DRUG ALLERGIES
Definitions and clinical manifestations
Interactive tool
The content of this publication has been written and edited by the Institut national d’excellence en santé et en services sociaux (National Institute of Excellence in Health and Social Service) (INESSS). This is an excerpt from l’Avis sur la standardisation des pratiques relatives aux allergies aux bêta-lactamines (Notice on the Standardization of practices regarding beta lactam allergies).

The overall opinion and all the other tools are available here.

Authors
Eve-Marie Bisaillon, B.pharm., M.Sc.
Fatiha Karam, Ph. D.
Geneviève Robitaille, Ph. D.

Collaborators
Philippe Bégin, M. D., Ph. D., allergist / immunologist
Marie-Dominique Breault, M. D., emergency physician
Jonathan Lacombe-Barrios, M. D., allergist / immunologist
Georgette Leclerc, M. D., dermatologist
Isabelle Levasseur, RN, nurse practitioner
Hélène Paradis, B. Pharm., pharmacist
Matthieu Picard, M. D., allergist / immunologist
Frédéric Poitras, B. Pharm., pharmacist

Scientific coordinator
Mélanie Tardif, Ph.D.

Scientific leadership
Sylvie Bouchard, B. Pharm., D.P.H., M. Sc., M.B.A.

Knowledge transfer
Amina Yasmine Acher, graphic design
Magali Bérubé, graphic design
Renée Latulippe, coordinator
Mélanie Samson, knowledge transfer
# Table of Contents

Table of adverse drug reactions (ADR) ................................................................. 1
Adverse drug reactions (ADR) ............................................................................. 2
Predictable adverse reactions ............................................................................ 2
Unpredictable adverse reactions ....................................................................... 2
  Intolerance ........................................................................................................ 3
  Pseudoallergic reactions .................................................................................. 3
  Serum sickness-like reactions ........................................................................ 4

**Allergic drug reactions** .................................................................................. 5
  Immediate allergic reactions ........................................................................... 6
  Delayed allergic reactions .............................................................................. 6
  Type I immediate allergic reaction ................................................................ 7
  Type II delayed allergic reactions ................................................................ 7
  Type III delayed allergic reactions ................................................................ 8
  Type IV delayed allergic reactions ................................................................ 8

Table of classification of the different types of allergic reactions caused by medications ................................................................. 9

**Anaphylaxis** .................................................................................................... 10
  Clinical criteria relating to the diagnosis of anaphylaxis ................................ 11

**Angioedema** .................................................................................................. 12

**Urticaria** ........................................................................................................ 12

**Serum sickness** ............................................................................................ 13

**Palpable purpura** ........................................................................................ 13

**Maculopapular rash** ..................................................................................... 14

**Drug reaction with eosinophilia and systemic symptoms (DRESS Syndrome)** ..................................................................................... 14

**Stevens-johnson syndrome (SJS)** ................................................................ 15

**Toxic epidermal necrolysis (TEN)** ................................................................. 15

**Acute generalised exanthematous pustulosis (AGEP)** .................................. 16
Acronyms:
AGEP: Acute generalized exanthematous pustulosis; DRESS: Drug reaction with eosinophilia and systemic symptoms; RASH: Maculopapular rash (also known as maculopapular eruption); SJS: Stevens-Johnson syndrome; TEN: Toxic epidermal necrolysis.
## ADVERSE DRUG REACTIONS (ADR)

**DEFINITION**
Any adverse or unintended drug reactions resulted from a normal dosage, overdose, intoxication or a sub-standard product use.

**CLASSIFICATION**
- Predictable adverse reactions;
- Unpredictable adverse reactions.

### PREDICTABLE ADVERSE REACTIONS
*Synonym: Type A reactions*

**DEFINITION**
Any adverse reaction related to a pharmacological effect that is predictable on the basis of the known pharmacological properties of a drug.

**CLASSIFICATION**
- No activation of the immune system;
- Represent between 85% and 90% of adverse drug reactions;
- Generally dose-dependent, reproducible and often identified prior to the marketing of the drug.

**EXAMPLES**
- Diarrhea following antibiotic use;
- Gastritis during prolonged use of nonsteroidal inflammatory drugs;
- Abuse, intoxication, medication error, therapeutic inefficiency or defective or sub-standard product.

### UNPREDICATBLE ADVERSE REACTIONS
*Synonym: Type B reactions*

**DEFINITION**
Reactions of immunological or non-immunological origins that occur in a subgroup of patients and which signs and symptoms are different from the expected pharmacological action of the drug.

**CLASSIFICATION**
- Activation of the immune system possible depending on the type of reaction;
- Represent between 10% to 15% of adverse drug reactions;
- The effects are not dose-dependent.

**EXAMPLES**
- Allergic reaction;
- Intolerance;
- Pseudoallergic reaction.
### INTOLERANCE

**DEFINITION**

*Non-immunological* reaction attributable to a *pronounced* adverse pharmacological effect which results from the taking of a small or normal dose of a drug and which mechanism is often unknown.

**MECHANISM**

- No activation of the immune system;
- Reactions must be important enough to interfere with daily activities.

**EXAMPLES**

- Headache;
- Digestive symptoms such as vomiting and/or severe diarrhea.

### PSEUDOALLERGIC REACTIONS

*Synonym: non-specific reactions*

**DEFINITION**

Reactions that have apparently the same clinical signs as allergic reactions but *do not involve any activation of the immune system*. These reactions can sometimes be serious (anaphylaxis).

**MECHANISM**

- No activation of the immune system (non-IgE-mediated);
- Degranulation of mast cells and basophils caused by the drug;
- Non-specific release of several mediators (e.g. histamine).

**EXAMPLES**

- Immediate reaction to radiological contrast products;
- Immediate reaction to opiates or vancomycin (red man syndrome);
- Reaction of angioedema or urticaria following the taking of anti-inflammatories.
# SERUM SICKNESS-LIKE REACTIONS

| DEFINITION | Reaction that is similar to clinically known serum sickness and usually occurs one to two weeks after the administration of certain medications. Serum sickness-like reactions to penicillins are rare. The prognosis is usually very favorable and healing takes place 10 to 15 days after stopping the intake of the concerned antibiotic. |
| MECHANISM | • The physiology and pathogenesis of the serum sickness-like reactions are still poorly defined and presumed to be, in the majority of cases, of non-allergic and rather infectious origin (especially in children). |
| CLINIC SYMPTOMS | • Same symptoms as classic serum sickness (severe cutaneous eruptions, mild fever and arthralgia; kidney or liver damage is very rare). |
| EXEMPLE | • Reaction to cefaclor. |
ALLERGIC DRUG REACTIONS

**DEFINITION**
Unexpected reactions that are not related to the dose or to the pharmacological effect for which a clear immunological mechanism is demonstrated.

**MECHANISM**
- Activation of the immune system (production of IgE, IgG or IgM antibodies and/or drug specific CD4 +T lymphocytes);
- Occurs after a sensitization period.

**CLASSIFICATION**
- **Immediate reactions** (Type I);
- **Delayed reactions** (Types II, III et IV).

**CAUTION**
Allergic reactions occur after a period of sensitization.

SENSITIZATION

**DEFINITION**
Phase in which the immune system recognizes, for the first time, the drug as an allergen.

**MECHANISM**
- Production of allergen-specific IgE antibodies that bind to the surface of basophils and mast cells or production of memory CD4 + T cells;
- Asymptomatic phase: the patient does not usually feel any particular symptoms.

**CAUTION**
In the clinic, during the anamnesis, it is often difficult, if not impossible, to identify or confirm a first exposure to an allergen.
# IMMEDIATE ALLERGIC REACTIONS

**Synonym:** IgE-mediated reactions

### DEFINITION
Reactions that usually occur in **less than an hour** but can sometimes take as long as 6 hours to emerge after a drug intake.

### MECHANISM
- Production of specific antibodies of the IgE type.

### CLASSIFICATION
- **Type I** (Gell-Coombs classification)

### EXAMPLES
- Anaphylaxis;
- Angioedema;
- Bronchospasm;
- Hypotension;
- Urticaria.

# DELAYED ALLERGIC REACTIONS

**Synonym:** non-immediate reactions

### DEFINITION
Reactions that may occur at any time **from one hour** after the administration of a drug (usually from a few hours to several days after the drug intake).

### MECHANISM
- Production of specific antibodies of the IgG or IgM type;
- Activation of the complement;
- Production of antigen-specific CD4 + and CD8 + T cells.

### CLASSIFICATION
- **Type II** (Gell-Coombs classification);
- **Type III** (Gell-Coombs classification);
- **Type IV** (Gell-Coombs classification).

### EXAMPLES
- Haemolytic anemia;
- Serum sickness;
- Maculopapular rash;
- Stevens-Johnson Syndrome and Toxic Epidermal Necrolysis (SJS / TEN);
- DRESS syndrome (Drug Reaction with Eosinophilia and Systemic Symptoms);
- Acute Generalized Exanthematous Pustulosis (AGEP).
| **TYPE I IMMEDIATE ALLERGIC REACTION**  
*Synonym: IgE-mediated reactions* |  |
<table>
<thead>
<tr>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>DEFINITION</strong></td>
<td>Reactions that usually occur in <strong>less than an hour</strong>, but can sometimes take as long as 6 hours to emerge after a drug intake.</td>
</tr>
</tbody>
</table>
| **MECHANISM** | • Binding of the drug to the specific IgE present on the surface of mast cells and basophils;  
• Degranulation of cells and release of vasoactive mediators;  
• Recruitment of inflammatory cells. |
| **EXAMPLES** | • Anaphylaxis;  
• Angioedema;  
• Bronchospasm;  
• Hypotension;  
• Urticaria. |

| **TYPE II DELAYED ALLERGIC REACTIONS**  
*Synonym: cytotoxic reactions* |  |
<table>
<thead>
<tr>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>DEFINITION</strong></td>
<td>Allergic reactions usually occur within a few hours after taking the drug, but can sometimes take several days to emerge.</td>
</tr>
</tbody>
</table>
| **MECHANISM** | • Binding of an antibody (IgG or IgM) to a drug which is attached to a cell;  
• Destruction of the cell. |
| **EXAMPLES** | • Haemolytic anemia induced by certain beta-lactams: e.g. penicillin, cephalosporin. |
**TYPE III DELAYED ALLERGIC REACTIONS**
*Synonym: immune complex reactions*

**DEFINITION**
Allergic reactions that usually occur within a few hours after the drug take. Sometimes, however, these reactions can emerge several days later.

**MECHANISM**
- Formation of large immune complexes (drug / IgG or IgM);
- Local or generalized deposition of immune complexes in tissues or in blood vessels;
- Activation of the complement, polynuclear cell and monocytes recruitment as well as cytokine release;
- Tissue damage.

**EXAMPLES**
- Serum sickness;
- Urticaria;
- Palpable purpura;
- Glomerulonephritis;
- Vasculitis;
- Arthritis / arthralgia.

---

**TYPE IV DELAYED ALLERGIC REACTIONS**
*Synonym: cell-mediated reactions*

**DEFINITION**
Allergic reactions that usually occur after 3 days of treatment. However, they can start earlier or occur a few days after stopping treatment (up to 6 weeks for DRESS syndrome).

**MECHANISM**
- Recruitment and activation of CD4 + helper T lymphocytes (Th1, Th2 or Th17) or antigen specific cytotoxic CD8 +;
- Recruitment of monocytes / macrophage and other polynuclear cells (neutrophils and eosinophils).

**EXAMPLES**
- Maculopapular rash;
- SJS / TEN;
- DRESS syndrome;
- AGEP.
<table>
<thead>
<tr>
<th>Type</th>
<th>Common name</th>
<th>Mediators</th>
<th>Pathophysiological features</th>
<th>Clinical manifestations</th>
<th>Time of onset of the symptoms (post-exposure to the medication)</th>
</tr>
</thead>
</table>
| I    | Immediate   | IgE       | • Binding of the drug to the specific IgE present on the surface of mast cells and basophils;  
• Degranulation of cells and release of vasoactive mediators;  
• Recruitment of inflammatory cells. | • Anaphylaxis;  
• Angioedema;  
• Bronchospasm;  
• Hypotension;  
• Urticaria. | From a few minutes to an hour (can take up to 6 hours) |
| II   | Delayed cytotoxic | IgG, IgM | • Binding of an antibody (IgG or IgM) to a drug which is attached to a cell. | • Hemolytic anemia | From a few hours to several days |
| III  | Delayed and immune complex-mediated | IgG, IgM, complement | • Formation of large immune complexes (drug / IgG or IgM);  
• Local or widespread deposition of immune complexes in tissues or in blood vessels;  
• Activation of complement, recruitment of polynuclear cells and monocytes, as well as release of cytokines. | • Serum sickness  
• Purpura palpable  
• Vasculitis | From a few hours to several days |
| IV   | Delayed cell-mediated | CD4 + helper T cells (Th1, Th2 or Th17) or antigen specific cytotoxic CD8 +. | • Recruitment and activation of lymphocytes T (CD4 +, CD8 +), monocytes, eosinophils and neutrophils. | • Rash  
• DRESS syndrome  
• SJS/TEN syndrome  
• AGEP | From a few hours to several days (can take up to 6 weeks for the DRESS) |

Acronyms: AGEP: Acute generalized exanthematous pustulosis; DRESS: Drug reaction with eosinophilia and systemic symptoms; Rash: Maculopapular rash (also known as maculopapular eruption); Ig: immunoglobulins; SJS: Stevens-Johnson syndrome; TEN: Toxic epidermal necrolysis; Th: CD4 helper T cells.
**DEFINITION**

Severe and systemic reaction that appears rapidly following degranulation of mast cells, whether or not it is mediated by IgE*, and involves more than one system of the human body.

*Note: Radiation contrast products and vancomycin may cause non-immunological (non-IgE-mediated) anaphylaxis following systemic and non-specific mast cell degranulation (pseudoallergic reaction).

**CLINICAL MANIFESTATIONS**

**Skin:** hives, itching, angioedema (lips, tongue, throat, face), redness, rash, etc.;

**Gastrointestinal system:** nausea or vomiting, diarrhea or abdominal cramps;

**Respiratory system:** coughing, wheezing, choking, impaired voice, stinging and watery nose, sneezing, difficulty swallowing or breathing, etc.;

**Cardiovascular system:** pale or bluish complexion, weak pulse, unconsciousness, dizziness, vertigo, shock;

**Other systems:** anxiety, feeling of distress, headache.

**CHARACTERISTICS**

<table>
<thead>
<tr>
<th>Reaction type</th>
<th>IgE-mediated</th>
<th>Degree of severity</th>
</tr>
</thead>
<tbody>
<tr>
<td>Immediate (of type I)</td>
<td>yes</td>
<td>severe or very severe if anaphylactic shock (with or without intubation)</td>
</tr>
<tr>
<td>Pseudoallergic</td>
<td>no</td>
<td>severe</td>
</tr>
</tbody>
</table>

**CAUTION**

✓ Anaphylaxis is very likely when one of the three clinical criteria for diagnosis is met.
✓ Intramuscular epinephrine is the only effective treatment for anaphylaxis.
Anaphylaxis is very likely if any one of the following three signs is observed after exposure to an allergen:

1. **Acute** onset of symptoms (from a few minutes to several hours) in the skin, mucous membranes, or both (e.g., generalized urticaria, pruritus or redness, inflammation of the lips, tongue, and uvula), and at least one of the following:
   a. **Respiratory compromise**
      (e.g., dyspnea, wheezing or bronchospasm, stridor, reduced peak expiratory flow [PEF], hypoxemia);
   b. **Reduced blood pressure (BP)** or symptoms associated with target organ dysfunction
      (e.g., hypotonia [collapse], syncope, incontinence).

2. Two or more of the following symptoms that occur rapidly after exposure to an allergen which is probable for this patient (from a few minutes to several hours):
   a. **Involvement of the skin or mucous membranes**
      (e.g., generalized urticaria, pruritus or redness, inflammation of the lips, tongue or uvula);
   b. **Respiratory compromise**
      (e.g., dyspnea, wheezing or bronchospasm, stridor, reduced PEF, hypoxemia, change of voice);
   c. **Reduced blood pressure (BP)** or associated symptoms
      (e.g., hypotonia [collapse], syncope, incontinence);
   d. **Persistent gastrointestinal symptoms**
      (e.g., abdominal cramps, vomiting).

3. **Reduced blood pressure after exposure to a known allergen for that patient**
   (from a few 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 deviation greater than 30% from that person’s baseline.

**CAUTION**
Low systolic blood pressure in children is a function of age and is defined as:
- ✓ <70 mm Hg from 1 month to 1 year;
- ✓ <70 mm Hg + [2 × age] from 1 to 10 years;
- ✓ <90 mm Hg from 11 to 17 years old.

**ANGIOEDEMA**

**DEFINITION**
- Localized and short-term edema (which persists from a few hours to a few days);

**CLINICAL MANIFESTATIONS**
- Can reach skin, mucous membranes, deep dermis and subcutaneous tissue (e.g., eyelid, lip, tongue, throat);
- May occur alone, with urticaria or as part of an anaphylactic reaction.

**CHARACTERISTICS**

<table>
<thead>
<tr>
<th>Reaction type</th>
<th>IgE-mediated</th>
</tr>
</thead>
<tbody>
<tr>
<td>Immediate</td>
<td>yes</td>
</tr>
<tr>
<td>Delayed</td>
<td>no</td>
</tr>
</tbody>
</table>

**URTICARIA**

**DEFINITION**
- Dermatological lesions:
  - nettles (resembling a stinging of nettle);
  - pink or red;
  - separated from each other (papule ≤ 1 cm) or in large plates (≥ 1 cm);
  - change shape or disappear in a **few hours** (less than 2-3 hours).

*Note:* An IgE-mediated urticarial reaction usually lasts **less than 24 hours**.

**CLINICAL MANIFESTATIONS**
- Elevation of the epidermis;
- Itching is often intense.

**CHARACTERISTICS**

<table>
<thead>
<tr>
<th>Reaction type</th>
<th>IgE-mediated</th>
</tr>
</thead>
<tbody>
<tr>
<td>Immediate</td>
<td>yes</td>
</tr>
<tr>
<td>Delayed</td>
<td>no</td>
</tr>
</tbody>
</table>

**CAUTION**

<table>
<thead>
<tr>
<th>Type of urticarial reaction</th>
<th>Allergic</th>
<th>Duration</th>
</tr>
</thead>
<tbody>
<tr>
<td>Immediate of IgE-mediated type</td>
<td>Yes</td>
<td>≤ 24 hours</td>
</tr>
<tr>
<td>Acute (often post-infectious)</td>
<td>No</td>
<td>3 to 6 weeks</td>
</tr>
<tr>
<td>Idiopathic chronic</td>
<td>No</td>
<td>≥ 6 weeks</td>
</tr>
</tbody>
</table>
SERUM SICKNESS

**DEFINITION**
A reaction that occurs after the administration of certain foreign proteins (e.g. horse serum or other species, monoclonal antibodies) and usually emerges 5 to 14 days after injection of the allergen. Serum sickness is rare.

**CLINICAL MANIFESTATIONS**
- Fever;
- Arthralgia;
- Rash (usually pruritic urticaria);
- Lymphadenopathy (sometimes);
- Renal or hepatic impairment (rarely).

**CHARACTERISTICS**

<table>
<thead>
<tr>
<th>Reaction type</th>
<th>IgE-mediated</th>
<th>Severity degree</th>
</tr>
</thead>
<tbody>
<tr>
<td>Delayed (of type III)</td>
<td>no</td>
<td>severe</td>
</tr>
</tbody>
</table>

PALPABLE PURPURA

**DEFINITION**
Macule or purplish red papule that does not fade on pressure and is usually located at the lower extremities and the lumbar region.

**CLINICAL MANIFESTATIONS**
- The lesion is slightly elevated and sometimes painful.

**CHARACTERISTICS**

<table>
<thead>
<tr>
<th>Reaction type</th>
<th>IgE-mediated</th>
</tr>
</thead>
<tbody>
<tr>
<td>Delayed (of type III)</td>
<td>no</td>
</tr>
</tbody>
</table>
**MACULOPAPULAR RASH**
*Synonym: maculopapular eruption*

**DEFINITION**
Erythematous eruption that is often itchy and may temporarily subside under pressure.

**CLINICAL MANIFESTATIONS**
- **Macular lesions**: superficial erythema without relief and without infiltration (macula ≤ 1 cm, spot ≥ 1 cm);
- **Papular lesions**: localized lesions of the dermis, elevated and without infiltration (papule ≤1 cm, plate ≥ 1 cm);
- These lesions may remain separate from each other or join into large plaques (coalescence).

**CHARACTERISTICS**

<table>
<thead>
<tr>
<th>Reaction type</th>
<th>IgE-mediated</th>
<th>Severity degree</th>
</tr>
</thead>
<tbody>
<tr>
<td>Delayed (of type IV)</td>
<td>no</td>
<td>very severe</td>
</tr>
</tbody>
</table>

**DRUG REACTION WITH EOSINOPHILIA AND SYSTEMIC SYMPTOMS (DRESS SYNDROME)**

**DEFINITION**
Serious allergic syndrome which is attributable to a drug and very often characterized by a severe cutaneous eruption.

**CLINICAL MANIFESTATIONS**
- Very inflammatory maculopapular eruption affecting > 50% of body surface area;
- Facial edema often associated;
- General state decreased;
- Fever;
- Lymphadenopathy;
- Lymphocytosis and marked eosinophilia;
- At least one internal organ is impaired (most often hepatitis).

**CHARACTERISTICS**

<table>
<thead>
<tr>
<th>Reaction type</th>
<th>IgE-mediated</th>
<th>Severity degree</th>
</tr>
</thead>
<tbody>
<tr>
<td>Delayed (of type IV)</td>
<td>no</td>
<td>very severe</td>
</tr>
</tbody>
</table>

**CAUTION**
The drugs most commonly associated with DRESS syndrome are beta-lactams, sulfonamides, allopurinol and aromatic anticonvulsants.
**DEFINITION**

Acute and severe dermatological diseases, most often caused by drug allergy.

**CLINICAL MANIFESTATIONS**

- **Sudden destruction and detachment of the superficial layer of the skin** (Nikolsky sign, presence of vesicles or bubbles);
- Mucous membrane damage (e.g. labial and oral mucosa).

<table>
<thead>
<tr>
<th></th>
<th><strong>SJS</strong></th>
<th><strong>TEN</strong></th>
<th><strong>Overlap syndrome</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Form</strong></td>
<td>limited</td>
<td>extended</td>
<td>intermediate</td>
</tr>
<tr>
<td><strong>% Epidermal necrolysis and detachment</strong></td>
<td>≤ 10%</td>
<td>≥ 30%</td>
<td>10-30%</td>
</tr>
</tbody>
</table>

**CHARACTERISTICS**

<table>
<thead>
<tr>
<th>Reaction type</th>
<th>IgE-mediated</th>
<th>Severity degree</th>
</tr>
</thead>
<tbody>
<tr>
<td>Delayed (of type IV)</td>
<td>no</td>
<td>very severe</td>
</tr>
</tbody>
</table>

**STEVENS-JOHNSON SYNDROME (SJS)**  **OR**  **TOXIC EPIDERMAL NECROLYSIS (TEN)**

*Synonym: Lyell syndrome*
ACUTE GENERALISED EXANTHEMATOUS PUSTULOSIS (AGEP)

DEFINITION
Bright red erythematous eruption which is edematous and associated with multiple non-follicular sterile pustules mainly located in the trunk, neck and large folds regions.

CLINICAL MANIFESTATIONS
- Febrile condition frequently associated;
- Leukocytosis with neutrophilia;
- In general, there is no internal organ impaired.

CHARACTERISTICS

<table>
<thead>
<tr>
<th>Reaction type</th>
<th>IgE-mediated</th>
<th>Severity degree</th>
</tr>
</thead>
<tbody>
<tr>
<td>Delayed (of type IV)</td>
<td>no</td>
<td>very severe</td>
</tr>
</tbody>
</table>