

Allergic contact dermatitis to topical antibiotics: Epidemiology, responsible allergens, and management

Kathryn A. Gehrig, MD,^a and Erin M. Warshaw, MD, MS^{b,c}
Minneapolis, Minnesota

Topical antibiotics are widely used to treat cutaneous, ocular, and otic infections. Allergic contact dermatitis to topical antibiotics is a rare but well-documented side effect, especially in at-risk populations. The purpose of this article is to review the epidemiology, responsible allergens, and management of allergic contact dermatitis to topical antibiotics. (J Am Acad Dermatol 2008;58:1-21.)

Learning objective: After completing this learning activity, participants should be able to describe the epidemiology of allergic contact dermatitis related to topical antibiotics; show knowledge of the most common allergenic topical antibiotics; and understand the allergenic cross-reactivity pattern amongst topical antibiotics.

Topical antibiotics are commonly used for the prevention and treatment of superficial skin, ocular, and otic infections. A rare but well-documented side effect of topical antibiotic therapy is allergic contact dermatitis (ACD). ACD may be seen following topical treatment regimens, either self-administered or iatrogenic, or following occupational exposure. In general, prolonged use and an impaired skin barrier increase the risk of developing ACD from topical antibiotics. While the overall prevalence of ACD from topical antibiotics is low, recognition of this problem by health care professionals is important because of the widespread use of topical antibiotics, especially in selected populations. The epidemiology, risk factors, allergens, and management of ACD to topical antibiotics are addressed in this review.

Abbreviations used:

ACD:	allergic contact dermatitis
CI:	confidence interval
CVI:	chronic venous insufficiency
NACDAG:	North American Contact Dermatitis Group
OR:	odds ratio
pet:	petrolatum
PR:	prevalence ratio
RR:	relative risk

METHODS

A literature search was conducted using various terms, including “allergic contact dermatitis,” “topical antibiotic,” “occupational contact dermatitis,” and the individual names of topical antibiotics. Hand searching of published manuscripts was also performed. We limited our review to patch-test proven ACD. If not reported in the original manuscript, we calculated percentages and averages when necessary for comparison. Pooled statistics were also calculated. These analyses are identified as “calculated” in the text.

EPIDEMIOLOGY

Prevalence

The prevalence of ACD to individual topical antibiotics in the general population is unknown. In patients presenting for patch testing in select tertiary referral centers in North America over the last 20 years, the prevalence of ACD to neomycin and bacitracin ranged from 7.2-13.1% and 1.5-9.1%, respectively (Table I).¹⁻⁶

From the School of Medicine^a and the Department of Dermatology,^b University of Minnesota, and the Minneapolis Veterans Affairs Medical Center,^c Minneapolis.

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Correspondence to: Erin M. Warshaw, MD, MS, Dept 111 K VAMC, Dermatology, 1 Veterans Dr, Minneapolis, MN 55417. E-mail: erin.warshaw@med.va.gov.

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Table I. Prevalence of allergic contact dermatitis to bacitracin and neomycin reported by the North American Contact Dermatitis Group

Test period	Neomycin 20% pet			Bacitracin 20% pet		
	n	Pos (%)	Rank	n	Pos (%)	Rank
1985-1989 ¹	3983	7.2	2	NR	1.5	NR
1992-1994 ²	3538	9.0	5	3511	7.8	6*
1994-1996 ³	3104	11.6	3	3079	9.1	8
1996-1998 ⁴	3436	13.1	2	4103	8.7	10
1998-2000 ⁵	5822	11.5	3	5812	9.2	7*
2001-2002 ⁶	4904	11.6	2	4900	7.9	9
2003-2004 [†]	5137	10.6	2	5143	7.9	9

n, number of patients tested; NR, not reported; Pos (%) = no. of patients with allergic reaction/no. of patients tested.

*Tied with another allergen.

[†]Unpublished data, personal communication, North American Contact Dermatitis Group.

Age and gender

While there are many studies evaluating the association of age and gender with ACD, in general, studies specific to topical antibiotics are limited and inconclusive. Two studies involving a total of 1725 subjects found that the overall frequency of sensitization was similar for men and women and among all age groups for various chemicals, including neomycin (*P* value for neomycin not reported separately; *P* > .2 for male age groups, *P* > .05 for female age groups).^{7,8} Conversely, Nethercott et al⁹ found that the odds of neomycin contact allergy increased significantly with increasing age (odds ratio [OR] = 1.02; *P* < .001) among 3983 patients with suspected contact dermatitis. Menezes de Pádua et al¹⁰ conducted a retrospective multifactorial analysis of 47,559 patients with suspected ACD who were patch tested to several antigens, including neomycin sulfate 20% pet. Patients younger than 40 years of age were at least 75% less likely to be allergic to neomycin (*P* < .05); on the contrary, patients more than 60 years of age were at least 150% times more likely to have neomycin allergy (*P* < .05). Green et al¹¹ studied 4384 patients suspected of having a contact allergy, and found that contact allergy to topical antibiotics (neomycin sulfate, gentamycin, soframycin, and fusidic acid) was more common in patients over 70 years (7.8%) compared with patients under 70 years (4.4%) (*P* value not reported).

Data on the role of gender in topical antibiotic sensitization prevalence are also limited and focus primarily on neomycin. In a study of 1158 subjects, Prystowsky et al⁷ found that women had higher rates of exposure than men for the four contactants studied, including neomycin, but not higher rates of sensitization. In a retrospective analysis of 47,559

patients, Menezes de Pádua et al¹⁰ reported that female patients did not have an elevated risk of neomycin sensitization (PR = 0.97; 95% CI, 0.86-1.09). Similarly, Green et al¹¹ did not find a gender difference among 4384 patients with suspected contact allergy to topical medicaments, including neomycin sulfate, gentamycin, soframycin, and fusidic acid (*P* > .05). Nethercott et al^{9,12} in a study involving 5040 subjects with suspected dermatitis, reported an overall equal distribution of ACD to 38 screening chemicals between males (47.6%) and females (49.3%; *P* > .05). However, for neomycin sulfate 20% petrolatum (pet), there was a significantly higher proportion of positive patch test results among females compared to males in both univariate (*P* < .05) and multivariate (OR = 1.56; *P* < .01) analyses.

Race and ethnicity

DeLeo et al¹³ evaluated the prevalence of ACD to a standard series of 41 allergens, including neomycin sulfate 20% pet and bacitracin 20% pet, in 8610 white and 1014 African American individuals patch tested over a 6-year period. The prevalence of ACD to both neomycin and bacitracin did not statistically differ between these two groups (*P* > .05).¹³

SPECIAL POPULATIONS AT RISK

Several studies have documented that ACD to topical antibiotics is more common in patients with chronic venous insufficiency (CVI), chronic otitis externa, postoperative or posttraumatic wounds, chronic eczematous conditions, and in certain occupations involving contact with antibiotics. It is thought that the presence of an impaired skin barrier, prolonged use of topical antibiotics, and occlusion for extended periods predispose these patient populations to developing ACD.¹⁴

Chronic venous insufficiency

It is well known that patients with venous insufficiency are more prone to secondary pyoderma and cutaneous ulcers, often requiring the chronic use of topical antibiotics. Several studies have established that individuals with CVI have an increased rate of sensitization to any product used on the legs.¹⁵ Prevalence rates from individual studies range from 50% to 85%, with a calculated pooled average of 67% from studies involving a total of 2631 patients with venous insufficiency (Table II).¹⁵⁻³² Gallenkemper et al³⁰ found that 25% of 36 patients with CVI were patch test positive to a topical antibiotic. Calculated pooled averages show that bacitracin is the most common sensitizer (19.7%), followed by framycetin (15.95%), neomycin (15.8%), and

Table II. Calculated pooled average sensitization rates in special populations

Publication	Year	Sensitization n	Overall sensitization (%)	Neomycin (%)	Bacitracin (%)	Gentamicin (%)	Chloramphenicol (%)	Polymyxin B (%)	Framycetin (%)	Oxytetracycline (%)
Venous insufficiency										
Breit ¹⁶	1972	326	71.5	—	—	—	—	—	—	—
Malten ¹⁷	1973	100	69	12	—	—	—	—	—	—
Rudzki ¹⁸	1974	166	68	4.2	—	—	10.3	—	—	7.3
Angelini ¹⁹	1975	306	57.8	16.3	—	0	4	—	—	—
Breit ²⁰	1977	118	53.4	16.9	—	7.7	—	—	—	—
Blondeel ²¹	1978	88	85.2	25	—	—	22.7	—	—	—
Dooms- Goossens ²²	1979	163	63	7.4	—	—	—	—	—	—
Fraki ²³	1979	192	69.2	34	13.1	—	—	—	31.2	1.3
Angelini ²⁴	1985	849	58.1	—	—	—	—	—	—	—
Paramsothy ²⁵	1988	100	55	14	—	—	—	—	—	—
Shupp ²⁶	1988	46	60.9	17.4	—	—	—	—	—	—
Wilson ²⁷	1991	81	67	19.8	—	—	—	—	—	—
Zaki ²⁸	1994	85	81	21	22	12	—	14	20	13
Rudzki ²⁹	1997	111	—	—	—	—	—	—	—	10.8
Gallenkemper ³⁰	1998	36	77.7	16.7	—	—	13.9	—	5.6	—
LeCoz ³¹	1998	50	76	2	—	—	—	—	—	—
Perrenoud ³²	1999	153	—	18	—	—	—	—	—	—
Saap ¹⁵	2004	54	63	13	24	—	—	—	7	—
Pooled		2631	67.2*	15.8*	19.7*	9.9*	15.6*	14[†]	16.0*	8.1
Chronic otitis externa										
Holmes ³³	1982	40	35	15	2	10	—	5	15	—
Fraki ³⁴	1985	142	40	16.2	2.8	1.4	4.2	4.2	16.2	0
Lembo ³⁵	1988	23	4.3	—	—	—	—	—	—	—
Pigatto ³⁶	1991	64	23.5	—	—	—	—	—	—	—
Onder ³⁷	1994	40	30	15	—	10	—	—	—	—
Devos ³⁸	2000	79	44.3	15.2	—	—	—	—	—	—
Pooled		388	29*	15.4*	2.4*	7.1*	4.2[†]	4.6*	15.6*	0**
Other eczematous conditions										
Rudzki ¹⁸	1974	2078	—	0.8	—	—	1.6	—	—	0.6
Blondeel ²¹	1978	242	54.6	7	—	—	5.4	—	—	—
Dooms- Goossens ²²	1979	1149	37	2.7	—	—	—	—	—	—
Pooled		3469	45.8*	3.5*	—	—	3.5*	—	—	0.6[†]

n, No. of patients tested.

*Calculated average.

[†]Based on one study, not a true pooled average.



Fig 1. Patient with fingertip dermatitis.



Fig 3. Patient in Figs 1 and 2 with positive patch test to neomycin.



Fig 2. Patient in Fig 1 with positive patch test to bacitracin.



Fig 4. Patient in Figs 1-3 with positive patch test to products containing both bacitracin and neomycin.

chloramphenicol (15.6%) in patients with CVI (Table II).

Topical antibiotic sensitivity may be associated with ulcer duration. Paramsothy et al²⁵ found that leg ulcer duration was significantly associated with positive patch test results to various substances, including neomycin, in 90 patients with CVI ($P < .01$). The authors found a linear association between the number of positive reactions and leg ulcer duration (Spearman rank correlation coefficient $r_{98} = 0.41$; $P < .001$). Another study by Saap et al,¹⁵ however, did not find a statistically significant correlation between ulcer duration and the number of positive allergen sensitivities in 54 patients with CVI (Spearman rank correlation coefficient = -0.013 ; $P = .93$).

Chronic otitis externa

Several studies have evaluated the prevalence of ACD in individuals with chronic otitis externa. Devos et al³⁸ found that 27.8% of their 79 patients with chronic otitis externa were sensitized to a topical medication or to the ingredients of topical medications. Our calculated prevalence rates from six studies involving 388 patients show that framycetin and neomycin are the most common antibiotic sensitizers in this population, with average prevalence rates of 15.6% and 15.4%, respectively (Table II).³³⁻³⁸

Other chronic eczematous conditions

The reported prevalence of sensitization to any antigen in chronic eczematous conditions excluding stasis dermatitis (seborrheic, atopic, and nummular) ranges from 37% to 55% in a total of 3469 patients with eczematous dermatitis.^{18,21,22} Table II summarizes the prevalence rates for individual topical antibiotics. The most common sensitizers in this population are neomycin and chloramphenicol. An example of a patient with chronic, fissured, fingertip dermatitis which was self-treated with topical antibiotics and later found to be allergic to those topical antibiotics is shown in Figs 1-4.

Atopy

The prevalence of atopy in the general population is approximately 20%.³⁹ It has been suggested that atopy is more common in patients with ACD; however, for topical antibiotic sensitization, this association is unclear. Angelini et al²⁴ studied more than

8000 patients with eczematous dermatitis and reported that 8.9% of patients with atopic dermatitis had a contact allergy to either a topical medicament (specific antigens not reported) or a medicament component. In an uncontrolled study, Epstein⁴⁰ reported evidence of atopy in 55% to 75% of 120 neomycin-sensitive patients. Wereide⁴¹ did not find an increased prevalence of contact allergy to neomycin in 88 patients with atopic dermatitis compared to 664 patients with other types of dermatitis ($\chi^2 = 0.92$; $P > .1$). In a study of 232 patients with eyelid dermatitis, Cooper and Shaw⁴² found that the frequency of atopy in patients with ACD to various substances, including neomycin, gentamicin, and chloramphenicol, was 49%, which was not statistically significantly different from the frequency of atopy in patients without ACD (52%), although the rates for individual antibiotics were not reported separately. In a retrospective analysis of 47,559 patients, Menezes de Padua et al¹⁰ found that past or current atopic dermatitis was not a risk factor for neomycin sensitivity.

Postoperative wounds

Posttraumatic eczema describes the occurrence of dermatitis at the site of previous skin trauma and, in some cases, can be caused by an allergy to topical antibiotics.⁴³ In a nonrandomized prospective study, Gette et al⁴⁴ evaluated the frequency of ACD to topical antibiotics in postoperative patients. Two hundred and fifteen patients who had undergone dermatologic surgery were instructed to apply neomycin (n = 94), bacitracin (n = 91), or any available topical antibiotic (n = 30) to the wound. On post-surgical follow-up, patients with a dermatitis suggestive of ACD were patch tested. Nine (4.2%) of the 215 patients (5 using neomycin and 4 using bacitracin) developed an eczematous reaction consistent with ACD; however, only 7 agreed to patch-testing. Six of the seven patients with positive patch test results reported a history of exposure to the topical antibiotic to which they were assigned. Angelini et al²⁴ found that 70.2% of 282 patients with post-traumatic eczema were sensitized to medicaments (specific antigens not reported) or the medicament components. The authors defined posttraumatic eczema as contact dermatitis induced by topical agents applied to traumatic lesions or areas of loss of skin continuity, excluding ulcers.

Occupational risk

Health care and pharmaceutical workers, as well as farmers, who handle antibiotics are at risk for developing ACD to antibiotics. Rudzki and Rebandel⁴⁵ studied 81 patients with occupational

dermatitis and found that 48.1% of pharmaceutical workers (n = 27), 45.8% of nurses (n = 24), and 26.6% of veterinary surgeons (n = 30) were sensitive to antibiotics, an overall prevalence of 39.5%. Penicillin was the most common sensitizer in pharmaceutical workers and nurses and the third most common sensitizer in veterinary surgeons. The second most common sensitizers were semisynthetic penicillins (ampicillin and cloxacillin). Streptomycin was the most common sensitizer in veterinary surgeons. Angelini et al²⁴ reported that 21.9% of 1488 patients with dermatitis had occupational contact allergy to medicaments and/or their components; individual antibiotics were not reported separately.

CLINICAL PRESENTATION

Type IV hypersensitivity

ACD, a type IV hypersensitivity reaction, presents acutely as pruritic, erythematous, edematous papules, vesicles, and plaques at the site of contact.³² It may also present as a worsening chronic dermatitis or a wound with delayed healing.^{46,47} In the early stages, the dermatitis is usually limited to the cutaneous site of principal exposure. However, spread to more distant sites is not uncommon, and autoeczematization ("id reactions") can result in dramatic clinical presentations.⁴⁷ To the untrained eye, the appearance may mimic cellulitis, not uncommonly resulting in hospital admission, expensive diagnostic work-ups, and/or systemic antimicrobial therapy. Thus, the proper evaluation by a dermatologist can save valuable resources.⁴⁶ Patch testing is considered a key diagnostic procedure for diagnosis of ACD.

ANTIBIOTICS

Aminoglycosides

The aminoglycoside antibiotics are structurally similar, accounting for their high rate of cross-reactivity (Fig 5).⁴⁸ All aminoglycosides in clinical use, with the exception of streptomycin, share a deoxystreptamine group.⁴⁹ Furthermore, neomycin, butirosin, and paromomycin share a neosamine group and a 4,5-di-O-substituted deoxystreptamine group, accounting for increased cross-reactivity among these three aminoglycosides.⁴⁹⁻⁵¹

Neomycin. Neomycin is an aminoglycoside antibiotic that inhibits bacterial protein synthesis by irreversibly binding to 30S ribosomal subunits. It is effective against many aerobic Gram-negative and some aerobic Gram-positive microorganisms.⁵² Neomycin is used topically in the prevention or treatment of superficial skin infections, and as a genitourinary irrigant to prevent bacteriuria and bacteremia associated with in-dwelling catheters.⁵³

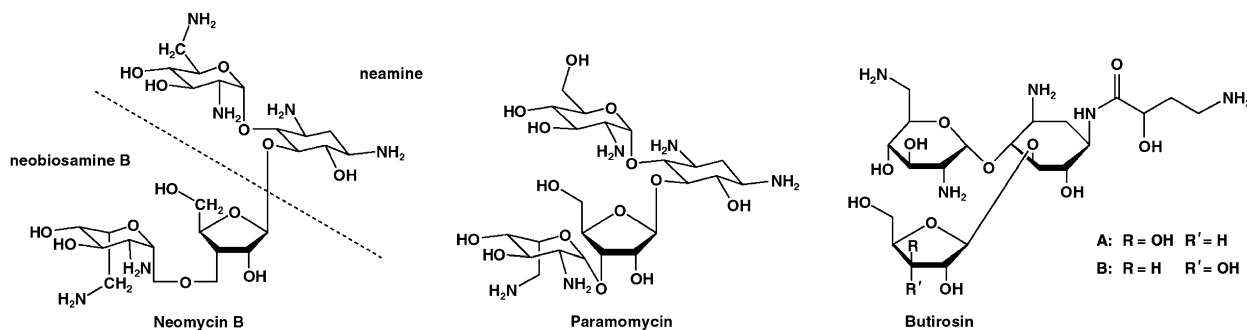
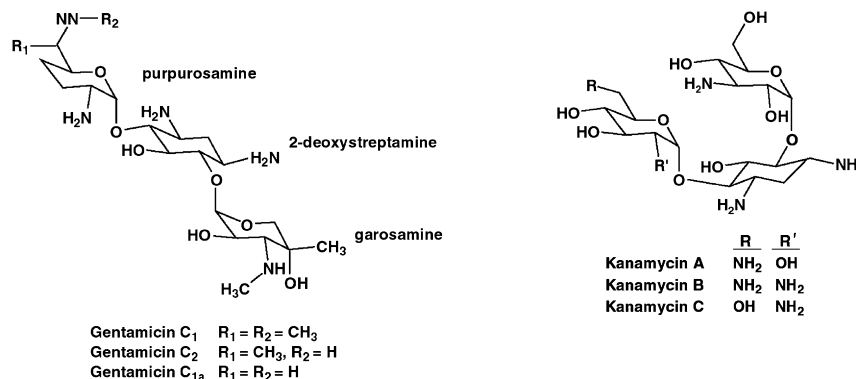
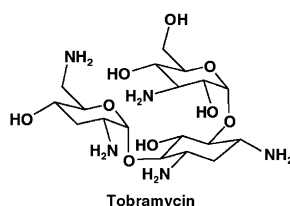
NEOSAMINE (the diamino sugar moiety)**4-6-di-O-SUBSTITUTED DEOXYSTREPTAMINE****4-6-di-O-SUBSTITUTED DEOXYSTREPTAMINE WITH RING A = -3-DEOXYNEOSAMINE**

Fig 5. Chemical structures of aminoglycoside antibiotics. Adapted from Schorr et al.⁴⁹

It is one of the most widely used topical antibiotics because of its low cost and perceived efficacy.⁵⁴

Neomycin allergy was first reported in 1952,³⁹ and it is estimated that, in the general population, approximately 1% to 6% of individuals are patch test sensitive to neomycin.^{7,21,32,39,54} Data from the North American Contact Dermatitis Group (NACDG) shows that approximately 7% to 13% of patch tested patients in the last 2 decades were allergic to neomycin (Table I).¹⁻⁶ Our pooled calculated rate in patients with CVI is 16% (Table II).

When used postoperatively on minor surgical wounds, the rate of patch test positive ACD from neomycin was reported to be 5.3% among 94 patients, likely because of a compromised cutaneous surface. While intermittent use on minor cutaneous wounds is not associated with an increased rate of

sensitization,⁵⁵ neomycin use for a week or more on an inflammatory dermatosis is thought to increase the risk of sensitization. Prystowsky et al⁷ found that 10 of 12 patients who were patch test positive to neomycin endorsed a history of using neomycin for at least 1 week compared to only 6 of 36 age-, race-, and sex-matched controls who were not sensitized to neomycin. In this small study, individuals who used neomycin for at least 1 week were 13 times more likely than controls to have a positive patch test reaction to neomycin (relative risk [RR] = 13; χ^2 = 14.4; P < .001).

Gentamicin. Gentamicin is an aminoglycoside antibiotic that inhibits bacterial protein synthesis by irreversibly binding to 30S ribosomal subunits. It is effective against many aerobic Gram-negative and some aerobic Gram-positive bacteria. Gentamicin is

used topically in the treatment of superficial infections of the skin and eye.⁵² The calculated prevalence of gentamicin contact allergy is approximately 10% in patients with CVI, and about 7% in patients with chronic otitis externa, based on a review of the literature involving 203 and 222 subjects, respectively (Table II).

Lynfield⁵⁶ first reported a case of contact sensitivity to gentamicin 0.1% cream in a 49-year-old male, with no previous exposure to gentamicin or neomycin, who was applying gentamicin cream 3 times daily to leg ulcers. On the thirty-seventh day of treatment, the patient experienced itching, redness, and swelling around the ulcers. The patient was patch test positive to gentamicin cream 0.1% and to neomycin sulfate 20% pet.⁵⁶ Sanchez-Perez et al⁵⁷ described a 55-year-old woman who developed pruritic, erythematous, scaly plaques on her eyelids 24 hours after starting gentamicin eyedrops. The patient was patch test positive to gentamicin 20% pet, to the gentamicin eyedrops as is, and to kanamycin 10% pet.

Streptomycin. Streptomycin is an aminoglycoside antibiotic used to treat tuberculosis and other mycobacterial infections, enterococcal and streptococcal infections, urinary tract infections, and plague.⁵² Contact allergy to streptomycin is usually seen occupationally, in health care and pharmaceutical workers or farmers who handle the drug tablets.

Strauss and Warring⁵⁸ first reported ACD to streptomycin in nurses administering streptomycin to patients with tuberculosis. Four of twelve nurses handling the drug developed dermatitis of the hands and subsequently were shown to be patch test positive (patch test concentrations not reported). Gauchía et al⁵⁹ reported a cattle breeder with a 10-year history of chronic hyperkeratotic fissured eczema of his hands and face. His condition improved while he was on vacation, and he noticed that it was associated with disease outbreaks among the animals. During these periods, he had administered neomycin, nitrofurazone, penicillin, and streptomycin to the cattle. Patch testing was positive only to streptomycin 2% pet.⁵⁹

Tobramycin. Tobramycin is an aminoglycoside antibiotic that inhibits bacterial protein synthesis by irreversibly binding 30S ribosomal subunits. It is effective against many aerobic Gram-negative and some aerobic Gram-positive microorganisms. Tobramycin is used topically for ophthalmic and otic bacterial infections.⁵² The prevalence of ACD to tobramycin alone is not reported in the literature. However, in patients who are sensitized to neomycin, we calculated an average cross-reactivity of 58% based on published reports of 32 subjects.

Cross-reactions among aminoglycoside antibiotics

Cross-reactivity is defined as a reaction to two or more allergens caused either by common chemically comparable structures or by common degradation products.⁶⁰ For true cross-reactivity, there must be no history of previous exposure to the cross-reactive allergen. Because of the high prevalence of neomycin sensitivity, cross-reactions are usually reported relative to neomycin. A summary of the average rates of reported cross-reactivity is presented in Table III.^{49,50,60-67} Paromomycin and butirosin have the highest frequency of cross-reactivity with neomycin at 90%, because of the common chemical structures of neosamine and 4,5-di-O-substituted deoxystreptamine. Streptomycin lacks the deoxystreptamine group common to all other aminoglycosides, accounting for a lower cross-reaction rate of only 4%.

Ramos et al⁶⁸ reported a case of severe dermatitis of the external auditory meatus in a 32-year-old female who was using eardrops containing tobramycin. The patient was patch test positive to tobramycin (20% aqueous [aq]) as well as kanamycin, ribostamycin, and sisomycin, but not neomycin.⁶⁸ This case is likely the first published case of primary contact allergy to tobramycin with cross-reactivity to aminoglycosides other than neomycin.

Polypeptides

Bacitracin. Bacitracin is a polypeptide antibiotic, produced by *Bacillus subtilis*, that inhibits bacterial cell wall synthesis. It is active against many Gram-positive organisms.⁵² Bacitracin is commonly used for the prevention or treatment of superficial skin infections and is restricted to topical application because of potential nephrotoxicity.⁵⁴ Bacitracin is prepared as either plain bacitracin or zinc-containing bacitracin. It is thought that zinc bacitracin is less sensitizing than plain bacitracin.^{69,70}

In Finland in the 1960s, bacitracin sensitization was relatively common, with sensitization rates of 7.8% in a study of 17,500 patients suffering from eczema.⁷¹ On the other hand, 200 dermatologists surveyed in the United States in 1962 believed that sensitivity to bacitracin was very rare.⁷² In 1973, Bjorkner and Möller⁷⁰ reported only 3 cases of bacitracin contact allergy in 1000 patients. Two more cases of ACD to bacitracin were reported in 1978,⁷³ and 11 additional cases were reported in 1987.^{69,74} Before 1987, bacitracin sensitivity was only reported in patients with neomycin sensitivity. Katz and Fisher⁶⁹ and Held et al⁷⁴ were the first to report cases of bacitracin allergy without neomycin allergy.

In the last 15 years, the prevalence of bacitracin allergy in North America has risen dramatically.

Table III. Calculated average proportion of neomycin-sensitive patients with cross-reactions to other aminoglycosides

Antibiotic	n	% Cross-reactive		Reference(s)
		Average	Range	
Aminosylin	12	91.7	—	Jerez ⁶¹
Paromomycin	80	90.0	83.3-97	Jerez, ⁶¹ Rudzki, ⁶² Pirila ⁶³
Butirosin	20	90.0	—	Schorr ⁴⁸
Ribostamycin	12	83.3	—	Jerez ⁶¹
Framycetin	32	67.2	56.5-77.8	Pirila, ⁶⁴ Carruthers ⁶⁵
Kanamycin	344	60.0	10-67	Epstein, ⁶⁰ Jerez, ⁶¹ Rudzki, ⁶² Pirila, ^{63,64,66} Rudzki ⁶⁷
Gentamicin	305	58.0	40-79.5	Schorr, ⁴⁹ Jerez, ⁶¹ Rudzki, ⁶² Pirila, ⁶⁶ Rudzki ⁶⁷
Tobramycin	32	57.5	50-65	Schorr, ⁵⁰ Jerez ⁶¹
Sisomycin	12	50.0	—	Jerez ⁶¹
Amikacin	12	33.3	—	Jerez ⁶¹
Streptomycin	203	4.3	0-11	Epstein, ⁶⁰ Jerez, ⁶¹ Pirila, ⁶⁴ Rudzki ⁶⁷

n, No. of patients tested.

According to data from the NACDG, the prevalence of bacitracin sensitization between 1985 and 1990 was only 1.5%, increasing to 7.7% to 9.2% in the last 15 years (Table I).¹⁻⁶ It has been suggested that the rise in bacitracin sensitization may be related to the perception by health care providers that bacitracin is safer than neomycin, thereby increasing its use. The most recent NACDG data reported a bacitracin sensitization prevalence of 8% to 15% among nearly 6000 subjects with suspected ACD.^{6,75} Bacitracin was named the "Contact Allergen of the Year for 2003" by the American Contact Dermatitis Society to raise awareness about this increasingly common sensitizer.⁴⁶

While data on the prevalence of bacitracin sensitization in the general population has not been documented, its prevalence in selected populations has been studied. Based on a review of the literature, the calculated average prevalence of bacitracin sensitization among a total of 331 patients with venous insufficiency was 19.7%, making bacitracin allergy more common than neomycin allergy in this population (Table II). When used for postoperative wound care, Gette et al⁴⁴ reported a 2% prevalence of ACD to bacitracin in 215 patients. Our calculated average rate of bacitracin sensitization is 2.4% among 182 patients with chronic otitis externa (Table II).

It has been suggested that the frequency of bacitracin sensitivity may be underestimated, because it is not included in the T.R.U.E. test series and it is a "late" reaction. Patch test readings at 48 hours may miss up to 50% of positive reactions, as many positive reactions do not manifest until 96 hours.⁶⁹

Polymyxin B. Polymyxins are cationic, basic proteins, produced by *Bacillus polymyxa*, that bind to the cell membranes of bacteria and disrupt their osmotic properties. Polymyxins are active against

Gram-negative organisms including *Pseudomonas aeruginosa*, but lack activity against Gram-positive organisms. Polymyxin B is used topically to treat bacterial ocular infections, otitis externa, and superficial skin infections.^{52,54}

In a guinea pig experiment comparing the sensitizing potentials of topical antimicrobials, polymyxin B was shown to be a very weak sensitizer (0/10 sensitizing index).⁷⁶ However, in 85 patients with leg ulcers, the prevalence of contact sensitivity to polymyxin B was 14%.²⁸ Our calculated prevalence of ACD to polymyxin B among 182 leg ulcer patients was 4.6% (Table II).

Möller⁷⁷ reported sensitization to polymyxin B sulphate in 10 patients with stasis dermatitis and leg ulcers who were treated with a commercial petrolatum ointment containing oxytetracycline chloride 3 g/100 g, polymyxin B sulphate 10⁶ IU/100 g, liquid paraffin and white petrolatum to 100 g. Van Ketel⁷⁸ reported contact dermatitis of the feet in a patient using topical polymyxin B sulphate. The patient had positive reactions to a related polymyxin (polymyxin E) and to bacitracin. Van Ketel⁷⁸ suggested that the latter was a cross-reaction, because both polymyxin and bacitracin are produced by similar strains of *Bacillus* bacteria.

Of note, polymyxin B sulphate and polymyxin E can be used parenterally to treat gastro-intestinal infections, mainly from *P. aeruginosa*. Thus, if a patient is topically sensitized to polymyxin B sulphate or bacitracin, it is theoretically possible to develop a systemic contact dermatitis from parenteral administration of polymyxin.⁷⁹ However, our literature search found no such reports.

Virginiamycin/pristinamycin. Virginiamycin is a cyclic polypeptide complex belonging to the streptogramin group that inhibits bacterial protein

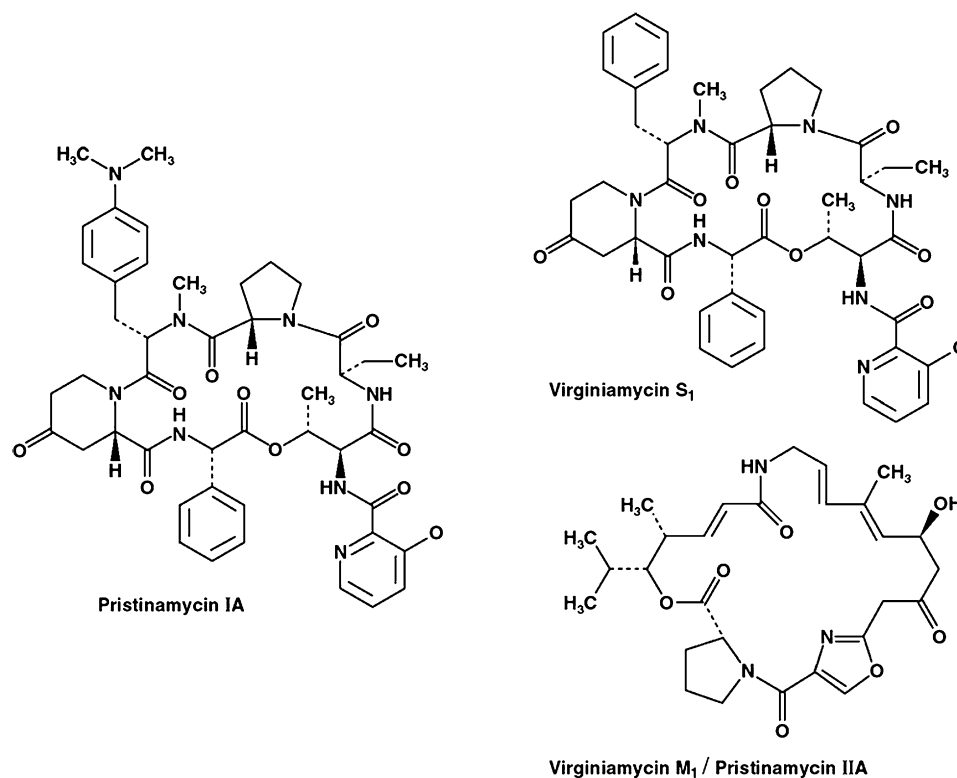


Fig 6. Chemical structures of virginiamycin and pristinamycin.⁴⁷

synthesis.⁸⁰ It consists of two factors: factor M (the main factor) and factor S.⁸¹ Virginiamycin is used topically in Europe to treat Gram-positive infections. It is also used as a growth promoter in cattle, swine, and poultry, and therefore can result in occupational contact dermatitis in livestock workers. Pristinamycin is a related streptogramin antibiotic made up of two fractions, IA and IIA.⁸² Chemically, factor M of virginiamycin and fraction IIA of pristinamycin are identical (Fig 6).⁴⁸ Therefore, one would expect that all patients sensitive to factor M of virginiamycin would also be sensitive to factor IIA of pristinamycin, and the literature supports this assumption. To our knowledge, there have been no reported cases of contact allergy to factor S of virginiamycin or to factor IA of pristinamycin.

Baes⁸² reported eight cases of contact allergy to virginiamycin. The patients were patch tested with factor M and factor S of virginiamycin as well as fraction IA and fraction IIA of pristinamycin. All eight patients were positive to factor M of virginiamycin 1% pet and fraction IIA of pristinamycin 1% pet. Lachapelle and Lamy⁸³ reported five cases of virginiamycin sensitivity to factor M of virginiamycin 5% pet and to pristinamycin 5% pet. (individual fractions not tested). Two of the five patients were also sensitized to neomycin sulfate 20% pet (virginiamycin is often combined with neomycin sulfate in

topical antibiotic preparations in Belgium).⁸³ Bleumink and Nater⁸⁰ reported one case of contact allergy to virginiamycin factor M in a burn patient. The patient reacted to 2% and 5% concentrations but not 0.5%. The patient was also sensitive to pristinamycin at all tested concentrations (individual fractions not tested).

There is one reported case of occupational contact dermatitis from virginiamycin. Tennstedt et al⁸¹ reported a 31-year-old male who handled a food additive which contained virginiamycin and other antibiotics. He had positive patch test reactions to factor M of virginiamycin 5% pet and to pristinamycin 5% pet (individual fractions not tested).

β -lactams. β -Lactam antibiotics inhibit mucopolypeptide synthesis in the bacterial cell wall.⁵² Currently, they are rarely used topically, because contact sensitivity is so common. Therefore, most cases of ACD to β -lactams present as occupational contact dermatitis in health care workers, pharmaceutical workers, or farmers who handle these drugs.

Penicillin. In the 1940s, there were three documented reports of topical penicillin sensitization. Following these reports, it was recommended that the use of topical penicillin should be limited to the shortest time possible, and if no immediate benefit was observed, the application should be discontinued.⁸⁴ In 1978, Girard⁸⁵ reported a patient who had

applied topical penicillin to a stasis ulcer and developed severe contact dermatitis around the ulcer 2 days later. Physicians now recognize the strong sensitizing potential of penicillin, and its topical use is largely avoided.⁸⁶

Occupational cases of ACD to penicillin have been reported in health care and pharmaceutical workers as well as in farmers.^{45,87} In a study of 81 patients with occupational dermatitis, penicillin was found to be the most common sensitizer in pharmaceutical workers and nurses and the third most common sensitizer in veterinary surgeons.⁴⁵ Rudzki et al⁸⁸ hypothesized that the frequency of occupational penicillin sensitivity parallels its use. In Poland over the last 30 years, the prevalence of occupational penicillin sensitivity has fluctuated to as high as 9.8% and as low as 0.7%, presumably as the result of reduction in the use of benzyl penicillin and an increase in the use of semisynthetic penicillins. In 1976 in Malaysia, where topical penicillin was available over-the-counter, penicillin was the most common cause of contact dermatitis caused by antibiotics.⁸⁹

Theoretically, penicillin could cross-react with the semisynthetic penicillins and cephalosporin antibiotics, all of which share a β -lactam ring. However, in practice, the different types of penicillin do not cross-react in a predictive fashion.⁸⁶

Semisynthetic penicillins. Cloxacillin was reported to cause ACD in two patients who applied topical cloxacillin intended for parenteral use on venous leg ulcers. The first patient developed an erythematous, edematous, and vesiculated dermatitis 8 hours after application, while the second patient developed a similar dermatitis 4 days after treatment. Both patients were patch test positive to cloxacillin 50 mg/ml in water. Cross-reactions to other β -lactams were not observed in these cases.⁹⁰

Ampicillin is a common cause of occupational contact dermatitis among health care workers.⁹¹ In a study of 62 health care workers with occupational eczema, ampicillin was found to be the most common allergen, responsible for ACD in 39% of the workers.⁹² In a separate study of occupational contact dermatitis among 81 health care workers, the semi-synthetic penicillins (ampicillin and cloxacillin) were the second most common group of sensitizers, after penicillins.⁴⁵

Cephalosporins. Most topical hypersensitivity reactions to cephalosporins result from occupational exposures. Case reports have described ACD from cephalosporins in pharmaceutical workers, nurses, and a chicken vaccinator.⁹³⁻⁹⁸

Foti et al⁹⁴ reported a 45-year-old nurse who had dermatitis on her hands, forearms, face, and neck for

4 years. During a leave of absence, the lesions disappeared completely. The patient noticed that the dermatitis followed handling cephalosporins for parenteral use. She reported that she had never ingested cephalosporins. She was patch tested and had positive reactions to five third-generation cephalosporins but not to any first- or second-generation cephalosporins. She also had negative reactions to both penicillin and ampicillin. Based on her patch test results, the authors concluded that her allergy was not to the β -lactam ring, but to the aminothiazolyl-methoxyl-iminic group and 7-amino-cephalosporanic acid, which are common to all third-generation cephalosporins.⁹⁴

There is only one case report of a patient who used cephalosporins in an exclusively topical manner. Milligan and Douglas⁹⁹ reported a patient who used cephalexin unconventionally on a stasis leg ulcer by applying the contents of cephalexin capsules to the ulcer under an occlusive dressing intermittently for many months. The patient developed dermatitis affecting the legs, face, and ears, and was patch test positive to cephalexin 1% in olive oil.

Cross-reactions are often observed within each cephalosporin generation, but the antibiotics' structural similarities must also be taken into account. Valsecchi et al¹⁰⁰ reported cross-reactivity between a penicillin and a cephalosporin in a patient with generalized urticaria, mucous membrane edema, and itching following the administration of parenteral ampicillin. The patient had no known previous exposure to topical compounds containing either antibiotic, but had positive patch test reactions to ampicillin and cephalexin (patch test concentrations not reported).

Macrolides

Erythromycin. Erythromycin is a macrolide antibiotic that inhibits bacterial protein synthesis by reversibly binding to 50S ribosomal subunits inhibiting translocation of aminoacyl t-RNA. It is active against most aerobic and anaerobic Gram-positive bacteria as well as a few Gram-negative bacteria. Topical erythromycin is used to treat acne vulgaris, superficial skin infections, and ophthalmic infections.⁵²

ACD to topical erythromycin is extremely rare. Van Ketel¹⁰¹ described a patient with delayed hypersensitivity to 0.1%, 1%, and 5% erythromycin stearate in petrolatum following application of erythromycin stearate (5% pet) to venous leg ulcers. Lombardi et al¹⁰² reported a patient with chronic dermatitis surrounding his leg ulcers, which had been treated with various topical antibiotics including erythromycin. The patient was patch test positive to

erythromycin sulphate 25% pet. Bernstein and Roenigk¹⁰³ analyzed 27,655 surgical procedures (excluding biopsies) in which erythromycin 2% pet was used for wound care. They found 6 cases of sensitization (0.022%; patch test concentration not reported).

Initially, the erythromycin base was thought to be nonsensitizing because Fisher¹⁰⁴ reported using the base on 60 patients with stasis ulcers and found no cases of allergic sensitization. However, in the mid-1990s, three cases of sensitization to the erythromycin base were reported.¹⁰⁵⁻¹⁰⁷

Miscellaneous antibiotics

Benzoyl peroxide. Benzoyl peroxide is primarily marketed as an antimicrobial agent effective against *Propionibacterium acne*, but it also has antifungal, antipruritic, and keratolytic properties. It is used topically in the treatment of acne and leg ulcers.^{52,108} Benzoyl peroxide is also used in the manufacture of plastic materials, resins, and elastomers, as a polymerization initiator in vinyl resins, and as a hardener in silicone elastomers.¹⁰⁹

Benzoyl peroxide is well known to cause irritant contact dermatitis, but allergic sensitization, while rare, has also been reported. Lindemayr and Drobil¹¹⁰ patch tested 222 patients with 5% benzoyl peroxide gel, and found positive allergic reactions in 3 of 94 (3.1%) inpatients with various skin diseases, in 4 of 69 (5.8%) patients with eczematous dermatoses, and in 3 of 59 (5.1%) patients with acne vulgaris who were using a benzoyl peroxide preparation for a mean of 10.7 months.

The prevalence of sensitization to benzoyl peroxide in patients with chronic leg ulcers is much higher than in patients with acne and eczematous dermatoses. Vena et al¹¹¹ patch tested 120 patients suffering from chronic leg ulcers with benzoyl peroxide 1% pet. Positive patch test reactions were found in 12 of the 120 patients (10%). Agathos and Bandmann¹¹² patch tested 41 patients with leg ulcers with benzoyl peroxide 1% pet, and when negative, treated them for 4 weeks with 20% benzoyl peroxide lotion. When patch tested following treatment, the authors reported a sensitization rate of 76%. Angelini et al¹⁹ reported a sensitization rate to benzoyl peroxide 1% pet of 7.6% in 118 patients with stasis dermatitis of the lower leg with or without ulceration.

There are several case reports of contact dermatitis to benzoyl peroxide in the workplace. Two cases of airborne contact dermatitis were found in podiatrists who pumiced insoles containing benzoyl peroxide. Both podiatrists were patch test positive to benzoyl peroxide 1% pet.¹⁰⁹ Forschner et al¹¹³ reported a 32-year-old male orthopedic technician

who had recurrent eczema of the face, neck, and arms for 2 years while heating and cutting materials such as plaster. He was patch test positive to benzoyl peroxide 1% and 2.5% pet. Bonnekoh and Merck¹¹⁴ reported another case of ACD to benzoyl peroxide in a sacristan. Benzoyl peroxide was used as a bleaching agent in candle wax. Quirce et al¹¹⁵ described airborne contact sensitization to benzoyl peroxide in an electrician sawing insulation plastics. Benzoyl peroxide has also been reported as a contact allergen in adhesive tape,¹¹⁶ a marble hardener,¹¹⁷ swimming goggles,¹¹⁸ and dental prostheses.¹¹⁹

Chloramphenicol. Chloramphenicol inhibits bacterial protein synthesis by binding reversibly to the 50S ribosomal subunit.¹²⁰ It is used topically in ophthalmology, laryngology, dermatology, and gynecology, with most ACD reactions elicited from eyedrops.¹²¹

Overall, chloramphenicol has a low frequency of sensitization.¹²¹ Van Joost et al¹²² described eight patients with periocular and periauricular dermatitis of possible allergic origin. All eight were patch test positive to chloramphenicol powder 100% (dilutions not reported). Moyano et al¹²³ reported a farmer who developed dermatitis on both eyelids and the upper face following treatment with eyedrops containing chloramphenicol for conjunctivitis. Following the initial episode, the patient had accidentally handled medicaments containing chloramphenicol for use in animals, and he developed dermatitis on areas of contact. He was patch test positive to chloramphenicol 1% pet.

Chloramphenicol-induced ACD has also been reported in patients with leg ulcers,¹²⁴ conjunctivitis,^{121,125} and vaginal infections.¹²¹ Cross-sensitization has been demonstrated to thiamphenicol 5% pet, a semisynthetic derivative of chloramphenicol with a similar chemical structure.¹²⁵ There is one case report of occupational contact dermatitis from chloramphenicol in a health care worker with daily contact to this antibiotic.¹²⁶

Because false negative reactions may occur when patch testing in petrolatum, ethanol or water is recommended when patch testing to chloramphenicol.¹²⁷

Clindamycin. Clindamycin, a semisynthetic derivative of lincomycin, inhibits bacterial protein synthesis by binding to 50S ribosomal subunits. It is effective against aerobic Gram-positive cocci and several anaerobic and microaerophilic Gram-negative and Gram-positive microorganisms. Clindamycin is used topically for the treatment of acne vulgaris and bacterial vaginosis.⁵²

Clindamycin was first used topically to treat acne in 1976.¹²⁸ The first case of clindamycin contact

allergy was reported in 1978.¹²⁹ Clindamycin is a weak allergen accounting for only five case reports in the literature.¹³⁰ An illustrative case is that of a 21-year-old male who was treated for acne vulgaris with clindamycin lotion 1%. He developed facial erythema and papules after 1 month of treatment. He was patch test positive to clindamycin hydrochloride 0.5% aq and clindamycin phosphate 0.1% aq, but was negative to lincomycin and several other antibiotics.¹³¹

Cross-reactions may occur between clindamycin and lincomycin. Conde-Salazar et al¹²⁸ reported a patient exposed to systemic and topical clindamycin who developed widespread eczema and had positive patch test reactions to both clindamycin hydrochloride and phosphate 1% aq as well as lincomycin hydrochloride 1% aq.

Clioquinol. Clioquinol is a halogenated hydroxyquinoline antibiotic. It inhibits the growth of Gram-positive cocci, such as Staphylococci or Enterococci, and various mycotic organisms, such as Microsporon, Trichophyton, and *Candida albicans*. It is also directly amebicidal. It is used topically in the treatment of eczema, infected leg ulcers, and fungal infections.¹³²

Clioquinol is a rare sensitizer. Lazarov et al¹³³ found that only 3 of 2156 patients in a contact dermatitis clinic were patch test positive to clioquinol 5.0% pet. Similarly, Morris et al¹³⁴ found that 8 of 1119 patients (0.7%) in a contact dermatitis clinic were sensitized to clioquinol 5% pet. Agner and Menne¹³⁵ reported that 21 of 4556 patients were patch test positive to clioquinol 3% and 5% pet. Sensitization to clioquinol seems to be more common in patients with leg ulcers. Le Coz et al³¹ patch tested 50 patients with leg ulcers and found that 3 (6%) were patch test positive to clioquinol 5% pet.

There is the possibility of cross-reactions among clioquinol and other topical and systemic halogenated hydroxyquinolines and some antimalarial drugs with a quinoline nucleus.¹³⁶ Kernekamp and van Ketel¹³⁷ reported that 40% of patients previously sensitized to clioquinol were patch test positive to the antimalarial drugs quinine, resorquine, and amodiaquin. Clioquinol was also found to cross-react with other topically applied halogenated hydroxyquinolines such as chlorquinaldol and broxyquinoline.^{137,138}

Fusidic acid. Fusidic acid, also known as sodium fusidate, is a topical antimicrobial agent used for skin infections caused by Gram-positive bacteria, mainly *Staphylococcus aureus*.^{134,139} Fusidic acid appears to be a rare sensitizer. The first reported case was in 1970 by Verbov¹⁴⁰ who described contact allergy to sodium fusidate (2% aq) in a patient with leg ulcers.

Morris et al¹³⁴ found that only 3 of 1119 patients (0.3%) from a contact dermatitis clinic were patch test positive to fusidic acid 2% pet. The authors also collected data from 1980 to 2000 on fusidic acid sensitivity in 3307 patch tested patients with contact dermatitis. A total of 48 patients were patch test positive to fusidic acid 2% pet over the 20-year study.¹³⁴

Single case reports or case series have also included 10 patients with stasis eczema,¹⁴¹ 7 patients with leg ulcers,^{139,140,142-144} 2 patients with otitis externa,¹⁴¹ and 2 patients with atopic eczema.¹⁴³

Metronidazole. Metronidazole is a synthetic, nitroimidazole-derivative antibacterial and antiprotozoal agent, which also has direct antiinflammatory and immunosuppressive effects. It is used topically for the treatment of inflammatory lesions associated with rosacea, and for the treatment of bacterial vaginosis, trichomoniasis, decubitus and other ulcers, perioral dermatitis, and alveolar osteitis.⁵²

ACD to topical metronidazole is rare. Beutner et al¹⁴⁵ patch tested 215 healthy patients with metronidazole 1% pet, and none of the patients had a patch test reaction indicative of contact sensitization. Jappe et al¹⁴⁶ patch tested five patients with suspected metronidazole allergy and found only one case of contact sensitization. There are only five case reports of contact dermatitis caused by topical metronidazole in the literature.¹⁴⁶⁻¹⁴⁹

Cross-reactivity to imidazole antifungals has been reported. Izu et al¹⁵⁰ reported a patient with tinea pedis who developed severe dermatitis following treatment with tioconazole cream. The patient was patch test positive to tioconazole 1, 10, 20 and 50% pet (a phenethyl imidazole), as well as metronidazole 2% pet (a nitroimidazole) and bifonazole 2% pet (a phenmethyl imidazole), despite having no previous contact to these latter two medications. The authors recommended that patients with contact allergy to any imidazole should be patch tested with other imidazoles because of the possibility of cross-reactivity.¹⁵⁰

Mupirocin. Mupirocin is produced by fermentation of the organism *Pseudomonas fluorescens* and inhibits bacterial protein synthesis by reversibly and specifically binding to bacterial isoleucyl t-RNA synthetase.⁵² It is effective against aerobic Gram-positive bacteria.⁵⁴ Mupirocin is used topically in the treatment of primary and secondary skin infections, atopic eczema, leg ulcers, and in the elimination of nasal carriage of *S aureus*.^{52,54,151}

ACD from mupirocin appears to be very rare. Mupirocin sensitization was first reported in 1995 in a patient who applied mupirocin ointment to venous leg ulcers. The patient was patch test positive to the

commercial ointment, a calcium mupirocin free base ointment at 1% and 10%, but was negative to the vehicle.¹⁵¹ In 1997, a second case report described a patient who applied mupirocin ointment after removal of a basal cell carcinoma. The patient was patch test positive to the 2% mupirocin ointment and negative to the polyethylene glycol vehicle provided by the manufacturer.¹⁵²

Two small studies have stressed the low sensitizing potential of mupirocin. In 25 healthy volunteers, no sensitization occurred in detergent-damaged skin.¹⁵³ In 13 patients who had used mupirocin for postoperative wound care, sensitization was not observed.⁴⁴ Zaki et al²⁸ reported a 2% prevalence of mupirocin sensitization in 85 patients with leg ulcers.

Because of its unique mechanism of action and structure, mupirocin does not appear to cross-react with other antibiotics.

Nitrofurazone. Nitrofurazone is a broad-spectrum antibacterial agent used topically to treat ulcers, burns, and skin infections.¹⁵⁴ In 1948, Downing and Brecker¹⁵⁵ reported a 6% prevalence of nitrofurazone sensitization in 233 patients with various types of dermatitis. Currently, its use has largely been abandoned in Western countries because of the high incidence of allergic reactions.¹⁵⁶ In India in the 1980s, nitrofurazone was still widely used topically as a first-aid medicament and was readily available. In a study of 390 patients from India with suspected contact dermatitis to topical medicaments, nitrofurazone was the most common sensitizer, with 36.2% of patients having a positive patch test reaction.¹⁵⁷

Cases of nitrofurazone sensitization have been reported in patients with varicose ulcers, traumatic ulcers, abrasions, and as a secondary ACD in a patient with cumulative irritant contact dermatitis.^{156,158} While topical use in humans has decreased, nitrofurazone is still used in veterinary medicine and as an animal feed additive, allowing for the potential of occupational contact dermatitis.¹⁵⁶ Caplan⁸⁷ reported a feed store employee with sensitivity to nitrofurazone 1%. Neldner¹⁵⁹ reported a hog rancher with dermatitis who was strongly patch test positive to a commercial feed additive containing nitrofurazone. Conde-Salazar et al¹⁵⁴ reported a case of nitrofurazone 1% pet sensitization in a cattle breeder handling uterine ovules containing the drug.

Cross-reactions involving nitrofurazone have not been reported in the literature.

Rifamycin. Rifamycin is produced by *Streptomyces mediterranei* and inhibits bacterial protein synthesis.⁵² It has activity against Gram-positive and Gram-negative microorganisms. Rifamycin is used topically for the treatment of infectious conjunctivitis, infected wounds, and for some leg ulcers.¹⁶⁰

Riboldi et al¹⁶¹ published the first case of rifamycin contact allergy in an 11-year-old boy who developed dermatitis after applying a topical medicine containing rifamycin and mercurochrome to minor wounds. The boy had positive patch test reactions to rifamycin and mercurochrome (concentrations not reported). ACD from topical rifamycin has also been described in patients who have applied rifamycin to a postsurgical wound,¹⁶² a biopsy site,¹⁶³ and to leg ulcers.^{162,164}

Cross-reactions to rifamycin have not been documented in the literature.

Oxytetracycline. Oxytetracycline inhibits bacterial protein synthesis by reversibly binding to 30S ribosomal subunits, thereby inhibiting the binding of aminoacyl t-RNA to those ribosomes. It is active against many aerobic and anaerobic Gram-negative and Gram-positive bacteria, including *Rickettsia*, *Chlamydia*, *Mycoplasma*, and spirochetes. Oxytetracycline is used topically in the treatment of acne vulgaris, ophthalmic infections, and in the prevention or treatment of skin infections.⁵²

Based on our analysis of the literature, the calculated average prevalence of oxytetracycline sensitivity was 8.1% in a total of 443 patients with venous insufficiency. Bojs and Moller¹⁶⁵ initially reported three cases of contact sensitization to oxytetracycline with cross-sensitization to other tetracyclines. Moller⁷⁷ reported an additional seven cases in patients with stasis ulcers and/or dermatitis. In this study, Moller described 10 patients with stasis ulcers and/or dermatitis who were using an ointment containing oxytetracycline and polymyxin B. Nine of the ten patients were sensitized to oxytetracycline, and all 10 patients were sensitized to polymyxin B. Rudzki and Rebandel²⁹ evaluated a total of 1267 patients with various types of dermatitis for oxytetracycline sensitivity. The authors found oxytetracycline sensitivity in 10.8% of 111 patients with stasis dermatitis, 1.8% of 276 patients with conjunctivitis, 0.7% of 832 patients with contact dermatitis, and none of 48 patients with atopic dermatitis.

CO-SENSITIZATION

Simultaneous sensitization to two antigens which are not structurally related is termed "co-sensitization"; the two antigens are often present in the same topical preparation, such as triple antibiotic ointment.¹⁶⁶ The co-sensitization rate of neomycin and bacitracin was 88% in a study of 50 patients.⁶⁴ Before 1987, there were no reports of reactions to bacitracin without neomycin. Grandinetti and Fowler¹⁶⁷ reported an illustrative case of a 39-year-old female who developed an acute, erythematous, vesicular dermatitis following treatment with a triple

Table IV. Topical antibiotics known to cause immediate, Type I hypersensitivity reactions

Antibiotic	Reference	Risk factor	Reaction
Bacitracin	Comaish ¹⁶⁸	Ulcer	A
	Dyck ¹⁶⁹	Tattoo	A
	Roupe ¹⁷⁰	Atopic dermatitis	A
	Schechter ¹⁷¹	Ulcer	A
	Sarayan ¹⁷²	Abrasions	A
Bacitracin irrigation	Blas ¹⁷³	Intraoperative	A
	Sprung ¹⁷⁴	Intraoperative	A
Bacitracin and neomycin	Goh ¹⁷⁵	Burn	A/CU
Bacitracin/polymyxin B	Eedy ¹⁷⁶	Ulcer	CU
Benzoyl peroxide	Minciullo ¹⁰⁸	Acne	CU
	Tkach ¹⁸⁶	Acne/abrasive scrub	CU
Clioquinol	Katsarou ¹⁸⁷	None	CU
Cefotiam hydrochloride	Chiba ¹⁷⁷	Nurse	CU
Chloramphenicol	SchewachiMillet ¹⁷⁸	Otitis externa	A
	Lipshitz ¹⁸⁸	Eyedrops	A
Erythromycin	Van Ketel ¹⁷⁹	Leg ulcer	CU
Framycetin	Agathos ¹⁸⁰	Postsurgical wound	A
Fusidic acid	DeCastro Martinez ¹⁸⁴	Impetigo	CU
Metronidazole	Knowles ¹⁸⁵	Recurrent vaginitis	A
	Schulze ¹⁹⁰	Vaginitis	A
Neomycin	Pippen ¹⁸¹	Chronic venous insufficiency	A
Rifamycin	Garcia ¹⁶⁰	Eyedrops	A
	Grob ¹⁸⁹	Ulcer	CU
Rifamycin SV	Scala ¹⁸²	Traumatic wound	A
Streptomycin solution	Romano ¹⁸³	Chronic hand eczema	A
		Wound	CU

A, Anaphylaxis; CU, contact urticaria.

antibiotic ointment for impetigo. The ointment was stopped, and oral and topical steroids were started with resolution of the dermatitis. The patient later applied the triple antibiotic ointment to a breast biopsy site and a similar dermatitis developed. She was patch test positive to neomycin, polymyxin B, and bacitracin, the three active components of the commercial ointment.

TYPE I HYPERSENSITIVITY

Several topical antibiotics may also cause type I, IgE-mediated hypersensitivity reactions. Symptoms range from contact urticaria to life-threatening anaphylaxis. Prick or scratch testing is most commonly used to diagnose type I hypersensitivity. Table IV^{108,160,168-190} lists topical antibiotics known to cause immediate reactions. In all but one reported case, an interruption of the skin barrier was present. Therefore, it has been suggested that access to systemic circulation seems to be a requirement for the development of anaphylaxis from externally applied agents.¹⁷¹ Despite the low likelihood of a life-threatening, immediate type I reaction occurring during patch testing, if the patient's symptoms and history suggest a type I reaction, it is suggested that

resuscitation equipment be available and the patient observed for at least 1 hour after patches are applied.

Bacitracin is the most common topical antibiotic known to cause anaphylaxis.¹⁷¹ Comaish and Cunliffe¹⁶⁸ reported an illustrative case of a 49-year-old female who developed facial swelling, generalized pruritis and urticaria, chest tightness, sweating, and hypotension 15 minutes after applying bacitracin to a venous leg ulcer. Months later, an intradermal test was positive to bacitracin 1/1000 (0.03 ml) with systemic symptoms. The patient later recalled two previous urticarial reactions following application of bacitracin to her ulcer. In three patients who were patch test positive to bacitracin, Bjorkner and Möller⁷⁰ reported that bacitracin injection caused a local wheal-and-flare reaction. Severe life-threatening anaphylactic shock from topical administration of bacitracin has also been reported after application to stasis ulcers,^{168,171} atopic dermatitis,¹⁷⁰ recent tattoos,¹⁶⁹ abrasions,¹⁷² and intraoperatively when used in irrigation.^{173,174}

Baes⁸² reported an interesting case suggesting topical sensitization to virginiamycin with a subsequent type I reaction to systemic administration of pristinamycin. A 44-year-old male applied a virginiamycin-containing salve for a presumed bacterial

infection and developed an acute ACD. A few months later, he developed a furuncle on his nose and ingested one 250 mg tablet of pristinamycin. Four hours later, he developed generalized urticaria with edema of the lips and eyelids, severe itching, emesis, fever, and stupor. During patch testing to virginiamycin 1% pet and pristinamycin 1% pet, the patient experienced transient edema of the lips and eyelids and a wheal next to the patch test reaction.

Van Ketel¹⁷⁹ reported a 7-year-old girl who developed contact urticaria after the application of an erythromycin stearate suspension for treatment of bronchitis. She developed a generalized urticarial eruption and the treatment was discontinued. The patient was patch test negative to erythromycin stearate suspension, but was strongly scratch test positive to a drop of the suspension.

Lipshitz and Loewenstein¹⁸⁸ reported a patient who developed an anaphylactic reaction following the application of chloramphenicol eye ointment 5%. Two years later, the man experienced anaphylaxis again after applying topical chloramphenicol to his daughter's finger. Schewach-Millet and Shpiro¹⁷⁸ reported two other cases of urticaria and angioedema caused by topically applied chloramphenicol ointment 3% for treatment of otitis externa and a finger wound, respectively.

Grob et al¹⁸⁹ published a case of type I and type IV hypersensitivities to rifamycin in a leg ulcer patient. Rifamycin had been applied to an ulcer as a compress. After 15 minutes, a wheal developed; within 40 minutes, generalized urticaria developed without respiratory or hemodynamic complications. The patient was patch test and scratch test positive to rifamycin sodium salt 1% aq. Rifamycin has also been reported to cause anaphylaxis after the use of an eyedrop and when applied to postsurgical or to other wounds.^{160,182}

Knowles et al¹⁸⁵ reported a case of type IV hypersensitivity reaction to intravaginal metronidazole followed by a type I hypersensitivity reaction to oral metronidazole. A 35-year-old female had previously experienced localized erythema to intravaginal metronidazole. Within 1 hour of receiving oral metronidazole, she developed fever, chills, generalized erythema, and a maculopapular rash. The following day, she developed shortness of breath and worsening edema of the extremities. Patch testing was not performed.¹⁸⁵ Schulze et al¹⁹⁰ reported another anaphylactic reaction to vaginal application of metronidazole in a 57-year-old female. The patient developed acute urticaria, facial edema, laryngeal discomfort, tachycardia, and shivering. The patient was scratch-test positive to metronidazole 0.5% pet.

Tkach¹⁸⁶ reported a case of contact urticaria to topical benzoyl peroxide. A 13-year-old female with acne developed hivelike lesions occurring about 30 minutes after application of 5% topical benzoyl peroxide. The patient experienced a moderate wheal and flare reaction with pruritis when patch tested with benzoyl peroxide 5% in water with occlusion. Minciullo et al¹⁰⁸ published a separate case of allergic contact angioedema to benzoyl peroxide in a 26-year-old female with acne. The patient developed an itchy erythematous reaction and strong edema localized to the face 2 weeks after she began applying a 10% benzoyl peroxide gel to her face. She was patch test positive to benzoyl peroxide 1% pet and to the 10% benzoyl peroxide-containing gel.

Katsarou et al¹⁸⁷ reported cases of both type I and type IV hypersensitivities to topical clioquinol. Of the 664 patients studied with suspected contact dermatitis, 13 had an immediate patch test reaction (wheal and flare) to clioquinol (conc and vehicle not reported), while 6 had a delayed patch test reaction.

SYSTEMIC CONTACT DERMATITIS

De Castro Martinez et al¹⁸⁴ reported a case of systemic contact dermatitis to oral fusidic acid with previous topical sensitization. A 51-year-old male with an impetiginized skin lesion was first treated with a topical ointment containing fusidic acid 2% in lanolin and pet with no adverse effects. Four days later, he was treated with an oral dose of fusidic acid (250 mg) and developed a pruritic micropapular generalized exanthema 4 hours later. The patient was patch test positive to the commercial ointment (fusidic acid 2% in lanolin and pet) and negative to lanolin and petrolatum alone.

Systemic antibiotics have been increasingly recognized as causative agents for the baboon syndrome, a type IV reaction to systemically administered allergens thought to be mediated by hematogenous spread of the allergen. It can occur in persons with or without previous skin sensitization. The characteristic clinical feature is a light-red diffuse erythema of the buttocks, upper inner surface of the thighs, and axillae. The onset is acute, occurring a few hours to a few days after oral exposure to the antigen.¹⁹¹⁻¹⁹³ In persons without previous cutaneous sensitization, baboon syndrome has been reported to be caused by the following antibiotics: amoxicillin, amoxicillin/clavulanic acid, ampicillin, pivampicillin, ceftriaxone, cefuroxime, cephalixin, clindamycin, erythromycin, penicillin V, and roxithromycin. In persons with previous cutaneous sensitization, ampicillin and neomycin have been reported to cause baboon syndrome.¹⁹³

Table V. Recommended patch test concentrations¹⁹⁴

Antibiotic	Concentration	Vehicle
Neomycin sulfate	20%	pet
Gentamicin sulfate	20%	pet
Streptomycin	0.1%-1%	aqua
	1%	pet
	1%	aqua
Tobramycin	20%	pet
	20%	aqua
Bacitracin	20%	pet
Polymyxin sulfate	3%	pet
Pristinamycin	5%	pet
Virginiamycin	5%	pet
	2.5%	pet
Penicillin comm prep	1%	pet
	10,000 IU/gr	pet
	100,000 IU/ml	pet
Cloxacillin	Pure	
Ampicillin	Pure	
	1%	pet
	5%	aqua
Cephalosporins	5%	pet
	1%-5%	aqua
	Pure or scratch test	
Cephalexin	0.5%	aqua
	1%	oo
	1%	oo
Erythromycin	Pure	
	1%	pet
	10%	pet
Sulfate	2%, 25%	
Stearate	1%	
Benzoyl peroxide	1%	pet
Chloramphenicol	5%	pet
Clindamycin hydrochloride	1%	aqua
	1%	pet
Clioquinol	5%	pet
Fusidic acid sodium salt	2%	pet
	2%	aqua
Metronidazole	2%	pet
Mupirocin	NA	
Nitrofurazone	1%	pet
Rifamycin	0.5%	pet
	0.5%-2.5%	pet
Oxytetracycline	3%	pet
	10%	pet

DIAGNOSIS AND MANAGEMENT

Diagnosis of allergy to topical antibiotics requires a heightened degree of suspicion, especially in high-risk patients, such as those with CVI, leg ulcers, or chronic otitis externa. It is important for clinicians to note that the symptoms of ACD may be masked by the skin changes of venous insufficiency. Stasis

dermatitis and ACD can appear morphologically similar.³² Because the sensitization rate of 67% is alarmingly high in this population, some experts recommend routinely patch testing all patients suffering from chronic stasis dermatitis and/or treatment-resistant leg ulcers. Similarly, ACD should be considered in all cases of chronic otitis externa resistant to treatment.

Patch testing is an important tool for diagnosing ACD. In addition to active ingredients, it is important to patch test with the components of suspected products, including vehicles, preservatives, and other additives. Table V¹⁹⁴ provides the recommended patch test concentrations for the topical antibiotics discussed in this review.

Once the allergen(s) have been determined, patient education is fundamental. The patient must also be made aware of cross-reacting allergens. Physicians can consult the Contact Allergen Database (CARD) for a frequently updated electronic database of ingredients in over-the-counter and prescription topical preparations (www.contactderm.org; CARD is accessible to members of the American Contact Dermatitis Society). Patients should also be encouraged to read the labels of topical medications.

It should also be stressed that a topical antibiotic is not always needed. In the case of minor surgical wounds, white petrolatum may function as well as a topical antibiotic ointment. In a randomized, controlled trial of 922 patients who had dermatologic surgery, Smack et al¹⁹⁵ found no significant difference in the incidence of infection ($P = .37$; 95% CI, -0.4% - 2.7%) or healing ($P = .98$ on day 1, $P = .86$ on day 7, and $P = .28$ on day 28) between those treated with bacitracin ointment and those treated with white petrolatum. Patients who experienced extensive itch around the wound site were patch tested with 20% bacitracin, 20% neomycin, and white petrolatum. Although this study found no difference in the rate of ACD ($P = .12$), in light of bacitracin's rising rate of sensitization and risk of anaphylaxis, physicians should consider using petrolatum instead of topical bacitracin for minor procedures. It has also been suggested that using hydrocolloid or foam dressings instead of antibiotic ointments as treatment modalities for patients with leg ulcers may improve healing and lower sensitization rates.¹⁹⁶

SUMMARY

ACD to topical antibiotics is not uncommon. Physicians should be aware of high risk groups, including patients who have an impaired skin barrier. Life-threatening anaphylaxis from the topical administration of some antibiotics is also possible,

especially with bacitracin. Further research is needed regarding the cross-reactivity and prevalence of contact allergy to specific topical antibiotics.

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