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Antibiotics for Acne—A Pilot Study of Collateral Damage to the Skin Microbiome

Tiffany C. Scharschmidt, MD

A decade has passed since modern sequencing methods were first used to investigate the microbial communities present on healthy human skin.[1,2] These studies of the skin microbiome, a term that broadly encompasses the skin's resident microorganisms (bacteria, archaea, fungi, viruses) as well as their genomic content and metabolic byproducts, have illuminated the diversity of microorganisms inhabiting the skin surface and invigorated research aimed at understanding their contributions to human health and disease. Attention by the lay media highlighting these investigations has heightened public awareness and interest in the human microbiome. In the clinic, this interest manifests as a wide range of patient inquiries regarding the role of microorganisms in skin disease, the influence of prescribed therapies on the microbiome, and strategies or products to "optimize" skin flora for health or cosmesis. Satisfactory answers to these questions are still forthcoming and will likely prove highly nuanced based on the complexity and contextuality of the skin-microbiota relationship.[3]

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The role of the skin microbiome in acne vulgaris is of particular interest to patients, clinicians, and researchers. This interest stems in part from the long-standing view that *Cutibacterium* (formerly *Propionibacterium*) *acnes* has a causative role in acne pathogenesis and the efficacy of topical and oral antibiotics in acne treatment. Multiple studies have now used sequencing-based methods to profile *C acnes* strains and the broader bacterial skin community associated with acne.[4-6] Collectively, these profiles have highlighted qualitative shifts in skin microbiota, that is, altered metagenomic content or metabolic activity indicated by specific subsets or ribotypes of *C acnes* that appear to be associated more with acne risk than overall *C acnes* abundance.[7]

In this issue of *JAMA Dermatology*, Chien et al[8] report results of a small pilot study profiling the facial skin microbiome of 4 women with acne prior to and following treatment with oral minocycline. Analysis of surface swabs of the bilateral forehead, cheek, and chin were performed at baseline, after completion of a 1-month minocycline course, and 1 and 8 weeks after completion of the course of antibiotics. Bacterial taxonomic assignment was performed by amplification and sequencing of V3/V4 hypervariable region of the bacterial 16S ribosomal gene. As in prior studies[2,4-6] of sebaceous skin sites in both healthy participants and those with acne, Chien et al[8] found that *C acnes* constituted a large proportion of the facial microbiome. Both at baseline and throughout the sampling period, composition of samples from a given participant were most similar to each other compared with those from a different participant. This is consistent with data showing that aspects of the skin microbiome are highly individualized and that specific strains may persist on a given person for months to years.[9]

Within a given participant, dynamic shifts in bacterial community composition were observed across the 4 time points,

potentially suggesting antibiotic-induced selection pressure. Pooled analysis of samples from all 4 participants demonstrated a roughly 25% reduction in relative abundance of *C acnes* immediately following the course of oral minocycline. This reduction persisted at 1 week but was largely reversed at 1 month posttherapy. Importantly, minocycline was also associated with sustained decreases in the relative abundance of several other bacterial genera, that is, *Corynebacterium*, *Prevotella*, and several *Lactobacillus* species, as well as temporary or sustained increases in others (several *Pseudomonas* species and *Streptococcus* species respectively).

As the authors correctly point out, the small sample size, the lack of an untreated control arm, and the omission of mock sampling controls represent considerable limitations[10] that restrict the generalizability of their study's findings. However, the longitudinal sampling constitutes a strength of the study and yields interesting, albeit preliminary, insight into the influence of a commonly used therapeutic intervention. Studies that use this design provide distinct and complementary information to those studies that investigate disease-associated microbial communities at a single time point. Although the reduced abundance of *C acnes* following minocycline therapy is expected based on prior studies using conventional culture[11] or 16S sequencing,[12] the short- and longer-term alterations in other bacterial genera are intriguing and may help explain complications of antibiotic treatment for acne vulgaris such as gram-negative folliculitis and pharyngitis.

It will be important to determine whether future investigations describe similar shifts in bacterial community composition in response to minocycline or other acne treatments and whether these changes correlate with the clinical response described by Chien et al.[8] It will also be powerful to pair this type of longitudinal, interventional study design with metagenomic and proteomic assays to detect altered functional capacity of the skin microbiome, such as prevalence of specific *C acnes* ribotypes, "pathogenicity" islands, and production of related products.

Independent of disease status, this study contributes to a small, but growing amount of literature addressing composition and resilience of the skin microbiome in response to antimicrobial agents. Recent examination of the short-term action of topical antiseptics on the back and forearm of 13 healthy participants revealed that the treatment effects depended heavily on the initial composition of the bacterial microbiome, a highly personalized and body site–specific feature.[13] Similarly, baseline differences in the microbiome composition of the 4 individuals evaluated by Chien et al[8] may have contributed to the distinct trajectories of the bacterial communities, as measured by alpha diversity, following minocycline treatment.

Future longitudinal studies should incorporate analysis algorithms and sample size calculations that account for these person-specific differences in skin bacterial community composition. Studies of the long-term treatment effects of oral antibiotics on the gut microbiome have documented changes in bacterial community structure and the prevalence of antibiotic resistance genes that persist for months following therapy. Recovery of composition of the gut community is further impaired with repeated antibiotic courses.[14] Whether oral antibiotics have a comparably enduring influence on the skin microbiome remains to be determined.

Short-term changes to the skin microbiome structure and function are likely not limited to a response to antimicrobial agents. Indeed, just as gut microbial communities are influenced by diet (eg, low vs high fiber), so is skin microbial ecology likely influenced by agents that affect factors accounting for age- and site-specific differences in skin microbiome, such as sebaceous content, salinity, pH, and moisture.[15] Any topical or oral treatment that alters these parameters and the skin microbial community might mitigate or promote disease depending on the context. Although the prospect of studying the entire array of prescribed, over-the-counter and lightly regulated or unregulated skin products is daunting, we might prioritize for study those products that result in a sustained benefit in a relevant disease context, such as isotretinoin in acne.

How can we address our patients' questions regarding the skin microbiome? I believe we can be enthusiastic about the potential of microbial-derived or microbial-directed therapies as future weapons in our therapeutic arsenal while acknowledging that there is much we still do not understand about the influence of current therapies on the delicate symbiosis we maintain with our cutaneous microbiota. In the context of a growing market of over-the-counter products designed to "restore" the skin microbiome, we should further emphasize that there is no universally good or bad skin microbiome. Microbes have highly contextual roles in skin biology, and a variety of factors, including the host's genetics, might influence whether a given strain contributes to host health or exacerbates a disease state.[3] As a specialty, continued basic research as well as translational studies, such as those highlighted here, place us on a strong trajectory toward deciphering these complexities.

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Early Use of Laser for Port-Wine Stains
Timing, Efficacy, and Shared Decision Making

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In this issue of *JAMA Dermatology*, Jeon and colleagues[1] report on the safety and efficacy of pulsed dye laser (PDL) use in the treatment of port-wine stains (PWS) in a cohort of nearly 200 infants treated without the use of general anesthesia. The authors retrospectively analyzed photographs from short-term follow-up and found a high rate of excellent clearance and no major cutaneous adverse events. They emphasize the feasibility of treating young infants without general anesthesia, an approach that is increasingly relevant because of recent concerns raised about possible developmental effects of general anesthesia in children younger than 3 years. Although the authors' treatment approach is similar to ours in many respects, there are several aspects of their study that are worthy of further discussion. We base our comments on published literature on this topic as well our experiences as pediatric dermatologists with a busy laser practice that has used PDL for PWS treatment since 1989 (in the case of the senior author).

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Concerns regarding associations of general anesthesia use with brain and neurocognitive development in young infants have recently been emphasized.[2] In 2014, the US Food and Drug Administration and the International Anesthesia Research Society convened a diverse group of experts and issued a consensus statement on the use of anesthetic and sedative drugs in infants and toddlers.[3] This statement emphasized avoidance of elective and repeated general anesthesia in young infants, a caution that is highly relevant for the treatment of PWS with PDL.

There is broad consensus that PDL is a painful procedure and increases in pain as PWS size increases because more pulses are required. Although Jeon and colleagues acknowledge this as an issue, they also note that dynamic cooling devices, which spray a cryogen prior to the laser pulse, "significantly diminish pain during PWS treatment."[1] We agree that dynamic cooling devices may reduce pain, but they certainly do not eliminate it. Pain experienced during infancy has been shown to have both short-term and potentially long-term effects, including possible effects on the developing neural circuitry that result in long-lasting differences in pain perception.[4,5] For example, higher numbers of same-day preschool vaccines have recently been shown to contribute to "needle phobia" in school-aged children and adolescents.[6] Even though the short-term or long-term effects of repeated PDL treatment on emotions and pain perception have not been studied systematically, we cannot assume that there is no effect. The patients in the study by Jeon and colleagues[1] received an average of 10 treatments. Although all patients started treatments before 1 year of age, the mean age at initiation was 3.38 months, so some of these patients continued treatment into the second year after birth. Our own experience is that by age 12 to 15 months, many infants show signs of fear and struggle more with laser treatments, particularly if multiple treatment sessions have already occurred.

In considering infant reactions to PDL, the total number of treatments is also worthy of discussion. Some authors have found that the degree of PWS improvement with PDL treatment diminishes after an average of 5 treatments,[7] whereas the mean number of treatments in the study by Jeon and colleagues[1] was 10. It would be helpful to know, either in this cohort or in future studies, how much additional benefit accrues with each additional treatment, particularly in infants receiving more than 5 to 10 treatments. Of note, the authors treated eyelid PWS in awake infants after inserting metal eye shields. A supplementary video shows this being done fairly easily in a young infant for a very brief period of time. We ques-