Contact Allergy to Polymyxin B Among Patients Referred for Patch Testing

Maisa Alfalah, MD, Hanieh Zargham, Linda Moreau, MD, FRCPC, Monica Stanciu, MD, FRCPC, and Denis Sasseville, MD, FRCPC

Backgound: **Polymyxin B is not included in most standard contact allergen series. The aim of this study was to determine the prevalence of contact sensitization to polymyxin B in a population of patients referred for patch testing.**

Methods: **A retrospective cohort study design was used to collect data on 795 patients referred to the contact dermatitis clinic of the McGill University Health Centre, as well as to the office of one of the authors (L.M.), between March 2014 and November 2015. Patients were patch tested to the North American Contact Dermatitis Group baseline series and polymyxin B sulfate 3% in petrolatum.**

Results: **Out of 795 tested individuals, 18 were allergic to polymyxin B, for a prevalence of 2.3%. The eruptions affected almost all body parts, but mostly the face. The degree of reaction ranged from 1+ to 2+. Isolated reactions to polymyxin B occurred in 9 (50%) patients, whereas reactions to bacitracin and polymyxin B were seen in the other 9. Only 1 patient reacted to bacitracin, polymyxin B, and neomycin (11.1%). Most reactions (12/18) were from past exposure to polymyxin B.**

Conclusions: **Allergic reactions to polymyxin B are not rare, and this antibiotic warrants inclusion in the standard patch testing series.**

Polymyxins belong to a family of cyclic decapeptide antibiotics that are active only against gram-negative bacteria. They were discovered in 1947 and consist of 5 structurally related compounds (polymyxins A-E) derived from various subspecies of *Bacillus polymyxa*, an endospore-forming bacterium.[1] Polymyxin B and polymyxin E (colistin) are the only members of the group to be used in clinical practice. Polymyxin E is administered parenterally to fight multiple-drug–resistant organisms, such as *Pseudomonas aeruginosa*.[2,3] Present only in topical preparations, often in combination with other antimicrobial agents, polymyxin B has been extensively used for decades to treat skin, ear, and eye infections. Polymyxin B, bacitracin, and neomycin are combined in *triple antibiotic* ointments and are sold over the counter in many parts of the world, including the United States.

Previous studies done by the North American Contact Dermatitis Group (NACDG) showed that neomycin and bacitracin are constantly among the 10 most common contact allergens.[4] The NACDG has estimated the rate of neomycin allergy to range between 7% and 13% among patch tested patients and reported an increasing incidence of bacitracin allergy, from 1.5% between 1985 and 1990 up to 7.7% and 9.2% between 2000 and 2004.[4] These figures have remained constant until now.[5] The NACDG chose bacitracin as the "Contact Allergen of the Year" in 2003,[6] and neomycin received this recognition in 2010.[7] In addition, the postoperative use of neomycin on minor surgical wounds has been shown to cause allergic contact dermatitis in 5.3% of the patients.[8]

Unlike bacitracin and neomycin, polymyxin B is not included in most standard contact allergen series. Partly for this reason, contact allergy caused by polymyxin B is infrequently reported in the literature. Furthermore, most of the described reactions have occurred when polymyxin B is compounded with other known topical sensitizers such as neomycin and bacitracin. The aim of this study was to determine the prevalence of contact sensitization to polymyxin B and to evaluate the possibility of its independent occurrence in a population of patients referred for patch testing.

METHODS

Study design

A retrospective cohort study design was used to collect data on patch testing performed between March 2014 and November 2015, first at the Royal Victoria Hospital (RVH) and subsequently at the Montreal General Hospital (MGH) as well as at the office of one of the authors (L.M.). The study end points were positive reaction to polymyxin B alone or reactions to multiple antibiotics

From the Division of Dermatology, McGill University Health Centre, Montreal, Quebec, Canada.

Address reprint requests to Denis Sasseville, MD, FRCPC, McGill University Health Centre, Montreal General Hospital, Room L8.201, 1650 Cedar Ave, Montreal, Quebec, Canada H3G 1A4. E-mail: denis.sasseville@mcgill.ca.

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including polymyxin B. All required ethical approvals were obtained before starting data collection.

Population

Consecutive male and female patients aged between 18 and 74 years who were referred to the contact dermatitis clinics of the RVH and MGH (631 patients) and to the office of one of the authors (L.M., 164 patients) represented the study population. Patients with severe generalized eczema, those on systemic corticosteroid therapy (>25 mg of prednisone per day) for more than 2 weeks, and those with a recent suntan were excluded from the study to avoid false-positive or false-negative testing reactions.

Testing

All patients were patch tested to the NACDG baseline series (AllergEAZE; SmartPractice, Calgary, Canada) and polymyxin B sulfate 3% in petrolatum (Chemotechnique Diagnostics, Vellinge, Sweden). At the RVH and MGH, the standard series was applied on Finn Chambers (SmartPractice, Phoenix, USA), whereas IQ Ultra Chambers (Chemotechnique Diagnostics) were used to test polymyxin B and patients seen at one of the authors' office. Readings were performed according to the criteria of the International Contact Dermatitis Research Group after 48 hours (D2) and 96 hours (D4) at the RVH and MGH, and after 96 hours (D4) at the office of one of the authors (L.M.).

TABLE 1. Characteristics of the Patients Allergic to Polymyxin B

Number	Sex	Age (y)	Site of Eruption	Positive Reactions	D2	D4	Independence	Relevance
1	Female	43	Hands	Polymyxin B	—	++	Multiple reactions	Past relevance
				Bacitracin	—	+		
2	Male	48	Face, neck, legs, and abdomen	Polymyxin B	—	+	Single reaction	Past relevance
3	Female	59	Eyelids	Polymyxin B	—	++	Multiple reactions	Past relevance
				Bacitracin	—	+		
4	Male	74	Genital area	Polymyxin B	—	++	Multiple reactions	Definite relevance
				Bacitracin	—	++		
				Mix of bacitracin, polymyxin B, & gramicidin	—	++		
5	Male	39	Face and hands	Polymyxin B	+	+	Single reaction	Past relevance
6	Female	44	Lips	Polymyxin B	—	+	Single reaction	Past relevance
7	Female	53	Face, scalp, and arms	Polymyxin B	—	++	Multiple reactions	Past relevance
				Bacitracin	—	+		
				Mix of bacitracin and polymyxin B	—	++		
8	Female	57	Neck, trunk, and arms	Polymyxin B	—	++	Multiple reactions	Past relevance, Maculopapular eruption
				Bacitracin	—	++		
				Neomycin	—	+		
				Framycetin	—	+++		
				Fusidic acid	—	++		
9	Female	68	Face	Polymyxin B	—	+	Single reaction	Past relevance
10	Male	51	Face	Polymixin B	—	+	Single reaction	Past relevance
11	Female	42	Face	Polymixin B	—	++	Multiple reactions	Undetermined
				Bacitracin	—	++		
12	Male	41	Feet	Polymyxin B	ND	++	Multiple reactions	Undetermined
				Bacitracin		++		
13	Female	45	Scalp	Polymyxin B	ND	+	Multiple reactions	Undetermined
				Bacitracin		++		
14	Female	23	Face	Polymyxin B	ND	+	Single reaction	Past
15	Male	72	Hands	Polymyxin B	ND	+	Single reaction	Past
16	Female	44	Right buttock and ankle (tattoo sites)	Polymyxin B	ND	+	Multiple reactions	Present
				Bacitracin		+		
17	Female	64	Scalp	Polymyxin B	ND	+	Single reaction	Undetermined
18	Female	51	Face	Polymyxin B	ND	+	Single reaction	Past

Patients 1 to 11 were seen at the RVH/MGH Contact Dermatitis Clinic. Patients 12 to 18 were seen at the office of one of the authors (L.M.).
ND indicates not done.

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RESULTS

Out of 795 patients, a total 18 patients were allergic to polymyxin B, which represented a prevalence of 2.3%. The details of patients with a positive reaction are shown in Table 1. Two thirds of the affected patients were women (12/18), and their average age was 51 years. The eruptions, as reported by the referred patients, were localized to almost all parts of the body with the face being the most commonly affected site. The degree of the reaction to polymyxin B ranged from 1+ to 2+. An isolated reaction to polymyxin B was seen in 9 (50%) patients whereas concomitant reactions to bacitracin and polymyxin B were seen in the other 9 (50%) patients. Only 1 patient had reactions to bacitracin, polymyxin B, and neomycin (11.1%). Most (12/18) of the reactions represented previous exposure to polymyxin B, and were therefore considered to be of past relevance.

DISCUSSION

To the best of our knowledge, this is the first study to examine the prevalence of polymyxin B in a large cohort. The current study estimated the prevalence of allergic reactions to polymyxin at 2.3% among patients referred to patch testing. Our study demonstrates that sensitization to polymyxin B can occur more frequently than currently recognized. Previous data estimating such prevalence are rare and have several methodological limitations. There have been isolated case reports describing allergy to polymyxin B but no large study documenting the rate of sensitization through routine patch testing of large cohorts. For example, Jiaravuthisan and DeKoven[9] reported what they believe to be the first case of contact allergy to polymyxin B in the absence of concomitant positive reactions to either bacitracin or oxytetracycline.

Previous studies have reported reactions to polymyxin B when it is compounded with other common topical sensitizers such as neomycin and bacitracin. For example, Fraki et al[10] examined 142 patients treated with otic preparations and reported reactions to polymyxin B in 4.2%, to bacitracin in 2.8%, and to neomycin in 16% of the patients. Similarly, Van Ginkel et al[11] examined delayed-type contact allergy among 34 patients using otic preparations and reported a relevant positive reaction in 19 patients (56%). In this study, the most frequent allergens were aminoglycosides (35%) whereas polymyxin B sensitization was found in 5 patients (17%).[11] One patient, hospitalized because of otitis externa resistant to topical and oral anti-infectious agents, was found to be allergic to neomycin, bacitracin, polymyxin, and dexamethasone.[12] In addition, Grandinetti and Fowler[13] described 2 patients who showed simultaneous contact allergy to neomycin, bacitracin, and polymyxin B.

True cross-sensitization was presumed to exist between bacitracin and polymyxin B because both are derived from bacillus species.[14] However, even though both molecules are cyclical polypeptides, they have different chemical structures that would make cross-reactions extremely unlikely (Fig 1). Polymyxin B also may have been implicated as the cause of anaphylactic reactions in

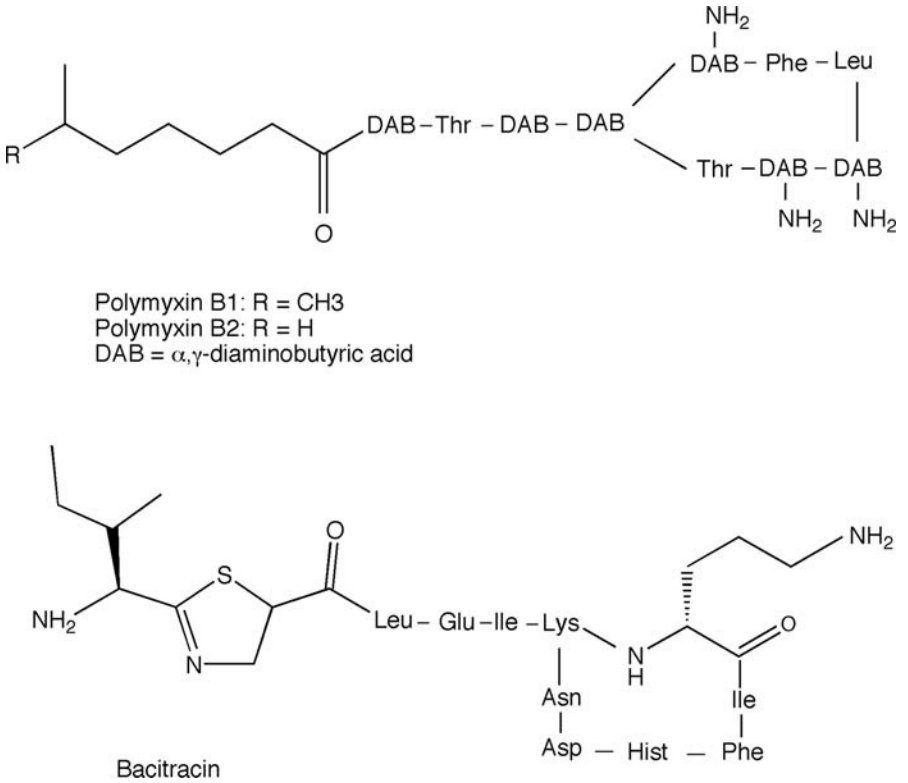

Figure 1. Chemical structures of polymyxins and bacitracin.

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patients using topical antibiotics. For example, both Eedy et al and Knowles and Shear[15,16] reported cases of anaphylactic reactions to topical antibiotic combinations. However, bacitracin was present in the preparations that triggered the reactions and is the most likely culprit. In fact, one of the patients had a similar reaction after exposure to a topical preparation that contained bacitracin but not polymyxin B. Unfortunately, none of these patients were investigated, and the cause of their immediate reactions remains hypothetical.

In large cohorts of consecutively patch tested patients, a sensitization rate of 1% or higher for a given allergen is considered sufficient to include it in a standard series. Because the current study estimated the prevalence of allergic reactions to polymyxin B at 2.3%, we recommend including this antibiotic on the European or the North American standard series to increase the diagnostic yield of patch testing because many reactions are likely missed.

In conclusion, we are reporting a rate of 2.3% of allergic reactions to polymyxin B among patients referred for patch testing, with 50% of these reactions occurring in the absence of concomitant positive reactions to other topical antimicrobial agents. Interestingly, most reactions were positive only on D4, emphasizing the need for late readings when testing topical antibiotics, as is already known with neomycin, a notoriously late reactor.

REFERENCES

1. Newton BA. The properties and mode of action of the polymyxins. *Bacteriol Rev* 1956;20(1):14–27.
2. Falagas ME, Kasiakou SK. Colistin: the revival of polymyxins for the management of multidrug-resistant gram-negative bacterial infections. *Clin Infect Dis* 2005;40(9):1333–1341.
3. San Gabriel P, Zhou J, Tabibi S, et al. Antimicrobial susceptibility and synergy studies of Stenotrophomonas maltophilia isolates from patients with cystic fibrosis. *Antimicrob Agents Chemother* 2004;48(1):168–171.
4. Gehrig KA, Warshaw EM. Allergic contact dermatitis to topical antibiotics: epidemiology, responsible allergens, and management. *J Am Acad Dermatol* 2008;58(1):1–21.
5. Warshaw EM, Maibach HI, Taylor JS, et al. North American Contact Dermatitis Group patch test results: 2011–12. *Dermatitis* 2015;26(1):49–59.
6. Sood A, Taylor JS. Bacitracin: allergen of the year. *Am J Contact Dermat* 2003;14(1):3–4.
7. Sasseville D. Neomycin. *Dermatitis* 2010;21(1):3–7.
8. Gette MT, Marks JG Jr, Maloney ME. Frequency of postoperative allergic contact dermatitis to topical antibiotics. *Arch Dermatol* 1992; 128(3):365–367.
9. Jiaravuthisan MM, DeKoven JG. Contact dermatitis to polymyxin B. *Contact Dermatitis* 2008;59(5):314–316.
10. Fraki JE, Kalimo K, Tuohimaa P, et al. Contact allergy to various components of topical preparations for treatment of external otitis. *Acta Otolaryngol* 1985;100(5–6):414–418.
11. Van Ginkel CJ, Bruintjes TD, Huizing EH. Allergy due to topical medications in chronic otitis externa and chronic otitis media. *Clin Otolaryngol Allied Sci* 1995;20(4):326–328.
12. Vilaça S, Lobo I, Selores M. Simultaneous contact allergy to neomycin, bacitracin, polymyxin, and dexamethasone: an often unrecognized cause of allergic contact dermatitis in patients using topical antibiotics. *J Am Acad Dermatol* 2012;66(4, Suppl 1):AB74.
13. Grandinetti PJ, Fowler JF Jr. Simultaneous contact allergy to neomycin, bacitracin, and polymyxin. *J Am Acad Dermatol* 1990;23(4 Pt 1):646–647.
14. Van Ketel WG. Polymyxin B sulfate. *Contact Dermatitis Newsletter* 1974;15:445.
15. Eedy DJ, McMillan JC, Bingham EA. Anaphylactic reactions to topical antibiotic combinations. *Postgrad Med J* 1990;66(780):858–859.
16. Knowles SR, Shear NH. Anaphylaxis from bacitracin and polymyxin B (Polysporin) ointment. *Int J Dermatol* 1995;34(8):572–573.

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