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Authors

Del Rosso, James Q
Webster, Guy F
Rosen, Ted
et al.

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[REPORT]

Status Report from the Scientific Panel on Antibiotic Use in Dermatology of the American Acne and Rosacea Society

Part 1: Antibiotic Prescribing Patterns, Sources of Antibiotic Exposure, Antibiotic Consumption and Emergence of Antibiotic Resistance, Impact of Alterations in Antibiotic Prescribing, and Clinical Sequelae of Antibiotic Use

[a]JAMES Q. DEL ROSSO, DO; [b]GUY F. WEBSTER, MD; [c]TED ROSEN, MD; [d]DIANE THIBOUTOT, MD; [e]JAMES J. LEYDEN, MD; [f]RICHARD GALLO, MD, PhD; [g]CLAY WALKER, PhD; [h]GEORGE ZHANEL, PhD; [i]LAWRENCE EICHENFIELD, MD

[a]Dermatology Adjunct Faculty, Touro University Nevada, Henderson, Nevada; [b]Department of Dermatology, Jefferson Medical College, Philadelphia, Pennsylvania; [c]Department of Dermatology, Baylor College of Medicine, Houston, Texas; [d]Department of Dermatology, Penn State University, Hershey, Pennsylvania; [e]Department of Dermatology, University of Pennsylvania, Philadelphia, Pennsylvania; [f]Department of Dermatology, University of California San Diego, San Diego, California; [g]University of Florida Dental School, Gainesville, Florida; [h]Department of Medical Microbiology and Infectious Diseases, University of Manitoba, Winnipeg, Canada; [i]Department of Dermatology (Pediatrics), University of California San Diego, San Diego, California

ABSTRACT

Oral and topical antibiotics are commonly prescribed in dermatologic practice, often for noninfectious disorders, such as acne vulgaris and rosacea. Concerns related to antibiotic exposure from both medical and nonmedical sources require that clinicians consider in each case why and how antibiotics are being used and to make appropriate adjustments to limit antibiotic exposure whenever possible. This first article of a three-part series discusses prescribing patterns in dermatology, provides an overview of sources of antibiotic exposure, reviews the relative correlations between the magnitude of antibiotic consumption and emergence of antibiotic resistance patterns, evaluates the impact of alterations in antibiotic prescribing, and discusses the potential relevance and clinical sequelae of antibiotic use, with emphasis on how antibiotics are used in dermatology. (*J Clin Aesthet Dermatol.* 2016;9(4):18–24.)

Oral and topical antibiotics are among the most commonly prescribed therapies in dermatologic practice, used predominantly for acne vulgaris (AV) and rosacea, but also for many other inflammatory and infectious skin diseases.[1–3] Antibiotic agents are vital to the optimal management of many skin diseases. Nevertheless, emerging national and global concerns related to antibiotic exposure from both medical and nonmedical sources require that all healthcare professionals take a closer look at why and how antibiotics are being used and to make appropriate adjustments in an attempt to limit antibiotic exposure whenever possible. This is not suggesting that antibiotics be withheld in cases where they are clearly indicated, especially in cases of cutaneous infections. The

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ADDRESS CORRESPONDENCE TO: James Q. Del Rosso, DO; E-mail: jqdelrosso@yahoo.com

notable decrease in the development of novel topical and systemic antibiotic agents (especially within dermatology), has created additional concern in both the inpatient and outpatient settings, as clinicians face a greater number of cases where antibiotic resistance is encountered.[4–10] Consideration of alternative options, or adjustments in how antibiotics are administered, may optimize therapy and reduce associated risks, especially with inflammatory skin disorders, and in some clinical scenarios where antibiotics are routinely given, but are not needed.[4–8,10]

Started in 2005, The Scientific Panel on Antibiotic Use in Dermatology (SPAUD) represents the first organized and dedicated attempt in the United States within dermatology to evaluate how antibiotic and antimicrobial agents are utilized within the specialty and to consistently publish and present in this area.[4–6] In 2014, the SPAUD project joined with the American Acne and Rosacea Society (AARS) and functions solely within the AARS. Importantly, other major dermatology groups involving dermatologists from both the United States and other countries have become very active in evaluating antibiotic use and promoting antibiotic stewardship in publications and through presentations.[7–10] Multiple initiatives emphasizing the significance of bacterial resistance to antibiotics, antibiotic stewardship, measures to reduce both medical and environmental antibiotic exposures, and increased research on antibiotic alternatives have emerged worldwide.[7–16] Although not all countries and regional sectors, including within the United States, have fully adopted formal and organized measures to reduce antibiotic resistance, some positive improvements and clinically relevant observations have been noted, and are discussed below.

In this first part of a three-part article series, the authors depict antibiotic prescribing patterns in dermatology, provide an overview of sources of antibiotic exposure, review the relative correlations between the magnitude of antibiotic consumption and emergence of antibiotic resistance patterns, assess the impact of alterations in antibiotic prescribing, and discuss the potential relevance and clinical sequelae of antibiotic use, especially in patients treated for AV. The second article in the series will discuss alterations of the microbiota and microbiome with antibiotic use, evaluate antibiotic and antimicrobial effects associated with medical therapies for AV and rosacea, and review data on subantibiotic therapy. The final article in the series will cover management of uncomplicated skin and skin structure infections (USSTIs) and provide an overall conclusion with some suggestions to minimize antibiotic resistance.

HOW COMMONLY ARE ANTIBIOTICS USED IN DERMATOLOGY?

Data ranging from 2003 through 2013 has shown that dermatologists in the United States prescribe approximately 8 to 9 million antibiotic prescriptions annually, accounting for at least 20 percent of all prescriptions written by dermatologists, with up to two-thirds of these antibiotic prescriptions being given for treatment of AV.[1,17–19] Over the past several years, among topical antibiotics, clindamycin is the most commonly prescribed by dermatologists, accounting for up to one-fourth of prescriptions for AV.[17,18] Tetracyclines, especially doxycycline and minocycline, comprise approximately 75 percent of all oral antibiotics prescribed by dermatologists (Table 1).[1,17–19]

TABLE 1. Practical considerations related to oral antibiotic use in dermatology[1,17–19]

- Approximately 11.5 million prescriptions and 6.9 million topical antibiotic prescriptions were dispensed for dermatologic conditions*
- Dermatologists prescribe approximately 8.2 million oral antibiotic prescriptions annually#
- Approximately two-thirds of oral antibiotic prescriptions written by dermatologists are for doxycycline and minocycline.+ Tetracycline agents account for approximately three-fourths of all prescriptions written by dermatologists
- Dermatologists prescribe antibiotics more commonly than any other physician group based on the prescribing rate per clinician
- The prescribed duration of antibiotic therapy is often markedly longer with therapies treated by dermatologists. The majority of antibiotic prescriptions written by dermatologists are for chronic inflammatory skin disorders, such as acne and rosacea, and not for cutaneous infections

*2015; #2010; +2011

Data from 2010 reported that 258 million courses of oral antibiotics were prescribed overall, with dermatologists accounting for 8.2 million prescriptions (3%).[17–19] Interestingly, based on this data, among the top five specialties in oral antibiotic prescribing, the number of prescriptions written per provider were highest among dermatologists.[17–19] This is not surprising due to the high volume of cases of AV and rosacea seen in dermatology practices, and also accounts for the high relative percentage of tetracycline prescriptions (75%) as compared to other oral antibiotics prescribed in dermatology.[1,17–19] Importantly, many diseases treated with antibiotic therapy by dermatologists involve much longer courses of active exposure (e.g., AV, rosacea) than those typically used to treat USSTIs, such as folliculitis and impetigo.[1,4–6] This latter factor differentiates how antibiotics are often used in dermatology and can impact bacterial resistance patterns and microbiome alterations through selection pressure, emergence of resistance genes, and other antibiotic resistance mechanisms.

WHAT ARE THE OVERALL PATTERNS OF ANTIBIOTIC EXPOSURE?

The two major sources of antibiotic exposures are

agriculture (livestock, poultry) (78.7%) and human (19.1%); aquaculture, crops, and companion animals comprise less than three percent collectively.[20] Despite the recommendation of the United States Food and Drug Administration (FDA) for judicious use of antibiotics in agriculture, 29,000,000 tons of antibiotics are used annually in the United States, mostly in livestock and poultry feed, primarily to promote animal growth and reduce infections that can lead to costly animal loss.[21,22]

What consequences have emerged from use of antibiotics in agriculture that may be clinically relevant to infectious disorders and/or antibiotic resistance patterns encountered by clinicians in their patients?

- Antibiotic residues, antibiotic-resistant bacterial strains, and antibiotic resistance genes gain access into wastewater from livestock and poultry farms; this can alter microbial ecology and potentially cause disease.[21]
- Tetracycline feeding to hogs led to emergence of methicillin-resistant *Staphylococcus aureus* (MRSA) strains (European ST398 variants), which were recovered from humans with infection, supermarket beef and pork (30%), and shopping cart handles (10%).[22]
- Tetracycline-resistant MRSA nasal colonization was present in 30 percent of workers from farms using tetracycline-containing feed compared to two percent in workers from antibiotic-free farms.[23]

Since 1999 and 2000, throughout Europe and in Denmark, respectively, use of antibiotics in feed for animal growth promotion has been banned.[22] In the United States, organized banning of antibiotics in animal feed has been minimal, and no effort has been made by China, the world leader in hog farms. It is difficult to determine whether or not banning antibiotics in agriculture has reduced the rate and morbidity/mortality of bacterial infections in humans. However, increases in infection rate in the farm animals and in animal death rate from acute infections have been noted.[22]

CAN ADJUSTMENTS IN WHEN AND HOW ANTIBIOTICS ARE USED IN CLINICAL PRACTICE MAKE AN IMPACT ON REDUCING ANTIBIOTIC RESISTANCE?

When one considers the widespread global use of antibiotics in agriculture, it is tempting to think that prescribing of antibiotics by clinicians in clinical practice contributes negligibly to the overall body of antibiotic-resistant bacteria. As a corollary to this, it is also easy to assume that measures to reduce antibiotic resistance by adjusting prescribing patterns would have very little impact on reduction of antibiotic resistance. In fact, there is evidence that consumption of antibiotics from prescribing is associated with emergence of antibiotic resistance in human populations, and measures to limit antibiotic exposure can lead to a reduction in antibiotic-resistant bacteria in involved communities, including both commensal and pathogenic strains.[1,4–6,9,24–33] Some representative examples include the following:

- Macrolide antibiotic consumption in Finland, defined as daily doses/1000 patients/day, decreased from 2.40 in 1991 to 1.38 in 1992, and remained around this lower level through 1996. The reduction in macrolide consumption was correlated directly with a progressive decrease in erythromycin-resistant group A streptococcal isolates from 16.5 percent in 1992 to 8.6 percent in 1996.[24]
- Skin colonization by antibiotic-resistant *P. acnes* among patients treated for AV and untreated close contacts, evaluated at six centers in Europe, demonstrated strong overall correlations with regional prescribing patterns (91% erythromycin/clindamycin resistance in Spain; 26.4% tetracycline resistance in United Kingdom).[30] Thorough literature analysis has reported both an increase in the overall incidence of antibiotic-resistant *P. acnes* from 20 percent in 1978 to 62 percent in 1996, and a direct correlation between poor therapeutic response and presence of antibiotic-resistant propionibacteria.[33]
- In the United States and many other countries, the frequency of recovery of insensitive strains of *P. acnes* and the magnitude of increase in minimum inhibitory concentrations (MICs) is highest with erythromycin, followed by clindamycin, and tetracycline; resistance to doxycycline is lower and is least with minocycline.[5,6,27,28,30,32,33] A more recent antibiotic-resistance analysis reported in 2008 completed in adults who exhibited high baseline *P. acnes* counts on forehead skin and carriage of high MICs to multiple antibiotics demonstrated resistance to erythromycin, clindamycin, tetracycline, doxycycline, and minocycline in 100 percent (30/30), 100 percent (25/25), 97 percent (29/30), 83 percent (25/30), and 63 percent% (19/30) of subjects, respectively; high-level resistance for erythromycin and the tetracyclines (tetracycline, doxycycline, minocycline), and intermediate to high resistance for clindamycin was present in 100 percent (30/30), 50 percent (15/30), 33 percent (10/30), 27 percent (8/30), and 52 percent (13/25) of subjects, respectively.[34]
- An *in vivo* analysis evaluated the effect of clindamycin 1% gel applied once daily for six weeks in subjects with facial AV. Greater *P. acnes* reductions were noted in subjects with clindamycin MICs of ≤256 µg/mL than in those with clindamycin MICs ≥512 µg/mL (P=0.0001). These results support that topical clindamycin produces variable *in vivo* antimicrobial effects on *P. acnes*, with an MIC breakpoint of 256 µg/mL separating the relative magnitudes of *P. acnes* reduction. It was observed that topical clindamycin appeared to be more effective *in vivo* in patients with MIC levels of ≤256 µg/mL as compared to higher MIC levels.[35]
- Thorough analyses of multiple clinical studies evaluating the efficacy of topical antibiotics used to

treat AV from 1977 through 2002 showed a significant decrease in the efficacy of erythromycin with both inflammatory and comedonal lesion counts (P=0.001 and P=0.001, respectively), likely due to the marked prevalence of high level *P. acnes* resistance to erythromycin.[34–37] Lesion count reductions with topical clindamycin have remained more stable over time since the 1970s.[36,37] This is likely due at least partially to greater *in vitro* variability in susceptibility of *P. acnes* based on MICs (as described above), although approximately two-thirds of individuals are likely to have facial skin colonized by clindamycin-resistant *P. acnes*.[35–37]

It is important to recognize that there are factors other than antibiotic consumption that influence the development of antibiotic-resistant bacteria. Differences among chemical classes of antibiotics (i.e., tetracyclines vs. macrolides vs. cephalosporins) and between antibiotics within the same class (i.e., doxycycline vs. minocycline) exist regarding relative propensity for emergence of resistance and specific mechanisms of resistance (i.e., encoded genes, cell envelope alterations, efflux pumps, biofilms).[5,6,27,28,30–33,38–44]

WHAT IS THE CLINICAL RELEVANCE OF ANTIBIOTIC PRESCRIBING AND EMERGENCE OF ANTIBIOTIC RESISTANCE IN DERMATOLOGY?

The high overall prevalence of both *P. acnes* strains and coagulase-negative staphylococci that are resistant or less susceptible to antibiotics commonly used to treat AV is well described, with some evidence directly correlating *P. acnes* resistance with a decrease in therapeutic effect.[5,6,27,28,30–33,35,45] Measures to reduce *P. acnes* resistance when prescribing antibiotics have been reviewed elsewhere.[3,5,6–8,34,37] However, the effect of oral and topical antibiotics on other cutaneous and mucosal bacteria, such as staphylococci and streptococci, are important to consider.[3–8,46] This is especially relevant when utilizing more prolonged courses of antibiotic therapy (weeks or months) for disorders such as AV and rosacea. The following outcomes from literature on antibiotic use for AV and other medical conditions summarizes important observations that are clinically relevant in the management of patients with AV:

- Facial application of erythromycin 2% gel compared to vehicle gel for 12 weeks (N=208) increased the quantity of erythromycin-resistant coagulase-negative staphylococci on the face and at remote sites (i.e., anterior nares, back), and also increased *S. aureus* nasal carriage.[46–48] The rate of erythromycin-resistant *S. aureus* among previous carriers rose from 15 to 40 percent over a duration of 12 weeks.[47] The prevalence and quantity of the erythromycin-resistant bacteria have been shown to persist over durations of four and six weeks after discontinuation of antibiotic treatment.[47,48]
- Among subjects with AV (N=105), a three-fold greater incidence of oropharyngeal colonization with *Streptococcus pyogenes* was noted in subjects using oral and/or topical antibiotics for at least three months (33%; 13/39) compared to control subjects not treated with antibiotics for at least six months (10%; 6/63); resistance of *S. pyogenes* to at least one tetracycline antibiotic was noted in 85 percent (11/13) of antibiotic-treated subjects compared to 20 percent (1/5) of control subjects.[49]
- Data from a retrospective cohort analysis of diagnosis and prescription data from a large population database (N=118,496) suggested that patients treated with oral and/or topical antibiotics for AV exhibit a 2.15-fold greater risk of developing an upper respiratory tract infection (URTI), although the microbiologic etiology of the URTI was not evaluated (i.e., bacterial, viral).[50] In addition, among household contacts of patients with AV (N=98,094), contacts of AV patients with a URTI were 43 percent more likely to develop an URTI compared to those in contact with AV patients who did not have an URTI; however, use of antibiotics in AV patients did not independently increase the risk of URTI among contacts.[51]
- In a cross-sectional study of AV patients, 43 percent (36/83) were colonized with *S. aureus*, six percent (2/36) had MRSA, 56 percent (2/36) had *S. aureus* throat colonization, 25 percent (9/36) exhibited *S. aureus* nasal carriage, and 19 percent (7/36) were colonized with *S. aureus* in their nose and throat.[52] The use of tetracyclines over 1 to 2 months lowered the prevalence of *S. aureus* colonization and did not increase resistance to the tetracycline antibiotics. *S. aureus* resistance rates to clindamycin and erythromycin were 40 and 44 percent, respectively, especially the nasal isolates; tetracycline resistance remained low (< 10%).
- A prospective cohort study from 1995 through 2002 of invasive pneumococcal infection (N=3339) demonstrated that knowledge of antibiotic use during the three months before presentation was important for determining appropriate antibiotic therapy.[53] Infection with trimethoprim-sulfamethoxazole (TMP-SMX)-resistant pneumococci was 1.7-fold higher with previous use of penicillin (P = .03), 4.7-fold higher with previous use of TMP-SMX (P<0.001), and 3.5-fold higher with previous azithromycin use (P=0.001). Infection with macrolide-resistant isolates was 3.9-fold higher with previous use of clarithromycin (P<0.001), and 9.9-fold higher with prior use of azithromycin (P<0.001). Infection with fluoroquinolone-resistant pneumococci was 12.1-fold higher with previous fluoroquinolone use (P<0.001). Importantly, this data demonstrates that prior antibiotic use, at least within the previous three months, directly affects the antibiotic resistance profile of the causative bacterial pathogen.[53]

SUMMARY "TAKE HOME" POINTS

- Antibiotics are important in the management of bacterial infections and some dermatologic disorders that are not infectious in etiology. It is important for

World Health Organization and Centers for Disease Control and Prevention Initiatives Related to Antibiotic Use and Resistance

The World Health Organization (WHO) has outlined several important recommendations that address regional and global measures and cooperative alliances to incorporate measures to reduce antibiotic resistance, encourage antibiotic stewardship, and decrease environmental exposures, with a strong emphasis on surveillance and actions plans. (http://apps.who.int/gb/ebwha/pdf_files/WHA67/A67_R25-en.pdf). Among the many recommendations are the following:

- Develop and/or strengthen national strategies with international collaboration to contain antibiotic resistance.
- Monitor the magnitude of antibiotic resistance including antibiotic use in all relevant sectors (especially health care and agriculture).
- Improve awareness of the threat posed by antibiotic resistance.
- Encourage and support research to combat antibiotic resistance and promote responsible use of antibiotic agents.
- Develop methods to expand the usable lifespan of existing antibiotics.
- Stimulate the development of new diagnostic methods and novel antibiotic and antimicrobial agents.
- Establish global action plans to mitigate antibiotic resistance, including antibiotic resistance surveillance systems in inpatients, in outpatients, in animals, and with nonhuman usage of antibiotics and antimicrobial agents.

In the United States in 1995, the Centers for Disease Control and Prevention (CDC) began the National Campaign for Appropriate Antibiotic Use in the Community, which was later renamed the "Get Smart: Know When Antibiotics Work" program in 2003 (www.cdc.gov/getsmart).

- The Get Smart program provides several educational services for health care professionals and patients, including handout materials and other tools to assist clinicians in their practice.
- Although this CDC initiative began with a focus on reducing the frequent prescribing of antibiotics within primary care for upper respiratory infections that are frequently viral in origin, the CDC has more recently increased its awareness of antibiotic prescribing in other disciplines, including dermatology. The participation of the CDC at the SPAUD meeting in September 2014 was a major first step in establishing cooperative efforts between the AARS and the CDC, both dedicated to assisting clinicians with optimal antibiotic prescribing and antibiotic use.

clinicians to prescribe antibiotics judiciously in order to limit the potential for antibiotic resistance and preserve their efficacy for treatment of infections.

- The potential consequences of antibiotic resistance related to antibiotic use may not be readily detectable or easy to perceive by prescribing clinicians. Administration of oral and/or topical antibiotics is consistently associated with emergence of resistant bacterial strains due to selection pressure. As a result, antibiotic use is associated with the unavoidable "side effect" or "selection" of antibiotic-resistant organisms.
- Due to the marked increase in treatment-resistant bacterial pathogens in both inpatient and office-based settings, clinicians are encouraged to evaluate if an antibiotic is needed and how it should best be utilized to achieve treatment success while also minimizing unnecessary exposure and creating "collateral damage" to the microbiome. Antibiotic exit strategies will be discussed later in this article series.
- Clinical significance of the emergent antibiotic-resistant strains may not always be present, or may not be readily apparent, as the microbiologic consequences may or may not affect the treated patient. Additionally, antibiotic-resistant bacteria may be transmitted to other personal contacts who may or may not manifest an associated infection, or may serve solely as a carrier.
- Antibiotic resistance occurs with both topical and systemic antibiotic use. Use of a topical antibiotic may alter microbial colonization and antibiotic resistance patterns at anatomic sites remote from the site of application, including the anterior nares.
- The prevalence of antibiotic-resistant *P. acnes* and many other cutaneous bacteria increase with greater antibiotic consumption. Measures to reduce the use of specific antibiotic classes or individual agents can decrease the prevalence of antibiotic-resistance with many bacterial strains.
- *P. acnes* resistance to clindamycin, and to a lesser extent doxycycline and minocycline, have progressively increased over time. It is strongly recommended that antibiotics not be used as monotherapy in the management of AV.
- Many unanswered questions remain regarding the "ecologic mischief" associated with antibiotic use. More studies are needed within dermatology and other disciplines to address the clinical relevance of antibiotic resistance. Recommendations regarding the optimal use of antibiotics are admittedly "a moving target" and are based on evaluation and interpretation of information that is currently available. Nevertheless, it is clear that limiting antibiotic use appropriately is an important goal that directly supports reduction in antibiotic-resistant bacteria.

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REFERENCES

1. Kim S, Michaels BD, Kim GK, Del Rosso JQ. Systemic antibacterial agents. In: Wolverton SE, ed. *Comprehensive Dermatologic Drug Therapy.* 3rd ed. Philadelphia, PA: Elsevier-Saunders; 2013:61–97.
2. Bhatia N. Use of antibiotics for noninfectious dermatologic disorders. *Dermatol Clin*. 2009;27(1):85–89.
3. Gollnick H, Cunliffe W, Berson D, et al. Management of acne:

report from a global alliance to improve outcomes in acne. *J Am Acad Dermatol.* 2003;49(1):S1–S37.
4. Del Rosso JQ. Report from the scientific panel on antibiotic use in dermatology: introduction. *Cutis.* 2007;79(6S):6–8.
5. Leyden JJ, Del Rosso JQ, Webster GF. Clinical considerations in acne vulgaris and other inflammatory skin disorders: focus on antibiotic resistance. *Cutis*. 2007;79(suppl 6):9–25.
6. Leyden JJ, Del Rosso JQ, Webster GF. Clinical considerations in the treatment of acne vulgaris and other inflammatory skin disorders: a status report. *Dermatol Clin.* 2009;27(1):1–15.
7. Thiboutot D, Dreno B, Gollnick H, et al. A call to limit antibiotic use in acne. *J Drugs Dermatol.* 2013;12(12):1331–1332.
8. Dreno B, Thiboutot D, Gollnick H, et al. Antibiotic stewardship in dermatology: limiting antibiotic use in acne. *Eur J Dermatol.* 2014;24(3):330–334.
9. Lawes T, Lopez-Lozano JM, Nebot CA, et al. Effects of national antibiotic stewardship and infection control strategies on hospital-associated and community-associated methicillin-resistant *Staphylococcus aureus* infections across a region of Scotland: a non-linear time-series study. *Lancet Infect Dis.* 2015;15(12):1438–1449.
10. Stanton TB. A call for antibiotic alternatives research. *Trends Microbiol.* 2013;21(3):111–1113.
11. Woolhouse M, Farrar J. Policy: An intergovernmental panel on antimicrobial resistance. *Nature*. 2014;509(7502):555–557.
12. Gould IM. Coping with antibiotic resistance: the impending crisis. *Int J Antimicrob Agents*. 2010;36 Suppl 3:S1–S2.
13. Van Boeckel TP, Gandra S, Ashok A, et al. Global antibiotic consumption 2000 to 2010: an analysis of national pharmaceutical sales data. *Lancet Infect Dis.* 2014;14(8): 742–750.
14. Cantón R, Bryan J. Global antimicrobial resistance: from surveillance to stewardship. Part 2: stewardship initiatives. *Expert Rev Anti Infect Ther*. 2012;10(12):1375–1377.
15. Struelens MJ, Monnet D. Prevention of methicillin–resistant *Staphylococcus aureus* infection: is Europe winning the fight? *Infect Control Hosp Epidemiol*. 2010;31(Suppl 1):S42–S44.
16. Allerberger F, Lechner A, Wechsler-Fördös A, et al. Optimization of antibiotic use in hospitals—antimicrobial stewardship and the EU project ABS international. *Chemotherapy*. 2008;54(4):260–267.
17. Get Smart About Antibiotics Week 2015. Centers for Disease Control and Prevention. http://www.cdc.gov/media/dpk/2015/dpk-antibiotics-week-2015.html.
18. Sanchez G. Presented at Scientific Panel on Antibiotic Use in Dermatology (SPAUD); September 6, 2014; Las Vegas, Nevada.
19. Del Rosso JQ. Oral doxycycline in the management of acne vulgaris: current perspectives on clinical use and recent findings with a new double-scored small tablet formulation. *J Clin Aesthet Dermatol.* 2015;8(5):19–26.
20. Hollis A, Ahmed Z. Preserving antibiotics, rationally. *N Engl J Med.* 2013;369(26):2474–2476.
21. Tao CW, Hsu BM, Ji WT, et al. Evaluation of five antibiotic resistance genes in wastewater treatment systems of swine farms by real-time PCR. *Sci Total Environ.* 2014;496: 116–121.
22. Mole B. Farming up trouble. *Nature*. 2013;499(7459): 398–400.
23. Rinsky JL, Nadimpalli M, Wing S, et al. Livestock-associated methicillin and multidrug resistant *Staphylococcus aureus* is present among industrial, not antibiotic-free livestock operation workers in North Carolina. *PLoS One.* 2013;8(7):e67641.
24. Seppala et al. The effect of changes in the consumption of macrolide antibiotics on erythromycin resistance in group A streptococci in Finland. Finnish Study Group for Antimicrobial Resistance. *N Engl J Med.* 1997;337(7): 441–446.
25. Bergman M, Huikko S, Pihlajamäki M, et al. Effect of macrolide consumption on erythromycin resistance in *Streptococcus pyogenes* in Finland in 1997–2001. *Clin Infect Dis.* 2004;38(9):1251–1256.
26. Goossens H. Antibiotic consumption and link to resistance. *Clin Microbiol Infect.* 2009;15(Suppl 3):12–15.
27. Eady AE, Cove JH, Layton AM. Is antibiotic resistance in cutaneous propionibacteria clinically relevant? Implications of resistance for acne patients and prescribers. *Am J Clin Dermatol.* 2003;4(12):813–831.
28. Ross JI, Snelling AM, Eady EA, et al. Phenotypic and genotypic characterization of antibiotic-resistant *Propionibacterium acnes* isolated from acne patients attending dermatology clinics in Europe, the U.S.A., Japan and Australia. *Br J Dermatol.* 2001;144(2):339–346.
29. Song M, Seo SH, Ko HC, et al. Antibiotic susceptibility of *Propionibacterium acnes* isolated from acne vulgaris in Korea. *J Dermatol.* 2011;38(7):667–773.
30. Ross JI, Snelling AM, Carnegie E, et al. Antibiotic-resistant acne: lessons from Europe. *Br J Dermatol.* 2003;148(3): 467–478.
31. Hsueh PR, Chen WH, Luh KT. Relationships between antimicrobial use and antimicrobial resistance in Gram-negative bacteria causing nosocomial infections from 1991–2003 at a university hospital in Taiwan. *Int J Antimicrob Agents.* 2005;26(6):463–472.
32. Coates P, Vyakrnam S, Eady EA, et al. Prevalence of antibiotic-resistant propionibacteria on the skin of acne patients: 10-year surveillance data and snapshot distribution study. *Br J Dermatol.* 2002;146(5):840–848.
33. Cooper AJ. Systematic review of *Propionibacterium acnes* resistance to systemic antibiotics. *Med J Aust.* 1998;169(5):259–261.
34. Leyden JJ, Wortzman M, Baldwin EK. Antibiotic-resistant *Propionibacterium acnes* suppressed by a benzoyl peroxide cleanser 6%. *Cutis*. 2008;82(6):417–421.
35. Leyden JJ. *In vivo* antibacterial effects of tretinoin-clindamycin and clindamycin alone on *Propionibacterium acnes* with varying clindamycin minimum inhibitory. *J Drugs Dermatol.* 2012;11(12):1434–1438.
36. Simonart T, Dramaix M. Treatment of acne with topical antibiotics: lessons from clinical studies. *Br J Dermatol.* 2005;153(2):395–403.
37. Del Rosso JQ. Topical antibiotics. In: Shalita AR, Del Rosso JQ, Webster GF, eds. *Acne Vulgaris.* London, United

Kingdom: Informa Healthcare; 2011:95–104.
38. Sardana K, Gupta T, Garg VK, et al. Antibiotic resistance to *Propionobacterium acnes*: worldwide scenario, diagnosis and management. *Expert Rev Anti Infect Ther*. 2015;13(7): 883–896.
39. Roberts MC. Tetracycline resistance determinants: mechanisms of action, regulation of expression, genetic mobility, and distribution. *FEMS Microbiol Rev.* 1996;19(1):1–24.
40. Eady EA, Jones CE, Gardner KJ, et al. Tetracycline-resistant propionibacteria from acne patients are cross-resistant to doxycycline, but sensitive to minocycline. *Br J Dermatol.* 1993;128(5):556–560.
41. Shivekar S, Menon T. Molecular basis for erythromycin resistance in group A streptococcus isolated from skin and soft tissue infections. *Diagn Res.* 2015;9(11):21–23.
42. Schafer F, Fich F, Lam M, et al. Antimicrobial susceptibility and genetic characteristics of *Propionibacterium acnes* isolated from patients with acne. *Int J Dermatol.* 2013;52(4):418–425.
43. Abdollahi S, Ramazanzadeh R, Khiabani ZD, et al. Epidemiological and inducible resistance in coagulase-negative staphylococci. *Glob J Health Sci.* 2015;8(4):51675.
44. Eady EA, Cove JH. Staphylococcal resistance revisited: community-acquired methicillin resistant *Staphylococcus aureus*--an emerging problem for the management of skin and soft tissue infections. *Curr Opin Infect Dis.* 2003;16(2): 103–124.
45. Cove JH, Eady EA, Cunliffe WJ. Skin carriage of antibiotic-resistant coagulase-negative staphylococci in untreated subjects. *J Antimicrob Chemother*. 1990;25(3):459–469.
46. Bowe WP, Leyden JJ. Clinical implications of antibiotic resistance: risk of systemic infection from Staphylococcus and Streptococcus. In: Shalita AR, Del Rosso JQ, Webster GF, eds. *Acne Vulgaris.* London, United Kingdom: Informa Healthcare; 2011:125–133.
47. Mills O, Thornsberry C, Cardin CW, 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;82:260–265.
48. Vowels BR, Feingold DS, Sloughfy C, et al. Effects of topical erythromycin in ecology of aerobic cutaneous bacterial flora. *Antimicrob Agents Chemother*. 1996;40:598–604.
49. Levy RM, Huang EY, Roling D, et al. Effect of antibiotics on the oropharyngeal flora in patients with acne. *Arch Dermatol.* 2003;139(4):467–471.
50. Margolis DJ, Bowe WP, Hoffstad O, et al. Antibiotic treatment of acne may be associated with upper respiratory tract infections. *Arch Dermatol*. 2005;141(9):1132–1136.
51. Bowe WP, Hoffstad O, Margolis DJ. Upper respiratory tract infection in household contacts of acne patients. *Dermatology*. 2007;215(3):213–218.
52. Fanelli M, Kupperman E, Lautenbach E, et al. Antibiotics, acne, and *Staphylococcus aureus* colonization. *Arch Dermatol.* 2011;147(8):917–921.
53. Vanderkooi OG, Low DE, Green K, et al. Predicting antimicrobial resistance in invasive pneumococcal infections. *Clin Infect Dis.* 2005;40(9):1288–1297.