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## ACNE MICROBIOME: FROM PHYLA TO PHYLOTYPES

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## ABSTRACT

Acne vulgaris is a chronic inflammatory skin disease with a complex pathogenesis. Traditionally, the primary pathophysiologic factors in acne have been thought to be: 1) altered sebum production, 2) inflammation, 3) excess keratinization, and 4) colonization with the commensal *Cutibacterium acnes*. However, the role of *C. acnes* has been unclear, since virtually all adults have *C. acnes* on their skin yet not all develop acne. In recent years, understanding of the role of *C. acnes* has expanded. It is still acknowledged to have an important place in acne pathogenesis, but evidence suggests that an imbalance of individual *C. acnes* phylotypes and an alteration of the skin microbiome that trigger acne. In addition, it is now believed that *Staphylococcus epidermidis* is also an actor in acne development. Together, *C. acnes* and *S. epidermidis* maintain and regulate homeostasis of the skin microbiota. Antibiotics, which have long been a staple of acne therapy, induce cutaneous dysbiosis. This finding, together with the long-standing public health edict to spare antibiotic use when possible, highlights the need for a change in acne management strategies. One fertile direction of study for new approaches involves dermocosmetic products that can support epidermal barrier function and have a positive effect on the skin microbiome.

## INTRODUCTION

Acne vulgaris is a highly prevalent skin disease with a multifactorial pathophysiology.<sup>1</sup> Acne is characterized by a waxing/waning natural history and a variable clinical presentation involving papules, pustules, and comedonal lesions as well as cysts or nodules in severe cases.<sup>2</sup> Acne occurs in areas of skin that have pilosebaceous ducts (face and torso).<sup>3</sup> Often highly visible, acne lesions can cause short-term embarrassment and diminished quality of life.<sup>3-7</sup> In addition, acne can lead to longer term problems, such as scarring and excess pigmentation at the site of former acne lesions.<sup>4, 8, 9</sup> Approximately 40% of acne sufferers develop clinically relevant scars and in darker skinned populations half or more develop pigmentary problems;<sup>9, 10</sup> as with active lesions, these sequelae have an impact on life quality.<sup>3, 4</sup> Further, they are often difficult to manage adequately.<sup>11</sup>

A variety of efficacious topical and systemic medical therapies for acne have been approved by regulatory bodies; however, their use can be limited by high costs, cutaneous irritation, possible teratogenicity, accessibility, and efficacy – especially when patients are not able or are unwilling to use the medication for a suitable duration. Large-scale population-based studies have shown that overall medication adherence is low in acne.<sup>12, 13</sup> As reported by Grada and colleagues, persistence to acne medications at 3 months is 12% and this dips to just below 2% by 12 months.<sup>13</sup> It is perhaps unsurprising, then, that patients and clinicians continue to search for new solutions for acne management – including preventative strategies – given the difficulty in reversing scarring and pigmentation once they have occurred.

In recent years, research has shed increasing light onto the interaction between microbes on the skin and host immunity overall, as well as its role in acne pathophysiology.<sup>1</sup> This publication will discuss emerging information about acne pathophysiology and how new therapeutic approaches may include dermocosmetic products. These non-prescription products may improve acne by supporting a healthy epidermal barrier and protecting the diversity of the skin microbiome.

## NEW INFORMATION ABOUT ACNE PATHOPHYSIOLOGY

Traditionally, it has been thought that acne pathophysiology primarily involves a quartet of factors: sebum overproduction (with qualitative change in composition) secondary to stimulation of the sebaceous gland, abnormal keratinization in the pilosebaceous duct, inflammation, and colonization by *C. acnes* (formerly *Propionibacterium acnes*).<sup>14, 15</sup> These changes together lead to the formation of a microcomedo, the acne precursor, which in turn can evolve into comedonal or inflammatory lesions.<sup>15</sup> This viewpoint has evolved in recent years, to acknowledge that simple overabundance of *C. acnes* in and around the sebaceous follicle does not adequately describe the role of this microbe in acne (Fig 1).<sup>16</sup> Now, it is known that *C. acnes* population and other microbiota interact intimately with the innate immune system, and further, the six main different phlotypes of *C. acnes* produces different types and amount of hemolytic toxins and have differing effects on innate immune activation.<sup>17, 18</sup> In addition, sebum may be involved in encouraging growth of particular subtypes of *C. acnes*.<sup>17</sup> The role of the microbiome and, more specifically, *C. acnes* and *S. epidermidis* are discussed below.

## Emerging information about the skin microbiome

The human skin's microbiome includes a dense range of microorganisms, such as bacteria, fungi, and viruses.<sup>1</sup> In healthy skin, commensal microbes act in symbiosis with the physical structure of the skin to create a barrier against external insults; this publication focuses on the role of bacteria in skin health and disease.<sup>17</sup> The microbiome is dominated by four main bacterial phyla: Actinobacteria, Firmicutes, Proteobacteria, and Bacteroidetes.<sup>17</sup> Among bacterial genera, *Cutibacterium*, *Staphylococcus*, and *Corynebacterium* are most common, but the relative proportions vary depending on the skin microenvironment and the topography.<sup>16</sup> Skin surfaces can be moist, sebaceous, and dry; thus, the face and back have microbial systems that differ from those of the feet, hands, or limbs. Sebaceous sites, which are involved in acne, have the least bacterial diversity since only a few species thrive in these anaerobic, lipid-rich areas.<sup>16</sup>

Beyond anatomical/topographical factors, the delicate balance of the composition of microbes within the microbiome can be affected by environmental factors such as pathogenic microbes and use of skincare products or medications like antibiotics.<sup>19, 20</sup> Alterations in the microbiota composition are associated with skin diseases, including acne, psoriasis, and atopic dermatitis.<sup>17, 21, 22</sup> Such alterations can include changes in both the relative proportion of species as well as the strains that are present.<sup>19</sup>

Study of the microbiome has shown that *C. acnes* and *S. epidermidis* have essential roles in regulation of skin homeostasis.<sup>19, 23, 24</sup> *C. acnes* is a ubiquitous Gram-positive anaerobic bacterium belonging to the *Actinobacteria* phylum and predominantly resides deep within the

sebaceous follicle.<sup>25,19</sup> Under healthy conditions, *C. acnes* has a role in protecting barrier function and the follicle by maintaining an acid pH caused by secretion of propionic acid (which, in turn, has a central role in the low surface pH of skin).<sup>26</sup> *S. epidermidis* is also a skin commensal that can become pathogenic when it penetrates through skin into the bloodstream.<sup>19,15</sup> Both *Cutibacterium* and *Staphylococcus* can prevent colonization of pathogenic bacteria and produce bacteriocins to compete with other skin flora for nutrients.<sup>27-29</sup> Moreover, other coagulase-negative staphylococci such as *S. capitis* can secrete antimicrobial compounds (phenol soluble modulins), killing specifically *C. acnes* strains.<sup>30</sup> Additionally, these bacteria stimulate production of antimicrobial peptides (AMPs) from keratinocytes and sebocytes to help maintain a balanced skin microbiome.<sup>31</sup> The AMPs help maintain an inflammatory homeostasis *via* suppression of excess cytokine release secondary to minor injuries of the epidermis.<sup>32</sup>

As alluded to in Figure 1, a complex signaling system connects the colonizing microorganisms with the host's innate and adaptive immune responses.<sup>17</sup> Host inflammatory responses can be triggered by alterations in epidermal barrier function, dysbiosis, or both.<sup>33</sup> Now, it is becoming clear that all of these factors have an important role in acne pathophysiology.

### **Update on *C. acnes* and *S. epidermidis* in acne**

*C. acnes* was first reported in acne lesions in 1891, and was long considered the likeliest microbial actor in acne.<sup>16, 34, 35</sup> It was originally named *Bacillus acnes*, but was later renamed *Corynebacterium acnes* due to morphologic similarity to *Corynebacterium*. In the 1940s, it was discovered that these bacteria produce propionic acid, and annexed to genus *Propionibacterium* as *Propionibacterium acnes*. Most recently, the name *Cutibacterium acnes* was proposed, when

genus *Propionibacterium* was divided into four genera as a result of the latest whole genome-based taxonomical clarification.<sup>25</sup> *C. acnes* is uniquely well suited to living in the pilosebaceous duct, and comprises up to 90% of the microbiota in sebaceous rich areas.<sup>16</sup>

*C. acnes* is grouped into three phylotypes (I-III) based on the cellular morphology, inflammatory and immune-inducing properties, virulence factors, and biochemical characteristics, which may help explain their differing roles in health and disease (Table 1).<sup>15, 16</sup> Type I is further subdivided by whole genome sequencing into the major type I clade encompassing IA<sub>1</sub>, IA<sub>2</sub>, IB, IC, II and III.<sup>15</sup> Acne-related strains produce porphyrins, which in turn generate reactive oxygen species (ROS) and inflammation.<sup>16</sup> As shown in Figure 1, *C. acnes* strains associated with acne interact with keratinocytes and monocytes to induce release of inflammatory cytokines.<sup>16</sup>

Acne is more prominently associated with loss of diversity of *C. acnes* phylotypes than to *C. acnes* proliferation.<sup>1</sup> Unlike in healthy skin, acne skin is characterized by a predominance of *C. acnes* phylotype IA<sub>1</sub> (Fig 2).<sup>33, 36-38</sup> Isolates of other phylotypes are present in acne skin, but in substantially lower proportions.<sup>15</sup> It has been shown that loss of phylotype diversity and predominance of type IA<sub>1</sub> strains represents a dysbiotic shift within the pilosebaceous duct, which could in turn be due to microenvironmental changes that lead to formation of microcomedones.<sup>1, 15</sup> In either case, phylotype IA<sub>1</sub> is associated with both stimulation of innate immunity and cutaneous inflammation.<sup>1</sup> As one example of this, significant up-regulation of innate immune markers (interleukins) has been shown in skin explants exposed to *C. acnes* IA<sub>1</sub>; this up-regulation did not occur when explants were incubated with a mixture of phylotypes IA<sub>1</sub>, II, and III.<sup>39</sup>



*C. acnes* and *S. epidermidis* interactions also have a role in acne. *S. epidermidis* can inhibit growth of *C. acnes* and minimize *C. acnes*-induced cutaneous inflammation.<sup>17, 40, 41</sup> Further, *S. epidermidis* affects *C. acnes* proliferation by releasing a fatty acid fermentation product known as succinic acid and suppresses *C. acnes*-induced release of cytokines from keratinocytes.<sup>1</sup> *C. acnes* can also inhibit the development of *S. epidermidis* by controlling the pH of the pilosebaceous follicle, metabolizing serum triglycerides, and excreting propionic acid.<sup>1</sup> Finally, both *C. acnes* and *S. epidermidis* affect survival of monocytes, which may indicate a role in acne associated hyperpigmentation.<sup>1</sup> Thus, maintaining the balance between these two bacterial species is important. *S. capitis* and *S. lugdunensis* and other CNS can interact, the skin homeostasis depending on this eubiotic equilibrium.<sup>42</sup>

*C. acnes* phylotypes IA and II are associated with a high percentage of biofilm formation, consisting of bacteria embedded in a matrix of extracellular polymeric substance, and these biofilms can adhere to surfaces.<sup>28</sup> *C. acnes* phylotypes IB and III, which are associated with healthy skin, have shown a low tendency toward forming biofilm.<sup>28</sup> In acne, sessile *C. acnes* (cells growing in a biofilm) can occur deep within the pilosebaceous follicle.<sup>28</sup> The biofilm is associated with increased production of exopolysaccharide “glue” that adheres corneocytes together, which is thought to contribute to the formation of microcomedones.<sup>28</sup> When in biofilm form, *C. acnes* has increased persistence, tolerance and resistance to antimicrobials as well as host inflammatory cells.<sup>16, 43</sup> It is thought that this resistance is due to slow growth (low-metabolic bacterial cells) and/or stimulation of a stress response, as well as other resistance mechanisms.<sup>44</sup>

*C. acnes* releases extracellular vesicles (EVs) capable of modulating the proliferation and differentiation of keratinocytes.<sup>1</sup> Contact between keratinocytes and *C-acnes* EVs results in abnormal regulation of antigen Ki67, keratin 10, filaggrin, and desmocollin 1, and upregulate production of inflammatory cytokines.<sup>45</sup> In this manner, the interaction between *C. acnes* and follicular keratinocytes plays a role in the development of microcomedones and comedones.<sup>1</sup> Recently, Chudzik et al showed that different *C. acnes* phylotypes have distinct protein and lipid compositions, indicating they convey different cell-to-cell communications and contribute to separate bacterial functions.<sup>46</sup>

Also important is the association between *C. acnes* and activation of the helper T-cell Th17 inflammatory pathway.<sup>47</sup> Stimulation of Th17 inflammatory responses in skin cells is linked to loss of *C. acnes* phylotype diversity in acneic skin.<sup>47</sup> It is now accepted that inflammation occurs at all stages of acne lesions, including the earliest non-clinical lesions.<sup>48</sup> Image analysis of microcomedones has shown that they have a pouch-like structure with an outer layer of corneocytes that is filled with lipids and bacterial clusters. The presence of bacteria and blockade of the pilosebaceous unit due to microcomedones further exacerbates inflammation and recruits immune cells, which leads to acne papules and pustules.<sup>47, 48</sup> The formation of biofilm and secretion of virulence factors (CAMP hemolysis, lipase, RoxP enzyme) by *C. acnes* phylotype IA<sub>1</sub> stimulates production of interleukin-17 by Th17 lymphocytes.<sup>47, 49</sup> Thus, the various *C. acnes* phylotypes can modulate T cell responses leading to either acne development or homeostasis.<sup>47</sup>

## IMPLICATIONS FOR CLINICAL PRACTICE

As mentioned early on in this publication, these new findings about the microbial interactions in acne skin should alter the management approach in acne. First, it is becoming clear that acne treatment should not target killing all *C. acnes* subpopulations but instead should aim for preventing or correcting the intra-species dysbiosis.<sup>1</sup> Antimicrobial resistance is a worldwide problem, and acne experts have expressed clinical concerns with the use of antibiotics to treat acne, and even more so with the discovery of resistance plasmid (encoding for macrolide-clindamycin resistance gene *erm(50)* and tetracycline resistance gene *tet(W)*), in *C. acnes* that can be transmitted to other *Cutibacterium* species, thus modifying the skin microflora.<sup>50, 51</sup> These concerns arise from the large population of patients with acne around the world at any given time and the fact that antibiotics are often used for prolonged periods of time in acne patients.<sup>50</sup> Together, these are arguments for limiting use of antibiotics in acne. This is particularly true for topical antibiotics, because they induce high levels of resistance not only among *C. acnes* but also with *S. epidermidis* leading to horizontal resistance transfer to pathogens such as *S. aureus*. Use of oral antibiotics, even those like tetracyclines that are not commonly used for other diseases, poses a population-based risk and lengthy treatment courses, and thus should be discouraged whenever possible. Further, there are effective non-antibiotic antimicrobial agents available for acne including benzoyl peroxide alone and in combination and active cosmetics.

### **Maintenance and protection of microbiome: Cleansers and moisturizers**

Second, effective acne treatment has been shown to increase diversity of skin bacteria and cosmetics that modulate the microbiome are showing promise.<sup>16, 28</sup> Figure 3 shows a schematic

of how supporting and improving the skin barrier function and microbiome influences cutaneous health and disease.<sup>52</sup> While the studies evaluating the effects of dermocosmetics on the microbiome and barrier in acne are currently sparse, some examples are presented here.

Dermocosmetic that included an ethanolic extract of myrtle leaves has been shown to reduce *C. acnes* biofilm and maintain acne clearance in a greater proportion of adult females compared to a control cream (85% vs 67%, respectively).<sup>53</sup> Similarly, a separate dermocosmetic based on thermal water showed a marked antibiofilm activity on both *C. acnes* and *S. aureus*.<sup>54</sup> In 2021, Hwang et al reported that daily use of a moisturizer for 4 weeks (n=25 women) increased bacterial diversity, considered a marker of healthy skin.<sup>55</sup>

Both *Cutibacterium* and *Staphylococcus* species increased, along with changes in the skin microbial network, and improved hydration. Thus, the authors suggest use that skincare regimen can “affect the microbial structure of facial skin as well as the biophysical properties.”<sup>55</sup>

Ciardiello et al and Kong et al also reported that use of skin care products could increase microbial diversity.<sup>56, 57</sup> Thermal water is interesting because its physicochemical characteristics may include soluble minerals and trace elements such as selenium or strontium.<sup>52</sup> Thermal water has probiotic bacteria that thrive on this natural mineral profile and thermal water and niacinamide have both been associated with a decrease in *Staphylococcus* species.

### **Bacteriophages**

Bacteriophages, viruses that replicate in bacteria, may provide an alternative to antimicrobial agents.<sup>58</sup> Indeed, they can replicate so much within the cell that they induce bacterial lysis.<sup>58</sup> They may also integrate into bacterial DNA to alter the bacteria and reduce pathogenicity.<sup>58</sup>

Phages offer the potential for targeting specific bacteria with minimal disruption to the remainder of the microbiome.<sup>58</sup> Lytic bacteriophages to *C. acnes* have been developed but their clinical applications have not been well studied.<sup>58, 59</sup> Further research in the field of dermatology must be performed to assure safety (respect of the balanced microbiota) and efficacy (*C. acnes* specific treatment) in humans.<sup>60</sup>

### Prebiotics

Today's skincare products are developed with an objective of nourishing a healthy microbiome. Ingredients that help achieve this goal include prebiotics such as *Vitreoscilla filiformis* and aqua posae filiformis the postbiotic heat-killed strain of lysate of *V. filiformis*, ceramides, and niacinamide.<sup>52, 61-63</sup> Pre- and post-biotics, ingredients that selectively stimulate growth and/or activity of individual bacterial strains, have the potential to normalize the balance of the skin microbiome.<sup>52</sup> Research is ongoing to determine the exact impact of these as ingredients, but benefits have been shown in patients with seborrheic dermatitis and atopic dermatitis.<sup>52</sup>

Ceramides can provide nutrients such as carbon and nitrogen, and maintenance of adequate ceramide levels seems to have an important role in skin health.<sup>52</sup> Indeed, *S. epidermidis* secretes a sphingomyelinase that acquires essential nutrients for the bacteria and assists the host in producing ceramides, the main constituent of the epithelial barrier that averts skin dehydration and aging.<sup>64</sup>

Dreno et al showed the importance of *S. epidermidis* in acne during a 28-day exploratory study in patients with acne (n=26) treated with topical erythromycin 4% or a dermocosmetic.<sup>17</sup> At

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baseline, microbiota sampling revealed a greater abundance of *Staphylococcus* on acne lesions vs non-lesional skin, and the degree of growth correlated with acne severity ( $P < 0.05$  for all).<sup>17</sup> At day 28 sampling, only the dermocosmetic reduced *Staphylococcus*, while erythromycin had no effect.<sup>17</sup>

## CONCLUSIONS

Manipulating the skin microbiome is an exciting but still ill-defined area in dermatology. Skincare products are being developed that contain synthetic chemicals and antimicrobial agents that may impact the balance of the microbiota. Biome friendly skincare products may support or help restore beneficial bacteria while preventing growth of harmful bacteria by improving skin hydration and the epidermal barrier.<sup>65</sup> Skin dryness can lead to irritation while elevated pH contributes to skin disease and use of appropriate skin care products may restore and preserve skin health.<sup>55</sup> Cleansers with pH close to normal physiologic levels (approximately 5) are a good choice for acne skin to minimize impact on the skin barrier and to favor microbial balance. Conversely, “poor choices made by an uninformed patient may derail an otherwise ideal therapeutic approach.”<sup>33</sup>

In the future, acne therapeutic approaches may include bacteriophages, pre- and post-biotics, and other manipulations of specific bacteria within the microbiome. Research is ongoing to determine which of these may have clinical utility.

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### Figure Legends

Figure 1. Model of main acne pathologic processes activated by *C. acnes*. From Lee YB, Byun EJ, Kim HS. Potential Role of the Microbiome in Acne: A Comprehensive Review. et al. *J Clin Med* 2019;8(7):987. doi: 10.3390/jcm8070987. EPS=extracellular polymeric substances; CAMP=cyclic adenosine monophosphate; TLR=toll like receptor; IL=interleukin; TNF=tumor necrosis factor; LTB=leukotriene B; CD36=cluster of differentiation 36; GMCSF=granulocyte-macrophage colony stimulating factor; hBD=human beta-defensin; MMPs=matrix metalloproteinases.

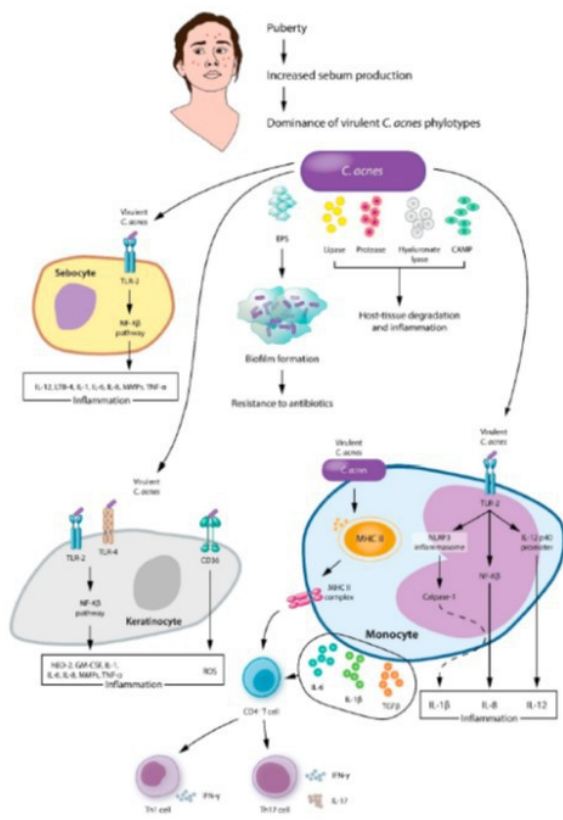
Figure 2. Distribution of *C. acnes* phylotypes in acne and healthy skin; proportions of type IA1 and III were significantly different ( $P<0.001$ ) between samples. Reprinted from Dagnelie MA, Corvec S, Timon-David E, et al. *Cutibacterium acnes* and *Staphylococcus epidermidis*: The unmissable modulators of skin inflammatory response. *Exp Dermatol* 2022;31(3):406-12. doi: 10.1111/exd.14467. 15, 66

Figure 3. Example of how improving characteristics of skin barrier and microbiome affect skin health and disease.

**Table 1.** *C. acnes* phylotypes\* and associations with acne and healthy skin.

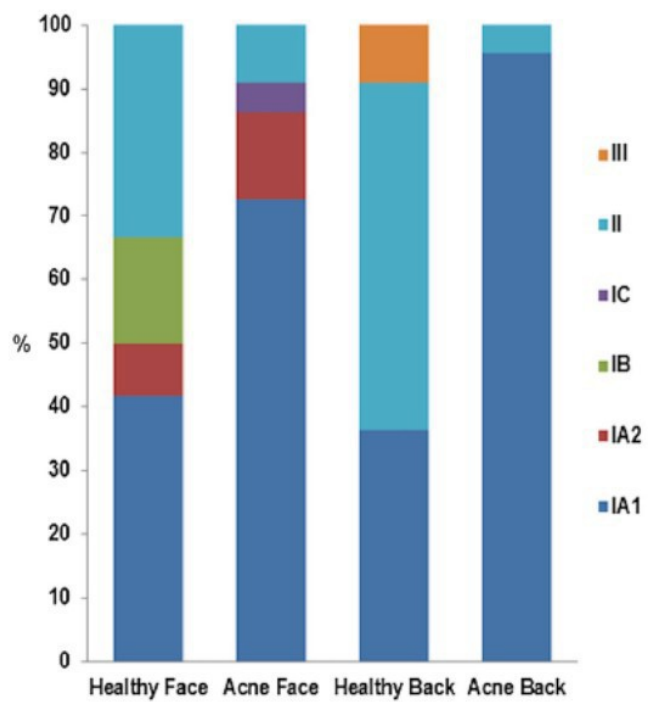
	<b>Acne</b>	<b>Healthy</b>
IA <sub>1</sub>	+	+
IA <sub>2</sub>	+	
IB	+	
IC	+	
II		+
III		+

\*Based on whole genome sequencing

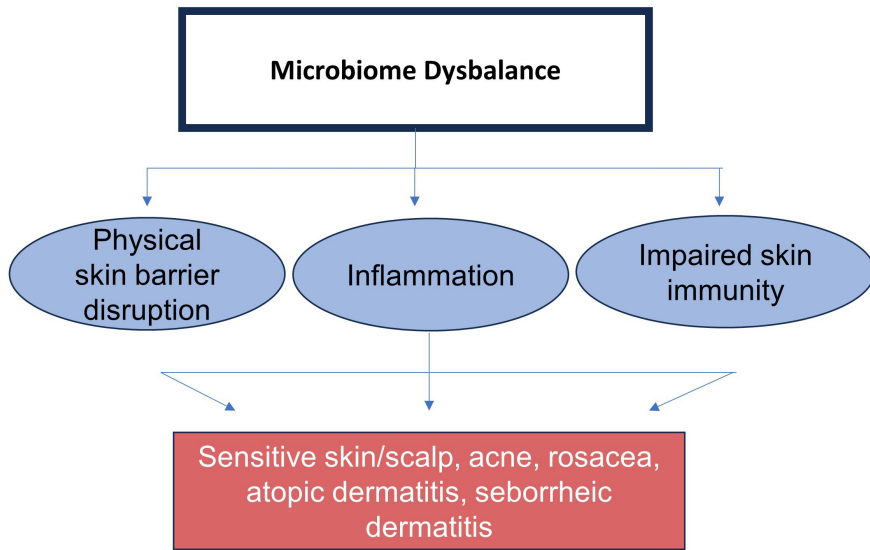


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