IN-DEPTH REVIEWS

Antibiotic Resistance Considerations of Importance to Clinical Dermatologists

James Q. Del Rosso, DO[a]

[a]Adjunct Clinical Professor (Dermatology), Touro University Nevada, Henderson, Nevada; Research Director, JDR Dermatology Research, Las Vegas, Nevada; Dermatology and Cutaneous Surgery, Thomas Dermatology, Las Vegas, Nevada.

ABSTRACT

Antibiotic resistance is a major health concern worldwide as the list of bacterial pathogens that are insensitive to available antibiotics continues to grow in both hospitals and outpatient communities. The slow development of newer antibiotics adds to the formidable challenge that clinicians face with treatment of infections caused by antibiotic-resistant bacteria. This article discusses important caveats related to antibiotic use in dermatology. These include understanding that both topical and oral antibiotics contribute to the emergence and spread of resistant bacteria, that antibiotic monotherapy is to be avoided for treatment of acne vulgaris, that effective treatment of rosacea does not require the use of an antibiotic, that antibiotic therapy in the management of atopic dermatitis is best limited to treatment of an active clinical infection, and that routine post-operative use of a topical antibiotic is not suggested after most office-based dermatologic procedures. By following principles of antibiotic stewardship, dermatologists are major players in the battle against antibiotic resistance.

INTRODUCTION

The topic of antibiotic resistance has gained progressive attention globally in the lay press, in the medical literature, and among several organizations who are actively promoting antibiotic stewardship in the United States (US) and many other countries.[1-10] In fact, many countries, such as in Europe, have preceded the US in strongly promoting initiatives to limit antibiotic prescribing over the past few decades due to concerns related to the consequences of widespread antibiotic resistance and the slow development of new antibiotics.[1-3,8,9] In the US and within the specialty of dermatology, The Scientific Panel on Antibiotic Use in Dermatology (SPAUD), a project administered by the American Acne & Rosacea Society (AARS), has been evaluating antibiotic use within the dermatology specialty since 2005 and has provided educational initiatives and publications related to the subject of bacterial resistance to antibiotics and optimal antibiotic prescribing.[2,3,11-15] Several leading dermatologists with strong clinical and academic interest in

this subject area have contributed to the activities of SPAUD and its publications.[15] This article highlights five important top line observations that may assist dermatologists in optimal antibiotic prescribing, avoiding antibiotic use where it is not needed, and reducing the emergence of antibiotic-resistant bacteria.

(1) TOPICAL ANTIBIOTICS CONTRIBUTE TO ANTIBIOTIC RESISTANCE AT SITES OF APPLICATION AND AT SITES REMOTE FROM WHERE THEY ARE APPLIED

Topical antibiotic agents, especially clindamycin and erythromycin, are commonly used for treatment of acne vulgaris (AV). It has been recommended that they be applied concomitantly with benzoyl peroxide (BP) to reduce emergence of resistant strains of *Propionibacterium acnes*.[16-18] However, this may not occur reliably, either because the prescriber does not combine both agents, or the patient does not acquire or utilize both agents together. It has been demonstrated that topical antibiotic therapy (ie erythromycin) induces resistant strains of *P acnes* and staphylococci on the face where it was applied, but also resistant bacteria on the back and anterior nares where it was not applied.[19-21] It has also been shown that clindamycin-resistant Group B *Streptococcus* strains are not uncommon, including in pregnant women where untoward sequelae may occur, and may be associated with multi-drug resistance. [22,23] Topical use of clindamycin, especially monotherapy, may contribute to the increase in resistant bacterial pathogens, including streptococci, staphylococci, and *P acnes*.[13,24]

(2) ANTIBIOTIC MONOTHERAPY IS NOT RECOMMENDED IN THE TREATMENT OF ACNE VULGARIS

Although the concept of avoiding antibiotic monotherapy for AV is practically intuitive among almost all dermatologists, it is important that it be stressed, especially in an era when patients do not always get access to all the medications that are prescribed. Factors that contribute to this include the amount of prescription copays, insurance coverage, attempts by pharmacies to change what is prescribed, patients running out of some medications and not making contact to arrange refills, and patients electing not to use some of the medications that were prescribed. Therefore, it is important to verify at each visit what patients are actually using day to day to treat their AV to assure that antibiotic monotherapy is avoided. The rationale for avoiding monotherapy with oral and/or topical antibiotics is reduction in emergence of antibiotic-resistant bacteria, both *P acnes*, and other organisms that comprise the commensal and transient flora.[1,3,11-13] To add, normal flora bacteria such as *Staphylococcus epidermidis* are capable of transferring resistance genes to potentially pathogenic bacteria such as *S aureus*.[21-23,25] This compounds the ecologic mischief related to antibiotic use, whereby emergence of resistant bacteria in a given individual can affect larger communities as individuals pass bacteria to others they are in close contact with, and the bacteria may pass resistance genes to other bacteria that are of different genus and/or species. Importantly, topical antibiotics affect the microbiota of the skin and regional mucosa (ie anterior nares); oral antibiotics have a more widespread impact, affecting the microbiota of the skin/nares, oropharyngeal region, gastrointestinal tract, and genitourinary tract.[3,13] The clinical efficacy

of antibiotic therapy for AV can be adversely impacted by the emergence of an adequate magnitude of antibiotic-resistant *P acnes* strains.[3,11,12,24,26] In addition, reducing antibiotic use in a given community can reduce the prevalence of bacteria resistant to that antibiotic over time, supporting the importance of judicious prescribing of antibiotic therapy.[27-29]

(3) MANAGEMENT OF ROSACEA DOES NOT REQUIRE AN ANTIBIOTIC EFFECT TO ACHIEVE THERAPEUTIC BENEFIT

Available evidence supports that the pathophysiology of rosacea, including cases presenting as diffuse centrofacial erythema with or without papulopustular lesions, involves both cellular and neurovascular inflammatory pathways, and is not related to the presence/proliferation of a specific bacterium.[30-34] As a result, many of the studies of therapies used to treat rosacea (eg tetracyclines, azelaic acid, ivermectin) especially with presence of papulopustular lesions, appear to affect inflammatory pathways/modes of action unrelated to an underlying bacterial trigger that appear to be operative in rosacea pathophysiology (eg inhibition of matrix metalloproteinases, downregulation of cathelicidin pathway, reduction in number of *Demodex* mites).[35-43]

The large body of evidence supporting an inflammatory pathogenesis of rosacea that is not triggered by a bacterial etiology has led globally to rosacea management recommendations supporting that avoidance of an antibiotic effect whenever possible is favorable in order to reduce the emergence of antibiotic-resistant bacteria.[44-47] In their rosacea medical management guidelines, the American Acne & Rosacea Society stated the following: “The lack of data supporting a bacterial component definitively related to the pathogenesis of rosacea suggests overall that medical therapies which are anti-inflammatory in nature are best considered for initial treatment of rosacea, especially the inflammatory (papulopustular) subtype, with oral antibiotic agents used in cases that are poorly responsive to a reasonable trial of topical therapy and/or oral anti-inflammatory therapy”.[44] To achieve this, available topical agents with demonstrated anti-inflammatory effects, efficacy, and safety in rosacea would include azelaic acid and ivermectin.[41,42,44-49] Sub-antibiotic dose doxycycline (such as the modified-release 40 mg capsule once daily or 20 mg immediate-release tablet twice daily) provides anti-inflammatory effects with efficacy and favorable safety for rosacea, without inducing antibiotic selection pressure.[40,44-47,50]

(4) ANTIBIOTIC USE IN ATOPIC DERMATITIS IS BEST LIMITED TO TREATMENT OF SKIN INFECTION WITH AVOIDANCE OF CHRONIC SUPRRESSIVE ORAL OR TOPIC ANTIBIOTIC THERAPY

Atopic skin is commonly colonized with *S aureus*, with presence on eczematous skin, uninvolved skin, and within anterior nares in 85%, 60%, and 60% of cases, respectively.[51-54] This skin colonization information, coupled with the suggestion that certain strains of *S aureus* may induce and/or prolong exacerbations of atopic dermatitis (AD) via production of specific toxins and other exoproducts, has led to a greater frequency of antibiotic use to manage and suppress AD.[52,54] When a cutaneous infection is diagnosed clinically, antibiotic therapy is therapeutically beneficial in AD. However, chronic topical or oral antibiotic therapy is not recommended as a treatment to manage or suppress AD in the absence of a true skin infection, and it

serves only to promote antibiotic resistance.[3,14,52] In fact, in the management of AD, topical corticosteroid therapy and topical epidermal barrier repair can reduce the density of *S aureus* that is present on eczematous dermatitis by decreasing skin inflammation and by mitigating both the permeability barrier and antimicrobial barrier dysfunctions associated with atopic skin and AD.[14,52,56-58] To summarize, it is recommended that antibiotic therapy be limited in the management of AD to treatment of actual clinical skin infection; chronic suppressive therapy is not suggested as this approach has not been shown to be effective and promotes the development of antibiotic-resistant bacterial strains such as *S aureus*.

(5) USE OF A TOPICAL ANTIBIOTIC AGENT IS NOT SUGGESTED FOR ROUTINE USE AFTER SUPERFICIAL CUTANEOUS SURGERIES PERFORMED IN THE OUTPATIENT OFFICE SETTING

A meta-analysis based on data pooled from four studies failed to demonstrate a statistically significant difference between application of topical antibiotics versus topical petrolatum/paraffin in preventing post-surgical infections after dermatologic procedures.[58] This is especially relevant clinically in the office-based dermatology setting where many cutaneous surgeries are superficial (eg most biopsies, curettage, saucerization, cryotherapy) and involve clean or clean-contaminated surgical wounds.[14,52,58] Another study (N=1207 wounds) compared post-procedure application of white petrolatum ointment or bacitracin ointment used daily over a duration of 7 to 10 days (N=1207 wounds); contact dermatitis was noted in 0.9% of patients who applied bacitracin daily as compared to none of the patients applying white petrolatum daily.[59] Available evidence suggests that routine postsurgical use of a topical antibiotic is not recommended overall after office-based dermatologic procedures, especially those that are not at high risk of infection; this includes clean and clean-contaminated wounds, after procedures in patients that are immunocompetent and not at high risk of infection, after surgeries performed in regions above the knee, and after surgeries not involving the groin, ears, or mucosal region of the nose or mouth.[14,52,60,61] In selected cases where the risk of post-operative infection is deemed to be high and avoidance of infection is a major priority due to patient-related risk factors, it is believed to be a better choice to utilize oral antibiotic prophylaxis as topical therapy alone is not as likely to provide adequate prevention of infection in such cases.[14,52]

SUMMARY

Antibiotic resistance continues to be a major health concern worldwide. The list of pathogens that are less sensitive to available antibiotics both within hospitals/health care facilities, and within urban and rural communities continues to grow. Coupled with the slow development of new and novel antibiotics and other alternative antibiotic approaches, the increase in antibiotic-resistant bacteria present a formidable challenge for clinicians. Each clinician can assist in the fight against resistance by using antibiotics only when they feel they are clearly needed to treat a given patient, and in regimens that are optimal for treatment of the disease state being targeted. This article emphasizes the importance of recognizing that both topical and oral antibiotics contribute to the emergence and spread of resistant bacteria, that antibiotic monotherapy is to be avoided for treatment of AV, that effective treatment of rosacea does not necessitate the use of

TABLES

Topical antibiotics used to treat acne vulgaris can induce the emergence of antibiotic-resistant bacteria.

- **Facial application of topical erythromycin was associated with an increase in resistant staphylococci and *P acnes* on the face and on the back; resistant staphylococci were also noted in the anterior nares.**

Antibiotic monotherapy is not recommended for the treatment of acne vulgaris.

- **Increased emergence of antibiotic-resistant bacteria such as *P acnes* occurs especially in the absence of concomitant benzoyl peroxide use.**
- **Decreased activity against *P acnes* has been correlated with decreased therapeutic effect in acne vulgaris.**

Evidence to date supports that the pathophysiology of rosacea does not involve pathways induced by a bacterium. An antibiotic effect is not needed for effective treatment of rosacea, nor does it appear to contribute to therapeutic activity in this disease.

- **Anti-inflammatory therapies that appear to modulate inflammatory pathways operative in rosacea, especially when papulopustular lesions are present, include some topical agents and sub-antibiotic dose doxycycline therapy.**

Use of topical or oral antibiotic therapy in atopic dermatitis is suggested for treatment of an active skin infection.

- **Chronic antibiotic use is not suggested for management or suppression of atopic dermatitis as this approach is not effective and contributes to the emergence of antibiotic-resistant bacteria.**

Available evidence supports that routine use of a topical antibiotic after office-based elective dermatologic procedures is not recommended, especially in those cases that are not at high risk of infection such as with clean and clean-contaminated wounds, and in immunocompetent patients.

- **Overall, the potential for skin infection after superficial dermatologic procedures is low, and is not reduced by application of a topical antibiotic ointment as compared to white petrolatum ointment.**
- **Use of a topical antibiotic (such as those containing bacitracin and/or neomycin) is associated with a definite risk of allergic contact dermatitis; patients may often confuse these reactions with post-operative infection.**

TABLE 1: Clinical Caveats Related to Antibiotic Use in Dermatology[3,11-14,16,17,19,20,26,44-56,58-60]

an antibiotic, that antibiotic therapy in the management of AD is best limited to treatment of an active infection, and that routine post-operative use of a topical antibiotic is not suggested after most office-based dermatologic procedures. Over time, the collective benefit of dermatologists complying with principles of antibiotic stewardship as best as possible will assist in reducing the challenges clinicians face related to antibiotic resistance.

Conflict of Interest Disclosures:
Dr. Del Rosso is a consultant, investigator, and/or speaker for Allergan, Aqua/Almirall, Bayer, BioPharmX, Celgene, Cipher (Innocutis), Cutanea, Dermira, Ferndale, Foamix, Galderma, Genentech, Innovaderm, LeoPharma, Novan, Pfizer (Anacor), Pharmaderm, Promius, Regeneron, Sanofi/Genzyme, Sebacia, SunPharma, Taro, Unilever, Valeant (Ortho Dermatologics), and Viamet. This article was developed and written solely by the author. The author did not receive any form of compensation, either directly or indirectly, from any company or agency related to the development, authorship, or publication of this article.

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Corresponding Author:
James Q. Del Rosso, DO
JDR Dermatology Research
9080 West Post Road
Suite 100
Las Vegas, Nevada 89148
702-331-4123
jqdelrosso@yahoo.com

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