

Neomycin

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FIRST isolated in 1949 from the gram-positive bacillus *Streptomyces fradiae*, neomycin belongs to the aminoglycoside family of antibiotics. It consists of a mixture of two isomers, neomycin B and neomycin C, along with small amounts of a degradation product, neamine or neomycin A.¹ It exerts its antibacterial activity through irreversible binding of the nuclear 30S ribosomal subunit, thereby blocking bacterial protein synthesis.² Neomycin is effective against most gram-negative organisms except *Pseudomonas aeruginosa* and anaerobic bacteria. Its activity against gram-positive microorganisms is more or less limited to staphylococci, but bacterial resistance super-venes after prolonged use.

Percutaneous absorption after topical application is minimal, and absorption through intact gastrointestinal mucosa is poor, ranging between 1% and 3%. Parenteral administration is associated with severe oto- and nephrotoxicity, at times irreversible. Neomycin is therefore used (1) in topical formulations for the prevention and treatment of superficial skin, ear, and eye infections; (2) in solutions for urinary instillations to prevent bacteriuria from indwelling catheters; and (3) in peritoneal irrigation solutions used to treat contaminations in abdominal surgery. Dentists may use a neomycin-containing paste in root canal treatment. Given orally in doses of 200 to 1,000 mg two to four times per day, neomycin is used to sterilize the gut before digestive tract surgery and is also used in the treatment of hepatic coma (to reduce the number of ammoniagenic intestinal bacteria). In addition, trace amounts of neomycin are present in numerous vaccines as a result of its use to prevent bacterial contamination during the vaccines' manufacture (Table 1).

Contact Hypersensitivity to Neomycin

Allergic contact dermatitis from neomycin was first described in 1952.³ Prystowsky and colleagues determined the frequency of neomycin sensitization in the general population to be 1.1%.⁴ Reported sensitization rates in selected patient populations referred for patch testing vary from one country to another. In 10 European centers, the rates varied from 1.1 to 3.8% and averaged 1.9%.⁵ A multifactorial analysis of German data found a global prevalence of neomycin sensitization of 2.5% in patch-tested patients.⁶ Published results from the North American Contact Dermatitis Group reveal sensitization rates that are much higher and that have remained remarkably stable through the years, from 11.6% in the 1994–1996 study period to 10% in the 2005–2006 period.⁷ According to this group's database, neomycin is now the fifth most common allergen in North America and was the third most common in the previous study period. This higher rate of sensitization stems from the availability of this antibiotic in numerous over-the-counter preparations, especially "triple antibiotic" creams and ointments. Subgroups at higher risk include patients with stasis dermatitis and leg ulcers, anogenital dermatitis, and otitis externa.⁸

Because antibiotic preparations are applied to already damaged skin, allergic contact dermatitis from neomycin is not always easily recognized. It often presents as the persistence or worsening of a preexisting dermatitis.⁹ An intensification of itch and the progression of lesions beyond the initial site of involvement may offer clues to the correct diagnosis. Occupational dermatitis involving the hands (and sometimes the face) can occur in nurses, physicians, pharmacists, dentists, and veterinarians.¹⁰

Patch Tests with Neomycin

The usual concentration of neomycin in topical formulations is 0.5%. However, patch testing on normal skin with the commercial preparation almost always yields negative results owing to poor penetration through an intact epidermal barrier. To overcome this difficulty, patch testing with neomycin is done with a concentration of

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Dermatitis Contact Allergens of the Year

2009 (Volume 20, Number 1)

Mixed Dialkyl Thioureas

Bryan E. Anderson

2008 (Volume 19, Number 1)

Nickel

Rachel Komik

Kathryn Zug

2007 (Volume 28, Number 1)

Fragrance

Frances J. Storrs

2006 (Volume 17, Number 2)

P-Phenylenediamine

Vince DeLeo

2005 (Volume 16, Number 1)

Corticosteroids

Marlene Isaksson

Magnus Bruze

2004 (Volume 15, Number 1)

Cocamidopropyl Betaine

Joseph Fowler

2003 (Volume 14, Number 1)

Bacitracin

Apra Sood

James Taylor

2002 (Volume 13, Number 1)

Thimerosal

Donald Belsito

2001 (Volume 12, Number 1)

Gold

Joseph Fowler

2000 (Volume 11, Number 1)

Disperse Blue Dyes

Frances Storrs

Table 1. Vaccines Containing Neomycin

Type	Name
Chickenpox	Varivax, Varilrix
Measles	Attenuvax
Mumps	Mumpsavax
Rubella	Meruvax II
Measles and rubella	Eolarix
Rubella and mumps	Biavax
Measles, mumps, and rubella	MMR II, Priorix
Influenza	Fluvirin, Fluad, Fluvax, Vaxigrip
DPT and polio	Infanrix IPV
DPT and polio and hepatitis B	Infanrix Penta
DPT and polio and hepatitis B and <i>Haemophilus influenzae</i>	Infanrix Hexa
Hepatitis A	Avaxim, Havrix 1440, Havrix Junior
Hepatitis A and B	Twinrix 720/20, Twinrix Junior 360/10
Hepatitis A and <i>Salmonella</i> <i>typhi</i>	Vivaxim
Polio	Ipol, Orimune Trivalent, Polio Sabin
Rabies	Imovax

DPT = diphtheria and tetanus toxoids and pertussis.

tests with the commercial preparation⁴ or patch tests with a 20% aqueous solution of neomycin¹² may eliminate the need for intradermal tests. When intradermal tests are required, a 1% sterile solution of neomycin is used.¹¹

Patch-test reactions to neomycin are notoriously slow to appear, peaking at 96 hours (day 4) or even at 168 hours (day 7).¹² Readings must therefore be performed after 48 hours if a certain number of cases are not to be missed. Similar to what occurs with gold, positive reactions may persist for days to weeks.

Neomycin Cross-Reactions

Neomycin is composed of four rings joined by glycosidic bonds (Fig 1). One of the rings, the amino hexose 2-deoxystreptamine, is common to all aminoglycosides except streptomycin. In streptomycin, the hexose is streptidine, and the entire structure of the molecule differs from that of other antibiotics of the same group. Framycetin is 99% neomycin B whereas paromomycin and butirosin share close structural similarities with neomycin. Antibiotics of the kanamycin family include tobramycin and amikacin; these antibiotics share with neomycin the neosamine moiety, with slight modifications

20% in petrolatum (230 µg/cm² in the Thin-Layer Rapid Use Epicutaneous [T.R.U.E.] Test [Mekos Laboratories A/S, Hillerød, Denmark]). Even at that concentration, false-negative reactions may occur in 10% of cases.¹¹ When contact allergy is strongly suspected in the face of a negative patch-test result, repeated open application

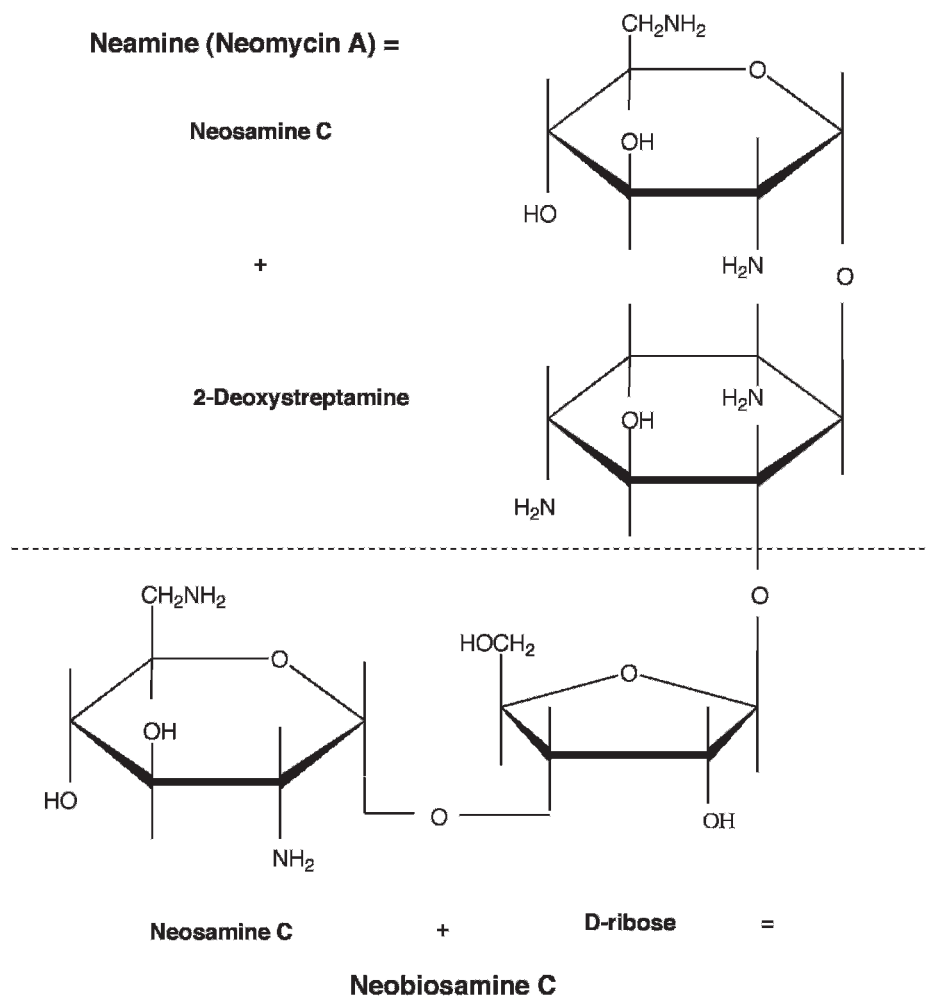


Figure 1. Chemical structure of neomycin C.

on the 2-deoxystreptamine ring. Antibiotics of the gentamicin family, including netilmicin and sisomicin, have only 2-deoxystreptamine in common with neomycin.^{1,13}

Considering the above, it is not surprising that the percentage of cross-reactions with neomycin is about 90% for paromomycin and butirosin, 70% for framycetin, 60% for tobramycin and kanamycin, 50% for gentamicin, and only 4% for streptomycin.^{1,2,13–18}

Neomycin Co-reactions

Because neomycin and bacitracin (2003 Allergen of the Year) are often present in the same topical preparations, it is not uncommon to observe sensitization to both antibiotics.¹⁹ Bacitracin is extracted from a strain of *Bacillus subtilis*, and its chemical structure bears no resemblance to that of neomycin. Thus, the frequent reactions seen with both molecules are not cross-reactions but concomitant sensitizations.

Triple antibiotic creams or ointments contain polymyxin B in addition to neomycin and bacitracin. Grandinetti and Fowler reported on the simultaneous sensitization to all three antibiotics.²⁰ Because polymyxin B is not routinely used in standard series, the rate of sensitization to this antibiotic is unknown. Polymyxins are derived from bacteria of the genus *Bacillus* (*Bacillus polymyxa*). Because of this common source, Van Ketel believed that both antibiotics would cross-react.²¹ Here again, however, the chemical structure of each compound is very different, and true cross-reaction appears unlikely.

Neomycin and Systemic Reactions

In an individual previously sensitized by topical exposure, the small amount of neomycin absorbed from the gastrointestinal tract may be enough to trigger widespread dermatitis or a flare-up at the site of prior contact dermatitis.^{22–24} Morton and colleagues described a case of

acute, widespread, and weeping dermatitis in a neomycin-sensitive patient from the subconjunctival injection of framycetin after cataract surgery. The patient later developed a local delayed reaction and a mild flare-up following intradermal testing with a 1% aqueous solution of framycetin.²⁵ A flare-up of positive patch-test reactions may be seen after oral administration of neomycin,⁸ and patch testing has induced flare-up of previous sites of allergic contact dermatitis from neomycin.²⁶

Systemic administration of a related aminoglycoside such as streptomycin, kanamycin, or gentamicin may be responsible for systemic contact dermatitis in patients who have been sensitized to neomycin by topical exposure. Guin and Phillips reported a case of erythroderma from systemically administered gentamicin in a neomycin-allergic patient.²⁷ To prevent infection following joint replacement, gentamicin is added to acrylic-based joint cement. Release of the antibiotic is maximal after 24 hours but continues for 6 months. One case report described the occurrence of self-limited but widespread dermatitis 3 days after knee replacement in a gentamicin-sensitive patient.²⁸ Similar events are likely to occur through cross-reaction in patients with neomycin allergy.

Vaccination with neomycin-containing preparations poses a theoretical risk of systemic reaction. One case report described the occurrence of a type I hypersensitivity reaction from the measles, mumps, and rubella vaccine in a 7-year-old boy not known to be allergic to egg protein.²⁹ The authors suspected neomycin as the culprit but did not perform prick or intradermal testing with the antibiotic; therefore, the true cause of their patient's reaction remains unknown. A history of anaphylaxis from neomycin would obviously preclude the administration of any vaccine that contains this antibiotic. However, Rietschel rightly pointed out that allergy to neomycin is usually of the delayed type and that the threshold for elicitation of sensitivity is 100 to 1,000 µg.³⁰ Given that vaccines contain 25 µg of neomycin, reactions to their administration are bound to cause minimal or no local transient reactions. The Committee on Infectious Diseases of the American Academy of Pediatrics no longer considers contact hypersensitivity to neomycin a contraindication to vaccination.²⁹

Conclusion

In countries such as Germany, where neomycin is available as a prescription drug, the rate of sensitization is around 1% of patients referred for patch testing. By contrast, in North America, where neomycin-containing preparations are available over the counter, the North American

Contact Dermatitis Group's results show a relatively constant rate of sensitization that varied between 10% and 13% from 1994 to 2006.⁷ Neomycin is not a new allergen, but it is an allergen that does not want to die. For its illustrious and long career, it is awarded the title of Allergen of the Year.

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References

1. Macdonald RH, Beck M. Neomycin: a review with particular reference to dermatologic usage. *Clin Exp Dermatol* 1983;8:249–58.
2. Gehrig KA, Warshaw EM. Allergic contact dermatitis to topical antibiotics: epidemiology, responsible allergens and management. *J Am Acad Dermatol* 2008;58:1–21.
3. Baer RI, Ludwig JS. Allergic eczematous sensitization to neomycin. *Ann Allergy* 1952;10:136–7.
4. Prystowsky SD, Nonomura JH, Smith RW, Allen AM. Allergic hypersensitivity to neomycin. Relationship between patch test reactions and “use” tests. *Arch Dermatol* 1979;115:713–5.
5. Uter W, Rämisch C, Aberer W, et al. The European baseline series in 10 European countries, 2005/2006—results of the European Surveillance System on Contact Allergies (ESSCA). *Contact Dermatitis* 2009;61:31–8.
6. Menezes de Padua CA, Schnuch A, Lessman H, et al. Contact allergy to neomycin sulfate: results of a multifactorial analysis. *Pharmacoepidemiol Drug Saf* 2005;14:725–33.
7. Zug KA, Warshaw EM, Fowler JF Jr, et al. Patch-test results of the North American Contact Dermatitis Group, 2005–2006. *Dermatitis* 2009;20:149–60.
8. Rietschel RL, Fowler JF Jr. Topical antimicrobials. In: Rietschel RL, Fowler JF Jr, editors. *Fisher's contact dermatitis*. 6th ed. Hamilton (ON): BC Decker; 2008. p. 210–29.
9. Andersen KE, White IR, Goossens A. Allergens from the standard series. In: Frosch PJ, Menné T, Lepoittevin JP, editors. *Contact dermatitis*. 4th ed. Berlin: Springer; 2006. p. 453–92.
10. Phillips DK. Neomycin sulfate. In: Guin JD, editor. *Practical contact dermatitis*. New York: McGraw-Hill Inc.; 1995. p. 167–77.
11. Epstein E. Contact dermatitis to neomycin with false negative patch tests: allergy established by intradermal and usage tests. *Contact Dermatitis* 1980;6:236–7.
12. Bjarnason B, Flosadóttir E. Patch testing with neomycin sulfate. *Contact Dermatitis* 2000;43:295–302.
13. Kimura M, Kawada A. Contact sensitivity induced by neomycin with cross-sensitivity to other aminoglycoside antibiotics. *Contact Dermatitis* 1998;39:148–50.
14. Schorr WF, Ridgway HB. Tobramycin-neomycin cross-sensitivity. *Contact Dermatitis* 1977;3:133–7.
15. Förström L, Pirlä V. Cross-sensitivity within the neomycin group of antibiotics. *Contact Dermatitis* 1978;4:312.

16. Samsoen M, Metz R, Melchior E, Foussereau J. Cross-sensitivity between aminoglycoside antibiotics. *Contact Dermatitis* 1980;6:141.
17. Carruthers JA, Cronin E. Incidence of neomycin and framycetin sensitivity. *Contact Dermatitis* 1976;2:269–70.
18. Rudzki E, Zakrzewski Z, Rebandel P, et al. Cross reactions between aminoglycoside antibiotics. *Contact Dermatitis* 1988;18:314–6.
19. Sood A, Taylor JS. Bacitracin: allergen of the year. *Am J Contact Dermat* 2003;14:3–4.
20. Grandinetti PJ, Fowler JF. Simultaneous contact allergy to neomycin, bacitracin and polymyxin. *J Am Acad Dermatol* 1990;23:646–7.
21. Van Ketel WG. Polymixine 8-sulfate and bacitracin. *Contact Dermatitis Newsl* 1974;15:445.
22. Ekelund AG, Möller H. Oral provocation in eczematous contact allergy to neomycin and hydroxyquinolines. *Acta Derm Venereol (Stockh)* 1969;49:422–6.
23. Menné T, Weismann K. Hämatogenes Kontaktekzem nach oraler Gabe von Neomycin. *Hautarzt* 1984;35:319–20.
24. Bouffieux B, Heid E. Eczéma endogène à la néomycine. *Nouv Dermatol* 1990;9:25.
25. Morton CA, Evans CD, Douglas WS. Allergic contact dermatitis following subconjunctival injection of framycetin. *Contact Dermatitis* 1993;29:42–3.
26. Jacob SE, Barland C, ElSaie ML. Patch-test-induced “flare-up” reactions to neomycin at prior biopsy sites. *Dermatitis* 2008;19:E46–8.
27. Guin JD, Phillips D. Erythroderma from systemic contact dermatitis: a complication of systemic gentamicin in a patient with contact allergy to neomycin. *Cutis* 1989;43:564–7.
28. Haeberle M, Wittner B. Is gentamicin-loaded bone cement a risk for developing systemic allergic dermatitis? *Contact Dermatitis* 2009;60:176–7.
29. Kwittken PL, Rosen S, Sweinberg SK. MMR vaccine and neomycin allergy. *Am J Dis Child* 1993;147:128–9.
30. Rietschel RL. Neomycin sensitivity and the MMR vaccine. *JAMA* 1981;245:571.