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Contact dermatitis from topical antibiotics

This review describes the antibiotics available for topical application and discusses their propensity to cause delayed and immediate allergic contact reactions.

Key words: allergic contact dermatitis, anaphylaxis, antibiotics, contact urticaria

Antibiotics are commonly used topically to prevent and treat cutaneous, otic and ophthalmic infections. They are often combined to increase their spectrum of activity. Most are also available for systemic administration, but some are restricted to topical use because of their inherent toxicity.

Almost every topical antibiotic has caused allergic reactions, most often in patients who suffer from stasis dermatitis and leg ulcer, atopic dermatitis or other chronic eczema, otitis externa, and hemorrhoids or perianal dermatitis. These conditions share an impaired epidermal barrier that predisposes to allergic sensitization. In addition, health professionals are prone to occupational sensitization from repeated contact with antibiotic preparations for human and animal use. Nowadays, allergic contact dermatitis from penicillin and other betalactam antibiotics occurs only in the occupational setting, as they are no longer used topically because of their high allergenicity.

This article reviews the topical antibiotics responsible for cutaneous allergic reactions, the clinical presentation and investigation of these adverse events, and the cross-reactions that occur among each class of therapeutic agents.

Aminoglycosides

More than two thirds of commercialized antibiotic and antifungal agents are extracted from actinobacteria, Gram-positive organisms that belong to the *Streptomycetaceae* family. Streptomycin was isolated in 1943 from *Streptomyces griseus* [1]. In later years, neomycin, paromomycin, kanamycin, gentamicin, tobramycin and amikacin became available. These molecules share a common structure of amino sugars linked to a hexose by glycosidic bonds. The hexose, or aminocyclitol, is either streptidine in streptomycin, or 2-deoxy-streptamine in other compounds (figure 1).

Neomycin

Extracted in 1949 from *Streptomyces fradiae*, neomycin is a mixture of 2 isomers, neomycin B or framycetin, and

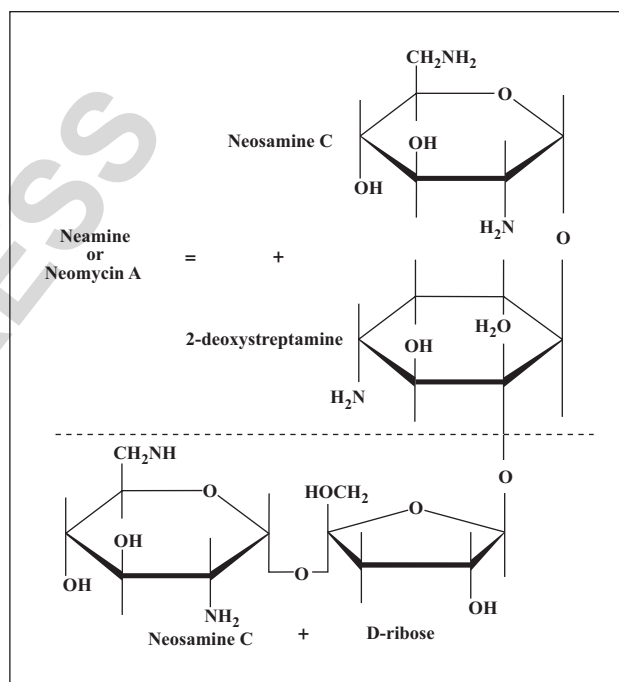


Figure 1. Chemical structure of neomycin.

neomycin C, together with a small amount of a degradation product, neomycin A or neamine (figure 1) [2]. Neomycin exerts its bactericidal effect by binding to the 30S ribosomal subunit, thereby interfering with protein synthesis [3]. Susceptible microorganisms include most Gram-negative bacteria except *Pseudomonas aeruginosa* and some anaerobes. The activity of neomycin against Gram-positive organisms is limited to staphylococci. Parenteral neomycin is severely oto- and nephrotoxic, and its administration is thus limited to topical cutaneous, auricular and ocular formulations, to vesical instillations in patients with indwelling catheters, and to peritoneal irrigation during contaminated abdominal surgery. Neomycin absorption from the gastro-intestinal tract is poor, in the range of 1% to 3%, hence its oral use to sterilize the bowel before surgery and at times to treat hepatic coma.

leg ulcers, and 7 had otitis externa. Despite wearing gloves, 3 young nurses acquired occupational hand dermatitis by exposure to gentamicin in acrylic bone cement.

Ghadially and Ramsay described an 89-year-old woman who developed a generalized eczematous drug eruption within hours of the intravenous administration of a single dose of gentamicin [26]. This patient was hospitalized for treatment of stasis ulcers infected with *Pseudomonas aeruginosa* that had been unsuccessfully managed at home with a gentamicin cream. When admitted, she presented with oozing eczema from the knee to the ankle. Patch tests were positive with gentamicin 20% and neomycin 20%. A recent report describes widespread but transient dermatitis in a 74-year-old woman, 3 days after a prosthetic knee replacement. The bone cement contained gentamicin. When patch tested 2 months later, the patient reacted to gentamicin and framycetin [27].

Tobramycin

An aminoglycoside extracted from *Streptomyces tenebra-rius*, tobramycin is structurally closely related to gentamicin (figure 2). Both antibiotics share common antibacterial activities and pharmacokinetic properties [1]. Topical preparations are limited to 0.3% eye drops and ointments, with and without dexamethasone.

Reports of contact allergy are scarce. Caraffini *et al.*, as well as Alvarez and Brancaccio, have described isolated allergy from tobramycin [28, 29]. Both cases involved acute blepharo-conjunctivitis secondary to ophthalmic preparations. Both patients had positive patch tests to their own eye drops and ointments, while the patient reported by Caraffini *et al.* also reacted to tobramycin 5% and 25% pet.

Menéndez-Ramos *et al.* reported the occurrence of acute otitis externa in a 32-year-old woman treated with an otic solution containing betamethasone, sulfamethazine and tobramycin [30]. Her patch tests were positive with tobramycin, kanamycin, ribostamycin and sisomycin, but negative with neomycin, gentamicin, amikacin, netilmycin and streptomycin. Schorr and Ridgway conducted a study to determine the frequency of cross-reactions between tobramycin and neomycin [31]. They tested 2 dilutions of tobramycin in 20 neomycin-allergic subjects: 12 individuals tested positively to tobramycin 10% pet., and 13 to the 20% preparation.

Polypeptides

Bacitracin

This mixture of cyclic polypeptides is produced by a strain of *Bacillus subtilis* (figure 3). This strain was isolated in 1943 from an open fracture in a young girl named Tracy, who thus contributed her name to the discovery. Its effectiveness against many Gram-positive microorganisms is mediated by inhibition of bacterial cell wall peptidoglycan synthesis. Topical creams and ointments, often combined with neomycin and polymyxin B, are sold over-the-counter in many countries. Bacitracin is also available as powder for the b6 re b6 re sos.8.1(is)JTJ T* 0C90.6secon434eBacitr434e

other ingredients of the lotion. A few months later, Herstoff published another case, characterized by a facial pruritic, papulo-nodular eruption that had begun 12 days after the onset of acne treatment with topical clindamycin [69]. Subsequent publications bring the total number of cases to only 8 in the English literature [68-75]. Six of these patients had acne and the contact dermatitis involved the face. The patient described by De Kort and De Groot developed, after 3 days of using Dalacin-T[®] lotion, an acute facial pustular eruption that resolved with topical corticosteroids. Patch tests were positive with the lotion and with 1% clindamycin phosphate in aqueous and alcoholic solutions [71]. The patient of Veljstrup and Menné was using Dalacin-T[®] lotion to treat crural and axillary hidradenitis suppurativa. After 2 months of twice-daily applications she developed eczematous lesions at the sites of contact, with subsequent generalization. Patch tests were positive with 1% clindamycin phosphate in water. [74]. Conde-Salazar's patient was a 55-year-old man whose atopic dermatitis had been treated with oral and topical clindamycin [73]. After 25 days, he presented with generalized eczema. Patch tests were positive with 1% clindamycin and 1% lincomycin, both diluted in water. Because both oral and topical clindamycin had been given simultaneously, it was impossible to distinguish between systemic or cutaneous sensitizations.

Synergistins (virginiamycin – pristinamycin)

Virginiamycin (Staphylomycine[®]) and pristinamycin (Pyostacine[®]) were isolated in 1955 from *Streptomyces virginiae* and *pristinaespiralis*, respectively. These streptogramin antibiotics are composed of 2 cyclic polypeptides that act synergistically. Virginiamycin fractions are called M and S, while those of pristinamycin are known as IA and IIA [3]. Cyclic depsipeptides, the S and IA compounds differ slightly from one another, while the identical M and IIA compounds are macrocyclic peptolides related to macrolides. The latter molecules are responsible for most of the antibacterial activity when they bind the 50S ribosomal subunit of susceptible microorganisms. These antibiotics are effective against Gram-positive cocci and bacilli, including staphylococci, against Gram-negative cocci, and against intracellular microorganisms such as *Chlamydia* and rickettsiae. Virginiamycin has been used topically to treat cutaneous, ocular and auricular infections, and as growth promoter in cattle, pork and poultry breeding. Pristinamycin is systemically administered in staphylococcal infections.

Bleumink and Nater initially reported allergic contact dermatitis from virginiamycin in a burn patient with positive patch test reactions to fraction M1 2% and 5% pet [76]. This patient also reacted to pristinamycin. Baes' 8 patients were tested with all 4 streptogramin fractions and reacted only to M and IIA, both 1% pet. [77]. Baes correctly interpreted these results as pseudo cross-reactions, as the 2 molecules are identical. Lachapelle and Lamy are the only investigators who showed, in one of their 5 patients, sensitization to the S fraction of virginiamycin [78]. The main allergen of synergistins is therefore fraction M or IIA. Tennstedt *et al.* later published the first report of occupational dermatitis from virginiamycin, in a 31-year-old pharmaceutical industry maker of animal feed additives [79]. The dermatitis was

airborne and the patient showed positive patch tests to the feed, as well as to virginiamycin 5% pet. and pristinamycin 5% pet.

Virginiamycin is no longer available in Belgium and France [80], but is still used in North American agriculture. Orally available pristinamycin has caused drug eruptions. Michel *et al.* have published 4 cases of generalized eczematous eruptions occurring within 24 to 48 hours after oral administration of pristinamycin in 3 cases and virginiamycin in 1 case [81]. These 4 patients had a past history of contact allergy to virginiamycin, later confirmed by patch testing. Barbaud *et al.* studied 29 cases of pristinamycin drug eruptions and demonstrated the value of skin testing in their investigation [82]. They were unable to establish whether their patients had been previously exposed to topical virginiamycin or not. In addition, 7 of 8 patients tested with dalfoprastine/quinupristine (Synercid[®]), a recently introduced synergistin, had positive reactions, exemplifying the high rate of cross-reactions among members of this family of antibiotics [82].

Chloramphenicol

Another bacterial protein synthesis inhibitor, chloramphenicol was isolated from *Streptomyces venezuelae* in 1946 (figure 6). Chloramphenicol attaches to the 50S ribosome subunit, close to the binding site of Macrolides and Lincosamides [55]. Nowadays, this antibiotic is rarely used systemically, as it is frequently responsible for severe blood dyscrasias. Topical preparations treat cutaneous, vaginal, auricular and ocular infections. Ophthalmic preparations are implicated in most cases of contact allergy [3].

Already in 1963, Schwank and Jirasek had described a number of cases of chloramphenicol sensitization in patients with stasis dermatitis or ulcers [83]. Van Joost *et al.* investigated 8 patients presenting with periorcular or periauricular dermatitis [84]. All reacted to 100% chloramphenicol powder, but only 3 had positive patch test to 1% pet. A 9-year-old child, reported by Kubo *et al.*, became sensitized from Chloromycetin[®] cream applied to a skin abrasion [85]. Patch tests were positive with the cream, and with 2% chloramphenicol in water and ethanol, but negative in petrolatum. The authors concluded that water and ethanol are better vehicles to reveal contact allergy to chloramphenicol.

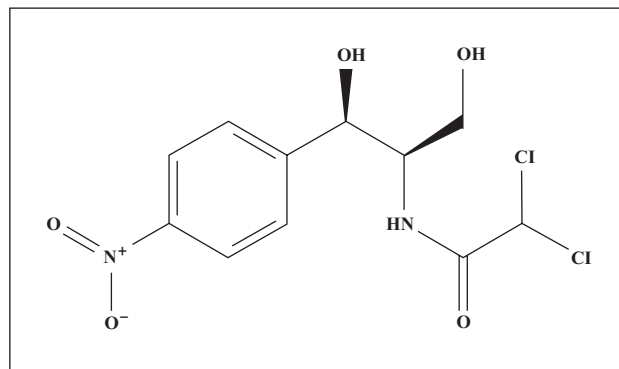


Figure 6. Chemical structure of chloramphenicol.

reacted to propylene glycol or cetyl alcohol, but no patient reacted to silver sulfadiazine. In the same study, 10 patients sensitized to a topical sulfonamide were tested with a series of sulfonamide antibiotics. Many cross-reactions were found, including 3 with sodium sulfadiazine, but none with silver sulfadiazine.

Similarly, sulfacetamide appears to be well tolerated, as no report of contact dermatitis has been published in the English literature. Use of eye drops has caused 1 case of erythema multiforme, 2 cases of Stevens-Johnson syndrome, and 1 case of toxic epidermal necrolysis [112-115]. These patients had all been previously treated with sulfamethoxazole-trimethoprim and could have become sensitized by oral exposure. Topical administration of sulfacetamide should therefore be avoided in sulfonamide-allergic patients.

Metronidazole

This synthetic nitro-imidazole derivative has antibacterial, amebicidal, and antiprotozoal properties (figure 8). Susceptible microorganisms transform metronidazole into DNA-altering metabolites. Topical metronidazole is used to treat rosacea, as well as bacterial and trichomonal vaginitis. Considering its widespread use, it remains an uncommon sensitizer. In a multicenter retrospective study among rosacea patients, only 3 needed to be patch tested with metronidazole, and only one had a positive test [116]. More recently, the same authors prospectively studied 78 rosacea patients [117]. All were tested to a comprehensive series of medicaments and vehicles, and none showed sensitization to metronidazole.

Vincenzi *et al.* reported facial contact dermatitis in a 26-year-old woman treated with 1% metronidazole gel [118]. Patch tests were positive with the gel and with metronidazole 1% pet., but were negative with many imidazole

antifungals. A 68-year-old woman developed acute facial dermatitis 24 hours after application of metronidazole gel [119]. She reacted to a 0.5% metronidazole solution, and also to methylchloroisothiazolinone/methylisothiazolinone (MCI/MI), a finding suggestive of cross-reaction, given the structural similarity between metronidazole and isothiazolinones.

In the past 3 years, 5 new cases have been published [120-122]. These rosacea patients suffered from acute dermatitis after treatment with topical metronidazole. One patient was also allergic to MCI/MI [122]. Another was patch tested to numerous imidazole antifungals but reacted to metronidazole only [121]. Finally, 2 nurses could have become sensitized by prior handling of metronidazole tablets or solutions before personal use of topical preparations [122].

Rifamycin

Rifamycins A, B, C, D, E, S and SV form a group of macrocyclic antibiotics isolated from *Streptomyces mediterranei*. Rifampicin and rifabutin are semi-synthetic derivatives of rifamycin B. These molecules bind to the enzyme RNA-polymerase and block the synthesis of ribonucleic acids. Rifamycins are effective against Gram-positive bacteria, mycobacteria, and some Gram-negative microorganisms. Rifamycin SV (Rifocine®) is only available for topical use. Allergic contact dermatitis from rifamycin is rare. Riboldi *et al.* reported an 11-year-old child simultaneously sensitized to Mercurochrome™ and rifamycin used on cutaneous lacerations [123]. Milpied *et al.* have seen 2 cases of contact allergy from rifamycin applied to damaged skin [124]. When patch tested, one patient reacted to rifamycin 0.5% pet., while the other reacted to sodium metabisulfite from the vehicle. The patient of Balato *et al.* became sensitized to a 5% aqueous solution of rifamycin applied to a leg ulcer [125]. Three patients published by Guerra *et al.* were patch test positive to rifamycin 2.5% pet., and 2 had been using the antibiotic on leg ulcers [126].

Immediate reactions have occurred, including a case of contact urticaria with secondary generalization after application on a stasis ulcer [127]. Open tests, occluded patch tests, and scratch tests were positive after 20 minutes with rifamycin 1% and rifampicin 1% aqueous solutions. A similar case, published by Mancuso and Masara, progressed to anaphylactic shock [128]. Two patients described by Erel *et al.*, with decubitus or stasis ulcers, experienced anaphylaxis after multiple exposures to Rifocine® solution [129]. A case of palpebral angioedema with generalized urticaria occurred after use of rifamycin eye drops [130]. Intra-operative anaphylaxis has been reported with rifamycin irrigation solutions [131-133]. Subsequent investigation of one case has demonstrated the presence of specific IgE antibodies [132].

Fusidic acid

Fusidic acid is a steroid-like antibiotic extracted from the fermentation of the deuteromycete *Fusidium coccineum* (figure 9). It inhibits bacterial protein synthesis by binding

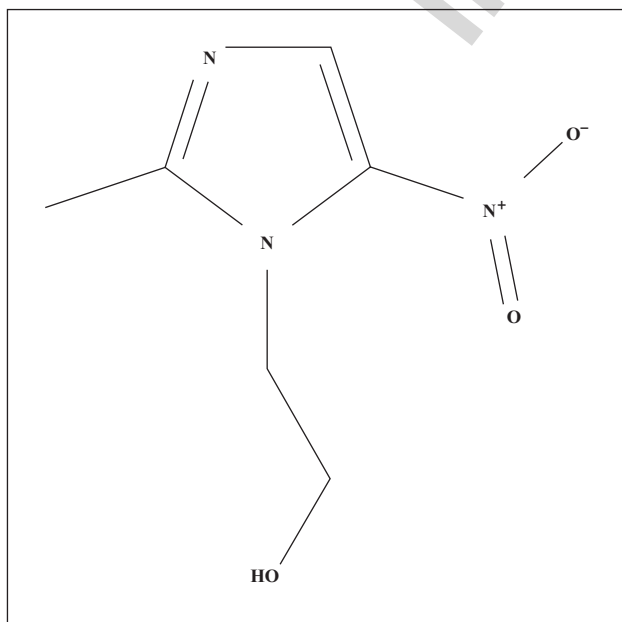


Figure 8. Chemical structure of metronidazole.

retapamulin is a semi-synthetic derivative obtained from *Clitopilus passeckerianus*. It interferes with bacterial protein synthesis by binding to the 50S ribosomal subunit, but on different sites than traditional antibiotics [160]. Active against Gram-positive cocci, retapamulin is available topically for the treatment of impetigo. Commercialized since 2007 in the USA under the trade name Altabax[®], it is called Altargo[®] in Europe. Altabax[®] contains 1% retapamulin in white petrolatum, but Altargo[®] also contains butylhydroxytoluene.

Two publications describe a total of 4 cases of contact allergy to retapamulin. Schalock's patient, a 79-year-old man, was applying Altabax[®] ointment after cryotherapy of facial actinic keratoses [161]. He became sensitized 3 weeks later. Patch tests were positive with the ointment, and it was assumed that the active ingredient was the allergen. The 3 patients of Warshaw *et al.* were between 6 and 40 years of age [162]. They were respectively treated for infected atopic dermatitis, folliculitis, and impetigo. The authors do not specify the duration of exposure before sensitization, but in each case improvement quickly followed discontinuation of the ointment. Each patient developed a vesicular reaction when patch tested with Altabax[®] ointment.

Conclusion

Topical antibiotics remain an important cause of iatrogenic allergic contact dermatitis. Aminoglycosides and bacitracin are the most common sensitizers. Individuals at risk are those who suffer from stasis dermatitis or ulcers, perianal or atopic dermatitis, and otitis externa. As far as possible, topical antibiotics should be avoided in these patients. Physicians should be able to recognize the clinical manifestations that suggest the occurrence of contact allergy, and proceed with appropriate patch testing with the active and inert ingredients of the culprit preparation. Finally, it is worth remembering that topical antibiotics may at times give rise to severe reactions, such as those described with bacitracin and rifamycin. □

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