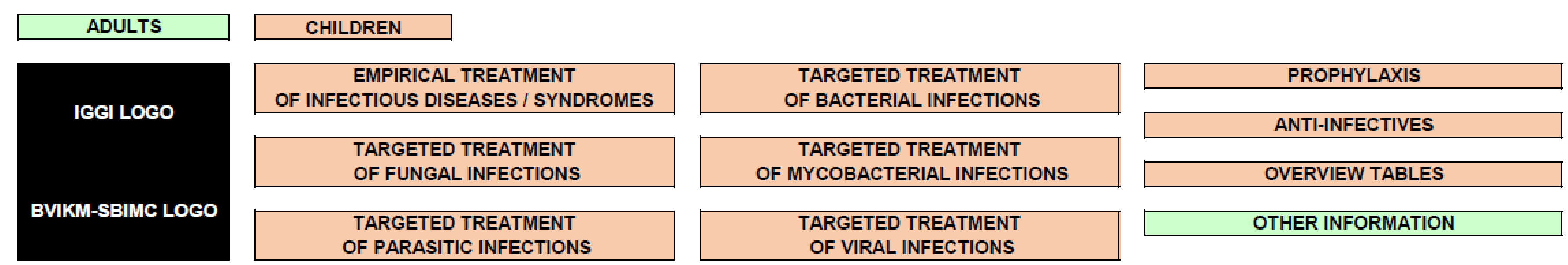
Richtlijn delabeling penicilline-allergie



PENICILLIN ALLERGY

WORKING GROUP COMPOSITION

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APPROACH TO PATIENTS WITH A PENICILLIN ALLERGY LABEL

FLOWCHART FOR PATIENTS WITH AN UNSPECIFIED PENICILLIN ALLERGY LABEL

DID THE PATIENT EXPERIENCE A POSSIBLE ALLERGIC REACTION IN THE PAST?

* Which was what the culprit drug (the specific antibiotic, not the class)?
* Which were the complaints at the time of the reaction?
* When did the reaction occur? A long time ago or recently (exact date)?
* How much time elapsed between the administration of the drug and the start of the reaction (< 1 hour, 1 to 6 hours, > 6 hours) and how many doses were administered to the patient before the reaction started?
* Why was the drug administered?
* How was the reaction treated?
* Was the administration of the drug discontinued and, if not, did the reaction progress?
* How long did the reaction last?

YES → Was there a re-exposure to the culprit drug without any reaction?
- YES[1] → NO PENICILLIN ALLERGY. The patient can be delabeled and treated with a first-choice antibiotic.
- NO → SUSPECTED PENICILLIN ALLERGY

NO → NO PENICILLIN ALLERGY

DID ANY OF THE FOLLOWING REACTIONS OCCUR?

* Anaphylaxis, angio-oedema[2], hypotension, bronchospasm.
* Urticaria occurring after < 1 hour, after the first dose and lasting < 24 hours (1-1-1 criterion).
* Severe cutaneous adverse drug reaction [SCAR (DRESS, SJS/TEN, AGEP) or severe MPE.
* Organ toxicity [hepatic, renal, haematological (cytopenia), other severe organ involvement].
* Reaction requiring emergency treatment or emergency medical attention.

SEVERE REACTION → HIGH-RISK LABEL

How long after the exposure did the reaction occur?

Immediate onset (< 6 hours).

Penicillins must be avoided.
β-lactam antibiotics that can be used.

* Cefazolin (refer to 8)
* Second to fifth generation cephalosporins3 (refer to 8)
* Carbapenems [4]
* Monobactams[5]

The patient must be informed and observed during the administration of the first dose.

Delayed onset (≥ 6 hours up to several days).

All β-lactam antibiotics must be avoided.
Case-by-case decision.

* In urgent need, a carbapenem[4] or a monobactam[5] can be used.
* Some other β-lactam antibiotics can potentially be used (only after consultation with an infectiologist-allergologist).

These patients must be referred for further validation/invalidation of the findings and for the identification of safe alternatives, especially if they:

* experienced severe reactions in the past.
* are labeled with allergy for multiple antibiotic classes.
* are immunocompromised (or expected to be in the future) or female patient with childwish

NON-SEVERE REACTION → LOW-RISK LABEL

β-lactam antibiotics that can be used without additional challenge or precautions.

* Carbapenems.
* Cephalosporins with dissimilar[6] side-chains (cefazolin and second to fifth generation cephalosporins[3]).
* Monobactams.

Use of penicillins if recommended as first choice.

* Not indicated in patients with risk factors (cardiopulmonary instability, pregnancy, …).
* If initial reaction occurred > 10 years ago or during childhood or adolescence: 1-step challenge procedure[7].
* If initial reaction occurred ≤ 10 years ago: 2-step challenge procedure[8].

If the challenge procedures is negative: inform the patient and general practitionner and **delabel** 1

FOOTNOTES

1. In case of an unspecified penicillin allergy label, **tolerated re-exposure** to amoxicillin or penicillin G/V allows for delabeling and for writing down in the file "no penicillin allergy".

2. Angio-oedema.

* Life threatening (orolaryngeal, ...) or generalised angio-oedema should be treated cautiously.
* Isolated, mild angio-oedema (extremities, ...) is less likely to be due to IgE mediated allergy.

3. Cephalosporins.

* Second generation: cefuroxime, cefuroxime axetil.
* Third generation: cefotaxime, ceftazidime, ceftazidime-avibactam, ceftriaxone.
* Fourth generation: cefepime.
* Fifth generation: ceftaroline, ceftolozane-tazobactam.

4. Carbapenems: meropenem, meropenem-vaborbactam.

5. Monobactams: aztreonam.

6. Similar or identical side chains are present in:

* amoxicillin, penicillin G, piperacillin, cefadroxil and cefalexine.
* aztreonam, ceftazidime and cefiderocol.

7. 1-step challenge procedure: administration of a single dose of amoxicillin (500 mg to 1 g) followed by close patient observation for at least 30 minutes (up to 60 minutes). **Ensure emergency medi**

8. 2-step challenge procedure.

* Not for patients with risk factors (cardiopulmonary instability, pregnancy). In hospital setting (medical supervision, **ensure emergency medications is standby**).
* Administration of a first dose of the antibiotic (10% of the therapeutic dose, liquid po formulation if available), followed 30 minutes later by a second dose (remaining 90% of the therapeutic dose)
* Vital parameters must be measured at the start and every 30 minutes until 1 hour after the administration of the entire second dose.
* In case of parenteral administration, the antibiotic must be injected slowly (bolus administration must be avoided).
* Depending on the urgency, this can be converted into a single step administration.
* A single-dose administration can be used for cefazolin for surgical prophylaxis, provided that is is done under careful anesthesiological supervision
* In case of true, confirmed, IgE mediated penicillin allergy: 2-4% risk of cross-reactivity, severe in only <1%.

ALLERGIC CROSS-REACTIONS BETWEEN β-LACTAM ANTIBIOTICS

OVERVIEW

Class	Gen.	Drug	CEFADROXIL	CEPHALEXIN	CEFAZOLIN	CEFUROXIME	CEFUROXIME AXETIL	CEFOTAXIME	CEFTAZIDIME	CEFTAZIDIME-AVIBACTAM	CEFTRIAXONE	CEFEPIME	CEFIDEROCOL	CEFTAROLINE	CEFTOLOZANE-TAZOBACTAM	MEROPENEM	MEROPENEM-VABORBACTAM	AZTREONAM	AMOXICILLIN	AMOXICILLIN-CLAVULANATE	BENZATHINE PENICILLIN G	FLUCLOXACILLIN	PENICILLIN G	PHENETICILLIN	PIPERACILLIN-TAZOBACTAM	TEMOCILLIN
CEPH.	1ST GEN.	CEFADROXIL																								
		CEPHALEXIN																								
		CEFAZOLIN																								
	2ND GEN.	CEFUROXIME					R1	R1'r2	r1"	r1"	R1"	R1"	r1"	R1"	R1"			r1"								
		CEFUROXIME AXETIL				R1		R1'r2	r1"	r1"	R1"	R1"	r1"	R1"	R1"			r1"								
	3RD GEN.	CEFOTAXIME				R1'r2	R1'r2		R1'	R1'	R1	R1	R1'	R1"	r1			R1'								
		CEFTAZIDIME				r1"	r1"	R1'		R1	R1'	R1'	R1	r1	R1"			R1								
		CEFTAZIDIME-AVIBACTAM				r1"	r1"	R1'	R1		R1'	R1'	R1	r1	R1"			R1								
		CEFTRIAXONE				R1"	R1"	R1	R1'	R1'		R1	R1'	R1"	r1			R1'								
	4TH GEN.	CEFEPIME				R1"	R1"	R1	R1'	R1'	R1		R1'r2	R1"	r1			R1'								
	5TH GEN.	CEFIDEROCOL				r1"	r1"	R1'	R1	R1	R1'	R1'r2		r1	R1"			R1								
		CEFTAROLINE				R1"	R1"	R1"	r1	r1	R1"	R1"	r1		R1'			r1								
		CEFTOLOZANE-TAZOBACTAM				r1"	r1"	r1	R1"	R1"	r1	r1	r1	R1"				R1"								
CARB.		MEROPENEM																								
		MEROPENEM-VABORBACTAM																								
MONOB.		AZTREONAM				r1"	r1"	R1'	R1	R1	R1'	R1'	R1	r1	R1"											
PEN.		AMOXICILLIN																								
		AMOXICILLIN-CLAVULANATE																								
		BENZATHINE PENICILLIN G																								
		FLUCLOXACILLIN																								
		PENICILLIN G																								
		PHENETICILLIN																								
		PIPERACILLIN-TAZOBACTAM																								
		TEMOCILLIN																								

Very low risk of cross-reaction.

Low risk of cross-reaction (~~partial similarity of sidechain or common structure~~ dissimilar).

Moderate risk of cross-reaction (similarity of sidechain or common structure)

High risk of cross-reaction (identical R1 sidechain).

All penicillins have a common core structure (thiazoline structure), as do cephalosporins (dihydrothiazine structure). So, cross-reactions between antibiotics belonging to the same class are always possible.

COMMENTS

* Allergy to all β-lactam antibiotics exists, but is exceedingly rare.

Based on Romano et al. Towards a more precise diagnosis of hypersensitivity to beta-lactams - an EAACI position paper. Allergy 2020 https://pubmed.ncbi.nlm.nih.gov/31749148/ PMID 31749148; Chaundhry et al. Cephalosporins: A Focus on Side Chains and β-Lactam Cross-Reactivity. Pharmacy (Basel). 2019 Jul 29;7(3):103. doi: 10.3390/pharmacy7030103