

PENICILLIN ALLERGENIC DETERMINANTS (DAP)

DESCRIPTION

Main allergenic determinants involved in type I or immediate hypersensitivity to benzylpenicillin and related antibiotics (beta-lactam), isolated, modified, and stabilised by means of lyophilisation. For exclusive use in the diagnosis of type I or immediate hypersensitivity to benzylpenicillin and related antibiotics (beta-lactam) by means of cutaneous tests (prick and intradermal tests).

QUALITATIVE AND QUANTITATIVE COMPOSITION

Penicillin Allergenic Determinants are classified and labelled as:

- Major Determinant Benzylpenicilloyl poly-L-lysine (PPL): formed by the bonding of the primary determinant of benzylpenicillin and related antibiotics (beta-lactam) to lysine chains.
- Minor Determinant Mix (MDM): formed by Sodium benzylpenicillin, Benzylpenicilloic acid, and Sodium benzylpenicilloate, which are involved in the sensitisation to benzylpenicillin and related antibiotics (beta-lactam).

The DAPs' quali-quantitative composition is the following:

PPL Vial:	Benzylpenicilloyl poly-L-lysine	0.04 mg
	Mannitol	20 mg
MDM Vial:	Sodium benzylpenicillin	0.5 mg
	Benzylpenicilloic acid	0.5 mg
	Sodium benzylpenicilloate	0.5 mg
	Mannitol	20 mg
Diluent Vial:	Sodium Chloride.	
	Potassium dihydrogen phosphate	
	Disodium hydrogen phosphate 2 hydrate	
	Potassium chloride	
	Water for injection	c.s.p. 1 ml

PHARMACEUTICAL FORM AND CONTAINER CONTENT

Vials containing lyophilised powder and diluent for injectable solution.

DAP: diagnostic set

3 vials containing PPL (benzylpenicilloyl poly-L-lysine) lyophilised powder.

3 vials containing MDM, Minor Determinant Mix (Sodium benzylpenicillin, Benzylpenicilloic acid, and Sodium benzylpenicilloate), lyophilised powder.

6 diluent vials, each containing 1 ml of saline solution in phosphate buffer.

Individualised vials containing:

PPL:	Lyophilised powder of Benzylpenicilloyl poly-L-lysine (PPL)
MDM:	Lyophilised powder of Minor Determinant Mix (MDM) (Sodium benzylpenicillin, Benzylpenicilloic acid, and Sodium benzylpenicilloate).
Diluent	Saline solution in phosphate buffer (1 ml)

HOLDER AND MANUFACTURER

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THERAPEUTIC INDICATIONS

Diagnostic evaluation, by means of cutaneous tests (prick and intradermal tests), of allergic states, sensitisation, or type I hypersensitivity, in those cases in which allergy to beta-lactam antibiotics is suspected.

CONTRAINDICATIONS

A pathological dermal alteration of the area intended for the cutaneous tests, as well as any other pathological state which may considerably affect the patient's general condition, constitute contraindications for the performance of cutaneous tests.

The course of an acute allergic reaction induced by any allergenic substance constitutes a contraindication for the performance of cutaneous tests.

Antihistamines, corticosteroids, cromones and, in general, any medication which exhibits collateral anti-allergic activity, must be suspended 1 week prior to the cutaneous examination.

The use of beta-blocker or ACE inhibitor therapy also constitutes a contraindication for the performance of cutaneous tests; therefore, always in agreement with your prescribing physician and with blood pressure monitoring, it must be suspended during the 48 hours prior to the test.

Pregnancy, breastfeeding, and, generally, being under six years of age, constitute contraindications for the performance of cutaneous tests; however, it should always be left to the Specialist's discretion, who must determine the convenience of, and the best timing for, the diagnostic cutaneous examination on the basis of the risk – benefit required by each specific situation.

The contraindications derived from the administration of adrenaline must be considered, given the potential induction of a secondary allergic reaction.

SPECIAL WARNINGS

The performance of cutaneous tests during pregnancy is not recommended, given the additional risk the potential induction of an anaphylactic reaction entails.

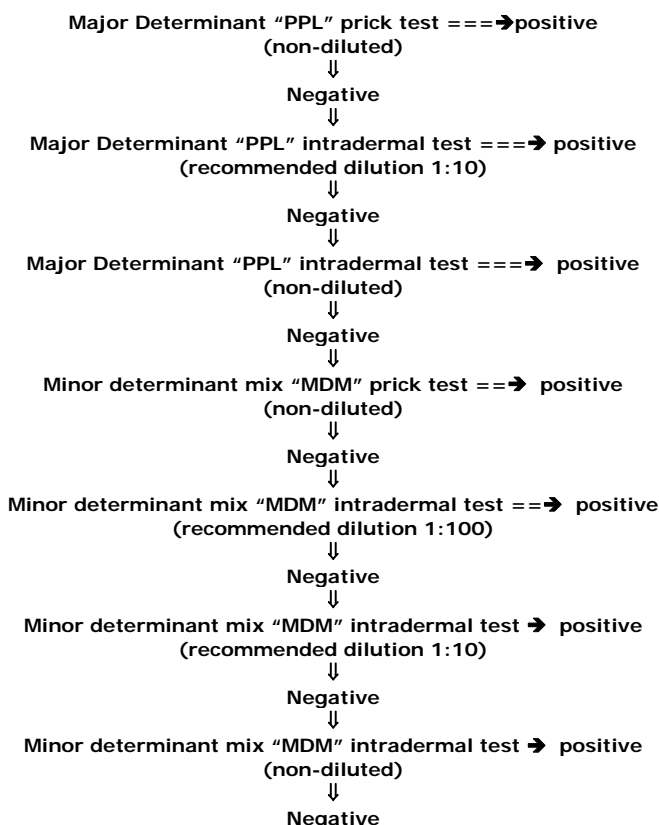
After performing the cutaneous tests, the patient must remain under observation for at least 30 minutes. In addition, it is advisable that the patient avoid alcohol consumption, intense physical exercise, and hot baths or showers during the hours prior and subsequent to the test.

In the event that the patient is under treatment with allergen immunotherapy, it is advisable that the cutaneous tests be performed with a 1-week minimum interval from the preceding immunotherapy dose. Similarly, the interval between the cutaneous tests and administration of an immunotherapy dose should be 2 or 3 days.

PRECAUTIONS FOR USE

Cutaneous tests using DAP must begin by studying cutaneous reactivity to the Major Determinant (PPL). The minor determinant mix (MDM) should only be used when the result of the cutaneous test using the Major Determinant (PPL) has been negative. Cutaneous tests must always start with the prick test technique. Intradermal tests should be used only when the prick tests are negative. As a preventive measure, it is advisable to apply a set of dilutions, at a ratio of 1:100 and 1:10, prior to starting the Major Determinant (PPL) and/or the minor determinant mix (MDM) intradermal tests. In patients with symptoms compatible with a severe reaction, or with a high risk, the dilutions for the cutaneous tests should begin at 1:1,000.

In cutaneous tests, it is advisable to follow the algorithm for the study of sensitivity to penicillin determinants shown below:



The dilutions must be performed while maintaining the required appropriate aseptic conditions and using the diluents which may be requested to that end.

INTERACTIONS

Antihistaminic, corticosteroids, cromones, and, in general, any medications which exhibit collateral anti-allergic activity have an interaction capacity which alters the results that may be obtained after performing the cutaneous tests. In the specific case of oral antihistaminic, it is necessary to suspend their administration 1 week before the cutaneous examination.

INSTRUCTIONS FOR USE

Preparation of the diagnostic solutions for cutaneous tests

Select and verify the expiration dates and the condition of the vials that are to be reconstituted. Under sterile conditions, and using a sterile syringe and needle, remove 1 ml of the diluent and transfer it to the DAP vial containing the lyophilised powder that is to be reconstituted, while shaking it lightly. It will then be ready for immediate use.

Cutaneous tests by means of the prick test technique

The prick test technique is one of the most widely used techniques for evaluation of the majority of allergic processes and which entails the lowest risk of inducing anaphylaxis. This cutaneous test, which is practically free of irritating effects, is performed by placing a drop of the allergenic determinant on the skin of the palmar face of the patient's forearm. Using a special 1-mm-tip lancet, the epidermis is pierced at a right angle, allowing for the solution to penetrate through the skin, and the excess liquid is removed immediately thereafter.

In no case should the result of a prick test be assessed if blood is produced. It is common for a small erythematous area to appear around the site where the test was performed.

Cutaneous tests by means of the intradermal technique

The intradermal test involves administration of an allergenic determinant dose close to 0.02-0.05 ml at the dermis level. This is done using a 4/10-caliber-needle tuberculin syringe, which is applied to the palmar face of the patient's forearm at a 10 – 15 degree angle, forming a small blister whose perimeter must be marked at the beginning of the test.

One must make sure not to injure any vessels while performing the test; should this occur, the result will not be assessed.

Patient conditions during the performance of cutaneous tests

Even though special skin care is not necessary prior to performing cutaneous tests, one must remember to assess dermatographism and clean the selected area, preferably with water and without vigorous rubbing.

Prior to performing the cutaneous tests, the patient must be tempered for at least 10 minutes.

Reading and interpretation of the cutaneous test results

The final cutaneous test results must be read once 15-20 minutes have elapsed since their performance, with periodical observation.

Interpretation of the cutaneous prick test results is based on the size of the induced papule; tests are considered positive when the papule has a diameter greater than 3 mm or exhibits pseudopod formation. The following assessment key may be used:

<u>Papule major diameter</u>	<u>Cutaneous test interpretation</u>
≤ 3 mm	Negative
> 3 mm	Positive

In intradermal tests, if the difference between the initial and the induced diameters is greater than 3 mm, the test is considered to be positive.

It is essential to observe and monitor the patient during the development of his/her cutaneous response, until the reading is done, in order to be able to act immediately in the event of any adverse, local or systemic reaction which may occur.

OVERDOSE

In the event of accidental overdose or incorrect performance of the cutaneous test, usually injury to a vessel and, consequently, endovenous administration, a more or less significant adverse reaction may appear, including anaphylaxis, which should be treated as indicated in the section on adverse reactions.

ADVERSE REACTIONS

Adverse reactions may be immediate or delayed, depending on how long the symptoms take to appear: seconds or minutes and hours, respectively, after performing the cutaneous test, and may be classified as:

Local reactions

In terms of symptoms, they entail the development and persistence of an erythema, edema, or inflammation, with or without pruritis, on the cutaneous test site, which usually appears after 10 to 60 minutes and persists for several hours.

They usually do not require pharmacological treatment, although it is advisable to use oral antihistamines and/or topical corticoid creams when the induration persists and its diameter is greater than 5 cm. Only in the event of severe local reactions is it advisable to use a tourniquet above the cutaneous test site and infiltrate the adjacent area with subcutaneous 1:1,000 adrenaline at a dose of 0.01 ml/kg of body weight.

Moderate systemic reactions

In terms of symptoms, they entail the development of large-size papules, erythema, and pruritis, which may reach a generalised urticaria or exanthematic condition, with the presence of oculo-nasal symptoms and Quincke's edema. The appearance of symptoms usually takes place between a few minutes and 4 - 6 hours after the test is performed.

A tourniquet must be placed above the test site and baseline pharmacological treatment must be started immediately. In those cases in which urticaria and Quincke's edema develop, it involves administering I.V. antihistamines, in addition to I.V. corticoids (100 mg of prednisolone or a glucocorticoid equivalent). If necessary, subcutaneous administration of 1:1,000 adrenaline at a dose of 0.01 ml/kg of body weight on a site adjacent to the cutaneous test site, which may be repeated every 15 minutes; as well as the use of bronchodilating aerosols and slow I.V. theophylline.

The patient's blood pressure and pulse must be constantly monitored.

Severe systemic reactions: anaphylaxis

The main symptoms in severe systemic reactions, which may develop within a few minutes after performing the cutaneous tests, are bronchospasm, dyspnea, laryngeal edema, and generalised urticaria.

Treatment involves placing a tourniquet above the test site and immediate subcutaneous or intramuscular administration of 1:1,000 adrenaline at a dose of 0.01 ml/kg of body weight on the site adjacent to the cutaneous test site, which may be repeated every 15 minutes if necessary. Administration of antihistamines by oral or intramuscular route, as well as high doses of corticoids (250-1,000 mg of prednisolone) by intravenous route, is mandatory in the case of considerable effects and edema. If respiratory compromise, in the form of severe or refractory bronchospasm, exists or co-exists, sympathomimetic bronchodilators and intravenous aminopylline (250 - 500 mg in adults and 5 - 7 mg/kg of body weight in children, every 24 hours) must be administered.

The patient's blood pressure and pulse must be constantly monitored.

Anaphylaxis may develop immediately and sequentially a few minutes after performing the cutaneous test. It usually exhibits prior standard symptoms, which involve the appearance of palmar and plantar pruritis, as well as pruritis above and below the tongue, which also affects the throat and leads to an intense, rapid collapse that affects several organs and systems: vascular collapse with marked hypotension, nasal congestion, laryngeal edema and bronchospasm; Generalized pruritis, urticaria and angioedema, abdominal pain, nausea, vomiting, and diarrhea; Metrorrhagia, tinnitus, vertigo, sphincter relaxation, seizures, and loss of consciousness.

Treatment involves applying a tourniquet above the test site, placing the patient in lateral decubitus position, and subcutaneous or intramuscular administration of 1:1,000 adrenaline at a dose of 0.01 ml/kg of body weight, which may be repeated every 10 - 15 minutes up to a total of 3 times. In the event that there is cardiac monitoring of the patient, the 1:1,000 adrenaline may be administered intravenously using a 1:10 dilution, which may also be repeated at 10 to 15 minute intervals up to a maximum of 3 times, always depending on the clinical evolution. Administration of oxygen and electrolytic solution fluid therapy must be considered, depending on the patient's clinical evolution. Administration of I.V. antihistamines, high doses of I.V. corticoids (250 - 1,000 mg of prednisolone). In the event that asthma appears, one must resort to sympathomimetic bronchodilators and I.V. aminophylline (250 - 500 mg in adults and 5 - 7 mg/kg of body weight in children, every 24 hours). Intubation or tracheotomy under certain circumstances and resuscitation in the event of circulatory failure must be anticipated and considered for immediate action.

The patient's blood pressure and pulse should be constantly monitored.

SPECIAL PRECAUTIONS FOR STORAGE

The vials containing the lyophilised powder for injection of PPL and MDM should not be stored at temperatures above 25°C.

Once reconstituted or diluted, they must be stored in a refrigerator at 2-8° C .

Medications should be kept away from children's reach and view.

SHELF LIFE

Do not use the vials containing lyophilised powder or diluent after the expiration date specified on the label.

After reconstitution or dilution, they must be used within a **maximum 24-hour period**.

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Bibliography: Position paper: "Diagnosis of Immediate Allergic Reactions to Beta - Lactam Antibiotics". Torres MJ, Blanca M, Fernández J, Romano A, Weck A, Aberer W, Brockow K, Pichler WJ, Demolí P; ENDA; EAACI Interest Group on Drug Hypersensitivity. Allergy. 2003 Oct;58(10):961-72.