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Position paper

Diagnosis of immediate allergic reactions to beta-lactam antibiotics

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Allergic reactions to betalactams are the most common cause of adverse drug reactions mediated by specific immunological mechanisms. Reactions may be induced by all betalactams currently available, ranging from benzylpenicillin (BP) to other more recently introduced betalactams, such as aztreonam or the related betalactamase-inhibitor clavulanic acid (Fig. 1) (1–5). Although the production process of betalactams has improved over the years, the number of reactions has not decreased,

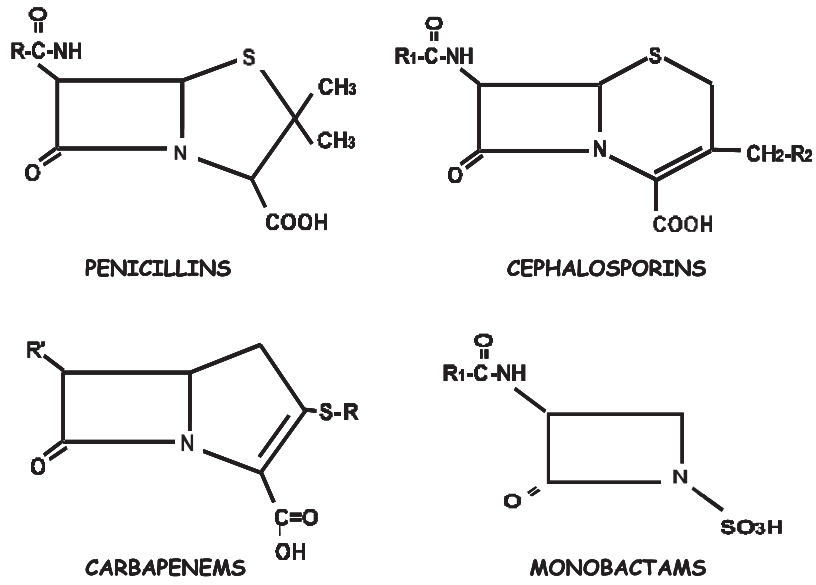

Figure 1. Betalactams chemical structure.

probably because the number of subjects exposed to these drugs has risen. The great diversity of chemical structures available has resulted in the generation of a larger number of hapten-carrier conjugates which can be recognised by the immunological system (6–9). Antibiotic consumption patterns change over time, and a recent study concerning their general use in Europe has shown that BP is now no longer the most common betalactam to which the population is exposed, having been replaced by other compounds, which vary from country to country (10). Amoxicillin (AX) is reported to be the most commonly consumed betalactam in many countries, such as Spain, France and USA (10, 11). Consumption of cephalosporins is increasing (10) and both betalactams are therefore gaining importance as a cause of allergy (12–15). In general, it can be inferred that these changes in consumption should be reflected in the pattern of allergic reactions. Evidence for changes in the clinical pattern of skin test reactivity has existed since the seventies, with increasing data supporting the role of side chain structures as unique determinants arising during the last fifteen years (12–17).

Depending on the time interval between drug administration and the occurrence of the reaction, Levine classified allergic drug reactions as immediate, accelerated or delayed (18). This has proved not only to be useful clinically but also to be in good agreement with the mechanisms responsible for the reaction. Immediate reactions usually appear within a maximum interval of one hour after drug intake and are mediated by specific IgE-antibodies. Symptoms are produced by a rapid release of histamine and other vasoactive inflammatory mediators immediately after hapten-antibody interaction. Immediate allergic reactions to betalactams can be evaluated by different methods: clinical history, skin tests, *in vitro* quantification of IgE-antibodies, and drug provocation test (DPT). The first three have generally been considered to be sufficient to confirm the diagnosis, if the history corresponds well with the results of the skin test and determination of specific IgE-antibodies (19). However, since the sensitivity of these tests is not a 100%, even in patients with a clear positive history, a DPT may be required to confirm the diagnosis (20). In this review, we describe the general ENDA/EAACI guidelines for evaluating and diagnosing subjects with a suspicion of immediate allergic reactions to betalactams.

Clinical evaluation

The most reliable approach for evaluating allergic reactions to betalactams is a detailed description of the symptoms which can be obtained from the patients themselves, or quite often from witnesses, and from parents in the case of children. Another source of information are the clinical records. Two important points to be noted are the time interval between both the first and last intake of the drug and the occurrence of the reaction and the type of symptoms. The former is needed for classifying reactions as being immediate or non-immediate, and the latter is to enable the reaction to be classified. Patients with immediate reactions develop symptoms within an interval of time ranging from minutes to one hour after drug intake. There is evidence indicating that the longer the interval between drug intake and appearance of the reaction the less the probability of being IgE mediated (19,20). Clinical pictures typical for immediate reactions to betalactams are urticaria, with or without angioedema, and anaphylaxis. Urticaria is defined as rapidly evolving and

transient pruriginous wheals occurring at different body sites (21). Anaphylaxis is considered, if several of the following symptoms appear: pruritus on palms or soles, later becoming generalized, generalised erythema, urticaria, dyspnea, difficulty in speaking or swallowing, hypotension, tachycardia and/or loss of consciousness (22). Urticaria can represent the first stage of an anaphylactic reaction which then proceeds to respiratory, gastrointestinal or cardiovascular involvement.

IgE-mediated skin reactivity decreases with time and diagnostic skin tests may become negative. In order to interpret negative skin tests, it is important to note the time elapsed between the occurrence of the clinical reaction and the evaluation by the specialist. Other details to be recorded are: age, sex, personal history of atopy and documented hypersensitivity to other drugs, family history of drug allergy, other drugs the patient was taking at the time, the illness for which the patient took the medication, the last time the patient tolerated any type of betalactam, how many days and at what dose the patient was taking the drug before the onset of the reaction, the treatment received for recovery from the reaction, and whether the patient had had previous episodes of reaction to betalactam. The ENDA/EAACI questionnaire proves very useful for the collection of all these data which can help to clarify many unknown aspects of drug allergy (23).

It may still be difficult to obtain a precise clinical history. The two clinical categories defined above, urticaria and anaphylaxis, may show overlapping associations. Nevertheless, all attempts should be made to classify the reaction within these two categories, as the presence of skin test positivity to major or minor determinants is associated with urticaria or anaphylaxis, respectively, and anaphylaxis is related with the development of side effects to skin testing (18, 24). It may be difficult to differentiate between immediate and accelerated reactions based on clinical history. Thus, some patients initially classified as anaphylactic have developed symptoms 1 to 6 hours after DPT (12, 25). These all indicate that patients, and even doctors, are frequently unable to recall and evaluate precisely all the data required in the clinical history, probably because the reaction being evaluated happened a long time before. Therefore, diagnostic procedures should be thorough and stereotyped.

Skin testing

Although skin testing in the diagnosis of immediate allergic reactions to betalactams is a well-known and widespread method, the way it is performed is very diverse and varies from country to country, from hospital to hospital, and even between doctors in the same hospital. Since the consumption of betalactams differs between countries, and even in the same country over time, the haptens used and the sensitivity of skin testing tend to undergo changes with time. Thus, general guidelines are needed in order to make accurate studies and comparisons between populations. These have been published recently by the ENDA/EAACI (26).

Skin test methods

There are three classical methods for skin testing: prick, intradermal and patch. Skin tests are normally done first by the skin prick test. Prick testing is done by pricking the skin with an appropriate needle through an allergen solution. If responses are negative intradermal tests are then carried out. Intradermal testing is done by the injection of 0.02–0.05 ml of the hapten solution, raising a small bleb that is marked initially. Both should be performed on the volar forearm, although other skin areas can be used. The role of patch testing in the diagnosis of immediate reactions to betalactams has not been clearly defined and is likely to be low.

Haptens. The haptens have to be freshly reconstituted and taken directly from the vial. Haptens are defined as chemical structures which become fully allergenic only after *in vivo* or *in vitro* conjugation to some suitable carrier molecule. For example, penicillins themselves or their derivatives, the so called minor determinants mixture (MDM) are haptens while benzylpenicilloyl poly-L-lysine (PPL) is a preformed, non immunogenic conjugate of BP to poly-L-lysine (27–30). Although the number of penicillin minor determinants of interest was initially higher, the instability of some has restricted the composition of the commercial MDM to BP and benzylpenicilloic acid (9, 27–29). The appearance of known side chain specific reactions has required the use of other determinants, of which the most relevant are AX and various cephalosporins (12–16).

The available commercial haptens to use are PPL and MDM (both from Allergopharma, Merck, Darmstadt, Germany) and AX. Ampicillin (AMP) and different cephalosporins can also be used. AX, AMP, or any other culprit drug must be prepared everyday fresh from the intravenous form under sterile conditions (14).

Concentrations. The maximum concentrations accepted nowadays for both prick and intradermal testing are: PPL 5×10^{-5} mmol/L, MDM 2×10^{-2} mmol/L, AX 20–25 mg/ml (51.67 mmol/L), AMP 20–25 mg/ml

Table 1. Concentrations recommended for both prick and intradermal testing with betalactams

Hapten	Dose	Units
BPO	5×10^{-5}	mmol/L
MDM	2×10^{-2}	mmol/L
Amoxicillin	20–25	mg/ml
Ampicillin	20–25	mg/ml
Cephalosporin	1–2	mg/ml

(54 mmol/L), and for most cephalosporins 1–2 mg/ml. Higher concentrations may cause unspecific irritative reactions also in subjects with good tolerance or no exposure to betalactams (Table 1).

Dilutions. In patients reporting symptoms compatible with severe reactions or who have experienced mild symptoms but are at special risk, the intradermal tests, and even the prick test, should begin with a thousand-fold dilutions, which are gradually increased until the appearance of a positive skin response or until reaching the maximum concentration described above.

Scoring. Readings should be taken after 15–20 minutes. In the skin prick tests a wheal larger than 3 mm accompanied by erythema with a negative response to the control saline is considered positive (26). In the intradermal tests the wheal area is marked initially and 20 minutes after testing, and an increase in diameter greater than 3 mm is considered positive (26). A late reading should be made in those cases with an unknown chronology or suspicion of non-immediate reactions; therefore all patients should be advised of the possibility of having a late reaction within an interval of 24–48 hours or even later.

General considerations. Some drugs have to be discontinued prior to undertaking the test, such as antihistamines (one week) and betablockers (48 hours) in cooperation with the prescribing physician and under monitoring of the blood pressure. The patient should be free of any infectious disease, fever or any inflammatory reactions at the time of testing.

Systemic reactions after skin testing

Reactions occurring after skin testing may resemble the original symptoms, although in general they are of lower intensity. Special care should be taken in order to avoid systemic reactions to skin tests, especially when the original reaction was severe. Typical symptoms include systemic pruritus, isolated maculopapulae, sometimes accompanied by angioedema, erythema, hoarseness and dizziness. In general these symptoms are noticed quite soon after the skin test. Occasionally, these may progress to tachycardia, abdominal pain, difficult breathing, and finally hypotension. Early monitoring and treatment, such as placement in a supine position, monitoring of blood pressure, and emergency medication have proved to be very valuable to control the symptoms.

One study performed over the years 1985–1995 showed that after intradermal skin testing with the maximum doses of penicillin, 11% of the patients, most skin test positive, developed systemic symptoms, with AX responsible in 50% of the cases, PPL in 29%, MDM in 15% and AMP in 6% (19).

Evolution of skin test reactions over time

As stated above one of the most important points to be taken into account when performing skin testing is the time interval between the clinical reaction and the test. Retrospective studies have shown that the longer the time interval between the initial reaction and the skin test, the less likely a positive response is obtained (31).

The description of side-chain-specific reactions and the identification of subgroups of patients allergic to specific betalactams has led to the re-evaluation of the spontaneous evolution of sensitivity in these subgroups. In a recent prospective study of allergic subjects who were all skin test positive initially, there was a different rate of persistence of skin test reactivity between patients with a response to a common penicillin determinant and those with a selective reaction to AX (32). After 5 years follow-up only 40% of cases in the first group became negative whereas 100% of patients with a selective response to AX had become negative. It is not yet known when subjects initially responding to other betalactam drugs, such as cephalosporins, become negative, and if loss of skin reactivity equals a loss of allergy. Further studies to determine the natural evolution of their specific antibodies are required.

Sensitivity and specificity of skin testing

To determine sensitivity and specificity of skin tests, a gold standard is needed, defined as the diagnostic method that can discriminate patients with allergic reactions to betalactams from those without. It is difficult to calculate the sensitivity of skin testing because DPT cannot be used as a gold standard for classifying subjects as allergic or not allergic. DPT can often not be performed for ethical reasons since it entails a high risk when challenging patients with a positive history and positive skin tests and false negative DPT results may also occur for various reasons (33).

Initially, skin tests to PPL were considered to be positive in more than 70% of patients with IgE mediated clinical reactions to penicillin, and most studies carried out over the years, mainly in the United States, have shown that PPL is the most relevant determinant (9, 25, 34–36). However, in one study encompassing 290 patients, the sensitivity of skin testing for any single hapten in patients with a clinical history of urticaria and/or anaphylaxis has recently been reported to be as low as 22% for PPL, 21% for MDM, 43% for AX and 33% for AMP (19). Subjects tended to be skin test positive to more than one penicillin determinant, and the combination of all four haptens gave a sensitivity of 70%. In the same study the specificity for each individual hapten ranged from 98–99%, and 97% when all the haptens were taken together. In this study the number of cases with a negative skin test but who were positive after DPT was of note, contrasting with

the previous data indicating that in subjects with a negative skin test to PPL and MDM the possibility of having a reaction after penicillin administration was negligible. However, at present, even including AX and AMP or other determinants in the skin test, the population that can be diagnosed by skin testing alone is lower than what has been reported in earlier studies (19). Regarding other betalactams, such as cephalosporins, no large studies and no definitive data about skin test sensitivity are available. Taking all immediate reactions together, whether selective or not, we can conclude that there seems to be a tendency to a decrease in the sensitivity of the skin test and, even with classical plus side-chain penicillin determinants, the number of subjects candidates for DPT is tending to increase (14, 37, 38).

To establish specificity, data from subjects with known good tolerance to betalactams are utilised. The specificity of skin testing has proved to be very good, from 97 to 99% (19).

Re-evaluation/Booster

As mentioned above the natural history of allergy to penicillins indicates that patients may lose sensitivity and become negative over time, but the percentage of cases who will become resensitized after one or more further contact with a betalactam is unknown. Although no prospective data are available, it has been recommended that in patients with a positive history and negative skin and *in vitro* tests with classical reagents, and even good tolerance after DPT, a re-evaluation may be considered, following the same protocol, from two weeks to one month later before further treatment can be attempted (39–43). In our opinion this has to be done only in those cases with severe reactions and when no other agents can be found responsible for the reactions. Different studies indicate that from 1 to 16% of subjects may become resensitized after re-administration of a betalactam (39–43). Such variation in numbers could be related to the age of the population, the inclusion criteria of the patients, and the time interval between the initial symptoms and the test.

In vitro tests

There are many methods reported to be useful in the diagnosis of patients with immediate allergic reactions to betalactams, but several methods have not been standardised and evaluated. We will focus on those methods that have been more widely studied.

Quantitation of specific IgE antibodies

The advantages of the *in vitro* quantitation of specific IgE antibodies compared to skin testing is that the former pose no direct risk to the patient. They are also less time consuming for those patients who require special measures to avoid risks, are useful in patients with skin diseases, can sometimes be positive in patients with negative skin tests and perhaps less expensive than DPT. These tests, however, are less sensitive and often more expensive than skin testing.

Methods. Many methods have been developed for the quantitation of specific IgE antibodies to betalactams but the most widely used are the immunoassays (ELISA, RIA or FEIA), and the most validated are the RIA, mostly by RAST, and the FEIA (44–48). All are based on the detection of the hapten-carrier-antibody complex. The disadvantage of RIA is that it uses an isotopic reagent that needs a special laboratory and equipment. We shall focus on the FEIA system because it is a commercial method available world-wide. In brief the Pharmacia CAP System FEIA method is as follows: the drug of interest, covalently coupled to Immuno-CAP, reacts with the specific IgE in the patient's serum specimen and the specific IgE measuring range is 0.35–100 kU_A/l, with a cut-off value ≥ 0.35 kU_A/l for positive test results and < 0.35 kU_A/l for negative test results.

Sensitivity and specificity. The sensitivity of specific IgE for benzylpenicilloyl (BPO) and amoxicilloyl (AXO) in a group of 19 patients who were skin test positive to AX, PPL or MDM has recently been reported to be 74%, and in a group of 29 patients with skin tests positive to AX and negative to PPL and MDM (selective AX group) the sensitivity of FEIA to AXO was 41%. Moreover 42% of 26 patients with skin tests negative and DPT positive were FEIA positive to BPO or AXO. Consequently this last group could have been diagnosed by FEIA alone, avoiding the DPT. The overall sensitivity among 48 patients skin test positive to AX and/or BP derived agents was 54%. The specificity of the test in this study was 95–100% (47).

In another study of 58 patients with immediate reactions to betalactams and positive skin test to at least one of the different allergens (MDM, PPL, BP, AMP, AX and cephalosporins) 22 patients had at least one positive specific IgE determination, as well as four controls. The sensitivity and specificity of the FEIA were therefore 37.9% and 86.7%, respectively (49). As we do not know what percentage of this group are selective, direct comparisons cannot be made with the previous study (47). A previous study (50) had found that among 35 patients with immediate reactions and positive skin tests 37% had a positive FEIA.

Differences in the reported sensitivities of the FEIA in patients undergoing similar skin testing procedures, as in these reported studies, may be due at least in part, to differences in the time elapsed between blood sampling and the occurrence of the clinical reaction or last exposure to the drug.

Comparison between skin testing and in vitro *quantification of specific IgE antibodies*. Studies comparing *in vivo* skin

tests and *in vitro* IgE results indicate that the two methods are not totally equivalent. Thus the skin test minor determinant response has no well-defined counterpart IgE test and subjects who are skin test positive to PPL (BPO-PLL) may have *in vitro* positivity to BPO-specific IgE tests, while some subjects positive to MDM and negative to PPL can also be *in vitro* positive to BPO-specific IgE reagents (12, 51). With respect to the AX selective response, those subjects who are skin test positive to AX are more frequently *in vitro* positive to AXO-specific IgE reagents (12), but a limited study has shown that these subjects who are *in vitro* positive to AXO-specific IgE reagents are skin test negative to AXO-PLL (data not published). Nevertheless, these tests have resulted in the more precise identification of side-chain-specific reactions.

Quantification of IgG antibodies

The quantification of specific IgG antibodies to betalactams has no diagnostic value in immediate allergic reactions to betalactams and non-allergic subjects can have high levels (24). The presence of these antibodies indicates contact more than an allergic reaction so they are not a recommended diagnostic method.

Study of inflammatory mediators

When mast cells and basophils are activated, after their interaction with the hapten-drug conjugate antigen, they release many mediators that can be measured in blood and different fluids. These measurements can have a diagnostic value if the patient is evaluated during the acute phase of the reaction which seldom occurs except in evaluating DPT. Two mediators that have been extensively studied are histamine and tryptase.

Histamine is released by both mast cells and basophils. In blood it can only be detected for a few minutes after the reaction as it is rapidly metabolised to N-methyl-histamine, which can be measured in urine. However, in non-allergic subjects high urine levels of N-methyl-histamine can also be detected, depending on many factors, such as the patient, the diet, or drugs. This method therefore is not recommended for diagnosing immediate allergic reactions to drugs.

The mast cell protease tryptase is released exclusively by mast cells, so its measurement is very useful in the diagnosis of immediate reactions to drugs (52). Until about 10 years ago, only the β-form of tryptase was measured, and non-anaphylactoid subjects generally had undetectable levels of β-tryptase in serum or plasma (53). High levels could be detected in blood from 1 to several hours after the onset of the reaction, depending on its intensity (54). Since about 10 years, total tryptase can be determined by a commercially available FEIA, which is more sensitive. Levels above 20 ng/ml are found in patients with anaphylaxis and in patients with systemic mastocytosis (55).

Histamine release test

This is an immuno-assay that measures *in vitro* the histamine release from peripheral blood basophils induced by drugs. It can be also performed by both RIA or EIA and the predictive capacity of this methodology in the diagnosis of patients allergic to drugs is not adequate (56).

Other tests

Various *in vitro* cellular tests have been described in recent years for the diagnosis of immediate-type allergy to betalactams. Most data exist on the Cellular Allergen Stimulation test (CAST), in which sulphidoleukotrienes (LTC4 and its metabolites LTD4 and LTE4) produced upon *in vitro* stimulation of blood leukocytes (predominantly basophils) by drugs are quantitatively evaluated (57–59). At present eight studies on a total of 146 patients with immediate reactions to betalactams and positive skin tests have shown an overall sensitivity of 46% (range 35–80%) while specificiy has varied between 79 and 89% (60). Some authors have judged the sensitivity too low for the test to be useful (58) while others judged it particularly suitable to detect patients with ananphylaxis (57). However, the ENDA opinion is that this test needs to be further validated before it can be used as a routine laboratory method.

The flow cytometric basophil activation test (FAST, FLOW-CAST or BASOTEST) has recently been described. This is based on the flow cytometric evaluation of CD63 on blood basophils, an activation molecule appearing following incubation of blood basophils with drugs or other allergens *in vitro* (49, 61, 62). This method has been recently studied and compared with FEIA in 58 patients with immediate allergic reactions to betalactam antibiotics and presenting positive skin tests to at least one of the allergens (MDM, PPL, BP, AMP, AX, Cephalosporins) and 30 subjects non-allergic to betalactams (49). The sensitivity of the technique was 50% and the specificity 93.3%. In spite of having a greater sensitivity and specificity than FEIA (37.9% and 86.7% respectively), differences between sensitivity and specificities of both techniques (CAP and FAST), taken individually, did not reach statistical significance. However, combination of both tests allowed the identification of 65.5 % of allergic patients. In a recent analysis of 57 patients with immediate reactions and positive skin tests to at least one of the penicillin reagents 67% were positive to one or both cellular tests and added to CAP 81% of the allergic patients could be detected (60). Although quite promising, these results still require confirmation and validation by other groups.

Drug provocation test

It has long been assumed that, even with a positive history, the presence of negative skin tests to major and minor determinants of BP is accompanied by a high probability of tolerance (25, 34–36). Recent evidence, however, indicates this is no longer valid and more determinants need to be included in skin testing (e.g. AX or AMP). Even using all possible determinants in skin testing, sensitivity is not 100% and in up to 17% of cases, with skin test and CAP-FEIA negative, the drug would have to be re-administered in a provocation test in order to confirm the diagnosis (19).

Patients with immediate reactions to betalactams can be allergic to several penicillins, to a subgroup of drugs with side chain similarities, or just to a single drug. Despite considerable work performed in the immunochemical basis for these variable specificities is not fully understood and many new betalactam determinants have still to be characterised (30, 33, 63). In general however, evidence indicates that, regardless of the betalactam inducing the clinical reaction, the first evaluation has to be made with BP and, if positive, the subject must be classified as allergic to the whole group of betalactams. But if this initial evaluation is negative the patient has to be tested with the culprit drug. If this is negative the adverse drug reaction can not be confirmed and if it is positive the patient is diagnosed as being selectively allergic to the culprit drug. If we do not know the culprit betalactam the first evaluation should be made with an aminopenicillin.

A DPT should be done only after performing skin tests, and possibly determination of specific IgE-antibodies. If either of these is positive, in combination with a compatible history, then DPT is not recommended because of the risk involved. The general considerations for carrying out a DPT are the same as described above for skin testing and in the ENDA general guidelines for DPT (manuscript in preparation). They are performed in a single blind placebo-controlled way under strict hospital surveillance with emergency room facilities. The drug is administered at increasing doses, with a minimum of 30 to 60-minute interval between each if good tolerance is established at the previous dose. The recommended doses are: BP intramuscularly 10^4 IU/ml, 10^5 IU/ml and completing 5×10^5 IU/ml (cumulative dose: no more than 10^6 IU/ml), and similarly, AX and penicillin V are given by oral route at the following doses: 1–5 mg, 50–65 mg, 100–150 mg, 250–300 mg, 400–800 mg (cumulative dose: no more than 1000 mg). The first two doses should be even lower in the case of a patient with a history of severe reaction (0.1–5 mg). Even though from the clinical history we are considering the possibility of an immediate reaction, this may not in fact be the case. Therefore, since the patient may react within an interval of several hours to even a few days afterwards, sufficient time should pass before proceeding with the next DPT. The symptoms developing after DPT enable classification of the reaction, as for example urticaria, or anaphylaxis.

There is a significant, direct association between the dose of the drug to which the subject responds in the DPT and the type of reaction; the greater the dose the longer the interval before the response. In those cases where this interval is longer, urticaria is the usual clinical reaction (20). Such patients may develop an accelerated urticaria. This has been described as one of the clinical entities induced in penicillin allergic patients with a variable time interval between drug administration and onset, which can be as short as two hours, and although this entity has been claimed to be IgE mediated, this has never been adequately demonstrated (9, 37).

High risk patients, ethical considerations and informed consent

There are two types of high risk patients: those who develop a life-threatening reaction, such as anaphylactic shock, and those who have any concomitant illness, such as cardiovascular disease, respiratory or oncologic problems or who are taking certain drugs, such as beta-blockers, which increase the risk of anaphylaxis. A risk-benefit analysis to decide whether the patient needs to be investigated for penicillin allergy should always be undertaken. If there is no other alternative, skin testing should begin with a higher dilution of the test reagents and all tests are performed under controlled conditions, with emergency treatment readily available.

The diagnostic methods described above for the detection of betalactam hypersensitivity reactions are in common use in different centres in many countries. In the case of a patient with a possible allergic reaction to a drug, these tests do not require the authorisation of the local ethics committee, though they do require informed consent. The authorisation of the local ethics committee is required, however, when these diagnostic methods are performed in the context of clinical studies, for example to establish the correct doses for skin testing or the validation of skin testing by DPT, and also when the data are to be collected, stored or distributed in a database.

Diagnostic evaluation of children

The diagnosis of immediate allergic reactions to betalactams in children follows the same practice as for that in adults. The lowest age at which these studies can be performed is at present not known and probably it is difficult to perform under six years old because of fear. In such cases, *in vitro* tests may be particularly useful. Clinical entities reported vary from urticaria to anaphylactic shock, although evidence indicates that a very high

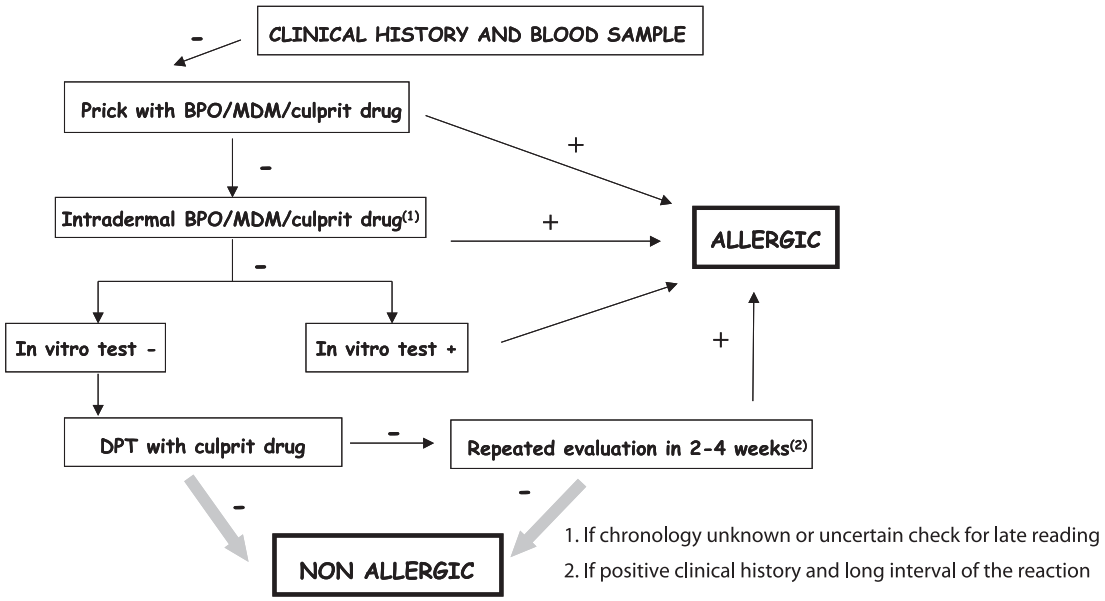

Figure 2. Short algorithm.

percentage of children who develop an immediate cutaneous reaction after administration of a betalactam have a negative skin test and FEIA and good tolerance in the DPT (42). This indicates that the reaction, often a rash, was induced by another agent, such as a viral disease. Though anaphylaxis has been reported, in some instances with severe respiratory symptoms, the same protocol as for adults is valid for the evaluation of children with immediate allergic reactions to betalactams (39, 42, 64).

Diagnostic algorithm

In order to provide a practical approach for patient evaluation two algorithms will be described, with the main difference being the time required to reach a final diagnosis. The first protocol is shorter and enables diagnosis of the patient as allergic or otherwise, though the reaction cannot be confirmed as selective or non-selective. The second protocol is longer and enables the evaluator to identify selective responders.

Short algorithm

The first step is to take a clinical history and a blood sample for performing *in vitro* tests, basically CAP-FEIA, although in the future other tests, such as cellular tests, can be performed. In the first evaluation, skin prick tests with all reagents are performed, followed by intradermal tests, if the formers are negative. If any of the skin and *in vitro* tests are positive, the patient is considered as, allergic; if both are negative, a DPT with the apparent culprit drug may be considered. At least in high risk patients and preferably in all, the results of the *in vitro* tests should be known before beginning with the skin tests, not to put the patients at unnecessary risk. If DPT results in good tolerance, two possibilities exist: either the patient can be considered as non allergic but, if the history is clearly positive and there is a long interval between the reaction and the diagnostic evaluation, a re-evaluation following the same protocol at least 2 to 4 weeks thereafter has to be performed before considering the patient as non allergic. This algorithm (Fig. 2) is quicker and cheaper than the long algorithm, but has the disadvantage that patients with a positive response cannot be clearly defined as selective or non-selective reactors. If we do not know which betalactam induced the reaction but know that it was some kind of penicillin, AX is the drug to be selected for DPT.

Long algorithm

This algorithm (Fig. 3) is basically the same as the first one but we perform skin tests and DPT in at least two steps. At the first evaluation, we begin skin testing with benzylpenicillin determinants by prick and intradermal methods. If they are negative, if the clinical reaction was not life-threatening and if the clinical situation requires it, we then proceed to a DPT of BP. If this is positive, the patient is considered to be allergic, but if it is negative, a second evaluation with the culprit drug has to be undertaken. If this second evaluation is positive at any step, the patient is considered to be a selective reactor to the culprit drug, but if it is still negative the patient is considered to be non allergic. If we do not know which betalactam induced the reaction but know that it was some kind of penicillin, AX is the drug to be selected in the second evaluation. We follow the same rules for

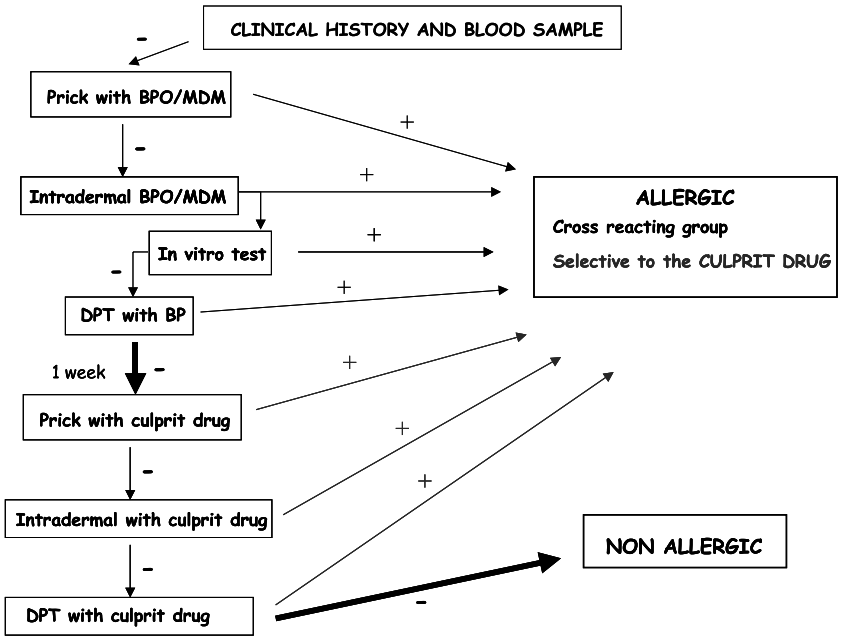

Figure 3. Long algorithm.

re-evaluating patients and for in vitro testing than in the first algorithm.

Search for alternatives

Patients are considered to have a selective reaction to one betalactam when they are diagnosed of an immediate allergic reaction to a betalactam, by skin test or DPT, and have good tolerance to benzylpenicillin in DPT. The advantage of detecting patients with selective reactions to some betalactams and good tolerance to others means that in a number of situations, such as cystic fibrosis, bone marrow transplantation, severe infections with specific micro-organisms, and AIDS, the existence of an allergic reaction to one betalactam does not prohibit the use of other betalactams. Cross-reactivity between penicillins had been reported specially to cephalosporins of the first and second generation (9). The frequency may have been overestimated because of traces of penicillin contaminating cephalosporins in the production process (9). Cross-reactivity between penicillins and the third and fourth generation cephalosporins have become rare (14). Prohibition of the whole group may imply more risk than benefit because of the potential adverse consequences of the choice of another drug that can be more toxic, more expensive or with the capacity of inducing bacterial resistance. Because of the suboptimal sensitivity of skin and *in vitro* testing, the only definitive approach to establish good tolerance of penicillin is DPT, provided other tests are all negative (8, 12–16). Thus, in the case of AX for example, before the patient can be considered a strictly selective reactor, he must be skin test negative to PPL and MDM, possess good clinical tolerance to BP and be either skin test or DPT to AX.

Concluding remarks

Changes in the use and choice of betalactam antibiotics, in particular the increased use of AX, have caused epidemiological modifications in the population of patients allergic to such drugs and justify a revision of past diagnostic guidelines.

Immediate reactions to betalactam antibiotics may be clinically classified as urticaria or anaphylaxis, occurring within one hour of drug administration. A detailed clinical history of the patient's reaction is required, including the symptoms, the time elapsed between administration of the drug and the appearance of symptoms as well as the time elapsed between the clinical reaction and the allergological evaluation, and previous reactions to betalactam antibiotics.

Skin testing by prick and intradermal techniques should not be limited to the classical reagents PPL and MDM, derived from BP, but should include AX and AMP, as well as any other possible culprit drug. Particular caution and testing, starting with 1,000-fold dilutions of the stock reagents, should be used in patients who have experienced severe or life-threatening reactions such as anaphylaxis. Skin testing with betalactams should be performed under controlled conditions with emergency treatment available, since systemic side effects may occur in up to 10% of cases.

The sensitivity of skin testing, when using the four reagents mentioned above, appears to be about 70%, which means that negative skin tests do not suffice to exclude penicillin allergy, as shown by a number of patients with a positive history and negative skin tests but positive DPT to the culprit drug. In this respect, additional *in vitro* tests, such as specific IgE determination to BPO and AXO determinants and new cellular tests still under validation may be helpful in order to confirm the clinical diagnosis.

A number of patients experiencing clinical allergic reactions to AX may be reacting specifically to AX and tolerating other betalactam antibiotic. The identification of such patients is based on negative skin tests to BP-derived reagents, negative in vitro tests to BP-derived reagents and negative challenge to BP under DPT. DPT must be performed with the required cautions and with correct indications.

In view of the wide use and of the high frequency of allergic reactions to betalactam antibiotics, accounting for the majority of allergic reactions to drugs, it is important that updated allergological diagnostic procedures become widely known and available to the medical profession.

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