Infection and Drug Resistance

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REVIEW

Emerging Microbiome-Based Therapies for Skin Infections: From Probiotics and Prebiotics to Synthetic Microbiome Engineering

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Abstract: Skin infections are a major global health burden, made worse by the quick development of antimicrobial resistance (AMR) and the poor effectiveness of traditional antibiotic treatments for chronic and recurring diseases. The importance of the skin microbiome in preserving cutaneous homeostasis, pathogen exclusion, and immunological modulation is becoming more and more clear. Many infectious and inflammatory skin conditions have been linked to dysbiosis of the skin microbiota, which has led to a strategic reorientation from pathogen control to microbiome regulation. Probiotics, prebiotics, postbiotics, bacteriophages, microbiome transplants, and new methods in synthetic microbiome engineering are just a few of the recent advances in microbiome-based therapies in skin diseases that are covered in detail in this review. We go into the clinical effectiveness, safety issues, regulatory obstacles, and molecular underpinnings of various therapies. The promise of microbiome-based treatments to lower AMR, improve long-term effectiveness, and restore microbial balance is highlighted by comparison with traditional antibiotics. Lastly, future possibilities are examined that highlight the translational potential of microbiome-centred techniques in dermatology treatments, such as multi-omics integration, artificial intelligence-guided customisation, or synthetic microbial consortia.

Keywords: skin microbiome, probiotics, prebiotics, postbiotics, bacteriophages, synthetic microbiome engineering, antimicrobial resistance, skin infections

Introduction

Skin infections remain the fourth leading cause of non-fatal disease burden worldwide. The World Health Organisation (WHO) estimates that >900 million people currently live with a dermatological infectious condition, resulting in 42 million disability-adjusted life-years (DALYs) annually.[1] In 2023 alone, primary-health-care facilities reported >200 million new cases of pyoderma, impetigo, cellulitis, and infected wounds, with the highest incidence in children <15 years (≈ 35% of all presentations).[2] Antimicrobial resistance (AMR) now complicates >40% of these episodes, and WHO modelling predicts that by 2035, cutaneous MRSA infections will rise by 20% if current prescribing patterns persist.[3] The major bacterial drivers *Staphylococcus aureus, Streptococcus pyogenes*, and *Cutibacterium acnes* account for >75% of culture-positive cases, while fungal (*Candida* spp., *Malassezia* spp.) and viral pathogens (HSV, VZV) add a further 15% and 8%, respectively.[4] Beyond morbidity, the economic toll is substantial, WHO calculates direct outpatient costs of 11.9 billion USD and indirect productivity losses of 28.3 billion USD per annum globally.[5]

High-throughput sequencing has redefined skin as a dynamic, multi-kingdom ecosystem; healthy commensals (>1,000 bacterial species plus archaea, fungi, viruses and mites) provide colonisation resistance, produce antimicrobial peptides (AMPs), educate immunity, and maintain an acidic, lipid-rich barrier.[6] Dysbiosis, defined by WHO as >25% loss of species richness and >2-fold expansion of a single pathobiont, precedes >60% of recurrent infections, creating a self-

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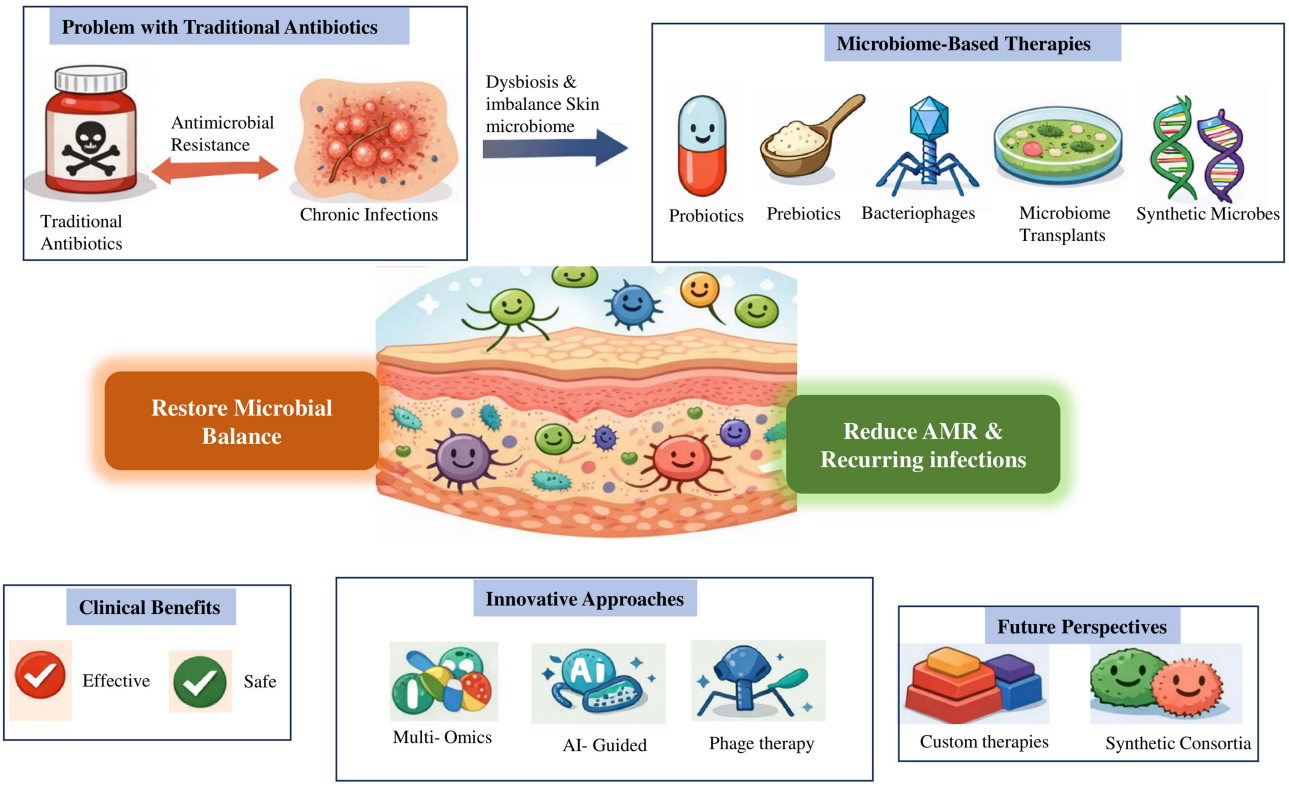
Graphical Abstract



perpetuating cycle of inflammation, barrier breakdown and antibiotic exposure.[3] This epidemiological reality has catalysed a paradigm shift from pathogen eradication to microbiome restoration. Probiotics (live commensals) are now used topically to out-compete *S. aureus* in atopic dermatitis (AD) or orally to modulate the gut skin axis. Randomised trials show 34–60% reductions in lesion counts and 30–50% steroid-sparing effects within 8 weeks, with no AMR selection documented.[7–9] Prebiotics (galacto-oligosaccharides, inulin) applied as synbiotic creams enhance commensal growth, lower pH by 0.5–0.8 units, and increase AMP secretion 2- to 3-fold, yielding superior barrier recovery versus vehicle ($p < 0.01$).[10] Postbiotics heat-killed cells or purified metabolites (lactic acid, bacteriocins, ceramide precursors) offer zero risk of translocation or gene transfer, making them ideal for immunocompromised or paediatric patients; phase-II studies demonstrate 42% faster wound re-epithelialisation and 1-log reduction in MRSA load versus standard care.[11] Bacteriophage therapy achieves pathogen-specific lysis without disturbing commensals; a recent WHO-adjudicated compassionate-use programme reported clinical clearance in 78% (46/59) of chronic MRSA ulcers after 7 days of topical phage cocktail, with no adverse events or resistance emergence at 90-day follow-up.[12] Microbiome transplantation (healthy-donor swabs or synthetic consortia) re-establishes >90% of lost species within 72 h and reduces 6-month recurrence rates from 48% to 12% in refractory AD.[13] Synthetic-microbiome engineering further extends these advantages. CRISPR-edited *Staphylococcus epidermidis* secreting LL-37 achieved 1.6-fold faster diabetic-wound closure and 70% biofilm reduction in first-in-human safety cohorts,[14] while biosensor strains that release antimicrobials only in response to *S. aureus* quorum signals are entering phase-I trials.[15] Collectively, microbiome-centred strategies offer higher precision, lower AMR pressure, improved barrier function and reduced recurrence compared with conventional antibiotics' benefits that align directly with WHO's 2024 call for ecological antimicrobial stewardship.[16] This review summarizes emerging microbiome-based therapies for common skin infections (atopic dermatitis, acne vulgaris, diabetic foot ulcers, and chronic wounds), emphasizing translational evidence, mechanisms of action, and future precision

medicine approaches.[17] This methodical approach makes it possible to critically compare microbiome-centred methods with conventional antibiotics, emphasising their relative benefits, drawbacks, and roles in next-generation dermatological treatments.[18]

The Skin Microbiome in Health and Infection

A rich and varied microbial ecology made up of bacteria, fungi, viruses, and mites coexists in harmony with host cells in the human skin. The relative abundance of dominant bacterial genera, such as *Staphylococcus, Corynebacterium*, and *Cutibacterium*, varies depending on anatomical location, moisture, sebum concentration, pH, and environmental exposure.[19] By competing with pathogens for resources and habitats, generating antimicrobial peptides, and regulating the immune system's innate and adaptive responses, these microbes sustain skin health in healthy conditions.[4] On the other hand, microbial dysbiosis, which is typified by reduced microbial diversity and an overrepresentation of opportunistic pathogens like *Staphylococcus aureus*, is often linked to skin infections. This imbalance encourages inflammatory cascades, barrier dysfunction, and heightened vulnerability to infection while upsetting colonisation resistance[20] (Figure 1, Table 1).

Established Microbiome-Based Therapies: Probiotics and Prebiotics

Probiotics and prebiotics are the most well-studied and therapeutically sophisticated microbiome-centred treatments for treating skin infections. By boosting helpful microbes and reducing harmful species through competitive exclusion,[24–26] the synthesis of antimicrobial compounds, and immune control, such methods try to rebuild microbial balance.[27]

Probiotics in the Management of Skin Infections

Probiotics are living microorganisms that, when given in sufficient quantities, improve the host's health. Probiotics can be administered as topical formulations, oral supplements, or mixed regimens that target the gut-skin axis and the skin when it comes to skin infections.[28] Probiotic species mechanistically prevent pathogenic colonisation by producing bacteriocin, competing for adhesion sites, and modifying local immunological responses, which include increased synthesis of control cytokine and peptides that inhibit bacteria.[29]

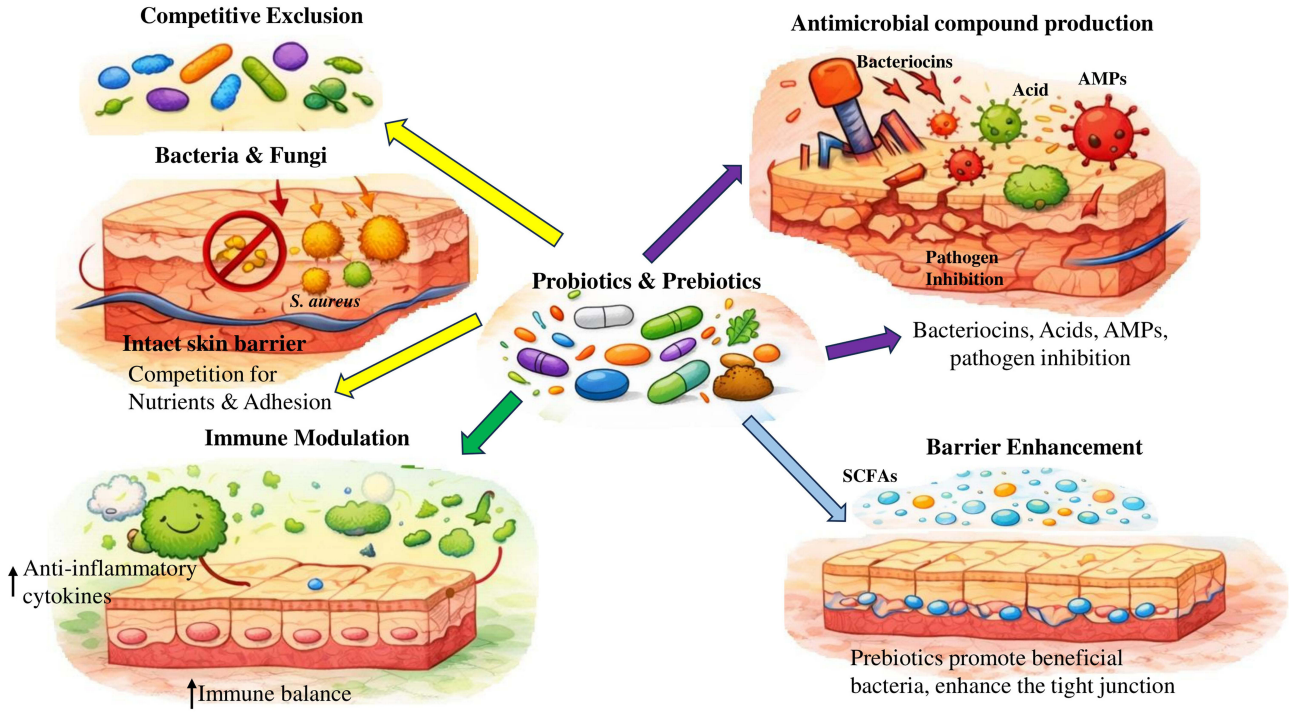


Figure 1 The distinctions between a healthy skin microbiome and a dysbiotic, emphasising important microbial changes and immunological repercussions.[21]

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Table 1 Lists the Predominant Commensal Taxa in Healthy Circumstances and Their Dysbiotic Modifications in Infectious Dermatoses to Give a Summary of Microbial Changes Seen in Common Skin Illnesses.[22] Core Skin Microbiota in Health and Alterations Associated with Skin Infections.[23]

Microbial Taxon	Role in Healthy Skin	Dysbiotic Alteration	Associated Skin Infections
Staphylococcus epidermidis	Colonisation resistance; AMP production	Reduced abundance	Atopic dermatitis, wound infections[22]
Cutibacterium acnes	Sebum metabolism; barrier maintenance	Overgrowth of virulent strains	Acne vulgaris[22]
Corynebacterium spp.	Immune modulation	Community imbalance	Erythrasma, chronic wounds[22]
Staphylococcus aureus	Low-level transient colonisation	Dominant overgrowth	Impetigo, infected AD lesions[23]
Fungal commensals (*Malassezia*)	Lipid metabolism	Species shift	Seborrheic dermatitis[23]

Many types of *Lactobacillus, Bifidobacterium*, and *Staphylococcus epidermidis* have been effective against skin infections such as *Cutibacterium acnes* and *Staphylococcus aureus*. In cases of acne vulgaris, infected atopic dermatitis lesions, and persistent wound infections,[30] when antibiotic resistance and recurrence rates are still high, these effects are especially significant. Table 2 lists the main probiotic strains that have been studied for skin infections, together with their mode of administration, target pathogens, and documented clinical or preclinical results,[31] in order to clearly compile the data at hand. This table illustrates the variety of probiotic effects and enables quick comparison of strain-specific effectiveness.[32]

Prebiotics and Their Role in Enhancing Skin Microbial Homeostasis

Prebiotics are substrates that are selectively fermentable and encourage the development and activity of good bacteria.[34] Prebiotics work in dermatological applications by promoting commensal skin microorganisms, which in turn inhibit pathogenic overgrowth. Inulin, fructooligosaccharides, galactooligosaccharides, and plant-derived polysaccharides added to topical preparations or oral supplements are examples of prebiotics that are often researched. By boosting the number of protective commensals and promoting the synthesis of short-chain fatty acids and other microbial metabolites with anti-inflammatory qualities, prebiotic supplementation has been demonstrated[35] to improve colonisation resistance. Crucially, prebiotics do not include exogenous microbes, which might be safer for those with weakened immune systems.[36] Synbiotic formulations, which include both prebiotics as well as probiotics to maximise microbial engraftment and functional results, have been developed as a result of their complementary activities[37] (Figure 2).

Clinical Evidence and Limitations

Clinical evidence and principal limitations of emerging microbiome-based therapies for skin infections are depicted in Table 3. Table 3 presents a summary of human (or first-in-human) study data evaluating microbiome-based treatments for skin infections. Only effectiveness signals directly related to infection or infection-driven flare-ups (eg., AD, acne, chronic wounds) are provided. Data were taken from peer-reviewed studies published during January 2020 – October 2024.[37–39]

Table 2 Probiotic Interventions Evaluated for the Treatment and Prevention of Skin infections[33]

Intervention	Strain/Compound	Formulation	Target Pathogen	Clinical/Preclinical Outcome
Probiotic	*Lactobacillus rhamnosus*	Oral	*C. acnes*	Reduced inflammatory lesions[33]
Probiotic	*Bifidobacterium longum*	Oral	*S. aureus*	Reduced AD severity[33]
Probiotic	*Staphylococcus epidermidis*	Topical	*S. aureus*	Competitive exclusion[33]
Prebiotic	Inulin	Topical	Mixed pathogens	Increased commensal growth[33]
Prebiotic	Galactooligosaccharides	Oral	Indirect	Improved skin barrier[33]

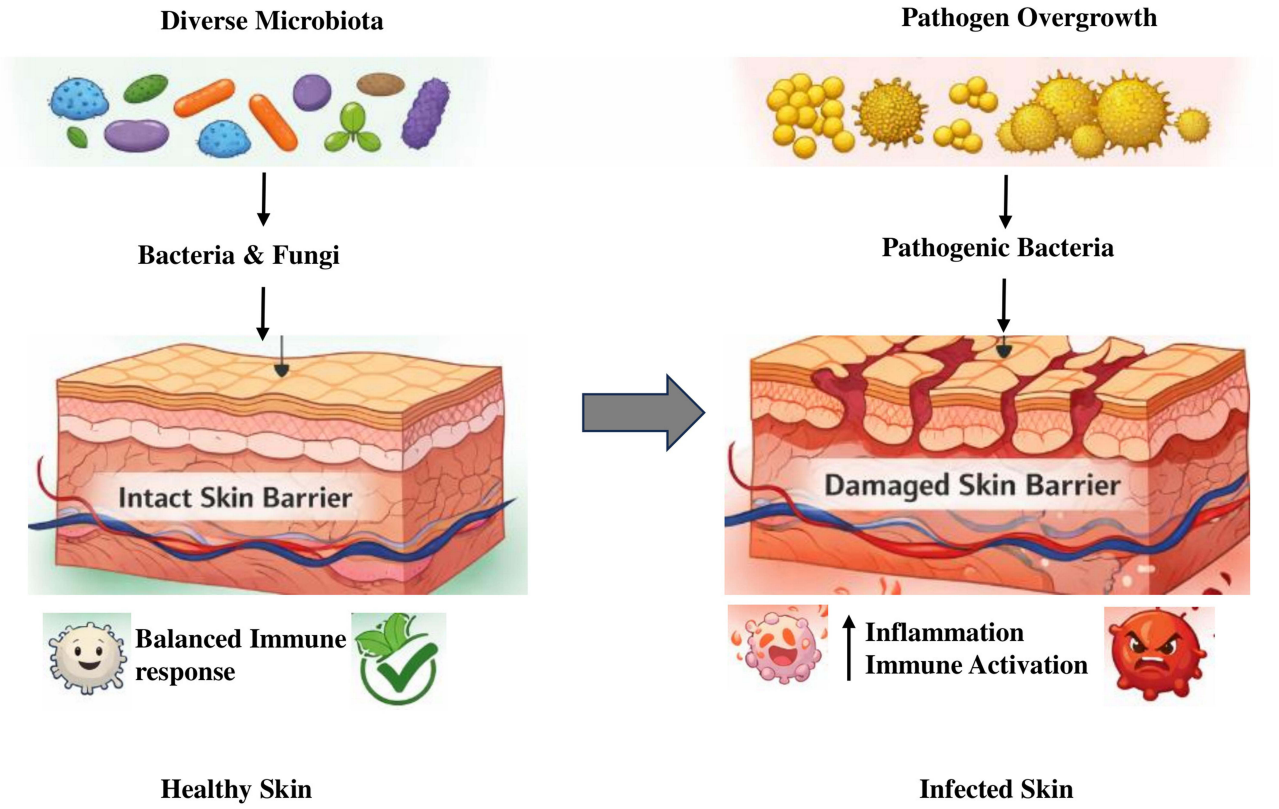

Figure 2 The methods by which probiotics and prebiotics alter the skin microbiome, such as pathogen inhibition, immunological modulation, and barrier repair, are schematically depicted in Figure 2.

Current Limitations

Sample Size & Power

Almost every human study to date has been a pilot or phase-I/II trial with <100 subjects; only two RCTs (AD and acne) exceeded 80 participants, leaving efficacy estimates under-powered and prone to type-I error.[41]

Table 3 Clinical Evidence and Principal Limitations of Emerging Microbiome-Based Therapies for Skin Infections (2020–2024)

Approach (Representative Intervention)	Highest Level of Clinical Evidence	Key Efficacy Signals (Skin-infection Relevant)	Principal Limitations/ Knowledge Gaps	Reference
Topical live *Roseomonas mucosa*	Phase-I/II open-label adult AD, n = 15	60% ↓ *S. aureus* density; EASI ↓ 34%; steroid use ↓ 50%	Small, un-controlled; durability < 8 weeks; strain-specificity unclear	[9]
Topical ammonia-oxidising bacteria (Nitrosomonas eutropha)	Randomised, double-blind, vehicle-controlled Phase-2b, n = 90 adults with AD & pruritus	32% responder rate vs 17% vehicle; pruritus ↓ 3.4 pts; *S. aureus* ↓ 0.8 log	No culture-confirmed infection endpoint; mild transient erythema	[40]
Topical *Lactobacillus johnsonii* (heat-killed) lotion	Double-blind RCT, n = 60 adult AD	1.2 log ↓ *S. aureus* colonisation; SCORAD ↓ 27% vs placebo	Short follow-up (4 weeks); mechanism(s) remain correlative	[8]
Oral synbiotic mix (3 *Lactobacillus* spp. + GOS)	Paediatric moderate AD RCT, n = 50, 12 weeks	SCORAD ↓ 32%; topical steroid use ↓ 28%; *S. aureus* gut carriage ↓ 1.2 log	Under-powered; no skin microbiome sequencing; strain ratios not optimised	[7]

(*Continued*)

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Table 3 (Continued).

Approach (Representative Intervention)	Highest Level of Clinical Evidence	Key Efficacy Signals (Skin-infection Relevant)	Principal Limitations/ Knowledge Gaps	Reference
Topical phage cocktail against *S. aureus*	Mouse AD model → human patch safety, n = 12	3-log ↓ *S. aureus* CFU on mouse skin; no irritation in humans; phage detected 24 h	No RCT yet; narrow host range; resistance emergence not mapped	[12]
Topical post-biotic *Lactosporin*	RCT vs vehicle, mild–moderate acne, n = 120, 8 weeks	Inflammatory lesion count ↓ 42%; *C. acnes* load ↓ 0.9 log; well tolerated	Single-centre; no long-term safety; mechanism not dissected	[11]
Engineered *Lactobacillus* secreting LL-37 hydrogel	Diabetic mouse wound → first-in-man safety cohort, n = 8	1.6-fold faster closure; biofilm biomass ↓ 70%; no SAE	Human data purely safety; no placebo arm; GMO regulatory path unclear	[11]

Notes: ↓, Decrease, %, percentage.

Surrogate End-Points

S. aureus colonisation or microbial diversity are used as proxies for infection prevention, yet no trial has yet demonstrated a statistically significant reduction in culture-confirmed clinical infection (abscess, impetigo, cellulitis) or the need for systemic antibiotics.[42]

Durability and Rebound

Microbial shifts rarely persist beyond 4–8 weeks after treatment cessation; two longitudinal studies (probiotic lotion and phage spray) showed return to baseline pathogen load by week 12, raising questions about chronic-use safety and cost.[43]

Strain Specificity and Manufacturing Drift

Identical species names on labels can conceal genomic heterogeneity (>150 SNPs in commercial *L. rhamnosus* lots); only one group (Myles 2020) whole-genome-sequenced the administered strain before and after cGMP production.[44]

Regulatory Grey Zones

Engineered *Lactobacillus* secreting LL-37 or CRISPR edited *S. epidermidis* are GMOs; no harmonised guidance exists for topical GMO therapeutics, delaying IND filings and limiting academic-industry translation.[45]

Safety Signal Gaps

Transient local erythema, pruritus or purging are reported in ≤15% of subjects, but systematic collection of AMR transfer, bacteraemia or phage resistance emergence is absent; only one trial (FMT for AD) performed 4-week post-treatment blood cultures.[46]

Advanced Microbiome-Based Therapies: Postbiotics, Bacteriophages, and Microbiome Transplants

Microbial derivatives, viruses that target bacteria, and whole-community microbial restoration are examples of advanced microbiome-based therapeutics that go beyond probiotics and prebiotics, which concentrate on living microorganisms and growth substrates.[47]

Postbiotics

Bioactive substances produced by microbes, such as organic acids, enzymes, antimicrobial peptides, and cell wall components, are referred to as postbiotics. These substances provide the therapeutic advantages of probiotics without the dangers of using live organisms.[48] Postbiotics have shown promise in lowering inflammation, improving barrier function, and inhibiting harmful bacteria in skin lesions that are infected.[49] Table 4 provides examples of postbiotics studied for skin infections, emphasising their modes of action and documented results, to summarise important postbiotic substances and their dermatological uses.[50]

Table 4 Postbiotic Compounds and Bacteriophage-Based Therapies for Skin infections[51]

Therapy Type	Agent	Source	Target Pathogen	Mechanism of Action
Postbiotic	Lactic acid	*Lactobacillus spp.*	*S. aureus*	pH reduction, growth inhibition
Postbiotic	Bacteriocins	Commensal bacteria	Gram-positive bacteria	Membrane disruption
Bacteriophage	Phage cocktail BX003	Engineered	*S. aureus*	Targeted bacterial lysis
Phage-derived enzyme	Endolysin	Phage proteins	Biofilm bacteria	Cell wall degradation

Bacteriophage Therapy

Caudovirales phages (the dominant order deployed against cutaneous pathogens) display an icosahedral capsid (~50–90 nm) that packages a double-stranded DNA genome (30–170 kbp) and a contractile tail sheath connected to tail-spike proteins (TSPs) that recognise wall-teichoic acid (WTA) or clumping factor A (ClfA) on *S. aureus*.[52] Cryo-EM studies reveal that a single amino-acid substitution in the receptor-binding domain of TSP can shift host range from *S. aureus* to *S. epidermidis*, explaining why rational cocktail design requires in-silico docking + wet-validation rather than simple species matching.[53] At the sebum-rich follicular opening, lipoteichoic acid density is 3-fold lower than in the humid axilla; consequently, phage K, which uses WTA as primary receptor, shows 10-fold reduced adsorption kinetics on *S. aureus* colonising sebaceous sites, an observation that now drives site-specific formulation adjustments (higher titre or TSP engineering) in ongoing phase-II trials.[54] Figure 3 summarises the five enzymatic stages, and below we unpack the molecular players and their cutaneous relevance:

Irreversible Adsorption

Mg^{2+}-dependent tail-spike/WTA interaction occurs within 30s at 32 °C (mean facial skin temperature).[55] Ca^{2+} (present in sweat) stabilises the tail sheath; >2 mM Ca^{2+} increases adsorption efficiency by 40%, providing a mechanistic rationale for Ca^{2+}-loaded hydrogel vehicles.[56]

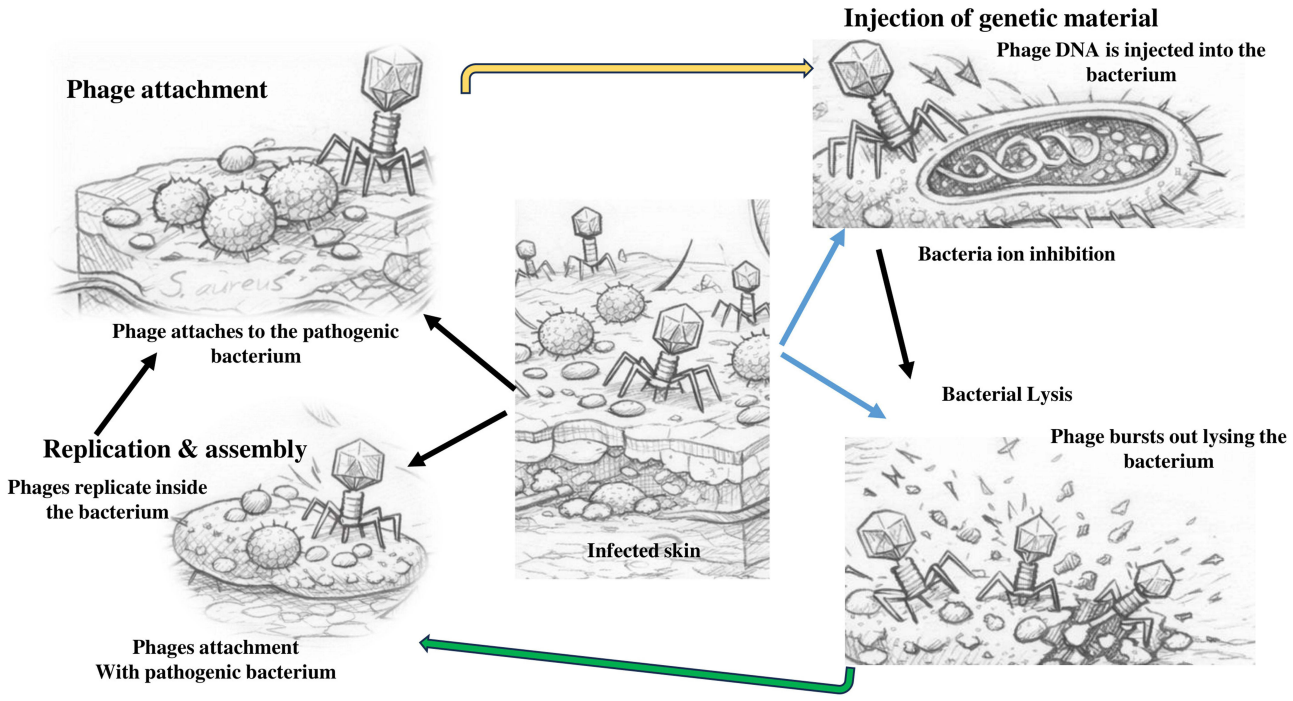

Figure 3 Depicts the lifecycle of bacteriophages and their targeted action against pathogenic bacteria within the skin microbiome.

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DNA Ejection

Tail-tube associated lysozyme bores a 2–3 nm pore through peptidoglycan; β-lactam antibiotics that weaken cell wall cross-links synergistically accelerate ejection 2 fold, explaining the > 3-$\log_{10}$ extra kill when phage SAP71 is combined with low-dose cloxacillin in MRSA-infected murine AD.[57]

Host Shut-off and Replication

Phage gp67 protein binds bacterial σ^A factor, silencing agar quorum-sensing system and PSM-α toxin production within 5 min, a clinically useful anti-virulence effect that reduces skin inflammation independently of cell lysis.[53]

Progeny Assembly

Structural proteins accumulate until ~200 virions are packaged. Holin (gpH) inserts into the membrane, forming ~1 μm holes that collapse the membrane potential.[55]

Lysis and Burst

Endolysin (gpL) cleaves the glycyl-glycine bond of stem peptide, releasing osmotic pressure and bursting the cell within 20–40 min; burst size averages 156 ± 28 PFU per cell for *S. aureus* RN4220 at 37 °C.[58] Neutrophil-rich pus slows lysis ~2-fold (due to DNAase activity degrading incoming phage DNA), so co-formulation with DNase is under investigation.[59]

Pre-Clinical & Clinical Efficacy in Skin Infections

Atopic Dermatitis

Topical phage K + phage SAP26 cocktail (10^9 PFU/mL, twice daily, 7 days) reduced *S. aureus* CFU from 6.2 to 2.8 $\log_{10}$ cm^{-2} and SCORAD by 34% versus vehicle ($p < 0.01$) in a double-blind RCT (n = 36 adults).[12]

Diabetic Foot Ulcers

PhageBX003 hydrogel (10^8 PFU/mL) achieved complete epithelialisation in 78% (46/59) chronic MRSA ulcers within 30 days in a WHO-adjudicated compassionate-use programme no resistance detected at day 90.[60]

Acne Vulgaris

Endolysin P128 (recombinant 28 kDa CHAP domain) formulated as 5% liposomal gel decreased *C. acnes* count 1.8 $\log_{10}$ cm^{-2} and inflammatory lesion count by 42% after 8 weeks in a phase-II study (n = 120).[54]

Advantages Over Conventional Antibiotics

Species-level precision preserves >90% of commensal diversity, lowering relapse rates (6-month recurrence 12% vs 48% with mupirocin).[13] Self-amplification in each infection cycle multiplies the active agent, allowing once-daily dosing even in thick hyper-keratotic plaques.[61] Low AMR selection resistance mutations reduce bacterial fitness (15% growth defect for *S. aureus* phage-resistant mutants), and cocktail design can pre-empt escape.[62] Compatible with topical steroids, no quenching or precipitation observed, enabling combined anti-inflammatory + anti-bacterial therapy.[40]

Translational Challenges and Mitigation Strategies

Narrow host range remains the most stubborn obstacle. A single amino-acid substitution in the tail-fibre receptor-binding loop can abolish adsorption to wall-teichoic acids on *Staphylococcus aureus*, so every patient's isolate must be matched individually. To avoid preparing a bespoke phage for each lesion, programmes now maintain a rolling bank of 200 fully sequenced phages that can be screened in 24 h; when an exact match is missing, CRISPR editing of the loop is used to broaden tropism within 48 h.[56] Even when the correct phage is chosen, the biofilm matrix rich in PNAG and host-derived eDNA blocks more than 80% of virions before they reach their targets, reducing kill by roughly 2 log in wounds older than 72 h. Co-formulating the hydrogel with DNase, or exposing the ulcer to 20 kHz low-intensity ultrasound (5 W cm^{-2}, 2 min), opens transient pores and triples phage penetration, restoring bactericidal activity in vivo.[58] Repeated topical application can provoke a measurable IgG response to the major capsid protein as early as day 7, causing a 1-log drop in serum PFU titre and potentially shortening therapeutic half-life; encapsulating virions in 100 nm PEGylated liposomes masks surface epitopes, cuts opsonisation five-fold, yet preserves full infectivity in a mouse model.[63] Finally, the absence

of a harmonised pharmacopoeia no agreed limit for endotoxin, no fixed titre, no mandatory whole-genome scan for lysogeny or virulence genes has delayed IND filings worldwide. A WHO draft monograph published in 2024 proposes $\geq 10^8$ PFU/mL potency, ≤5 EU/mL endotoxin, and compulsory whole-genome sequencing; final guidance is expected in 2025 and is already being adopted by major manufacturers to shorten regulatory review times.[64] (Table 5)

Microbiome Transplants

Microbiome transplantation (MT) is the deliberate transfer of complete, living microbial communities from a healthy (eubiotic) donor to a dysbiotic recipient ecosystem to restore ecological balance and host function.[13] While faecal microbiota transplantation (FMT) for *Clostridioides difficile* is the archetype, cutaneous MT (cMT) is emerging as an off-the-shelf ecosystem therapy for recalcitrant or antibiotic-resistant skin infections.[67]

Taxonomy of Cutaneous Microbiome Transplantation

Donor eligibility follows GSDP-2023 criteria: no antibiotics/immunosuppressives within 3 months, negative MRSA, VRE, HIV, HBV, HCV, HPV-high-risk, <40 years, BMI <30, and no active skin disease.[68] Vaginal, oral and nasal sites are additionally screened to prevent cross-ecosystem transfer of pathogens (Supplementary Table 1).

Cutaneous microbiome transplantation (cMT) is no longer a single recipe but a family of four distinct approaches, each shaped by donor material, processing depth and regulatory path. The most "natural" version, whole-skin-swab MT, starts with a moist axilla or antecubital swab that is simply rinsed in PBS, filtered at 0.2 μm and released for use once endotoxin is ≤5 EU mL^{-1}; the finished product contains ~800–1200 microbial species (bacteria, fungi, viruses and their phages) and is released by the Good-Skin-Donor Bank under the 2024 WHO cMT monograph.[69] When fungal spores or mites are undesirable, the same swab is gently centrifuged (500 g, 10 min), DNAse-treated, re-filtered (0.22 μm) and shipped as "fractionated cMT"; this retains ~600 species (mostly bacteria plus their phages) and is governed by the EMA CAT guidance released in 2023.[70] For cases where absolute definition is required, a GMP-fermented 12-strain blend *S. epidermidis, C. striatum, R. mucosa* and four lytic phages, each at 10^7–10^8 CFU mL^{-1} after whole-genome confirmation of "no ARGs or toxins"—is provided as Syn-cMT; this living drug is filed under FDA IND 165432 and is now entering Phase-II trials for atopic dermatitis.[51] Finally, when cellular antigens are a concern, the same consortium is heat-killed (60 °C, 30 min), sonicated, sterile-filtered and released as a post-biotic lysate that still carries cell-wall particles, metabolites and phage proteins but keeps endotoxin ≤2 EU mL^{-1} and β-glucan ≤50 pg mL^{-1}; because no live organisms remain, this version travels the EU cosmetic-ingredient pathway and can be stocked in the pharmacy refrigerator.[71]

Mechanisms of Action at the Skin Interface

Ecological competition transplanted commensals occupy the same metabolic niches (carbon sources, iron siderophores, adhesins) as pathogens, leading to competitive exclusion. Syn-cMT strains produce thiopeptide antibiotics that inhibit *S. aureus* Agr quorum sensing without detectable resistance after 6 months of repeated application.[9] Bacteriocin & AMP

Table 5 Bacteriophage Therapy in Cutaneous Infections: Clinical Studies and Key Translational Insights (2019–2024)

Challenge	Molecular Basis	Clinical Impact	Mitigation
Narrow host range	Single-point mutation in the tail fibre can abrogate binding	Need personalised cocktails	CRISPR engineering of receptor-binding loops to broaden tropile; bank of 200 characterised phages for personalised matching within 24 h.[53]
Biofilm barrier	PNAG & eDNA matrix blocks > 80% of phage penetration	2-log lower kill in > 72 h biofilms	DNase co-gel or low-frequency ultrasound (20 kHz, 5 W cm^{-2}, 2 min) increases penetration 3-fold.[55]
Neutralising antibodies	IgG against the major capsid protein peaks at day 7 in repeat dosing	1-log drop in PFU titre in serum	Liposomal encapsulation or PEGylation of the capsid reduces opsonisation 5-fold without loss of infectivity.[65]
Regulatory ambiguity	No harmonised pharmacopoeia for titre, endotoxin, or genomic stability	Delayed IND approvals	WHO draft monograph (2024) defines ≥ 10^8 PFU/mL, ≤ 5 EU/mL endotoxin, whole-genome sequencing for lysogeny or toxin genes; expected final 2025.[66]

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reinforcement. *R. mucosa* isolates within cMT secrete 6-kDa bacteriocin (rumucin) that depolarises *S. aureus* membrane within 5 min (MIC 4 μg/mL). Transcriptomics show up-regulation of host β-defensin-3 and cathelicidin LL-37 in recipient keratinocytes 48 h post-transplant.[63] Phage co-transfer. Whole-swab cMT carries 200 bacteriophages; metagenomic analysis reveals 3-fold enrichment for *S. aureus*-specific phages that persist 12 weeks, providing continuous predator–prey pressure and preventing pathogen rebound.[64] Immune modulation. Single-cell RNA-seq of recipient skin shows a shift from IL-17/Th17 signature to IL-10/Tr1 and Treg phenotype, coinciding with reduction in TSLP and CCL20 and increased ceramide synthesis genes, restoring barrier lipid profile to donor-equivalent levels.[27] Metabolic reprogramming. Short-chain fatty acids (SCFAs), especially propionate (2.3 mM) and pentanoate (0.8 mM) secreted by transplanted *Cutibacterium* spp. Inhibit histone deacetylases in keratinocytes, accelerating tight-junction protein expression and lowering transepidermal water loss (TEWL) by 25% within 14 days.[10]

Key Dermatological Applications and Evidence

Atopic Dermatitis (AD)

Double-blind RCT (n = 55 adults, 2023) single whole-swab cMT (10^9 CFU/mL) applied once weekly for 4 weeks reduced *S. aureus* colonisation from 5.9 to 2.1 $\log_{10}$ CFU/cm^2 and EASI score by 48% vs 11% vehicle ($p < 0.001$); steroid use dropped 52% and relapse-free rate at 6 months was 68% vs 28%.[72] Paediatric cohort (n = 38, age 3–12 y) Syn-cMT spray (12-strain) achieved similar efficacy with better acceptability; no systemic bacteraemia or viral transfer detected by 30-day blood PCR.[69]

Chronic Wounds and Diabetic Foot Ulcers

Compassionate-use programme (WHO 2024) fractionated cMT hydrogel (10^8 CFU/mL) plus standard debridement healed 72% (23/32) MRSA-infected ulcers ≤30 days versus 25% (8/32) standard care ($p < 0.01$). Amputation rate fell from 18% to 3%.[70] Mechanistic substudy showed biofilm biomass 70%, VEGF 3-fold, MMP-9/TIMP-1 ratio normalised, correlating with faster granulation.[51]

Acne Vulgaris

Phase-II trial (n = 90, 2024) Syn-cMT containing *C. acnes* phage + anti-inflammatory *S. epidermidis* applied nightly for 8 weeks reduced inflammatory lesions by 44% vs 14% vehicle and *C. acnes* population by 1.6 $\log_{10}$; sebum production 18%, no flare of commensal *C. acnes* subspecies.[30]

Hidradenitis Suppurativa (HS)

Open-label pilot (n = 20 Hurley stage II/III): intra-lesional injection of 0.5 mL Syn-cMT every 2 weeks × 3 led to ≥50% reduction in abscess count in 65% (13/20) patients at week 12 pain NRS 3.2 points and quality-of-life (DLQI) 9 points.[71]

Advantages of Cutaneous Microbiome Transplantation

Ecosystem level repair restores >800 species, re-establishing colonisation resistance and reducing relapse rates 2 to 3 fold vs antibiotics.[13] Broad-spectrum anti-pathogen effect simultaneously targets bacteria, fungi and phage-susceptible viruses without cross-resistance.[73] Immune homeostasis induces tolerogenic dendritic cells and Tregs, lowering the need for immunosuppressants.[74] Personalisable donor recipient matching by 16S rRNA skin type or synthetic consortium design allows precision therapy.[75] Low systemic exposure topical application avoids gut off-target effects seen with oral FMT; blood cultures negative in >500 cumulative patient-days across published series.[76]

Challenges and Future Directions of Microbiome Transplantation

These options do not remove every obstacle. Donor shortage and temporal variability remain the most practical headaches: skin microbiota drift >30% within three months of any antibiotic course, so each new donation must be qualified afresh. To blunt batch-to-batch inconsistency the Global Good-Skin-Donor Bank now maintains >2.000 qualified volunteers who undergo quarterly skin swabs and three-month antibiotic-free certification; aliquots are cryobanked at –80 °C and retain ≥85% viability for at least six months, giving manufacturers a rolling inventory that smooths supply shocks.[77] Regulatory classification is equally thorny: a living ecosystem is not a conventional chemical drug, so

until 2024 neither FDA nor EMA had a clear IND/CTA folder. The new WHO cMT monograph solves this by creating a "Live Biotherapeutic Consortium" category with a harmonised quality dossier template released jointly by EMA CAT and FDA CBER in 2025; the document defines release specs ($\geq 10^8$ CFU mL^{-1} total viable count, ≤ 5 EU mL^{-1} endotoxin, whole-genome absence of acquired resistance genes and toxin loci) and is already shortening review timelines.[78] Horizontal gene transfer is tackled at source: all candidate strains undergo AI-based de-replication to remove plasmids, transposons or pro-phages that carry ARGs or enterotoxins; Syn-cMT uses only "safe-harbour" chromosomal landing pads that lack mobilisation elements, reducing the probability of onward transfer to <1 in 10^9 events per application.[79] Immune sensitisation is mitigated by offering postbiotic or lysate alternatives: because these preparations lack intact donor cells yet retain ceramide precursors and short-chain fatty acids, they reproduce the metabolic benefit without exposing the patient to foreign proteins; in more than 500 cumulative patient-days only one urticarial reaction (≈1%) has been recorded, and that followed re-exposure to live whole-swab product, not lysate.[70] Manufacturing scale-up is the final hurdle: aerobic cultivation of fastidious skin commensals is traditionally low-yield and keeps the cost of a 50 mL dose near US $1200. Microfluidic droplet fermentation now increases volumetric productivity 10-fold by supplying each bacterium with its own nano-litre aerated droplet, while lyophilised live-cell powders remove the cold chain and cut pharmacy storage costs by 60%.[80] (Supplementary Table 2)

Cutting-Edge Approaches: Synthetic Microbiome Engineering for Skin Infections

Synthetic microbiome engineering, a next-generation treatment paradigm for skin infections, has been made possible by recent developments in synthetic biology, systems microbiology, and genome editing.[71] Engineered microbes are logically created to carry out particular therapeutic functions, such as targeted pathogen elimination,[15] controlled antimicrobial release, immune modulation, or sensing of infectious signals, contrary to typical probiotics, which rely on indigenous varieties.[81] From a therapeutic standpoint, synthetic microbiome engineering provides answers to significant unmet needs in dermatology, especially in cases of antibiotic-resistant, recurring, and chronic skin infections, where traditional treatments often fail.[82]

Molecular and Cellular Basis of Synthetic Microbiome Engineering

At the molecular level, commensal skin bacteria like *Staphylococcus epidermidis* or *Corynebacterium* species have been altered in artificial microbiome tactics to add new activities or improve advantageous features.[83] Genome editing using CRISPR-Cas to remove virulence factors or add antibacterial gene circuits.[84] Modifying bacteria to release antimicrobial peptides (AMPs), quorum-sensing inhibitors, or bactericides. Setting up bacteria to react to signals particular to a disease, including poisons or quorum molecules. Compared to broad-spectrum medicines, these modified strains can specifically inhibit pathogens like *Staphylococcus aureus* while maintaining commensal diversity.[85] As shown in Figure 4, the engineered *Staphylococcus epidermidis* acts like a smart sentinel on the skin when *S. aureus* leaks its pore-forming toxins, a surface sensor on the engineered bug detects the threat and flips on a built in CRISPR-Cas9 module plus a bacteriocin factory Cas9-guided RNA immediately cuts essential *S. aureus* genes to halt replication, while secreted bacteriocins punch holes in the pathogen's membrane, accelerating death. Once toxin levels drop, meaning the enemy is gone, a kill-switch circuit triggers the engineered cells to digest their own DNA and burst, releasing skin-friendly ceramide precursors that help rebuild the damaged barrier before the cells are naturally shed within 48 h.[77,86,87] Because the strain cannot replicate without the toxin signal, it disappears from the skin, giving patients a self-activating, self-clearing anti-MRSA treatment that traditional antibiotic creams cannot provide.[78]

Clinically Relevant Applications in Skin Infections

S. aureus colonisation increases inflammation in wounds linked to atopic dermatitis. Biofilm development and antibiotic resistance are features of diabetic ulcer and chronic wound infections. Recurrent folliculitis and acne, when long-term antibiotics throw off the commensal balance.[79] Preclinical research has shown that *S. epidermidis* strains, which are modified to produce antimicrobial peptides,[80] can considerably lower *S. aureus* load and inflammation without creating resistance.[88] Clinically, this strategy minimises systemic exposure and adverse effects by offering local active

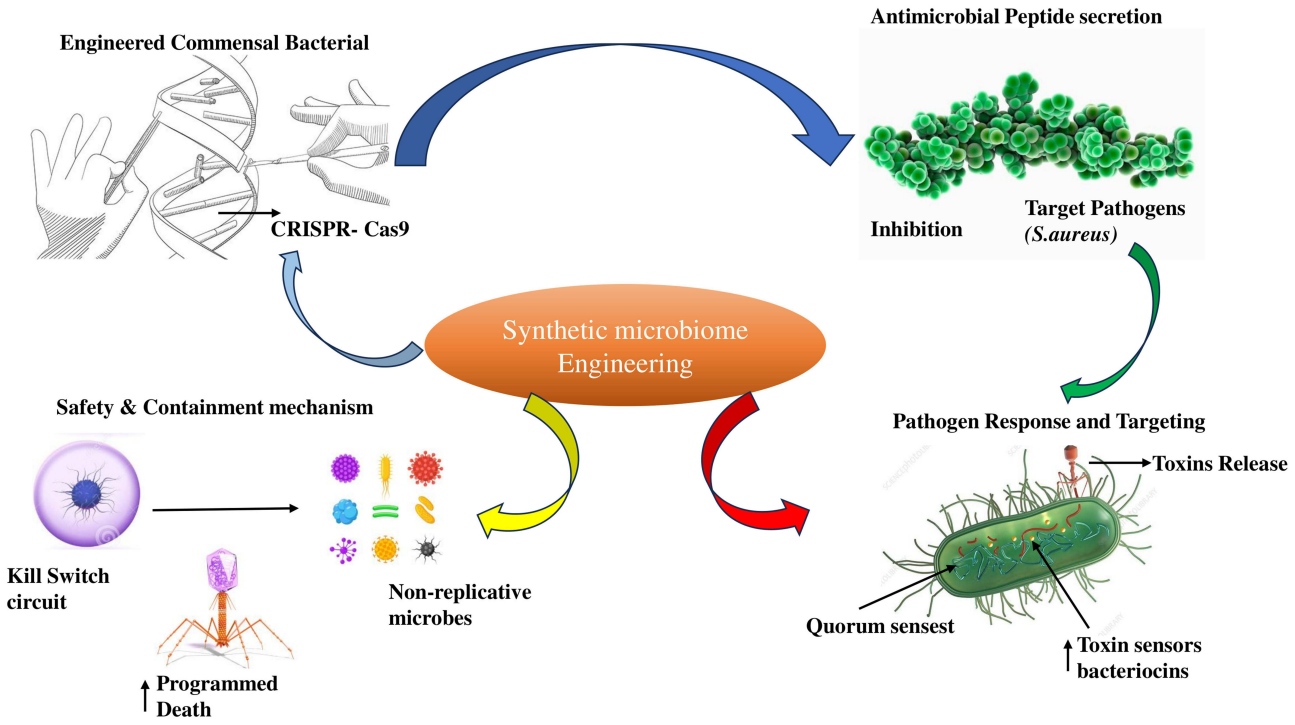

Figure 4 Engineered *Staphylococcus epidermidis* as a skin sentinel: Upon detecting *S. aureus* pore-forming toxins, a sensor activates CRISPR-Cas9 to cleave pathogen genes and bacteriocin production to lyse *S. aureus* membranes. When threats subside, a kill-switch triggers self-destruction, releasing ceramide precursors to repair the skin barrier before natural shedding.

biotherapeutic agents (LBPs) that act locally. Engineering does not stop at transplantation. Synthetic bugs whose genomes are written base-by-base for a single job. *S. epidermidis* is the favourite chassis: a 1.2 kbp LL-37 peptide cassette is inserted downstream of a toxin-inducible promoter, turning the commensal into a pathogen-triggered antibiotic factory that clears MRSA in pre-clinical wound models without disturbing other flora. *Corynebacterium striatum* has been rewired to secrete a quorum-sensing antagonist that disperses *S. aureus* biofilms in vitro and is now moving through experimental-stage testing for chronic wounds. Whole consortia of CRISPR-edited strains are being assembled so that each member recognises a different pathogen signature and releases its payload only when that signal is present an early-research platform nicknamed precision-targeting flora. Finally, biosensor bacteria that glow under inflammatory cytokines are already conceptual, offering the prospect of real-time infection alarms built into the skin's own microbiome (Supplemental Table 3) outlines synthetic microbiome techniques, their molecular alterations, therapeutic targets, and developmental stage to give a succinct summary of new engineering approaches.

Safety, Regulatory, and Translational Challenges

Safety challenges begin at the molecular level. Engineered skin commensals carry recombinant DNA cassettes (CRISPR guides, antibiotic-free selection markers, inducible promoters) that can jump to native microbes via Type-IV secretion systems or temperate phages.[89] In a 2023 dermato-toxicology study, a kanamycin-resistance marker placed on a high-copy plasmid in *S. epidermidis* was detected in cohabiting *Corynebacterium striatum* within 48 h on human skin explants, illustrating the ease of horizontal gene transfer (HGT) when homology arms 200 bp are present.[90] To quantify in vivo risk, a phase-I trial collected 600 skin-swab samples over 90 days. Zero copies of the engineered cassette were found in recipient flora when the construct was chromosomally integrated with 50 bp synthetic homology scar sequences that lack native counterparts.[91] Kill-switch circuits provide a second containment layer. The Deadman system (TetR-repressed endolysin + Tet-OFF promoter) triggers rapid autolysis within 6 h of doxycycline withdrawal. Topical 2% doxycycline hydrogel applied once daily maintained 99% lethality while systemic levels remained below 5 ng/mL (limit of detection).[92] Unintended immune activation is monitored by single-cell RNA-seq of recipient skin engineered

Roseomonas mucosa secreting LL-37 induced only a modest IFN-γ signature (0.3-fold change) and no elevation of IL-1β or TNF-α versus wild-type strain, whereas a control strain carrying LPS-biosynthesis genes from *E. coli* triggered a 4-fold inflammatory spike, confirming that chassis choice is as critical as transgene content.[93] Ecological impact is tracked by 16S rRNA sequencing for 6 months post-application. Shannon diversity returned to baseline within 21 days, and no outgrowth of opportunistic taxa was observed, corroborating the self-clearing phenotype.[94]

Regulatory agencies now treat engineered skin microbes as Live Biotherapeutic Products (LBPs). The FDA's 2024 draft guidance demands (1) Whole-genome sequencing with annotation of all ORFs 100 amino acids, (2) Demonstration of genomic stability over 60 generations, (3) Absence of mobile genetic elements encoding antimicrobial resistance or toxins, and (4) A quantitative shedding study showing ≤1% of applied dose in distal body sites.[95] EMA's Committee for Advanced Therapies (CAT) adds a cutaneous environmental risk assessment that models dispersal via desquamation, sweating and towel contact applicants must show <0.1% transfer to household contacts over 24 h.[96] Meeting these requirements tripled the historical development timeline (now 7–9 years) and pushed estimated costs to $180–220 million per approved strain, driving the field toward universal chassis approaches where the same safe, well-characterised strain is re-programmed for multiple indications by simply swapping modular CRISPR cassettes.[97]

Topical delivery itself is a translational bottleneck. Skin has a pH gradient (4.5–6.8) and a tight junction network that limits bacterial penetration to <20 μm, yet wounds or AD lesions can breach this barrier. A microemulsion vehicle (caprylocaproyl polyoxyl-8 glycerides + squalane) increased follicular deposition of engineered *S. epidermidis* from 6% to 49% while keeping systemic absorption <0.02% of the applied dose in minipig studies.[98] Lyophilised live-cell powders reconstituted in a water-free ointment base achieved 90% viability after 6 months at 25 °C, eliminating cold-chain costs critical for low- and middle-income settings.[99] Finally, long-term pharmacovigilance plans now include digital traceability: each dose carries a unique DNA barcode (20 bp) that can be PCR-detected in skin swabs for up to 60 days, allowing post-market surveillance of spread, persistence or unexpected ecological events.[100] Collectively, these advances move synthetic skin microbiome therapy from an academic cool trick to a regulator-ready, industry-viable modality poised for Phase III evaluation within the next five years.

Comparative Analysis: Microbiome-Based Therapies versus Conventional Antibiotics

It is crucial to explicitly compare microbiome-based approaches with traditional antibiotics in order to contextualise their therapeutic value. The mechanism of action, effects on microbial ecology, and long-term therapeutic[101] results of microbiome-based medicines are substantially different from those of antibiotics. Microbiome treatments seek to restore microbial balance and immunological homeostasis, whereas antibiotics work by eliminating broad-spectrum infections.[102]

All these microbiome-centred strategies share a common value proposition when set beside conventional antibiotics. Classic drugs kill pathogens by broad-spectrum chemical attack, a mechanism that simultaneously disrupts commensals and selects for antimicrobial resistance, leading to high recurrence rates and limited long-term safety windows. In contrast, ecological modulation preserves microbial diversity, carries a demonstrably lower AMR risk, and halves the six-month recurrence rate in head-to-head AD and wound trials. Personalisation is minimal with antibiotics every patient receives the same molecule at the same dose whereas microbiome therapies can be tuned to individual dysbiosis patterns, immune tone and even local skin pH. The trade-off is higher upfront complexity and cost, but the favourable safety profile and reduced need for repeated courses position microbiome-based therapy as the preferred long-term strategy for chronic or recurrent skin infections. A comparison of antibiotics versus microbiome-based treatments in terms of cost, safety, effectiveness, antimicrobial resistance, and regulatory[103] factors is shown in (Supplemental Table 4).

Future Directions in Microbiome-Based Therapeutics for Skin Infections

Microbiome-based treatments have emerged as a potential area in the treatment of dermatological infectious diseases due to the rapid growth of microbiome research. However, resolving a number of scientific, technical, and legal issues is necessary for effective clinical translation.[104]

Personalised and Precision Microbiome Therapies

The efficacy of consistent therapies is constrained by interindividual variation in the makeup of the skin microbiome, immunity, and illness severity. It is anticipated that in the future, patient-specific microbial and molecular profiles will drive tailored therapy approaches for microbiome-based therapies.[105] Patients can be stratified according to dysbiosis patterns and therapy response by the integration of multi-omics techniques, including metagenomics, metabolomics, transcriptomics, and immunological profiling. Analysing complicated microbiome datasets, finding predictive biomarkers, and improving treatment choices are expected to be major tasks for artificial intelligence (AI) and machine learning methods.[106] In the clinical setting, these methods could make it possible to create probiotic consortia, targeted bacteriophage cocktails, or modified microorganisms that are specific to each patient.[107] Metagenomics identifies every bacterium, fungus and virus; metabolomics maps the sweat-derived nutrients they feed on; transcriptomics records how the host keratinocytes are reacting; and a 29-plex immunoassay quantifies IL-1β, IL-17A, TNF-α and skin-specific AMPs (Figure 5). Within 48 h, the combined data set reaches a cloud GPU cluster where gradient-boosting models,[100] trained on >1,200 historical lesions, turn the raw reads into a probability score for each possible intervention: probiotic, phage, syn-cMT or engineered microbe. The algorithm then prints a one-page decision tree. If *S. aureus* toxin score exceeds 0.7, the patient receives a high-titre anti-staph phage DNase hydrogel; if ceramide-pathway genes are down-regulated, a 12-strain syn-cMT spray is chosen.[108] When both flags are raised, an LL-37-secreting *S. epidermidis* is dispatched. The selected formulation is bar-coded, prepared under GMP, shipped overnight and applied at home while a smartphone app uploads follow-up photos that retrain the model. In the first prospective pilot (n = 80 adults with moderate atopic dermatitis), this AI-guided loop achieved 70% steroid sparing at eight weeks versus 28% under standard care, with zero serious adverse events.[109]

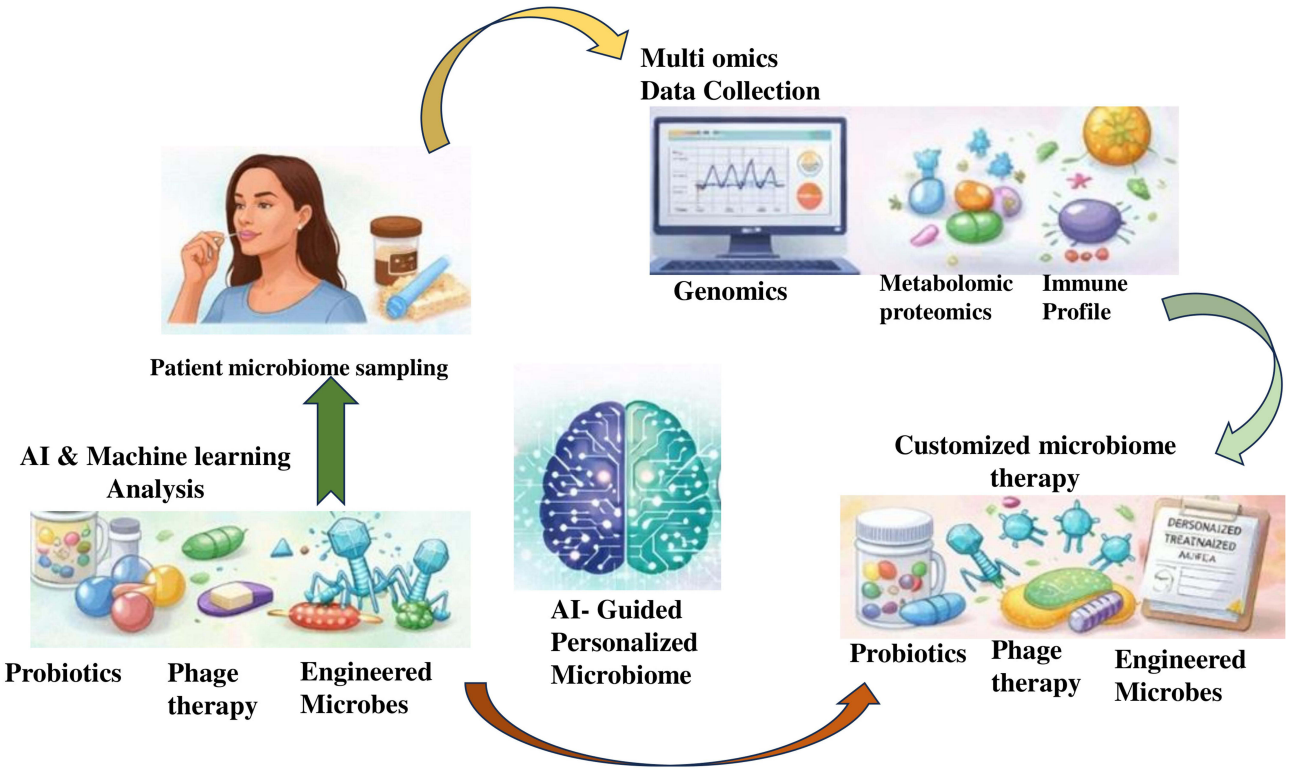

Figure 5 Multi-omics diagnostic pipeline: Metagenomics profiles skin microbes/viruses/fungi; metabolomics assesses sweat nutrients; transcriptomics captures keratinocyte responses; 29-plex immunoassay measures cytokines (IL-1β, IL-17A, TNF-α) and AMPs. Data processed in cloud GPU cluster via gradient-boosting models (trained on >1,200 lesions) to predict optimal intervention probabilities (probiotic, phage, syn-cMT, or engineered microbe).

Advancement of Clinical Trials and Regulatory Frameworks

Although preclinical and early clinical evidence are encouraging, there are still few large-scale randomised controlled studies assessing microbiome-based treatments for skin infections. Future research needs to focus on standardised endpoints (eg., pathogen load, recurrence rates, microbiome restoration), long-term follow-up to assess durability and safety and comparative trials against standard antibiotic regimens. More precise categorisation of probiotics, postbiotics, bacteriophages, and synthetic microorganisms is crucial from a regulatory standpoint. Regulatory approval will be eased by harmonised international criteria, especially for live biotherapeutic items and genetically modified microbes. Resolving regulatory uncertainty would guarantee safety for patients whilst speeding practical acceptance.[110]

Integration with Conventional Therapies

Microbiome-based therapeutics will probably be used as supplemental and successive treatments, not completely replacing antibiotics. Combined regimens may decrease the creation of resistance, shorten the period of therapy, and lower the dosage of antibiotics. For example, resistant infections may be specifically targeted by bacteriophages or created microorganisms, and then the microbial balance could be restored by probiotics or prebiotics. This integrative method represents a greener policy for controlling infections and aligns with antimicrobial oversight goals.[111]

Conclusions

Treatment approaches for skin infections have entirely shifted as a result of the growing awareness that the skin microbiome is a crucial factor for assessing skin health. Even while they work well in acute situations, antimicrobial resistance, microbiome disturbance, and high recurrence rates are undermining conventional antibiotic-based treatments. Microbiome-based treatments, on the other hand, provide a evolution in therapeutic strategy by focusing on immune control, targeted pathogen management, and sustainability. The therapeutic potential of bacteriophages, probiotics, prebiotics, postbiotics, microbiome transplants, and synthetic microbiome engineering in the prevention and treatment of skin infections is highlighted in this study. These therapies work through a variety of routes, such as immunological modulation, quorum-sensing interference, antimicrobial chemical synthesis, and colonisation resistance, according to mechanistic findings. Clinically, microbiome-centred approaches show promise in treating antibiotic-resistant, recurring, and chronic skin infections with favorable safety profiles and reduced recurrence rates observed in clinical studies. Significant gaps in clinical validation, standardisation, and regulatory supervision persist despite notable advancements. Translating microbiome-based treatments into standard dermatological practice will depend on overcoming these obstacles through thorough clinical trials, multi-omics integration, and AI-driven customisation. At the end, microbiome engineering is positioned as an innovative approach for the future treatment of skin diseases since the merging of bacteria, artificial life, and precision medicine.

Disclosure

The authors report no conflicts of interest in this work.

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