

Occupational allergy to  $\beta$ -lactam antibiotics

**Key words**  
nurse – contact  
urticaria –  
penicillin –  
cephalosporin  
– anaphylaxis

**Background**

Contact urticaria in atopic patients was described by Hannuksela [1], among others, in 1980. It generally appears within 30 min of allergen contact and, in the majority of cases, is restricted to the areas of contact; however, local spread and generalized urticaria in the sense of anaphylaxis are seen. Allergic rhinoconjunctivitis and asthma may also subsequently occur [2]. Von Krogh and Maibach [3] subdivide contact urticaria into four degrees of severity: Grade I and II are restricted to the skin, i. e., localized urticaria (Stage I) and generalized urticaria (Stage II). Extracutaneous and systemic reactions (asthma, rhinitis, conjunctivitis, orolaryngeal symptoms, and gastrointestinal symptoms) are characterized as Grade III, and Grade IV refers to anaphylactic reactions. The prevalence of contact urticaria among healthcare workers is not known. It varies in Europe from 5 % to 10 %, whereas between 1 % and 3 % of the normal population in Russia is believed to be affected [4]. In the case of regular contact, the prevalence of sensitization to drugs increases with working years (6.7 % after 1 year vs. 47 % after 7 years) [5]. The prevalence of occupational allergy to natural rubber latex in the 1990s was 8 %–17 % [6].

Contact urticaria can be triggered by a non-immunological mechanism or an immunoglobulin-E (IgE)-mediated immune response. In the former, vasoactive mediators are released, which cause mast cell degranulation without prior sensitization. The immunological form exhibits an allergic immediate-type reaction that is mediated by specific IgE and which occurs in previously sensitized individuals. A dose dependence has been described for contact urticaria [7].

**Case report**

A 24-year-old nurse employed on a neuropsychiatric unit presented at our clinic. She gave a 2-3 month history of recurrent urticaria on the hands and neck becoming manifest only during work hours. The wheals appeared approximately 10 min after the preparation of intravenous antibiotics, in particular cefotaxime and cefuroxime infusions. During the preceding 2 weeks, she had experienced dyspnea while in the infusion preparation room. The nurse's scope of functions had not changed recently. Treatment with oral antibiotics had always been well tolerated in the past. The most recent pulmonary function test, performed 1 year previously due to allergic rhinoconjunctivitis to grass pollen, showed no evidence of bronchial asthma.

The patient exhibited urticarial dermographism on clinical examination. Since swelling or wheals occurred only during work hours, this finding was borne in mind in the further evaluation, but was not considered a clinical trigger of symptoms.

Graduated allergy testing [8] (**Tab. 1**) showed a strongly positive reaction in the rub test with cefuroxime after 5 min (**Fig. 1**), a finding that was still slightly visible 24 h later. In comparison, the saline control was weakly positive (urticarial).

Subsequent prick testing with penicilloyl (PPL, major determinant of penicillin; Diater, Spain) and cephalosporin (250 mg/ml; Hikma) failed to induce a positive reaction.

Prick-to-prick testing with cephalosporin (500 mg, in paste form; ratiopharm) showed a strongly positive reaction, whereas the control with 0.9 % saline solution was negative.

The intradermal test with minor determinant mixture (MDM; Diater, Spain) was carried out in a 1 : 10 dilution. This induced a moderately positive reaction after 20 min. 40 min later she developed lower-lip swelling and wheals on the dorsum of the contralateral hand, i. e., an early systemic reaction. The patient unequivocally ruled out the possibility that she had rubbed her lip or hand. She was treated with an oral antihistamine (180 mg Fexofenadine).  $\beta$ -Lactam allergy requires a cautious and graduated diagnostic approach, as shown in detail in **Tab. 1**.

Due to the pronounced symptoms and unequivocal test results, no further diagnostic steps involving oral provocation with cephalosporins and/or penicillin were undertaken.

Tryptase was within the normal range at 2.71  $\mu$ g/l. Specific IgE (in CAP fluorescence enzyme immunoassay, CAP-FEIA) to amoxicillin, penicillin derivatives, and natural rubber latex could not be detected.

**Abbreviations**

OC	Occupational disease
CAP-FEIA	CAP-fluorescence enzyme immunoassay
IgE	Immunoglobulin E
MDM	Minor determinant mixture
NaCl	Sodium chloride
PPL	Penicilloyl

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**Tab. 1: Graduated allergy diagnostics**

Open patch test	Substance	Concentration	Vehicle	20 min	
	Cephazolin Na	0.1 %	NaCl	negative	
	Cephalexin 500 mg, suspension	pure		negative	
	Cefuroxime 100 mg/ml	pure	Aqua	negative	
	Cefotaxime 100 mg/ml	pure	Aqua	negative	
Rub test	Substance	Concentration	Vehicle	20 min	24 h
	Cephazolin Na	0.1 %	NaCl	negative	
	Cephalexin 500 mg, suspension	pure		negative	
	Cefuroxime 100 mg/ml	pure	Aqua	strongly positive reaction after 5 min	erythema, discret swelling
Prick test	Substance	Concentration	Vehicle	15 min	
	PPL (Diater)	pure		erythema	
	Ampicillin	0.1 %	NaCl	negative	
	Penicillin G 1,000 E/ml	pure		negative	
	MDM (Diater)	pure		negative	
	Cephazolin Na	0.1 %	NaCl	erythema	
Intradermal test	Substance	Concentration	Vehicle	20 min	30 min
	PPL (Diater)	pure		negative	negative
	Ampicillin	0.1 %	NaCl	negative	negative
	Penicillin G 1,000 E/ml	pure		negative	negative
	MDM (Diater)	1 : 10 diluted		moderately positive	lower-lip swelling, wheals on dorsum of contralateral hand
	Cephazolin Na	0.01 %	NaCl	negative	
	Cephazolin Na	0.1 %	NaCl	negative	
Prick-to-prick	Substance	Concentration	Vehicle	15 min	
	Cephalexin 500 mg, suspension	pure		strongly positive	
Controls					
Rub test	Substance	Concentration	Vehicle	20 min	
	NaCl	pure		small wheal after 10 min	
Prick test	Substance	Concentration	Vehicle	15 min	
	NaCl	0.9 %	Aqua	weakly positive	
	Histamine 1 : 100	pure		moderately positive	
Intradermal test	Substance	Concentration	Vehicle	20 min	
	NaCl	0.9 %	Aqua	negative	
	Histamine 1 : 10,000	pure		strongly positive	
<p>Graduated diagnostics: initiated with the PPL prick test, followed by the intradermal PPL test in the case of a negative reaction. This is followed by prick testing with ampicillin, penicillin G, MDM 1:10, as well as pure MDM in the case of a negative reaction. The next step is intradermal testing with ampicillin, penicillin G, MDM 1:10, as well as pure MDM in the case of a negative reaction. Since, based on the history, cephalosporins were considered causative in this particular case, an open epicutaneous test with 0.1% cephazolin was performed as a first step, followed by a rub test with cephazolin. Since both were negative, prick testing and intradermal testing with cephazolin (0.01% and 0.1%) followed. A patch test with cephalexin (500 mg, in paste form) was then performed, followed by a friction test with cephalexin. Since both were negative, a cephalexin prick-to-prick test was carried out and showed a distinctly positive reaction. At 1 week later, an open patch test with cefuroxime (750 mg) was performed, yielding a negative result. This was therefore followed by a rub test that induced a positive reaction, which was still visible 24 h later. Further testing with cephalosporins was dispensed with. Due to the case history, skin testing was performed after gaining intravenous access.</p>					
<p><i>NaCl, sodium chloride; MDM, minor determinant mixture; PPL, Penicilloyl</i></p>					



**Fig. 1:** Rub test with cefuroxime (proximal forearm). A strongly positive reaction, which remained slightly visible after 24 h, was observed. In comparison the saline control (distal forearm) was weakly positive (urticarial).

A diagnosis of occupational contact urticaria caused by  $\beta$ -lactam antibiotics complicated by dermatographism was made.

The patient made a renewed attempt to work on treatment with 5 mg desloratadine while at the same time avoiding  $\beta$ -lactam antibiotics. Since the patient's symptoms continued to worsen, an occupational disease (OD) was stated (BK 5101).

### Conclusion

In a prospective study by Cetinkaya et al. [9] on the prevalence of sensitization to antibiotics among medical personnel, 12% of the nurses investigated exhibited sensitization to penicillin despite no previous history of penicillin allergy. Increased numbers of sensitization to penicillin, reaching their height between 1981 and 1985, were observed as a result of topical use of benzylpenicillin by Polish nurses [10]. In the case of negative skin tests to penicillin (including minor and major allergens), immediate-type allergic reactions, though generally mild and self-limiting, are seen

in 1%–3% of cases upon systemic administration. To our knowledge, severe anaphylaxis following negative skin testing has not been described to date. On the other hand, in the case of positive skin testing, an immediate-type allergic reaction is seen in 40%–100% of cases [11]. Sensitization to penicilloyl (major determinant) suggests cross-reactivity with all  $\beta$ -lactam antibiotics. The risk of cross-reactions between penicillin and cephalosporins differs for the individual cephalosporin generations: 5%–16.5% for the first generation, 4% for the second, and 1%–3% for the third and fourth generations [12].

The case of a nurse who complained of facial swelling and eczema of the fingers on contact with penicillin was reported in the 1950s. These symptoms appeared even upon contact with a patient receiving penicillin treatment (so-called derivative allergy, i.e., an allergy mediated by an intermediate carrier). Conjunctival provocation with sweat from one such patient produced conjunctival injection, foreign body sensation, and pruritus. No symptoms were observed in controls [13].

The increased rate of sensitization (in particular to natural rubber latex and drugs) among health-care personnel is due to regular contact with the relevant allergens. The prevalence of occupational allergies to natural rubber latex is 8%–17%; asthma due in particular to occupational allergy to natural rubber latex is reported to be 2.5%–6% [6].

Antibiotics are generally in powder form and contained in glass vials. When preparing infusions for patients, the vacuum in the bottle is released and the powder brought into solution. The antibiotic solution may escape due to excess pressure and come into contact with the skin of the individual preparing the infusion. If the skin barrier is damaged due to fissures or dry skin, the antibiotic reaches the dermis and may cause sensitization [14]. Epicutaneous sensitization appears to be possible even in the absence of skin damage [15], meaning that, ultimately, a mechanical barrier, e.g., waterproof protective gloves, is essential.

This case report illustrates the central importance of prevention in high-risk occupations. Instruction on skin protection measures is essential in order to counteract sensitization in a timely manner [14]. Such measures include not only bland emollients, and protective gloves, but also surgical masks in the case of contact with dust and aerosols (preparation of medications). A closed dust and fume extraction system is the most effective method of preventing contact with medications.

However, not only individuals with high-risk occupations are at greater risk of sensitization to antibiotics; given the increase in sensitization following topical  $\beta$ -lactam antibiotic application,

antibiotic treatment should not be administered topically.

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#### **Conflict of interest**

The authors state that there are no conflicts of interest.

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