Antibiotic desensitization as a potential tool in antimicrobial stewardship programs: retrospective data analysis and systematic literature review

Alicia Rodríguez-Alarcón, Jaime Barceló-Vidal, Daniel Echeverría-Esnaïl, Luisa Sorli, Roberto Güerri-Fernández, Sofía Martina Ramis Fernández, Adela Benitez-Cano, Elena Sendra, Inmaculada López Montesinos, Estela Membrilla-Fernández, Olivia Ferrández, Ramón Adalia, Juan Pablo Horcagada, Fernando Escolano, Silvia Gómez-Zorrilla and Santiago Grau, on behalf of PROA-PSMAR group.

4Pharmacy Service, Hospital del Mar, Infectious Pathology and Antimicrobials Research Group (IPAR), Institut Hospital del Mar d’Investigacions Mèdiques (IMIM), Universitat Autònoma de Barcelona (UAB), Universitat Pompeu Fabra (UPF), Barcelona, Spain; 5Infectious Diseases Service, Hospital del Mar, Infectious Pathology and Antimicrobials Research Group (IPAR), Institut Hospital Del Mar d’Investigacions Mèdiques (IMIM), Universitat Autònoma de Barcelona (UAB), Universitat Pompeu Fabra (UPF), Barcelona, Spain; 6Spanish Network for Research in Infectious Diseases (REIP), Centro de Investigacion Biomedica en Red Enfermedades Infecciosas, CIBERINFEC, Instituto de Salud Carlos III, Madrid, Spain; 7Pediatrics Service, Hospital del Mar de Barcelona. Institut Hospital del Mar d’Investigacions Mèdiques (IMIM), Barcelona, Spain; 8Surgery Service, Parc de Salut Mar. Institut Hospital del Mar d’Investigacions Mèdiques (IMIM) Fabra, Barcelona, Spain

ABSTRACT

Objectives: Antibiotic allergy labels (AAL) are related to worse therapeutic results. Strategies to improve the management of these patients, such as the implementation of antibiotic desensitization, are essential for Antimicrobial Stewardship Programs (ASP). The aim of our study is to evaluate the efficacy and safety of antibiotic desensitization procedures for the management of patients with AAL.

Methods: A retrospective study from 2015 to 2022 was performed to describe all antibiotic desensitization conducted in our institution, within the framework of ASP. A systematic literature review using electronic databases, such as PubMed, was also done to identify studies describing antibiotic desensitization between 2000 and 2022.

Results: Sixteen antibiotic desensitization protocols were carried out in our institution. In fourteen cases, the desensitization was successfully completed, and the antibiotic could be used to treat the infection. In the systematic review, twenty-two studies were included, with a total of 202 desensitization episodes. In 97% of them, the desensitization was completed successfully. No desensitization-related mortality was observed neither in our cohort nor in literature review.

Conclusions: Antibiotic desensitization strategies should be considered a safe and effective tool that can be included in ASP for patients with a high risk of or confirmed allergy to penicillin.

1. Introduction

Antibiotics are widely used in the hospital setting, with an estimated 25–40% of admitted patients receiving treatment with these drugs [1,2]. Beta-lactams are considered the first-line treatment choice for most infections, due to their high efficacy and acceptable safety profile [1]. Penicillin allergy is associated with worse clinical outcomes, higher risk of mortality [3] and adverse effects, such as renal insufficiency, Clostridioides difficile infection (37%) and selection of methicillin-resistant Staphylococcus aureus (MRSA) and other microorganisms [4].

A high percentage of the population, around 15–20%, is classified as allergic to penicillin [5,6]. This may lead to the use of alternative options that are less effective and safe, often associated with a broader antibiotic spectrum [1,5,7]. High rates of penicillin-allergy labeling pose a major public health challenge, leading to the use of less effective antibiotic options and overuse of broad-spectrum antibiotics with a consequent increase in antimicrobial resistance and economic burden [8]. While more than 95% of patients labeled penicillin-allergic could probably tolerate another member of the family of penicillins [1,5,6,9], skin testing to confirm the allergy is not usually performed [5,6]. In this scenario, strategies to improve the management of patients with antibiotic allergy labels (AAL) are essential for Antimicrobial Stewardship Programs (ASP). Prior studies have demonstrated the utility of such interventions, mainly by incorporating antibiotic allergy testing into the ASP [10–13]. However, in most hospitals, when patients with AAL require antibiotics during hospitalization, skin testing is not always available. In addition, skin testing and drug provocation tests can carry the potential risk of severe, life threatening reactions in high-risk patients [14].

CONTACT Silvia Gómez-Zorrilla sgomezzorrilla@psmar.cat Infectious Diseases Service, Hospital del Mar (Barcelona, Spain), Passeig Marítim de la Barceloneta, 25-29 08003, Barcelona, Spain
Silvia Gómez-Zorrilla and Santiago Grau are joint senior authors in this work.

Supplemental data for this article can be accessed online at https://doi.org/10.1080/14787210.2022.2122443

© 2022 Informa UK Limited, trading as Taylor & Francis Group
this context, drug desensitization could be another useful tool for ASP, especially in complicated infections such as endocarditis or central nervous system infections where beta-lactams are essential.

Antibiotic desensitization is a method of inducing drug tolerance by administering the diluted compound to the patient in progressively increasing concentrations until the required dose is reached [8]. Desensitization success rates range from 58% to 100%, although with limitations such as lack of precision concerning the reconstitution, storage, stability, and administration of the administered agent in the desensitization process, which may pose significant risks [15]. For this reason, standardized protocols are warranted [16].

Desensitization is mentioned as a valid option for treating allergic patients in the latest Scientific Statement published by the American Health Association (AHA), and most experts consider it a safe practice [17]. However, the implementation of desensitization protocols as part of an ASP is less widespread [18–20]. Since 2015, our institution, with the collaboration of infectious diseases and pharmacy departments, has piloted antibiotic desensitization protocols within the framework of the local ASP (PROA-PSMAR, Programa de Optimización de Antibióticos, Parc de Salut Mar). The aim of this study is to report experience of antibiotic desensitization in our center and to perform a systematic review of the available literature.

2. Materials and methods

2.1. Literature review

A systematic review of the literature published between January 2000 and March 2022 was conducted and reported in accordance with the quality standards described in the PRISMA 2009 checklist [21]. Studies were identified by searching electronic databases (PubMed, Embase, Cochrane Plus Library and Google Scholar) for articles published in English. Using the PICO query tool to identify potentially relevant studies, we looked for AAL patients, antibiotic desensitization interventions and desensitization efficacy and safety as main outcomes. The key words used for this search were ‘desensitization,’ ‘beta-lactams,’ ‘allergy,’ ‘antibiotics,’ ‘penicillin,’ ‘cephalosporin’ and ‘carbapenem.’ All antibiotic agents in each of the above antimicrobial families were also searched individually.

Following deduplication, titles and abstracts were screened independently and blind-reviewed by two authors (A.R. and J.B.). Articles were included according to the criteria set out below. All potentially eligible papers underwent full-text review. Disagreements between reviewers were evaluated by a third reviewer (S.G-Z) and resolved by consensus.

All studies describing antibiotic desensitization were included. Exclusion criteria were publications prior to 2000; no antibiotics or beta-lactams; no description of the patient or desensitization, which means no description of patient’s clinical background and reasons for hospitalization, and no description of desensitization process, including process completion, complications or the need of antihistamine medication; no desensitization protocol included, which means no description of antibiotic diluted bags’ preparation or administration speeds; and no description of outcomes or complications occurred during desensitization, which were the main variables required for our review.

Data were extracted from included studies using Microsoft Excel. Studies were characterized according to year of publication, setting, population, number of patients and desensitization, study design, antibiotic involved, study variables, outcomes, and complications.

2.2. Retrospective study

2.2.1. Study design and participants

A retrospective study was performed at the Hospital del Mar, a tertiary care university hospital in Barcelona (Spain) from 2015 to 2022. All patients over 18 years of age who had undergone antibiotic desensitization were selected from the pharmacy registry and included. Desensitization was indicated by the responsible physician, in accordance with the ASP. This strategy was reserved for patients with a history of severe allergy or doubtful allergy but at high risk of complications if penicillin-related antibiotics were not administered. Accordingly, desensitization was performed in: a) patients with confirmed allergy and the results of previous positive penicillin skin tests, b) patients with a history of immediate hypersensitivity reactions (including anaphylactic reaction), c) patients with a penicillin allergy label in whom hypersensitivity was not confirmed but who were in a compromised clinical situation and required penicillin or a penicillin-related antibiotic [1].

2.2.2. Desensitization protocol

Based on previous studies [8], different dilution bags were prepared in sterile laminar flow cabinets in the pharmacy. We prepared 11–16 bags, starting with the lowest drug concentration (1/10,000 of the usual dose) and increasing these progressively until the regular dose was reached. The protocols for each antibiotic are detailed in the supplementary material. Administration of these preparations began between 30 and 60 minutes after preparation. In all cases, the last antibiotic solution for desensitization was administered no later than 6 h after preparation.

Since desensitization strategies carry the risk of complications, all patients were transferred to an intensive care unit (ICU) and were strictly monitored and followed during desensitization. The physicians who supervised the desensitization were properly trained for the procedure and the nursing team followed a checklist provided by Pharmacy department.

2.2.3. Data collection and definitions

Demographic, clinical and epidemiological data were collected from hospital medical and nursing records and included the following: age and sex; comorbidities and severity of underlying diseases as assessed by the age-adjusted Charlson comorbidity index [22,23]. Severity of illness was calculated by Quick SOFA (Sepsis related Organ Failure Assessment) [24] on the day of the desensitization procedure. Definition of infection was based on Centers for Disease Control and Prevention criteria [25]. Prior antibiotic exposure was defined.
as administration of antibiotics for more than 48 h during hospital admission before desensitization.

Microbiological data: bacterial identification was confirmed by MALDI-TOF MS (Bruker Daltonics, Bremen, Germany). Antimicrobial susceptibility was interpreted following European Committee for Antimicrobial Susceptibility Testing (EUCAST) guidelines [26]. The multidrug-resistant (MDR) profile was defined according to current international standard definitions: Isolates were defined as MDR when they showed non-susceptibility to ≥1 agent in ≥3 antibiotic classes and as extensively drug-resistant (XDR) when they showed non-susceptibility to ≥1 agent in all but ≤2 antibiotic classes [27].

Allergy history data collected included family allergy, the antibiotic involved, confirmation of allergy by skin prick test and/or intradermal skin test, date of allergy diagnosis, allergy symptoms at the time of the reaction and time elapsed since the last reaction (unknown, less than 1 year, 1 to 5 years, more than 10 years, childhood).

With respect to the desensitization procedure, the following data were collected: indication (therapeutic failure, absence of alternative treatments, severity, other), the antibiotic involved, duration of treatment after desensitization, completion of desensitization, reactions during and after desensitization, need for antihistamines.

2.2.4. Outcomes and Follow-up
The primary outcome was to evaluate the efficacy and safety of antibiotic desensitization strategies for the management of patients with AAL. Efficacy was defined as the ability to complete desensitized antibiotic for the treatment of the infection episode. Safety was defined as the absence of adverse events during and after the desensitization. Secondary outcomes were clinical cure at the end of antibiotic treatment, in-hospital mortality, 30-days mortality and the need for rescue treatment with another antibiotic. Patients were followed up to 30 days from the date of beta-lactam desensitization.

2.3. Ethical approval
The study design was revised and approved by the Clinical Research Ethical Committee of Parc de Salut Mar (CEIC Parc de Salut Mar, registration no. 2021/9829/I). Patients gave informed consent prior to the desensitization procedure.

3. Results
3.1. Literature review
A total of 157 studies were found through the database search: 22 were included for analysis and 135 excluded (Figure 1). Thirty-seven studies were excluded because they were published before 2000, 22 did not describe a desensitization protocol or case reports, 21 did not describe any case report, two did not include the desensitization protocol, one did not describe desensitization outcomes, one desensitization was not a beta-lactam and one was not an antibiotic.

The included studies are reviewed in Table 1. Two hundred and two cases of desensitization of 54 beta-lactams: 23 (42.6%) cephalosporin, 18 (33.3%) penicillin, 10 (18.5%) carbenpenem and three (5.6%) monobactam.

All studies were retrospective descriptive studies. A total of 197 (97.5%) desensitizations were successfully completed and generally well tolerated. The most common adverse event during desensitization was rash and urticarial reaction, generally mild in severity. Five patients did not complete desensitization; three patients suffered anaphylaxis, one had a generalized skin rash, and one was a pregnant patient who

Figure 1. Flow diagram of search and study selection process.
Table 1. Literature review on beta-lactam desensitization.

| Source (country) | Population | N° patients/ desensitizations | Study design          | Antibiotics            | Variables       | Outcome                  | Complications |
|------------------|------------|-------------------------------|-----------------------|------------------------|----------------|--------------------------|---------------|
| Yusin et al., 2013 (USA) [28] | Allergy background and serious infection requiring beta-lactam as their only option | 12/13 | Retrospective chart review | Imipenem, Penicillin G, Ceftazidime, Cefepime, Meropenem, Amoxicillin, Piperacillin/Tazobactam, Penicillin | Outcome | Complications | Successful | None |
| Chen et al., 2019 (USA) [15] | Hypersensitivity reactions during or after antibiotic administration | 36/61 | Retrospective study | Ceftazidime/Ambicil, Meropenem, Cefepime, Ceftriaxone, Cefazolin | Outcome | Complications | 59 (97%) desensitizations were successfully completed | 6 rash, urticaria, 2 cases of anaphylaxis |
| Foer et al., 2019 (USA) [29] | Anaphylaxis experience and ECMO | 3/3 | Case reports | None | Outcome | Complications | Successful | None |
| Win et al., 2005 (USA) [30] | Positive skin test results to cephalosporins | 8/8 | Retrospective chart review | Ceftriaxone, Cefazolin, Meropenem, Aztreonam, Piperacillin/Tazobactam, Cefepime | Time of desensitization protocol | Successful | 2: 7–8 h, 6: 2 h | None |
| Breuer et al., 2014 (ISRAEL) [31] | Allergy background | 8/8 | Retrospective review | Ceftrazidime, Meropenem, Aztreonam, Piperacillin/Tazobactam, Cefepime | Outcome | Complications | 7 successful, 1 complication | 1 case of anaphylaxis on day 2 after desensitization |
| Gorman et al., 2003 (CANADA) [32] | 40-year-old, benzylpenicillin allergy background (erythema) | 1/1 | Case report | Imipenem | Outcome | Complications | Successful | None |
| Pham et al., 2017 (USA) [33] | Positive prick test and intradermal skin test | 1/1 | Case report | Penicillin | Toleration of desensitization protocol | Successful | None |
| Dalle et al., 2018 (BRAZIL) [34] | Pregnant women with syphilis and a diagnosis of allergy | 10/10 | Descriptive study | Penicillin V, Benzathine penicillin | Outcome | Complications | 9 completed treatment | 1 had urticarial reaction |
| Jones et al., 2015 (USA) [35] | 32-year-old woman with multidrug allergy | 1/1 | Case report | Ceftrazidime, Cefazolin | Outcome | Complications | Successful | None |
| Kuhlen et al., 2015 (USA) [36] | 29-year-old pregnant woman with multiple beta-lactam allergy | 1/1 | Case report | Ceftrazidime | Outcome | Complications | Successful | None |
| Gupta et al., 2016 (USA) [16] | History of allergy | 5/5 | Retrospective study | Ertapenem, Ceftriaxone, Cefazidime, Meropenem, Aztreonam, Cefazidime, Cefepine | Outcome | Complications | Successful | Not described |
| De Maria et al., 2002 (USA) [37] | Pediatric patients with positive skin test for antimicrobial allergy | 2/3 | Case report | Ertapenem, Ceftrazidime, Cefazidime, Meropenem, Aztreonam, Cefazidime, Cefepine, Ertapenem, Ceftrazidime, Cefepine | Outcome | Complications | Successful | Not described |
| Kwong et al., 2018 (AUSTRALIA) [38] | 60-year-old man with confirmed immediate hypersensitivity limited to flucloxacillin | 1/1 | Case report | Flucloxacillin | Outcome | Complications | Successful | Not described |
| Guglielmi et al., 2012 (USA) [39] | Cystic fibrosis patient highly allergic to aztreonam | 1/1 | Case report | Aztreonam | Outcome | Complications | Successful | None |
| Marin et al., 2018 (SPAIN) [40] | 79-year-old woman with clinical suspicion of allergy to beta-lactams | 1/1 | Case report | Cloxacinil | Outcome | Complications | Successful | None |
| Wilson et al., 2003 (USA) [41] | 20-year-old man with cystic fibrosis and positive intradermal test to imipenem | 1/1 | Case report | Meropenem | Outcome | Complications | Successful | None |
| Source (country) | Population | N° patients/ desensitizations | Study design | Antibiotics | Variables | Outcome | Complications |
|-----------------|------------|-------------------------------|-------------|-------------|-----------|---------|---------------|
| Cernadas et al., 2012 (PORTUGAL) | 12-year-old boy with cystic fibrosis and Pseudomonas aeruginosa in sputum | 1/1 | Case report | Ceftazidime | Toleration of desensitization | Successful | None |
| Kumar et al., 2021 (AUSTRALIA) | 60-year-old man with penicillin anaphylaxis history and endocarditis due to Abiotrophia defectiva | 1/1 | Case report | Penicillin | Treatment completion | Successful | Not described |
| Staso et al., 2017 (USA) | 17-year-old male with mast cell activation syndrome with a history of antibiotic hypersensitivities presented with pneumonia | 1/1 | Case report | Ceftriaxone | Outcome Complications | Successful | None |
| Shah et al., 2019 (USA) | 30-year-old female with past medical history of mast cell activation syndrome presented with MSSA bacteremia | 1/1 | Case report | Cefazolin | Treatment tolerance Complications | Successful | None |
| Legere et al., 2009 (USA) | Cystic fibrosis patients who underwent antibiotic desensitization between 1998 and 2009 | 15/52 | Retrospective study | Meropenem Piperacillin/ tazobactam Ceftazidime Cefepime Cefoxitin | Outcome Complications | Successful (100% completed desensitization) | None |
| González-García et al., 2021 (Spain) | Patients admitted to their hospital who underwent beta-lactam antibiotic desensitization between 2018 and 2021 | 17/28 | Retrospective study and literature review | Meropenem Ceftazidime Amoxicillin Amoxicillin/ Clavulanate Ceftolozane/ Tazobactam Ceftriaxone Penicillin G Piperacillin/ Tazobactam Cloxacillin | Outcome Complications | 27 successful 1 did not complete | 1 skin rash 1 vesicular lesions with erythema |

aSix cases of rash or urticarial reaction were mild in severity and completed desensitization. Two cases that were categorized as anaphylaxis manifested urticaria, angioedema, oxygen desaturation, bronchospasm and/or hypotension and were treated with diphenhydramine, methylprednisolone and/or epinephrine. The desensitization process was prematurely aborted with resolution of symptoms in both patients. The antibiotics involved were ceftriaxone and amikacin. 

bThe antibiotic involved was ceftazidime and the patient required hospitalization in the intensive care unit.

Pregnant patient did not complete desensitization because of a mild urticarial reaction. However, the reaction was not severe and a second penicillin desensitization was conducted and completed without complications after the second dose of penicillin.

Four patients had non-severe reactions, such as urticaria, erythema, nausea, and diarrhea, which resolved with diphenhydramine. One patient had acute respiratory failure and required intubation, although desensitization was not stopped and he completed the treatment.

One patient had a generalized skin rash during ceftazidime desensitization and was forced to discontinue desensitization. Another patient had vesicular lesions with erythema and flaking on the arms, chest, back, armpits and thighs after completion of meropenem desensitization and did not complete antibiotic treatment.
suffered a non-severe urticarial reaction and desensitization was discontinued as a precaution due to pregnancy. However, the same patient underwent a second penicillin desensitization due to a syphilis infection without complications.

3.2. Retrospective study

A total of 16 desensitizations in 14 patients were performed at our center. The data corresponding to these patients are shown in Table 2. Ten (62.5%) women were included, median age was 74 (58–84) years with a median age-adjusted Charlson comorbidity index of 6 (2–12). The most common comorbidities were respiratory disease eight (50%) episodes, followed by cardiovascular six (37.5%) and neurologic diseases five (31.3%), diabetes mellitus five (31.3%), chronic kidney disease five (31.3%) and solid neoplasm, five (31.3%). Sources of infection are recorded in Table 2. Ten out of 16 episodes (62.5%) were bloodstream infections. In terms of site of acquisition, six out of 16 (37.5%) were hospital-acquired infections and six out of 16 (37.5%) were postoperative infections (two intrahospital pneumonia, two intraabdominal infections, one skin/soft tissue and one community-acquired osteoarticular infection).

The microbiological data are shown in Table 3. Regarding Enterobacterales, five out of nine (55.6%) were extended-spectrum beta-lactamase-producing (ESBL) strains. MDR Pseudomonas aeruginosa was present in one patient, and two patients had an XDR profile. Methicillin-resistant S. aureus was found in four patients. All Enterococcus isolates were E. faecalis.

When we analyzed previous antibiotics prescribed before desensitization, we observed that six (37.5%) cases had previously been exposed to molecules similar to those used in desensitization. The potentially allergy-triggering molecules previously used were imipenem, meropenem, ceftazidime, cefotaxime, and penicillin G.

Regarding allergy history, AAL was previously confirmed in only four (25%) cases by ID physician but not with specific allergy tests. In 10 (62.5%) cases, the patient did not know when the last allergic reaction occurred, three (18.8%) reactions occurred more than 10 years previously, two (12.5%) less than a year and one (6.5%) between one and five years previously. The clinical manifestations of allergy were six (37.5%) unknown, five (31.3%) rash, two (12.5%) anaphylaxis, one (6.3%) uvular edema, one (6.3%) fever, one (6.3%) pruritus.

The indications for desensitization were: five (31.3%) indications were due to absence of therapeutic alternative options, five (31.3%) to therapeutic failure, four (25%) to treatment optimization and two (12.5%) to severity.

With respect to tolerability, 11 (68.7%) cases showed no adverse reactions during the desensitization procedure. Three subjects (18.8%) showed some reaction: one patient suffered a mild cutaneous reaction, but desensitization was completed without problems and in the remaining two, desensitization was stopped due to anaphylactic shock in one patient, and the presence of dyspnea, rash and pruritus in the other.

Seven (43.7%) cases needed antibiotic rescue: four episodes of XDR Pseudomonas aeruginosa infection (carbapenem-resistant) required ceftolozane/tazobactam, one episode due to toxicity required dalbavancin, and the two patients who did not complete desensitization required amikacin and ceftazidime/avibactam.

There were no occurrences of desensitization-related mortality in our cohort. Overall, mortality during hospitalization occurred in two (12.5%) patients and both were infection-related.

4. Discussion

Desensitization can be a useful tool in the ASP setting. Overall, of the 202 episodes reviewed in the literature, a high percentage showed desensitization without complications and only five patients did not complete the whole procedure. In our series of 16 episodes, three had mild symptoms such as rash or pruritus and only two did not complete desensitization due to dyspnea and anaphylactic shock. This shows that antibiotic desensitization is well tolerated and safe. In our cohort, patients had a high age-adjusted Charlson comorbidity index (median 6), suggesting that the strategy is safe, even for complex patients with high comorbidity scores.

Drug hypersensitivity is an immunologic response to medication, classified by pathogenesis and time relative to antigen exposure. Type 1 or IgE-mediated hypersensitivity reactions are of greatest clinical concern because they occur immediately and can be severe and life-threatening [15,28]. The drug antigen interacts with IgE bound to receptors on mast cells, triggering degranulation and the release of inflammatory mediators and cytokines [15,29]. Antibodies against penicillin target the beta-lactam ring, a chemical structure common in agents belonging to the penicillin drug class [30]. Although IgE-mediated hypersensitivity reactions can be life-threatening, previous literature has demonstrated that most patients labeled as allergic to penicillin are not truly allergic [1,5,6,9]. Consistent with these studies, only 25% of patients in our cohort were based on a clinical history of high-risk allergy, although none had undergone skin testing to confirm allergy. In 37% of patients, the clinical manifestations of allergy were unknown, 62% did not know when the last allergic reaction occurred and 18% of reactions had occurred more than 10 years previously. AAL is associated with receiving suboptimal treatment using drugs that are less effective and safe [3,4] and every effort should be made to de-label AAL in clinical practice.

The aim of desensitization is to induce tolerance to a drug and prevent anaphylaxis [8]. Suboptimal doses of antigen, as low as 1/10 the optimal dose administered before an optimal dose, render mast cells and basophils unresponsive to antigens but not to other activating stimuli [29]. It is considered a valid option in patients with allergies confirmed by skin test or oral challenge and in those with a history of high-risk allergy (including previous anaphylactic reactions, previous recurrent allergic reactions or reactions to multiple beta-lactam antibiotics) [31] for whom the antibiotic to which they are allergic is the first therapeutic choice [8]. It is also indicated in patients without a confirmed allergy or history of high-risk allergy but who are in a compromised or unstable clinical situation, and in patients with severe infection where the first antibiotic option is the agent for desensitization [1].
Table 2. Case reports of desensitization performed at our hospital.

| Case (Year) | Patient age/Sex | Main comorbidity | Infection: clinical presentation | Antibiotics used prior to desensitization | Desensitized Antibiotic | Duration of procedure | Desensitization Outcome | Desensitization Complications | Antihistamines | Antibiotic duration (days) | Infection outcome |
|-------------|-----------------|-------------------|----------------------------------|-------------------------------------------|--------------------------|----------------------|------------------------|-----------------------------|----------------|--------------------------|------------------|
| 1 (2018)    | 65/F            | Pancreatic cancer | Pneumonia                        | Aztreonam                                 | Meropenem                | 3 h 45 min           | Completed             | Rash                        | Yes            | 10                       | Rescue therapy |
| 2 (2015)    | 76/F            | Colorectal cancer | Intraabdominal                   | Tigecycline, Imipenem                     | Cefotolozane/Tazobactam  | 3 h 30 min           | Completed             | None                         | No             | 10                       | Rescue therapy |
| 3 (2015)    | 76/F            | Colorectal cancer | Skin and soft tissue             | None                                      | Meropenem                | 3 h                  | Completed             | None                         | Yes            | 11                       | Rescue therapy |
| 4 (2018)    | 84/M            | Chronic kidney disease | Endovascular                 | Vancomycin                                 | Cefaroline               | 3 h 45 min           | Completed             | None                         | No             | 25                       | Curation         |
| 5 (2019)    | 74/F            | Ovarian cancer    | Intraabdominal                   | Tigecycline, Amikacin, Tigecycline         | Meropenem                | 3 h 45 min           | Completed             | None                         | No             | 7                        | Rescue therapy |
| 6 (2018)    | 65/M            | Hemorrhagic ictus | Pneumonia                        | Tigecycline, Ciprofloxacin, Tigecycline    | Meropenem                | 3 h 45 min           | Completed             | None                         | No             | 7                        | Curation         |
| 7 (2019)    | 75/F            | Chronic kidney disease | Endovascular                 | Vancomycin                                 | Cloxacillin              | 3 h 30 min           | Completed             | None                         | No             | 15                       | Curation         |
| 8 (2019)    | 82/F            | Cholangiocarcinoma | Pancreatobiliary                 | Tigecycline, Aztreonam                    | Cefotaxime               | 4 h                  | Completed             | None                         | No             | 14                       | Curation         |
| 9 (2019)    | 70/F            | Parkinson disease | Skin and soft tissue             | Tigecycline, Aztreonam                    | Meropenem                | 3 h 45 min           | Completed             | None                         | No             | 6                        | Lost to follow-up |
| 10 (2017)   | 80/M            | Diabetes mellitus | Endovascular                     | Daptomycin                                 | Penicillin G             | 4 h                  | Completed             | None                         | No             | 13                       | Curation         |
| 11 (2017)   | 80/M            | Diabetes mellitus | Endovascular                     | Daptomycin                                 | Ceftriaxone              | 4 h                  | Completed             | None                         | No             | 50                       | Curation         |
| 12 (2020)   | 70/F            | Congestive heart failure | Endocarditis                  | Daptomycin                                 | Cefaroline               | 3 h 45 min           | Completed             | Rash                         | Yes            | 7                        | Rescue therapy |
| 13 (2020)   | 65/F            | None               | Meningoencephalitis              | Cotrimoxazole, Aztreonam                   | Ampicillin               | 4 h                  | Completed             | None                         | No             | 8                        | Exitus          |
| 14 (2016)   | 74/F            | None               | Osteoarticular                   | Cotrimoxazole, Amikacin                    | Ceftriaxime              | 2 h 40 min           | Not completed         | None                         | No             | 0                        | Rescue therapy |
| 15 (2021)   | 58/M            | Cirrhosis          | Pneumonia                        | Levofoxacin, Cefazidime/Avibactam, Colistin | Meropenem                | 3 h 45 min           | Completed             | None                         | No             | 6                        | Curation         |
| 16 (2021)   | 71/M            | Chronic bronchitis | Pneumonia                        | Cefazidime/Avibactam, Colistin             | Cotrimoxazole            | 3 h 25 min           | Not completed         | None                         | Yes            | 0                        | Rescue therapy |
Although desensitization is considered a safe practice [17], implementation of desensitization protocols as part of an ASP is less widespread [18–20] and the published literature on desensitization is scarce.

The advantages of desensitization are the possibility of using first-line antibiotics with fewer adverse effects and a reduction in costs. The disadvantages are the need to perform it in a strictly monitored area such as an ICU, the requirement to desensitize again if drug exposure is interrupted, and the need to desensitize for each specific agent regardless of molecular family.

The most common indications for desensitization in our hospital’s experience were the absence of alternative therapeutic options and therapeutic failure. In fact, the strategy of desensitization allowed us to use first-line antibiotics and new beta-lactams in combination when there were no other options. In our cohort, desensitization also proved to be an effective strategy, even though new molecules such as ceftolozane/tazobactam or ceftaroline were being used.

The carbapenem family was the one most desensitized in our hospital (37.5%), followed by cephalosporins (31.2%). However, cross-reactivity between penicillin and cephalosporins is around 2% [1], and between 0.8 and 1% for carbapenems [32], which is attributed to the different R1 chains in their molecular structures [7,32]. This was a retrospective study and skin tests were not performed to confirm allergy, so that desensitization of patients who were not really allergic cannot be ruled out. Six patients in fact received a molecule from the same family as the desensitized agent. These molecules had a low percentage of cross-reactivity (3 carbapenem and 2 cephalosporins), so that the fact of receiving them does not rule out allergy. However, one of the previously received antibiotics was penicillin G, so that de-labeling was probably possible in this patient. Even so, skin allergy tests are not available at the time of acute infection in routine clinical practice and consequently patients with questionable allergies would benefit from desensitization.

Desensitization protocols should be included as part of an ASP [15,16,19,20]. However, as noted in this study and in the literature, the rates of confirmed allergy are low [5,6] and the addition of allergy skin testing and other delabeling procedures to ASPs would also be warranted [11–13].

Our study has certain limitations arising from the fact that the results of the review come from retrospective case series or case reports. Another limitation is that allergy was not confirmed by allergy testing in any case report or in our series. Also, most of the desensitized antibiotics were carbapenems or cephalosporins with low risk of cross-reactivity. Moreover, reviewed studies were mainly from North America and Europe, which cannot be representative for the whole global population. Nevertheless, several strengths of this study can be highlighted. First, all information was reviewed by trained investigators. Second, this study is useful since it summarizes the published literature, as well as our hospital’s experience of desensitization, and the protocols included in the supplementary material can be used in routine clinical practice. Unlike one recently published study [33], in our experience, the stability of the prepared solutions was not tested, since this information was obtained from the published literature [34]. Finally, one important strength is the inclusion of patients with high comorbidity scores, some of whom were affected by life-threatening infections.

This paper explored the safety and feasibility of antibiotic desensitization through clinical practice and literature review. The incidence of complications resulting from desensitization treatment was low, and no deaths were observed. This study can provide valuable reference for the safe and rational use of antibiotic desensitization in clinical practice. Antibiotic desensitization strategies, using standardized protocols and conducted in strictly monitored conditions, should be considered a safe procedure. The high effectiveness rates and few adverse events found in literature and our clinical practice place desensitization as a tool that need to be implemented more often in ASP to improve the management of patients labeled penicillin-allergic.

5. Conclusion

Desensitization should be considered a safe and effective strategy that can be included in ASP for patients with a high risk of or confirmed allergy to penicillin. Other strategies for confirmation of allergy or de-labeling, such as directed anamnesis and bedside skin testing, should also be included in an ASP to compensate for the lack of population screening.

Acknowledgments

We would like to thank Janet Dawson for English editing. This study is part of a PhD program in Medicine of the Universitat Autònoma de Barcelona (Spain). Silvia Gómez-Zorrilla has received a research grant from the Spanish Society of Infectious Diseases and Clinical Microbiology (SEIMC) to support her research and the project "P21/00509 "funded by Instituto de Salud Carlos III (ISCIII) and co-funded by the European Union. These data were previously presented, in part, in the 32nd European Congress of Clinical Microbiology and Infectious Diseases (2022), number 1673.

Funding

This paper was not funded.

Declaration of interest

The authors have no relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript. This includes employment, consultancies, honoraria, stock ownership or options, expert testimony, grants or patents received or pending, or royalties.
Reviewer disclosures
Peer reviewers on this manuscript have no relevant financial or other relationships to disclose.

Author contributions
A Rodríguez-Alarcón has substantially contributed to the conception and design of the review article and interpreting the relevant literature (1). J Barceló-Vidal has substantially contributed to the conception and design of the review article and interpreting the relevant literature (1). D Echeverría-Ensain has substantially contributed to the conception and design of the review article and interpreting the relevant literature (1). L Sorli has been involved in writing the review article or revised it for intellectual content (2). R Güeri-Fernández has been involved in writing the review article or revised it for intellectual content (2). S Martina Ramis Fernández has been involved in writing the review article or revised it for intellectual content (2). A Benítez-Cano has been involved in writing the review article or revised it for intellectual content (2). E Sendra has been involved in writing the review article or revised it for intellectual content (2). I López Montesinos has been involved in writing the review article or revised it for intellectual content (2). E Membriña-Fernández has been involved in writing the review article or revised it for intellectual content (2). O Fernández has been involved in writing the review article or revised it for intellectual content (2). R Adalia has been involved in writing the review article or revised it for intellectual content (2). J Pablo Horcajada has been involved in writing the review article or revised it for intellectual content (2). F Escolano has been involved in writing the review article or revised it for intellectual content (2). S Gómez-Zorrilla has substantially contributed to the conception and design of the review article and interpreting the relevant literature (1). S Grau has substantially contributed to the conception and design of the review article and interpreting the relevant literature (1).

ORCID
Alicia Rodríguez-Alarcón http://orcid.org/0000-0002-3697-2552
Elena Sendra http://orcid.org/0000-0002-4374-2173
Juan Pablo Horcajada http://orcid.org/0000-0001-9873-5459
Silvia Gómez-Zorrilla http://orcid.org/0000-0002-5987-068X

References
Papers of special note have been highlighted as either of interest (•) or of considerable interest (••) to readers.

1. Shenoy ES, Macy E, Rowe T, et al. Evaluation and management of penicillin allergy: a review. J Am Med Assoc. 2019;321(2):188–199.
2. of considerable interest. Review of evaluation and management of penicillin allergy and the importance in antimicrobial stewardship.
3. Rodríguez-Baño J, Paño-Pardo JR, Alvarez-Rocha L, et al. Programas de optimización de uso de antimicrobianos (PROA) en hospitales españoles: documento de consenso GEIH-SEIMC, SEFH y SEMPSPH. Farm Hosp. 2012;36(1):33.e1–33.e30.
4. Blumenthal KG, Lu N, Zhang Y, et al. Recorded penicillin allergy and risk of mortality: a population-based matched cohort study. J Gen Intern Med. 2019;34(9):1685–1687.
5. Blumenthal KG, Lu N, Zhang Y, et al. Risk of meticillin resistant Staphylococcus aureus and Clostridium difficile in patients with a documented penicillin allergy: population based matched cohort study. Bmj. 2018;361:k2400.
6. Blumenthal KG, Wickner PG, Hurwitz S, et al. Tackling inpatient penicillin allergies: assessing tools for antimicrobial stewardship. J Allergy Clin Immunol. 2017;140(1):154–161.e6.
7. Blumenthal KG, Peter JG, Trubiano JA, et al. Antibiotic allergy. Lancet. 2019;393(10167):183–198.
8. Castells M, Khan DA, Phillips E. Penicillin Allergy. N Engl J Med. 2019;381(24):2338–2351.
9. •• of considerable interest. Review of management of patients with penicillin allergy label.
10. Trubiano JA, Franklin Adkinson N, Phillips EJ. Penicillin allergy is not necessarily forever. J Am Med Assoc. 2017;318(1):82–83.
11. Estep PM, Ferreira JA, Dupree LH, et al. Impact of an antimicrobial stewardship initiative to evaluate β-lactam allergy in patients ordered aztreonam. Am J Heal Pharm. 2016;73(S_Supplement_1):S8–S13.
12. Trubiano JA, Beekmann SE, Worth LJ, et al. Improving antimicrobial stewardship by antibiotic allergy delabeling: evaluation of knowledge, attitude, and practices throughout the emerging infections network. Open Forum Infect Dis. 2016;3(3):1–4.
13. •• of interest. Review of current practice of antibiotic-allergic patients and emerging practices for antimicrobial stewardship programs.
14. Unger NR, Gauthier TP, Cheung LW. Penicillin skin testing: potential implications for antimicrobial stewardship. Pharmacotherapy. 2013;33(8):856–867.
15. Harmon S, Richardson T, Simons H, et al. The clinical and financial impact of a pharmacist-driven penicillin skin testing program on antimicrobial stewardship practices. Hospital Pharmacy. 2020;55(1):58–63.
16. Doña I, Torres MJ, Montañez MI, et al. In vitro diagnostic testing for antibiotic allergy. Allergy, Asthma Immunol Res. 2017;9(4):288–298.
17. Habib G, Lancellotti P, Antunes MJ, et al. ESC Guidelines for the management of infective endocarditis. Eur Heart J. 2015;36(44):3075–3123.
18. Chastain DB, Hutzley VJ, Parekh J, et al. Antimicrobial desensitization: a review of published protocols. Pharmacy. 2019;7(3):112.
19. •• of considerable interest. Antimicrobial desensitization protocols.
20. Jones BM, Jozefczyk C, Maguire C, et al. Beta-lactam allergy review: implications for antimicrobial stewardship programs. Curr Treat Options Infec Dis. 2019;11(2):103–114.
21. Wunderink RG, Sinrivasan A, Barie PS, et al. Antibiotic stewardship in the intensive care unit: an official American thoracic society workshop report in collaboration with the aacn, chest, cdc, and scmr. Ann Am Thorac Soc. 2020;17(5):531–540.
22. Moher D, Liberati A, Tetzlaff J, et al. preferred reporting items for systematic reviews and meta-analyses: the PRISMA Statement. Ann Intern Med. 2009;151(4):264–269.
23. Charlson ME, Pompei P, Ales KL, et al. A new method of classifying prognostic comorbidity in longitudinal studies: development and validation. J Chronic Dis. 1987;40(5):373–383.
24. Charlson M, Szatrowski TP, Peterson J, et al. Validation of a combined comorbidity index. J Clin Epidemiol. 1994;47(11):1245–1251.
25. Seymour CW, Liu ITJsVX, Iwashyna TJ, et al. Assessment of clinical criteria for sepsis for the third international consensus definitions for sepsis and septic shock (sepsis-3). J Am Med Assoc. 2016;315(8):762–774.
26. CDC/NHSN. Surveillance definitions for specific type of infections. Surveill Defin. 2020;21–24.
27. European Committee on Antimicrobial Susceptibility Testing. Breakpoint tables for interpretation of MICs and zone diameters, Version 1.3 [Internet]. 2011. Available from: http://www.eucast.org/clinical_breakpoints.
27. Magiorakos AP, Srinivasan A, Carey RB, et al. Multidrug-resistant, extensively drug-resistant and pandrug-resistant bacteria: an international expert proposal for interim standard definitions for acquired resistance. Clin Microbiol Infect. 2012;18(3):268–281.

28. Legendre DP, Muzny CA, Marshall GD, et al. Antibiotic hypersensitivity reactions and approaches to desensitization. Infect Dis (Auckl). 2013;58(8):1140–1148.

29. Castells M. Rapid desensitization for hypersensitivity reactions to medications. Immunol Allergy Clin North Am. 2009;29(3):585–606.

30. Yates AB. Management of patients with a history of allergy to beta-lactam antibiotics. Am J Med. 2008;121(7):572–576.

31. Jeimy S, Ben-Shoshan M, Abrams EM, et al. Practical guide for evaluation and management of beta-lactam allergy: position statement from the Canadian Society of Allergy and Clinical Immunology. Allergy, Asthma Clin Immunol. 2020;16(1):1–10.

32. Zagursky RJ, Pichichero ME. Cross-reactivity in β-Lactam Allergy. J Allergy Clin Immunol Pract. 2018;6(1):72–81.e1.

33. González-García R, Albanell-Fernández M, Aranda L, et al. Evaluation of desensitization protocols to betalactam antibiotics. J Clin Pharm Ther. 2021;46(1):1–8.

34. Trissel LA, Ashworth LD, Ashworth J. Trissel’s stability of compounded formulations. 6th (United States: Apha Publications) ed. 2018.