

Occupational allergic contact dermatitis caused by antibiotics in healthcare workers – relationship with non-immediate drug eruptions

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Summary

Background. Occupational allergic contact dermatitis (ACD) in healthcare workers (HCWs) is common, but systemic antibiotics are rarely reported as the cause.

Objectives. Characterize occupational ACD by handling systemic antibiotics.

Method. A retrospective analysis was performed of ACD caused by systemic antibiotics among HCWs patch tested between 2010 and 2016 with a series of systemic antibiotics.

Results. We studied 4 female nurses aged 28–47 years who developed ACD while working in surgical departments. They had eczema of the hands, and forearms or face, and 1 patient, who previously had exanthema caused by flucloxacillin, also developed a generalized rash following airborne exposure to systemic antibiotics. Patch tests showed positive reactions to ampicillin and cefazolin in 1 patient, to cefotaxime and ceftriaxone in 2 patients, and to several penicillins in another patient. Three patients also reacted to rubber allergens, fragrances, and/or preservatives. All patients admitted having direct and sporadic exposure to systemic antibiotic solutions. Avoidance resulted in a significant improvement of ACD, but 1 patient had to change job.

Conclusions. Occupational ACD caused by β -lactam antibiotics, particularly cephalosporins, is significant in HCWs. Cross-reactions between β -lactams are similar to those described in non-immediate drug eruptions. A relationship between systemic delayed drug hypersensitivity and ACD, as observed in 1 case, suggests that patients should avoid future use of the antibiotic to which they are sensitized.

Key words: allergic contact dermatitis; β -lactam; cephalosporins; healthcare workers; non-immediate drug eruptions; occupational; patch test.

Occupational skin diseases, namely allergic contact dermatitis (ACD), are among the most common occupational diseases (1, 2), although they may be underreported in many countries (1–3). Healthcare workers (HCWs) are

most frequently affected (4), with a high prevalence of contact dermatitis, mainly hand eczema, ranging from 17% to 70% (5–7). Occupational risk factors include frequent hand washing, prolonged glove use, and exposure to disinfectants and drugs, which all may be responsible for irritant contact dermatitis or ACD (8, 9), or immediate reactions, such as contact urticaria/protein contact dermatitis (8, 10, 11). Occupational ACD caused by systemically administered drugs has been occasionally reported in HCWs, mostly caused by systemic antibiotics such as penicillins, cephalosporins, and aminoglycosides, but does not appear to be frequent (12–15). We report 4 cases related to the handling of intravenous antibiotics,

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and discuss the relationships with reactions on systemic exposure to the antibiotics.

Methods

We performed a retrospective analysis of clinical data and patch test results from HCWs patch tested in the Department of Dermatology of Coimbra Hospital and University Centre (CHUC) between 2010 and 2016, and analysed those with positive reactions to systemic antibiotics. All patients were tested with the European baseline series, the preservative and excipient series, and additional series (Chemotechnique Diagnostics, Vellinge, Sweden or Trolab® allergens, Almirall, Reinbek, Germany), according to exposure. Eight nurses involved in the preparation of drugs for intravenous administration and 4 physicians were also patch tested with a series of antibiotics regularly used in the study of drug eruptions, with no false-positive results and no cases of active sensitization (16), and with other drugs that these workers handled most frequently. Systemic antibiotics and other intravenous drugs that were not commercialized by Chemotechnique Diagnostics were prepared in-house from intravenous powder to achieve a final concentration of the active drug of 10% pet., as recommended for the study of non-immediate drug eruptions (17). Allergens were applied on the back in Finn Chambers® (Epitest, Almirall) or IQ Chambers® (Chemotechnique), fixed with Mefix® adhesive tape for 48 h. Readings were performed on day (D) 2–3 and D4–7, according to ESCD guidelines (18). Only + or stronger reactions were considered to be allergic. Occasionally, semi-open testing was additionally performed with rinse-off products from the workplace.

Results

Between 2010 and 2016, among a total of 1858 patch tested patients (503 males and 1356 females), we studied 125 HCWs (11 males and 114 females) with contact dermatitis, mostly nurses (n = 56) with hand eczema. We observed at least one positive patch test reaction in 90 (72%) of the HCWs, with occupational relevance in 47 (52.2%), as previously reported (13). Among them, there were 4 nurses with ACD caused by systemic antibiotics, described here in detail (Table 1).

Patient 1, with a long history of allergic rhinitis, and who had been working as a nurse for 11 years, suffered from bilateral hand eczema for 2 years, with aggravation at work, namely, at the main hospital operating theatre. She had to inject patients with antibiotics during surgery

or in the immediate preoperative or postoperative period, and she mentioned symptoms after using different types of latex gloves. Chronic eczema of the dorsa of the hands, which was more intense on the right hand, was associated with lesions on the fingers, particularly the interdigital webs. Apart from cobalt chloride 1% pet. (+), sodium tetrachloropalladate 3% pet. (+), thiuram mix 1% (++), carba mix 3% pet. (++), and pieces of several gloves used (++), PTs showed positive reactions to ampicillin 10% pet. (?+/+) and cefazolin 10% pet. (+/+)(Table 2).

Patient 2 developed lesions while working in the orthopaedics ward, and the lesions persisted when she moved into internal medicine. She had chronic plaques of eczema on the dorsa of the hands (Fig. 1a) and often also on the forearms, lips, and face (Fig. 1b), which she related to the preparation of intravenous drugs. She reported an episode of urticaria and facial oedema 10 years ago she attributed to direct skin contact with an intravenous preparation of piperacillin/tazobactam, but no allergy testing was performed then. Patch testing showed positive reactions to ceftriaxone 10% pet. (++/+++), cefotaxime 10% pet. (+/+), and cefoxitin 10% pet. (?+/+) (Fig. 2a), as well as reactivity to nickel, methylisothiazolinone, ethylenediamine, colophonium, and abietic acid. Patch testing with piperacillin/tazobactam gave a negative result. This patient also had weak positive reactions to omeprazole and pantoprazole (Table 2).

Patient 3 worked as a nurse for 27 years, most recently in the department of cardiac surgery, where she developed hand eczema 3 years ago. Initial lesions were localized mainly on the fingers, but more recently also on the palms and forearms (Fig. 1c). She reacted on patch testing to rubber additives and fragrances (Table 2), and also to cefotaxime 10% pet. (++) and ceftriaxone 10% pet. (++) (Fig. 2b).

The youngest patient developed eczema in 2015, after 2 years of working as a nurse in a general surgery ward. Lesions were initially localized on the dorsa of the hands and face, and were triggered by the preparation of intravenous antibiotics. More recently, eczema of the exposed areas developed whenever she entered an area where other nurses were preparing antibiotics. Moreover, she had two episodes of airborne eczema followed, within 12–24 h, by a maculopapular rash that took a few days to resolve with the use of oral steroids. This patient, who had been taking carbamazepine for epilepsy for 8 years, developed drug reaction with eosinophilia and systemic symptoms (DRESS) in 2014, beginning on the third day of treatment with flucloxacillin for an oropharynx infection. She stopped taking flucloxacillin immediately, and started to use oral steroids, but cutaneous lesions and systemic symptoms (fever and hepatic cytolysis)

Table 1. Characterization of the 4 patients (nurses) with allergic contact dermatitis (ACD) caused by systemic antibiotics

	Patient 1	Patient 2	Patient 3	Patient 4
Year of diagnosis	2012	2012	2014	2016
Age (years)	31	38	47	28
Years of experience	11	18	27	2
Job	Operating theatre	Orthopaedics	Cardiac surgery	General surgery
Atopic history	Allergic rhinitis	No	Allergic conjunctivitis	No
Site of ACD	Hands (dorsa), fingers	Hands (dorsa), forearms, face	Hands (palms), forearms	Hands, face, exanthema
Duration of symptoms	2 years	2 years	3 years	1 year

Table 2. Positive patch test reactions to systemic antibiotics tested 10% pet. with readings on day (D) 2/3 and D4-D7, and positive reactions to other allergens

	Patient 1	Patient 2	Patient 3	Patient 4
Antibiotics for systemic use	Cefazolin +/+ Ampicillin? +/+	Ceftriaxone ++/+++ Cefotaxime +/+ Cefoxitin? +/+	Ceftriaxone ++/++ Cefotaxime ++/++	Dicloxacillin ++/+++ Flucloxacillin ++/+++ Penicillin G ++/+++ Amoxicillin ++/+ Piperacillin/tazobactam +/+
Other allergens	Thiuram mix ++ Carba mix ++ 1,3-Diphenylguanide ++ Glove pieces ++ Cobalt + Palladium + Lifoscrub™ ++* Softaskin™ ++*	Methylisothiazolinone ++ Colophonium ++ Abietic acid ++ Ethylenediamine ++ Nickel ++ Pantoprazole? +/+ Omeprazole? +/+	Thiuram mix ++ Fragrance mix I ++ Hydroxycitronellal ++, geraniol ++ Fragrance mix II ++ HICC ++ <i>Myroxylon pereirae</i> ++	

HICC, hydroxyisohexyl 3-cyclohexene carboxaldehyde.

*Open test.

only began to improve when she stopped taking carbamazepine after 7 days. Patch tests performed in 2014 gave negative results with carbamazepine, which was later reintroduced with no further problems, and positive reactions to flucloxacillin (++), dicloxacillin (++), penicillin G (++), and amoxicillin (+), all 10% pet. In 2016, owing to the frequent reactivation of lesions at work, patch tests with systemic antibiotics were repeated, and showed, as well as positive reactions to flucloxacillin, dicloxacillin, penicillin G, and amoxicillin, a positive reaction to piperacillin/tazobactam (+). Moreover, on D2 of patch testing, the patient developed a minor exanthema with no systemic symptoms that resolved without the use of systemic steroids. This patient has remained free of skin lesions after moving to a primary healthcare facility where she does not handle intravenous systemic antibiotics. All other patients reported significant improvement of their skin lesions after avoiding the allergens, namely the preparation of the culprit systemic antibiotics.

Discussion

HCWs are frequently affected by hand eczema, either irritant contact dermatitis or ACD, mostly caused by

gloves, disinfectants, and cleansing solutions (3–8, 13, 19, 20), as observed in 3 of our cases, and less frequently caused by the handling of drugs for topical, oral or systemic use (12–15). Systemic antibiotics have been reported as a cause of ACD in HCWs, and, among them, β -lactams constitute one of the main causes (12–15). Cephalosporins, which gave positive test results in 3 nurses, represent a particular problem, with several cases of ACD (13, 21–24), and immediate contact reactions in HCWs exposed to these systemic antibiotics (15), having been reported.

ACD affected 4 nurses working in surgical departments, in which systemic administration of antibiotics is frequent, and spilling of the systemic antibiotic solutions may occur during the preparation of the syringe for administration. Involvement of the dorsa of the hands and interdigital webs suggests possible exposure during this process, as patients reported occasional handling without gloves – owing to intolerance to gloves in 2 of our patients. Moreover, thin latex gloves may be permeable to these allergens, as is the case with many small chemicals that induce ACD (3, 25, 26). Involvement of the forearms and face can be caused by hand transport



Fig. 1. Eczema of (a, b) the dorsa of the hands, forearms and chin in patient 2, and (c) of the palms and interdigital folds in patient 3.

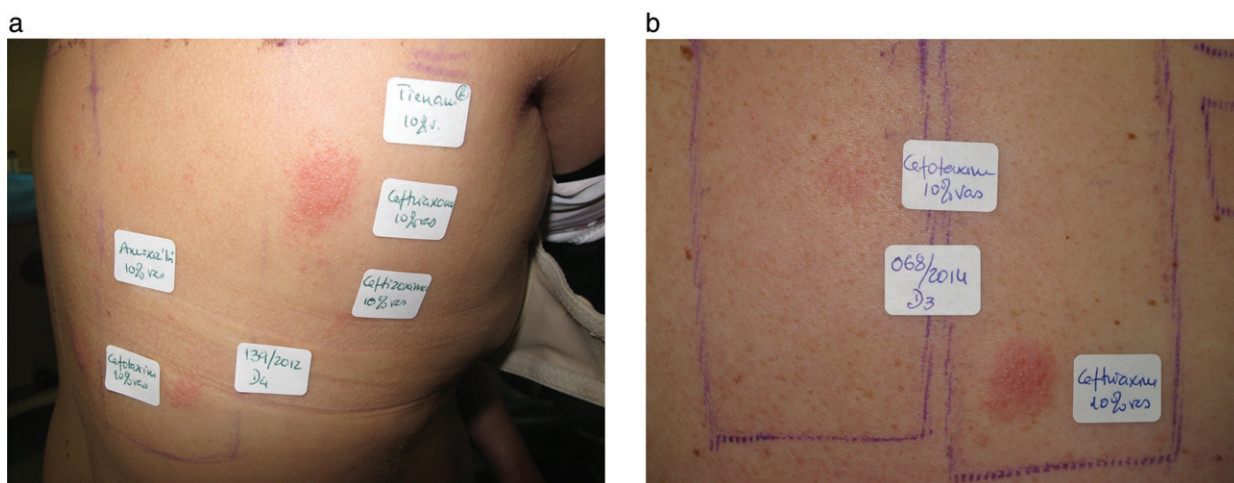


Fig. 2. Positive patch test reactions to systemic antibiotics. (a) Patient 2 with positive reactions on day 4 to ceftriaxone 10% pet. (+++), cefotaxime 10% pet. (++), and cefoxitin 10% pet. (?). (b) Patient 3 with positive reactions to ceftriaxone 10% pet. (++) and cefotaxime 10% pet. (+) on day 3.

or contamination of working surfaces, but airborne exposure can also occur (14, 27). One of the patients also reacted, although weakly, to proton pump inhibitors, which are frequently responsible for occupational ACD in HCWs (12–15). In 3 patients, reactivity to other allergens (rubber chemicals, methylisothiazolinone, and fragrances) found in their occupational environments or in their homes may also have contributed to dermatitis or facilitated sensitization to systemic antibiotics, but the dermatitis improved significantly on avoidance of exposure to the culprit systemic antibiotic(s) (1, 9, 28).

In patient 4, previous systemic exposure to flucloxacillin in the context of a non-immediate drug eruption fulfilling the criteria for DRESS (29) was very probably the source of sensitization to β -lactam antibiotics. Patch tests gave positive reactions as early as

2014, and, as reported for non-immediate drug eruptions (30), reactivity was maintained for 2 years thereafter, with additional reaction to piperacillin/tazobactam. By analogy with systemic allergic dermatitis, where patients sensitized through the skin develop lesions when systemically exposed to the same chemical or a similar molecule, this suggests that patients sensitized systemically may also develop lesions on contact exposure to the same chemical. This is indeed the basis for the reactivity of patch testing with drugs in the study of non-immediate cutaneous drug eruptions (10, 11, 16). Even though we did not perform oral provocation tests in the other 3 nurses, and we found no report of a drug eruption in previous cases of occupational ACD caused by systemic antibiotics, we recommended that they should not use the antibiotic to which they were sensitized.

As reported in patients with ACD, and similarly in those with non-immediate cutaneous drug eruptions, there is frequent cross-reactivity among penicillins (31–33), as in case 4. Cross-reactivity among cephalosporins also occurs both in non-immediate cutaneous drug eruptions (33) and ACD (21–24), particularly between cephalosporins that share identical R1 side chains, such as the two third-generation cephalosporins (ceftriaxone and cefotaxime) (32), as observed in 2 of our patients. The rate of cross-reactivity between penicillins and cephalosporins in non-immediate reactions is much lower (2.8–31.2%), and occurs especially with aminocephalosporins (32). In the present study, in the only case with a reaction to both classes of systemic antibiotic, this occurred between ampicillin and cefazolin, a first-generation cephalosporin that does not share identical side chains, suggesting the possibility of concomitant sensitivities (34). As reported by Romano et al. in non-immediate drug eruptions, we observed no cross-reactions with carbapenems, imipenem/cilastatin, or meropenem (35).

ACD and delayed exanthema caused by systemic exposure to systemic antibiotics, although apparently

different on clinical grounds, share many aspects, namely pathophysiological mechanisms (drug-specific effector T cells), reactivity in patch testing, cross-reactivity, and possible triggering either by cutaneous or by systemic exposure (10, 11). There is therefore a strong link between ACD and non-immediate cutaneous drug hypersensitivity.

Conclusion

ACD in HCWs caused by systemic drugs, particularly systemic antibiotics, is mostly related to incorrect handling of drugs, and presents mainly as hand eczema, but airborne dermatitis and generalized exanthema also occur. Similarly to what is found in systemic allergic dermatitis, we observed a case of a non-immediate drug eruption caused by flucloxacillin, later followed by occupational ACD when the patient was exposed to the same systemic antibiotic. Avoiding unnecessary occupational risks and limiting sensitization to systemic antibiotics is important to prevent eczema and eventual drug eruptions when these patients later use these or similar systemic antibiotics.

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