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

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Content

Guideline navigation **4**

Summary and scope of the guideline **5**

Flowchart of the approach towards a reported penicillin allergy **6**

Synopsis of recommendations **7**

General principles **16**

General introduction *17*

Methodology *22*

Literature search strategy (general information) *24*

Quality assessment of literature and formulation of recommendations *25*

Implementation and dissemination of the guideline **27**

Conflicts of interest policy and funding **27**

Updates **27**

Conflicts of interest of members of the SWAB approach to antibiotic allergy guideline **28**

Definitions and abbreviations **29**

Guideline definitions of severity of drug hypersensitivity and risk indication 31

Key questions **34**

I Allergy history and data collection *34*

1. What is the probability of a current true antibiotic allergy - as assessed by means of skin tests and/or drug provocation tests - in unselected patients with a reported history of antibiotic allergy? 34

2. Which factors are associated with increased or decreased probability of the presence of a true antibiotic allergy? 40

II Registration of antibiotic allergy *43*

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 result of an allergy, and to assess the severity of a reaction) 43

4. When is, based on patient derived information, a reported reaction to be classified as 'not allergic' and can the allergy label be removed ? 46

III Re-exposition in patients with a beta-lactam allergy label *51*

5. Which patients with a reported beta-lactam antibiotic allergy have a very low risk of an actual allergy and can therefore be re-exposed to the same antibiotic for which they are labelled allergic? 51

IV Cross reactivity in beta-lactam allergy (penicillins) *57*

6. What are the determinants of cross-reactivity between beta-lactam antibiotics of the same subclass; and between different subclasses of beta-lactam antibiotics? 59

7. In which patients with a reported allergy to a penicillin, a different penicillin can be administered with an acceptable low risk of an allergic reaction? 62

8. In which patients with a reported allergy to penicillin, a cephalosporin can be administered with an acceptable low risk of an allergic reaction? 66

8a. In which patients with a reported immediate type allergy to a penicillin, a cephalosporin can be administered with an acceptably low risk of an allergic reaction? 66

CONCEPT

Download van SWAB.nl | 2026-11-21 21:43

8b. In which patients with a reported delayed type allergy for a penicillin, a cephalosporin can be administered with an acceptably low risk of an allergic reaction? 71
9. In which patients with a reported allergy to penicillin, a monobactam or carbapenem can be administered with an acceptable low risk of an allergic reaction? 73

V. Cross reactivity in beta-lactam allergy (cephalosporin, carbapenem and monobactam allergy)..... 78
10. In which patients with a reported allergy to a cephalosporin, a penicillin can be administered with an acceptable low risk of an allergic reaction? 78
11. In which patients with a reported allergy to a cephalosporin, a different cephalosporin can be administered with an acceptable low risk of an allergic reaction? 84
12. In which patients with a reported allergy to a cephalosporin, a monobactam or carbapenem can be administered with an acceptable low risk of an allergic reaction? 89
13. In which patients with a reported allergy to a monobactam or carbapenem, a penicillin can be administered with an acceptable low risk of an allergic reaction? 93
14. In which patients with an allergy for a monobactam or carbapenem, a cephalosporin can be administered with an acceptable low risk of an allergic reaction? 94

VI. Non B-lactam antibiotic allergy..... 97
15. Which patients with a non-B-lactam allergy label can be re-exposed to the same antibiotic with an acceptable low risk of an allergic reaction? 97
16. In which patients with a non-B-lactam antibiotic allergy, a different antibiotic from the same class (of non-beta-lactam antibiotics) can be administered with an acceptable low risk of a severe allergic reaction?..... 98

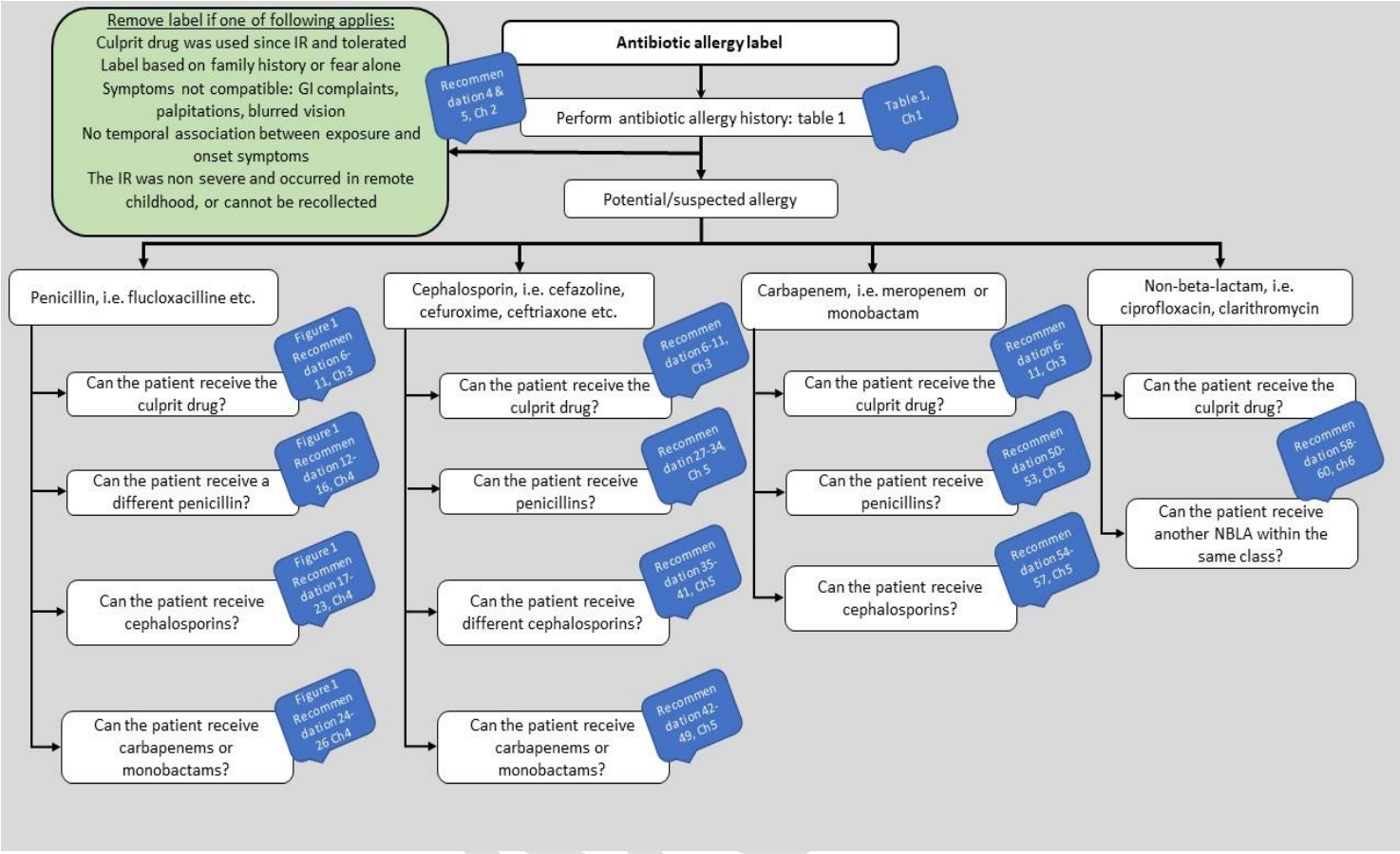
VII In hospital delabeling 107

References 112

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Guideline navigation



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Summary and scope of the guideline

The 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 work-up. The aim of this guideline is 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 at presentation. The guideline was restricted to the most important antibiotics classes used in the clinical practice. Although the primary focus of this guideline is hospital care, part of the guideline is applicable in primary care. The definitions used in this guideline are specified in the “definitions and abbreviations” section. This guideline is intended for the use by all specialties that prescribe antimicrobial treatment or are otherwise involved in patients that need treatment for infection, or are involved in antimicrobial policy making.

Patients with antibiotic allergy comprise a very heterogeneous population and in the individual patient there are always nuances and uncertainties in diagnosis of true antibiotic allergy or potential multi drug hypersensitivity. It is therefore possible that the recommendations in this guideline may not be applicable in an individual patient case. The implementation of the guideline is the responsibility of the attending physician. There may be facts or circumstances in which non-adherence to the guideline is desirable in the interest of good patient care.

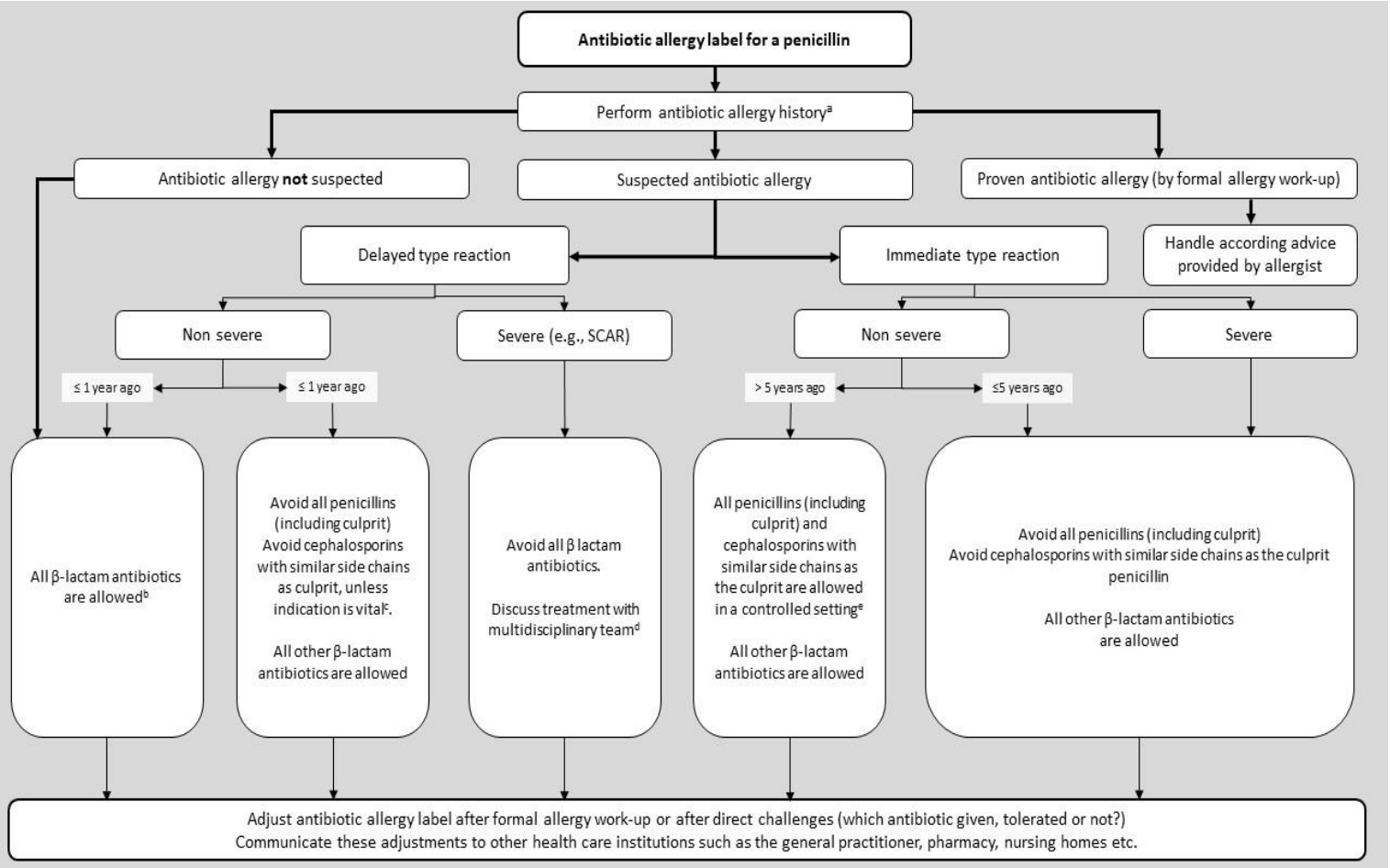
The Dutch Working Party on Antibiotic Policy (SWAB), established by the Dutch association of infectious disease specialists, the Dutch society for medical microbiology and the Dutch association of hospital pharmacists, coordinates activities in the Netherlands with the aim to optimize antibiotic use, 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 on 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).(1)

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Flowchart of the approach towards a reported penicillin allergy

Figure 1. Approach towards a reported penicillin allergy



Legend:
(**a)** See Table 1 (link);
(**b**) In case of severe side effect, do not re-exposure to culprit;
(**c**) Vital indication: if no other options with similar effectiveness are available;
(**d**) 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 antibiotic should be balanced against each other followed by shared decision making with the patient;
(**e**) 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.

Abbreviations: SCAR: severe cutaneous adverse reactions, see table 3 (link)

For classification of severity of the index reaction see table 8 (link). For similarity of side chains yes or no see table 11 (link).

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Synopsis of recommendations

Allergy history and data collection (Chapter I)

What is the probability of a current true antibiotic allergy - as assessed by means of skin tests and/or drug provocation tests - in unselected patients with a reported history of antibiotic allergy?

Recommendation	**Strength**	**Quality of evidence**
1. Because the vast majority of patients, including children, that report a beta-lactam allergy are in fact not truly allergic, we recommend against the standard avoidance of the culprit antibiotic.	Strong	Moderate
2. A detailed antibiotic allergy history (**table 1**) should be performed in patients with documented or (self) reported antibiotic allergy.	Strong	GPS
3. When, according to clinical history, the clinician suspects a true immediate or delayed type beta-lactam allergy, we suggest a formal allergy work up to confirm or rule out a true allergy.	Weak	Very low

Registration of antibiotic allergy (Chapter II)

When is, based on patient derived information, a reaction not allergic and can the allergy label be removed?

Recommendation	**Strength**	**Quality of evidence**
4. 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 occurrence of an allergic reaction. • The allergy label was *solely based on positive family history* of allergy or on *fear* of allergy. • The reported symptoms are *not compatible* with an allergic reaction (i.e. GI complaints only, palpitations, blurred vision). • There was *no temporal association* between exposure and the onset of symptoms.	Strong	Moderate
5. 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 childhood.	Weak	Low

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• The patient is *not aware* of the antibiotic allergy label or *cannot recollect* clinical signs and symptoms of a reaction at all.		

Re-exposition in patients with a beta-lactam allergy label (Chapter III)

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

Recommendation	**Strength**	**Quality of evidence**
6. 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 longer ago, the smaller the chance of an allergic reaction occurring.	Weak	Low
7. We suggest that patients with suspected* *non-severe*, immediate type index reactions that occurred >5 years ago, can receive a therapeutic dose of the culprit beta-lactam antibiotic in a controlled setting**.	Weak	Low
8. We recommend that patients with suspected* *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	Low
9. We suggest that if formal allergy testing is not available, patients with a suspected* *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**.	Weak	Low
10. We suggest that patients with suspected* *non-severe*, delayed type index reactions that occurred >1 year ago can receive the culprit beta-lactam antibiotic without formal allergy testing.	Weak	Low
11. We recommend against re-exposure to the culprit drug in patients with suspected *severe* delayed type index reactions (**table 3**), irrespective of the time since the index reaction. In the absence of acceptable alternative antimicrobial treatment, the use of the culprit should be discussed in a multidisciplinary team***.	Strong	GPS

*In case of a proven allergy by formal allergy work up, handle according to the advice of the consulted allergist.
**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.
*** 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 antibiotic should be balanced against each other followed by shared decision making with the patient.

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Cross reactivity in beta-lactam allergy, penicillin allergy (Chapter IV)

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

Recommendation	**Strength**	**Quality of evidence**
12. We recommend that in patients with a suspected* immediate type allergy to penicillins, irrespective of severity, that occurred ≤ 5 years ago, all other penicillins, (**table 2**) should be avoided.	Strong	Low
13. We recommend that in patients with a suspected* *non-severe* immediate type allergy to penicillins,, that occurred >5 years ago, all other penicillins can be used in a controlled setting**.	Strong	Low
14. We suggest that in patients with suspected* *non-severe* delayed type allergy to penicillins that occurred ≤ 1 year ago, all other penicillins should be avoided.	Weak	Low
15. We suggest that in patients with a suspected* *non-severe* delayed type allergy to penicillins that occurred > 1 year ago, all other penicillins can be used.	Weak	Low
16. We recommend that in patients with suspected *severe* delayed type allergy (**table 3**) to penicillins, all other penicillins should be avoided, irrespective of time since the index reaction. In the absence of acceptable alternative antimicrobial treatment, the use of penicillins should be discussed in a multidisciplinary team***.	Strong	GPS

*In case of a proven allergy by formal allergy work up, handle according to the advice of the consulted allergist.
**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.
*** 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 antibiotic should be balanced against each other followed by shared decision making with the patient.

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

Recommendations for Immediate type allergy	**Strength**	**Quality of evidence**
17. We recommend that patients with a suspected or proven immediate type allergy to penicillins can receive cephalosporins with dissimilar side chains, irrespective of severity and time since the index reaction.	Strong	Moderate
18. Cefazolin does not share any side chains with the currently available penicillins and can be used in cases of suspected or proven immediate type allergy to a penicillin, irrespective of severity or time since the index reaction.	Strong	Moderate

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19. We suggest that patients with a suspected or proven *non-severe*, immediate type index reaction to a penicillin can receive a therapeutic dose of cephalosporins with similar side chains (e.g. cefalexin, cefaclor, cefamandole) in a controlled setting*	Weak	Low

*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.

Recommendations for Delayed type allergy	**Strength**	**Quality of evidence**
20. We recommend that patients with suspected or proven *non-severe*, delayed type allergy to penicillins, can receive cephalosporins with dissimilar side chains, irrespective of time since the index reaction.	Weak	Low
21. We suggest to avoid cephalosporins with similar side chains (e.g. cefalexin, cefaclor, cefamandole) in patients with suspected or proven *non-severe,* delayed type allergy to amoxicillin, penicillin G, V or piperacillin, with an index reaction that occurred ≤1 year ago.	Weak	Low
22. We suggest that cephalosporins with similar side chains (e.g. cefalexin, cefaclor, cefamandole) can be used in patients with suspected or proven *non-severe*, delayed type allergy to amoxicillin, penicillin G, V or piperacillin with an index reaction that occurred > 1 year ago.	Weak	Low
23. We recommend that in patients with suspected *severe* delayed type allergy (**table 3**) to penicillins, all cephalosporins should be avoided, irrespective of time since the index reaction. In the absence of acceptable alternative antimicrobial treatment, the use of cephalosporins should be discussed in a multidisciplinary team*.	Strong	GPS

* 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 antibiotic should be balanced against each other followed by shared decision making with the patient. If the multidisciplinary team concludes the cephalosporin may be used in case of a suspected or proven severe delayed type penicillin allergy, the cephalosporin should be administered under prolonged medical supervision.

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

Recommendation	**Strength**	**Quality of evidence**
24. We recommend that patients with suspected or proven immediate type penicillin allergy, irrespective of severity or time since the index reaction, can receive *any* monobactam or carbapenem, without prior allergy testing.	Strong	Low

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25. We recommend that patients with a suspected or proven *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	Low
26. We recommend that in patients with suspected *severe* delayed type allergy (**table 3**) to penicillins, all monobactams and carbapenems should be avoided, irrespective of time since the index reaction. In the absence of acceptable alternative antimicrobial treatment, the use of monobactams or carbapenems should be discussed in a multidisciplinary team*.	Strong	GPS

*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 antibiotic should be balanced against each other followed by shared decision making with the patient. If the multidisciplinary team concludes the monobactam or carbapenem may be used in case of a suspected or proven severe delayed type penicillin allergy, the monobactam or carbapenem should be administered under prolonged medical supervision.

Cross reactivity in beta-lactam allergy, cephalosporins and carbapenem allergy (Chapter V)

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

Recommendations for Immediate type allergy	**Strength**	**Quality of evidence**
27. We recommend that referral for allergy work-up should be considered to prove or disprove suspected immediate type allergy to cephalosporins in patients	Strong	GPS
28. We recommend that patients with a suspected or proven immediate type allergy to cephalosporins can receive penicillins with dissimilar side chains, irrespective of severity and time since the index reaction.	Strong	Low
29. We recommend to avoid penicillins with similar side chains in patients with a suspected or proven immediate type allergy to cefaclor, cefalexin and/ or cefamandole, irrespective of severity and time since index reaction.	Strong	Low
30. Cefazolin does not share any side chains with the other currently available penicillins and penicillins can therefore be used in cases of suspected or proven immediate type allergy to cefazolin, irrespective of severity and time since the index reaction.	Strong	Low

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Recommendation for Delayed type allergy	Strength	Quality of evidence
31. We recommend that patients with a suspected or proven *non-severe*, delayed type allergy to a cephalosporin can receive penicillins with dissimilar side chains, irrespective of time since index reaction.	Strong	Low
32. We suggest to *avoid* penicillins with similar side chains in patients with suspected or proven *non-severe*, delayed type allergy to cefalexin, cefaclor and/ or cefamandole, when the index reaction occurred ≤ 1 year ago.	Weak	Low
33. We suggest that penicillins with similar side chains can be used in patients with suspected or proven *non-severe*, delayed type allergy to cefalexin, cefaclor and/ or cefamandole, when the index reaction occurred > 1 year ago.	Weak	Low
34. We recommend that in patients with suspected *severe* delayed type allergy (**table 3**) to cephalosporins, all penicillins should be avoided, irrespective of time since the index reaction. In the absence of acceptable alternative antimicrobial treatment, the use of penicillins should be discussed in a multidisciplinary team*.	Strong	GPS

*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 antibiotic should be balanced against each other followed by shared decision making with the patient. If the multidisciplinary team concludes the penicillin may be used in case of a suspected or proven severe delayed type cephalosporin allergy, the penicillin should be administered under prolonged medical supervision.

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

Recommendations for Immediate type allergy	Strength	Quality of evidence
35. We recommend that cephalosporins with a dissimilar side chain can be used in patients with a suspected or proven immediate type allergy to a cephalosporin, irrespective of severity and time since index reaction.	Strong	Moderate
36. Cefazolin does not share any side chains with the other currently available cephalosporins and can be used in cases of suspected or proven immediate type allergy to a cephalosporin, irrespective of severity and time since the index reaction.	Strong	Moderate
37. We suggest that patients with suspected *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**.	Weak	Low

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Recommendations for Delayed type Allergy	Strength	Quality of evidence
38. We recommend that cephalosporins with a dissimilar side chain can be used in patients with a suspected or proven *non-severe* delayed type allergy to a cephalosporin, irrespective of time since index reaction.	Strong	Low
39. We suggest *against* the administration of cephalosporins with similar or identical side chains to the culprit drug in patients with a suspected or proven, *non-severe*, delayed type allergy to a cephalosporin, when the index reaction occurred ≤ 1 year ago.	Weak	Low
40. We suggest cephalosporins with similar or identical side chains to the culprit drug can be used in patients with a suspected or proven, *non-severe*, delayed type allergy to a cephalosporin, when the index reaction occurred > 1 year ago.	Weak	Low
41. We recommend that in patients with suspected *severe* delayed type allergy (**table 3**) to cephalosporins, all other cephalosporins should be avoided, irrespective of time since the index reaction. In the absence of acceptable alternative antimicrobial treatment, the use of cephalosporins should be discussed in a multidisciplinary team*.	Strong	GPS

*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 antibiotic should be balanced against each other followed by shared decision making with the patient. If the multidisciplinary team concludes the other cephalosporin may be used in case of a suspected or proven severe delayed type cephalosporin allergy, the cephalosporins should be administered under prolonged medical supervision.

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

Recommendations for Immediate type allergy	Strength	Quality of evidence
42. We suggest that aztreonam can be used in patients with a suspected or proven immediate type allergy to cephalosporins other than ceftazidime or cefiderocol, irrespective of severity and time since index reaction.	Weak	Low
43. We suggest to *avoid* aztreonam in patients with a suspected or proven immediate type ceftazidime or cefiderocol allergy.	Weak	Low
44. We suggest that *any* carbapenem can be used in a clinical setting in patients with suspected or proven, immediate type allergy to a cephalosporin, irrespective of severity or time since index reaction.	Weak	Low

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Recommendations for Delayed type allergy	Strength	Quality of evidence
45. We recommend that aztreonam can be used in patients with a suspected or proven, *non-severe,* delayed type allergy to cephalosporins other than ceftazidime or cefiderocol, irrespective of time since the index reaction.	Strong	Low
46. We suggest to *avoid* aztreonam in patients with a suspected or proven, *non-severe,* delayed type ceftazidime or cefiderocol allergy, when the index reaction occurred ≤ 1 year ago.	Weak	Very low
47. We suggest that aztreonam can be used in patients with a suspected or proven, *non-severe,* delayed type allergy to ceftazidime and/or cefiderocol, when the index reaction occurred > 1 year ago.	Weak	Very low
48. We suggest that *any* carbapenem can be used in patients with suspected or proven *non-severe,* delayed type allergy to cephalosporins, irrespective of time since index reaction	Weak	Very low
49. We recommend that in patients with suspected *severe* delayed type allergy (**table 3**) to cephalosporins, all monobactams and carbapenems should be avoided, irrespective of time since the index reaction. In the absence of acceptable alternative antimicrobial treatment, the use of monobactams and carbapenems should be discussed in a multidisciplinary team*.	Strong	GPS

*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 antibiotic should be balanced against each other followed by shared decision making with the patient. If the multidisciplinary team concludes the monobactam or carbapenem may be used in case of a suspected or proven severe delayed type cephalosporin allergy, the monobactam or carbapenem should be administered under prolonged medical supervision.

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

Recommendations	Strength	Quality of evidence
50. Referral for allergy work-up should be considered to prove or disprove suspected immediate type allergy to monobactam or carbapenem in patients.	Strong	GPS
51. We suggest that penicillins can be used in a clinical setting in patients with a suspected or proven immediate type allergy to monobactams or carbapenems and no history of penicillin allergy, irrespective of severity or time since the index reaction.	Weak	Very Low
52. We suggest that penicillins can be used in a clinical setting in patients with a suspected or proven *non-severe*, delayed type allergy to monobactams or carbapenems and no history of penicillin allergy, irrespective of time since the index reaction.	Weak	Very Low

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53. We recommend that in patients with suspected *severe* delayed type allergy (**table 3**) to monobactams or carbapenems, all penicillins should be avoided, irrespective of time since the index reaction. In the absence of acceptable alternative antimicrobial treatment, the use of cephalosporins should be discussed in a multidisciplinary team*	Strong	GPS

*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 antibiotic should be balanced against each other followed by shared decision making with the patient. If the multidisciplinary team concludes the penicillin may be used in case of a suspected or proven severe delayed type monobactam or carbapenem allergy, the penicillin should be administered under prolonged medical supervision.

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

Recommendations	**Strength**	**Quality of evidence**
54. We suggest that in patients with a suspected or proven 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	Very low
55. We suggest that in patients with a suspected or proven 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	Very Low
56. We suggest that in patients with a suspected or proven *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	Very low
57. We recommend that in patients with suspected *severe* delayed type allergy (**table 3**) to monobactams or carbapenems, all cephalosporins should be avoided, irrespective of time since the index reaction. In the absence of acceptable alternative antimicrobial treatment, the use of cephalosporins should be discussed in a multidisciplinary team*	Strong	GPS

*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 antibiotic should be balanced against each other followed by shared decision making with the patient. If the multidisciplinary team concludes the cephalosporin may be used in case of a suspected or proven severe delayed type monobactam or carbapenem allergy, the cephalosporins should be administered under prolonged medical supervision.

Non B-lactam antibiotic allergy (Chapter VI)

Which patients with a non-beta-lactamallergy label can be re-exposed to the same antibiotic with an acceptable low risk of an allergic reaction?

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In which patients with a non-beta-lactamantibiotic allergy, a different antibiotic from the same class (of non-beta-lactam antibiotics) can be administered with an acceptable low risk of a severe allergic reaction?

Recommendations	**Strength**	**Quality of evidence**
58. We recommend avoiding re-exposure to the culprit NBLA and all other NBLA within the same class when the index reaction was severe.	Strong	GPS
59. 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.	Weak	Low
60. 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*	Strong	GPS

*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.

**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 antibiotic should be balanced against each other followed by shared decision making with the patient.

General principles

While formulating the recommendations for each key question, the guideline committee noticed that some principles and recommendations were consistently returning, these were the following:

- Always perform a detailed allergy history (**Table 1**).
- If cross-allergy is not to be expected because of absence of side chain similarity, the patient can be exposed to the BLA. An exception to this rule are the severe delayed type reactions.
- In case of *severe* delayed type reactions, do not challenge without consultation of a multidisciplinary team.
- In case of *non-severe* delayed type reactions, re-exposure to the culprit antibiotic (or a BLA with similar or identical side chains) is allowed after 1 year.
- In case of *non-severe* immediate type reactions, re-exposure to the culprit BLA (or a BLA with similar or identical side chains) is allowed after 5 years in a controlled setting.
- In case of *non-severe* immediate type reactions that occurred <5 years ago or *severe* immediate type reactions, re-exposure to the culprit drug (or a BLA with similar or identical side chains) should be avoided.

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General introduction

Ten to twenty percent of clinically admitted patients have some form of drug allergy or hypersensitivity registered in their electronic file. Based on formal allergy test studies however, less than 10% of patients with an allergy label are truly allergic.(2-4) The most frequent drug involved is an antibiotic of the penicillin class (**table 2**).(2) Often, in case of a possible history of antibiotic allergy, an agent (or group of agents) is erroneously avoided. As a result, the optimal antimicrobial therapy (i.e. the antibiotic that is most effective, has a narrow spectrum and little toxicity) is not administered. This is undesirable, not only because of the direct disadvantages for the patient, but also because of a negative influence on the development of resistance when using more broad-spectrum antibiotics. For example, patients with a reported ß-lactam antibiotic allergy who present with sepsis frequently receive empiric non-ß-lactam antibiotic treatment options such as aminoglycosides, fluoroquinolones or trimethoprim/ sulfamethoxazole. These non-ß-lactam antibiotics have been associated with increased risk of clinical failure(5-8) or side effects and complications such as clostridium difficile infections.(9, 10) However, a documented allergy could also be a true allergy and an actual threat to the patients' health.(11) Prudent decision-making regarding reported antibiotic allergy and antibiotic use is therefore an important part of antibiotic stewardship.

Most allergy labels are self-reported by the patients and rarely or only partially substantiated by the healthcare professional (general practitioner or specialist) that observed or identified the drug reaction. The extent of the risk of recurrence of an allergic reaction upon re-exposure to the antibiotic depends on several factors. Estimating this risk requires a systematic clinical approach.(2) The questions that must be answered to assess this risk are at least the following: 1) Is a true allergy suspected or is the reaction caused by toxicity (e.g. intolerance) or another cause such as a viral exanthema. 2) What type of allergy occurred: immediate or delayed, and what was the severity of the reaction. 3) What is the chance of recurrence of a reaction after re-administration of the culprit drug. 4) What is the risk of cross-allergy with other antibiotics and 5) What are the pros and cons of the alternative antimicrobial treatment.(2, 12, 13) To be able to answer the previous questions a formal allergy history should be taken in each patient reporting an antibiotic allergy (**Table 1**). For some index reactions there is too limited information available to classify the symptoms as immediate or delayed type allergy. For example the symptoms are consistent with immediate type allergy, but the course of index reaction is suggestive for a delayed type reaction. For these reactions it is especially important to determine the severity of the index reaction. If the index reaction was non-severe, but included symptoms suggestive of immediate type allergy, the advice is the same as

CONCEPT

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in non-severe immediate type index reactions. If the index reaction was non-severe and included no symptoms consistent with immediate type allergy, the advice is the same as non-severe delayed type allergy.

Table 1: Detailed allergy history *modified from Salkind et al. 2001 and Lambregts et al. 2020 (2, 14)*

Question	Explanation
What was the culprit antibiotic (the antibiotic used/ administrated) that elicited the index reaction?	Identify the specific antibiotic, not the class (e.g., amoxicillin, not penicillins or BLA)
What was the patients' age at the time of the reaction, and when did it occur (how many years ago?)	It has been shown that skin tests for penicillin become negative over time (though not always confirmed with negative drug provocation). The longer ago the index reaction occurred, the smaller the risk of a reaction after re-exposure.
What was time between the first dose of the antibiotic and the onset of the first symptoms of the reaction?	Immediate type reactions usually occur <1 hour after drug administration and delayed reactions occur generally >24 hours after administration.
How long did the symptoms last?	The symptoms of a delayed type reaction generally last longer than those of an immediate type reaction. Immediate type reactions tend to resolve within minutes/hours after discontinuation of the culprit drug. Delayed type reaction after days to weeks.
What were the characteristics or symptoms of the reaction?	This is to classify the symptoms as pointing to an immediate or a delayed type reaction and severe or non-severe: see table 3 and 8
Was the reaction observed by a doctor or other health care workers?	Documented observations can be of value to be able to classify the type and severity of the reaction.
Why was the patient using the culprit antibiotic at that time?	Could the symptoms have been part of the clinical picture/disease at that time (viral exanthems, infection induced urticaria, respiratory symptoms induced by pneumonia).
Did the reaction result in hospital admission, ICU admission or the administration of adrenalin?	This identifies the severity of the reaction and the probability of an immediate type reaction.
Has the patient used the culprit antibiotic since the index reaction? If yes, did a reaction occur?	If re-exposure was previously successful, the antibiotic allergy label should be removed.
Was an alternative antibiotic from the same class of antibiotics used after the index reaction occurred? If yes, did a reaction occur?	For example, in case of penicillin allergy, did the patients receive cephalosporins?

In order to interpret the available information, health care workers should be educated about adverse drug reactions (ADRs). For antibiotics, non-immunologic reactions include predictable adverse effects and toxicity and are therefore not truly allergic reactions. The immunologic reactions

CONCEPT

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to antibiotics (i.e., true allergy) are traditionally subdivided into type I to IV according to the classification of Gell and Coombs (**table 3**). In current clinical practice , a different approach is preferred based on the time between administration and the formation of a reaction (immediate vs. delayed type reactions). Immediate type reactions can be IgE mediated (**table 3**), or other factors may be involved such as direct mast cell stimulation. In the IgE mediated immediate reactions, re-exposure to the antibiotic can trigger anaphylactic reactions resulting in life threatening situations.(12) These reactions are truly allergic reactions. In immediate reactions where direct mast cell activation results in the reaction (i.e. non IgE-mediated, immediate reactions), the reactions have an immunological phenotype but immunological memory is not formed. Vancomycin and fluorquinolones are the most commonly recognized mast cell activators. These reactions are not considered to be true allergic reactions.(12) Delayed type reactions are either antibody or T cell mediated reactions. This reactions include maculopapular exanthema (MPE) and the more severe cutaneous adverse reactions (SCAR).(15) (**Table 3**)

This guideline provides recommendations and a flow chart (**Figure 1**) for the use of antibiotics in patients with an antibiotic allergy label (AAL) in the clinic, both self-reported or registered by health care workers (HCWs). A detailed history can be helpful to estimate the risk of recurrence of an allergic reaction.(2, 16) However, clinical history alone is not always a good predictor of antibiotic allergy or sufficient to discriminate between immediate and delayed reactions.(17) In reactions where an immunologically mediated reaction is suspected, referral to an allergist for further work-up is frequently advised. Skin tests and drug provocation tests can help establish a true allergy and test for cross-reactivity with alternative antibiotics. More often allergists will be able to rule out an actual allergy, resulting in removal of the AAL. This could result in the reduction of the use of alternative antibiotics and increase the use of β lactam antibiotics without causing more hypersensitivity or adverse reactions.(7, 18) Obviously, a problem with allergy testing is that it would delay optimal empiric antimicrobial treatment in such a way that it would increase morbidity and mortality due to the untreated infection. The general objective of the SWAB antibiotic allergy guideline is to guide medical professionals in empirical and targeted antibacterial treatment for children and adults with a self-reported or documented antibiotic allergy in hospitals in the Netherlands.

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Table 2: classification of beta lactam antibiotics, used in the Netherlands

Group	Compound	Formulation
Penicillins		
Natural penicillins	Penicillin G (benzylpenicillin)	Parenteral
	Penicillin V (Phenoxymethylpenicillin)	Oral
	Pheneticillin	Oral
Penicillinase resistant	Flucloxacillin	Oral and parenteral
Aminopenicillins	Amoxicillin*	Oral and parenteral
Extended penicillin spectrum	Piperacillin*	Parenteral
Cephalosporins		
Amino-cephalosporins **(Common R1 aminobenzyl group)**	Cefaclor	Oral
	Cefalexin	Oral
Benzyl-cephalosporins (amino-benzyl group)	Cefamandole	Parenteral
Methoxyimino cephalosporins **(Common R1 Methoxyimino group*)***	Cefuroxime	Oral and parenteral
	Ceftriaxone, Cefotaxime	Parenteral
Alkoxy-imino cephalosporins	Ceftazidime, Cefiderocol	Parenteral
Unique R1 group	Cefazolin	Parenteral
Other Cephalosporins	Ceftibuten, Ceftolozane, ceftarolinefosamil	Oral and parenteral
Carbapenems		
	Meropenem	Parenteral
	Imipenem*	
	Ertapenem	
Monobactams		
Alkoxy-imino group	Aztreonam	Parenteral

* Often used in combination with beta lactamase inhibitors: co-amoxiclav, tazobactam, cilastatin, relebactam

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Table 3: General classification and pathogenesis of allergic reactions *modified from (12, 19)*

Type of reaction according to the Gell and Coombs classification	Type of allergy (relative frequency)	Mechanism	Signs/symptoms	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	<1h typical, can be up to 6h 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 hours, 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 (type IV) = T-cell activation by specific antigens				
Cutaneous only				
Maculopapular rash (*MPE*)	Delayed (common)	Eosinophilic infiltration or infiltration of cytotoxic T cells	Morbilliform rash, eosinophilia	Days to weeks, typically 4-14 days
Symmetrical drug related intertriginous and flexural exanthem (SDRIFE)	Delayed (rare)	Infiltration of cytotoxic T cells	Similar to MPE, with involvement of the gluteal and intertriginous areas and symmetry of lesions.	Up to 7 days
Fixed drug eruption (*FDE*)	Delayed (rare)	IFN gamma and cytotoxic granules released by CD8 T cells	Painful/ burning erythematous or edematous round plaques with gray/dusky center at same sites (lip, tongue, face, genitals)	Days to weeks, minutes upon re-challenge
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
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 desquamation, mucosal lesions, fever, upper respiratory tract symptoms	4 -28 days
Acute generalized exanthematous pustulosis (*AGEP*)	Delayed (rare)	T cells via IL-8 and granulocyte-macrophage colony stimulating factor	Acute pustular eruption with widespread non-follicular sterile pustules with fever, facial edema and or neutropenia, oral involvement	1-12 days

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Methodology

The guideline committee defined the scope of the guideline and key questions to be answered. **Table 4** shows the final key questions. Questions covering interventions were structured into the PICO format (Population; Intervention; Control; Outcomes, see appendix). Guideline committee members were assigned to one or more key questions. As the PICO search did not always yield randomized control trials (RCTs) and most of the literature concerns observational studies, the committee decided to use additional quality criteria whilst reviewing the literature. Drug provocation was considered as gold standard, skin tests were considered as good indicators of drug allergy, provided that validated test protocols were used. Skin test should ideally be validated by drug provocation. Intracutaneous testing was considered as delivering stronger evidence as skin prick testing. Epicutaneous testing was considered as delivering strong evidence for delayed reactions, as were late readings of intracutaneous testing, again provided that validated test protocols were used. Theoretical considerations were regard as least strongest evidence, as were results based on serological responses. It has been shown that skin tests for penicillin become negative over time (however, not always confirmed with negative drug provocation tests).

The guideline was written according to the Appraisal of Guidelines for Research & Evaluation (AGREE) instrument.(20) In line with the AGREE instrument, the Guideline committee followed a guideline development process comparable to that of the Infectious Diseases Society of America (IDSA), 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).(21)

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Table 4. Key questions for the SWAB guideline for the approach to a reported antibiotic allergy

Chapter I – Allergy history and data collection

1. What is the probability of a current true antibiotic allergy - as assessed by means of skin tests and/or drug provocation tests - in unselected patients with a reported history of antibiotic allergy?

2. Which factors are associated with 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 beta-lactam allergy label

5. Which patients with a reported beta-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 beta-lactam allergy (penicillin allergy)

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

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

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

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

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

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

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

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

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

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

Chapter VI – Non B-lactam antibiotic allergy

15. Which patients with a non-B-lactam allergy label can be re-exposed to the same antibiotic with an acceptable low risk of an allergic reaction?

16. In which patients with a non-B-lactam antibiotic allergy, a different antibiotic from the same class (of non-beta-lactam antibiotics) can be administered with an acceptable low risk of a severe allergic reaction?

Chapter VII – In hospital delabeling

No questions formulated, this is a descriptive chapter

Literature search strategy (general information)

For each key question a literature search was developed, with guidance of a medical librarian, to identify all published articles that report outcomes regarding the PICO. When available in literature; RCTs, systematic reviews and meta-analysis were included to answer the PICO and formulate conclusions and recommendations. If appropriate, case-control and cohort studies were used in the paragraph " additional literature review". Studies that did not report outcomes on the specific questions were excluded. The search 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. Search strategies are included in the Supplementary Material.

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Quality assessment of literature and formulation of recommendations

One guideline member (coordinator) performed quality assessment of the literature for individual key questions, which was subsequently verified by other guideline members. The quality of evidence per outcome variable was graded according to the GRADE (Grading of Recommendations Assessment, Development and Evaluation) system, adopted by SWAB. Quality of evidence is determined by several factors, the most important of these was study design (**Figure 2**).(21) The remaining factors (e.g. risk of bias) can downgrade or upgrade the quality of evidence based on design. For example, an observational study with a serious risk of bias is considered to have a very low quality of evidence. In the final step of the process recommendations were made. The strength of recommendations was graded as Strong or Weak, taking the quality of evidence, patients' values, resources and costs, and the balance between benefits, harms and burdens into account (**Figure 2**).(21) The SWAB Stewardship Guideline committee and for example the WHO are of the opinion that a low quality of evidence does not necessarily lead to a weak recommendation. Likewise, strong evidence for a certain intervention can sometimes nevertheless result in a weak recommendation. The reasons for the guideline committee to give strong or weak recommendations are discussed for each recommendation in the section: Other considerations. When evidence could not be obtained, assigned guideline group members for the key question proposed recommendations on the basis of opinions and experiences. These good practice statements (GPS) were not graded using the GRADE approach and were developed according to criteria in **Table 5**.(22)

Drafted recommendations for each key question were presented to the complete guideline working group and consensus was reached by discussion and voting. Preparation of the guideline text was carried out by a multidisciplinary committee consisting of experts regarding antibiotic allergy, pharmacology, and treatment of infectious diseases (see list of committee members on frontpage) The recommendations were summarized. The draft guideline was subsequently submitted to the members of relevant professional societies for external review. The guideline working group adjusted the guideline according to comments in the external review through group discussion. The final version was presented to the SWAB executive board, that consisted of mandated representatives of the professional societies, for formal authorization.

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Figure 2. Overview of GRADE methodology. Approach and implications to rating the quality of evidence and strength of recommendations using the Grading of Recommendations Assessment, Development and Evaluation (GRADE) methodology. [21]

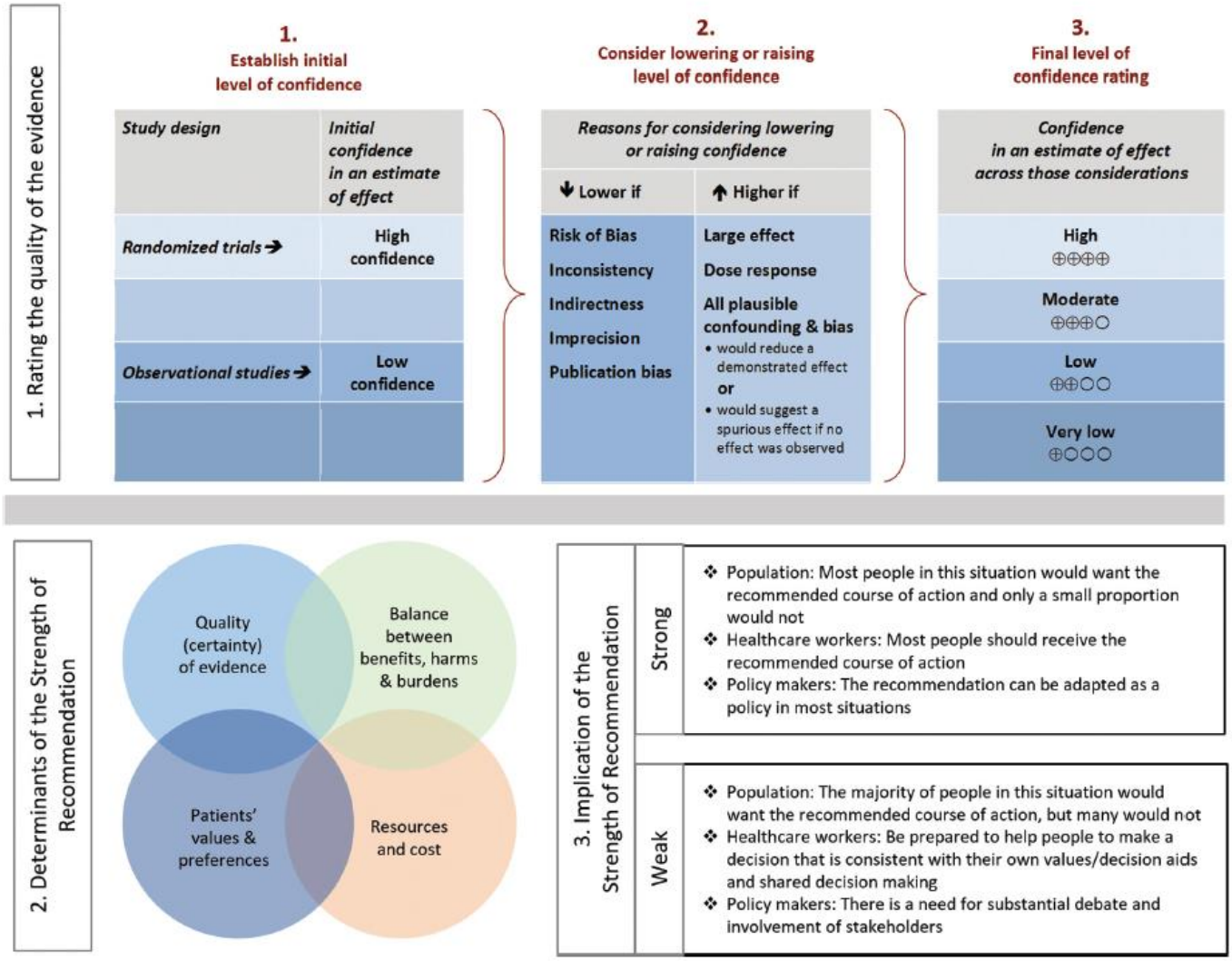


Table 5. Criteria for the development of good practice statements (GPS) (22)

A question applicable to any recommendation (but often violated in good practice statements)
1. Is the statement clear and actionable?
Questions particular to good practice statements
2. Is the message really necessary in regard to actual health care practice?
3. After consideration of all relevant outcomes and potential downstream consequences, will implementing the good practice statement result in large net positive consequences.
4. Is collecting and summarizing the evidence a poor use of a guideline panel's limited time and energy (opportunity cost is large)?
5. Is there a well-documented clear and explicit rationale connecting the indirect evidence?
The answers to all questions 2 - 5 should be yes to proceed with a good practice statement.

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Implementation and dissemination of the guideline

The formal publication of the guideline is announced to all relevant professional societies and presented at relevant national conferences. The recommendations in the guideline are made available online at https://swab.nl.

Conflicts of interest policy and funding

The SWAB employs strict guidelines with regard to potential conflicts of interests, as described in the SWAB Format for Guideline Development (www.swab.nl). For the development of this guideline, the SWAB was funded by the Ministry of Health via the Dutch National Institute for Public Health and the Environment (CIb-RIVM). See **table 6** for disclosures of the members of the Guideline committee.

Updates

SWAB intends to revise their guidelines every 5 years. The potential need for earlier revisions will be determined by the SWAB board at annual intervals, based on current literature. If necessary, the guideline committee will be reconvened to discuss potential changes.

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Conflicts of interest of members of the SWAB approach to antibiotic allergy guideline

Table 6: committee member disclosures

Member	Potential conflict of interest
Lieke de Vrankrijker	None
Suzanne Lutgens	None
Maja Bulatovic Ćalasan	None
Ananja Middel	None
Lonneke Bode	None
Kim Sigaloff	None
Maurits van Maaren	None
Bart Hendriks	None
Chris Nieuwhof	None
Eveline Roelofsen	None
Aline Sprikkelman	None
Masja Loogman	None
Mark de Boer (Chair)	None
Roos Wijnakker (coordinator)	None

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Definitions and abbreviations

Table 7. Definitions and abbreviations

Allergy		
Term	*Abbreviation*	*Definition*
Adverse drug reaction	ADR	Unintended, harmful events attributed to the use of medicines, *on target ADR* are predictable based on drug action (e.g. side effects, for example C. diff) and *off target ADR* can be non-immunologically mediated (for example non IgE mediated mast cell activation) or immunologically mediated (antibody or T cell)
Anaphylactic reaction		An acute onset of an illness (minutes to several hours) with simultaneous involvement of the skin, mucosal tissue or both and at least one of the following: respiratory compromise, reduced blood pressure or associated symptoms of end organ dysfunction, severe gastrointestinal symptoms.
Antibiotic allergy		A reaction that is the result of activation of the immune system by the antibiotic
Antibody mediated allergy or reaction		Antibody mediated allergies include Type I, II and III hypersensitivity reactions according to the Gell and Coombs classification of allergic reactions, see table 2.
Basophil activation tests	BAT	A functional assay that measures the degree of degranulation following stimulation with allergen or controls by flow cytometry. It correlates directly with histamine release. From the dose-response curve resulting from BAT in allergic patients, basophil reactivity (%$CD63^+$ basophils) and basophil sensitivity (EC_{50} or similar) are the main outcomes of the test.
Controlled setting		A clinical setting with trained personnel where rapid and adequate treatment can be administered when a reaction occurs.
Cross reactivity		In case of immediate type allergy: an immune-mediated phenomenon of an IgE antibody recognizing, binding, and inducing an immune response to similar allergenic molecules (homologues). In case of delayed type allergy: T cell mediated reactivity.
Delayed reaction		A reaction that usually occurs > 24 hours after exposure to the antibiotic (mostly 1-10 days after exposure). The reaction can occur after drug discontinuation.
Direct challenge	DC	Direct administration of the antibiotic (therapeutic or as challenge) without previous allergy testing.

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Drug provocation test	DPT	In case of a suspected allergy and negative sensitization test or little suspicious history and positive sensitization test, a provocation test is indicated to prove or reject the allergy.
Drug re-exposure		Re administration of the culprit antibiotic drug (i.e. the antibiotic that resulted in the index reaction).
Formal allergy work-up		Performing allergy diagnostics (skin tests and provocations) to reject or confirm the diagnosis of antibiotic allergy.
Hypersensitivity reaction	HSR	An exaggerated or inappropriate immunologic response occurring in response to an antigen or allergen
Immediate reaction		A reaction that occurs typically <1 hour after exposure, but can be considered within 6 hours after exposure. They can be either mediated by IgE or by other factors (such as direct mast-cell stimulation)
Immune mediated reaction	IM	Reactions that are antibody- or pure T cell mediated
Index reaction	IR	The first reaction that occurred after administration of an antibiotic
In vitro allergy tests		Tests that are not performed directly on the body: for example: tryptase and histamine determination, sIgE or RAST, Basophil activation tests (BAT), Lymphocyte transformation testing (LTT)
In vivo allergy tests		All tests performed directly on the body: immediate and delayed skin tests, patch skin tests, drug provocation tests
Lymphocyte transformation testing	LTT	A test based on the activation and expansion of the drug-specific memory T cells following co-incubation of the patient's peripheral mononuclear cells (PMBC) with the suspected drug in vitro. The read-out parameter in the classical LTT is T cell proliferation which can be measured as counts per minute following the addition of radiolabeled thymidine to the cell culture.
Medical supervision		Frequent patient control by a medical specialist, for immediate type reactions preferably in a clinical setting.
Multidisciplinary team		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 antibiotic should be balanced against each other followed by shared decision making with the patient.
Non-immune mediated reaction	NIM	Reactions that are not immunologically mediated but result from cellular toxicity and disrupted physiology or (non-) immune cell receptor interaction. Previously called pseudo-allergic or anaphylactoid reactions. For example non-IgE mediated mast-cell stimulation.

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Prolonged medical supervision		Frequent (e.g. twice a week) check-ups for an emerging reaction by a medical specialist until treatment is stopped
Specific IgE	sIgE	A blood test to detect specific IgE antibodies, to determine the substances a subject is allergic to.
Remote reaction		A reaction that occurred more than 10 years ago
Reported antibiotic allergy		A documented or self-reported reaction to an antibiotic
Side chain		The side chains (R) of β lactam antibiotics are potentially immunologic. Penicillins have one side chain (R1) and cephalosporins have two side chains (R1, R2).
Skin test	ST	Epicutaneous skin testing (i.e., prick, puncture, patch or scratch) and intradermal skin testing
T cell mediated allergy or reaction		Reactions that are induced by various T cell subsets.
Type A reaction		Augmented or intrinsic reaction, result from an exaggeration of normal pharmacological actions of the drug when given at the usual therapeutic dose and are normally dose-dependent and predictable.
Type B reaction		Idiosyncratic reactions not clearly related to increasing dose and are associated with drug-specific and patient-specific characteristics and environmental risks.

Guideline definitions of severity of drug hypersensitivity and risk indication

Multiple systems are known to classify the severity of drug hypersensitivity reactions and/or systemic allergic reactions. None of these classifications is universally accepted as the preferred system. The current classification systems can be further divided into those based on the symptoms of the reaction and those based on the consequences and interventions needed. The guideline committee decided to use the WAO symptom-based classification system for anaphylaxis with additions from the EAACI position paper on classification of cutaneous manifestations of drug hypersensitivity, as well as the CIOMS criteria which are based on consequences of the reaction. It is important to note that the reaction can be classified as severe if the criteria of one of the two system is fulfilled, and that it is not needed to fulfill the criteria of both systems.(19, 23, 24)

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Table 8. Classification of severity of a suspected allergic reaction by the definitions used in this guideline

Definition used in this guideline	By Symptoms of reaction, WAO/EAAIC criteria(19, 24)	OR	By consequences of reaction, CIOMS criteria(23)
Severe	1. Acute onset of an illness (minutes to several hours) with simultaneous involvement of the skin, mucosal tissue, or both (eg, generalized hives, pruritus or flushing, swollen lips-tongue-uvula) AND at least one of the following: a. Respiratory compromise (eg, dyspnea, wheeze-bronchospasm, stridor, reduced PEF, hypoxemia) b. Reduced BP or associated symptoms of end-organ dysfunction (eg, hypotonia [collapse], syncope, incontinence) c. Severe gastrointestinal symptoms (eg, 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 SCAR: a. Tiny vesicles or crusts, grey-violaceous or dusky color of lesions, painful or burning skin and/or mucosa in addition to fever and malaise, hemorrhagic erosions of mucous membranes and skin detachment (SJS/TEN) b. Exanthema with pustules (AGEP) 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) (DRESS). e. Facial oedema, edematous and infiltrated skin inflammation. Acute fever of 38.5°C and higher. (AGEP/DRESS)		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: a. Cutaneous: Urticaria, erythema-warmth, pruritus, tingling, itching of the lips. b. Upper respiratory: Nasal symptoms (eg, sneezing, rhinorrhea, 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

Legend: The description of severe symptoms was derived from the WAO allergy anaphylaxis guidance position paper 2020 definitions for 'likely anaphylaxis' (**table 2**, (19)), as well as from the EAACI position paper on how to classify cutaneous manifestations of drug hypersensitivity (24). Abbreviations: WAO, World Allergy Organization, EAAIC, 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

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Table 9. Terms used with regard to risk indication in this guideline

Estimate of the %	Terms used in guideline	
>90%	High risk	Proven
>50%	High risk	Probable
5-50%	Intermediate risk	Possible
1-5%	Low risk	Unlikely
<1%	Very low risk	Negligible

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Key questions

I Allergy history and data collection

Introduction

Despite the high frequency with which antibiotic allergy is reported, true antibiotic allergy remains rare. In addition, serious allergic reactions such as anaphylaxis or Steven Johnson syndrome are seen even less frequently.(4) This chapter examines the probability of true antibiotic allergy in patients that report an antibiotic allergy and highlights the importance of allergy history taking to be able to stratify the risk of occurrence of a serious drug reaction.

1. What is the probability of a current true antibiotic allergy - as assessed by means of skin tests and/or drug provocation tests - in unselected patients with a reported history of antibiotic allergy?

PICO

P: Patients with an antibiotic allergy label (AAL) or reported antibiotic allergy

I: Skin test and/or drug provocation test

C: Not applicable

O: True antibiotic allergy (immune mediated)

Evidence summary

Systematic reviews and meta-analyses

Four systematic reviews (including two meta-analyses) were identified, that assessed the probability of a true antibiotic allergy in patients that reported having an antibiotic allergy. Salkind et al. included 14 studies, of which 4 compared clinical history with skin test (ST) results for penicillin allergy, among patients (adults and children) with and without a positive history of penicillin allergy (n=9526). Of the patients reporting a history of penicillin allergy, 10-20% were found to be truly allergic based on skin testing. Out of patients with a positive history of penicillin allergy and negative ST results, ≥98% (6739 patients) were able to tolerate penicillins. The likelihood ratio (LR) of a positive ST in patients with a history of penicillin allergy was 1.9 (95% CI 1.5-2.5) while the LR of a positive ST in patients without a history of penicillin allergy was 0.5 (95% CI 0.4-0.6).(2) The second systematic review included 24 studies of inpatient adult (>18 years) cohorts with a documented penicillin allergy, in which an evaluation was performed to rule out penicillin allergy, mostly by ST or intradermal test (IDT) with or without subsequent drug provocation test (DPT) with an oral penicillin. In this study the

CONCEPT

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population weighted mean probability for a negative penicillin ST was 95.1% (95% CI 93.8-96.1%). The authors conclude that this is similar to data from studies that included outpatients and peri-operative patients.(25) In a systematic review and meta-analysis, 5065 patients (mean age >18 years) with a reported history of penicillin allergy received a systemic dose challenge with a penicillin (595 patients received a DPT without prior skin testing). The DPT was tolerated well in 94% (95% CI 93.7-95%) of patients. Participants challenged based on history alone tolerated penicillin more frequently than those undergoing ST prior to drug challenge, suggesting that higher-risk patients were more likely to be selected for testing.(4) In another systematic review and meta-analysis 14 studies investigating either adults (n=1511), children (n=1822) or both (n=823 children and adults) were analysed. In 9 out of 14 studies, STs were performed and followed by DPT when ST was negative (and N/A in 5/14 studies). The pooled estimate of the prevalence of a reaction to penicillin in patients reporting a beta-lactam hypersensitivity 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. The relatively high percentage of an immediate reaction to penicillin might partly be explained by the inclusion of delayed type reactions in one of the studies and the high study heterogeneity.(26)

Additional literature overview

Included studies from the literature search were published in the past 15 years and had >500 patients per study. When specifically searching for penicillins there were 56 full text available prospective studies, of which 26 were already included in the described systematic reviews. Of the 22 full text available retrospective studies 7 were already included in the systematic reviews. When searching for beta-lactam antibiotic (BLA) allergy in general, an additional 17 full text prospective studies were found of which 4 were included in the systematic review. Of the additional retrospective studies there were 8 full text available articles, none of which were included in the systematic reviews.

Children

For penicillins specifically, a prospective study was performed including 723 children with a median age of 5.5 years, who reported adverse events to penicillins. STs and specific IgE tests were performed; regardless of these results, a DPT was carried out. In 35 patients (4.8%) allergy to penicillins was confirmed: 6 children had an immediate type reaction and 29 children had a delayed type reaction. Amoxicillin was the trigger in 96.9% of these reactions. Of note, the outcome on DPT was not associated with allergist diagnosis based on clinical history.(27) A second study included 818 children with suspected amoxicillin hypersensitivity, who were challenged with 550-1500 mg amoxicillin based on weight. Of these patients, 770 (94.1%) tolerated the DPT and 17 (2.1%)

CONCEPT

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developed mild immediate reactions, whereas 31 (3.8%) children developed non-severe delayed reactions.(28)

For BLA allergy in children, a prospective study described 1078 patients (mean age 7.62 years) with suspected immediate type reactions to cephalosporins and penicillins. ST and IDT was performed according to ENDA/EAACI recommendations, and sIgE. If STs were found to be negative, a DPT was performed. Based on *in vivo* testing (ST, including IDT or DPT) 58.3% were found to be positive (94.4% to penicillins and 35.3% to cephalosporins). All children with negative *in vivo* tests (41.7%) had generalized urticaria and/or angioedema in their history suggesting a coinciding or underlying disease.(29) In another prospective study by the same author, 1026 patients (mean age 7.7 years) with a history of a delayed reaction to BLA (defined as a reaction >1 hour after administration) were included. A patch test or ST was performed and if negative a DPT was done. Delayed type BLA allergy was confirmed in 76 patients (7.4%): 57 patients upon delayed reading of IDT and 19 upon a positive DPT (symptoms were urticaria and maculopapular exanthema (MPE)). Of note, 66/300 patients had positive tests for viruses or Mycoplasma and two of these patients had positive allergy tests.(30)
A prospective study of 550 children reporting delayed type hypersensitivity to BLA (mean age 8.5 years) was performed using patch tests or IDT (late reading) and a prolonged DPT. Delayed type hypersensitivity was confirmed in 63 children (11.5%), reporting 66 reactions (9.8%), based on ST (n= 17, 25.8%), DPT (n=43, 65.2%) and clinical history (n=6, 9.1%).(31) A retrospective study of 1431 children with a suspected hypersensitivity to BLA (immediate or delayed type, mean age 5.5 years) was reported. ST and IDT were performed in all children, and patch tests in 286 children with delayed type reactions. Challenge tests were performed in those with negative STs except those with severe reactions to non-essential BLA (especially first generation cephalosporins), in whom an alternative BLA was used for the challenge test. Allergy to BLA was diagnosed in 227 children (15.9%). Of the children with immediate reactions, 50/162 (30.9%) were diagnosed with BLA allergy; in those with delayed type reactions, 177/1087 (16.7% $p<0.001$) were confirmed allergic.(32) A second retrospective study analysed 756 children (mean age 11 years) reporting skin reactions occurring within 6 hours after BLA administration. Children previously known with bronchospasm, anaphylaxis and severe delayed reactions were excluded. Skin prick test (SPT) and IDT were performed and when both were negative, patients underwent a DPT. When all tests were negative, a second round of evaluation was performed 2-4 weeks later. Based on responses in ST (n=21) or DPT (n=4) 25 children were diagnosed allergic (3.3%). Of these children, 22 were diagnosed in the first round of testing and 3 children (2 based on ST and 1 based on DPT) in the second round 2-4 weeks later. The latter finding points to a very low risk of resensitization by oral provocation in children with non-severe reactions.(33)

CONCEPT

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Adults

A retrospective study observed that of 3469 patients with a history of penicillin allergy, 255 patients (7.3%) had a positive ST result. A total of 36 patients had a reaction upon DPT; 5.1% of those with negative ST and 0.72% of those with a positive ST.(34) In a study that retrospectively evaluated 1759 adult patients with a history of penicillin allergy, 4 percent (64 patients) had a positive ST reaction.(35) Another retrospective study reviewed the skin tests (penicillin ST and amoxicillin determinant) of 1068 inpatients with a history of penicillin allergy in a tertiary hospital. The overall rate of skin test positivity was 29.1% (243/834 patients).(36)

Combined (children and adults)

A prospectively performed study included 563 patients, aged 21 years or younger with a reported penicillin hypersensitivity, not further specified. Skin tests were performed with penicillin G and graded DPT was performed when the ST results were negative. A total of 33% results were positive (185 skin tests and 18 DPTs). This high rate could be explained by a shorter time between the index reaction and work-up (2.6 years).(37) One thousand and thirty patients with a self-reported penicillin allergy (aged 15-94 years) were retrospectively studied in a pre-operative clinic. Four percent (43 patients) had a positive ST result to penicillin. No DPTs were performed. Of the patients with a history of beta-lactam antibiotic allergy, 85% (947 patients) received an advise to use a beta-lactam antibiotic.(38) The last retrospective study evaluated 596 patients (50.3% inpatient, 25.3% outpatient and 24.3% intensive care unit (ICU) patients) with a history of beta-lactam antibiotic allergy. The penicillin skin test was positive in 8.2% of patients and indeterminate in 3.4%. Patients admitted to the ICU were less likely to be positive (3.4%) versus patients tested in the outpatient setting (16.4%) (*P* .001). Adult patients were less likely as well to be positive to penicillin ST (6.0%) versus patients younger than 18 years (16.1%) (*P* .001).(39)

CONCEPT

Specific populations

Pregnant women

A systematic review of 18 observational studies (including 231 patients) described women with various histories of penicillin allergy who were evaluated due to a need for treatment for Group B streptococcal infection or syphilis during pregnancy. These studies included 203 participants who underwent penicillin skin testing and in 4 studies DPTs were performed. Most patients (83.7%) had negative penicillin ST results, and only 1.5% had allergy related reactions to penicillin ST (pruritus, 2 anaphylactic type of which one resulted in intra-uterine foetal demise), and none of the patients had an allergy related reaction to DPT.(40)

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Elderly patients

Five hundred and sixty five elderly patients with a history of hypersensitivity reaction to BLA (or were labelled as such during their stay) and who were either admitted to the internal medicine ward or who were referred to the allergy outpatient clinic for evaluation were evaluated by clinical history, ST, sIgE and DPT.(41) Patients were divided into age groups (group A >60-79 years and group B ≥80 years). The median time since the initial hypersensitivity reaction was 5 years in group A and 30 years in group B. In group A (n=285) STs were positive in 17.8% of patients, while in group B (n=267) 2.9% were positive (p<0.01). DPT was performed in 235 patients in group A and 270 patients in group B, and was well tolerated in 89.4% and 97.8% respectively (p<0.01). Retesting was done in 128 patients (group A 84 patients, group B 44 patients), upon which only two patients became positive (1.6%).(41)

Acute rheumatic fever (ARF)

In 535 children with a diagnosis of ARF, case files were reviewed for immediate and delayed type allergic reaction to prophylactic penicillin treatment. In patients with suspected allergic reactions STs (SPT and IDT) and DPT were performed. Out of 535 patients, 11 (2.1%) were suspected to have allergic reactions after a total of 17.641 penicillin injections and only 1 patient (0.18%) was diagnosed to have penicillin allergy (immediate type hypersensitivity) after detailed evaluation.(42)

Conclusions

Conclusion	**Level of evidence**
Overall, in patients with a reported history of a penicillin allergy and a mean age >18 years, approximately 5% of patients are truly allergic to penicillins.	Moderate
When patients are selected based on characteristics of their index reaction, higher percentages have been reported.	Low

Other considerations

Based upon the included literature the risk of a true allergy in *unselected* patients is considered low. The percentages of a true allergy as reported in the systematic reviews and meta-analyses were largely consistent, as were the studies in children specifically. The studies done in adult populations however showed more variable results: percentages of true allergies ranged from 4% (Park et al.) to 29.1% in a study based largely on ST alone (Lin et al.). Possible explanations for these higher numbers were the selection of patients in a tertiary center, the fact that not all studies included DPT and the possibility of a clinical diagnosis of allergy being more likely associated with a true allergy. We

CONCEPT

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concluded that in unselected patients the likelihood of a true allergy is low and warrants recommending against standard avoidance of the culprit drug.

The previous presented studies all investigate the likelihood of a true allergy in *unselected* patients with an allergy label or a positive history for an allergic reaction. Several studies have evaluated the likelihood of a true allergy in *selected* patients, based on their allergy history. The following four studies evaluated the likelihood of a true allergy in patients with an *immediate type reaction*. The first study observed that of the 410 adult patients with a history of immediate type allergy to penicillin, 290 tested positive on ST. Of these 290 patients, 71% had anaphylaxis and 29% acute urticaria or angioedema, mostly upon amoxicillin.(43) The second study included 1031 patients with a history of immediate type hypersensitivity to benzylpenicillins and/or aminopenicillins and found that 281 patients (27.2%) had positive results on ST (264 patients), DPT (16 patients) or sIgE (1 patient).(44) The third study observed that an immediate type allergy for beta-lactam antibiotics could be confirmed by ST, sIgE or DPT in 16.4% (170/1032) of patients with such a history.(45) In a prospective study of 1779 patients who consulted with the allergy service for immediate allergic reaction to BLA (urticaria or anaphylaxis), the authors showed that 28.6% were found truly allergic by formal allergy work-up.(46) For *delayed type reactions*, a study showed that of the 105 patients with suspected delayed type reactions to cephalosporins, 5 patients (4.6%) had a positive ST (with delayed reading). None of the negatively tested patients had a reaction upon drug provocation.(47) A second study found that 7.6% (28/380) of patients with a cutaneous reaction to penicillin had a confirmed delayed type allergy based on positive ST with delayed reading or DPT.(48) Bousquet et al. showed that in 1218 patients who were selected by their primary physician (immediate or delayed type reactions) 21.1% had a true BLA allergy (69.3% ST, 30.7% DPT). Urticarial and angioedema (36.6%) and anaphylactic shock (18.3%) were their most common reactions.(49) In these specific studies, again, selection of patients referred to an allergy service possibly accounted for these higher probabilities. However, these findings do support the notion that based on the clinical history of the index reaction, when clinicians suspect a true allergy, further work-up is warranted.

Recommendations

Recommendation	**Strength**	**Quality of evidence**
1. Because the vast majority of patients, including children, that report a beta-lactamallergy are in fact not truly allergic, we recommend against the standard avoidance of the culprit antibiotic.	Strong	Moderate

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2. A detailed antibiotic allergy history (**table 1**) should be taken in patients with documented or (self) reported antibiotic allergy.	Strong	GPS
3. When, according to clinical history, the clinician suspects a true immediate or delayed type beta-lactam allergy, we suggest a formal allergy work up to confirm or rule out true allergy.	Weak	Very low

2. Which factors are associated with increased or decreased probability of the presence of a true antibiotic allergy?

No PICO formulated

Evidence summary

RCTs, Systematic reviews and meta-analyses

There were no RCT's, systematic reviews or meta analyses that investigated which factors are associated with increased or decreased probability of a true antibiotic allergy.

Additional literature review

From the search results of chapter 2.1 we identified 1 position paper and 1 guideline that addressed this question. Furthermore, 22 clinical studies and 4 reviews evaluated factors associated with the presence of a true antibiotic allergy which are classified as either drug or patient related factors. A 2019 EAACI position paper of the Drug Allergy Interest Group states that a risk stratification can be made on severity of the index reaction.(19) Furthermore, regarding drug related risk factors, they advise to also consider route of administration and type of treatment. A clinical review on risk factors in drug allergy published in 1984 already noticed that the parenteral route was associated with an increased risk of anaphylaxis compared to the oral route when administrating penicillin.(50) However, severe reaction rates for similar doses of oral and parenteral penicillin may be comparable. Within the BLA group, involvement of a penicillin was associated with a 1.53 times higher risk of being allergic compared to other BLA.(51) Aminopenicillins accounted for more than 70% of all cases, probably also because they are the most frequently prescribed group of antibiotics.(45) 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 to penicillin allergy.(12)

A shorter time between the index reaction and evaluation of a possible allergy (less than a year) was associated with a higher odds of having a true immediate type BLA allergy (OR 38.66, p=0.003, Siew 2019) and was reported as an independent clinical predictor of genuine BLA allergy.(51, 52) Children

CONCEPT

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tend to have a lower risk of having a true BLA allergy when compared to adults, although more severe reactions in children are associated with true allergy and the risk of allergy to BLA decreases again with older age (>60 years).(26, 31, 41, 51) A prospective study evaluated 72 patients with cephalosporin allergy for 5 years and found that 45/72 patients (63%) became negative upon skin testing and sIgE.(53) Similarly, another study prospectively evaluated 41 patients over a 4-year period, and found that after 4 years only 2.4% of patients remained IgE positive.(54)

Regarding a very suggestive history, Arikoglu et al. described 180 allergic reactions in 97 children of which 104 involved a BLA and concluded that patients with index reactions that were observed by healthcare personnel or who had their antibiotic allergy recorded in the medical record, were 3.5 times more likely to have a confirmed drug allergy compared to patients with a weak history (p=0.015, CI 1.27-9.60).(55) Furthermore, a more severe index reaction (e.g. anaphylaxis, angioedema, serum sickness like reaction or SCAR) has been evaluated – in multiple studies - as a higher likelihood and independent predictor of having a true BLA hypersensitivity (p<0.001).(27, 32, 41, 51, 52, 56-58) On the contrary, the combination of absence of anaphylaxis, unknown name of the index drug and a reaction occurring more than 1 year before testing had a 98,4% NPV for type 1 BLA allergy.(57)

Whether gender is a risk factor remains unresolved. A study that analyzed 3469 adults with a history of penicillin allergy saw no difference in a confirmed penicillin allergy between men and women in ST, although in the group of women more allergies were reported.(34) On the contrary, a study evaluated 100 adults with a suspected penicillin allergy by ST and DPT and concluded that women were more likely than men to have a true penicillin allergy (odds ratio [OR] 4.0 (95% CI 1.23-13.2).(59) Similar findings were concluded from a review that included 1759 patients with a reported penicillin allergy.(35)

There are retrospective case studies suggesting that a positive family history of drug or penicillin allergy might be associated with a true penicillin allergy in the patient.(55, 60) A prospective cohort of 51 children and adults with suspected BLA allergy did not report any significant differences regarding age, sex and family history of drug allergy between patients with confirmed or ruled out diagnoses of penicillin or amoxicillin allergy. No associations have been found between a positive family history and risk of true BLA allergy.(61)

CONCEPT

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Conclusions

Drug related risk factors

Conclusion	Level of evidence
There is limited evidence that antimicrobial therapy administered via the oral route is less likely to cause reactions than parenteral (or other) routes.	Very low
Frequent courses of the same antibiotic are more likely to sensitize, i.e. to cause an allergy to antibiotics.	Low
Reactions are more commonly caused by penicillins, in particular amoxicillin and ampicillin as compared to other antibiotics.	Low
A history of cephalosporin allergy is associated with an increased odds of true antibiotic allergy as compared to penicillins.	Very low

Patient related risk factors

Conclusion	Level of evidence
In adults with a history of any antibiotic allergy, the probability of a confirmed allergy decreases with advancing age (i.e. with time elapsed since the index reaction)	Moderate
In young children the probability of having a true antibiotic allergy is lower than in adults and increases with age.	Low
An index reaction that is observed by health care personnel (inpatient or at the emergency department) and classified as allergy or potential allergy, is more likely to be later confirmed as a true allergy	Low
Multiple episodes of reactions with 1 BLA (single reactors) or multiple BLAs (multiple reactors) increase the risk of presence of a true allergy.	Very low
The severity of the index reaction (both immediate as delayed type reactions) is associated with the risk of a true antibiotic allergy.	Low
The time elapsed between the reported index reaction and the allergy work up is inversely associated with the probability of the presence of a true allergy.	Low
A shorter time between the index reaction and evaluation of a possible allergy (< 1 year) is associated of higher odds of having a true immediate type BLA allergy.	Low

CONCEPT

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II Registration of antibiotic allergy

Introduction

Registration of allergy labels in health care systems is often incomplete and insufficient to distinguish between an adverse event and a true allergic reaction. Several papers report or state that in the general population approximately 10% carry a penicillin allergy label.(62, 63) In more than 90% of patients with a penicillin allergy label, the label can be removed after proper assessment.(62, 64) Inappropriate labels can lead to unfortunate use of broad spectrum or second choice antibiotic regimens. This results in an increased risk of adverse outcomes, antibiotic resistance and Clostridium difficile infection, consequently posing a considerable burden on patients and the health systems.(10, 62, 65, 66)

To determine the risk of the actual presence of a true antibiotic allergy in patients who report such an allergy or carry a label in their medical file, specific information is needed regarding the suspected allergic event. This chapter describes the minimum set of information required to estimate whether the index reaction is “suspected of true antibiotic allergy” or “not compatible with true antibiotic allergy”. In addition, this information is relevant to classify the index reaction as a type A (common and predictable) or type B (rare and unpredictable) adverse drug reaction and in case of suspected true allergy as immediate or delayed type reactions. This information is also relevant to determine the severity of the index reaction. Preferably this information should be included in the antibiotic allergy label (AAL), since it can determine the policy with regard to whether or not a patient can or cannot be exposed to an antibiotic regimen or only under certain conditions. A formal delabeling strategy however, is not provided in this chapter (see chapter VII).

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 result of an allergy, and to assess the severity of a reaction)

For this question no PICO was formulated. A literature search was conducted including search terms for (allergy) label, allergy reporting, medical record, the reaction type, anti-allergic medication combined with antibiotic allergy.

CONCEPT

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Evidence summary

Systematic reviews and meta-analyses

The literature search yielded no systematic reviews or meta-analyses.

Additional literature review

Further literature review did not provide an unequivocal answer to the key question. There are no clinical studies on the minimum of information that should be described in an antibiotic allergy label. However, there are several studies and reviews that provide information on the risk assessment of an antibiotic allergy. Studies described in chapter II, question 4, all use a risk stratification in order to determine the likelihood of presence of a true antibiotic allergy. Chapter I discussed the importance of time interval between administration and onset of symptoms (< 60 minutes for immediate type) and severity of the index reaction as well the time that has elapsed since the registered allergy.

Two narrative reviews and one position statement from the Canadian Society of Allergy and Clinical Immunology describe specific assessments of a suspected penicillin allergy.(62, 67, 68) The first narrative review defines 3 core elements of drug allergy; patient details, medication details and treatment details. Patient details are symptoms of reaction, date of reaction, concurrent medication, exposure since and coincident infections. Medication details are drug, route, timing and dose. Treatment details are described as setting, time to resolution and management. The elements of importance in the other papers can be categorised in these categories as well.(67) The second narrative review lists antibiotic, date of index reaction, route of exposure time to symptom onset, symptoms and treatment given, while the position statement adds the indication of the medication, the number of courses and doses, co-medication and reintroduction of the culprit drug.(62, 68) All these studies use additional questions to specify the reaction and optimize the information in an antibiotic allergy label. Information that was considered important include the involvement of vital organs, systemic reactions, severe cutaneous or haematologic reactions and the specific treatment including the administration of epinephrine/adrenaline, corticosteroids, antihistamines, (dis) continuation of the antibiotic, no treatment and the administration of another antibiotic and whether this was tolerated. Several other reviews – not identified by our primary literature search - and a EAACI position paper have described which information is relevant to be able to classify drug allergy and severity.(19, 69-71) The results are similar to the abovementioned elements.

The conclusion section formulated in this chapter lists the minimum of information that should be included in the allergy label based on the concordance in the literature and the expert opinion of the guideline committee.

CONCEPT

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Conclusions

Conclusion #	Level of evidence
Minimum of information that should be included in the allergy label: • Specific antibiotic involved in the index reaction (not only the class) • Indication for prescription of the antibiotic at the time the index reaction occurred: Could the infection have been the cause of an unwanted cutaneous reaction (infection induced urticaria or viral induced exanthema)? Was the antibiotic prescribed as peri-operative prophylaxis in which other drugs could have been the cause of the reaction? • Date of the index reaction • Concurrent medication used at time of the index reaction • Comorbidity • Time to onset of symptoms of the reaction after the 1st dose of antibiotic (<1h, 1-6h, >6h) • Symptoms of the index reaction • Hospital admission due to the reaction yes or no • Duration of symptoms • Treatment: antibiotic stopped, epinephrine/adrenaline, oxygen, mechanical ventilation, corticosteroids, antihistamines, no treatment (self-limiting), alternative antibiotic given (tolerated?). • Outcome of reaction: fully recovered or permanent injury • Culprit antibiotic re-administered at any time after index reaction (tolerated?) until present.	Low

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4. When is, based on patient derived information, a reported reaction to be classified as 'not allergic' and can the allergy label be removed ?

PICO

P: Patients with a reported allergy or allergy label

I: Detailed allergy history

C: Challenge tests (gold standard)

O: Direct delabeling without formal allergy testing, allergy occurring upon re-exposure yes / no

Evidence summary

Randomized trials, systematic reviews and meta-analyses

No randomized trials, systematic reviews or meta-analyses were found regarding this PICO.

Additional literature review

Ten clinical studies were identified that studied potential direct delabeling based on patient derived information alone. One study reported on eligibility for direct delabeling or further testing. The other nine performed skin tests and/or an oral challenge with amoxicillin. Five of these studied the delabeling of patients that were deemed to have a low risk of having had a true allergic reaction and/or a low risk for an allergic reaction upon re-exposure, while the remaining 4 studies encompassed all risk categories.

Torda et al. studied the direct delabeling of low risk patients and the eligibility of the patient for further testing in higher risk groups. Three hundred fifty two adult patients with a history of antibiotic allergy were interviewed. This study showed that based on history alone, 25.6% (n=109) of patients were eligible for direct delabeling as they provided a history of a non-allergic reaction. In 21.6% (n= 92) of patients the allergy history was considered vague (not useful) and in 52.8% (n=225) convincingly useful.(72)

The other nine studies focused on the delabeling of low or all-risk patients after a skin test or an oral challenge. These studies however differ in their definition of low risk patients. Some of these studies include patients with a Type A reaction (adverse reaction which is predictable from the known pharmacology and effects of the drug) for an oral challenge and some directly delabel these patients based on history alone.

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Four studies included patients with a type A reaction for an oral challenge. The first study identified 56 adult patients labelled with a penicillin allergy as low risk using a questionnaire. 'Low risk' patients were defined as patients with nausea, vomiting, diarrhoea, non-itchy rash, thrush or did not know/could not remember symptoms that had not been admitted to the hospital. All 'low-risk' patients received a direct challenge with amoxicillin. Fifty five (98.2%) patients were delabeled, with no serious reactions observed. One patient had urticaria, which had also occurred during the index reaction but the patient had failed to mention this during prior history taking.(73) The second study identified 195 low risk Medical Intensive Care Unit (MICU) patients labelled with a penicillin allergy. Low risk was defined as: urticaria only, a reaction >5yrs ago, self-limited cutaneous rash at any point, gastro-intestinal (GI) complaints only, remote childhood reaction with limited details, family history only, avoidant from fear of allergy only, known tolerance of penicillin since index reaction and other non-allergic symptoms. Two patients had a positive skin test. One hundred and eighty four patients agreed to undergo an oral challenge with amoxicillin. All (100%) patients tolerated amoxicillin. The negative predictive value (NPV) of low-risk categorization was 99% (95% CI, 96–100%).(74) The third study categorized a total of 231 adult patients based on clinical history as likely immediate type Hypersensitivity Reaction (HSR) (n=27), likely delayed type HSR (n=65), indeterminate (n=111) and HSR unlikely (n=28). HSR unlikely was defined by: no temporal association, subsequent exposure to same drug without reaction, symptoms not suggesting an immune mediated reaction (i.e. headache, blurred vision or isolated GI symptoms). Penicillin allergy was excluded in 100% of HSR unlikely patients by means of allergy testing.(75) The last study used a risk stratification resulting in 5 classes:

1) Reported symptoms not compatible with an allergic reaction (GI, headache, palpitation) AND/OR Time interval not suggestive of allergy AND/OR Cannot remember a clinical reaction at all (48 cases)

2) Reaction confined to the skin during or after antibiotic therapy in childhood or adolescence (≤16yr) (36 cases)

3) Acute urticaria with or without angioedema during antibiotic therapy AND recurrence of urticaria for several days despite stopping the administrated antibiotic. (17 cases)

4) Maculopapular exanthema (MPE) during or <1 week after stopping AND no evidence of potentially severe. (29 cases)

5) Signs of anaphylaxis, mucous membrane erosions, pustules or blisters, liver or kidney involvement and decrease of blood cell numbers.

Class 1 to 4 were challenged with the suspected antibiotic in 28/48 cases, 23/36 cases, 11/17 cases, and 20/29 cases respectively and all tolerated.(76)

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Five studies directly delabeled patients with a Type A reaction or an inconsistent history.(77-81) The first study reports a total percentage of patients that could be delabeled of 62% (355/558) in adult patients with a low risk of penicillin allergy. Low risk was defined as: a known reaction <10yrs ago, type A reactions where direct delabeling was not accepted by the patient, history of unspecified childhood rash, localized to injection site reaction only, or MPE >10yrs ago. In total, 161 patients (28,9%) were directly delabeled without performing challenge tests of which 133 due to a type A adverse reaction. Forty eight patients were delabeled by patient history, pharmacy dispensing and/or medical reconciliation as they had subsequently tolerated the implicated penicillin.(77) In the second study 224 patients with a penicillin allergy label were screened for low risk. Low risk patients were defined as those with a limited cutaneous reaction (including rash and hives), or unknown symptoms occurring ≥ 6 months ago and >1 hour after drug administration and who did not meet any of the criteria for intermediate or high risk. Of the 162 patients that were classified as low risk, 71 (31.7%) could be delabeled without a challenge with amoxicillin because they had either tolerated penicillins or had a non-allergic history.(78) The third study screened 363 patients and 21 patients (5,8%) could be delabeled based on history alone and 4 due to a positive family history alone. These patients were not challenged with amoxicillin.(79) The fourth study identified 250 adult patients with a penicillin allergy label. A total of 199 (80%) could be delabeled either directly or after oral challenge or referral to an immunologic clinic. One hundred and sixty (64%) patients were directly delabeled as the interview clearly revealed their index reaction was not consistent with a true allergy. Of the 160 patients, 127 (79%) had received and tolerated a course of penicillin antibiotic prior to inclusion without adverse effect. Sixty nine percent (110 of 160) described an adverse event: nausea, vomiting or headaches. Many patients fell into both groups (77 of 160, 48%). Of the 186 delabeled patients available for follow-up, 103 were prescribed penicillin antibiotics in the year following intervention (55%). Three (2%) experienced a delayed HSR.(80) The last study identified 22 patients out of 106 patients (20,8%) with a penicillin allergy label as non-immune-mediated Type A reactions. Of these, 15 patients (68.2%) were reported to have penicillin allergy labels relating to gastrointestinal symptoms (such as nausea, vomiting, diarrhoea or abdominal pain). Of the 22 patients, 14 (63.6%) had their penicillin AAL removed from the EMR demonstrating that prescribing teams recognized Type A reactions, yet were still reluctant to remove these labels from the EMR.(81)

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Conclusions

Conclusion	Level of evidence
Most antibiotic allergy labels (AAL) can be removed after drug challenge; however, several studies show that a variable percentage of AAL can be directly removed based on clinical history alone.	Low
Headache, blurred vision, palpitations and gastro-intestinal complaints (vomiting, nausea, diarrhea) are symptoms that are *not compatible* with an allergic reaction.	Moderate
A true allergic reaction can be ruled out when the patient tolerated the culprit drug since the index reaction	n/a
When adults cannot recollect a clinical reaction at all, the likelihood of presence of a true allergy is very low.	Low
When a label is based solely on positive family history of allergy, the label is inaccurate	n/a
The time interval between first dose of the antibiotic and onset of symptoms is useful to address the likelihood of allergy	Moderate
In case of a suspected allergy that occurred > 10 years ago and/ or a reaction that occurred at a young child's age, the chance that an allergy can be confirmed is very low	Low

Other considerations

The definition of 'no' or 'low' risk for true antibiotic allergy varied in these studies. Most studies considered headache, blurred vision, palpitations and gastro-intestinal complaints (vomiting, nausea, diarrhoea) as a non-immune reaction. Other categories that were defined as 'no' or 'low' risk were: no temporal association between the exposure to the culprit antibiotic and the symptoms of the alleged allergic reaction, subsequent exposure to same drug without reaction, a positive family history alone, no recollection of the incident. Two studies (Stone et al., Mohamed et al.) reported good negative predictive values (NPV) of low-risk categorization.(74, 75)

Three additional studies, not retrieved by the previous literature review, developed an algorithm or questionnaire to be able to diagnose patients as low risk of true allergy. The first study included 259 patients and compared penicillin allergy work up with an algorithm. Details that were used in the algorithm were: 1) Time first dose penicillin and onset of symptoms (<2h, ≥2h or not known) and 2) Definition of low risk (new administration of penicillin without reaction, skin involvement without pruritis or with pruritis duration >24h, manifestations such as diarrhea, asthenia). In total 41/259 patients (15.8%) were confirmed penicillin allergic. The algorithm however misclassified 3 of these 41 patients with confirmed immediate type allergy as low risk patients.(82) A second study used a questionnaire and composite reference standard to exclude allergy in 163 children with a recorded allergy. In 51.5% of cases, no characteristics of the recorded allergic reaction were reported in their medical files. Based on the composite reference standard, allergy could be excluded in 19 patients

CONCEPT

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(11.7%). In these patients allergy was defined as improbable when the time to symptoms was > 14 days OR any time AND there were no symptoms of urticaria, angioedema, rash, exanthema, dyspnea or collapse AND/OR there was no reaction to re-exposition to the culprit antibiotic.(83) In a questionnaire study that included 86 patients with a self-reported allergy to BLA, 60 patients were identified as potentially allergic (skin or mucosa involvement), 14 with intolerance of side effects (GI only) and 12 patients not able to classify. The author concluded that up to one fifth of patients with self-reported beta-lactam allergy has a non allergic side effect.(84)

The recommendations formulated result in safe removal of inappropriate antibiotic allergy label because of non-allergic reactions. This will result in the use of smaller spectrum antibiotic regimens, less resistance development and other negative effect of antimicrobial therapy (e.g. Clostridium difficile).

Recommendations

Recommendation	**Strength**	**Quality of evidence**
4. We recommend that an antibiotic allergy label can be removed *directly* without previous 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 occurrence of an allergic reaction. • The allergy label was *solely based on positive family history* of allergy or on *fear* of allergy. • The reported symptoms are *not compatible* with an allergic reaction (i.e. GI complaints only, palpitations, blurred vision). • There is *no temporal association* between exposure and onset symptoms.	Strong	Moderate
5. 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/mild, confined to the skin and occurred in remote* adolescence or childhood. • The patient is *not aware* of the antibiotic allergy label or *can not recollect* clinical signs and symptoms of a reaction at all.	Weak	Low

*An index reaction that occurred >10 years ago.

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III Re-exposition in patients with a beta-lactam allergy label

Introduction

The previous chapter showed that the percentage of true antibiotic allergy is low. The risk of mislabeling patients with an antibiotic allergy can result in less effective and more expensive antimicrobial therapy. The majority of patients with a history of penicillin allergy will not have subsequent reactions to penicillins or other beta-lactam antibiotics after re-exposition. This chapter investigates whether patients can be identified who have a (very) low risk of developing an allergic reaction upon reintroduction of the culprit drug.

5. Which patients with a reported beta-lactam antibiotic allergy have a very low risk of an actual allergy and can therefore be re-exposed to the same antibiotic for which they are labelled allergic?

PICO

P: patients with a beta-lactam antibiotic allergy label

I: re-exposure of (culprit) beta-lactam in patients with low risk of actual allergy

C: no re-exposure or alternative antibiotic given

O: allergic reaction yes or no

Evidence summary

<u>RCTs, systematic review and meta-analyses</u>

The literature search identified no RCTs, 1 systematic review and 1 narrative review.

In a systematic review, Macy and Vyles included 6 studies, with data about 3299 children and adults, in which patients with a low risk of penicillin allergy received a direct DPT.(85) Low risk was defined as a history of a reaction >12 months ago and any of the following: any benign rash, gastro-intestinal symptoms, headaches, other benign somatic symptoms or unknown history. Of these patients, 42 (1.3%, 95% CI 0.9-1.7%) had immediate type reactions; 130 patients (3.9%, 95% CI 3.3-4.7%) had delayed type reactions. None of the included studies reported severe reactions to DPT. Stone et al. highlights the importance of the evaluation of a penicillin allergy label in the context of antimicrobial stewardship.(74)

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Additional literature overview

9 additional clinical studies were found.

An allergists' diagnosis based on clinical history was not associated with DPT outcome in a study by Ibanez et al.(27) They prospectively studied 732 children with reported adverse events to penicillin (excluding severe reactions). Based on clinical history alone, 31 (4.2%) patients were deemed clearly positive by allergists, none of whom were found positive upon DPT. Of the 518 patients (70.8%) classified as clear negative, 23 (4.4%) were confirmed allergic and of the 183 children (25%) classified as doubtful, 12 (6.6%) had positive DPT. In addition, the reactions elicited in positive DPT results were all of mild intensity.

Three other studies evaluated the risk of an allergic reaction in children based on direct provocation tests.(68, 86, 87) In these studies children with a suspected BLA hypersensitivity reaction were subjected to direct DPT if the risk a true allergy was considered low. The first study described 597 children with a history of parent-reported penicillin allergy (median age of testing 9 years, median age of allergy diagnosis 1 year). They offered allergy testing to children aged 4 years or older if the reported symptoms were classified as 'low risk of a severe IgE-mediated or severe T-cell driven process'. Low risk symptoms included rash, itching, diarrhoea, vomiting, runny nose, nausea, cough or a reported family history of allergy. High risk reactions were defined as either IgE-mediated (respiratory or cardiovascular involvement: wheezing, difficulty breathing, airway swelling, syncope, blood pressure drop or cutaneous involvement with a severe reaction i.e. orofacial or limb angioedema; and any report of anaphylaxis) or T-cell driven reactions (any report consistent with bullous cutaneous reaction), and additionally drug reactions with eosinophilia and systemic symptoms (diffuse erythema). These reactions were considered a high clinical risk for an allergic reaction upon re-exposure to a penicillin by any route. Of the 597 children with completed questionnaires, 434 (72.6%) were considered to have symptoms that indicated a low-risk of allergy to penicillin and 163 (27.3%) children had at least one high-risk symptom. A total of 100 children (33%) with low risk symptoms underwent allergy testing including direct oral challenge and all had negative results (100%, 95% CI 96.4-100%).(68) The second study included 78 children and identified 56 low risk patients (those with a single episode with mild, delayed skin symptoms after the administration of a BLA via the oral route) for direct DPT. Only 1 patient had a positive DPT (a mild delayed reaction).(86) The third study included 91 children with suspected non-severe, delayed BLA hypersensitivity. Upon direct DPT, 78 children (86%) had no reaction and 13 children (14%) had a non-severe hypersensitivity reaction (n=3 immediate (urticarial), n=10 delayed (MPE)). Of those

CONCEPT

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without a reaction, 30 children (38%) were re-exposed to the same antibiotic: 28 (93%) did not have any reaction and 2 (7%) had MPE.(87)

The literature search yielded five studies in which adult patients were evaluated based on history and direct DPT. In two studies patients with a penicillin allergy label were delabeled based on history alone upon first evaluation. The results of these studies strongly differed: 13.2% (Devchand et al.(81)) and 64% (Du Plessis et al.(80)) were directly delabeled. In both studies further workup (STs and DPT) yielded a total percentage of patients that could be delabeled of 37.7% (Devchand) and 80% (Du Plessis). In studies performed in outpatient populations, both authors describe low risk patients (based on non-severe cutaneous reactions and/or the absence of symptoms possibly associated with IgE-mediated allergy and considering the time since reaction) receiving uneventful direct DPT's in 98% and 98.5% respectively.(73, 88) Lin et al. also described adult inpatient populations in whom a direct DPT was performed in patients with low risk of immediate type reactions. Of these patients, 95% tolerated direct DPT. In these studies, patients who did react to direct DPT had isolated mild cutaneous reactions generally.(89)

In order to develop a clinical decision rule that enables point-of-care risk assessment, a prospective study was performed with a validation cohort in which 622 patients were included, together with a retrospective cohort of 945 patients for external validation.(90) They identified four features associated with positive penicillin allergy test result: reaction ≤5 years ago, anaphylaxis/angioedema, severe cutaneous adverse reactions (SCAR) (both these criteria were considered major criteria, 2 points), and treatment required for allergy episode (considered minor criterion, 1 point). Internal validation showed minimal mean optimism of 0.003 with internally validated area under the curve of 0.805. A cut-off of less than 3 points was considered a low risk for penicillin allergy: only 17/460 patients (3.7%) had positive results and negative predictive value was 96.3% (95% CI 94.1%-97.8%). External validation resulted in similar findings. The 4 features associated with a positive penicillin allergy test result upon validation were summarized in the mnemonic PEN-FAST: penicillin allergy, five or fewer years ago, anaphylaxis/ angioedema or severe cutaneous adverse reaction [SCAR], and treatment required for allergy episode. The risk of a positive penicillin allergy test can be accurately predicted from these criteria: 0 points – Very low risk of positive penicillin allergy test <1%; 1-2 points – Low risk of positive penicillin allergy test 5%; 3 points – Moderate risk of positive penicillin allergy test 20% and 4 points – High risk of positive penicillin allergy test 50%.(90)

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Conclusions

Conclusion	Level of evidence
Clinical history taking alone can identify some allergy labels as low risk of true antibiotic allergy, but faulty memories and mistakes occur.	Low
Risk stratifications by immediate versus delayed and severe versus non-severe index reactions are useful to identify patients at low or high risk for having a true antibiotic allergy.	Low
Direct drug provocation testing (oral/intravenous) can be safely performed in patients at low risk for true antibiotic allergy, both in children and adults. (see chapter VII)	Low
Patients with non-severe, delayed type index reactions >1 year ago are considered at low risk for true antibiotic allergy upon re-exposure.	Low
Patients with severe, delayed type index reactions are considered at high risk for true antibiotic allergy upon re-exposure, irrespective of time elapsed since index reaction.	n/a
For patients with immediate type index reactions, the severity of the index reaction, time since the IR and previous required treatment are useful to identify the risk of allergy upon re-exposure.	Low

Other considerations

Throughout the world, antibiotics are the most prescribed drugs in which penicillin and BLA in general are most used due 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 reported prevalence up to 16% in the United States. Although the prevalence in the Netherlands is much lower with 0,6%-2% in primary care and 5,6% in a tertiary care, these reported BLA allergy labels are not a benign finding (65, 83, 91, 92). Especially in hospitalized patients, due to avoidance of the 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 re-admissions, higher use of reserve antibiotics, more complications like *Clostridium difficile* infections, higher costs and not at the least of interest higher resistance rates to antibiotics. For example, in infective endocarditis caused by *Enterococcus* spp., the preferred treatment contains amoxicillin. Vancomycin treatment as an alternative in case of an alleged penicillin allergy has a longer duration of therapy, needs therapeutic drug monitoring and side effects of nephrotoxicity are more common. Also, due to overestimation of cross-reactivity between penicillins and cephalosporins, cephalosporins are often erroneously avoided. Taking all these negative consequences of an alleged penicillin label into account,

CONCEPT

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evaluation of an antibiotic allergy should be part of antimicrobial stewardship, as Stone et al. also state in their narrative review.(74)

The literature included in this chapter consistently showed that if the index reaction was classified as non-severe or history indicated a low-risk of an actual penicillin allergy, there were none or no severe reactions upon reintroduction of the culprit drug by direct DPT, both in children and adults. Although Ibanez et al. 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.(27) We concluded that clinical history taking and/or using risk stratifications can both identify whether a patient has a low risk of an actual BLA allergy and therefore recommend that these patients can receive the culprit drug without formal allergy testing. Since classifying severity of immediate type index reactions remains challenging and consequences of a faulty diagnosis might be huge, we suggest that patients classified as having an immediate type index reaction receive the first therapeutic dose of the culprit drug in a controlled setting. The implementation of a "controlled setting" differs depending on the severity of the index reaction and the time that has elapsed since. 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, 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.. Since 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 (MPE) are considered as part of the low risk group by the guideline committee based on the systemic review of Macy and Vyles and additional literature by Stevenson et al, and therefore reintroduction of the culprit drug after 1 year is considered as safe in this situation.(85, 93) Of note, re-exposure to the culprit drug in patients with residual risk for occurrence of an immediate type index reaction should be performed on a clinical ward, with monitoring of vital signs, under supervision of a physician.

Recommendations

Recommendation	**Strength**	**Quality of evidence**
6. 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 longer ago, the smaller the chance of an allergic reaction occurring.	Weak	Low

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7. We suggest that patients with suspected* *non-severe*, immediate type index reactions that occurred >5 years ago, can receive a therapeutic dose of the culprit beta-lactam antibiotic in a controlled setting**.	Weak	Low
8. We recommend that patients with suspected* *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	Low
9. We suggest that if formal allergy testing is not available, patients with a suspected* *non-severe*, immediate type index reaction that occurred ≤ 5 years ago OR a suspected *severe* immediate type index reactions, 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**.	Weak	Low
10. We suggest that patients with suspected* *non-severe*, delayed type index reactions that occurred >1 year ago can receive the culprit beta-lactam antibiotic without formal allergy testing.	Weak	Low
11. We recommend against re-exposure to the culprit drug in patients with suspected *severe* delayed type index reactions (**table 3**), irrespective of the time since the index reaction. In the absence of acceptable alternative antimicrobial treatment, the use of the culprit should be discussed in a multidisciplinary team***.	Strong	GPS

*In case of a proven allergy by formal allergy work up, handle according to the advice of the consulted allergist.
**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.
*** 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 antibiotic should be balanced against each other followed by shared decision making with the patient.

CONCEPT

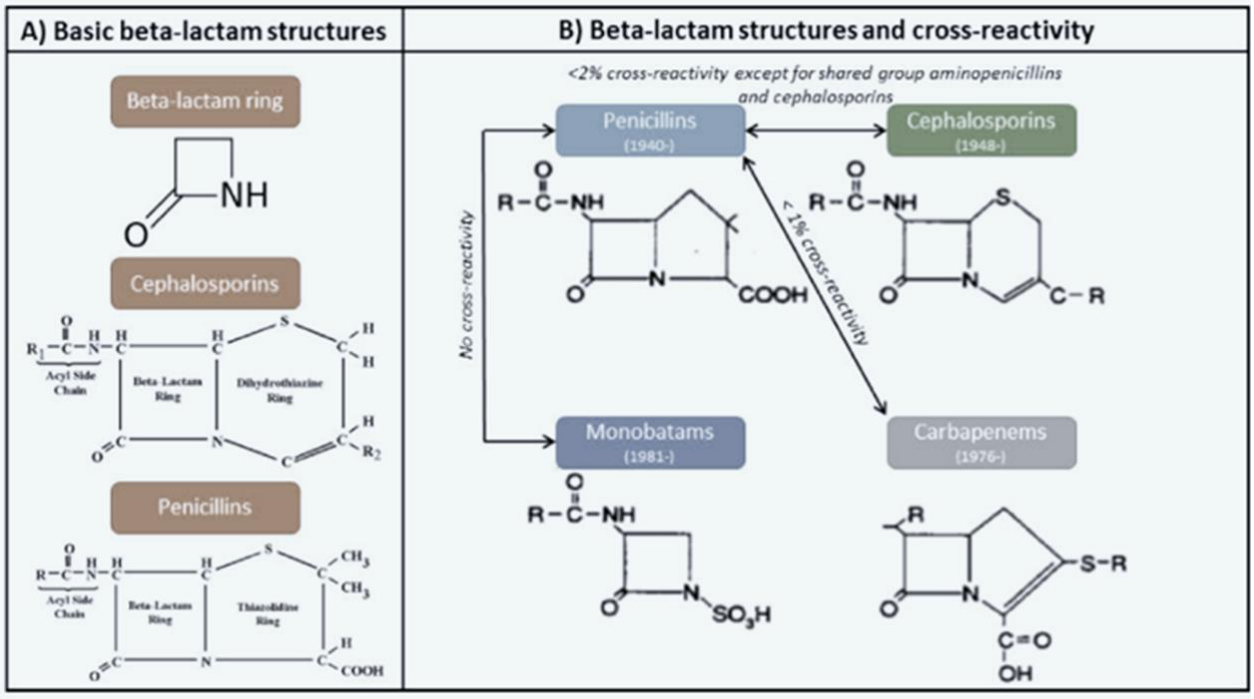
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IV Cross reactivity in beta-lactam allergy (penicillins)

Introduction

The class of beta-lactam antibiotics comprises four groups: penicillins, cephalosporins, carbapenems and monobactams. All antibiotics belonging to one of these groups share a so called beta-lactam ring. Beta-lactam antibiotics belonging to different groups have no or a different second ring structure and one or more different side chains attached to one of the ring structures. Penicillins have a thiazolidine ring structure and one R1 side chain attached to the 6th carbon position of the beta-lactam ring. The penicillins differ from each other because each penicillin has a unique side chain. Cephalosporins have a dihydrothiazine ring and two side chains; one R1 side chain attached to the 7th carbon position of the beta-lactam ring and a R2 side chain attached to the 3th carbon position of the dihydrothiazine ring. Carbapenems are similar to penicillins but the beta-lactam ring is attached to a 5-member carbon-only cyclic ring and a sulfur-atom linked to C2. Monobactams are structurally unique in that the beta-lactam ring is not fused to another ring structure. Monobactams have one side chain.

Figure 3: structure of penicillin, cephalosporin, carbapenem and monobactam (adapted from (94))



An allergic reaction is the result of a part of structure of a beta-lactam antibiotic being recognized by an immune receptor and the immune system being consequently activated.

Cross-reactivity evolves when two beta-lactam antibiotics are structurally related; i.e. these two beta-lactam antibiotics share a molecular part that is recognized by immune receptors or antibodies with the same specificity. Theoretically if the core beta-lactam structure is recognized, broad cross

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reactivity between beta-lactam antibiotic belonging to different groups can be expected. If the side chain is recognized, cross reactivity between beta-lactam antibiotics that share an identical or similar side chain can be expected. However, side chains similarity is not the exclusive cause for cross-reactivity in beta-lactam allergy but sporadically also other molecular similarities may be responsible for cross-reactivity such as identical three-dimensional structures.(95) **Table 11** shows the potential of cross-allergy between the different beta-lactams based on the molecular structure.

Table 11: risk of cross allergy in beta-lactam antibiotics

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

■	Allergy possible based on formation of PPL, or cross-tabulation similar.
■	Potential cross allergy based on 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

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

No PICO formulated.

Evidence summary

Systematic reviews and meta-analyses

In several systematic reviews the literature evaluating the cross-reactivity between the different beta-lactam antibiotics is reviewed. Some are specifically focused on cross-reactivity between beta-lactam antibiotics of the same subclass (94, 96), others on cross reactivity between penicillins and cephalosporins (15, 97-99), again others between penicillins and carbapenems (98-100) or on cross-reactivity between penicillins and monobactams.(100) The most common reason for beta-lactam cross-reactivity is caused by side chain similarity, which is explained below.

Penicillin – penicillin

In patients that have a penicillin allergy it is possible to remain sensitized to other penicillins, including the aminopenicillins (amoxicillin) and anti-staphylococcal penicillins (flucloxacillin, piperacillin), via the thiazolidine ring, rather than the beta-lactam ring. Isolated allergy to a single penicillin (amoxicillin) is also possible if a R1 side chain is involved.(94) This is further explained elsewhere (Chapter IV, Q7).

Penicillin – Cephalosporin

The incidence of cross-reactivity among penicillins and cephalosporins is lower than the historically reported 10%. This considered to be due to contamination of cephalosporin preparations with penicillins. Instead, there is evidence that the beta-lactam side chains (dis)similarities are highly predictive of cross-reactivity. Penicillins have one side chain at the 6-position (R1) while cephalosporins have two side chains at the 7- and 3- position (R1 and R2) (**figure 3**) Drugs with similar 6- or 7- position side chains may exhibit cross-allergenicity with each other, just as drugs with similar 3-position side chain structures.(15) The side chain on the 6-position of penicillins or the 7-position of cephalosporins is called the R1 side chain. It is this side chain, rather than the beta-lactam ring itself, that is the determining factor for the rate of cross reactivity. After degradation, penicillins forms a stable ring, whereas cephalosporins undergo rapid defragmentation of their rings. Therefore

CONCEPT

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immunologic cross-reactivity based in molecular similarities in the beta-lactam ring is very unlikely. Amoxicillin has the same R1 side chain as several first- and early second- generation cephalosporins.(63, 96, 97). The finding that cross-reactive, immunoglobulin E (IgE)- mediated and T-cell mediated immune responses between penicillins and cephalosporins are based on molecular side chain similarities of the antibiotics rather than in the identical beta-lactam rings is further supported by other reviews.(94, 98, 101) Pichichero et al. found that side chain specific antibodies predominate in the allergic immune response to cephalosporins thereby explaining the lack of cross-reactivity between second- and third generation cephalosporins and penicillins. Therefore, cross-allergic reactions occurred predominantly among patients receiving first generation cephalosporins with related chemical side chains to penicillin or amoxicillin.(101) Side chain similarity does not necessarily predict a clinical reaction, this is further explained elsewhere in key question 8.

Several studies suggest that cephalosporin induced anaphylaxis occurs no more frequently among patients with known penicillin allergy than among those without such allergy and both immediate and delayed cross allergic reactions appear to be commonly associated with the side chain structures of the penicillins and cephalosporins.(94, 96)

Penicillin - Carbapenem

The structural similarity between penicillin and carbapenem antibiotics is the bicyclic core, composed of a 5-membered ring attached to the beta-lactam ring. This commonality is generally believed to be responsible for the cross-reactivity between these classes of antibiotics.(100) Greanya et al. found that when a penicillin allergy is confirmed by skin tests or is reported as anaphylaxis, the cross-reactivity between penicillins and carbapenems is higher than when only a self-reported allergy status is available.(99) However, Zagursky et al. state that the molecular structure of carbapenems are sufficiently dissimilar from those of penicillins and cephalosporins that cross-allergy among these would not be predicted.(102)

Penicillin – monobactam

Studies show that there is no evidence of any clinical cross-reactivity between aztreonam and penicillins except the development of sensitization reactions in cystic fibrosis patients.

Cephalosporin – cephalosporin

Cross-reactivity between cephalosporins is based on R1 side chain similarity and to a lesser degree on R2 side chain similarity on the 3-position of cephalosporins.(96, 98, 102) The cross reactivity is not based on the shared cephalosporin dihydrothiazine ring.(94) The cephalosporins which are

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commonly used in clinical practice in the Netherlands do not share similar R2 side chains. If a patient had an allergic reaction to a specific cephalosporin, the risk of a reaction with a different cephalosporin is very low to nonexistent if the side chain of the 2 drugs are dissimilar.(96)

Cephalosporin –monobactam

Cross-reactivity may exist between ceftazidime and aztreonam, due to similarity of side chains.(100)

Conclusions

Conclusion	Level of evidence
Conclusions (general)	
Occurrence of cross-allergic reactions based on selective recognition of the beta-lactam ring is unlikely.	Low
The risk of allergic cross reactivity is based on the a-priori risk on true beta-lactam antibiotic allergy; when there is a (very) low risk on true antibiotic allergy the risk of cross reactive allergy is negligible.	Low
Cross reactivity within a class (penicillins OR cephalosporins)	
Cross-reactivity between aminopenicillins is based on the R1 side chain similarity of amoxicillin, ampicillin and piperacillin.	Low
Cross-reactivity between other penicillin derivates is not based on side chain similarity.	Low
Cross-reactivity within cephalosporins is based on side chain similarity.	Low
Cross reactivity between classes (penicillins and cephalosporins)	
Cross-reactivity between penicillins and cephalosporins is based on side chain similarity in both immediate and delayed type reactions.	Low
When there is no side chain similarity between penicillins and cephalosporins, the risk of cross-reactivity is negligible (*<1%)*	Low
The presence of side chain similarity between penicillins and cephalosporins does *not* mean that an allergic reaction necessarily will occur.	Low

CONCEPT

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

PICO

P: Patients with a reported allergy (proven or history) for a penicillin

I: Patient treated with another penicillin than the culprit penicillin

C: Patient treated with different antibiotic, not being a penicillin

O: Occurrence of an allergic reaction (immediate or delayed)

Evidence summary

RCTs, systematic reviews and/or meta-analyses

On this subject several studies were found, but no randomized controlled trials or systematic reviews met the search criteria.

Additional literature overview

Several studies evaluated immediate-type IgE mediated reactions. The following studies evaluated the risk of allergic reactions to penicillin V or G in amoxicillin allergic patients. Out of a total of 177 patients, Vega et al. described 54 cases diagnosed with immediate type amoxicillin allergy but with good tolerance of penicillin G. Immediate amoxicillin allergy was confirmed by skin test, amoxicillin-RAST or when negative by immediate positive DPT with amoxicillin. Tolerance of penicillin was demonstrated by negative ST and/or DPT.(103) In another study 16 of 76 selected subjects were allergic to amoxicillin, while tolerating penicillin G. Amoxicillin allergic subjects had positive skin test or positive DPT. All penicillin tolerant subjects had negative parenteral DPTs.(104) In a study by Blanca-Lopez et al. 40 of 58 (78%) patients were amoxicillin allergic based on positive skin tests or oral challenge results and showed good tolerance to penicillin G and V based on skin prick tests, intra-dermal tests and/or drug provocation tests.(105) These patients were considered selective allergic for amoxicillin. Isolated allergy to amoxicillin is possible if a R side chain is involved.(94) Also a group of 11 selective clavulanic acid responders were found to tolerate Penicillin G and V, and amoxicillin. They found that 35% of patients taking the combination of amoxicillin with clavulanic acid, developed a selective response to clavulanic acid. The absence of cross-reactivity between clavulanic acid and other penicillins is explained by the fact that clavulanic acid had a oxazolidine ring instead of a thiazolidine ring.(105)

CONCEPT

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Other studies evaluated delayed-type (cell mediated) reactions. One study evaluated whether 27 patients with cell-mediated allergy to aminopenicillins could safely use alternative beta-lactam antibiotics.(106) Time elapsing between administration of aminopenicillin and onset of symptoms was about 2 days. All 27 patients tested negative for immediate-type skin prick and intradermal tests for aminopenicillins and also to other penicillins. Patch tests were positive for all aminopenicillins and negative for all other beta-lactam antibiotics. Oral or intramuscular challenge tests for all other beta-lactam antibiotics (among which the following penicillins: penicillin G, penicillin V, piperacillin, mezlocillin, ticarcillin) were negative. This finding was confirmed by another study showing that of 71 patients with delayed-type non-IgE-mediated allergy (based on skin test and oral challenge), 51 patients had negative skin tests for benzyl and phenoxymethyl penicillin and could tolerate phenoxymethyl penicillin. The other 20 patients had positive skin tests with benzyl or phenoxypenicillin.(107)

Both immediate and delayed type reactions were evaluated in a group of 40 patients with confirmed allergy to flucloxacillin and studied for cross-reactivity against other beta-lactam antibiotics.(108) Thirty-three patients had immediate hypersensitivity to flucloxacillin based on skin prick tests, intra-dermal tests and/or oral challenges and 7 had delayed hypersensitivity to flucloxacillin based on intra-dermal tests or oral challenge. Although groups were small, 75% (3 of 4) of patients in the delayed group cross-reacted with other penicillins based on IDTs and/or oral challenge while only 35% (6 of 17) of patients with IgE-mediated allergy cross-reacted with other penicillins based on skin prick tests, intra-dermal tests, specific IgE testing and sometimes oral challenges.(108) A group of 59 patients with IgE-mediated reactions to a penicillin derivate and a positive skin test were evaluated. (109) The patients were divided in two groups and skin tested to several determinants, i.e. benzylpenicilloyl (BPO, major determinant of benzylpenicillin), minor determinant mix (MDM), amoxicillin (AX), ampicillin (AMP), specific IgE, IgG antibodies to BPO-PLL (benzylpenicillin conjugated to polylysine) and AXO-PLL (Amoxicillin conjugated to polylysine). One group consisted of 30 patients with symptoms limited mostly to the skin, consisting of urticaria and/or angioedema, and the other contained 29 patients having symptoms of an anaphylactic shock. Results showed that patients who developed an anaphylactic reaction were more frequently ST positive to MDM, AX and AMP, than those with urticaria, and the latter were more frequently ST positive to BPO. The authors concluded that skin test positivity to minor determinants of penicillin, including amoxicillin and ampicillin may be more frequent in cases of anaphylactic shock than urticaria.(109)

CONCEPT

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The previous literature yielded no studies on cross reactivity between piperacillin and other penicillin derivatives. An additional search for piperacillin was performed later on, during review of this chapter. Two recent articles regarding piperacillin allergy and cross reactivity with other penicillins were found. One article concluded that there was an increase in both piperacillin/tazobactam (PT) prescriptions and number of reported allergies between 2015 and 2019.(110) Skin tests were performed in 36 patients with suspected PT allergy: 2 had positive results and 32/34 patients had negative results. The patients with a negative ST results underwent a DPT of which 9 were positive. Overall 11/34 (32.4%) were diagnosed with PT allergy, meaning there is a high rate of genuine PT allergy and a poor NPV of STs (up to 70%). The study was unable to fully study the cross reactivity of PT allergy since they did not perform DPTs with different penicillins in confirmed PT allergy.(110) The second study included 87 patients who underwent SPT and IDT with PT, major (penicilloyl-polylysine) and minor (sodium penilloate) determinants, amoxicillin, benzylpenicillin, flucloxacillin, co-amoxiclav, clavulanic acid and meropenem, with immediate and, where appropriate, delayed reading.(111) ST negative patients underwent DPTs to the various penicillins including PT. Forty-eight of 87 patients (55%) were diagnosed with PT allergy by either positive ST or DPT results. Twenty-six (54%) with immediate type reactions and 22 (45%) with delayed type. One-third of patients (cross) reacted to other penicillins with a pattern suggesting tazobactam allergy in 3 patients. In 21 patients with PT allergy (12 immediate, 9 delayed), tolerance to other beta lactams was demonstrated using DPTs. Although most patients were selectively allergic to PT and tolerated other penicillins, potential cross reactivity with other penicillins was around 30%. Some of these cross reactions however, may have been caused by the beta-lactamase.(111) When looking at these two studies, it is striking that the chance of a negative DPTs is high in the case of negative ST results in the second study, which is in contrast to the previous mentioned study by Wong et al.

Conclusions

Conclusion	Level of evidence
A true allergy for amoxicillin does not necessarily indicate co-sensitivity (or cross-allergy) to other penicillins.	Low
Without the use of skin tests and/or provocation tests, there is no sufficient body of literature that a different penicillin can be given safely to patients with immediate type penicillin allergy	Very low

Other considerations

The studies mentioned in the evidence summary are all based on confirmed allergies with skin tests and/or provocation tests and sometimes sIgE. The recommendations however, are formulated not

CONCEPT

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only for patients with a proven penicillin allergy, but also for patients with suspected penicillin allergy based on allergy history (**Figure 1**). Also, in practice, most antibiotic allergy labels are incomplete and do not specify which penicillin resulted in the reaction. The scarce available studies show cross reactivity between flucloxacillin and amoxicillin or penicillin G/V, between amoxicillin and penicillin G/V and between piperacillin/tazobactam with other penicillins. Since the antibiotic allergy label is often incomplete and the potential risk of cross reactivity is shown by the previous studies, the guideline committee decided to ban all penicillins in case of a suspected or proven immediate type allergy to one of the penicillins if the index reaction occurred ≤ 5 years ago. However, since patients have been shown to be selectively allergic to amoxicillin or PT, one could argue that banning all penicillins is a bit of a stretch in some situations.

Recommendations

Recommendation	**Strength**	**Quality of evidence**
12. We recommend that in patients with a suspected* immediate type allergy to penicillins, irrespective of severity, that occurred ≤ 5 years ago, all other penicillins, (**table 2**) should be avoided.	Strong	Low
13. We recommend that in patients with a suspected* *non-severe* immediate type allergy to penicillins,, that occurred >5 years ago, all other penicillins can be used in a controlled setting**.	Strong	Low
14. We suggest that in patients with suspected* *non-severe* delayed type allergy to penicillins that occurred ≤ 1 year ago, all other penicillins should be avoided.	Weak	Low
15. We suggest that in patients with a suspected* *non-severe* delayed type allergy to penicillins that occurred > 1 year ago, all other penicillins can be used.	Weak	Low
16. We recommend that in patients with suspected *severe* delayed type allergy (**table 3**) to penicillins, all other penicillins should be avoided, irrespective of time since the index reaction. In the absence of acceptable alternative antimicrobial treatment, the use of penicillins should be discussed in a multidisciplinary team***.	Strong	GPS

*In case of a proven allergy by formal allergy work up, handle according to the advice of the consulted allergist.
**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.
*** 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 antibiotic should be balanced against each other followed by shared decision making with the patient.

CONCEPT

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

Whether or not a cephalosporin can be administered with an acceptably low level of risk in a patient with a reported allergy for a penicillin depends, in part, on the type of reaction reported. For the purposes of clarity, this chapter will be divided in two sections that separately describe patients who report immediate and delayed type reactions.

8a. In which patients with a reported immediate type allergy to a penicillin, a cephalosporin can be administered with an acceptably low risk of an allergic reaction?

PICO

P: Patients with a reported immediate type allergy (proven or history) for a penicillin

I: Patient treated (or skin tested) with a cephalosporin

C: None applicable

O: Occurrence of an allergic reaction (immediate type)

Evidence summary

Systematic reviews, meta-analyses and randomized controlled trials

Six systematic reviews and meta-analyses have described the literature evaluating the safety of cephalosporins in patients that report an immediate type allergy to penicillins. DePestel et al. included 5420 patients with a (self-reported) allergy to a penicillin from different studies. Of these, 2.55% had a reaction after oral rechallenge with a cephalosporin. Of note, the majority of these reactions occurred when a first generation cephalosporin with a side chain structure similar to penicillin or amoxicillin was administered.(15) The more widely used cephalosporins with a side chain similar to amoxicillin include cefaclor, cefalexin and cefamandole. Comparable results were reported by the next systematic review: 2.55 % of 5462 patients with a confirmed allergy to a penicillin exhibited cross sensitivity to cephalosporins.(97) It should be noted that “Cross sensitivity” is different from “cross allergy”, since not all reactions that occur in skin tests or oral challenge tests are true allergic reactions. This percentage decreases to approximately 1 % in patients with only a self-reported allergy to a penicillin. The authors note that cross-sensitivity appears to be dependent on side-chain similarity between penicillins and first- or second generation cephalosporins. Therefore, they conclude that it is safe to administer third- and fourth generation cephalosporins and

CONCEPT

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other cephalosporins with dissimilar side-chains to patients with an immediate type allergy to a penicillin.(97)

In a publication of Pichichero the results of 23 reviews were summarized. The author calculated that patients with an allergy to a penicillin have a three-fold increased risk of adverse reactions to structurally unrelated drugs. When this finding is taken into account, the apparent cross-sensitivity between penicillins and first generation cephalosporins is no longer statistically significant (p=0.18). It should be noted that the vast majority of patients included in the analysis had a history of penicillin allergy which was not confirmed by skin testing. Many patients may not have been actually allergic, thus confounding the results of these analyses. Furthermore, the author concludes that if cross-sensitivity exists, it must be side-chain mediated (see also chapter III, question 4).(101) This conclusion was confirmed by 2 meta-analysis later performed, but by the same author.(96, 112) The study published in 2006 summarized publications evaluating 38.846 children and adults with and without a history of penicillin allergy. The database included 2435 patients with a history of penicillin allergy and 961 patients with a history of penicillin allergy and positive skin-test results for penicillin or amoxicillin (total penicillin-allergic patients = 3396). The allergic reaction rate was compared with 34.047 patients without a history of penicillin allergy and 1403 patients without a history of penicillin allergy and negative ST results for penicillin or amoxicillin (total penicillin-nonallergic patients = 35.450). When patients with a positive history of penicillin-allergy received first generation cephalosporins, which share a chemical side chain similar to penicillin or amoxicillin (cephalothin, cephaloridine, cefalexin, cefadroxil, and cefazolin, plus the early second-generation cephalosporin, cefamandole), they showed an increased risk of an allergic reaction to the cephalosporin. The risk of allergy to cefazolin which shares no side chain with penicillins, was only slightly increased In penicillin allergic patients (RR difference +3.5, 95% CI 1.4-5.5, P=0.008).(96)

A meta-analysis published in 2007 included 9 articles as source material. A meta-analysis was performed that included six studies that compared the rate of allergic reactions to the administered cephalosporin in patients with and without a penicillin/amoxicillin allergy. The presence of an allergy was based on medical history alone. A statistically significant increase in allergic reactions to cephalothin (OR 2.5; 95% CI:1.1 to 5.5), cephaloridine (OR 8.7; 95% CI: 5.9 to 12.8), and cefalexin (OR 5.8; 95% CI:3.6 to 9.2), and all first generation cephalosporins plus cefamandole (OR 4.8; 95% CI:3.7 to 6.2) were observed in penicillin allergic patients. No cross reactivity was observed with second generation cephalosporins (OR 1.1; 95% CI: 0.6 to 2.1) or third generation cephalosporins (OR 0.5; 95% CI: 0.2 to 1.1). Based on these results it was concluded by the investigators that first-generation cephalosporins have cross-allergy with penicillins, but that cross-allergy is negligible with second and

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third-generation cephalosporins.(112) However, it should be noted that many of the included studies that reported the largest effect sizes were performed before 1980, when cephalosporins were likely to have contained traces of penicillins due to the manufacturing process, see also chapter III, question 4. These studies hence overestimated the actual likelihood of cross-sensitivity. Of particular importance is that data from this meta-analysis showed that patients with a known penicillin allergy did not have an increased risk of anaphylaxis (i.e. a severe immediate type reaction) when they received treatment with a cephalosporin.(96, 112)

In a more recent meta-analysis only studies that confirmed an immediate type allergy to a penicillin by a skin test or a direct provocation test were included.(98) To prevent confounding due to penicillin contaminated cephalosporin products, only subjects that had been evaluated after 1980 were included in the analyses. To reduce the risk of underestimating cross-allergy, a risk-of-bias assessment was performed to differentiate between studies that did- or did not confirm a negative penicillin skin test result by a direct provocation test for a substantial proportion of patients. Lastly, to quantify the similarity between R1 side chains of penicillins and cephalosporins on the basis of structural and physicochemical properties a bioinformatics model was applied.
Twenty-one observational studies were included, involving 1269 penicillin allergic patients. 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 aminocephalosporins, 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 cephalosporin generation. The higher risk associated with aminocephalosporins 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, cefalexin and cefaclor respectively. No increased risk of cross-reactivity for cefazolin was observed. The authors concluded that cephalosporins that are associated with cross-reactivity are either first or second-generation cephalosporins and that this finding was attributable to the fact that these molecules had a R1 side chain with a high or intermediate similarity score. Cross-reactivity between aminopenicillins and aminocephalosporins was not restricted to patients selectively allergic to aminopenicillins (e.g., tolerant to other penicillins).(98)

Additional literature review

After the publication of abovementioned meta-analyses, several studies were published that confirmed the findings of these meta-analyses.(113-120) Stone et al, performed a retrospective 2

CONCEPT

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center cohort study including all patients reporting a cephalosporin or penicillin allergy with unknown tolerance of cephalosporins. Skin tests (SPT and IDT) with cefazolin and ceftriaxone were performed in 452 patients with a history of penicillin allergy, both immediate and delayed type. All ST results were negative.(119) A much higher percentage of cross reactivity to cephalosporins of 8.1% in 99 patients with a history of penicillin allergy was found in another study.(121) The authors raised the possibility that cross reactivity in the Asian population may differ from the Western populations. However, in this study no formal STs or DPTs were performed. Cross reactivity was defined as patients diagnosed as being allergic to both penicillin and cephalosporin according to their electronic medical record and using Naranjo's algorithm (a questionnaire for determining the likelihood of whether an ADR is actually do to the drug rather that the result of other factors).(121) **T**he use of perioperative antibiotics was studied in children with a registered penicillin allergy at a Nationwide Children's hospital in Ohio.(120) Cephalosporins were used in 153/624 surgical cases (24.5%), with cefazolin used in 83% of episodes. Only one case with a non-anaphylactic reaction was reported. A study by Vaisman et al. established that a structured allergy history, without skin testing, could be safely applied in the perioperative setting and increase cefazolin use as 1st choice preoperative antibiotic prophylaxis. Of the 485 patients with self-reported beta-lactam allergy (SRBA) that underwent structured allergy histories, 117 (24.1%) has a history compatible with a immediate type allergy; 267 (55.1%) patients received cefazolin prophylaxis and none subsequently experienced an adverse reaction. After implementation of the intervention, the overall use of alternative antibiotic prophylaxis at Michael Garron Hospital (Toronto, Canada) among those with SRBA decreased from 81.9% to 55.9%. The authors concluded that the use of cefazolin perioperative prophylaxis could be increased without any serious adverse events and in the absence of skin testing or diagnostic challenges.(122)

Conclusions

Conclusion	**Level of evidence**
The overall rate of cross-reactivity with cephalosporins in patients reporting a penicillin allergy is approximately 1%	Low
The risk of cross-reactivity strongly depends on side-chain similarity between the penicillin and the cephalosporin.	Moderate
The risk of cross-reactivity with cephalosporins in patients with proven penicillin allergy is negligible (<1%) for cephalosporins with dissimilar side chains and 5-17% in cephalosporins with similar or identical side chains.	Moderate
There is no cross-reactivity between penicillins and cefazolin	Moderate

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Cefalexin, cefaclor and cefamandole are the only cephalosporins currently available in the Netherlands that exhibit an intermediate risk of cross-reactivity with penicillins due to side-chain similarity**.**	Low

Other considerations

Due to their excellent efficacy and very low toxicity cephalosporins are the drugs of choice for peri-operative prophylaxis and both empirical and guided treatment of many life-threatening infections. Unnecessary avoidance of cephalosporins in favour of escalation to second line antibiotics (e.g. vancomycin, quinolones) leads to suboptimal outcomes and increased morbidity (including resistant infections), length of hospital stay and healthcare-associated costs.(25, 65) Other cephalosporins used in the Netherlands are ceftibuten and ceftolozane. The previous literature search yielded no publications regarding these two cephalosporins. An additional literature search was performed. For ceftibuten, a prospective study sought to assess the cross-reactivity between penicillins and ceftibuten in 131 subjects with immediate reactions (mostly anaphylaxis) to penicillins that had a positive skin test result to at least 1 penicillin reagent.(123) All patients underwent skin tests with cefazolin and ceftibuten. Patients with negative skin tests were challenged. Ceftibuten has a side chain that is different from those carried by penicillins. Only one patient had a positive ST result to both cefazolin and ceftibuten and to all other reagents tested including aztreonam and carbapenems. All 129 patients who underwent challenges with cefazolin and ceftibuten tolerated them. One patient refused challenges.(123) To our knowledge, no studies were available about ceftolozane.

Recommendations

Recommendations for Immediate type allergy	**Strength**	**Quality of evidence**
17. We recommend that patients with a suspected or proven immediate type allergy to penicillins can receive cephalosporins with dissimilar side chains, irrespective of severity of and time since the index reaction.	Strong	Moderate
18. Cefazolin does not share any side chains with the currently available penicillins and can be used in cases of suspected or proven immediate type allergy to a penicillin, irrespective of severity or time since the index reaction.	Strong	Moderate
19. We suggest that patients with a suspected or proven *non-severe*, immediate type index reaction to a penicillin, can receive a therapeutic dose of cephalosporins with similar side chains (e.g. cefalexin, cefaclor, cefamandole) in a controlled setting*	Weak	Low

*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.

CONCEPT

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8b. In which patients with a reported delayed type allergy for a penicillin, a cephalosporin can be administered with an acceptably low risk of an allergic reaction?

PICO

P: Patients with a reported delayed type allergy (proven or history) for a penicillin

I: Patient treated (or skin tested) with a cephalosporin

C: None applicable

O: Occurrence of an allergic reaction (delayed type)

Evidence summary

Systematic reviews, meta-analyses

The previously discussed meta-analysis by Picard et al (2019) also described studies that evaluated the risk of cross reactivity with cephalosporins in T cell mediated (i.e. delayed type) penicillin allergic patients. Ten studies were included, with a total of 636 penicillin allergic patients, mostly to amoxicillin. Cross reactivity was observed mainly with cefalexin and cefaclor.(98)

Additional literature review

Additional literature review of studies that investigated delayed type allergy did show similar results as previously reported by studies performed in immediate type allergy. Three studies determined whether cefazolin could be used safely in the peri-operative setting in patients with a non-IgE mediated reaction to penicillin. A prospective study observed no adverse reactions in 81 non-IgE mediated penicillin allergic patients who received cefazolin in a peri-operative setting.(124) The second study reviewed all primary hip and knee arthroplasty (n=2012) and revision (n=278) cases. The prevalence of reported penicillin allergy was 9.9% of which 75% was non-IgE mediated. Only 27% of the non-IgE mediated penicillin allergy patients received cefazolin. No adverse reactions were observed.(125) The last study retrospectively assessed the safety and tolerability of cefazolin in patients with methicillin sensitive gram-positive bacterial infections with non-IgE mediated hypersensitivity reactions to nafcillin. Sixty patients were switched to cefazolin because of immune mediated HSR to nafcillin and 17 (28.3%) of those because of non-IgE mediated reactions. All but one patient (94.1%) tolerated cefazolin and completed their therapy.(126)

Two studies included patients with severe delayed type reactions. A retrospective single centre study was performed that evaluated the cross-reactivity among penicillin subclasses and amino- and non-amino cephalosporins in patients with delayed cutaneous adverse drug reaction (CADR). Fifty-six

CONCEPT

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patients were included: 46 with amoxicillin-suspected allergy and 7 with a cephalosporin-suspected allergy. Twenty-nine had severe CADR, and 27 had MPE. Twenty-two had positive tests (18 for amoxicillin and 4 for non-aminocephalosporins). Among the 18 positive amoxicillin-suspected patients, 10 (55.6%) showed cross-reactivity with one or more other BLA: 9 (50%) with another penicillin and 3 (16.5%) with a non-aminocephalosporin.(127) The second study investigated cross reactivity with cephalosporins in patients with severe delayed and presumed T cell mediated reactions to penicillins.(128) A severe T-cell mediated hypersensitivity syndrome was defined as drug reaction with eosinophilia and systemic symptoms (DRESS), acute generalized exanthematous pustulosis (AGEP) or severe maculopapular exanthem (MPE). Patients experiencing Stevens-Johnson syndrome and toxic epidermal necrolysis (SJS/TEN) associated with a penicillin were excluded. All patients were tested with a routine IDT panel of penicillin reagents, cefazolin and ceftriaxone. Of the 32 patients with a severe delayed and presumed T-cell mediated hypersensitivity, 14 (44%) were negative to all reagents, 6 (19%) positive to 2 tested reagents and 12 (38%) had a positive IDT result documented to > 2 reagents from the routine IDT panel. The phenotypes of the 12 this patients were: DRESS (3/12; 25%), AGEP (3/12; 25%) and severe MPE (6/12; 50%). The primary implicated penicillins were piperacillin-tazobactam (6, 50%); amoxicillin (4, 33%) and flucloxacillin (2, 17%). Eleven of 12 (92%) patients tolerated an oral provocation to cefalexin and cefuroxime after IDT.(128)

Conclusions

Conclusion	**Level of evidence**
Patients with *non-severe*, delayed type allergy to penicillins can safely receive cefazolin.	**Low**
The risk of cross-reactivity of patients with *non-severe*, delayed type penicillin allergy was increased with cefalexin and cefaclor	Low
In patients with *non-severe*, delayed type penicillin allergy, the risk of cross-reactivity with cephalosporins with dissimilar side chains is unlikely.	Low
In patients with *severe*, delayed type penicillin allergies, cephalosporins may still be tolerated.	Very low

Other considerations

As is shown by the systematic review by Picard et al. the risk of cross reactivity varied with the degree of similarity between the R1 side chains, not only in IgE mediated allergy, but also in T cell mediated allergy. The risk of cross reactivity in penicillin allergic patients was highest with aminocephalosporins (cefalexin and cefaclor). For cefamandole, no sufficient data could be obtained. Patriarca et al. found cross reactivity with cefamandole in 1/29 (3.4%) and Schiavino et al. in 0/27

CONCEPT

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(0%) of patients.(106, 129) The guideline committee decided to align the recommendation for delayed-type allergy with regard to cefamandole with the previous recommendation for immediate-type allergy, based on theoretical grounds (based on side chain (dis)similarity).

Recommendations for Delayed type allergy	**Strength**	**Quality of evidence**
20. We recommend that patients with suspected or proven *non-severe*, delayed type allergy to penicillins, can receive cephalosporins with dissimilar side chains, irrespective of time since the index reaction.	Weak	Low
21. We suggest to avoid cephalosporins with similar side chains (e.g. cefalexin, cefaclor, cefamandole) in patients with suspected or proven *non-severe,* delayed type allergy to amoxicillin, penicillin G, V or piperacillin, with an index reaction that occurred ≤1 year ago.	Weak	Low
22. We suggest that cephalosporins with similar side chains (e.g. cefalexin, cefaclor, cefamandole) can be used in patients with suspected or proven *non-severe*, delayed type allergy to amoxicillin, penicillin G, V or piperacillin, with an index reaction that occurred > 1 year ago.	Weak	Low
23. We recommend that in patients with suspected *severe* delayed type allergy (**table 3**) to penicillins, all cephalosporins should be avoided, irrespective of time since the index reaction. In the absence of acceptable alternative antimicrobial treatment, the use of cephalosporins should be discussed in a multidisciplinary team*.	Strong	GPS

* 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 antibiotic should be balanced against each other followed by shared decision making with the patient. If the multidisciplinary team concludes the cephalosporin may be used in case of a suspected or proven severe delayed type penicillin allergy, the cephalosporin should be administered under prolonged medical supervision

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

PICO

P: Patients with a reported allergy (proven or history) for a penicillin

I: Patient treated (or skin tested) with a carbapenem or monobactam

C: Patient treated with different antibiotic, not a carbapenem, monobactam or penicillin

O: Occurrence of an allergic reaction (immediate or delayed)

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Evidence summary

Systematic reviews, meta-analyses and RCTs

The literature search yielded no RCTs, 3 systematic reviews and one meta-analysis regarding cross reactivity between penicillins and carbapenems and one systematic review evaluating cross reactivity with both carbapenems or monobactams.

Greanya et al. (2005) included 4 cross sensitivity studies of which 3 studies had a retrospective study design. A total of 360 patients with a *self-reported* penicillin allergy and 6 patients with a documented (observed by health care personnel) penicillin allergy were included. Penicillin skin tests were performed only in 40 patients, of which 20 tested negative, and 19 tested positive. Nine out of 19 (47.4%) penicillin ST positive subjects had a positive ST to imipenem or its metabolites, while only 1/20 (5%) penicillin ST negative subjects reacted to imipenem. Of the remaining 326 patients with reported or documented penicillin allergy, (without confirmation by STs or DPTs), 32 patients had a *reported* reaction to a carbapenem. Most of these reactions were non-severe. Severe reactions included one anaphylactic reaction and two reactions with respiratory distress or wheezing. The authors concluded that based on *self-reported* penicillin allergy patients (without confirmation), the risk of allergic cross reactivity of imipenem or meropenem to penicillin was approximately 10%.(99) Frumin et al. (2009) included an additional 3 prospective studies to the studies described in the review by Greanya et al. In these studies challenges with increasing doses of carbapenem were administered to penicillin allergic patients who were carbapenem ST negative. A total of 324 penicillin ST positive patients were included (both children and adults), of whom 0.9-1% reacted to a carbapenem. All carbapenem ST negative patients tolerated the carbapenem challenges.(100) Kula et al. (2014) included 10 studies and 12 case reports describing 854 patients. Of these 854 patients, 838 had proven, suspected or possible IgE-mediated penicillin reactions. The incidence of any type of suspected HSR to a carbapenem was 36/838 (4.3%, 95%CI 3.1-5.9%). Only 1/838 was a *proven* IgE mediated reaction, and 19/838 a *possible* IgE mediated reaction. When including only patients with positive penicillin STs (n = 295), 1 patient had a reaction to a carbapenem (0.3%, 95% CI 0.06%-1.9%) and this was a possible IgE-mediated reaction.(130) Terico et al. (2015) included the same 6 studies that evaluated cross reactivity between penicillin and carbapenems (3 retrospective and 3 prospective) as the previous mentioned systematic reviews. In addition, Terico et al. included 4 studies evaluating cross reactivity between penicillins and aztreonam. A total of 147 patients with ST or DPT proven penicillin allergy, and 6 patients with penicillin anaphylaxis without formal allergy testing, received aztreonam STs or DPTs. Only one patient reacted to the aztreonam ST, but not to

CONCEPT

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the challenge test. This patient also reacted to all penicillin determinants and to cefamandole skin tests.(11)

The meta-analysis by Picard et al. (2019) included 11 observational studies on carbapenem cross reactivity with 1127 proven (based on ST or DPT) penicillin allergic participants. Both IgE-mediated and T-cell mediated reactions were included. Cross reactivity had to be assessed to at least one carbapenem through ST or DPT, and if both test were performed, DPT was used as the criterion standard to confirm allergy. The overall risk of cross reactivity to any carbapenem was 0.87% (95%CI 0.32-2.32). Nine studies evaluated the cross-reactivity to imipenem in a total of 917 penicillin allergic subjects and observed a rate of 0.79% (96% CI 0.21-2.88). Five studies evaluated the risk of cross reactivity to meropenem and observed a rate of 0.30% (95% CI 0.08-1.19) and 3 studies evaluated this risk for ertapenem, resulting in a risk of cross reactivity of 0% (95% CI 0-0.01).(98)

Additional literature review

Six additional observational studies about cross reactivity between penicillins and carbapenems were found that were not included in the abovementioned systematic reviews. Three clinical studies reported on cross reactivity in proven penicillin allergic patients, the remaining 3 studies in reported penicillin allergic patients. Cross reactivity with aztreonam was evaluated in a prospective study in 214 patients with a proven delayed type penicillin allergy (mostly for aminopenicillins) based on positive patch test or delayed reading. All 214 patients tolerated aztreonam challenges.(131) Another study included adult patients, of which 78 reacted to penicillin allergy testing (SPT, IDT and if negative DPT). Of these 78 patients, 39 (50%) presented with anaphylaxis as the initial reaction and 39 (50%) with urticaria. In 28 patients (71.8%) of the anaphylaxis group and 22 (56.4%) among the urticaria group, alternative beta-lactam testing was performed. The remaining 28 patients refused further testing. Of the 50 patients, 45 patients were skin tested and if negative challenge tested for meropenem. Meropenem was tolerated in 43 patients and 2 patients reacted (one with positive IDT, another with delayed urticaria and facial angioedema).(116) Sanchez de Vincente et al. (2020) evaluated 137 adult patients with immediate type penicillin allergy proven by ST (n= 132) or DPT (n= 5). Fifty one patients presented with anaphylaxis and 86 with urticaria/angioedema within 1 hour after administration. These patients received STs and challenge tests with imipenem 1 gram intravenous when STs were negative. Forty-six patients were challenged with imipenem and no reactions were observed.(118)

CONCEPT

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Three studies included reported (e.g. not proven) penicillin allergic patients, both immediate and delayed type reactions.(113, 132, 133) Cunha et al. included 42 patients with a penicillin allergy and treated them with ertapenem, no reaction occurred.(132) Wall et al. included 324 penicillin allergic patients and 624 non penicillin allergic patients and observed 1 reaction with a carbapenem in the penicillin allergic patients and 4 reactions in the non-allergic group.(133) Crotty et al. included 175 patients with self-reported penicillin allergy and treated 56 of them with a full dose course of meropenem. Three (5%) patients reacted with a rash with or without pruritis.(113)
For aztreonam, 2 additional observational studies were found. The first included 40 patients with positive STs and/ or sIgE tests to penicillin determinants. Most patients had anaphylaxis or urticaria as their index reaction. All patients had negative IDTs with aztreonam and tolerated the intramuscular graded challenges.(134) The second study included 212 subjects aged >15 years with immediate type reactions to penicillins, proven by positive ST results to at least 1 penicillin reagent. These 212 patients underwent STs with aztreonam and if negative challenges with escalating doses. All subjects displayed negative skin test results to aztreonam and 211 accepted challenges and all were tolerated.(135)

Conclusions

Conclusion	Level of evidence
There is no molecular pattern that results in cross reactivity between penicillins and carbapenems (Key question 6)	Low
In patients with non-severe, delayed type penicillin allergy, the risk of cross-reactivity with any carbapenem is unlikely (<1%).	Moderate
In patients with an immediate type penicillin allergy, both severe and non-severe, the risk of cross-reactivity with any carbapenem is unlikely (<1%)	Moderate
The risk of cross-reactivity in patients with severe, delayed type penicillin allergy with any carbapenem is unknown.	Very low
No cross reactivity was observed between penicillins and aztreonam	Moderate

Other considerations

The first available prospective study by Saxon et al. (1988) led to the frequently quoted and cited cross reactivity rate of approximately 50% between penicillin and imipenem allergies.(136) Additional prospective studies however showed that this high rate was not accurate and that the risk of cross reactivity between penicillins and carbapenems was <1% (unlikely). In addition, carbapenems are generally well tolerated, with rash, pruritis and urticaria experienced by 0.3%-3.7% of patients in post marketing studies of imipenem, meropenem, doripenem and ertapenem.(11) The

CONCEPT

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guideline committee discussed that these results from the literature review led to the recommendation that carbapenems can be given without additional measures to patients with reported or proven penicillin allergy. For severe delayed type reactions no conclusions could be drawn since patients with a Severe Cutaneous Adverse Reaction (SCAR such ass DRESS, AGEP) were excluded in all available studies.

Recommendations

Recommendation	**Strength**	**Quality of evidence**
24. We recommend that patients with suspected or proven immediate type penicillin allergy, irrespective of severity or time since the index reaction, can receive *any* monobactam or carbapenem, without prior allergy testing.	Strong	Low
25. We recommend that patients with a suspected or proven *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	Low
26. We recommend that in patients with suspected *severe* delayed type allergy (**table 3**) to penicillins, all monobactams and carbapenems should be avoided, irrespective of time since the index reaction. In the absence of acceptable alternative antimicrobial treatment, the use of monobactams or carbapenems should be discussed in a multidisciplinary team*.	Strong	GPS

* 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 antibiotic should be balanced against each other followed by shared decision making with the patient. If the multidisciplinary team concludes the monobactam or carbapenem may be used in case of a suspected or proven severe delayed type penicillin allergy, the monobactam or carbapenem should be administered under prolonged medical supervision

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V. Cross reactivity in beta-lactam allergy (cephalosporin, carbapenem and monobactam allergy)

Introduction

Cephalosporin allergy has been investigated mainly in the context of patients with confirmed penicillin allergy. Moreover, a history of penicillin allergy often resulted in standard avoidance of all cephalosporins because of the historically reported high cross-reactivity of 10%. This high percentage can be explained by contamination of cephalosporin preparations with penicillins. Therefore the cephalosporin allergy label is often misleading. On the other hand, cephalosporins are used increasingly and have been shown to be the responsible drug of allergic reactions more frequently (up to 15%).(137, 138) Studies investigating the allergic reaction to cephalosporins are growing, but remain scarce. Particularly studies that investigate cross reactivity with penicillins, carbapenems and/or monobactams in cephalosporin allergic patients are limited. The overall reported incidence of carbapenem allergy is low (0.3-3.7%) resulting in limited available data regarding cross reactivity between cephalosporins and carbapenems. Clinical studies that examine cross reactivity within carbapenems are lacking.(139)

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

PICO

P: Patients with a proven allergy to a cephalosporin

I: Exposure to a penicillin, by means of skin tests, specific IgE and if available DPTs

C: Not applicable

O: Occurrence of an allergic reaction (immediate or delayed) indicated by specific Ige, positive skin test or provocation test results

Evidence summary

Randomized trails, systematic reviews and meta-analyses

No RCTs, systematic reviews and meta-analyses were retrieved.

Additional literature review

Ten studies were found that determined the risk of cross reactivity to penicillins in cephalosporin allergic patients. All of the selected studies are case series. Most of included patients had immediate

CONCEPT

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type reactions to cephalosporins and underwent skin tests with penicillins and/or assays for specific IgE.

Studies that investigated the risk of cross reactivity to cephalosporins in penicillin allergic patients have shown that cross reactivity exists between aminopenicillins (amoxicillin) and amino-cephalosporins (cefaclor and cefalexin) or benzyl-cephalosporin (cefamandole) (see chapter III). Unfortunately, no studies were found that examined the cross reactivity to amoxicillin in patients allergic to cefalexin or cefamandole, nor studies that determined cross reactivity to penicillins in patients with delayed type allergy to cephalosporins.

Three studies, all performed by Romano et al. used skin tests only, not DPTs. One study evaluated the IgE response to penicillins in subjects with immediate allergic reactions to cephalosporins.(140) In 30 subjects with immediate reactions to ceftriaxone, cefotaxime, ceftazidime, and cefuroxime, skin tests and sIgE antibody assays were performed for major and minor determinants of penicillin G, amoxicillin, and ampicillin, as well as for the culprit cephalosporins and other cephalosporins. Only the sensitization test results of penicillin determinants are discussed here. Twenty-six (86,7%) patients had positive STs to a cephalosporin and negative STs and negative sIgE assays to penicillin. Four Subjects (13,3%) had a positive response to penicillin determinants. The second study included 70 patients (>15 years old) with proven immediate type reactions to cephalosporins (mainly ceftriaxone, cefotaxime and ceftazidime) and observed a positive ST or sIgE result in 19 (27.1%) of them.(141) The last study included 148 children with cephalosporin allergy (mainly cefaclor and ceftriaxone), with both immediate type reactions (n=43) and delayed type reactions (n=105). Of the 35 patients with proven immediate type cephalosporin allergy (mostly cefaclor), 15 (42.9%) showed positive results on immunoassays (n=5) or STs to penicillin (n=10).(142)

Seven studies performed both STs as DPTs. In a study by Romano et al. published in 2010, subjects with immediate allergy to different cephalosporins and a positive skin test result to the responsible cephalosporin were included.(143) All subjects underwent skin tests with penicillins and the responsible cephalosporin. In all subjects sIgE to penicilloyl G, penicilloyl V, ampicilloyl, amoxicilloyl, and cefaclor (CAP-FEIA), was determined. Ninety-eight subjects (68 female and 30 male) aged 13 to 90 years (mean age 44.5 years) were included. Over 75% had experienced an anaphylactic reaction. The cephalosporins that most frequently caused allergic reactions were ceftriaxone, ceftazidime, cefaclor and cefotaxime. Twenty-five (25.5% [95% CI, 17.9% to 34.5%]) subjects had a positive ST and/or sIgE to one or more penicillin determinants. Positive results on allergologic tests for penicillin determinants were observed in 10 (55.5% [95% CI, 33.5% to 75.5%]) of 18 subjects who had reacted to cephalosporins that share similar (cephalothin or cefamandole) or identical (cefaclor, cefalexin, or

CONCEPT

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cefatrizine) side chains with penicillins versus 15 (18.7% [95% CI, 11.7% to 28.7%]) of 80 subjects who reacted to cephalosporins (ceftriaxone, ceftazidime, cefotaxime, cefuroxime, cefazolin, cefodizime, cefoperazone, or cefonicid) that have side chains different from those of penicillin. After reacting to a cephalosporin that shares a similar or identical side chain with a penicillin, the estimated relative risk ratio of cross-reacting with at least 1 penicillin was 3.0 (95% CI, 1.6-5.5%). The authors remarked that because all subjects had been treated with penicillins some time before their reaction to cephalosporins it is possible that subjects with positive results on allergologic tests with cephalosporins and penicillins that have dissimilar side chains, could be the result of a co-existing sensitivity, not cross-reactivity.(143)

A study by Antunez et al. included subjects with immediate reactions to different cephalosporins. In all subjects skin testing and sIgE assays ('RAST') were performed with a panel of penicillin determinants: benzylpenicilloyl-poly-L-lysine, minor determinant mixture, benzylpenicillin, amoxicillin, ampicillin. Only 24 patients, in which sIgE to the culprit cephalosporin could be demonstrated, were included. The culprit cephalosporins in these 24 patients, were cefaclor (N = 7), cefonicid (N = 1), cefotaxime (N = 2), ceftazidime (N = 2), ceftriaxone (N =3), and cefuroxime (N = 9). Two patients had a positive skin test result to penicillin determinants. No in vitro IgE antibodies to the penicillin derivatives used were detected to these penicillins. In one subject allergic to ceftriaxone, sIgE to benzylpenicillin and amoxicillin could be demonstrated. In the second subject allergic to cefuroxime, sIgE to ampicillin was observed. Twenty-two subjects had negative results to penicillin determinants and tolerated benzylpenicillin administration.(144)

Subjects presenting with a history of immediate type allergy to cephalosporins were investigated in a study by sIgE testing to penicillin, amoxycillin and cefaclor, followed by skin prick testing, intradermal testing and drug provocation testing with a panel of penicillins and cephalosporins. Fifty-five subjects had a history consistent with IgE-mediated reaction. Cefalexin was the most common index cephalosporin in 25 (45.4%) followed by cefazolin in 11 (20%) and ceftriaxone in 7 subjects (12.7%). Out of 55 subjects, 24 (43.6%) were found allergic to their index cephalosporin as confirmed by demonstration of sIgE and/or positive STs. Two cefaclor-allergic subjects confirmed by positive sIgE were also positive to other penicillins on sIgE (penicilloyl V in one and penicilloyl V, penicilloyl G and amoxicilloyl, in the other). Following negative IDT, both underwent DPT to amoxycillin which they tolerated.(138)

Another study diagnosed patients with IgE-mediated cephalosporin anaphylaxis based on suggestive clinical history supported by elevated mast cell tryptase, positive IDT to the culprit cephalosporin, and negative IDT to other perioperative drugs and substances tested. Fourty-four patients were

CONCEPT

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included (40 had anaphylaxis to cefazolin, two to cefalothin, and two to ceftriaxone). Penicillin STs were only performed in patients that had an anaphylaxis to a cephalosporin other than cefazolin. All 44 patients completed a 3-day amoxicillin challenge with no immediate adverse reaction reported. One patient reported a delayed benign rash after 24 hours and ceased amoxicillin. The authors remark that the study results suggest that that cefazolin allergy may be specific and patients may tolerate penicillins without the need for further evaluation.(145)

A total of 780 adult patients from 2 centers (Australia and USA) labeled with a cephalosporin allergy label (CAL) or penicillin allergy label (PAL) with unknown tolerance of cephalosporins underwent a standardized skin testing.(119) The standard protocol consisted of major determinant, minor determinant mix either or an in-house stock prepared solution of benzyl penicilloate, ampicillin, and penicillin G via SPT and IDT. Of 328 patients with a CAL, 245 had a history of immediate allergy of whom 22 tested positive and 83 had a history of delayed history of whom 6 tested positive. Of 328 patients with a CAL, 16 (4.8%) were ampicillin skin test positive. Eleven of these 16 patients had an initial allergy label to cefalexin. Of the patients with an initial CAL, 305 (80%) underwent an uneventful penicillin allergy challenge.(119)

Sixty six patients that were referred to the clinic after experiencing perioperative anaphylaxis, were exposed to cefazolin. Patients exhibiting a positive skin test with cefazolin had a panel of STs with other β-lactams and, if indicated, graded drug challenges to study cross-reactivity. Minor determinant mixture, penicilloyl-polylysine , benzylpenicillin and amoxicillin (clavulanic acid) were tested. Out of the 66 patients, 19 patients displayed positive ST responses to this cephalosporin. Challenges with alternative β-lactams were performed in 16 of 19 patients. Of the 16 patients, 14 were challenged with amoxicillin or amoxicillin-clavulanic acid, all challenges were negative.(146)

A total of 10 individuals with proven IgE-mediated cefazolin hypersensitivity were included in a study. All the index reactions were compatible with an acute IgE-mediated reaction. Cefazolin STs were positive in 7 individuals and cefazolin challenges were positive in 3 more. In the 8 cefazolin allergic patients who received challenges with amoxicillin, no one reacted.(147)

Conclusions

Conclusion	Level of evidence
The body of literature suggest the same mechanism of cross reactivity in patients with cephalosporin allergy who receive penicillins as for patients with penicillin allergy who receive cephalosporins (i.e. side chain similarity)	Low

CONCEPT

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The risk of skin test positivity with penicillin reagents, however, is not only related to structural side chain similarities with cephalosporins, but also due to co-sensitization.	Low

Other considerations

Patients with an immediate hypersensitivity to a cephalosporin have a small risk of reactivity to penicillins that have dissimilar side chains. Because the side chains are different the cause may not be cross reactivity but co-sensitisation. The workgroup accepts this small risk and advises not against use of penicillins in patient with cephalosporins, except when it concerns immediate type or recent (<1 year) non-severe delayed type allergies to cefaclor, cefalexin and cefamandole.

Cefazolin is a very commonly used pre-operative antibiotic. In patients with an immediate type hypersensitivity to cefazolin no cross reactivity can be demonstrated with penicillin determinants in several studies. Therefore patients with immediate hypersensitivity to cefazolin are allowed to use penicillins (and all other beta-lactam antibiotics).

Despite the that no studies could be found about cross reactivity to penicillins in patients with allergy to cefalexin and cefamandole, the workgroup advises against the use of aminopenicillins in these patients. The reason is, because cross-reactivity to these cephalosporins and cefaclor have been demonstrated in patients with allergy to amoxicillin due to R1 side chain similarity.

No conclusions can be drawn for ceftibuten or ceftolozane, since studies regarding cross reactivity are not available yet. Studies show no evidence for cross reactivity of cephalosporins with piperacillin.

Contrary to the literature available for penicillin allergy, there is very limited literature on the half-life of cephalosporin allergy. Romano et al. showed that of 72 patients with cephalosporin allergy, 45 became skin test or sIgE negative after 5 years.(53) Fernandez et al. observed only 2.4% of 41 patients with cephalosporin allergy showed sIgE positivity after 4 years.(54) For the non-severe delayed type allergy the guideline committee has adopted the advice from chapter III, where re-exposure to the culprit is allowed if the index reaction had occurred > 1 year ago. For the non-severe immediate type reactions, the guideline committee has adopted the advice from chapter III, where re-exposure to the culprit is allowed if the index reaction had occurred > 5 years ago. If one wants to administer an antibiotic with potential cross reactivity in view of side chain similarity, because of a vital indication, our advice is to consult with an allergist. A potential cross reactivity based on side chain similarity does not necessarily result in cross allergy.

CONCEPT

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Recommendations

Recommendations for Immediate type allergy	Strength	Quality of evidence
27. We recommend that referral for allergy work-up should be considered to prove or disprove suspected immediate type allergy to cephalosporins in patients	Strong	GPS
28. We recommend that patients with a suspected or proven immediate type allergy to cephalosporins can receive penicillins with dissimilar side chains, irrespective of severity and time since the index reaction.	Strong	Low
29. We recommend to avoid penicillins with similar side chains in patients with a suspected or proven immediate type allergy to cefaclor, cefalexin and/ or cefamandole, irrespective of severity and time since index reaction.	Strong	Low
30. Cefazolin does not share any side chains with the other currently available penicillins and penicillins can therefore be used in cases of suspected or proven immediate type allergy to cefazolin, irrespective of severity or time since the index reaction.	Strong	Low

Recommendation for Delayed type allergy	Strength	Quality of evidence
31. We recommend that patients with a suspected or proven *non-severe*, delayed type allergy to a cephalosporin can receive penicillins with dissimilar side chains, irrespective of time since index reaction.	Strong	Low
32. We suggest to *avoid* penicillins with similar side chains in patients with suspected or proven *non-severe*, delayed type allergy to cefalexin, cefaclor and/ or cefamandole, when the index reaction occurred ≤ 1 year ago.	Weak	Low
33. We suggest that penicillins with similar side chains can be used in patients with suspected or proven *non-severe*, delayed type allergy to cefalexin, cefaclor and/ or cefamandole, when the index reaction occurred > 1 year ago.	Weak	Low
34. We recommend that in patients with suspected *severe* delayed type allergy (**table 3**) to cephalosporins, all penicillins should be avoided, irrespective of time since the index reaction. In the absence of acceptable alternative antimicrobial treatment, the use of penicillins should be discussed in a multidisciplinary team*.	Strong	GPS

*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 antibiotic should be balanced against each other followed by shared decision making with the patient. If the multidisciplinary team concludes the penicillin may be used in case of a suspected or proven severe delayed type cephalosporin allergy, the penicillin should be administered under prolonged medical supervision.

CONCEPT

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

PICO

P: patients with a reported allergy (proven or history) for a cephalosporin

I: patient treated (or skin tested) with a different cephalosporin than the culprit drug

C: patients treated with an alternative antibiotic

O: Occurrence of an allergic reaction (immediate or delayed)

Evidence summary

No studies with a randomized design nor systematic reviews or meta-analysis could be included.

Additional literature review

As already mentioned in the general introduction, the incidence of allergy against cephalosporins is rather low. Cefazolin is implicated as a cause of perioperative anaphylaxis, as used in many national protocols for perioperative prophylaxis.

Immediate type reactions

A recent study by Lin et al. showed that of the almost 500 patients included in an antibiotic stewardship program in a teaching hospital in the Netherlands, almost 10 percent have a label of penicillin, cephalosporin and carbapenem allergy. This is inconsistent with the published incidence of cephalosporin and carbapenem allergy and suggests that there still is an important misconception about the prevalence of cephalosporin and carbapenem allergy in first line health care (I.e. general practitioners and pharmacists).(89, 139, 148) Khan et al. observed that the incidence of cephalosporin hypersensitivity was 0.8 % for oral and 0.64% for parenteral cephalosporins in the USA. While cephalosporin induced anaphylaxis was 5 in 901.908 oral courses and 8 in almost 500.000 parenteral courses.(148)

Three retrospective studies and 7 prospective studies were found dealing with *immediate reactions* (10) and *delayed reactions* (2). One extensive study looked into the structural similarities of cephalosporins. In the *retrospective* studies, a recently published study in 55 adults with a history of cephalosporin allergy could confirm the allergy in 24/55 patients with sIgE test, skin tests or drug provocations.(138) Twenty patients were allergic to the index cephalosporin only and four patients proofed to be allergic for different beta-lactam antibiotics. Of those, two when a similar R1 chain was

CONCEPT

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present, and two who had a random pattern, reflecting probable co-sensitization. In this study cefaclor allergy was solely diagnosed using serological tests. However, it is known that serological tests can become false positive when high total IgE titers are present (product information Thermo Fisher Immunocap). Another retrospective study investigated 97 children suspected for beta-lactam allergy, ten out of them had a proven cephalosporin allergy and 4/10 reacted only to the index cephalosporin, not to a cephalosporin with a different R1 chain.(149) Pipet et al. looked at 25 patients in a French Drug allergy database who had a history implicating cefazolin as a suspect cause of anaphylaxis. In 10 patients this could be confirmed with a skin test (7) and drug provocation test (3). Nine patients were also tested with various cephalosporins, either by skin testing or provocation (4): none of the proven cefazolin allergic patients reacted with another cephalosporin (ceftriaxone, cefuroxime, cefamandole, cefalothin, cefotaxime, cefoxitine and ceftazidime).(147) Several other case reports corroborate the concept of side chain specific reactions to cefazolin (but ceftezole, used only in Asia, can cross react with cefazolin).

Romano et al. prospectively studied 30 subjects (aged 6-79 years) with reactions to one or more cephalosporins (ceftriaxone (15), cefotaxime (9), ceftazidime (7) and cefuroxime (4). Indication for analysis were urticaria and anaphylactic shock. The majority of patients (26) had only one allergic episode induced by a cephalosporin. Four patients had reactions to different BLA. Skin tests and in vitro specific IgE antibody assays were performed for major penicillin determinants as well as for culprit cephalosporins. Four patients had skin test and/or serological positive results for one or more penicillin determinants. Of the group with selective skin test positivity to cephalosporins (26 patients); 15 responded only to the culprit cephalosporin and 11 to the culprit cephalosporin but also to different cephalosporins. Among patients with reactions to ceftriaxone, selective responses to this drug were found in 9 patients. Two patients with ceftriaxone allergy reacted to cefotaxime (same R1 chain) and one patient showed cross reactivity between cefotaxime and cefuroxime (similar side chain). No drug provocations, however, were performed.(140) Somech et al. studied 6 patients aged 12-56 years. Responsible compounds were cefuroxime (3), cefaclor (1), cefazolin (1) cefalexin (1) and clinical reactions included urticaria, anaphylaxis and angioedema <1h. One patient had a positive DPT to cefalexin and cefaclor (with a similar 7-position side chain) but tolerated amoxicillin (with a similar but not identical 7 position side chain). One patient who was challenge positive to cefuroxime also reacted to cefalexin, which shares no side chains or structural similarities. Cross reactivity in medications with no structural side chain similarities in this small cohort is 7.1%.(150) Antunez et al. described 24 patients who were studied with in vitro responses, RAST inhibition assays and skin tests. Twenty patients were mono-sensitized for cephalosporins (cefaclor (7), cefonizid (1), cefotaxime (2), ceftazidime (2), ceftriaxone (3) and cefuroxime (9)). Two third of the patients reacted only with the

CONCEPT

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culprit cephalosporin, one third showed cross reactivity, mainly with cephalosporins with a similar side chain and only incidentally with a cephalosporin with different side chains.(137) Atanaskovic-Markovic et al. studied 1170 children of which 241 reacted to cephalosporins, often in combination with positive reactions on penicillin (skin) tests. One child reacted to all (skin) tested cephalosporins, roughly one quarter of the children reacted to the first generation cephalosporins cefalexin and cefaclor and 1-0.3% to the third generation ceftriaxone and cefotaxime. When individual cephalosporins are evaluated: in patients with ceftriaxone allergy (7): 2 reacted to cefalexin (28.6%) and 4 (57.1%) to cefaclor. In cefotaxime allergy (2): 1 reacted to cefaclor (50%) and in cefaclor allergy (199), 137 reacted to cefalexin (68.8%) which shares the same side chain.(29) Romano et al. described 102 patients with immediate type reactions to cephalosporins, often with anaphylaxis. The patients were analyzed with several skin tests, serological tests and drug provocations. The study showed that *all* patients (73) with an index reaction to ceftriaxone, cefuroxime, cefotaxime, cefepime, cefodizime or ceftazidime tolerated an aminocephalosporin (in casu cefaclor). All subjects who had initially reacted to aminocephalosporins (13), tolerated provocation with cefuroxime and ceftriaxone. Moreover, all above mentioned patients (86) tolerated provocations with cefazolin and ceftibuten (which do not have any common side chain). The authors concluded that cross reactivity for different cephalosporins was R1 side chain dependent, both among aminocephalosporins and penicillins, and among cephalosporins: cross reactivity was shown between cefuroxime and ceftriaxone and between cefotaxime and cefodizime, which indeed share an identical R1 chain.(151) Uyttebroek et al. tested 19 cefazolin allergic patients who presented with perioperative anaphylaxis and had a positive skin test at 2 or 20 mg/ml and provoked them with alternative beta-lactam antibiotics, including aztreonam (in 5 cases). None of the patients reacted, with different sets of beta-lactam antibiotics, including cefuroxime, ceftriaxone, and ceftazidime. They concluded that cefazolin-allergy is a selective allergy with proven good tolerance of other beta-lactam antibiotics.(146) Sadleir et al. describes twenty-one patients, of whom 19 had a definite diagnosis of perioperative anaphylaxis due to cefazolin. In all these patients intracutaneous testing of cephalothin was negative. Subsequent incremental dosing of cephalothin i.v. was well tolerated, and three patients underwent new perioperative exposure to cephalothin, which was well supported. Though both cephalosporins are first generation, they do not share common side chains allowing for good tolerability of cephalothin in cefazolin allergy. Both cephalosporins are available in The Netherlands (according to the G-standard).(152)

Delayed type reactions

When delayed reactions to cephalosporins are considered, Lammintausa et al. performed 270 patch tests in suspected cephalosporin delayed type allergy.(153) Thirteen patients tested positive, most

CONCEPT

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often to ceftriaxone and cefuroxime. One of these patients showed also a positive reaction to cefalexin, cefadroxil and cefaclor, while another reacted to both cefuroxime and ceftriaxone. Overall, patch and skin prick testing in 935 patients had a sensitivity of 90%. Two hundred forty six patients were challenged. Of the 17 test positive patients, 14 showed a clinical reaction upon challenge, while in 229 test negative patients, 207 (90.4 %) did not react to the challenge.(153) A prospective study examined 105 patients, aged 14-84 years, with histories of delayed reactions to cephalosporins. They could confirm the allergy in seven patients with skin testing. Of 98 patients with negative skin testing, 86 patients tolerated the suspected cephalosporin, illustrating a good predictive value of skin testing (intradermal and patch testing) for delayed type reactions to cephalosporins, but no data about cross reactivity were degenerated.(47) Bérot et al. reported amongst others on cephalosporin related delayed reactions. Four of seven patients had positive patch testing: two showed positive test results to amoxicillin and a cephalosporin (cefoxitin, cefuroxime), one patient only to a single culprit and the last patient with an initial reaction to ceftriaxone had positive patch tests for cefuroxime, cefoxitin (not available in the Netherlands), cefotaxime and ceftazidime.(127) When structural considerations are used in predicting whether there will be cross reactivity between cephalosporines, Pichichero developed an extensive overview of structural overlaps within cephalosporins, which has been adapted to the available cephalosporins in the Netherlands (**table 11).**(154)

Conclusions

Conclusion	**Level of evidence**
A cephalosporin allergy label does not always represent a current and true allergy (chapter I)	Moderate
In patients with a confirmed cephalosporin allergy, the risk of a cross-allergic reaction is high in the case of cephalosporins with similar or identical side chains and low for cephalosporins with different side chains.	Low
Cefazolin does not share an identical side chain with any other cephalosporin and is therefore almost always a selective allergy i.e. to cefazolin only.	Low
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.	Very low

Other considerations

Data from annual prescriptions show that several hundred prescriptions are delivered in general practices in the Netherlands. (Cefalexin and ceftriaxone each 684 prescriptions in 2019, source Gip databank).(155) However, preliminary data from allergy registrations for beta-lactam

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allergy in the general practice, show that almost one quartier of all allergy registrations are registrations of cephalosporin allergy, largely overestimating the real incidence of cephalosporin allergy. It is also important to keep in mind that several potential cross reactivities between cephalosporins are based upon in structural similitudes, where similar or identical side chains probably predict cross reactivity, but not all have been formally verified by skin testing and provocations.

Recommendations

Recommendations for Immediate type allergy	**Strength**	**Quality of evidence**
35. We recommend that cephalosporins with a dissimilar side chain can be used in patients with a suspected or proven immediate type allergy to a cephalosporin, irrespective of severity and time since index reaction.	Strong	Moderate
36. Cefazolin does not share any side chains with the other currently available cephalosporins and can be used in cases of suspected or proven immediate type allergy to a cephalosporin, irrespective of severity.	Strong	Moderate
37. We suggest that patients with suspected *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**.	Weak	Low

Recommendations for Delayed type Allergy	**Strength**	**Quality of evidence**
38. We recommend that cephalosporins with a dissimilar side chain can be used in patients with a suspected or proven *non-severe* delayed type allergy to a cephalosporin, irrespective of time since index reaction.	Strong	Low
39. We suggest *against* the administration of cephalosporins with similar or identical side chains to the culprit drug in patients with a suspected or proven, *non-severe*, delayed type allergy to a cephalosporin, when the index reaction occurred ≤ 1 year ago.	Weak	Low
40. We suggest cephalosporins with similar or identical side chains to the culprit drug can be used in patients with a suspected or proven, *non-severe*, delayed type allergy to a cephalosporin, when the index reaction occurred > 1 year ago.	Weak	Low

CONCEPT

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41. We recommend that in patients with suspected *severe* delayed type allergy (**table 3**) to cephalosporins, all other cephalosporins should be avoided, irrespective of time since the index reaction. In the absence of acceptable alternative antimicrobial treatment, the use of cephalosporins should be discussed in a multidisciplinary team*.	Strong	GPS

*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 antibiotic should be balanced against each other followed by shared decision making with the patient. . If the multidisciplinary team concludes the other cephalosporin may be used in case of a suspected or proven severe delayed type cephalosporin allergy, the cephalosporins should be administered under prolonged medical supervision

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

Introduction

Monobactams are beta-lactam antibiotics containing a monocyclic ring structure, which differs from the bi-cyclic ring structure in the nucleus of cephalosporins. Of the monobactam antibiotics, aztreonam is currently the only available drug. The side chain of aztreonam is identical to that of ceftazidime and cefiderocol, but not to that of other cephalosporins (Chaudry, 2019). Cefiderocol is a relatively new cephalosporin with activity against certain carbapenem-resistant Gram-negative bacilli.

Carbapenems, like meropenem, imipenem/cilastatine(-relebactam) and ertapenem, also structurally differ from cephalosporins with regard to their side chains. Based on side chain similarity, no cross-reactivity of cephalosporins with monobactams or carbapenems would be expected, with one exception: based on identical side chains, cross-reactivity between ceftazidime, cefiderocol and aztreonam is expected.

PICO

P: Patients with a reported allergy (proven or history) for a cephalosporin

I: Patient treated (or skin tested) with a carbapenem or monobactam

C: Patient treated with different antibiotic, not a carbapenem or monobactam

O: Occurrence of an allergic reaction (immediate or delayed)

Evidence summary

<u>RCTs, systematic reviews and meta-analyses</u>

No RCTs or meta-analyses were retrieved on the safety of monobactam administration in patients with a reported allergy for cephalosporins. One systematic review was found by the literature search

CONCEPT

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that reviewed all published data about children and adults who reported to have a clinical history of a suspected IgE-mediated (i.e. immediate type) reaction to a penicillin and/or cephalosporin, and who were subsequently given a carbapenem.(130) Twelve out of 854 patients had a suspected or possible IgE-mediated cephalosporin allergy. Of these 12 patients, 25% (n=3) showed any drug reaction to a carbapenem (imipenem or meropenem). Two of these reactions were non-IgE-mediated and one was possibly IgE-mediated. Four patients had previous reactions with both a penicillin and cephalosporin. Of these patients, one had a suspected IgE-mediated reaction to a carbapenem.(130)

Additional literature overview

A retrospective study evaluated 6 cystic fibrosis patients allergic to ceftazidime. One of them (16.7%) became sensitized to aztreonam upon re-exposure to this drug and developed angioedema and bronchospasm. Concern of cross reactivity existed since then between ceftazidime and aztreonam because of side chain similarity.(156) A prospective study included 98 subjects aged >12 years, with 106 immediate reactions (>75% anaphylaxis) to cephalosporins proven by positive skin tests. All subjects underwent skin tests with aztreonam, imipenem/cilastatin and meropenem and if negative, they were gradually challenged with meropenem i.v., imipenem/cilastatin i.m. and aztreonam i.m. Of these subjects, 3.1% reacted to aztreonam, 2% to imipenem/cilastatin and 1% to meropenem. Seventy-two subjects (73.5%, 95CI% 63.9-81.2%) had negative responses in allergic tests including challenges, with all β-lactams other than cephalosporins. The only patient that had positive skin test result for imipenem and meropenem also had positive results to all other reagents including aztreonam. The IgE antibodies in this patient were probably directed against parts of the beta-lactam ring. For the other 2 subjects that reacted to aztreonam, there was side chain similarity (cefodizime and ceftazidime). The negative predictive value of skin tests with the alternative beta-lactams was very high in this study.(143)

A study was performed in 13 patients with proven cephalosporin allergy (9 had an episode of anaphylaxis and 4 had urticaria). Seven patients underwent a drug provocation test with meropenem, all with negative results.(116) A prospective study tested 10 patients with a positive ST to a cephalosporin (none with a reaction to ceftazidime) to aztreonam using STs and if negative patients were challenged with intramuscular aztreonam. All patients had negative skin tests and tolerated the challenges.(134) Seventy eight patients with a history of a cell-mediated, non-immediate (accelerated or delayed) reaction to a beta-lactam antibiotic of which 2 reported a cephalosporin as the culprit drug (ceftriaxone and cefalexin) were investigated.(157) All patients had a positive patch test to at least 1 antibiotic; 26 patch tests to cephalosporins were positive, none of

CONCEPT

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the patch tests to aztreonam or ceftazidime were positive. All patients who were challenged with aztreonam i.m. (n=65) tolerated the drug.(157) A retrospective monocenter study observed no cross reactivity between cephalosporins and aztreonam or carbapenems in 7 patients with a delayed-type cephalosporin allergy (severe or maculopapular exanthema), tested with patch tests and intradermal tests.(127)

Conclusions

Conclusion	Level of evidence
Ceftazidime, cefiderocol and aztreonam share an identical side chain resulting in a higher risk of cross reactivity.	Moderate
No cross reactivity has been observed between aztreonam and other cephalosporins than ceftazidime and cefiderocol.	Low
The risk of cross reactivity between cephalosporins and carbapenems is considered low when cephalosporin allergy is proven based on skin test (1-2%).	Very low
No reactions to aztreonam or carbapenems have been observed in patients with a suspected delayed-type allergy to cephalosporins.	Low

Other considerations

Aztreonam, currently the only monobactam antibiotic clinically available, shares an identical side chain with ceftazidime and cefiderocol. As aztreonam exposure in patients with a reported ceftazidime allergy leads to an increased risk of an allergic reaction, it is recommended to avoid aztreonam in patients with a suspected ceftazidime allergy. Based on the hypothesis that side chain similarity accounts for the higher risk of allergy to aztreonam in ceftazidime allergic patients, it would be logic to recommended to also avoid aztreonam in case of cefiderocol allergy. In the literature, no cross reactivity has been reported between aztreonam and other cephalosporins than ceftazidime. Theoretically, among the cephalosporins currently available, only ceftazidime and cefiderocol has a side chain identical to that of aztreonam. 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 numbers of studies and included patients are very low, we recommend to avoid aztreonam in patients with a suspected ceftazidime or cefiderocol allergy. This is based on the knowledge that side chains are an important potential epitope with regard to developing an allergy to cephalosporins

CONCEPT

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as well as that the as side chains of the aforementioned cephalosporins and aztreonam are identical.

Recommendations

Recommendations for Immediate type allergy	**Strength**	**Quality of evidence**
42. We suggest that aztreonam can be used in patients with a suspected or proven immediate type allergy to cephalosporins other than ceftazidime or cefiderocol, irrespective of severity and time since index reaction.	Weak	Low
43. We suggest to *avoid* aztreonam in patients with a suspected or proven immediate type ceftazidime or cefiderocol allergy.	Weak	Low
44. We suggest that *any* carbapenem can be used in a clinical setting in patients with suspected or proven, immediate type allergy to a cephalosporin, irrespective of severity or time since index reaction.	Weak	Low

Recommendations for Delayed type allergy	**Strength**	**Quality of evidence**
45. We recommend that aztreonam can be used in patients with a suspected or proven, *non-severe,* delayed type allergy to cephalosporins other than ceftazidime or cefiderocol, irrespective of time since the index reaction.	Strong	Low
46. We suggest to *avoid* aztreonam in patients with a suspected or proven, *non-severe,* delayed type ceftazidime or cefiderocol allergy, when the index reaction occurred ≤ 1 year ago.	Weak	Very low
47. We suggest that aztreonam can be used in patients with a suspected or proven, *non-severe,* delayed type allergy to ceftazidime and/or cefiderocol, when the index reaction occurred > 1 year ago	Weak	Very low
48. We suggest that *any* carbapenem can be used in patients with suspected or proven *non-severe,* delayed type allergy to cephalosporins, irrespective of time since index reaction	Weak	Very low
49. We recommend that in patients with suspected *severe* delayed type allergy (**table 3**) to cephalosporins, all monobactams and carbapenems should be avoided, irrespective of time since the index reaction. In the absence of acceptable alternative antimicrobial treatment, the use of monobactams and carbapenems should be discussed in a multidisciplinary team*.	Strong	GPS

*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 antibiotic should be balanced against each other followed by shared decision making with the patient. If the multidisciplinary team concludes the monobactam or carbapenem may be used in case of a suspected or proven severe delayed type cephalosporin allergy, the monobactam or carbapenem should be administered under prolonged medical supervision.

CONCEPT

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

PICO

P: patients with a reported allergy (proven or history) for a monobactam or carbapenem

I: Patients treated (or skin tested) with a penicillin

C: Patients treated with an alternative antibiotic, not including a carbapenem, monobactam or penicillin

O: Occurrence of an allergic reaction (immediate or delayed)

Evidence summary

RCTs, systematic reviews or meta-analysis

No studies with a randomized design nor systematic reviews or meta-analysis could be identified.

Additional literature overview

There are no studies that evaluate the rate of suspected or proven penicillin allergy in patients who are allergic to a carbapenem. Vice versa, several studies evaluated the rate of carbapenem allergy in patients who are allergic to penicillins. The studies are described in chapter IV and were used by the guideline committee to draw conclusions about the anticipated rate of penicillin allergy in carbapenem allergic patients.

Conclusions

Conclusion	Level of evidence
The overall incidence of carbapenem allergy is low (0.3-3.7%)	Low
There is no or ample evidence regarding cross reactivity with penicillins in patients with an allergy to carbapenems.	n/a

Other considerations

Since there were no studies found on which conclusions and recommendations could be based, the guideline committee used the literature described in chapter IV to formulate guidance.

CONCEPT

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Recommendations

Recommendations	Strength	Quality of evidence
50. Referral for allergy work-up should be considered to prove or disprove suspected immediate type allergy to monobactam or carbapenem in patients.	Strong	GPS
51. We suggest that penicillins can be used in a clinical setting in patients with a suspected or proven immediate type allergy to monobactams or carbapenems and no history of penicillin allergy, irrespective of severity or time since the index reaction.	Weak	Very Low
52. We suggest that penicillins can be used in a clinical setting in patients with a suspected or proven *non-severe*, delayed type allergy to monobactams or carbapenems and no history of penicillin allergy, irrespective of time since the index reaction.	Weak	Very Low
53. We recommend that in patients with suspected *severe* delayed type allergy (**table 3**) to monobactams or carbapenems, all penicillins should be avoided, irrespective of time since the index reaction. In the absence of acceptable alternative antimicrobial treatment, the use of cephalosporins should be discussed in a multidisciplinary team*	Strong	GPS

*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 antibiotic should be balanced against each other followed by shared decision making with the patient. If the multidisciplinary team concludes the penicillin may be used in case of a suspected or proven severe delayed type monobactam or carbapenem allergy, the penicillin should be administered under prolonged medical supervision.

CONCEPT

14. In which patients with an allergy for a monobactam or carbapenem, a cephalosporin can be administered with an acceptable low risk of an allergic reaction?

PICO

P: patients with a reported allergy (proven or history) for a monobactam or carbapenem

I: Patients treated (or skin tested) with a cephalosporin

C: Patients treated with an alternative antibiotic, not including a carbapenem or cephalosporin

O: Occurrence of an allergic reaction (immediate or delayed)

Evidence summary

RCTs, systematic reviews and meta-analyses

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No studies with a randomized design and no meta-analyses could be included for the above-mentioned PICO. A Systemic review by Kula et al. reported that the incidence of cross-sensitivity in patients with a previous proven, possible, or suspected IgE-mediated cephalosporin reaction to carbapenems was 25% (3 out of12 patients) (130)

Additional literature overview

There are no studies that evaluate the rate of cephalosporine hypersensitivity in patients who are allergic to a carbapenem. Vice versa, Romano et al evaluated, in the largest prospective study published so far, the rate of allergic reactions to carbapenems in patients with a confirmed cephalosporine allergy. In this study, of 98 patients with confirmed IgE-mediated hypersensitivity to cephalosporines, only one had positive skin test to both cephalosporines and carbapenems (imipenem and meropenem). The authors point out that this patient had positive skin test results for all other penicillins and aztreonam speculating that this one patient could have reacted to the beta-lactamring shared by all classes of the beta lactam antibiotics. In the remaining 97 patients with a negative skin test a challenge was performed; only one patient did not tolerate the challenge and developed mild urticaria to imipenem after 30 minutes. Taking into account this patient as well as the patient with a positive skin test, the rate of cross-reactivity to imipenem was 2% (2/98 patients). The authors state that a negative skin test is a useful indicator of tolerability with a high negative predictive value.(143) Within a larger study by Al-Ahmad et al, a smaller case series of 13 patients with a proven cephalosporine allergy showed no reactions to meropenem in 7 patients tested with a challenge.(116)

Conclusions

Conclusion	**Level of evidence**
The overall incidence of carbapenem allergy is low (0.3-3.7%)	Very low
There is no or ample evidence regarding cross reactivity with cephalosporins in patients with an allergy to carbapenems.	n/a

Other considerations

Since there were no studies found on which conclusions and recommendations could be based, the guideline committee used the literature described in chapter V, question 12, to formulate guidance.

CONCEPT

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Recommendations

Recommendations	Strength	Quality of evidence
54. We suggest that in patients with a suspected or proven 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	Very low
55. We suggest that in patients with a suspected or proven 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	Very Low
56. We suggest that in patients with a suspected or proven *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	Very low
57. We recommend that in patients with suspected *severe* delayed type allergy (**table 3**) to monobactams or carbapenems, all cephalosporins should be avoided, irrespective of time since the index reaction. In the absence of acceptable alternative antimicrobial treatment, the use of cephalosporins should be discussed in a multidisciplinary team*	Strong	GPS

*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 antibiotic should be balanced against each other followed by shared decision making with the patient. If the multidisciplinary team concludes the cephalosporin may be used in case of a suspected or proven severe delayed type monobactam or carbapenem allergy, the cephalosporins should be administered under prolonged medical supervision

CONCEPT

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VI. Non B-lactam antibiotic allergy

Introduction

Non-beta-lactam antibiotics (NBLA) constitute a large collection of heterogeneous, chemically diverse group of medications. Some NBLA have been used for over 60 years, while new antibiotics are continuously being introduced into clinical use. Numerous studies about allergy to antibiotics focused on reactions to beta-lactams, while studies on specific NBLA, or the group as a whole, are scarce. For this guideline, a literature search was performed regarding the five most frequently prescribed NBLA in Dutch Hospitals according to Nethmap 2019:

- Fluoroquinolons (e.g. ciprofloxacin);
- Aminoglycosides (e.g. gentamicin);
- Imidazol derivatives (e.g. metronidazole);
- Macrolides (e.g. clarithromycin);
- Lincosamides (e.g. clindamycin).

Additionally, descriptive summaries were formulated, without performing a formal literature review, for:

- Glycopeptides (e.g. vancomycin)
- Sulfonamides (e.g. cotrimoxazole)

Hypersensitivity reactions can be mediated by immunologic (allergic) or non-immunologic mechanisms. Due to limited skin testing options, discrimination between immunologic and non-immunologic reactions to NBLA agents is often not possible.(158)

15. Which patients with a non-B-lactam allergy label can be re-exposed to the same antibiotic with an acceptable low risk of an allergic reaction?

PICO

P: Patient with an NBLA allergy label

I: Re-exposure to the culprit NBLA

C: Not applicable

O: Allergic reaction yes/no (immediate and delayed type reaction)

CONCEPT

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16. In which patients with a non-B-lactam antibiotic allergy, a different antibiotic from the same class (of non-beta-lactam antibiotics) can be administered with an acceptable low risk of a severe allergic reaction?

PICO

P: Patients with an NBLA allergy label (one of the 5 most frequently prescribed NBLA)

I: Exposure to a different NBLA within the same class

C: Not applicable

O: Allergic reaction yes/no (immediate and delayed type reaction/cross-reactivity)

Evidence summary

The overall quality of the evidence regarding re-exposure with the same antibiotic or a different antibiotic from the same class after presumed NBLA allergy was low or very low. The literature search yielded no systematic reviews, meta-analyses or randomized controlled trials. The identified relevant studies were small in sample size and consisted mainly of case reports, carrying a high risk of publication bias. Furthermore, the identified studies lacked precision, and often no clear distinction was made regarding immediate and delayed type reactions. Regarding the immediate type reactions it was unclear whether these were IgE mediated or non-IgE mediated. The bulk of the literature evaluated the usefulness of various types of allergy tests for NBLA, which is outside the scope of this guideline.

Among the studies on NBLA allergy, the majority of available data was for either presumed macrolide or fluoroquinolone allergies. Agent-specific recommendations were formulated for these two antibiotic drug classes only. For the other NBLA listed above, descriptive summaries were formulated based on available literature and input from the guideline committee.

Additional literature review of specific NBLAs

Macrolide allergy or hypersensitivity in adults

Macrolides are classified according to the number of carbon atoms in the lactone ring: erythromycin, troleandromycin, roxitromycin, dirithromycin, clarithromycin with 14 members; azithromycin with 15 members and spiramycin, josamycin, midecamycin with 16 members.(159) 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.(159, 160) Benahmed et al. studied suspected allergic reactions to macrolides in 107 adult patients visiting their outpatient ward. The majority of patients had experienced urticaria (41), followed by maculopapular exanthema

CONCEPT

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(MPE, 26), angioedema (16) as well as anaphylaxis (5). All patients underwent a single blinded oral drug provocation test (DPT). Only 8 out of 107 patients (7.5%) had a positive DPT, predominantly after re-exposure to spiramycin and to roxithromycin. Reactions ranged from anaphylaxis (1 patient) to urticaria (3 patients) and MPE (4 patients).(160)

Considering the low percentage of positive drug provocation tests, clinical history alone was not sufficient to ascertain a diagnosis of hypersensitivity to macrolide antibiotics. Seitz et al. also demonstrated that clinical history alone grossly overestimates the number of hypersensitivity reaction to macrolides that will occur after re-exposure.(161) In this study, 125 patients (53 with an immediate type allergic reaction and 72 with a delayed type allergic reactions) were analyzed. Forty seven out of 53 patients with an immediate type allergic reaction received a drug provocation test and all of them had negative results. In the group with delayed type allergic reactions, 66/72 were exposed to a provocation, out of whom 4 developed an allergic reaction (and 1 patient had a positive skin test but was not provoked). All 4 (3.5%) patients developed exanthema upon the DPT. Overall, 109 patients out of 113 patients tolerated the DPT (96.5%). The authors emphasized that false negative results can occur due to missing co-factors such as viral infection or exercise. It is noteworthy that only one patient demonstrated a positive skin prick test, showing the unreliable nature of skin testing for macrolides.

In a smaller study 25 patients with a history of immediate (21; of whom 3 with anaphylaxis) and delayed type (4) allergic reactions to macrolides underwent skin testing followed by a single blind DPT.(162) The most common culprit was clarithromycin in 20 (female) patients followed by azitromycin and spiramycin (each 2 patients) and dirithromycin (1 patient). Skin prick tests with clarithromycin were positive only in 2 patients who had an anaphylactic reaction as index reaction according to their medical history. These patients, along with another 4 patients with a history of anaphylaxis and 6 patients who did not give informed consent, were not challenged with the culprit drug. The remaining 13 patients underwent DPT and all experienced hypersensitivity reactions. The authors conclude that the high rate of a positive response to DPT with culprit drugs can be explained by the appropriate selection of patients through a detailed history. This study also demonstrated data on cross-reactivity between different macrolide: 2 of 20 clarithromycin-allergic patients reacted to dirithromycin and 2 reacted to azithromycin, whereas 1 of 2 azithromycin-allergic patients reacted to clarithromycin. Reactions ranged from erythema to urticaria and pruritus as well as anaphylaxis. The author concluded that performing a DPT is the only reliable method to predict macrolide hypersensitivity as well as to detect cross-reactivity between macrolides.(162) Although macrolides are similar in chemical structure, data supporting cross-reactivity are limited. Shaeer et al. suggest

CONCEPT

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that in case of a severe hypersensitivity reaction, it may be more convenient and safer to change to an alternative class of antibiotics whenever there is an option available.(163)

Macrolide allergy or hypersensitivity in children

There are 4 studies that evaluated macrolide hypersensitivity reactions in children. In a study that evaluated 64 children with histories of clarithromycin hypersensitivity by performing intradermal tests (IDT) and subsequent exposure to the culprit drug, 9 patients had an immediately positive IDT of which 2 patients had an immediate urticarial skin reaction upon clarithromycin provocation. Another 2 patients had a delayed reaction (itchy papulo-erythematosus skin) during prolonged use (5 days) of clarithromycin (also confirmed with a repeated placebo-controlled double blind challenge). Therefore, 4 of 64 children (6%) with a previously described reaction had a positive DPT result.(164)

Another study evaluated 66 patients: 22 with an immediate reaction (anaphylaxis in 3 children: 2 to azithromycin and 1 with reaction to both azithro- and clarithromycin) and 44 with a delayed reaction to clarithromycin and azithromycin.(165) In the group of 22 patients with a reported immediate reaction, 18 patients (2 azithromycin and 16 clarithromycin) with a negative cutaneous test were provoked; none of them reacted to the culprit antibiotic upon drug provocation. The three children with a reported anaphylactic reaction had positive skin testing (either skin prick test or intradermal test). They did not undergo drug provocation tests because parental consent was not obtained. In the group of 44 patients with a reported delayed reaction, 35 patients underwent a DPT, of whom only 1 (2.5%) developed late generalized urticaria upon the last clarithromycin intake. Nine patients refused a DPT because of positive skin testing. The authors conclude that cross-reactivity may occur between different macrolide antibiotics, particularly in case of anaphylaxis. Furthermore it was concluded that azithromycin seemed to be more prone to induce an allergic reaction than clarithromycin, while clarithromycin is more frequently prescribed in children.(165) The authors of another study arrive at the same conclusion showing that azithromycin appeared more 'allergenic' than clarithromycin.(166) They included 90 patients with immediate and delayed type reactions; 77 out of 90 patients completed the allergy work-up with skin testing and drug provocation tests. Fifty-eight children had a reaction to clarithromycin (immediate: 21; delayed: 37) and 19 children reacted to azithromycin (immediate: 6; delayed: 13). Overall, 9 of 58 (15.5%), patients with either immediate or delayed reactions to clarithromycin had a confirmed allergic reaction using either drug provocation testing or skin testing whereas 9 of 19 (47.3%) patients with either immediate of delayed reactions to azithromycin had a confirmed allergic reaction using either drug provocation testing or skin testing.(166) In a study performed in children, 45 patients with both immediate and delayed type reactions to clarithromycin were tested with either a combination of skin testing and drug

CONCEPT

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provocation tests or with drug provocation tests directly.(167) Of 20 patients undergoing both skin testing and provocations, 9 patients had a positive skin test, however none had a confirmed allergic reaction to clarithromycin during DPT. Of 11 patients having a negative skin test, 2 had a positive DPT (urticaria) and the remaining 9 did not develop a reaction during the drug provocation. Twenty-five patients were directly assessed with a drug provocation and none of them had an allergic reaction. This study underscored the limited frequency of persisting clarithromycin reactions with only 2/45 patients (4%) having a confirmed allergic reaction.(167)

Fluoroquinolones

No RCTs were available. For fluoroquinolones 18 clinical studies, 5 small case series and 7 reviews were identified that assessed which patients with a fluoroquinolone allergy label can either be re-exposed to the same antibiotic and/or in which of these patients, a different fluoroquinolone can be administered with an acceptable low risk of a severe allergic reaction.

Although the true prevalence in the general population is unknown, fluoroquinolone allergy is the most frequently reported NBLA allergy. The literature agrees on 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 to other frequently used fluoroquinolones 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.(159) 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.(168) This makes the interpretation of an immediate type allergic reaction and skin tests more difficult. In delayed type allergies, MPE is most frequently reported and mainly related to ciprofloxacin use.(159, 169-171)

Several risk factors were identified for developing a fluoroquinolone allergy. An atopic constitution was reported in up to 24.8% of patients with a history of fluoroquinolone allergy.(172) Both Blanca lopez et al. and Dona et al. concluded that the risk of confirmation of a hypersensitivity reaction to fluoroquinolones is highest if the index reaction involved moxifloxacin versus other fluoroquinolones (OR 3.09 95%CI 1.16-8.23).(173, 174) A previous history of intolerance to other antibiotics, in particular beta lactam allergy, was also associated with a higher risk for an actual allergy to fluoroquinolones (OR:4.571; 95% CI: 0.987–21.171; adjusted OR: 23.654; 95% CI: 1.529–365.853)(169), as well as a confirmed IV contrast allergy, allergy to neuromuscular blocking agents and older age in comparison to penicillin allergy. (170, 175)

CONCEPT

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Regarding cross-reactivity, evidence is very limited and no clinical rules exist for predicting cross-reactivity.(169-171) Several authors have claimed that cross-reactivity within the fluoroquinolone group particularly appears in patients with a history of other immediate type reactions.(176)

Conclusions: NBLA in general

Conclusion	Level of evidence
A detailed history alone is useful, but results in overestimation of NBLA allergy*	Low
There is a lack of reliable in vitro tests** to diagnose NBLA allergy	Low
Definite diagnosis of NBLA allergy can only be based on a drug provocation test	Low
The risk on true allergy depends on the history of the index reaction and the specific type of antibiotic that was used (fluorquinolones > macrolides)	Very low

* the term allergy is used, but as explained in the introduction it may be uncertain if it is a true allergy or hypersensitivity caused by other mechanisms.
** Skin tests (SPT and IDT), BAT, sIgE, LTT

Conclusions: macrolides

Conclusion	Level of evidence
Allergy* to macrolides are uncommon	Low
Allergy to macrolides is mostly non-severe	Very low
Cross-reactivity to marcolides is unlikely, but the risk of cross-reactivity increases if the index reaction was an anaphylactic reaction.	Very low
Skin tests are not useful for diagnosis; drug provocation tests remain the golden standard.	Low

* the term allergy is used, but as explained in the introduction it may be uncertain if it is a true allergy or hypersensitivity caused by other mechanisms.

Conclusions: Fluoroquinolones

Conclusion	Level of evidence
Allergy* to fluoroquinolones is the most frequently reported NBLA allergy. The absolute number of hypersensitivity reactions (HSR) has increased over the years due to increasing usage.	Low
Risk factors for allergy* to fluoroquinolones are: atopic constitution, immediate type index reaction, use of moxifloxacin, history of allergy to BLA, intravenous contrast or neuromuscular blocking agents, e.g. succinylcholine, rocuronium.	Low
Immediate type reactions are more frequently confirmed by drug provocation tests than delayed type reactions to fluoroquinolones.	Low
Within the fluoroquinolone drug class, moxifloxacin is most frequently involved in severe allergic reactions.	Low

CONCEPT

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Levofloxacin and ciprofloxacin are relatively more frequently associated with non-severe reactions.	Low
Skin tests are frequently false positive because of direct mast cell release.	Low
Cross-reactivity between fluoroquinolones seems to occur most frequently in immediate type reactions, but evidence is limited and conflicting.	Low
The rate of cross-reactivity for severe delayed type (e.g., SJS/TEN, AGEP) is unknown.	n/a

* the term allergy is used, but as explained in the introduction it may be uncertain if it is a true allergy or hypersensitivity caused by other mechanisms.

Other considerations

Provided that the data on NBLA allergy is limited, and that the available evidence regarding 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.

Brief summaries with information about aminoglycosides, imidazole deratives, lincosamides, lipoglycopeptides and sulfonamides were constructed:

Aminoglycosides (e.g. gentamicin)

Aminoglycosides are classified in two groups: streptidine group: e.g., streptomycin and desoxystreptamine group: e.g., kanamycin, amikacin, gentamicin, tobramycin, neomycin. Contact dermatitis from topical aminoglycoside is the most frequent clinical manifestation associated with these antibiotics, since neomycin, gentamicin and tobramycin are widely used as cream, ointment, and eye or ear drops.(159) Other cutaneous manifestations like urticaria, maculopapular rash, fixed drug eruption and toxic epidermal necrolysis (TEN) have been reported. Anaphylaxis is very uncommon.(159) Cross-reactions among aminoglycosides neomycin and paromomycin (sharing the desoxystreptamine group) is common, as well as between tobramycin, kanamycin, amikacin, gentamicin (also sharing the desoxystreptamine group) in patients with reported contact dermatitis to one of these aminoglycosides. Cross-reactivity between neomycin and other aminoglycosides with a desoxystreptamine group is around 50%, whereas there is low (1-5%) or no cross-reactivity with streptomycin.(159) Some experts recommend avoidance of all aminoglycosides in neomycin-sensitive patients.

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Imidazol derivatives (e.g. metronidazole)

T cell-mediated ADRs have been reported for nitroimidazoles (e.g., metronidazole, tindazole), with cross-reactivity noted probably due to similar chemical structures. Immediate drug reactions to metronidazole can also occur.(177-179)

Lincosamides (e.g. clindamycin)

Clindamycin is a chemical derivative of lincomycin with activity against aerobic Gram positive and anaerobic Gram negative bacteria. Hypersensitivity reactions are relatively uncommon. The most common presentation is a delayed maculopapular exanthem, usually 7-10 days after initiation of the drug. However, other drug reactions have been reported including anaphylactic shock, urticaria, angioedema, FDE, bullous eruptions, AGEP, Sweet's Syndrome, SJS, and DRESS. Most clindamycin delayed maculopapular exanthems do not require specific therapy and resolve spontaneously with cessation of the drug.(159) In case of an MPE and subsequent need for clindamycin use, a new challenge should be considered. If MPE occurs again treating through or desensitization should be considered.

Glycopeptides (e.g. vancomcyin)

The most common cutaneous adverse event related to vancomycin is the "vancomycin infusion reaction" (formerly referred to as "red man syndrome").(180) Vancomycin infusion reaction is a rate-dependent infusion reaction. It is not considered a true allergic reaction, but is mediated by histamine release from mast cells.(159, 181) This phenomenon can be diminished or ended by reducing the infusion rate of vancomycin. Some experts recommend premedication with an antihistamine.(182) The occurrence of vancomycin infusion reaction does not preclude future repeated administration of vancomycin. In case of reintroduction, administration with prolonged infusion rate is recommended.

True allergic, immediate-type reactions to vancomycin have been described but are considered rare.(183) A cross-allergic reaction between vancomycin and other glycopeptides has been described for teicoplanin but not for other glycopeptides.(184)

Severe delayed cutaneous adverse reactions (SCARs) have also been described in association with vancomycin use, such as drug rash with eosinophilia and systemic symptoms (DRESS), and less commonly IgA bullous dermatosis (LABD), Stevens–Johnson (SJS) syndrome and TEN. These reactions require specific treatment and avoidance of glycopeptides in the future.

CONCEPT

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Sulfonamides (e.g. cotrimoxazole)

Cotrimoxazole, or trimethoprim-sulfamethoxazole (TMP-SMX), has been associated with many side effects, mostly associated with the SMX component and only rarely with TMP. Immediate-type reactions can occur but are less common than other hypersensitivity reactions. Among the delayed type reactions, cutaneous manifestations are most common and consist mainly of maculopapular exanthemas, i.e. “rashes”, of variable intensity. The occurrence of rash appears higher in patients treated with high dose therapy. SCARs have also been described: SJS/TEN occurs more commonly with SMX than DRESS.(159)

Cotrimoxazole remains the standard of care for prevention and treatment of Pneumocystis Jirovecii pneumonia (PCP) in patients with impaired cellular immunity due to HIV or other causes. In the HIV population, a high frequency of hypersensitivity reactions has been described. The majority of patients develop maculopapular exanthema (typically after a median of 9 days), but SCARs have also been described.(185) Because of concerns for SJS/TEN, the safest approach is to discontinue cotrimoxazole in case of a benign rash. However, in some patients continuation of therapy is possible without aggravation of symptoms.(186) “Treating through” can be attempted in patients with a vital indication for cotrimoxazole and a non-severe rash without signs of mucosal or extra-cutaneous symptoms. This approach requires monitoring for evidence of progression or systemic involvement (fever, eosinophilia, lymphadenopathy, hepatitis).

The absence of cross-reactivity between sulfonamide antimicrobials and non-antimicrobials has been shown in a large cohort.(187) Therefore, withholding non-antimicrobial sulfonamides in patients allergic to sulfonamide antimicrobials is no longer standard of care. However, cross-reactivity is presumed for sulfonamide antimicrobials as a class.(188)

Summary

Severe reactions to NBLA, including macrolide or fluoroquinolone allergy, were more likely to be confirmed by DPT. Subsequently, re-exposure to the culprit NBLA in case of severe reactions should be avoided. If, however, the index reaction was mild, an attempt at a renewed treatment can be undertaken.(189) Data regarding cross-reactivity is limited; the available evidence suggests that cross-reactivity within NBLA classes occurs infrequently. In general the risk of cross-reactivity increases if the index reaction was a (severe) anaphylactic reaction. Therefore, in case of a severe reaction, not only the culprit NBLA but all other NBLA within the same class should be avoided.

CONCEPT

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Recommendations

Recommendations	Strength	Quality of evidence
58. We recommend avoiding re-exposure to the culprit NBLA and all other NBLA within the same class when the index reaction was severe.	Strong	GPS
59. 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.	Weak	Low
60. 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*	Strong	GPS

*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.

**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 antibiotic should be balanced against each other followed by shared decision making with the patient.

CONCEPT

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VII In hospital delabeling

Introduction

It is currently very clear that many allergy labels that have previously been generated, are inaccurate or no longer relevant. Inaccurate allergy labels lead to second best antibiotic choices with deleterious effects for the individual patients, hospitals and general health care. In this chapter the guideline committee describes several ways to delabel patients. The focus of this chapter is delabeling in a hospital setting. General practitioners can delabel partially, but re-exposure (or drug provocation) to the culprit antibiotic in the general practitioners offices has not been described so far.

Delabeling can be done in several ways :

1. Direct removal of the label, without provocation.
2. Direct provocation with the culprit antibiotic, without previous skin testing
3. Skin testing, with subsequent drug provocation, usually only of the negatively tested antibiotic.

1. <u>Direct removal of allergy label</u>

Revision of inaccurate allergy registrations can be done in different ways. Chapter II specified which elements in patient history can lead to *direct removal* of the allergy label. This delabeling strategy can also be used in general practice. In short, direct label removal can be performed for the following scenarios (see chapter III, Question 5):

- Re-exposition to the culprit antibiotic without complaints
- Label based positive family history
- Complaints incompatible with an allergic reaction (akin to type A reactions)
- Inability to recall the complaints
- Lack of temporal association between exposure and the onset of symptoms

2. <u>Provocation with or without prior skin testing</u>

Delabeling can be done either by skin testing followed by provocation with the culprit antibiotic or by direct provocation without previous skin testing. Delabeling procedures, albeit often including skin tests, have been investigated in many different clinical settings, including in emergency units, intensive care units, paediatric (emergency) units, cancer units and in pregnancy care settings. Several different medical and paramedical specialists have been involved in delabeling, including infectious diseases specialists, pharmacists and allergists. Such delabeling procedures have been typically performed in low risk patients. In this guideline, low risk patients is defined as those who

CONCEPT

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had had a *non-severe* delayed type reaction more than 1 year ago or *non-severe* immediate type reactions more than 5 years ago.

Scope

The current chapter will focus on delabeling procedures without previous skin testing in (very) low risk patients, referred to as direct provocation test/challenge. The reason for this limitation lies in the fact that delabeling is a part of antibiotic stewardship and as such can be performed in settings where there is no physical presence of an allergist and/or availability of skin prick facilities. Several patient categories should NOT be subjected to further delabeling procedures: in short, patients with severe immediate type reactions less than 5 years ago, severe cutaneous allergy reactions (SCARs) (severe Gell and Coombs type 4 reactions) and/or haematological or other organ involvement (type 2 and 3 Gell and Coombs reactions), as already mentioned elsewhere.

Safety and efficacy data

Several studies have addressed the issue of safety of direct provocation without previous skin testing. A retrospective study of 402 marine recruits was performed, in which they initially performed skin tests in 74 recruits, but due to 74 negative skin tests and time constraints, 328 recruits subsequently underwent a direct drug provocation with a single dose amoxicillin. Five recruits reacted objectively: 4 had isolated cutaneous symptoms and 1 had a globus sensation. All recovered with antihistaminic treatment and epinephrine to avoid progression of symptoms. Thus, in 98,8 % of the recruits the penicillin allergy label could be removed. Only 1.5 % of the recruits who had prior skin testing reacted to the provocation.(88) They later expanded the study group to 708 marine recruits, where 8 patients reacted.(190) In another study, 1205 patients with only Type A adverse drug effects or isolated cutaneous symptoms more than 10 years ago or in childhood were investigated, identifying these patients as having low risk. Two hundred (200) low risk patients were directly exposed to the culprit beta lactam antibiotic, 194 did not react at all and could be delabeled. Six patients reacted, out of whom none had an immediate reaction; 3 patients reacted with late cutaneous symptoms and 3 patients had symptoms possibly related to other causes: fever during concurrent urosepsis (1), isolated vomiting (1) and pruritus without cutaneous lesions (1). Thus 3-6% patients reacted and no specific treatment was needed.(77)

A study that reported on the safety and efficacy of an oral penicillin challenge in cancer patients showed that of 195 patients that carried a penicillin allergy label, 98 had a low risk profile. Low risk was similarly defined as in the previous study. Fifty patients met an exclusion criterion like hemodynamic instability, pregnancy, history of anaphylaxis or angioedema, organ or severe skin involvement and cognitive impairment. Forty-six low risk patients were exposed to a single or

CONCEPT

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prolonged dose of penicillin and followed 5 days after provocation. None of these patients reacted (2 patients refused).(191)

A prospective audit of a pharmacist-led penicillin allergy delabeling ward round delabed 20 of 21 eligible patients (1 declined) by direct provocation, with 1 patient reporting late cutaneous symptoms.(81) A more recent study reported on the efficacy and safety of penicillin delabeling, amongst others comparing direct provocation (when isolated skin symptoms had been present > 20 years ago) with provocation preceded by skin testing, showing that 1 out of 47 patients reacted to the direct provocation with immediate red swollen eyes responding to antihistamine treatment. They also showed that direct provocation was half as expensive (206 dollar) as provocation preceded by skin tests.(192) Li et al. performed two studies.(193, 194) In the first study (2019) they performed a direct provocation test followed by a 3-day amoxicillin challenge in 7 patients reporting a Type A reaction, resulting in no reactions. Furthermore, In 56 of 63 patients reporting a type B reaction, direct drug provocation followed by a 3-day amoxicillin challenge was performed. Of those challenged 56 patients, 21 had a history suggestive of an immediate type reaction (patients with a recent (<10 years) anaphylaxis were excluded) and the remaining 35 had a history compatible with a delayed allergic reaction. Out of all 56 patients reporting a type B reaction, 54 tolerated the prolonged course of amoxicillin and 2 patients (reporting a history of non-immediate reaction) developed mild cutaneous reactions. In this study, skin testing was indeed performed in all patients in order to collect data, however direct provocation testing was performed regardless of the result.(193) The study group continued to enrol 149 patients, both inpatients (41) and outpatients (108), with similar inclusion and exclusion criteria, exposing them to a single dose of amoxicillin, followed by a three day course of amoxicillin. Of included patients, 85 patients reported a history of immediate type reactions, including 40 patients with a history of anaphylaxis more than 10 years ago. One patient developed pruritus after a single dose, 5 patients developed an maculopapular rash and three developed diarrhoea. Patients reacting were similarly divided between the low risk group and the group with an immediate type history.(194) A prospective study investigated 165 patients older than 7 years of age (mean age around 50 years), 6 of whom were excluded due to anaphylaxis (5) or blistering disease with desquamation (1). One hundred fifty nine patients were subjected to a blinded, placebo controlled oral graded challenge, of whom 3 reacted to placebo. The remaining 156 patients completed the graded provocation, 120 patients showed no reaction at all, 16 patients had placebo reactions and 19 patients reacted to the active dose. Of these 19 patients, 4 had genuine allergic reactions (3 mild delayed cutaneous symptoms, no treatment needed in 2, and 1 pruritus resolving after antihistamine treatment) and 15 patients had non -allergic symptoms.(195) Another study was performed in an outpatient setting: 185 patients were older than 5 years (mean age 35 years). All had only skin symptoms and all tolerated a direct provocation with amoxicillin. Thirteen

CONCEPT

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patients older than 5 years underwent skin testing due to extra cutaneous symptoms, 2 of whom tested positive. Of the remaining 159 patients 80 patients underwent skin testing and when negative it was followed by provocation and 79 underwent direct provocation. Both groups were similar and all were considered low risk patients. In the skin testing group, 10 (13%) patients tested positive and were not exposed to amoxicillin provocation, 70 patients tested negative on skin testing and provocation. In the direct provocation group, 3 (4%) patients reacted with skin related symptoms only and 76 underwent a direct provocation without complaints. This study suggests that skin testing a low risk population may in fact overestimate real allergic patients, as positive skin testing is rarely followed by provocation.(79) Similarly to the previous clinical trial, 432 children (<18 years) and 207 adults were investigated in a study with both skin testing and provocation, excluding patients with a history of an immediate reaction. Provocation was performed at an outpatient clinic, followed by a prolonged provocation at home. Thirty patients had a positive skin test, of these 29 tolerated the first day challenge, 1 patient reacted immediately with skin symptoms (urticaria) responding to antihistamine, 1 patient showed a delayed skin reaction (rash without systemic symptoms) and all other patients completed a prolonged provocation. In total, 24 patients reacted to the first day provocation and skin testing did not differentiate between reactors and non-reactors. Additionally, 6 patients reacted to the prolonged provocation. All reactors had skin complaints or abdominal discomfort which resolved without treatment.(196)

Special categories**:**

Pregnancy:

Zhang et al. describes 66 pregnant patients, of whom 28 patients were considered low risk and directly received an oral provocation, while 14 patients were considered as medium risk, and received skin prick testing prior to oral exposure. All 66 patients tolerated the provocation, with no immediate reactions occurring.(197)

Children:

Mill et al. described 818 children who were subjected to a graded provocation, using 10% and subsequently 90% dosing of amoxicillin after 20 minutes. Seven hundred seventy children could tolerate the provocation without complaints: 250 responders of 346 children eligible for annual follow-up showed that 55 children had a full course of amoxicillin, with 6 responding with a delayed reaction and 49 without any problems. Of the 818 children, 17 (2%) had an immediate reaction (consisting of hives only, reacting to antihistamine treatment), and 31 (4%) had a delayed

CONCEPT

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maculopapular reaction (one patient had serum sickness like reaction). Both groups were treated with a cephalosporin without complaints.(28)

Summary

- Direct oral provocation with single or repeated dose without skin testing in low risk patients (*non-severe* delayed type reaction more than 1 year ago or *non-severe* immediate type reactions more than 5 years ago) is an efficient method for delabeling incorrect beta-lactam antibiotic allergy registrations.
- Direct oral provocation with single or repeated dose without skin testing in previously defined low risk patients is a safe method for delabeling incorrect beta-lactam antibiotic allergy registrations.
- Direct provocation without skin testing has to be done in a setting where any immediate type reaction can be treated. A small percentage (1-3%) of patients undergoing direct provocation will react to the provocation.
- Drug provocation and/or skin testing should not be performed in patients with recent anaphylaxis (<5 years ago), severe cutaneous allergy reactions (SCARs) and/or patients with haematological or other organ involvement.

Safety considerations

Direct provocation without previous skin testing needs to be performed by adequately trained medical personnel trained in basic life support and able to recognize and treat anaphylaxis, urticaria, hyperventilation or vagal complaints. Extended life-saving support should be available, usually covered by an acute intervention team (SIT team). Medication necessary on the site of provocation should include injectable adrenaline 0.3-0.5 mg for adults and relevant dosing for children based on weight (auto-injector possible), injectable and oral antihistamines and corticosteroids. Oxygen supply should be accessible. During provocation blood pressure, heart rate, oxygen saturation and clinical symptoms should be monitored. Patients subjected to oral provocation should be well informed and followed by telephone call 3-4 days afterwards to correctly identify complete tolerance.

CONCEPT

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