[R E P O R T]

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

Part 2: Perspectives on Antibiotic Use and the Microbiome and Review of Microbiologic Effects of Selected Specific Therapeutic Agents Commonly Used by Dermatologists

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ABSTRACT

In this second part of a three-part series addressing several issues related to antibiotic use in dermatology, potential effects of antibiotic use on the human microbiota and microbiome are reviewed. Data from available literature on the microbiologic effects of specific therapeutic agents commonly used in dermatology, including oral isotretinoin, tetracycline agents, and sub-antimicrobial (sub-antibiotic) dose doxycycline, are also discussed. (*J Clin Aesthet Dermatol.* 2016;9(5):11–17.)

In Part 1 of this three-part article series, antibiotic exposure, prescribing patterns, and clinical sequelae of antibiotic consumption were discussed. The information gleaned from available literature and from the perspectives of professionals with knowledge and strong interest in this area will hopefully guide clinicians in using antibiotics more judiciously and responsibly.
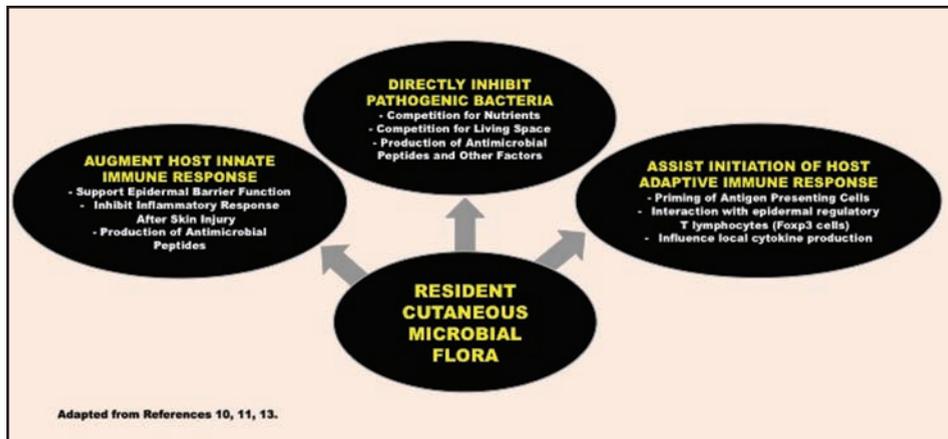
In this second part of the series, potential effects of antibiotic use on the human microbiome are discussed along with data on oral isotretinoin, subantimicrobial (sub-antibiotic) dose doxycycline, and other therapeutic agents commonly used in dermatology.

WHAT IS MEANT BY "HUMAN MICROBIOME"?

Recent widespread interest in the human microbiome and its relationships with health and disease are exemplified by several recent review publications.[1–10] The term human microbiome refers to the totality of microbial organisms and their collective genetic material present in or on anatomic regions (communities) within the human host, such as the gastrointestinal (GI) tract, oral cavity, skin, and genital tract. Although the terms microbiome and microbiota are often used interchangeably, the term human microbiota originally was used to refer to all of the microorganisms, whether commensal, symbiotic, or pathogenic,

Figure 1. Normal bacterial flora of the human skin microbiota provide host-protective effects through multiple mechanisms.

that literally share the human body space.

In general usage, the term human microbiota refers to the roughly 100 trillion microbes, predominantly GI tract bacteria, that are present within or on the human body; while the human microbiome refers more specifically to the collective genomes that are harbored by these organisms.[7,8] Technologic advances in DNA sequencing and genetic analysis have allowed for the emergence of highly detailed research in this area; however, interpretation of the data warrants careful analysis before definitive conclusions can be made about correlations with health and disease. It is important to be critical when comparing studies identifying the "skin microbiome," as the anatomic site studied and environment exposures can drastically impact the array of microbes that are identified.[10]

WHAT IS THE SIGNIFICANCE OF THE HUMAN SKIN MICROBIOTA AND MICROBIOME TO THE HOST?

The wide diversity of species that make up the human microbiota, its dynamic nature in response to exogenous antimicrobial exposures, and the range of genetic variations within the microbiome, are very difficult to conceptualize or to definitively correlate with clinical relevance. It has been calculated that on skin there are approximately 33 bacteria per cell, and within the GI tract approximately 2,500 bacteria per cell.[9] It is believed that the human skin microbiota plays a cooperative role in concert with the immune and endogenous antimicrobial peptide systems to provide a homeostatic balance that serves to inhibit growth of pathogenic bacteria and support both innate and adaptive immunity (Figure 1).[10] Interestingly, the wide range of microbial diversity both between different individuals and within the same person that are observed in studies of the human skin microbiota and microbiome confound the ability to draw firm conclusions. As noted above, the anatomic site sampled is a major determinant of the microbial composition, as different microbes colonize different anatomic locations on

the human body. Although some body sites exhibit marked similarities in their microbial flora among different individuals, a significant amount of inter-personal variability has been identified overall.[10–12] Nevertheless, some important observations have been made regarding relationships between normal skin flora and protection against pathogenic bacteria.

WHAT IS THE CONCEPT OF COMMENSAL COMPETITION?

When pathogenic bacteria are introduced onto the skin surface, commensal organisms inhibit their ability to gain access to skin and proliferate through "competition for nutrients and space."[10] Some commensal bacteria, such as *Staphylococcus epidermidis*, as well as other bacterial taxa, are able to inhibit or restrict the growth of similar or closely related bacteria by producing antimicrobial molecules called bacteriocins.[13,14] In addition, cutaneous commensal bacteria also work in harmony with host immunologic functions to mitigate the potential for invasion by pathogenic bacteria.[10]

S. epidermidis, although a potential pathogen in selected circumstances, is one of the most abundantly cultured commensal bacteria on human skin.[10] There are data to demonstrate that some isolates of *S. epidermidis* "possesses several weapons that contribute to the innate immune defense arsenal present in human skin" that can inhibit the growth of pathogenic bacteria.[10] These weapons include:

- Production of a serine protease (Esp) by *S. epidermidis* augments the antimicrobial properties of human β-defensin 2 (hBD2). Introduction of Esp-producing *S. epidermidis* into the nasal cavity of volunteers who were nasal carriers of *S. aureus* produced clearance of colonization.[14]
- Esp produced by *S. epidermidis* has been shown to degrade several proteins produced by *S. aureus* that are involved in biofilm formation and many human receptor proteins important for staphylococcal colonization and infection by *S. aureus*.[15]
- *S. epidermidis*-derived molecules, such as phenol-soluble modulins (PSMs), can inhibit growth of cutaneous pathogens by inducing leakage of lipid membranes. The antimicrobial effects of *S. epidermidis* against potential skin pathogens, such as *S. aureus* and *Streptococcus pyogenes* are modulated via cooperative activity with host-derived antimicrobial peptides and through incorporation into neutrophil extracellular traps (NETs), which also provide innate host defense against infection.[10,15–17]
- Detection of *S. epidermidis* by keratinocytes via Toll-

like receptor-2 (TLR2) augments host immune response to *S. aureus* infection by increasing the expression of antimicrobial peptides, such as hβD2 and hβD3.[18,19]

S. epidermidis represents one of the commensal organisms that has been extensively studied, as briefly reviewed above, that can inhibit pathogenic bacteria. However, other bacterial organisms have been reported to exhibit symbiotic and mutualistic behaviors when colonizing human skin that are host-protective, including *Corynebacterium spp, Propionibacterium species, and Streptococcus spp*.[20] Importantly, when antibiotics or antimicrobial agents modify the cutaneous flora, there may be sequelae that alter host defense if host-protective commensal bacteria are reduced.

WHAT EFFECTS HAVE BEEN NOTED WITH USE OF ANTIBIOTICS ON THE HUMAN MICROBIOTA AND MICROBIOME?

The use of topical antibiotics, especially as monotherapy, for treatment of acne vulgaris (AV) have been shown to increase the emergence of resistant *Propionibacterium acnes* and *S. epidermidis*, and promote *S. aureus* nasal colonization.[21–30] It has also been established that use of oral antibiotics for AV is associated with increased emergence of antibiotic-resistant *P. acnes* and oropharyngeal *S. pyogenes* colonization.[21–23,29–31] However, two areas that are sometimes overlooked are the duration of persistence of antibiotic-resistant bacterial strains that emerge during a course of antibiotic therapy and the less apparent adverse effects of dysbiosis that oral antibiotics may induce by altering GI tract microbiota, including oropharynx. Although a complete review of these considerations are beyond the scope of this article, some important observations that are likely to be clinically relevant are as follows:

- An evaluation of distal GI tract bacterial flora measured through stool samples before and after repeated exposures to courses of oral ciprofloxacin administered six months apart demonstrated a rapid change in the diversity and composition of bacteria within 3 to 4 days. The overall GI flora began to return to baseline status starting one week after completion of therapy after each of the two courses of oral ciprofloxacin. However, the return was often incomplete suggesting that antibiotic use may possibly alter the baseline status of distal gut microbiota.[32,33]
- Assessments of a wide variety of systemic antibiotics such as amoxicillin, amoxicillin/ clavulanate, ciprofloxacin, and clindamycin showed a definite tendency toward rapid and marked changes in GI flora within days. Return to baseline state of bacterial flora generally occurred within a few months after therapy was completed; however, partial or incomplete return to baseline status was common.[34]
- A 1-year study evaluating antibiotic resistance characteristics of Gram-negative fecal bacteria in volunteers treated with amoxicillin, minocycline, or placebo showed 1) that healthy individuals carry bacteria harboring resistance to several antibiotics within their GI tract at baseline and 2) that antibiotic administration in some individuals can select for bacteria that are multi-antibiotic resistant with persistence for up to one year.[35]
- The use of a two-week course of oral clarithromycin was shown to induce marked and sustained antibiotic resistance in oropharyngeal flora that persisted for at least eight weeks after therapy.[36]
- An analysis of pharyngeal carriage of macrolide-resistant streptococci was completed in healthy volunteers treated with standard oral courses of azithromycin, clarithromycin, or placebo, with microbiologic evaluations completed before and after study treatment through 180 days. Both agents markedly increased the proportion of macrolide-resistant streptococci as compared to placebo, with the largest difference between the two active drugs noted at Day 28 (higher for azithromycin); some macrolide-resistant strains were noted to persist through 180 days.[37]

There has been a large body of emerging interest on potential relationships between the microbiota and microbiome, especially of the GI tract, and the potential health-related effects of microbial dysbiosis, including changes that may be associated with antibiotic use; examples include potential relationships to inflammatory bowel disease and other disorders, such as rheumatoid arthritis, type 1 diabetes, metabolic syndrome, atopy, and obesity.[34,38–49]

Although no definitive conclusions may be drawn at present, it is important for clinicians to be aware that research is in progress. As more research is completed over time, clinically relevant data on this topic is likely to be forthcoming, which may provide important insights regarding optimal use of antibiotic therapy.

WHAT ARE POTENTIAL CONSEQUENCES RELATED TO SKIN AND OTHER BACTERIAL FLORA WITH SELECTED SYSTEMIC AGENTS COMMONLY USED IN DERMATOLOGY?

Potential microbiologic consequences associated with topical antibiotic use were reviewed in Part 1 of this article series. The following discusses alterations to the cutaneous and other bacterial flora that can occur with selected systemic agents.

Oral isotretinoin. Changes in microbial flora have been shown to occur in association with the use of oral isotretinoin in patients with AV. Marked reduction in *P. acnes* and Gram-negative bacilli have been noted in both skin and anterior nares with a significant increase in recovery of *S. aureus* also observed.[50–52] Although oral isotretinoin causes a dramatic reduction in *P. acnes*, including strains resistant to several antibiotics commonly used to treat *P. acnes*, there are some antibiotic-resistant *P. acnes* strains that remain viable and persist after completion of oral isotretinoin therapy. Rates of nasal

- **Survey of 809 patients with acne vulgaris and 210 parents of patients**
  - **Approximately two-thirds of respondents were *not* aware that use of a topical antibiotic can cause a carrier-state for antibiotic-resistant bacteria**
  - **More than half of the respondents reported that they did not discuss with their doctor about the risks of resistance associated with antibiotic use**
  - **Approximately two-thirds of respondents stated that they prefer to avoid use of antibiotics unless they are the only option for treatment of their acne**
  - **One-third of respondents who were prescribed a regimen containing an antibiotic were aware of the existence of antibiotic-free treatment options**
  - **28% of respondents who were prescribed a regimen containing an antibiotic recalled discussing non-antibiotic treatments with their doctor or health care provider**

Reference 79

Figure 2. Perceptions of patients and parents of patients about antibiotic use for treatment of acne vulgaris.

carriage of *S. aureus* associated with use of oral isotretinoin range from 15 to 70 percent and may persist for at least six months after completion of therapy.[52,53] Although data are limited, there is some evidence to suggest that oral isotretinoin may increase fecal colonization with extended spectrum beta-lactamase (ESBL)-producing *Escherichia coli*.[53]

Oral tetracyclines. Oral tetracyclines represent the vast majority of oral antibiotics prescribed in dermatology, comprising approximately three-fourths of all antibiotics written by dermatologists.[54,55] Doxycycline and minocycline are currently the most frequently used oral antibiotics in dermatology, with the majority of prescriptions written for AV and rosacea.[55] Importantly, these two agents are also commonly utilized to treat uncomplicated skin and soft tissue infections caused by methicillin-resistant *S. aureus* (MRSA).[54] Although some reports do not demonstrate a clear association with use of oral tetracyclines and emergence of increased *S. aureus* colonization (including MRSA), the literature does suggest that oral tetracycline use can select for resistant bacterial organisms.[53,56] Some data support that prolonged antibiotic therapy for AV, including oral tetracycline therapy, may be associated with increased skin, nasal, and/or oropharyngeal carriage of *S. aureus*; may lead to emergence of resistant bowel flora (i.e., *E. coli*); and that antibiotic-resistant staphylococci may be transmitted to other close personal contacts.[53,56–62]

Sub-antimicrobial (sub-antibiotic) dose doxycycline. Tetracyclines have been shown to exhibit a variety of biologic properties that exhibit anti-inflammatory effects and are unrelated to any antibiotic activity. These biologic properties have been reviewed in detail elsewhere, with several of these non-antibiotic effects believed to correlate with the therapeutic effects of the tetracyclines for inflammatory disorders, such as AV and rosacea.[54,63–65] Among the tetracyclines, it has shown through both basic science and clinical research that sub-antibiotic dosing of doxycycline can be achieved without loss of the anti-inflammatory properties of the drug.[54,63–71] Sub-antibiotic dosing of doxycycline has been referred to in the literature

as both sub-antimicrobial dose doxycycline and anti-inflammatory dose doxycycline. Sub-antimicrobial (sub-antibiotic) doses provide the anti-inflammatory effects associated with doxycycline, but provide serum levels significantly below the concentrations required to be inhibitory for most bacteria.[54,63,66–71]

The sub-antibiotic pharmaco-kinetic profile has only been established with doxycycline 40mg modified-release (MR) capsule once daily and doxycycline immediate-release 20mg tablets twice daily; a dose of ≥50mg daily does exceed minimum inhibitory concentration (MIC) levels to produce antibiotic activity for some bacteria.[54,64,66–74] A variety of studies confirmed the aforementioned sub-antibiotic properties in placebo-controlled microbiologic studies completed over a range of 6 to 24 months that evaluated the microbiota of the oral cavity, GI tract, skin, and vaginal region, with antibiograms demonstrating no changes in sensitivities to multiple commonly used antibiotics.[54,63,64,66–69,72–75] It has not been shown that simultaneous administration of two immediate-release 20mg doxycycline tablets maintains sub-antibiotic activity and is best avoided.

The efficacy and safety of sub-antimicrobial dose doxycycline, especially with use of doxycycline 40mg-MR capsule once daily, has been demonstrated in several studies of patients with papulopustular rosacea, and in a case series of patients with perioral dermatitis.[54,68–71] Sub-antimicrobial dose doxycycline has also been shown to exhibit efficacy in some patients with AV, although data are limited, and more studies are needed.[67,77] The major advantage of sub-antimicrobial dose doxycycline is the avoidance of antibiotic selection pressure, especially in disorders that do not require an antibiotic effect to achieve therapeutic benefit (i.e., rosacea).[54,78]

CONCLUDING REMARKS

It is extremely important to appreciate the importance of preserving our arsenal of effective antibiotics, as these agents significantly reduce the morbidity and mortality associated with infection. Research evaluating the plethora of effects that antibiotics can have on human microbiota and the microbiome is rapidly emerging. However, the ability to establish definitive conclusions and clear clinical recommendations from the available data is difficult, as research in this field is in its infancy and is at present a moving target. Nevertheless, it is clear that all clinicians be encouraged to utilize antibiotics thoughtfully and responsibly, and only when they are truly needed. In addition, clinicians and their staff can also serve to educate their patients about appropriate use of antibiotics, including situations where they are not needed. Recent survey results related to antibiotic use for AV support the

need for greater education of patients by physicians and their staff (Figure 2).[79]

ACKNOWLEDGMENT

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