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Belgian consensus-based recommendations on the management of hospitalized patients with a penicillin allergy label

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ABSTRACT

Objectives: Penicillin allergy labels are common among hospitalized adults and are frequently inaccurate, potentially leading to inappropriate antibiotic use and avoidable harm. This Belgian consensus-based recommendation aims to provide a pragmatic framework for the management of penicillin allergy labels in hospitalized adults (>18 years), with particular emphasis on distinguishing low- to high-risk labels.

Methods: Recommendations were developed through a structured, multidisciplinary expert consensus process and are presented as a stepwise clinical algorithm.

Results: The recommendations highlight a structured approach to evaluate reactions through a series of questions, delineating between severe and non-severe signs. It offers a pragmatic algorithm for managing low-risk penicillin allergy labels through re-administration procedures while ensuring emergency preparedness for rare adverse reactions. Comparisons with existing protocols revealed differences in approaches to delabeling, referral criteria for allergy evaluation, and liberalization of antibiotic choices based on reaction severity, timelines, and individual patient risk factors. The recommendation favors a patient-centric risk-assessment approach, offering distinctions between severe and non-severe reactions and includes precautions based on reaction types and timelines.

Conclusion: This consensus-based recommendation offers a structured approach to managing penicillin allergy labels in hospitalized adults.

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KEYWORDS
Penicillin allergy; drug allergy; delabeling; betalactam antibiotics

Introduction

The prevalence of penicillin allergy labels varies from 10%–20% in United States (US), United Kingdom (UK) and Australian studies to 3%–6% in Belgium or the Netherlands, respectively [1,2], with higher prevalences in selected populations [3]. Most penicillin allergy labels can be removed after a drug allergy workup (including skin and provocation testing), ranging between 95%–99% (US, Australian) and 77%–91% (France or Belgium, respectively) [3–6].

A penicillin allergy label, irrespective of its correctness, results in an increased use of second-line/broad-spectrum antibiotics, delay in time-to-first-dose, increased odds for infection with antibiotic resistant organisms, increased length-of-stay, mortality, intensive care unit (ICU) admission rate [4,7–10], although diverging findings have been reported [11–13]. Therefore, an incorrect allergy label can be considered harmful for the individual patient.

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Penicillin allergy delabeling protocols have been evaluated in several healthcare systems, including the US and Australia [5,14–16]. These resulted in updates of national guidelines, notably in the US through the American Academy of Allergy and Clinical Immunology (AAAAI) guidelines [17] and in the Netherlands through the Dutch Working Party on Antibiotic Policy (SWAB) [18]. At the time of generation of this Belgian consensus document, the corresponding recommendations from the European Network of Drug Allergy and the Drug Hypersensitivity Interest Group of the European Academy of Allergy and Clinical Immunology (ENDA-EAACI) had not yet been updated [19]. These guidelines indicate a more liberal approach in the case of penicillin allergy labels than previously proposed, to improve the benefit–risk balance, aiming for more first-choice antibiotic use [20].

To provide a Belgian consensus to guide clinicians confronted with hospitalized patients with a penicillin allergy label but necessitating β-lactam antibiotics, a pragmatic, literature- and consensus-based algorithm and accompanying text was generated.

Methods

In February 2023, an invitation to participate in a national working group on IgE-mediated allergy to β-lactam antibiotics was disseminated within Belgium by the *Belgische Vereniging voor Infectiologie en Klinische Microbiologie – Société Belge d'Infectiologie et de Microbiologie Clinique* (BVIKM-SBIMC). BVIKM-SBIMC is a non-profit professional organization for infectious disease physicians, clinical microbiologists, and hospital pharmacists, aiming to develop guidance on the treatment and prevention of infectious diseases. These guidelines are compiled in the Infectiologiegids – Guide d'Infectiologie (IGGI), which is available (for a fee) to healthcare professionals working in Belgian hospitals. The consensus was developed to reconcile different recommendations in existing guidelines, incorporate recent evidence, and translate these findings into a pragmatic framework for the Belgian inpatient setting while preserving broader applicability.

Under the coordination of the IGGI Steering Committee, the call for participation was issued to assemble a multidisciplinary group tasked with revising and updating the existing IGGI guidelines on IgE-mediated β-lactam allergy. The predefined composition criteria included at least one hospital pharmacist, two physicians with expertise in allergology, and one infectious disease physician, all participating on a voluntary basis. Eligibility requirements comprised a minimum of 3 years of professional experience and a commitment to attend at least 80% of the scheduled meetings. The working group was formally established on 28 March 2023 and consisted of six members (RS, JC, FP, AT, GVDS, XVDB), supported by the IGGI Steering Committee (BD, FJ, MB), an IGGI scientific collaborator, and the IGGI coordinator (JVC). The final composition included one hospital pharmacist (GVDS), four physicians with expertise in allergology (RS, FP, AT, XVDB), and four infectious disease specialists (JC, BD, FJ, MB).

Meetings were organized by the Steering Committee and conducted online on seven occasions (4 May 2023, 23 June 2023, 7 September 2023, 5 October 2023, 30 November 2023, 25 January 2024, and 23 February 2024). In addition, iterative email-based discussions were used to refine and finalize the draft text and recommendations. During the course of the process, the scope of the working group was refined to focus specifically on patients carrying a penicillin allergy label. The outcomes of the consensus process are presented as a structured clinical flowchart, detailing guiding principles, intended population, definitions, and decision steps for the management of hospitalized adults with a penicillin allergy label. The recommendations were launched on 26 June 2025. Open access publication of the flowchart was agreed on earlier.

Results

The clinical flowchart (Figure 1) constitutes the primary output of the consensus process and is presented as a structured, stepwise algorithm with footnotes clarifying practical considerations. Below, several clarifications are provided in a question-answer model.

What is the general principle of the flowchart?

To improve antibiotic choices, we aim to distinguish *low*- from *high*-risk penicillin allergy labels. The central position is that a patient with a *low-risk penicillin allergy label* is considered to expect more harm by avoiding

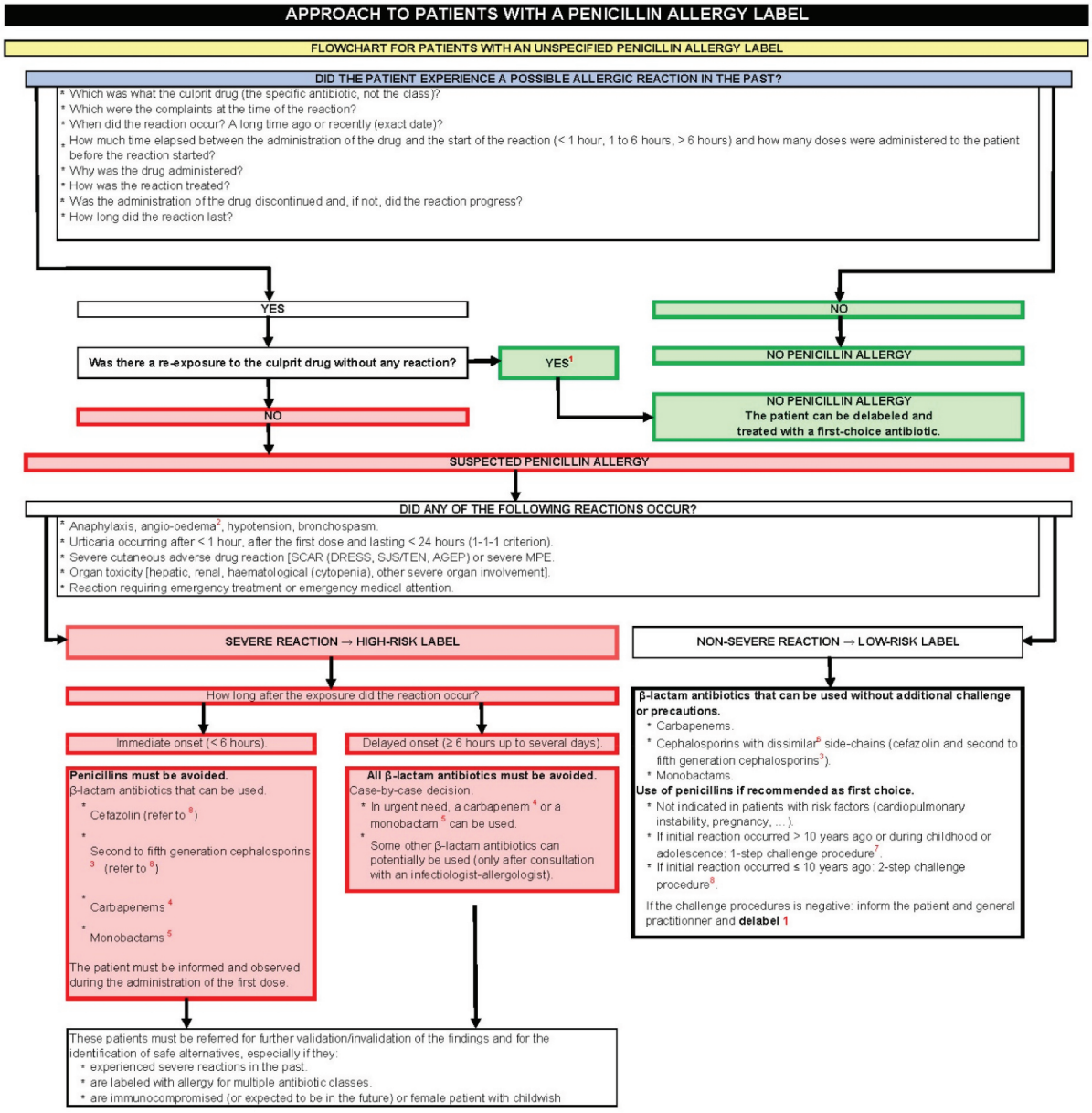

Figure 1. Flowchart for patients with an unspecified penicillin allergy label. **Footnotes: 1.** In case of an unspecified penicillin allergy label, tolerated re-exposure to amoxicillin or penicillin G/V allows for delabeling and for writing down in the file 'no penicillin allergy'. **2.** Angio-oedema. Life threatening (oropharyngeal, . . .) or generalized angio-edema should be treated cautiously. Isolated, mild angio-edema (extremities, . . .) is less likely to be due to IgE-mediated allergy. **3.** Cephalosporins. Second generation: cefuroxime, cefuroxime axetil. Third generation: cefotaxime, ceftazidime, ceftazidime-avibactam, ceftriaxone. Fourth generation: cefepime. Fifth generation: ceftaroline, ceftolozane-tazobactam. **4.** Carbapenems: meropenem, meropenem-vaborbactam. **5.** Monobactams: aztreonam. **6.** Similar or identical side chains are present in: amoxicillin, penicillin G, piperacillin, cefadroxil and cefalexin; aztreonam, ceftazidime and cefiderocol. **7.** 1-step challenge procedure: administration of a single dose of amoxicillin (500 mg to 1 g) followed by close patient observation for at least 30 min (up to 60 min). **8.** 2-step challenge procedure. Administration of a first dose of the antibiotic (10% of the therapeutic dose, liquid oral formulation if available), followed 30 min later by a second dose (remaining 90% of the therapeutic dose). Not necessary when cefazolin is used in the operating room. Vital parameters must be measured at the start and every 30 min until 1 h after the administration of the entire second dose. In case of parenteral administration, the antibiotic must be injected slowly (bolus administration must be avoided). Box underneath '*Did the patient experience a possible allergic reaction in the past*' indicates questions you have to ask your patient to judge the penicillin allergy label. *Abbreviations*: AGEP, acute generalized exanthematous pustulosis; DRESS, drug reaction, eosinophilia, systemic symptoms; MPE, maculopapular exanthema; SCAR, severe cutaneous adverse drug reaction(s); SJS, Stevens-Johnson syndrome; TEN, toxic epidermal necrolysis.

Box 1. Key elements

Key elements

- General principle: This flowchart and document is for adult patients (>18y) in a hospital setting with an unspecified penicillin allergy label. It aims to differentiate low-risk versus high-risk penicillin allergy labels, emphasizing that patients with low-risk labels might face more harm by avoiding penicillins than by re-exposure if these are the first-choice antibiotics.
- Key actions: Ascertain this is a valid allergy label on the basis of the reported complaints and possible re-exposure. In case of a valid label: ascertain if it is a low-risk or high-risk penicillin label.
- Outcome: Most patients will have a low-risk penicillin allergy label and can proceed to use first-choice penicillin antibiotics, with or without a graded rechallenge. In patients with a high-risk penicillin allergy label, alternative β-lactam antibiotics can be considered in most cases.

penicillins than by being re-exposed to penicillins, if these are first-choice antibiotics. We aim to allow safe delabeling where possible and to encourage proper first-choice antibiotic use, whilst maintaining patient safety.

For which patients is this consensus-based recommendation intended (or not)?

This document is meant to guide treatment for adult patients (>18y) in a hospital context where allergy counseling is not directly available (Box 1).

What are penicillins? What are β-lactams? What is meant by 'penicillin' in the flowchart?

β-lactam antibiotics consist of the following groups: penicillins, cephalosporins, monobactams and carbapenems. The group of penicillin antibiotics currently available in Belgium contains the following drugs: penicillin G, feneticillin (pheneticillin), amoxicillin, flucloxacillin, piperacillin and temocillin. Many patients do not recall which drug/penicillin they reacted to but most reactions refer to prior use of penicillin (G or V) or amoxicillin. This document and flowchart (Figure 1) refer to penicillins '*not otherwise specified*', i.e. most likely penicillin G/V or amoxicillin. Allergy labels for penicillins that actually refer to reactions to flucloxacillin, piperacillin, or temocillin are considered rare and should require a specialist's advice.

What questions do I have to ask my patient to judge the penicillin allergy label correctly?

To assess if the reported allergy is indeed suggestive for a true allergy (or another severe side-effect) and whether subsequent tolerated exposure could allow for rapid non-invasive delabeling, first information should be gathered using pre-specified questions as a guidance (Figure 1, upper part of the flowchart).

What are severe and non-severe reactions?

The flowchart (Figure 1) and Table 1 list the symptoms of severe allergic reactions. Mild reactions are considered all those that lack any sign of severity. It is key to ask for the presence/absence of these severity signs. Mild non-severe signs are (for instance) mild rash, itch, nausea and vomiting, malaise (without arguments for anaphylaxis), rhinitis, nasal congestion, orofacial paresthesia. Importantly, nausea, vomiting, digestive problems, orofacial paresthesia on their own are not symptoms of allergy. Secondly, when the signs reported by the patient are incompatible with allergy, delabel.

How do I recognize anaphylaxis?

Anaphylaxis is a severe and potentially life-threatening reaction that occurs rapidly after exposure to the allergen. It is characterized by the involvement of at least 2 organ systems, including skin (urticaria/angioedema), respiratory (bronchospasm), cardiovascular (hypotension–collapse), and/or gastrointestinal systems (infrequent in drug allergy). Although cutaneous manifestations are frequently

Table 1. Classification of the severity of a suspected allergic reaction.

Definition	By symptoms of reaction, wao/eaaci 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, vulva/scrotum) and at least one of the following: (2) Respiratory compromise (e.g. dyspnea, wheeze, bronchospasm, stridor, reduced PEF, hypoxemia) (3) Reduced BP or associated symptoms of end-organ dysfunction (e.g. hypotonia (collapse), syncope, incontinence) (4) Severe gastrointestinal symptoms (e.g. severe crampy abdominal pain, repetitive vomiting), **OR.** (5) 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.** (6) Danger signs for SCAR: (7) Tiny vesicles or crusts, gray-violaceous or dusky color of lesions, painful or burning skin and/or mucosa in addition to fever and malaise, hemorrhagic erosions or mucous membranes and skin detachment (SJS/TEN) (8) Exanthema with pustules (AGEP) (9) Purpura (vasculitis) (10) 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) (DRESS) (11) Facial edema, edematous and infiltrated skin inflammation. Acute fever of 38.5°C and higher (AGEP/DRESS) Note: If an MPE meets the symptom or CIOMS-criteria for a severe reaction, it should be considered as such.		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
Non-severe	(1) Symptom(s)/sign(s) from 1 organ system present: (2) Cutaneous: urticaria (with onset >6 h after exposure and/or duration >1 day), flushing, pruritus, tingling, itching of the lips. (3) Upper respiratory: Nasal symptoms (e.g. sneezing, rhinorrhea, nasal pruritus, and/or nasal congestions), Throat-clearing (itchy throat), Cough not related to bronchospasm. (4) Conjunctival: Erythema, pruritus, or tearing, **OR.** (5) Maculopapular exanthema without organ involvement or other danger signs, duration <7 days [21], **OR.** (6) Other (not symptoms of hypersensitivity): Nausea, metallic taste		All Other reactions

Classification of severity of a suspected allergic reaction based on SWAB 2022 guidelines [18]; *Clinical Microbiology and Infection*, Vol. 29, Wijnakker R et al., "The Dutch Working Party on Antibiotic Policy (SWAB) guideline for the approach to suspected antibiotic allergy," pp. 863–875, 2023, with permission from Elsevier.

Abbreviations: WAO: World Allergy Organization, EAACI: European Academy of Allergy and Clinical Immunology, CIOMS: Council for International Organizations of Medical Sciences, PEF: Peak expiratory flow, BP: blood pressure, SCAR: Severe Cutaneous Adverse Reactions, SJS/TEN: Stevens Johnson Syndrome/Toxic Epidermal Necrolysis, AGEP: Acute Generalized Exanthematous Pustulosis, DRESS: Drug Reaction with Eosinophilia and systemic symptoms, MPE: maculopapular exanthema.

observed (>90%), their absence does not preclude the diagnosis of anaphylaxis, and treatment should not be delayed while awaiting mucocutaneous symptoms. Important clues are its acute onset (<1 h), after the first dose of a regimen, with resolution within 1 day. These elements can be referred to as the 1–1–1 criterion.

What does the 1–1-1 criterion stand for?

It means a reaction occurred after the first intake (of that regimen), within 1 h and resolved within 1 day. These are typical findings in the case of an IgE-mediated reaction. Although isolated urticaria does not

represent a severe symptom per se, it is considered a severity sign when meeting this 1–1-1 because of a higher risk for an underlying IgE-mediated allergy [22].

Why is angioedema specified as a severe reaction?

Angioedema can be part of the mucocutaneous signs in anaphylaxis and can be the only element the patient initially remembers. Isolated but life-threatening angioedema of the larynx or oropharyngeal cavity should be dealt with caution. However, some episodes of isolated angioedema (such as angioedema of the hands or eyes), without any other signs of organ involvement, are less likely to be caused by a drug allergy (as this would be expected to provoke a more systemic reaction). In case of doubt, specialist advice should be sought. If not available immediately, the advice for *high-risk label* should be followed.

What if my patient does not recall the reaction or if I cannot obtain information?

If the patient does not recall the reaction and none of the high-risk features can be identified, the patient can be considered for the low-risk group. If no information can be obtained, indicating that high-risk features cannot be excluded with sufficient confidence, referral or a more cautious approach is recommended.

What are the different types of allergic reactions?

According to the underlying pathogenetic mechanism, allergic reactions to penicillins and the overarching β-lactam antibiotics can be subdivided into type I to IV, following the Gell and Coombs classification for immune-mediated hypersensitivity reactions (Table 2). Clinically, reactions are stratified on the basis of a morphological (i.e. the appearance of the skin lesions, the complex of symptoms caused) and a chronological criterion [23] (i.e. immediate vs non-immediate onset, based on the time between administration and onset of the reaction). The combination of the two criteria allows for the most appropriate diagnosis and stratification. Both immediate and non-immediate (also termed delayed) type reactions can be either severe or non-severe.

My patient has multiple drug/antibiotic allergy labels, what can I do?

True multiple drug allergy exists but is rare. In some patients, the multiple drug allergy label refers to adverse drug reactions that are incompatible with hypersensitivity. This is also called multiple drug intolerance syndrome, which is distinct from allergy [24]. In case of doubt (signs possibly compatible with allergy), these patients can be referred to an allergy specialist to (in)validate their labels and rationalize their potential antibiotic use in the future.

What about cross-reactivity or cross-allergies?

Cross-reactivity or cross-allergies can occur (Figure 2):

(a) within the group of penicillins,
(b) within the group of cephalosporins,
(c) between different groups, in those with similar or identical side chains, such as between amoxicillin, penicillin G/V, piperacillin, cefadroxil and cefalexine and between aztreonam, ceftazidime and cefiderocol. Cross-reactivity between piperacillin and other penicillins has been described in one third of cases, but data remain limited to smaller cohorts or case series [26].
(d) Allergy for all β-lactams is exceedingly rare [19].

Additional patterns that are incompletely explained by structural similarities can be observed occasionally (referred to as co-reactivity, instead of cross-reactivity).

Table 2. Classification and pathogenesis of allergic reactions.

Type of reaction according to the Gell and Coombs classification	Type of Allergy (relative frequency)	Mechanism	Signs/symptoms (Classification of severity of symptoms in table 2)	Chronology of onset
Antibody-mediated				
Type I	Immediate (common)	IgE-mediated reaction based on cross linking of IgE on the surface of mast cells and subsequent degranulation.	Urticaria, angio-edema, bronchospasm and anaphylaxis	<1 h typical, can be up to 6 h post exposure
Type II	Delayed (rare)	Antigen binding to IgM or IgG antibody on cell surfaces or extra cellular matrix proteins. Complement mediated phagocytosis and cytotoxicity.	Cytopenia, hemolytic anemia, vasculitis, thrombocytopenia, probably medication induced pemphigus	Often <72 h, up to 15 days
Type III	Delayed (rare)	Deposition of antibody-antigen complexes in tissues and capillaries with subsequent inflammation (IgM, IgG, complement)	Serum sickness, fever, vasculitis (purpura, petechial) arthritis, glomerulonephritis	Days to weeks (1–3 weeks)
Cell-mediated: T-cell activation by specific agents				
Type IV				
Cutaneous only				
Maculopapular rash (MPE)	Delayed (common)	Eosinophilic infiltration or infiltration if cytotxic T cells	Morbiliform rash, eosinophilia	Days to weeks, typically 4–14 days
Symmetrical drug-related intertriginous and flexural exanthema (SDRIFE)	Delayed (rare)	Infiltration of cytotoxic T cells	Similar to MPE, with involvement of the gluteal and intertriginous areas and symmetric lesions.	Up to 7 days
Fixed drug eruption (FDE)	Delayed (rare)	IFN gamma and cytotoxic granules relased by CD8 T cells	Painful/burning erythematous or edematous round plaques with gray/dusky center at same sites (lip, tongue, face, genitals)	1–12 days to weeks, minutes upon rechallenge
Contact dermatitis	Delayed	Monocytic inflammation	Erythema and edema with vesicles or bullae	Days to weeks
Primary single organ				
Acute interstitial nephritis	Delayed (rare)	CD4/monocyte immune injury	Rash, acute kidney injury, white cell casts in urinary sediment, eosinophilia	3 days-4 weeks, up till 10–12 weeks
Liver injury	Delayed (rare)	CD4 then CD8 T cell activation and TNFα with perforin	Transaminitis (cholestatic or mixed), sometimes rash, fever or eosinophilia	5 days-12 weeks
Severe Cutaneous Adverse Reactions (SCAR), involve systemic symptoms				
Drug reaction eosinophilia and systemic symptoms syndrome (DRESS)	Delayed (rare)	CD4 and CD8 T cells implicated	Fever, rash, peripheral blood eosinophilia, lymphadenopathy, organ involvement (liver/kidney)	2–8 weeks
Steven Johnson Syndrome and toxic epidermal necrolyses (SJS/TEN)	Delayed (rare)	CD8 cytotoxic T cells	Rash with detachment, mucosal lesions, fever, upper respiratory tract symptoms	4–28 days
Acute generalized exanthematous pustulosis	Delayed (rare)	T cells via IL-8 and granulocyte-macrophage colony stimulating factor	Acute pustular euption with widespread non-follicular sterile pustules with fever, facial edema, neutropenia, oral involvement	1–12 days
Other SCARSs, e.g. drug induced IgA dermatosis	Delayed (rare)	Diverse	Diverse	variable

Classification and pathogenesis of allergic reactions obtained from SWAB 2022 guidelines [18];Clinical Microbiology and Infection, Vol. 29, Wijnakker R et al., "The Dutch Working Party on Antibiotic Policy (SWAB) guideline for the approach to suspected antibiotic allergy," pp. 863–875, 2023, with permission from Elsevier.

Who needs an allergy evaluation, where, and how?

Any patient who had a potential severe β-lactam allergy should preferentially be referred for definitive diagnosis and to identify safe alternatives. This evaluation occurs preferably <6 months after the event. Timely referral is mandatory.

Patients with a low-risk penicillin allergy label generally do not need to be referred. In case, they have (or are expected to have in the future) an increased need for antibiotics (e.g. immunocompromised status), have allergy labels for multiple antibiotic classes, have a pregnancy wish (testing is usually avoided during

pregnancy), and/or if the patient disagrees with the proposed approach and/or seeks additional reassurance, referral is recommended.

During a drug allergy evaluation, patients can first undergo skin testing where applicable, before undergoing (mostly oral) tolerance testing in a hospital setting.

How do I manage re-administration of a penicillin in case of a low-risk penicillin allergy label?

The flowchart showed that your patient has a *low-risk* penicillin allergy label, and the first-choice regimen contains a penicillin.

Exclude host risk factors: pregnancy and cardiopulmonary instability. In the latter case, a penicillin could still be envisioned depending on the indication and setting (e.g. emergency room, intensive care setting) and using a 2-step challenge (e.g. ~10%, ~90%).

Inform patients: '*Many patients have a penicillin allergy label but in most cases this turns out to be incorrect (or perhaps it was correct at the time, but not anymore). We know that avoiding penicillins also can have a negative impact on your health. Therefore, we propose to administer amoxicillin, a penicillin, orally in a "single or 2-step procedure (see flowchart)", while monitoring you clinically. We do not expect to re-provoke symptoms. We expect to demonstrate that you tolerate penicillins, so you could use these antibiotics now and in the future. We have the necessary medication to revert a possible reaction here at hand, in the rare case this would be necessary. This advice is based on a consensus on penicillin allergy labels.*'

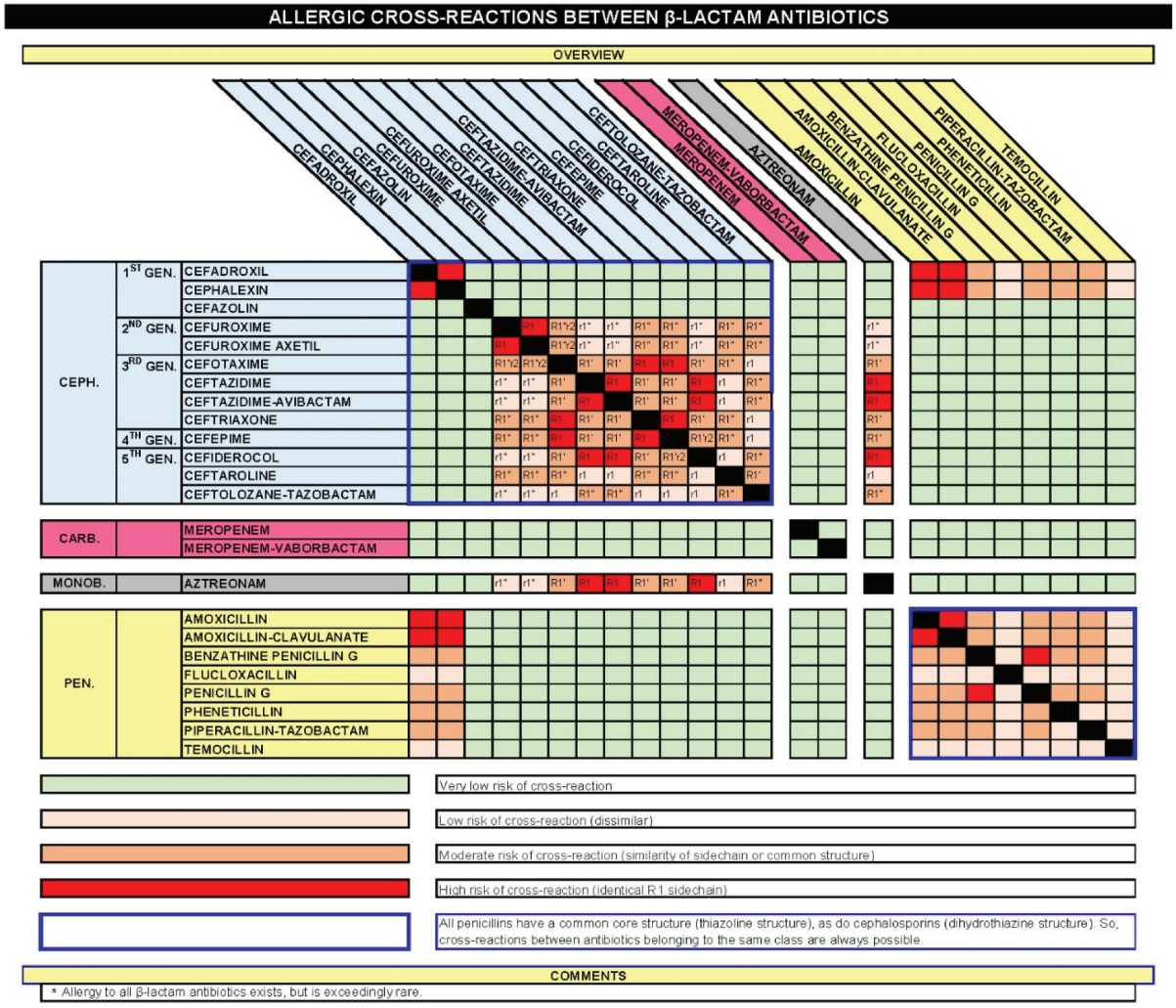

Figure 2. Cross-reactivity and structural similarity within β-lactams. Cross-reactivity and structural similarity within β-lactams based on [19,25].

Verify the presence of emergency medication and the ability to cope with an immediate reaction (the presence of a doctor that is immediately available during the procedure). Although the likelihood is considered low in the case of a *low-risk* penicillin allergy label, it remains imperative to be prepared for this rare event.

Use an oral dose of amoxicillin (0.5 or 1 g) using a single or 2-step challenge procedure according to the flowchart (Figure 1) and observe for 60 min afterward. After this time period, we do not expect immediate (possible IgE-mediated) reactions to occur. We also recommend this observation period to allow objectification of any event that might occur. Some patients may experience non-allergic side effects that could be erroneously attributed an allergy. Of note, it has been shown that 10% of patients who thought they were challenged to amoxicillin in an outpatient allergy practice 'reacted' to placebo [22].

What do I do if the first-choice regimen is not amoxicillin-, but flucloxacillin- or piperacillin- or temocillin-based?

First, a challenge with amoxicillin can be performed, and if negative, *any* penicillin can be started.

Alternatively, a single (or 2-step) oral dose of 0.5 g flucloxacillin or a single (or 2-step) IV challenge of piperacillin/temocillin (bearing in mind to avoid bolus administrations) can also be performed analogously. When tolerated, this does not allow full delabeling of the penicillin allergy, because specific allergy to the drug amoxicillin may exist (which, epidemiologically, is the most likely culprit when patients cannot recall which specific penicillin was involved in their history). To rule this out, subsequently, an oral challenge for amoxicillin would be required.

What do I do if the first-choice regimen is not amoxicillin-based, but is an aminocephalosporin (i.e. cefadroxil, cefalexine)?

The same flowchart applies for these aminocephalosporins. Amoxicillin can be interchanged with one of these cephalosporins. However, a successful rechallenge with an aminocephalosporin in a patient with a penicillin allergy does not rule out an underlying penicillin allergy.

What should I do if my patient did react?

Treat accordingly [27], then document (i.e. take photographs, write up the sequence in the medical file and perform a serum tryptase determination 1–4 h after the start of the manifestation) and refer for formal allergy workup and registration. Based on literature, this should be the exception (and not the rule).

What should I do if a re-challenge was successful?

We expect that this is the rule (and not the exception). We strongly encourage to write this down in the medical file. We prefer stating that there is *NO PENICILLIN ALLERGY*, based on tolerance testing, rather than simply removing the label from the electronic health care record since these labels have been shown to re-appear afterward [19]. Inform the patient and the general practitioner, ideally both verbally as in writing (to avoid reappearance of the label in case of a next encounter with health care). Of note, rarely, after a single dose rechallenge a non-immediate hypersensitivity can occur, mostly up to 48 h [28]. A follow-up contact (in person or via phone) after 1 week could be performed to verify tolerance.

What should I do if my patient has a high-risk penicillin allergy label?

In cases where patients have a *high-risk* penicillin allergy label, all penicillins should be avoided. Alternative β-lactam antibiotics may be considered if they are a first-choice and the benefits of their use outweigh the risks of a possible reaction.

In these patients, a distinction must be made between those with a suspected history of immediate *versus* non-immediate allergy to penicillin. In those with a history of immediate reaction (i.e. onset within 6 h after the last dose), cefazolin, meropenem and aztreonam may be used with the first dose under close medical

monitoring. The patient must be observed for 60 min after administration and medication to treat a possible reaction must be readily available.

If the facilities of the unit and the clinical scenario allow, it is advisable to perform the first administration with a 2-step challenge procedure, i.e. ~10% of the dose followed by the rest of the dose 30 min later. Again, observation for 60 min after the last dose is recommended.

Also, 2nd–5th generation cephalosporins with a different side chain than amoxicillin (e.g. cefuroxime, cefotaxime, ceftazidime, ceftriaxone, cefepime, cefiderocol, ceftaroline, ceftolozane) may be used but only with a 2-step challenge procedure as described above.

These recommendations are based on the structural differences that underlie the known patterns of cross-reactivity between β-lactam antibiotics. As stated above, there is always a risk of co-sensitization following unpredictable structural patterns. Therefore, caution is recommended when deciding to use an alternative β-lactam.

In cases of severe non-immediate reactions (i.e. onset >6 hours or several days after the first dose), the use of β-lactam antibiotics is virtually excluded. Data on cross-reactivity in this patient category are limited. In cases of necessity, when β-lactam antibiotics are irreplaceable, meropenem and aztreonam may be used. Other β-lactam antibiotics may be considered only after consultation with an infectiologist and allergist.

Of note, the distinction between severe immediate and severe non-immediate reactions is clinically important. It affects both the mechanism that is most likely involved and the extent to which alternative β-lactams can still be considered, as indicated in the flowchart (Figure 1). In particular, severe immediate histories raise concern for IgE-mediated reactions and selected alternative β-lactams may still be used cautiously under monitored conditions, whereas severe delayed phenotypes such as SCAR or severe organ involvement require a more restrictive approach because data on safe β-lactam reuse are limited.

What about desensitization, is it still an option?

Yes. It can be performed in patients with a confirmed (or presumed) immediate type (IgE-mediated) allergy to a drug, under strict medical supervision and immediate availability of emergency treatment. However, the indications for a desensitization procedure in the context of a penicillin allergy label are limited. In case of need, please refer to an allergist-specialist and take into account that the effect of desensitization wanes once the drug is stopped (desensitization will have to be re-performed upon every new start of this specific regimen). A calculator can be found online [29].

What if my patient takes a beta-blocking agent?

Beta-blocking agents can reduce the efficacy of adrenaline in the case of an IgE-mediated reaction. When the penicillin allergy label has been identified as 'low-risk', we estimate the risks of interrupting the treatment is greater than maintaining it. Therefore, we do not recommend on changing maintenance therapy or divert the procedure because the maintenance treatment contains a beta-blocking agent.

In an elective allergy evaluation, a risk-benefit estimation must be performed to see if the beta-blocking agent can be temporarily paused or not (duration of interruption depending on the half-life of the agent).

Discussion

This Belgian consensus provides a pragmatic, clinically oriented framework for the management of hospitalized adults with a penicillin allergy label, with the aim of reducing unnecessary avoidance of first-choice β-lactam antibiotics while maintaining patient safety. The recommendations align with a growing international shift toward risk-based delabeling strategies.

A strength of this consensus is the prioritization of clinical phenotype and severity as the principal determinant of risk over a chronological categorization since accurate timing of historical reactions is often unreliable, particularly in non-specialist inpatient settings. In addition, the consensus broadens the definition of severe reactions by including severe non-allergic reactions and urticaria fulfilling the 1–1–1 criterion, thereby enhancing its applicability to real-world settings. Finally, the consensus emphasizes the importance of non-invasive delabeling by instructing users to critically evaluate the initial penicillin allergy

label and actively search for tolerated re-exposures since installation of the label [30,31], in line with previous guidelines [17–19]. This includes evaluating the medical record, contacting the general practitioner, and the pharmacist for potential inadvertent exposure(s) to the culprit drug or family members.

Although considered, the working group decided not to adopt the PEN-FAST score. PEN-FAST has been prospectively validated in Australia and North America, but its performance in European cohorts remains unknown [15,32,33]. Retrospective European data suggest a lower negative predictive value and potential misclassification of patients with severe reactions [34,35]. In line with the Dutch SWAB guideline and the AAAAI practice parameter [17,18,36], this Belgian consensus endorses direct penicillin re-administration in patients with *low-risk* labels, including those with benign cutaneous reactions or vague historical complaints. Importantly, additional safeguards are introduced through the consideration of host-related risk factors (e.g. pregnancy, cardiopulmonary instability), and specifying requirements for the re-administration (Figure 1).

In patients with a history of severe immediate reactions, this consensus aligns with international guidance in allowing the use of carbapenems and monobactams, and – via a 2-step challenge, as in [14,20] – other cephalosporins with a dissimilar side chain (cefazolin, 2nd–5th generation cephalosporins). This is a smaller group of patients (5% of labels are due to anaphylaxis, 12% angioedema), with a low risk for (unexpected) cross-reactivity (2.11% (95% CI 0.98–4.46%)) [37] but a potentially severe reaction. Blumenthal et al. observed in this setting a repeated reaction in 2.6%–3.8% of patients (mostly with cefepime, more than ceftriaxone, more than ceftazidime), although only <1% (of the total administrations) was deemed severe (i.e. necessitating adrenaline, demonstrating severe organ toxicity or severe cutaneous adverse drug reaction (SCAR) occurrence) [14,16,20]. For cefazolin, the risk is expected to be lower [38], which is why we are retaining a more cautious approach (a two-step procedure) when possible, while leaving the option for single-dose administration under medical supervision in the operating room, to align with the SWAB guidelines that had been partially implemented in Belgium at the time of consensus generation [18].

For non-severe immediate and non-severe non-immediate reactions, which constitute the majority of penicillin allergy labels, this consensus is intentionally permissive. Penicillin re-administration is considered appropriate regardless of reaction latency, and provided severity criteria (including urticaria and 1–1–1 criterion) are absent and is supported by evidence demonstrating the safety of direct challenges in these patients [15, 39–42]. While re-occurrence of benign rashes is acknowledged, the consensus emphasizes that such events rarely progress to severe disease and should not perpetuate unnecessary lifelong labeling.

The SWAB guidelines recommend direct removal of an antibiotic allergy label when the index reaction was non-severe, limited to the skin, and occurred in remote childhood or adolescence, or when patients are unaware of the label or unable to recall the reaction [18]. These latter scenarios were not incorporated into the present consensus. Although this consensus supports direct delabeling in the absence of a documented index event, lack of patient recollection may have multiple explanations and was therefore not adopted as a criterion.

In the future, nurse-led assessments, structured allergy questionnaires, and multidisciplinary involvement – particularly of clinical pharmacists – represent practical and increasingly evaluated strategies to support antibiotic allergy delabeling [30,43,44]. Incorporating these approaches into stewardship programs may improve identification of low-risk patients, expand delabeling capacity, and help address the growing burden of inaccurate allergy labels.

Finally, this consensus underscores the importance of documentation and communication. Explicitly stating 'no penicillin allergy' after a negative challenge – rather than merely removing the label – addresses the well-documented problem of label reappearance across care settings.

In summary, this Belgian consensus aims for a balanced position between safety and antibiotic optimization. By favoring a clinically intuitive, severity-based approach, it provides guidance for clinicians dealing with hospitalized adults with a penicillin allergy label in settings where allergy expertise is not immediately available.

Author contributions

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Ethical approval and informed consent were not required, as this manuscript reports a consensus of expert opinions and does not include primary research involving human participants or patient-level data.

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