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Guidelines

ESCMID clinical guidelines on the evaluation and management of a reported antibiotic allergy

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ABSTRACT

Scope: Antibiotic allergies remain one of the most frequently documented drug allergies in clinical records. It is well established that only a small proportion—estimated at 5% to 10%—represents true immune-mediated hypersensitivity. Mislabelling can contribute to the development of antimicrobial resistance via prescription of suboptimal antimicrobial therapy (i.e. unnecessary avoidance of first-line antibiotics), increased use of broad-spectrum agents, and complications such as drug toxicity. This guideline, developed by the European Society of Clinical Microbiology and Infectious Diseases, provides evidence-based recommendations for the clinical evaluation and management of patients with reported antibiotic allergies. It is aimed at nonallergist clinicians and seeks to harmonize practice across healthcare settings in Europe and beyond.

Methods: The guideline was developed by a multidisciplinary panel of 16 experts in infectious diseases, allergy, pharmacy, paediatrics and clinical microbiology, following a modified GRADE-ADOLOPMENT process. Systematic searches were conducted in PubMed and the Trip Database (2015–2023) to identify relevant guidelines, complemented by an additional systematic search for primary studies (2021–2024). The included guidelines were assessed using the AGREE Global Rating Scale. Four existing guidelines, from 2022 and 2023, met methodological quality criteria and were included. Key questions were identified and prioritized by the panel, and relevant data were extracted using piloted Evidence to

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Decision framework sheets. The panel developed recommendations by adopting, adapting or formulating new recommendations, through an iterative work-up and consensus process. All recommendations were finalized through panel discussion and formal voting, with consensus defined as agreement by $\geq$ 80% of members.
Recommendations: The guideline recommends a structured clinical assessment to evaluate a reported antibiotic allergy, taking into consideration the characteristics of the index reaction. Where the clinical history suggests a very low or low likelihood of true allergy, direct delabelling or performing a controlled drug challenge test is appropriate. By supporting allergy evaluation and prudent prescribing practices, the recommendations aim to improve individual patient outcomes and reinforce antimicrobial stewardship goals. **Oana Joean, Clin Microbiol Infect 2026;32:767**

Context

This guideline addresses reported allergies to antibiotics. β-Lactam antibiotics, in particular penicillins, are among the most commonly prescribed antimicrobials because of their effectiveness, safety and narrow spectrum of activity [1]. However, they are also the cause of most reported drug allergies in medical records, with consequences that extend beyond individual patient care [2].

The prevalence of true β-lactam antibiotic allergy is significantly lower than medical records suggest, with only 1 to 2 out of every 20 allergy labels being accurate [3,4]. Incorrect labels are associated with poorer clinical outcomes and increased use of broad-spectrum antibiotics [2,5]. The mislabelling of penicillin allergies leads to unnecessary avoidance of first-line antibiotics, resulting in suboptimal therapy, longer hospital stays, higher healthcare costs, more complications—such as *Clostridioides difficile* infections—and greater reliance on second-line agents [2,5]. These factors contribute to rising antimicrobial resistance, highlighting the need for antimicrobial stewardship programmes that prioritize re-evaluating reported antibiotic allergies.

Allergic reactions to antibiotics are classified as being either immediate or delayed type. Immediate reactions, generally IgE-mediated, typically manifest within 1 hour of drug administration, although onset may be delayed up to 6 hours. Non-immediate, i.e. delayed reactions, predominantly T-cell–mediated, usually occur more than 6 hours after exposure and may develop over several days [5–7]. The risk of an allergic reaction upon re-exposure to the suspected drug or a related agent is contingent on multiple variables. A comprehensive clinical assessment of the index reaction, covering the antibiotic causing the reaction (its indication, route of administration, dose and frequency), the nature, severity, timing and duration of symptoms, as well as any treatment received, enables a structured analysis of whether the event was likely immune mediated, its timing (immediate versus delayed) and its severity. Furthermore, an evaluation of the risks and benefits of alternative treatments is essential, particularly in scenarios where the clinical history lacks detail or the classification of the reaction is uncertain [3,6].

Despite advances in understanding the nature of reported antibiotic allergies, their management remains highly variable [8,9]. This inconsistency has prompted the development of several evidence-based national guidelines to standardize practices and improve patient outcomes [5,7,10,11]. This guideline aims to provide nonallergist clinicians with clear, implementable recommendations for evaluating and managing reported antibiotic allergies.

Panel composition

This clinical guideline was developed by the European Society of Clinical Microbiology and Infectious Diseases (ESCMID) after an initiative of the ESCMID Study Group for Antimicrobial Stewardship. A multidisciplinary panel of 16 experts were convened, comprising clinicians specialized in infectious diseases, allergy, paediatrics, pharmacy and clinical microbiology. The panel was chaired by M.G.J.D.B., and methodological supervision and guidance were provided by the ESCMID methodologist (B.N.).

Aim and scope

This guideline offers clinical guidance for managing reported antibiotic allergies in children and adults. It outlines decision pathways and strategies to optimize treatment in patients with reported antibiotic allergies, addressing safety concerns and special considerations. The guideline supports antimicrobial stewardship by helping to (a) enable use of first-line, narrow-spectrum antibiotics, and (b) reduce inappropriate use of broader-spectrum second-line agents, which carry higher risks of adverse events, increased costs and potential treatment failure. It also highlights evidence gaps to guide future research and policy making. The guideline is primarily intended to support hospital-based clinicians in managing patients with a suspected antibiotic allergy.

Methods

This guideline was developed using the GRADE-ADOLOPMENT methodology [12], as several recent guidelines on the topic were already available. However, some adjustments herein were needed because none of the source guidelines had published GRADE evidence profiles or Evidence to Decision (EtD) tables, as recommended in the GRADE-ADOLOPMENT process. In short, ADOLOPMENT is a pragmatic approach to guideline development that combines the processes of adoption, adaptation and *de novo* development of recommendations. It allows efficient use of already existing high-quality clinical practice guideline on handling reported antimicrobial allergies by either adopting them directly, modifying them according to relevance and new insights or creating new recommendations when necessary. The guideline panel considered it essential to develop an umbrella guideline by systematically identifying and incorporating scientific data and recommendations from all relevant existing guidelines, rather than relying on a single source. This allowed for broader clinical guidance and the opportunity to assess variability across existing guidelines. Therefore, systematic searches for relevant clinical guidelines were undertaken.

Literature searches and evidence synthesis

Systematic literature searches for published guidelines on this topic were performed in PubMed and Trip Databases, covering the period from January 2015 to September 2023, without language or study design filters (see supplementary materials). Additional

manual searches were conducted via Google and the websites of 26 international and national societies active in this field.

Study selection followed a two-phase screening process (title/abstract and full-text review), conducted in Rayyan (www.rayyan.ai) [13]. Two independent reviewers screened the records, with disagreements resolved by a third reviewer. Eligible records included clinical guidelines published: (a) from 2015 onwards, (b) by a society or organization, (c) by at least three authors, (d) by national or international societies and (e) published in English. Detailed inclusion criteria and Preferred Reporting Items for Systematic reviews and Meta-Analyses flow diagrams, including reasons for exclusion, are provided in the supplementary materials.

Quality of evidence and recommendations

The quality of included guidelines was assessed using the AGREE Global Rating Scale [14] by two independent reviewers (supplementary material). Only guidelines based on a systematic review of evidence and using a formal evidence grading system were retained for further consideration. Wherever possible, this umbrella guideline synthesizes recommendations from previously published guidelines to broaden the scope and provide a consolidated reference. The original evidence grading systems were retained to preserve methodological rigour and ensure alignment with the source guidelines.

Selecting key questions

From the included guidelines, all research questions were extracted by one reviewer and verified by another. Panel members then rated the importance of each question using a Likert scale (1 = least important, 5 = most important). On the basis of these ratings, the panel agreed on a final list of key questions to be included.

Data extraction

Data extraction was performed by one reviewer and verified by a second reviewer, using standardized forms. Three types of extraction sheets were used. The first form collected general information about each included guideline. The second form focused on individual PICO (Population-Intervention-Control-Outcome) questions, detailing the question itself, the corresponding recommendations and the primary studies cited. The third form documented each issued recommendation along with the underlying information, using the EtD framework [15].

Consensus and issuing recommendations

Working groups (WGs) were formed based on thematic clusters of topics. Each WG included at least one junior and two senior panel members. Using the EtD framework, WGs assessed whether to adopt, adapt or reject recommendations, according to GRADE recommendations [16]. In an iterative process, each WG presented their findings and proposed recommendations to the full panel. After one or more rounds of discussion, recommendations were finalized through voting. All panel members had voting rights, except the ESCMID methodologist, who remained impartial. Consensus was defined as agreement by at least 80% of panel members with a voting right.

Literature search update for primary studies

To ensure up-to-date evidence, it was planned to replicate primary study searches from the source guidelines. However, this was not possible because search strategies were incompletely described, and therefore nonreproducible. Instead, independent systematic searches were conducted in PubMed and Embase for recent studies published between January 2021 and December 2024. Study selection followed a two-phase process using Rayyan systematic review software [13]. Two independent reviewers screened articles, with a third resolving disagreements. Primary studies were assessed for their potential to change the direction or strength of recommendations. Relevant studies were extracted, and Risk of Bias was evaluated using tools from the ESCMID methodological manual [17]. Data were synthesized narratively. Inclusion criteria, search strategies and Preferred Reporting Items for Systematic reviews and Meta-Analyses flow diagrams are detailed in the supplementary material.

Conflict of interest management

All panel members declared any potential conflicts of interest according to ESCMID's policies [17].

Results

Seven relevant guidelines were identified and assessed for their quality. For use in the ADOLOPMENT procedure, four high-quality national guidelines published between 2022 and 2023 were included: the Dutch SWAB guideline [11], the British Society for Allergy and Clinical Immunology (BSACI) guideline [10], the Spanish multidisciplinary guideline (SEIMC/SEAIC/SEFH/SEMICYUC) [7] and the 2022 Drug Allergy Practice Parameter Update [5]. From these documents, 24 recommendations were adopted or adapted, which are summarized in Table 1.

Some of these recommendations are based upon a risk stratification system derived from integrative adaptations of the BSACI [10] and the Dutch SWAB [11] guidelines. Eventually, three categories are defined (Figs. 1 and 2, Table 1): very low risk, low risk and high risk of true antibiotic allergy. Depending on those categories and on the nature of the reported (or suspected) reaction, flowcharts (Figs. 1 and 2) are provided to support clinical decision-making.

In this guideline, definitions of immediate and delayed reactions (see Introduction) were adopted from the Spanish multidisciplinary guideline [9] and the 2022 U.S. Practice Parameter Update [5]. Definitions of severe or nonsevere reactions (Table 2) were adapted from the Dutch SWAB guideline [11], which used an international consensus-based classification including World Allergy Organization/European Academy of Allergy and Clinical Immunology [18,19] and Council for International Organizations of Medical Sciences criteria [20]. Of note, relevant considerations on urticarial reactions are additionally provided in the rationale text of recommendation 2.4, in the footnotes of Figs. 1 and 2 and in paragraph 6 of the results section.

Table 3 provides a risk classification of cross-allergy to β-lactam antibiotics, adopted from the Dutch SWAB Guideline [11]. Guidance on drug challenge procedures and contraindications is shown in Table 4 (see also 3. Details of performing a controlled drug challenge test (CDCT)). In the following paragraphs, the evidence and rationale are presented per recommendation topic.

Table 1
Summary of recommendations

Topic	Recommendation	Source guideline/ adolopment status	Strength	Evidence grading (method)	Important remarks
1. General recommendations on the approach and work-up of suspected penicillin- or other β-lactam allergy					
Can nonspecialist healthcare professionals identify low-risk patients and safely perform controlled drug challenge test?	1.1. All patients labelled as 'penicillin allergic' should have a penicillin-allergy assessment using needs-based prioritization.	British (BSACI)/ adapted	Strong	Grade E (SIGN)	Dutch (SWAB) has a similar recommendation, and separately recommends performing an antibiotic allergy anamnesis.
	1.2. Nonallergists should perform controlled drug challenge test in low-risk patients in a setting where allergic reactions including anaphylaxis can be treated.	British (BSACI)/ adopted	Strong	Grade E (SIGN)	See recommendation 3.1 for further details
2. Recommendations on direct removal of the allergy label and on performing a controlled drug challenge					
When is, based on patient-derived information, a reaction not allergic and can the allergy label be removed?	2.1. We recommend that an antibiotic allergy label can be removed directly without previous allergy testing when one of the following criteria applies (very low* risk of antibiotic allergy): > The culprit drug has been used since the index reaction without occurrence of an allergic reaction. > The allergy label was solely based on positive family history of allergy or on fear of allergy. > The reported signs and symptoms are not compatible with an allergic reaction (i.e. GI complaints only, palpitations, blurred vision, headache, candidiasis).	Dutch (SWAB)/ adapted	Strong	Moderate (GRADE)	*Very low risk was further defined by the guideline panel. The recommendation extents to all settings otherwise defined in this guideline as very low risk (of developing an allergic reaction upon exposure)
Which patients with a reported ß-lactam antibiotic allergy have a low risk of an actual allergy and can therefore be re-exposed to the culprit antibiotic?	2.2.a We recommend that patients with a history of a 'low-risk' index reaction can receive a controlled drug challenge of the culprit ß-lactam antibiotic in an appropriate clinical setting: > Patients with a history of a nonsevere cutaneous reaction >5 years ago (independent of the type—immediate or delayed—of the reaction) > The patient reports only a rash with no other history available[#] > The patient cannot remember the index reaction symptoms[#] [#]Under the condition that the patient was either told it was not serious/severe AND/OR the reaction did not require hospitalization or treatment specific for allergy	Dutch (SWAB) and British (BSACI)/ adapted	Strong	Low (GRADE)	This recommendation was the result of a fused adaptation of three recommendations: (I) Dutch (SWAB): we suggest that patients with suspected nonsevere, immediate-type index reactions that occurred >5 years ago, can receive a therapeutic dose of the culprit ß-lactam antibiotic in a controlled setting. (II) Dutch (SWAB): we suggest that patients with suspected nonsevere, delayed-type index reactions that occurred >1 year ago can receive the culprit β-lactam antibiotic without formal allergy testing. (III) British (BSACI) GL: all patients identified as low risk for true penicillin allergy should be offered direct drug provocation testing (controlled drug challenge test), providing no exclusion criteria are met
	Recommendation 2.2.b We suggest that hospitalized patients with a suspected nonsevere, delayed-type index reaction that occurred >5 years ago (low-risk category) can receive the culprit β-lactam antibiotic without controlled drug challenge testing.* *Follow-up is warranted; if no reaction occurs during treatment, the label should be removed	Dutch (SWAB), British (BSACI) and supported by USA (AAAAI-ACAAI)/ adapted	Weak	Low (GRADE)	This recommendation is aimed at—and can be applied to—a subpopulation of the patient population captured in recommendation 2.2.a. Importantly, both recommendations must not be read as contradictory guidance. Rather, recommendation 2.2.b must be read as a specific additional recommendation in this section, that

					allows to us follow this recommendation instead of 2.2.a for the subpopulation mentioned.
Which patients with a reported ß-lactam antibiotic allergy have a low risk of an actual allergy and can therefore be re-exposed to the culprit antibiotic?	2.3. We recommend against re-exposure to the culprit drug class in patients with severe delayed-type index reactions (high risk for an antibiotic allergy).	Dutch (SWAB)/ adapted	Strong	GPS	The sentence 'In the absence of acceptable alternative antimicrobial treatment, the use of the culprit should be discussed in a multidisciplinary team' will be added as a separate statement in the text of the GL-document.
	2.4. We recommend that patients with suspected nonsevere, immediate-type index reactions that occurred ≤5 years ago OR a suspected severe immediate-type index reaction irrespective of time elapsed, should be referred for formal allergy work up before re-exposure can be considered. (high risk for an antibiotic allergy)	Dutch (SWAB)/ adapted	Strong	Low (GRADE)	
3. Details of performing a controlled drug challenge					
What are the minimum safety requirements for direct controlled drug challenge test?	3.1. We recommend that the principles for the conduct of a drug provocation test (controlled drug challenge test) be applied as follows in patients identified as low-risk for penicillin allergy: - Inform the patient and obtain consent - CDCT should be performed in a setting where vital signs can be measured, and allergic reactions can be treated. - Single-dose or graded-dose CDCT can be used depending on local preference o Single-dose CDCT: Administer 100% of a full dose of the index antibiotic, preferably orally, or via an alternative route if necessary. If the index drug is unknown but probably a penicillin, amoxicillin (500 mg for adults) should be used ◦ Graded-dose CDCT according to local protocol* - Should symptoms consistent with anaphylaxis develop during the test, treat the patient in accordance with local protocol or national guidelines for the management of anaphylaxis - The patient should be observed for 1 h after the last dose. - The patient should be provided with clear written instructions about what to do if symptoms develop after leaving the hospital. - A system should be in place to inform the GP and other relevant healthcare professionals about the result of the CDCT. The patient should receive clear (preferably) written information about the test result and its implications	British (BSACI)/ adapted	Strong	Grade E (SIGN)	Amoxicillin 500 mg dose taken from another PICO/key question and incorporated here. In the text, brief note on absence of evidence for either graded or full dose challenge. *Graded-dose CDCT suggested by the BSACI 2022 Guideline [8]: Administer 10% of a full dose of the index antibiotic (i.e. 50 mg amoxicillin for adults); observe for 30 min; administer 50% of a full dose of the index antibiotic (i.e. 250 mg amoxicillin for adults); observe for 30 min; administer remainder of a full dose of the index antibiotic (i.e. 200 mg amoxicillin for adults); observe for 60 min.
Should multiple-day challenges be performed in patients with reported penicillin allergy?	3.2. We recommend against the routine use of multiple-day drug challenge testing in the evaluation of penicillin allergy.	USA (AAAAI-ACAAI)	Strong	Not graded	
4. Cross-allergy between β-lactams Part I. Penicillins)					
In which patients with a reported allergy to a penicillin, a different penicillin can be administered with an acceptable low risk of an allergic reaction?	4.1. We recommend that in patients with a suspected immediate-type allergy to penicillins, irrespective of severity, that occurred ≤5 years ago, all other penicillins should be avoided	Dutch (Dutch (SWAB)/adopted	Strong	Low (GRADE)	
	4.2. We suggest that in patients with a suspected nonsevere immediate-type allergy to a certain penicillin, that occurred >5 years ago (low risk), a controlled drug challenge test with other penicillins can be performed based on indication.	Dutch (SWAB)/ adapted	Weak	Low (GRADE)	See corresponding recommendation 2.2a on using the culprit penicillin in case of low-risk allergy
	4.3. We suggest that in patients with a suspected nonsevere delayed-type allergy to penicillins that occurred >5 years ago (low risk), all other penicillins can be used in a controlled setting.	Dutch (SWAB)/ adapted	Weak	Low (GRADE)	If doubt between immediate-type or delayed-type use recommendation above, perform a controlled drug challenge/controlled drug challenge test

(*continued on next page*)

Table 1 (*continued*)

Topic	Recommendation	Source guideline/ adolopment status	Strength	Evidence grading (method)	Important remarks
Part II. Penicillins vs. cephalosporins or carbapenems					
In which patients with a reported immediate-type allergy to a penicillin, a cephalosporin can be administered with an acceptably low risk of an allergic reaction?	4.4. We recommend that patients with a suspected or proven immediate-type allergy to penicillins* can receive cephalosporins, but only those with dissimilar side chains.	Dutch (SWAB)/ adapted	Strong	Moderate (GRADE)	*With the exception of patients with severe anaphylaxis, in which case the panel recommends to seek expert evaluation first
In which patients with a reported delayed-type allergy for a penicillin, a cephalosporin can be administered with an acceptably low risk of an allergic reaction?	4.5. We suggest that patients with suspected or proven nonsevere, delayed-type allergy to penicillins, can receive cephalosporins with dissimilar side chains, irrespective of time elapsed since the index reaction.	Dutch (SWAB)/ adopted	Weak	Low (GRADE)	
In which patients with a reported immediate-type allergy to a penicillin, a cephalosporin can be administered with an acceptably low risk of an allergic reaction?	4.6. Cefazolin does not share any side chains with the currently available penicillins and can be used in cases of suspected or proven immediate-type allergy to a penicillin, irrespective of severity or time elapsed since the index reaction.	Dutch (SWAB)/ adapted	Strong	Moderate (GRADE)	*With the exception of patients with severe anaphylaxis, in which case the panel recommends to seek expert evaluation first
In which patients with a reported allergy to penicillin, a monobactam or carbapenem can be administered with an acceptable low risk of an allergic reaction?	4.7. We recommend that the following patients can receive any monobactam or carbapenem, without prior allergy testing: - patients with suspected or proven immediate-type penicillin allergy (low and high risk*) - nonsevere, delayed-type penicillin allergy (low risk)	Dutch (SWAB)/ adapted	Strong	Low (GRADE)	*With the exception of patients with severe anaphylaxis, in which case the panel recommends seeking expert evaluation first.
Part III. Cephalosporins vs. cephalosporins					
In which patients with a reported allergy to cephalosporin, a different cephalosporin can be administered with an acceptable low risk of an allergic reaction?	4.8. We suggest that referral for allergy work-up should be considered to prove or disprove suspected immediate-type allergy to cephalosporins in patients.	Dutch (SWAB)/ adapted	Weak	GPS	Allergy to cephalosporins is relatively rare but has consequences as cephalosporins are among the most frequently used broad spectrum antimicrobials for empiric and targeted treatment in hospitalized patients in Europe
	4.9. We recommend that cephalosporins with a dissimilar side chain can be used in patients with a suspected or proven immediate-type allergy to a cephalosporin.*	Dutch (SWAB)/ adapted	Strong	Moderate (GRADE)	*With the exception of patients with severe anaphylaxis, in which case the panel recommends to seek expert evaluation first
	4.10. We recommend that cephalosporins with a dissimilar side chain can be used in patients with a suspected or proven nonsevere delayed-type allergy to a cephalosporin, irrespective of time since index reaction	Dutch (SWAB)/ adopted	Strong	Low (GRADE)	
Part IV. Cephalosporins vs. monobactams and carbapenems					
In which patients with a reported allergy to a cephalosporin, a monobactam or carbapenem can be administered with an acceptable low risk of an allergic reaction?	4.11. We suggest that any carbapenem can be used in a clinical setting in patients with suspected or proven, immediate-type allergy to a cephalosporin, irrespective of time elapsed since index reaction.	Dutch (SWAB)/ adapted	Weak	Low (GRADE)	*With the exception of patients with severe anaphylaxis, in which case the panel recommends to seek expert evaluation first
	4.12. We recommend that aztreonam can be used in patients with a suspected or proven, nonsevere, delayed-type allergy to cephalosporins other than ceftazidime or cefiderocol, irrespective of time since the index reaction.	Dutch (SWAB)/ adopted	Strong	Low (GRADE)	
	4.13. We suggest that any carbapenem can be used in patients with suspected or proven nonsevere, delayed-type allergy to cephalosporins, irrespective of time since index reaction	Dutch (SWAB)/ adapted	Weak	Low (GRADE)	
5. Suspected allergy for non−β-lactam antibiotics					
Which patients with a non−ß-lactam antibiotics allergy label can be re-exposed to the same antibiotic with an acceptable low risk of an allergic reaction?	5.1. We recommend avoiding re-exposure to the culprit non−ß-lactam antibiotic (NBLA) and all other NBLA within the same class when the index reaction was severe (high risk).	Dutch (SWAB)/ adopted	Strong	Low (GRADE)	
	5.2 We suggest a controlled drug challenge in patients with a nonsevere index reaction (low risk) to reintroduce the culprit NBLA or any other NBLA within the same class	Dutch (SWAB) and USA (AAAAI-ACAAI)/adapted	Weak	Low (GRADE)	

BSACI, British Society for Allergy and Clinical Immunology; CDCT, controlled drug challenge test; GP: General Practitioner; GPS: Good practice statement; PICO: population-intervention-control-outcome question.

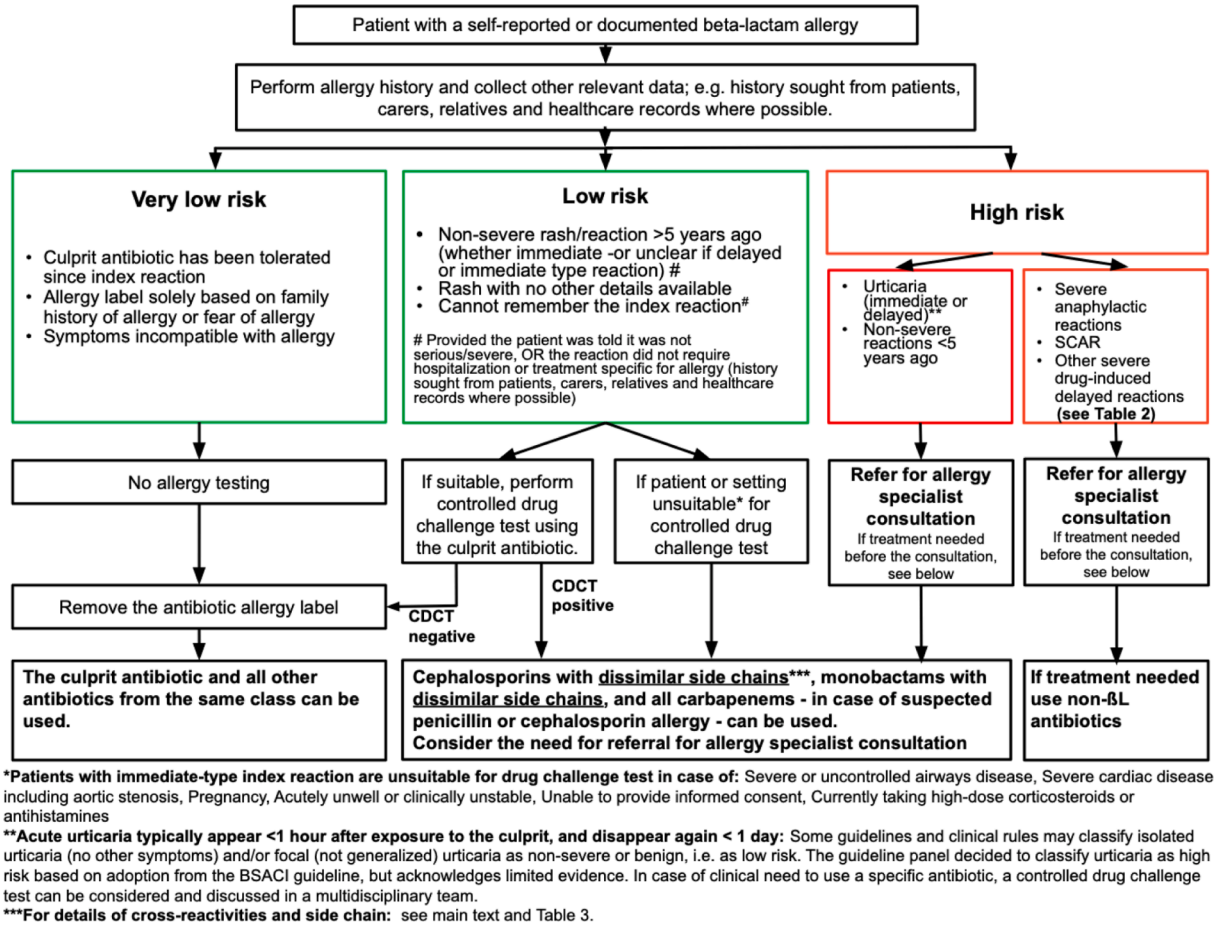

Fig. 1. Flow diagram for the approach towards a reported penicillin allergy. Legend: ßL, beta-lactam; CDCT, controlled drug challenge test; SCAR, severe cutaneous adverse reaction.

General recommendations on the approach towards a suspected penicillin- or other β-lactam allergy

Key question: Which patients with a reported β-lactam antibiotic allergy have a low risk of an actual allergy and can therefore be re-exposed to the culprit antibiotic?

Recommendation 1.1. All patients labelled as 'penicillin allergic' should have a penicillin-allergy assessment using needs-based prioritization. (Strong recommendation, SIGN grade E).

Source guideline: This recommendation was adapted from the 2022 BSACI guideline [10].

Evidence summary: The recommendation is based on extensive data showing that 90–95% of patients with a penicillin-allergy label do not have a true allergy when formally tested [21,22]. In addition, carrying a penicillin-allergy label is associated with increased risks of mortality, treatment failure, *C. difficile* infection, Methicillin-resistant *Staphylococcus aureus* infection, toxicity and harm from non–β-lactam alternatives [23–25]. Recent studies have demonstrated that clinical evaluation strategies, using readily available patient history or medical records, can effectively and safely remove incorrect antibiotic allergy labels. This has allowed many patients to receive β-lactam antibiotics again [26–32]. Depending on the strategy used, patients may undergo direct delabelling, allergy specialist referral or a drug challenge test conducted by trained medical personnel (not necessarily allergy specialists). Implementation studies estimate that up to 85% of patients with a penicillin-allergy label may benefit from such an assessment [26,33].

The updated literature search identified 22 relevant studies: 3 randomized trials, 5 prospective cohorts, 3 retrospective studies and 11 systematic reviews, including 3 meta-analyses. All studies reported high rates of successful delabelling after risk assessment, with a low incidence of adverse events (0.5–3.5% with a vast majority of mild positive reactions) [3,4,34–47]. Three studies showed that allergy assessment programmes can be effectively implemented in hospital care without the need for continued on-site supervision or care by allergy specialists [41], including surgery [48–51] and intensive care unit (ICU) departments [48], with successful interventions also led by nurses [50] and pharmacists [43].

Rationale.

This recommendation aims to emphasize the need for broader hospital-based implementation of evidence-based penicillin-allergy assessment, enabling a substantial number of patients to be safely delabelled outside specialist allergy clinics. It is cost-effective [52] and may reduce the need for drug challenges by allowing direct delabelling when appropriate, making it more acceptable to patients by avoiding testing. The reason for adapting the original recommendation by adding the formulation 'needs-based prioritization' was to reflect the pragmatic reality in Europe and beyond, where limited resources may yet prevent universal implementation.

Recommendation 1.2. Nonallergists should perform drug challenge tests in low-risk patients in a setting where allergic reactions, including anaphylaxis, can be treated (Strong recommendation/SIGN grade E).

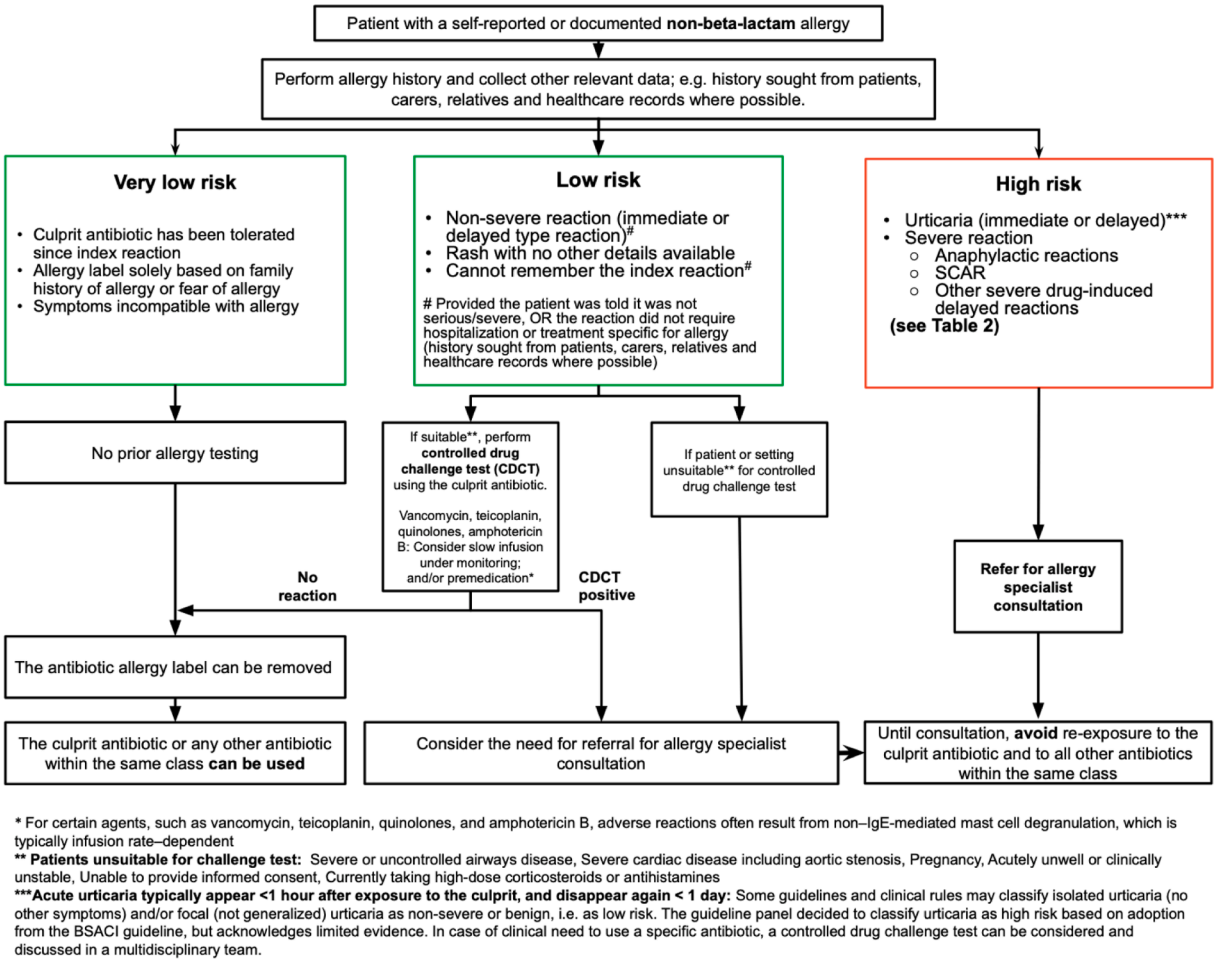

Fig. 2. Flow diagram for the approach towards non−β-lactam antibiotics. Legend: ßL, β-lactam; CDCT, controlled drug challenge test; SCAR, severe cutaneous adverse reaction.

Source guideline.

This recommendation was adopted from the 2022 BSACI guideline [10].

Evidence summary.

The frequency of severe anaphylactic reactions after drug challenge tests in patients with a low risk of having a true β-lactam allergy is very low, but not absent [21,22,26–29,53–56]. The updated literature search identified 13 relevant studies—2 randomized trials, 1 prospective cohort, 1 retrospective study and 9 systematic reviews (6 with meta-analyses)—reporting severe adverse event rates between 0% and 0.42% [3,4,34,35,37,38,40,42,43,45,48,49].

Rationale.

By this recommendation, nonallergy specialists are supported to use single-day/dose drug challenge testing in a certain patient population to reassure both patients and clinicians that a patient does not have a severe IgE-mediated allergy to the selected antibiotic and can safely be treated with that antibiotic. A single-day/dose drug challenge test cannot reliably rule out delayed-onset reactions and these may still occur during subsequent therapy, but evidence suggests these are mild. The recommendation reflects a pragmatic, safety-first approach, as no studies specifically define the optimal setting for drug challenge testing. Performing drug challenge tests in settings prepared to treat anaphylaxis remains a core patient safety requirement, regardless of the low event rate.

Recommendations on direct removal of the antibiotic allergy label and on performing a controlled drug challenge

Key question: When, based on patient-derived information, is a reaction not allergic, and can an allergy label be removed?

Recommendation 2.1. We recommend that an antibiotic allergy label can be removed directly without previous allergy testing when one of the following criteria applies (very low risk of antibiotic allergy).

- The culprit drug has been used since the index reaction without the occurrence of an allergic reaction.
- The allergy label was solely based on a positive family history of allergy or fear of allergy.
- The reported signs and symptoms are not compatible with an allergic reaction (i.e. gastro-intestinal complaints only, palpitations, blurred vision, headache, candidiasis).

(Strong recommendation, moderate quality of evidence – GRADE).

Source guideline: This recommendation was adapted from the Dutch Working Party on Antibiotic Policy (SWAB) guideline for the approach to suspected antibiotic allergy [11].

Evidence summary: The recommendation is supported by consistent findings from multiple observational studies showing that patients at very low risk for true antibiotic allergy can be

Table 2
Definitions of severe and nonsevere manifestations of a suspected antibiotic allergic reaction

Definitions	By symptoms of reaction (WAO/EAACI criteria [18,19])	OR	By consequences of reaction (CIOMS criteria [20])
Severe	1. Acute onset of an illness (minutes to several hours) with involvement of the skin OR/AND mucosal tissue (e.g. generalized urticaria[a], pruritus or flushing, swollen lips-tongue-uvula) AND at least one of the following: a Respiratory compromise (e.g. dyspnoea, wheeze-bronchospasm, stridor, reduced PEF, hypoxemia) b. Reduced BP or associated symptoms of end-organ dysfunction (e.g. hypotonia [collapse], syncope, incontinence) 2. Acute onset of hypotension or bronchospasm or laryngeal involvement after exposure to a known or highly probable allergen for that patient (minutes to several hours), even in the absence of typical skin involvement. 3 Danger signs for severe cutaneous adverse reactions: a Tiny vesicles or crusts, grey-violaceous or dusky colour of lesions, painful or burning skin and/or mucosa in addition to fever and malaise, haemorrhagic erosions of mucous membranes and skin detachment (SJS/TEN) b. Exanthema with pustules (AGEP) c. Purpura (vasculitis) d. Macules/papules together with noncutaneous organ involvement; progression to more than 50% of the body surface area, deviating laboratory values (differential blood count, liver and kidney parameters) (DRESS). e. Facial oedema, oedematose and infiltrated skin inflammation. Acute fever of 38.5°C and higher. (AGEP/DRESS)	OR	Those reactions that are fatal, life threatening, cause hospitalization, result in persistent or significant disability or incapacity, require intervention to prevent permanent damage, or cause congenital anomalies
Nonsevere	1. Symptom(s)/sign(s) from one organ system present: a. Cutaneous: urticaria[a] (localized) erythema-warmth, pruritus, tingling, itching of the lips, OR b. Upper respiratory: nasal symptoms (e.g. sneezing, rhinorrhoea, nasal pruritus, and/or nasal congestion), throat-clearing (itchy throat), cough not related to bronchospasm. OR c. Conjunctival: erythema, pruritus, or tearing 2. Maculopapular exanthema without organ involvement. OR 3. Other: nausea, metallic taste, gastrointestinal symptoms (e.g. cramping abdominal pain, repetitive vomiting)	OR	All other consequences

This table is adapted from the WAO allergy guidance position paper [18], the EAACI position paper [19] and CIOMS criteria [20] on how to classify cutaneous manifestations of drug hypersensitivity. AGEP, acute generalized exanthematous pustulosis; BP, blood pressure; CIOMS, Council for International Organizations of Medical Sciences; DRESS, drug rash with eosinophilia and systemic symptoms; EAACI, European Academy of Allergy and Clinical Immunology; PEF, peak expiratory flow; SJS, Stevens–Johnson Syndrome; TEN, toxic epidermal necrolysis; WAO, World Allergy Organization.

[a] Acute urticaria typically appear <1 hour after exposure to the culprit and disappear again <1 day: some guidelines and clinical rules may classify isolated urticaria (no other symptoms) and/or focal (not generalized) urticaria as nonsevere. The guideline panel decided to classify urticaria as high risk (independently of the severity) based on adoption from the BSACI guideline but acknowledges limited evidence.

safely delabelled without prior allergy testing. Very low-risk criteria include non–immune-mediated symptoms (e.g. nausea, vomiting, diarrhoea, headache, blurred vision), lack of temporal association with drug exposure, documented tolerance on re-exposure or labels based solely on family history or fear of allergy. Although criteria varied slightly across studies, some studies used oral challenge testing, whereas in others, patients were delabelled based on history alone. All demonstrated that such approaches reliably identify suitable patients, with a very low risk of severe allergic reactions (<1%) and a low overall reaction rate (0–3%) [26,29,30,57–65].

The updated literature search identified two relevant studies. The first, a prospective multicentre cohort, reported that 337 of 490 patients were safely delabelled based on history alone, with a low re-labelling rate because of mild reactions (0.9%) [44]. The second, a systematic review by Powell et al. [41], included 69 studies and found that 689 of 4350 patients (15.8%) were safely delabelled without harm through non–allergist-led, history-based approaches.

Rationale: Collectively, the evidence supports a structured, history-based delabelling pathway executed by nonallergists for patients at very low risk of true allergies. This is a safe, feasible strategy that promotes antimicrobial stewardship across healthcare settings. The recommendation was adapted, rather than fully adopted, to include additional common signs and symptoms—such as headache and candidiasis—referenced in the BSACI guideline. In addition, the criterion in the original recommendation 'If there is no temporal association between exposure and onset of symptoms' was excluded because of a lack of clarity and definition. Of note, ideally, the physician responsible for conducting the direct delabelling should verify that all medical records under his or her management have been updated to

Table 3
Risk of cross-allergy between β-lactam antibiotics

Beta-lactam Antibiotic	Amoxicillin	Penicillin G	Penicillin V	Flucloxacillin	Feneticillin	Piperacillin	Cefalexin	Cefazolin	Cefalothin	Cefuroxime	Cefaclor	Cefamandole	Ceftibuten	Ceftriaxone	Cefotaxime	Ceftazidime	Cefepime	Cefiderocol	Ceftaroline	Ceftolozane	Meropenem	Imipenem	Ertapenem	Aztreonam
Amoxicillin	■	▒	▒	▒	▒	▒	■	✓	✓	✓	■	■	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
Penicillin G	▒	■	▒	▒	▒	▒	■	✓	✓	✓	■	■	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
Penicillin V	▒	▒	■	▒	▒	▒	■	✓	✓	✓	■	■	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
Flucloxacillin	▒	▒	▒	■	▒	▒	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
Feneticillin	▒	▒	▒	▒	■	▒	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
Piperacillin	▒	▒	▒	▒	▒	■	■	✓	✓	✓	■	■	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
Cefalexin	■	■	■	✓	✓	■	■	✓	✓	✓	■	■	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
Cefazolin	✓	✓	✓	✓	✓	✓	✓	■	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
Cefalothin	✓	✓	✓	✓	✓	✓	✓	✓	■	■	✓	✓	✓	✓	■	✓	✓	✓	✓	✓	✓	✓	✓	✓
Cefuroxime	✓	✓	✓	✓	✓	✓	✓	✓	■	■	✓	✓	✓	■	■	■	■	■	■	■	✓	✓	✓	■
Cefaclor	■	■	■	✓	✓	■	■	✓	✓	✓	■	■	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
Cefamandole	■	■	■	✓	✓	■	■	✓	✓	✓	■	■	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
Ceftibuten	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	■	■	■	■	■	■	■	■	✓	✓	✓	■
Ceftriaxone	✓	✓	✓	✓	✓	✓	✓	✓	✓	■	✓	✓	■	■	▪	■	■	■	■	■	✓	✓	✓	■
Cefotaxime	✓	✓	✓	✓	✓	✓	✓	✓	■	■	✓	✓	■	▪	■	■	▪	■	■	■	✓	✓	✓	■
Ceftazidime	✓	✓	✓	✓	✓	✓	✓	✓	✓	■	✓	✓	■	■	■	■	■	▪	■	■	✓	✓	✓	▪
Cefepime	✓	✓	✓	✓	✓	✓	✓	✓	✓	■	✓	✓	■	■	▪	■	■	■	■	■	✓	✓	✓	■
Cefiderocol	✓	✓	✓	✓	✓	✓	✓	✓	✓	■	✓	✓	■	■	■	▪	■	■	■	■	✓	✓	✓	▪
Ceftaroline	✓	✓	✓	✓	✓	✓	✓	✓	✓	■	✓	✓	■	■	■	■	■	■	■	■	✓	✓	✓	■
Ceftolozane	✓	✓	✓	✓	✓	✓	✓	✓	✓	■	✓	✓	■	■	■	■	■	■	■	■	✓	✓	✓	■
Meropenem	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	■	■	■	✓
Imipenem	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	■	■	■	✓
Ertapenem	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	■	■	■	✓
Aztreonam	✓	✓	✓	✓	✓	✓	✓	✓	✓	■	✓	✓	■	■	■	■	■	■	■	■	✓	✓	✓	■

■	Cross-tabulation similar
▒	Allergy possible based on the formation of Penicilloyl-poly-L-lysine (PPL)
■	Potential cross allergy based on similarity in R1 or R2 side chain and/or clinical studies
■	Potential cross allergy based on identical in R1 or R2 side chain
✓	No risk of a cross allergic reaction

Table 4
Principles for performing a controlled drug challenge test

Principles for performing a controlled drug challenge test (CDCT)
1) Inform the patient and obtain consent, check for patient suitability.[a]
2) CDCT should be performed in a setting where vital signs can be measured, and allergic reactions can be treated.
3) Single-dose or graded-dose CDCT can be used depending on local preference
• Single-dose CDCT: administer 100% of a full dose of the index antibiotic, preferably orally, or via an alternative route if necessary. If the index drug is unknown but probably a penicillin, amoxicillin (500 mg for adults) should be used
• Graded-dose CDCT according to local protocol[b]
4) Should symptoms consistent with anaphylaxis develop during the test, treat the patient in accordance with local protocol or national guidelines for the management of anaphylaxis
5) The patient should be observed at least for 1 h after the last dose.
6) The patient should be provided with clear written instructions about what to do if symptoms develop after leaving the hospital.
7) A system should be in place to inform the GP and other relevant healthcare professionals about the result of the CDCT. The patient should receive clear (preferably) written information about the test result and its implications

GP: General Practitioner.

[a] Patients with immediate-type index reaction are unsuitable for drug challenge test in case of: severe or uncontrolled airways disease, severe cardiac disease including aortic stenosis, pregnancy, acutely unwell or clinically unstable, unable to provide informed consent, currently taking high-dose corticosteroids or antihistamines.

[b] Example of graded-dose CDCT as suggested by the BSACI 2022 Guideline [8]: administer 10% of a full dose of the index antibiotic, (i.e. 50 mg amoxicillin for adults); observe for 30 min; administer 50% of a full dose of the index antibiotic (i.e. 250 mg amoxicillin for adults); observe for 30 min; administer remainder of a full dose of the index antibiotic (i.e. 200 mg amoxicillin for adults); observe for 60 min.

remove the relevant label and—if possible—undertake efforts so that other care providers and institutional correspondents are appropriately informed of this modification.

Key question: Which patients with a reported β-lactam antibiotic allergy have a low risk of an actual allergy and can therefore be re-exposed to the culprit antibiotic?

Recommendation 2.2a. We recommend that patients with a history of a low-risk index reaction can receive a CDCT of the culprit β-lactam antibiotic in an appropriate clinical setting.

Low-risk patients are defined as:

- Patients with a history of a nonsevere cutaneous reaction >5 years ago (independent of the type—immediate or delayed—of the reaction)
- The patient reports only a rash with no other history available*
- The patient cannot remember the index reaction symptoms*

*Under the condition that the patient was either told the reaction was not serious/severe AND/OR the reaction did not require hospitalization or medical treatment specific for allergy.

(Strong recommendation, low quality of evidence – GRADE).

Recommendation 2.2.b We suggest that hospitalized patients with a suspected nonsevere, delayed-type index reaction that occurred >5 years ago (low-risk category) can receive the culprit β-lactam antibiotic without controlled drug challenge testing*

*Follow-up is warranted; if no reaction occurs during treatment, the label should be removed.

(Weak recommendation, low quality of evidence – GRADE).

Source guidelines: These two recommendations resulted from merging and adapting three recommendations from the Dutch Working Party on Antibiotic Policy (SWAB) guideline for the approach to suspected antibiotic allergy—2.2. a and 2.2. b— [11] and the 2022 BSACI guideline—2.2. a— [10].

Evidence summary: The source guidelines cite several studies [27–30,54,58,66,67] showing that the above-mentioned criteria identify approximately 50% of patients labelled as penicillin allergic who are at low risk of having a true penicillin allergy. This applies across various settings—including outpatient, hospitalized, paediatric, ICU and geriatric populations—and allows safe delabelling via controlled drug challenge testing. Ultimately, this approach could reduce testing costs and benefit patients by removing incorrect allergy labels [68].

The updated literature search identified 11 relevant new studies. Three randomized controlled trials [38,46,48], one prospective cohort study [36], two retrospective studies [69,70] and six systematic reviews [3,34,39,41,42,45,49], five of which included meta-analyses. Collectively, these studies reinforced the previously established criteria and benefits, confirming a very low risk (0–0.3%) of severe adverse reactions [3,4,42,45].

Rationale: These adapted recommendations merge similar guidance from the two above-mentioned guidelines. They avoid interpretations of 'appropriate clinical setting' across countries and simplify risk stratification for easier implementation.

A separate recommendation (2.2b) was developed for hospitalized patients with nonsevere delayed reactions. This recommendation is aimed at—and can be applied to—a subpopulation of the patient population captured in recommendation 2.2. a. Importantly, both recommendations must not be interpreted as contradictory guidance. Rather, recommendation 2.2. b must be read as a specific additional recommendation in this section, which allows us to follow this recommendation instead of 2.2. a for the subpopulation mentioned. The reason behind this is that a single-dose drug challenge test is reliable for detecting IgE-mediated allergies but probably fails to identify delayed reactions. Therefore, in case the reported reaction is (almost) certainly a delayed-type reaction, it is more logical to follow the approach suggested in recommendation 2.2. b. In summary, for hospitalized patients with a history of nonsevere delayed reactions occurring more than 5 years ago, and who require treatment with the culprit β-lactam, we suggest initiating the therapeutic course. If the history does not clearly distinguish between immediate and delayed reactions, follow the approach recommended in 2.2a.

Key question: Which patients with a reported β-lactam antibiotic allergy have a low risk of an actual allergy and can therefore be re-exposed to the culprit antibiotic?

Recommendation 2.3. We recommend against re-exposure to the culprit drug class in patients with severe delayed-type index reactions (high risk for an antibiotic allergy).

(Strong recommendation, good practice statement – GRADE).

Recommendation 2.4. We recommend that patients with suspected nonsevere, immediate-type index reactions that occurred ≤5 years ago OR a suspected severe immediate-type index reaction irrespective of time elapsed should be referred for formal allergy work-up before re-exposure can be considered (high risk for an antibiotic allergy).

(Strong recommendation, low quality of evidence – GRADE).

Source guideline.

Both recommendations were adapted from the Dutch Working Party on Antibiotic Policy (SWAB) guideline for the approach to suspected antibiotic allergy [11].

Evidence summary.

The source guideline presents evidence linking a high risk of β-lactam allergy to two key factors: (I) a shorter interval between the index reaction and allergy evaluation [71,72] and (II) a history of severe immediate (e.g. anaphylaxis, angioedema) or severe delayed reactions [71–77]. Severe delayed reactions are commonly accepted as life threatening. The updated literature search identified five studies that were considered relevant in relation to recommendation 2.4: two prospective cohorts [37,78], one retrospective study [69] and two systematic reviews [34,40]. All but one—likely due to high heterogeneity [40]—supported the association between increased allergy risk and the two (I+II) outlined key factors.

Rationale.

Recommendation 2.3 follows a precautionary principle, emphasising that those patients with a severe delayed reaction to any antibiotic—cutaneous or noncutaneous—must not be re-exposed to the culprit drug because of the high risk of true allergy and potential for life-threatening outcomes. In such cases, the risk outweighs any potential benefit. The recommendation was adapted to advise avoidance of the entire drug class, as cross-reactivity studies in β-lactam allergy consistently exclude patients with severe delayed reactions. The phrase "irrespective of the time since the index reaction" was removed to improve clarity. Recommendation 2.4 outlines criteria for evaluating patients at high risk of true immediate β-lactam allergy in settings that involve allergy specialists, where the risk of severe reactions and the need for testing can be assessed in detail.

Because of their strong association with (IgE-mediated) immediate-type reactions, urticaria were classified as high-risk by the panel (Figs. 1 and 2) as a conservative and safety-first approach. The panel acknowledges that the term 'urticaria' is sometimes used incorrectly to describe nonspecific rashes and may encompass nonallergic and/or delayed hypersensitivity reactions. In cases of isolated, focal urticaria, a CDCT may be considered after evaluation by a multidisciplinary team as recommended in some guidelines. This topic is additionally addressed in paragraph 6 of the results section: Identified knowledge gaps and future research needs.

Details of performing a CDCT

Key question: What are the minimum safety requirements for a CDCT?

Recommendation 3.1. We recommend that the principles for the conduct of a CDCT be applied as follows in patients identified as low risk for penicillin allergy.

(Strong recommendation, SIGN grade E) (see Table 4).

- Informed consent is required.
- Single-dose OR graded-dose CDCT can be used depending on local preference.
- Single-dose CDCT: administer 100% of a full dose of the index penicillin, or, if unknown, amoxicillin (500 mg = adult dose).
- Graded-dose CDCT* should be performed according to local protocol.
- Should symptoms consistent with anaphylaxis develop during the test, treat the patient following local protocol or national guidelines for the management of anaphylaxis.
- The patient should be observed for 1 hour after the last dose.
- The patient should be provided with clear written instructions about what to do if symptoms develop after leaving the hospital.
- A system should be in place to inform the GP and other relevant healthcare professionals about the result of the CDCT. The patient should receive clear (preferably) verbal and written information about the test result and its implications.

*We here provide the graded-dose CDCT suggested by the BSACI 2022 Guideline [8] as an example: administer 10% of a full dose of the index antibiotic, (i.e. 50 mg amoxicillin for adults); observe for 30 minutes; administer 50% of a full dose of the index antibiotic (i.e. 250 mg amoxicillin for adults); observe for 30 minutes; administer remainder of a full dose of the index antibiotic (i.e. 200 mg amoxicillin for adults); observe for 60 minutes.

Patients are unsuitable for a CDCT in case of:

- Acutely unwell or clinically unstable condition.
- Severe or uncontrolled airways disease.
- Severe cardiac disease (e.g. severe aortic stenosis).
- Pregnancy.
- Impossibility to obtain informed consent (from patient or legal representative).
- Currently taking high-dose corticosteroids.
- Currently taking antihistamines and unable to withhold prior to testing.

Source guideline: This recommendation was adapted from the BSACI guideline for the approach to suspected antibiotic allergy [10].

Evidence review: Consistent evidence from prospective and retrospective studies shows that drug challenge testing is safe in patients with a low likelihood of true penicillin allergy [21,22,26–30,53]. When reactions do occur, they are generally mild to moderate and tend to manifest several days after the challenge. Across studies involving over 1400 adults and children, hypersensitivity reaction rates to challenge tests were low (0.8–6%), with extremely rare severe reactions and no confirmed anaphylaxis. These findings indicate that basic safety measures, such as appropriate clinical observation, are sufficient to manage the low risk of adverse events. Stricter precautions may unnecessarily hinder the delabelling process without improving patient safety.

The literature search update retrieved six relevant studies: two meta-analyses [34,42], one prospective cohort [51], two retrospective studies [36,47] and one systematic review [35]. All reported that severe reactions to drug challenge tests were rare in patients with reported penicillin allergy. One meta-analysis of 112 studies involving 26 595 participants estimated the incidence of severe reactions at 0.06% (95% CI: 0.01–0.13%; I^2 = 57.9%) [34]. Another meta-analysis, focused on 8334 paediatric tests, reported a 5.23% overall positive reaction rate, with immediate reactions at 0.8%, delayed reactions at 3.69%, and only three severe events (0.036%) [42].

Rationale.

The panel endorses controlled drug challenge testing in low-risk patients as a safe, evidence-based approach with extremely low risk of severe adverse events. Minimum safeguards—appropriate clinical setting, appropriate observation and patient education—are sufficient to manage potential reactions and maintain safety and trust in the process. In contrast, more excessive restrictions (like intubation readiness in the case of patients with a low risk of allergy) may hinder delabelling and limit access to testing.

Key question: Should multiple-day challenges be performed in patients with reported penicillin allergy?

Recommendation 3.2. We recommend against the routine use of multiple-day drug challenge testing in the evaluation of penicillin allergy (Strong recommendation, not graded).

Source guideline.

This recommendation was adopted from the 2022 Drug Allergy Practice Parameter Update [5].

Evidence review.

The recommendation is supported by consistent evidence from multiple prospective and retrospective studies showing that multiday CDCT offers no added benefit over single-day testing in low-risk penicillin-allergy patients [79–83]. Reported delayed reaction rates after negative skin testing or repeated β-lactam exposure were very low (0–1.8%) [79–83]. Furthermore, most delayed reactions were safely detected with a single-day challenge [76,77]. For example, in one study using a 7-day washout after a single-dose challenge before starting therapy at home, only two patients developed a mild rash during the washout, and one additional mild exanthema occurred during treatment in 116 patients [83]. An updated literature search identified one relevant study—a systematic review and meta-analysis of 42 studies and over 10 000 challenge tests [45]. It compared prolonged (2–10 days) vs. single-day tests in suspected β-lactam allergy. The confirmed hypersensitivity rate was 6.96%: 3.31% on day one and 3.65% during extended testing. Although detection increased slightly (~3%), the added yield was modest. Half of the additional positives occurred on days 2–3. Severe reactions were very rare (0.02%), and detecting one extra mild case required testing 28 more patients [45]. These findings suggest single-day testing is sufficient for identifying most delayed reactions in low-risk patients.

Rationale.

Routine multiday drug challenge testing after a negative single-day challenge is not recommended in patients with low-risk penicillin allergy. Evidence shows that single-day testing is safe, effective and identifies most clinically relevant reactions, which are typically mild and self-limiting. In contrast, prolonged testing adds limited diagnostic value while increasing unnecessary antibiotic exposure. Prolonged regimens may contribute to antimicrobial resistance, *C. difficile* infection and other avoidable harms, potentially increasing the healthcare burden. Although

both approaches are low-cost, the added risks and minimal benefit of multiday testing do not justify its routine use.

Cross-allergy between β-lactams

Part I. Penicillins

Key question: In which patients with a reported allergy to a penicillin, a different penicillin can be administered with an acceptable low risk of an allergic reaction?

Recommendation 4.1: We recommend that in patients with a reported (suspected) immediate-type allergy to penicillins, irrespective of severity, that occurred ≤5 years ago, all other penicillins should be avoided (strong recommendation, low quality of evidence – GRADE).

Recommendation 4.2: We suggest that in patients with a reported (suspected) nonsevere immediate-type allergy to a certain penicillin, that occurred >5 years ago (low risk), a CDCT with other penicillins can be performed based on indication (Weak recommendation, low quality of evidence – GRADE).

We suggest that in patients with a reported (suspected) nonsevere delayed-type allergy to penicillins that occurred >5 years ago (low risk), all other penicillins can be used in a controlled setting (Weak recommendation, low quality of evidence – GRADE).

Source guideline: Recommendation 4.1 was adopted and recommendations 4.2. and 4.3. were adapted from the Dutch Working Party on Antibiotic Policy (SWAB) guideline for the approach to suspected antibiotic allergy [11].

Evidence summary: Evidence on penicillin cross-reactivity comes primarily from observational studies using formal allergy testing, which indicated some risk of cross-reactivity between various penicillins [84–90]. However, in practice, most patients labelled as allergic can safely tolerate penicillins, possibly because most labels are false [91–93]. Overly cautious interpretation of cross-reactivity data may lead to unnecessary avoidance and increased use of second-line antibiotics, which are associated with poorer outcomes [24,94,95]. The 5-year threshold for identifying high-risk patients was based on the criteria established by Trubiano et al. [31]. In their study, four factors were linked to positive penicillin-allergy test outcomes: a reaction occurring within the past 5 years, a history of anaphylaxis or angioedema, severe cutaneous adverse reactions and the need for treatment during the initial episode. The PALACE clinical trial, which assessed this clinical decision rule to support direct oral challenges using a randomized design, further highlighted the safety of this approach [38]. The updated literature search did not retrieve additional relevant, high-quality studies.

Rationale.

As a safety-first approach, the panel recommended avoiding all penicillins in cases of suspected or confirmed immediate-type allergy if the reaction occurred within the past 5 years. If penicillin use is clinically necessary, formal allergy testing may be warranted. Alternatively, a cephalosporin with a dissimilar side chain (as detailed below in Part II, Penicillins vs. Cephalosporins or Carbapenems, and in Fig. 1) may be used. For patients who report a reaction that occurred more than 5 years ago and who require treatment with another penicillin, the recommendations allow for a CDCT when clinically indicated. For suspected nonsevere delayed (low-risk) reactions, a conservative 5-year threshold was adopted—in contrast to the Dutch guideline's 1-year threshold—because of limited supporting evidence. The 5-year threshold is acknowledged as arbitrary, based on the PEN-FAST score and evidence on penicillin-allergy half-life [31,38,96]. Of note, in recommendation 4.3 'controlled setting' refers to a setting in a hospital environment and not to a 'controlled drug challenge test'. When there is uncertainty whether it concerns an immediate or delayed-type reaction, the guideline panel advises using the approach as if it was an immediate-type reaction (per recommendation 4.2).

Part II. Penicillins vs. cephalosporins or carbapenems

Key questions:

In which patients with a reported immediate-type allergy to a penicillin, a cephalosporin can be administered with an acceptably low risk of an allergic reaction?

In which patients with a reported delayed-type allergy for a penicillin, a cephalosporin can be administered with an acceptably low risk of an allergic reaction?

In which patients with a reported allergy to penicillin, a monobactam or carbapenem can be administered with an acceptable low risk of an allergic reaction?

Recommendation 4.4. We recommend that patients with a suspected or proven immediate-type allergy to penicillins* can receive cephalosporins, but only those with dissimilar side chains (Strong recommendation, moderate quality of evidence – GRADE).

*With the exception of patients with severe anaphylaxis (e.g. anaphylactic shock), in which case the panel recommends seeking expert evaluation first.

See Table 3 to compare side chains (dis-)similarity.

Recommendation 4.5. We suggest that patients with suspected or proven nonsevere, delayed-type allergy to penicillins can receive cephalosporins with dissimilar side chains, irrespective of the time elapsed since the index reaction (Weak recommendation, low quality of evidence – GRADE).

Recommendation 4.6. Cefazolin does not share any side chains with the currently available penicillins and can be used in cases of suspected or proven immediate-type allergy to a penicillin*, irrespective of severity or time elapsed since the index reaction (Strong recommendation, moderate quality of evidence – GRADE).

*With the exception of patients with severe anaphylaxis (e.g. anaphylactic shock), in which case the panel recommends seeking expert evaluation first.

Recommendation 4.7. We recommend that the following patients receive any monobactam or carbapenem, without prior allergy testing: patients with suspected or proven immediate-type penicillin allergy (low and high risk*), patients with nonsevere, delayed-type penicillin allergy (low risk).

(Strong recommendation, low quality of evidence – GRADE).

*With the exception of patients with severe anaphylaxis (e.g. anaphylactic shock), in which case the panel recommends seeking expert evaluation first.

Source guideline.

Recommendation 4.5. was adopted and recommendations 4.4., 4.6. and 4.7 were adapted from the Dutch Working Party on Antibiotic Policy (SWAB) guideline for the approach to suspected antibiotic allergy [11].

Evidence summary.

The original Dutch guideline recommendations are based on six systematic reviews assessing cross-reactivity between penicillins and cephalosporins in patients with confirmed or suspected penicillin allergy. Outcomes included positive skin tests or clinical reactions to cephalosporins across various generations [97–102].

Patients allergic to penicillins may exhibit cross-reactivity to other β-lactams, either through shared core structures or because of similar or identical R1 side chains [103]. The risk of cross-reactivity with cephalosporins depends almost entirely on side chain similarity. Observational studies consistently show that cephalosporins with dissimilar R1 side chains to the culprit penicillin carry a negligible (<1%) risk [99], whereas those with

similar or identical side chains pose a significantly higher risk, ranging from 5% to 17%, and even greater in some subgroups [98,100].

A recent meta-analysis by Picard et al. [100] included 21 observational studies with 1269 patients with confirmed immediate-type penicillin allergy (via skin testing or drug challenge test). The analysis found a strong correlation between cross-reactivity and R1 side chain similarity: 16.45% (95% CI: 11.07–23.75) for amino-cephalosporins (similarity score = 1), 5.60% (95% CI: 3.46–8.95) for intermediate similarity (score 0.563–0.714) and 2.11% (95% CI: 0.98–4.46) for low similarity scores (<0.4), regardless of cephalosporin generation. This elevated risk applied to both IgE-mediated and T-cell–mediated (delayed) hypersensitivity reactions.

Supporting this, Pichichero [98] analysed data of over 35 000 patients and found that those with confirmed or suspected penicillin allergy had a significantly elevated reaction rate to first-generation cephalosporins with similar side chains (risk difference +7.0%, 95% CI: 6.1–7.8%), particularly in those with confirmed allergy (+7.3%, 95% CI: 1.2–13.6%). Cephalosporins with dissimilar side chains did not show an increased risk. No cross-reactivity has been observed between penicillins and aztreonam in patients with confirmed allergy, according to Picard et al. [100] and Gaeta et al. [104]. Monobactams and carbapenems can therefore be administered without prior testing in both nonsevere immediate and nonsevere delayed-type reactions. However, in severe delayed-type allergy (e.g. Stevens–Johnson syndrome), the cross-reactivity risk remains unclear.

In the literature search update, one study relevant to the recommendations above was identified. In a systematic review and meta-analysis [68], 6147 patients from 77 studies were included. Forty-four patients were allergic to a penicillin and cefazolin, resulting in a frequency of 0.7%. The low rate of penicillin-cefazolin dual allergy strongly suggests that most patients should receive cefazolin regardless of a positive penicillin-allergy history, further supporting recommendation 4.6.

Rationale.

Despite structural similarities within β-lactam antibiotics, evidence indicates that cross-reactivity between penicillins and cephalosporins is primarily driven by R1 side chain similarity. Multiple systematic reviews and meta-analyses repeatedly demonstrated a low risk (<1%) of cross-reactivity when cephalosporins with dissimilar side chains are used in skin tests or proven penicillin-allergic patients. For cephalosporins with similar side chains, the risk increases (5–17%), but can be mitigated through careful selection based on molecular structure. Notably, cefazolin, commonly used for perioperative antimicrobial prophylaxis, shows no increased risk of cross-reactivity. In patients with confirmed penicillin allergy, both monobactams (e.g. aztreonam) and carbapenems have shown no clinically relevant cross-reactivity in immediate- or delayed-type reactions. Therefore, these agents can be considered safe alternatives. For antimicrobial stewardship reasons, a cephalosporin is preferred over a monobactam or carbapenem if the indication permits. The panel could not reach consensus about patients with severe anaphylaxis (anaphylactic shock, ICU admission) because of penicillin allergy. Ultimately, it was decided to exclude these patients from recommendations 4.4. and 4.7.

Part III. Cephalosporins vs. cephalosporins

Key question: In which patients with a reported allergy to cephalosporin, a different cephalosporin can be administered with an acceptable low risk of an allergic reaction?

Recommendation 4.8. We suggest that referral for allergy work-up should be considered to prove or disprove suspected immediate-type allergy to cephalosporins in patients (Weak recommendation, good practice statement – GRADE).

Recommendation 4.9. We recommend that cephalosporins with a dissimilar side chain can be used in patients with a suspected or proven immediate-type allergy to a cephalosporin* (Strong recommendation, moderate quality of evidence – GRADE).

*With the exception of patients with severe anaphylaxis (e.g. anaphylactic shock), in which case the panel recommends seeking expert evaluation.

Recommendation 4.10. We recommend that cephalosporins with a dissimilar side chain can be used in patients with a suspected or proven nonsevere delayed-type allergy to a cephalosporin, irrespective of time since index reaction (Strong recommendation, low quality of evidence – GRADE).

Source guideline.

Recommendations 4.8. and 4.9. were adapted and recommendation 4.10. was adopted from the Dutch Working Party on Antibiotic Policy (SWAB) guideline for the approach to suspected antibiotic allergy [11].

Evidence summary.

Data from cohort analyses show that cephalosporins are extensively utilized in both inpatient and outpatient settings. Reported cephalosporin allergies rank second only to penicillin allergies in certain patient cohorts [105–107]. Using alternative antimicrobial agents, particularly for perioperative prophylaxis, has been associated with a higher incidence of surgical site infections, prolonged hospitalizations and increased morbidity [58,108]. Current evidence indicates that cross-reactivity among cephalosporins is primarily driven by structural similarity of the R1 side chain and, to a lesser extent, by similarity of the R2 side chain (Table 3) [109]. Observational studies involving formal allergy testing have provided most of the available data on suspected immediate- and delayed-type cephalosporin allergies [110–118].

The updated literature search identified two relevant studies. Cox et al. [78] developed and validated a clinical decision rule to assess cephalosporin allergy risk and guide drug challenge testing and delabelling, using cohorts from Australian and U.S. allergy clinics. Touati et al. [37] retrospectively reviewed 476 patients with suspected cephalosporin allergy at a French clinic; only 25% had confirmed allergy. Delayed reactions were rare and exclusively mild, cutaneous cases, consistent with earlier data from a study performed in Italy, which reported a 4.7% delayed reaction rate, all mild [118].

Rationale.

The WG agreed that formal allergy testing can aid in selecting appropriate antibiotics for suspected cephalosporin allergy. However, access and feasibility vary across healthcare systems, and that limited allergy service availability can be a barrier. Considering the resource demands of allergy workups, the panel issued a weak recommendation and adapted recommendation 4.8 from the Dutch guideline to avoid overburdening healthcare systems. A recently developed clinical decision rule may aid in streamlined risk stratification, guide drug challenge testing and delabelling in patients with a cephalosporin allergy label, pending further external validation [78].

Recommendations 4.9 and 4.10. are based on indirect evidence. The panel weighed the low cross-reactivity risk of cephalosporins with dissimilar sidechains, along with their safety, availability and alignment with antimicrobial stewardship principles, against the harms of second-line antibiotic use. Delayed mild reactions to cephalosporins are uncommon, even in specialized allergy settings [37,118]. In nonspecialist settings, most reported reactions are not confirmed as true allergies, suggesting a low overall risk of harm.

In line with recommendations 4.4. and 4.7, it was advised that in case of severe anaphylaxis (anaphylactic shock, ICU admission) patients are referred for specialist evaluation.

Part IV. Cephalosporins vs. monobactams and carbapenems

Key question: In which patients with a reported allergy to a cephalosporin, a monobactam or carbapenem can be administered with an acceptable low risk of an allergic reaction?

Recommendation 4.11. We suggest that any carbapenem can be used in a clinical setting in patients with suspected or proven, immediate-type allergy to a cephalosporin, irrespective of time elapsed since index reaction*.

(Weak recommendation, low quality of evidence – GRADE).

*With the exception of patients with severe anaphylaxis (e.g. anaphylactic shock), in which case the panel recommends seeking expert evaluation first.

Recommendation 4.12. We recommend that aztreonam can be used in patients with a suspected or proven, nonsevere, delayed-type allergy to cephalosporins other than ceftazidime or cefiderocol, irrespective of time since the index reaction.

(Strong recommendation, low quality of evidence – GRADE).

Recommendation 4.13. We suggest that any carbapenem can be used in patients with suspected or proven nonsevere, delayed-type allergy to cephalosporins, irrespective of time since the index reaction. (Weak recommendation, very low quality of evidence – GRADE).

Source guideline.

Recommendation 4.11. was adapted, recommendations 4.12. and 4.13. were adopted from the Dutch Working Party on Antibiotic Policy (SWAB) guideline for the approach to suspected antibiotic allergy [11].

Evidence summary.

These recommendations are supported by six observational studies and one systematic review involving both adults and children referred to allergy clinics [37,67,116,118–124]. Overall, the evidence suggests good tolerability. However, aztreonam, ceftazidime and cefiderocol share a common side chain, which may increase the risk of cross-reactivity [120]. As a result, monobactams are generally considered safe, except in cases of presumed immediate-type hypersensitivity to ceftazidime or cefiderocol. The updated literature search did not retrieve additional relevant, high-quality studies.

Rationale.

Carbapenems are widely used for empiric treatment of severe infection and have a strong safety profile. Cohort studies report a low risk of cross-reactivity in patients with cephalosporin allergy [37]. The panel concluded that the benefits of carbapenem use in patients with suspected or confirmed immediate or mild delayed-type cephalosporin allergies outweigh the very low risk of an allergic reaction. The panel recommends referral to a specialist for patients with severe anaphylaxis (ICU admission, anaphylactic shock) to cephalosporins, adapting the recommendation from the source guideline.

Aztreonam-avibactam is one of the few treatment options against certain carbapenemase-producing bacteria. Cross-reactivity is primarily driven by side-chain similarity. Hence, the use of aztreonam is generally safe unless the implicated cephalosporin is ceftazidime or cefiderocol [116,120,122–124]. Delayed cephalosporin reactions are uncommon [37], and many reported reactions are not confirmed allergies. On the basis of this evidence, the panel concluded that the use of aztreonam is appropriate for patients with suspected or confirmed mild delayed-type cephalosporin allergy.

Approach to antibiotic allergy in case of reported allergy to a non–β-lactam antibiotic

Key question: Which patients with a non–β-lactam antibiotics allergy label can be re-exposed to the same antibiotic with an acceptable low risk of an allergic reaction?

Of note: For direct delabelling of a reported allergy to a non–β-lactam antibiotic, see recommendation 2.1 (intended for all antibiotic classes).

Recommendation 5.1. We recommend avoiding re-exposure to the culprit non–β-lactam antibiotic and all other non–β-lactam antibiotics within the same class when the index reaction was severe (high-risk, see Table 2) (Strong recommendation, low quality of evidence – GRADE).

Recommendation 5.2. We suggest performing a CDCT in patients with a nonsevere index reaction (low risk) to reintroduce the culprit non–β-lactam antibiotic or any other non–β-lactam antibiotic within the same class (Weak recommendation, low quality of evidence – GRADE).

Source guidelines.

Recommendation 5.1 was adopted from the Dutch Working Party on Antibiotic Policy (SWAB) guideline for the approach to suspected antibiotic allergy [11]. Recommendation 5.2 was adapted from the Dutch Working Party on Antibiotic Policy (SWAB) guideline and the 2022 Drug Parameter Update [5,11].

Evidence summary.

The Dutch guideline systematically reviewed data on suspected allergies to non–β-lactam antibiotics, mainly focusing on adverse reactions to macrolides and quinolones. For glycopeptides and sulphonamides, only descriptive summaries were available. All included studies were observational and conducted in formal allergy testing settings. Skin testing has limited diagnostic value for non–β-lactam antibiotic allergies [125–130]. Although severe reactions are rarely reported, they are more likely to be confirmed through drug challenge testing [125–127,130–132]. In contrast, patients with suspected mild immediate or delayed reactions face a low risk of severe adverse events upon re-exposure [125–131,133–135]. For certain drugs—such as vancomycin, teicoplanin, quinolones and amphotericin B—reactions are often due to non–IgE-mediated mast cell degranulation, typically related to the infusion rate rather than true allergy [130,136–142]. The updated literature search identified four new studies on suspected hypersensitivity to cotrimoxazole. Krantz et al. [143] report that 94% of 204 patients with suspected nonsevere reactions to cotrimoxazole tolerated an oral challenge test, with longer time since the initial reaction significantly associated with tolerance. An Australian study adapted the PEN-FAST tool to create the SULF-FAST score, which showed high negative predictive value at a threshold of <3 and was validated in two independent cohorts [45,144]. In immunocompromised patients, re-evaluation and reintroduction of cotrimoxazole for Pneumocystis pneumonia prophylaxis after a successful challenge yielded significant cost savings [145].

Rationale.

Considering the limited amount of evidence as well as the absence of reliable tools to predict within-class cross-reactivity, re-exposure to an antibiotic from the same antibiotic class should be avoided in patients with a history of severe (high-risk) reactions to a non–β-lactam antibiotic. Although the supporting evidence is of low quality, the data suggest that severe reactions after mild immediate or delayed responses are uncommon. Reactions to vancomycin, teicoplanin, quinolones and amphotericin B are often due to non–non-IgE–mediated mast cell degranulation from rapid infusion and typically do not preclude re-use. Growing evidence also supports safe cotrimoxazole re-challenge in patients with

mild suspected reactions, particularly relevant for immunocompromised individuals.

Identified knowledge gaps and future research needs

Despite recent advances in the clinical evaluation and management of presumed antibiotic allergies, several important knowledge deficits remain. The current 5-year cutoff for mild delayed-onset index reactions requires further refinement. In this guideline a one-size-fits-all time-window is applied, derived from larger cohort studies and validation of the PEN-FAST rule [144]. However, the guideline panel found that the data supporting this time-window for mild delayed-type reactions are dispersed and difficult to summarize comprehensively. In particular, shorter times since index reactions could be as safe. With regard to severe delayed cutaneous reactions, it is unresolved whether safe re-exposure in patients would be possible within the β-lactam class if similar principles as for immediate-type reactions, i.e. considering side-chain (dis)similarity, are followed.

For immediate-type reactions, the classification of reported (acute) urticaria as either low or high-risk reaction—despite some guidelines and published protocols already considering isolated or focal urticaria as nonsevere—represents an area with limited supporting evidence. Moreover, in real-life practice, there is a substantial potential for misclassification of other rashes as being urticaria or vice versa. Future research should assess the true risk these presentations represent and clarify whether a CDCT can be safely offered when there is a clinical need for a specific antibiotic. In the case of the patients with the most severe clinical phenotype of immediate-type reactions, i.e. severe anaphylaxis/anaphylactic shock, the guideline panel discussed whether they should be excluded from applying the recommendations presented in the section on cross-allergic reactions. Here, expert insights diverged. Hence, on the topic of cross-allergy, more research is needed to address this issue.

Regarding the recommendations about performance of a CDCT, more research may be needed to assess single-versus multiday challenge protocols to determine safety and clinical effectiveness as well as impact on healthcare use and patient adherence. Through the use of the ADOLOPMENT procedure for development of this guideline, the panel is confident that current recommendations on this topic are adequate but acknowledges that other practices in performing a CDCT may be as safe and effective—or better.

Actual implementation strategies may differ between hospitals but through the guideline development process it became clear that more data are needed on feasibility, acceptability, equity and cost-effectiveness of controlled drug challenge testing approaches, as well as the integration of decision support tools into clinical workflows. Finally, sustainable delivery of antibiotic allergy evaluation will require adequate staffing, training and other resources that must be addressed while developing implementation strategies. In addition, research is needed to identify effective prioritization strategies for settings where full implementation of the recommended practices is not feasible.

Discussion

Antimicrobial resistance is a global threat to health, and recent estimates suggest 4.71 million deaths were associated with bacterial AMR in 2021 [146]. Antibiotics are among the most common drugs associated with allergy labels and have a profound effect on antibiotic therapy. Although patients with a genuine allergy must continue to avoid the antibiotics that cause a reaction, over recent decades, it has emerged that antibiotic allergy labels are harmful for patients and often incorrect [147]. The focus of antibiotic allergy research has been on penicillin allergy because this is by far the most frequently reported drug allergy. Penicillin-allergy labels, in particular, affect antibiotic prescribing [148], but are also associated with antimicrobial resistance and worse patient health outcomes [148,149]. Whether all of these negative consequences can be reversed is not yet known but prescribing of penicillins can be safely and cost-effectively increased, while also reducing using use of broader-spectrum β-lactams and non−β-lactam antibiotics [30,32,150]. As such, antimicrobial stewardship guidance from the European Union [151], Infectious Diseases Society of America [152] and WHO [153] all encourage penicillin-allergy evaluation. However, implementation of these recommendations has been slow and penicillin-allergy assessment has largely remained in the domain of allergy specialists in many places. Although non-specialist assessment of antibiotic allergy has been found to be safe and effective [41], the lack of well-defined, standardized guidance on how to assess patients with antibiotic allergies is one of the reasons for this lack of progress.

As there was a clear unmet need for a standardized approach to this problem across Europe, The ESCMID therefore undertook to develop a guideline that could be widely applied. To make optimal use of existing guidance and maximize efficiency, an ADOLOPMENT process was used. This supports evidence-based decision-making, whereas the guideline panel was able to accommodate differences such as variation in healthcare infrastructure, medical-cultural values and resource availability. This guideline provides recommendations that are intended to be applicable across healthcare systems in Europe and beyond that considering antimicrobial stewardship principles, patient safety and practicality of implementation.

Awareness of variation in the provision of healthcare across different countries has led to some recommendations being less forceful than we would have liked, as, e.g. there would be no point in making recommendations that were impossible to implement. The recommendations are aimed at all healthcare professionals, but particularly nonallergy specialists, to facilitate the need for expansion of antibiotic allergy assessment beyond specific allergy clinics. Flow diagrams and charts have been included to aid ease of use. Patient safety considerations weighed heavily throughout the guideline development process and where sufficient data were lacking, a more cautious approach was taken.

No guideline can be used as a stand-alone resource, and local implementation in most situations will require a multidisciplinary approach, preferably led/supervised by antimicrobial stewards. Healthcare professionals who are to undertake allergy assessment need to be appropriately trained to perform this task. Even with carrying out assessment in a simulated patient environment, as well as observations of routine practice, potentially major errors in decision-making can be made [154,155].

Limitations

Several methodological limitations should be acknowledged. First, some source guidelines lacked clarity on how certain decisions were reached; this was addressed through panel discussions and appraisal of the supporting evidence. Second, although decisions were made through a consensus process, not all were unanimous, which is not unexpected. Third, much of the evidence informing the source guidelines—and this field in general—was observational and therefore subject to bias, a limitation that could not be resolved here. Fourth, because this guideline synthesizes four previously published guidelines, multiple evidence grading systems were retained. Although this deviates from standard practice and prevented updating the quality of evidence when new

studies became available, it was necessary to maintain alignment with the original documents. Although this may be viewed as a limitation, it was an intentional choice to broaden the scope and enhance the utility. At the same time, the umbrella approach is a strength, consolidating dispersed guidance into a single, more accessible resource.

Implications

The European Union has set a target of a 20% reduction in antibiotic use by 2030 [151]. Penicillin-allergy assessment can reduce total antibiotic use [32] and is therefore a potential means to work towards this target. The WHO has assigned all antibiotics to one of three groups, Access, Watch and Reserve, known as the AWaRe categories, with antibiotics in the Access group intended to minimize the risk of driving antimicrobial resistance [156,157]. The latest UK 5-year National Action Plan to combat AMR has set a target of 70% of total antibiotic use to comprise Access category antibiotics by 2029 [157,158]. Antibiotic allergy assessment provides a means to increase Access category antibiotics compared with Watch and Reserve. Above all, patients with allergies to other antibiotics, and particularly those with multiple antibiotic allergy labels, are at higher risk of suboptimal therapy and implementing this guideline aims to achieve better outcomes for these patients.

Conclusions

In this guideline, we defined and explained 24 recommendations for the assessment and medical management of patients with antibiotic allergies based on four previously published national guidelines and an additional systematic literature review, that are intended to be applicable across Europe and beyond. There is a clear need to widen access to antibiotic allergy assessment for patients, and the provision of a standardized approach should enhance the implementation of this. The guideline can be used and incorporated into antimicrobial stewardship programmes and used to initiate a process that empowers all prescribers to be more involved in providing optimal antimicrobial therapy.

Author Contribution Statement

All authors contributed to the conceptualization of the guideline and the constitution of the final recommendations. BN provided methodological support. MGJdB constructed the first draft of the guideline and supervised the writing process. All other authors contributed to the text by delivering raw paragraph text and reviewing subsequent versions. OJ and KS performed a central role in writing and revising subsequent versions as well as in improvement of tables and figures. BN supervised the construction of the supplement.

Updating

The guideline will be updated according to ESCMID recommendations.

Transparency declaration

Potential conflict of interest

O.J. reports receiving honoraria for lectures and educational events from the German Society of Infectious Medicine and financial support from ESCMID to attend ESCMID global meetings. K.B. reported receiving royalties for authorship from UptoDate, and consulting fees from Denali Therapeutics. S.G.-Z. received funding for research from the Spanish government's National Institute of Health Research (projects PI21/00509 and PI25/00018) funded by Insitituto de Salud Carlos III (ISCIII), cofunded by the European Union and a research grant from the Spanish Society of Infectious Diseases and Clinical Microbiology (SEIMC). E.K. reported receiving grants from theHorizon2020 Marie Skłodowska-Curie International Training Network 'the European Sepsis Academy'. E. Kh. reported financial support from Gilead to attend an ESCMID meeting in 2024. N.P. reported consultancy honoraria from GSK and Pfizer, and honoraria from Thermo Fisher and bioMérieux for providing presentations. J.A.T. has received research funding from the Engineering and Physical Sciences Council, National Institute for Health and Care, Research, Wellcome Trust and Medical Research Council and is supported in part by the NIHR Leeds Biomedical Research Centre (NIHR203331). M.G.J.D.B. reported receiving research grants from ZonMW and Health Holland research councils. All other authors declare that they have no conflicts of interest.

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Declaration of AI and AI-assisted technologies in the writing process

During the preparation of this work the authors used ChatGPT (ver. 4.0), as an assistive tool for spelling checks and improving text flow. After using this tool, the authors reviewed and edited the content as needed and take full responsibility for the content of the publication.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.cmi.2026.02.011.

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