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URTICAIRE CHRONIQUE SPONTANÉE, MALADIE SYSTÉMIQUE ?

Audrey Nosbaum, Florence Hacard, Frédéric Bérard, Marc Vocanson, Jean-François Nicolas

Allergologie et Immunologie Clinique, CHU Lyon-Sud
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URTICAIRE CHRONIQUE SPONTANÉE, SYNDROME D'ACTIVATION MASTOCYTAIRE?

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Allergologie et Immunologie Clinique, CHU Lyon-Sud
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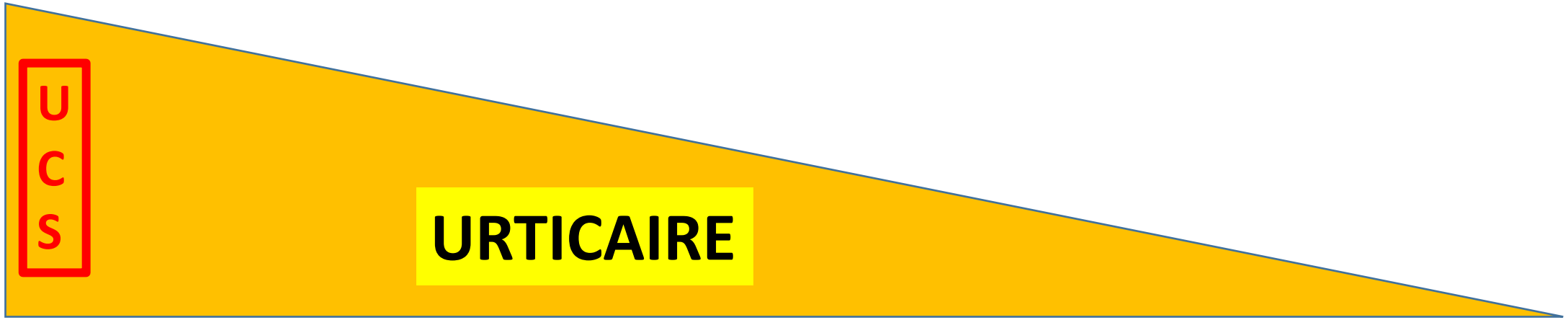
Outline

- Urticaire, maladie ou symptôme ?
- Urticaire Chronique Spontanée
- Mastocytes / Désordres d’activation mastocytaire / Syndromes d’ activation mastocytaire
- Physiopathologie de l’activation mastocytaire
- Urticaire aux médicaments

Urticaire
Maladie ou symptôme ?



Mast cell activation disorders

Mast cell activation syndromes

Urticaire = Activation mastocytaire

Messages clés

- UCS: dermatose inflammatoire chronique
- UCS: activation des mastocytes cutanés dont la physiopathologie est encore inconnue
- UCS + signes systémiques: fréquent (digestifs, asthénie, céphalées)
- Diagnostic des UCS + signes systémiques :
  - UCS
  - SAM si critères diagnostiques réunis

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Chronic Urticaria

- Frequent (2% population)
- Chronic skin inflammatory disease

(not an allergic disease)

- Transient hives (<24h)
- Wheal and Flare

Pathophysiology

- Mast cells are pre-activated

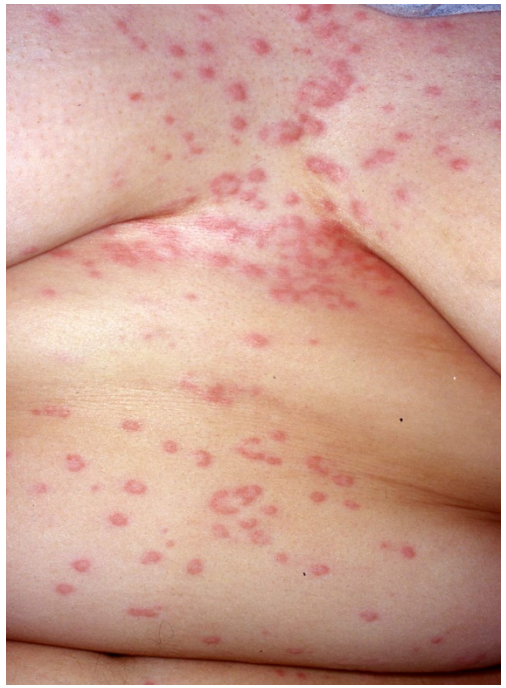
(auto-immune, atopic urticaria)

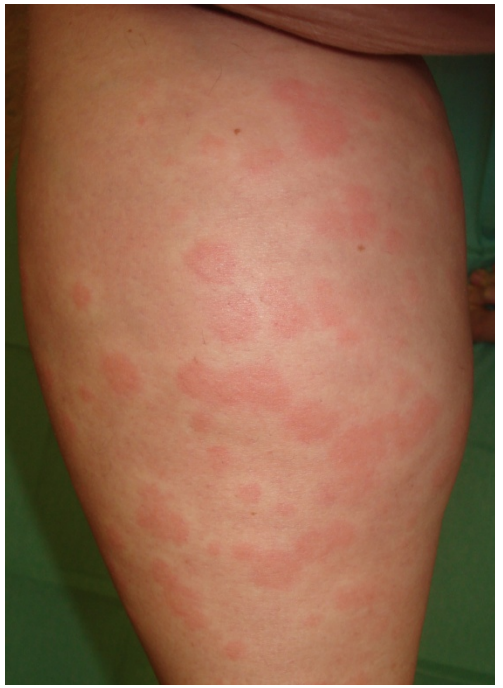
- Full activation induced by different triggers

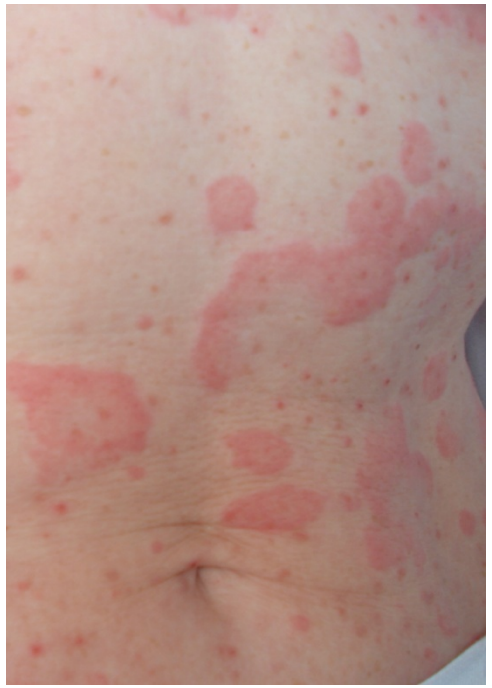
(food, drugs, infection, stress, trauma, etc.)

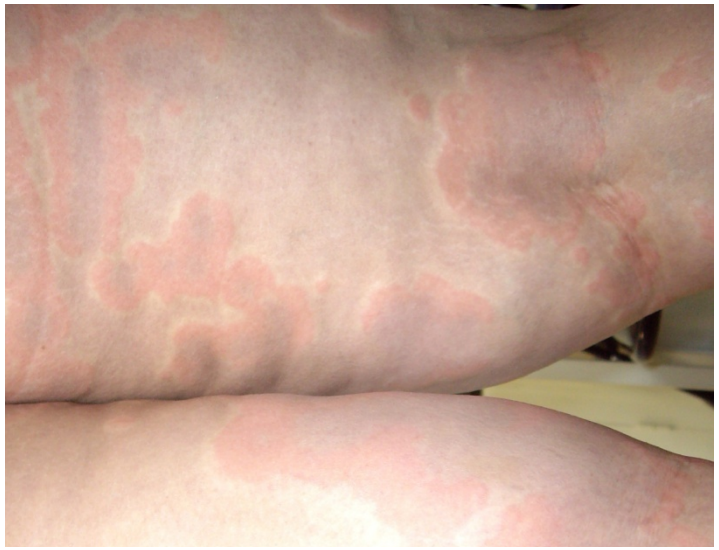
Treatment

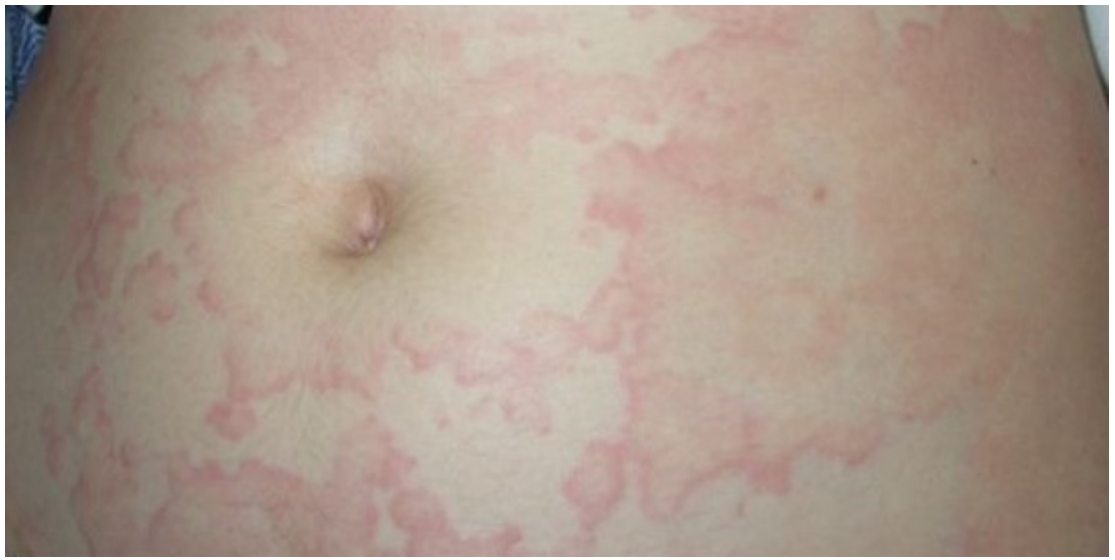
- Anti-H1R efficient
- Anti-IgE mAbs (omaluzimab)



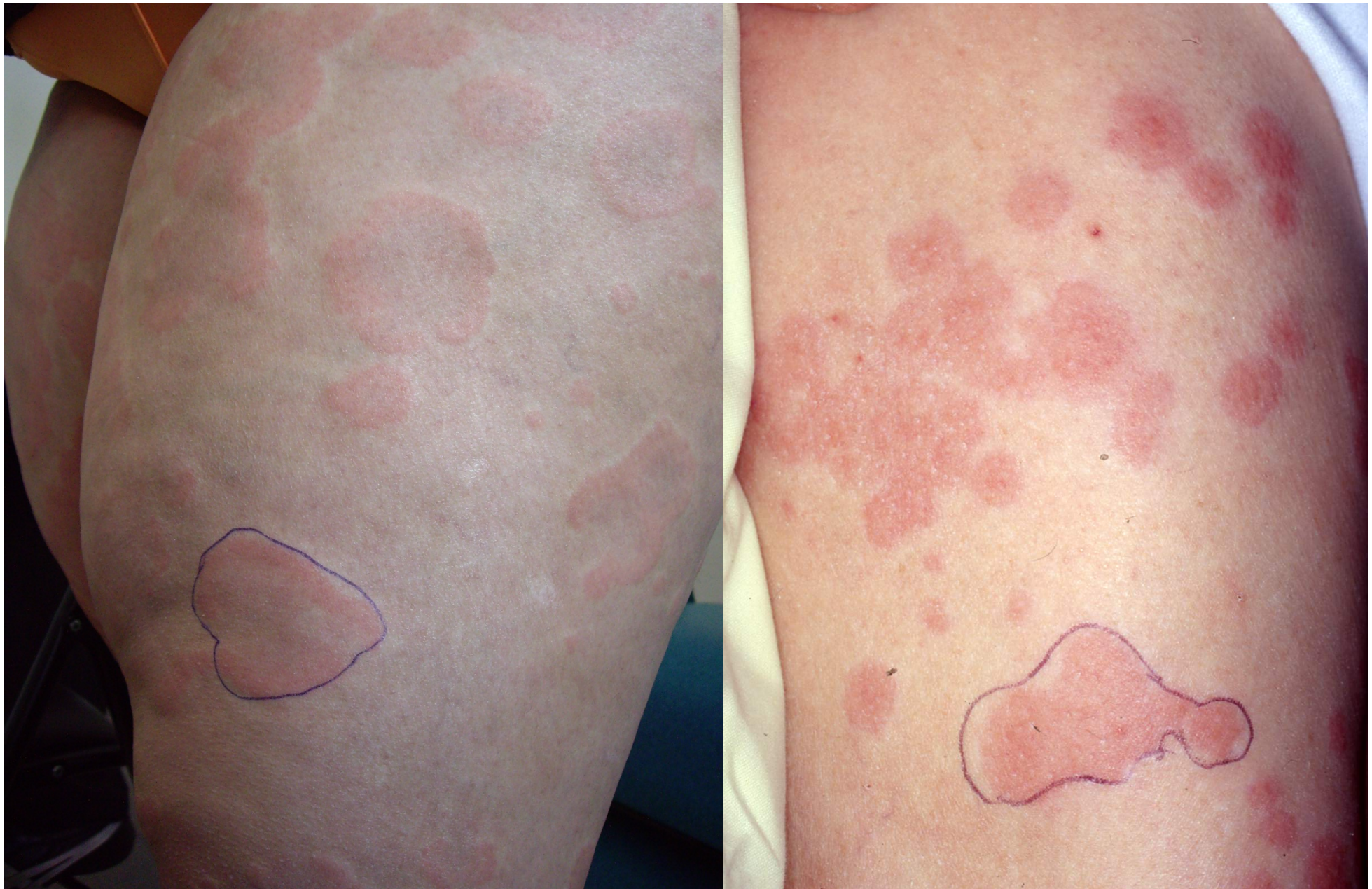




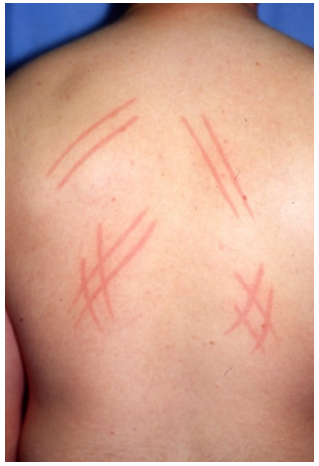


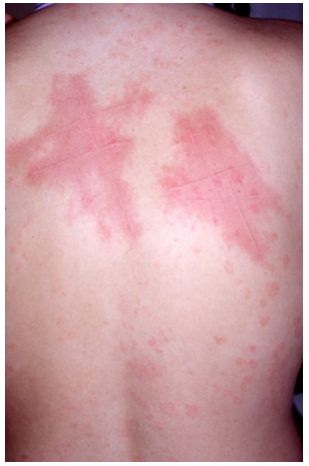


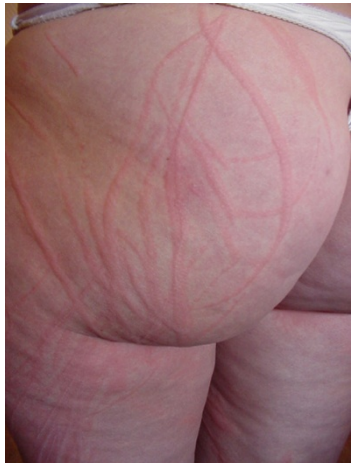
Chronic Urticaria – Delayed form

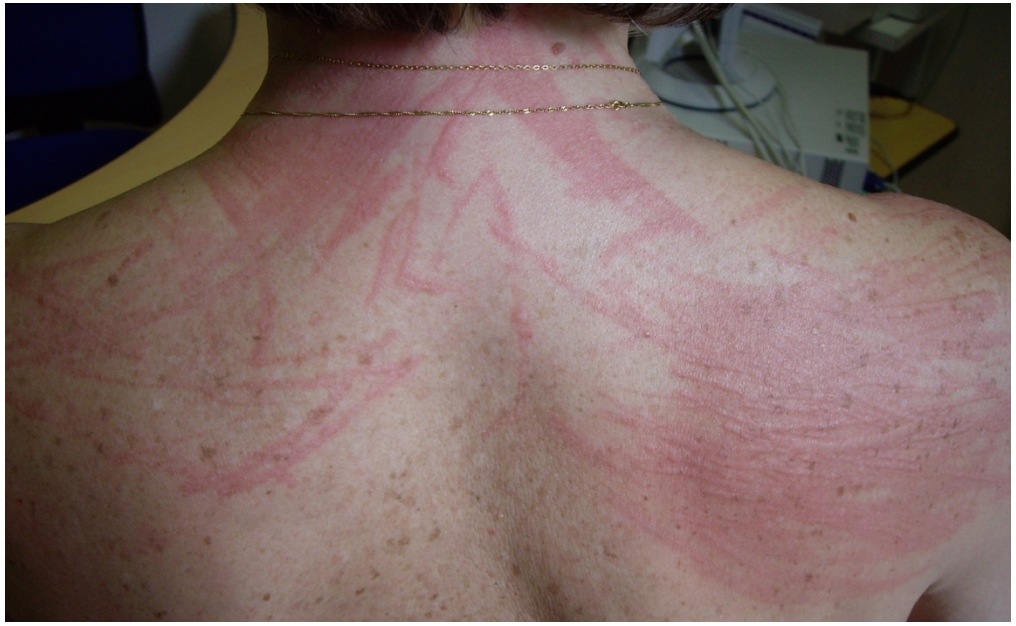


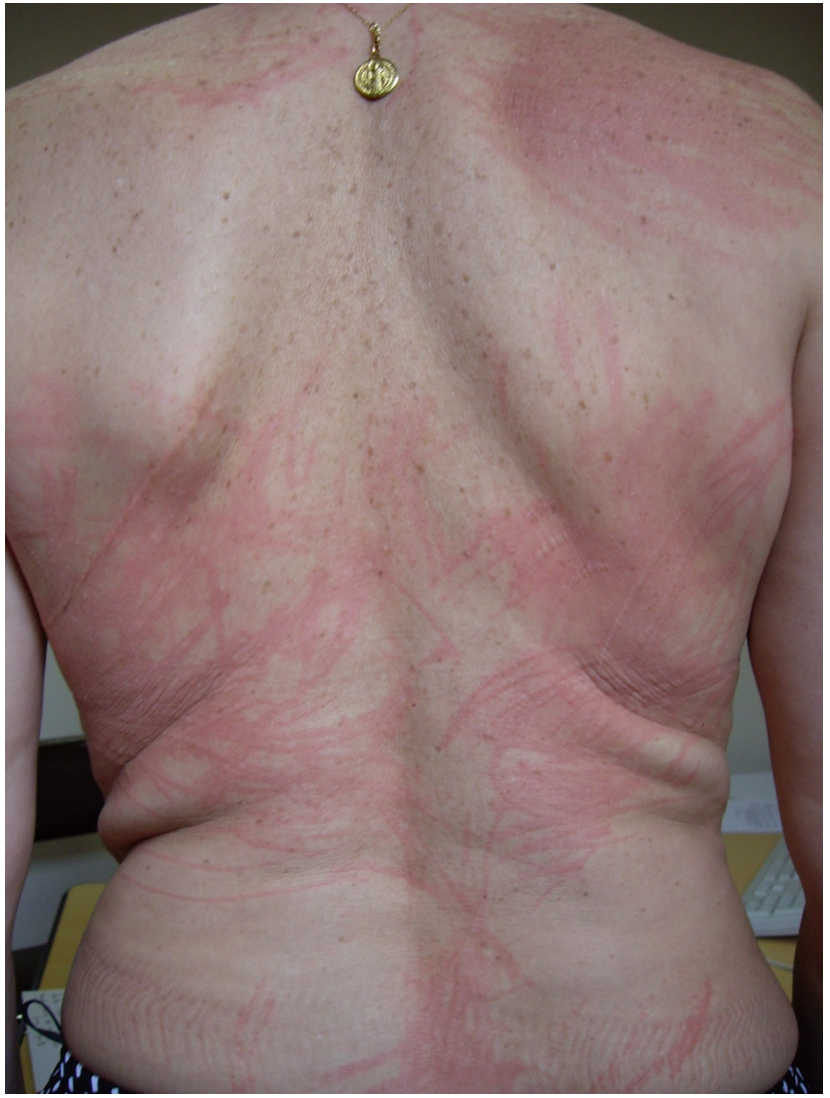
Chronic Urticaria – Physical urticaria



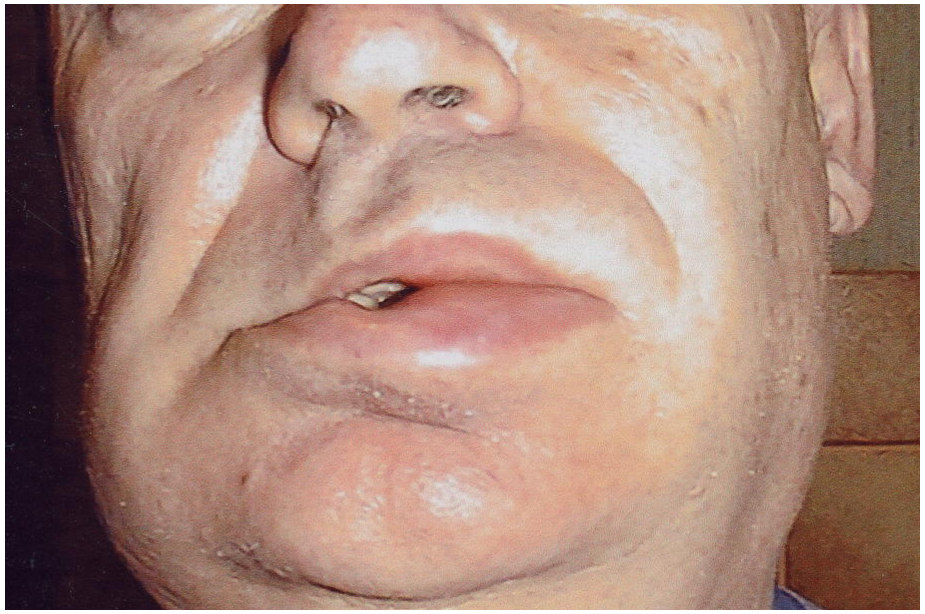


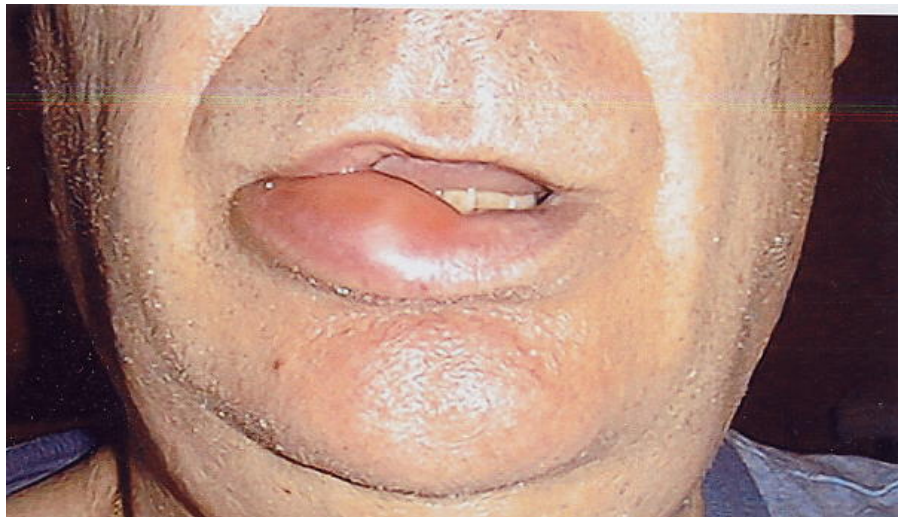


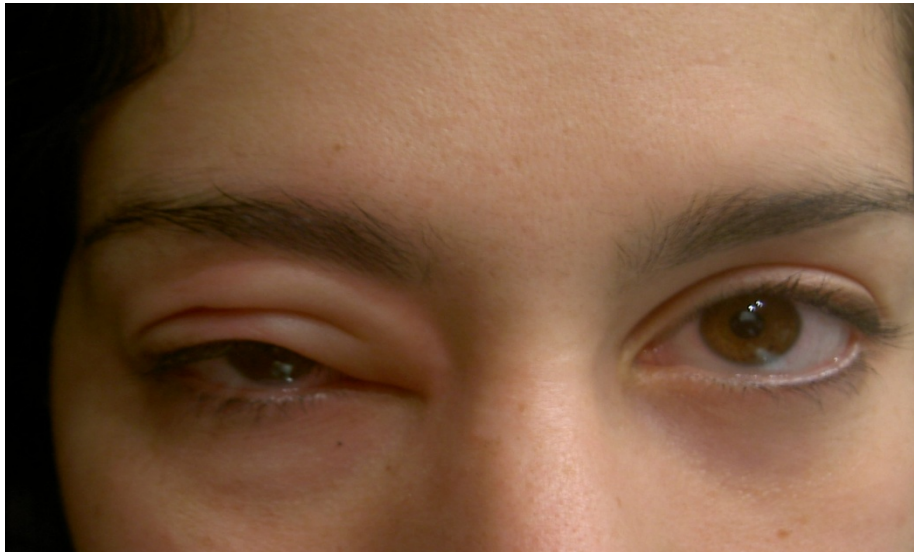


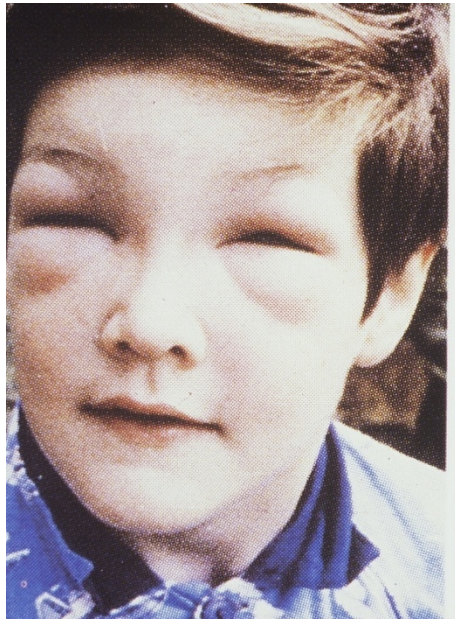


Chronic urticaria – Face urticaria - Angioedema









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Mast cells

- Mast Cells (MC) are widely distributed, long lived cells found predominantly in connective and mucosal tissues, in proximity to blood vessels, nerves and lymphatic vessels
- MC are particularly abundant in epithelia and mucosae: skin, respiratory tract, gastrointestinal tract, eye, nose, buccal mucosae
- MC are the primary effector in immediate hypersensitivity (HS) that could be allergic (IgE) or (most importantly) non allergic (non IgE)
- MC are implicated in both acquired and innate immune responses, wound healing, fibrosis, angiogenesis
- MC are implicated in all types of HS and in the pathophysiology of several (if not all) chronic inflammatory, autoimmune and allergic diseases.

Mast cell activation disorders

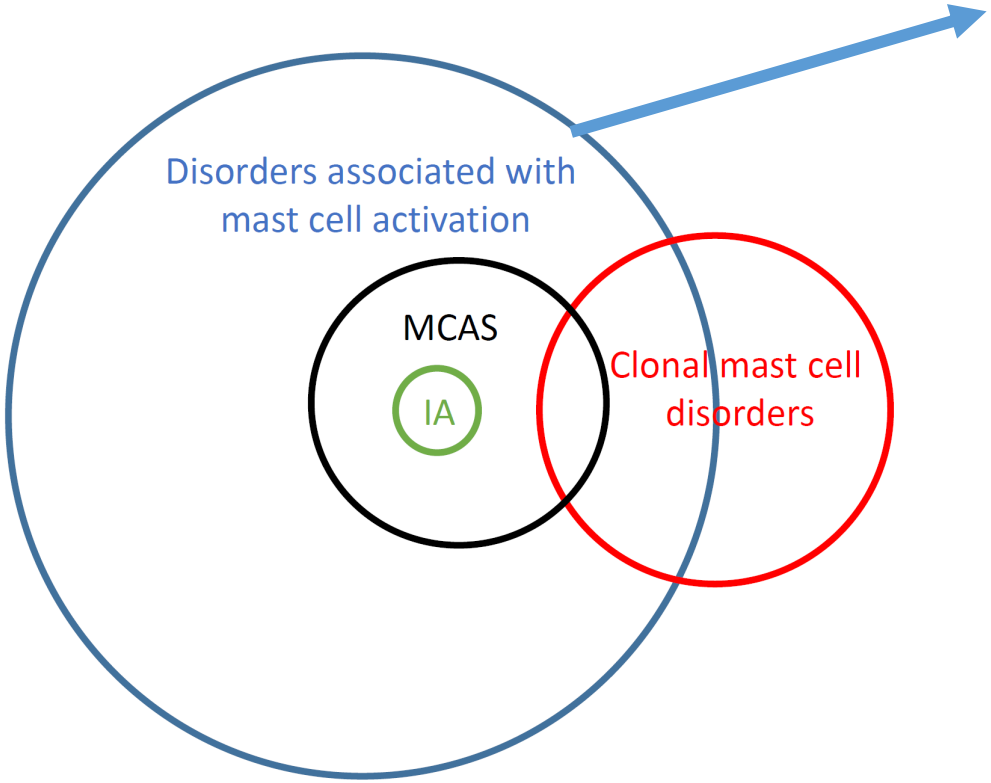

FIG 1. Relationship between clonal mast cell disorders, mast cell activation syndrome *(MCAS)*, and idiopathic anaphylaxis *(IA)*. *Circle sizes* do not represent prevalence.

Disorders (diseases or symptoms) associated with mast cell activation

- **Localized**
  - Asthma
  - Rhinitis
  - Conjonctivitis
  - Urticaria
  - GI: nausea, diarrhea, abdominal cramps (IBD)
  - Neurological symptoms: asthenia, headaches
- **Systemic**
  - Anaphylaxis
  - Idiopathic anaphylaxis
  - Mast cell activation syndrome
  - Clonal mast cell disorders

Mast cell activation syndromes (MAS)

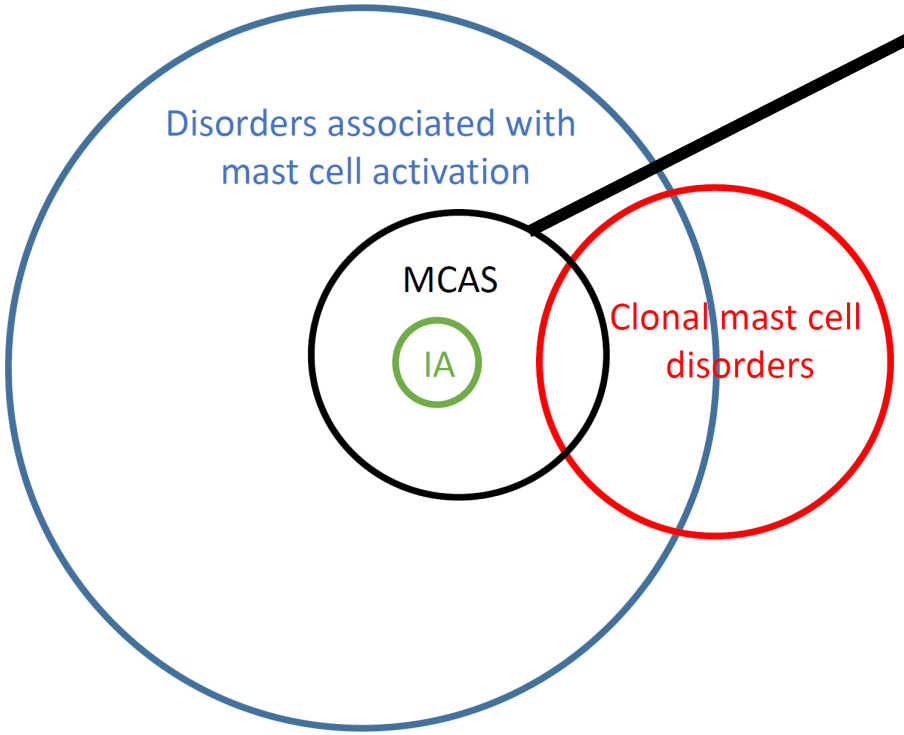

FIG 1. Relationship between clonal mast cell disorders, mast cell activation syndrome *(MCAS)*, and idiopathic anaphylaxis *(IA)*. *Circle sizes* do not represent prevalence.

Criteria for mast cell activation syndrome (all 3 must be present)

1. Episodic **multisystem symptoms** consistent with MC activation
2. Documented **increase in serum tryptase levels** during a symptomatic period compared with the patient's baseline values
3. Appropriate **response to medications** targeting MC-derived mediators, MC-stabilizing agents, or both

Akin C. Mast cell activation syndromes. J Allergy Clin Immunol. 2017;140:349-355
Valent P et al. Mast cell activation syndrome: Importance of consensus criteria and call for research. J Allergy Clin Immunol. 2018;142:1008-1010

Outline

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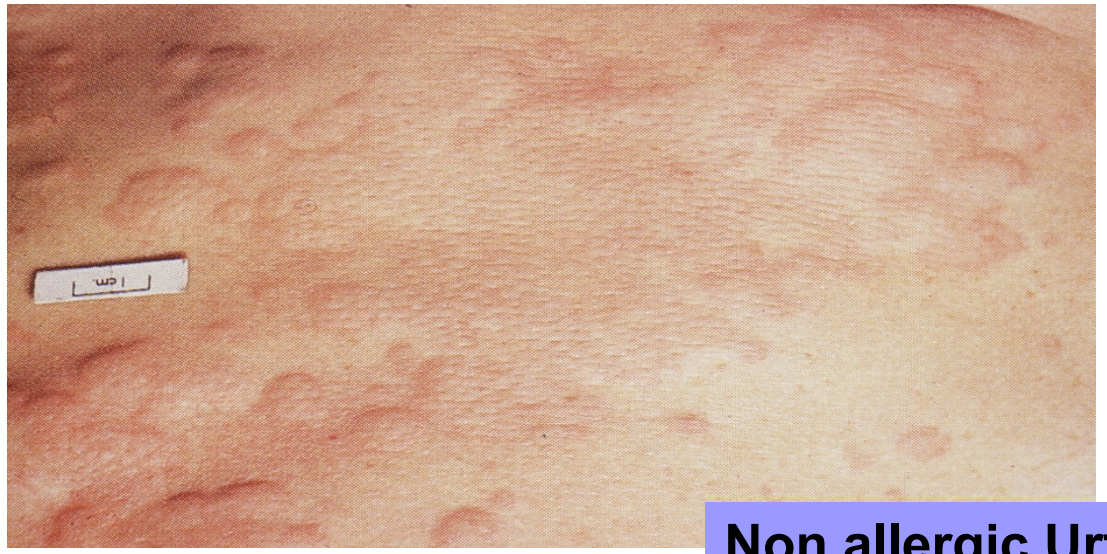
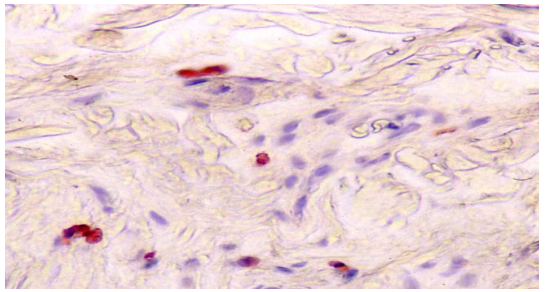
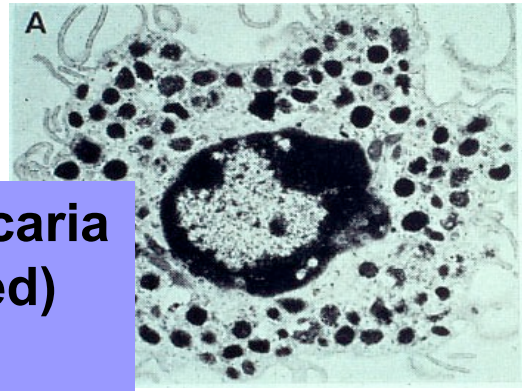
URTICARIA: pathophysiology

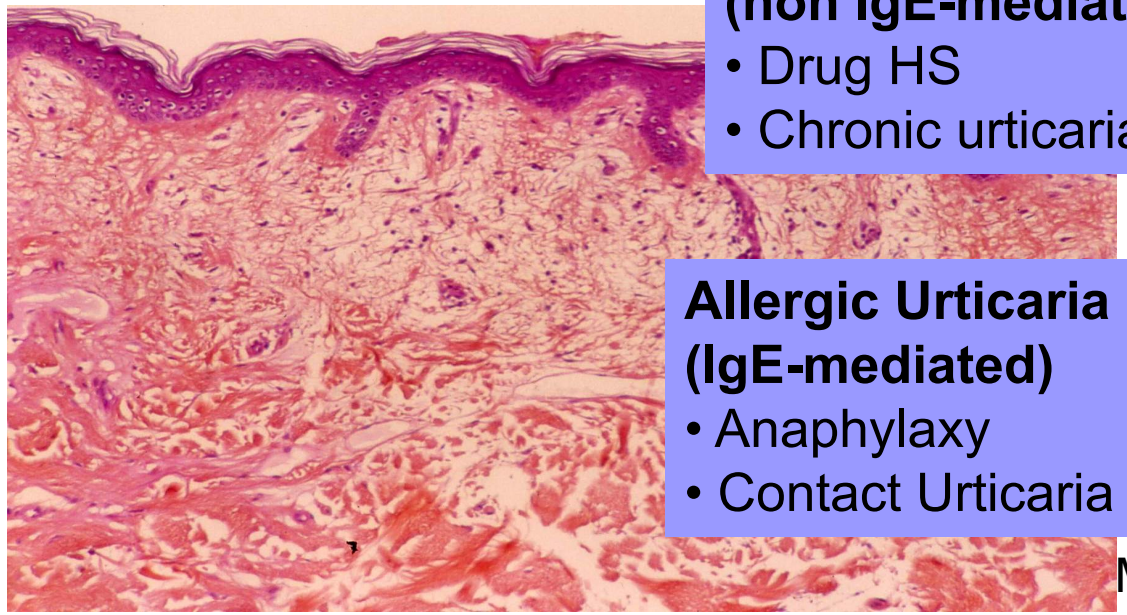


Œdème du derme / Vai

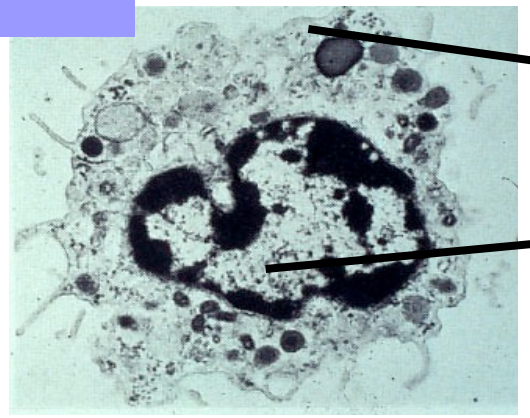




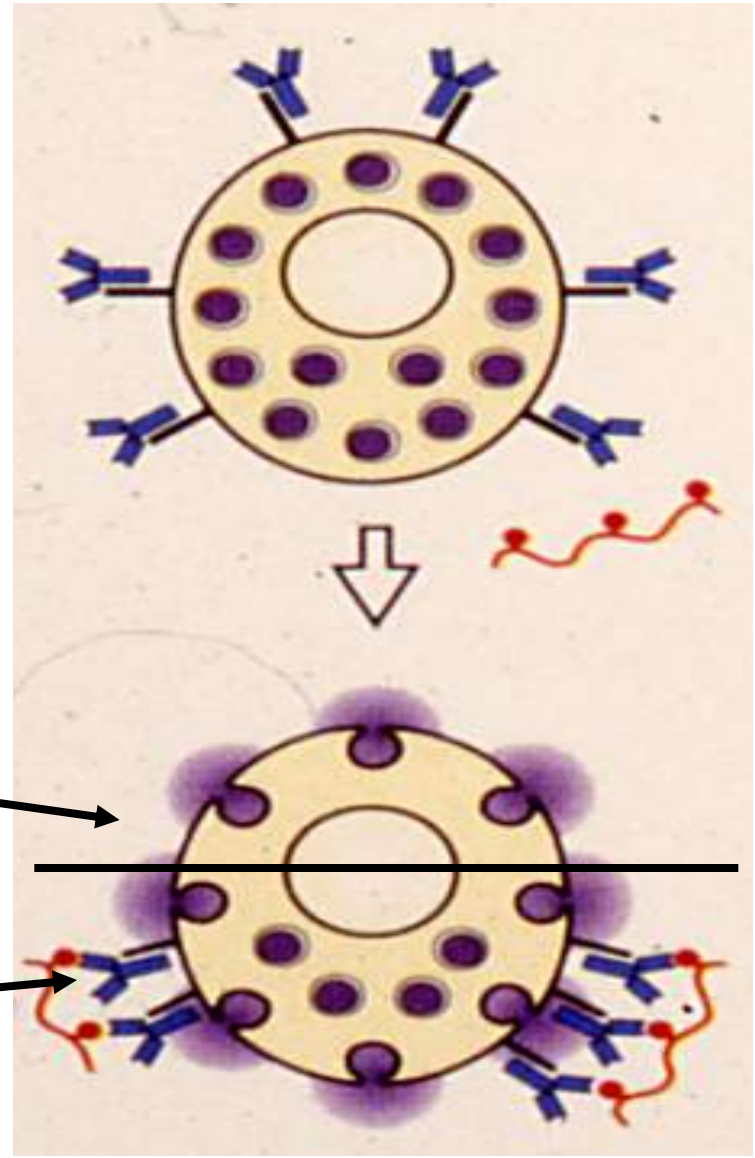
Non allergic Urticaria (non IgE-mediated)
- Drug HS
- Chronic urticaria



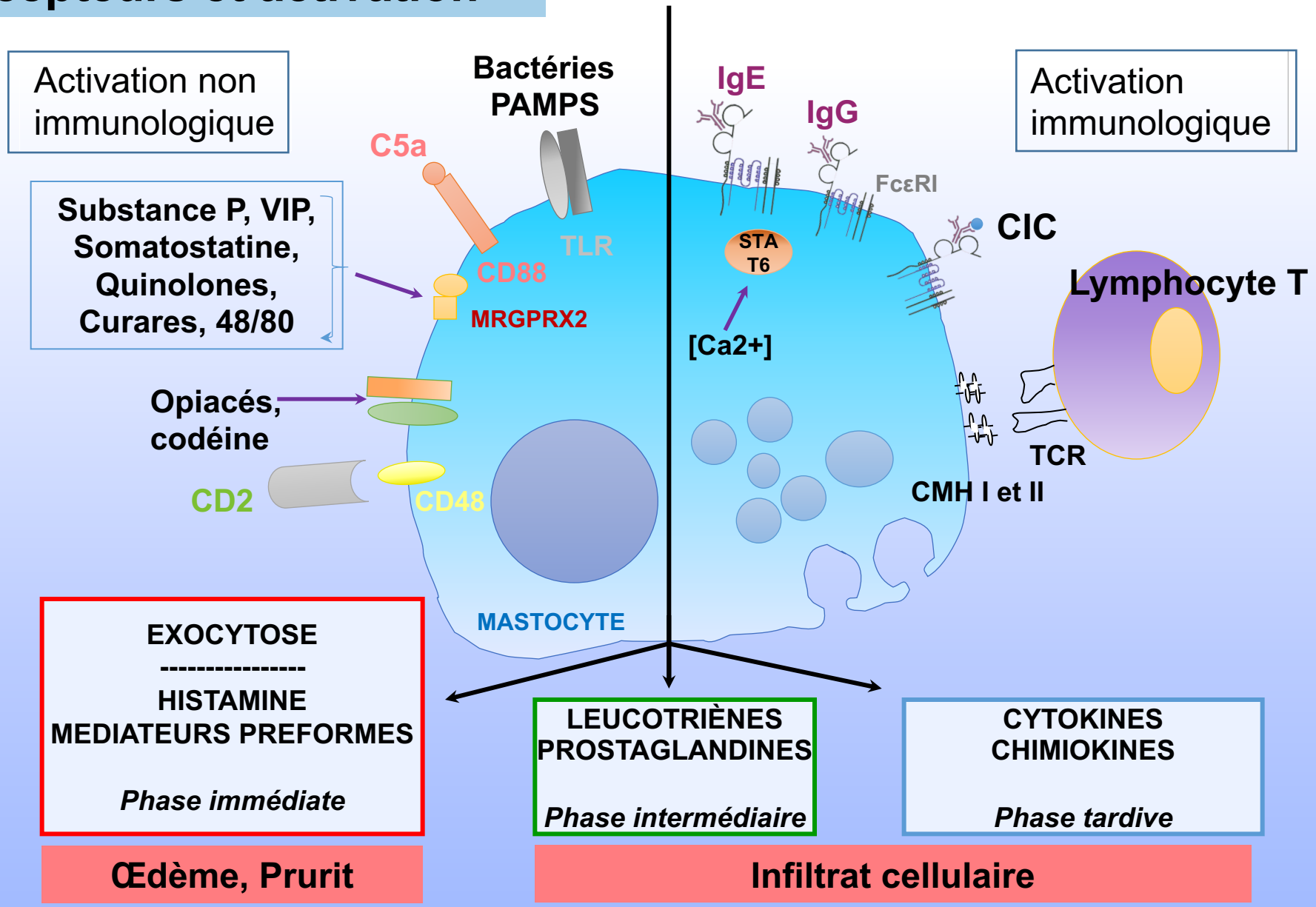
Allergic Urticaria (IgE-mediated)
- Anaphylaxy
- Contact Urticaria



Mast cell / Histamine

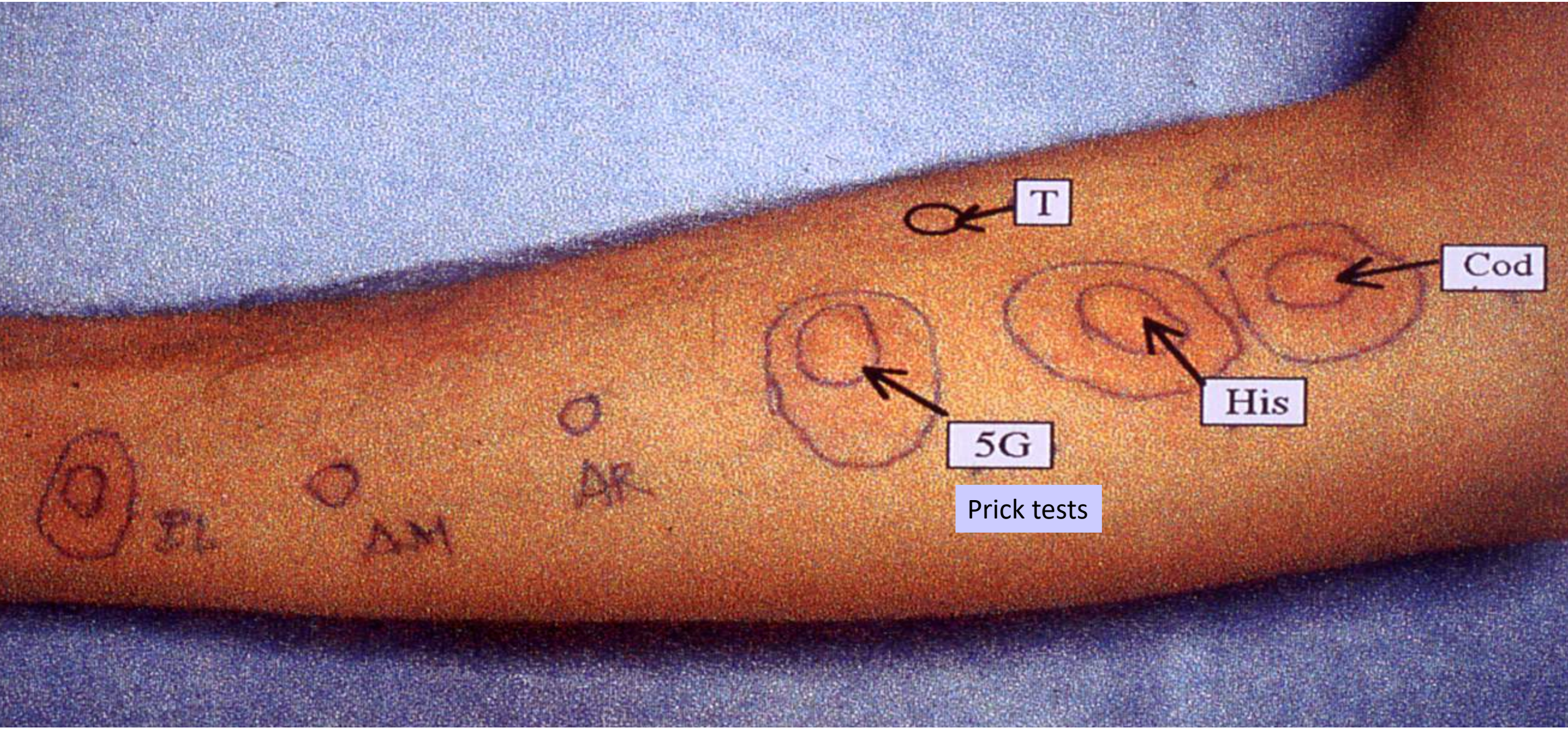


MASTOCYTES
Récepteurs et activation

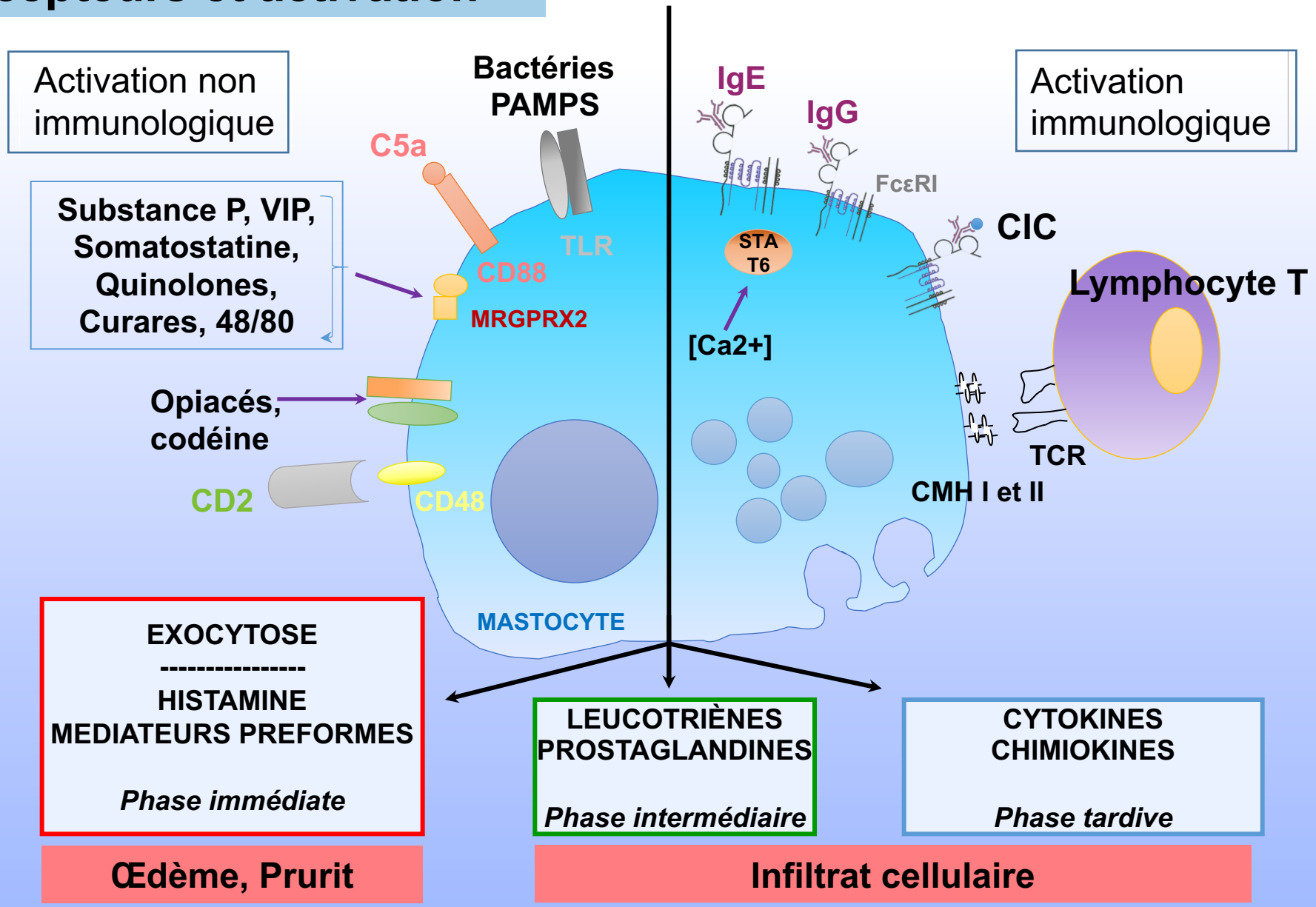


Urticaria – Immediate phase

Skin prick tests of allergens on the forearm



MASTOCYTES
Récepteurs et activation



Urticaria – Late phase

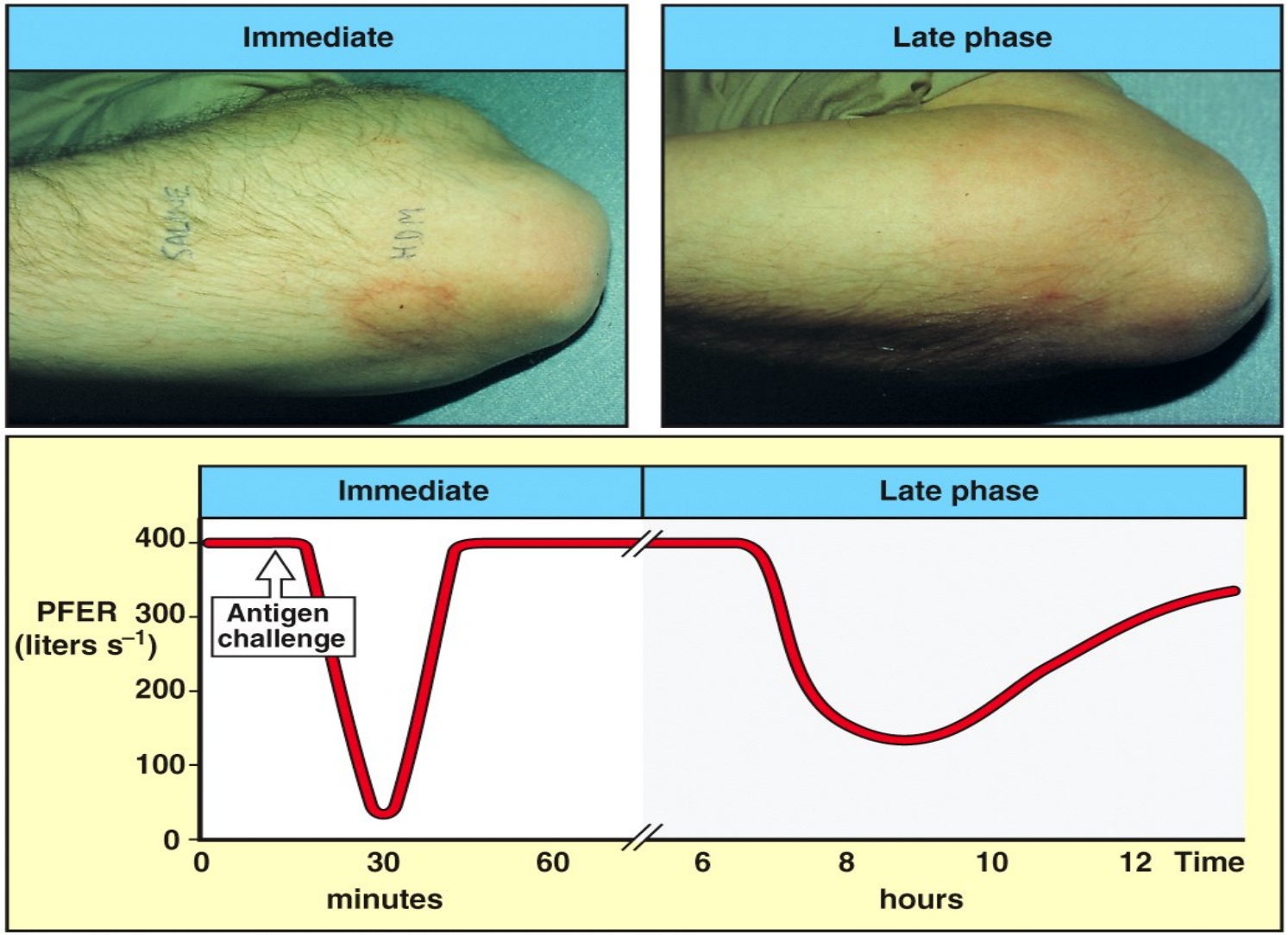
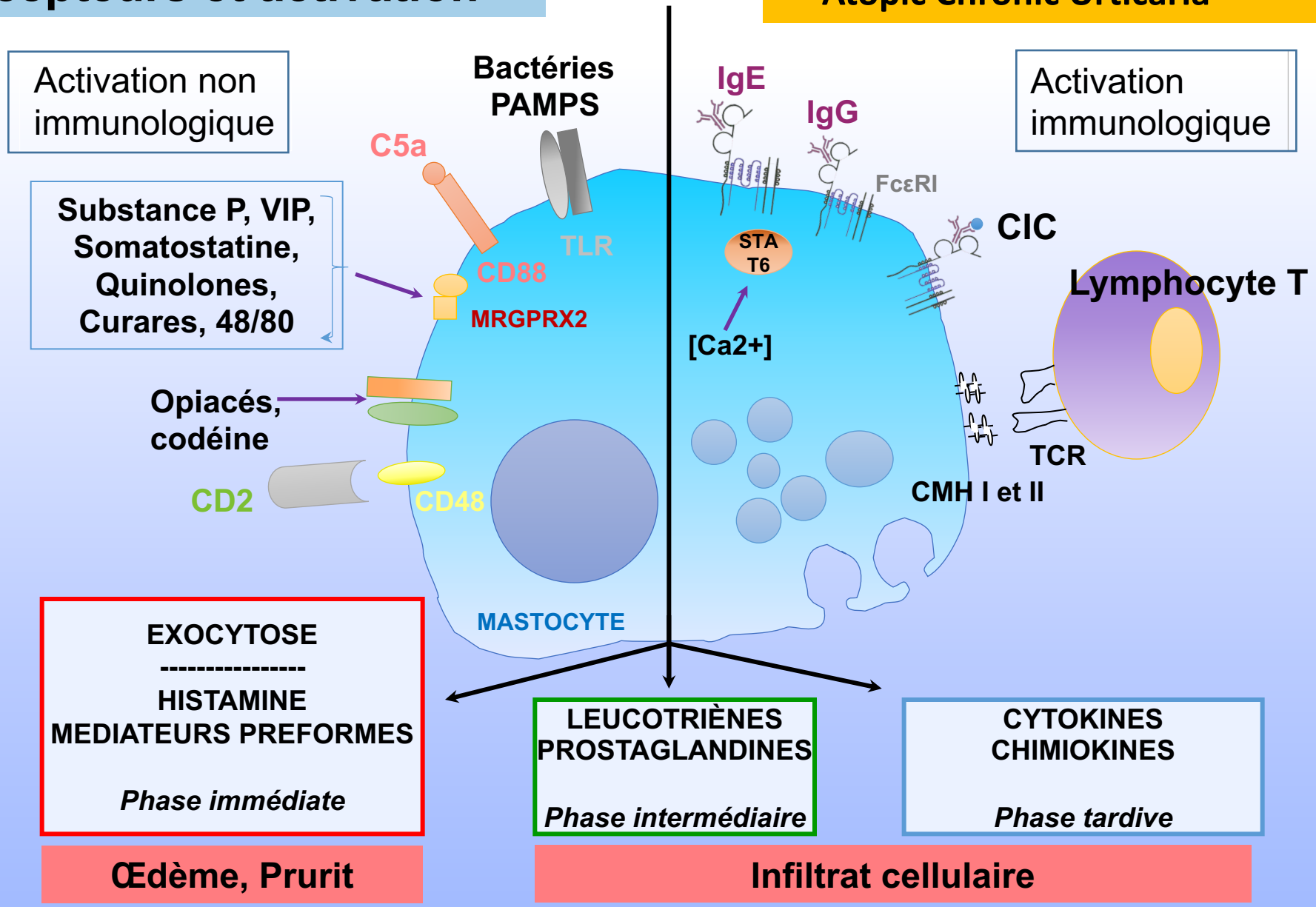


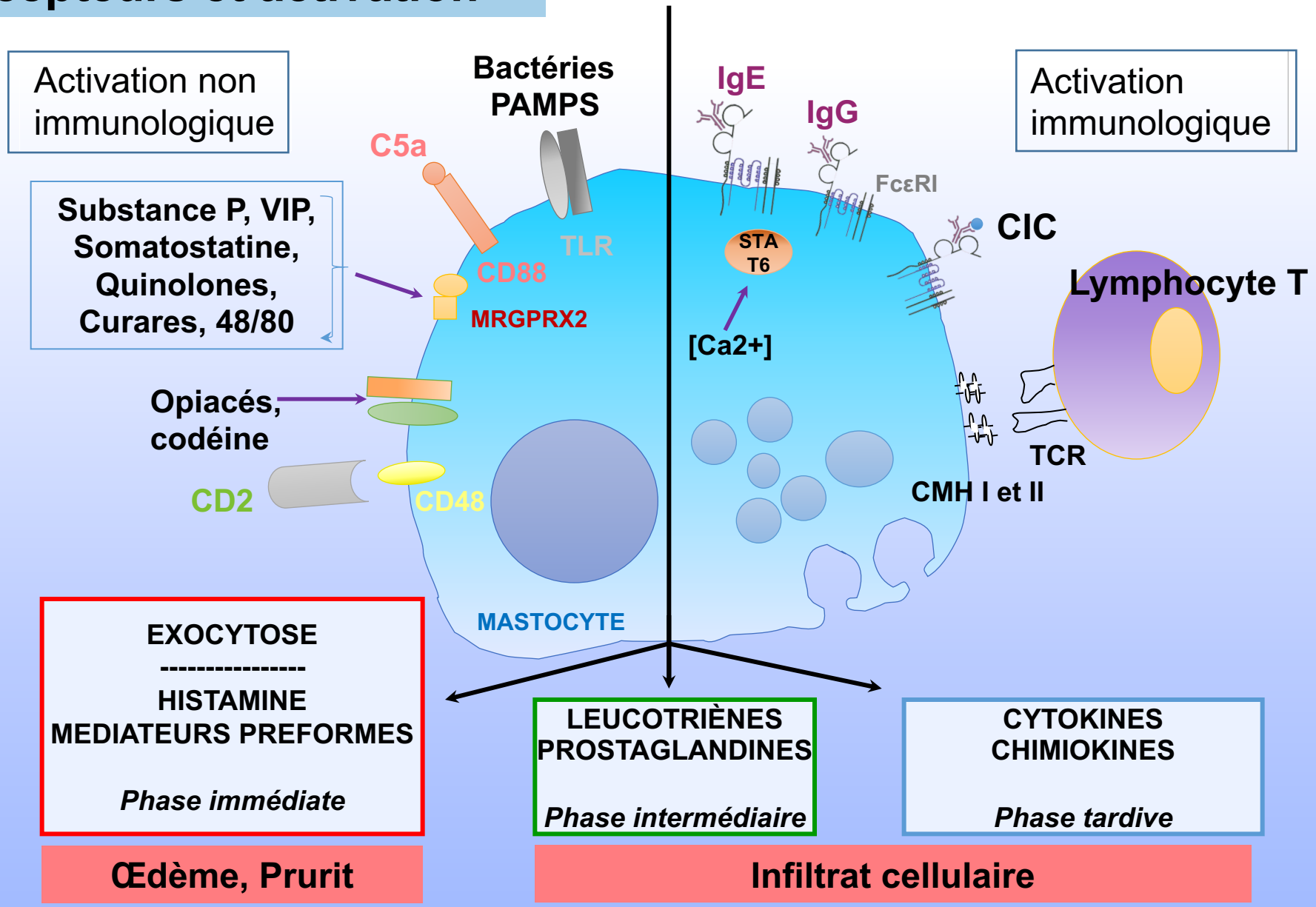
Figure 12-16 Immunobiology, 6/e. (© Garland Science 2005)

MASTOCYTES
Récepteurs et activation

- Autoimmune Chronic Urticaria
- Atopic Chronic Urticaria



MASTOCYTES
Récepteurs et activation



LETTER 12 MARCH 2015 | VOL 519 | NATURE | 237

doi:10.1038/nature14022

Identification of a mast-cell-specific receptor crucial for pseudo-allergic drug reactions

Benjamin D. McNeil[1], Priyanka Pundir[2], Sonya Meeker[3], Liang Han[1], Bradley J. Undem[3], Marianna Kulka[2,4] & Xinzhong Dong[1,5]

Mast cells are primary effectors in allergic reactions, and may have important roles in disease by secreting histamine and various inflammatory and immunomodulatory substances[1,2]. Although they are classically activated by immunoglobulin (Ig)E antibodies, a unique property of mast cells is their antibody-independent responsiveness to a range of cationic substances, collectively called basic secretagogues, including inflammatory peptides and drugs associated with allergic-type reactions[1,3]. The pathogenic roles of these substances have prompted a decades-long search for their receptor(s). Here we report that basic secretagogues activate mouse mast cells *in vitro* and *in vivo* through a single receptor, Mrgprb2, the orthologue of the human G-protein-coupled receptor MRGPRX2. Secretagogue-induced histamine release, inflammation and airway contraction are abolished in Mrgprb2-null mutant mice. Furthermore, we show that most classes of US Food and Drug Administration (FDA)-approved peptidergic drugs associated with allergic-type injection-site reactions also activate Mrgprb2 and MRGPRX2, and that injection-site inflammation is absent in mutant mice. Finally, we determine that Mrgprb2 and MRGPRX2 are targets of many small-molecule drugs associated with systemic pseudo-allergic, or anaphylactoid, reactions; we show that drug-induced symptoms of anaphylactoid responses are significantly reduced in knockout mice; and we identify a common chemical motif in several of these molecules that may help predict side effects of other compounds. These discoveries introduce a mouse model to study mast cell activation by basic secretagogues and identify MRGPRX2 as a potential therapeutic target to reduce a subset of drug-induced adverse effects.

Substance	Mrgprb2 EC_{50}	MRGPRX2 EC_{50}
Compound 48/80	3.7 ± 0.5 μg/ml	470.1 ± 139.6 ng/ml
Substance P	54.3 ± 4.9 μM	152.3 ± 48.0 nM
Cortistatin-14	21.3 ± 0.9 μM	106.7 ± 39.3 nM
PAMP (9-20)	12.4 ± 1.6 μM	166.0 ± 35.7 nM
Mastoparan	24.0 ± 3.6 μM	3.9 ± 0.7 μM
Icatibant	32.5 ± 2.0 μg/ml	15.8 ± 2.7 μg/ml
Cetrorelix	23.4 ± 1.4 μg/ml	221.7 ± 63.1 ng/ml
Sermorelin	29.1 ± 1.2 μg/ml	4.5 ± 0.9 μg/ml
Octreotide	10.0 ± 1.1 μg/ml	6.6 ± 0.7 μg/ml
Leuprolide	152.0 ± 7.1 μg/ml	9.1 ± 0.7 μg/ml
Atracurium	44.8 ± 1.4 μg/ml	28.6 ± 2.4 μg/ml
Rocuronium	22.2 ± 3.3 μg/ml	261.3 ± 14.4 μg/ml
Ciprofloxacin	126.5 ± 5.1 μg/ml	6.8 ± 0.5 μg/ml
Moxifloxacin	14.1 ± 2.1 μg/ml	9.9 ± 0.6 μg/ml
Levofloxacin	807.6 ± 47.1 μg/ml	22.7 ± 0.4 μg/ml
Ofloxacin	225.0 ± 25.4 μg/ml	30.1 ± 1.5 μg/ml

LETTER 12 MARCH 2015 | VOL 519 | NATURE | 237
doi:10.1038/nature14022

- Récepteur non sélectif
- Tous les mastocytes n'expriment pas MRG
- Variants avec gain ou perte de fonction
- Lie des peptides et molécules aux propriétés physico-chimiques particulières
  - -Cationique, Hydrophobiques,
  - -Peptides toxines
  - -Neuropeptides
  - -Peptides anti-microbiens
  - -Other endogenous peptides: kallicreine
  - -Peptides médicaments

ell-specific receptor crucial reactions

Han[1], Bradley J. Undem[3], Marianna Kulka[2,4] & Xinzhong Dong[1,5]

we show that drug-induced symptoms of anaphylactoid responses are significantly reduced in knockout mice; and we identify a common chemical motif in several of these molecules that may help predict side effects of other compounds. These discoveries introduce a mouse model to study mast cell activation by basic secretagogues and identify MRGPRX2 as a potential therapeutic target to reduce a subset of drug-induced adverse effects.

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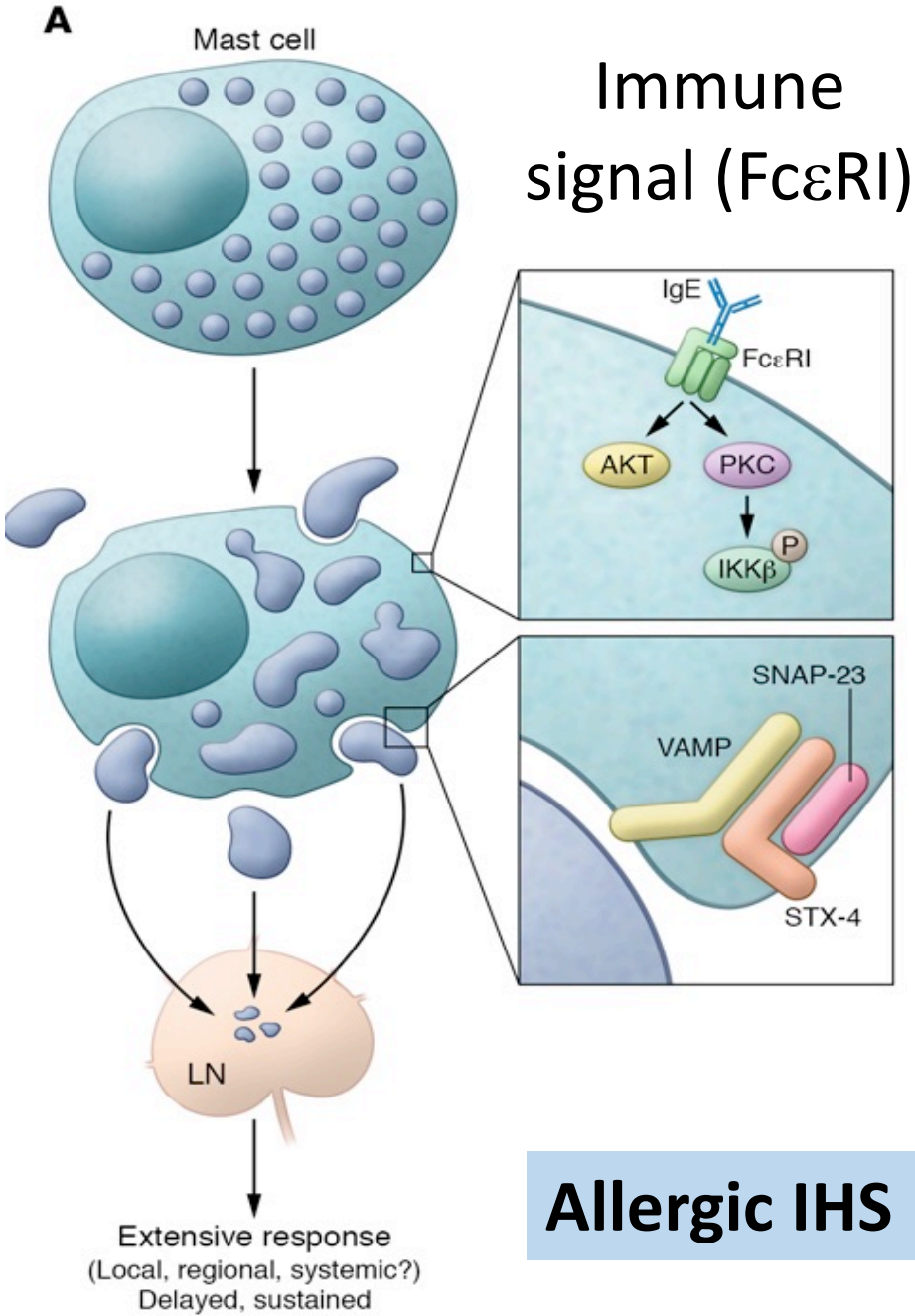
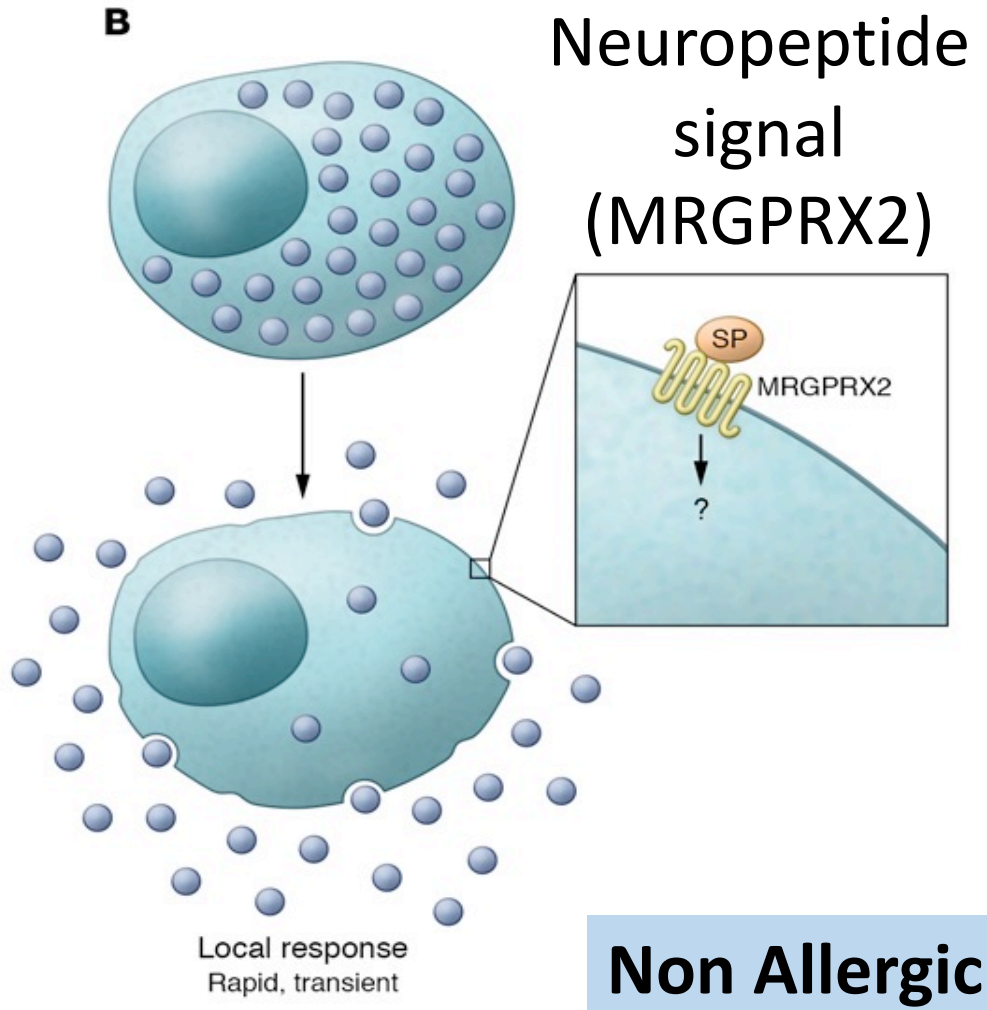
Two fundamental degranulation pathways in mast cells



Immune signal (FcεRI)

Allergic IHS



Neuropeptide signal (MRGPRX2)

Non Allergic IHS

Gaudenzio et al. ***J Clin Invest*** *2016*

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Drug-induced urticaria and angioedema

- **Allergic (IgE)**: rares (5%) and exceptionally isolated

- **Non allergic**: frequent (95%) and almost always benign

- Cousin F, Philips K, Favier B, Bienvenu J**,** Nicolas JF**.** Drug-induced urticaria. **Eur J Dermatol** 2001;11(3):181-7.

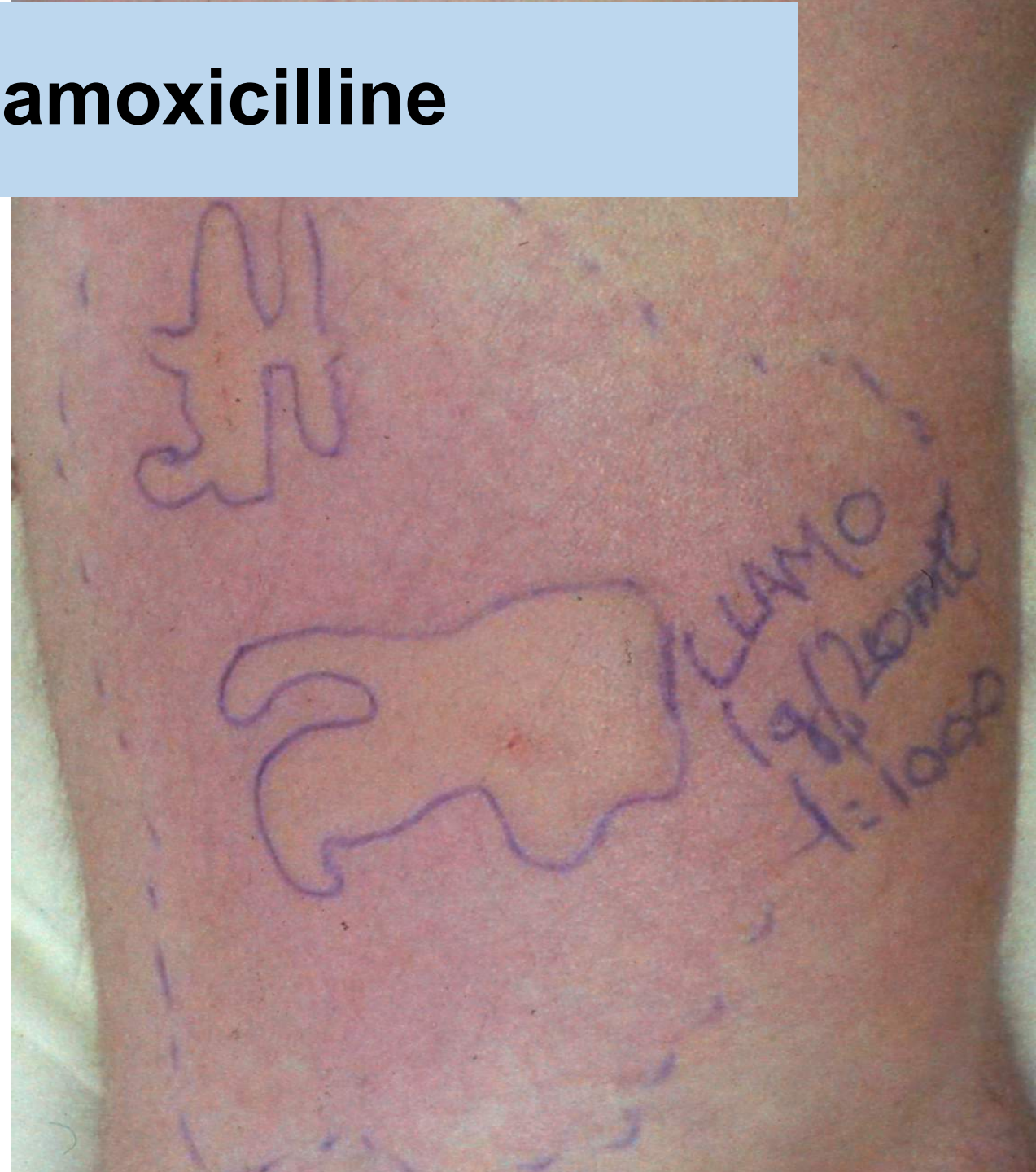
Anaphylactic shock : e.g. amoxicilline

2 minutes after the first tablet
of Amoxicilline 1g

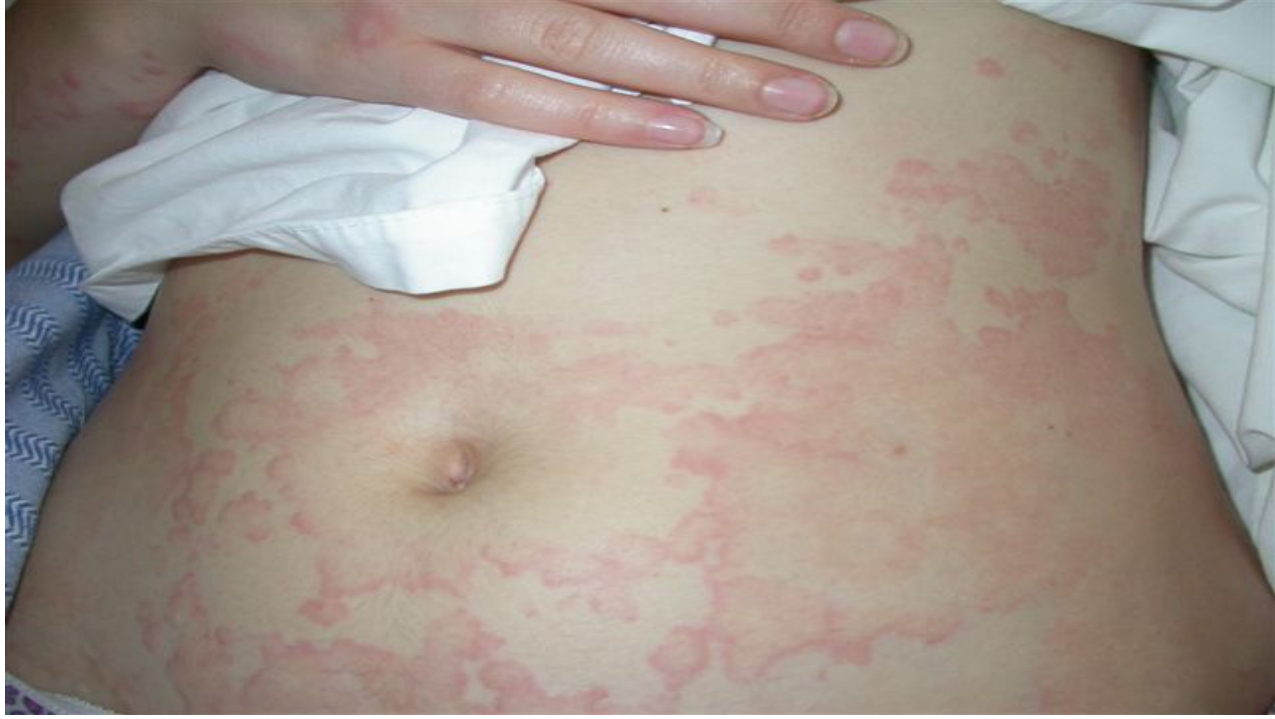
- Bronchospasm
- Cardiac failure
- Vomiting, Diarrhea
- Epinephrine necessary
- Urticaria was not a problem

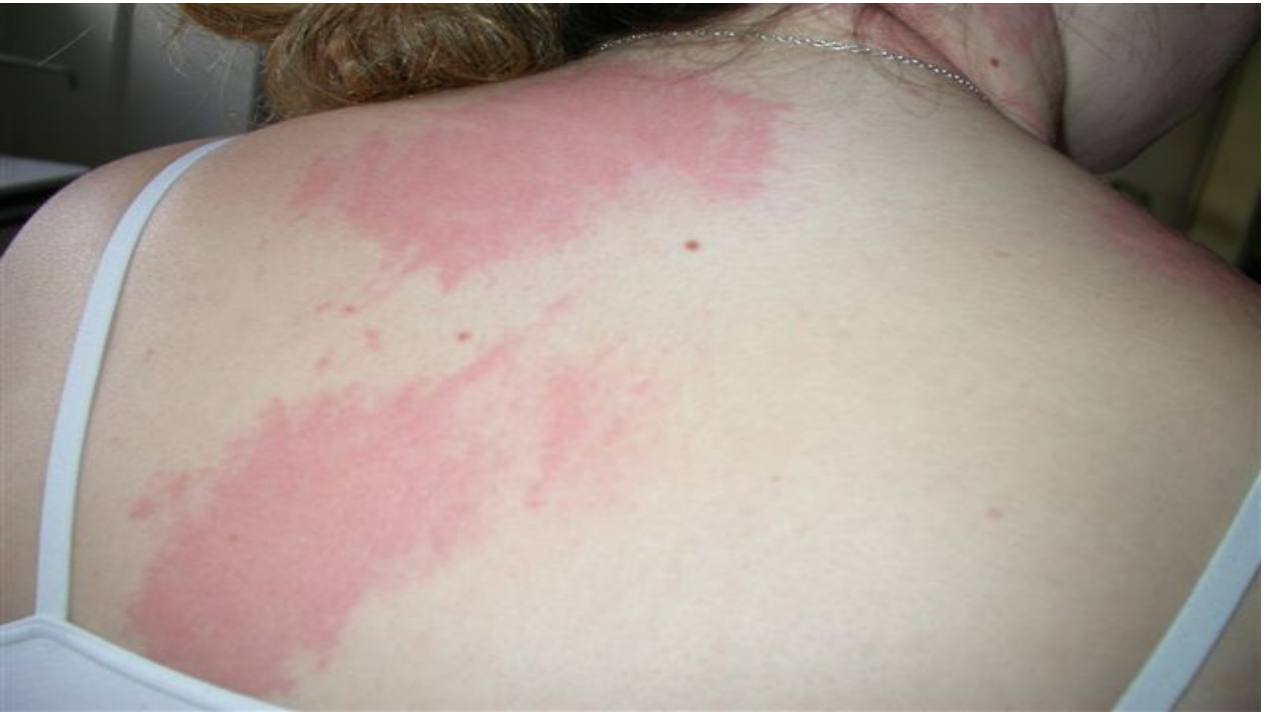
IMMUNOALLERGO work-up
(prick tests, IDT 1:1000 puis 1:100)
- Amox, ampi positive
- C1G positive
- C2G et C3G negative

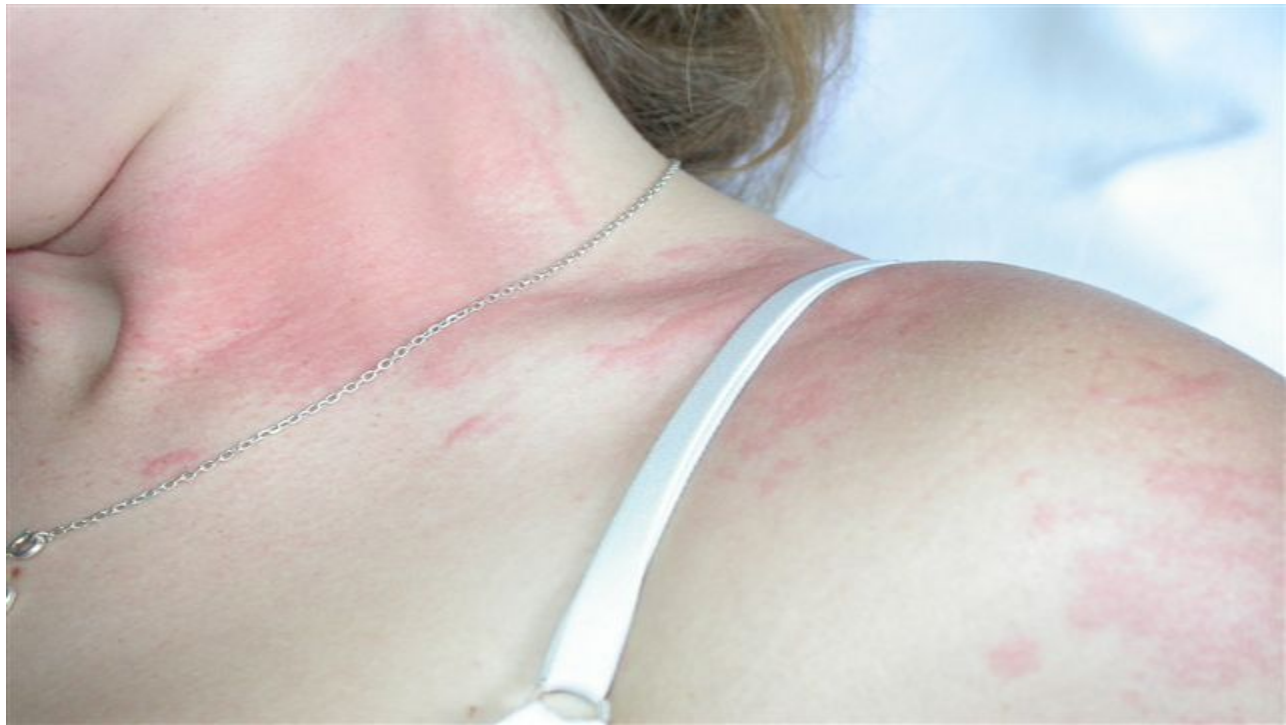
C3G adminisitred to the amox-allergic patient and well tolerated



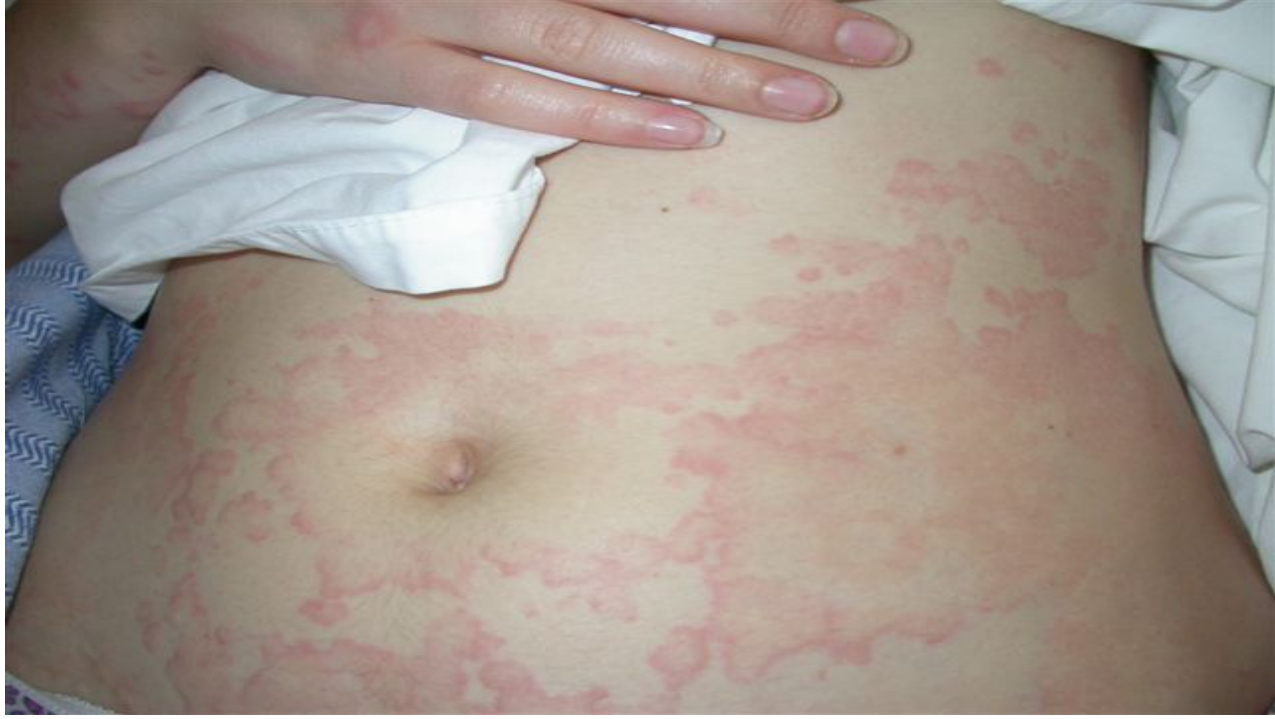

Third day of treatment
Amoxicilline 1g at 7AM
Urticaria at 7:20 AM

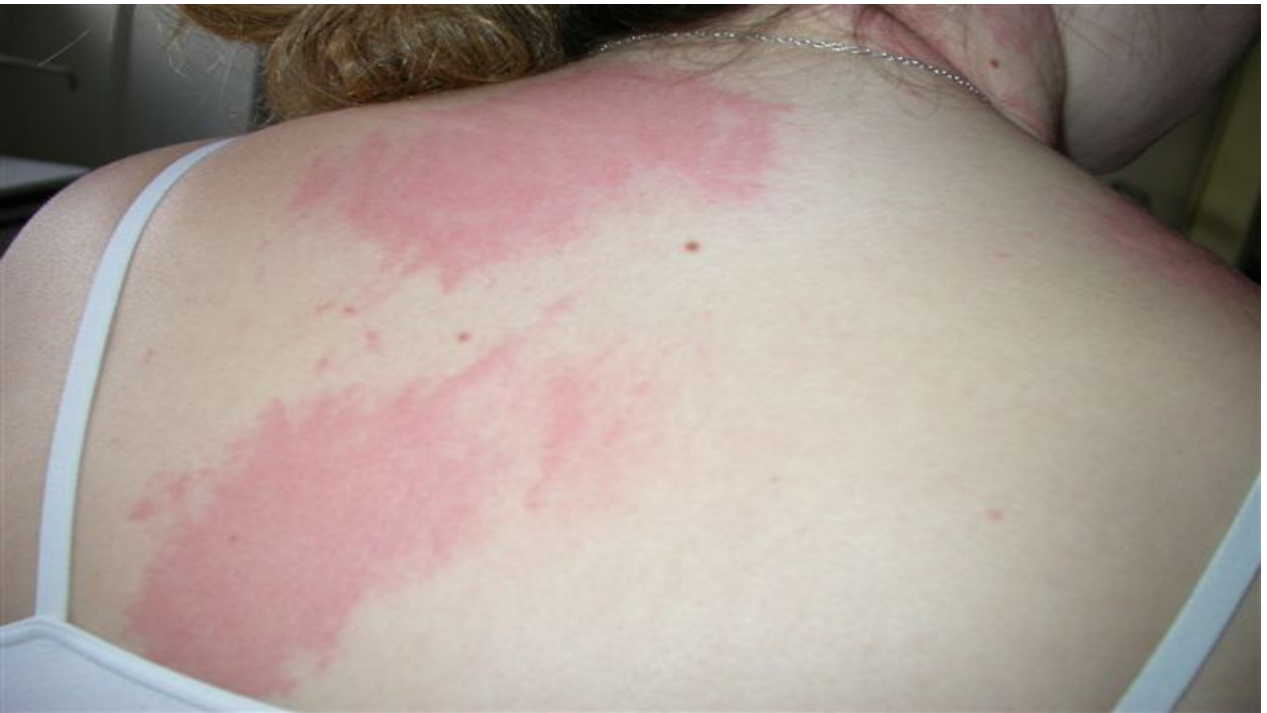


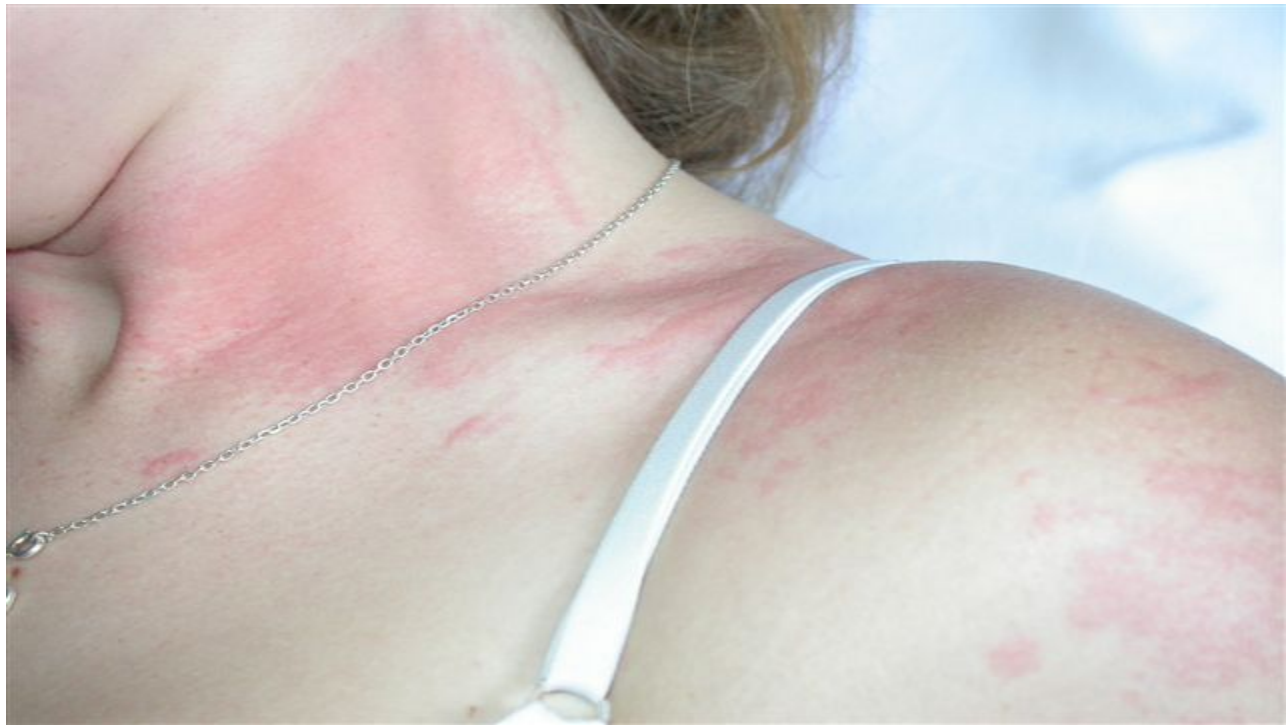


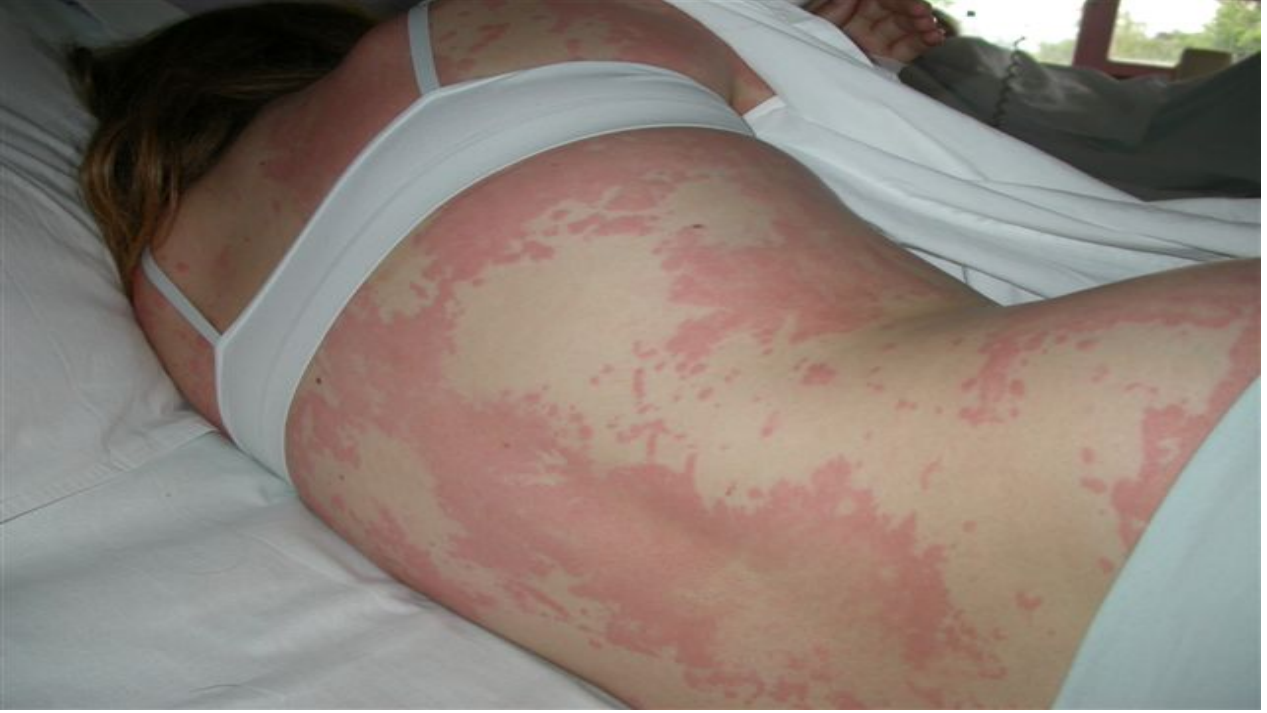


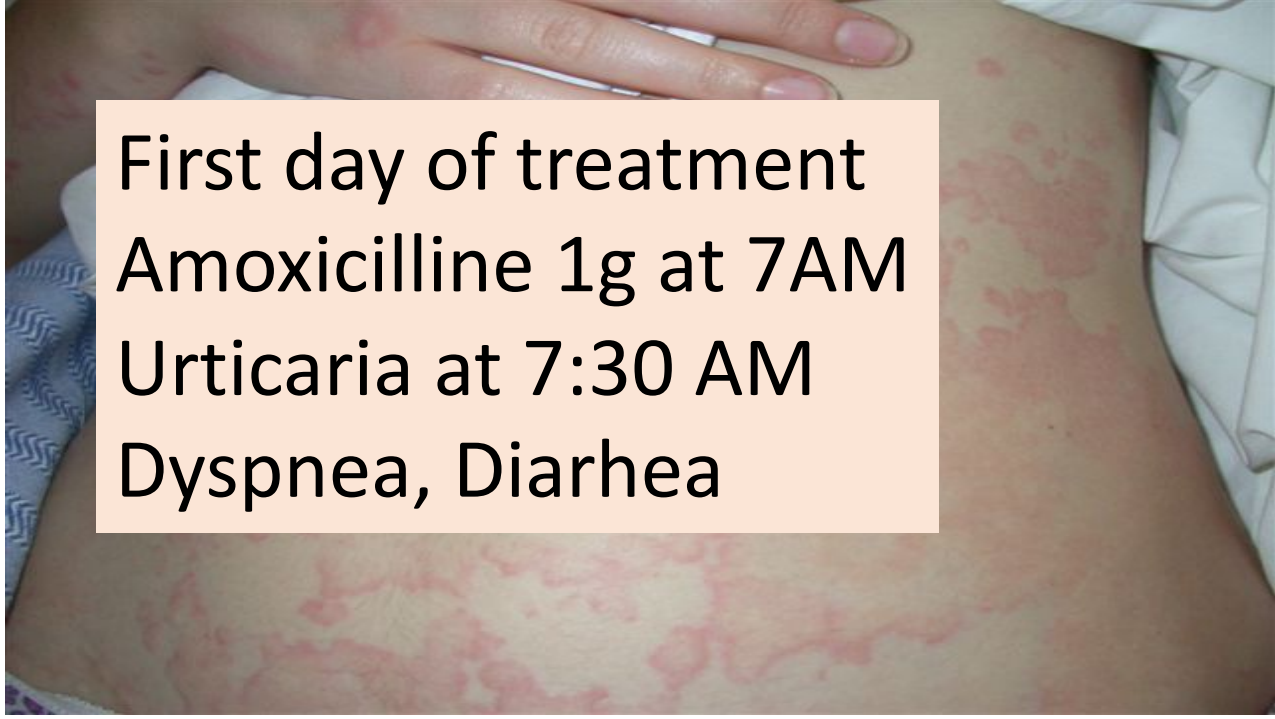

First day of treatment
Amoxicilline 1g at 7AM
Urticaria at 11 AM



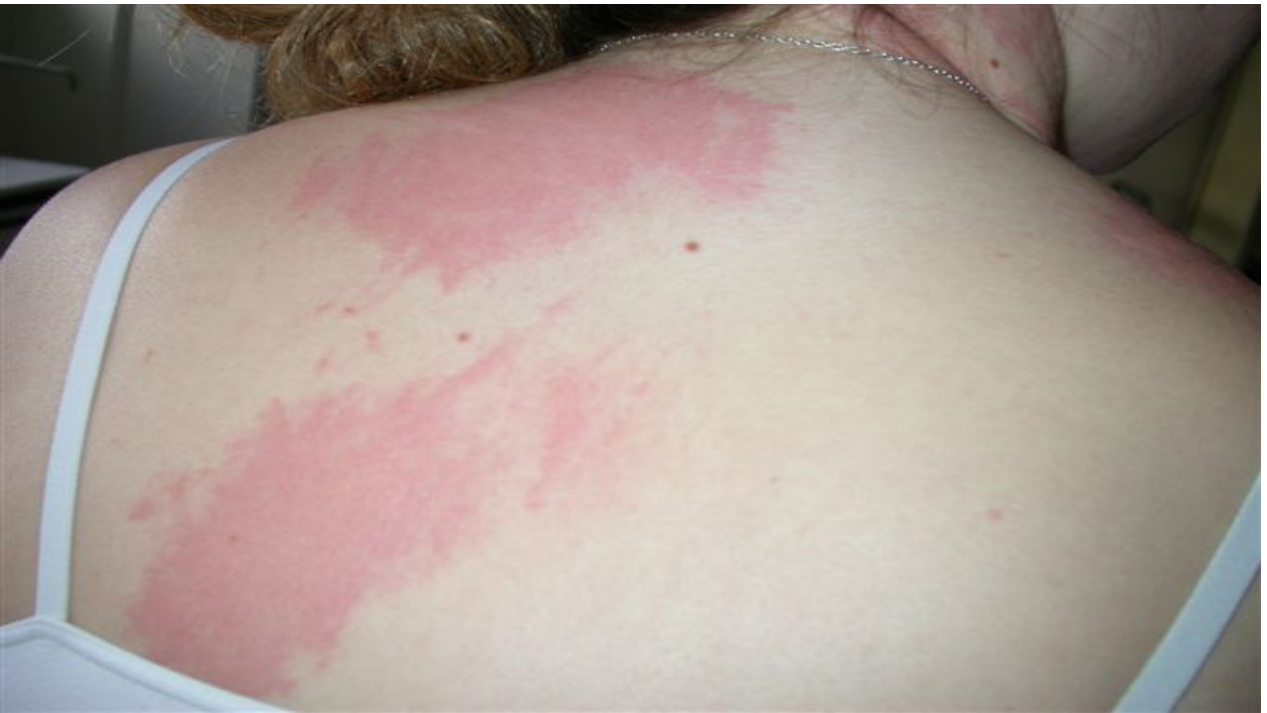


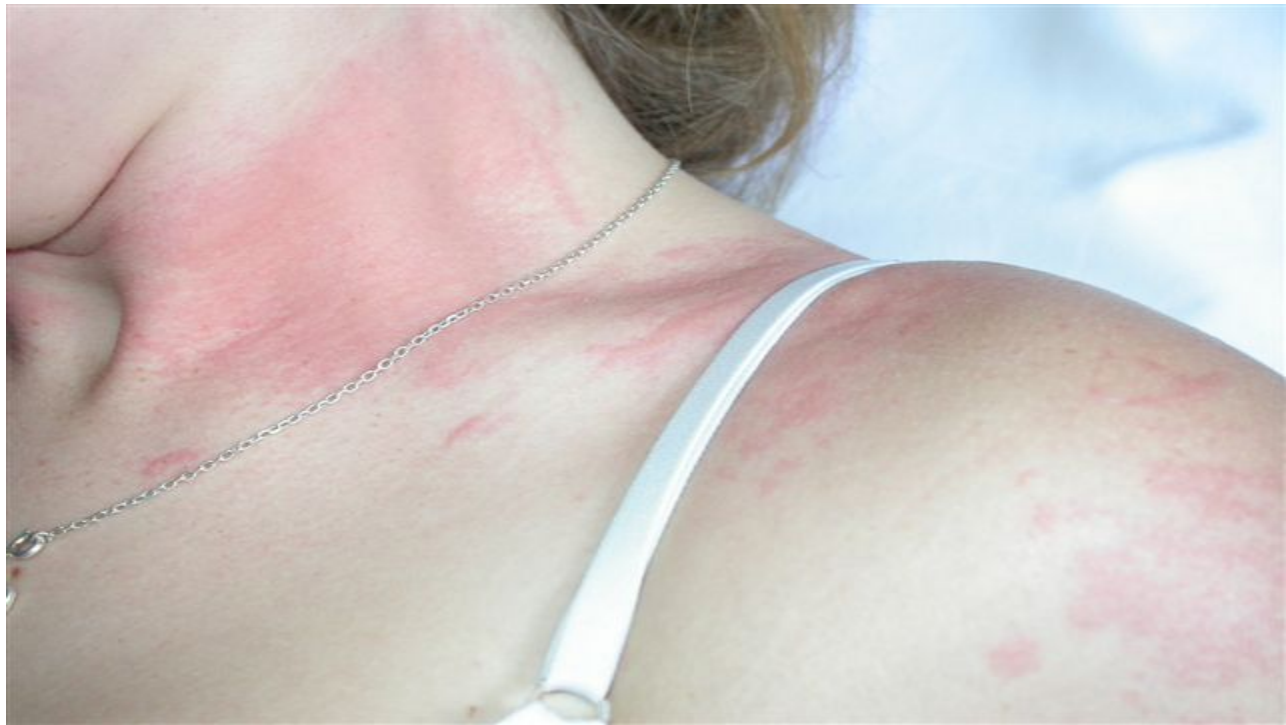






First day of treatment
Amoxicilline 1g at 7AM
Urticaria at 7:30 AM
Dyspnea, Diarhea





Messages clés

- UCS: dermatose inflammatoire chronique
- UCS: activation des mastocytes cutanés dont la physiopathologie est encore inconnue
- UCS + signes systémiques: fréquent (digestifs, asthénie, céphalées)
- Diagnostic des UCS + signes systémiques :
  - UCS
  - SAM si critères diagnostiques réunis

Département Allergologie et Immunologie Clinique

Clinical Research Unit

INSERM translational research team

Allergology & Clinical Immunology Department