

Evaluation of desensitization protocols to betalactam antibiotics

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Abstract

What is known and objective

Betalactam antibiotics are the most frequent cause of hypersensitivity reactions. Rapid drug desensitization (RDD) is a technique that induces temporary tolerance to a drug allowing a patient to receive the optimal agent. The increased use of RDD and the lack of standardization among available protocols in terms of formulation, starting dose, number of steps and dosing frequency make it essential to determine the safety and appropriate management of these protocols, especially regarding reconstitution, diluents, stability and drug administration in order to guarantee reproducibility. We reviewed betalactam desensitization protocols in a tertiary hospital, in accordance with currently published practices and evaluated its use on patients over a period of three years.

Methods

(a) We performed a literature search in PubMed, MEDLINE and Google Scholar databases for case reports and/or systematic reviews describing desensitization protocols for

betalactam antibiotics. Pharmacokinetic parameters and physicochemical stability were checked for each antibiotic. (b) We retrospectively reviewed inpatients undergoing our antibiotic desensitization protocols from February 2018 to January 2021. Data and outcomes of desensitization procedures were analysed.

Results

We developed nine RDD protocols: meropenem, ceftriaxone, ceftazidime, ampicillin, ceftolozane/tazobactam, cloxacillin, piperacillin/tazobactam, amoxicillin/clavulanate and penicillin G sodium. Five antibiotics have RDD protocols for two different doses, adjusted to patients with impaired renal function. Detailed data (diluent, total dose, volume, concentrations, duration and stability) of the protocol of each antibiotic used are provided. 28 desensitizations were performed in 17 patients, three of them with confirmed allergies by skin test. 26 out of 28 (92.9%) of them were successfully completed, including those three with positive skin results. The pathogens most frequently involved were *E. faecalis* and *P. aeruginosa*; both frequently associated with bacterial resistance. Meropenem, ceftriaxone and ceftazidime were the antibiotics most desensitized. 25 out of 26 (96.1%) procedures were successful in resolving the infection.

What is new and conclusions

Detailed information about compounding, dilution and stability is crucial to ensure safe and successful desensitization processes, as well as good coordination between the Allergy and Pharmacy departments. The increase in bacterial resistance to many of the commercially available antibiotics limits the therapeutic options for treating multidrug-resistant infections; in those situations, antibiotic desensitization may be a key therapeutic option. Although there is a broad consensus in limiting the use of RDD to patients with confirmed allergy, in usual clinical practice its application in those strongly suspected of having type I hypersensitivity is still observed. Our betalactam desensitization protocols have shown themselves to be safe and effective, as evidenced by data from the 17 patients on whom they have been tested.

1 WHAT IS KNOWN AND OBJECTIVE

Betalactam antibiotics are the most frequent cause of hypersensitivity reactions mediated by specific immunological mechanisms, with there being two main types, IgE reactions and T cell-dependent responses.¹ Type 1 hypersensitivity reactions are characterized by flushing, pruritus, urticaria, shortness of breath, hypotension and life-threatening anaphylaxis.^{1, 2}

In case of suspected allergy to betalactams, second line antibiotics such as vancomycin or fluoroquinolones are usually prescribed. Nevertheless, during the last decade, rising antibiotic resistance along with slow antimicrobial drug development has limited the pharmacotherapy options available for allergic patients.³

Rapid drug desensitization (RDD) is an option for patients with suspected IgE-mediated antibiotic allergies when no other alternative exists. This technique induces temporary tolerance to a drug allowing patients to receive the optimal agent for his or her disease.⁴ Drug desensitization allows safe and progressive administration of the drug, starting at low doses until a full therapeutic dose is clinically tolerated. It produces induction of a temporary clinical unresponsiveness to drug antigens in patients who have previously presented severe hypersensitivity reactions.⁵ There are various hypotheses that may explain how RDD is able to prevent cell activation: (a) depletion of activating signal transduction components such as syk kinase, (b) sub-threshold depletion of mediators and (c) internalization of FcεRI through progressive cross-linking at a low antigen concentration.⁶

The scientific evidence on the safety and efficacy of rapid desensitization to betalactam antibiotics largely consists of case reports and case series, especially in cystic fibrosis patients, a population frequently affected by recurrent infections (particularly by *Pseudomonas aeruginosa*), antibiotic allergies and resistant organisms.⁴ The largest series reported are those of Legere et al. (40 betalactam desensitizations in 12 patients),⁷ Yusin et al. (13 desensitizations in 12 patients)⁸ and Chen et al. (44 betalactam desensitizations in 35 patients),³ all of them with rates of successful complete desensitization above 95%.^{3, 4, 7}

Indication of antibiotic desensitization needs a multidisciplinary approach, including an allergist and an infectious disease physician, to do a good risk-benefit assessment. Besides, the role of pharmacists should be noted. For instance, pharmacokinetic and pharmacodynamic (PK-PD) parameters should be considered in treatment schedules, and therefore, also in desensitization protocols. Betalactamic effect is time-dependent, which means the time that free concentrations are above the minimum inhibitory concentration (MIC) correlates best with bactericidal effect and bacterial eradication. Dosages that do not achieve specific PK/PD targets may increase the likelihood of treatment failure and even the emergence of antibiotic resistance.^{9, 10} With regard to betalactams' PK-PD characteristics, continuous infusion is the best method to maintain optimal concentrations above MIC, as well as to maintain stable plasma concentrations of the allergen in order to ensure successful desensitization. Antibiotic half-life is also important, especially to decide the time schedule between the end of the desensitization protocol and the first therapeutic dose.³

Physicochemical aspects of the formulation are equally important. Most betalactam antibiotics have a short period of stability once they are diluted so the diluent, concentration and storage conditions should be carefully chosen in order to ensure the correct antibiotic concentration throughout the procedure.^{3, 10}

A recent review of published protocols about antimicrobial desensitization highlights the lack of standardization and the differences among available protocols in terms of formulation, starting dose, number of steps and dosing frequency.

The increased use of RDD in our institution encouraged us to review our betalactam

desensitization protocols in accordance with best practices currently published and to evaluate its use on patients admitted to a tertiary hospital (728 beds) over a period of three years. Detailed information about preparation, stability, storage conditions and dose adjustment is provided.

2 METHODS

A literature search in PubMed, MEDLINE and Google Scholar databases was performed, looking for case reports and/or systematic reviews describing desensitization protocols for betalactam antibiotics. Additionally, antibiotic pharmacokinetic parameters and the physicochemical stability in different diluents were reviewed for each antibiotic in the technical information data sheet and specialized websites.^{11, 12} Our current protocols were contrasted with the ones found in the literature research, and the most relevant points were discussed.

At the same time, we retrospectively reviewed the medical records of all patients admitted to our hospital who underwent betalactam antibiotic desensitization from February 2018 to January 2021. The study was approved by the hospital's Research Ethics Committee. From the beginning of the study period, inpatients labelled as allergic to betalactams (confirmed or strongly suspected) and who underwent an RDD process to one or more betalactam antibiotics were analysed and reviewed retrospectively.

Data of the following variables were extracted from the electronic clinical history (SAPMedication®): demographic data, type of infection, causative microorganism, applied desensitization protocol, desensitized antibiotic, reason why the desensitization was indicated, tolerance and results of the procedure. Those processes were successfully completed with no need for interruption due to allergic reactions and that allowed the continued antibiotic treatment at full doses to be considered effective.

3 RESULTS

3.1 Literature review

Cases of penicillin desensitization have been reported since the 1940s, the first reports were very often associated with significant allergic reactions during or soon after the procedure.¹³ In the 1980s, Sullivan et al. established a relatively safer form of penicillin desensitization, based on a 17 step protocol adapted to intravenous and oral administration.^{13, 14} Later, the group of Castells M. extended the use of their 12 step protocol, previously checked in chemotherapy and monoclonal antibodies, to different antibiotics, including betalactams.⁴ More recently, Chen et al. developed a series of specific RDD protocols, taking into account pharmacokinetic considerations such as the antibiotic half-life, and stability issues.³ Some reviews have also been published; all of them agree that no universal antimicrobial desensitization protocols exist but most of them have been successful in allowing patients to receive therapeutic doses of the antimicrobial that previously caused a hypersensitivity

reaction.^{4, 13, 15}

According to the available literature, as well as respecting the indications and contraindications of this procedure, the main key points when designing RDD protocols for betalactam allergy would include starting dose, dosing frequency, number of steps, formulation and the use of premedication.

3.2 Our protocols

We developed RDD protocols for meropenem, ceftriaxone, ceftazidime, ampicillin, ceftolozan/tazobactam, cloxacillin, piperacillin/tazobactam, amoxicillin/clavulanate and penicillin G sodium. Detailed information on the protocols is summarized in Table 1. Five antibiotics have RDD protocols for two different doses, adjusted for patients with impaired renal function.

TABLE 1. Summary of antibiotics used in desensitizations

Antibiotic	Diluent	Total dose	Volume (in each bag)	Concentrations	Duration (hours)	Stability
Meropenem	NS, D5W	1 g	250 ml	0.04 mg/ml	3.75 ^(3, 19)	NS ^(16, 17) : 48 hours at 2–8°C,
		2 g	250 ml	0.4 mg/ml	3.75 ^(3, 7)	24 hours at 22–25°C
				3.97 mg/ml		
				0.08 mg/ml		D5W ^(16, 17) : 18 hours
				0.8 mg/ml		2–8°C,
				7.94 mg/ml		3–4 hours at 25°C
Ceftriaxone	NS, D5W	1 g	100 ml	0.1 mg/ml	3.75 ^(3, 20)	NS and D5W: 10 days at 2–8°C,
		2 g	100 ml	1 mg/ml	3.75 ^(3, 20)	48 hours at 25°C
				9.8 mg/ml		
				0.2 mg/ml		
				2 mg/ml		

Diluent, total dose, volume, and concentrations tested, duration of the procedure and stability of the preparations in different diluents. NS: sodium chloride. D5W: dextrose 5% in water. Duration of desensitization: defined as the total time of desensitization, from the beginning of the first bag administered until the end of the third bag before the start of the therapeutic dose.

We performed 12-step protocols using three solutions at escalating rates: 1/100 (bag 1), 1/10 (bag 2) and 1/1 (bag 3); bags 1 and 2 were not finished, while bag 3 must be finished to reach the total antibiotic dose prescribed. This is based on the proposal of the group of Castells M.^{1, 4, 5} with which we already had previous experience in the desensitization of cytostatics. The starting dose using this strategy is about 10^{-4} the therapeutic dose. The infusion rate was doubled every 15 minutes if no adverse effect was observed so the total length of the procedures was between 3.75 and 5.5 hours. Desensitizations were conducted in a hospital ward or in an intensive care unit (ICU) at our institution under the supervision of an allergist. Methylprednisone 60 mg IV and cetirizine 10 mg PO were used as premedication 30 minutes before starting the procedure.

Antibiotic dilutions were prepared by the pharmacy service in aseptic conditions with multi-step pump equipment purged of medication and protected from light. In accordance with stability information, and seeking to standardize as much as possible, we used normal saline (NS) in all our preparations, even though some of the antibiotics can be also diluted in dextrose 5% in water (D5W). Equally, the volume of dilution was 100 ml for all the antibiotics prescribed, except for meropenem; in this case, a total volume of 250 ml was chosen since it is shown that more dilute concentrations (<10 mg/ml) of this antibiotic are more stable.^{16, 17} The stability of amoxicillin/clavulanate was very short; barely 4 hours at room temperature,¹⁸ for this reason, it was necessary to coordinate the preparation between the pharmacy service and the administration in the ward, to be able to supply bags on time inside the stability range.

3.3 Evaluation of practice

During a three-year period, 128,544 patients were admitted to the hospital, of which 4745 (3.7%) were labelled as allergic to betalactams. Data about the characteristics of patients and the desensitized antibiotics are provided in Tables 2 and 3. Our protocols were evaluated in 17 patients. All patients included had a clinical history consistent with a Type I hypersensitivity reaction (HSR), and three of them also had positive skin tests. All patients gave their prior consent before the procedure. We performed 28 desensitizations in 17 patients, of which 92.9% (26 out of 28) were successfully completed without incident, continuing with the chosen antibiotic. In two patients, the desensitization was not successful. One of the cases (patient 2) had a generalized skin rash during the desensitization to ceftazidime, and the second one (patient 14), after complete desensitization to meropenem, had vesicular lesions with erythema, and flaking on the

arms, chest, back, armpits and thighs. In both cases, these reactions forced us to stop the betalactam antibiotic and look for an alternative.

TABLE 2. Clinical characteristics and results

No of admissions (Feb 2018–Jan 2021)	128,544
No patients labelled as allergic to betalactams	4745 (3.7%)
Desensitizations (Patients)	17
- Mean age (years)	69 (55–70)
- Gender (F/M)	7/10
No. Desensitizations (Procedures)	28
Desensitized Antibiotics	9
•Meropenem	7 (25.0%)
•Ceftriaxone	5 (17.9%)
•Ceftazidime	5 (17.9%)
•Ampicillin	4 (14.3%)
•Ceftolozane/Tazobactam	2 (7.1%)
•Cloxacillin	2 (7.1%)
•Piperacillin/Tazobactam	1 (3.6%)
•Amoxicillin/Clavulanate Acid	1 (3.6%)

Demographic characteristics of the patients (age, gender). Desensitized antibiotics, most common causes of infections and most frequent pathogens. Adverse reactions during infusion and allergological reports. SSTI: Skin and soft-tissue infection.

^a Some infections were ongoing at the same time.

TABLE 3. Patient characteristics and outcomes of desensitization

Patient	Age	Sex	Diagnostic	Causative microorganism	Skin test	Alternative treatment
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Patient	Age	Sex	Diagnostic	Causative microorganism	Skin test	Alternative treatment
1	78	M	Prosthesis infection	<i>S. maltophilia</i>	+	Linezolid + Nebulized colistine + Aztre
			Prosthesis infection	<i>S. maltophilia</i>	+	Linezolid + Nebulized colistine + Mero
2	69	M	Bacteremia	<i>E. faecalis</i>	ND	Imipenem + Daptomycin
			Bacteremia	<i>E. faecalis</i>	ND	Ciprofloxacin + Metronidazol
			Pneumonia	<i>P. aeruginosa</i>	ND	Amikacin
			SSTI	<i>E. faecalis</i>	ND	Levofloxacin + Metronidazole + Linez
			SSTI	<i>P. aeruginosa</i>	ND	Amikacin + Tigecycline + Daptomycin
			SSTI	<i>P. aeruginosa</i>	ND	Amikacin + Tigecycline + Daptomycin

Demographic characteristics of the patients (age, gender), diagnostic, causative microorganism, skin test results before the desensitization procedure, alternative treatment proposed, desensitization antibiotic, stopped or adverse reaction during the desensitization procedure and completed the process without incidents. ND, No data; SSTI, Skin and soft tissue infection.

Meropenem, ceftriaxone and ceftazidime were the antibiotics most desensitized, 25.0% (7 out of 28), 17.9% (5 out of 28) and 17.9% (5 out of 28), respectively. The most common cause of infection affecting desensitized patients was infected skin and soft tissue, present in 11 out of 31 cases. It is worth noting that some patients were suffering from more than one ongoing infection at the same time. Pathogens most frequently related to these infections included *E. faecalis* 25.8% (8 out of 31) followed by *P. aeruginosa* 22.6% (7 out of 31).

Of the 26 procedures completed, 25 (96.1%) were successful in resolving the infection; one of the patients (patient 17) died within a few days due to an external cause, so we were unable to assess the efficacy of the procedure (Table 3).

Antibiotic desensitization was prescribed in accordance with medical criteria from a multidisciplinary perspective, weighing the risk/benefit ratio. In most cases, the chosen antibiotic was considered to be the most suitable among the available alternatives in terms of its spectrum of action and the infection to be treated (Table 3). However, sometimes

there was no alternative treatment; for example, this was the case of a pregnant woman (patient 6) infected by *T.pallidum*. Desensitization to penicillin is recommended for pregnant women with syphilis who are allergic to betalactams. Oral and intravenous desensitization regimens had been studied in this group of patients, with effective results in both administration routes. Our patient was effectively treated with IV penicillin G to cure her infection.^{27, 28}

4 WHAT IS NEW AND CONCLUSIONS

We developed protocols for nine different betalactam antibiotics, including latest generation drugs, such as ceftolozane/tazobactam, a novel fifth-generation cephalosporin/ β -lactamase inhibitor combination, with limited available data regarding desensitization³ and also to amoxicillin/clavulanate, which is mostly absent in available published protocols. Our protocols were critically revised in accordance with the last evidence published in this field. We standardized as much as possible to avoid prescription and/or administration errors, choosing the 12 step strategy (broadly tested by the group of Castells M. et al.), and taking into account pharmaceutical considerations in the formulation to guarantee the safety and efficacy of the procedures.

Once the therapeutic dose is reached, that the drug concentration in plasma is always above the MIC for the pathogen causative of the infection should be cautiously controlled. Unlike Chen et al., who established a specific time to start the therapeutic dose after antibiotic desensitization, the usual practice in our centre is to maintain the therapeutic schedule of the antibiotic, paying special attention to avoid delays in administration. Betalactam antibiotics usually have a short stability period once they are diluted, due to physicochemical reactions such as hydrolysis and oxidation, which are more likely to happen in a solution. The administration of a drug beyond its recommended shelf-life involves a risk of lack of efficacy and/or toxicity that should be avoided. That is especially noticeable with amoxicillin/clavulanate, ampicillin and meropenem, with just a few hours of stability once they are diluted. In those cases, it is mandatory not just to adjust protocol duration to stability data, but also to coordinate the preparation with the pharmacy service to ensure a successful desensitization.

The diluent and concentration of the drug in the solution are other factors affecting stability. In some cases, such as meropenem, the stability is different depending on the solvent and NS is preferred in this case due to longer stability (24 hours in NS vs. 3–4 hours in D5W at 25°C). Other antibiotics, such as ampicillin, amoxicillin/clavulanate and penicillin G sodium, are only stable in NS.^{3, 16, 17}

The use of premedication has been discussed by some authors; for instance, Chen XJC et al. did not administer premedication before RDD, to allow accurate and prompt detection of any early signs of reaction.^{3, 13} Nevertheless, premedication is used in routine desensitization practice in our centre because it has been shown to significantly reduce the

risk of developing acute hypersensitivity reactions during the desensitization process.²⁹

The increasing rate of antimicrobial resistance and the critical need to preserve antimicrobial agents makes desensitization a worthwhile option for consideration in our antimicrobial stewardship toolkit.¹⁵ Drug desensitization is a safe and effective method to keep patients on first-line preferred therapy³⁰; Chastain et al. even raised the future possibility of desensitizing a patient when using a first-line option, including where alternatives exist.¹⁵

In our study, *E. faecalis* and *P. aeruginosa* were the most common pathogens involved in infections, both considered to be multiresistant. In *E. faecalis*, betalactam resistance is due to hyperproduction or alterations in PBP5, while betalactamase production is anecdotal. In Spain, *Enterococcus* resistance to betalactams and high-level resistance to aminoglycosides is common, but *E. faecalis* is almost uniformly sensitive to ampicillin.³¹ Related to *P. aeruginosa*, one of the most common resistance mechanisms is the production of betalactamases; so when other options have failed the use of drugs such as ceftolozane/tazobactam and ceftazidime/avibactam, new generation antibiotics might be a good alternative as they are not affected by the main resistance mechanisms of bacteria thanks to the addition of betalactamase inhibitors with good activity against serine-betalactamases Amp C.³²

RDD protocols are usually very efficient with success rates ranging from 58% to 100%.^{3, 4, 7, 8, 13} The success rate in our series was similar to previous studies; however, we only had skin test confirmation of allergy in three patients; the rest had a clinical history consistent with type I HSR, but not allergological confirmation by the time of desensitization. Unfortunately, this is the real-life practice in those clinical scenarios; although it would be better to perform desensitization only in those patients with a positive skin test, in the series of cases published desensitization in most cases was performed empirically, guided by the patient's clinical history and his/her current infection. Some authors, like Yusin et al. or Legere et al., state that skin testing was not commercially available at the time they performed desensitizations.^{7, 8} In the series of Chen et al., the majority of allergies were self-reported, 'with considerable reactions reported as only rash/pruritus'.³ Moreover, Yusin et al. were concerned because many betalactam antibiotics have metabolites that are major causes of allergic reactions, as is the case of carbapenems. Skin testing without the metabolized component could produce a false negative result.⁸

In our literature review, only Legere et al. detail in their series of cases those patients with a positive skin test (3 of 15); only one of the three had some adverse effects during the procedure, but she was able to finish desensitization successfully.⁷ Similarly in our series patients who developed some reaction during desensitization had a clinical history consistent with type I HSR without skin test confirmation, and the three with skin test results managed to successfully complete the procedure without incident (Table 3).

4.1 Conclusion

- i. Detailed information about compounding, dilution and stability is crucial to ensure safe and successful desensitization processes, as well as good coordination between the Allergy and Pharmacy departments.
- ii. The increase in bacterial resistance to many of the commercially available antibiotics to date limits the therapeutic options for treating multidrug-resistant infections; in those situations, antibiotic desensitization may be a key therapeutic option.
- iii. Although there is a wide consensus in limiting the use of RDD to patients with confirmed allergy, in the usual clinical practice its application in those strongly suspected to have Type I hypersensitivity is still observed.
- iv. Our betalactam desensitization protocols have shown themselves to be safe and effective, as evidenced by data from the 17 patients tested.

CONFLICTS OF INTEREST

The authors declare that they have no conflicts of interests.

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DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available on request from the corresponding author. The data are not publicly available due to privacy and/or ethical restrictions.

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