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Antibiotic Allergy: A Clinical Review

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Abstract

Introduction: Antibiotics are commonly associated with hypersensitivity reactions. These can be expressed through clinical manifestations that range from mild symptoms to severe life-threating reactions. Nevertheless, these are often mistaken with adverse events. Incorrect labeling off a patient as allergic, leads to increase in costs and morbidity in the health care setting.

Objectives: Review currently available information on evaluation, diagnosis and treatment of allergic antibiotic reactions.

Methods: A search was conducted in the PubMed, filtering results to articles published in the last ten years, in English, in adults and with full texts available. Out of the eight hundred and twenty-six results, seventy-three were selected.

Results: Diagnosis of allergic events requires a detailed anamnesis. Confirmation of the diagnosis is influenced by the clinical features and the type of reaction, immediate or nonimmediate. The first can be evaluated with skin tests and drug provocation tests. The latter are studied with delayed-reading skin tests and drug provocation tests. Management of these patients should follow avoidance and application of an alternative tolerated drug. However, if the drug in question is indispensable for the treatment of the patient, then desensitization can be tried.

Discussion: Clinical history is a fundamental component in the management of these patients. Skin tests are less well validated to antibiotics other than β-lactam. *In vitro* tests have not been fully validated in large samples of subjects. Desensitization has been validated for patients with β-lactam immediate reactions, but further investigation is required for non-immediate reactions, as well as, for non β-lactam antimicrobials.

Conclusion: Management of antimicrobial hypersensitivity follows specific considerations in function of the type of allergic reaction and antibiotic class. Further investigation regarding immunochemistry and validation of diagnostic tests for non β-lactam antibiotics is required.

Keywords: Anti-Bacterial agents; Cross-reactivity; Desensitization; Skin testing; Drug provocation test

Introduction

Anti-bacterial drugs not only represent one of the most prescribed pharmaceuticals in the clinical practice, but also are one of the major causes of drug allergy reported in epidemiological studies [1]. Estimates of prevalence of antibiotic allergy are highly variable. For instance, allergy to beta-lactam antibiotics constitutes the most common form of medication allergy, occurring in 8-12% of patients [2,3].

Although being one of most prevalent adverse effects of antibiotic use, the term "allergy" is frequently misused in clinical practice [4]. An allergic reaction as to be immunologically mediated [2]. Immunological reactions can be divided as immediate and non-immediate (delayed) hypersensitivity reactions. Immediate hypersensitivity are IgE-mediated occurring minutes to one hour after exposure to the last dose. Non-immediate hypersensitivity is T cell mediated, taking place hours to days after last dose administration [1,5].

Furthermore, antibiotic allergic reactions can present themselves in a large spectrum of ways, possibly affecting a great variety of organ systems, in variable severity. The most common clinical manifestations of antimicrobial allergy are cutaneous (maculopapular skin eruptions, urticaria, and pruritus). Nevertheless, antibiotic hypersensitivity can present with organ-specific (e.g. interstitial nephritis) and/or systemic symptoms (e.g. anaphylaxis), but also with potentially fatal reactions such as Stevens Johnson syndrome (SJS) or toxic epidermal necrolysis (TEN) [1,2].

Therefore, it is vital for all medical practitioners to be able to correctly evaluate, diagnose and treat patients presenting with allergic reactions, and thus reducing the substantial morbidity, mortality and increased health care costs associated with this disease. In this regard, this consists on a review on currently available information on how to evaluate, diagnose and treat allergic antibiotic reactions.

Methods

Published papers associated with this topic were examined using the PubMed data base. PubMed has resources covering more than 26 million of published papers from Medline and life science journals, being regularly updated with newly content. The online paper search was conducted using the MeSH terms: "Anti-Bacterial Agents" (Mesh) and "Hypersensitivity" (Mesh). After that, the papers were examined and filtered on the following inclusion and exclusion criteria: being "published in English", being "published between 2006 and 2016", the content referred to "adults of the age 19 or higher" and the articles were available in full text through PubMed. This search wielded eight hundred and twenty-six results.

From this initial sample, the abstract of every article was analysed and the additional criteria for inclusion and exclusion were applied: do not refer to both anti-bacterial agents and hypersensitivity; not following the age criteria; do not provide information on evaluation, diagnose or treatment of allergic antibiotic reactions; focus of the article on populations with specials considerations, such as cystic fibrosis. After examining all these criteria, seventy-four were considered for the elaboration of this review.

Results

Antibiotics are amongst the most frequent prescribed pharmaceuticals in medical practice, being also reported as one of the most common causes of drug allergy reaction [1,2,4,6]. Prevalence of antibiotic allergy label range between 10-20%, but only 10-20% of this patients have true allergy confirmed by allergologic work-up [7-9]. Frequently, patient claims that any type of adverse reactions constitutes allergic reactions. However, only when a definite immunologic mechanism is established can these reactions be classified as allergic [4,6]. Consequently, patient reported history of antibiotic allergy is frequently unfounded, leading to the use of alternative, second choice drugs, with negative implications regarding cost, safety, duration of inpatient stay, and efficacy of treatment [4,10].

Hypersensitivity reactions to antibiotics have been explained by the hapten and pro-hapten model. High molecular weight protein drugs (>800 Dalton) induce hypersensitive reactions in a similar process to the immunological response to foreign antigenic proteins. The pharmaceutical compound is recognized and bound by compatible B cell receptors (BCRs) on B cells. However, this interaction is not sufficient to induce B cell proliferation and differentiation. For that to occur, interaction between B cells with T helper 2 is mandatory. Activation of naive T helper cells bearing T cell receptors (TCRs) with appropriate specificity requires the presentation of the drug by antigen-presenting cells (APC), as an antigenic peptide, on the major histocompatibility complexes (MHCs). Interaction between drug peptide-presenting B cells with activated T helper cells induces proliferation, differentiation and production of drug-specific antibodies [11].

However, antibiotics are low molecular weight substances (<800 Dalton) and cannot be presented by APC. In order to induce a hypersensitivity reaction these compounds will act as haptens, low-molecular weight substances that can covalently bind to carriers such as proteins or polypeptides. The subsequently formed drug–protein complex can now be incorporated by APCs, presented on MHC molecules and act as immunogenic peptides that can be recognized by B and T cells triggering antibody manufacture or T cell differentiation and clonal expansion of different T cell types, responsible for the various types of allergic reactions [11]. Pro-haptens are compounds that are immunologically inactive in their original form, requiring metabolization to form the reactive metabolites involved in the allergic reaction [11].

The allergic reactions can be classified according to the Coombs and Gell classification system, regarding the pathophysiology and immunological mediators, into four types: I (mediated by drug specific IgE antibodies), II (cytotoxic), III (mediated by drug specific IgG or IgM antibodies), and IV (mediated by drug-specific T lymphocytes) [6,12]. Clinically, hypersensitivity reactions are classified in functions of the time elapsed between last drug dose administration and symptom onset, into two types: immediate or nonimmediate [2,4,6].

Immediate type hypersensitivity occurs within one hour after administration of the drug and are type I reactions, causing mast cells degranulation, producing large amounts of vasoactive substances and histamine [6,13]. These types of reactions not only are rapidly progressive and potentially lethal, but they also have the tendency to become more severe with repeated exposure. Normally, this reaction manifest as urticaria, angioedema, conjunctivitis, rhinitis, bronchospasm, gastrointestinal symptoms, and anaphylaxis [2,4,6,12,13].

Nonimmediate reactions arise more than one hour after drug administration and include type II to IV allergic reactions. Type II reactions result of circulating antibodies (IgG and IgM) binding to the surface of circulating blood cells, inducing the destruction of these cells (haemolytic anaemia, neutropenia and thrombocytopenia) [6]. On the other hand, Type III reactions occur due to the formation of antibody-antigen complexes that precipitate in tissues and activate complement resulting in a variety of clinical syndromes including serum sickness and small-vessel vasculitis, potentially affecting any organ system. Clinical manifestations may comprise fever, malaise, nausea, vomiting, diarrhea, abdominal pain, arthralgias, myalgias, lymphadenopathy, glomerulonephritis and rash. Type IV reactions are mediated by T-cell activation and cytokine expression in response to the drug allergen. Although the precise role of T-cells is not completely understood, several situations such as exfoliative dermatitis, acute generalized exanthematous pustulosis (AGEP), SJS, TEN, immune hepatitis and drug-induced hypersensitivity syndrome (DRESS) can be included in this category [1,2,6]. The DRESS syndrome is characterized by a severe skin eruption, fever, hematologic abnormalities (eosinophilia or atypical lymphocytes), and internal organ involvement. It has a mortality rate of 10%, occurring between 2–6 weeks after the beginning of a new drug and may last despite drug discontinuation [6,14].

Therefore, the clinical features of antibiotic allergy include a broad spectrum of symptoms, depending of the type, severity and organ systems affected [2]. Also, variables such as the type of drug used, disease being treated and immunological state of the patient, influence the organic response of the patient [2].

The clinical management and assessment of antibiotic allergy requires a detailed medical history. Differentiating between drug adverse reactions and true allergy is a crucial step in the patient evaluation. Information regarding the specific symptom, the time interval between drug administration and the appearance of symptoms, as well as the time between clinical symptoms and allergic evaluation, other medication used by the patient and subsequent reactions to related drugs [2,6]. The assessment of these patients also includes a physical examination of all the systems that can be

implicated in the clinical manifestations. Since cutaneous manifestations are the most common symptoms involved in drug allergic reactions, the evaluation of this organ system should be emphasized during physical examination [15]. The absence of a detailed history may lead to an erroneous classification of the patient as allergic, leading to higher costs, longer hospital admission and development of resistant microorganisms [2,5].

Confirmation of the diagnosis of allergic reaction should be based on *in vivo* or *in vitro* allergy tests. The tests to apply are chosen taking in consideration the symptoms expressed by the patient and clinical classification of the allergic reaction, as immediate or nonimmediate, but also the nature of the antibiotic [12]. In the case of immediate reactions, this can be evaluated by *in vitro* tests such as serum-specific IgE assays and flow cytometric basophil activation tests (BAT), and *in vivo* by immediate-reading skin tests (skin prick tests (SPT) and intradermal tests (IDT)) and drug provocation tests (DPTs), in some selected patients. On the other hand, nonimmediate reactions are assessed *in vitro* test such as lymphocyte transformation tests (LTT), lymphocyte activation tests (LAT), and enzyme-linked immunospot (ELISpot; Millipore, Bedford, Mass) assays for analysis of antigen-specific, cytokine-producing cells; the *in vivo* test includes delayed-reading skin prick tests, patch tests, and DPTs [1,2,12].

It´s important to refer that the *in vitro* tests have not been fully validated in large samples studies [16]. Also, the *in vivo* tests, have been specially more validated to β-lactams, and in an inferior degree for the other classes of antibiotics. Therefore, separate considerations must be made regarding β-lactams and to non β-lactams antimicrobials [2,12].

β-lactams antimicrobials

The β-lactams antimicrobials are a group of compounds that include four families of chemically related substances that share a β-lactam ring: penicillins, cephalosporins, carbapenems and monobactams.

Penicillins are formed by a thiazolidine ring attached to a β-lactam ring that carries a secondary amino group side chain [17,18]. This group of antibiotics is almost completely metabolized (over 95%) in the organism into benzylpenicilloyl, which quickly combines proteins conjugates and forms antigenic haptens. These are known as the major determinant of penicillin allergy and are responsible for the majority of allergies. Unmetabolized penicillin and other minor metabolites (penilloate, penicilloate and specific metabolite side chain derivatives) can also work as sensitizers, however in a minor significance, and are referred to as minor determinants [19]. Therefore, it is possible to conclude that cross-reactivity between different penicillins can happen if the allergy is induced by a major determinant. However, if the allergic reaction is instigated by unique metabolites or side-chain determinants of semisynthetic penicillins, cross-reactivity will not occur [6].

Immediate hypersensitivity

In the case of the suspicion of an immediate hypersensitivity reaction to a penicillin, the first step in the confirmation of this diagnose is a skin test [20]. Initially, an SPT is performed with the administration of benzylpenicilloyl-poly-L-lysine (PPL), minor determinant mixture (MDM) and amoxicillin (AX) [20]. In 2004 because cessation of production this test became unavailable. However, in 2009 a new company, Diater, initiated the commercialization of a new kit. This new kit contains PPL, yet the MDM now only comprises benzylpenicilloate, eliminating benzylpenicillin and benzyl penicilloic acid from the classical evaluation [5]. Although some concern remains that the elimination of this compounds will lead to a reduction of sensitivity in the skin test evaluation, multiple studies carried so far have reveal that these two formulations are equivalent [21-23].

In the PST, a wheal diameter of at least 3 mm in comparison with the negative control supports a positive result [24]. American centres recommend a wheal diameter of at least 5 mm to increase specificity. If these tests are negative at 15 minutes, they are followed by intradermal tests. Increase in wheal size of more than 3 mm from the initial bleb with flare is considered positive [5].

It is important to highlight four considerations. Firstly, the negative predictive value of skin tests is not 100%. In fact, approximately 1/3 of patients with penicillins allergy will have a negative skin test result [5,25]. These patients require DPT, considered the gold standard test to confirm or exclude IgE-mediated penicillin allergy. Skin test is used to reduce the number of DPT and possible oral challenge reactions [16].

Secondly, skin test sensitivity is reduced over time and resensitization, conversion to skin test positivity, has been reported in patients revaluated after 4 weeks of negative allergological test, especially in patients who have experienced immediate reactions [26]. Therefore, European guidelines recommend that these tests be carried out shortly after reaction and advice revaluating patients who experienced immediate reactions to β-lactams and display negative results in the first allergic evaluation, including DPTs, after a period of 2-4 weeks [5,12].

Thirdly, skin testing can trigger systematic reactions in approximately 1% of all patients and 9% in positive skin test patients [27]. Therefore, antibiotic skin testing should only be performed by qualified professionals, in a space capable to treat potential systemic reactions such as anaphylaxis [28]. Also, in patients with history of severe allergic reaction patch tests should be performed before skin testing [29]. In case of patch-test negativity, for intradermal testing, the drug should be initially tested with the highest dilution [12].

Lastly, laboratory investigations serum-specific IgE assays and BAT have a higher specificity than skin tests. Nevertheless, their lower sensibility and higher costs make them be considered in selected patients, namely in situations of severe anaphylactic risk, contra-indicating DTP, and skin test negative [30].

Non-Immediate hypersensitivity

In the identification of non-immediate antibiotic allergic reactions, a detailed clinical history is important, since the variety of the clinical manifestations can mimic the symptoms of infectious or autoimmune diseases. Furthermore, these reactions can be associated with a concomitant viral infection, such as HIV, cytomegalovirus, human herpes virus 6, or Epstein Barr Virus [20,31].

Evaluation of non-immediate hypersensitivity begins with skin test, with the classic penicillin reagents, to exclude immediate hypersensitivity. If these tests are negative, a late intradermal reading of these tests is made three to five days afterwards. Patients negative in all the previously referred test, are subjected to DPT [5,12,20].

While skin testing is an effective test to evaluate IgE-mediated reactions, the sensitivity of these *in vivo* tests is low in the context of non-immediate allergic reactions, meaning that DPT may be required to establish the diagnosis [5,12,20]. Moreover, *in vitro* tests such as BAT, LTT, LAT and enzyme-linked immunospot have not been

completely validated in studies with large samples of patients, requiring further validation until their complete usefulness can be properly evaluated [5,12,20].

Cephalosporins

Cephalosporins are antibiotics chemically structured by a β -lactam ring bound to a six-membered dihydrothiazine ring. Furthermore, cephalosporins have a side chain in C7 and different substitutions in C3 position [17,18].

In opposition to penicillins, the immunochemistry of cephalosporins is not completely understood. Nevertheless, recent studies revealed that like penicillin, cephalosporins are metabolize into a major compound, cephalosporoyl. Although, in contrast with benzylpenicilloyl, cephalosporoyl is unstable and suffers rapid fragmentation in the dihydrothiazine (six-membered) ring, leading to the formation of new molecules that have no structural similarity to benzylpenicilloyl or to the minor determinants. The importance of this data is that cross-reactivity between penicillin and cephalosporins is normally not induced by major determinant of penicillin, but by sensitization to fragmentation of the side chain [6,32-34]. Therefore, cross-reactivity among penicillin and cephalosporins with similar side chain can occur in >30%, and be reduced to less than 10% if no similar side chain [34].

Cross-reactivity between cephalosporins follows the same logic, meaning that cephalosporins with similar side chain are more likely to present cross-reactivity. However, there are cases where there is only selective reaction to one cephalosporin, leading to the conclusion that in this case the reaction be mediated to allergic response to the culprit cephalosporin in question [34].

In regards to the diagnose of cephalosporin allergy, the collection of a detailed is fundamental to elicit the suspicion of this process. Confirmation of the diagnose follows similar principles between all β-lactam anti-microbials, for both immediate and non-immediate reactions [12,32-35].

Nevertheless, while skin testing is an effective test to evaluate IgE-mediated reactions, most of the appropriate antigens have not been identified for most drugs. Meaning that apart from penicillin, there are no valid *in vivo* or *in vitro* diagnostic reagents available for identifying most antibiotic-specific IgE antibodies [2]. Consequently, in skin tests frequently the whole antibiotics are used, diluted in saline solution [12,32-35]. Moreover, skin test must also contain penicillin derivatives (PPL, MDM and AX), so to determine if the reaction was caused by elements also present in penicillins (β -lactam ring or similar side chain) [34,36].

Carbapenems, monobactams and clavulanic acid

Carbapenems are chemically similar to penicillin, being formed by a β -lactam ring connected to a five-membered ring and two variable chains. However, they contrast with penicillin by the absence of sulphur atom in the five-membered ring and by the substitution of the nitrogen in position R1 for a carbon. Monobactams constitute a separate group of β -lactam antibiotics, since they are formed by only a β -lactam ring, being only effective against gram-negative bacteria. Clavulanic acid is compounds that chemically resemble β -lactam molecules, but they have weak antibacterial activity, instead acting has inhibitors to β-lactamases [17,18].

Carbapenems immunochemistry has not been entirely clarified. These compounds are metabolized into a main molecule, carbapenoyl, structurally comparable to benzylpenicilloyl and also capable to induce sensitization [6]. Because of their biochemical similarities, initially was expected that cross-reactivity between penicillins and carbapenems would be high. Early studies reported cross-sensitization between penicillin allergic patients to carbapenems in the order of nearly 50% [37]. However, more recent prospective studies have revealed that the risk of cross-ractivity to carbapenems in patients with IgE-mediated reaction to penicillin is very low (1%) [38,39]. In the case of non-immediate reactions to penicillins studies report a prevalence of cross-reactivity to carbapenems between 0-5.5% [40,41]. In summary, cross-reactivity is inferior to what was initially considered and therefore carbapenems should not be completely avoided [42].

About the immunochemistry of monobactams, these compounds are not processed into structures chemically resembling penicilloyl acids or minor determinants of penicillin allergy [6]. Thus, immunological cross-reactivity does not occur with this agent [43-46]. Nevertheless, cross-reactivity between aztreonam and ceftazidime has been reported due to side chain homology, yet it is still a rare phenomenon [47]. Consequently, aztreonam is largely tolerated in patients with confirmed hypersensitivity reactions to β-lactams, granting that rarely cross-sensitization can happen with ceftazidime [5].

Finally, clavulanic acid (CLV) has been reported to be responsible for immediate hypersensitivity reaction in patients with IgE-mediated allergic reactions to AX-CLV [48,49]. Accordingly, hypersensitivity to CLV should be evaluated in cases of allergy to AX-CLV, specifically in situations of negative results to AX separately [5].

Non β-lactams antimicrobials

In the evaluation of potentially hypersensitivity reactions to non β-lactams antibiotics, the diagnostic procedure follows a similar logistics. However, they are being separately considered because the diagnostic tests have been mainly validated for β-lactams antibiotics [12]. According to Mirakian et al. [50] and Romano et al. [12], assessment of this patients should being with the collection of a careful clinical history. If the suspicion of an immunological aetiology is considerate, the distinction between immediate non-immediate hypersensitivity must be made. In case of immediate hypersensitivity, skin testing with SPT and IDT should be considered. If both are negative, DPT can be used to clarify possible allergic reaction. On the other hand, in non-immediate hypersensitivity patch test and/or delayed reading intradermal test should be used. If both are negative, DPT can be used to clarify possible non IgE mediated allergic reaction.

Macrolides

Macrolides are a group of chemically related antibiotics that are characterized by a macrocyclic lactone ring to which are attached one or more deoxy sugars [17,18]. Allergic reactions to these antibiotics are unusual occurring in 0.4%-3% of treatments [51]. Clinical manifestations of hypersensitivity reactions to these antibiotics include urticaria, angioedema, rhino conjunctivitis, anaphylaxis (IgE mediated); maculopapular rash, SJS and TEN [1,2,12].

In the diagnose of macrolide allergy, the immunochemistry is not known. Consequently, skin testing is made with the use of non-irritating concentrations of the antibiotics (0.05 mg/mL for erythromycin, 0.01 mg/mL azithromycin according to a study by

Empedrad et al. [52]; 0.5 mg/ml for clarithromycin in a study Mori et al. [53]). In the study by Seitz et al. [54], all the 53 patients with immediate suspected reactions, were skin test and DPT negative, and of the 72 patients with history of non-immediate reactions solely one was skin test positive. Mori et al. [53], reported that the sensitivity and specificity of skin tests in the diagnosis of clarithromycin allergy was of 75% and 90%, respectively, in a pediatric group of 64 children with a history of clarithromycin allergic reaction. Therefore, the significance of skin testing in evaluation of macrolide hypersensitivity is still unknown and DPT is frequently required to confirm diagnosis.

Lastly, macrolides with a 14-membered lactone ring (erythromycin, clarithromycin and roxithromycin) have been reported to express cross-reactivity in single cases reports. Moreover, azithromycin, a 15-membered lactone ring semisynthetic derivate of erythromycin, cross-reactivity with erythromycin has also been described. Nevertheless, there is insufficient evidence to clearly support a common sensitization between macrolides antibiotics. Thus, individual macrolides are generally well tolerated [12].

Tetracyclines

Tetracycline antibiotics are a group of chemically related antimicrobial substances, that share a octahydrotetracene-2-carboxamide skeleton, in other words a tetra hydrocarbon ring structure [17,18]. This antibiotic class has been reported to cause allergic reactions expressed as urticaria, angioedema, anaphylaxis, pericarditis, polyarthralgia, exacerbation of systemic lupus erythematosus, pulmonary infiltrates with eosinophilia, photosensitivity, photo-onycholysis, SJS, TEN and DRESS [1,2,55-58].

Minocycline has been reported to induce grave hypersensitivity reactions, such as SJS, DRESS, anaphylactic shock, serum sickness and drug-induced lupus. These symptoms normally arise within 4 weeks of therapy, except for minocycline-induced lupus that typically expresses itself 2 years after the initiation of therapy. Hypersensitivity reactions to doxycycline and tetracycline are relatively rare, being the photodermatoses and photo-onycholysis the most common [1].

Clindamycin

Clindamycin is a synthetic derivate of lincomycin [17,18]. This antibiotic has been reported to be associated with immediate hypersensitivity, but more frequently with non-immediate reactions (described to happen in a rate of between less than 1% to 10.5% of treated subjects), such as maculopapular exanthemas, TEN, SJS, AGEP and DRESS [59,60]. The importance of skin testing in the evaluation of delayed or non-immediate reactions is datable. Seitz et al. [60], retrospectively studied clindamycin skin allergy testing in 33 patients with reported history of non-immediate reactions to clindamycin. From his analysis, a rate of positive testing of 15% was observed, as well as a 14.3% of false negatives results, posteriorly confirmed by DPT. Similarly, Pereira et al. [59], presents a rate of positive testing of 30%. Therefore, DPT remains the gold standard for confirmation of the diagnosis of clindamycin allergy. However, because of the risk of severe complication inherent to this test, skin testing is used to select patients and reduce the number of DPT complications.

Fluoroquinolones

Fluoroquinolones are synthetic fluorinated analogues of nalidixic acid. These antibiotics can be further divided in function of their generation: first (cinoxacin and nalidixic acid), second (ofloxacin, norfloxacin, ciprofloxacin, and enoxacin), third (levofloxacin), and fourth (gemifloxacin and moxifloxacin) [17,18].

Fluoroquinolones have been reported to be associated with immediate and non-immediate allergic reactions. Maculopapular rash is the most frequent clinical symptom. Studies report moxifloxacin has the fluoroquinolone associated with the highest rate of hypersensitivity reactions [61,62].

The usefulness of skin testing in evaluation of hypersensitivity to quinolones is debatable. Seitz et al. [63], assessed 64 patients with suspected immediate hypersensitivity. Three of six patients with positive result to skin testing were negative, when tested with DPT, as well as three of the forty-two patients negative to skin testing, were positive to DPT. Consequently, skin testing generated a sensitivity of 50%, specificity of 93%, PPV of 50% and NPV of 93%. Venturini et al. [64], reported a 5% rate of false negative skin tests and only half the subjects with positive skin tests had a positive DPT. Uyttebroek et al. [65], reported moxifloxacin skin test to have a sensitivity and specificity of 57% and 12.5%, respectively.

This alert to the fact skin testing can produce false positive results. This has been attributed to the inherent ability of fluoroquinolones to induce degranulation and release of histamine [66]. Therefore, DPT remains the gold standard in the diagnostic of hypersensitivity to fluoroquinolones.

Regarding cross-reactivity amongst fluoroquinolones, these have been reported more frequently between first and second generation quinolones. However, cross-reactivity with third and fourth generations is more complex. Patients with hypersensitivity to moxifloxacin tolerated ciprofloxacin, but patients with allergic reaction to ciprofloxacin responded to moxifloxacin [67]. In conclusion, cross-reactivity in this class is unpredictable and in case of hypersensitivity to this class, different antibiotic class should be used.

Aminoglycosides

Aminoglycosides consist of two or more amino sugars joined in glycosidic linkage to a hexose nucleus [17,18]. These antibiotics can be further divided into two groups: the streptidine group (eg: streptomycin) and the desoxystreptamine group (eg: kanamycin, amikacin, gentamicin, tobramycin, and neomycin).

Immediate and non-immediate allergic reactions have been reported to aminoglycosides, being the latter the most frequent. Of the non-immediate hypersensitivity reactions, the most frequently reported is contact dermatitis, but maculopapular rash, TEN and DRESS, have also been reported. Neomycin has been indicated has the aminoglycoside, with the highest rate of hypersensitivity reactions [12].

Because the immunochemistry of aminoglycoside antibiotic allergy is not fully understood, skin testing uses native antibiotic. Since the culprit native drug may not contain all the pertinent antigenic determinants, false negatives may arise. Therefore, diagnosis confirmation might need DPT [12].

Regarding cross-reactivity, common sensitization amongst aminoglycosides of the the desoxystreptamine group reaches at least 50%, according to Romano et al. [12]. However, cross-reactivity between the desoxystreptamine group and streptomycin has not been reported. It is considered that this is due to the different chemical structure of streptomycin, which produces different antigenic determinants compared to the other aminoglycosides. Therefore,

transition between the streptidine group and the desoxystreptamine group, can be made safely, when hypersensitivity is reported.

Sulfonamides

Sulfonamides are sulfonyl arylamines, characterized by a sulfonamide (SO2-NH2) moiety directly attached to a benzene ring, which carries an unsubstituted amine (-NH2) at the N4 position [68]. Sulfonamides antibiotics can induce immediate and non-immediate reactions, being the latter the most frequent. Non-immediate reactions can range between maculopapular rashes, to serious complications such as TEN, SJS and DRESS. In fact, Sulfonamide antibiotic are associated with the highest risk of SJS-TEN, when compared to other antibiots [12].

Two details must be highlighted. Firstly, allergic reactions to sulfonamide antibiotics arise in two to four percent of patients treated, but the prevalence rate rises to 50-60% in HIV infected patients. Secondly, immunological mediated reactions between different sulphonamides antibiotics have been described, because the reactions is directed against the sulfonyl arylamines [68]. Therefore, extension of the allergic reactions to sulphonamides compounds that are not sulfanilamides, such as celecoxib, furosemide, topiramate, has not been reported. Nevertheless, there is an exception, sulfasalazine, because this compound used in the treatment of rheumatoid arthritis, is metabolized to sulfapyridine, a sulfanilamides [68,69].

Glycopeptides

Vancomycin has been reported to induce allergic reactions such as anaphylaxis, drug fever, eosinophilia, skin eruptions (including exfoliative dermatitis), SJS, TEN and vasculitis, but these manifestations are rare [1,12,70]. The most common manifestation is the "red man syndrome", characterized by flushing, warmth, pruritus, and hypotension. This syndrome results of the stimulation of histamine release from mast cells derivated of rapid intravenous administration [1,12,70]. Teicoplanin, another glycopeptide antimicrobial, can produce hypersensitivity reactions similar to those reported above. However, in opposition to vancomycin, it has less side effects and infrequently produces "red man syndrome", since this antibiotic thus not induce mast cell histamine release. Cross-reactivity between this two antibiotics is complex, since some reports express common allergic reaction [71,72], while others refer tolerability between them [73].

Management and Treatment

The management of antimicrobial hypersensitivity beings with the collection of a complete clinical history and identification of a possible relation between the adverse effects and the administered pharmaceutical compound. After this, confirmation of the diagnosis should follow the principles discussed above. If a positive result is obtained and hypersensitivity is diagnosed, the adequate approach to this patient will vary according to the type of allergic reaction presented by the patient.

Immediate hypersensitivity

In the case of immediate or IgE-mediated hypersensitivity, management and treatment should follow: avoidance of the suspected drug, with the application of an alternative compound and, if adequate, allergic evaluation of this substance. Nevertheless, if the antimicrobial is fundamental to the treatment of the subject or an alternative medication is not available, then desensitization can be tried [5,50].

Desensitization

Desensitization is defined as the induction of a state of temporary unresponsiveness to a compound responsible for a type I or IgE-mediated hypersensitivity reaction [74]. After cessation of the drug, tolerability to the pharmaceutical agent is lost in 24-36 h and if new administration of the compound is necessary, desensitization is required [5,50,74].

The mechanism by which this state is obtained is not completely understood. However, it is considered that mast cells and basophils are the cellular targets of this process, in which sub-therapeutic doses reduce the membrane expression of IgE and cause the cell to be unresponsive [1,5,50,74].

This procedure consists of the administration of increasing doses of the antimicrobial agent, during a period of several hours, until the pretended therapeutical dose is obtained [1,2,5,50,74]. Initial dose 1/10 000 to 1/100 of the full therapeutic one and this are doubled every 15 to 30 minutes. The drug can be administrated orally or intravenously, but oral route has been reported to have less reaction [5,50].

Nevertheless, desensitization can induce allergic reaction in about 1/3 of the patients submitted to this procedure. According to Cernadas et al. [74], the great majority of this are mild reactions (90%), which can be treated with simple cessation of the drug. Then, new sensitization can be tried from the last tolerated dose, since these reactions are most frequent on the first desensitization. However, if severe reaction occurs (AGEP, SJS, TEN, etc), then desensitization is contra-indicated. Desensitization success has been reported to be range between 58%-100% [75].

Non-Immediate hypersensitivity

In the case of delayed hypersensitivity, avoidance of the drug and allergic evaluation of alternative compound, if appropriate, is the correct clinical approach [5,50]. Although desensitization was designed for immediate reactions, the procedure has been reported to be successful in non-immediate allergic reactions, and protocols are available for several β-lactams and non-β antibiotics. Though, until now no controlled clinical trials are available, most of the documented cases do not include previous confirmation of the diagnosis with full allergic evaluation, and the pathophysiology is largely unknown [76]. Therefore, further considerations and research must be made is this area.

Discussion

Adverse events related to the use of antimicrobial agents are commonly reported. Amongst the great myriad of symptoms and signs, only a smaller group of adverse reactions are immunologically mediated and correspond to true hypersensitivity reactions. Therefore, it is fundamentally important that a detailed medical history and physical examination are conducted in order to help the physician to differentiate between drug adverse reactions and hypersensitivity.

In the presence of a high suspicion of an allergic reaction, it stands logical the need for the execution of a confirmatory diagnostic test. Although, *in vitro* tests have shown promising results, they have not been fully validated in large samples studies. Meaning that *in vivo* tests

are the unique auxiliary resource available for the confirmation of diagnosis, namely skin prick tests, patch tests, and DPTs.

Skin tests have unsatisfactory low rates of sensitivity, specificity and predictive negative and positive values, more so when used outside the context of immediate hypersensitivity reactions to β-lactams. On the other hand, DPT are the gold standard diagnostic test, with very high negative predictive value, but are associated with the potential risk of severe allergic reaction. Therefore, to increase sensitivity in the diagnostic process and reduce the risk and number of DPT, a sequential approach of skin test followed by DPT is recommended.

Furthermore, apart from penicillin, the great majority of the appropriate antigens has not been identified for most pharmaceuticals agents, implicating the frequent use off whole antibiotics, diluted in saline solution, for the preparations in skin tests. This can lead to an important number of false negatives results for reasons such as the antigenic agent might be a metabolite of the drug not produced from skin application; or concentration or vehicle used might not be adequate. Consequently, further research must be conducted in this area, in order to develop the comprehension on the immunochemistry processes involved in the mediation of hypersensitivity to non-penicillin antibiotics.

On the other hand, the majority of allergies to penicillin are determined by benzylpenicilloyl, and in a minor significance, to the minor determinants (penilloate, penicilloate and specific metabolite side chain derivatives). Therefore, cross-reactivity between penicillins and other β-lactam antimicrobials are determined by unique metabolites or side-chain determinants. Consequently, for patients allergic to penicillin, the alternative use of another β-lactam antimicrobials, namely a cephalosporin with side chains that differ from penicillin or amoxicillin, is associated with a low risk off cross-reactivity and their use is defensible by available evidence.

Regarding non β-lactam antimicrobials, evidence suggests that every antibiotics class has its own particularities. Cross-reactivity amongst antibiotics of the same class is not linear and individual considerations should be made in the treatment of patients presenting with hypersensitivity reactions, considering the antibiotic used, but also the disease being treated and immunological state of the patient.

Desensitization is a valid approach in the management of patients with IgE mediated hypersensitivity reactions, in cases where the culprit drug is fundamental for the treatment. Nevertheless, although only in the minority of cases, desensitization can induce severe allergic reactions. Therefore, this process must be executed in an appropriate environment and by trained professionals. Moreover, is contra-indicated in patients presenting with severe reactions. Although desensitization was designed for immediate reactions, the procedure has been reported to be successful in non-immediate allergic reactions, and protocols are available for several β-lactams and non-β antibiotics. Nonetheless, until now no controlled clinical trials are available, most of the documented cases do not include previous confirmation of the diagnosis with full allergic evaluation, and the pathophysiology is largely unknown. Therefore, further considerations and research must be made is this area.

Conclusion

Antibiotics are one of the drugs most commonly associated with allergic events, ranging from mild symptoms to severe life-threating reactions. However, this are often mistaken with adverse events associated with the therapeutical use of this drugs. Therefore, a careful clinical history is required to determined true allergic reactions, from adverse reactions, and avoid the over diagnose of antibiotic allergy, associated with increased incidence of antimicrobial resistance and medical costs.

If a high suspicion of hypersensitivity reaction exists, then a full allergic evaluation should be made to confirm diagnosis. The work up follows specific considerations in function of the type of allergic reaction presented. Nevertheless, with the exception of β-lactam antimicrobials, not only immunological mechanisms are not fully understood, but also the sensitivity and specificity of the diagnostic procedures are lower than desirable. Therefore, further investigation in this area is needed.

After confirmation of the diagnosis of allergic reaction, the management of this patients should follow avoidance and application of an alternative tolerated drug. If the drug in question is indispensable for the treatment of the patient, then desensitization can be tried. However, once again, for non-immediate reactions, for non β-lactam antimicrobials, more research is required to further validate this approach.

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