

How does skin microbiota act in atopic dermatitis?

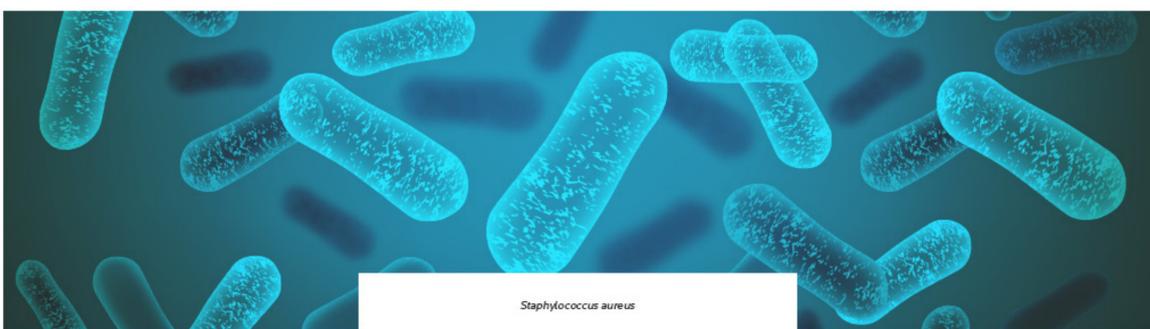
SKIN & MICROBIOTA

BASIC

Atopic dermatitis (AD) is one of the most common chronic inflammatory skin diseases with psoriasis.¹ AD, whose prevalence is increasing in industrialized countries, has been associated with dysbiosis of the skin microbial community since 1974. These early observations were repeated and extended with modern 16S sequencing approaches in 2013.^{2,3}

AD: an overabundance of Staphylococci

Atopic dermatitis is a complex condition with common features: very dry itchy skin and abnormalities of the immune, skin and microbial barrier, including a deficiency in the epithelial barrier protein filaggrin, colonization by *S. aureus*, and immune hypersensitivity.⁴

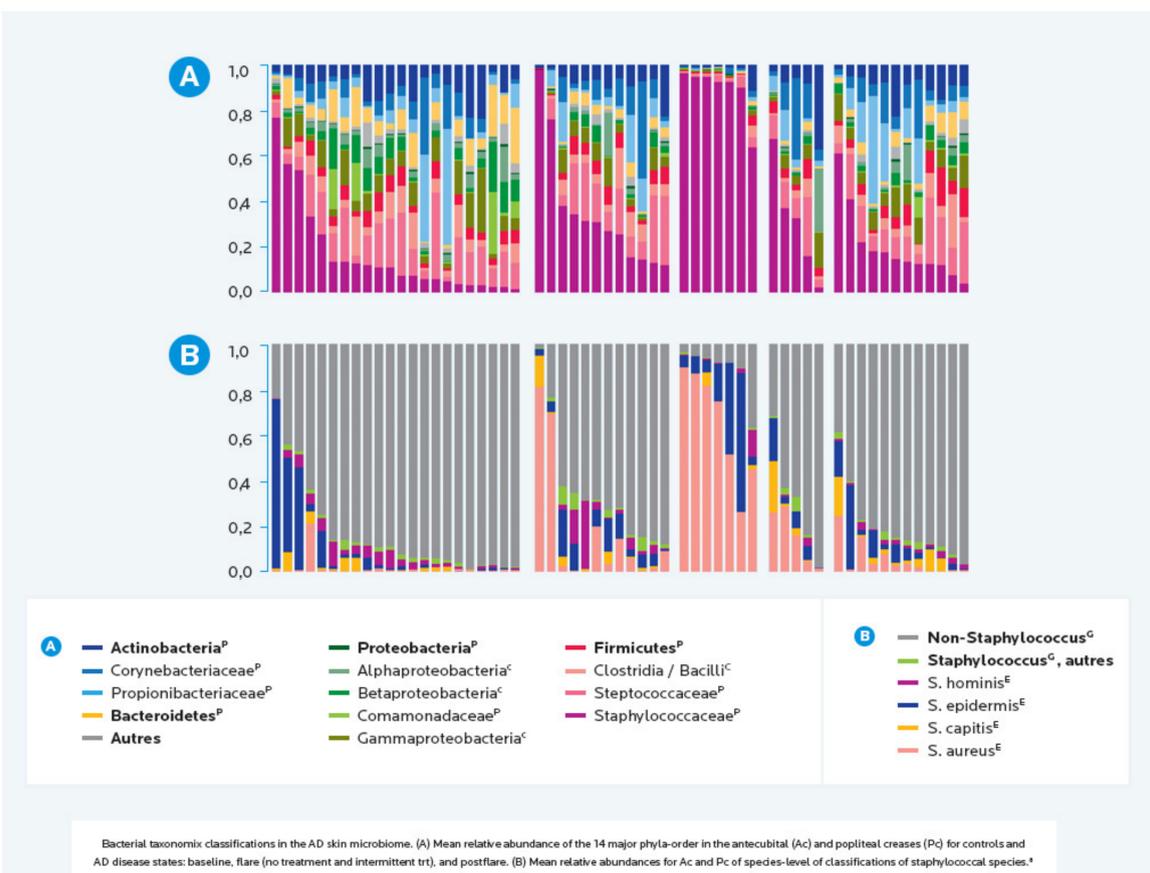


AD lesion areas show a dramatic drop in bacterial diversity with up to 90% of their community being just one type: *Staphylococcus* is present on the skin of >90% of AD patients.^{4,5} This presence is at least partially explained by an antimicrobial peptide deficiency and the poor quality of the skin barrier, which allows easy access to complex substrates.² Furthermore, during flares, the loss of bacterial diversity and predominance of *Staphylococcus species*, *S. epidermidis* and *S. aureus*, worsen in correlation with severity.⁵⁻⁹

In AD, the microbial distribution differs according to affected or unaffected sites

The skin's topography and microenvironments are powerful determinants of microbial community structure at particular skin sites. AD preferentially involves the antecubital and popliteal regions, moist sites that harbor similar groups of organisms and share distinct compositions of microbial communities.⁸

However, it has been demonstrated that bacterial communities vary between closest affected (AF) or lesional and unaffected (UAF) or non-lesional skin from the same individual, providing a deeper insight into those involved in the skin dysbiosis associated with AD. Staphylococci and lower microbial diversity especially dominate AF skin compared with adjacent UAF skin.^{5,9}



The role of *S. aureus* remains unclear

Deciphering complex cutaneous host-microbe and microbe-microbe interactions and their roles in skin disease and innate immunity is a daunting task. Recent evidence suggests that nonpathogenic bacteria alleviate AD-related skin inflammation. Conversely, AD-related perturbations in *S. aureus* populations may be secondary to the disease process, largely a result of the disrupted barrier function rather than representing primary etiologic events. Whether *S. aureus* contributes to the pathophysiology or merely reflects the abnormal environment has never been conclusively established.⁷

In 2012, a metagenomic study showed that Staphylococci species increased from 35% to 90% of the microbiota during flares, but surprisingly both *S. aureus* and *S. epidermidis* increased.^{4,8,10} These increases will result in an inflammatory process and will worsen the deregulation of the cutaneous immune system. Therefore, microbiota data suggest that understanding how *S. aureus* affects AD will require understanding of its fluctuations as part of a larger, complex ecosystem. *S. epidermidis* can produce molecules that selectively inhibit *S. aureus*, arguing that *S. epidermidis* may be antagonistic, or competitive, to *S. aureus*.^{4,8}

In addition to the obvious changes in *S. aureus* and *S. epidermidis* abundance, many unrelated, non-staphylococcal species also appear to change in abundance during an AD flare. Future research should examine whether a change in host skin first triggers changes in species composition, thereby allowing for Staphylococci overgrowth, or if Staphylococci overgrowth is a primary event that then forces other species to change in abundance.⁴

Rebalance atopic skin microbiota: an achievable therapeutic challenge

There is evidence that decreasing inflammation, and improving barrier function and hydration of skin may suffice to reduce *S. aureus* and *S. epidermidis*, and normalize AD bacterial compositions.^{7,9}

Interestingly, effective AD treatment is associated with higher bacterial diversity, indicating that current treatments that promote bacterial diversity trigger disease improvement.²

However, adjunctive therapy may be of great help to restore and control the skin microbiota. A study conducted in sixty patients with moderate AD in 2017 showed that application of an emollient* twice a day is able to normalize skin microbiota and significantly reduce the number and severity of flare-ups.⁵

*containing a Vitreoscilla Biformis dead biomass grown in a medium containing Thermal Spring Water

And in the future...

Similar to fecal microbiota transplantation therapies to treat *Clostridium difficile* infections, skin microbiota transplantations could be considered to ameliorate transiently *S. aureus* colonization and AD symptoms without relying on antibiotic therapies that encourage the acquisition of resistance.

Some evidence suggests that gastrointestinal probiotics and prebiotics may offer benefits in preventing and reducing the severity of AD. In addition, low diversity in the gut microbiota during early infancy has been associated with development of atopic eczema later in life. These observations imply that there is a connection between the gut microbiota and the skin, potentially through stimulation and/or education of immune cell populations. Further exploration of this connection may provide insight into the mechanism of allergic and atopic conditions, while providing an additional target, the gut microbiota, for manipulation (via probiotics, prebiotics, postbiotics or microbiota transplant) in the treatment and/or prevention of skin disease.¹¹

GOING FURTHER

Inflammatory mechanisms in Atopic Dermatitis

AD patients exhibit alterations in T-cell homeostasis, suppression of cathelicidin and b-defensin antimicrobial responses, and physical barrier defects. The combination of physical barrier and antimicrobial barrier defects are likely to drive the microbial dysbiosis, which disrupts further the cell immunity balance needed to maintain inflammatory equilibrium with the external environment.

Regulatory T (Treg) cells are crucial mediators of the balance between tolerance to antigens (both "self" and foreign) and immune responses. The secretion of anti-inflammatory cytokines such as IL-10 is one mechanism by which this balance is achieved. Although it remains controversial whether defects in Treg cells contribute to the pathogenesis of AD, depletion of FoxP3+ Treg cells in mice drives AD-like symptoms such as expression of Th2 cytokines and elevated serum IgE. Because of the recognized associations between bacteria products and Treg cell function, AD provides an ideal model system to appreciate the potential benefits of a "normal" microbiome.²

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