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Clinical Microbiology and Infection 29 (2023) 863–875

Contents lists available at ScienceDirect

Clinical Microbiology and Infection

journal homepage: www.clinicalmicrobiologyandinfection.com

Guidelines

The Dutch Working Party on Antibiotic Policy (SWAB) guideline for the approach to suspected antibiotic allergy

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ARTICLE INFO

Article history:
Received 12 January 2023
Received in revised form
28 March 2023
Accepted 7 April 2023
Available online 15 April 2023

Editor: L. Leibovici

Keywords:
β-Lactam
Antibiotic allergy
Antimicrobial stewardship
Delabeling
Non−β-lactam antibiotics
Relabeling

ABSTRACT

Objectives: Prudent handling of reported antibiotic allergies is an important aspect of antibiotic stewardship. The Dutch Working Party on Antibiotic Policy (SWAB) constituted a multidisciplinary expert committee to provide evidence-based recommendations for bedside decision-making in antibiotic therapy in patients that report an antibiotic allergy.
Methods: The guideline committee generated 12 key questions, most of which were population, intervention, comparison, and outcome questions relevant to both children and adults with suspected antibiotic allergies. For each question, a systematic literature search was performed and reviewed for the best available evidence according to the Grading of Recommendations Assessment, Development and Evaluation (GRADE) system. The quality of evidence was graded from very low to high, and recommendations were formulated in structured discussions as strong or weak.
Results: Sixty recommendations were provided for suspected allergy to β-lactam antibiotics (BLAs) and non−β-lactam antibiotics. Owing to the absence of randomized controlled trials in this field, the underlying evidence was predominantly graded as low or very low. Available data support that a detailed allergy history should always be performed and critically appraised. When cross-allergy between BLA groups is not to be expected due to the absence of molecular similarity of the side chains, the patient can be safely exposed to the alternative BLA. An exception to this rule is severe delayed-type reactions in which re-exposure to a BLA should only be considered after consultation with a multidisciplinary team.
Conclusions: Accumulated scientific data now support a more liberal approach that better balances the benefits of treatment with first choice and usually smaller spectrum antibiotics with appropriate avoidance of antibiotics in case of a truly high risk of a (severe) allergic reaction. In The Netherlands, a formal guideline was developed that provides recommendations for the approach toward suspected

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https://doi.org/10.1016/j.cmi.2023.04.008

allergy to BLA and frequently used non–β-lactam antibiotics, thereby strongly supporting antimicrobial stewardship. **Roos Wijnakker, Clin Microbiol Infect 2023;29:863**

Scope

Throughout the world, antibiotics are among the most prescribed drugs. Penicillins, and β-lactam antibiotics (BLAs) in general, are used most frequently owing to their high safety profile, narrow spectrum of activity, and low cost. At the same time, a penicillin allergy label is the most documented drug allergy label with a reported prevalence of up to 16% in the United States. Although the estimated prevalence in The Netherlands is much lower (0.6–2% in primary care and 5.6% in tertiary care), these reported BLA allergy labels are not a benign finding [1]. Owing to the avoidance of first-line antibiotic therapy for certain infections, an alleged penicillin allergy label is associated with poorer clinical outcomes, longer duration of therapy and in-hospital stay, more readmissions, higher use of reserved antibiotics, more complications like *Clostridioides difficile* infections, higher costs and not at the least of interest: higher resistance rates to antibiotics [1–3]. Based on formal allergy test studies <10% of patients with an allergy label are truly allergic [4–6]. Often, in case of a possible history of antibiotic allergy, an antibiotic is erroneously avoided. Additionally, owing to an overestimation of cross-reactivity between penicillins and cephalosporins, cephalosporins are often erroneously avoided. Prudent decision-making regarding reported antibiotic allergy and antibiotic use is therefore an important component of antibiotic stewardship.

The risk of recurrence of an allergic reaction upon re-exposure to the antibiotic or the risk of cross-allergy with other antibiotics depends on several factors [4]. Information retrieved about the index reaction, including the date of occurrence, nature, intensity, onset, and duration of symptoms concerning the use and indication of the suspected drug enables the clinicians to evaluate the following aspects: (a) is a true allergy suspected or is the reaction caused by an intolerance or another cause such as a viral exanthema; (b) what type of allergy occurred? Immediate or delayed; and (c) what was the severity of the reaction? In addition, the pros and cons of an alternative antimicrobial treatment should be evaluated [4,7,8]. The first step of a systematic clinical approach to estimate the risk of recurrence is recording a formal allergy history in each patient reporting an antibiotic allergy. For some index reactions, there is too limited information available to classify the symptoms as either immediate- or delayed-type allergy. For these reactions, it is particularly important to determine the severity of the index reaction (Table 1).

Table 1
Definitions of the severity of an allergic reaction

Definitions used in this guideline	By symptoms of a reaction; World allergy organization and the European academy of allergy and clinical immunology criteria	OR	By consequences of reaction, CIOMS criteria
Severe	1. Acute onset of an illness (minutes to several hours) with simultaneous involvement of the skin, mucosal tissue, or both (e.g. generalized hives, pruritus or flushing, swollen lips-tongue-uvula) AND at least one of the following: a. Respiratory compromise (e.g. dyspnoea, wheeze-bronchospasm, stridor, reduced peak expiratory flow, hypoxaemia) b. Reduced blood pressure or associated symptoms of end-organ dysfunction (e.g. hypotonia (collapse), syncope, incontinence) c. Severe gastrointestinal symptoms (e.g. severe crampy abdominal pain, repetitive vomiting), OR 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. OR 3. Danger signs for severe cutaneous adverse reactions: a. Tiny vesicles or crusts, the 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 (Stevens-Johnson Syndrome/toxic epidermal necrolysis) b. Exanthema with pustules (acute generalized exanthematous pustulosis) c. Purpura (vasculitis) d. Macules/papules together with non–cutaneous organ involvement; progression to more than 50% of the body surface area, deviating laboratory values (differential blood count, liver and kidney parameters)(drug reaction with eosinophilia and systemic symptoms). e. Facial oedema, oedematous, and infiltrated skin inflammation. Acute fever of 38.5 °C and higher. (acute generalized exanthematous pustulosis/drug reaction with eosinophilia and systemic symptoms) *Note:* if maculopapular exanthema meets the symptom or CIOMS criteria for a severe reaction, it should be considered as such.		These 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
Non-severe	1. Symptom(s)/sign(s) from 1 organ system present: a. Cutaneous: urticaria, erythema-warmth, pruritus, tingling, and itching of the lips. b. Upper respiratory: Nasal symptoms (e.g. sneezing, rhinorrhoea, nasal pruritus, and/or nasal congestion), Throat-clearing (itchy throat), Cough not related to bronchospasm. c. Conjunctival: erythema, pruritus, or tearing. OR 2. Maculopapular exanthema without organ involvement. OR 3. Other: nausea, metallic taste		All other reactions

CIOMS, Council for International Organizations of Medical Sciences.

The current guideline articulates the prevailing professional standard in the approach towards a reported antibiotic allergy and contains general recommendations for the antimicrobial treatment of hospitalized children and adults with an antibiotic allergy label (AAL) without prior formal allergy workup. This guideline aims to provide an overview of the quality of available evidence and to provide evidence-based recommendations for antibiotic use in patients (both children and adults) with an AAL or who report an antibiotic allergy in the anamnesis.

The Dutch Working Party on Antibiotic Policy (SWAB), established by the Dutch Association of infectious disease specialists, the Dutch Society for Medical Microbiology, and the Dutch Association of Hospital Pharmacists, coordinates activities in The Netherlands to optimize antibiotic use, to contain the development of antimicrobial resistance, and to limit the costs of antibiotic use. For this purpose, SWAB develops evidence-based guidelines on antibiotic treatment. SWAB also yearly reports on the use of antibiotics and trends in antimicrobial resistance in The Netherlands in NethMap (available on www.swab.nl), in collaboration with the Centre for Infectious Diseases Control, National Institute for Public Health and the Environment (CIb-RIVM) [9].

Please see supplementary material S1, for completed guidelines, text, and rebuttal of the received commentaries which can also be found at www.swab.nl.

Methods

The guideline committee generated 12 key questions of which 10 were population, intervention, comparison, and outcomes (PICO) questions relevant to patients with an AAL. For each key question, a literature search was performed, with the guidance of a medical librarian, to identify all published articles that report outcomes regarding the PICO. The search was performed separately for each key question starting in February 2020 until December 2020 and was conducted with English and Dutch language restrictions. Case reports, animal-only studies, and studies before 1980 were also excluded. The search was performed in PubMed, EMBASE, and the Cochrane Library. Search strategies consisted of controlled vocabulary, using Medical Subject Headings (i.e. MeSH terms) in combination with text words. Please see the supplementary material S2, for the search strategies used in this study. When available in the literature, randomized controlled trials, systematic reviews, and meta-analyses were included to answer the PICO questions and formulate conclusions and recommendations. If appropriate, case-control and cohort studies were reviewed as an additional literature review. Studies that did not report outcomes on specific questions were excluded. The committee decided to use the following additional principles while reviewing the literature. Drug provocation was considered as a reference standard and skin tests as good indicators of drug allergy. Skin tests should ideally be validated by drug provocation. Intracutaneous testing was considered to deliver stronger evidence than skin prick testing. Epicutaneous testing was regarded as delivering strong evidence for delayed reactions, as were late readings of intracutaneous testing, provided that validated test protocols were used. Theoretical considerations were regarded as the least strong evidence, as were results based on serological responses.

The guidelines were written according to the Appraisal of Guidelines for Research & Evaluation instrument. In line with the Appraisal of Guidelines for Research & Evaluation-II instrument, the Guideline committee followed a guideline development process comparable to that of the Infectious Diseases Society of America, which includes a systematic method of grading both the quality of evidence (very low, low, moderate, and high) and the strength of the recommendation (weak or strong) [10,11]. The quality of evidence per outcome variable was graded according to the GRADE (Grading of Recommendations Assessment, Development and Evaluation) system, adopted by SWAB. When evidence could not be obtained, assigned guideline group members for the key question proposed recommendations based on opinions and experiences. These Good Practice Statements (GPS) were not graded using the GRADE approach and were developed according to the criteria created by Guyatt et al. [12]. Drafted recommendations for each key question were presented to the complete guideline working group, and a consensus was reached by group discussion.

Key questions and recommendations

Below, we summarize the most important literature and recommendations for the clinical approach to a suspected antibiotic allergy in adults and children. See Box 1 for a summary of the key questions formulated for the construction of this guideline. Of note, both hypersensitivity and allergy are terms used in the literature to define a reaction to antibiotics. In a strict sense, the term allergy should be used to describe proven immune-mediated reactions to the antibiotic. For clarity reasons and to adhere to the clinical setting, the word 'allergy' is used in the guideline and in this article to refer to suspected as well as confirmed (i.e. proven immune-mediated or 'true') reactions to antibiotics. The culprit antibiotic denotes the 'offending antibiotic' (i.e. the antibiotic that is held responsible for the reported-allergic reaction).

Box 1
Summary of key questions

Chapter I – Allergy history and data collection

1. What is the probability of a current true antibiotic allergy—as assessed using skin tests and/or drug provocation tests—in unselected patients with a reported history of antibiotic allergy?
2. Which factors are associated with an increased or decreased probability of the presence of a true antibiotic allergy?

Chapter II – Registration of antibiotic allergy

3. What is the minimum of information that should be described in an antibiotic allergy label? (i.e. which information is essential to assess if a reaction is likely the cause of an allergy, and to assess the severity of a reaction)
4. When is, based on patient-derived information, a reaction not allergic and can the allergy label be removed?

Chapter III – Re-exposition in patients with a β-lactam allergy label

5. Which patients with a reported β-lactam antibiotic allergy have a very low risk of an actual allergy and can therefore be re-exposed to the culprit antibiotic.

Chapter IV – Cross-reactivity in β-lactam allergy (penicillin allergy)

6. What are the determinants of cross-reactivity between β-lactam antibiotics of the same subclass, and between different subclasses of β-lactam antibiotics?

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

Chapter V – Cross-reactivity in β-lactam allergy (cephalosporin and carbapenem allergy)

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

Chapter VI – Non–β-lactam antibiotic allergy

11. Which patients with a non–β-lactam allergy label can be re-exposed to the same antibiotic with an acceptable low risk of an allergic reaction?
12. In which patients with a non–β-lactam antibiotic allergy, a different antibiotic from the same class (of non–β-lactam antibiotics) can be administered with an acceptable low risk of a severe allergic reaction?

Epidemiology of antibiotic allergy and probability of a reaction upon re-exposure

Overall, in patients with a reported history of a penicillin allergy and a mean age >18 years, approximately 5% of patients can be demonstrated to be truly allergic to penicillins. When patients were selected based on the characteristics of their index reaction, higher percentages have been reported [13,14]. In a systematic review and meta-analysis, 5065 patients (mean aged >18 years) with a reported history of penicillin allergy received a systemic dose challenge with penicillin, 595 patients received a drug provocation test (DPT) without prior skin testing. The DPT was tolerated well in 94% (95% CI, 93.7–95%) of patients [6]. In another systematic review and meta-analysis, 14 studies were analysed that investigated either adults (n = 1511), children (n = 1822) or both (n = 823; children and adults) reporting a β-lactam allergy. In 9 of 14 studies, skin tests were performed and followed by DPT when negative. The pooled estimate of the prevalence of a reaction to penicillin in these patients was 1.98% (95% CI, 1.35%, 2.60%) in children, 7.78% (95% CI, 6.53%, 9.04%) in adults, and 2.84% (95% CI, 1.77%, 3.91%) in the combined group [15].

Different studies have evaluated the risk factors for the presence of a true antibiotic allergy. Within the BLA group, involvement of penicillin was associated with an approximately 1.5 times higher risk of being allergic than that in other BLAs [16]. Aminopenicillins accounted for >70% of all cases, probably because they are also the most frequently prescribed group of antibiotics [17]. A reported cephalosporin allergy was associated with an increased odds of confirmed allergy (odds ratio [OR], 2.96; 95% CI, 1.34–6.58) compared with penicillin allergy [7]. A shorter time between the index reaction and evaluation of a possible allergy (less than a year) was associated with higher odds of having a true immediate-type BLA allergy (OR, 38.66; p 0.003) and was reported as an independent clinical predictor of genuine BLA allergy [16,18]. Children tend to have a lower risk of having a true BLA allergy than adults, although more severe reactions in children are strongly associated with true allergy. The risk of allergy to BLA decreases again with older age (>60 years) [15,16,19,20]. An index reaction that is observed by health care personnel (inpatient or at the emergency department) and classified as an allergy or potential allergy, is more likely to be later confirmed as a true allergy [21]. In multiple studies, a more severe index reaction (e.g. anaphylaxis, angioedema, serum sickness-like reaction, or severe cutaneous adverse reactions) was shown to be independently associated with the presence of a true BLA hypersensitivity [16,18–20,22–26]. On the other hand, the combination of the absence of anaphylaxis, unknown name of the index drug, and a reaction occurring >1 year before testing had a 98.4% negative predictive values for type 1 BLA allergy [25]. Whether gender is a risk factor remains unresolved [13,27,28].

Recommendations

Because most patients, including children, that report a β-lactam allergy are in fact not truly allergic, we recommend against standard avoidance of the culprit antibiotic. *(Strong recommendation, moderate quality of evidence)*

We suggest that the time that has elapsed since the index reaction should be factored in the probability that an allergy will occur upon re-exposure to the culprit drug: the long ago, the smaller the chance of an allergic reaction occurring. *(Weak recommendation, low quality of evidence)*

Antibiotic allergy labels

Registration of allergy labels in health care systems is often incomplete and insufficient to distinguish between an adverse event and a true allergic reaction. In >90% of patients with a penicillin allergy label, the label can be removed after a proper assessment based on history alone or using additional skin tests or DPTs [29].

The minimum of information that should be included in the allergy label was assessed based on the concordance in the literature and the expert opinion (i.e. the lowest level of medical evidence) of the guideline committee [29,30]. In brief, this includes (a) patient details: symptoms of the reaction, the date of the reaction, the concurrent medication, comorbidity; (b) medication details: drug, route, timing, and dose; and (c) treatment details: setting, time to resolution, management, and outcome of the reaction.

The definition of ‘no’ or ‘low’ risk for true antibiotic allergy varied in the included studies. Most studies considered headache, blurred vision, palpitations, and gastrointestinal complaints only (vomiting, nausea, diarrhoea) as a non-immune reaction. Other categories that were defined as ‘no’ or ‘low’ risk were as follows: no temporal association between the exposure to the culprit antibiotic and the symptoms of the alleged allergic reaction, subsequent exposure to the same drug without reaction, a positive family history alone, and no recollection of the incident. Two studies (Stone et al. [31], Mohamed et al. [32]) reported good negative predictive values of low-risk categorization.

Recommendations

We recommend that an antibiotic allergy label can be removed *directly* without allergy testing when one of the following criteria applies (*no/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 on *fear* of allergy.
- The reported symptoms are *not compatible* with an allergic reaction (i.e. gastrointestinal complaints only, palpitations, and blurred vision).
- There was *no temporal association* between exposure and the onset of symptoms.

(Strong recommendation, moderate quality of evidence)

Half-life of BLA allergy

Several studies have shown that patients lose skin test sensitivity to penicillin over time. The longer the interval between the reaction and the skin test, the greater the likelihood of having a negative test result. In addition, patients with a selective response to amoxicillin tended to lose sensitivity faster than those who responded to several penicillin determinants [33,34]. Contrary to the literature available for penicillin allergy, there is very limited literature on the half-life of cephalosporin allergy. Romano et al. [35] showed that of 72 patients with cephalosporin allergy, 45 demonstrated negative skin test results or showed serum IgE negativity after 5 years [35]. Fernandez et al. [36] observed only 2.4% of 41 patients with cephalosporin allergy showed serum IgE positivity after 4 years.

Recommendations

We suggest 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 index reaction was not severe, confined to the skin, and occurred in remote adolescence or remote childhood.
- The patient is *not aware* of the antibiotic allergy label or *cannot recollect* clinical signs and symptoms of a reaction at all.

(Weak recommendation, low quality of evidence)

Re-exposition in patients with a β-lactam allergy label

Literature review consistently showed that when the index reaction was classified as non-severe and/or history indicated a low risk of an actual penicillin allergy, the risk of occurrence of a severe reaction upon the reintroduction of the culprit drug by direct DPT was very low, both in children and adults. Although Ibáñez et al. [24] showed that the diagnosis of a true but non-severe allergy by history alone was not consistent with direct DPT outcome, none of the patients that were faulty classified as having no or a doubtful allergy to penicillin had a severe reaction upon direct DPT (Table 2).

Patients with a *non-severe*, immediate-type index reaction that occurred >5 years ago can be re-exposed to the culprit drug in a clinical setting in which the patient is observed, with trained personnel and where rapid and adequate treatment can be administered when an allergic reaction occurs. Severe, immediate-type index reactions should be evaluated by formal allergy testing. Because severe, delayed-type index reactions are less common and history is mainly clear, we recommend against re-exposure to the culprit drug in this situation. Non-severe, delayed-type index reactions (maculopapular exanthema) are considered as part of the low-risk group by the guideline committee based on the systemic review of Macy and Vyles [37] and additional literature by Stevenson et al. [38], and therefore the reintroduction of the culprit drug after 1 year is considered safe in this situation. Severe, delayed-type index reactions are less common and history is mainly clear. We therefore recommend against re-exposure to the culprit drug in this situation.

Recommendations

We suggest that patients with suspected[a] *non-severe*, immediate-type index reactions that occurred >5 years ago, can receive a therapeutic dose of the culprit β-lactam antibiotic in a controlled setting[b]. *(Weak recommendation, low quality of evidence)*

We recommend that patients with suspected[a] *non-severe*, 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. *(Strong recommendation, low quality of evidence)*

We suggest that if formal allergy testing is not available, patients with a suspected[a] *non-severe*, immediate-type index reaction that occurred ≤5 years ago OR a suspected *severe* immediate-type index reaction, irrespective of time elapsed, in which the indication for a specific antibiotic is vital, re-exposure could be considered if the antibiotic is administered in a controlled setting[b]. *(Weak recommendation, low quality of evidence)*

We suggest that patients with suspected[a] *non-severe*, delayed type index reactions that occurred >1 year ago can receive a culprit β-lactam antibiotic without formal allergy testing; and to avoid exposure if this index reaction occurred <1 year ago. *(Weak recommendation, low quality of evidence)*

We recommend against re-exposure to the culprit drug in patients with suspected[a] *severe* delayed-type index reactions, irrespective of the time since the index reaction. In the absence of acceptable alternative antimicrobial treatment, the use of the culprit should be discussed with a multidisciplinary team[c]. *(Strong recommendation, GPS)*

[a] In case of a proven allergy by formal allergy workup handled according to the advice of the consulted allergist.

[b] A clinical setting in which the patient is observed by trained personnel and where rapid and adequate treatment can be administered when an allergic reaction occurs.

[c] An expert team that consists of an infectious diseases' specialist and/or microbiologist, pharmacist, and if available an allergist. The risk of side effects and benefits of use of proper antibiotics should be balanced against each other followed by shared decision -making with the patient.

Table 2
Cross-reactivity in β-lactam antibiotics

β-Lactam Antibiotic	Amoxicillin	Penicillin G	Penicillin V	Flucloxacillin	Feneticillin	Piperacillin	Cephalexin	Cefazolin	Cefalothin	Cefuroxime	Cefaclor	Cefamandol	Ceftibuten	Ceftriaxone	Cefotaxime	Ceftazidime	Cefepime	Cefiderocol	Ceftaroline	Ceftolozane	Meropenem	Imipenem	Ertapenem	Aztreonam
Amoxicillin	■	■	■	■	■	■	■	✓	✓	✓	■	■	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
Penicillin G	■	■	■	■	■	■	■	✓	✓	✓	■	■	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
Penicillin V	■	■	■	■	■	■	■	✓	✓	✓	■	■	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
Flucloxacillin	■	■	■	■	■	■	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
Feneticillin	■	■	■	■	■	■	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
Piperacillin	■	■	■	■	■	■	■	✓	✓	✓	■	■	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
Cephalexin	■	■	■	✓	✓	■	■	✓	✓	✓	■	■	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
Cefazolin	✓	✓	✓	✓	✓	✓	✓	■	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
Cefalothin	✓	✓	✓	✓	✓	✓	✓	✓	■	■	✓	✓	✓	✓	■	✓	✓	✓	✓	✓	✓	✓	✓	✓
Cefuroxime	✓	✓	✓	✓	✓	✓	✓	✓	■	■	✓	✓	✓	■	■	■	■	■	■	■	✓	✓	✓	■
Cefaclor	■	■	■	✓	✓	■	■	✓	✓	✓	■	■	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
Cefamandole	■	■	■	✓	✓	■	■	✓	✓	✓	■	■	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
Ceftibuten	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	■	■	■	■	■	■	■	■	✓	✓	✓	■
Ceftriaxone	✓	✓	✓	✓	✓	✓	✓	✓	✓	■	✓	✓	■	■	■	■	■	■	■	■	✓	✓	✓	■
Cefotaxime	✓	✓	✓	✓	✓	✓	✓	✓	■	■	✓	✓	■	■	■	■	■	■	■	■	✓	✓	✓	■
Ceftazidime	✓	✓	✓	✓	✓	✓	✓	✓	✓	■	✓	✓	■	■	■	■	■	■	■	■	✓	✓	✓	■
Cefepime	✓	✓	✓	✓	✓	✓	✓	✓	✓	■	✓	✓	■	■	■	■	■	■	■	■	✓	✓	✓	■
Cefiderocol	✓	✓	✓	✓	✓	✓	✓	✓	✓	■	✓	✓	■	■	■	■	■	■	■	■	✓	✓	✓	■
Ceftaroline	✓	✓	✓	✓	✓	✓	✓	✓	✓	■	✓	✓	■	■	■	■	■	■	■	■	✓	✓	✓	■
Ceftolozane	✓	✓	✓	✓	✓	✓	✓	✓	✓	■	✓	✓	■	■	■	■	■	■	■	■	✓	✓	✓	■
Meropenem	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	■	■	■	✓
Imipenem	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	■	■	■	✓
Ertapenem	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	■	■	■	✓
Aztreonam	✓	✓	✓	✓	✓	✓	✓	✓	✓	■	✓	✓	■	■	■	■	■	■	■	■	✓	✓	✓	■

Legenda Table 2.

■	Cross-tabulation was similar
■	Allergy possible based on the formation of PPL
■	Potential cross-allergy based on an identical R1 side chain
■	Potential cross-allergy based on similarity in R1 or R2 side chains or clinical studies
✓	No risk of a cross-allergic reaction

PPL, polyvalent penicilloyl polylysine (a major penicillin determinant)

Cross-reactivity in β-lactam allergy

An allergic reaction is the result of a part of the structure of a BLA being recognized by an immune receptor and the immune system being consequently activated. Cross-reactivity can evolve when 2 BLAs are structurally related, i.e. these 2 BLAs share a molecular part that is recognized by the immune receptors or antibodies with the same specificity. If the side chain is recognized, cross-reactivity between BLAs that share an identical or similar side chain can be expected. However, side chain similarity is not the exclusive cause for cross-reactivity between different β-lactam groups; sporadically also other molecular similarities may be responsible for cross-reactivity such as identical three-dimensional structures [39].

For cross-reactivity between different subclasses of BLAs, there is evidence that the β-lactam side chain (dis)similarities are highly predictive of cross-reactivity. Penicillins have one side chain at the 6-position (R1), whereas cephalosporins have 2 side chains at the 7- and 3- position (R1 and R2) drugs with similar 6- or 7- position side chains that may exhibit cross-allergenicity with each other, just as drugs with similar 3-position side chain structures [40]. It is the R1 side chain, rather than the β-lactam ring itself, which is the determining factor for the rate of cross-reactivity. Side chain similarity, however, does not necessarily result in a clinical reaction. Several studies suggest that cephalosporin-induced anaphylaxis occurs no more frequently among patients with known penicillin allergy than among those without such allergies. Both immediate and delayed cross-allergic reactions appear to be commonly associated with the side-chain structures of the penicillins and cephalosporins [41]. The molecular structure of carbapenems are sufficiently dissimilar from those of penicillins and cephalosporins, resulting in a very low risk of cross-allergy among these BLAs [42].

Cross-reactivity in penicillin allergy

Patients that are allergic to a penicillin can be sensitized to other penicillins via the thiazolidine ring rather than the β-lactam ring. Isolated allergy to single penicillin (amoxicillin) is also possible if an R1 side chain is involved [41].

For cephalosporins with dissimilar side chains to the suspected penicillin, the risk of cross-reactivity is negligible (<1%). For cephalosporins with similar or identical side chains to the culprit penicillin, the risk increases (5–17%) [37]. Some studies show even higher percentages for similar side chains. In a recent meta-analysis, only studies that confirmed an immediate-type allergy to penicillin by a skin test or a DPT were included [43]. Twenty-one observational studies were included, involving 1269 patients with penicillin allergy. A substantial variation was seen in the absolute risk of cross-reactivity, with a strong correlation with the calculated similarity score: 16.45% (95% CI, 11.07–23.75) for amino-cephalosporins, which share an identical side chain with a penicillin (similarity score (1), 5.60% (95% CI, 3.46–8.95)) for a few cephalosporins with an intermediate similarity score (range, 0.563–0.714), and 2.11% (95% CI, 0.98–4.46) for all those with low similarity scores (below 0.4), irrespective of the cephalosporin generation. The higher risk associated with amino-cephalosporins was observed in both IgE- (immediate type) or T-cell-mediated (delayed type) penicillin allergy. For cephalosporins available in The Netherlands, a significantly increased absolute risk of cross-reactivity of 5.3%, 12.9%, and 14.5% was observed for cefamandole, cephalexin, and cefaclor, respectively. No increased risk of cross-reactivity for cefazolin was observed.

The meta-analysis by Picard et al. [37] (2019) ($n = 1127$ proven penicillin allergic participants, observational studies) showed no cross-reactivity between penicillins and aztreonam. Monobactams and carbapenems can therefore be administered without prior testing in both (non) severe immediate or non-severe delayed-type allergy. For severe, delayed-type allergy, the risk of cross-reactivity is unknown (Fig. 1).

Recommendations for immediate-type allergy

We recommend that in patients with a suspected[a] 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)*

We recommend that in patients with a suspected[a] *non-severe,* immediate-type allergy to penicillins, that occurred >5 years ago, all other penicillins can be used in a controlled setting[b]. *(Strong recommendation, low quality of evidence)*

We recommend that patients with a suspected[a] immediate-type allergy to penicillins can receive cephalosporins, but only those with dissimilar side chains, irrespective of severity and time since the index reaction. *(Strong recommendation, moderate quality of evidence)*

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

We suggest that patients with a suspected[a] *non-severe*, immediate-type index reaction to penicillin >5 years ago, can receive a therapeutic dose of cephalosporins with similar side chains in a controlled setting[b]. *(Weak recommendation, low quality of evidence)*

We recommend that patients with suspected[a] immediate-type penicillin allergy, irrespective of severity or time since the index reaction, can receive *any* monobactam or carbapenem, without prior allergy testing. *(Strong recommendation, low quality of evidence)*

Recommendations for delayed-type allergy

We suggest that in patients with suspected[a] *non-severe,* delayed-type allergy to penicillins that occurred ≤1 year ago, all other penicillins should be avoided *(Weak recommendation, low quality of evidence)*.

We suggest that in patients with a suspected[a] *non-severe,* delayed-type allergy to penicillins that occurred >1 year ago, all other penicillins can be used *(Weak recommendation, low quality of evidence)*

We recommend that patients with suspected[a] *non-severe*, delayed-type allergy to penicillins, can receive cephalosporins with dissimilar side chains, irrespective of time since the index reaction. *(Weak recommendation, low quality of evidence)*

We suggest to avoid cephalosporins with similar side chains (e.g. cefalexin, cefaclor, cefamandole) in patients with suspected[a] *non-severe,* delayed-type allergy to amoxicillin, penicillin G, V, or piperacillin, with an index

reaction that occurred ≤1 year ago. *(Weak recommendation, low quality of evidence)*

We suggest that cephalosporins with similar side chains (e.g. cefalexin, cefaclor, cefamandole) can be used in patients with suspected[a] *non-severe*, delayed-type allergy to amoxicillin and penicillin G, V, or piperacillin with an index reaction that occurred >1 year ago. *(Weak recommendation, low quality of evidence)*

We recommend that patients with a suspected[a] *non-severe*, delayed-type penicillin allergy, irrespective of severity or time since the index reaction, can receive *any* monobactam or carbapenem, without prior allergy testing. *(Strong recommendation, low quality of evidence)*

We recommend that in patients with suspected[a] *severe* delayed type allergy to penicillins, all beta-lactam antibiotics should be avoided, irrespective of time since the index reaction. In the absence of acceptable alternative antimicrobial treatment, the use of β-lactam antibiotics should be discussed in a multidisciplinary team[c]. *(Strong recommendation, GPS)*

Cross-reactivity in cephalosporin and carbapenem allergy

Current literature suggests the same mechanism of cross-reactivity in cephalosporin allergy (i.e. side chain similarity). Therefore, only in case of cefaclor, cephalexin, and/or cefamandole allergy, penicillins with similar side chains should be avoided. For other cephalosporin allergies, penicillins may be used, although there is a small risk of co-sensitization. Cefazolin is a very commonly used pre-operative antibiotic. In patients with an immediate-type hypersensitivity to cefazolin with no cross-reactivity can be demonstrated with penicillin determinants in several studies [44–48].

Seven prospective studies and 3 retrospective studies showed that cross-reactivity between different cephalosporins is R1 side chain-dependent [44,45,48–53]. Different studies concluded that cefazolin allergy is a selective allergy with tolerance of other cephalosporins because of dissimilar side chains [47–53]. In case of delayed-type reactions, limited information is available about cross-reactivity. Additional patch and intradermal testing has added value to guide subsequent antimicrobial courses, with a good predictive value of negative tests and a variable pattern of possible cross-reactivity [54].

Ceftazidime, cefiderocol, and aztreonam share an identical side chain resulting in a higher risk of cross-reactivity [45]. No cross-

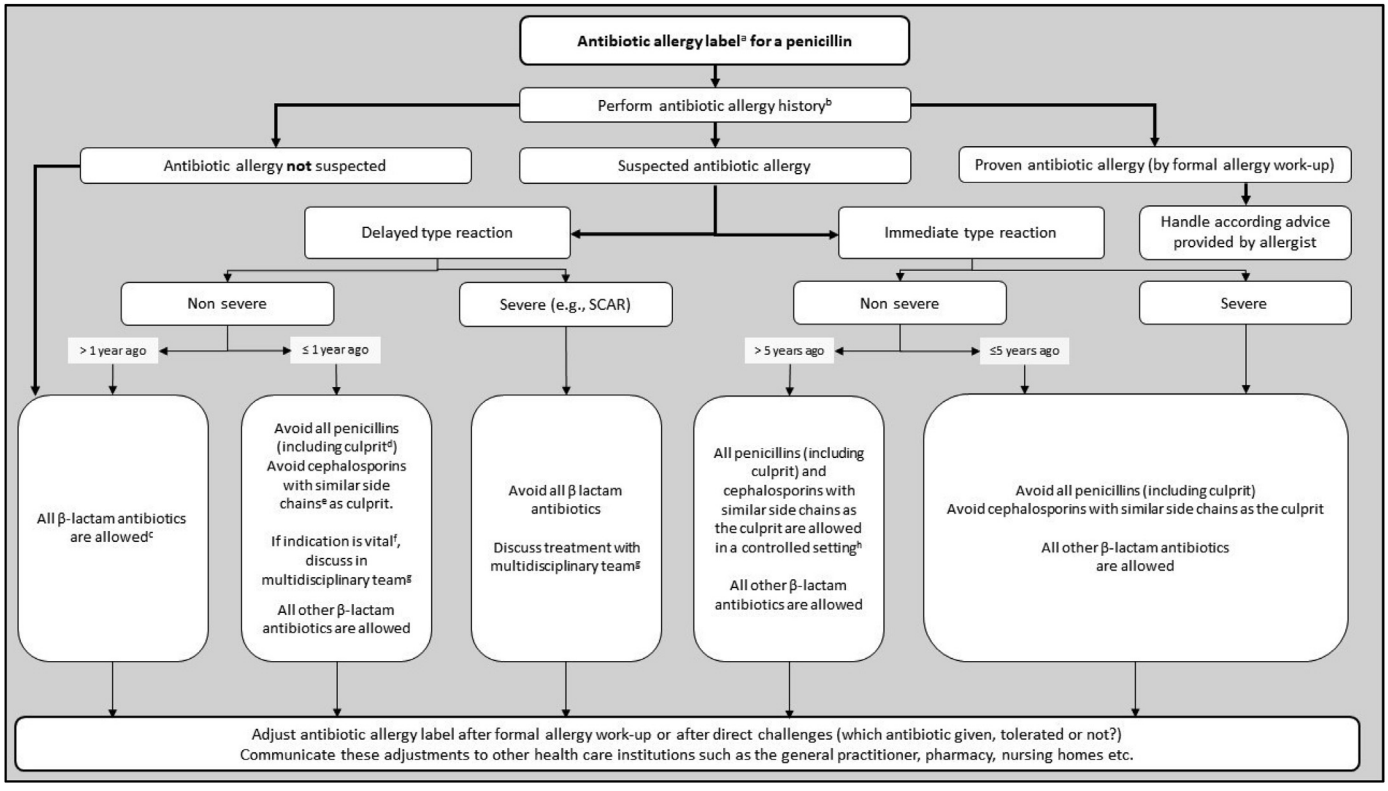

Fig. 1. Flowchart for the approach towards suspected penicillin allergy.
(a) Antibiotic allergy label: patient-reported antibiotic allergies, that may represent an unpredictable immune -mediated adverse drug reaction (e.g. anaphylaxis)
(b) See Table in Guidelines (https://swab.nl/en/aanpak-bij-vermoeden-van-antibiotica-allergie-algemene-informatie);
(c) In case of severe side effects that is not an allergy, do not re-expose to the culprit.
(d) Culprit drug: the antibiotic held responsible for the reported-allergic reaction;
(e) Side chain similarity: reflects to the similarity between side chains of penicillins and cephalosporins;
(f) Vital indication: if no other options with similar effectiveness are available;
(g) An expert team that consists of an infectious diseases specialist and/or microbiologist, pharmacist, and if available an allergist or specialized dermatologist. The risk of side effects and benefits of use of proper antibiotics should be balanced against each other followed by shared decision-making with the patient;
(h) A clinical setting, in which the patient is observed, with trained personnel, where rapid and adequate treatment can be administered when an allergic reaction occurs.
SCAR: severe cutaneous adverse reactions.

reactivity has been observed between aztreonam and other cephalosporins compared with ceftazidime and cefiderocol [54–56]. Therefore, it is considered safe to administer aztreonam without any additional measures in case of a suspected immediate-type cephalosporin allergy other than for ceftazidime or cefiderocol. No reactions to aztreonam or carbapenems have been observed in patients with a suspected delayed-type allergy. Therefore, aztreonam and carbapenems seem to be safe options in patients with a non-severe, delayed-type cephalosporin allergy. Nevertheless, because the number of studies and included patients are very low, we recommend avoiding aztreonam in patients with a suspected ceftazidime or cefiderocol allergy.

There are no studies that evaluate the rate of suspected or proven penicillin allergy in patients who are allergic to a carbapenem. In addition, there are no studies that evaluate the rate of cephalosporine cross-reactivity in patients who are allergic to a carbapenem. Conclusions were drawn from previous chapters that evaluated the rate of carbapenem allergy in patients who are allergic to penicillins or to cephalosporins.

Recommendations for immediate-type allergy

We recommend that patients with a suspected[a] immediate-type allergy to cephalosporins can receive penicillins with dissimilar side chains, irrespective of severity and time since the index reaction. *(Strong recommendation, low quality of evidence)*

We recommend to avoid penicillins with similar side chains in patients with a suspected[a] immediate-type allergy to cefaclor, cefalexin, and/or cefamandole, irrespective of severity and time since index reaction. *(Strong recommendation, low quality of evidence)*

We recommend that cephalosporins with a dissimilar side chain can be used in patients with a suspected[a] immediate-type allergy to a cephalosporin, irrespective of severity and time since the index reaction. *(Strong recommendation, moderate quality of evidence)*

We suggest that patients with suspected[a] *non-severe*, immediate-type index reactions to a cephalosporin that occurred >5 years ago, can receive a therapeutic dose of cephalosporins with similar or identical side chains in a controlled setting[b]. *(Weak recommendation, low quality of evidence)*

We suggest that aztreonam can be used in patients with a suspected[a] immediate-type allergy to cephalosporins other than ceftazidime or cefiderocol, irrespective of severity and time since the index reaction. *(Weak recommendation, low quality of evidence)*

We suggest to *avoid* aztreonam in patients with a suspected[a] immediate-type ceftazidime or cefiderocol allergy. *(Weak recommendation, low quality of evidence)*

We suggest that *any* carbapenem can be used in a clinical setting in patients with suspected[a] immediate-type allergy to a cephalosporin, irrespective of severity or time since the index reaction. *(Weak recommendation, low quality of evidence)*

We suggest that penicillins can be used in a clinical setting in patients with a suspected[a] immediate-type allergy to monobactams or carbapenems and no history of penicillin allergy, irrespective of severity or time since the index reaction. *(Weak recommendation, low quality of evidence)*

We suggest that in patients with a suspected[a] immediate-type allergy to a carbapenem and no history of cephalosporin allergy, cephalosporins can be administered in a clinical setting, irrespective of severity and time since the index reaction. *(Weak recommendation, low quality of evidence)*

We suggest that in patients with a suspected[a] immediate-type allergy to aztreonam, ceftazidime and cefiderocol should be avoided. Other cephalosporins used in The Netherlands can be used irrespective of severity or time since the index reaction. *(Weak recommendation, low quality of evidence)*

Recommendations for delayed-type allergy

We recommend that patients with a suspected[a] *non-severe*, delayed-type allergy to a cephalosporin can receive penicillins with dissimilar side chains, irrespective of time since the index reaction. *(Strong recommendation, low quality of evidence)*

We suggest to *avoid* penicillins with similar side chains in patients with suspected[a] *non-severe*, delayed-type allergy to cefalexin, cefaclor, and/or cefamandole, when the index reaction occurred ≤1 year ago. *(Weak recommendation, low quality of evidence)*

We suggest that penicillins with similar side chains can be used in patients with suspected[a] *non-severe*, delayed-type allergy to cephalexin, cefaclor, and/or cefamandole, when the index reaction occurred >1 year ago. *(Weak recommendation, low quality of evidence)*

We recommend that cephalosporins with a dissimilar side chain can be used in patients with a suspected[a] *non-severe,* delayed-type allergy to a cephalosporin, irrespective of time since the index reaction. *(Strong recommendation, low quality of evidence)*

We suggest *against* the administration of cephalosporins with similar or identical side chains to the culprit drug in patients with a suspected[a] *non-severe*, delayed-type allergy to a cephalosporin, when the index reaction occurred ≤1 year ago. *(Weak recommendation, low quality of evidence)*

We suggest that cephalosporins with similar or identical side chains to the culprit drug can be used in patients with a suspected[a] *non-severe*, delayed-type allergy to a cephalosporin, when the index reaction occurred >1 year ago. *(Weak recommendation, low quality of evidence)*

We recommend that aztreonam can be used in patients with a suspected[a] *non-severe,* delayed-type allergy to cephalosporins other than ceftazidime or cefiderocol, irrespective of time since the index reaction. *(Strong recommendation, low quality of evidence)*

We suggest to *avoid* aztreonam in patients with a suspected[a] *non-severe,* delayed-type ceftazidime or cefiderocol allergy, when the index reaction occurred ≤1 year ago. *(Weak recommendation, very low quality of evidence)*

We suggest that aztreonam can be used in patients with a suspected[a] *non-severe,* delayed-type allergy to ceftazidime and/or cefiderocol, when the index reaction occurred >1 year ago. *(Weak recommendation, very low quality of evidence)*

We suggest that *any* carbapenem can be used in patients with suspected[a] *non-severe,* delayed-type allergy to cephalosporins, irrespective of time since the index reaction. *(Weak recommendation, vert low quality of evidence)*

We suggest that penicillins can be used in a clinical setting in patients with a suspected[a] *non-severe*, delayed-type allergy to monobactams or carbapenems and no history of penicillin allergy, irrespective of time since the index reaction. *(Weak recommendation, vert low quality of evidence)*

We suggest that in patients with a suspected[a] *non-severe* delayed-type allergy to a monobactam or carbapenem and no history of cephalosporin allergy, cephalosporins can be administered in a clinical setting, irrespective of the time since the index reaction. *(Weak recommendation, very low quality of evidence)*

We recommend that in patients with suspected[a] *severe,* delayed-type allergy to cephalosporins, monobactams, or carbapenems, all β-lactam antibiotics should be avoided, irrespective of time since the index reaction. In the absence of acceptable alternative antimicrobial treatment, the use of beta lactam antibiotics should be discussed in a multidisciplinary team[c]. *(Strong recommendation, GPS)*

Non–β-lactam antibiotics

Studies on specific non–β-lactam antibiotics (NBLAs), or groups of NBLA, are scarce. For this guideline, a literature search was performed regarding the 5 most frequently prescribed NBLA in the Dutch Hospitals according to Nethmap 2019: (a) fluoroquinolones (e.g. ciprofloxacin); (b) aminoglycosides (e.g. gentamicin); (c) imidazol derivatives (e.g. metronidazole); (d) macrolides (e.g. clarithromycin); and (e) lincosamides (e.g. clindamycin). This profile roughly corresponds with the use of systemic antimicrobial drugs in hospitals in other European countries [57]. Additionally, descriptive summaries were formulated, without performing a formal literature review, for: (a) glycopeptides (e.g. vancomycin); (b) sulfonamides (e.g. cotrimoxazole). Owing to limited skin testing options, discrimination between immunologic and non-immunologic reactions to NBLA agents is often not possible [56]. Among the studies on NBLA allergy, most available data were for either presumed macrolide or fluoroquinolone allergies. Hypersensitivity reactions to macrolides are uncommonly reported in 0.4–3% of treatments, including both immediate and delayed-type reactions. Cutaneous reactions are observed most frequently [58,59]. Considering the low percentage of positive DPTs, clinical history alone is not sufficient to ascertain a diagnosis of hypersensitivity to macrolide antibiotics and grossly overestimates the number of hypersensitivity reactions to macrolides that will occur after re-exposure. Skin tests often give false negative results in macrolide antibiotic allergy [60]. Performing a DPT is the only reliable method to predict macrolide hypersensitivity as well as to detect cross-reactivity between macrolides [61]. Different studies in children have observed that azithromycin appeared more ‘allergenic’ than clarithromycin [62,63].

Although the true prevalence in the general population is unknown, fluoroquinolone allergy is the most frequently reported NBLA allergy. The literature agrees on the existence of both immediate as well as delayed-type allergies to fluoroquinolones. Immediate-type allergies are most described and moxifloxacin poses the highest risk of anaphylaxis compared with other frequently used fluoroquinolones, such as levofloxacin and ciprofloxacin. The absolute risk of a severe reaction is low with reported anaphylaxis in 1.8–2.3/100.000.000 days of treatment [58]. Of note, besides IgE-mediated reactions, fluoroquinolones can also cause pseudo-allergic reactions by stimulating the MrgprX2 receptor on mast cells, thereby causing direct mast cell release [64]. This makes the interpretation of an immediate-type allergic reaction and skin tests more difficult. In delayed-type allergies, maculopapular exanthema is most frequently reported and mainly related to ciprofloxacin use [58,65–67]. Risk factors for allergy* to fluoroquinolones are atopic constitution, immediate-type index reaction, use of moxifloxacin, history of

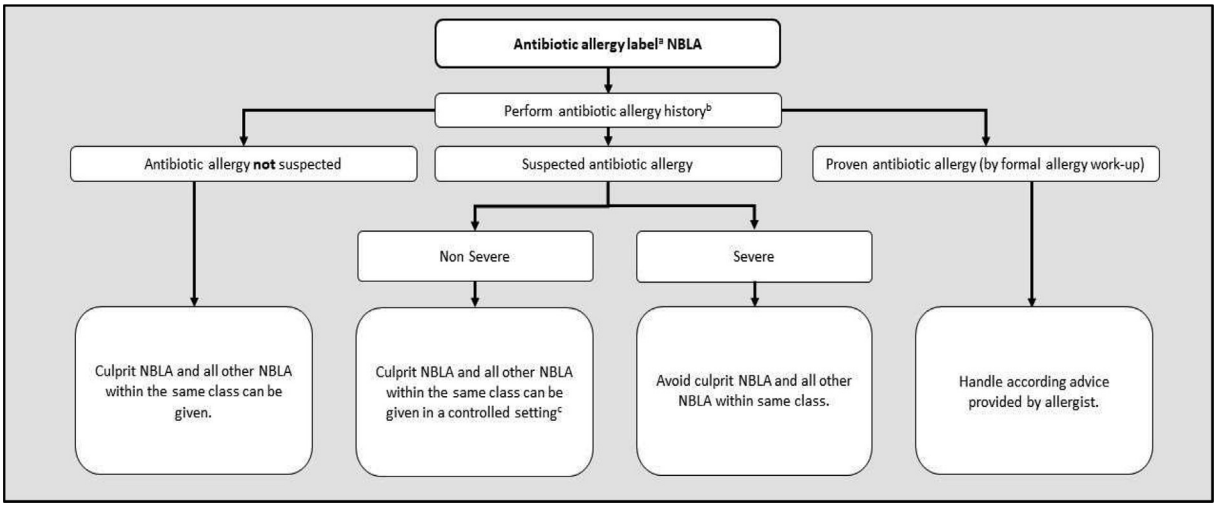

Fig. 2. Flowchart for the approach toward non–β-lactam antibiotic (NBLA) allergy.
(a) Antibiotic allergy label: patient-reported antibiotic allergies, that may represent an unpredictable immune-mediated adverse drug reaction (e.g. anaphylaxis). (b) Antibiotic allergy history (link to the guideline). (c) Controlled setting: a clinical setting in which the patient is observed by trained personnel and where rapid and adequate treatment can be administered when an allergic reaction occurs. NBLA, non–β-lactam antibiotics.

allergy to BLA, intravenous contrast, or neuromuscular blocking agents, e.g. succinylcholine and rocuronium [65,66,68–70]. Regarding cross-reactivity, evidence is very limited and no clinical rules exist for predicting cross-reactivity [65–67]. Several authors have claimed that cross-reactivity within the fluoroquinolone group particularly appears in patients with a history of other immediate-type reactions [71].

Provided that the data on NBLA allergy is limited, and that the available evidence regarding the macrolide or fluoroquinolone allergy, although different in frequency and severity, yielded similar recommendations for re-exposure, a 'one-size fits all' approach for NBLA allergy was proposed, discussed, and agreed upon by the guideline committee (Fig. 2).

Recommendations

We recommend avoiding re-exposure to the culprit NBLA and all other NBLA within the same class when the index reaction was severe. *(Strong recommendation, GPS)*

We suggest that, in general (see next recommendation), when the index reaction was *non-severe*, the culprit NBLA and all other NBLA within the same class can be re-introduced in a controlled setting[b]. *(Weak recommendation, low quality of evidence)*

For quinolones, we recommend that if the index reaction was generalized urticaria, the culprit quinolone and all other quinolones should be avoided (because of potential direct mast cell release mechanism) and discussed in a multidisciplinary team[c]. *(Strong recommendation, GPS)*

Limitations

The subject of antibiotic allergy remains a topic of interest in scientific research. Hence, additional research was—and will be—performed since this guideline was written. This potentially improves new insights regarding the key questions and recommendations stated above. The second limitation is that randomized controlled trials are not available on this topic and that most studies are considered as low quality of evidence resulting in weaker recommendations. The third limitation is that implementation was not a part of this guideline. The guideline committee, however, strived to formulate the recommendations in a way that would maximally facilitate implementation.

Conclusions

The scientific data reviewed for this guideline strongly support a more liberal approach towards patients with a suspected antibiotic allergy. Systematic literature review confirmed that far <10% of patients that report an antibiotic allergy is truly allergic, and that the risk of cross-reactivity is smaller than previously assumed. In addition, the time elapsed since the index reaction, and structured allergy anamnesis allows clinicians to assess the risk of recurrence of a (severe) allergic reaction. The implementation of the recommendations outlined in this guideline may, therefore, result in the use of smaller spectrum antibiotics with fewer side effects, less toxicity, and potentially lower risks of antibiotic resistance. At the same time, the data show that the avoidance of certain antibiotics in case of suspected true (and severe) antibiotic allergy should be strongly advised. With few exceptions, other infectious disease guidelines cannot be implemented elsewhere mainly due to differences in the epidemiology of antimicrobial resistance. In contrast, this newly developed formal guideline provides recommendations that can be used internationally for the approach towards suspected allergy to BLA as well as frequently used NBLA, thereby strongly supporting antimicrobial stewardship.

Author contributions

The first author is the corresponding author. The first and last author are main contributors. All other authors are listed in alphabetical order. We describe the author contributions to this article using the CRediT taxonomy. Writing and original draft: R. and M.G.J., Writing -Review and editing: R., M.S., and M.G.J. and all other listed authors revised it critically for important intellectual content, conceptualization: R. and M.G.J. Investigation: R., J.S., and M.G.J. Methodology: all listed authors, Formal analysis: all listed authors.

Transparency declaration

The authors have no conflict of interest to declare. M.G.J. de Boer is the chair of the Dutch Working Party on Antimicrobial Policies. There was no financial interest or funding for this article.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.cmi.2023.04.008.

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