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The Role of Epidermal Barrier Dysfunction and Cutaneous Microbiome Dysbiosis in the Pathogenesis and Management of Acne Vulgaris and Rosacea

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Dysbiosis, (Barrier) Dysfunction, and Dermatoses: A Chicken-and-Egg Dilemma

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Acne vulgaris (AV) and rosacea are two of the most common dermatoses diagnosed and managed by dermatologists.[1,2] Despite this and our improved understanding of the unique pathogenesis of each, there has been little focus on general skin care and how it may affect physiologic functioning of the epidermis until recently. Under optimal homeostatic conditions, the skin generally provides a physical, chemical, and immune layer that deftly balances moisture, temperature, and biochemical substrates.[3] These factors create biomes specific to different areas of the body including the skin, teeth, and internal/external mucosa, where various microorganisms (including bacteria, viruses, and fungi) can thrive.[3] Given that bacteria alone outnumber human cells more than 10 to 1 and have over 100 times more genes than humans, the microbiome, and the factors that support it, cannot be ignored.[4] While alterations in epidermal barrier function and the disruption of the cutaneous microbiome(CM) have been studied in a few dermatoses, most notably atopic dermatitis, these may not be the first to come to mind when treating AV and/or rosacea.

One of the most prominent pillars of AV pathogenesis is the follicular colonization with *Cutibacterium acnes*. Although typically a commensal organism, virulent strains of *C. acnes*—phylotype IA1 in particular—have been associated with AV and worsening acne severity.[5] With the onset of puberty, there is also a notable change in epidermal barrier function as measured by increased transepidermal water loss (TEWL).[6] TEWL is further compounded in patients with AV, which may be up to 50% greater depending on acne severity.[7]

Rosacea pathogenesis is thought to be a complex, interconnected web of dysregulated innate and adaptive immunity combined with hyperreactive neurovasculature. In practice, many of the secondary criteria for rosacea (eg, burning, stinging, edema, dryness)[8] are also symptoms of epidermal barrier deficiency. Multiple studies have demonstrated that the addition of physiologic moisturizers and/or cleansers to standard-of-care regimens may augment treatment outcomes for mild-moderate disease.[9-13] Unlike AV in which one organism has been implicated, rosacea has been associated with multiple organisms including bacteria (eg, *Streptococcus epidermidis, Bacillus oleronius*, and *Helicobacter pylori*), *Demodex* species, a decreased abundance of *C. acnes*, and even the general overgrowth of bacteria in the small intestine (SIBO).[14] Although a singular perpetrator has not been conclusively identified, multiple studies have found dysbiosis within the rosacea cutaneous (and enteric) microbiome.

Both AV and rosacea have varying degrees of epidermal barrier dysfunction, which may be further altered by topical and even systemic therapies. Similarly, AV and rosacea have unique cutaneous microbiomes and microbiome derangement that can be both directly and indirectly affected by common treatment options, including the indiscriminate use of broad-spectrum antibiotics. With derangements at baseline that may be further exacerbated by current therapeutic paradigms, discussion of proper skin care is close to becoming a cornerstone of care. Every acne and rosacea encounter should endeavor to discuss key factors in moisturizers and cleansers: physiologic to slightly acidic pH; scent-/fragrance-free; emollients to soften the skin; humectants, such as glycerin and hyaluronic acid, to attract water; occlusives like petrolatum to seal them in, and proper lipid composition to potentially supplement those deficient in disease states.

A final interesting concept to consider: the chicken and the egg. A healthy microbiome is dependent on a functioning epidermis with adequate moisture and nutrients for survival and balance. In turn, a healthy microbiome can quell virulent organisms and provide a suitable pH to optimize biochemical and immunological epidermal processes. In AV and rosacea, there are data to suggest that both dysbiosis and epidermal barrier dysfunction have roles to play. But does one precede (or even supersede) the other? And, more importantly, if dermatologists have the potential to repair and even restore both, how much might it matter in clinical practice? While research continues to elucidate the role of both dysbiosis and barrier dysfunction in acne and rosacea, it behooves us to employ quality skin care to restore and repair so the chicken and egg concept is irrelevant. No visit for either disease is complete until quality skin care has been discussed.

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 ORIGINAL ARTICLE

The Role of Epidermal Barrier Dysfunction and Cutaneous Microbiome Dysbiosis in the Pathogenesis and Management of Acne Vulgaris and Rosacea

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ABSTRACT

Background: Dysregulation of either the cutaneous microbiome (CM) or epidermal barrier function (EBF) is thought to play an increasingly important role in acne vulgaris (AV) and rosacea pathogenesis.

Objective: To review the literature regarding epidermal barrier dysfunction (EBD) and cutaneous dysbiosis in AV and rosacea and provide clinical pearls for dermatologists.

Methods: A Medline literature search was performed for relevant literature regarding EBD and dysbiosis and either AV or rosacea. An expert consensus panel was then convened to discuss article merits and distill findings into clinical pearls.

Results: Final review included 138 articles. Puberty may alter natural stratum corneum lipid ratios, instigating and/or exacerbating EBD in AV. Patients with severe AV have an abundance of virulent *Cutibacterium acnes* phylotype IA1. EBD may manifest as classic signs of rosacea and improve with treatment. While several microbial populations are dysregulated in rosacea, the effect from any singular species is unclear. Current AV and rosacea treatment regimens may mitigate inflammation but may also indiscriminately damage CM and EBF. Physiologic moisturizers and cleansers that harness pre-/pro-/postbiotics may have a role in restoring CM, EBF, and potentially improving dermatosis severity.

Limitations: Limited prospective clinical trial data especially regarding over-the-counter (OTC)/non-prescription skincare products.

Conclusion: Appropriately developed prescription and OTC preparations may selectively influence the microbiome and potentially maintain/restore EBF. By understanding this relationship, dermatologists will be better able to educate patients on the importance of appropriate skin care.

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INTRODUCTION

The cutaneous microbiome (CM) is a sprawling ecosystem comprising various microorganisms and their metabolites that dwell on every surface of the human body.[1-4] Together, the human body and microbiome create a functional synergy that is increasingly thought to modulate local and systemic inflammation.

While CM composition varies with moisture, sebaceous gland activity, and anatomical region, these microbes exist symbiotically with other commensal organisms and the surfaces on which they dwell, receiving necessary nutrients (eg, amino acids, fatty acids, moisture) while providing a slightly acidic pH, priming host immune response (eg, induced antimicrobial peptides [AMP] and bacteriocins) and outcompeting classic pathogenic organisms (eg, pathogenic biofilm-producing, strains of *Streptococcus epidermidis* and *Staphylococcus aureus*).[4-10] In this regard, the CM functions as a distinct, organized, and unique layer atop the stratum corneum (Figure 1).[11]

When appropriately functioning, the CM and the epidermal barrier exist in homeostasis.[12-15] The loss of epidermal barrier function (EBF), dysbiosis, or both may result in a dysregulated inflammatory response, as is classically seen in atopic

FIGURE 1. Skin barrier anatomy and function. In addition to division by anatomic layers, the skin can also be divided into functional layers (including a physical, chemical, immunological, and microbiome layer) that work in conjunction to promote epidermal (barrier) function.

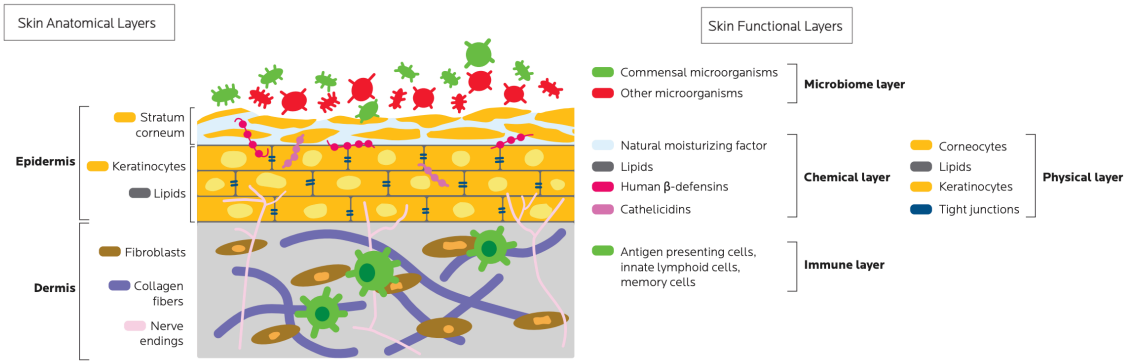
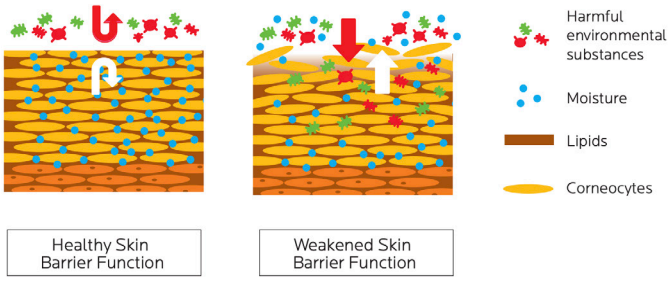


FIGURE 2. Epidermal barrier dysfunction. A functioning epidermal barrier is capable of keeping harmful substances out, retaining moisture, minimizing inflammation, and promoting effective innate immune function. Insults may disrupt the anatomic and/or functional layers and propagate inflammation through the skin.



dermatitis (AD) (Figure 2).[13] Despite increasing understanding in how EBD and dysbiosis may affect inflammation, therapeutic options are limited and still poorly understood.

The purpose of this paper is to review the literature regarding (1) the role that dysbiosis and EBD play in the pathogenesis of acne vulgaris (AV) and rosacea and (2) provide pearls and potential therapeutic interventions to restore CM homeostasis and EBF.

MATERIALS AND METHODS

A panel of United States (US) dermatologists recognized for their contributions and prior expertise in the diagnosis and management of AV/rosacea, and/or history of academic achievement were convened on August 4th, 2021.

Prior to meeting, a Medline literature search was performed for original studies, meta-analyses, clinical guidelines, and reviews regarding "epidermal barrier dysfunction", "epidermal barrier function", "transepidermal water loss", "cutaneous microbiome", "dysbiosis", "probiotics", "prebiotics", and "postbiotics". The Boolean term "AND" was used to find intersections between these phrases and either "acne vulgaris" or "rosacea".

Authors discussed topics including: the role of EBD and dysbiosis in AV and rosacea; the role of skin care in AV and rosacea; and agent/ingredients which may complement current standard-of-care prescription regimens.

Results of the discussion and a follow-up survey containing 8 summative statements voted on by panelists (using a 5-point Likert scale with 1 being "Strongly Disagree" and 5 being "Strongly Agree") that was performed on October 14th, 2021 are presented below.

TABLE 1.

Post-Meeting Summative Survey Results		
Statements		**Mean Score**
There were sufficient data to conclude that:	ACNE is a barrier deficiency disorder	4.0
	ROSACEA is a barrier deficiency disorder	4.7
	ACNE is associated with an alteration of the healthy microbiome	5.0
	ROSACEA is associated with an alteration of the healthy microbiome	4.5
	Water and therefore moisturizers are prebiotics	4.2
	Quality skin care can help to restore/normalize the healthy microbiome	4.5
	Normalization of a healthy microbiome can improve ACNE	4.7
	Normalization of a healthy microbiome can improve ROSACEA	4.3

Mean score was calculated from a 5-point Likert scale with 1 being "Strongly Disagree" and 5 being "Strongly Agree".

RESULTS

All 8 post-meeting statements received a mean score of ≥4 (Table 1). The authors emphasized that, although potentially limited by temporal or logistic constraints, dermatologists should endeavor to discuss skin care during every AV/rosacea visit. Optimal skin care may improve both diseases, potentially with minimal pharmacotherapy. Furthermore, poor choices made by an uninformed patient may derail an otherwise ideal therapeutic approach.

Acne Vulgaris

Barrier Dysfunction

Epidermal barrier dysfunction (EBD) is well-known in AV as adverse effects of over-the-counter (OTC) products, and prescription and adjunctive procedural therapies.[16] These effects, clinically noted as xerosis, abnormal sensations (eg, stinging, burning, tingling, pruritus), pain, tightness, and/or an irritant dermatitis, are all signs of increased transepidermal water loss (TEWL) and may be partially mitigated with concurrent use of appropriate moisturizers.[16-21]

Data suggest AV patients may have pre-existing EBD.[22-25] Untreated Japanese male AV patients ages 14-26 (moderate, n=11; mild, n=25) had significantly greater TEWL that correlated with AV severity than age/gender-matched controls (n=29) (TEWL g/m2/h±SD: Control 10.3±2.4; Mild, 14.4±2.5; Moderate, 16.8±3.8, *P*<.01).[22]

TEWL may worsen as patients approach puberty, regardless of AV, with one study finding among 132 healthy children (boys, n=67; girls, n=65) ages 6-13 that TEWL was significantly greater by age 9 for girls and 11 for boys vs their 6-year-old counterparts (*P*<.05).[25]

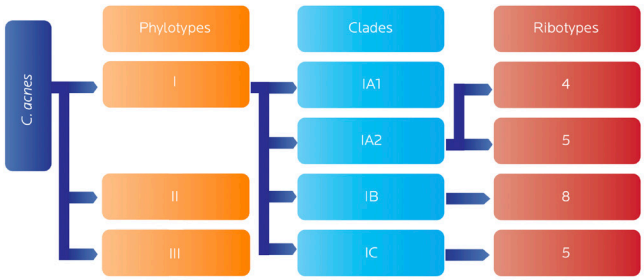
Compared against an internal ceramide standard, a decrease in total stratum corneum (SC) ceramides in AV (µg±SD: moderate 3.4±0.45; mild 4.07±.87) vs control (6.49±0.98) (*P*<.05) had a significant negative correlation with increased TEWL.[23] After isolating total ceramide and sphingosine from other SC lipids, there was also a significant negative correlation with decreasing total ceramide (*P*<0.1) and free sphingosine (*P*<0.1) with worsening AV severity.[23] Of note, similar ceramide derangements have been found in and are thought to pathologically contribute to EBD in psoriasis and AD.[26]

Together these data suggest increases in TEWL may be a result of ceramide imbalances due to adrenarche-induced ceramide synthetic dysfunction. Although these changes may not be specific to AV, EBD may be associated with, and potentially precede and/or exacerbate, clinically-evident AV.

Microbiome Dysbiosis

In AV, there are two broadly distinct CMs: superficial and follicular.[27] Superficial facial and truncal CM are dominated by *Staphylococci spp.* (eg, *S. epidermidis*) which account for >27% of bacteria, while anaerobic *Propionibacteria* (including *Cutibacterium acnes*) account for <2%.[28] Conversely, the physiologically-healthy follicular CM is more homogenous, with *C. acnes* comprising 89% to 94% of the bacterial population, functioning as a commensal organism in healthy skin.[14,29] This disparity may suggest that, unlike in the superficial CM, the sebum-abundant follicular milieu may self-select for lipophilic organisms and that the absence of microbiota species diversity could be the norm.[14]

FIGURE 3. *Cutibacterium acnes* phylotypes. Single and multi-locus sequencing have found phylotypes IA1 to be predominantly associated with additional virulence factors that instigate/propagate acne vulgaris while phylotypes II (and III) are thought to be predominantly commensal species.



Counterintuitively, *C. acnes* follicular colonization is one of the 4 dogmatic factors of AV pathogenesis and may correlate with severity.[25,30-32] During puberty there is a significant increase in absolute abundances of organisms[25] and relative abundance of *C. acnes* that parallels increase in sebum production.[33-35] Conversely, the decreased incidence and prevalence of AV (~3-5% of individuals) by the fifth decade of life coincides with up to a 49.9% of the reduction in *Propionibacterium spp.* and may be due to age/age-related changes, a significant decrease in sebum production, and increase in overall CM diversity.[36-38]

C. acnes phylotypes are distinct between individuals with and without AV (Figure 3).[27,29,39-42] *C. acnes* phylotype IA1 (and to a lesser degree IA2) represents 55-67% of all *C. acnes* in mild and severe AV (respectively), whereas, in healthy skin, IA1 exists alongside other phylotypes including IA2, II, and III.[42] This homogenization of *C. acnes* phylotypes may correlate with increasing AV severity, as one study found phylotype IA1 comprised 84.4% and 95.6% of all *C. acnes* on the face and back (respectively) of individuals with severe AV compared with healthy individuals who had ~39% phylotype IA1 and ~43% phylotype II.[43]

Compared with *C. acnes* phylotype II, a commensal strain, phylotype IA1 (Figure 3) has pro-inflammatory capabilities via increased activation of toll-like receptor 2 (TLR2) Th1/Th17 axis, decreased interleukin-10 (IL-10) response,[29,44] and a combination of virulence factors including: increased triacylglyceride lipase activity generating short-chain fatty acids,[45,46] β-hemolytic,

membrane pore-forming toxins termed Christie-Atkins-Munch-Petersen (CAMP) factors that may stimulate TLR-2;[47-52] plasmids that promote bacterial adhesion and biofilm formation;[29] lyases that degrade hyaluronic acid and the extracellular matrix, propagating inflammation;[46] porphyrins that induce oxidative stress/damage;[53,54] and reduced loss of clustered regularly interspaced short palindromic repeats (CRISPR) loci allowing increased horizontal acquisition of virulent traits.[55] Furthermore, virulent *C. acnes* may also have an increased resistance to erythromycin, clindamycin, and tetracycline classes of antibiotics.[56,57]This presents potential concern for indiscriminate, inadvertent eradication of commensal organisms (including *C. acnes* phylotype II and III) within already pathologic follicular and superficial CM, allowing any remaining phylotype IA1 to flourish.

While *C. acnes* typically dominates the follicular microbiome, even in AV-prone skin, it does coexist with other microbes (eg, *Malassezia spp*. fungi, *S. epidermidis*, and bacteriophages).[58] Of particular interest is *S. epidermidis*, which has shown potential to limit *C. acnes* growth in vitro,[59] and (*C. acnes* specific) bacteriophages.[60-63] These bacteriophages, which are significantly more abundant in healthy skin vs. acne-prone skin (P<.05) may modulate the microbiome in vitro by facilitating the exchange of virulence factors and preferentially killing specific bacteria.[14,60,61]

Harnessing the natural "predator-prey" relationship of these organisms may have potential as a targeted, non-antibiotic AV therapy.[59] Studies also suggest that isotretinoin may achieve its durable therapeutic response by inducing a "sebaceous drought", resetting the follicular microbiome, and allowing a more diverse CM to repopulate.[64-66]

Rosacea

Barrier Dysfunction

Many of the clinical signs of EBD (hyperirritability, burning, stinging, and sensitivity to common OTC skincare products) are hallmarks of rosacea.[17,67,68] EBD may also explain rosacea triggers, including extreme climates and UV exposure and increased likelihood of positive patch test (and risk of allergic/irritant contact dermatitis).[67,69] This may be due in part to a significantly more alkaline central facial skin (pH 5.7 vs 5.2, P=.026) and materially different skin surface lipid composition.[70]

EBD in rosacea appears localized to areas of (and those adjacent to) inflammation.[71-73] In a study of unaffected nasolabial-fold and volar-arm skin in rosacea patients (n=28) and age/gender-matched controls (n=32), nasolabial-fold skin in rosacea patients had materially higher TEWL than healthy controls (21.1 vs 16.8, P=0.127) and significantly lower SC hydration (SCH) (16.5 vs 24.4, P<.001); these trends were not observed in the volar forearm.[71] Evaluations using topically-applied lactic acid to elicit irritation (ie, lactic acid stinger test [LAST]) have found individuals with erythematotelangiectatic-predominant (ETR) and papulopustular-predominant (PPR) rosacea to be significantly more likely to have a positive (75% vs 18.8%, P<.001) and greater LAST response (P<.001).[72,74] Worsening TEWL and SCH also correlated with LAST scores and patients' perception of sensitive skin.[72]

EBD may also correlate with rosacea severity. Not only does concomitant use of more physiologic pH cleansers and moisturizers minimize adverse effects of prescription therapy, but they may also have additive effects in reducing rosacea severity (Table 2).[75-79] A 6-week investigative trial with oral minocycline 100 mg daily, in the absence of topical intervention, has also

TABLE 2.

Epidermal Barrier Outcomes Following Topical and Systemic Management of Rosacea

Study	Study Type & Size (n)	Rosacea Phenotype & Severity	Participant Age	Sex (%F)	Study Length	Treatment Regimen	Results
Del Rosso[77]	Split Face (102)	PPR, mild-moderate	20-39: n=29 40-59: n=52 >60: n=21	85	7 days	Twice daily: Azelaic acid 15% gel and cleanser to full face. Moisturizer to only right half of face.	Significant reduction in CSS with moisturizer use vs baseline (P=.008) and vs side without moisturizer (P=.015)
Subramanyan[78]	RCT (70)	--, moderate	--	--	4 weeks	Metronidazole. Synthetic detergent (syndet) vs soap bar	Significantly less patient self-reported itching, irritation, tingling with syndet vs soap bar (P=--)
Draelos et al[79]	RCT (67)	PPR and ETR, mild-severe	Range 19-66	100	12 weeks	Twice daily: Azelaic acid 15% gel Gluconolactone cleanser (4%) and moisturizer (10%) vs nonstandardized patient self-selected products	improved facial erythema (week 8, P=.012; week 12, P=.001), itching (week 8, P=.045), stinging (week 12, P=.029). self-reported significant improvement (P<.05) in skin sensitivity, dryness, texture, and smoothness compared with baseline vs controls
Ní Raghallaigh et Powell[80]	Open-label, case-control (29)	PPR, --	< 40: n=6 40-55: n=12 >55: n=11	48.2	6 weeks	Once daily: Minocycline 100 mg	Significant improvement in erythema (P=.003) and hydration vs baseline (Central face: 41.4 vs 38.5, P=.041; Cheeks: 42 vs 37.4, P=.012)

-- Data not reported. CSS, cumulative symptom score (comprising itching, burning, stinging, tingling); ETR, erythematotelangiectatic-predominant rosacea; PPR, papulopustular-predominant rosacea; RCT, randomized controlled trial.

been shown to significantly improve erythema (*P*=.003) and SCH (Central face, *P*=.041; Cheeks, *P*=.012).[80] This may suggest that underlying (systemic) inflammation may exacerbate rosacea severity and EBD in a positive-feedback loop.

Microbiome Dysbiosis

Rosacea has several potential key microbes: *Demodex spp.* (*Demodex folliculorum*, *Demodex brevis*), *Bacillus oleronius, Staphylococcus epidermidis*, and *Cutibacterium acnes*.[81]

Demodex spp., specifically *D. folliculorum* and *D. brevis*, are commensal mites that dwell within the pilosebaceous follicle and consume sebum.[82] The highest concentrations of *Demodex spp.* have been found in areas typically affected by rosacea (ie, cheeks, forehead).[83] A 5-year epidemiological study of 3213 patients found PPR was associated with a mean Demodex density (Dd) of 36 D/cm^2 (range: 8-112 D/ cm^2) compared with ≤5 D/cm2 in normal skin.[84] Non-invasive skin samples have found *Demodex spp.* more frequently in individuals with rosacea vs healthy age-matched controls (96% vs 74%, *P*<.01); in one study the Dd was ≥5.7x in rosacea patients.[82] This appears to be unique to rosacea as other inflammatory conditions of the face failed to show excess Demodex presence.[83] Clinicohistological studies have found mixed results but suggest that heavy *Demodex spp.* burdens may cause follicular rupture, dermal invasion, and cell-mediated reaction with granuloma formation along with activation of a plurality of inflammatory signals (including matrix metalloproteinase-9 (MMP-9), interleukin-8 (IL-8), tumor necrosis factor alpha (TNF-alpha), and LL-37).[82,85] However, it is unclear if *Demodex spp.* instigates inflammation in rosacea or that underlying inflammatory changes enable proliferation of *Demodex spp.*.[86]

Bacillus oleronius is a non-commensal gram-negative bacteria that has been cultivated from *Demodex* mite in PPR patients and is capable of stimulating a mononuclear cell response more readily in rosacea patients (n=16/22, 73%) vs healthy controls (n=5/17, 29%, *P*=.01).[87] 62 and 83 kilodalton (kDa) antigens isolated from *B. oleronius* have been found to preferentially stimulate serum reactivity in ETR individuals (n=21/26, 80%) over controls (n=9/22, 40%; *P*=.004) as well as in individuals with ocular involvement.[88,89] *Demodex spp.* count was noted to be significantly greater in rosacea patients (6.6±9.0 vs 1.9±2.2, *P*=.014), suggesting *Demodex* may be a vector for *B. oleronius*-induced inflammation.[89] Inflammatory cascades downstream of *B. oleronius* include many factors associated with *Demodex*-associated inflammation, including MMP-9, IL-8, TNF-alpha.[90]

S. epidermidis is a gram-positive coccus that, although capable of mitigating pathogenic *S. aureus* strain activity,[91,92] has capacity for virulence.[93,94] Cultures taken from PPR patients have found *S. epidermidis* within pustules but not from unaffected ipsilateral cheek skin.[95] Furthermore, studies comparing *S. epidermidis* strains isolated from untreated PPR patients with controls found *S. epidermidis* from PPR pustules were significantly more likely to have β-hemolytic activity than from control isolates and also to secrete different (potentially virulent) proteins at higher temperatures (ie, 37°C vs 30°C).[96] Such temperatures are not uncommon in the vasodilated cheeks of a rosacea patients.

The lack of *C. acnes* may also play a role in rosacea.[97,98] A small study (n=58) comparing superficial cutaneous swabs from individuals with PPR (n=15), ETR (n=21) with controls (n=22) found significantly less *C. acnes* isolated from the bilateral malar cheeks in rosacea patients (ETR: 27.3%; PPR: 23.3%) compared with controls (62.6%, *P*<.01).[98] Another study found that healthy individuals age ≥60 have significantly less (*P*=.018) *C. acnes* than those <60.[97] These observations may explain why AV is more prevalent among teens while another unrelated facial dermatosis, rosacea, is more common in those in the fourth/ fifth decade of life.

The authors also note that there is growing evidence of "cross-talk" between the enteric microbiome and CM in rosacea patients.[99-105] Population studies have found individuals with rosacea were more likely to have celiac disease (Hazard Ratio 1.46, 95%CI 1.11-1.93, *P*<.001), Crohn's disease (HR 1.45, 95%CI 1.19-1.77, *P*<.001), ulcerative colitis (HR1.19, 95%CI 1.02-1.39, *P*<.001), and irritable bowel syndrome (IBS) (HR 1.34, 95%CI 1.19-1.50, *P*<.001).[100] A randomized-control trial using rifaximin (a non-systemic, intestinal-limited antibiotic) for the management of small intestine bacterial overgrowth (SIBO) found that rosacea lesions completely cleared (n=20/28) or greatly improved (n=6/28) after treatment with rifaximin compared with those who received placebo (no change, n=18/20; worsened, n=2/20; *P*<.001).[102] Other studies have also implicated alterations in the relative abundance of different species in rosacea including those of the genera *Gordonia* and *Geobacilus, Corynebacterium, Actinomyces, Vellonella*, and *Chloroplast*.[103-105]

Although these findings may imply a correlation between disease and dysbiosis, they cannot yet establish causality as it is unclear if dysbiosis is a primer or symptom of inflammation.[104] Furthermore, studies have not consistently identified a single organism tying dysbiosis to rosacea, suggesting that dysbiosis itself may be sufficient to stimulate inflammation.[103,104]

Current Therapeutic Regimens and the Microbiome

Acne Vulgaris

Topical retinoids and benzoyl peroxide (BPO) are mainstays of mild-moderate AV management.[106] BPO has been found to increase TEWL and deplete SC levels of α-tocopherol.[107] Topical retinoids have been found to transiently thin the SC, increase cell turnover, and increase TEWL.[18] Clinically, patients perceive these effects as irritation, inflammation, and xerosis, which may be partially alleviated by concurrent application of a gentle, non-comedogenic moisturizer.[19-21] Topical treatment may also influence the microbiome (at least in the acute [post-]

treatment period) by creating an inhospitable environment for some microbes and a boon for others, with yet unclear long-term post-treatment implications.[108,109] Despite this, it should be noted these medications are all capable of (at least transiently) improving acne severity.

Systemic antibiotic therapy is the cornerstone for moderate-severe AV therapy.[106] While broad-spectrum antibiotics may achieve transient improvements, they may also induce long-term CM alterations. In one longitudinal prospective study, 4 women ages 25 to 32 with recently diagnosed AV were given oral minocycline 100 mg twice daily for 4 weeks. Superficial cutaneous swabs found a 1.4-fold reduction in *C. acnes* counts with a trend towards *C. acnes* abundance recovery 8 weeks after minocycline discontinuation, but a sustained reduction in *Lactobacillus spp.* and *Corynebacterium spp.* over the same time interval.[110]

Isotretinoin is one of the few prescription AV therapies that consistently achieves durable response.[106,111] Several studies suggest this may be due in part to modulations of the microbiome.[64-66,109] CM samples post-isotretinoin therapy have found up to a 100-fold decrease in *C. acnes* colonies (including strains resistant to erythromycin, clindamycin, and tetracycline) 1 month after completion of 18-week isotretinoin course[65] and increased diversity of other taxa.[66] This CM recalibration may be a result of an isotretinoin-induced sebaceous drought that induces a microbial survival "bottleneck", which allows non-virulent *C. acnes* strains to repopulate the follicles.[64]

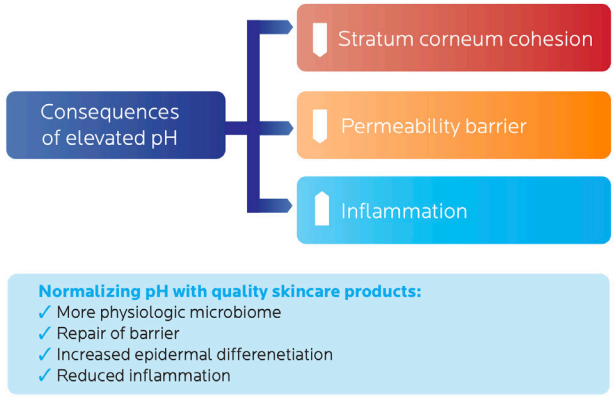
Rosacea

Systemic antimicrobials have demonstrated efficacy in management of rosacea, primarily PPR.[112,113] In a longitudinal cohort study of 12 PPR patients treated with doxycycline, superficial skin swabs found a significant 3.43-fold increase in *Weissela confusa* relative abundance (P=.008)[97] and also a material change in the predominant genera with a baseline composition of *Staphylococcus* (28%), *Cutibacterium* (13%), *Pseudomonas* (9%), *Corynebacterium* (8%), *Acinetobacter* (7%), and *Snodgrassella* (6%) being replaced by *Staphylococcus* (22%), *Stenotrophomonas* (33%), *Corynebacterium* (8%) and *Cutibacterium* (7%) after 6 weeks of doxycycline 100 mg twice-daily.[97] The significance, if any, of this microbiome shift is unknown.

Present Practices and Potential Paradigms

Dermatologists may consider the nature between EBD and dysbiosis akin to an interdependent positive feedback loop. However, clinically, the directional relationship between dysbiosis and EBD may be irrelevant if patients are counseled on therapeutic options with the potential to improve both anomalies. The authors note that skincare and OTC products, including cleansers and moisturizers, are a grossly underappreciated and overlooked cornerstone in patient education that may complement prescription therapy.

FIGURE 4. Relationship between pH, barrier (dys)function, and the microbiome. Adapted from Lynde CW et al. *J Clin Aesthet Dermatol.* 2014;7(3):40-48 and *Proksch J Dermatol.* 2018;45:1044-1052.



Quality moisturizers are composed of: humectants (eg, glycerin, hyaluronic acid) to attract water; occlusives that seal in moisture (eg, petrolatum); and emollients that soften and smoothen the skin.[70] Effective implementation can maintain a healthy epidermal barrier, and even rescue a deficient one (Figure 4).[70,115,116] For AV patients, moisturizers should also be non-comedogenic to avoid instigating additional lesions.[20,21,117] Individuals with AV may also benefit from using moisturizers with ceramides to supplement their prescription regimens.[23,70,117-118] Given the increased skin sensitivity seen in rosacea, moisturizers should avoid fragrances, surfactants and other potential instigators of allergic or irritant contact dermatitis, and have an acidic or physiologic pH.[70]

An ideal cleanser should remove debris, cosmetics, and transient bacteria without perturbing EBF or CM.[70] For both AV and rosacea, cleansers should be close to physiologic skin pH (~4-6) to avoid excessive burning, stinging, and dryness and to preserve the metabolic functions, including lipid processing (Figure 4).[70] Lipid-free cleansers and synthetic detergents allow for superior preservation of the skin's natural lipids thereby decreasing irritancy.[70]

Therapeutic Probiotics

In addition to these essential qualities of skincare regimens, the authors note the clinical potential to augment current skincare products by utilizing pro-/pre-/postbiotics to further mend EBD and restore microbiome diversity and richness.

Probiotics are foods (eg, yogurts, fermented products such as kefir and kombucha) and topical/oral supplements that contain live microorganisms such as *Nitrosomonas eutropha, Lactobacillus spp. Lactococcus spp.*, *Streptococcus spp.*, and

TABLE 3.

Epidermal Barrier Outcomes Following Topical and Systemic Management of Rosacea

Study	RoA	Study Type & Size (n)	Acne Location, Severity	Participant Age	Study Length	Treatment Regimen	Results
Kang et al[123]	Topical	RCT (70)	Face, mild-moderate	≥12	8 weeks	Fecal E. faecalis anti-bacterial isolate lotion	Significant (*P*<.05) reduction in inflammatory lesions (pustules) vs vehicle
Muizzuddin et al[124]	Topical	Open-label (10)	Face & Trunk, --	Range 18-50	4 days	*Lactobacillus spp.* 5% lotion spot application QD	Significant (*P*<.05) reduction in acne lesion size and erythema compared with untreated lesions
AOBiome[125]	Topical	RCT, clinical trial phase 2b (358)*	--, Mild-moderate	--	12 weeks	Topical *Nitrosomonas eutropha*-containing spray	Significantly (*P*=.03) more participants had 2-grade IGA reduction and greater reduction in inflammatory lesions (*P*=.028) than vehicle
Jung et al[126]	Oral	RCT (45)	Face, mild-moderate	Range 18-35	12 weeks	BPO 5% and facial cleanser and: A) Minocycline QD or B) *Lactobacillus spp.* & *Bifidobacterium bifidum* BID or C) Both A&B	C had significantly greater reduction in total lesion count than group A (week 8: 67% vs 52%, *P*<.001; week 12: 82% vs 67%, *P*<.001) and B (week 8: 67% vs 56%, *P*=.006; week 12: 82% vs 67,% *P*<.001) C also had significantly less NIL and IL count at week 12 than A (NIL: 77% vs 70%, *P*=.03; IL: 77% vs 70%, *P*<.001) and B (NIL: 77% vs 65%, *P*=.001; IL: 77% vs 70% *P*<.001)
Fabbrocini et al[127]	Oral	RCT (20)	Trunk, --	Mean (SD): 33.7±3.3	12 weeks	*Lactobacillus rhamnosus* liquid	Significant decrease 32% (*P*<.001) in IGF-1 and 65% (*P*<.001) increase in FOXO1 from biopsied acne lesions Participants taking probiotic were more likely to be rated as having (markedly) improved based on IGA (aOR 28.4, 95%CI 2.2-411.1, *P*<.05)

-- Data not available from source document. *ClinicalTrials.gov ID: NCT02832063. [a]OR, adjusted odds ratio; BID, twice daily; CI, confidence interval; IGA, investigator's global assessment; IL, inflammatory lesion; NIL, non-inflammatory lesion; QD, once daily; RCT, randomized controlled trial; RoA, route of administration; *spp.*, species.

Bifidobacteria spp.[119-120] Theoretically, introduction of these species may mitigate and outcompete pathogenic organisms,[121] thereby improving CM homeostasis.

Several clinical trials have found success in using probiotics as monotherapy or in conjunction with traditional AV therapy (Table 3).[119,122-127] Studies are investigating "grafting" autologous microbes cultured from non-lesional skin in individuals with dermatoses onto affected areas.[128] In the future, we may be able to extract the contents of an AV-prone follicle, apply a cocktail of *C. acnes* (IA1)-specific bacteriophage to deplete pathogenic strains and reintroduce commensal *C. acnes* phylotypes II and III.[42,62] This dual-pronged approach may provide a personalized, targeted means to improve disease severity while promoting a healthy CM.[129]

More than Moisture: Water, Prebiotics, and Postbiotics

Prebiotics are topical/oral supplements or foods that selectively support and stimulate the growth and/or activity of the microbiome.

Different microorganisms have been found to tolerate decreased SCH, such as *S. aureus*, whose abundance correlates temporally with AD flares,[130] and therefore may outcompete commensal microbes under more "arid" conditions.[12,131] Therefore adequate moisturization and water-retention may not only promote EBF but also microbiome diversity. In this way water, by cultivating and stimulating CM growth and/or activity, may be considered a prebiotic.[132]

Postbiotics (or bacterial byproducts, metabolites, and excreted compounds from lysed organisms, such as Xanthomonas, and *Enterococcus faecalis*) may also have potential to affect dermatoses. An 8-week double-blind, randomized, vehicle-controlled trial of 70 mild-moderate AV patients found that topically-applied anti-bacterial isolate from fecal *Enterococcus faecalis* significantly (*P*<.05) reduced more pustules than the vehicle.[123] Postbiotics from *Vitreoscilla filiformis*, a gram-negative filamentous, non-pathogenic bacterium that is naturally found in thermal springs and spa water[133] has been found to have antioxidant abilities mediated via mitochondrial superoxide dismutase in vitro[134] and anti-inflammatory activity via interleukin-10 (IL-10) mediated regulatory T cells within murine models of AD.[135] Preliminary data also suggest that addition of *V. filiformis* lysate to emollients may provide a method to improve EBF and CM diversity.[136-138]

DISCUSSION AND FUTURE DIRECTIONS

While the flow of causality between EBD and dysbiosis is not yet clear for AV and rosacea, they do appear to play a material role in the pathogenesis and development of clinical symptoms. Repairing the barrier and restoring the microbiome are essential, and quality skin care may help patients achieve this goal. It is vital that dermatologists are aware of the growing

role that EBD and dysbiosis may play in AV and rosacea, and how best to select prescription and OTC agents to address these deficiencies.

Currently, there are limited clinical studies investigating the use of adjunctive skincare products, especially in AV and rosacea.

Studies investigating the role of pro-/pre-/postbiotics have traditionally focused on AD (and psoriasis).

Future studies, and specifically clinical trials, should assess the implementation of skincare products in AV and rosacea, with particular attention afforded to pro-/pre-/postbiotics and how they may complement current prescription regimens to longitudinally augment clinical improvement and minimize adverse effects and local skin irritation.

CONCLUSION

AV and rosacea are multifaceted inflammatory dermatoses that both have varying degrees of intrinsic EBD, which may be affected by selected therapy. Similarly, AV and rosacea have unique CM abnormalities that can be further perturbed by indiscriminate use of systemic broad-spectrum antibiotics. The interplay between EBF and the CM is critical for the research and development of new therapies and methods to approach these diseases. Appropriately developed prescription and OTC agents have the potential to selectively influence the microbiome in a beneficial direction and maintain, if not restore, EBF. By understanding this intricate interplay, dermatologists will be better able to educate their patients on the importance of appropriate skin care and potentially improve their quality of life.

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