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Skin Microbiome Dysbiosis in Atopic Dermatitis: The Impact of *Staphylococcus aureus* and Emerging Bacteriophage Therapy

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ABSTRACT

Atopic dermatitis (AD) is a chronic, relapsing inflammatory skin disease characterized by pruritus, impaired epidermal barrier function, and immune dysregulation. In recent years, mounting evidence has highlighted the critical role of skin microbiome alterations in disease pathogenesis, particularly the overcolonization by *Staphylococcus aureus*. This bacterium is strongly associated with disease severity, flares, and resistance to conventional therapy through the production of virulence factors that amplify cutaneous inflammation and barrier dysfunction. Traditional antimicrobial strategies, including topical and systemic antibiotics, are limited by the rise in antimicrobial resistance and their detrimental effects on commensal skin flora. In this context, bacteriophages—viruses that selectively infect bacteria—have emerged as a promising, microbiome-sparing therapeutic approach. Bacteriophages targeting *S. aureus* demonstrate high specificity, the ability to disrupt biofilms, and minimal impact on beneficial microorganisms. This review summarizes the pathogenic role of *S. aureus* in atopic dermatitis, examines the biological rationale for bacteriophage therapy, and critically evaluates current preclinical and early clinical evidence supporting its use. The key message of this review is that bacteriophage-based therapy represents a novel, targeted strategy that may complement existing treatments and support personalized, microbiome-oriented management of atopic dermatitis.

Keywords: Atopic dermatitis; bacteriophages; inflammation; phage therapy; skin microbiome; *staphylococcus Aureus*.

INTRODUCTION

Atopic dermatitis is one of the most common chronic inflammatory skin diseases, affecting both children and adults worldwide.[1] Clinically, it is characterized by intense pruritus, eczematous lesions, recurrent infections, and significant impairment of quality of life.[1,2] Despite advances in anti-inflammatory and biologic therapies, long-term disease control remains challenging for many patients.

Beyond epidermal barrier defects and immune dysregulation, alterations in the skin microbiome have emerged as a central component of AD pathogenesis.[1] Numerous studies have demonstrated a marked reduction in microbial diversity during disease flares, accompanied by pronounced colonization with *Staphylococcus aureus*.[3,4] This shift in microbial balance contributes to inflammation, disease persistence, and therapeutic resistance.[1,3]

Antibiotics are frequently used to control secondary infection or colonization; however, their repeated use promotes antimicrobial resistance and disrupts commensal bacteria essential for skin homeostasis. These limitations have driven interest in alternative, targeted antimicrobial strategies.

This review examines the role of *S. aureus* in atopic dermatitis and evaluates bacteriophages as an emerging therapeutic option. Particular emphasis is placed on biological mechanisms, therapeutic potential, and current limitations of phage-based approaches.

REVIEW

Skin microbiome and dysbiosis in atopic dermatitis

The skin microbiome is a complex ecosystem composed of bacteria, viruses, fungi, and other microorganisms that play a crucial role in maintaining epidermal barrier integrity and immune homeostasis.[1,5] Disruption of microbial balance leads to impaired barrier function, reduced local immune defense, and excessive colonization by pathogenic microorganisms.[1,4]

Dysbiosis is considered a major determinant of disease severity in atopic dermatitis.[1,3] Numerous studies have demonstrated that *S. aureus* is isolated from lesional skin in a high proportion of patients with active AD.[1,3] Microbial composition differs significantly between flare and remission phases: disease exacerbation is preceded by increased *S. aureus* colonization and a marked reduction in microbial diversity,[3] whereas higher abundance of coagulase-negative staphylococci and protective commensal-derived antimicrobials is associated with milder disease phenotypes.6

Genotypic characteristics of *Staphylococcus aureus* in atopic dermatitis

The strains of *S. aureus* colonizing the skin of patients with atopic dermatitis may differ genetically and functionally from those detected in non-AD populations, and these differences can correlate with disease severity and host barrier genetics (including filaggrin-related associations).[4] Such variability may contribute to differences in virulence factor expression and immune activation in AD.[1,7]

These genotypic and functional differences support the pathogenic specificity of *S. aureus* in atopic dermatitis.[1,4,7]

Mechanisms of barrier disruption and inflammation

In atopic dermatitis, *S. aureus* exacerbates epidermal barrier damage through multiple virulence factors and host–microbe

interactions, thereby amplifying cutaneous inflammation and barrier dysfunction.[1] Microbial products and toxins further influence inflammatory pathways linked to AD.[1,8]

The secreted cytotoxin α-hemolysin (alpha-toxin) is produced by skin-colonizing *S. aureus* and has been implicated in immune activation relevant to AD.[8] Together, these mechanisms support a role for *S. aureus* in perpetuating inflammation and barrier impairment in susceptible hosts.[1,8]

Superantigens, pruritus, and steroid resistance

Staphylococcus aureus strains isolated from patients with atopic dermatitis frequently produce superantigens, and infected AD lesions may contain pharmacologically relevant amounts of staphylococcal superantigens.[9] Superantigen-driven pathways can promote allergic skin inflammation in experimental models.[10]

These superantigens induce massive activation of antigen-presenting cells and T lymphocytes by directly binding to MHC class II molecules and T-cell receptors, bypassing conventional antigen presentation, leading to excessive cytokine production and increased disease activity.[10] The presence of superantigens in infected AD lesions further supports their contribution to disease exacerbation.[9]

Superantigen-related immune activation has also been proposed as a mechanism that can reduce responsiveness to immunosuppressive therapy in inflammatory skin disease.[9,10]

Neural mechanisms of pruritus

Experimental studies have demonstrated that *S. aureus* can directly induce pruritus through interaction with peripheral nerve signaling. In particular, inhibition of protease-activated receptor-1 (PAR1) signaling reduces itch induced by *S. aureus*, supporting a neuroimmune itch pathway relevant to AD symptomatology.[11]

Antimicrobial defense, biofilm formation, and persistence

Rapid elimination of *S. aureus* from the skin depends in part on endogenous antimicrobial peptides; in atopic dermatitis, deficiencies in antimicrobial peptide responses are associated with increased susceptibility to skin infections and colonization.[12] In addition, a deficiency in protective antimicrobials produced by commensal skin bacteria has been demonstrated in AD, further supporting a dysbiosis-driven vulnerability to *S. aureus* overgrowth.[13]

Staphylococcus aureus persistence is also facilitated by biofilm formation. Staphylococcal biofilms have been demonstrated in atopic dermatitis and are associated with bacterial persistence and reduced susceptibility to antimicrobial interventions.[14]

Bacteriophages as a novel therapeutic strategy

Conventional systemic and topical antibiotics are frequently used in patients with atopic dermatitis during exacerbations and secondary infections; however, prolonged antibiotic use increases selective pressure on resistant strains and can disrupt the commensal skin microbiota.[15,16]

Recent work characterizing the human skin phageome has demonstrated differences between normal and inflamed skin, supporting the concept that alterations in the bacterial–phage ecosystem may be relevant to inflammatory skin conditions, including AD.[17] Bacteriophages—viruses that specifically infect bacteria—have therefore emerged as a promising alternative antimicrobial strategy.[15-18] Phages exhibit high specificity for target bacteria, bactericidal activity, and the capacity to act at the site of infection; phage-derived enzymes and related mechanisms may also contribute to activity against bacterial biofilms.[15,19]

Phage cocktails and personalized ("sur-mesure") approaches have been proposed to improve efficacy and address host-range limitations.[19,20] Key reviews summarize pharmacologic principles, accumulated evidence, and clinical implementation considerations for phage therapy. These properties position phage therapy as a strategic, microbiome-oriented approach for the management of atopic dermatitis.

CONCLUSIONS

The management of atopic dermatitis increasingly requires strategies that address not only inflammation but also microbial dysbiosis. *Staphylococcus aureus* plays a pivotal role in disease exacerbation and persistence, making it a critical therapeutic target. Bacteriophage therapy represents a novel, biologically rational approach that enables selective control of *S. aureus* while preserving the integrity of the skin microbiome. Although current clinical evidence remains limited, existing clinical frameworks and emerging skin phageome research support the continued development of phage-based interventions for inflammatory skin disease. Future research should focus on well-designed clinical trials, optimization of topical formulations, and integration of phage therapy into personalized treatment paradigms for atopic dermatitis.

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