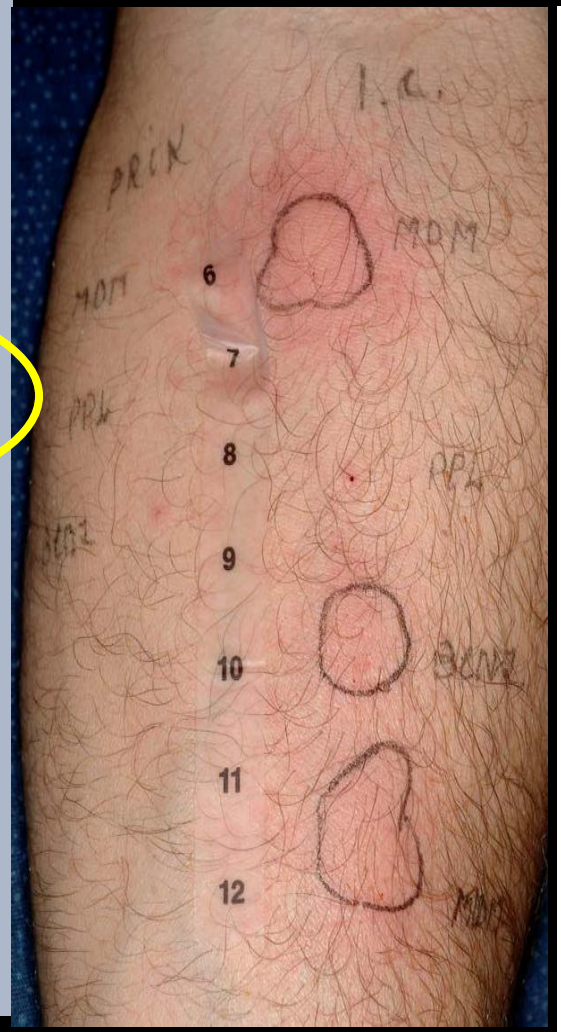
| HAPTEN | DOSE | UNIT |
|---|---|---|
| PPL | $5x10^{-5}$ | mMol/l |
| MDM | $2x10^{-2}$ | mMol/l |
| AMOXICILLIN | 20 | mg/ml |
| BENZYLPENICILLIN | 10,000 | IU/ml |
| CULPRIT DRUG | | |
| • Cephalosporin | 2 | mg/ml |
| • Amoxicillin-clavulanic | 20 | mg/ml |
| • Ampicillin | 20 | mg/ml |

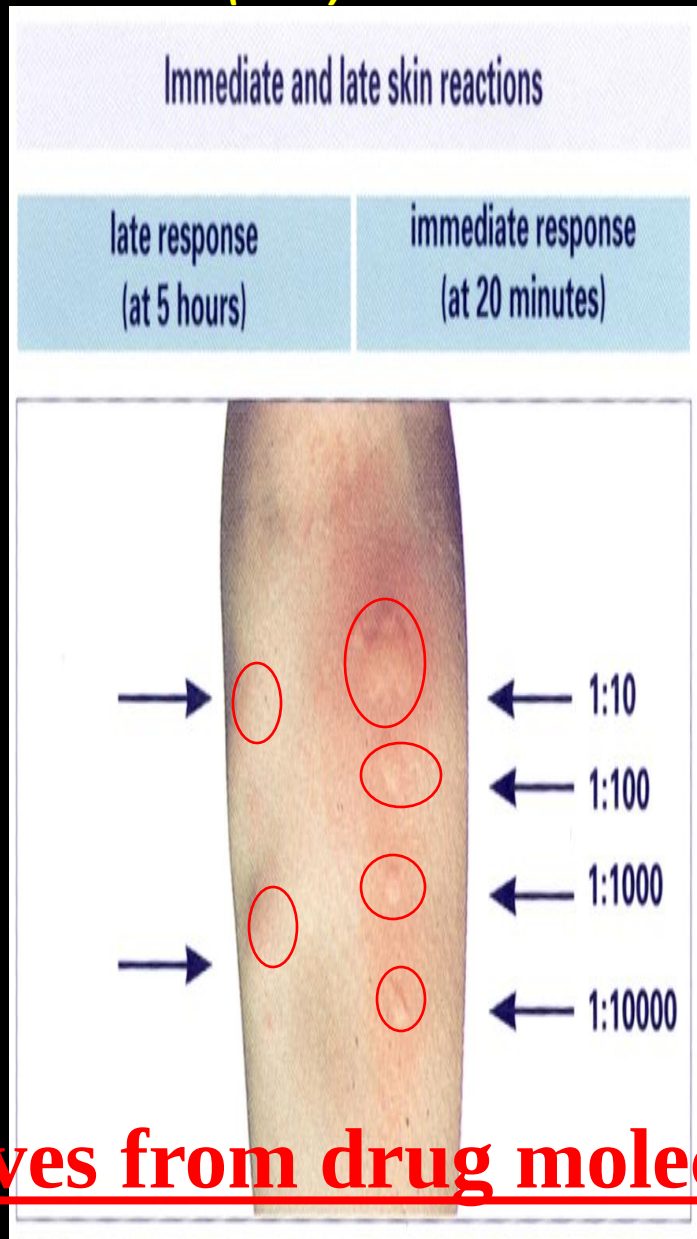
M Blanca et al, Allergy 2009

# Diagnosing IgE mediated Drug Allergy- Anaphylaxis

- ✓ 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.

*Intradermal Test (IDST)*

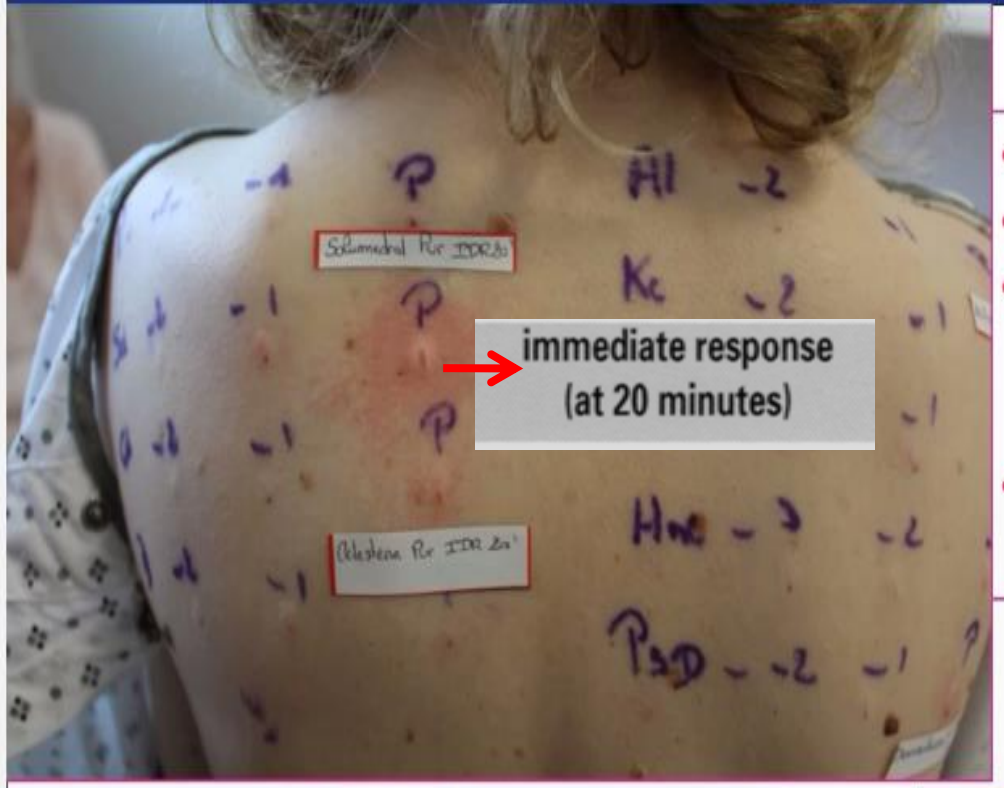


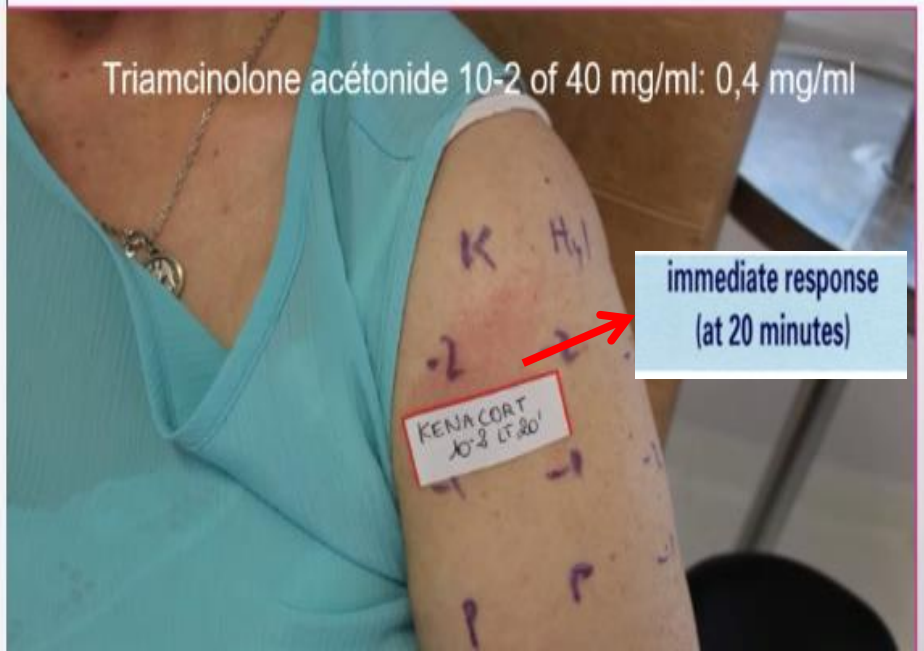



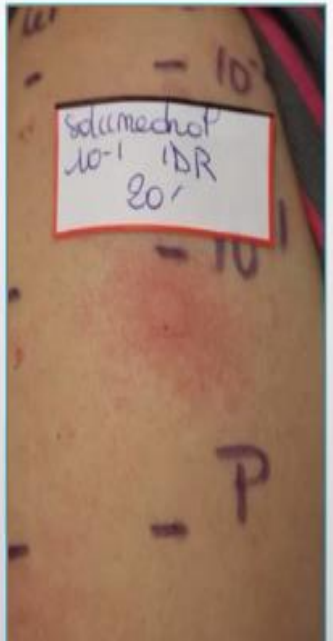

**Do Serial dilutions test to r/o preservatives from drug molecular**

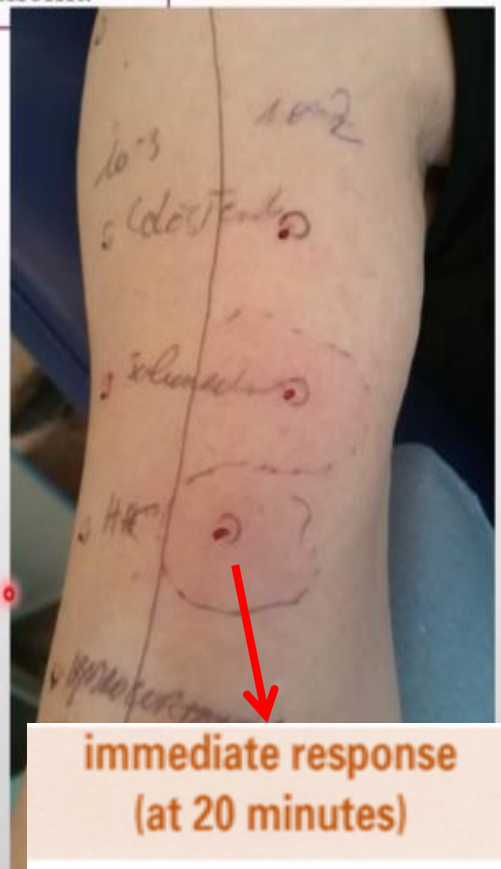
# Intradermal tests

- Use only injectable forms
- Inject 0.02 ml
- At 20 mns, results must be recorded as follows: Wi/W20E20
- Positive if W20 > Wi + 3 mms and a surrounding erythema



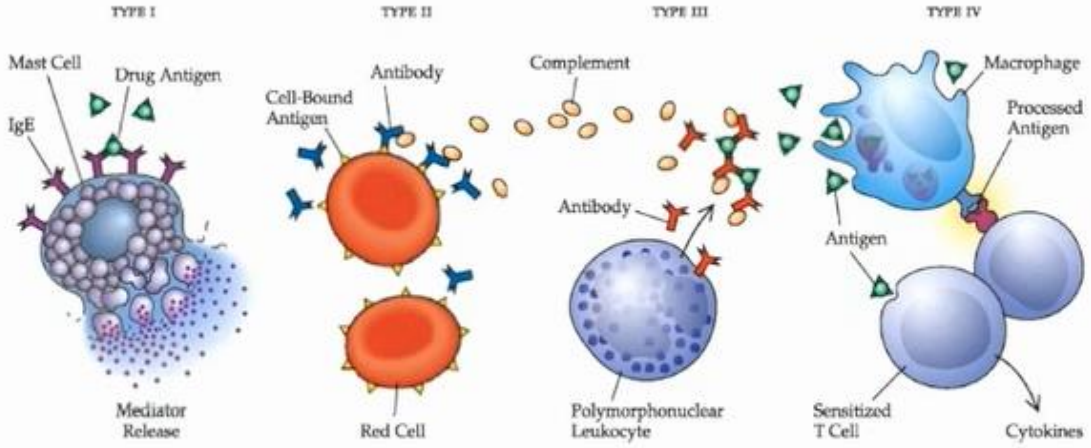



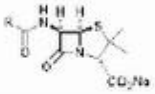


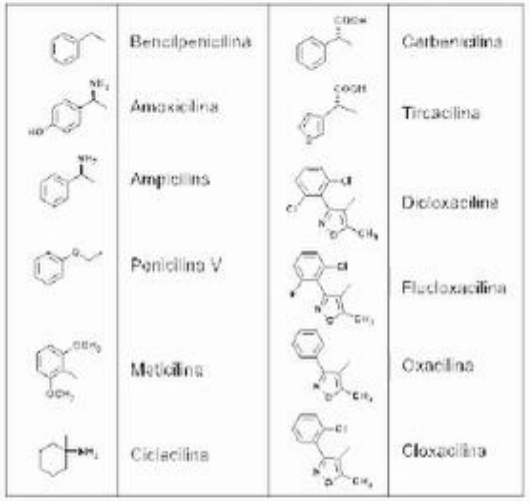
# Clinical History

1. Drug involved
2. Clinical Symptoms
3. Time period drug administration-reaction

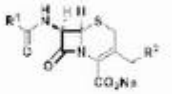


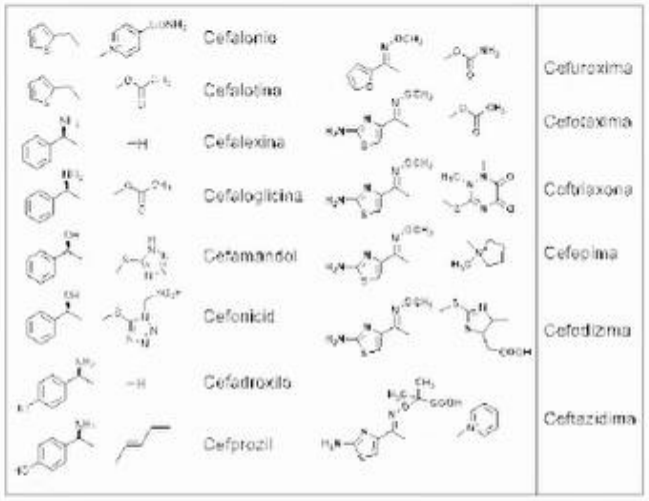

## PENICILLINS



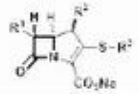


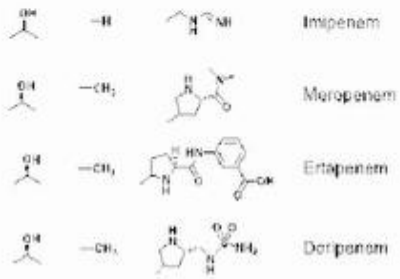

## CEPHALOSPORINS



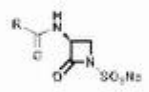


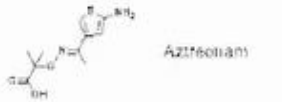

## CARBAPENEMS



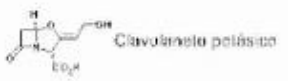



## MONOBACTAMS






## CLAVAMS



doi: 10.1111/j.1365-2222.2008.03155.x



Clinical and Experimental Allergy, 39, 43–61



# BSACI guidelines for the management of drug allergy

R. Mirakian*, P. W. Ewan*, S. [illegible]* and S. M. Nasser*
*Cambridge University, NHS Found[illegible] 'HLI, London, UK, ‡The
London Allergy Clinic, London, UK, [illegible] spital, Dermatology
Department, Level F South Block, Tr[illegible] ust, Clifton Boulevard,
Nottingham, UK and **British Soci[illegible]

Text box 1: *Indications for investigating patients with penicillin allergy*

1. Patients with a history of an allergic reaction when on multiple drugs, e.g. during GA
2. Patients allergic to multiple antibiotics
3. Patients with an absolute requirement for penicillin, e.g. those with central nervous system syphilis, immunodeficiency, post-splenectomy, or with cardiac valve disorders requiring prophylaxis.

Clinical an
Experiment
Allerg

*Correspondence:*
Dr S. M. Nasser, Cambridge University, NHS Foundation Trust, Allergy Clinic, Cambridge CB2 0QQ, UK. E-mail: shuaib.nasser@addenbrookes.nhs.uk
*Cite this as:* R. Mirakian, P. W. Ewan, S. R. Durham, L. J. F. Youlten, P. Dugué, P. S. Friedmann, J. S. English, P. A. J. Huber and S. M. Nasser, *Clinical and Experimental Allergy*, 2009 (39) 43–61.

OCC) of the British allergists and t available for the of allergic drug iagnosis of drug gement of drug nd adequate s are evidence-based but where evidence was lacking consensus was reached by the panel of specialists on the committee. The document encompasses epidemiology, risk factors, clinical patterns of drug allergy, diagnosis and treatment procedures. In order to achieve a correct diagnosis we have placed particular emphasis on obtaining an accurate clinical history and on the physical examination, as these are critical to the choice of skin tests and subsequent drug provocation. After the diagnosis of drug allergy has been established, communication of results and patient education are vital components of overall patient management.

**Keywords** aspirin, BSACI, classification of drug allergy, drug allergy, drug allergy investigations, drug challenge, drug desensitization, drug intradermal tests, drug patch tests, drug provocation, drug skin prick, general anaesthetic, guidelines, local anaesthetic, muscle relaxants, NSAID, penicillin, specific IgE drug testing, Standards of Care Committee, tryptase

# Penicillin Hypersensitivity Pathway

## Type II-IV HSR

Serum sickness

Stevens-Johnson Syndrome

Toxic Epidermal Necrolysis

Acute Interstitial Nephritis (AIN)

Drug Rash Eosinophilia Systemic Symptoms (DRESS) Syndrome

Systmic Cutaneous Adverse reactions

Drug Fever

↓

**Avoid using PCN, cephalosporin, or carbapenem**

Use alternative agents by microbial coverage*

Alternative Drugs

***If clinical indication for a beta-lactam, please involve the Infectious Disease service and Allergy/Immunology, if available.***

## Type I (IgE-mediated) HSR

Anaphylaxis

Anaphylaxis

Angioedema

Wheezing

Laryngeal edema

Hypotension

Hives/urticaria

**OR**

**Unknown reaction WITHOUT mucosal involvement, skin desquamation or organ involvement**

↓

**OK to:**

Use 3rd/4th/5th generation cephalosporins or carbapenems* by Test Dose Procedure

OR

Use alternative agent by microbial coverage‡

Pennicillin Skin Testing

Aztreonam*

OR

***If a PCN or a 1st/2nd generation cephalosporin is preferred, PCN skin testing is indicated. Call/consult Allergy/Immunology, if available. If not available, desensitization may be considered.***

## Mild reaction

Minor rash (not hives)

Maculopapular rash (mild Type IV HSR)

Record lists allergy, but patient denies

Maculo Papular Eruption

↓

**OK to:**

Use full dose 3rd/4th/5th generation cephalosporin

OR

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

OR

Use carbapenem*

Oral Provocation Test

# Cephalosporin Hypersensitivity Pathway

**Type II-IV HSR**

Serum sickness

Stevens-Johnson Syndrome

Toxic Epidermal Necrolysis

Acute interstitial nephritis (AIN)

Drug Rash Eosinophilia Systemic Symptoms (DRESS) syndrome

Systmic Cutaneous Adverse reactions

Drug Fever

**Type I (IgE-mediated) HSR**

Anaphylaxis

Angioedema

Wheezing

Laryngeal edema

Hypotension

Hives/urticaria

OR

Unknown reaction WITHOUT mucosal involvement, skin desquamation, or organ involvement

Anaphylaxis

**Mild reaction**

Minor rash (not hives)

Maculopapular rash (mild Type IV HSR)

Record lists allergy, but patient denies

Maculo Papular Eruption

**Reaction to:**

1st/2nd Generation

3rd/4th Generation

**Avoid using PCN and cephalosporins**

Use alternative agents by microbial coverage§

Alternative Drugs

*If clinical indication for a PCN or cephalosporin, please involve the Infectious Disease service and Allergy/Immunology, if available*

**OK to:**

Administer 3rd/4th/5th generation cephalosporin if dissimilar side chains by Test Dose Procedure

OR

Use alternative agents by microbial coverage§

OR

Penicillin Skin Testing

*If a PCN or 1st/2nd generation cephalosporin is preferred, penicillin skin testing is indicated. Call/consult Allergy/Immunology, if available. If not available, desensitization may be considered.*

**OK to:**

Administer PCN or cephalosporin if dissimilar side chains by Test Dose Procedure

OR

Use alternative agents by microbial coverage§

Cephalosporin Skin Test

**OK to:**

Use a cephalosporin with dissimilar side chains

OR

Administer PCN, the same cephalosporin, or cephalosporin with similar side chains by Test Dose Procedure

Oral Provocation Test

OR

Use alternative agents by microbial coverage§

# Correction to: Guideline for the diagnosis of drug hypersensitivity reactions

ENDA

DAP® AMOXICILLIN

DAP® CLAVULANIC

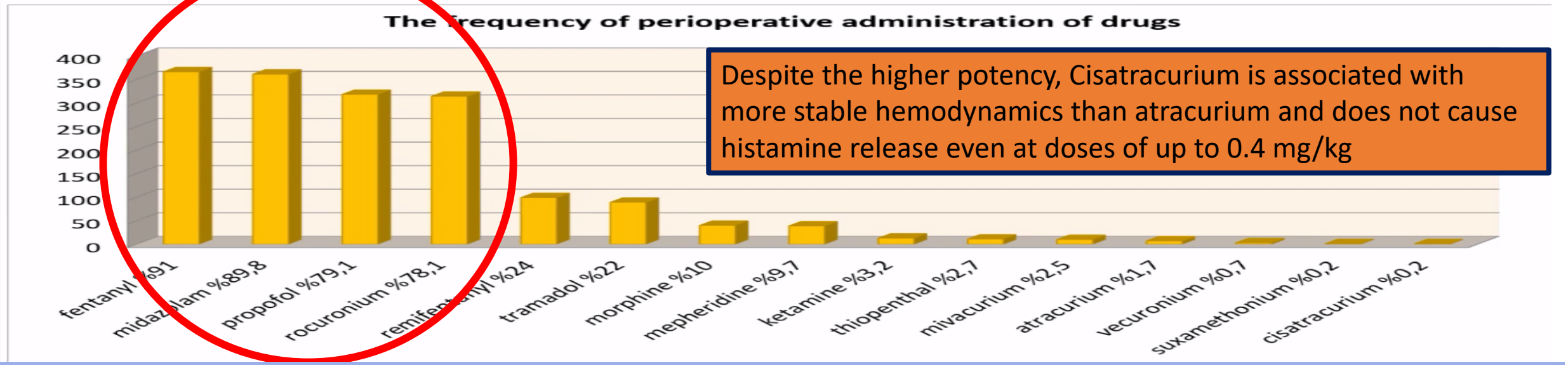
- The **only** kit marketed with the major (BP-OL) and minor (MD) antigenic determinants of penicillin.
- **100%** specificity.
- The **ENDA group** recommends the use of DAP-Penicillin for the diagnosis of immediate hypersensitivity.
- The ENDA group believes that **DAP-Penicillin and DAP-Amoxicillin** should always form part of the betalactam **hypersensitivity diagnosis.**

# NMBA's- classification

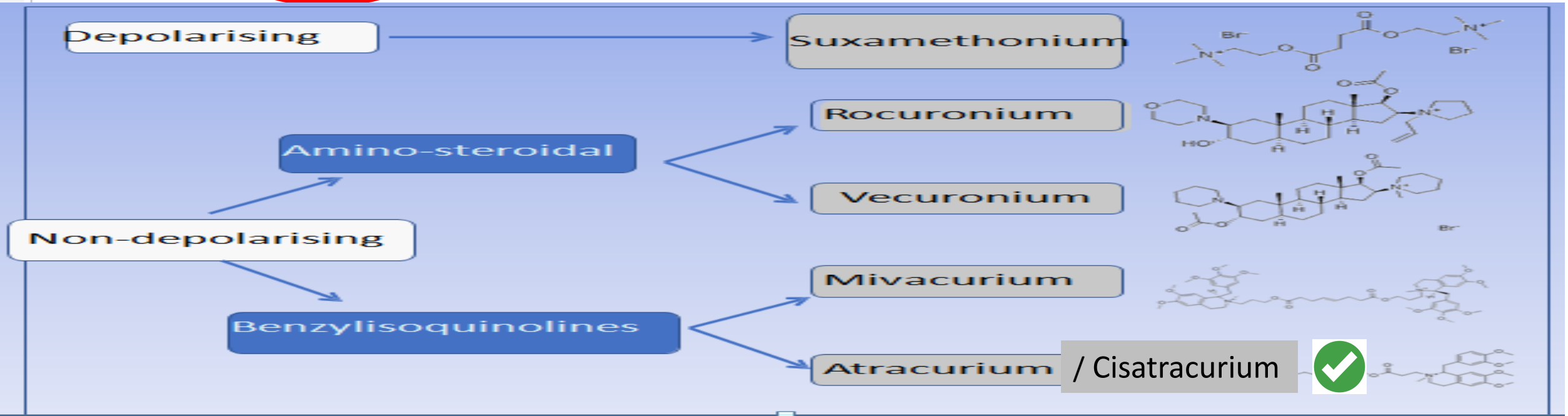
Original Article

**Cisatracurium versus Atracurium for Abdominal Surgeries Regarding Condition of Intubation and Hemodynamic Effect: A Randomized Double-Blind Study**

Rahul Ranjan, Mohammad Faseehullah Alam, Raja Avinash
Department of Anaesthesiology and Critical Care Medicine, Indira Gandhi Institute of Medical Sciences, Patna, Bihar India




Despite the higher potency, Cisatracurium is associated with more stable hemodynamics than atracurium and does not cause histamine release even at doses of up to 0.4 mg/kg



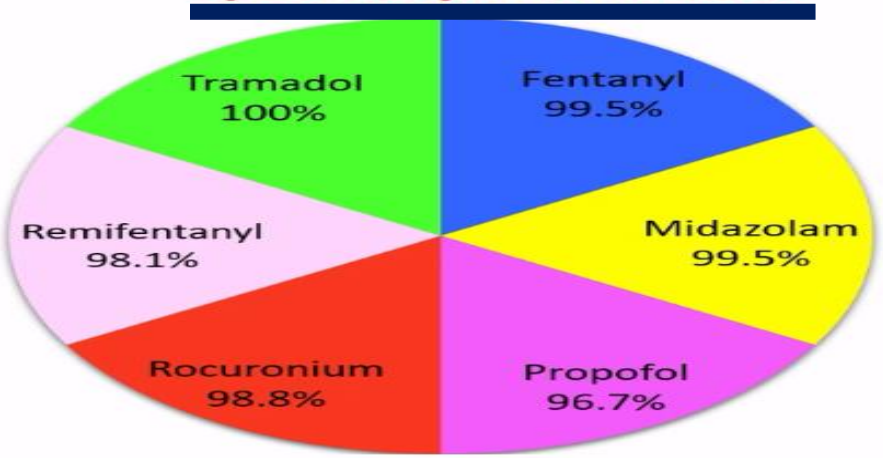
# The negative predictive values (NPV) of skin tests for anesthetics

**Patients with drug allergies**

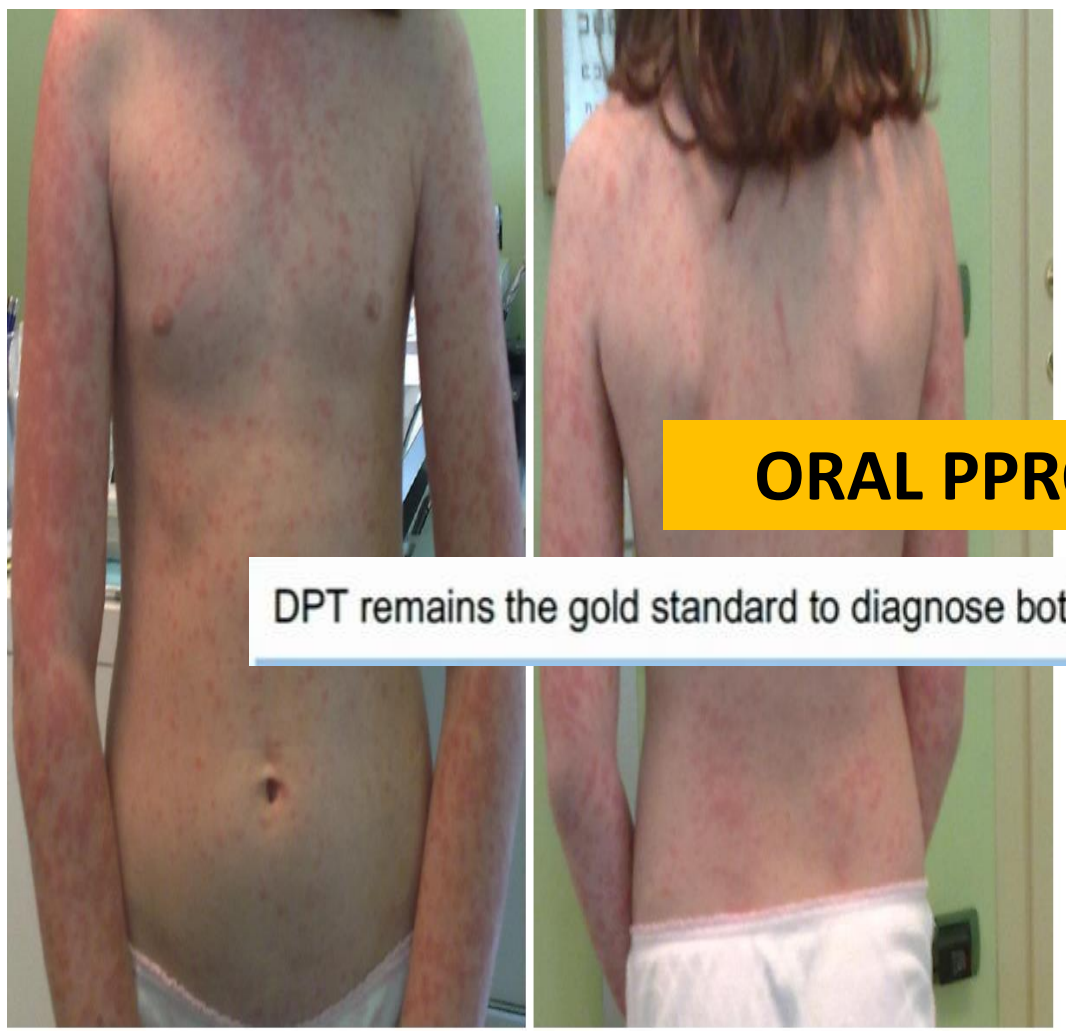

**Atopic patients**


## The specificity of skin tests for anesthetics in patients who received general anesthesia previously

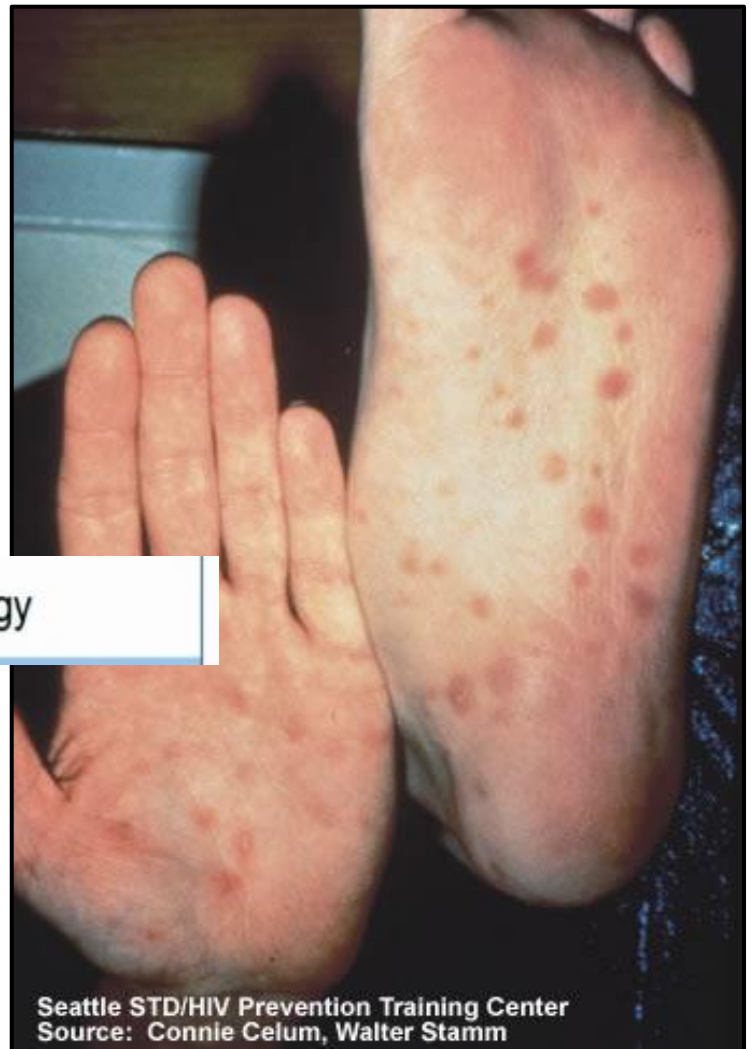
**Specificity of skin tests**



# Maculo Papular Eruption





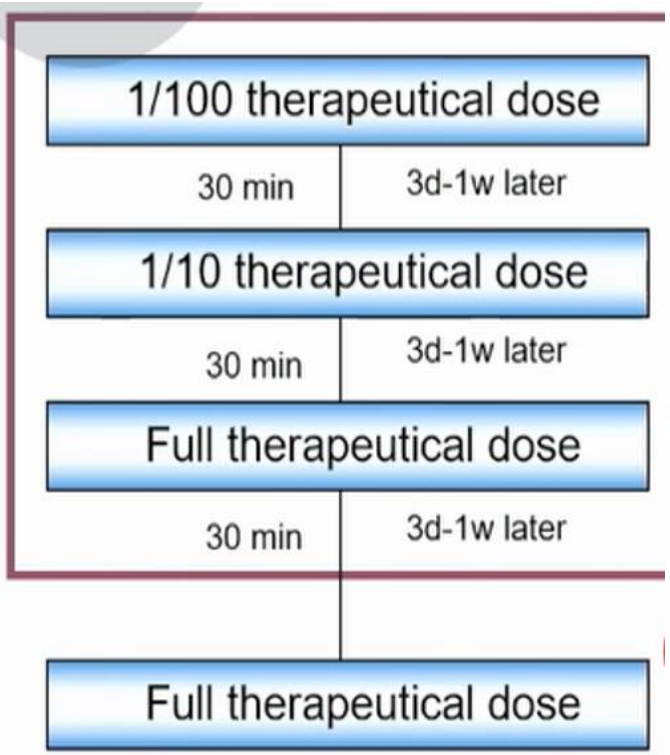

**ORAL PPROVOCATION TEST**

DPT remains the gold standard to diagnose both immediate and non-immediate BL allergy

# Test Dose Protocol successfully applied to patient

- Administer medication and monitor
  - standardized, 2-step

| | Step 1<br>Test Dose | Monitor<br>30 minutes | Step 2<br>Target Dose | Monitor<br>60 minutes* |
|---|---|---|---|---|
| Oral tablet<br>Cefpodoxime<br>Penicillin | 25% | | Full dose (100%) | |
| Oral Suspension<br>Amoxicillin<br>Cefixime<br>Cephalexin | 10% | | 90% | |
| Intravenous | 10% | | Full dose (100%)** | |




* After completion of Target Dose
** Follow Policy administration vs Standard Administration Rate

# Doses recommended for drug provocation tests in subjects with immediate reactions

| Low-risk subjects | High-risk subjects |
| --- | --- |
| 10% → 40% → 50% of the maximum single unit dose<br><br>Interval between doses: 30-60 minutes (depending on that of the index reaction) | 1% → 10% → 40% → 49% of the maximum single unit dose<br><br>*[or 1% → 5% → 15% → 30% → 49% of the maximum single unit dose]*<br><br>Interval between doses: 30-60 minutes (depending on that of the index reaction) |

# ORAL PROVOCATION TEST-Quinolones

## OFX & LFX – Cross reactivity

Poor CR
CFX/ MFX/
GFX

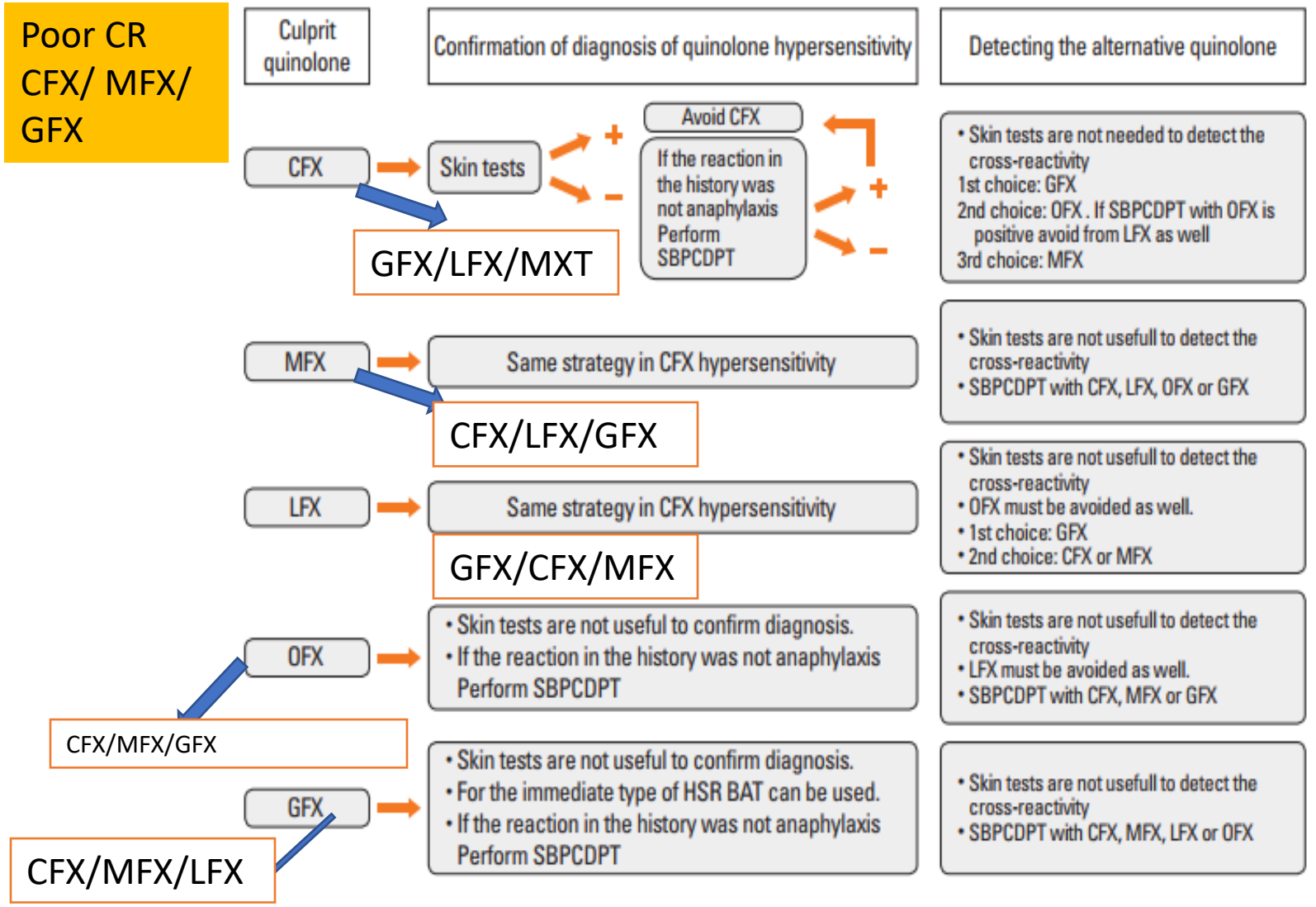



Fig. 4. Suggestions which were extrapolated from the study for choosing alternative quinolone in a quinolone hypersensitive patient. CFX, ciprofloxacin; MFX, moxifloxacin; LFX, levofloxacin; OFX, ofloxacin; GFX, gemifloxacin; BAT, basophil activation test; SBPCDPT, single blind placebo controlled drug provocation test.

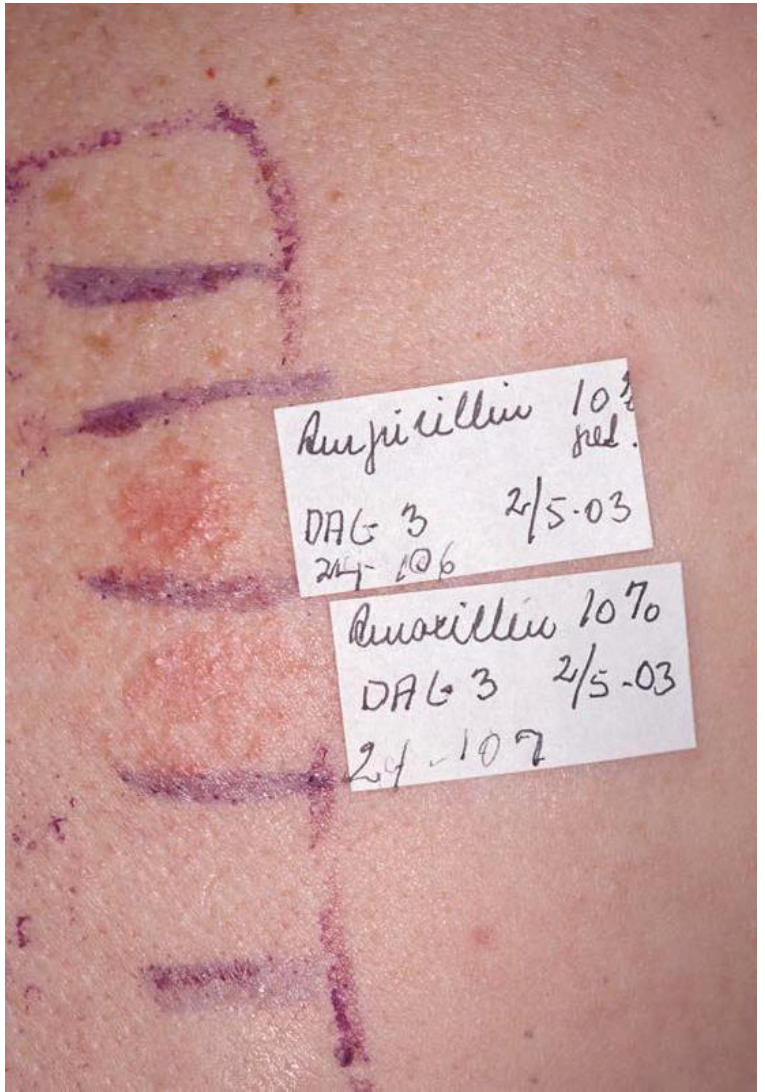
# Diagnosing T-cell mediated Drug Allergy

## Delayed readings for IDT

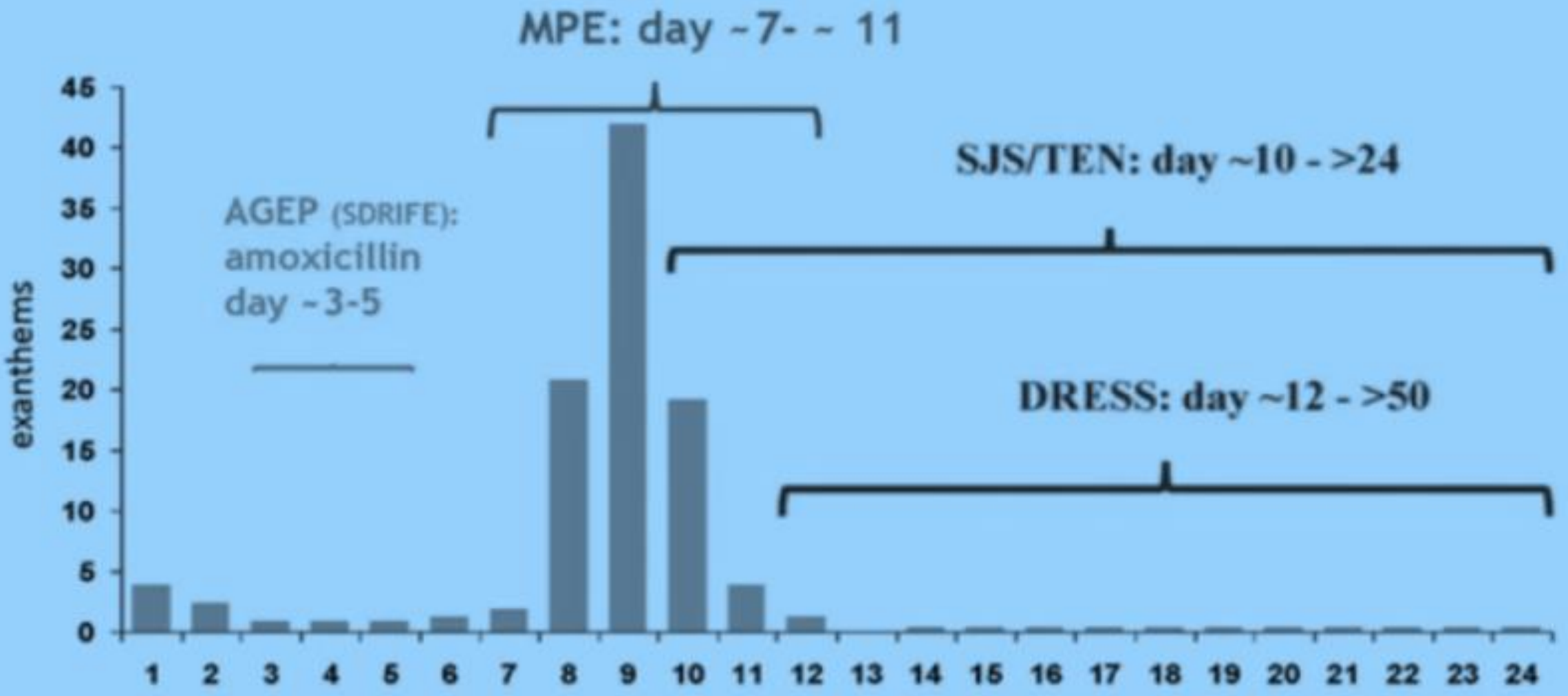
- Readings have to be done at 24h or 48h
- Or later:
- Are considered positive when there is an erythematous induration at the skin test site

✓ ***Controversial in systemic drug reactions.***

## Patch Test



# Time of appearance of delayed skin reactions

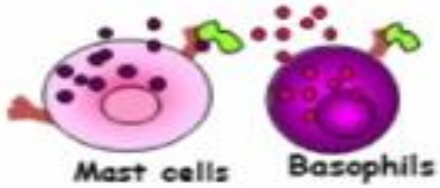



Demoly and Castells World Allergy Organization Journal (2018)

# CLINICAL ENTITIES AND INVOLVED MECHANISMS

**IMMEDIATE REACTIONS**

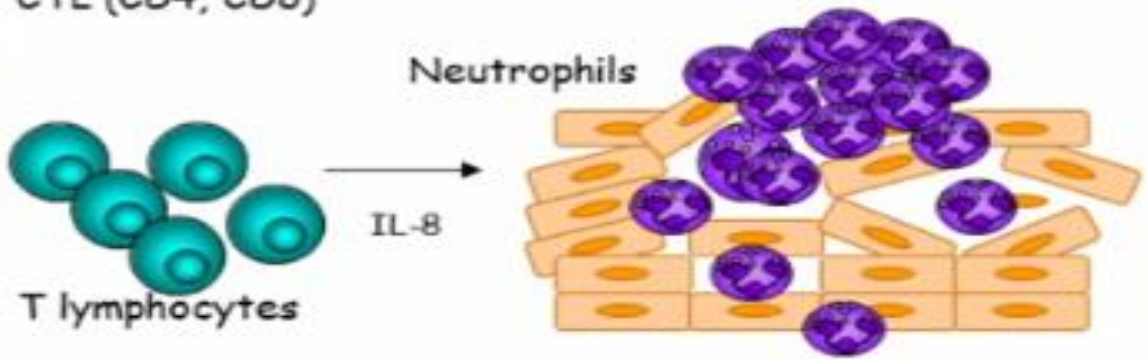
Urticaria/angioedema
Anaphylaxis



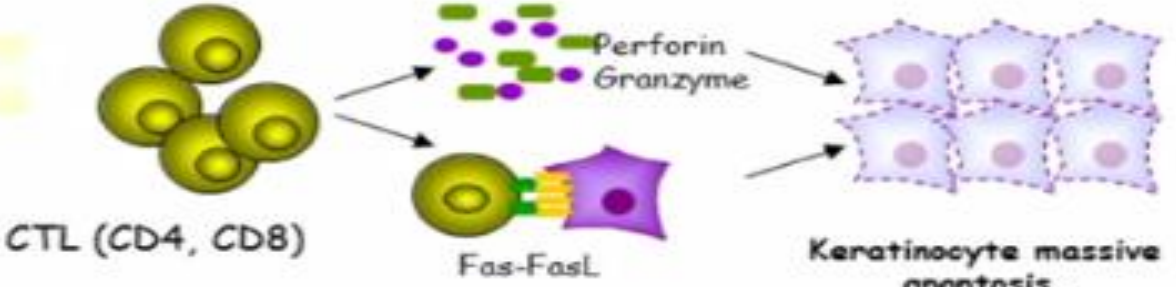

**NON IMMEDIATE REACTIONS**

Multiforme erythema
Exanthema
Urticaria
Fixed drug eruption
DRESS/DHIS

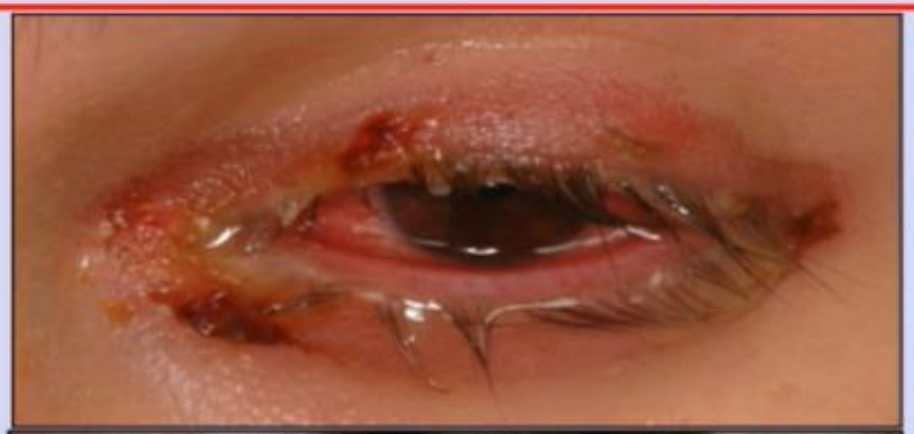

Acute generalized exanthematous pustulosis

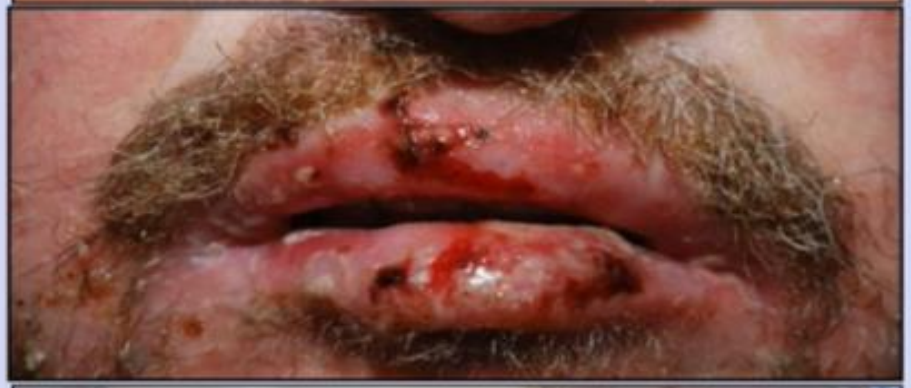


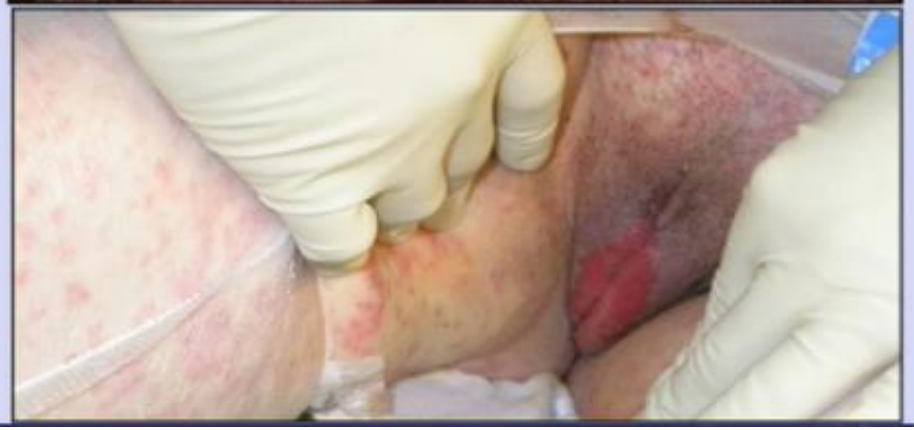

SJS/TEN



# Stevens-Johnson syndrome (SJS) / Toxic epidermal necrolysis (TEN)







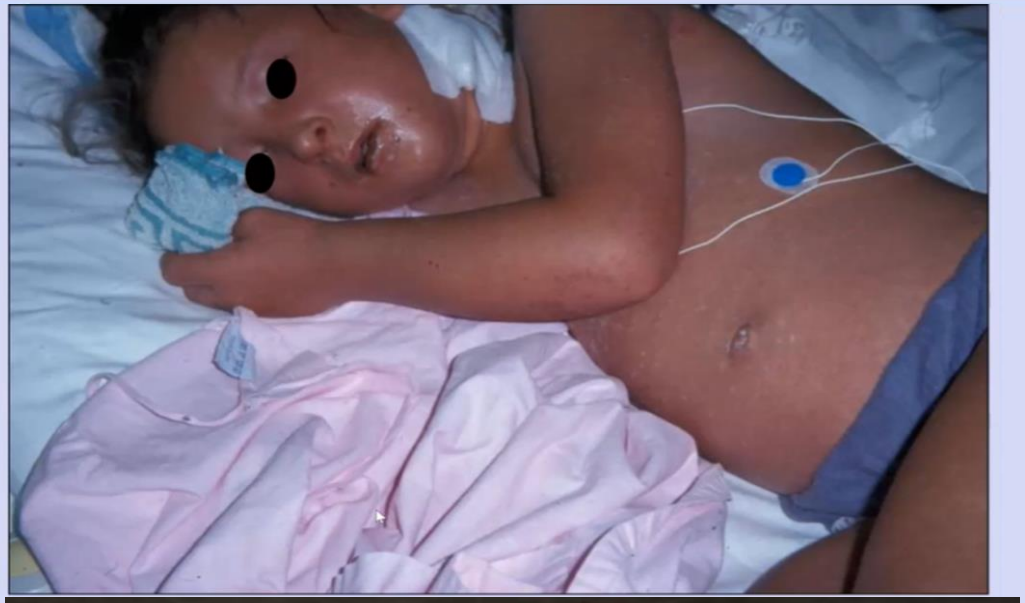
- in the early phase confluent macules and flat atypical targets
- dark colour with necrosis and detachment of the epidermis
- hemorrhagic erosions of mucous membranes

# DRESS

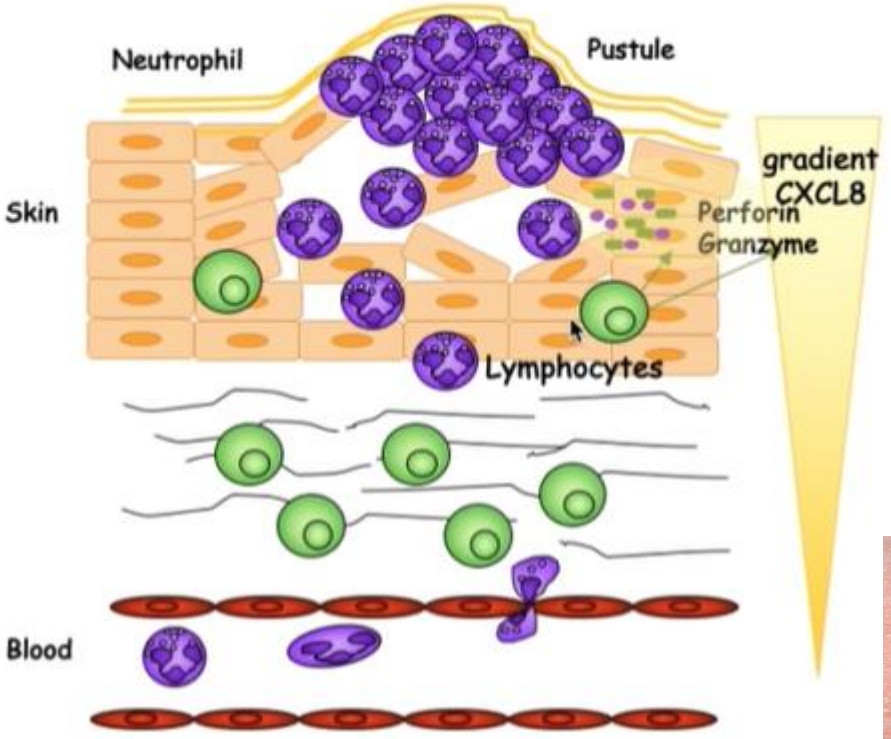
**Eosinophils**

- Multisystem disease
- Drug-induced
- Fever
- „Rash“
- Eosinophilia & atypical lymphocytes
- Lymphadenopathy
- Involvement of liver and other organs

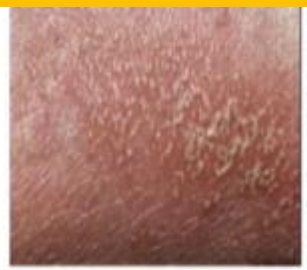
→ Other explanation for symptoms excluded!



# Severe cutaneous adverse drug reactions: AGEP

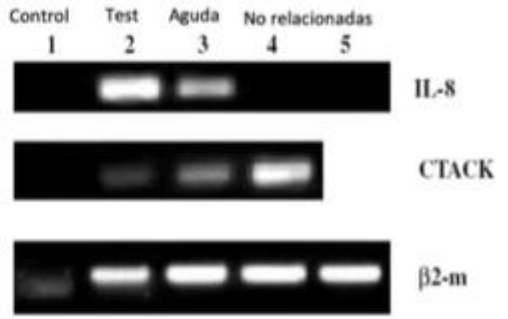



**Neutrophils**

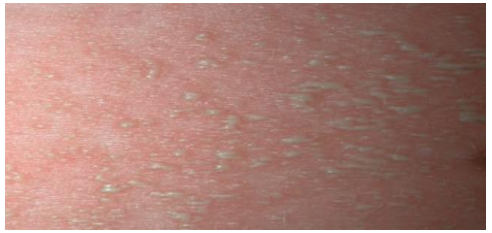


Roujeau JC. Toxicology 2005

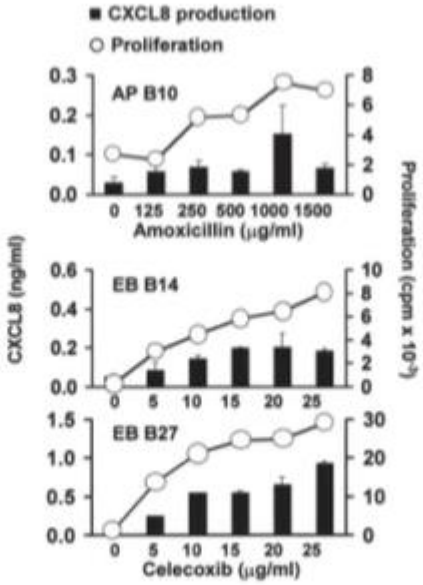
## Skin biopsies




Padial MA. Br J Dermatol 2004



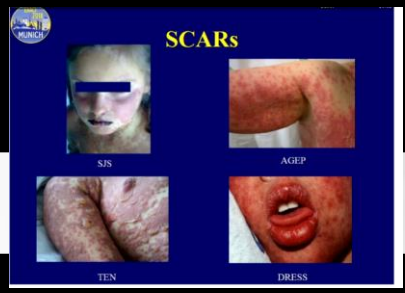
## T cell clones



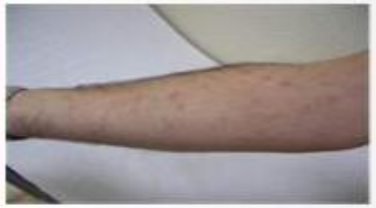

Schaerli P. J Immunol 2004

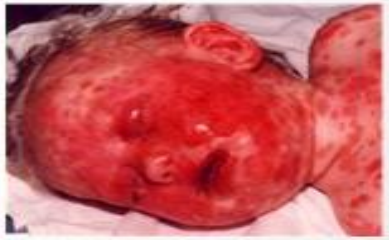
- Drug-specific T cells infiltrate the epithelium, induce blistering through **perforin/granzyme B and Fas ligand to induce apoptosis.**
- Also express **IL-8 attracting neutrophil** which form pustules. A leucocytosis, typically a neutrophilia may be present.

# Individual T cell response and immune mediators



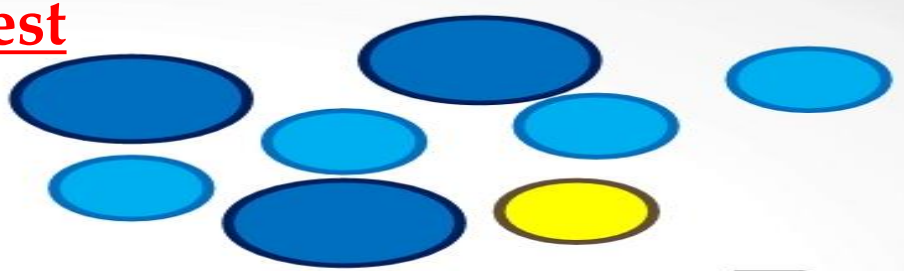

| Category of Type IV reaction | | Immune mediator | Clinical features Cell type |
|---|---|---|---|
| Type IVa | TH1 cells: IFN-γ and TNF-α | T cells, macrophages | Contact dermatitis Tuberculin reaction |
| Type IVb | TH2 cells: IL-4, IL-5, IL-13 | Eosinophils | Maculopapular rash |
| Type IVc | Cytotoxic 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) |

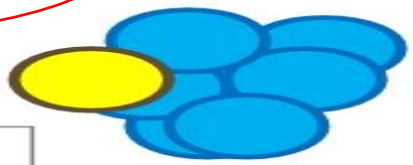


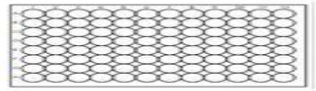


# Lymphocyte Transformation Test

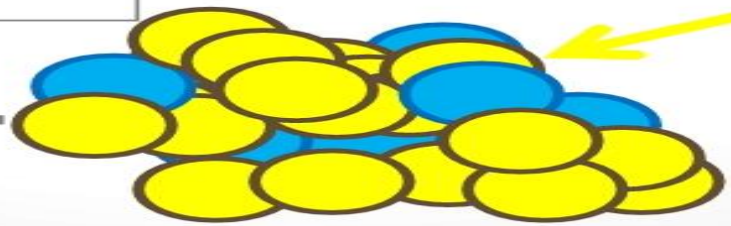
Activation of T-Cell conjugated with Drugs



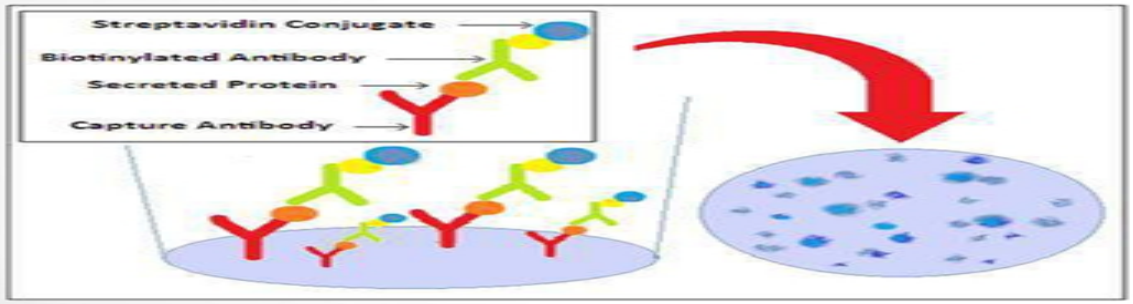




Radioactive THY



## 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.

**Non-allergic** (Pharmacological / Pseudo-allergic)

# NSAIDs Hypersensitivity

## Acute

## Delayed

Respiratory

Cuteneous / Anaphylaxis

Various organs

**NERD**

Non Cox-1 allergic Inhibition

**NECD**

Cox-1 inhibition

**NIUA**

Unknown probability COX-1 inhibition

**SNIUAA**

Allergic IgE mediated

**SNIDHR**

T cell mediated

**Non-immunologically Mediated(cross-reactive) Hypersensitivity reaction**

Immunologically mediated (selective) hypersensitivity reaction)

# Non-allergic (Pharmacological / Pseudo-allergic)

NERD

Asthma/ sinusitis / Nasal polyp

NECD/ NIUA

Urticaria

Anaphylaxis/ Urticaria Angioedema-IgE

Cutaneous reaction DHR- T cell

SNIUAA/SNIDHR

# ASA challenge as a first approach is safe and useful to establish the diagnosis of NSAIDs HS


NSAID

## A.Cross- reactors

## B. Selective-reactors

Blanca-Lopez N, et al. J Allergy Clin Immunol Pract. 2018.

Sanchez-Borges M, et al. J Allergy Clin Immunol Pract. 2018.

# NSAIDs hypersensitivity in children

- Prevalence 0.6–5.7% in the general population
- 1° or 2° cause of HRs in children according to different studies

**Selective-reactors**

SR= selective reactor

Alternative group of NSAIDS

Immunological mechanism to a single or single subclass of NSAID

- selective NSAID-induced urticaria, angioedema, and anaphylaxis (SNIUAA).
- selective NSAID-induced delayed-type reactions (SNIDR)

**Cross- reactors**

NO NSAIDS

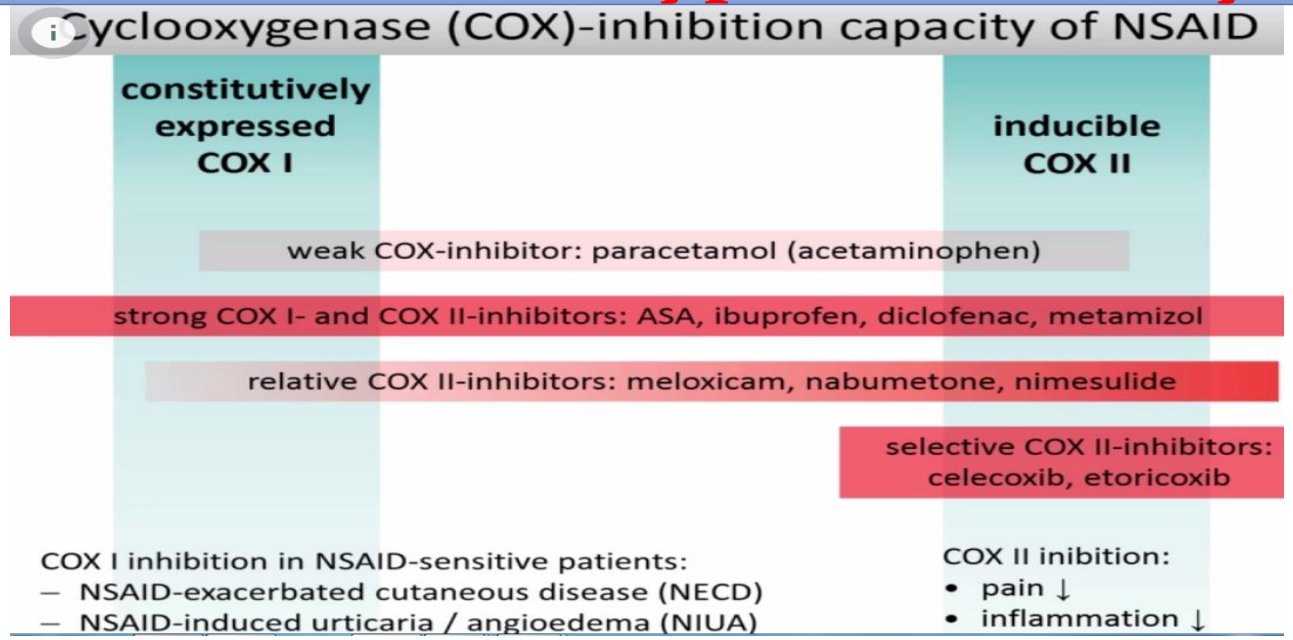
CI= Cross-Intolerant

Related to the COX-1 inhibition and decrease in prostaglandin-E2 [PGE2] synthesis

- NSAIDs-induced urticaria and angioedema (NIUA)
- NSAIDs-exacerbated respiratory disease (NERD)
- NSAIDs-exacerbated cutaneous disease (NECD)

Kowalski ML, et al. Allergy. 2013;68:1219–1232.

# NSAIDs Hypersensitivity




| **Salicylates** | **Propionic acids** | **Enolic acids** |
|---|---|---|
| Aspirin | Ibuprofen | Meloxicam |
| Salsalate | Naproxen | Piroxicam |
| Diflunisal | Ketoprofen | |
| | Fenoprofen | **Fenamic acids** |
| **Acetic acids** | | Mefenamic acid |
| Diclofenac | **Nonacidic/ carboxylic acid** | |
| Etodolac | Nabumetone | **Coxibs** |
| Indomethacin | | Celecoxib |
| Ketorolac | | Etoricoxib |

# Management of NSAIDs cross – reactive hypersensitivity

## NSAIDs avoidance and alternative drugs

Avoidance of NSAIDs with strong COX-1 inhibitory activity is recommended

**NSAIDs tolerance in patients with cross-reactive type of hypersensitivity.**

AVOIDANCE

**Group A: NSAIDs cross-reacting in majority of hypersensitive patients (60–100%)**

- Diclofenac, Ibuprofen, Ketoprofen, Nabumetone, Flurbiprofen, Indomethacin, Ketorolac, Naproxen

TOLERANCE

**Group B: NSAIDs cross-reacting in minority of hypersensitive patients (2–10%)**

- Rhinitis/asthma type
  - acetaminophen (< 1000 mg), meloxicam, nimesulide
- Urticaria/angioedema type
  - Acetaminophen, meloxicam, nimesulide, celecoxib, rofecoxib)

SAFE

**Group C: NSAIDs well tolerated by all hypersensitive patients***

- Rhinitis/asthma type
  - celecoxib, parvocoxib, trisalicylate, salsalate
- Urticaria/angioedema type
  - etoricoxib, pavocoxib

*Single cases of hypersensitivity have been reported

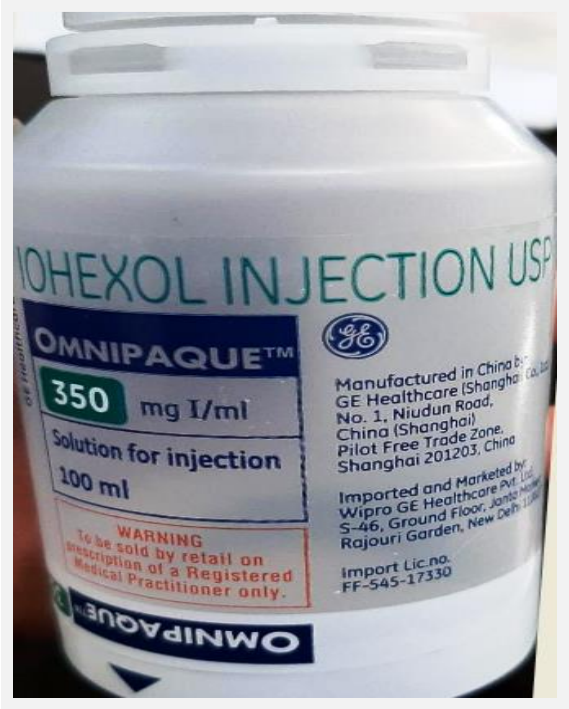
# Radiocontrast media (RCM)

1. **RCM are associated with both allergic and pseudo-allergic reactions.**
2. The incidence of reactions to RCM, including severe, life-threatening reactions,appears to be **lower with *non-ionic* versus *ionic (high osmolar)* agents.**
3. Pseudo-allergic reactions to RCM can usually **be preventedthrough the use of pre-treatment regimens** e.g. corticosteroidsand H1-antihistamines

# RADIOLOGICAL IV CONTRAST MEDIA

IODIXANAL INJECTION (VISIPAQUE 270 mgI/ml)


IOHEXOL INJECTION (OMNIPAQUE 350 mg I/ml)



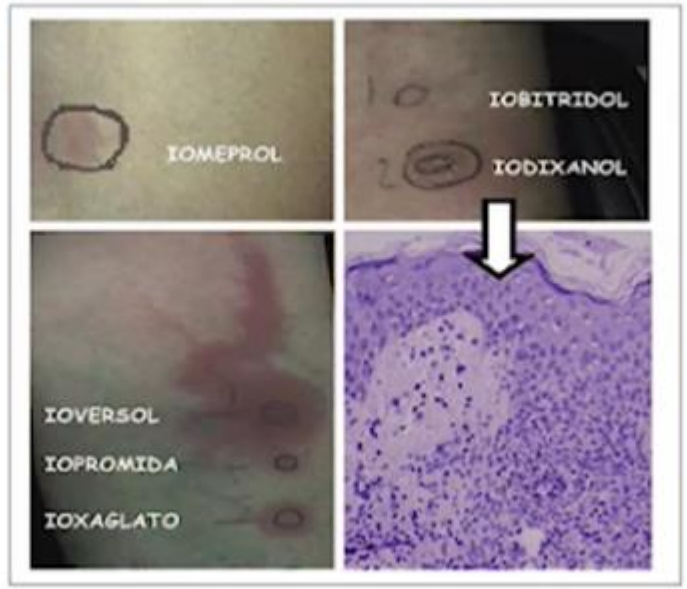

GADODIAMIDE INJECTION (OMNISCAN 0.5 mmol/ml)

# RCM skin test sensitivity -Low sensitivity but Good Specificity

| Skin test + | DPT + | Reference |
|---|---|---|
| 50% (I)<br>47% (NI) | nd<br>nd | Brockow K et al, Allergy 2009 |
| 60% (I) | 40% | Salas M. Allergy 2013 |
| 43,6% (NI) | 56,4% | Torres MJ. Allergy 2012 |

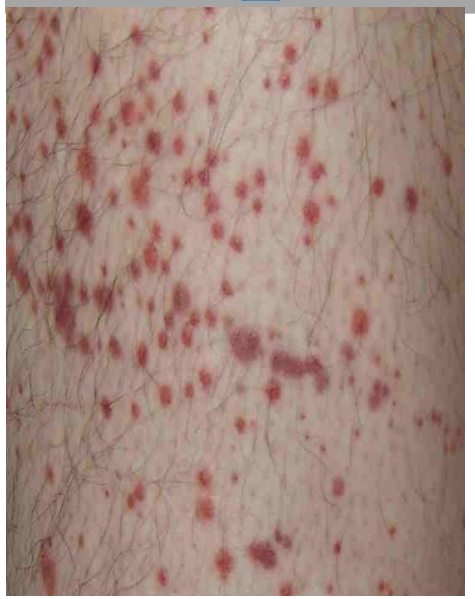
## Skin Test (Grade of recommendation C)

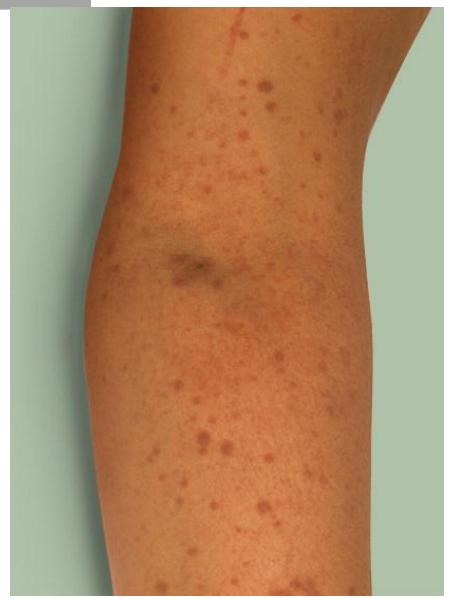
| | Immediate | Non-Immediate |
|---|---|---|
| Prick | 1/1 | -------- |
| Intradermo | 1/10 | 1/1 |
| Patch | -------- | 1/1 |
| Sensitivity | 4,2-7,3% | 21-47% |
| Specificity | 96,3% | 95% |
| NPV | 60-96,6% | 65% |



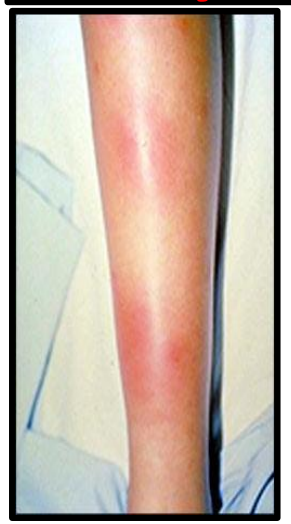
Gell & Coomb- TYPE II & TYPE III REACTION

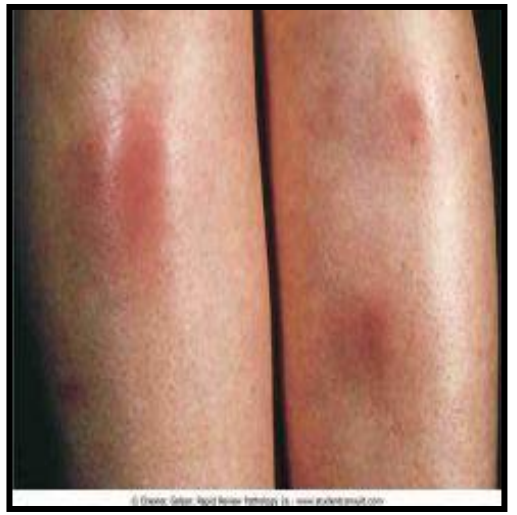
# Purpura

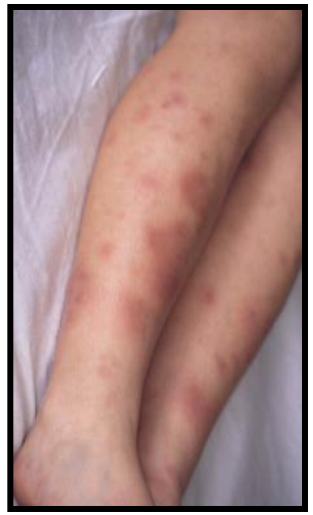




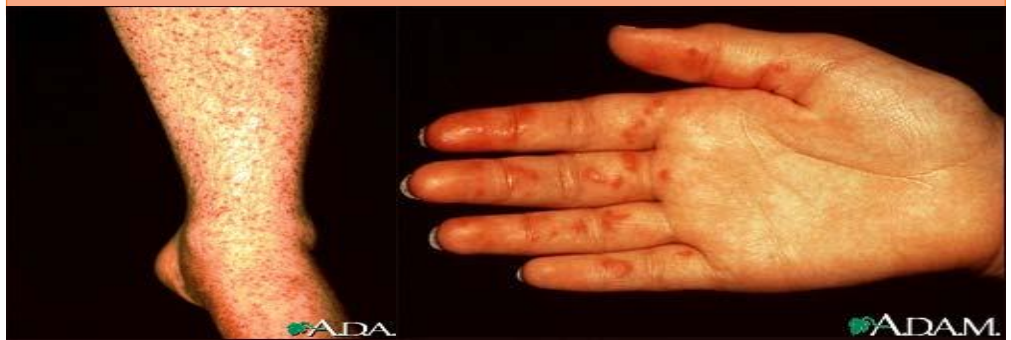
# Erythema Nodosum



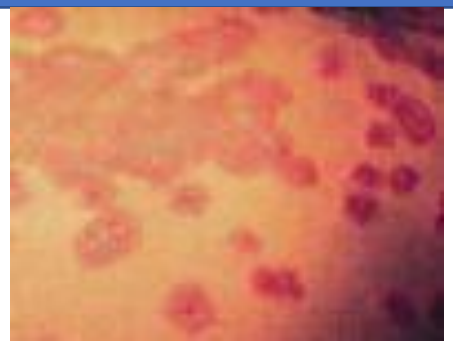


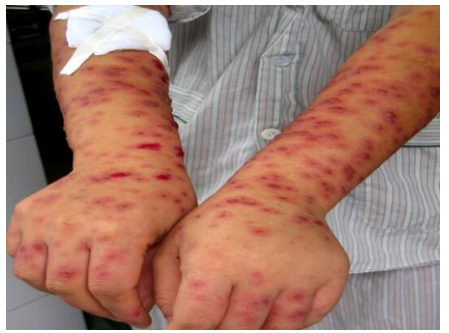


# Vasculitis



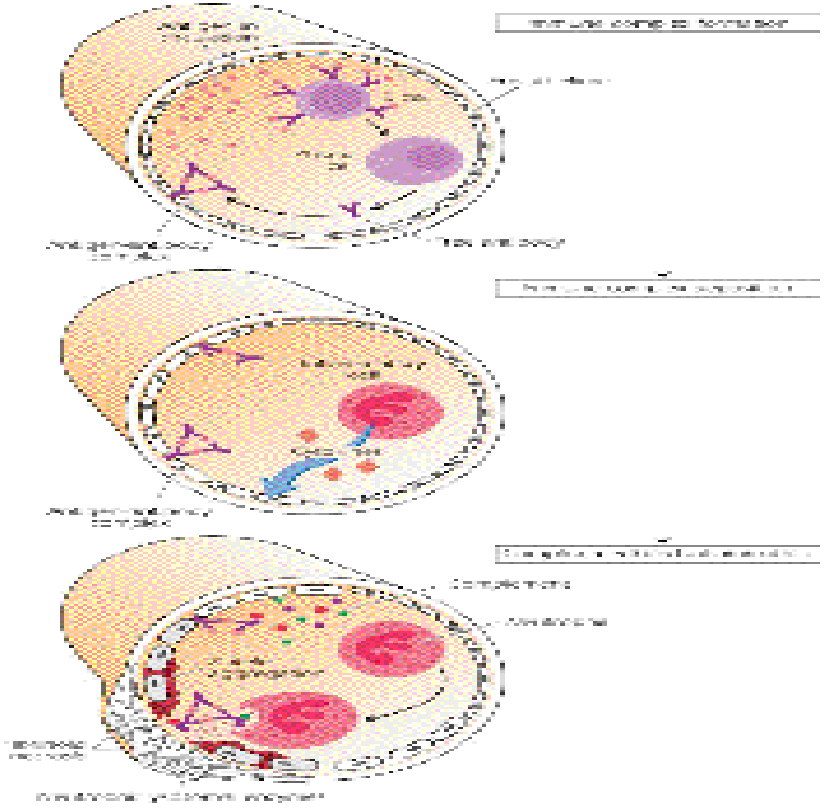

## Erythema Exudativum Multiform

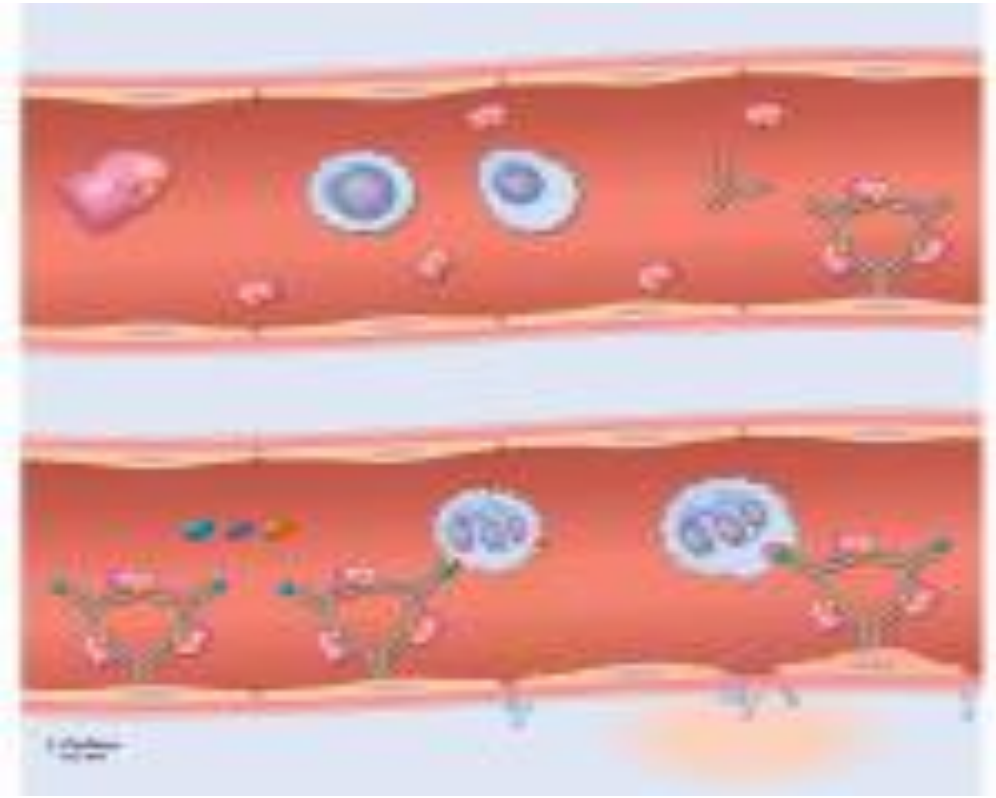




# Immune complex Type III reaction

## 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."*

# Drug Allergy

## IMMEDIATE

- IgE-Mediated Mast Cell activation
- Non- IgE mediated mast Cell activation
- Cytotoxic T Cells ag Mabs (Cytokine storm)

## Delayed

- T-cell mediated
  - Single organ eg Maculo-papular rash
- HLA associated drug T-cell mediated Hypersensitivity reactions
  - Severe coetaneous adverse Reaction (SCAR)
    - •DRESS
    - •AGEP
    - •SjS/TEN

# Diagnostic pathways: *In vitro* testing

- **Still limited applicability and poor generalised validation**
- **Tryptase** can be used as a biomarker of mast cell degranulation

Madrigal-Burgaleta R, et al. Importance of Diagnostics Prior to Desensitization in New Drug Hypersensitivity: Chemotherapeutics and Biologicals. Curr Treat Options Allergy. 2020. doi:10.1007/s40521-020-00238-y (available on Research Gate)

- **IL-6** can be used as a biomarker of cytokine release

Silver J, et al. Endophenotyping Oxaliplatin Hypersensitivity: Personalizing Desensitization to the Atypical Platin. J Allergy Clin Immunol Pract. 2020;8(5)

Jakubovic B, et al. Interleukin-6: A novel biomarker for monoclonal antibody and chemotherapy-associated hypersensitivity confirms a cytokine release syndrome phenotype-endotype association. Allergy. 2021;76:1571-3

- Alvarez-Cuesta *et al.* validated **oxaliplatin-specific IgE** in a cohort with a large sample size with well-characterised patients (allergy workup including drug provocation testing). The authors found that these technique was very specific but not so sensitive.

Alvarez-Cuesta E, et al. Delving into cornerstones of hypersensitivity to antineoplastic and biological agents: Value of diagnostic tools prior to desensitization. Allergy. 2015;70(7).

- Some authors have explored the role of sIgE in the study of **cross-reactivity** in platinum drugs

Caiado J, et al. Carboplatin-, Oxaliplatin-, and Cisplatin-specific IgE: Cross-reactivity and Value in the Diagnosis of Carboplatin and Oxaliplatin Allergy. J Allergy Clin Immunol Pract. 2013;1(5)

- Patients reacting to **cetuximab** can be sensitised to galactose-alpha-1,3-galactose, and sIgE alpha-gal is commercially availbale

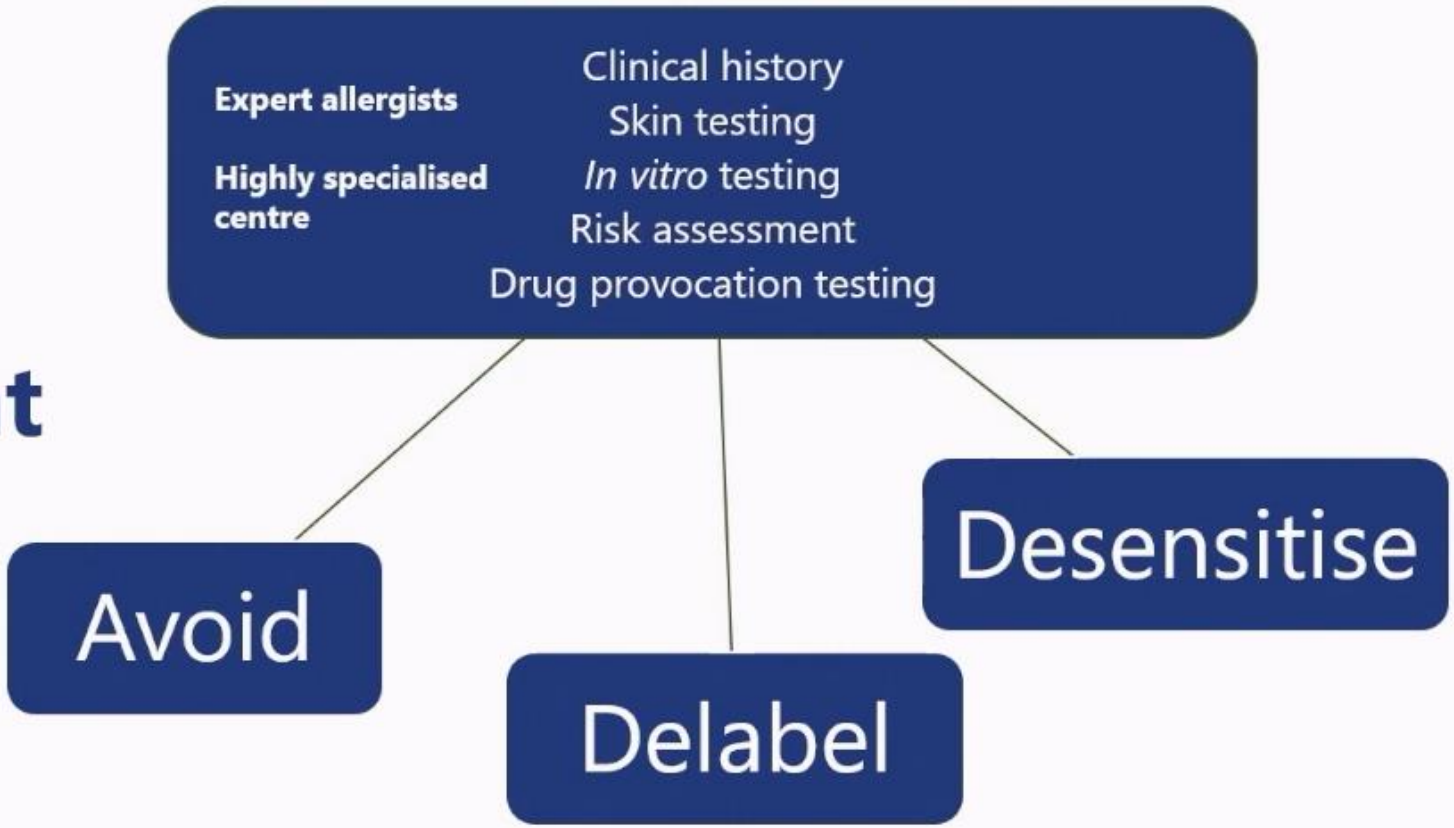
García-Menaya JM, et al. Successful desensitization to 1452 cetuximab in a patient with a positive skin test to cetuximab and specific IgE to alpha-gal. J Investig Allergol Clin Immunol. 2016;26(2)
Steinke JW, et al. The alpha-gal story: Lessons learned from connecting the dots. J Allergy Clin Immunol. 2015;135(3)
Chung CH, et al. Cetuximab-induced anaphylaxis and IgE specific for galactose-α-1,3- galactose. N Engl J Med. 2008;358(11)

- **Basophil activation test** have been used in the diagnosis of these reactions, and even in the follow as a risk marker of breakthrough reactions during desensitisation

Iwamoto T, et al. Evaluation of basophil CD203c as a predictor of carboplatin-related hypersensitivity reaction in patients with gynecologic cancer. Biol Pharm Bull. 2012;35(9):1487-95
Piva E, et al. Adverse reactions in patients with B-cell lymphomas during combined treatment with rituximab: In vitro evaluation of rituximab hypersensitivity by basophil activation test. Am J Hematol. 2012;87(11)
Castells M. Drug hypersensitivity and anaphylaxis in cancer and chronic inflammatory diseases: The role of desensitizations. Front Immunol. 2017;8
Madrigal-Burgaleta R, et al. Importance of Diagnostics Prior to Desensitization in New Drug Hypersensitivity: Chemotherapeutics and Biologicals. Curr Treat Options Allergy. 2020. (available on Research Gate)

# Veni, vidi, vici – come, understand, and delabel, avoid, or desensitise

## Management




Editorial

Drug allergy

Veni, vidi, vici—come, understand, and delabel, avoid, or desensitize


Madrigal-Burgaleta R, et al. Medical algorithm: Diagnosis and treatment of hypersensitivity reactions to cancer chemotherapy. Allergy. 2021; in press.

Madrigal-Burgaleta R, et al. Importance of Diagnostics Prior to Desensitization in New Drug Hypersensitivity: Chemotherapeutics and Biologicals. Curr Treat Options Allergy. 2020. doi:10.1007/s40521-020-00238-y (available on Research Gate)

Hong DI, et al. Controversies in Allergy: Chemotherapy reactions, desensitize or de-label? J Allergy Clin Immunol Pract. 2020;8(9):2907-2915.

Castells M. Drug allergy: Veni, vidi, vici-come, understand, and delabel, avoid, or desensitize. Ann Allergy Asthma Immunol. 2019;123(1):1–2.

# Diagnostic pathways: Consensus

Controversies in Allergy

**Controversies in Allergy: Chemotherapy Reactions, Desensitize, or Delabel?**

David I. Hong, MD[a,*], Ricardo Madrigal-Burgaleta, MD, PhD[b,*], Aleena Banerji, MD[c], Mariana Castells, MD, PhD[d,e], and Emilio Alvarez-Cuesta, MD, PhD[f,g] *Boston, Mass; London, United Kingdom; and Madrid, Spain*

**† Risk assessment is dynamic and should include at least:**

(1) Phenotype and endotype-related factors, such as the results on the allergy workup risk markers, both *in vivo* and *in vitro* (ST, specific IgE, tryptase, IL-6, basophil activation test, etc,).

(2) Drug/reaction-related, such as type of drug, severity of the reaction, previous life-threatening reaction (such as a history of intubation or cardiovascular collapse), type of reaction (immediate, nonimmediate), more than one drug involved in the reaction.

(3) Exceptional situations like pregnancy, acute infections, critically ill patients, urgency to receive treatment, or clinical trials.

(4) Institutional-related factors, such as access to expert allergists with clinical expertise in drug allergy, access to a multidisciplinary team approach for each individual patient, trained staff, specific resources, appropriate facilities (special dedicated areas for these techniques, and access to intensive care), risk-management strategies and worst-case scenario recovery plans.

(5) Patient-related, such as comorbidities where exposure might provoke situations beyond medical control.

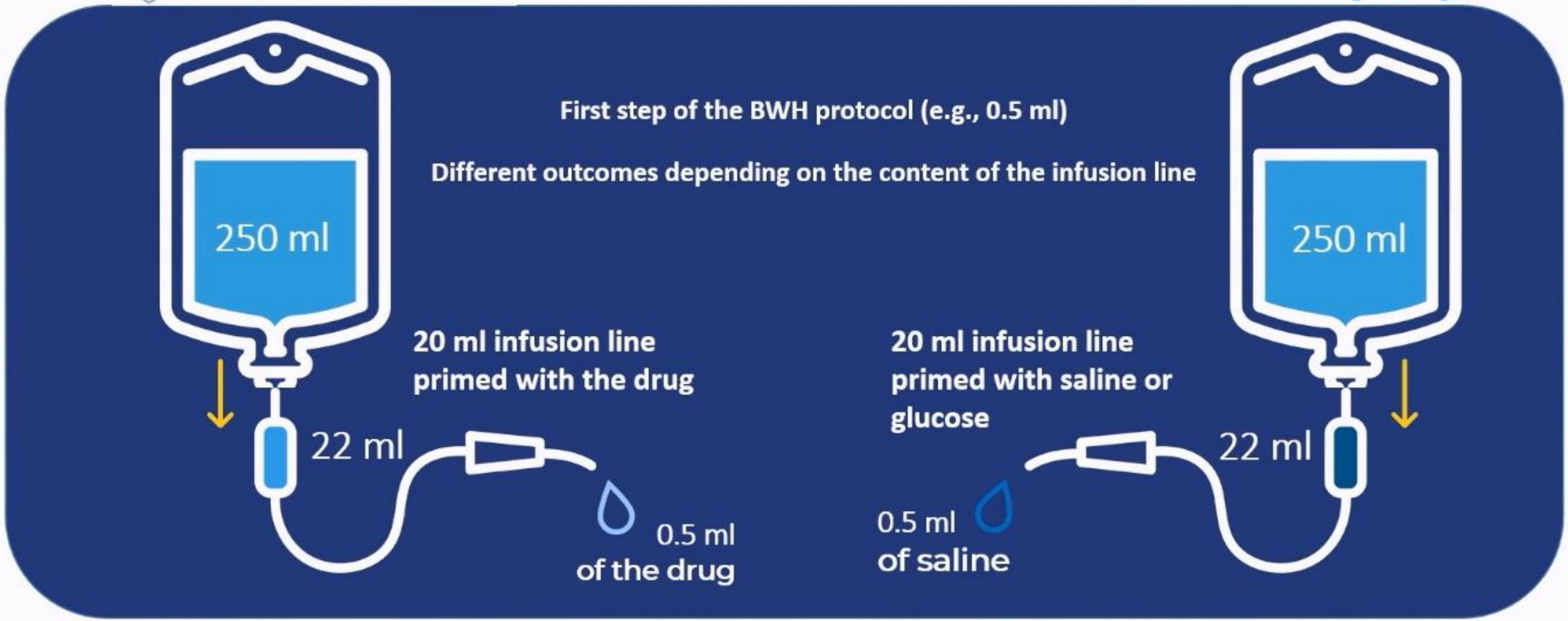
(6) social factors (travel distance to center, level of anxiety, inclination toward challenge vs desensitization, and so forth).

Designed by Emilio Alvarez-Cuesta & Ricardo Madrigal-Burgaleta, 2020

# Rapid Drug Desensitisation: Protocols

BRIGHAM AND WOMEN'S HOSPITAL

Hospital Universitario Ramón y Cajal



# Thanks

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# “ Man is made by his belief. As he believes, so he is ”

– The Bhagavad Gita

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