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Review Article

# Hypersensitivity to the Bêtalactames

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**Abstract**

Bêtalactames are the antibiotic family the most commonly used both in prophylaxy and therapy. Allergic reactions to penicillin's have been reported since the 1950s, shortly after their introduction as therapeutic agents. An increasing number of reported anaphylactic reactions and other adverse effects proved this to be a serious public health problem. Hypersensitivity to the Bêtalactames is often overestimated with 80% to 90% of patients who report an allergy even without arguments. Documented allergy to betalactames antibiotics is rare but it can be seriously lethal. We are going through this present review, detailing the semiological aspects, the etiopathogenic mechanisms, as well as the risk factors of the Hypersensitivity to the Bêtalactames.

**Keywords:** Drug; Bêtalactames; Hypersensitivity; Allergy

## Introduction

Drug hypersensitivity his immunological reaction characterized by two essential characteristics: it is unpredictable and it is independent of antibiotic dose administered [1]. It constitutes a major clinical problem. Its prevalence remains little known. It is estimated that it affects approximately 10% of hospitalized patients and 7% of ambulatory patient [2]. All medicines may be responsible of a hypersensitivity reaction, although the frequency and the severity of the reaction depend on the molecule. The bêtalactames antibiotics are the most frequently drugs involved in severe reactions [3]. It is classically admitted that almost 10% of the subjects treated by the bêtalactames report suspected bêtalactames allergic reactions to [4].

### Bêtalactames

The β-lactam antibiotics represent a broad class of antibiotics which includes: penicillin's; cephalosporin's; the monobactams; the carbapenems;

Their common structure is molecular defined by a β-lactam ring to which is added a péneme kernel /cephem and the side chains, allowing to define the different classes cited above (Figure 1).

### Mechanisms of allergy to penicillin's

Because of their low molecular weight, the β-lactams can induce a humoral and cellular immunological response. They are capable to cause all types of immunological reactions described by Gell and Coombs. The allergy mediated by immunoglobulin E (IgE) is the most frequent form. It is responsible for the immediate reaction occurring in the hour following the drug therapy. The Delayed hypersensitivity reactions are responsible of Delayed reactions [5]. The clones T as the specific IgE, of allergic patients, recognize the kernel β-lactame as much as the rest of the molecule, which explains the heterogeneity of immune responses [5-9].

The mechanisms involved are numerous and are linked to both the drug chemical properties and the host and are not yet well known

### Mechanisms related to the molecule

The penicillin's are responsible of a large number of allergic reactions due to the high chemical reactivity of the kernel β-lactame and its derivatives [4]. During the penicillin metabolism, it appears that intermediate compounds reagents are able to attach on proteins, to change the structure and thus become immunogenic by production of specific antibodies. Moreover, the native penicillin can also be set directly, on proteins as the HLA molecules antigen presenting cells, to modify the structure and reactivate some specifically clones specific T [10].

### Mechanisms related to the host

The risk to develop drug hypersensitivity depends also on the host itself because of the stimulation level of immune system during antibiotic administration [10].

### The Classifications

The Gell and Coombs classification distinguishes between four types of hypersensitivity (Table 1) [11,12].

### Epidemiology

The hypersensitivity to BL is the most reported in the literature. Penicillin are the most purveyor of allergic reactions. It is reported that 1 to 10% of patients developed a clinical history of penicillin allergy [4], with 0.02% of Anaphylaxis Severe and sometimes fatal [5]. The cephalosporin's allergy varies from 1 to 3% [13]. Now, Amoxicillin is the most beta lactam involved in allergy reaction because of its high prescription [4].

### Risk factor

There are several risk factors associated to development of allergy:

- Treatment itself: character immunogenic of the drug, administration route, repeated exposures
- Environmental factors: in particular viral infections in the Drug Allergies delayed
- Genetic predisposition: The first study, published in 1998 by an Italian team. Romano et al. [14], had showed an association between certain alleles of the CMH (HLA-A2, DRw52) and a delayed hypersensitivity medicinal. Later, it had demonstrated the association




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**Table 1:** Classification of immunological reactions caused by antibiotics [12].

| Classification of Gell and Coombs scope | | Type of immune response | The pathophysiological characteristics | Clinical signs | Usual period of onset of symptoms (after the beginning of treatment) |
|---|---|---|---|---|---|
| Type I | | IgE | Activation of mast cells and basophils, and | Anaphylactic Shock | From a few minutes to 1 hour after the last drug therapy |
| | | | | Angiedema | |
| | | | | Urticaria | |
| | | | | Bronchospasm | |
| Type II | | IgG and FCR* | Dependent cytotoxicity of the RCF | Cytopenias | 5-15 days |
| Type III | | IgG or IgM and complement or rcfs | Filing of Immune Complex | Serum sickness | 7-8 days for the serum sickness |
| | | | | Urticaria | |
| | | | | Vasculitis | 7-21 days for vasculitis |
| | | | | Induced lupus | |
| Type IV | Has | Th1 (INFγ) | Activation of monocytes | Eczemas | 5-21days |
| | B | Th2 (IT-4 and IT-5) | Eosinophilic inflammation | Rash maculopapular bullous and | 2-6 weeks for the syndrome of hypersensitivity drug (DRESS**) |
| | C | T lymphocyte (LT) cytotoxic. | Lysis of keratinocytes mediated by the LT CD4 or CD8 | Rash maculopapular bullous pustular and | < 2 days for the pigmented erythema fixed; 7-21 days for the Stevens-Johnson syndrome and toxic epidermal necrolysis |
| | Of | LT (IT-8/CXCL8) | Recruitment and activation of the Neutrophil | Pustulose exanthématique acute generalized | < 2 days |

*rcfs : Receiver cell membrane for the immunoglobulins;
**Dress: Drug reaction with Eosinophilia and Systemic Symptoms.

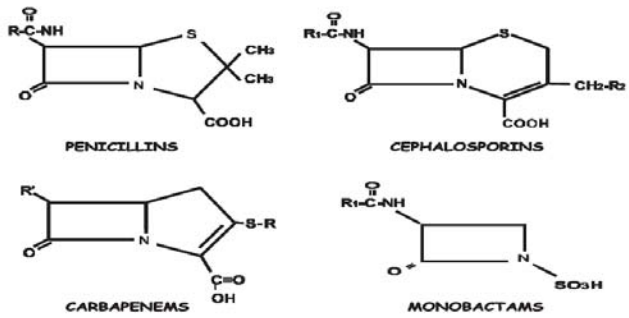


**Figure 1:** Chemical structure of β-lactam antibiotics.

between particular alleles and penicillin allergy [14].

The betalactames antibiotics have the capacity to bind to the amino acids present on various antigenicepitopes of the same protein carrier [15]. These epitopes are modified by a connection of bêtalactams and are presented to the surface of the CPA by HLA molecules of the patient to T lymphocytes. The activation of lymphocytes therefore depends on presence of these epitopes modified and of the alleles HLA-specific HAS capable to present this complex. The molecular heterogeneity of modified epitopes and of HLAalleles could explain the allergic symptoms variations induced by bêtalactames antibiotics. Furthermore, the heterogeneity of allergenic determinants related to penicillin's also explains the absence of associations described up to now with the HLA specificallele.

## Conclusion

The waning of symptoms of suspected hypersensitivity to betalactam antibiotics: exploration by skin tests validated more or less a challenge test can often rule out a true hypersensitivity. Anamnestic information is often insufficient to clear hypersensitivity. For benign eruptions delayed onset, the most common, reintroduction can be achieved in the absence of skin tests, but it is recommended under medical supervision, at least the first outlet. Hypersensitivity to the true therapeutic alternative should be sought, and in some cases, the proposed desensitization protocols.

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