Topical Antibiotic Trends from 1993 to 2007: Use of Topical Antibiotics for Non-Evidence-Based Indications

Whitney J. Lapolla, MD,* Michelle M. Levender, MD,* Scott A. Davis, MA,*
Brad A. Yentzer, MD,* Phillip M. Williford, MD,* and Steven R. Feldman, MD, PhD*†‡

BACKGROUND Systemic antibiotic use has become more conservative with the emergence of drug resistance. Topical antibiotics are employed for a variety of indications, although there are only a few evidence-based indications.

OBJECTIVE To examine topical antibiotics use in the outpatient setting.

METHODS Topical antibiotic use was characterized using data from the 1993 to 2007 National Ambulatory Medical Care Survey. Visits were identified at which a topical antibiotic was used and analyzed according to patient demographics, diagnoses, procedures, concomitant medications, and provider specialty. Topical antibiotic use over time was analyzed using linear regression.

RESULTS The most frequent diagnoses associated with topical antibiotic use were benign or malignant neoplasm of skin, impetigo, insect bite, and cellulitis. Data revealed a significant downward trend in topical antibiotics associated with dermatologic surgery ($p < .001$) and a nonsignificant downward trend in use in conjunction with skin biopsies ($p = .09$). Topical antibiotic use by dermatologists was noted to be decreasing over time, whereas among non dermatologists, it was noted to be increasing, although neither of these trends was statistically significant.

CONCLUSION Topical antibiotics continue to be used for non-evidence-based indications, despite data that suggest that such use may be detrimental for patients and represents significant costs to the health care system.

The authors have indicated no significant interest with commercial supporters.

Ten years ago, the Centers for Disease Control and Prevention, the U.S. Food and Drug Administration (FDA), and health organizations around the world identified emerging microbial resistance and the need for more conservative use of antibiotics. Over time, bacteria have developed genetic mutations that allow them to elude the antibiotics to which they were previously sensitive. The effort to promote judicious antibiotic use has focused predominantly on oral and intravenous antibiotics, but the implications of drug resistance extend to topical antibiotics as well. Although bacterial resistance to topical antibiotics is not widespread, some resistance has been observed. A 2008 Cochrane review revealed that there is evidence of resistance to mupirocin, particularly when used for prolonged periods.[1]

Evidence supports the use of topical antibiotics for several indications including treatment of impetigo, eradication of nasal carriage of *Staphylococcus aureus*, and treatment of acne.[2,3] Topical antibiotics are also used for a variety of other indications for which there is limited or no data to support their use.[4,5] In addition to emerging drug resistance, topical antibiotics have been associated with adverse effects, including allergic contact dermatitis (ACD) and poor wound healing.[5–7]

The purpose of this study was to examine how topical antibiotics are being used in the outpatient setting in the United States, with particular emphasis on patient age, race ethnicity, and sex; associated diagnoses and procedures; concomitant medications; types of physician prescribers; and notable trends

*Departments of *Dermatology and †Pathology, Center for Dermatology Research and ‡Department of Public Health Sciences, School of Medicine, Wake Forest University, Winston-Salem, North Carolina*

ISSN: 1076-0512 • Dermatol Surg 2011;37:1427–1433 • DOI: 10.1111/j.1524-4725.2011.02122.x

over time of topical antibiotics in general, in addition to particular topical antibiotic agents.

Methods

Data from the National Ambulatory Medical Care Survey (NAMCS) were used to characterize the clinical settings in which topical antibiotics are used. The NAMCS is a nationwide collection of data from outpatient physician practices of non-federally funded U.S. physicians. For each year of data, the multistage probability sampling design is stratified according to primary sampling unit (county, contiguous counties, or standard metropolitan statistical area), then according to physician practices within the sampling unit, and finally according to patient visit within the 52 weekly randomized periods. For each visit sampled, the physician provider completed a patient log including data on demographics, reason for visit, diagnoses, procedures performed, and associated medications. Sampling weights were then applied to sample data to project national estimates describing outpatient services in the United States.[8]

The NAMCS database was queried for all visits between 1993 and 2007 in which a topical antibiotic was used or recommended for further patient use. Specific topical antibiotics queried included mupirocin, neomycin, Polysporin (polymyxin plus bacitracin), Neosporin (neomycin, bacitracin, plus polymyxin), and bacitracin. The frequency of visits associated with each topical antibiotic over time was analyzed using linear regression. The data were further examined to determine ordering physician characteristics (particularly dermatologist vs other) reason for patient visit, patient race ethnicity, concomitant medications, and associated diagnoses and procedures. To better evaluate diagnoses associated with topical antibiotics, the data set was limited to single diagnosis visits to more definitively establish the relationship between diagnosis listed for visit and the use of a topical antibiotic. To determine whether topical antibiotics were being used in association with dermatologic procedures the data set was queried for procedure codes for biopsy (International Classification of Diseases, Ninth Revision (ICD-9) procedure code 86.11) and dermatologic surgery (ICD-9 procedure code 86.3), and the frequency of procedures associated with a topical antibiotic over time was analyzed using linear regression. All data analysis was performed using SAS software (SAS Institute, Inc., Cary, NC).

Results

The top three prescribers of topical antibiotics were dermatologists (27%), pediatricians (22%), and family practitioners (18%) (Table 1). Topical antibiotics were used with similar frequency in men (49.3%) and women (50.7%, Table 2). The most common single-diagnosis visits associated with topical antibiotic use in order of frequency were malignant or benign neoplasm of the skin, impetigo, and insect bite and cellulitis, which had equivalent frequency (Table 3). Of the patient visits with a single diagnosis of benign or malignant neoplasm of the skin, 84.7% had an associated surgery, biopsy, or destruction listed. A slight downward trend was noted in the use of any topical antibiotic in conjunction with a biopsy over time ($p = .09$). There

TABLE 1. Percentage of Patient Visits Associated with Topical Antibiotics According to Type of Physician Prescriber

Physician Specialty	*Visits Associated with Topical Antibiotic, %*
Dermatology	27
Pediatrics	22
Family practice	18
Internal medicine	7.1
Ophthalmology	6.1
Otolaryngology	4.8
General practice	4.3
General surgery	2.0
Plastic surgery	1.9
Obstetrics and gynecology	0.65
Orthopedic surgery	0.55
Emergency medicine	0.53
Pediatric ophthalmology	0.53
Allergy	0.47
Urology	0.42

TABLE 2. Proportion of All Visits Involving Topical Antibiotic Use According to Sex and Age

Characteristic	*Visits,* n *(%)*
Sex	
Male	32,090,368 (49)
Female	32,991,240 (51)
Age	
0–9	15,090,656 (23)
10–19	6,651,422 (10)
20–29	4,262,648 (7)
30–39	5,117,377 (8)
40–49	6,767,208 (10)
50–59	7,001,926 (11)
60–69	6,837,339 (11)
70–79	7,324,023 (11)
80–89	5,256,835 (8)
≥90	772,174 (1)

was a significant decrease in topical antibiotics associated with dermatologic surgery over time ($p < .001$).

Analysis of race/ethnicity of visits associated with topical antibiotics revealed that Caucasian patients accounted for the majority of topical antibiotic use (84.0%), followed by African Americans (7.1%) and Asians (4.9%) (Table 4). When examining frequency of topical antibiotic use during visits of a particular race/ethnicity, rates were comparable in all racial/ethnic groups (multiracial patients, 1.59%; Asians, 0.73%; Caucasians, 0.52%; Native Hawaiians and Pacific Islanders, 0.44%; American Indians and Alaskan Natives, 0.44%; and African Americans, 0.40%; Table 4). The most common diagnosis in visits with topical antibiotics varied according to race/ethnicity, with malignant or benign neoplasm of the skin being the most common diagnosis in Caucasian patients and impetigo in African American and Asian patients.

TABLE 3. Most Common Diagnoses Associated with Topical Antibiotic Use

Diagnosis	*Topical antibiotic visits, %*
Benign or malignant neoplasm of the skin	11.9
Impetigo	8.5
Cellulitis	3
Insect bite	3
Epistaxis	2.2
Sebaceous cyst	1.8
Rash	1.6
Abrasion or friction	1.3
Actinic keratosis	1.2
Carbuncle and furuncle	1.2

All diagnoses accounting for at least 1% of visits in which topical antibiotics were used are reported.

TABLE 4. Distribution of Topical Antibiotic Use According to Race/Ethnicity

Race/ Ethnicity	*Visits Associated with Topical Antibiotics,* n *(%)*	*Visits in Which Topical Antibiotics Were Used, %*
White	54,652,879 (84)	0.52
Black	4,641,661 (7.1)	0.40
Asian	3,173,677 (4.9)	0.73
Not reported	2,040,157 (3.1)	0.65
More than one reported race	281,025 (0.4)	1.59
Native Hawaiian and Pacific Islander	188,686 (0.3)	0.44
American Indian and Alaska Native	103,523 (0.2)	0.44

Medications most commonly used at visits in which topical antibiotics were used included antiseptics (Hibiclens, Betadine, and hydrogen peroxide), tetanus toxoid, anesthetics such as lidocaine and Xylocaine, and oral antibiotics, most commonly cephalexin and amoxicillin/clavulanate.

From 1993 to 2007, there was a nonsignificant downward trend in the frequency of visits associated with a topical antibiotic by dermatologists and a nonsignificant upward trend in the frequency of visits with topical antibiotics by all other physicians (Figure 1). There was a significant decrease over time in the use of Polysporin (bacitracin plus polymyxin) by dermatologists ($p < .05$) and other physicians ($p < .0001$). There was a significant increase in the use of mupirocin by nondermatologists ($p < .001$).

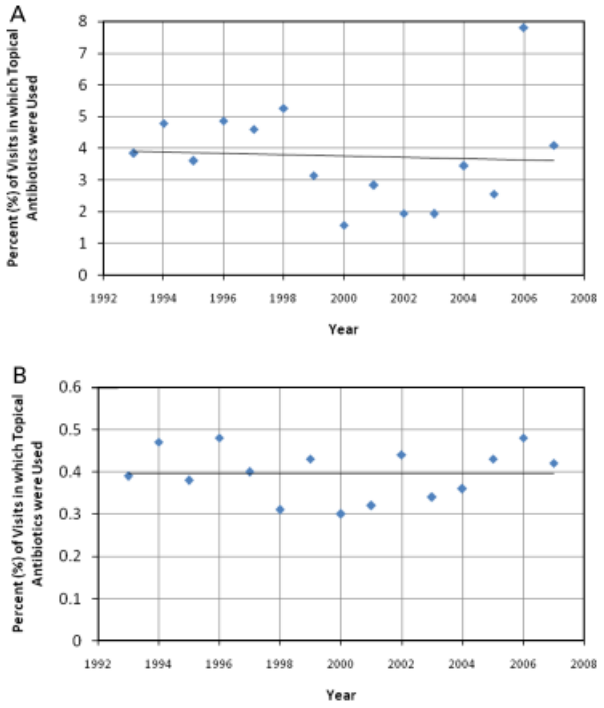

Figure 1. Percentage of total visits by year in which topical antibiotics were used in visits to (A) dermatologists and (B) all other physicians (nondermatologists).

Discussion

Topical antibiotics can be useful in the management of certain conditions when used appropriately, but as with all medicines, inappropriate use carries some risk. Topical antibiotics allow patients to achieve a high concentration of medication at the intended treatment site while limiting systemic absorption and toxicity. Several studies have demonstrated adverse outcomes after the administration of topical antibiotics. One study of 118,496 patients with acne vulgaris demonstrated 2.15 greater odds ($p < .001$) of topical antibiotic-treated patients developing an upper respiratory infection than those treated with other therapy.[9] Topical antibiotics alter normal skin flora. In a study of facial application of erythromycin for 12 weeks, there was a greater prevalence of coagulase-negative staphylococcus on treated and untreated areas.[10] Pharyngeal colonization with *Streptococcus pyogenes* occurs after chronic application of topical antibiotics for acne vulgaris, in particular high concentrations of *S. pyogenes* strains resistant to tetracycline. Studies such as these demonstrate that topical antibiotics are breeding resistant bacteria, although the clinical significance remains unclear.[11,12]

Certain topical antibiotics are potent contact allergens. In a group of patch-tested patients, neomycin was the most common cause of ACD (11%); bacitracin was also found to be allergenic, causing ACD in 8% of individuals in the patch-tested population.[13] In a number of case reports, bacitracin has been associated with anaphylaxis.[13–15] Unnecessary use of topical antibiotics also contributes to antibiotic resistance.[16] Resistance of methicillin-resistant *S. aureas* (MRSA) to mupirocin increased from 1.6% to 7.0% between 1995 and 2004.[17]

This study demonstrated that dermatologists are the physicians most often associated with topical antibiotic use. Based on an estimate using data from 2003, dermatologists account for 3 million to 4 million topical antibiotic prescriptions annually.[18] Some of this use is appropriate. Patients aged 0 to 9 years account for the majority of visits associated with topical antibiotics, and much of this use could be for impetigo. In treatment of impetigo, topical antibiotics are a preferred first-line therapy and can be more effective than systemic antibiotics.[19] Mupirocin specifically has been compared with oral erythromycin and oral cephalexin and was more effective for impetigo treatment in both cases.[20,21] Of greater significance is that much of the topical antibiotic use identified in our analysis may not be appropriate.

Benign or malignant neoplasm of the skin was the diagnosis most commonly associated with topical antibiotic use. Of the single-diagnosis visits for benign or malignant neoplasm of the skin in which a topical antibiotic was used, 84.7% had an associated procedure code listed. This association suggests that, in these cases, topical antibiotics are being used for prophylaxis.[22] The information available in the database limited this study, and therefore it is not possible to ascertain definitively that the use of

topical antibiotics in these visits was for prophylaxis, but this is the assumption we are making. Data analysis also revealed that topical antibiotics were frequently used in association with other agents commonly used at surgical procedures (antiseptics such as Hibiclens, Betadine, and hydrogen peroxide and local anesthetics including lidocaine, epinephrine, and Xylocaine). Antiseptics are broad-spectrum chemicals that inactivate microbes and have a broader mechanism of action than antibiotics. They are routinely employed preoperatively for antimicrobial prophylaxis.[23,24] Regional anesthetics such as lidocaine, epinephrine, and Xylocaine are used routinely in dermatologic surgery to decrease sensitivity to pain.[25] The common association between these agents and topical antibiotic visits lends further support to the assumption that, at visits with a diagnosis of benign or malignant neoplasm of the skin, topical antibiotics were being used as postoperative prophylaxis.[25]

Routine prophylaxis of surgical wounds with topical antibiotics is not necessary and may be detrimental to patients.[18] The rate of wound infection after clean dermatologic surgery is low (1.3%), whereas the occurrence of neomycin- and bacitracin-induced ACD is moderately higher (11% and 8%, respectively).[18] In a study of 1,207 surgical wounds treated with white petrolatum or bacitracin for 7 to 10 days postoperatively, the group treated with bacitracin had a higher rate of wound complications. The wound infection rates were not significantly different between the groups, leading to the conclusion that, in clean dermatologic surgery, plain petrolatum rather than topical antibiotic prophylaxis is the preferred postoperative treatment.[6] Our data suggest that despite this evidence, physicians are routinely using topical antibiotics as surgical prophylaxis. Nevertheless, there was a significant downward trend noted in the use of topical antibiotics in dermatologic surgery procedures and a nonsignificant downward trend in the use of topical antibiotics in dermatologic biopsies, suggesting an encouraging shift toward more evidence-based practice.

Tied for the position of third-most-common diagnosis associated with topical antibiotic use were insect bite and cellulitis. For treatment of minor wounds such as insect bites, abrasions, and burns, the data for topical antibiotic use are not clear. Topical antibiotics lessen bacterial contamination of the wound and eradicate local skin flora, but whether this effect yields a clinical advantage has not been demonstrated.[3,26] More surprising was the association between topical antibiotics and cellulitis. Topical antibiotics are not indicated for management of cellulitis. Used as a single entity, this practice is not adequate and would be inappropriate for patient care.[27]

In contrast to surgical prophylaxis, insect bites, and cellulitis, eradication of nasal colonization with *Staphylococcus aureus* is one of the evidence-based indications for use of topical antibiotics. Nasal application of topical mupirocin has been shown to be effective in eradicating such colonization.[28] The NAMCS data did not reveal any significant association between topical antibiotics and the diagnosis of bacterial colonization or other related nasal conditions. An explanation for this may be that the NAMCS data is based on outpatient visits, and screening for *S. aureus* colonization in the outpatient setting is not common. Some studies have found that treating known carriers before scheduled surgery results in lower postoperative *S. aureus* infection rates.[1] Although further research is needed, this practice might be seen more often in the future.

Although prescribing patterns of systemic antibiotics have changed significantly over the last 10 years in the setting of emerging drug-resistant bacteria, we have not found this change paralleled in the prescribing patterns of topical antibiotics. There has been a nonsignificant downward trend in overall topical antibiotic use by dermatologists but also a nonsignificant upward trend in use by all other physicians. Data are available demonstrating growing resistance to the topical antibiotic mupirocin, which the finding of a significant increase over time in mupirocin use by nondermatologists may explain.

Of concern is that, based on our data, topical antibiotics are being used for prophylaxis in dermatologic surgery and in the management of cellulitis, despite the lack of evidence to support these practices, although there has been a shift toward less use of topical antibiotics in dermatologic surgery, which is reassuring. Considering the high incidence of ACD associated with topical antibiotics and the direct and indirect costs of their overuse, a significant effort should be undertaken to change the practice of using topical antibiotics for non-evidence-based indications.

Acknowledgments The Center for Dermatology Research is supported by an unrestricted educational grant from Galderma Laboratories, L.P. Dr. Feldman is a consultant and speaker for Galderma, Connetics, Abott Labs, Warner Chilcott, Centocor, Amgen, Photomedix, Genentech, Biogenidec, and Brystol Myers Squib. Dr. Feldman has received grants from Galderma, Connetics, Astellas, Abott Labs, Warner Chilcott, Centocor, Amgen, Photomedix, Genentech, Biogenidec, Coria, Pharmaderm, Dermatology Foundation, American Society of Dermatologic Surgery, National Psoriasis Foundation, Ortho Pharmaceuticals, Aventis Pharmaceuticals, Roche Dermatology, 3M, Brystol Myers Squib, Stiefel, GlaxoSmithKline, and Novartis and has received stock options from Photomedix.

References

1. van Rijen MM, Kluytmans JA. New approaches to prevention of staphylococcal infection in surgery. Curr Opin Infect Dis 2008;21:380–4.
2. Thornton SC, Taylor SC, Weinberg JM. Topical antimicrobial agents in dermatology. Clin Dermatol 2003;21:70–7.
3. Hirschmann JV. Topical antibiotics in dermatology. Arch Dermatol 1988;124:1691–700.
4. Rosengren H, Dixon A. Antibacterial prophylaxis in dermatologic surgery: an evidence-based review. Am J Clin Dermatol 2010;11:35–44.
5. Haas AF, Grekin RC. Antibiotic prophylaxis in dermatologic surgery. J Am Acad Dermatol 1995;32:155–76.
6. Smack DP, Harrington AC, Dunn C, Howard RS, et al. Infection and allergy incidence in ambulatory surgery patients using white petrolatum vs bacitracin ointment. A randomized controlled trial. JAMA 1996;276:972–7.
7. Campbell RM, Perlis CS, Fisher E, Gloster HM Jr. Gentamicin ointment versus petrolatum for management of auricular wounds. Dermatol Surg 2005;31:664–9.
8. About the ambulatory care surveys. Office of Information Services. The Center for Disease Control and Prevention. 7-14-2009.
9. Margolis DJ, Bowe WP, Hoffstad O, Berlin JA. Antibiotic treatment of acne may be associated with upper respiratory tract infections. Arch Dermatol 2005;141:1132–6.
10. Mills O Jr., Thornsberry C., Cardin CW, Smiles KA, et al. Bacterial resistance and therapeutic outcome following three months of topical acne therapy with 2% erythromycin gel versus its vehicle. Acta Derm Venereol 2002;82:260–5.
11. Leyden JJ, Del Rosso JQ, Webster GF. Clinical considerations in the treatment of acne vulgaris and other inflammatory skin disorders: focus on antibiotic resistance. Cutis 2007; 79:9–25.
12. Harkaway KS, McGinley KJ, Foglia AN, Lee WL, et al. Antibiotic resistance patterns in coagulase-negative staphylococci after treatment with topical erythromycin, benzoyl peroxide, and combination therapy. Br J Dermatol 1992;126:586–90.
13. Sheth VM, Weitzul S. Postoperative topical antimicrobial use. Dermatitis 2008;19:181–9.
14. Cronin H, Mowad C. Anaphylactic reaction to bacitracin ointment. Cutis 2009;83:127–9.
15. Greenberg K, Espinosa J, Scali V. Anaphylaxis to topical bacitracin ointment. Am J Emerg Med 2007;25:95–6.
16. Brian MJ. Mupirocin-resistant MRSA transmission associated with community hospitals and nursing homes. J Hosp Infect 2010;75:141–2.
17. Mulvey MR, MacDougall L, Cholin B, Horsman G, et al. Community-associated methicillin-resistant *Staphylococcus aureus*, Canada. Emerg Infect Dis 2005;11:844–50.
18. Del Rosso JQ, Kim GK. Topical antibiotics: therapeutic value or ecologic mischief? Dermatol Ther 2009;22:398–406.
19. George A, Rubin G. A systematic review and meta-analysis of treatments for impetigo. Br J Gen Pract 2003;53: 480–7.
20. Mertz PM, Marshall DA, Eaglstein WH, Piovanetti Y, et al. Topical mupirocin treatment of impetigo is equal to oral erythromycin therapy. Arch Dermatol 1989;125: 1069–73.
21. Rist T, Parish LC, Capin LR, Sulica V, et al. A comparison of the efficacy and safety of mupirocin cream and cephalexin in the treatment of secondarily infected eczema. Clin Exp Dermatol 2002;27:14–20.
22. Wright TI, Baddour LM, Berbari EF, Roenigk RK, et al. Antibiotic prophylaxis in dermatologic surgery: advisory statement 2008. J Am Acad Dermatol 2008;59:464–73.
23. Alsterholm M, Karami N, Faergemann J. Antimicrobial activity of topical skin pharmaceuticals—an in vitro study. Acta Derm Venereol 2010;90:239–45.
24. McDonnell G, Russell AD. Antiseptics and disinfectants: activity, action, and resistance. Clin Microbiol Rev 1999;12: 147–79.

25. Koay J, Orengo I. Application of local anesthetics in dermatologic surgery. Dermatol Surg 2002;28:143–8.

26. Gelmetti C. Local antibiotics in dermatology. Dermatol Ther 2008;21:187–95.

27. Stevens DL, Eron LL. Cellulitis and soft-tissue infections. Ann Intern Med 2009;150:ITC11.

28. Laupland KB, Conly JM. Treatment of *Staphylococcus aureus* colonization and prophylaxis for infection with topical intranasal mupirocin: an evidence-based review. Clin Infect Dis 2003;37:933–8.

Address correspondence and reprint requests to: Michelle M. Levender, MD, Department of Dermatology, Wake Forest University School of Medicine, Medical Center Boulevard, Winston-Salem, NC 27157-1071, or e-mail: mlevende@wfubmc.edu