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Allergy to Penicillins – Hypersensitivity: Identification, in vivo Testing, Induction of Tolerance

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ABSTRACT

Penicillin allergy is an immune reaction that can range from mild manifestations, such as urticaria, to severe reactions like anaphylaxis. The present review emphasizes that penicillin allergy is often overreported, underscoring the necessity for proper diagnostic confirmation to prevent the unjustified use of alternative antibiotics, which can contribute to antimicrobial resistance. Desensitization protocols are reviewed as safe options for patients requiring penicillin therapy. The importance of careful patient management, including allergy documentation, patient education, and desensitization strategies, is underscored for optimizing clinical outcomes.

Distinguishing between true allergic reactions and non-immunological side effects is essential to avoid incorrect labeling and to expand the safe use of penicillins, which are crucial in treating severe infections. Accurate diagnosis allows for management strategies such as periodic re-evaluation, patient education, updated records, and the possibility of desensitization when necessary. Additionally, understanding the role of penicillin metabolites, especially penicilloic acid determinants-minor (5% of metabolites), namely benzylpenicillin (penicillin G), benzylpenicilloate and benzylpeniloate, which are important for understanding the pathogenesis of allergic reactions.

Recent advances in developing more precise diagnostic tests and educating healthcare professionals have been made. Nonetheless, there remain gaps in the complete understanding of immunological mechanisms, particularly regarding cross-reactivity with other beta-lactams, which calls for future research. Implementing systematic protocols and maintaining ongoing awareness are essential to improve clinical safety, reduce antimicrobial resistance, and enhance outcomes for patients with penicillin allergy.

Introduction

Penicillins: Structure, Classes, and Clinical Importance of Allergy

Penicillin: A Brief History

The history of penicillin dates back to 1928, when British microbiologist Alexander Fleming, then working at St. Mary's Hospital in London, was investigating new approaches to control pathogenic bacteria, with a particular emphasis on *Staphylococcus aureus*. During his experiments, Fleming observed a remarkable

phenomenon upon returning from a period of absence: one of the bacterial culture plates left inadvertently in the laboratory showed contamination by a fungus previously identified as *Penicillium notatum*. Surprisingly, he found that the cultivated bacterial colonies did not grow in the vicinity of the fungus, resulting in a zone of inhibition characterized by the absence of bacterial growth around the fungus.

Motivated by this observation, Fleming isolated the fungus

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and confirmed that it produced a substance with antibacterial properties, later named "penicillin," marking a revolutionary breakthrough in the development of antimicrobial agents and starting a new era in the treatment of bacterial infections. This discovery represented a milestone in microbiology and the field of antimicrobials, significantly influencing modern medicine.

Despite the initial recognition, large-scale production of penicillin faced significant challenges, and its first clinical applications only occurred in the 1940s. This was made possible through the efforts of researchers such as Howard Florey, Ernst Boris Chain, and Norman Heatley, who purified the substance and developed methods to produce the antibiotic in sufficient quantities. This achievement enabled the mass use of penicillin during World War II, revolutionizing the treatment of bacterial infections and saving millions of lives. The significance of this discovery was recognized with the Nobel Prize in Physiology or Medicine in 1945, awarded to Fleming, Florey, and Chain. The discovery of penicillin marked the beginning of the era of effective antibiotics against a wide range of infectious diseases, catalyzing the development of an entire class of beta-lactam drugs and fundamentally transforming modern medicine. Since then, penicillin has remained a symbol of medical innovation: a revolution that forever changed the fight against infections [1,2].

Structure and Classes of Penicillins

Penicillins represent one of the earliest classes of beta-lactam antibiotics discovered and remain a fundamental cornerstone in the treatment of bacterial infections. The basic chemical structure of penicillin consists of a beta-lactam ring, which is a four-membered cyclic structure containing one nitrogen atom and three carbon atoms which is essential for its antimicrobial activity. In beta-lactam antibiotics, the beta-lactam ring (BL), additional rings, and side chains are described as potential epitopes responsible for allergic reactions mediated by IgE and T lymphocytes. Under physiological conditions, the BL ring is unstable and, in the case of penicillins, results in the generation of major (major-95%) and minor (minor-5%) determinants, which covalently bind to host proteins (hapten-carrier complex). The BL ring binds to lysine residues on serum proteins and creates the main antigenic determinant, penicilloyl-polysine, that accounts for 95% of penicillin metabolites. When covalent binding occurs to carboxyl and thiol groups, it generates several secondary determinants, minor, with benzylpenicillin (penicillin G), benzylpenicilloate, and benzylpenilloate being the most important [3].

This capacity of penicillins to interfere with bacterial cell wall synthesis by targeting penicillin-binding proteins (PBPs) gives penicillins their effectiveness primarily against Gram-positive bacteria, although some also exhibit activity against Gram-negative bacteria. The core structure of penicillins includes a thiazolidine ring attached to the beta-lactam ring, to which different side chains can be linked. These side chains modify the chemical and pharmacological properties of the antibiotic, leading to the classification of various penicillin types [3].

Main Classes of Penicillins and Their Clinical Uses

1. Natural Penicillins: These include penicillin G (benzylpenicillin)

and penicillin V (phenoxymethylpenicillin). They are mainly effective against Gram-positive cocci, such as *Staphylococcus aureus* and *Streptococcus* spp., and some Gram-negative bacteria. Penicillin G requires parenteral administration, while penicillin V can be administered orally due to its better gastrointestinal stability [3].

- 2. Beta-lactamase Resistant Semi-synthetic Penicillins:** Developed to overcome resistance conferred by beta-lactamase produced by staphylococci. Examples include oxacillin, cloxacillin, and methicillin. These penicillins retain activity against Gram-positive bacteria, particularly beta-lactamase-producing staphylococci, without being destroyed by these enzymes [3].
- 3. Aminopenicillins:** they are semi-synthetic penicillins, available since 1960, after the addition of an amino group to the side chain, and have a broader spectrum of action compared to benzylpenicillins including some Gram-negative bacteria such as *Haemophilus influenzae*, *E. coli*, and *Salmonella*. They are often used in respiratory, urinary tract, and other infections. They exhibit good absorption, both orally and parenterally. The aminopenicillins available for clinical use in Brazil are Ampicillin and Amoxicillin [3].
- 4. Antipseudomonal Penicillins:** Exemplified by piperacillin, these penicillins were developed to act against resistant bacteria, especially *Pseudomonas aeruginosa* and other difficult-to-treat Gram-negative bacteria. They are often administered in combination with beta-lactamase inhibitors to broaden their spectrum and efficacy [3].

In addition to these classifications, the development of modified derivatives aims to improve stability, activity, and resistance to beta-lactamase enzymes, as well as to broaden their spectrum of action. Understanding these structures and classes is essential for guiding appropriate therapeutic choices and for the development of new antibacterial agents.

Penicillin Allergy

Penicillin allergy is an adverse reaction of the immune system triggered by exposure to antibiotics in the penicillin group, which includes medications such as penicillin G, penicillin V, amoxicillin, and ampicillin, among others. It is a specific immune response mediated by hypersensitivity mechanisms that primarily involve the production of IgE antibodies. This condition results in sensitization of the immune system after the first exposure to the antibiotic, creating an immunological memory that, on subsequent exposures, leads to the activation of mast cells and basophils with subsequent release of inflammatory mediators. These mediators cause a range of clinical manifestations that can vary from mild, such as light rashes, urticaria, pruritus, erythema, and angioedema, to more severe reactions like anaphylaxis, a medical emergency characterized by symptoms such as respiratory difficulty, sudden drop in blood pressure, and edema, requiring immediate intervention. It is crucial to differentiate a real IgE-mediated penicillin allergy from non-allergic side effects, such as nausea or diarrhea, which are common with any antibiotic use [4].

The prevalence of penicillin allergy varies across different regions of the world and can be influenced by various factors, including population characteristics. Although generally well

tolerated, reports of allergies to beta-lactam antibiotics affect between 11% and 15% of hospitalized patients [5,6]. However, despite the estimate that approximately 10% of the global population are allergic to penicillin, studies have shown that the true prevalence of immediate hypersensitivity, mediated by IgE, is only about 1% to 3% of the population [7-9]. Penicillin sensitization decreases every 10 years, and after 20 years, less than 1% of patients with initial clinical symptoms consistent with an allergic reaction continue to maintain their sensitivity [10]. The discrepancy between reported and actual penicillin allergy may be explained by the decrease in IgE antibodies to penicillin over time, by the misclassification of an adverse reaction, or a drug reaction that was actually an infectious condition [11,12].

It is essential to distinguish between true allergic reactions and mistaken reports of allergy, as approximately 90% of individuals who believe they are allergic to penicillin can tolerate it after appropriate allergy testing. For this reason, allergy testing is important, especially in pregnant women suspected of having syphilis and a history of penicillin allergy. We could also say that skin testing for penicillin immunoglobulin E-mediated reactions to syphilis in pregnant women with a history of penicillin allergy, used in conjunction with clinical history and tolerance induction, can help improve identification of the culprit and be of great value in treating the mother and fetus. Many diagnoses are based on clinical history without adequate confirmatory testing [6].

In Brazil, the prevalence follows a similar trend observed globally, although there are no specific and broadly representative data for the country. Allergy tests such as skin tests and challenge tests can be used to confirm or rule out allergies in individuals who report being allergic to penicillin. Awareness of the need for accurate allergy verification is very important to ensure that antibiotic prescriptions are as appropriate and safe as possible, since incorrect diagnoses can lead to unnecessary use of alternative antibiotics, which may be less effective or more costly.

Clinical Importance of Penicillin Allergy

Due to its clinical significance, it is recommended that healthcare professionals carefully assess patients' allergy histories to penicillins and consider allergy testing when appropriate, in order to optimize treatment and minimize risks. In these cases, the following points should be considered:

1. **Limited Antibiotic Choices:** Since penicillins are a broad class of antibiotics, when a patient is labeled as allergic to penicillins, treatment options become more limited, often leading to the use of alternative antibiotics that may be less effective, more toxic, or more expensive [6,13].
2. **Antibiotic Resistance:** Unnecessary use of second-line antibiotics when penicillin allergy is not confirmed can contribute to the development of bacterial resistance. This is a public health concern because it reduces the effectiveness of available antibiotics [14].
3. **Differentiation of True Allergic Reactions:** Many people who believe they are allergic to penicillin may not have a true IgE-mediated allergy (the classic form of allergy), but rather side effects or idiosyncratic reactions. Confirming the allergy with appropriate tests can allow many patients

to safely use penicillins [15].

4. **Impact on the Treatment of Severe Infections:** In cases of severe infections, such as endocarditis or infections caused by Group A streptococci, the use of penicillins can be crucial. Inability to use penicillins due to allergy can complicate treatment [16].
5. **Cross-Reactivity Among Beta-Lactam Antibiotics:** There is a common concern about cross-reactions between penicillins and other beta-lactam antibiotics, such as cephalosporins. Although the risk of cross-reactivity is lower than previously thought, it remains an important consideration when choosing antibiotics [17].

Mechanisms of Penicillin Allergy

Immune response

Understanding the different forms of hypersensitivity is crucial for accurate diagnosis and management of penicillin allergy, allowing for safer and more effective interventions for the patient. Therefore, the relationship between each type of hypersensitivity and allergic reactions to penicillin can be summarized as follows:

- i. **Type I hypersensitivity (Immediate):** This type of reaction occurs within the first 15 minutes to 6 hours after the dose, representing an IgE-mediated delayed reaction triggered by IgE antibodies specifically sensitized to penicillin. It is the classic form of IgE-mediated allergy. It is the most common and well-studied form related to penicillins. When a person previously exposed to penicillin comes into contact with the drug again, the IgE antibodies already attached to the surface of mast cells and basophils recognize penicillin metabolite as an antigen. This recognition leads to the immediate release of histamine and other inflammatory mediators. These manifestations can occur minutes to hours after exposure and include urticaria, angioedema, conjunctivitis, respiratory symptoms (rhinitis, bronchospasm, cough, dyspnea), gastrointestinal symptoms (nausea, vomiting, diarrhea, abdominal pain) and/or anaphylaxis, which require urgent medical attention [18]. It is important to consider the possibility of a delayed IgE-mediated reaction, which could occur up to 6 hours later.
- ii. **Type II hypersensitivity (Cytotoxic):** This involves IgG or IgM antibodies directed against cellular antigens or components of the cell surface, leading to cell destruction. In the context of penicillins, these reactions are rare but can occur, resulting in conditions such as hemolytic anemia or thrombocytopenia [19];
- iii. **Type III hypersensitivity (Immune complexes):** Characterized by the formation of immune complexes that deposit in tissues, leading to activation of the complement system and systemic inflammatory reactions. This results in reactions such as serum sickness, which features fever, arthralgia, and rash [20]. Although less common, these reactions can occur days to weeks after exposure to penicillin, and finally,
- iv. **Type IV hypersensitivity** that does not involve antibodies but rather immune system cells, such as T lymphocytes. Exposure to penicillin can sensitize these cells, which respond excessively upon re-exposure to the drug. Typical manifestations include contact dermatitis and maculopapular rashes, which do not appear immediately

but rather days after exposure [21]. This type of reaction is mediated by cytokines and the infiltration of immune cells, causing inflammation and tissue damage.

Delayed hypersensitivity reactions (DTH - Type IV) are mediated by cellular immune mechanisms. Recent modifications subdivide these reactions into four categories based on the predominant immune cells involved: monocytes (IVa), eosinophils (IVb), CD4 or CD8 T cells (IVc), and neutrophils (IVd) [22]. The classic example of this category is contact dermatitis, a condition characterized by topical sensitization and elicitation of immune response limited to the skin.

DTH are also responsible for delayed cutaneous eruptions (maculopapular exanthems) caused by antibiotics (e.g., amoxicillin and sulfonamides) and acute generalized exanthematous pustulosis (AGEP). Additionally, drug allergy can be classified based on the predominant tissue or organ involved (e.g., systemic, cutaneous, hepatic), which can be useful given the occasional difficulty in identifying the specific immunologic mechanism (Table 1).

Drug Hypersensitivity

Role of penicillin metabolites in the allergic response

The allergic response to penicillin is a complex process mediated by the interaction of its metabolites with the immune system. When penicillin is administered, it can be metabolized into various reactive forms, known as metabolites. Penicillin presents a major determinant [benzylpenicilloyl group or (BPO)/major determinant hapten penicilloyl-polylysine (PPL)] and a minor determinant mix (MDM, constituted by (benzylpenicillin [penicillin G], benzylpenicilloate, benzylpenicilloyl-amine, and benzylpenicilloic acid, among others, which binds to host proteins, forming hapten-protein conjugates [20]. These conjugates are recognized by the immune system as antigens, stimulating the production of specific antibodies, mainly IgE, in susceptible individuals [23].

The binding of major determinant (benzylpenicilloyl group or BPO-PPL) and or minor determinants antigenic-MDM (benzylpenicillin [penicillin G], benzylpenicilloate, benzylpenicilloyl-amine, and benzylpenicilloic acid to plasma proteins forms antigenic determinants that are essential for sensitization and subsequent allergic reactions. In a sensitized individual, re-exposure to penicillin

leads to IgE antibodies binding to these determinants, which are anchored on mast cells and basophils, provoking the release of histamine and other inflammatory mediators. This results in symptoms of an allergic reaction, such as urticaria or anaphylaxis [18]. In addition to penicilloic acid, other smaller metabolites may also contribute to Type I (immediate) hypersensitivity reactions or participate in delayed hypersensitivity reactions (Type IV), which involve T cell activation [24,25]. These non-immediate reactions can manifest as maculopapular eruptions or even more severe conditions such as Stevens-Johnson syndrome. Therefore, the precise identification of the role of penicillin metabolites in allergic responses helps to understand the pathogenesis of allergic reactions associated with these antibiotics and facilitates the development of more effective diagnostic and treatment strategies.

Importance of Drug Allergy Diagnosis

Accurate diagnosis of drug allergy is essential for both patient safety and efficient clinical practice. Many reactions reported by patients do not actually represent IgE-mediated allergy. Non-immunological reactions, common side effects, idiosyncratic reactions, or adverse effects from other mechanisms can also cause diagnostic uncertainties. When a drug allergy is unknown or misdiagnosed, it can lead to serious adverse reactions. Additionally, false labeling of allergy can limit the use of first-line medications, resulting in the use of less effective, more expensive alternatives, or those with potentially greater side effects. This contributes to antimicrobial resistance, which is currently an increasing global concern.

Drug Allergy Diagnosis

The primary method for diagnosing drug allergies involves a combination of detailed clinical evaluation, skin tests, in vitro tests, and, in some cases, controlled challenge tests. The assessment begins with a comprehensive medical history to identify the nature, timing, and symptoms of previous reactions.

This history helps differentiate between allergic reactions and non-immunological side effects [23]; The most useful test for detecting IgE-mediated drug reactions caused by many large-molecular-weight biologicals and penicillin is the skin tests (prick test and intradermal testing), frequently used to diagnose allergies to beta-lactam antibiotics, such as penicillin [25]. In cases of suspected immediate hypersensitivity to

Table 1: Hypersensitivity and allergic reactions to penicillins: Mechanisms and Clinical Presentations.

Hypersensitivity Type	Cellular/Immune Mechanism	Clinical Manifestations	Examples of Related Reactions
Type I (Immediate)	IgE-mediated, mast cells	Urticaria, anaphylaxis	Allergic reactions to medications, foods, insect stings
Type II (Cytotoxic)	IgG/IgM antibody-mediated	Hemolysis, drug-induced cytopenias	Penicillin-induced hemolysis, incompatible transfusions
Type III (Immune Complexes)	Immune complex deposition	Vasculitis, serum sickness, Arthus reaction	Vasculitis induced by drugs, serum sickness
Type IVa (Cell-mediated)	Macrophages, T cells	Contact dermatitis, Stevens-Johnson syndrome, TEN, erythema multiforme	Contact dermatitis, severe reactions like SJS, TEN
Type IVb (Eosinophilic)	T cells, eosinophils	Severe drug reactions with eosinophilia and systemic symptoms	Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS)
Type IVc (Delayed)	CD8+ T cells	Erythema multiforme, drug eruptions	Various agents, including medications
Type IVd (Neutrophilic)	Neutrophils	Acute inflammation, tissue damage	Drug-induced neutrophilic dermatoses

These different manifestations reflect the complexity of the immunological mechanisms involved and the diversity of clinical presentations in patients with suspected penicillin allergy.

penicillin, the first step is to attempt to confirm the allergy with epicutaneous tests. Skin testing is the most useful biomarker for both immediate- and delayed-type reactions available. Challenge drug provocation testing (DPT) is the gold standard for investigation. Skin tests are recommended prior to challenge but may be omitted in low-risk patients.

The ENDA task force suggests a strict definition of such low-risk patients in both children and adults. An algorithm for beta-lactam allergy, outlining how to adjust DPT according to risk and when to omit skin tests before DPT, was also presented [26]. European guidelines recommend that these tests be performed soon after the reactions occur and recommend reassessing patients with a history of immediate reactions and negative patch tests at the first evaluation, including provocation tests, after a period of 2 to 4 weeks. There are indications that the detection of hypersensitivity is less successful with increasing time interval to the suspected clinical reaction [27]. We explicitly do not recommend allergological workups in patients without a previous history of drug hypersensitivity reactions, among other reasons, due to the theoretical risk of iatrogenic sensitization [28]. This practice, often referred to as "prophetic testing," is discouraged [29]

The Penicillin Skin Test

Penicillins, metabolized or spontaneously, can give rise to substances called haptens, which are not capable of stimulating the immune system. Therefore, these metabolites need to bind to a host protein called a carrier protein so that the hapten-antigen complex becomes an immunogen.

The allergenic determinants of penicillin are classified and labeled as follows:

<http://www.medecapharma.com/dap/dap-penicillin-en.pdf>

Major Determinant: Benzilpenicilloil poli-L-lysine (PPL) formed by the linkage of the primary determinant of benzylpenicillin and related beta-lactam antibiotics to lysine chains. Usually, approximately 95% of penicillin is degraded into penicilloil.

Minor Determinant Mixture (MDM): composed of benzylpenicillin sodium, benzylpenicilloate acid, and benzylpenilloate sodium, which are involved in sensitization to benzylpenicillin and related beta-lactam antibiotics, represents 5% of degraded penicillin. Major haptens induce an antibody-mediated response involving IgG and/or IgM, which do not produce an anaphylactic reaction. In contrast, the minor determinant is responsible for IgE-mediated, anaphylactic reactions [30].

For patients with a history of IgE-mediated reaction to penicillin, or whose past history is unclear, American and European guidelines recommend skin testing with major penicillin antigenic determinants (penicilloyl-polylysine [PPL]) and minor antigenic determinants (benzylpenicillin [penicillin G], benzylpenicilloate, and benzylpenilloate) [31-33]. In the United States, penicillin G is the only commercially available minor determinant and is used in combination with PPL (PRE-PEN; AllerQuest LLC, West Hartford, Conn), while in Europe benzylpenicilloyl-octa-lysine and sodium benzylpenilloate (DAP; Diater, Madrid, Spain) are available as majores and minor determinants, respectively.

The European Network on Drug Allergy (ENDA) and European Academy of Allergy and Clinical Immunology (EAACI) Interest Group on Drug Allergy have already published guidelines and position papers on procedures, such as history taking [34], general approach to skin testing [35], drug provocation tests [36], as well as recommendations for the management of betalactam hypersensitivity [37], perioperative anaphylaxis [38], radiocontrast media reactions [39], hypersensitivity to nonsteroidal anti-inflammatory drugs (NSAID) [40] and on rapid desensitization [41].

It is estimated that skin testing with PPL and penicillin G, without the use of penicilloate and penilloate, may miss 10% to 20% of individuals sensitized with penicillin [42,43]. The clinical utility of penicilloate and penilloate is controversial because studies in North America found a negative predictive value (>95%) between skin testing for PPL and penicillin G alone versus PPL and minor determinant mixture reagent in patients challenged with penicillin [44]. Skin testing with penicillin G alone without the use of PPL is not recommended, as up to 70% of patients who have a positive skin test react only to PPL, and these patients may still have a severe reaction [45]. Furthermore, patient populations who underwent skin testing with PPL and penicillin G alone are not comparable to those who had all reagents used for testing. Therefore, it is not possible to compare the negative predictive value. Additionally, recent or severe historical reactors are not typically included when only PPL and penicillin G are used for skin testing. The final epicutaneous and intradermal concentration used for penicillin G varies between 5,000 and 10,000 U/mL and between 0.01 and 0.02M for the other minor determinants (penicilloate and penilloate) [31,42] (Table 2).

It is recommended that dilutions use saline solution instead of sterile water to decrease the possibility of false-positive reactions. A 1:10 or 1:100 dilution of PPL and minor determinants can be selectively used in patients who have had extremely severe reactions. In most guidelines, a positive result is a wheal with its largest diameter at least 3 mm greater than that observed with a negative control, although some authors suggest a 5 mm wheal to increase sensitivity, especially for PPL, for which a 5 mm wheal for puncture testing is recommended on the package insert [31,42,46]. The concentrations for penicillin skin testing are presented in table 3.

Table 2: Recommended Hapten Concentrations for Prick and Intradermal Tests.

Reagent	Puncture	Intradermal
Penicilloyl-polylysine-PPL (PRE-PEN)	5 × 10 ⁻⁵ M	6 × 10 ⁻⁵ M
Penicillina G	10,000 units/mL	100 Unit/mL*
		1.000 Unit/mL*
		10.000 Unit/mL
Penicilloate	0.01-0.02 M	0.01-0.02 M
Penilloate	0.01-0.02 M	0.01-0.02 M
Amoxicillin	20 mg/mL	20 mg/mL

M, Molar Adapted from K. Brockow, 2013

*Optional, based on physician discretion

**Optional, based on physician discretion

Table 3: Maximum non-irritating concentrations for skin testing with beta-lactams.

Hapten	Maximum Non-Irritating Concentration	Application Method
Benzilpenicilina	10.000 UI/mL	Puncture and intradermal
Amoxicilina	20 mg/mL	Puncture and intradermal
Ampicilina	20 mg/mL	Puncture and intradermal
Cefepime	2 mg/mL	Puncture and intradermal
Outras Cefalosporinas	20 mg/mL	Puncture and intradermal
Imipenem	0,5 mg/mL	Puncture and intradermal
Meropenem	1 g/mL	Puncture and intradermal
Aztreonam	2 mg/mL	Puncture and intradermal

Source: Adapted from Broyles et al., 2021.

Several studies confirm the safety of skin testing in children, with a rate of 1% to 3% of patients experiencing systemic reactions to skin tests [47,48], with a negative predictive value of an allergy assessment that includes skin tests and drug challenge tests exceeding 97% in children.

Patients who have had negative skin test results to penicillin major and minor determinants may receive penicillin with minimal risk of an IgE-mediated reaction. Depending on the reaction history, the first dose may need to be given via graded challenge [49].

Caution in interpreting epicutaneous tests

Skin tests with Penicillin Allergic Determinants (PAD) should begin with the assessment of skin reactivity to the Major Determinant (PPL). The Minor Determinant Mixture (MDM) should only be used when the skin test result with the PPL is negative. Skin tests should always start with the prick test technique. Intradermal tests should be used only when prick test results are negative. As a precaution, it is advisable to apply a series of dilutions at ratios of 1:100 and 1:10 before starting intradermal testing of the major determinant (PPL) and/or the minor determinant mixture (MDM). In patients with symptoms compatible with a severe or high-risk reaction, skin test dilutions should begin at 1:1.000. When performing skin tests, it is recommended to follow an algorithm for assessing sensitivity to penicillin determinants shown below (testing is stopped when a positive result is observed) Figure 1.

In vitro tests

Specific serum IgE assays offer the most common in vitro method for evaluating immediate reactions to penicillins in Europe and the United States. The most widely used commercial method is the fluoroimmunoassay (ImmunoCAP; Thermo-Fisher, Uppsala, Sweden), available for a limited number of penicillins: penicillin G, penicillin V, amoxicillin, and ampicillin. Caution in interpreting epicutaneous tests.

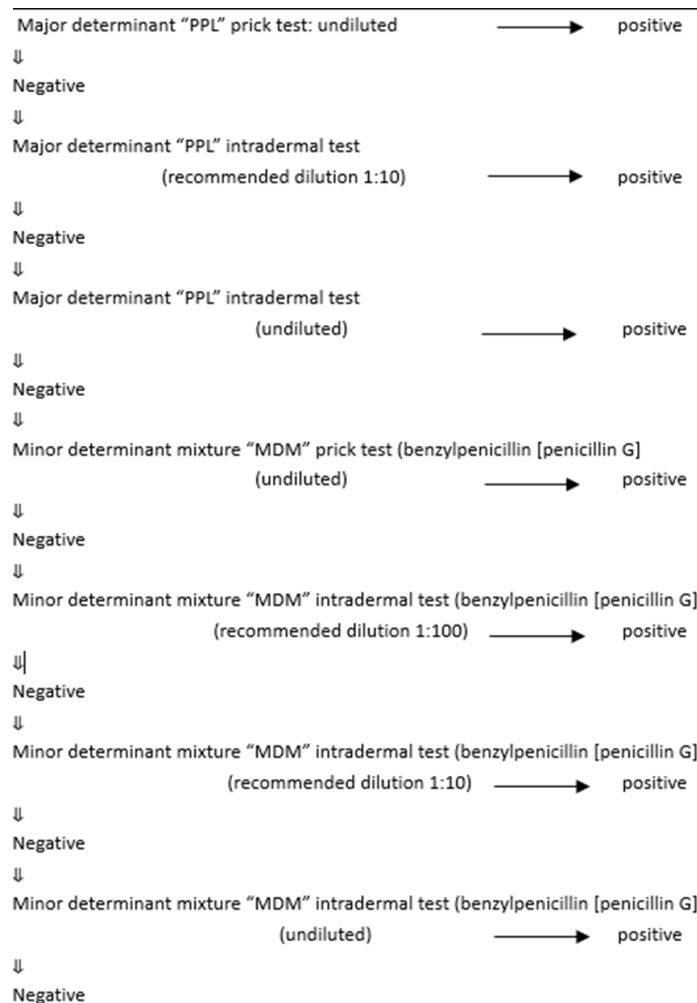


Figure 1: Algorithm for performing skin tests.

PPL: Penicilil poli-L-lysina (Major determinant), **MDM:** Minor determinant mixture/(benzylpenicillin [penicillin G]).

After a negative penicillin skin test result, amoxicillin is administered as a drug challenge, often as a single full dose or as 1/10 of the final dose followed by the full dose.

Amoxicillin is the most commonly used penicillin for drug challenges because it has both structures, the immunologically significant penicillin core and the potentially significant R-group side chains. A challenge with the drug that caused the reaction, such as amoxicillin-clavulanate, may also be considered in the right doses (Table 4).

Table 4: Drugs Culprit of Reactions for Challenge Testing.

Drug	Dose	Unit
Cephalosporin	2	mg/mL
Amoxicillin-clavulanic	20	mg/mL
Ampicillin	20	mg/mL

Delayed Hypersensitivity Reactions

Both delayed reading of intradermal tests (IDTs) and patch tests have been described as diagnostic tools for non-immediate reactions.

Typically, the intradermal test (IDT) is performed using penicillin G, as well as any other suspected penicillins or β -lactam antibiotics. The role of penicillin major and minor determinants in skin testing has been studied, and it has been found that late skin testing with PPL and other minor determinants has limited diagnostic value. Penicillin G is administered at a concentration of 10,000 IU/mL, while a concentration of 1 to 20 mg/mL can be used for other suspected penicillins (e.g., ampicillin and amoxicillin). The clinician should begin with an epicutaneous prick test. If results are negative after 15 to 20 minutes, the test should proceed with intradermal testing. Again, results are read after 20 minutes to evaluate any immediate responses. Additional readings for delayed reactions are performed after 48 and 72 hours. Erythema infiltrated with a diameter greater than 5 mm is considered a positive reaction. Syed B Ali et al. in 2023 stated that in patients suspected of penicillin allergy, benzyl penicillin and amoxicillin alone may be sufficient for *in vivo* testing in individuals with suspected penicillin allergy [30].

A contact test for penicillin and other suspected penicillins/ β -lactams is performed using a concentration of 5% to 10% penicillin in petrolatum. The patch should be kept in place for 48 hours, with readings taken 15 minutes after removal and again 24 hours later. The specificity of delayed readings of IDTs and patch tests is high (90%–100%), but sensitivity is lower, ranging from 50% to 60%. Delayed readings of intradermal tests appear to be more sensitive than patch testing but may also be less specific. The contact test and delayed intradermal readings can be useful for diagnosing maculopapular eruptions, AGEP, and DRESS. Although patch testing may be considered in SJS and TEN, delayed readings of IDT are contraindicated in these two conditions.

The **basophil activation test (BAT)** is a recently described method that has also been assessed as a diagnostic tool for immediate hypersensitivity reactions to penicillin and other

β -lactams evaluating expression of CD63 on basophils after stimulation with an allergen. Its sensitivity is approximately 50%, with a specificity of over 90% [50]. There are limited data using this method to evaluate patients with possible allergies to beta-lactam [51]. This test has not been validated, is not commercially available, and is not currently recommended for clinical use.

In a systematic review recently published in *The Journal of Allergy and Clinical Immunology (JACI)*, Sousa-Pinto and colleagues found that skin tests and blood tests (specific IgE quantification) demonstrate low sensitivity but high specificity for detecting penicillin allergy. The researchers estimated that both types of tests yield negative results in over 95% of individuals who do not actually have a penicillin allergy. Conversely, skin tests return positive results in only about one-third of patients with a true penicillin allergy, and this proportion drops to one-fifth for blood tests. Furthermore, the authors projected that less than half of the patients with positive skin or blood tests truly have a penicillin allergy [51].

Overall, penicillin allergy skin and blood tests have suboptimal diagnostic accuracy, particularly in patients who report mild non-immediate reactions. In clinical practice, taking a thorough patient history can aid in identifying those patients who would benefit most from these tests and those who might safely undergo an allergist-supervised, direct graded challenge with the suspected penicillin. Penicillin allergy skin and blood tests have limited accuracy [52].

Challenge tests are considered the gold standard when history and skin tests are inconclusive. These involve the gradual, controlled administration of the drug under medical supervision and monitoring for adverse reactions [53]. These diagnostic procedures are crucial to ensure that the patient receives the most effective and safe treatment, avoiding potentially serious complications associated with inappropriate medication use.

Preventions and Contraindications for Performing Drug Provocation Tests (DPTs)

The route of administration and preparation used when drug provocation test (DPT) is performed with the suspected culprit drug must be considered. The use of the exact product and the same route causing the initial reaction is recommended. The route of administration for DPT should be guided by initial reaction severity, patient comorbidity, and the setting where DPT is performed. Traditionally, it has been suggested that the oral route is the safest due to slower absorption and this is still the most used route. Concerning oral or IV routes for DPT no recommendation is made [54].

Drug provocation tests (DPTs) are contraindicated in uncontrolled and/or severe hypersensitivity reactions with life-threatening risks. These include severe skin reactions such as SJS, TEN, DRESS, vasculitis, and systemic reactions like DRESS with any internal organ involvement or hematologic reactions. Anaphylaxis can be tested after a thorough risk/benefit assessment.

DPTs are not indicated when the offending drug is unlikely to be necessary, especially when there are several structurally unrelated alternative medications. Additionally, DPTs should not be performed during pregnancy or in the presence of severe concomitant illness unless the medication is essential for the treatment of the concomitant condition or is required during pregnancy or delivery.

DPTs must be conducted under the highest safety precautions: a trained team aware of the procedure, prepared to recognize early signs of a positive reaction, and ready to manage a potentially life-threatening event, with emergency resuscitation equipment readily available [55].

After a negative skin test with penicillin, amoxicillin is typically administered as a drug challenge, often as a full single dose and occasionally as one-tenth of the final dose, followed by the full dose (Table 5).

Amoxicillin is the most commonly used penicillin for drug challenges because it contains both the immunologically significant core structure of penicillin and the potentially relevant R-group side chains. Challenge with the medication that caused the reaction, such as amoxicillin-clavulanate, may also be considered. The DPT test is often performed in two or three steps (placebo, 10% of the dose, followed by 90% /100% of the dose after 30 to 60 minutes). Amoxicillin is the preferred BL for the test, due to the presence of the BL ring and the R1 side chain, but other options are shown in (Table 6). If an allergy to amoxicillin-clavulanate is suspected, use this medication in the Provocation Test.

Table 5: Drug Provocation Test (DPT) - Haptens and Recommended Doses for (epicutaneous tests: negatives).

Drug	Benzylpenicillin	Penicillin V	Amoxicillin
Dose	103 IU/mL (*)	5mg*	5mg
	104 IU/ mL (*)	50mg*	50mg*
	105 IU/mL (*)	150mg*	100mg
	5X105 IU/mL (*)	200mg*	150mg
			200mg
			500mg*
Route	IM	Oral	Oral
Acumulative Dose	6 x 105 IU/ML	405mg	550mg
Interval in minutes	45/60 min	45/60 min	45/60 min.

benzilpenicillin = penicillin G. BL: betalactam. (*): preferred doses.

Table 6: Groups of β -Lactam antibiotics that share identical R-Group Side Chain.

Group	Antibiotic
1	Amoxicillin, Cefadroxil, Cefprozil, Cefatrizine
2	Ampicillin, Cephaloglycin, Cefaclor, Cephalexin, Cephadrine, Loracarbef
3	Ceftizoxime, Ceftriaxone, Cefotaxime, Cefmenoxime, Cefpodoxime, Cefditoren
4	Cefoxitin, Cephaloridine, Cephalothin
5	Cefamandole, Cefonicid
6	Ceftazidime, Aztreonam

Adapted from Ann Allergy Asthma Immunol. 2010 doi: 10.1016/j.anai.2010.08.002.²³

Symptoms of Penicillin Allergy

The symptoms of penicillin allergy can vary widely, from mild to potentially life-threatening, depending on the severity of the reaction. Among the most common symptoms associated with this allergy are: **i) Skin Reactions** such as urticaria (red patches and itching on the skin), maculopapular rash (a skin eruption resembling spots), and angioedema (subcutaneous swelling, usually around the eyes and lips); **ii) Respiratory Symptoms:** (difficulty breathing, wheezing, nasal congestion, rhinitis, bronchospasm, cough, dyspnea); **iii) Gastrointestinal Symptoms:** (nausea, vomiting, diarrhea, abdominal pain); and **iv) Systemic Symptoms:** (anaphylaxis, fever, dizziness). In addition, penicillins can cause exfoliative dermatitis, Acute Generalized Exanthematous Pustulosis (AGEP), and more severe blistering rashes such as Stevens-Johnson Syndrome (SJS) and Toxic Epidermal Necrolysis (TEN).

Hematological changes with certain penicillins, such as methicillin and ampicillin, can cause interstitial nephritis, pneumonitis, hepatitis, and/or vasculitis, arthralgia with or without signs of serum sickness. Drug-induced hypersensitivity syndrome or Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS) is the combination of skin eruptions, visceral involvement, hematological change, fever, lymphadenopathy, and eosinophilia.

Management, Treatment, and Handling

Immediate Approach to Allergic Reactions to Penicillin - The immediate response to a penicillin allergic reaction must be rapid and effective to alleviate symptoms and prevent serious complications. The first step is the immediate discontinuation of the antibiotic. For this, the healthcare professional must quickly assess the severity of the reaction and act accordingly. For mild reactions such as urticaria or pruritus, monitoring and additional medications may be sufficient. In more severe cases, especially if anaphylaxis is suspected, it is crucial to follow well-established emergency protocols, which include the administration of adrenaline/ epinephrine, oxygen supply, and respiratory support as needed [18].

Use of Antihistamines - Antihistamines are frequently used to treat mild to moderate allergic symptoms associated with penicillin, such as urticaria and rhinitis. They work by blocking histamine receptors, reducing itching, redness, and swelling [56]. Second-generation antihistamines are preferred due to their lower risk of sedation.

Epinephrine in Cases of Anaphylaxis - Epinephrine is the first-line treatment and should be administered immediately in cases of anaphylaxis, a severe and rapidly occurring allergic reaction. Intramuscular injection of epinephrine is the preferred route, typically given in the lateral aspect of the thigh, and can be repeated if necessary [57]. Epinephrine helps counteract vasodilation, smooth muscle contraction, and increased vascular permeability, as well as alleviating respiratory and circulatory symptoms.

Strategies for Managing Allergic Patients - For the management of patients with penicillin allergy, it is essential to adopt a structured approach, employing strategies aimed at improving

patient safety, ensuring that antibiotic use is rational and safe, and avoiding potentially fatal consequences of unplanned allergic reactions. This approach involves:

- **Accurate Diagnosis and Diagnostic Confirmation:** Conduct a detailed clinical assessment and, when necessary, use skin and challenge tests to confirm or rule out true allergy. Many times, intolerance or side effects are mistakenly classified as allergy [58].
- **Patient Education** - Explain to patients the nature of their allergies and the early identification of allergy signs (symptoms of allergic reactions), emphasizing the need to avoid the use of penicillin and its derivatives. Patients with a history of severe reactions should be informed about the use of auto-injector devices for adrenaline.
- **Updating Health Records:** Regularly review and update patients' allergy histories in medical records, performing re-evaluations when appropriate, to avoid permanent allergy labels that may be incorrect. These updates should be communicated to other healthcare professionals. Medical alert bracelets can also be considered.
- **Desensitization:** In situations where penicillin use is absolutely necessary, desensitization under strict medical supervision may be considered, in a hospital environment prepared for emergency situations [59].

Alternative Antibiotics in Cases of Penicillin Allergy

When penicillin allergy is confirmed, choosing effective and safe alternative antibiotics is crucial. Among the available options there are: i) Macrolides, such as erythromycin and azithromycin, frequently used in respiratory infections; ii) Clindamycin, effective against anaerobic infections and some Gram-positive bacteria; iii) Tetracyclines, such as doxycycline, used for a variety of infections including those caused by *Rickettsia* and *Borrelia*; iv) Fluoroquinolones, such as ciprofloxacin, although their use should be carefully evaluated due to possible side effects and resistance concerns.

VIRUS Pathogenesis in Drug Hypersensitivity Reactions (DHRS)

Viral infections are particularly frequent in children, in which allergic reactions to beta-lactams are less common than in adults. Thus, children treated with beta-lactams may develop skin rashes (maculopapular or urticarial lesions) and mimic drug hypersensitivity reactions but these lesions, diagnosed as allergies, may be caused by viral infections and enteroviruses [60]. In these cases, this rash is rarely reproduced by challenge. Some aspects of drug-induced hypersensitivity (DH) and management differ with age, although the same tools are used for DH management in adults and also for children [60].

When questioned, about 10% of the parents report suspected hypersensitivity to at least one drug in their children. However, only a few of these reactions can be confirmed as allergic after a diagnostic workup. In children There is a lack of knowledge on drug hypersensitivity (DH) epidemiology, and appropriate diagnostic methods. some aspects of DH and management differ with age, although same tools are used for DH management in adults and also for children.

Considerations on Cross-Reactivity with other Beta-Lactams

Historically, it was believed that there was a high rate of cross-reactivity between penicillins and other beta-lactam antibiotics, such as cephalosporins. However, modern studies show that the risk of cross-reactivity is lower than previously estimated. The β -lactam ring structure is common, but the side chains differ, impacting cross-reactivity [61]. Cross-reactivity is more probable with first-generation cephalosporins and decreases with later generations [62].

The European Network for Drug Allergy (ENDA)

ENDA assess the possibility of cross-allergic reactions between different classes of beta-lactam antibiotics. ENDA provides specific guidelines for identifying these risks and guiding the for a safe use of these medications in patients with suspected or confirmed penicillin allergy (Table 7).

Table 7: Percentage of cross-reactivity between penicillin G and other beta-lactam antibiotics.

Aminopenicillin:	<2% -	Although cross-reactivity with penicillins like amoxicillin and ampicillin is generally low, it can occur in patients who have a documented penicillin allergy.
Cephalosporin:	3%	Cephalosporin antibiotics share a chemical structure similar to penicillins. While the risk of cross-reactivity is higher with first-generation cephalosporins, it significantly decreases in the second and third generations.
Monolactams (such as aztreonam)	0%	These are often considered safe for use in patients with penicillin allergies due to their distinct structure, except in cases of specific allergy to ceftazidime, which shares a similar side chain.
Carbapenems	< 1%	Studies have shown that cross-reactivity between penicillins and carbapenems is low, but use should be carefully monitored in individuals with a history of severe penicillin reactions.

The ENDA Protocol - A Rapid Algorithm for Diagnosing Allergic Reactions to Beta-Lactams BP: benzylpenicillin (Figure 2).

To be performed in 1 day – each step of 15 / 15 minutes
Clinical history consistent with Type-I hypersensitivity (IgE-mediated)

Desensitization After Allergy Tests

Tests for beta-lactams and cephalosporins, when negative, should be repeated after 4 weeks as follow:

High-Risk Patients

Individuals with demonstrated sensitivity to penicillin, whether through a positive skin test or drug challenge tests, should avoid the responsible medication as well as those with potential cross-reactivity. It is reasonable to repeat skin testing if many years have passed since the previous skin test.

If there are no reasonable alternatives, both oral and intravenous desensitization protocols have been well established in guidelines in the United States and Europe [63,64]. Examples

are provided in Tables 8.

Oral Desensitizing

It is primarily indicated for patients with a confirmed clinical history of penicillin allergy, with positive epicutaneous tests, and also for pregnant women who need to use penicillin. Protocols are available with the variable dilutions that should be observed for each test and each substance.

A typical protocol for desensitization to intravenous penicillins and cephalosporins begins with a 1:10,000 or 1:100,000 dilution of the target dose, with doses doubled every 15 to 20 minutes over several hours until the target dose is reached [63].

Rapid Desensitization to Beta-Lactam Antibiotics Penicillin and Cephalosporins

The important rapid induction of tolerance, with increasing oral doses of penicillin, is indicated for pregnant women with syphilis who are confirmed to be penicillin-allergic [63]. Different publications have validated the efficacy and safety of various protocols. Up to 30% of cystic fibrosis patients develop hypersensitivity reactions after multiple exposures to beta-lactams, which requires rapid desensitizations. Failure of desensitization is related to symptoms not mediated by IgE [65].

A protocol for desensitization to penicillin and intravenous cephalosporins starts with one-tenth to one-hundredth of the target dose, with doses doubled every 15 to 20 minutes over several hours until the target dose is reached [66].

Desensitization with ceftazidime has been performed in cystic fibrosis patients to treat IgE-mediated hypersensitivity reaction with no significant systemic reactions during desensitization [67].

Table 8: Rapid Desensitization for Hypersensitivity Reactions to Medications.

Step	V Penicillin oral (Unit/mL)	mL	Unit	Cumulative dose (Unit/mL)
1	1.000 (*)	0.1(*)	100	100
2	1.000 (*)	0.2 (*)	200	300
3	1.000 (*)	0.4(*)	400	700
4	1.000 (*)	0.8 (*)	800	1.500
5	1.000 (*)	1.6 (*)	1.600	3.100
6	1.000 (*)	3.2 (*)	3.200	6.300
7	1.000 (*)	6.4 (*)	6.400	12.700
8	10.000 (**)	1.2 (**)	12.000	24.700
9	10.000 (**)	2.4 (**)	24.000	48.700
10	10.000 (**)	4.8 (**)	48.000	96.700
11	80.000 (***)	1.0 (***)	80.000	176.700
12	80.000 (***)	2.0 (***)	160.000	336.700
13	80.000 (***)	4.0 (***)	320.000	656.700
14	80.000 (***)	8.0 (***)	640.000	1.296.700

NOTE: 1) 1mL/80,000UI (***) a) dilute 1/10: 1mL 8,000UI. b) dilute 1/8: 1mL 1,000UI (*) Adapted from Castells M, 2009

2) 1mL/80,000UI. a) dilute 1/8: 1mL 10,000UI (**); 3) Every 30 minutes

Cefotaxime desensitization was performed in a 51-year-old man with bacterial spondylitis; treatment continued for 4 weeks without adverse events [68].

Patients with positive skin tests for penicillin and cephalosporins (cefepime, ceftriaxone, and cefazolin) were desensitized to beta-lactam medications using a 2-hour and 15-minute protocol, in which tripled doses were administered every 15 minutes, without significant side effects [69].

Low-Risk Patients

For patients at low risk of an immediate hypersensitivity

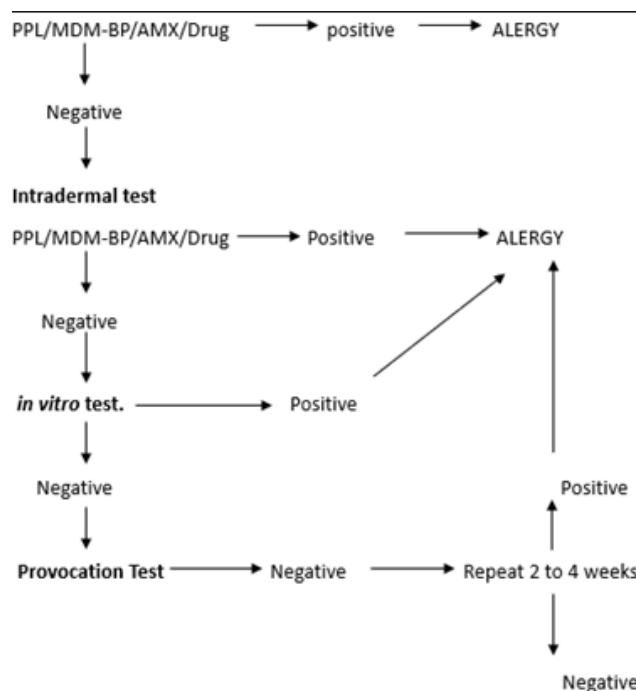


Figure 2: Puncture Test.

Adapted from: Blanca M, et al 2009. 37

PPL: Penicilol poli-L-lysina (Major determinant), MDM: Minor determinant mixture; BP: Benzilpenicillin; AMX: Amoxicillin; Drug: Other drugs or substances tested.

reaction, including those with a history of itching without urticaria, mild maculopapular rash (i.e., duration less than 1 week), or other benign skin rash, a test drug challenge may be considered without the use of skin tests [70].

Prevention of Future Reactions

Prevention of future reactions relies on proper guidance for the patient and their family. Contact with the family doctor to report the patient's medication allergy during hospitalization should be documented on a note or even on the door of the room with a medication allergy alert. For everyday use, a bracelet should be worn indicating the medication name, especially in patients with reactions that pose a risk of death.

Cephalosporins

Cephalosporins can cause a variety of hypersensitivity reactions, ranging from mild reactions and delayed responses to life-threatening anaphylactic reactions. The most common reactions to cephalosporins are maculopapular rashes and drug fever. Urticaria is less common, and anaphylaxis is rare.

Patients with positive penicillin tests have about a 3% chance of allergic reactions to first-generation cephalosporins, although these conclusions are based on studies using epicutaneous testing rather than challenge tests.

For patients allergic to penicillin, it is advisable to avoid first-generation cephalosporins. However, this approach can be avoided if epicutaneous tests for cephalosporins are negative. In penicillin-allergic patients, cross-reactivity with second- and third-generation cephalosporins is limited, especially with amino-penicillins [71].

In general, adverse drug reactions (ADRs) to cephalosporins affect approximately 0.5% to 2.5% of patients. ADRs include nephropathy and colitis [g]. Although cephalosporin allergy is about ten times less common than penicillin allergy, it remains one of the most frequently reported drug allergies in the United States [72].

Main symptoms: Cephalosporins can provoke various types of hypersensitivity reactions, including IgE-mediated responses characterized by urticaria, angioedema, rhinitis, bronchospasm, and anaphylaxis. Notably, cephalosporins, especially cefaclor and cefprozil, can cause reactions similar to serum sickness. 13 They can also, less frequently, lead to severe cutaneous adverse reactions (SCARs) and isolated eosinophilia [73].

Diagnosis

Immediate Hypersensitivity Skin Test

Most hypersensitivity reactions to cephalosporins are directed against the R group of the side chain rather than the β -lactam ring molecule of the core [74]. However, it may also be useful to perform a penicillin skin test when patients present with possible sensitivity to cephalosporins, particularly those in earlier generations, which include aminocephalosporins (Table 9). Although skin testing for native cephalosporins is not standardized, a positive skin test result at a non-irritating concentration suggests the presence of specific IgE antibodies to the drug.

Table 9: Cutaneous test: cephalosporin immediate hypersensitivity.

Drugs	Stage 1: epicutaneous	Step 2: Intradermal	Etapa 3: Intradermal
Cephalexin	25 mg/mL	NA	NA
Cefazolin	330mg/mL	3.3mg/mL	1mg/mL
Cefuroxime	100mg/mL	1mg/mL	10mg/mL
Cefotaxime	100mg/mL	1mg/mL	10mg/mL
Ceftazidime	100mg/mL	1mg/mL	10mg/mL
Ceftriaxone	100mg/mL	1mg/mL	10mg/mL
Cefepime	200mg/mL	2mg/mL	220mg/mL
Cefixime	2mg/mL	1mg/mL	10mg/mL

"NA" indicates that the step was not applicable or not performed for that drug.

Cephalosporin Challenge

STEP 1:	1/ 4 of oral dose/tablet/ 1/10 of parenteral liquid dose or oral, observe for 30-60 min
STEP 2:	1 TOTAL DOSE. observe for 60 min

Conclusions and Important Points

Penicillin allergy is one of the most commonly reported drug allergies, but it is often misdiagnosed, with true hypersensitivity being significantly less prevalent than perceived. Accurate identification and proper management of this allergy are essential to avoid the overuse of alternative antibiotics, which may be less effective, more costly, and contribute to antimicrobial resistance.

Important points

Clarification of Penicillin Allergy Prevalence - Accurate diagnostic assessment, including skin testing in accordance with current standards, is essential to reduce mislabeling, expand the safe use of penicillins, and contribute to the control of antimicrobial resistance [58]. Solensky et al. reported a Penicillin Skin Test Kit, containing all relevant penicillin allergenic determinants, demonstrating a very high Negative Predictive Value. Removal of a penicillin allergy label in a large majority of currently mislabeled patients has substantial personal and public health implications [75].

Mechanisms of Penicillin Allergy - Allergic reactions involve complex immunological processes, predominantly IgE-mediated Type I hypersensitivity, in which hapten-protein conjugates, such as penicilloic acid bound to proteins, sensitize the immune system, leading to the release of inflammatory mediators [9]. This understanding is vital for improving diagnostic and therapeutic strategies, including the use of skin tests that evaluate these sensitization mechanisms with high specificity [75].

Evaluation of Diagnostic Methods - Skin tests, including prick, intradermal, and controlled provocation tests, remain the gold standard for confirming or ruling out penicillin allergy, with studies showing that tests incorporating the main antigenic determinants, such as those presented by Solensky et al., have high sensitivity and high negative predictive value [23,75]. This enables a safer assessment, reducing false positives, avoiding unnecessary restrictions, and facilitating the reclassification of patients who are incorrectly labeled.

Clinical Management of Patients with Confirmed or Suspected Allergies - A detailed clinical assessment, combined with the use of validated laboratory tests, should guide the management strategy. The availability of high-validity testing kits, facilitates the identification of patients who may tolerate penicillins, as well as enabling provocation tests under supervision, including the use of desensitization protocols [63].

The Need for Further Research in This Field

Despite current advances, there are still areas within the diagnosis and management of penicillin allergy that require more research, including: to improve clinical outcomes, optimize the choice of antibiotic therapies, and reduce antimicrobial resistance worldwide. Among strategic point to be considered are:

- **Development of New Diagnostic Tests:** Improving the accuracy and accessibility of laboratory and in vivo tests for drug allergies.
- **Immunological Mechanisms:** Further exploration of the immunological mechanisms underlying penicillin allergies and cross-reactivity with other beta-lactams.
- **Educational Interventions:** Developing and evaluating educational programs for patients and healthcare professionals regarding proper management of antibiotic allergies.

Future Perspectives in the Treatment and Management of Penicillin Allergy

The management of penicillin allergy is undergoing a transformation, driven by technological advances, improved understanding of immunological mechanisms, and the increasing emphasis on personalized medicine. Future prospects promise to significantly optimize how penicillin allergies are diagnosed, treated, and managed in clinical settings. Here are some promising directions:

1. **Development of Advanced Diagnostic Tests:** One of the most critical areas is improving diagnostic tests to make them more accurate, rapid, and accessible. The use of molecular diagnostic platforms and biochips that detect specific sensitivity to antigenic determinants, such as enhanced versions of skin testing that cover a broader range of determinants, can reduce the occurrence of false diagnoses and provide clarity about the true prevalence of penicillin allergies [76].
2. **Immunomodulatory Therapies:** Research in immunotherapy offers hope for more effective desensitization. Approaches that modulate the immune response, possibly through treatments that introduce small peptides to reprogram the immune system's response, are in experimental stages but promise to offer an alternative for patients with severe allergies [77].
3. **Personalized Medicine:** Advances in genomics and proteomics studies may allow for the identification of specific biomarkers of susceptibility to allergic reactions to penicillins. Personalized medicine, considering the patient's genetic profile, can prevent the development of adverse reactions by guiding therapy choices and the selection of appropriate dosages [78].
4. **Education and Awareness:** The continuous and systematic training of healthcare professionals and increasing the

general public's awareness of drug allergies are essential. With digital advancements, educational platforms, e-learning, and mobile applications can provide real-time updates and personalized information for doctors and patients [79].

5. **Health Policies and Collaborative Research:** Coordinating global efforts to collect high-quality epidemiological data and develop evidence-based guidelines for managing penicillin allergies is a priority. Funding collaborative research that crosses national borders can accelerate progress in the detection and management of allergies [80].
6. **Development of Alternative Antibiotics:** Against the backdrop of antimicrobial resistance, research to discover and develop new antimicrobials that do not provoke allergic reactions is critical. This includes not only new compounds but also modifications of existing structures to reduce their allergenic potential while maintaining antimicrobial efficacy [81].

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