SUPPLEMENTARY MATERIAL

1. Epidemiology

1.1. How frequently are antibiotic allergies reported?

Summary

- Antibiotics overall are the most common cause of drug allergy or drug hypersensitivity reactions.
- 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.
- 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.

Drug hypersensitivity reactions (DHR) belong to type B adverse drug reactions, which are defined as dose-independent, unpredictable, noxious, and unintended response to a drug taken at a dose normally used in humans.[1,2] DHR can either be allergic, when they are immune-mediated, or non-allergic if they are not. Pathophysiologically, immune-mediated DHR can be classified into four categories (type I to type IV).[2] Clinically, DHRs can be classified as immediate or nonimmediate depending on the time interval between the drug administration and symptoms onset. Immediate reactions are mediated by specific IgE-antibodies and subsequent mast cell activation, occur within 1 hour, and up to 6 hours, after the drug administration and can present as urticaria and/or angioedema, rhinitis, bronchospasm, and anaphylactic shock.[2] Nonimmediate reactions occur more than 6 hours after the drug administration and they are usually mediated by specific T-cells.[2] The most common non-immediate manifestations are maculopapular exanthems and delayed-appearing urticaria but other severe systemic reactions can occur (i.e. Stevens-Johnson syndrome, toxic epidermal necrolysis, DRESS syndrome…).[2–4] Although clinical presentation is critical in order to identify DHR, confirmatory diagnosis frequently needs a specific workup based on *in vivo* tests because of nonspecific DHR presentation and the concomitant use of multiple drugs.[4]

Antibiotics overall, and more specifically penicillins, some of the most frequently prescribed drugs worldwide, are the most commonly reported cause of drug-induced hypersensitivity reactions.[5–9] Doña et al evaluated 4460 consecutive patients referred to a Spanish Allergology Unit between 2005 and 2010 because of a reported drug hypersensitivity reaction. Most of the episodes (44.4%) were reported allergy to antibiotics (ß-lactams 29.4%; non β-lactams 15%) followed by nonsteroidal anti-inflammatory drugs (NSAIDs)[10]. Among the 1683

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patients (37.45%) finally confirmed as allergic, hypersensitivity to multiple NSAIDs was the most common finding (47.29%), followed by immediate reactions to β-lactams (18.12%). There

was an increase in reactions to non β–lactams (from 21.2% to 31.9%; P<.03) over the study period, mainly due to an increase in allergy to quinolones, which might reflect an increased use of this antibiotic class (from 0.5% to 6.8%; P<.02). Other Spanish studies offers similar results[11].

The estimated incidence of reported antibiotic allergies varies depending on the gender, age, antibiotic drug and, perhaps, sociocultural factors. Macy et al retrospectively estimated the incidence of antibiotic allergy among 411,513 patients belonging to a healthcare network in California and found that the incidence of antibiotic allergy steadily increased with age and it was systematically higher in females for all antibiotic classes. The estimated incidence of antibiotic allergy was highest among sulfonamides (1.91% to 3.74%), followed by penicillin (1.01% to 1.51%), cephalosporins (0.49% to 1.21%), macrolides (0.38% to 1.54%), quinolones (0.42% to 1.14%) and tetracyclines (0.36% to 1.46%).[9] However, some selection bias should be present in this study. Nested in a large US health insurance claims, Johannes et al designed a cohort study to determine the incidence of severe DHR, defined as those requiring hospitalization or visit to the emergency department, in the 14 days following administration of penicillins, cephalosporins and quinolones. The incidence of severe DHR ranged from 4.5/10,000 first doses (moxifloxacin) to 7.5/10,000 first doses (cephalosporins).[12] An analysis of the National Electronic Injury Surveillance System–Cooperative Adverse Drug Event Surveillance between 2004 and 2006 showed that most (78.4%) of emergency department visits for antibiotic-associated adverse events were due to antibiotic allergies and the highest risk was observed with sulfonamides (4.3 Emergency Department (ED) visits/10,000 prescriptions) followed by clindamycin (2.8 ED visits/10,000 prescriptions), quinolones (2.4 ED visits/10,000 prescriptions) and penicillins (2.2 ED visits/10,000 prescriptions).[13].

Unless a specific workup proves tolerance, allergy labels frequently last for the rest of patients´ lives and thus, prevalence is probably a more accurate measure of the burden of antibiotic allergies. The prevalence of antibiotic allergy labels depends not only on the individual DHR risk for every antibiotic but also on the frequency of antibiotic use as well as on the probability of antibiotic exposure, which might vary in specific populations. Table 1 summarizes the estimated prevalence of antibiotic allergy in several countries and in various healthcare settings. Overall, approximately 10-12% of adult population is reported to be penicillin allergic. Prevalence of allergy labels to other antibiotics such as sulfonamide (4-7%), cephalosporins (2-4%) and quinolones (0.6-1.3%) is lower than penicillin. However, as historic perspective of antibiotic allergy should be shorter, the prevalence of sulfonamide hypersensitivity could be lower and the fluoroquinolones one, higher(10).

The presentations of DHR and non-immune mediated drug adverse reactions often overlap. Moreover, signs and symptoms of coexisting diseases (e.g. rash occurring in the setting of a febrile viral infection) may easily be misinterpreted as DHR when there is concomitant antibiotic exposure. Therefore, differentiating DHR from other mimicking entities is often hard in the absence of a systematic workup that may include a careful and systematic clinical history as well as skin testing, specific laboratory tests and drug provocation. Consequently, a variable proportion of patients with antibiotic allergy label have not ever had a DHR, leading to the overestimation of the frequency of true antibiotic allergy.

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First author	Year of Publication	Country	Setting	Number of patients	Penicillin allergy label rate N / %
Biagtan[14]	2013	USA	Hospitalized patients	35,268	7,968 / 22.6%
Lee[15]	2000	USA	Hospitalized patients (Tertiary centre)	1893	295 / 15.6%
Khasawneh[16]	2013	USA	Hospitalized patients (Internal Medicine. Community Hospital)	2,589	387 / 14.9%
McConeghy[6]	2017	USA	Hospitalized patients	10,800,000	1,410,080 / 13% Sulphonamides 558,653 / 5.1%
Trubiano[17]	2015	Australia	Hospitalized patients (Tertiary centre)	509	68 / 13% Cephalosporins 24 / 5% Sulphonamides 22 / 4%
Zhou[5]	2016	USA	Hospitalized patients (Tertiary centre)	1,766,328	225,957 / 12.8% Cephalosporins 30,272 / 1.7% Sulphonamides 130,029 / 7.4% Macrolides 40,269 / 2.6% Fluoroquinolones 22,147 / 1.3% Tetracyclines 20,454 / 1.2%
MacPherson[18]	2006	Australia	Preoperative assessment	1,260	147 / 11.7%
Albin[19]	2014	USA	Outpatient population (Internal Medicine)	11,761	1348 / 11.5%
Doña[10]	2012	Spain	Outpatient population (Allergy Department)	4,460	1070 / 24%
Trubiano[20]	2016	Australia	Hospitalized patients* (Countrywide survey)	21,031	2307 / 11% Cephalosporins 488 / 2.3% Sulphonamides 450 / 2.1% Macrolides 271 / 2.3% Tetracycline 158 / 0.8% Fluoroquinolones 125 / 0.6%
Blumenthal[21]	2018	USA	Preoperative assessment	8,335	911 / 10.9%

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Branellec[22]	2008	France	Primary Care	1,057	99 / 9.4%
Moskow[23]	2015	USA	Outpatient population	319,051	β-lactam 29,051 / 9.1%
Macy	2009	USA	Outpatient population	411,543	37,059 / 9% Cephalosporins 5365 / 1.3% Sulphonamides 22,232 / 5.42% Quinolones 2275 / 0.5%
Fernández[24]	2018	Spain	Hospitalized patients (Internal Medicine; elderly patients [> 80 years-old])	1723	106 / 6.2%
Inglis[25]	2017	Australia	Hospitalized patients	96,708	5,023 / 5.2%
Borch[26]	2006	Denmark	Hospitalized patients (Tertiary centre)	3,642	96 / 2.6%
Salden[27]		Netherlands	Primary Care	8,288	β-lactam 168 / 2%
Gomes[28]	2004	Portugal	Outpatient population	2309	37 / 1.6%
Beltran[29]	2015	USA	Preoperative assessment (pediatric)		513 (no denominator available)

Table 1. Studies reporting the prevalence of reported antibiotic allergy.

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

Summary

- 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).

Penicillin allergy labels preclude the use of penicillin and in many instances other β-lactam antibiotics despite these are first-line therapy for several infectious syndromes, leading to inappropriate or suboptimal antimicrobial regimes.[20,30–35] As second-line antibiotics are frequently less efficacious and/or more toxic and costly, patients labeled with penicillin or β-lactam allergy experience are expected to have worse outcomes that patients who are treated with penicillin or other β-lactams.[36–39]

Large cohort studies have shown prolonged hospitalization, increased readmission rate, intensive care unit admission and/or mortality among hospitalized patients that had been labeled with antimicrobial, mainly penicillin, allergy.[31,33,40–42] Charneski et al observed longer hospital stay (1.16 days), an increased adjusted risk of ICU admission (OR 1.42, 95% IC 1.21 to 1.67) and an increased risk of death (OR 1.56 95% IC 1.20 to 2.04) in a cohort study that included 1324 hospitalizations of patients with antimicrobial allergy label hospitalized in nonsurgical wards of a US urban tertiary center.[33] In a retrospective cohort study with patients hospitalized in a large hospital network in Southern California between 2010 and 2012, Macy et al observed longer hospital stay among patients with penicillin allergy label (6.3 days in females and 7.1 days in males) as compared with a main diagnosis, sex and age matched cohort of patients without penicillin allergy label (5.6 days in females and 6.8 days in males; p<0.001 and 0.0067, respectively).[31] Similarly, in a cohort of 1,718 hospitalizations of Portuguese children labelled penicillin allergic from 2010 to 2014 hospital stay was significantly longer (5 days vs 4 days ; p=0.003) than in a matched cohort of children without a penicillin allergy label.[40] Readmission rates have also been found to be higher among patients with penicillin allergy labels. In an Australian sample of 725 patients from a tertiary center with reported penicillin readmission rates were significantly higher than in matched patients without reported allergy (OR = 1.57, 95% CI, 1.04-2.37; p = 0.0331).[41] Readmissions were mostly (85%) caused by severe infections.[43]

In more specific populations, such as immunocompromised patients, some authors have found higher mortality in those with penicillin allergy label. For instance, Huang et al observed that among 660 patients with hematological malignancies and penicillin allergy label that required antibiotics, 30-day and 180-day mortality was higher than in patients without reported penicillin allergy (7.6% vs 5.3%, p <0.001 and 15.8% vs 12.2%, p< 0.001, respectively). Similarly, hospital stay was longer among patients with reported penicillin allergy (11.3 vs 7.6 days; p = 0.01).[44] In contrast, Trubiano et al found an increased risk of readmission rates (53% vs 28%; p < 0.001) but neither increased mortality nor prolonged

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hospitalization among 198 Australian cancer patients with an antimicrobial allergy label who required antibiotics.[30] Patients with bloodstream infections are also at higher risk of poorer outcomes when first-line therapy is not possible. In a small 1:2 matched cohort study that included patients with bloodstream infections Young observed increased rate of infection-related readmission (32.6% vs 14.0%, p = 0.012).[45]

Clinical outcomes have also been found to be worse among patients who receive second-line antibiotic prophylaxis because of a penicillin allergy label. In the largest available study, Blumenthal et al reported that among 911 penicillin allergy reporters, cefazolin, first-line antibiotic for surgical site infection (SSI) prophylaxis was used marginally as compared with non-penicillin allergy reporters (12% vs 92%; p <0.001) in favor of second-line drugs such as clindamycin (49% vs 3%**;** p < 0.001), vancomycin (35% vs 3%; p < 0.001) and gentamicin (24% vs 3%; p <0.001). The adjusted risk of SSI was significantly higher among penicillin allergy reporters (OR 1.51, 95% IC 1.02-2.22).[21] Several authors have found an increased risk of prosthetic joint infection after arthroplasty when non-cefazolin antibiotics are prophylactically administered in patients with reported penicillin allergy.[46,47] For instance, Robertsson et al observed higher risk of revision surgery for infection (RR =1.5, 95% CI: 1.2-2.0; p = 0.001) among patients who underwent total knee arthroplasty and received clindamycin (n= 5,771) as antibiotic prophylaxis than among patients who received cloxacillin (n= 72,232).[46]. Nevertheless, other authors did not find and increased risk of prosthetic joint infection among patients who received vancomycin as antibiotic prophylaxis due to reported penicillin allergy [48,49] In a crossed match of two large databases of antibiotic prophylaxis and drug adverse effects reporting, Thornhill et al found an increased number of fatal reactions (3 vs 0 per million prescriptions) and non-fatal reactions (149 vs 22.62 per million prescriptions) when clindamycin, first-line antibiotic drug for penicillin allergic patients, was received as compared with first-line standard agents.[50]. Regarding antibiotic prophylaxis before dental procedures, French et al found an increased risk of dental implant failure (2.1% vs 0.8%; p = 0.002).[51] and infections (3.4% vs 0.6%; p= 0.005) among the 470 patients with reported penicillin allergy as compared with the 5,106 patients without penicillin allergy label.

Used of second-line, more expensive antibiotics, increased duration of antibiotic therapy, prolonged hospitalization, increased number of readmissions and need for additional surgical procedures observed in patients with penicillin allergy label have additional costs for healthcare systems.[38] The cost of second-line antibiotics among hospitalized patients with penicillin allergy label was 1.82 to 2.58 times higher in a selected sample of 102 hospitalized patients in a British centre.[52] Similarly, King et al found that the antibiotic cost during admission of patients with reported penicillin allergy was nearly $300 lower after delabelling.[53] Huang et al estimated global (direct and indirect) costs among hospitalized hematological patients with reported β-lactam allergy were almost $50,000 per patient higher than in those without penicillin allergy label ($223,046 vs $173,256; p<0.001).[44]

Importantly, patients with penicillin allergy label have been found to be at increased risk of acquiring infections caused by multi-drug resistant microorganisms and C. *difficile*. In the largest study to date, a population-based matched cohort study including more than 300,000 adults Blumenthal el al observed an increased risk of methicillin-resistant *S. aureus* -MRSA- (HR 1.69; IC95 1.51 to 1.90) and *C. difficile* (HR 1.26; IC95 1.12 to 1.40) infections among patients with reported penicillin allergy. These findings concur with those provided by other researchers.[31,45,50,54]

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

Summary

- 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 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.
- 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**).

A significant, although variable proportion of antibiotic allergy labels do not represent true DHR, leading to antibiotic allergy overreporting. Antibiotic allergy overreporting may be determined by several factors. First, non immune-mediated antibiotic adverse events are frequently misinterpreted as true DHR. Several questionnaire-based studies have found that between 6% and 27% of all penicillin or β-lactam allergy labels do represent non immune-mediated drug adverse reactions, such as nausea, vomiting and diarrhea.[23,25,27,34,55] Antibiotic allergy labels tend to persist over time despite proven incorrect. Well-tolerated subsequent exposure to culprit antibiotics can be documented in a variable proportion of up to 35% of patients with a penicillin allergy label.[16,26]

Both non immune-mediated antibiotic drug reactions and inadvertent tolerance to alleged culprit antibiotics can be identified clinically through a systematic approach. Unfortunately, a significant proportion of antibiotic allergy labels are deficiently documented. Several studies have found empty or missing allergy description in 20 to 47% of patients with antibiotic allergy labels[14,23,25,56].

Clinical manifestations of coexisting illnesses, such as virus-mediated exanthema as happens in patients with several viral infections, especially in children, that are mistreated with antibiotics can lead to inappropriate antibiotic allergy labels, too.[2] Polypharmacy observed in many patients with true DHR may also hamper clinical identification of the culprit drug, leading to multiple drug allergy labels.

While a detailed drug history is essential in the evaluation of β-lactam allergy, it is usually insufficient to determine the presence of a drug allergy. Drug history can be imprecise in many cases as when the patient is evaluated many years after the reaction. Indeed, up to one-third of patients with vague symptoms have positive skin tests.[25] Therefore, in a significant proportion of patients, the frequency of antibiotic DHR can only be determined on the basis of a systematic workup that includes *in vivo* and *in vitro* tests. In a Spanish population, Doña et al evaluated 1471 patients with a clinical history of β-lactam allergy during a six year period (2005-2010) and after an allergy study only 305 (23%) were finally confirmed as allergic with 78% with good tolerance[10]. In a recently published systematic review including inpatients with reported penicillin allergy, penicillin skin tests were found to be negative in 95.1% of the tested patients.[57] Overall, when an allergic evaluation is performed, between 70% and more than 95% of patients considered as allergic are able to tolerate β-lactams (Table 2).

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First author	Year of Publication	Country	Population	Number of patients	β-lactam DHR confirmed (N / %)
Arnold[58]	2015	Australia	Pediatric	109	4/ 3.3%
Zambonino[59]	2014	Spain	Pediatric (1-14 yo)	783	62 / 7.9%
Doña[10]	2012	Spain	Adult	1471	305 / 23%
Bourke[60]	2015	Australia	Pediatric / Adult (>15 yo)	401	51 / 12.7%
Kopac[61]	2012	Slovenia	Pediatric / Adult (14-85 yo)	606	82 / 13.5%
Mota[62]	2016	Portugal	Pediatric / Adult	234	43 / 18%
Moreno[63]	2016	Spain	Adult	1779	509 / 28.6%

Table 2. Frequency of β-lactam allergy confirmation rate after in vivo and in vitro testing.

The variability in the proportion of true allergy is probably due to differences in the pre-test probability of DHR due to the heterogenous documentation of reactions and variability in the studied populations. The percentage of confirmed penicillin allergy is lower in children than in adults.[59,64] Also, the frequency of positive results in hospitalized patients with a documented penicillin allergy seems lower than on outpatient adult population.[57,60,63]

In conclusion, a high proportion of patients with a label of penicillin allergy have inaccurate and/or unverified allergy histories. Therefore, diagnostic workup for evaluation of β-lactam hypersensitivity should be a key component of antibiotic stewardship and can significantly improve health care quality.

The European Network of Drug Allergy (ENDA) and the Drug Allergy Interest Group in the European Academy of Allergy and Clinical Immunology (DAIG-EAACI) have developed various diagnostic algorithms for the evaluation of immediate and nonimmediate reactions to β-lactams. These algorithms are still useful in the evaluation of patients with a history of allergy to β-lactam antibiotics. [65–67]

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2. Risk assessment of antibiotic allergy labels

2.1. Can the risk of allergic reactions in patients with antibiotic allergy label be stratified by the means of clinical assessment?

Summary

- 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 **(Table 3). (A-II)**
- Patients who report having had anaphylaxis, bronchospasm, angioedema, laryngeal edema, or hypotension should be considered high-risk Type I immediate drug hypersensitivity reaction (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 (**Table 3** and **Table 4**) 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**. (A-II)**

Although most patients with reported penicillin allergy are not at risk of DHR when they are re-exposed to penicillin, use of penicillin and many other β-lactams is avoided in most patients labelled as penicillin allergic on the grounds of severe, potentially lethal reactions, exposing them to suboptimal antimicrobial therapy, which is associated with poorer outcomes.[20,30,32,34]

The most desirable scenario in patients with reported antibiotic allergy is delabelling so that they can receive first-line antibiotic therapy. The reference standard to delabel a patient with reported antibiotic allergy is to perform a complete allergological study, including skin tests and drug provocation tests if indicated.[4] Nevertheless, the approach to patients with antibiotic allergy label should be individualized, according to the risk and severity of drug reactions if subsequently exposed to the culprit or alternative, but related antibiotics. Indeed, the first step when approaching patients labeled as antibiotic allergic should be to identify those incorrectly labeled due to non immune-mediated drug adverse reactions.

Stratifyng the risk in patients in which an immune-mediated reaction cannot be ruled out is especially important in children, in whom it is not necessary to perform skin tests before drug provocation tests if presented with mild and moderate exanthema and no other accompanying symptoms.[68–70] These drug provocation tests can even be performed in a unique dose, especially in small children, in whom viral infections are the most important cause of exanthema.[71] Nevertheless, recently, several randomized and non-randomized trials in adults have shown that direct antibiotic oral challenges in “low risk” individuals can be a safe and faster alternative to the classical approach.[72–76] Moreover, safe administration of alternative β-lactam antibiotics in patients with penicillin allergy label is an often acceptable desirable outcome even if complete delabelling is not feasible. Risk stratification of patients with reported antibiotic allergy is therefore useful to guide further allergy tests, especially to decide in which patients direct antibiotic challenge can be performed and which patients can

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safely receive alternative β-lactams. Nevertheless, it should also be considered that favorable outcomes observed in studies assessing direct antibiotic challenge might confer a false of safety when making decisions in patients with a clear clinical history of allergy, since they included patients with non immune-mediated drug adverse reactions and excluded some high-risk patients such as those with as anaphylaxis.[72–76]

High-risk patients are those at significant risk of severe DHR. Some severe DHR reactions are Type I, immediate IgE mediated reactions, such as angioedema, bronchoespasm and anaphylaxis. This is why those patients who report having had anaphylaxis, bronchospasm, angioedema, laryngeal edema, or hypotension should be considered high-risk because these symptoms are compatible with a severe Type I DHR.[73,77–79] Although most authors consider hives and urticaria as high risk other authors do not.[73,80]

Other severe, reactions are non-immediate Type II-IV HSR such as Stevens-Johnsons Syndrome, Toxic Epidermal Necrolysis, Acute Interstitial Nephritis, Drug Rash Eosinophilia Systemic Symptoms (DRESS) and hemolytic anemia.[73,77]

One of the main problems when stratifying the risk of reported drug allergies is the reliability of the drug allergy history, mainly due to the time elapsed since exposure and recall bias. Several clues can indirectly help to assess the type and severity of the reported reaction. For instance, reactions that occurred immediately (from 1h to 6 hours) after the first dose suggest a Type I, IgE mediated DHR. How the reaction was treated, for example if epinephrine was administered or the patient had to be hospitalized point out severity.[73] Remote, IgE mediated allergic reactions, i.e. those occurred >10 years before, pose a lower risk than non-remote reactions because allergic antibodies decline and can disappear with time, resulting in most patients becoming skin-test negative after a decade.[81] Subsequent, documented tolerance of the culprit antibiotic should be looked upon as part of the clinical assessment. Notwithstanding, in patients with remote IgE mediated allergic reactions, drug exposure, even if well tolerated may experience a boosting response, similar to those induced by vaccines, that could lead to a reaction if subsequent exposures occur. Previous formal allergy assessments, if available, are an invaluable source to estimate patients' risk. Finally, the presence of significant cardiorespiratory comorbidity should also be considered since it may increase the risk of adverse outcomes, regardless of the severity of the reaction. All available information regarding the drug history should be used to categorize patients as low or high-risk, with regards to antibiotic DHR (**Table 3** and **Table 4**), keeping in mind that although severe reactions are unlikely in low-risk patients (1-2%) and thus, antibiotic allergy cannot be ruled out.[82].

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Non immune-mediated adverse drug reaction	Low-risk patients	High-risk patients
• Isolated gastrointestinal symptoms • High suspicion of mucocutaneous candidiasis as the sole symptom • Headache as the sole symptom • Family history of antibiotic allergy in the absence of exposure or symptoms after exposure • Rash in the absence of exposure to any antibiotic • Culprit antibiotic tolerated after the occurrence of the reaction[§]	• Mild and moderate maculopapular rash in children • Mild maculopapular rash in adults • **Other rash**: Fixed drug eruption, Contact dermatitis, Palmar exfoliative exanthema • Isolated generalized pruritus • Local infiltrated reaction to intramuscular administration in the absence of hematoma • Unknown reaction without mucosal involvement, skin desquamation or organ involvement in the infancy • Presyncope	**Type I, immediate, IgE mediated reactions** • Upper and/or lower respiratory symptoms • Urticaria • Bronchospasm • Angioedema • Collapse • Poorly described symptoms (not deemed serious) in patients with significant cardiovascular comorbidity • Need of epinephrine or hospital care during the alleged episode of allergy
		Type II-IV, delayed reactions • Moderate-severe maculopapular rash in adults • Desquamative maculopapular exanthema with or without mucosal involvement (SJS, TEN) • Drug reaction with eosinophilia and systemic symptoms • Systemic vasculitis/Serum-sickness–like reaction • Specific organ reactions (i.e. acute interstitial nephritis) • Haemolytic anaemia • Need of hospital care during the alleged episode of allergy

Table 3. Risk stratification of patients with reported antibiotic allergy. Adapted from Mohamed et al[73], Blumenthal et al[77], and Ramsey et al.[79] Patients with symptoms or diagnosis belonging to more than one risk category should be assigned to the category of the symptom / diagnosis representing the highest-risk. Immediate reaction (1-6 hours) after first administration suggests Type I, IgE mediated reaction.[§] Amoxicillin tolerance in a patient with previous reaction to benzylpenicillin does not rule out benzylpenicillin allergy and viceversa.

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Questions	Answers
1. How many years ago was the reaction?	____ years • < 1y • 1-5y • 5-10y • >10y
2. Was it a first time reaction?	• Yes • No • Unknown
3. Was it an immediate (minutes* to hours*) or delayed reaction (days*)? * Time from drug administration to reaction	• Immediate • Delayed • Unknown
4. How was it treated?	• Hospitalization • ER • Epinephrine • Others
5. With which drug did the patient experience the reaction?	_____
6. Has the patient tolerated similar medications subsequently?	• Yes • No If yes, specify: • Amoxicillin • Ampicillin • Cefuroxime • Other:_____
7. Symptoms of adverse reaction	
7.1. **Raised erythematous pruritic rash lasting <24h**	• Yes • No
7.2. **Other type of rash: mild or delayed in onset, non-hive like.**	• Yes • No
7.3. **Swelling of the tongue, mouths, lips or eyes**	• Yes • No
7.4. **Respiratory changes (Wheezing / bronchospasm)**	• Yes • No
7.5. **Hemodynamic instability, hypotension or syncope**	• Yes • No
7.6. **Lesions or ulcers involving the mouth, lips, or eyes;** skin desquamation (Stevens Johnson Syndrome (SJS), Toxic Epidermal Necrolysis (TEN), and other severe type IV reactions)	• Yes • No
7.7. **Organ involvement such as kidneys or liver** (Acute Interstitial Nephritis (AIN). Drug Rash Eosinophilia and Systemic Symptoms (DRESS) syndrome, and other severe type IV reactions)	• Yes • No • Yes • No
7.8. **Joint pains (Serum-sickness like reaction)**	
7.9. **Nausea, vomiting, diarrhea, headache, paresthesias or local injection reactions**	

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Table 4. Questionnaire to guide drug allergy history. Adapted from Blumenthal el al[77].

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

Summary

- 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 **(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.

The diagnostic approach of patients labelled as allergic to antibiotics overall, and more specifically to β-lactams, depends on the risk assessment (based on the type of reactions and patient risk factors), the need of receiving a β-lactam antibiotic, the organization of the Healthcare System, and accessibility to an Allergy Unit. Consequently, the approach to patients labelled as allergic to β-lactam may have significant country or regional variations. For instance, in the US the evaluation has been traditionally based on signs and symptoms, an approach that has the disadvantage of overdiagnosis. Characteristically, in this country a diagnostic approach was applied in patients with history of non-severe reactions, avoiding allergy testing in high-risk patients. On the other hand, in many European countries, the standard approach has consisted in clinical assessment and allergy tests, skin testing, and drug provocation tests if necessary.

Clinical assessment includes a thorough drug allergy history, including the type of symptoms presented by the patient; time elapsed between administration of the drug and the appearance of symptoms, as well as between the clinical reaction and the clinical assessment; the antibiotic involved in the reaction and presence of underlying diseases, especially viral infections.

Although clinical history has low reliability and has a limited diagnostic value, it is useful to differentiate allergic reactions from non immune-mediated adverse reactions, such as nausea, vomiting, diarrhoea, headache, or paraesthesia. These adverse reactions can be diagnosed by clinical history and do not need to be tested in an Allergy Unit.[35–37,73,75,83–87] Subsequent, documented tolerance to the culprit antibiotic (i.e. amoxicillin in patients with penicillin allergy labels) can be identified by medical record review and can lead to allergy de-labelling. To be able to differentiate between DHR and non immune-mediated reactions and to identify documented tolerance to the culprit antibiotic, all health care professionals dealing with patients with a history of β–lactam allergy, especially primary care physicians, need to be trained to obtain a structured drug allergy history.[83,88]

In recent years, there has been a growing interest in developing mathematical diagnostic models based only on data obtained from the clinical history.[82,89,90] This would permit the avoidance of high-risk procedures such as skin tests and drug provocation tests. These models try to generate a quantitative-punctuation scale based on the value of different clinical variables of each patient. If the scale result is higher than a cut-off point, the patient is diagnosed as allergic. To build these models, it is important to select the most optimal variables and this can be done based on expert opinion, which has shown low specificity (30%) and an important number of false positive results, or, alternatively, based on data obtained from patients. Noteworthy, these studies include patients with no confirmed diagnosis, low sample size, or

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are not prospectively validated, overestimating their utility.[89,90] As a result, no mathematical model based on clinical history is currently available for diagnosis.

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?

Summary

- 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.
- Skin tests are not recommended in patients with non-suggestive allergic adverse events. (**A-III**)
- It is hard to accurately estimate the sensitivity and specificity of skin tests, 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. (**A-II**)
- When the culprit antibiotic is an aminopenicillin or a cephalosporin, the reactivity is frequently specific against 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. Betablockers 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)** If no reaction is observed an intradermal test, should be performed, as they have higher sensitivity for drug-specific IgE. (**A-II**)
- In immediate hypersensitivity reactions to β-lactams readings should be taken after 15–20 minutes. (**A-II**)
- In the 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 for diagnosis of nonimmediate drug reactions to β-lactams. (**A-II**)

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- 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 made in those cases with an unknown chronology or suspicion of non-immediate reactions. (**A-II**)

In which patients is it necessary to perform skin tests?

Skin tests are the most validated method for confirming or excluding β-lactam allergy (R, moderate/strong). [4,91] Skin tests should be performed in all patients with a suggestive allergic reaction related to a previous β-lactam administration. They should be performed 4–6 weeks after the reaction to avoid false negative results due to a possible refractory period of the mast cells after the reaction (R, weak). [2] Is also important to emphasize that in immediate reactions to β-lactams, skin test reactivity is lost over time, with only 20% to 30% of patients remaining positive after 10 years. [92,93] Skin tests have to be applied depending on the suspected pathogenic mechanism [94]. Skin prick tests and intradermal tests are particularly important in order to demonstrate an IgE-dependent mechanism[4,65]. In order to demonstrate a T-cell-dependent mechanism for nonimmediate allergic reactions, patch tests and/or late reading intradermal tests should be performed. [4,66]

Skin tests are not recommended in patients with non-suggestive allergic adverse events such as gastrointestinal manifestations, headache, or paraesthesia. [2,94]

How to perform skin tests?

Skin tests for immediate reactions

For immediate drug hypersensitivity reactions to β–lactams, the prick test is recommended for initial screening. [95] Skin prick tests are performed by pricking the skin with a suitable needle through an allergic solution. If this does not cause a reaction, an intradermal test can then be done, by the injection of 0.02–0.05 ml of the drug solution. Compared to skin prick tests, intradermal tests have higher sensitivity for drug-specific IgE. [95] Both skin prick and intradermal tests are usually performed on the volar surface of the forearm. [65] Non-irritant skin tests concentrations have been recently reviewed in a position paper of EAACI-DAIG/ENDA. [91]

Reagents classically used for skin tests are the major and minor determinants of penicillin[4]. A metabolite of the β-lactam core structure of penicillins, benzylpenicilloyl (BPO), is considered the major antigenic determinant. Commercially preparations of major and minor determinants have been modified over time. In 2004, Diater (Spain) launched Diagnostic Allergy Penicillin (DAP), which included benzylpenicillin and penicilloate (as MDM -Minor determinant mixture-) and PPL -peniciloil poly L lysine-. In 2011, a purer and more stable benzylpenicilloyl octa-L-lysine (BP-OL), and the most stable minor determinant, sodium benzylpenilloate (penilloate) called “minor determinant” (MD) were commercialized as DAP® (Diagnostic Allergy Penicillin, Diater). [96] In addition, Romano described that a small percentage of β-lactam allergic patients presented negative skin tests to PPL and DM, but positive to benzylpenicillin, recommending its inclusion in the battery of skin tests. [97] However, a recent Spanish study did not find that the inclusion of benzylpenicillin to skin tests would increase the sensitivity of skin tests. [98]

Immediate hypersensitivity reactions to β-lactams can be due to reactivity to betalactam ring or the side chain. Skin tests with the major and minor determinants of benzylpenicillin appear adequate for diagnosis when benzylpenicillin is the culprit antibiotic, and the reactivity is

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against the betalactam ring. [4,91] However, when the culprit antibiotic is an aminopenicillin or a cephalosporin, the reactivity is frequently specific against the side chain. [3,63,99] In these cases, skin tests with classical determinants can be negative. At present, due to a widely use of amoxicillin it is necessary to use this antibiotic in the diagnostic evaluation of β-lactams allergy. [63,100,101] The injectable sodium salt amoxicillin and a commercial compound have been validated for diagnosing immediate reactions to amoxicillin. [101,102] Therefore, for optimal sensitivity European guidelines recommend skin tests with BPO-OL, DM, benzylpenicillin, amoxicillin and the suspected antibiotic (R, high/strong). [4,91] Histamine as a positive control and saline as negative control must be included. [65]

For diagnosis of suspected allergic reactions to cephalosporins, it is recommended that BPO-OL, DM, the suspected cephalosporin and β-lactams with similar side chains be used (R moderate/strong). [4,91] In recent years there have been reporting subjects with selective hypersensitivity to clavulanic acid. [103,104] Recently, clavulanic acid has been commercialized for skin tests. Therefore, the study of immediate allergy to β–lactams is now more complex due to the wide variety of β–lactams prescribed today.

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 (R, high/strong). [4,91]

Before skin tests, any medications that could interfere with the results of skin tests (e.g., antihistamines) should be temporarily discontinued[65]. Betablockers should be discontinued at least 24 hours, since they could interfere with the use of adrenalin if a systemic reaction occurs. The patient should be free of any infectious disease, fever or any inflammatory reactions at the time of testing. [4,65]

Skin tests in nonimmediate reactions

Intradermal skin tests and patch tests with delayed readings have been recommended for diagnosis of nonimmediate drug reactions to betalactams. [66] Intradermal skin tests with delayed readings generally have a higher sensitivity than patch test with similar specificity (R, low/weak). [105,106] Intradermal tests are performed in the same way as for immediate reactions[91]. Skin tests with BPO-OL and DM are scarcely useful (R, moderate/strong) since most nonimmediate reactions are selective to aminopenicillins. [107] Patch tests can be done with benzylpenicillin, amoxicillin, and the suspected antibiotic, using a concentration of 5-10% in petrolatum. [66]

How to interpret skin tests? Scoring

In immediate hypersensitivity reactions to β-lactams readings should be taken after 15–20 minutes. In the skin prick tests, a wheal larger than 3 mm accompanied by erythema with a negative response to the control saline is considered positive. [95] In the intradermal tests the wheal area is marked initially and 20 minutes after testing, and an increase in diameter greater than 3 mm is considered positive. [95] A late reading should be made in those cases with an unknown chronology or suspicion of non-immediate reactions; therefore, all patients should be advised of the possibility of having a late reaction within an interval of 24–48 hours or even later. In delayed intradermal readings, an infiltrated erythema with a diameter greater than 5 mm is considered as a positive result[66]. Patch tests readings should be done according to the European Environmental and Contact Dermatitis Research Group patch tests classification at 24 and 48 hours later.[3]

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Who should carry them out?

Skin tests are generally safe, but systemic reactions may occur, especially in patients with a previous history of anaphylaxis. [4] Systemic reactions have been reported in 0.7% to 11% of patients with positive skin tests results[101,108,109]. Systemic reactions occur especially when multiple β–lactams derivatives are tested simultaneously and when the highest recommended concentration is used. [108,109] Therefore, testing should be undertaken by professionals with the knowledge, experience, and training to interpret tests results and the ability to manage severe allergic reactions. [95,110]

What are the consequences of a positive result? And a negative one?

It is hard to accurately estimate the sensitivity and specificity of skin tests, since the diagnostic gold standard e.g., drug provocation test, is not performed in all the subjects due to ethical considerations. Therefore, drug provocation tests for a β–lactam positive in skin tests have been rarely performed; these patients will react in a majority of cases. The positive predictive value on very limited drug provocation tests in patients with positive skin tests has been estimated between 40% and 100%. [110,111]

The percentage of positive skin tests in patients with a clinical history of a β–lactam allergic reaction varies between less of 5% and up to 70% according to different studies. [60,63,112,113] The higher frequency of positive skin tests is shown in patients with very suggestive histories of immediate reaction, as urticaria and anaphylaxis, and also when skin tests are made just a short time after the reaction has occurred, because a long interval between the reaction and skin testing reduces the likelihood of a positive response. [4,93]

The major determinant of penicillin (PPL) has been historically the most relevant. The firsts studies found positive results in more of 70% of patients with penicillin allergy. [92,114] The use of the minor antigenic determinants of penicillin (MDM) has been also considered to be important as some studies suggested that 10-20% of patients with penicillin allergy were positive to these determinants and negative to PPL [65]. However, since the 1990s the sensitivity of penicillin skin tests using PPL and MDM has been progressively declining. [115] This is likely due to the decreasing use of parenteral penicillin, and the increased use of semisynthetic penicillins, such as aminopenicillins and cephalosporins, leading to an increase in patients with selective side-chain specific allergic reactions [63,101,115]. The sensitivity of skin tests is up to 70% if major and minor determinants of penicillin, amoxicillin and the suspected β–lactam are used [4,65]. The description of selective reactions to clavulanic acid has raised the need to include this drug in the diagnostic evaluation [103,104].

However, despite using a large panel of β–lactams, the sensitivity of skin tests in immediate reactions is not optimal. [3,4] In addition, in last decades, the sensitivity of skin tests seems to have been decreasing, diagnosing a significant percentage of patients through drug provocation tests. [101,116] Several European studies have reported that between 8.4% and 30.7% of patients with negative skin tests reacted on drug provocation tests [101,112,116]. Therefore, patients with negative skin tests require drug provocation tests in order to exclude β–lactam hypersensitivity.

For immediate reactions, sensitivity of skin tests decreases over time; the percentage of loss is even higher in the case of aminopenicillin. [93] It is unknown which percentage of cases become again positive after a new contact with a β–lactam, a phenomenon known as resensitization. Several studies indicate that between 1% and 27.9% of subjects may be re-sensitized after β–lactam administration. [63,112,117] For this reason, in patients with a clear history of having had an immediate reaction after the administration of a β–lactam derivative, which have negative skin and in vitro tests and good tolerance in drug provocation test, a

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reevaluation after one month is strongly suggested [2,63,65], particularly if the reaction occurred more than one year before.

The sensitivity of skin tests in nonimmediate reactions is lower than in immediate reactions, and it is ranging from 10% to 30%. [105,106] Unlike in immediate reactions, in non-immediate reactions sensitization especially to aminopenicillins is long-lasting. [66]

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

Summary

- The drug provocation test is considered to be 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.
- Drug provocation tests should be done only after performing skin tests (**A-III**). Nevertheless, in patients with severe infections and a 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.

A drug provocation test, also referred to as drug challenge, graded challenge, or test dosing, is the gold standard for the identification of the drug eliciting allergy (moderate/strong). [2] The EAACI-DAIG/ENDA defines drug provocation tests as "the controlled administration of a drug in order to diagnose drug hypersensitivity reactions". The drug provocation test can be harmful and thus should be performed after individual risk-benefit evaluation. The ENDA position paper specifies two main indications for drug provocation tests with the suspected compounds: 1 to exclude hypersensitivity in non-suggestive histories of drug hypersensitivity; 2 to establish a firm diagnosis in suggestive histories of drug hypersensitivity with negative, non-conclusive, or non-available allergy tests. [118] A positive drug provocation test result optimizes allergen avoidance, while a negative one allows a label of drug hypersensitivity to be removed. [118] For these reasons, drug provocation tests are often carried out to exclude a diagnosis of hypersensitivity to β-lactams when other allergic tests are negative. [4]

In what cases is it necessary to perform a drug provocation test?

The drug provocation test is considered to be the gold standard for establishing the diagnosis of drug hypersensitivity as well as for assessing tolerance to potentially cross-reactive drugs. [4,65,118] According to several European studies, up to one third of patients allergic to penicillins have a negative result in skin tests[101,116]. Therefore, patients with negative skin tests will require a drug provocation to confirm or exclude betalactam allergy. [4]

The drug provocation test should be done only after performing skin tests, and when these are negative[4]. No skin tests nor drug provocation became necessary in patients with non-suggestive allergic adverse events as commented above. However, drug provocation tests could be recommended, without skin tests, in children with a history of mild cutaneous reactions coinciding with the administration of penicillins, since most of them are viral exanthemas. Several recent studies have demonstrated the safety of this approach in children who have not presented anaphylactic reactions or non-immediate severe cutaneous reactions[59,69,119,120].

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How and under what conditions?

Drug provocation tests should be performed in centers in which equipment, supplies, and personnel are present to manage serious reactions, and that personnel are well trained and experienced in performing this procedure[118]. The route of administration depends on the suspected drug, which should in principle be administered in the same way as it was given when the initial reaction occurred. However, all the guidelines agree that the oral route is preferred whenever possible (R, moderate). Drug provocation test is not well standardized. Drug provocation protocols can vary between centers, especially in regard to number of steps and time intervals between doses increases[59,119,121,122]. The drug provocation test is usually performed in a single blind placebo-controlled manner by escalating doses with intervals of 30 to 90 minutes[3]. The drug provocation test should stop and as soon as symptoms occur[118]. The variation in the protocols depends on several factors including the type of reaction (immediate *vs* nonimmediate reactions), its severity (anaphylaxis vs mild reactions) or, the population involved (children *vs* adults). Usually, the drug provocation test starts with a low dose; carefully increasing this, up to the full therapeutic dose. [118] However, when or how complete the protocol and declare negative result of drug provocation test is controversial. Some groups accept a full therapeutic dose to consider negative result, [121] while others prone prolonged drug provocation tests [59] or even full therapeutic course to ensure tolerance. [122] In case of non-immediate reactions could be appropriate the administration during several days at a therapeutic dose, to confirm that delayed reactions appeared. [66] Some authors recommend a full dose to exclude allergy in non-suggestive allergic reactions[123].

Drug provocation tests can be used to assess cross-reactivity among β-lactam antibiotics[4,66]. Patients with hypersensitivity to β-lactams may be allergic to several antibiotics, to a subgroup with similarities of side chains, or simply to a single beta-lactam. [4] In our country, where more than 50% of reactions to β-lactams are associated with amoxicillin with or without clavulanic acid, a significant percentage of patients have selective responses to side chain. For example, according to the diagnostic algorithms proposed by EAACI-DAIG/ENDA, the drug provocation test can be useful to confirm tolerance to benzylpenicillin if skin tests to the major and minor determinants of benzylpenicillin are negative. [4]

The drug provocation test is not recommended in pregnancy, in patients with uncontrolled asthma, or with uncontrolled underlying chronic disease (including heart disease that contraindicated the use of adrenaline). [118] The drug provocation test is contraindicated in in patients with a history of severe cutaneous reactions such as DRESS, Stevens-Johnson syndrome or TEN. [118]

What are the consequences of a positive test? And of a negative result?

The drug provocation test is considered the gold standard for diagnosis of drug hypersensitivity. [2] Therefore, a positive drug provocation contraindicates the use of culprit drug. The negative predictive value of drug provocation test in immediate hypersensitivity reactions is high. [124] In a European multicenter study the negative predictive value for β-lactam drug provocation test was 94.1%. [124] The high predictive value of drug provocation test has been found in a USA study where reactions were reported in 4.5% of patients re-exposed to penicillin after drug provocation test. [123]

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

Summary

- Drug desensitization (DD) is indicated when the antibiotic is irreplaceable or when the drug if more effective than the alternatives. (**A-III)**
- DD should generally not be performed in patients at increased risk of serious 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 have an extremely high level of risk and high complexity that must be conducted by an allergist and nursing staff with specific training in an hospital location where patients who develop a severe reaction can be treated. (**A-III**)

When is it necessary to perform a desensitization?

Desensitization is defined as the induction of a state of unresponsiveness to a compound responsible for a hypersensitivity reaction. Before performing any desensitization procedure, and individual risk-benefit evaluation has to be performed. [125,126]

Drug desensitization (DD) is indicated when the antibiotic is irreplaceable (for example, penicillin in pregnant women with syphilis[127,128] or when the drug is more effective than the alternatives (such as, specific antibiotic in cystic fibrosis[129–132]; antituberculosis drugs; [133,134] sulfonamides in HIV-positive patients for *Pneumocystis jirovecii* treatment or prevention[126,135,136], bone marrow transplantation[137,138] or lung transplantation. [139]

DD should generally not be performed in patients at increased risk of serious complications due to significant comorbidity, such as patients with uncontrolled asthma, hemodynamically unstable or uncontrolled cardiac diseases.

DD 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 like Stevens-Johnson Syndrome (SJS), Toxic Epidermal Necrolysis (TEN), Drug-induced Hypersensitivity Syndrome (DiHS) or Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS). [126,140]

DD should also be considered after a careful individual risk/benefit evaluation in patients treated with beta-blockers, patients who have suffered severe anaphylaxis and patients with hepatic, renal or other diseases, in whom exposure might provoke a potentially harmful complication. [125,126,141–143] DD can be done even in pregnant patients and if necessary the use of epinephrine in the course of an anaphylaxis had little to no immediate effects on the fetus. [144]

How to perform a desensitization?

DD have an extremely high level of risk and high complexity, either due to the potential severity of the reaction or to the increased risk associated with comorbidity. These procedures must be carried out in an hospital location where patients who develop a severe reaction can be treated. Material for immediate cardiopulmonary resuscitation (CPR) must be readily available if necessary as well as access to an Intensive Care Unit, Postoperative Recovery Unit or Emergency Department if DD is not of carried out in such units as it is recommendable at least for very high-risk DD. The procedure must be conducted by an allergist with specific training and nursing staff with experience. During the procedure, which can last up to more than 4 or 5 hours, the patient must remain under the supervision of the health care personnel. These

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requirements are specified in the document Safety and Quality Recommendations in Allergy Medicine (Spanish acronym, RESCAL), recently published by the Spanish Society of Clinical Allergology and Immunology (SEAIC). [145]

Desensitization procedures should take into account available protocols, and it is preferable to use protocols applied in samples larger than 10 patients. [125] Both oral and parenteral routes can be used in the procedure and it seems that both can be equally effective. For drugs that can be administered both orally and parenterally, the oral route seems to be safer, easier, and less expensive; however, this is not always advisable or feasible. [125] There are protocols that combine oral and parental routes of administration; and other routes as inhaled have been described. [146]

Immediate reactions:

A desensitization protocol for immediate reactions should be performed in an allergic patient requiring the culprit or another antibiotic from the same group with high cross-reactivity to which there is evidence of IgE-mediated allergy. In β-lactam allergy, cephalosporin desensitization should also be considered in a skin-test positive, penicillin-allergic patient requiring a cephalosporin to which the patient is skin test-positive; and also, penicillin desensitization should be considered in a cephalosporin-allergic patient requiring a penicillin to which the patient is skin-test positive. [147]

In published protocols, the starting dose ranges from 1/10,000 to 1/100 of the full therapeutic dose. The starting dose should be determined by taking into account the severity of reaction: in patients with histories of severe anaphylaxis, the initial dose should be between 1/1,000,000 and 1/10,000 of the full therapeutic dose. In patients with a positive skin test, the starting dose can be determined on the basis of the endpoint titration. The use of premedication also varies in published protocols. [125]

Most published protocols increase doses by doubling every 15–20 minutes over the course of several hours until the therapeutic dose is reached. If a reaction occurs during DD, it should be treated and when the patient is stabilized the DD should continue (usually repeating the last dose that was last tolerated) until complete the desensitization. Complete successful DD is achieved when the patient reaches the full therapeutic dose and tolerates repeated administrations of such dose until the therapeutic course is completed. [125]

Both oral and parenteral routes can be used in the procedure and it seems that both can be equally effective and safe, but for immediate reactions DD the intravenous route is used more frequently in the literature. [125]

Several DD for immediate reactions have been described for almost every group of antibiotics: β-lactams (penicillin, [127,148–151] cephalosporins, [150,152] monobactams, [146] and carbapenems [153,154]), quinolones, [129,155,156] macrolides, [157–160] tetracyclines, [161–163] nitroimidazoles, [164] aminoglycosides, [165] glycopeptides, [166,167] oxazolidinones, [168–170] or antituberculosis drugs. [171–175]

Nonimmediate reactions:

A desensitization protocol for nonimmediate reactions should be performed in a patient who developed a delayed-type hypersensitivity reaction requiring the culprit or another antibiotic from the same group with high cross-reactivity. Delayed drug reactions have a variety of manifestations and the pathways by which they occur have not been fully elucidated, and there is no evidence of IgE-mediated allergy [126,140]. As previously mentioned DD are absolutely contraindicated in severe delayed reactions.

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In published delayed DD protocols, the starting dose ranges from 1/1,000,000 to 1/8 of the full therapeutic one. [126,140] The use of premedication also varies in published protocols. The dosing interval for DD on nonimmediate reactions should be chosen according to the drug and the previous reaction of the patient. In patients with exanthems, most often slow protocols with gradually increasing doses have been used, which last from hours, to days to several weeks. Faster protocols have the advantage over slower ones that full therapeutic doses of the drug are reached within a few hours or one to two days, treating earlier the infection and with less chance of generating antibiotic resistance, but they have higher risks and failure rates. [126,140]

Both oral and parenteral routes can be used in the procedure and it seems that both can be equally effective and safe, but for nonimmediate reactions DD the oral route is used more frequently in the literature. [126,140]

Several DD for nonimmediate reactions to sulfonamide [125,126,176] in HIV and non-HIV patients have been described, but also for other antibiotics as β-lactams, [130–132] quinolones, [177,178] tetracyclines, [132] nitroimidazoles, [179] lincosamides, [180] or antituberculosis drugs. [134,181]

What implications does it have for the use of the antibiotic to which a patient has been desensitized?

Desensitization induces a temporary tolerant state, which can only be maintained by continuous administration of the medication. When the drug is discontinued, tolerance is lost over hours or days, because the desensitized state will only last for up to 4-5 half-lives (t½) of the drug[182,183]. Therefore, when the DD was successful the antibiotic should not be suspended until the therapeutic course is completed. After that, sensitivity is assumed to have returned, and future therapeutic courses will require repeated desensitization protocols.

In certain settings, reactions can be noted with delayed redosing after as little as 2 half-lives (t½), but reactions are also common in desensitized individuals even with continual dosing. [183]

There is no evidence that a change in the administration route during the treatment course (e.g., intravenous to oral) is problematic. [125]

It is possible to sustain a state of ongoing tolerance by daily administration of the drug, such as penicillin in patients with recurrent infections. [184,185] Also, in the setting of long-acting benzathine penicillin, patients appear to be capable of maintaining a desensitized state for as long as 3 weeks and repeat desensitization is not needed for subsequent injections.[127]

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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?

Summary

- In patients with history consistent with non immune-mediated adverse events to penicillins or cephalosporins, β-lactams can be administered unrestrictedly (**Table 3**). **(A-II)**
- To decide which β-lactam to choose in β-lactam allergy labelled patients, it is important to consider the chemical structure of the β-lactam responsible for the reaction and 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 (**Table 5**). 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, as well as 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 tests 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 (**Table 5 and Table 6**). **(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 history of severe Type II-IV drug hypersensitivity reactions, β-lactams should be avoided if at all possible. **(A-III)**

β-lactam antibiotics are chemical compounds that share a common structure that consists of a 4-member β-lactam ring that, in penicillins, is connected with a 5-member thiazolidine ring and, in cephalosporins, with a 6-member dihydrothiazine ring. Penicillins have one side chain (R1), and cephalosporins have two of them (R1 and R2). The substitution at the R1 and R2 side chains results in a large number of antibiotics with different chemical structures and antimicrobial activity. Even minor changes in the chemical structure can be recognized as different and discriminated by the immunologic system. This has relevant clinical implications as patients may be allergic to one group of β-lactams and tolerate others.[3] In that sense, to decide which alternative drugs to choose, it is important to consider the chemical structure of the β-lactam responsible for the reaction and the alternative one, as well as the type of reaction, as tolerance may differ between immediate and nonimmediate ones. The description of alternative β-lactams comes from the safest to the riskiest, according to cross-reactivity rates. [186]

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Monobactams and carbapenems are the safest option for adults and children allergic to penicillin or cephalosporin. Different studies have shown a very low rate of cross-reactivity between penicillins and aztreonam (0%)[187] or carbapenems (0.87%)[187–196] for immediate and non-immediate reactions [197,198]. Monobactams are a safe alternative that can be administered to patients allergic to penicillin and cephalosporin, except for those allergic to ceftazidime because both structures share the same side chain at R1 position.[199] Regarding carbapenems, although it has been classically recommended to perform skin tests and drug provocation tests before administration [190,191,200], due to the low cross-reactivity with penicillins, several authors propose unrestricted use in patients with low-risk reported penicillin allergy or use after a controlled drug-test in patients with high-risk reactions (**Table 5** and **Table 6**). [74,78,87,201–210]

Cephalosporins have been used in patients allergic to penicillin, observing cross-reactivity from 0%[69,193,197,211–216] to over 30%[216,217] in patients with immediate reactions, and from 20%[197] to 30%[218] in patients with nonimmediate reactions. Penicillins are also an alternative in patients allergic to cephalosporins, with positivity ranging from 8%[219] to 25%[220] in patients with immediate reactions. These significant differences in cross-reactivity are mainly due to variations in the chemical structure of the involved penicillin and cephalosporin, as the similarity on the R1 structure is more frequently related to cross-reactivity between penicillin and cephalosporins.[216,218,220,221] As a rule, differences in side chains between penicillins and cephalosporins are more marked in the case of higher cephalosporins generations, implying a lower risk of cross-reactivity (**Table 4**). Nevertheless, cefazolin, a broadly used, parenteral first generation cephalosporin is an exception to this rule since similarity score of cefazolin with penicillins is low, ranging from 0.032 (piperacillin) to 0.176 (penicillin G).[186] When prescribing a penicillin to patients allergic to cephalosporin, or a cephalosporin to patients allergic to penicillin, antibiotics with the most different structure of the side chain at the R1 position should be selected whenever possible (**Figure 1A and 1B**).

The classical strategy consists in performing skin tests and, if negative, a drug provocation test to confirm tolerance. [4,200,222] Nevertheless, several authors propose a more straightforward approach in hospitalized patients with moderate and severe infections: administering cephalosporins to penicillin allergic patients without performing skin tests, after a drug test procedure. [74,78,87,201–208,223–225] As a matter of fact, Blumenthal et al found that only 14/514 (2.7%) of penicillin allergic labeled patients (IgE or unknown history) that were challenged with third, fourth or fifth generation cephalosporins subsequently had a drug hypersensitivity reaction. [74] It is important to take into account that this recommendation comes from North America population where the rate of penicillin allergy false positive labelling is extremely high. Similarly, several studies found that the use of cefazolin as surgical prophylaxis in patients with penicillin allergy label without penicillin skin test, in the absence of previous documented or suspected anaphylaxis, was not associated with significant adverse reactions. [29,226–230] Moreover, Blumenthal et al found that 17/18 (94.6%) patients with ongoing suspected non-severe, non-immediate hypersensitivity reactions to nafcillin that were changed to cefazolin without performing penicillin skin tests had their symptoms resolved. [231] Therefore, the use of cephalosporins in patients with penicillin allergy after a controlled drug test may be an acceptable approach after a favorable risk / benefit analysis in hospitalized patients with moderate and severe infections, if skin testing is not feasible (**Table 5** and **Table 6**). Nevertheless, in patients with suspected penicillin or cephalosporin allergy, allergy label should not be removed without a standardized allergologic work-up and, thus, they should be referred to an allergist for delabeling purposes.

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Finally, the riskiest procedure is to prescribe alternative penicillins to a patient who is allergic to penicillin, or an alternative cephalosporin to a patient allergic to cephalosporin. Amoxicillin, itself or combined with clavulanic acid, is the penicillin involved most frequently in reactions. Data mainly coming from Spain indicate that patients can be allergic to amoxicillin and have good tolerance to benzylpenicillin [232], or be allergic to clavulanic and have good tolerance to amoxicillin and benzylpenicillin. [103,232] This has been also described in nonimmediate reactions. [105,107] However, 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.[221,233] The recommendation for prescribing an alternative penicillin is using benzylpenicillin in patients allergic to amoxicillin, after skin tests and drug provocation tests. [4,200] Again, in this case several authors propose direct penicillin / amoxicillin challenge without previous skin testing in low-risk patients. [69,70,72–76]

Regarding the administration of cephalosporins to patients allergic to this group of drugs, it is important to consider a recent study indicating that, basing on their chemical structure, three groups were identified: group A, which included those with a methoxyimino group in their R1 side chains (i.e., cefuroxime, ceftriaxone, cefotaxime, cefodizime, and cefepime) plus ceftazidime, group B, which was composed of aminocephalosporins; and group C, which included cephalosporins other than those belonging to groups A and B. It is important to follow this classification during the process of cepahalosporin selection. [234] The general recommendation for prescribing an alternative cephalosporin is using a cephalosporin from a different group after performing skin tests and drug provocation tests. [4]

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Cephalosporins		Type of penicillin allergy			
		IgE		T-cell	
Generation	**Name**	**n/N**	**AR**	**n/N**	**AR**
First	Cephalexin	40/310	12.9 (9.6-17.1)	57/383	14.9 (11.7-18.8)
	Cefadroxil	75/287	26.1 (21.4-31.5)	20/270	7.4 (4.8-11.2)
	Cephalothin	8/128	6.3 (2.7-11.9)	1/56	1.8 (0.3-11.6)
	Cefazolin	0/47	0.0 (0.0-7.5)	1/26	3.8 (0.0-19.6)
	Cefatrizine	NA	NA	1/56	1.8 (0.3-11.6)
	Cephaloridine	NA	NA	0/17	0.0 (0.0-19.5)
Second	Cefamandole	22/418	5.3 (3.5-7.9)	1/56	1.8 (0.3-11.6)
	Cefaclor	41/282	14.5 (10.9-19.2)	49/397	12.3 (9.5-16.0)
	Cefuroxime	7/490	1.1 (0.2-5.8)	7/423	0.5 (0.0-8.0)
	Cefprozil	NA	NA	3/39	7.7 (1.6-20.9)
	Cefpodoxime	NA	NA	1/71	1.4 (0.0-7.6)
Third	Ceftazidime	2/433	0.3 (0.0-4.7)	NA	NA
	Cefotaxime	5/380	1.3 (0.6-3.1)	0/56	0.0 (0.0-6.4)
	Cefixime	0/39	0.0 (0.0-9.0)	2/285	0.7 (0.2-2.8)
	Ceftriaxone	12/474	2.5 (1.4-4.4)	1/367	0.2 (0.0-9.5)
	Ceftibuten	NA	NA	0/153	0.0 (0.0-2.4)
Fourth	Cefepime	1/285	0.3 (0.0-10.3)	NA	NA

Table 5. Cross-reactivity of cephalosporins in patients with penicillin allergy. NA: does not apply. n: number of positive skin tests. N: number of tested patients. AR: absolute risk.

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Candidate antibiotic		Penicillin allergy risk stratification			
		Non-allergic reaction	**Low-risk allergic reaction**	**High-risk allergic reaction (IgE mediated)**	**High-risk allergic reaction (Type II-IV DHR)**
Penicillins	Benzylpenicillin	Unrestricted	Full allergy work-up	Full allergy work-up	Avoid β-lactams. If absolutely needed. referral to an allergist
	Amoxicillin				
	Cloxacillin / Flucloxacillin / Nafcillin				
	Piperacillin				
Cephalosporins	Cephalexin	Unrestricted	Full allergy work-up	Full allergy work-up	Avoid β-lactams. If absolutely needed. referral to an allergist
	Cefazolin		Controlled drug challenge	Controlled drug provocation after an individualized risk-benefit analysis	
	Cefuroxime		Controlled drug challenge	Full allergy work-up	
	Ceftriaxone		Controlled drug challenge	Controlled drug provocation after an individualized risk-benefit analysis	
	Cefotaxime				
	Ceftazidime				
	Cefixime				
	Cefditoren				
	Cefepime				
	Ceftolozane				
	Ceftaroline				
Carbapenems	Imipenem	Unrestricted	Controlled drug challenge	Controlled drug provocation after an individualized risk-benefit analysis	Avoid β-lactams. If absolutely needed. referral to an allergist
	Meropenem				
	Ertapenem				
	Doripenem				
Monobactam	Aztreonam	Unrestricted	Unrestricted	Unrestricted	Unrestricted

Table 6. Recommended strategies to use β-lactams in hospitalized patients with penicillin allergy label. These recommendations are not applicable to patients with suspected immune-mediated reactions to cephalosporins.

A

	Cephalosporins	Penicillins						
		Penicillin G	Penicillin V	Ampicillin	Amoxicilin	Cloxacillin	Piperacilin	Ticarcillin
1st	Cefadroxil	0,371	0,220	0,618	1,000	0,179	0,060	0,333
	Cephalexin	0,592	0,333	1,000	0,618	0,208	0,043	0,371
	Cefazolin	0,176	0,110	0,099	0,088	0,078	0,032	0,088
	Cefradine	0,344	0,200	0,517	0,371	0,155	0,082	0,263
	Cephalothin	0,563	0,321	0,337	0,295	0,154	0,035	0,268
	Cefatrizine	0,371	0,220	0,618	1,000	0,179	0,060	0,333
	Cephaloridine	0,563	0,321	0,337	0,295	0,154	0,035	0,268
2nd	Cefaclor	0,592	0,333	1,000	0,618	0,208	0,043	0,371
	Cefoxitin	0,330	0,245	0,211	0,180	0,148	0,043	0,180
	Cefprozil	0,371	0,220	0,618	1,000	0,179	0,060	0,333
	Cefuroxime	0,304	0,220	0,274	0,248	0,320	0,044	0,228
	Cefamandole	0,592	0,333	0,714	0,485	0,208	0,043	0,412
3rd	Cefixime	0,110	0,110	0,098	0,157	0,219	0,084	0,138
	Cefotaxime	0,141	0,090	0,138	0,142	0,249	0,049	0,182
	Ceftazidime	0,092	0,087	0,092	0,142	0,198	0,064	0,127
	Ceftriaxone	0,141	0,090	0,138	0,142	0,249	0,049	0,182
	Cefpodoxime	0,141	0,090	0,138	0,142	0,249	0,049	0,182
	Cefdinir	0,147	0,083	0,143	0,156	0,207	0,047	0,238
	Ceftibuten	0,167	0,127	0,148	0,165	0,237	0,079	0,165
4th	Cefepime	0,141	0,090	0,138	0,142	0,249	0,049	0,182

No-similarity — Identical

0.000 — 1.000

B

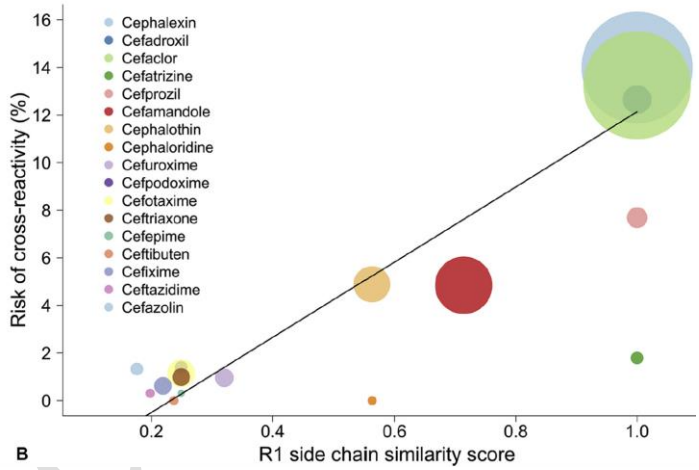

Figure 1. Similarity between R1 side chains of penicillins and cephalosporins and its association with the risk of cross-reactivity. A, Heatmap of similarities between R1 side chains. Score of "0" corresponds to no similarity and "1" to identical side chains. **B, Association between the AR of cross-reactivity and R1 side chain similarity.** Weights are inversely proportional to the estimated standard error of the AR of cross-reactivity obtained for each meta-analysis. From Picard et al.[186]

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?

β-lactams are the first antimicrobial choice for the most severe infectious syndromes due to their bactericidal mechanism of action, their safety profile and the broad experience of use with these drugs. When patients labeled with a non-confirmed penicillin and / or b-lactam allergy benefits from antimicrobial therapy and a β-lactam is of first choice for the infectious condition, they should be assessed systematically following a clinically based, risk-stratifying approach. Consequently, patients should be categorized as having had: 1) a non-immune mediated adverse drug reaction, 2) a low-risk immune mediated drug reaction and 3) high-risk immune mediated drug reaction (**Table 3**).

Patients considered to have had a non-immune mediated adverse drug reaction may receive any β-lactam without restrictions (**A-III**). Patients categorized as having had a low-risk or a high-risk immune mediated drug reaction should not receive any β-lactams, with the exception of aztreonam before being systematically assessed, what comprises sequentially performing skin tests and drug provocation tests by experienced staff (**A-III**). Nevertheless, carbapenems might be used after a controlled drug challenge in the absence of skin tests in patients with high-risk immune mediated drug reactions with severe infections if skin testing is not feasible at short term, as carbapenems have very low cross-reactivity with penicillins (<1%) (**B-III**). Similarly, in patients with low-risk immune mediated drug reaction to penicillins, third generation cephalosporins and cefazolin might be used after a controlled drug challenge in patients with severe infections if skin testing is not rapidly feasible (**B-III**) (**Table 6**). Patients with low-risk or high-risk immune mediated drug reaction to β-lactams who receive a β -lactam in the absence of fully systematically approach should be referred to an allergist before delabeling (**A-III**).

Non β-lactams frequently have a worse efficacy and safety profile and should be chosen considering the antibacterial spectrum needed, as well as the pharmacokinetic / pharmacodynamic properties required to adequately treat the infectious syndrome. The likelihood of antimicrobial resistance should be assessed taking into account epidemiological data and individual patient risk factors (**A-III**).

Table 7 summarizes recommended antibiotic choices for the most prevalent infectious syndromes in patients labelled with a possible penicillin allergy.

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Syndrome	Cause	Low-risk immune mediated drug reaction	High-risk immune mediated drug reaction or confirmed allergy[§]
Odontogenic infections	Polymicrobial	• Clindamycin 300-600 mg q8h PO If severe enough to warrant hospitalization: • Ceftriaxone[†] 2 g q24h IV + metronidazole 500 mg q8h IV **OR** • Clindamycin 600-900 mg q8h IV Duration: 5d	• Clindamycin 300-600 mg q8h PO • Clindamycin 600-900 mg q8h IV Duration: 5d
Acute pharyngitis	*Streptococcus* grupo A (SGA)	• Azithromycin 500 mg q24h PO (5d) **OR** • Clindamycin 300-600 mg q8h PO (10d) If severe enough to warrant hospitalization: • Ceftriaxone[†] 2 g q24h IV 10d **OR** • Clindamycin 600-900 mg q6h IV 10d	• Azithromycin 500 mg q24h PO (5d) **OR** • Clindamycin 300-600 mg q8h PO (10d) **OR** If severe enough to warrant hospitalization: • Clindamycin 600-900 mg q6h IV 10d

Parapharyngeal, sublingual or submaxillary abscess. **Ludwig's angina**	Polymicrobial	• Ceftriaxone† 2 g q24h IV + metronidazole 500 mg q8h IV **OR** • Clindamycin 600 mg q8h IV + aztreonam 1-2 g q8h IV Duration depends on the quality of source control	• Clindamycin 600 mg q8h IV + aztreonam 1-2 g q8h IV Duration depends on the quality of source control)
Epiglottitis (adults)	*H. influenzae, S. pneumoniae, S. pyogenes, S. aureus, N. meningitidis.*	• Levofloxacin 750 mg q24h PO If severe enough to warrant hospitalization: • Ceftriaxone † 2 g q24h IV **OR** • Levofloxacin 750 mg q24h IV Duration: 5-7d if favorable course	• Levofloxacin 750 mg q24h PO Duration: 5-7d if favorable course
Acute sinusitis	*S. pneumoniae, H. influenzae, M. catarrhalis*, vírus	• Levofloxacin 750 mg q24h PO If severe enough to warrant hospitalization: • Ceftriaxone† 2 g q24h IV **OR** • Levofloxacin 750 mg q24h IV	• Levofloxacin 750 mg q24h PO If severe enough to warrant hospitalization: • Levofloxacin 750 mg q24h IV

		Duration: 5 d if favorable course	Duration: 5 d if favorable course
Acute otitis media	*S. pneumoniae, H. influenzae, M. catarrhalis*, virus	• Azitromycin 500 mg q24h PO (3d) • Levofloxacin 750 mg q24h PO if failure to improve If severe enough to warrant hospitalization: • Ceftriaxone† 2 g q24h IV **OR** • Levofloxacin 750 mg q24h IV Duration: 5 d if favorable course	• Azitromycin 500 mg q24h PO (3d) **OR** • Levofloxacin 750 mg q24h PO if failure to improve If severe enough to warrant hospitalization: • Levofloxacin 750 mg q24h IV Duration: 5 d if favorable course
Malignant otitis externa	*P. aeruginosa*	• Ciprofloxacin 400 mg q8h IV/ 750 mg q12h PO (7-14d. If bone is involved, prolong duration as in osteomylelitis) If course is not favorable: • Ceftazidime† 2g q8h IV **OR** • Meropenem† 1-2g q8h IV Duration: 7-14d	• Ciprofloxacin 400 mg q8h IV/ 750 mg q12h PO (7-14d if osteomielitis)

Orbital cellulitis	*S. pneumoniae, H. influenzae, M. catarrhalis*, *S. aureus*, anaerobios, *S. pyogenes*	• Clindamycin 300 mg q8h PO If severe enough to warrant hospitalization: • Ceftriaxone† 2 g q24h IV ± clindamycin 600 mg q8h IV **OR** • Vancomycin 15-20 mg/Kg q12h IV + levofloxacin 750 mg q24h IV ± clindamycin 600 mg q8h IV Duration: 7-14d	• Clindamycin 300 mg q8h PO If severe enough to warrant hospitalization: • Vancomycin 15-20 mg/Kg q12h IV + levofloxacin 750 mg q24h IV ± clindamycin 600 mg q8h IV Duration: 7-14d
Endophthalmitis	Coagulase negative Staph, *S. aureus, P. acnes.* In postraumatic endophthalmitis, consider *B. cereus*, *P. aeruginosa,*hongos	Intravitreal: • Ciprofloxacin 2 mg and vancomycin 1 mg (each one diluted in 0.1 ml normal saline). Systemic: • Ceftazidime† 2 g q8 h IV + linezolid 600 mg q12h IV/VO. **OR** • Aztreonam 2 g q8 h IV + linezolid 600 mg q12h IV/VO.	Intravitreal: • Ciprofloxacin 2 mg and vancomycin 1 mg (each one diluted in 0.1 ml normal saline). Systemic: • Aztreonam 2 g q8 h IV + linezolid 600 mg q12h IV/VO. Duration: 7-14d

		Duration: 7-14d	
Acute bacterial meningitis	*Streptococcus pneumoniae, Neisseria meningitidis, Haemophilus influenzae.* **> 50 yo:** + *Listeria monocytogenes, S. agalactiae.* **Immunocompromised:** +*Listeria monocytogenes*, *enterobacteriacceae*. **Less frequent:** *Brucella sp*, TBC.... **CSF leak:** igual. If high risk for *P. aeruginosa* and/ or *S. aureus* treat as nosocomial (see below).	• Vancomycin 40-50 mg/kg/day IV (divided in 2-3 doses) + ceftriaxone† 2g q12h IV **OR** • Vancomycin 40-50 mg/kg/day IV (divided in 2-3 doses) + aztreonam 2 g q8h IV. **>50 yo or inmunocompromised:** • add cotrimoxazole IV 15-20 mg (trimethropim)/kg/day IV divided in 4 dosis Duration: according to aetiology (5 days if *Neisseria* sp., 10 days if pneumococci, 7-14 d if gram negatives, ≥21 d if Listeria)	• Vancomycin 40-50 mg/kg/day IV (divided in 2-3 doses) + aztreonam 2 g q8h IV. **>50 yo or inmunocompromised:** • add cotrimoxazole IV 15-20 mg(trimethoprim)/kg/day divided in 4 doses. Duration: according to aetiology (5 days if *Neisseria* sp., 10 days if pneumococci, 7-14 d if gram negatives, ≥21 d if Listeria)

Meningitis (postsurgical) or ventriculitis (shunt associated; either internal or external)	*Staphylococcus* spp., *enterobacteriacceae*, *P. aeruginosa.*	• (Vancomycin 30-45 mg/kg/d IV, in 2-3 doses OR linezolid 600 mg q12h IV/PO) + Ceftazidime† 2 g q8 h IV OR • (Vancomycin 30-45 mg/kg/d IV, in 2-3 doses OR linezolid 600 mg q12h IV/PO) + meropenem† 2 g q8 h IV Duration: 7-14d	• (Vancomycin 30-45 mg/kg/d IV, in 2-3 doses OR linezolid 600 mg/12h IV/PO) + aztreonam IV 2 g q8h IV Duration: 7-14d
Brain abcess	***Mixed****: Streptococcus virid ans,* anaerobes (*Enterobacterales* if inner ear associated) **Inmunocompromised*:*** *Li steria* sp *(*meningitis + abscess*), Nocardia* sp *(*lung abcess*),* Toxoplasma *(multiple abcess in RI), fungi.*	• Ceftriaxone† 2 g q12h IV + metronidazole 500 mg q8h IV **>50 yo or inmunocompromised:** • add cotrimoxazole IV 15-20 mg trimethoprim/kg/day IV divided in 4 dosis. Duration: according to source control.	• Vancomycin 30-45 mg/kg/d IV, in 2-3 doses or linezolid 600 mg q12h IV/PO + aztreonam 2 g q8h IV + metronidazol 500 mg q6-8h IV. Duration: according to source control.

COPD exacerbation	**50%**: *S. pneumoniae*, *H. influenzae, M. catarrhalis* **30%**: Virus. **20%:** *M.pneumoniae, C. pneumoniae.*	• Levofloxacin 750 mg q24h PO (3-5d) **OR** • Azitromycin 500 mg q24h PO (3d) If severe enough to warrant hospitalization: • Ceftriaxone† 2 g q24h IV **OR** • Ceftazidime† 2 g q8h IV (if risk factors for *P. aeruginosa*) **OR** • Levofloxacin 750 mg q24h IV Duration: 3-5 d	• Levofloxacin 750 mg q24h Duration: 5-7 d
Lung abcess or aspiration pneumonia	Anaerobes	• Ceftriaxone† 2 g q24h IV ± clindamycin 600 mg q8h IV Duration: according to source control.	• Clindamycin 600 mg q8h IV + aztreonam 2 g/8h IV (until drainage)
Community-acquired pneumonia	*S.pneumoniae, H.influenzae, Mycoplasma pneumoniae*, *enterobacteriacceae*	• Levofloxacin 750 mg q24h PO (3-5d) If severe enough to warrant hospitalization:	If severe enough to warrant hospitalization: • Levofloxacin 750mg q24h IV Duration: 5 d

		• Ceftriaxone† 2 g q24h IV +/- azithromycin 500 mg q24h PO **OR** Levofloxacin 750 mg q24h IV Duration: 5 d	
Nosocomial pneumonia	**- Early (<5º days of admission)**: *S.pneumoniae, H.influenzae, enterobacteriacceae*, *S. aureus.* **- Late (>5º days) or severe:** idem plus *P. aeruginosa.* Might vary significantly depending on local epidemiology	**- Early (<5º days of admission)**: • Ceftriaxone† 2 g q24h IV **OR** • Levofloxacin 750 mg q24h IV Duration: 8 d **- Late (>5º days) or severe:** • Ceftazidime† 2 g q8 h IV ± (linezolid 600 mg q12h OR vancomycin 30 mg/Kg/day divided in 2-3 doses IV) OR • Meropenem† 1-2 g q8 h IV ± linezolid 600 mg q12h OR vancomycin 30 mg/Kg/day divided in 2-3 doses IV Duration: 8 d	• Aztreonam 2g q8h IV + (linezolid 600 mg q12h OR vancomycin 30 mg/Kg/day divided in 2-3 doses IV). Duration: 8 d

Primary peritonitis (spontaneus bacterial periotinitis)	*E. coli*, *Klebsiella*, other enterobacterales, *S. pneumoniae.* Risk factors for ESBL_producers: previous cephalosporin or quinolone use, recurrent UTI, urinary catheter, diabetes mellitus.	• Ceftriaxone† 2 g q24h IV If increased risk of ESBL: • Ertapenem† 1 g q24h IV. Duration: 7 d	• Aztreonam 2 g q8h IV **OR**: • Tygecycline 50 mg q12h IV (loading dose 100 mg) Duration: 7 d
Secondary community peritonitis or intraabdominal abscess, complicated diverticulitis, complicate acute 39dem39ry39tis39.	Mixed: *E. coli*, other enterobacterales *+Bacteroides fragilis sp* Risk factors for ESBL_producers : see above	• Ceftriaxone† 2 g q24h IV + metronidazole 500 mg q8h IV If increased risk of ESBL: • Ertapenem† 1 g q24h IV. Duration: 4d after surgical source control	• (Aztreonam IV 1 g q8h or amikacin 15 mg/ kg q24h*) + metronidazole 500 mg q8h IV **OR** • Tygecycline 50 mg q12h IV (loading dose 100 mg) Duration: 4d after surgical source control

Secondary nosocomial peritonitis or postsurgical intraabdominal abscess	Idem+ *P.aeruginosa* + *Enterococcus* spp. Risk factors for ESBL_producers : see above. Risk of *Candida sp* if: multiple site 40dem40ry40tis40, intrabdominal surgery, parenteral nutrition, sepsis, previous admission to ICU, severe pancreatitis, previous antibiotic treatment, femoral catheter, sepsis.	• Ceftazidime† 2 g q8h IV + metronidazole 500 mg q8h IV +/- vancomycin 30 mg/Kg/day divided in 2-3 doses IV If septic shock or increased risk of ESBL: • Meropenem† 1-2 g q8h IV +/- vancomycin 30 mg/Kg/day divided in 2-3 doses IV If risk of *Candida* sp: • Fluconazole 400 mg q24h IV (loading dose 800 mg) Duration: 7d after surgical source control	• (Aztreonam IV 1-2 g q8h IV or amikacin 15 mg/ kg q24h*) + vancomycin 30 mg/Kg/day divided in 2-3 doses IV + metronidazole IV 500 q8h IV **OR** • Aztreonam IV 1-2 g q8h IV + tygecycline 50 mg q12h IV (loading dose 100 mg). If risk of *Candida* sp: • Fluconazole 400 mg q24h IV (loading dose 800 mg) Duration: 7d after surgical source control
Terciary peritonitis	Similar to nosocomial peritonitis + resistant gram negative bacilli, *Candida, S. aureus* and coagulase-negative *staphylococci*	• Meropenem† 1-2 g q8h + vancomycin 30 mg/Kg/day divided in 2-3 doses IV If risk of *Candida* sp:	• Tygecycline 50 mg q12h IV (loading dose 100 mg) + (aztreonam 1-2 g q8h IV or amikacin 15 mg/ kg q24h*) If risk of *Candida* sp:

		• Fluconazole 400 mg q24h IV (loading dose 800 mg) Duration: 7d after surgical source control	• fluconazole 400 mg q24h IV (loading dose 800 mg) Duration: 7d after surgical source control
Acute calculous cholescystitis and acute cholangitis	*E. coli*, other enterobacterales.	• Ceftriaxone† 2 g q24h IV If risk for ESBL: • Ertapenem† 1 g q24h IV Duration: 7d	• Aztreonam 1-2 g q8h IV **OR** • Amikacin 15 mg/ kg q24h* IV **OR** • Tygecycline 50 mg q12h IV (loading dose 100 mg) If risk for ESBL: • Tygecycline 50 mg q12h IV (loading dose 100 mg) **OR** • Amikacin 15 mg/ kg q24h* IV Duration: 7d
Emphysematous acute cholecystitis with no additional risk factors	Idem + anaerobes	• Ceftriaxone† 2 g q24h IV + metronidazole 500 mg q8h Duration: 7d	• (Aztreonam IV 1 g q8h or amikacin 15 mg/ kg q24h IV) + metronidazole 500 mg q8h IV **OR**

			• Tygecycline 50 mg q12h IV (loading dose 100 mg) Duration: 7d
Acute cholecystitis or cholangitis with associated complication (postsurgical or post billiary manipulation)	Enterobacterales (risk of ESBL producers: see above). *Enterococcus* spp (postsurgical infection, previous antibiotic, previous biliar drainage). Billiary manipulation or nosocomial: Ïdem + *P. aeruginosa.*	• Ceftazidime† 2 g q8h IV + metronidazole 500 mg q8h IV + vancomycin 30 mg/Kg/day divided in 2-3 doses IV If increased risk of ESBL or septic shock: • Meropenem† 1-2 g q8h IV +vancomycin 30 mg/Kg/day divided in 2-3 doses IV Duration: 7d, if surgical treatment need, 4d after surgical control	**Billiary manipulation or risk for *Enterococcus* sp**.: (Aztreonam IV 1 g q8h or amikacin 15 mg/ kg q24h) + vancomycin 30 mg/Kg/day divided in 2-3 doses IV **Sepsis or risk for ESBL producers:** Tygecicline 100 mg 1ª dose (followed by 50 mg q24h) + amikacin 15 mg/ kg q24h (if renal impairment consider ciprofloxacin 400mg q8h IV instead or amikacin) Duration: 7d, if surgical treatment need, 4d after surgical control
Acute pielonephritis	*E. coli*, other enterobacterales (>80%)	• Ceftriaxone† 2 g q24h IV	• Gentamicin or tobramycin 3 mg/kg q q24h IV **OR**

		Duration: 7d	• Amikacin 7,5 mg/kg q24h **OR** • Fosfomycin 6 g q8h IV Duration: 7d
Complicated pielonephritis or urinary sepsis	*E. coli*, other enterobacterales (>80%) Risk factors for ESBL_producers *E. coli o Klebsiella* spp : sepsis, previous cephalosporin or quinolones treatment, recurrent UTI, urinary catheter, diabetes mellitus. Risk pf *Enterococcus* spp: elderly, urinary catheter, previous chepalosporin treatment	• Ceftriaxone† 2 g q24h IV If increased risk of ESBL: • Ceftriaxone† 2 g q24h IV plus amikacin 15 mg/kg q24h IV **OR** • Ertapenem† 1 g q24h IV In increased risk of enterococci: • add vancomycin 30 mg/Kg/day divided in 2-3 doses IV Duration: 7d	• Aztreonam 1-2 g q8h + (amikacin 15 mg/kg q24h IV or Fosfomycin 6 g IV q8h IV) Risk of enterococci: • add vancomycin 1g q12h • Duration: 7d
Nosocomial urinary sepsis	*E. coli*, enterobacterales, *P. aeruginosa, Enterococcus* spp*, Candida*,	• Ceftazidime† 2 g q8h IV If increased risk of ESBL or septic shock:	• Aztreonam 1-2 g q8h + amikacin 15 mg/kg q24h IV If increased risk of enterococci:

	Polimicrobial Risk for ESBL producers or enterococci: see above	• Meropenem† 1-2 g q8h IV If increased risk of enterococci: • add vancomycin 30 mg/Kg/day divided in 2-3 doses IV Duration: 7d	• add vancomycin 30 mg/Kg/day divided in 2-3 doses IV Duration: 7d
Acute protatitis with admission criteria (sepsis)	*E. coli*, other enterobacterales (>80%)	• Ceftriaxone† 2 g q24h IV If increased risk of ESBL: • ertapenem† 1 g q8h IV If the isolated microorganism is susceptible the preferred sequential therapy is: • Ciprofloxacin 500-750 mg q12h PO **OR** • Cotrimoxazole 800mg-160mg q12h Duration: 14-28d	• Gentamicin or tobramycin 3 mg/kg q q24h IV **OR** • Amikacin 7,5 mg/kg qd **OR** • Fosfomycin 6 g q8h IV If the isolated microorganism is susceptible the preferred sequential therapy is: • Ciprofloxacin 500-750 mg q12h PO **OR** • Cotrimoxazole 800mg-160mg q12h Duration: 14-28d
Short-life catheter infection	*S. epidermidis, S. aureus,* Enterobacterales, *P.*	• Vancomycin 30-40 mg/Kg/day divided in 2-3 doses IV **OR**	• Vancomycin 30-40 mg/Kg/day divided in 2-3 doses IV **OR**

Infected phlebitis **Sepsis with suspected focus on vascular catheter**	*aeruginosa,* *Candida* spp	• Daptomycin 8-10 mg/Kg q24h IV If risk of Gram negative bacili: • add ceftazidime† 2g q8h IV **OR** • Meropenem†* 1-2 g q8h IV If septic shock or risk of fungi: • add caspofungin 70 mg IV inicial followed of 50 mg/24 h (maintainance dose of 70 mg is patient´s weight >80 kg) Duration: according to aetiology: 3-5 d for Coagulase-negative staphylococci at least 7 d for gram negative 14 days for *S. aureu*	• Daptomycin 8-10 mg/Kg q24h IV If risk of Gram negative bacilli: • add aztreonam 1 g q8h IV **OR** • Amikacin* 15 mg/kg q24h IV Duration: according to aetiology: 3-5 d for Coagulase-negative staphylococci at least 7 d for gram negative 14 days for *S. aureus* 14 days for *Candida sp* since first negative blood culture.

		14 days for *Candida sp* since first negative blood culture.	
Community-onset cellulitis (non specific exposures)	β-hemolytic streptocci *S. aureus*	• Clindamycin 300-600 mg q8h PO If severe enough to warrant hospitalization: • Cefazolin† 2 g q8h IV Duration: 5-7 d	• Clindamycin 300-600 mg q8h PO If severe enough to warrant hospitalization: • Vancomycin 30-40 mg/Kg/day divided in 2-3 doses IV **OR** • Linezolid 600 mg q12h IV/PO Duration: 5-7 d

Table 7. Recommended antimicrobial therapy for the most prevalent infectious syndromes in adult patients with suspected penicillin allergy. Antimicrobials are presented in preferential order. Duration (d=days) refers to the usual accepted duration of antimicrobial therapy for most patients in case of a favorable course. † In patients with severe infections that warrant hospitalization and have had a non-confirmed, low-risk, immune-mediated penicillin reaction a controlled drug challenge with cefazolin, a third generation cephalosporin or a carbapenem can be considered (See Section 4.1). § In patients with confirmed allergy consult the allergist's report for the selection of β-lactam antibiotics, if feasible. * Choose if increased risk of infection caused by ESBL-producing enterobacterales

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

Summary

- 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. **(A-III)**
- If a patient has prior allergy but 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**)

How should the label / allergy situation be reported in the clinical history? Updating information systems

All patients evaluated in an Allergology Department must receive a medical report on paper and must have a copy in the patient's medical history (paper-based and / or electronic patient records if available).

The minimum standards of the allergy medical report have been established by the Spanish Society of Allergology and Clinical Immunology (SEAIC)[235]. These minimum standards include common requirements to other allergic conditions (identification and age of the patient or date of birth, personal and family history, reason for consultation, origin of the patient, identification of the centre / doctor, date of issue of the report, signature of the doctor, physical examination, other allergic conditions, need for subsequent revisions) and specific minimum standards for drug allergy.

A detailed anamnesis of the allergic reaction to the medication subject to study should be done and reflected in the medical report: symptoms, drugs involved, reason why he was taking them, dosage and route of administration, latency time between taking of the drug and the onset of symptoms, duration of symptoms, possible residual lesions and drugs that have been tolerated since then. The allergy workup performed (in vitro tests, skin tests and drug provocation tests) must be also reflected. The diagnosis must clearly reflect the confirmation or non-confirmation of the allergy to the drug. In the treatment and recommendations should always include prohibited drugs and optionally therapeutic alternatives except that no drug is prohibited.

New technologies have enabled health centres to implement Electronic Health Records (EHRs) providing opportunity to register important health-related information, such as allergic conditions. These systems have been shown to improve the safety and quality of patient care by, for example, reducing the likelihood of medication errors and consequent patient harm. [236]

Health professionals have suboptimal understanding of classification of adverse drug reactions as allergy (immunological) or intolerance (non-immunological), and this is reflected in a inconsistent and inapropiate use of this labels in EHRs [25,237–239].

It is essential that the information shown in the EHRs is correct. To promote this it may be useful: increase health professional's training in the recognition and correct classification of adverse drug reactions and its correct registration in the EHRs; harmonize terminology; adequate communication between the different EHRs systems; cleaning up old documentation; developing tools to relabel inappropriate documentation and to facilitate accurate documentation in the future. [238,240]

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In the more advanced systems, Clinical Decision Support (CDS) have been implemented. CDS provide assistance with clinical decision-making tasks and represents an important tool for promoting patient safety and quality of care[241], and medication-related CDS is especially useful because simply having EHRs appears to have little impact on quality by itself. [242,243]

However, clinicians can be exposed to a high number of alerts, which can result in them experiencing “alert fatigue” (clinicians can often ignore or override both clinically important and unimportant alerts due the high number of alerts and the frequent inaccuracy of them)[244,245]. Ignoring alerts can potentially lead to patient harm and other unintended consequences, thus many efforts are underway to improve the accuracy of the alerts and reduce clinicians “alert fatigue”. [246,247]

5. Interventions to improve characterization and antimicrobial use in patients with self-reported β-lactam allergy (SRBA)

Summary

- 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. (**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 it is the case of patients with endocarditis and osteoarticular infections, or in patients receiving high valued antibiotics due to SRBA. (**A-II**)
- One of the circumstances that may diminish the potential impact of interventions designed to formally assess SRBA is inefficient delabeling of the discarded allergies. (**A-II**)

Several studies have proven the negative impact of self-reported β-lactam allergy (SRBA). As most SRBA do not represent true allergies, they lead to the unnecessary selection of second-line of antimicrobial agents, which not only are less effective but they are associated with more adverse effects, including and increased risk of secondary infections caused by antimicrobial-resistant microorganisms.[42] [248]

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Given the significant consequences of SRBA and as it affects up to 10-15% of the population, several interventions have been investigated to mitigate its burden on health outcomes and on the health system. Although heterogeneous, most of these interventions took place in hospitals, frequently integrated with other activities of antimicrobial stewardship programs (ASP). Most frequently, they were complex, meaning that they used a multimodal approach, with several activities within each intervention.

The impact of the interventions to improve the characterization of SRBA and antimicrobial use in these patients has been assessed either describing the outcomes observed in cohorts of patients subject to these interventions or by the means of, occasionally controlled, before-after quasiexperimental study designs. No clinical trials assessing the impact of these kind of interventions were found in the literature search, probably because this study design may well not be ethically acceptable. Regarding the outcomes, these studies frequently measured the use of first-line antibiotics (mostly β-lactams) as their primary outcome as well as economical (mainly direct cost) and seldom other clinical events (mortality, length of hospital stay and drug adverse events) as secondary outcomes.

Some of the interventions to further characterize SRBA and to improve antimicrobial use among these patients have been triggered by clinical events such as bloodstream infections[249] or certain high-risk surgeries needing antibiotic prophylaxis. Others have targeted certain high-risk or highly valuable antibiotics, such as aztreonam [204] [223] [224][230][250][251] or carbapenems [201], or have even been systematically applied on patients with SRBA who receive any antibiotic.
[36][52][202][203][252][253][254][255] [256][257] While some interventions have included the use of penicillin skin testing (PST) and drug challenge others have aimed to improve clinical characterization of the SRBA in the absence of penicillin skin [203,249] [201][203][204][223]. Pharmacists were the healthcare professionals most frequently involved in these interventions, followed by infectious diseases physicians and allergists.

Clinical assessment tools (CAT) such as guidelines or algorithms to categorize the SRBA as low or high-risk of immune-mediated drug reaction to subsequent exposure to β-lactams were frequently used. CAT were commonly put into practice by trained pharmacists, infectious diseases or allergists on the basis of active case-finding or by referral. Nevertheless some CAT pretend to be used at the point of care by the treating physicians. [223][201][203][249][250]. CAT have shown to safely identify patients unlikely to be allergic to β-lactams. Those SRBA consisting of gastrointestinal intolerance and those patients in which subsequent tolerance to penicillins could be proven were considered to be non-allergic and therefore unrestricted use of β-lactams, including penicillins was allowed in the absence of significant immune mediated drug-related events following exposure. [230][223][201][255][202][257][52][36][207] The subset of patients unlikely to be allergic to β-lactams represented a proportion that widely ranged between 4% and 40% of all assessed patients. [36][52]

In addition, some of these locally implemented CAT have proven the safe use of non-penicillin β-lactams, for instance cefazolin, in patients in which an IgE mediated reaction or a severe non-IgE related reaction, such as Stevens-Johnson, DRESS or serum sickness were not suspected. [201][223][224][230] For instance, Staicu *et al.* describe a single case of late-onset mild to moderate rash after β-lactam rechallenge, mainly with cephalosporins, in 56 patients with a SRBA clinically classified as mild to moderate allergy or intolerance to penicillin. [223] Vaisman *et al.* describe the eventless preoperatively administration of cefazolin to 267 patients with non-severe, non-clinically suspicious IgE mediated SRBA following a CAT. [230]

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Some interventions also included penicillin skin testing followed by antibiotic challenging. Although some targeted exclusively those patients with indeterminate SRBA[204][258], most also included SRBA likely to be Ig-E mediated. [36][79][207][251][252][253][254][255] Penicillin skin testing was performed by trained personnel, mainly allergists [36][53][79][253][258], pharmacists [207][251][252] and to a lesser extent infectious disease physicians. [254] In one study, penicillin skin testing was performed by a trained physician assistant supervised by an allergologist via telemedicine consult.[255]

In the non-controlled cohorts of patients with SRBA assessed a significant proportion of the included patients could safely receive β-lactams after the intervention (72-100%) [36][53][252][254][255], coherently with the known fact that most SRBA do not represent true allergies. Concomitantly a significant decrease in the used of second-line antimicrobials was observed. Before-after studies found a significant postintervention increase in the proportion of patients receiving first-line antibiotics, with an absolute increase in first line antibiotic use ranging between 15% and 71%.[207,256] [201][202][203][204][223][249][251][256] In a controlled quasiexperimental study Shannon *et al*. observed that in a hospital in which a formal antibiotic allergy assessment protocol was implemented, 56% of patients with SRBA received β-lactam as compared to 32% in a control hospital.[253] Although these results are unquestionably positive, they also show that there is still a great opportunity to increase the yield of these interventions. For instance, those interventions that integrated CAT in the electronic medical record, triggering in some instances specialized consultations to allergologists or infectious diseases physicians by default may contribute to increase the yield of the interventions. [201][223][248] The gap between the formal possibility of β-lactam use and its actual use may well partly explained by the fact that penicillin allergy labels many times persist despite a formal assessment has ruled out the allergy.[259]

Regarding the economic impact of interventions targeting patients with SRBA, most of them were associated with cost savings that range from $37 to $360 per patient.[203][255] As expected, those interventions triggered by high-cost antibiotics, such as aztreonam, were associated with greater cost savings than those not linked to any specific antibiotic. Several decision analysis models show that the maximum benefit of assessing SRBA should be expected in patients with severe infections in which β-lactams are associated with improved outcomes or in those infections that require longest durations, such as osteoarticular infections and endocarditis.[257][260][261]

Cost savings in primary care have been more modest than in the hospital setting. In 1998, Macy compared the per antibiotic cost in the year preceding PST with the per antibiotic cost in the year following PST found an average 5% decrease.[8] More recently, Vyles et al found that among 100 children with negative PST, 36 received antibiotics in the year following PST and the associated cost savings associated with penicillin allergy delabelling were $1,368.[262]

There are several limitations to the cost analysis of interventions designed to characterize SRBA and to improve antibiotics in these patients. Although the cost of penicillin allergy can be quite variable, depending on several factors such as the use of PST, the qualification of the personnel and the integration of PST and drug challenge, when the latter is necessary, most studies considered a fixed cost.[263] In addition cost analysis of these interventions is usually limited to a given period after the intervention while their benefit persists indefinitely. The clinical benefits of delabelling penicillin allergies have not been proven in the studies that have assessed them, which may be partly explained by the small sample size of the studies and the clinical heterogeneity of the patients included and their infections. [204][224][250][253]

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6. Implementation of the Clinical Practice Guideline

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

Summary

- 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-immunomediated reactions in the acute care settings and e) Insufficient human resources capabilities within antimicrobial stewardship programmes (ASPs).

The aim of this guideline is to contribute to improve the selection of antimicrobial therapy in patients with suspected or confirmed antibiotic allergy, mainly penicillin and other β-lactam agents. Unfortunately, several factors might hamper the implementation of the recommendations contained in this guideline. These factors, also known as barriers, should be acknowledged and addressed in order to increase the impact of the recommendations.

Large size and widespread distribution of affected population. Antibiotic allergy, either suspected or confirmed might affect over 10% of the population. These patients probably have the same distribution in the territory as the general population does.

Insufficient and unequitable access to allergists. This guideline recommends a risk-based, standardized management of suspected, not yet confirmed antibiotic allergy labels that includes skin testing and, eventually, subsequent drug challenge, which often require the kind of expertise that allergists provide. Unfortunately, access to these specialists is very far from being 24/7 and worse, it is significantly inequitable within the Spanish territory, partly due to geographical factors but also because of different priorities in healthcare planification among regional healthcare services.

Resistance of doctors and patients to the use of any β-lactam in patients labeled as penicillin allergic. Many patients and a significant amount of doctors are not aware of the detrimental impact of choosing second line antibiotics for the treatment of severe infections. Neither they know the odds of an antibiotic allergy label not representing a true hypersensitivity reaction to the antibiotic, nor the low cross-reactivity between penicillins and certain other β-lactam antibiotics. It is also frequently unknown that the risk of hypersensitivity reactions with repeated exposures wanes over time. Consequently, most patients and many doctors disproportionally fear the clinical and or legal consequences of an eventual, new hypersensitivity reaction. Although fear is perhaps a more visible barrier, it is likely founded on a lack of knowledge and motivation.

Lack of training and support for using alternate β-lactams in patients with low-risk and non-immunomediated reactions in the acute care settings. When facing the decision of using a β-lactam in a patient with severe infections and a low-risk antibiotic allergy label or even when the label is clearly due to a non-hypersensitivity mediated drug reaction, clinicians do not feel they have the institutional support to

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dismiss the label in the latter or to proceed with a controlled drug challenge in the former if skin testing is not available. In regard of controlled drug challenge in acute care settings when a formal allergy assessment is not feasible in the short-term, lack of protocols and / or formal training are significant barriers, too.

Limitations of health records. A negative standardized work-up that safely rules out antibiotic allergy is often unable to counteract a suspected allergy label, frequently because of lower visibility or inaccessibility of the allergy work-up that supports delabeling in the health records.

Insufficient human resources capabilities within antimicrobial stewardship programmes (ASPs). While ASPs are the ideal vehicle to implement this guideline, they are frequently understaffed and may not have the capability to assume the burden that implementing this guideline implies.

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

Summary

- 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 programmes (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.

We believe that a proactive assessment of all individuals with an antibiotic allergy label within the Spanish population, first clinically with skin tests and then eventually by the means of drug provocation could be framed as a broad Public Health intervention. We consider it a high-yield intervention since in most individuals the antibiotic allergy label does not represent a true hypersensitivity reaction and a one-step or a two-step approach would suffice to reverse most inappropriate allergy labels and their associated deleterious consequences. Nevertheless, the pertinence of such a large-scale intervention and its design should be carefully studied from a Public Health perspective.

While a population-based approach is considered appropriate and an intervention is eventually designed and implemented, individuals with antibiotic allergy who benefit most from a systematic approach should be prioritized. These 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).

We believe that antimicrobial stewardship programmes (ASP), widely distributed in our country, both in the hospital setting and in primary care are the best vehicle to

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implement the recommendations contained in this CPG. Therefore, ASPs should design and implement activities aiming antibiotic allergy delabeling and antibiotic selection in priority patients. These comprise the inclusion or update of empiric antimicrobial therapy recommendations for antibiotic allergic patients in local antimicrobial guidelines, setting up circuits to early detect, assess and eventually delabel priority patients and educational sessions for clinicians, among others. These activities should count with a leading allergist that should be actively involved in its planning and conduction.

In order to facilitate and to promote the implementation of this CGP by ASPs we plan to present the CGP to the coordination team of the Spanish Action Plan Against Antimicrobial Resistance (PRAN) for endorsement. We believe that PRAN endorsement would help the guideline to reach the various Spanish Autonomous Communities healthcare systems more expeditely, in a top-to-bottom strategy, in order to design and implement regional strategies.

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

Summary

- Specific protected time for ASP team members, as well as allergists and skilled nurses should 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 to decrease the workload associated with the implementation of the recommendations contained in this guideline for ASP members.

Local ASPs need to design and implement the protocols for identification and assessment of priority patients and need to be adequately staffed. ASPs also need to design and conduct educational activities locally, for which the availability of ready to use or easy to adapt, printed or in e-format, posters, leaflets and other informative materials such as infographics would significantly reduce the workload associated with the implementation of the guideline. Expectedly, the implementation of this guideline will increase the demand of specialized assessment by allergists and skilled nurses, what should be taken into account by healthcare authorities when planning and allocating the necessary resources.

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

Summary

- Table 8 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.

In **Table 8** we propose a set of indicators to help to monitor the implementation of this guideline.

Indicator	Type	Value	Comment
The institution specifies alternative antimicrobial therapy for patients with antibiotic allergy in the local antimicrobial therapy guideline	Process	Yes /No	>70% of infectious syndromes included in the guideline should have alternative therapy for allergic patients
The institution has established a circuit for identification and assessment of priority patients with antibiotic allergy labels	Process	Yes/No	
Priority patients targeted by the intervention	Process	0 / 20 /40/60/80/100%	Add 20% per each priority patient group targeted
The institution has protocolized how to adequately labeling and delabeling antibiotic allergies in the healthcare records	Process	Yes/No	
Number of patients referred to the Allergy Service	Process	Number	Yearly
Number of patients delabeled	Process	Number	Yearly
Proportion of patients delabeled	Process	$\frac{\text{Patients delabeled}}{\text{Patients assessed}}$	Yearly
Proportion of delabeled patients who receive first-line antimicrobial therapy in the following year when needed	Result	$\frac{\text{Delabeled patients receiving 1st line antibiotics}}{\text{Delabeled patients receiving antibiotics}}$	Yearly

Table 8. Potential indicators to monitor the implementation of the guideline

These indicators could be used locally by ASP, by regional healthcare systems or by PRAN to monitor the implementation of activities aiming to improve antibiotic use among patients labeled as antibiotic allergic. We believe that a survey, first when guideline is released and then, 2 years later would help to better understand its implementation nationwide.

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Annex I. Selected, rejected and added references from the original literature systematic review.

1.1. How frequently are antibiotic allergies reported?

Selected	Rejected (Title)	Rejected (Abstract)	Rejected (Full read)	Additional references	Total
28	151	48	35	4	274

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

Selected	Rejected (Title)	Rejected (Abstract)	Rejected (Full read)	Additional references	Total
18	171	48	32	9	271

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

Selected	Rejected (Title)	Rejected (Abstract)	Rejected (Full read)	Additional references	Total
18	151	68	33	8	278

2. Risk assessment of antibiotic allergy labels

2.1. Can the risk of allergic reactions in patients with antibiotic allergy label be stratified by the means of clinical assessment?

Selected	Rejected (Title)	Rejected (Abstract)	Rejected (Full read)	Additional references	Total
8	46	44	15	23	113

3.3. Desensitization

Selected	Rejected (Title)	Rejected (Abstract)	Rejected (Full read)	Additional references	Total
7	0	19	18	54	61

doi: 10.18176/jiaci.0859

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

Selected	Rejected (Title)	Rejected (Abstract)	Rejected (Full read)	Additional references	Total
47	282	66	7	17	402

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

Selected	Rejected (Title)	Rejected (Abstract)	Rejected (Full read)	Additional references	Total
0	33	58	13	14	14

5. Interventions to improve characterization and antimicrobial use in patients with self-reported β-lactam allergy (SRBA)

Selected	Rejected (Title)	Rejected (Abstract)	Rejected (Full read)	Total
30	7	37	1	75

doi: 10.18176/jiaci.0859