

# From Road Rash to Top Allergen in a Flash: Bacitracin

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**BACKGROUND.** Bacitracin is an antibiotic that is produced by *Bacillus subtilis*, which is used in several types of consumer products, including cosmetics and ophthalmic and cutaneous ointments.

**OBJECTIVE.** To call attention to the rising allergic contact dermatitis associated with bacitracin.

**RESULTS.** Mass usage has resulted in an increasing number of clinically relevant allergic contact dermatitis reactions and

near fatal anaphylaxis. The North American Contact Dermatitis Group has recorded its emergence as a leading allergen and continues to monitor the ever-growing allergic reaction rates.

**CONCLUSION.** The clinical impact, scientific evidence, and need for medical cost containment all advocate the discontinuation of routine usage of bacitracin in clean surgical wounds.

S. E. JACOB, MD, AND W. D. JAMES, MD HAVE INDICATED NO SIGNIFICANT INTEREST WITH COMMERCIAL SUPPORTERS.

THE TRACEY I strain of *Bacillus subtilis* was recovered from the damaged tissue and street dirt debrided from a patient's compound fracture 60 years ago. It was found that the decanted media filtrate had a powerful antibiotic action with a wide antibacterial spectrum and thus became "bacitracin."<sup>1</sup> Tentative Food and Drug Administration specifications were called to order in 1948 by the Surgeon General for interested parties to hear preliminary reports on bacitracin. In the 5 subsequent years after the discovery of bacitracin, 200 surgical infections had been treated with 87% "favorable results." "The dermatologists were particularly impressed with the high rate of cure and low incidence of allergic reactions to bacitracin [topically] as contrasted with penicillin and sulfonamides."<sup>1</sup>

Nephrotoxicity after parenteral use led to the use of bacitracin primarily as a topical antibiotic. Historically, it played a lead role in bacterial eradication of open cutaneous infections, suppurative conjunctivitis, and corneal ulcers. Current bacitracin preparations and uses include ophthalmic, antibacterial topical ointments of plain bacitracin and bacitracin zinc, cosmetics (Obagi Nuderm), and additives (Fascian) (Table 1). The purported low sensitizing potential and broad-spectrum activity have made it one of the most frequently prescribed medications in U.S. emergency rooms and hospitals, despite the continued increase in

associated allergic contact dermatitis (ACD). The National Occupational Exposure Survey reported 117,226 potential occupational exposures to bacitracin in 23 occupations surveyed; of these, 83,072 were registered nurses.<sup>2</sup> As expected, nursing is the occupation with the highest incidence of ACD.<sup>3</sup> In 1992, bacitracin was the seventh most frequently prescribed medication among the 34-million injury-related emergency room visits.<sup>4,5</sup>

Further perpetuating the mass use are television commercials encouraging the use of antibiotic ointments to promote wound healing and state regulation board requirements. For example, Alabama and Texas State regulation boards require antibiotic ointments be used after tattoo and body piercing, whereas other boards require either petrolatum or antibacterial ointment (South Dakota and Oregon).<sup>6</sup> Popular belief and the Internet have further compounded this problem. Petrolatum is discouraged in aftercare of tattoos by parlors because petroleum-based products tend to drain the color from a tattoo. Neosporin is openly advised against secondary to the "spotted" tattoo effects after resolution of allergic reactions. Bacitracin is the current "first choice" in ointments; however, many report a side effect known as the "weeping tattoo," fluid leakage from the tattoo in the first several days of healing.<sup>7</sup> To our knowledge, the "weeping tattoo" has not been investigated and may represent cases of ACD.

The widespread use encouraged by the belief of low sensitization potential has opened the door to rapidly increasing numbers of allergic eczematous contact reactions. Epstein and Wenzel surveyed 200 U.S.

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**Table 1. Some Bacitracin-Containing Products**

|                                                                    |
|--------------------------------------------------------------------|
| Amway Formucare                                                    |
| Ayfin                                                              |
| Baciguent Antibiotic Ointment <sup>+</sup> (Upjohn)                |
| Bacitracin Ointment <sup>+</sup> (American Pharmaceuticals)        |
| Betadine healing ointment                                          |
| BNP Ointment (Norwich-Eaton)                                       |
| Cortisporin Ointment* (Burroughs Wellcome)                         |
| Fascian TM (Human Allograf Fascia Material, bacitracin, polymyxin) |
| Fortracin                                                          |
| Industrial 5–10 person OSHA First Aid Kit                          |
| Mycitracin Antibiotic Ointment <sup>+</sup> (Upjohn)               |
| Neo-Polycin* (Merrell Dow)                                         |
| Neosporin Aerosol, Ointment, Powder* (Burroughs Wellcome)          |
| Obagi Nuderm                                                       |
| Penitracin                                                         |
| Polysporin Ointment* (Burroughs Wellcome)                          |
| Topitracin/Topisporin* (Pharmafair)                                |
| Zutracin                                                           |

<sup>+</sup>Plain, \* Zinc

dermatologists in 1962 and found that the clinical sensitivity to bacitracin was very rarely reported.<sup>8</sup> Conversely, in 1967, ACD to bacitracin was reported among the leading contact allergens in Finland, 7.8% positive reactions in 17,500 patients tested.<sup>9</sup> The early discrepancy in reporting may have reflected several variables, such as exposure rates, numbers of patients tested, reporting bias, relevancy, geographic location, formulations of the antibiotic, genetic background of the patients, and inclusion of delayed readings. It is well known that many positive bacitracin reactions are present only on delayed (96 hours) readings.<sup>10</sup>

Katz and Fischer<sup>10</sup> reported nine patients with ACD to bacitracin in 1987. They felt that such reactions were likely to be underreported in the United States. Within a few years of this report, bacitracin sensitivity began to be more frequently documented. Gette et al.<sup>11</sup> reported in 1992 that 9 of 215 patients who had used topical antibiotics (neomycin and bacitracin) postoperatively developed ACD. They confirmed the frequency with patch testing and found 5.3% and 2% positivity with neomycin and bacitracin, respectively. Early reports of bacitracin allergy stressed neomycin co-reactivity, which occurred with a 70% to 80% frequency. These co-reactions were thought to repre-

sent independent sensitization events, as the two compounds are chemically unrelated.<sup>9</sup>

Chronic leg ulcer patients are acknowledged as having a high incidence of ACD to a wide spectrum of topically applied agents. Zaki et al.<sup>12</sup> in 1994 patch tested 85 patients with either long-standing leg ulcers (more than 5 years) or ulcer patients with wound eczema complications. In this population, there was a high proportion of patients sensitive to neomycin (21%) and bacitracin (22%). Interestingly, the patients sensitive to bacitracin also had at least one other positive patch reaction.

The North American Contact Dermatitis Group (NACDG) periodically collects and reports the current trends in allergen reaction rates.<sup>13–16</sup> The data reflect the trends in testing, exposures, and sensitization. In the 1990s, as more patients were tested, bacitracin moved into the top 10 allergens reported by NACDG. In addition to larger numbers of patients being documented to have allergic reactions to bacitracin, realization of its relevance in explaining dermatitis improved (Table 2). Maouad et al. devised a construct in 1999, the Significance-Prevalence Index Number (SPIN). This combined the NACDG data with a mathematic parameter to assess the relative importance of different allergens. Between 1984 and 1985, bacitracin was not screened for nationally; yet in 1992 to 1994, bacitracin emerged as eighth most common allergen of 50 allergens tested with a SPIN of 200 (the higher the number the greater the prevalence and clinical significance). In a subsequent analysis in 1994 to 1996, bacitracin maintained the eighth rank yet increased in SPIN number to 311, denoting an improved appreciation of its clinical significance.<sup>17</sup>

Most recently, Shackelford and Belsito<sup>18</sup> confirmed the high incidence of bacitracin allergy in a 5-year retrospective analysis of patients with foot dermatitis. They found that this group of patients was more likely atopic and male with a bimodal age distribution (less than 19 and 41 to 60 years old). Of the 70 patients patch-tested bacitracin caused the most frequently observed relevant reactions. Such increasing levels of sensitization are being documented in spite of the fact that bacitracin is not part of the most common screening trays of allergens, the T.R.U.E. Test, International Standard Series, or European Standard Series.

**Table 2. NACDG Bacitracin Information<sup>13–16</sup>**

| Year                   | 1984–1985 | 1989–1990 | 1992–1994 | 1994–1996  | 1996–1998  | 1998–2000 |
|------------------------|-----------|-----------|-----------|------------|------------|-----------|
| % Positive (relevance) | N/A       | 1.5       | 7.8       | 9.1 (12.5) | 8.7 (50.4) | 9.2       |
| Rank number            | N/A       | N/A       | 8th       | 8th        | 10th       | 9th       |
| Number tested          | N/A       | –         | 3511      | 3079       | 4103       | –         |
| "SPIN" number          | N/A       | N/A       | 200       | 311        | –          | –         |

Contact urticaria and potentially life-threatening anaphylactic shock are also potential threats of exposure to bacitracin. These IgE-mediated events, as opposed to the cell-mediated ACD, are still rarely reported yet are dramatic in consequence. The initial clinical observation was by Comaish and Cunliffe<sup>19</sup> in 1967. They reported an anaphylactic episode in a woman shortly after she applied bacitracin to a stasis ulcer. She developed generalized itching, sweating, dyspnea, hypotension, and subsequent collapse. Later, she recalled two prior episodes of urticaria after bacitracin application to her ulcer. These life-threatening reactions are rare but are enumerated in Table 3. The cases represent a broad spectrum of exposures, including the intraoperative irrigation of wound sites, a youth with no underlying chronic skin diseases, and application on a skin graft in a previously sensitized patient.

Two decades ago, in 1983, the National Research Council found that humans are potentially exposed to 65,725 substances, 2800 of which are allergens, with an estimated annual cost to society for professionally treated contact dermatitis and eczema at \$237,804,000, not including the over-the-counter medicine costs.<sup>34,35</sup> Extrapolated to 2003, the figures are staggering. If exposures could be reduced, less sensitization to this allergen would result. It is clear that bacitracin does not need to be applied to clean surgical wounds. In a randomized, double-blinded, prospective trial of 922 patients with 1249 wounds, Smack et al.<sup>36</sup> compared the effect of white petrolatum versus bacitracin ointment on wound infection incidence, ACD incidence, and healing characteristics. They found that white petrolatum was safe and

effective, with no ACD compared with 0.9% in the bacitracin group, whereas no statistically increased wound infections or compromise in healing results occurred. Use of white petrolatum as a wound dressing for clean surgical procedures will reduce the chance of adverse reactions, including ACD and life-threatening contact urticaria and anaphylaxis.

## Conclusion and Future Directions

Sixty years ago marked the discovery of bacitracin produced by a *Bacillus* cultured from a dirty wound. Throughout the last 4 decades, the trend toward mass unregulated use of this antibiotic has led to an increasingly recognized incidence of ACD with a potential for life-threatening anaphylaxis. In most of the cases resulting in severe systemic reactions, patients had a known history of prior sensitization, and many were able to recall an allergic reaction when questioned.

Dermatologists need to help educate physicians and surgeons to be cognizant of the possibility of both immediate (IgE) and delayed (cell-mediated) reactions to bacitracin. Because white petrolatum is sufficient to dress clean surgical wounds, the use of bacitracin in this situation should be abandoned. In addition, the 1996 cost savings estimate of a switch from antibacterial ointments to white petrolatum by U.S. dermatologists (alone) would result in a health care savings of \$8 to \$10 million per year.<sup>36</sup> In an era of increasing managed care and cost containment, the discontinued routine use of bacitracin creates both the opportunity to eliminate potential medical hazards while reducing expenditures.

**Table 3.** Case Reports of Bacitracin Anaphylaxis

| Source, year                             | Drug                | Exposure                                                              | Prior Exposure |
|------------------------------------------|---------------------|-----------------------------------------------------------------------|----------------|
| Comaish and Cunliffe, <sup>19</sup> 1967 | Bacitracin          | Stasis Dermatitis/stasis ulcer SDSU                                   | Multiple       |
| Roupe & Strannegard, <sup>20</sup> 1969  | Bacitracin          | Atopic dermatitis-topical                                             | Multiple       |
| Vale et al., <sup>21</sup> 1978          | Bacitracin          | Skin Graft Donor site-topical                                         | Multiple       |
| Schechter et al., <sup>22</sup> 1984     | Bacitracin          | SDSU-topical                                                          | Multiple       |
| Goh, <sup>23</sup> 1986                  | Neomycin/bacitracin | Burn wound-topical                                                    | Multiple       |
| Netland et al., <sup>24</sup> 1987       | Bacitracin          | Lumbar laminectomy intraoperative irrigation                          | Bacitracin     |
| Elsner et al., <sup>25</sup> 1990        | Nebacetin           | Infected shoe contact dermatitis                                      | Unknown        |
| Eedy et al., <sup>26</sup> 1990          | Polyfax             | Venous ulcer-topical                                                  | Multiple       |
| Sprung et al., <sup>27</sup> 1990        | Bacitracin          | Nephrectomy intraoperative irrigation                                 | Multiple       |
| Farley et al., <sup>28</sup> 1995 Pt 1   | Bacitracin          | LSC                                                                   | Multiple       |
| Farley et al., <sup>28</sup> 1995 Pt 2   | Bacitracin          | Abrasion                                                              | Multiple       |
| Sarayan et al., <sup>29</sup> 1998       | Bacitracin          | Motor cycle accident-abrasion topical                                 | Multiple       |
| Gall et al., <sup>30</sup> 1999          | Bacitracin          | Nasal packing post septorhinoplasty                                   | Polysporin     |
| Carver et al., <sup>31</sup> 2000        | Bacitracin          | Insertion of ventriculoperitoneal shunt soaked in bacitracin          | Polysporin     |
| Blas et al., <sup>32</sup> 2000          | Bacitracin          | Sternal debridement and rewiring-intraoperative bacitracin irrigation | Neosporin      |
| Morales et al., <sup>33</sup> 2002       | Bacitracin          | Breast augmentation                                                   | —              |

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