

## CASE REPORT

# Successful desensitization to cloxacillin in a patient with sepsis, with infective endocarditis and clinical suspicion of hypersensitivity to penicillins, a case report

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## Summary

**What is known and objective:** Beta-lactam antibiotic (BLA) therapy is frequently needed to treat infective endocarditis (IE). Hypersensitive reactions to BLA restrict BLA therapy in allergic patients. In the current case, we aim to describe the utility of desensitization (DS) in this context. Although the evidence is limited, DS is recommended.

**Case description:** This case report deals with a 79-year-old woman with a clinical suspicion of allergy to BLA and a methicillin-sensitive *Staphylococcus aureus* (MSSA) IE. A cloxacillin DS protocol was developed to enable treatment with cloxacillin.

**What is new and conclusion:** Alternative antibiotic treatments may be less effective or not available in MSSA IE. In this case report, DS allowed optimal cloxacillin treatment.

## KEYWORDS

cloxacillin, desensitization, drug hypersensitivity, endocarditis, immunologic

## 1 | WHAT IS KNOWN AND OBJECTIVE

Infective endocarditis (IE) is a severe infectious disease related to high mortality and severe complications.<sup>1</sup> Bactericidal antibiotics and synergic effects are needed to completely eliminate the bacteria causing the IE. In patients with myocardial infection, beta-lactam antibiotics (BLA) are commonly needed to provide early effective treatment.<sup>2</sup>

Penicillin allergy (PA) is a highly frequent drug-induced allergy with an enormous impact on antibiotic treatment selection.<sup>3</sup> PA has a strong impact on the treatment of severe bacterial infections. Allergic patients may receive less effective or less safe antibiotic treatments.<sup>4</sup>

An allergic reaction to a drug is defined as a specific immunologic-mediated reaction to a specific drug.<sup>5</sup> Reactions to drugs that clinically resemble an allergy are usually identified as drug hypersensitivity reactions (DHR).<sup>6</sup> Nevertheless, most DHR are nonallergic

reactions (without a demonstrated immunologic mechanism) and reactions mediated by IgE represent a small part of the DHR.<sup>7</sup> DHR are classified according to the timing of the appearance of clinical symptoms, immediate reactions occurring 1–6 hours after last drug administration and delayed or nonimmediate reactions occurring from 1 hour to an indefinite time after the initial administration of the drug. Some immediate reactions can be type 1 IgE-mediated reactions.<sup>8</sup> Immediate DHR involve the most significant cases due to the risk of life-threatening situations different to delayed-type reactions commonly present as rashes or skin reactions.<sup>9</sup>

Desensitization (DS) is a process based on the continuous administration of increasing doses of a drug inducing temporary tolerance. The DS mechanism is not fully understood.<sup>10</sup> It is hypothesized that DS produces continuous low rates of mast cells degranulation, but not enough to produce a systemic reaction. DS is indicated in patients at risk of an immediate hypersensitivity reaction to a specific drug.<sup>9</sup> DS enables patients to be treated when alternative antibiotic

treatments are not available.<sup>11</sup> Understanding antibiotic hypersensitivity reactions and an accurate medical evaluation are essential to select the best alternative: DS or the use of an alternative antibiotic, for each case.<sup>12</sup>

DS is a safe and effective process, and it has been described as a safe process in more than 90% of the cases.<sup>13</sup> However, it is a complex process indicated in specific situations that must be carried out by a multidisciplinary team led by an allergist.

## 2 | CASE DESCRIPTION

We describe the case of a 79-year-old woman. Her medical history included arterial hypertension, dyslipidaemia, type II diabetes mellitus, heart failure attributed to hypertensive cardiopathy, bronchial hyperactivity with episodes of upper respiratory tract infections, colonic diverticulosis and obesity; an MSSA IE resolved by antibiotic treatment with vancomycin plus gentamycin and the insertion of a prosthetic mitral valve in 2002; and a history of allergy to penicillin recorded at patient's medical record. The patient received an intramuscular penicillin dose resulting in facial oedema and urticaria in the first hours after drug administration. This episode was correctly described in the medical record during hospital admission, but the patient was not evaluated by an allergist and a definitive diagnosis was not made. The patient had not been treated with beta-lactam since that episode, and no other related episode had been described.

On 14 November 2015, the patient suffered an accidental fall at home and was immobile for more than 2 days, before arriving at the hospital. On 16 November 2015, the patient was admitted to the emergency room due to a complicated right humerus bone fracture. The patient reported a hypovolemic shock, the consequence of a severe bruise in the fracture area in the context of anticoagulation treatment, and on 17th November, the patient was admitted to the ICU. An increase in hepatic transaminase (GOT 35.3UI/L, GPT 46.7UI/L, GGT 129.9UI/L), without alteration in the bilirubin and a neutrophil-mediated leukocytosis, was observed. Nevertheless, the surgical team evaluation discarded an abdominal acute pathology. After 2 days in the ICU, the patient was stabilized and transferred to the ward. During her stay in the ICU, the traumatology team postponed surgery. On 19 November 2015, the general health of the patient worsened and she suffered a flutter episode with cardiogenic shock.

On 20 November 2015, the patient developed fever and was admitted to the ICU again. Blood cultures were drawn identifying Gram-positive cocci in the samples. After this finding, vancomycin treatment was initiated and an urgent echocardiogram was required.

The echocardiogram showed no signs of endocarditis, or echocardiographic anatomical criteria such as vegetation, abscess or pseudoaneurysm. However, there was a high suspicion of IE. This outcome was assessed considering the limitations of a prosthetic valve evaluation. Microbiology tests identified MSSA in blood cultures.

In this situation, BLA intravenous administration was essential. Although over 90% of patients who stated to be allergic to BLA had negative skin tests and tolerated BLA treatment, a DHR was a possibility and DS was considered.<sup>12</sup> Unfortunately, we could not count on an allergy specialist at that moment to provide us with expert advice on this case. A specific skin or drug provocation test could not be performed to assess the patient's allergic condition.

Treatment for MSSA IE was initiated with a regimen of 240 mg of intravenous gentamicin every 24 hours, 600 mg of intravenous rifampicin every 12 hours and cloxacillin according to the desensitization protocol, designed by the pharmacy service and described below. The DS was successful, and no allergy signs were detected. After DS, the patient continued on an intravenous cloxacillin regimen of 2000 mg every 4 hours. Vancomycin treatment was stopped.

On 28 November 2015, after 8 days of treatment, renal function deteriorated and oligoanuria was detected so gentamicin treatment stopped.

Over the following days, the general condition of the patient worsened. After 14 days of stay in the ICU, limitation of therapeutic effort was decided on. The patient died on 14 December 2015. However, in the interests of this case study, a 10-day treatment with cloxacillin had been performed without the patient showing any allergic reaction. A description of important dates of the case is reported in Table 1.

### 2.1 | Desensitization protocol

The pharmacy service developed a DS protocol preparing 16 dilution bags with increasing concentrations. Each infusion bag doubled the cloxacillin concentration of the preceding bag. Cloxacillin dose and concentrations are given in Table 2. This protocol is a modification of the DS model proposed by Legere et al in 2009.<sup>13</sup> We prepared the dilutions using aseptic techniques. Sterile saline solution bags were used to prepare the dilutions. Cloxacillin in saline solution is commonly reported to be stable.<sup>14</sup> We removed a volume of 0.9 sterile saline solution from the infusion bag and replaced it with the calculated volume of cloxacillin. Each infusion bag had a total volume of 50 ml.

Administration of cloxacillin infusions was performed in the ICU. Intensive care physicians closely monitored the patient's clinical condition during DS. Administration of each cloxacillin infusion lasted 30 minutes and was administered every 15 minutes. When DS finished, the patient continued receiving common doses of cloxacillin for MSSA IE successfully.

## 3 | WHAT IS NEW AND CONCLUSION

This clinical case report can provide specific clinical experience in a particular situation. We successfully used a DS protocol for cloxacillin in a patient with MSSA IE. To our knowledge, this is the first DS protocol reported for cloxacillin in a patient with IE and suspected

**TABLE 1** Description of important dates and times in the case

| Description of important dates and times in the case |                                                                                                                                                                                                                      |
|------------------------------------------------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| November 2002                                        | Medical record of staphylococcal IE due to MSSA with a mitral valve replacement with a prosthetic valve and a tricuspid valvuloplasty                                                                                |
| 14 November 2015                                     | Accidental fall at home                                                                                                                                                                                              |
| 16 November 2015                                     | Admission to emergency room<br>Abdominal pathology dismissed by surgical team                                                                                                                                        |
| 17 November 2015                                     | Admission to the intensive care unit coming from the emergency room<br>Surgical treatment dismissed by the traumatology team                                                                                         |
| 19 November 2015                                     | Admission to the internal medicine unit coming from the intensive care unit                                                                                                                                          |
| 20 November 2015                                     | Admission to the intensive care unit coming from the emergency room<br>Positive blood cultures identifying Gram-positive cocci<br>Antibiotic regimen for IE due to MSSA<br>Successful desensitization to cloxacillin |
| 28 November 2015                                     | Gentamicin stopped due to renal function deterioration                                                                                                                                                               |
| 4 December 2015                                      | Limitation of therapeutic effort                                                                                                                                                                                     |
| 14 December 2015                                     | The patient died                                                                                                                                                                                                     |

IE, infective endocarditis; MSSA, methicillin-sensitive *Staphylococcus aureus*.

**TABLE 2** Desensitization protocol performed on this patient

| Step | Dose (Milligrams) | Concentration (Milligrams per millilitre) | Cumulative dose (Milligrams) |
|------|-------------------|-------------------------------------------|------------------------------|
| 1    | 0.1               | 0.002                                     | 0.1                          |
| 2    | 0.15              | 0.003                                     | 0.25                         |
| 3    | 0.3               | 0.006                                     | 0.55                         |
| 4    | 0.6               | 0.012                                     | 1.15                         |
| 5    | 1.2               | 0.024                                     | 2.35                         |
| 6    | 2.5               | 0.05                                      | 4.85                         |
| 7    | 5                 | 0.1                                       | 9.85                         |
| 8    | 10                | 0.2                                       | 19.85                        |
| 9    | 20                | 0.4                                       | 39.85                        |
| 10   | 40                | 0.8                                       | 79.85                        |
| 11   | 75                | 1.5                                       | 154.85                       |
| 12   | 125               | 2.5                                       | 279.85                       |
| 13   | 250               | 5                                         | 529.85                       |
| 14   | 500               | 10                                        | 1029.85                      |
| 15   | 1000              | 20                                        | 2029.85                      |
| 16   | 2000              | 40                                        | 4029.85                      |

allergy to penicillin. Due to the severity of this pathology and the lack of equally effective therapeutic alternatives, this study provides a possible approach.

Unfortunately, in this case we did not have an allergy specialist at the time of making the therapeutic decision and the patient's allergic condition could not be evaluated accurately. An allergy specialist should always be present in these situations to lead decision-making.

In this case, we used a modification of the desensitization model protocol proposed by Legere et al in 2009.<sup>13</sup> We designed a protocol of 16 bags administered at constant speed to minimize the possibility of error during administration.

The patient was a 79-year-old woman with MSSA IE, septic shock, prosthetic valve IE, history of diabetes mellitus and history of heart failure, all associated with a poor prognosis.<sup>15-17</sup>

DS is mentioned in the latest Scientific Statement published by the American Heart Association (AHA) as an option for patients with MSSA IE allergic to BLA, and most experts report it to be a safe practice.<sup>2</sup>

## CONFLICT OF INTEREST

The authors affirm that there are no conflict of interests.

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