

Review

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Hypersensitivity to non- β -lactam antibiotics

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Key words

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Abstract. Most allergic reactions to antibiotics are caused by β -lactam antibiotics; however non- β -lactam antibiotics are also capable of causing both immediate allergic reactions as well as late-type reactions to these drugs. This is especially true for fluoroquinolones and sulfonamides. Of these, the combination of sulfamethoxazole with trimethoprim (Cotrimoxazol, e.g., Bactrim) is most important. However, there are certain types of reactions to non- β -lactam antibiotics that are not associated with β -lactam antibiotics. These include photosensitivity to sulfonamides, tetracyclines, and fluoroquinolones as well as different patterns of drug metabolism and associations with HLA alleles that may influence their prevalence. This review is focused on recent findings regarding the pathogenesis of allergic reactions to non- β -lactam antibiotics.

mediated by specific IgE immunoglobulins in most – if not all – cases typically occurring within seconds to minutes following oral, parenteral, or even topical drug exposure. Most often, they occur within 1 hour after exposure. Sometimes they can develop after several hours – but rarely after more than 6 hours. One explanation for the latter may be delayed drug absorption. In contrast, delayed-type reactions can occur days after drug administration. More than 90% of these cutaneous reactions appear as maculopapular or morbilliform eruptions, are not life-threatening, and usually resolve spontaneously with or without topical therapy once the offending drug has been withdrawn. However, 5 – 10% of these reactions may result in more severe cutaneous adverse reactions (SCARs) such as bullous drug eruptions as well as fixed or multiple fixed drug eruptions, Stevens-Johnson Syndrome (SJS), toxic epidermal necrolysis (TEN) but also acute generalized exanthematous pustulosis (AGEP) and drug rash with eosinophilia and systemic symptoms (DRESS) [3]. Among these, TEN is the most severe type of delayed drug reaction, but fortunately it is quite rare with an incidence of 1 – 2/million people/year although up to one-third of these patients will not survive. The medical management of these allergic reactions does not differ significantly from corresponding reactions to β -lactam

Introduction

Compared to other drug families, antibiotics frequently trigger allergic drug reactions, and in particular β -lactam antibiotics are the major cause of these reactions [3]. This class of antibiotics is widely prescribed for the treatment of numerous infectious diseases. However, non- β -lactam antibiotics can also trigger immediate allergic reactions ranging from urticaria to anaphylactic shock as well as delayed-type reactions [21, 36]. Immediate-type allergic reactions are

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antibiotics. Diagnostic skin testing methods for immediate reactions include both prick tests and intracutaneous tests also known as intradermal tests, whereas in late reactions, patch testing is the preferred diagnostic procedure. The diagnosis of immediate reactions typically consists of obtaining a careful medication history along with the tests described above. Additionally, the determination of specific IgE antibodies and the basophil activation test can be used. The latter is a functional assay that measures the degree of degranulation following stimulation with allergens or controls by flow cytometry. In selected cases, a drug provocation test may be appropriate [26]. For delayed hypersensitivity reactions, the diagnostic methods also include a careful history along with the patch or intracutaneous test with delayed reading as well as in vitro tests including the lymphocyte transformation test or the ELISpot assay and, in selected cases, a drug provocation test [3, 31]. These procedures are performed only in patients with maculopapular exanthems and are in parts contraindicated in patients with SCARs. However, it is important to remember that doses of suspected drugs used for provocation tests are much less well-defined than such testing with β -lactam antibiotics, in particular with regard to penicillin allergy [4, 22, 29].

As mentioned above, there are unique reactions to non- β -lactam antibiotics that are not seen in patients with β -lactam antibiotics, including phototoxic or photoallergic reactions to various antibiotics including sulfonamides, tetracyclines, and fluoroquinolones [18]. The pathophysiologic mechanism of allergic drug reactions to sulfonamides involves metabolic activation by cytochrome P450 isoenzymes (CYP) into highly reactive sensitizing derivatives that can bind to macromolecules [27, 32]. In contrast, β -lactam antibiotics are for the most part not substrates for CYPs or other oxidizing enzymes [27]. Anaphylactic reactions to fluoroquinolones can be triggered by IgE-dependent pathways and by direct activation of mast cells [8, 25].

ics can trigger both phototoxic and photoallergic reactions [18]. Clinically, these reactions are characterized by the acute onset of erythema and/or an eczematous dermatitis after skin exposure to solar ultraviolet radiation (UVR) on sun-exposed body areas. Therefore, mainly the “sun terraces” of the skin including the back of the hands, the central face, the lower lip, the ears, and the balding scalp are typically affected in these reactions. In contrast, certain anatomic areas such as the upper eyelids are typically spared due to the photoprotective effects of the retraction of the open eyelids. Currently, it is the fluoroquinolones that are the major non- β -lactam antibiotics that cause these types of adverse reactions [18].

The mechanisms involved in these reactions are complex [11]. It is the combination of administering a drug that has an absorption spectrum between 320 and 400 nm (the ultraviolet A (UVA) range) followed by exposure to solar UVR that triggers the reaction [15, 17]. Photon absorption by the drug drives the generation of reactive oxygen species (ROS) and/or highly reactive drug metabolites (Figure 1). These chemically reactive drugs or their metabolites can bind to macromolecules to form a complete allergen after interacting with immunocompetent cells such as antigen-presenting dendritic cells and T lymphocytes and in the process induce a photoallergic reaction that is typically an eczematous dermatitis. Both ROS and the photoexcited drug may also have a non-immunogenic direct cytotoxic effect that induces a phototoxic reaction that manifests as erythema resembling an exaggerated sunburn [10]. The ultimate risk of developing these reactions is dependent upon drug concentration in the skin and the intensity of exposure to solar UVR. At the same time, the skin possesses a multitude of enzymatic and non-enzymatic photoprotective mechanisms to minimize phototoxic and photoallergic reactions. The enzymatic antioxidants include catalases, glutathione peroxidase, superoxide dismutase, and reductases, among others [14]. The non-enzymatic photoprotective agents include antioxidants such as glutathione, α -tocopherol, ascorbate and β -carotene, among others.

The suspicion of a photosensitivity is based upon the patient's history of exposure. The standard procedures for confirming the diagnosis are known as the minimum

Photosensitivity

Unlike β -lactam antibiotics, sulfonamides, fluoroquinolones, and tetracycline antibiot-

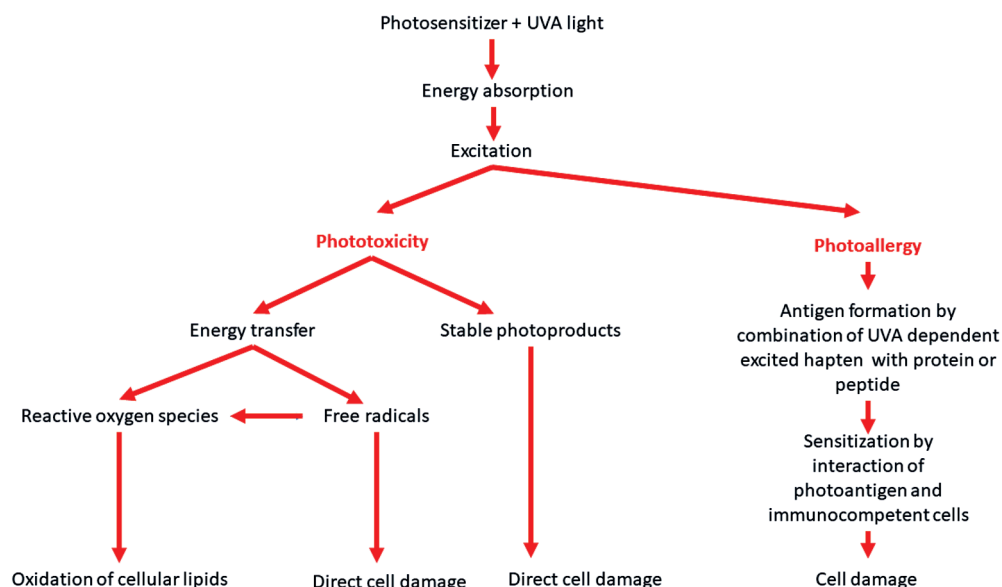


Figure 1. Hypothetical mechanisms of photosensitivity reactions including phototoxic and photoallergic reactions [12, 14].

erythema dose (MED) test and the photopatch test (PPT), and a detailed description of these procedures has recently been published [7].

Briefly, on day 1, photo tests are performed using artificial light sources that emit UVB and UVA radiation to determine the MED to UVB and UVA, and on that day up to 24 photoallergens (Chemotechnique Diagnostics AB, Malmö, Sweden), often supplemented with a baseline series and including any products that the patient may be using, are applied in duplicate to the back of the patient with a standardized technique using Finn Chambers (Epitest Ltd. Oy, Tuusula, Finland) on Scanpor tape (Norgesplaster Alfarma AS, Vennesla, Norway). On day 2 or day 3, the patches are removed and one of the duplicate sets are irradiated with UVA (10 J/cm^2). If the UVA MED was less than 10 J/cm^2 , a dose of at least one J/cm^2 less than the MED is used. The remaining set of allergens acts as non-irradiated control. Two readings of the test sites are performed in each patient, on day 3 or 4 and one of days 5 – 10. Patch test reactions are scored as +/- (weak/doubtful/macular erythema), + (mild), ++ (strong), or +++ (very strong). If both the non-irradiated and irradiated sites show equally positive reactions, this suggests the diagnosis of allergic contact dermatitis; if positive reactions occur only at the irradiated sites, a diagnosis of photoallergic contact dermatitis is established; if

both sites show positive reactions but the irradiated site is more intensely positive, a diagnosis of photo-aggravated contact dermatitis is likely. Positive reactions are considered to be clinically relevant if the patient has had known definite, probable, possible, or past contact with the suspected allergen and the timing of exposure coincides with the development of photodermatitis.

Sulfonamides

Allergic reactions to sulfonamides occur in ~ 2 – 4% of patients treated with these drugs. For unknown reasons, patients with HIV have a 10-fold increased risk of these reactions [29]. The clinical presentation in these patients includes maculopapular rash and/or SCARs, whereas anaphylactic reactions are quite rare. Currently, the most common source of exposure to sulfonamides comes from the administration of Cotrimoxazole which contains the combination of sulfamethoxazole (SMX) and trimethoprim e.g., Bactrim (Roche, Basel, Switzerland). Unfortunately, in most cases prick/intracutaneous tests and patch tests are not sufficiently sensitive to detect allergic reactions to either sulfonamides or trimethoprim. In the rare case of immediate-type reactions, prick and intracutaneous testing is recommended. It is of interest that certain HLA associations in

Table 1. HLA association with various phenotypes of drug hypersensitivity to non- β -lactam antibiotics in different populations [6].

Associated drug	HLA allele	Drug allergy	Ethnicity
Co-trimoxazole	B*15:02, C*06:02, C*08:01 B*13:01	SJS/TEN	Thai
Sulfa-methoxazole	B*38:02	SJS/TEN	European
Dapsone	B*13:01	DRESS	Han-chinese, Thai

some ethnic groups may influence susceptibility to SMX reactions as well as to dapsone, a sulfone derivative (Table 1) [28].

Sulfonamides including SMX are metabolized by xenobiotic-metabolizing enzymes including CYP450 isoenzymes. SMX is converted by cytochrome P450 (CYP) 2C9 or peroxidases to SMX-hydroxylamine, which spontaneously forms nitroso-SMX with oxygen, and nitroso-SMX in turn reacts with SMX-hydroxylamine to generate azo- and azoxydimers; furthermore nitroso-SMX is converted to the more stable NO-SMX. [9].

There is convincing evidence from *in vitro* and *in vivo* animal studies that this metabolic pathway plays an important role in both sensitizing and eliciting allergic reactions to these drugs, in particular SMX [35]. We have conducted studies using lesional T lymphocyte clones obtained from the involved skin of a patient suffering from SJS to SMX. These lymphocyte clones specifically recognized SMX; however, they reacted only after incubation of SMX together with liver microsomes, which we have shown to contain CYP isoenzymes [13]. The significance of the SMX oxidation to NO-SMX as a prerequisite for driving the allergic reactions was also demonstrated by immunohistological studies using specific antibodies directed against NO-SMX. Co-staining with NO-SMX antibodies and MHC I-binding antibodies was detected on keratinocytes, suggesting that this reactive metabolite is capable of binding to immunologically critical macromolecules [30].

More recently, using an *in vitro* priming assay consisting of T lymphocytes and antigen-presenting cells (APCs), sensitization to SMX was shown to be due to NO-SMX. This is produced by a CYP2C9-dependent metabolic activation [10].

As mentioned above, human exposure to SMX occurs most frequently in patients

receiving Cotrimoxazole, e.g., Bactrim. In addition, trimethoprim itself can also cause allergic reactions. Recent studies in an animal model of trimethoprim reactions showed that hydroxylated trimethoprim and its reactive sulfated metabolites can bind to skin proteins suggesting their involvement in an allergic reaction [5].

Cross-reactions between sulfonamides and drugs such as dapsone or non-antimicrobial drugs with a sulfonamide-like structure such as furosemide or celecoxib have not been documented [16]. However, T-cell clones have recently been isolated from HLA-B*13:01-positive patients. This HLA allele is associated with an increased risk of SCARs to SMX and dapsone in patients from Thailand (Table 1). Individual clones that reacted to SMX also reacted to nitroso-dapsone [28].

Antibiotics as ligands of MRGPRX2

Mas-related G-protein-coupled receptor member X2 (MRGPRX2) plays a role in the interaction between mast cells and the microbiome. It is expressed predominantly by mast cells, but also by basophils and eosinophils and can be activated by binding to various drug ligands including antibiotics [20, 34]. This mast cell-associated activation can lead to IgE-independent anaphylactic reactions. Fluoroquinolones are also known to bind to MRGPRX2. The incidence of fluoroquinolone-induced anaphylaxis was described as 0.2 per 1 million days of treatment [2]. Fluoroquinolones are also capable of inducing IgE-mediated allergic reactions as well as pseudo-allergic reactions by activation of mast cells after binding to MRGPRX2 [1, 23, 24]. In one review of severe hypersensitivity reactions to non- β -lactam antibiotics, fluoroquinolones were involved in at least half of the anaphylactic reactions [32]. The development of anaphylaxis immediately after an initial dose or within the first 3 days of administration suggests that not all reactions require prior sensitization and are therefore unlikely to be IgE-mediated [33]. Pseudo-allergic anaphylactic reactions to fluoroquinolones may also be dependent on their pharmacokinetics and their binding affinity to MRGPRX2 perhaps related to

LTT: Patient; Spiramycin

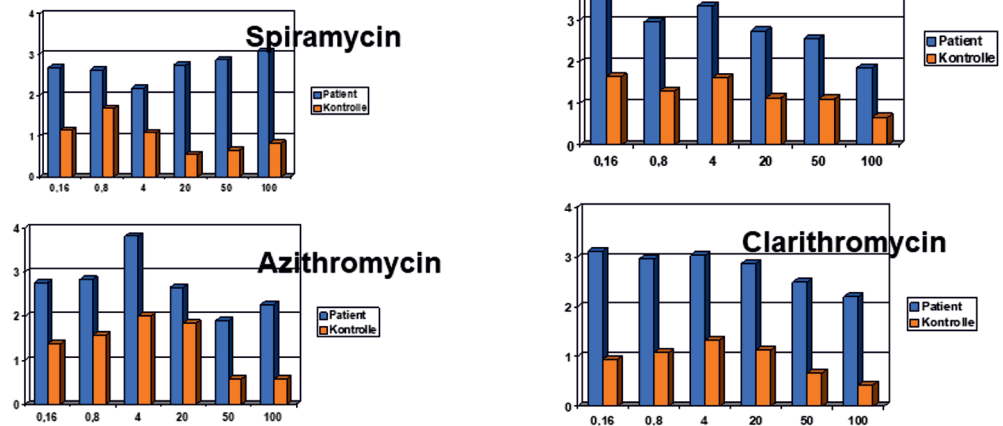


Figure 2. A lymphocyte transformation test was performed on a patient who developed a spiramycin-dependent drug rash while working at a chemical plant where this drug was manufactured. Cross-reactivity was observed with azithromycin, roxithromycin, and clarithromycin. SI = stimulationindex. PHA: 8.74 (control: 8.52); TT: 3.09 (control: 25.65); concentration of antibiotics in µg/mL.

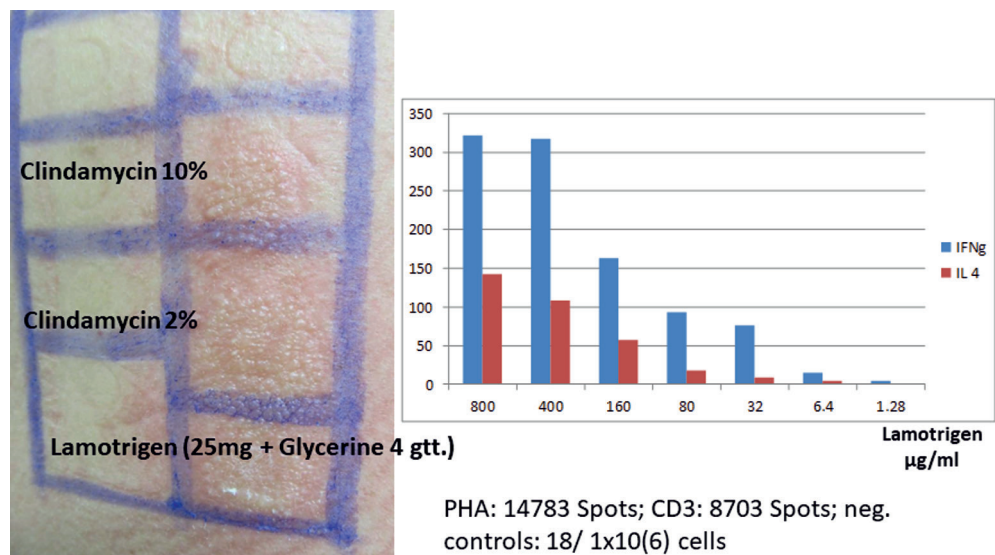


Figure 3. Example of a positive ELISpot assay with IFN- γ release after incubation with lamotrigine in a patient diagnosed with DRESS caused by lamotrigine together with clindamycin. There was no activation in the ELISpot assay to clindamycin; however, the patch test was for clindamycin as well as for lamotrigine. The patient was taking both medications when DRESS appeared.

delayed drug elimination [25]. Among the fluoroquinolones that bind to MRGPRX2, ciprofloxacin has the highest binding affinity with an EC_{50} value of 6.8 µg/mL, whereas for levofloxacin it is 22.7 µg/mL [25]. The basophil activation test may also be helpful as it would yield positive results only in the case of IgE-dependent reactions [8]. Mast cell activation by fluoroquinolones may also be associated with other adverse clinical effects of these antibiotics such as arthralgias, myalgias, or joint damage, as they accumulate

in cartilage tissue and then trigger local mast cell-dependent inflammatory responses [25].

Vancomycin is a glycopeptide antibiotic capable of inducing Red man syndrome due to its binding to MRGPRX2 that can also trigger anaphylactic reactions [25]. The method of administration (oral or IV) as well as the speed of the infusion may be risk factors. SCARs, in particular vancomycin-associated DRESS, have been described in association with HLA-A*32:01 [19].

Macrolide antibiotics

Allergic reactions to this group of non- β -lactam antibiotics that include erythromycin, troleandomycin, clarithromycin, spiramycin, and josamycin, are rare compared to the other antibiotics discussed above. Diagnostic skin testing procedures are considered to be less sensitive in assessing reactions to these antibiotics [29]. In our own observation of a morbilliform drug rash to spiramycin that was acquired occupationally in a manufacturing plant, we were able to confirm broad cross-reactivity across various macrolide antibiotics (Figure 2).

Clindamycin

Clindamycin is frequently associated with delayed-type reactions. Clindamycin can induce significant positive patch test reactions. As an example, in Figure 3 a patient was shown to be suffering from lamotrigine-associated DRESS based on positive reactions in the ELISpot assay and with patch testing; however, she also showed a positive patch test reaction to clindamycin, but the ELISpot assay was negative (Figure 3). The patient had been treated with both medications prior to developing the DRESS reaction.

Conclusion

In summary, this review demonstrates that in comparison to β -lactam antibiotics, skin and in vitro tests for reactions to non- β -lactam antibiotics have not been so rigorously tested in verifying their involvement in affected patients. Indeed, they are mostly based on published individual case reports. Nonetheless, these procedures may sometimes be helpful in confirming a suspected diagnosis, in particular in severe allergic drug reactions such as DRESS, for which provocation testing is contraindicated.

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Conflict of interest

No conflict of interest (H.M., D.R.B.).

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