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Anaphylaxis (M Sánchez-Borges, Section Editor)

Penicillin and Cephalosporin-Induced Anaphylaxis: an Update

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Abstract

Purpose of review Beta-lactams (BL) are the most widely used antibiotics and the first-choice drugs for many bacterial infections. Their consumption has increased in the last decades being now three times higher than the second most highly consumed group. However, they have a high potential for inducing allergic reactions, being the compounds most frequently involved in drug reactions induced by specific immunological mechanisms. The purpose of this review is to summarize the sensitization patterns, the methods used for diagnosing, and the management of BL-induced anaphylaxis.
Recent findings BL can cause severe reactions such as anaphylaxis; in fact, they have been estimated to account for 75% of all fatal anaphylactic episodes in the USA. As a result,

physicians often recommend individuals reporting previous reactions to a given BL to avoid all others in the future. However, we consider this practice to be outdated and in need of revision. The decision of what drugs to recommend should be made based on our knowledge of cross-reactivity between BL groups, based on clinical data and chemical structure. A complete and accurate diagnostic workup must be performed to confirm such cross-reactivity or lack thereof. Our improved knowledge regarding cross-reactivity coincides with recent improvements of in vitro tests, which has decreased the need to perform potentially risky procedures such as drug provocation tests in some situations. This will allow physicians to re-evaluate previous cases and lead to an increase in their therapeutic arsenal to fight against infections.

Summary This review summarizes the complex diagnostic approach and management of BL-induced anaphylaxis focusing in recommendation of alternative BL according to the cross-reactivity between BL groups based on clinical data and chemical structure.

Introduction

Anaphylaxis is a potentially life-threatening, systemic hypersensitivity reaction that results from the sudden release of mediators derived from mast cells and basophils via degranulation [1, 2]. Symptoms of anaphylaxis can involve any organ; however, the most commonly affected ones are the cutaneous (affecting around 88% of cases), respiratory (76.1%), cardiovascular (41.9%), and gastrointestinal systems (12.8%) [3].

Drugs are the most common triggers of anaphylaxis triggers in adults [4–6], being beta-lactams (BL) and non-steroidal anti-inflammatory drugs the most common culprits, accounting for up to 28.1% of all cases of anaphylaxis[7–9] and for 42.6% of all cases of severe drug-induced anaphylaxis.[10••] Amoxicillin is the BL that induces anaphylaxis most frequently.[5, 10••] Recently, clavulanic acid, usually prescribed in combination with amoxicillin, has also been implicated.[11•, 12] Cases induced by cephalosporins, carbapenems, and monobactams are rare.[10••, 13, 14]

BL-induced anaphylaxis has been reported to involve IgE-dependent mechanisms.[15–17] IgE can be directed to the central ring and/or to the side chains (R1 and R2) of the BL molecule. Immunological side chain recognition is particularly relevant for amoxicillin and cephalosporin reactions.[18••] Diagnosis is not always straightforward, and regularly requires the use of skin tests (ST) or in vitro tests, which can be performed during the acute phase (assessing tryptase or histamine levels in serum or histamine metabolites in urine) and after the reaction (serum-specific IgE quantification or basophil activation test (BAT), to confirm the culprit agent. Drug provocation testing (DPT) is not recommended for severe anaphylaxis, due to the high risk of inducing another reaction; it is only recommended in some cases to assess tolerance to potentially cross-reactive drugs.[19] Desensitization should be considered if there is an absolute requirement for a specific BL in the presence of positive ST or DPT.[20••]

Epidemiology and sensitization patterns

Changes in BL antibiotic consumption patterns over time have gradually modified the allergic determinants to which patients can be sensitized.[21] In the1950s, it was estimated that 25 anaphylactic episodes occurred for every 100,000 patients treated with benzylpenicillin.[22] Gradually, benzylpenicillin has been replaced by semisynthetic penicillins with differences in chemical structure, such as amoxicillin, resulting in an increase in the appearance of

selective reactions to these drugs.[23] In fact, amoxicillin is now considered the most frequent cause of anaphylaxis to BL.[5, 10••] Since clavulanic acid was introduced in the 1980s, anaphylactic reactions have also been reported to this drug.[11•, 12] In 2007, the rate of anaphylactic reactions to BL was estimated to lie between 0.001 and 0.002% for each treatment course, although these estimates have wide confidence intervals.[24, 25] BL account for up to 20% of all fatal anaphylactic episodes in Europe and up to 75% of all fatal anaphylactic episodes in the USA each year.[9] In the USA, this corresponds to 500–1000 deaths/year.[9] The risk of fatal anaphylaxis with penicillin has been estimated to be between 0.0015 and 0.002% of treated patients.[26] There were no cases of fatal anaphylaxis associated with oral amoxicillin use in a population exposed to 100 million treatment courses over 35-years period.[24]

Concerning cephalosporins, the incidence of anaphylaxis is not well established due to more limited data availability; however, it is generally thought to be lower than for penicillin with an estimated risk range around 0.0001% for each treatment course.[13, 27, 28] However, the incidence of severe anaphylactic reactions to cephalosporins is relatively high.[10••] Nowadays, cephalosporin-induced anaphylaxis is mainly due to the increased use of second-, third-, and fourth-generation cephalosporins,[29] being ceftriaxone, cephalexin, cefuroxime, and cefazolin the most frequent involved.[10••, 13, 28, 30] It is of note that there are more reported cases of anaphylaxis to cephalosporins in patients without known penicillin allergy compared to those with known penicillin allergy.[31, 32]

Penicillins and cephalosporin chemical structures and antigenic determinants

Investigation of allergic reactions requires knowledge of BL structural chemistry.

Chemical structure of penicillin and cephalosporin

Both penicillins and cephalosporins share a common BL ring that is attached to either a 5-membered thiazolidine ring or a 6-membered dihydrothiazine (cephem) ring, respectively. The former has 1 side chain (R1), and the latter has 2 (R1 and R2), with substitution at the R1 and R2 side chains resulting in different chemical structures with a broader spectrum of antibacterial activity and better pharmacokinetic properties.[18••, 33] The earliest generation of cephalosporins focused mainly on the R1 chemical group, whereas the later generations focused on modifications at both the R1 and R2 groups. The homology of aminopenicillin and cephalosporin side chains is shown in Table 1. Additional modifications to the basic core structures of both penicillins and cephalosporins have been made, leading to other types of BL-containing antibiotics such as carbapenems and monobactams.

Antigenic determinants

Penicillin undergoes spontaneous degradation because of a chemically unstable BL ring, forming reactive intermediate products which can bind to lysine residue aminogroups on soluble or cell-bound proteins.[34–36] This results in the

Table 1. Homology of side chains of the chemical structure of aminopenicillins and cephalosporins

Identical R1 side chain (C7 position)	Identical R2 side chain (C3 position)
• Amoxicillin, cefadroxil[1], cefatrizine[1], cefprozil[2]	• Cephalexin[1], cefadroxil[1], cephradine[1]
• Ampicillin, cephalexin[1], cephradine[1], cephaloglycin[1], cefaclor,[2] loracarbef[2]	• Cephapirin[1], cephalothin[1], Cephaloglycin[1], cefotaxime[3]
• Cephalotin[1], cephaloridine[1], cefoxitin[2]	• Cefuroxime[2], cefoxitin[2]
• Cefamandole[2], cefonicid[2]	• Cefotetan[2], cefamandole[2], cefmetazole[2], cefpiramide[3]
• Ceftriaxone[3], cefotaxime[3], cefpodoxime[3], cefditoren[3], ceftizoxime[3], cefmenoxime[3], cefepime[4]	• Cefaclor,[2] loracarbef[2]
	• Ceftibuten,[3] ceftizoxime[3]
Similar R1 side chain (C7 position)	**Similar R2 side chain (C3 position)**
• Cefadroxil[1], cefaclor[2]	• Cefuroxime[2], cefotaxime[3]
• Ceftazidime[3], ceftriaxone[3], cefotaxime[3], cefixime[3], cefpodoxime[3], cefepime[4]	

[1]First-generation cephalosporins
[2]Second-generation cephalosporins
[3]Third-generation cephalosporins
[4]Fourth-generation cephalosporins

formation of benzyl penicilloyl (BPO), known as the major antigenic determinant of penicillin.[35–38] The remaining part of the benzylpenicillin molecule degrades to a range of derivatives which can also act as haptens. These are minor determinants, accounting for allergic reactions in approximately 15–16% of patients.[20••] The minor determinants do not cross-react with each other and are known to provoke severe anaphylactic reactions.[33, 34] In addition to the BL ring, the side chains can also trigger allergic reactions.[35, 36]

The degradation process for cephalosporins leads to fragmentation of the BL ring as well as the thiazinic group, resulting in larger degradation products. This process is more rapid than the fragmentation of penicillin. The exact nature of these intermediate products has not been characterized,[39, 40] but the haptenization mechanism appears slower and possibly more complex than for penicillins.[41]

Because of these differences in degradation processes between penicillins and cephalosporins, the investigation of IgE-mediated reactions to BL must include major and minor penicillin determinants as well as to the whole molecule; conversely, the investigation of IgE-mediated reactions to cephalosporin should only include the native molecule.

Diagnosis

The diagnosis of BL-induced anaphylaxis is based on clinical history, physical examination (if signs or symptoms are present), ST, in vitro tests, and DPT.

Clinical history

Diagnosis of BL-induced anaphylaxis is based on recognition of characteristic signs and symptoms during the reaction (Table 2), which generally start within minutes after administration of the drug.[42] It essentially involves recording clinical history, including a detailed description of the symptoms and their

Table 2. Clinical criteria for the diagnosis of anaphylaxis, taken from Simons FE et al. World Allergy Organ J 2015[42]

Acute onset of an illness with skin-mucosal involvement and at least one of the following	Respiratory compromise Decreased blood pressure, syncope, or collapse
or	
Two or more of the following that occur rapidly after exposure to a likely allergen for that patient	Skin-mucosal involvement Respiratory compromise Decreased blood pressure, syncope, or collapse Gastrointestinal symptoms
or	
Decreased blood pressure after exposure to a known allergen for that patient	

severity.[43] However, the clinical history can be imprecise in many cases as the patient is evaluated a long time after the reaction. After the physician has established the diagnosis of anaphylaxis based on clinical symptoms and has identified the culprit agent, the patient should undergo an allergological study.

Skin test

ST has been shown to be an important method for confirming IgE-mediated allergy to BL.[21, 44] Firstly, the skin-prick test (SPT) technique is usually performed. If this does not cause a reaction, an intradermal test (IDT) can then be carried out. In patients who have previously suffered life-threatening anaphylactic reactions, IDT should start with a dilution of 1/1000 or 1/100 of the therapeutic drug concentration, increasing 10-fold until a non-irritating concentration is achieved (Table 3).[21, 45•] ST should be undertaken by trained personnel as systemic reactions may occur in up to 8% of patients with a previous history of anaphylaxis.[46]

The current benzylpenicillin determinants consist of BPO octa-L-lysine and benzylpenilloic acid in many European countries, and of BPO poly-L-lysine (PPL) in the USA and Canada. A minor determinant mixture (MDM) of the naturally metabolized penicillin G products must also be included for the initial ST.[16, 21, 45•] Currently, changes in patterns of consumption of BL

Table 3. Non-irritating concentrations for ST to BL antibiotics

Reagent	Concentration
BP-OL	0.04 mg/ml
MDM	0.5 mg/ml
Benzylpenicillin	10,000 UI/ml
Amoxicillin	20 mg/ml
Clavulanic acid	5 mg/ml
Cephalosporins	2 mg/ml

has led to a fall in ST positivity rates for major and minor benzylepnicillin determinants[22, 47] and the need for other determinants, such as amoxicillin.[21, 44] In fact, amoxicillin has become the most important determinant of penicillin allergy and its inclusion is essential in the diagnosis of BL anaphylaxis nowadays.[48–51] Indeed, the inclusion of amoxicillin in ST could increase positivity up to 70%.[48] In the case of amoxicillin, the equivalent determinant for benzylpenicilloic acid (amoxicilloic acid) and benzylpenilloic acid (amoxilloic acid) are not of value for ST, and amoxicillin itself with the intact BL ring is the reagent used.[52] There are no clear benefits to adding benzylpenicillin to ST that already include PPL and MDM, in populations where amoxicillin and amoxicillin-clavulanic acid are the main culprit drugs.[53] However, it can be useful if PPL and MDM are not available, as it has been reported that up to 5% of BL allergic patients with negative ST to PPL and MDM gives positive results to benzylpenicillin in ST.[54] In addition, ST should include amoxicillin and clavulanic acid separately if anaphylaxis occurred after administration of amoxicillin-clavulanic acid,[21, 45•] as cases of selective hypersensitivity reactions to clavulanic acid have been reported in recent years.[11•, 12, 55] Including clavulanic acid in ST has been shown to increased sensitivity from 9 to 18.7% in SPT and from 63.6 to 81.2% in IDT.[11•, 12]Concerning cephalosporins, ST are done with the native molecule (intravenous preparations or crushed tablets solubilized in buffer) and can predict hypersensitivity only to the specific cephalosporin ST reagent or cephalosporins with similar side chains.[18••] Moreover, concentrations for ST with native molecule cephalosporins have to be standardized.[56, 57]

In general, the percentage of positive ST in patients with a clinical history of a BL allergic reaction varies between 7 and 76% according to different studies,[51, 58, 59] with the higher results given by patients with suggestive clinical histories of immediate reactions (urticaria and anaphylaxis), as well as when ST are made a short time after the reaction.[21, 59, 60] Prospective studies show that ST reactivity decreases over time in penicillin-allergic patients, with only 30–50% of patients with initial positive ST remaining positive after 5 years[60]; this percentage is even higher in the case of aminopenicillins.[60] Several studies suggest that between 1 and 27.9% of subjects may become positive again after BL administration (resensitization).[51, 58, 61, 62] For this reason, it is necessary to re-evaluate the patient after 1 month if they experienced anaphylaxis to BL but the allergological study gives negative results,[44, 51, 63] particularly if the reaction occurred more than a year ago.

However, despite using a large panel of BL, the sensitivity of ST is not optimal[44] and even in recent years, it has been decreasing, meaning that diagnosis must be achieved through DPT in a significant percentage of patients.[48, 64]

In vitro

These methods can be performed whilst the reaction is still ongoing (acute phase), during which we can analyze the release of different mast cell mediators that occurs after the symptoms onset, in order to confirm the diagnosis of anaphylaxis. In vitro methods can be performed once the reactions is over (diagnostic phase), in order to identify the culprit BL.

Acute phase

Several mediators have been studied as possible biomarkers of an anaphylactic reaction, although the release of tryptase and histamine during the acute phase are the most frequently used in the clinical practice.[65•] Both mediators can be determined in plasma by immunoassay,[66] although histamine can also be determined in urine.[67] These mediators are continuously released by resting mast cells, and therefore mast cell diseases can influence basal levels,[68] thus it is important to compare the values obtained at the time of the event with a recent baseline.[69, 70] The half-life of tryptase in serum is 90–120 min; therefore, the optimal timing for measuring its levels is between 30 and 120 min after the initiation of symptoms. Basal levels must be measured at least 24 h after resolution of the reaction.[19, 71–73] In the case of histamine, due to its short half-life of only 20 min, blood must be collected during the first hour after symptoms onset, which limits its use in clinical practice.[74, 75] Another possibility is the measurement of two histamine metabolites, N-methylhistamine and N-methylimidazoleacetic acid, in urine. Both appear 30–60 min after the onset of a reaction and are detectable for 24 h.[67, 76, 77] There is a lack of studies with a sufficient number of cases to establish the sensitivity and specificity of this technique to diagnose penicillin and cephalosporin-induced anaphylaxis. In studies that also include other drugs, sensitivity of tryptase determination has been estimated to range between 37–94% and specificity between 92–94%,[65•, 78] depending on the cut-off point used.

Diagnostic phase

Immunoassays

Serum-specific IgE quantification can be performed using immunoassays, such as commercial assays or custom-made radioimmunoassays.[70] The sensitivity of these methods in patients with anaphylaxis to benzylpenicillin or amoxicillin is around 55%, with a specificity of 97%.[79]

Basophil activation test

It is a more functional cellular test that mimics the in vivo reaction. The technique is based on the measurement of basophil activation after drug stimulation using flow cytometry.[80] The use of BAT as a part of the allergological workup is increasing; in fact some authors have recommended its inclusion in diagnostic algorithms even before the performance of ST.[3] BAT can be of great value in decreasing the necessity to perform DPT, especially in patients suffering life-threatening reactions such as anaphylaxis.[81, 82] The sensitivity of BAT for penicillins has been estimated to be around 50%, with a specificity of 90%,[80, 83, 84] although when analyzing patients with more severe reactions sensitivity increases to 70%.[81] Interestingly, around 25% of amoxicillin allergic patients with a negative ST show a

positive BAT result.[81, 84] This value is even higher in clavulanic acid allergic patients, for whom nearly 50% of patients with a negative ST showed a positive BAT.[81] When combining the results of BAT and ST together, between 80 and 90% of patients suffering anaphylactic reactions after amoxicillin-clavulanic acid intake could be diagnosed without the need to perform DPT.[81]

Drug provocation test

DPT is considered to be the gold standard to establish or exclude the diagnosis of hypersensitivity to a certain substance.[85•] However, it is not recommended for severe anaphylaxis, due to the high risk of inducing another reaction. It is primarily indicated for patients where the drug being tested is thought unlikely to be the trigger, and for assessing tolerance to potentially cross-reactive drugs.[19] DPT is time and cost-consuming, and given the high possibility of inducing another allergic reaction, patients should undergo a risk–benefit analysis prior to the procedure. It should only be performed by trained personnel in a clinical setting where resuscitation facilities are available.[85•] Ideally, it should be performed 4–6 weeks after the episode due to the high rate of negativization of diagnostic tests over time.[60, 86•, 87] The drug is administered at increasing doses, with a minimum interval of 30 to 60 min between each administration, until the full therapeutic dose is reached.[33] Different protocols for DPT have been published,[21, 30, 55] with that of Messaad et al. being the most frequently used[88] (Table 4).

Management

This includes the treatment of the acute episode of anaphylaxis and its subsequent management, and a diagnostic workup that can include either recommendation of alternative BL or desensitization with the culprit BL.

Anaphylaxis treatment

An anaphylactic reaction is a life-threatening situation that needs urgent medical assessment, even in some cases intensive care.[89•, 90, 91] Immediate treatment is the same, regardless of the trigger (Airway, Breathing, Circulation, Disability, and Exposure approach). Intramuscular adrenaline (1 mg/ml) is recommended as the first-line treatment due to its agonist effects on α-1, β-1, and β-2 receptors.[92] Second-line treatment includes correct patient posture, fluids and oxygen support, and administration of short-acting β-2 agonists if bronchospasm symptoms are present. As a third-line treatment, H1 and H2 antihistamines and glucocorticosteroids should be given. It is important after a BL-induced anaphylactic reaction to provide the patient with oral and written information about BL avoidance in order to prevent another adverse event and to refer the patient for allergological study.

Recommendation of alternative BL: cross-reactivity between BL compounds

All too frequently, patients suffering anaphylaxis to a suspected BL are told to avoid all BL, without taking into account cross-reactivity between

Table 4. Doses recommended for DPT to BL. *CD* cumulative dose

Drug (route)	Messad et al. 2004[88] Doses every 30 min	Blanca et al. 2009[21] Doses every 45–60 min	Blanca-Lopez et al. 2015[55] Doses every 30 min	Romano et al. 2016[30] Doses every 60 min
Benzylpenicillin (intramuscular)		10^3, 10^4, 10^5, 5 × 105 IU/ml (CD 6 × 10^5 IU/ml)		
Penicillin V (oral)		5, 50, 150, 200 (CD 400 mg)		
Amoxicillin (oral)	1, 5, 25, 100, 500, 1000 (CD 1000–2000 mg)	5, 50, 100, 150, 200 (CD 500 mg)	5, 50, 125, 250, 500 (CD 1000 mg)	
Amoxicillin-clavulanic acid (oral)			50/12.5; 125/31.25; 250/62.5; 500/125 (CD 925/231.25 mg)	
Ampicillin (oral)	1, 5, 25, 100, 500, 1000 (CD 1000–2000 mg)			
Cloxacillin (oral)	1, 5, 25, 100, 500, 1000 (CD 2000 mg)			
Cefaclor (oral)				5, 50, 445 (CD 500 mg)
Cefadroxil (oral)	1, 5, 25, 100, 500, 1000 (CD 2000 mg)			
Cefazolin (intravenous/intramuscular)	1, 5, 25, 100, 500, 2000 (CD 1500–3000 mg)			10, 100, 890 (CD 1000 mg)
Cefuroxime (oral)	1, 5, 20, 80, 400 (CD 500 mg)			5, 50, 445 (CD 500 mg)
Ceftazidime (intravenous)	1, 5, 25, 100, 500, 2000 CD 3000 mg)			
Cefixime (oral)	1, 5, 25, 100, 225 (CD 400 mg)			
Ceftriaxone (intravenous/intramuscular)	1, 5, 25, 100, 500, 1000 (CD 1000–2000 mg)			10, 100, 890 (CD 1000 mg)

different BL compounds and the existence of selective responders. Subjects with an IgE response to the BPO structure usually respond to several penicillin derivatives (including aminopenicillins such as amoxicillin) and first-generation cephalosporins.[93] This IgE-response differs in subjects with selective allergy to amoxicillin or cephalosporins; in these cases, the

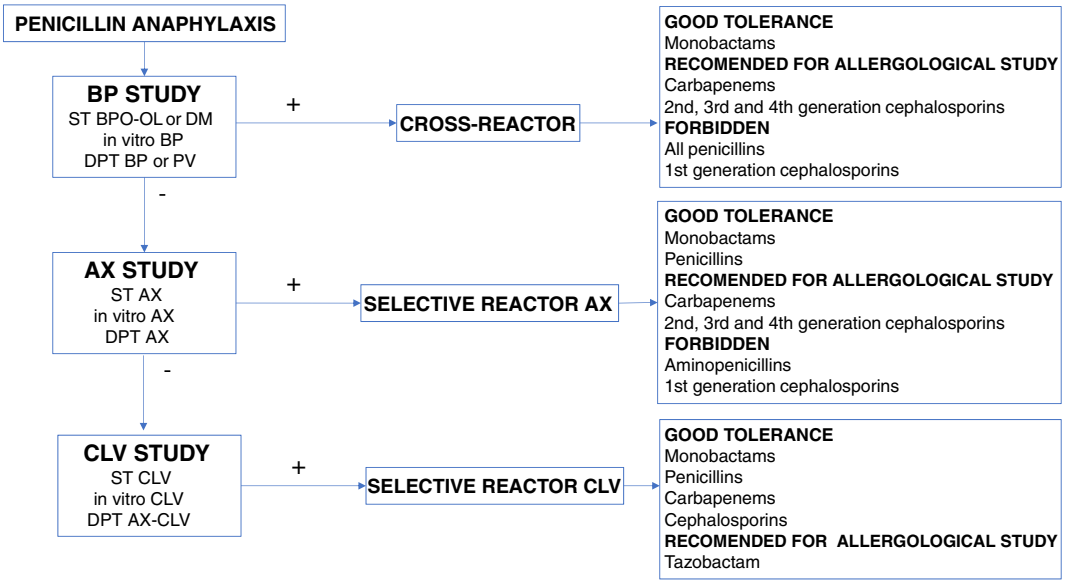

Fig. 1. Algorithm for management of penicillin anaphylaxis.

antigenic determinants are predominantly side chain structures (R1 for the amoxicillin; R1 and R2 for cephalosporins).[33, 94] Furthermore, other parts of the molecule also account for cross-reactivity. Thus, the attributable risk of an allergic cross-reactivity between penicillins and cephalosporins, for all but a few cephalosporins with similar side chain structures to penicillin, is essentially nil.[18••] With these preliminary concepts, the decision algorithm for the allergological workup is described in Figs. 1 and 2.

Desensitization

This procedure is recommended when alternative drugs are not available or not effective and the culprit drug is the only treatment option.[95] Desensitization is defined as the induction of a temporary state of tolerance to a compound that

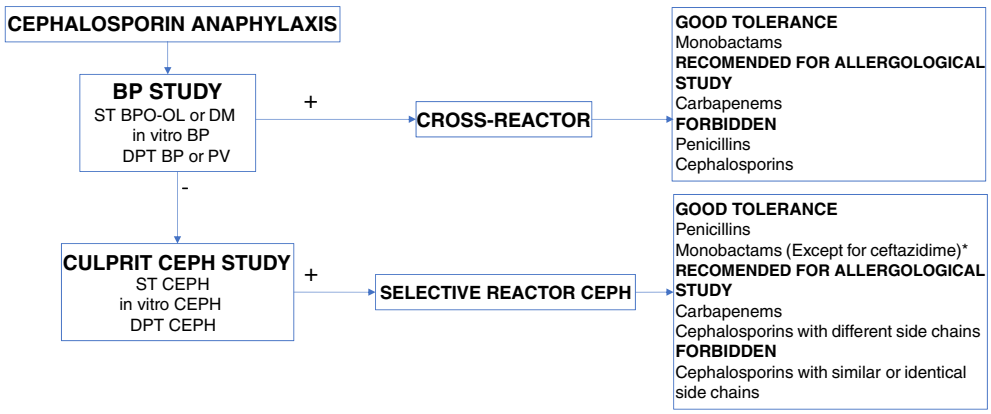

Fig. 2. Algorithm for management of cephalosporin anaphylaxis. *Clinical data support cross-reaction between aztreonam and ceftazidime 96

caused a hypersensitivity reaction previously. This tolerance is achieved after several hours by the administration of increasing doses of the drug involved until the therapeutic dose is reached.[20••, 97] Although desensitization protocols were first described for penicillin,[98, 99] there is a distinct lack of validated BL desensitization protocols in general, and the European Network on Drug Allergy has recommended that effort be put into establishing better protocols for desenzitation by replicating previous studies (consensus statement of the European Academy of Allergy and Clinical Immunology[95]). A good example of how to achieve this aim is provided by researchers at the Brigham and Women's Hospital in Boston.[100–102]

Conclusions

BL continue to be the most highly used antibiotics worldwide. They are also the most frequent triggers of hypersensitivity reactions to drugs. The rise in prescription of amoxicillin, clavulanic acid, and cephalosporins in recent decades means that the details of the original allergological assessments need to be updated. The major and minor determinants of benzylpenicillin are no longer the main allergenic molecules, side chains now play an important role, and the knowledge of cross-reactivity between BL is crucial for recommending alternatives. Additionally, the development of specific in vitro tests, particularly the BAT, is helping us to perform more accurate and safer diagnosis. Despite all these changes, desensitization remains essential in some cases, and more research is needed in this area to establish better procedures. We hope that this review will go some way towards improving BL hypersensitivity management, leading to a decrease in the use of risky procedures and unnecessary avoidance of important antibiotics.

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Compliance with Ethical Standards

Conflict of Interest

I. Doña declares that she has no conflict of interest. G. Bogas declares that he has no conflict of interest. N. Perez-Sanchez declares that she has no conflict of interest. T. D. Fernandez declares that she has no conflict of interest. E. Moreno declares that she has no conflict of interest. M. J. Torres declares that she has no conflict of interest.

Human and Animal Rights and Informed Consent

This article does not contain any studies with human or animal subjects performed by any of the authors.

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• Of importance
•• Of major importance.

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