

Management of Patients with Suspected or Confirmed Antibiotic Allergy. Executive Summary of Guidance from the Spanish Society of Infectious Diseases and Clinical Microbiology (SEIMC), the Spanish Society of Allergy and Clinical Immunology (SEaic), the Spanish Society of Hospital Pharmacy (SEFH) and the Spanish Society of Intensive Medicine and Coronary Care Units (SEMICYUC)

Short Title: Management of Antibiotic Allergy

Paño-Pardo JR¹, Moreno Rodilla E², Cobo Sacristan S³, Cubero Saldaña JL⁴, Periañez Párraga L⁵, del Pozo León JL⁶, Retamar-Gentil P⁷, Rodríguez Oviedo A⁸, Torres Jaén MJ⁹, Vidal-Cortes P¹⁰, Colás Sanz C⁴

¹ Division of Infectious Diseases. Hospital Clínico Universitario. Instituto de Investigación Sanitaria Aragón. Zaragoza, Spain. CIBER en Enfermedades Infecciosas (CIBERINFEC).

² Allergy Service, University Hospital of Salamanca, Salamanca, Spain. IBSAL (Institute for Biomedical Research of Salamanca), Salamanca, Spain. Department of Biomedical and Diagnostic Sciences, Salamanca Medical School, University of Salamanca, Salamanca, Spain. RETIC de Asma, Reacciones adversas y Alérgicas (ARADYAL), Madrid, Spain.

³ Department of Pharmacy, Hospital Universitari de Bellvitge-IDIBELL, Hospitalet de Llobregat, Barcelona, Spain.

⁴ Department of Allergy. Hospital Clínico Universitario. Instituto de Investigación Sanitaria Aragón. Zaragoza, Spain.

⁵ Farmacia hospitalaria. Hospital Universitari Son Espases. CIBER en Enfermedades Infecciosas (CIBERINFEC).

⁶ Division of Infectious Diseases. Department of Microbiology. Clínica Universidad de Navarra.

⁷ Unidad Clínica de Enfermedades Infecciosas y Microbiología, Hospital Universitario Virgen Macarena, Sevilla, Spain. Instituto de Biomedicina de Sevilla / Departamento de Medicina, Universidad de Sevilla / CSIC, Sevilla, Spain. Centro de Investigación Biomédica en Red en Enfermedades Infecciosas (CIBERINFEC) (Instituto de Salud Carlos III, Madrid, Spain).

⁸ Servicio de Medicina Intensiva. Hospital Universitari de Tarragona Joan XXIII. Tarragona, Spain. IISPV. CIBERES.

⁹ Allergy Unit. Hospital Regional Universitario de Málaga-HRUM. Medicine Department, Universidad de Málaga-UMA, IBIMA-ARADyAL, Málaga, Spain

¹⁰Servicio de Medicina Intensiva. Hospital Universitario de Ourense. Orense, Spain.

Corresponding authors:

Carlos Colás Sanz.

E-mail: ccolas@salud.aragon.es

José Ramón Paño-Pardo

E-mail: jrpanno@salud.aragon.es

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Abstract

Suspected or confirmed antibiotic allergy is a frequently encountered clinical circumstance that influences antimicrobial prescribing and often leads to the avoidable use of less efficacious and / or more toxic or costly drugs than first-line antimicrobials. Optimizing antimicrobial therapy in patients with antibiotic allergy labels has become one of the priorities of antimicrobial stewardship programs (ASP) in several countries. This guidance document aims to make recommendations for the systematic approach to patients with suspected or confirmed antibiotic allergy based on current evidence. A panel of eleven members of involved Scientific Societies with expertise in the management of patients with suspected or confirmed antibiotic allergy formulated questions about the management of patients with suspected or confirmed antibiotic allergy. A systematic literature review was performed by a medical librarian. The questions were distributed among panel members who selected the most relevant references, summarized the evidence and formulated graded recommendations when possible. The answers to all questions were finally reviewed by all panel members. A systematic approach to patients with suspected or confirmed antibiotic allergy is recommended to improve antibiotic selection and, consequently clinical outcomes. A clinically-oriented, 3-category risk-stratification strategy was recommended for patients with suspected antibiotic allergy. Complementary assessments should consider both clinical risk category and preferred antibiotic agent. Empirical therapy recommendations for the most relevant clinical syndromes in patients with suspected or confirmed β -lactam allergy were formulated. Recommendations on the implementation and monitoring of the impact of the guidelines were formulated. ASP and allergists should design and implement activities that facilitate the most adequate antibiotic use in these patients.

Key words: Antibiotic allergy. Drug hypersensitivity reaction. Skin tests. Drug provocation test. Allergy label. Antimicrobial stewardship

Resumen

En la práctica clínica, un antecedente de alergia a los antibióticos, confirmada o sospechada, es frecuente y condiciona la selección de antibióticos, requiriendo con frecuencia el uso de fármacos menos eficaces, más tóxicos o más caros que los antibióticos de primera línea. La optimización del uso de antibióticos en pacientes con este antecedente es una de las prioridades de los programas de optimización de uso de antibióticos (PROA) en varios países. Estas guías pretenden formular recomendaciones para evaluar de una manera sistemática a estos pacientes mediante una aproximación basada en la evidencia. Un panel multidisciplinar constituido por alergólogos, infectólogos, farmacéuticos hospitalarios e intensivistas formularon una serie de preguntas sobre el manejo de estos pacientes. Una documentalista realizó la revisión bibliográfica. Las preguntas se distribuyeron entre los miembros del grupo de trabajo, quienes seleccionaron las referencias más relevantes y formularon las correspondientes recomendaciones, que fueron revisadas y aprobadas por todos los miembros del grupo. Es necesaria una aproximación sistemática a los pacientes con antecedente de alergia a antibióticos para optimizar la selección del tratamiento antibiótico y a mejorar los resultados clínicos de estos pacientes cuando precisan antibioterapia. El presente documento recomienda una estrategia de estratificación clínica del riesgo en 3 categorías. La recomendación de realizar evaluaciones complementarias se basa en el riesgo clínico y el antibiótico de primera línea necesario. Además, se formulan recomendaciones de tratamiento antibiótico empírico para los principales síndromes infecciosos en pacientes con alergia confirmada o sospechada. Finalmente se formulan recomendaciones sobre la implementación y monitorización del impacto de las recomendaciones de la guía. Los programas PROA y los alergólogos deben trabajar conjuntamente en el diseño y ejecución de actividades dirigidas a facilitar el correcto uso de antibióticos en estos pacientes. Los programas PROA y los alergólogos deben trabajar conjuntamente en el diseño y ejecución de actividades dirigidas a facilitar el correcto uso de antibióticos en estos pacientes.

Palabras clave: Alergia a antibióticos. Reacción de hipersensibilidad a medicamentos. Test cutáneos. Test de provocación bronquial. Etiqueta de alergia. Administración antimicrobiana.

Introduction. Aims and scope of the Guideline

Antibiotic allergy, either suspected or confirmed, is a frequently encountered present or past diagnosis, also referred as antibiotic allergy label, that significantly influences antimicrobial therapy, mainly because it often leads to the selection of second-line agents that are frequently either less efficacious, more toxic, or more costly than first-line antibiotics. As this is a frequent problem and second line agents often have an increased potential of induction and / or selection of antimicrobial resistant microorganisms or *C. difficile*.

Many diagnoses of antibiotic allergy labels do not truly represent hypersensitivity or immune-mediated drug reactions, making necessary a clinical and, eventually the use of complimentary tests in order to better define the presence of antibiotic and the antibiotics that it might involve. In recent years, antimicrobial stewardship programs (ASP) have considered patients with diagnosis of antibiotic allergy as priority, multiple interventions targeting these patients have been designed and conducted in coordination with allergists, with significantly successful outcomes.

The Spanish Society of Infectious Diseases and Clinical Microbiology (SEIMC) and the Spanish Society of Allergy and Clinical Immunology (SEAIC) considered that there could be significant room for improvement in the selection of antibiotic therapy among patients with antibiotic allergy labels in Spain, mainly because of an heterogenous approach to these patients in the Spanish territory. As scientific production in this field has been quite fertile, SEIMC and SEAIC considered that a clinical practice guideline could contribute to improve clinical practice in regards of antibiotic selection and infection management in suspected or known allergic patients. It was deemed necessary to include other healthcare providers involved in the management of these patients, such as pharmacists, through the Spanish Society of Hospital Pharmacy (SEFH) and intensive care specialists through the Spanish Society of Intensive Medicine and Coronary Units (SEMICYUC).

The main aim of this guideline is to formulate evidence-based recommendations that contribute to improve the management of patients with suspected or confirmed antibiotic allergies. More specifically, it pretends to standardize the approach of both, clinicians when facing the need of prescribing antimicrobials in patients with an antibiotic allergy label, and allergists when need to confirm or exclude the antibiotic allergy label and to define its extent and the drugs that might and might not be safely prescribed. The scope of this guideline is not restricted to patients of any specific gender or specific age segments. Although, a comprehensive approach was sought and allergy to all antibiotic groups was considered, the available evidence is disproportionally skewed towards β -lactams overall and penicillins, specifically. Similarly, although we did not restrict the scope of the guideline to a specific level of care within the healthcare system a disproportionate proportion of the retrieved references were in the hospital care setting.

In addition, this guideline also aims to facilitate patient prioritization and articulation and monitoring of local or regional activities and interventions that help to put the recommendations contained in this guideline into practice.

Finally, an extensive and detailed version of this consensus, with all the items and tables developed and the corresponding bibliographic support, is available in the repository ([See also Supplementary Material](#)). All tables referred to can be found in the supplementary material.

Methods

SEIMC and SEAIC chose one coordinator each (JRPP and CCS, respectively). The coordinators proposed two experts in infectious diseases (JdPL and PRG) and three experts in Allergy (JLCS, EMR and MJTJ), accepted by SEIMC and SEAIC executive committees, respectively. SEFH and SEMICYUC were invited to participate through their executives' committees and proposed two hospital pharmacists (SCS and LPP) and two critical care specialists (PVC and ARO).

Coordinators followed the SEIMC recommendations to elaborate Clinical Practice Guidelines and the Agree II Collaboration guidance to draft an outline, which was shared, discussed and adapted with the rest of the panel members. It was decided to structure the document based on clinically relevant questions addressing the assessment of the antibiotic allergy label and its extent as well as recommended empiric antimicrobial therapy for the most frequent infectious syndromes. The questions were distributed among the panel members considering their expertise.

A specific systematic literature search was performed for each question by an expert in medical information retrieval from the Aragon Healthcare Sciences Institute (IACS). The original search was performed in July 2018. Retrieved references were distributed to the corresponding experts who selected relevant references, summarized the evidence, and formulated recommendations. Recommendations had to be graded in two domains, the strength of the recommendation (A: Good evidence to support a recommendation for or against use; B: Moderate evidence; C: Poor evidence), and quality of evidence (I: Evidence from >1 properly randomized clinical trial; II: Evidence from >1 well-designed clinical trial, without randomization; from cohort or case-controlled analytic studies from multiple time series; or dramatic results from uncontrolled experiments; III: Evidence from opinions of respected authorities, based on clinical experience, descriptive studies, or reports of expert committees), according to the Infectious Diseases Society of America (IDSA) grading system.

The systematic literature search did not retrieve the information needed to provide recommendations for the recommended empirical antimicrobial empirical therapy in patients with antibiotic allergy labels (Question 4.2.). Thus, the main infectious syndromes were selected once the panel members agreed upon the clinical risk-stratifying categories. Then, the main etiologies and the epidemiology of antimicrobial resistance were considered, and recommendations for empirical therapy for each clinical syndrome were subsequently formulated and shared for discussion among panel members.

Lastly, we analyzed potential barriers that might negatively affect the implementation of the guideline and provided input on how they could be overcome. Indicators to monitor the impact of the guideline were suggested, too. Before its publication, the guideline was distributed among SEIMC membership for review and comments.

We are planning to perform a new literature search in 2023. Analysis of the references retrieved in this literature search will determine if an update is necessary. In that case, healthcare professionals with other specialties, mainly from primary care and pediatrics, will be invited to join the panel.

1. Epidemiology

1.1. How frequently are antibiotic allergies reported?

- Antibiotics overall are the most common cause of drug allergy or drug hypersensitivity reactions. (See also Table 1 on Supplementary Material)
- The prevalence of reported antibiotic allergy is probably the best indicator to measure the burden of this public health problem. Penicillins are the antibiotics that account for most of antibiotic allergy labels. Although significant variations are observed between institutions, countries and in some specific populations, overall, 10-12% of the population reports to be penicillin allergy [1]. (See also Table 2 on Supplementary Material)
- The risk of reported antibiotic allergy (likelihood of reported antibiotic allergy in patients exposed to a given antibiotic) has been found to be highest for sulfonamides (2-4%) followed by penicillins (1%).
- Incidence of reported antibiotic allergy is higher in females for all antibiotic classes.
- Severe antibiotic hypersensitivity reactions account for a minority of all reported antibiotic allergies (4-7%). Sulfonamides may be associated with the highest risk of severe antibiotic allergic reaction followed by clindamycin, fluorquinolones and penicillins.
- Nevertheless, these figures overestimate the frequency of true antibiotic allergies given that many reactions labelled as antibiotic allergy are not hypersensitivity reactions but non-immune mediated reactions and even non drug-adverse reactions [2].

1.2. What are the consequences of receiving second-line antimicrobial therapy because of a β -lactam allergy label?

- Antimicrobial allergy label has been found to be associated with prolonged hospitalization, increased rate of readmissions, increased hospital costs and/or mortality in several large cohort studies with hospitalized patients. These findings have also been observed in more specific populations, such as hemato-oncological patients.
- Second-line antimicrobial agents used for prophylaxis in penicillin allergic patients are associated with increased risk of infection and increased toxicity.
- Patients labelled penicillin allergic have an increased risk of *C. difficile* and of infections caused by antimicrobial-resistant microorganisms. There is evidence of the association between penicillin allergy label and infections caused by multi-drug resistant microorganisms (MDRO), mainly methicillin-resistant *Staphylococcus aureus* (MRSA) [3].

1.3. How frequently an antibiotic allergy label does not represent an antibiotic hypersensitivity reaction?

- Antibiotic allergy labels, more specifically those to penicillin or β -lactam antibiotics, overestimate true antibiotic hypersensitivity reactions.
- Between 70% and more than 95% of patients with penicillin allergy labels have not had penicillin hypersensitivity reactions and may tolerate penicillins or other β -lactams.
- The frequency of true drug hypersensitivity reactions (DHR) among patients with penicillin allergy labels is lowest among children and outpatients.
- Poorly detailed drug allergy histories contribute to antibiotic allergy overestimation through misinterpretation of non-immune mediated adverse reactions as true DHR and failure to identify subsequent tolerance to the culprit antibiotic [4].

- Even with a comprehensive drug history many patients labeled as penicillin allergic would benefit of a specific allergy workup with *in vivo* and/or *in vitro* tests **(A-II)**.

2. Risk assessment of antibiotic allergy labels

2.1. Can the risk of allergic reactions in patients with antibiotic allergy labels be stratified using clinical assessment?

- Although the gold standard to delabel penicillin allergy is to perform a complete allergological study, the approaches to patients with antibiotic allergy label should be individualized. **(A-II)**
- A standardized clinical assessment of patients with antibiotic allergy labels should start by identifying those with a history of non-immune mediated symptoms as the isolated manifestation of a drug reaction (See also Table 3 on Supplementary Material). **(A-II)**
- Patients who report having had anaphylaxis, bronchospasm, angioedema, laryngeal edema, or hypotension should be considered high-risk Type I immediate DHR. **(A-II)**
- Other high-risk subjects are patients with suspected non-immediate Type II-IV HSR severe reactions, such as Stevens-Johnsons Syndrome, Toxic Epidermal Necrolysis, acute interstitial nephritis, drug rash eosinophilia systemic symptoms (DRESS), and hemolytic anemia. **(A-II)**
- Having received epinephrine and having had a reaction that required hospital care indirectly suggest severe DHR. **(A-II)**
- Although drug allergy history has significant limitations, mainly due to the time elapsed since the episode of alleged allergy and the non-specific clinical presentation of DHR, a risk-assessment, systematic approach (See also Table 3 and Table 4 on Supplementary Material) can help to stratify the clinical risk of reported drug reactions and to guide further allergy tests, especially to decide in which patients direct antibiotic challenge can be performed, and which patients could safely receive alternative β -lactams if necessary [5]. **(A-II)**

2.2. Can antibiotic allergy be ruled out in some patients with self-reported antibiotic allergy by means of clinical assessment? In which patients?

- Clinical assessment through a detailed drug allergy history and risk stratification is of limited value to rule out antibiotic allergy.
- Patients in whom the detailed drug allergy history is conclusive of non-immune-mediated drug adverse effects, such as nausea, vomiting, diarrhoea, headache, or paraesthesia, can be de-labelled, and further specialized evaluation or testing is not necessary [6]. **(A-III)**
- Patients in whom subsequent tolerance to the culprit antibiotic has been documented can be de-labelled, and further specialized evaluation or testing is not necessary. **(A-III)**
- Further research is needed on the efficacy and safety of mathematical diagnostic models based on data obtained from clinical assessment to de-label reported antibiotic allergies.

3. Assessment of patients with antibiotic allergy through complimentary tests

3.1. What is the role of skin tests in patients with clinically suspected antibiotic allergy?

- Skin tests are the most validated method for confirming or excluding β -lactam allergy, although skin test reactivity declines over time. Some cases become again positive after a new contact with a β -lactam [7].
- Skin tests are not recommended in patients with non-suggestive allergic adverse events. **(A-III)**
- It is hard to estimate the sensitivity and specificity of skin tests accurately since the diagnostic gold standard (e.g., drug provocation test) is not performed in all the subjects due to ethical considerations. Assuming this limitation, the sensitivity of skin tests is estimated to be up to 70% if major and minor determinants of penicillin, amoxicillin, and the suspected β -lactam are used.
- Based on the limited number of drug provocation tests performed in patients with positive skin tests due to ethical reasons, their positive predictive value has been estimated to be between 40% and 100%.
- Skin tests are generally safe, but systemic reactions may occur, especially in patients with a previous history of anaphylaxis.
- In severe reactions or in patients who have experienced mild symptoms but are at special risk, the intradermal tests, and even the prick test, should begin with a dilution of 1/1000 or 1/100, which are gradually increased until the appearance of a positive skin response or until a non-irritant concentration is reached [8]. **(A-II)**
- When the culprit antibiotic is an aminopenicillin or a cephalosporin, the reactivity is frequently due to the side chain.
- Benzylpenicilloyl (BPO-OL), sodium benzylpenilloate (MD), benzylpenicillin, amoxicillin and the suspected penicillin or cephalosporin should be tested, as well as β -lactams that share the same side chain. **(A-II)**
- Before skin tests, any medications that could interfere with the results of skin tests (e.g., antihistamines) should be temporarily discontinued. Beta-blockers should be discontinued at least 24 hours since they could interfere with the use of adrenalin if a systemic reaction occurs. **(A-II)**
- For immediate drug hypersensitivity reactions to β -lactams, prick tests are recommended for initial screening. **(A-II)** An intradermal test (ID) should be performed if no reaction were observed, as IDs have higher sensitivity for IgE mediated reactions [8]. **(A-II)**
- In immediate hypersensitivity reactions to β -lactams, readings should be taken after 15–20 minutes. **(A-II)**
- In skin prick tests, a wheal larger than 3 mm accompanied by erythema with a negative response to the control saline is considered positive. **(A-II)**
- We recommend intradermal skin tests and patch tests with delayed readings to diagnose nonimmediate drug reactions to β -lactams. **(A-II)**
- In the intradermal tests, the wheal area is marked initially and 20 minutes after testing, and an increase in diameter greater than 3 mm with erythema is considered positive. **(A-II)**
- A late reading should be done in those cases with an unknown chronology or suspicion of non-immediate reactions. **(A-II)**

3.2. What is the role of drug provocation tests in the assessment of patients with suspected antibiotic allergy?

- The drug provocation test is considered the gold standard for establishing the diagnosis of drug hypersensitivity. Up to one-third of patients allergic to penicillins have a negative result in skin tests [9].
- Drug provocation tests should be done only after performing skin tests **(A-III)**. Nevertheless, in patients with severe infections and non-confirmed penicillin or cephalosporin allergy, and if skin testing is not feasible, a controlled drug challenge with an alternative β -lactam with low cross-reactivity with the culprit drug might have a favourable risk/benefit balance and be could therefore be considered appropriate (See question 4.1).
- Drug provocation tests can be used to assess cross-reactivity among β -lactam antibiotics.

3.3. What is the role of desensitization in patients with antibiotic allergy?

- Drug desensitization (DD) is indicated when the antibiotic is irreplaceable or when the drug is more effective than the alternatives [10]. **(A-III)**
- DD should generally not be performed in patients at increased risk of severe complications due to significant comorbidity and is absolutely contraindicated in patients who have experienced severe, life-threatening immunocytotoxic reactions, vasculitis or bullous skin diseases and other severe cutaneous adverse drug reactions. **(B-III)**
- DD has an extremely high level of risk and complexity and must be conducted by an allergist and nursing staff with specific training in a hospital location where patients who develop a severe reaction can be treated. **(A-III)**

4. Antibiotic selection in patients with reported penicillin or cephalosporin allergy

4.1. Can β -lactams be used in patients labeled penicillin allergic? Which β -lactams? In which patients?

- In patients with a history consistent with non-immune mediated adverse events to penicillins or cephalosporins, β -lactams can be administered unrestrictedly (See also Table 3 on Supplementary Material) [11]. **(A-II)**
- To decide which β -lactam to choose in β -lactam allergy labelled patients, it is essential to consider the chemical structure of the β -lactam responsible for the reaction and that of the alternative one, as well as the type of reaction, as tolerance may differ between immediate and nonimmediate ones. **(A-II)**
- Of all β -lactams, aztreonam (0%) and carbapenems (0.87%) have the lowest cross-reactivity rates with penicillin and can be safely administered to most patients labelled penicillin allergic. **(A-II)**
- There are significant differences in the cross-reactivity rates of cephalosporins with penicillins (See also Table 5 at Supplementary Material). These differences are due to variations in the chemical structure, mainly the R1 and sometimes the R2 side chains, of the involved penicillin and cephalosporin. Patients allergic to ceftazidime might experience cross-reactivity with aztreonam due to structural similarities.
- There is a high degree of cross-reactivity among semi-synthetic penicillins, especially aminopenicillins (i.e., amoxicillin, ampicillin, bacampicillin, and pivampicillin), which share an amino group in their side chain. Nevertheless, some patients with amoxicillin allergy tolerate benzylpenicillin, and patients allergic to clavulanic acid may tolerate amoxicillin.

- The gold standard procedure to administer a β -lactam in patients with suspected immune-mediated reactions is to perform skin and drug provocation tests before administration and delabeling. **(A-II)**
- Nevertheless, in some hospitalized patients with moderate and severe infections and penicillin or cephalosporin allergy label, controlled drug challenge with an alternative β -lactam with low probability of cross-reactivity, in the absence of skin tests, has a favorable risk/benefit ratio (See also Table 5 and Table 6 at Supplementary Material) [12]. **(A-II)**
- Patients with suspected immune-mediated hypersensitivity reactions exposed to alternative β -lactams in the absence of a standardized allergy work-up, should be referred to an allergist before delabeling. **(A-III)**
- In patients with a history of severe Type II-IV drug hypersensitivity reactions, β -lactams should be avoided if possible. **(A-III)**

4.2. What is the recommended antimicrobial therapy for the main infectious syndromes in patients with a non-confirmed label of penicillin and / or β -lactam allergy?

See Table 7 at supplementary material

4.3. How should antibiotic allergy be reported in the medical records?

- All patients should receive an Allergology Department's medical report that must meet the established minimum recommended quality standards. **(A-III)**
- Antibiotic allergy should be reported in a prominent site within the medical record [13]. **(A-III)**
- If a patient had a prior allergy, but it has been delabeled, the current status of the antibiotic allergy should be updated in the medical record, specifying the date of delabeling. **(A-III)**
- Electronic Health Records (EHRs) have been shown to improve the safety and quality of patient care, especially when Clinical Decision Support (CDS) is implemented. **(A-II)**

5. Which interventions to improve characterization and antimicrobial use in patients with self-reported β -lactam allergy (SRBA) have been shown useful?

- Formal assessment of self-reported β -lactam allergy (SRBA) in hospitalized patients receiving antibiotics increases the likelihood of β -lactam use and decreases the chance of receiving second-line, more expensive, more toxic and less efficacious antibiotics [14]. **(A-II)**
- Formal assessment of SRBA in hospitalized patients is associated with cost savings that persist beyond the intervention. **(A-II)**
- Clinical impact of SRBA is still uncertain. **(A-II)**
- Clinical assessment tools (CAT) such as guidelines or algorithms, when implemented in the setting of an antimicrobial stewardship team, have proven to help identify patients unlikely to be allergic and patients at low-risk of severe immune-mediated reactions after a new β -lactam exposure who can safely receive some β -lactams other than aztreonam and carbapenems, such as cephalosporins and, in the former case, even penicillins. **(A-II)**

- The integration of CAT with penicillin skin testing and oral β -lactam challenge when appropriate, if performed by trained personnel, increases the yield of formal assessment of SRBA. (A-II)
- The cost effectiveness of the formal assessment of SBRA is highest among patients with severe infections, especially if prolonged therapy is needed, as is the case of patients with endocarditis and osteoarticular infections, or in patients receiving high valued antibiotics due to SRBA [15]. (A-II)
- One of the circumstances that may diminish the potential impact of interventions designed to assess SRBA formally is inefficient delabeling of the discarded allergies. (A-II)

6. Implementation of the guideline

6.1. Which barriers might interfere the implementation of the recommendations contained in this guideline? Are there any facilitators?

- The main barriers to the implementation of the recommendations contained in this guideline are: a) the large size and widespread distribution of the affected population, b) insufficient and unequitable access to allergists, c) Resistance of doctors and patients to the use of any β -lactam in patients labeled as penicillin-allergic, d) Lack of training and support for using alternate β -lactams in patients with low-risk and non-immune mediated reactions in the acute care settings and e) Insufficient human resources capabilities within antimicrobial stewardship programs (ASPs).

6.2. How should the recommendations contained in this guideline should be put into practice?

- Antibiotic allergy labeled patients to prioritize are: a) Patients with sepsis or septic shock b) Patients with infections leading to hospitalization c) Immunocompromised individuals d) Patients who are undergoing high-risk surgeries from the infectious perspective (i.e., oncological procedures) and e) Patients with recurrent infections (i.e. urinary tract or biliary infections).
- Antimicrobial stewardship programs (ASPs) are probably the best vehicle to implement the recommendations contained in this guideline, both in the hospital and in primary care.
- Activities to improve the management of patients with suspected or confirmed antibiotic allergy should count with the active participation of specialists in allergy.
- Endorsement of this guideline by the Spanish National Action Plan Against Antimicrobial Resistance (PRAN) might increase its impact, especially contributing to involve Autonomous Communities and regional healthcare systems.

6.3. What resources are needed for the implementation of the recommendations included in this guideline?

- Specific protected time for ASP team members, as well as allergists and skilled nurses should be allocated according to the estimated needs associated with the interventions.
- Ready to use or easily adaptable printed or in e-format educational materials of several kinds might help decrease the workload associated with implementing the recommendations contained in this guideline for ASP members.

6.4. How is the implementation of this guideline going to be monitored?

- Table 8 at Supplementary Material, summarized several indicators to monitor the implementation of this guideline
- A 2 time-point nationwide survey might help to understand the implementation of this guideline.

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