A Call to Limit Antibiotic Use in Acne

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With increasing urgency, national and international health authorities are calling for physicians to limit antibiotic use.[1] Generally, physicians are familiar with efforts to reduce antibiotic prescriptions to minimize bacterial resistance, particularly in regards to respiratory infections.[2] Many may be less familiar with the fact that there is significant antibiotic use in acne,[3, 4] with patients often taking prolonged courses of antibiotic therapy. Acne affects the vast majority of the world's population at some time in their lives,[5] and many clinicians who manage acne patients utilize antibiotics as a primary treatment.[3, 4] As dermatologists with special interest in acne, we call on our colleagues in medicine to review current information on antibiotic use in acne and prescribe these agents in a judicial manner. We discuss below some of the primary reasons to revise the current prescription pattern.

First, *Propionibacterium acnes* (the primary bacterial target) is only one of the 4 pathogenic factors in acne.[5, 6] Combination therapy involving a topical retinoid plus an antimicrobial is the recommended first-line approach, based on the premise that it is most efficacious to target multiple pathophysiologic mechanisms and the results of numerous clinical studies showing improved efficacy.*[5, 6] By tailoring the choice of antimicrobial and duration of antibiotic use, this combination approach can be utilized for almost all patients with acne, providing results that are faster and superior to antibiotic therapy alone.*[4,5]

Second, resistance among *P acnes* is increasing and can occur by selective pressure during antibiotic therapy.[3, 7, 8] Increases in *P acnes* resistance have been reported in all major areas of the world; many countries currently report more than 50% of *P acnes* strains are resistant, particularly to topical macrolides .[9-13] In acne, resistance can manifest as reduced response, no response, or relapse.[8, 14, 15] Further, antibiotic use results in resistance among both targeted and non-targeted bacteria and resistance gene pools are often shared by pathogens and non-pathogens.[8, 16, 17-19] The likelihood of *P acnes* resistance increases with the patient's age, duration of acne, and duration of treatment with topical or systemic antibiotics.[8]

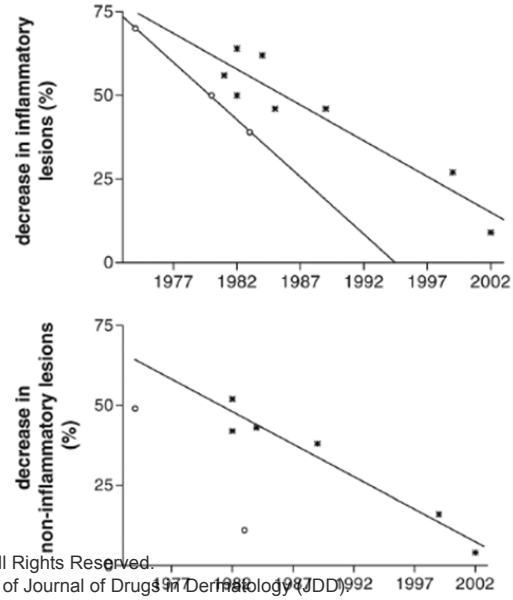
Third, acne is not an infection and killing *P acnes* does not always "cure" acne. *P acnes* is a skin commensal that is present in small numbers in most post-pubertal individuals, and is found in increased numbers in the abnormal environment of increased sebum and abnormally desquamated corneocytes found in sebaceous follicles of acne patients including those without acne.[20, 21] It is also clear that acne is not an infectious disease and simply killing *P acnes* may lead to an improvement but not necessarily to disease resolution.[6]

Fourth, the relative importance of antibacterial and anti-inflammatory effects of antibiotics in acne is unclear.[22, 23] The relative contribution of these actions to antibiotic efficacy in acne remains unknown and there is some speculation that the importance of the various actions may have changed since antibiotics were first used to treat acne.[22, 23] Antibiotics are thought to work by inhibiting inflammation;[24] it should be noted that this has not been proven in vivo, but rather is suggested by large amounts of in vitro data showing that antibiotics have actions independent of bacterial killing. Topical antibiotics act quite slowly on *P acnes* and have a poor suppressive effect compared with benzoyl peroxide (BPO); oral antibiotics are generally considered to be more effective than topical antibiotics.[24] Evidence suggests that adding BPO to a topical antibiotic improves efficacy and reduces the risk of antimicrobial resistance.[24, 25] BPO and systemic antibiotics should be used in combination with a topical retinoid, since retinoids target acne precursor lesions (microcomedones) and have a significant effect on comedones.*[5]

Changes to Consider in Acne Therapy

Topical antibiotics should never be used as monotherapy. Very sparse data support the use of topical antibiotics as monotherapy in acne.[26] Indeed, data from a meta-analysis of available data show a dramatic reduction in efficacy of topical erythromycin since its introduction (Figure 1). In some clinical studies,

FIGURE 1. Efficacy of topical erythromycin in acne over time (empty circles: studies evaluating treatment efficacy after 8 weeks; asterisks: studies evaluating treatment efficacy after 12 weeks).[31]



the efficacy of topical clindamycin alone is similar to what is observed in the vehicle arm of acne studies.[27, 28]

Oral antibiotics have a role in managing acne, but should be used judicially. Oral antibiotics, particularly lipophilic cycline antibiotics (such as doxycycline, lymecycline, and minocycline), continue to have a valuable role in management of patients with more severe acne. As with topical antibiotics, however, current guidelines recommend that oral antibiotics should not be used as monotherapy.[5, 6, 29] Currently, there is interest in the use of subantimicrobial-dose doxycycline to provide anti-inflammatory benefits without selective pressure on bacteria.[22, 23, 30]

First-line therapy for acne involves retinoid-based combinations. Updated acne management recommendations call for avoiding antibiotic monotherapy and prescribing antibiotics only in combination with benzoyl peroxide and retinoids. [6] Retinoid-based combination therapy should be considered as first-line therapy for almost all patients with acne since it reduces the risk of bacterial resistance and there is a large evidence base showing that combinations have greater efficacy.[6] Current recommendations also include limiting the duration of systemic antibiotic use, avoiding use of topical and systemic antibiotics together, adding BPO to retard emergence of resistant bacteria, including a topical retinoid to improve outcomes and using topical retinoids for maintenance therapy adding BPO if needed.*[6]

*A fully-referenced discussion of acne pathophysiology and clinical trial evidence supporting current recommendations is beyond the scope of this letter; thus, we encourage clinicians to review the detailed information summarized in Gollnick et al[5] and Thiboutot et al.[6]

Disclosures

D.T. has served as a consultant or investigator for Allergan, Inc, Anacor, Galderma, Intrepid, and Stiefel/GSK. B.D. has served as a consultant or investigator for Meda, Galderma, Fabre, and Labcatal. S.K. has served as a consultant or investigator for Anacor and Galderma. J.L. has served as a consultant or investigator for Anacor, Allergan, Galderma, Sol-Gel, Sienna, and Sebacia. V.T. has been a consultant and speaker for Galderma. H.G. has served as Consultant or Speaker for Intendis, GSK, Galderma, Merz, Pierre Fabre, Novartis, Roche, Basilea and Meda. V.B. and A.S. Have no relevant conflicts to disclose.

References

1. G8 ministers pledge to act on bacterial antibiotic resistance. Financial Times 2013;June 13.
2. Jenkins TC, Irwin A, Coombs L, Dealleaume L, Ross SE, Rozwadowski J et al. Effects of clinical pathways for common outpatient infections on antibiotic prescribing. *The American journal of medicine* 2013;126:327-35 e12.
3. Narahari S, Gustafson CJ , Feldman SR. What's new in antibiotics in the management of acne? *Giornale italiano di dermatologia e venereologia : organo ufficiale, Societa italiana di dermatologia e sifilografia* 2012;147:227-38.
4. Kinney MA, Yentzer BA, Fleischer AB, Jr. , Feldman SR. Trends in the treatment of acne vulgaris: are measures being taken to avoid antimicrobial resistance? *Journal of drugs in dermatology : JDD* 2010;9:519-24.
5. Gollnick H, Cunliffe W, Berson D, Dreno B, Finlay A, Leyden JJ et al. Management of acne: a report from a Global Alliance to Improve Outcomes in Acne. *Journal of the American Academy of Dermatology* 2003;49:S1-37.
6. Thiboutot D, Gollnick H, Bettoli V, Dreno B, Kang S, Leyden JJ et al. New insights into the management of acne: an update from the Global Alliance to Improve Outcomes in Acne group. *Journal of the American Academy of Dermatology* 2009;60:S1-50.
7. Cooper AJ. Systematic review of Propionibacterium acnes resistance to systemic antibiotics. *The Medical journal of Australia* 1998;169:259-61.
8. Mills O, Jr., Thornsberry C, Cardin CW, Smiles KA , Leyden JJ. Bacterial resistance and therapeutic outcome following three months of topical acne therapy with 2% erythromycin gel versus its vehicle. *Acta dermato-venereologica* 2002;82:260-5.
9. Luk NM, Hui M, Lee HC, Fu LH, Liu ZH, Lam LY et al. Antibiotic-resistant Propionibacterium acnes among acne patients in a regional skin centre in Hong Kong. *Journal of the European Academy of Dermatology and Venereology : JEADV* 2013;27:31-6.
10. Abdel Fattah NS , Darwish YW. In vitro antibiotic susceptibility patterns of Propionibacterium acnes isolated from acne patients: an Egyptian university hospital-based study. *Journal of the European Academy of Dermatology and Venereology : JEADV* 2012.
11. Leyden JJ , Del Rosso JQ. Oral antibiotic therapy for acne vulgaris: pharmacokinetic and pharmacodynamic perspectives. *The Journal of clinical and aesthetic dermatology* 2011;4:40-7.
12. Schafer F, Fich F, Lam M, Garate C, Wozniak A , Garcia P. Antimicrobial susceptibility and genetic characteristics of Propionibacterium acnes isolated from patients with acne. *International journal of dermatology* 2013;52:418-25.
13. Tzellos T, Zampeli V, Makrantonaki E , Zouboulis CC. Treating acne with antibiotic-resistant bacterial colonization. *Expert opinion on pharmacotherapy* 2011;12:1233-47.
14. Leyden JJ, McGinley KJ, Cavalieri S, Webster GF, Mills OH , Kligman AM. Propionibacterium acnes resistance to antibiotics in acne patients. *Journal of the American Academy of Dermatology* 1983;8:41-5.
15. Ozolins M, Eady EA, Avery AJ, Cunliffe WJ, Po AL, O'Neill C et al. Comparison of five antimicrobial regimens for treatment of mild to moderate inflammatory facial acne vulgaris in the community: randomised controlled trial. *Lancet* 2004;364:2188-95.
16. Levy RM, Huang EY, Roling D, Leyden JJ , Margolis DJ. Effect of antibiotics on the oropharyngeal flora in patients with acne. *Arch Dermatol* 2003;139:467-71.
17. Nord CE , Oprica C. Antibiotic resistance in Propionibacterium acnes. Microbiological and clinical aspects. *Anaerobe* 2006;12:207-10.
18. Ross JI, Eady EA, Carnegie E , Cove JH. Detection of transposon Tn5432-mediated macrolide-lincosamide-streptogramin B (MLSB) resistance in cutaneous propionibacteria from six European cities. *The Journal of antimicrobial chemotherapy* 2002;49:165-8.
19. Ross JI, Eady EA, Cove JH , Cunliffe WJ. 16S rRNA mutation associated with tetracycline resistance in a gram-positive bacterium. *Antimicrobial agents and chemotherapy* 1998;42:1702-5.
20. Leyden JJ. The evolving role of Propionibacterium acnes in acne. Seminars in cutaneous medicine and surgery 2001;20:139-43.
21. Leyden JJ, McGinley KJ, Mills OH , Kligman AM. Propionibacterium levels in patients with and without acne vulgaris. *The Journal of investigative dermatology* 1975;65:382-4.
22. Skidmore R, Kovach R, Walker C, Thomas J, Bradshaw M, Leyden J et al. Effects of subantimicrobial-dose doxycycline in the treatment of moderate acne. *Archives of dermatology* 2003;139:459-64.
23. Toossi P, Farshchian M, Malekzad F, Mohtasham N , Kimyai-Asadi A. Subantimicrobial-dose doxycycline in the treatment of moderate facial acne. *Journal of drugs in dermatology : JDD* 2008;7:1149-52.
24. Plewig GK, A. Acne and Rosacea. New York: Springer; 2000.
25. Seidler EM , Kimball AB. Meta-analysis comparing efficacy of benzoyl peroxide, clindamycin, benzoyl peroxide with salicylic acid, and combination benzoyl peroxide/clindamycin in acne. *Journal of the American Academy of Dermatology* 2010;63:52-62.
26. Del Rosso JQ , Kim GK. Topical antibiotics: therapeutic value or ecologic mischief? *Dermatologic therapy* 2009;22:398-406.
27. Kircik L. Rapid and efficacious fixed-combination monotherapy: desired results for the patient and improved adherence for the clinician. *Cutis; cutaneous medicine for the practitioner* 2009;84:5-11.
28. Lookingbill DP, Chalker DK, Lindholm JS, Katz HI, Kempers SE, Huerter CJ et al. Treatment of acne with a combination clindamycin/benzoyl peroxide gel compared with clindamycin gel, benzoyl peroxide gel and vehicle gel: combined results of two double-blind investigations. *Journal of the American Academy of Dermatology* 1997;37:590-5.
29. Nast A, Dreno B, Bettoli V, Degitz K, Erdmann R, Finlay AY et al. European evidence-based (S3) guidelines for the treatment of acne. *Journal of the European Academy of Dermatology and Venereology : JEADV* 2012;26 Suppl 1:1-29.
30. Monk E, Shalita A , Siegel DM. Clinical applications of non-antimicrobial tetracyclines in dermatology. *Pharmacological research : the official journal of the Italian Pharmacological Society* 2011;63:130-45.
31. Simonart T , Dramaix M. Treatment of acne with topical antibiotics: lessons from clinical studies. *The British journal of dermatology* 2005;153:395-403.

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