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# Mechanisms of drug hypersensitivity

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- Vifor, Switzerland: consultancy, honoraria

(e.g. employment, consultancy, honoraria, stock ownership, sponsored education, research grant, educational grant, expert witness, other relevant funding, etc ...)





EUROPEAN MEDICINES AGENCY  
SCIENCE MEDICINES HEALTH

28 June 2013  
EMA/377372/2013

## New recommendations to manage risk of allergic reactions with intravenous iron-containing medicines

[http://www.ema.europa.eu/docs/en\\_GB/document\\_library/Press\\_release/2013/06/WC500144874.pdf](http://www.ema.europa.eu/docs/en_GB/document_library/Press_release/2013/06/WC500144874.pdf)



*Controversies Conference on Iron Management in CKD | March 27-30, 2014 | San Francisco, California, USA*



EUROPEAN MEDICINES AGENCY  
SCIENCE MEDICINES HEALTH

13 September 2013  
EMA/549569/2013

## Assessment report for: Iron containing intravenous (IV) medicinal products

Procedure under Article 31 of Directive 2001/83/EC

Procedure number: EMEA/H/A-31/1322

[http://www.ema.europa.eu/docs/en\\_GB/  
document\\_library/Referrals\\_document/  
IV\\_iron\\_31/WC500150771.pdf](http://www.ema.europa.eu/docs/en_GB/document_library/Referrals_document/IV_iron_31/WC500150771.pdf)

# Contents

- Definitions of terms
- Allergens
- Mechanisms
  - Mast cell, basophils
- Clinical manifestations
- Diagnostic approaches



# Classification of ADR by pharmacologists

<b>A (Augmented)</b>	<b>Dose related</b>
<b>B (Bizarre)</b>	<b>Non-dose related</b>
<b>C (Chronic)</b>	<b>Dose and time related</b>
<b>D (Delayed)</b>	<b>Time related</b>
<b>E (End of use)</b>	<b>Withdrawal</b>
<b>F (Failure)</b>	<b>Unexpected failure</b>



# Type A (“augmented”)

- Toxic-pharmacologic pathogenesis
- Dose dependent, obligatory
- Adverse effects related to the pharmacologic drug effect
- predictable
  - Bleeding from overdose of anticoagulation
  - Skin atrophy from prolonged corticosteroid use

# Type B (“bizarre”)

- Immunologically-mediated
  - Only sensitized individuals (IgE, IgG, T cells)
- or hypersensitivity, not-immunologically mediated, but similar/identical clinical manifestation ( “non-IgE mediated”, “pseudoallergy”), in “hypersensitive” individuals
- Adverse effect unrelated to the pharmacologic, expected drug effect
- Minor dose dependency (rational of test dose)
- unpredictable
  - Drug rash (exanthem) to antibiotic
  - Urticaria to analgetic drug or iron product



# Type B (“bizarre”)

- Hypersensitivity reactions
  - Anaphylaxis to cephalosporin or penicillins (Allergy Type I)
  - Exanthem to aminopenicillin (Allergy Type IV)
  - Urticaria to acetylsalicylic acid (Pseudoallergy)
    - Often cross-reactivity to other NSAIDs or iron
  - Angioedema to ACE-Inhibitor (Idiosyncrasy)

# Four reactions according to Coombs & Gell

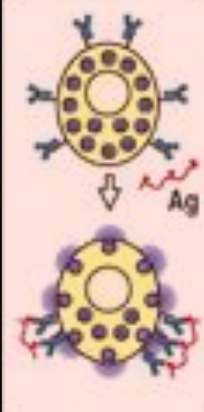

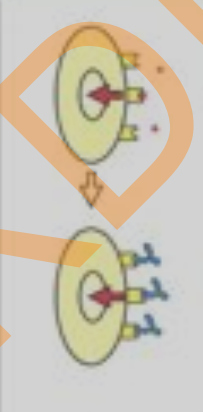
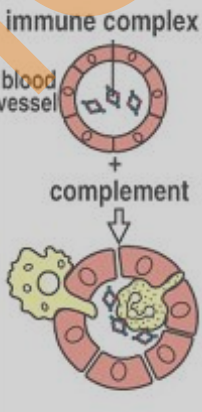
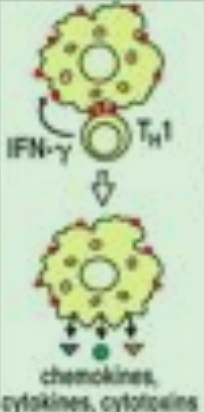
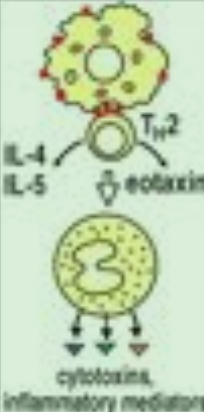

	Type I	Type II		Type III	Type IV		
Immune reactant	IgE	IgG		IgG	T <sub>H</sub> 1 cells	T <sub>H</sub> 2 cells	CTL
Antigen	Soluble antigen	Cell- or matrix-associated antigen	Cell-surface receptor	Soluble antigen	Soluble antigen	Soluble antigen	Cell-associated antigen
Effector mechanism	Mast-cell activation	Complement, FcR <sup>+</sup> cells (phagocytes, NK cells)	Antibody alters signaling	Complement, Phagocytes	Macrophage activation	IgE production, Eosinophil activation, Mastocytosis	Cytotoxicity
							
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)

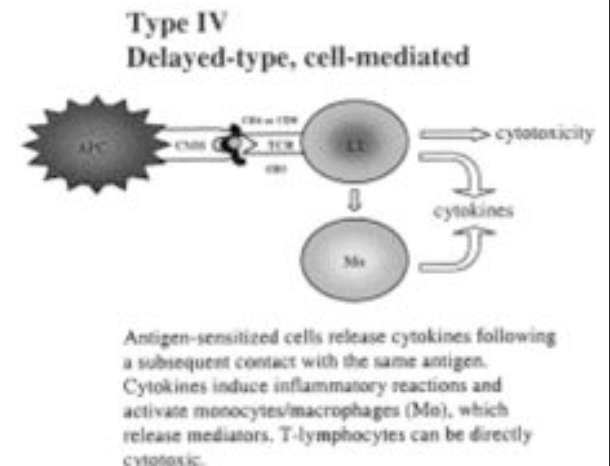
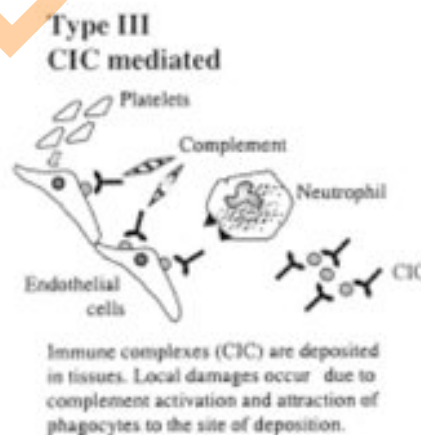
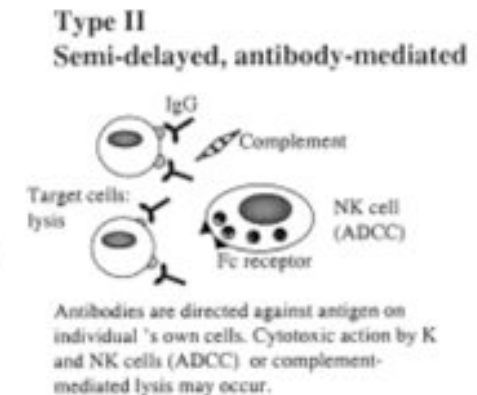
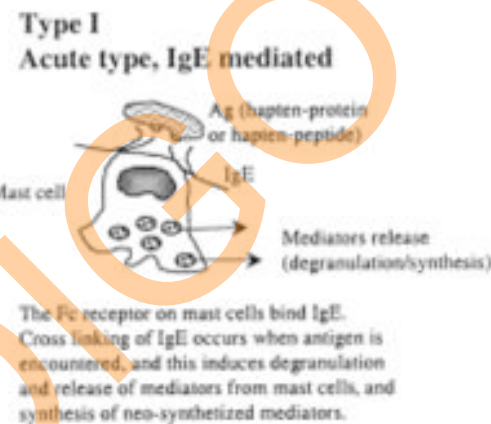
B lymphocytes/plasma cells  
(humoral)

T lymphocytes (cellular)  
CD4 CD8



# Coombs & Gell

- **Type I: IgE**
  - Mast cell, basophils
- **Type III: immune-complexes (IgG, IgM), Complement**
  - Neutrophils
- **Pseudoallergy type I similar/identical**
  - Mast cell, basophils



# Immunologically mediated reactions to drugs (Type IV, Type III and II, Type I)

First exposure, start of sensitization/or preexisting crossreactive Ab/Tc

Sensitization: days, weeks, months (at least 5-10 days)

IgE-Ab  
IgG-Ab  
T-Ly

If T-Ly and reexposure

Elicitation: one to several days

Plaques

Exantheams  
Contact dermatitis

Delayed type symptoms

If IgG and reexposure

Elicitation: few hours to some days

Cytopenia  
IC anaphylaxis

Cytopenia,  
immune  
complex  
anaphylaxis

If IgE and reexposure

Elicitation: minutes to several hours

Urticaria  
Angioedema  
Anaphylaxis  
Asthma

Immediate type symptoms

Phases of pseudoallergic drug reactions  
no specific Immune response (e.g. **Arachidonic acid cascade deviation, direct mast cell/basophil activation**)

First exposure

No sensitization, i.e. reaction upon first exposure possible

No IgE,  
IgG,  
T cells

I.e. at first or repeated exposures

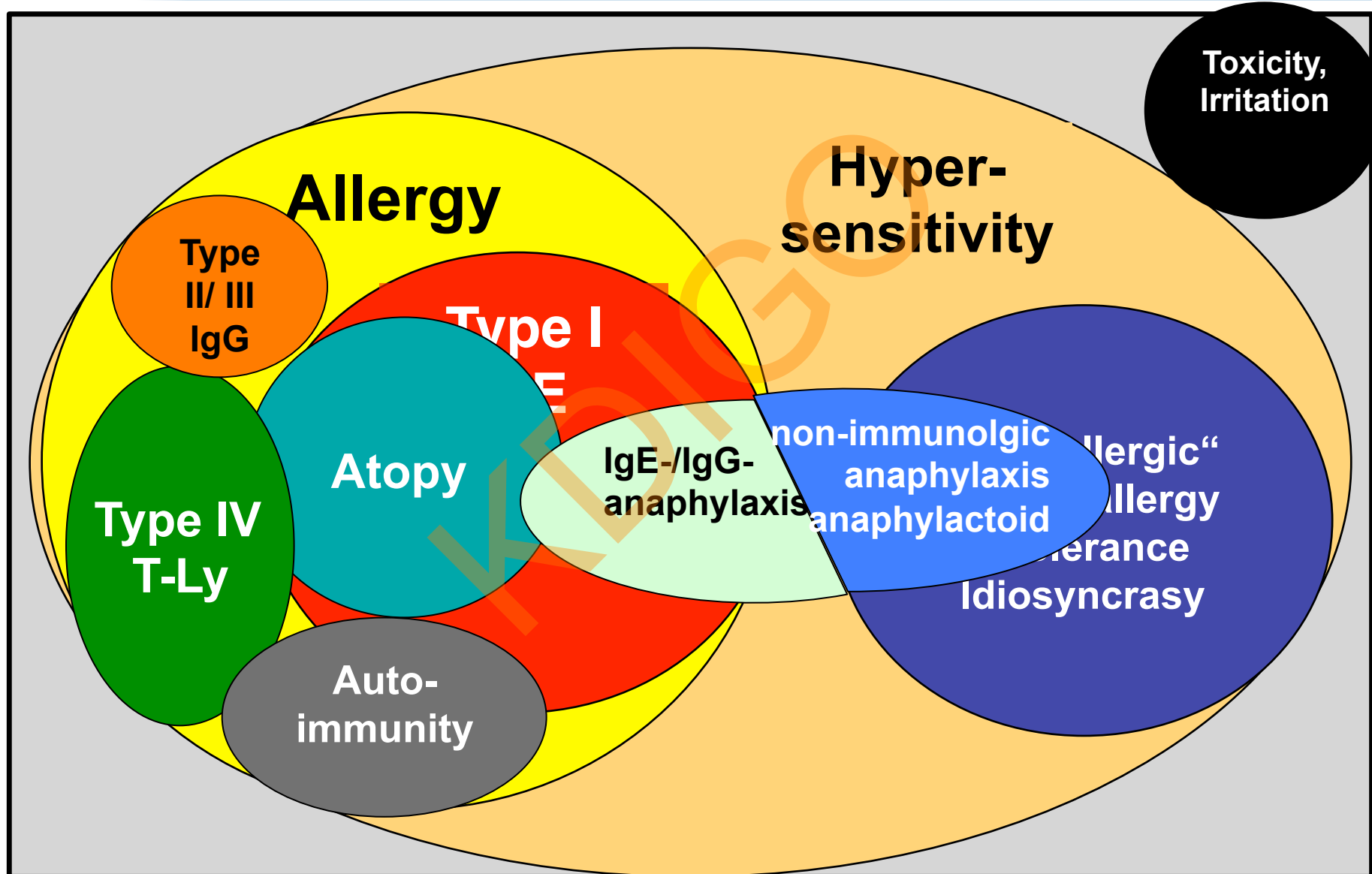
Elicitation: minutes to several hours

Urticaria  
Angioedema  
Anaphylaxis  
Asthma

Immediate type  
symptoms

Particularly analgetics NSAIDs, (COX-1- inhibitors), contrast media, opioids, **iron products?** (direct mast cell, basophil activation, complement)

# Terminology

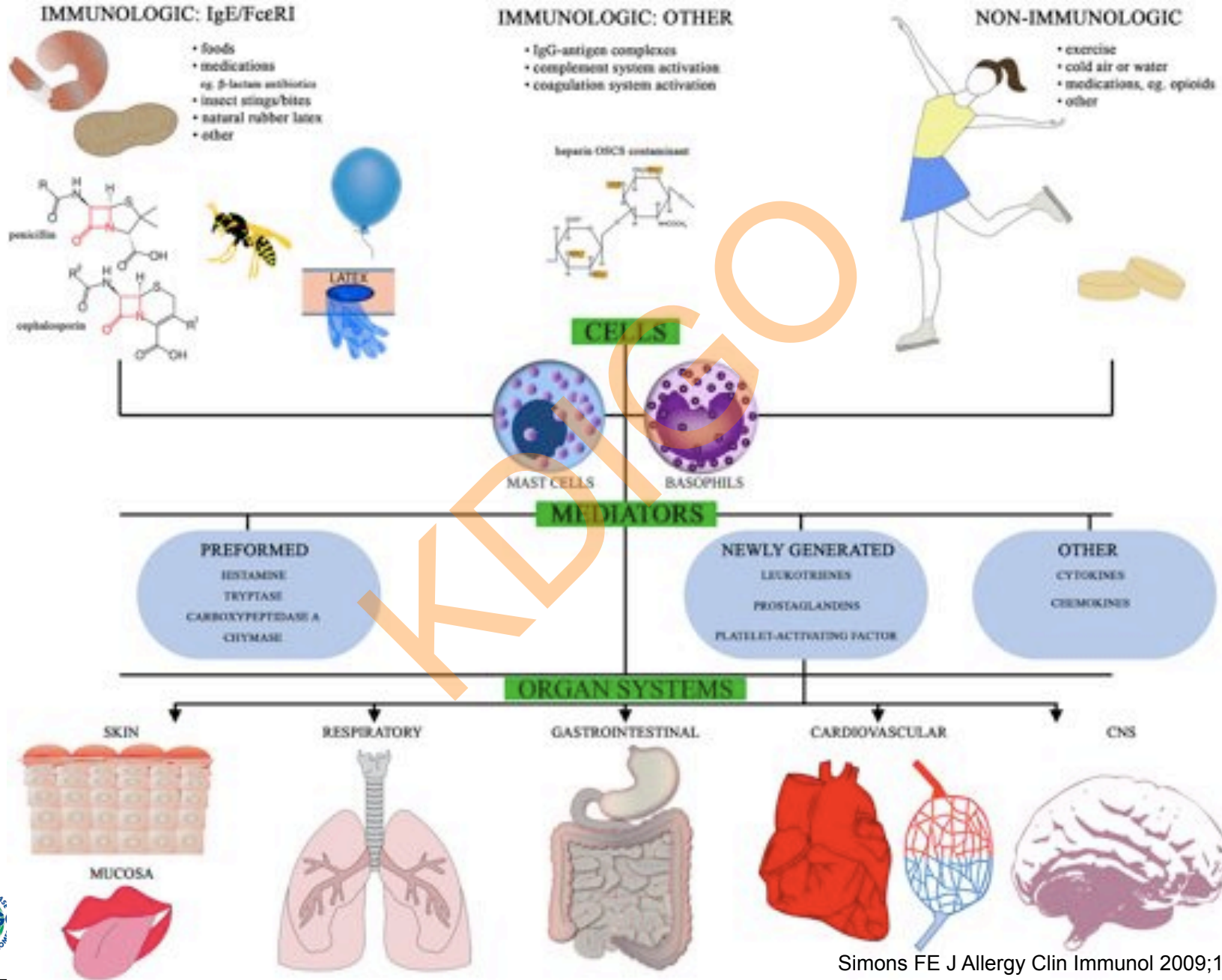


# Mediator systems in immediate hypersensitivity reactions

- Histamin, platelet activating factor
- Arachidonic acid cascade
  - Leukotrienes, prostaglandins
- Contact (kinin) system
  - Bradykinin
- Complement system
  - Anaphylatoxins (C3a, C5a)
- Coagulation cascade



# MECHANISMS AND TRIGGERS





# Classification

**Table 1. The Ring and Messmer classification**

<b>Grade</b>	<b>Symptoms</b>
I	Skin symptoms and or mild fever reaction
II	Measurable, but not life threatening Cardiovascular reaction (tachycardia, hypotension) Gastrointestinal disturbance (nausea) Respiratory
III	Shock, life threatening spasms of smooth muscles (bronchi, uterus)
IV	Cardiac and or respiratory arrest

**Table 3.** Classification of anaphylactic reactions according to severity of clinical symptoms [35]

Grade	Symptoms			
	skin	abdominal	respiratory	cardiovascular
I	pruritus flush urticaria angioedema			
II	pruritus flush urticaria angioedema (not mandatory)	nausea cramping	rhinorrhea hoarseness dyspnea	tachycardia ( $\Delta >20$ beats/min) blood pressure change ( $\Delta >20$ mm Hg systolic) arrhythmia
III	pruritus flush Urticaria angioedema (not mandatory)	vomiting defecation diarrhea	laryngeal edema bronchospasm cyanosis	shock
IV	pruritus flush urticaria angioedema (not mandatory)	vomiting defecation diarrhea	respiratory arrest	cardiac arrest



# Anaphylaxis: Some definitions

- Acute systemic reaction with symptoms of an immediate reaction, that may encompass the whole organism (1)
- Serious, allergic reaction, that is rapid in onset and may cause death (2)
- “A severe, life-threatening, generalized or systemic hypersensitivity reaction” (3)

<sup>1</sup> Ring et al; AWMF Leitlinie: Akuttherapie anaphylaktischer Reaktionen. Allergo J 2007; 16: 420–34

<sup>2</sup> Sampson HA et al; Second symposium on the definition and management of anaphylaxis. J Allergy Clin Immunol 2006; 117: 391-7

<sup>3</sup>. EAACI revised Nomenclature for Allergy. Allergy: 2001;56:813-24 and JACI 2004;113:832-6



# Definition of Anaphylaxis

**TABLE I. Clinical criteria for diagnosing anaphylaxis**

**Anaphylaxis is highly likely when any one of the following 3 criteria are fulfilled:**

1. Acute onset of an illness (minutes to several hours) with involvement of the skin, mucosal tissue, or both (eg, generalized hives, pruritus or flushing, swollen lips-tongue-uvula)  
**AND AT LEAST ONE OF THE FOLLOWING**
  - a. Respiratory compromise (eg, dyspnea, wheeze-bronchospasm, stridor, reduced PEF, hypoxemia)
  - b. Reduced BP or associated symptoms of end-organ dysfunction (eg, hypotonia [collapse], syncope, incontinence)
2. Two or more of the following that occur rapidly after exposure to a likely allergen for that patient (minutes to several hours):
  - a. Involvement of the skin-mucosal tissue (eg, generalized hives, itch-flush, swollen lips-tongue-uvula)
  - b. Respiratory compromise (eg, dyspnea, wheeze-bronchospasm, stridor, reduced PEF, hypoxemia)
  - c. Reduced BP or associated symptoms (eg, hypotonia [collapse], syncope, incontinence)
  - d. Persistent gastrointestinal symptoms (eg, crampy abdominal pain, vomiting)
3. Reduced BP after exposure to known allergen for that patient (minutes to several hours):
  - a. Infants and children: low systolic BP (age specific) or greater than 30% decrease in systolic BP\*
  - b. Adults: systolic BP of less than 90 mm Hg or greater than 30% decrease from that person's baseline

PEF, Peak expiratory flow; BP, blood pressure.

\*Low systolic blood pressure for children is defined as less than 70 mm Hg from 1 month to 1 year, less than  $(70 \text{ mm Hg} + [2 \times \text{age}])$  from 1 to 10 years, and less than 90 mm Hg from 11 to 17 years.

J Allergy Clin Immunol 2006;117:391-7



# Iron products

- high-molecular-weight iron dextrans
- low-molecular-weight iron dextrans
- iron dextrin
- saccharated iron oxide
- iron dextran
- iron sucrose (Venofer)
- ferric gluconate (Ferlecit)
- carboxymaltose iron (Ferinject)

# Antigens and Allergens

- Induce a specific immune response
  - Antibody (IgM, IgG, IgE), T cells
- MW >1000 (haptens <1000, typically bind to carrier proteins)
- Peptides > carbohydrates > lipids
- At least bivalent expression of epitope
- Haptens are low molecular chemicals (most drugs and contact allergens)
  - Induce preferentially T cell response > IgE, IgG

# Allergens

- Glycoproteins
  - Most protein antigens/allergens are glycosylated
    - Respiratory allergens
    - Food allergens
    - Some hymenoptera venom allergens
  - Many parasitic antigens (helminths, insects)
- Carbohydrate antigens/allergens
  - Dextrans (bacteria), particularly HMW dextrans
  - Bromelain, horseradish peroxidase (plant food, pollen)
  - Galactose-alpha-1,3-galactose (alpha-gal)
    - Mammalian meats, parasites, ticks, insects, cetuximab

# Metal allergens

- Nickel, Cobalt, Palladium, Chromium
  - Common contact allergens (T cell-mediated)
  - Allergic contact dermatitis
- Platinum, Cobalt
  - Very rarely IgE mediated allergy
  - Occupational asthma, cisplatin (oncology)
- Iron
  - Putative elicitation of contact dermatitis
  - Immediate hypersensitivity from iv iron
  - No hypersensitivity from oral iron





# Diagnostic test possibilities

- In vivo
  - Skin tests (→ *allergy*)
    - Skin prick, intradermal, (patch tests for T cell)
  - Provocation tests (→ *allergy and pseudoallergy*)
- In vitro test
  - Specific antibody levels (→ **IgE**; IgG) (allergy)
  - Basophil activation tests (experimental), (→ allergy and pseudoallergy)
  - Mediator measurements (e.g. **mast cell tryptase** 1-2h after acute reaction), (→ allergy and pseudoallergy)



# Skin tests „IgE-mediated“ allergy

- Standard procedures
  - Skin prick tests, intradermal tests
  - With **standardized** allergens
  - Test location: volar forearm, upper arm/back
  - Positive and negative controls
  - Readings: after 15 – 20 minutes
- *Special procedures*
  - *Scratch tests, Rub tests*

**Serum**  
*In vitro*  
**Monovalent binding**

**Mast cell**  
*in vivo*  
**bivalent binding**

**Denatured protein allergen**

**Low-molecular hapten**

**Anti-IgE-IgG**

**IgE**

**Low-molecular hapten**

**Denatured protein allergen**

**Carbohydrate determinant**

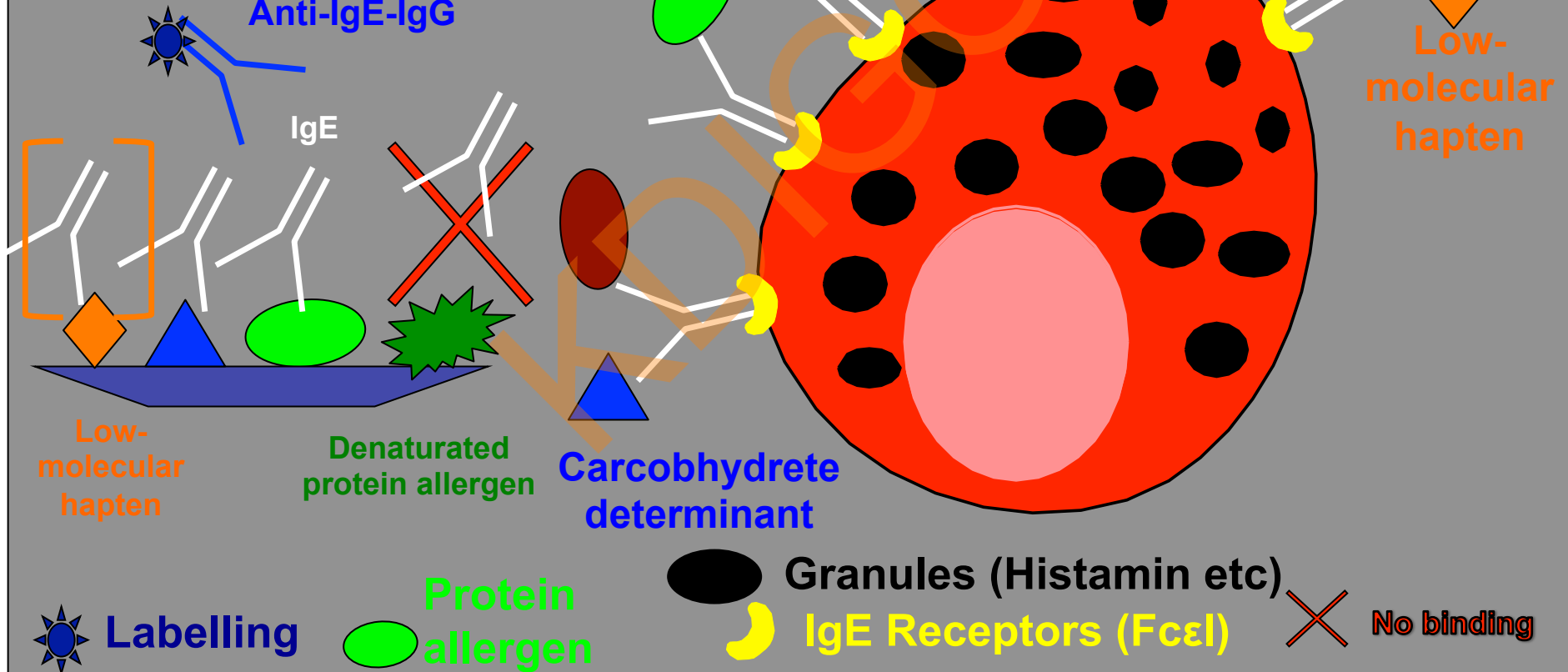
**Granules (Histamin etc)**

**IgE Receptors (Fcε1)**

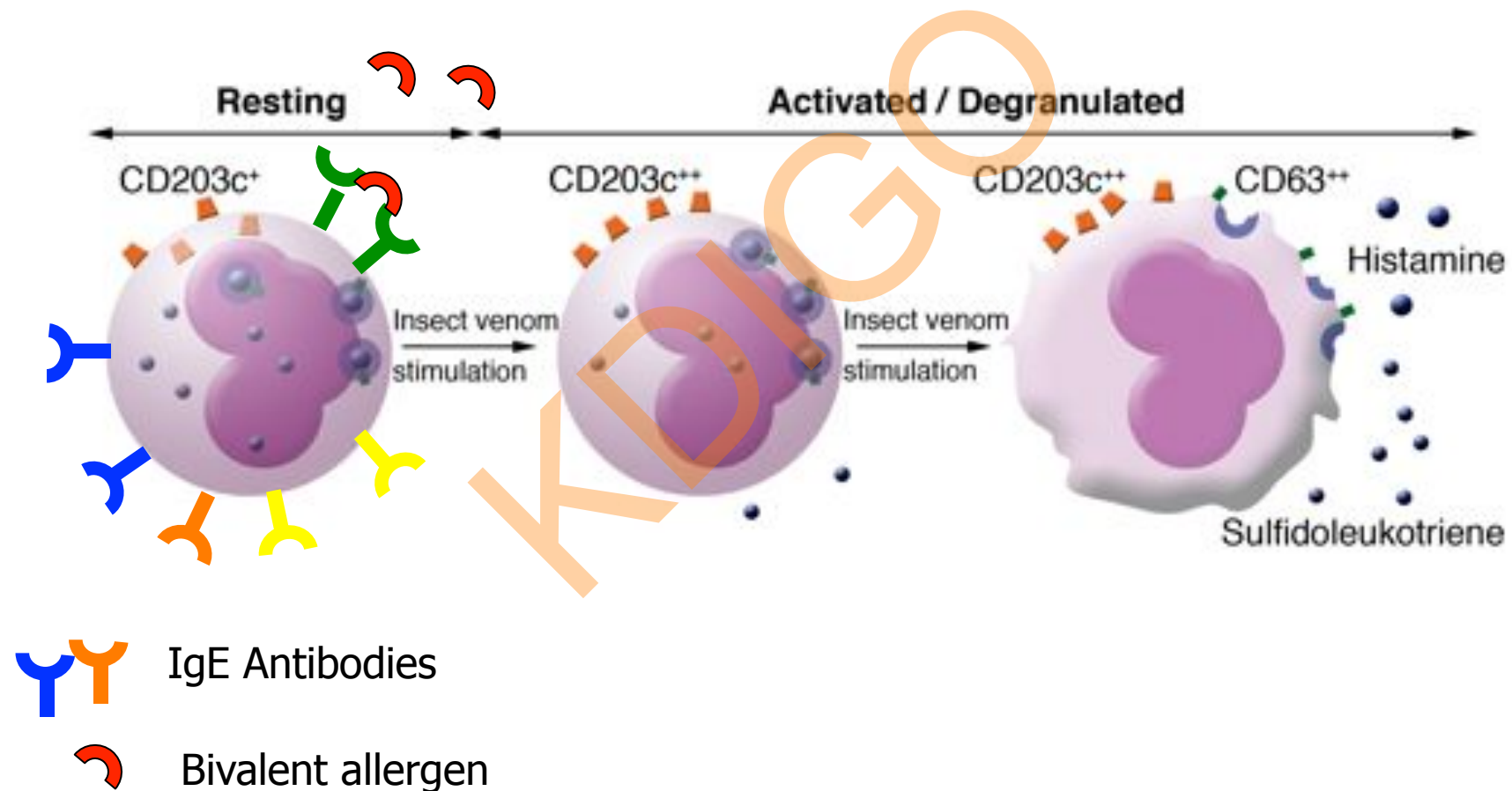
**No binding**

**Labelling**

**Protein allergen**



# Basophil activation & degranulation test (BADT) by FACS analysis



# Some drugs causing immediate (non-IgE-mediated) hypersensitivity

- NSAIDs
  - Asthma, urticaria, angioedema, non-IgE anaphylaxis (prostaglandins, leukotrienes, histamine?)
- Radio contrast media, local anesthetics
  - Non-IgE anaphylaxis (histamine, complement?)
- Biologics
  - Infusion reactions (cytokines, histamine etc)
- Vancomycin
  - Red man syndrome (histamine)
- ACE-Inhibitors
  - Angioedema (kinin system)

# Summary iron hypersensitivity

- Clinical features of immediate type hypersensitivity
  - HMW dextran irons IgG complex-mediated
  - Other carbohydrate-coated irons
    - No evidence for IgE, IgG mediated reactions
    - No evidence für T cell mechanisms
  - Activation of mast cells/basophils likely
    - Urticaria, angioedema, anaphylaxis
  - Diagnostic tools very limited
    - Test dosing, reexposure
- Mechanism of other symptoms largely unknown