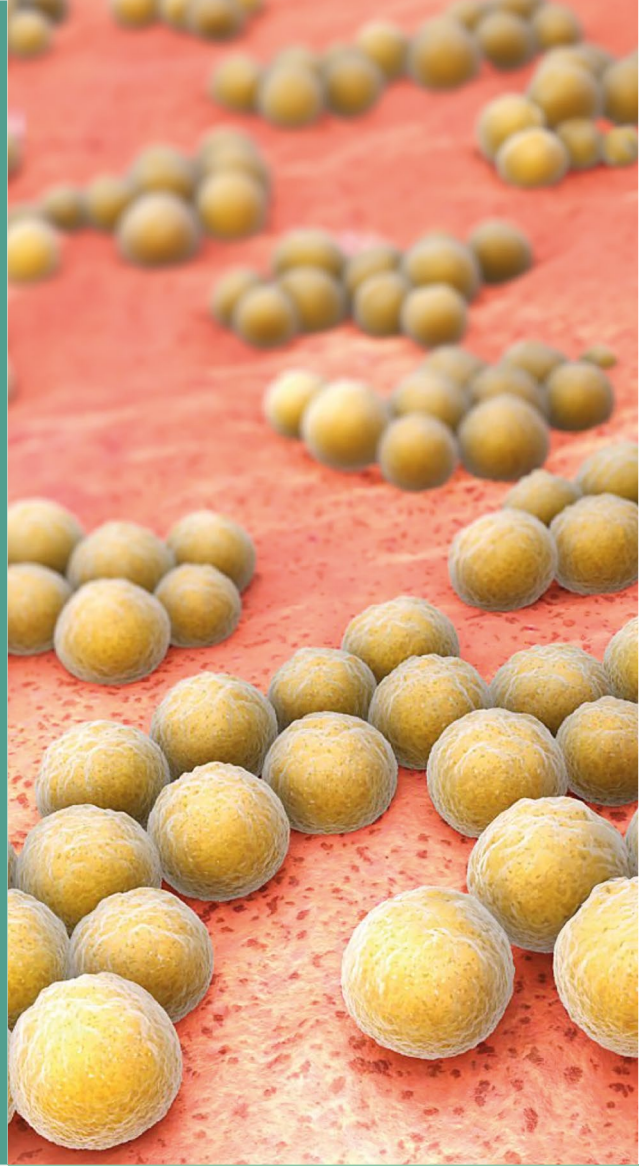


Staphylococcus aureus & atopic eczema



What are the therapeutic implications?

Fourth edition

Contents

A. Introduction

Atopic eczema (synonymous with atopic dermatitis) is a common chronic skin condition mainly affecting children and follows a remitting and relapsing course. It is characterised by intense itching, redness, inflammation and exudation. It affects mainly the flexor surfaces of the elbows and knees, or extensor surfaces in darker skin, as well as the face and neck.

Estimates of the prevalence of eczema vary but it has been reported that the recorded incidence and lifetime prevalence of patients with eczema has increased. With almost 1 in 9 of the population experiencing the condition at some point in their lives, eczema is now one of the most common chronic conditions to affect the population.¹

Estimates vary due to the different populations examined, but figures suggest that atopic eczema may affect as many as 10 to 30% of children and about 2 to 10% of adults.² There are incidence peaks in infants (< 1 year) and older adults (> 80 years) and eczema prevalence was highest in children aged 2. Differences in incidence and prevalence by ethnicity, sociodemographic characteristics and geography have been reported.³ Atopic eczema can continue into adolescence and adult life as a chronic disease, but it can be expected to clear in approximately 65% of children by the time they are seven years of age and in approximately 74% of children the eczema will have disappeared by 16 years of age.⁴

The severity of atopic eczema varies enormously, from an occasional dry, itchy patch to a debilitating disease where much of the body is covered by itchy, excoriated (scratched and abraded) and bleeding lesions, which can become infected. Its course may be continuous for prolonged periods or of a relapsing-remitting nature characterised by acute flare-ups.

Atopic eczema can have a significant impact on quality of life. In addition to the burden of daily treatment, the condition may affect everyday activities, such as work or school and sleep disturbance is common, especially during flare-ups. Severe atopic eczema in children can also have a significant impact on family life, with parents/carers having to cope with the demands associated with caring for a child with a chronic illness.

Immunological, genetic and environmental factors all play a role in causing atopic eczema. It often has a genetic component, whereby gene mutations result in a reduction in filaggrin. Filaggrin is a protein critical in the flattening of keratinocytes in the stratum corneum, which is crucial to the strength and integrity of the skin barrier. This breakdown of the skin barrier allows ingress of trigger factors such as irritants, allergens and microorganisms which can make the eczema worse.

Itchy skin (pruritus) is a major symptom of atopic eczema. A vicious circle can develop, where itching and scratching damage the skin and increase inflammation, which in turn increases the itch. Scratching can damage the skin and cause bleeding, secondary infection and thickening of the skin (lichenification).

The combination of an itch-scratch cycle with frequent flare-ups has long been known and the involvement of *Staphylococcus aureus* (*S. aureus*) in atopic eczema is now recognised following around 50 years of research.⁵ However, new information is emerging all the time as to how *S. aureus* affects atopic eczema and the interplay between the host factors and *S. aureus* virulence mechanisms affecting colonisation.

This booklet provides a review of key data published on the link between *S. aureus* and atopic eczema. Extracts from papers are provided for easy reference, together with a diagrammatic summary of the role of the bacteria in the exacerbation of the disease.



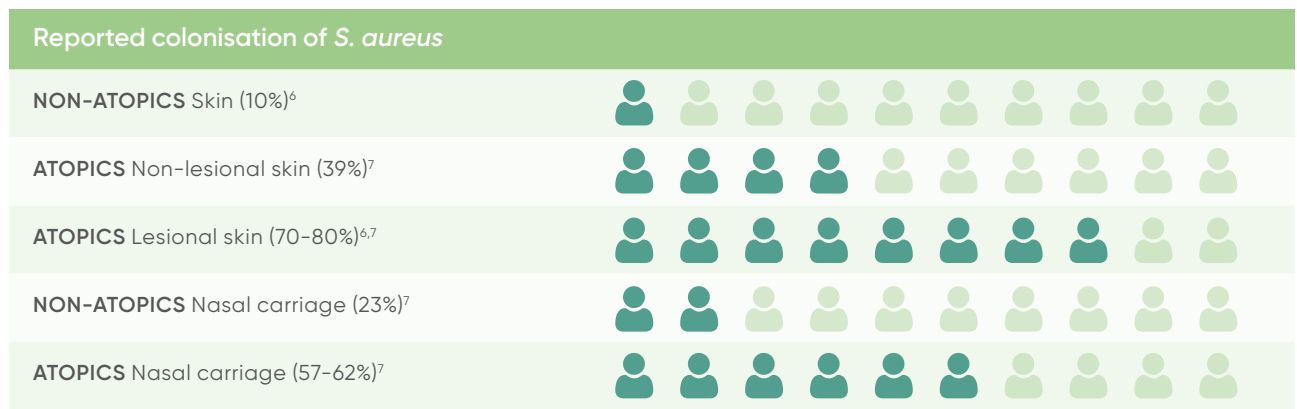
B. Prevalence of *Staphylococcus aureus*

A defective skin barrier

The skin acts as an effective barrier to the external environment, stopping the ingress of allergens and microbes while preventing water loss through the skin. In atopic eczema, the skin barrier is compromised, in part due to decreased production of skin lipids leading to dryness, fissuring and penetration of environmental toxins, allergens and potentially pathogenic microbes such as *S. aureus*. This results in inflamed, itchy and possibly infected skin.

Skin colonisation

In patients with atopic eczema there is an increased prevalence of *S. aureus* in both lesional and non-lesional skin. Nasal carriage of *S. aureus* is also higher in patients with atopic eczema.



Key: = *S. aureus* present = *S. aureus* absent

'The prevalence of *Staphylococcus aureus* (SA) colonization among patients with AE is typically above 80% for lesional skin and 40% for nonlesional skin versus 10% in healthy individuals, but this depends largely on the culture methods used. The density of the colonization correlates with the disease severity.'

Wollenberg A. et al. European guideline (EuroGuiDerm) on atopic eczema - part II: non-systemic treatments and treatment recommendations for special AE patient populations. *Journal of the European Academy of Dermatology and Venereology* 2022;36(11):1904-1926.

'...this systematic review and meta-analysis demonstrates that patients with AD are more frequently colonized with *S. aureus* than healthy controls and that colonization is increased in more severe AD.'

'Overall, 81 studies (5231 patients) reported on colonization of the lesional skin and 30 studies (1496 patients) reported on colonization of the nonlesional skin. Pooled analysis showed that 70% of the patients with AD carried *S. aureus* on the lesional skin (95% CI 66-74; I² = 88.31) and 39% on the nonlesional skin (95% CI 31-47; I² = 87.39). Pooled results of 43 studies (2476 patients) that address nasal colonization estimated that 62% of the patients with AD carry *S. aureus* in the nose (95% CI 57-68; I² = 85.20).'

'Pooled analysis of 19 of 21 studies that evaluated nasal colonization (1051 patients and 1263 controls) showed that 57% of the patients were positive for *S. aureus* in the nose vs. 23% of the controls (OR 4.50, 95% CI 3.00-6.75; P < 0.001; I² = 70.31).'

'The current use of antistaphylococcal therapies, together with literature that points to *S. aureus* as a driver in AD pathogenesis, underlines the importance of antistaphylococcal treatment in AD. However, long-term (preventive) use of antibiotics and glucocorticosteroids is undesirable as they can cause side-effects and antibiotic resistance.'

Totté J. E. E. et al. Prevalence and odds of *Staphylococcus aureus* carriage in atopic dermatitis: a systematic review and meta-analysis. *British Journal of Dermatology* 2016;175(4):687-695.

'Patients with atopic dermatitis, who are invariably colonised with *Staphylococcus aureus*, showed changes in the lipid compositions before and after treatment. Skin lipids which moderate microbial growth may be suppressed in atopic dermatitis permitting the overgrowth of *S. aureus*.'

'*Staphylococcus aureus* is usually transient on the normal skin surface, the common resident sites are the nose, axillae, perineum and toewebs. The relative rarity of colonisation by *S. aureus* on normal skin sites contrasts dramatically with the high carriage rate in all patients with atopic dermatitis and cutaneous infection is one of the factors that plays a role in the aggravation of this condition.'

'The role of *S. aureus* may be to aggravate atopic dermatitis or prevent the resolution of the lesions. Not only is it found in lesions, where it may be recovered with an average density of about 2×10^7 organisms/cm² in acute lesions, but it is also the dominant organism on the clinically normal skin of these patients, although the density is lower.'

Patel S.D. & Noble W.C. Changes in skin surface lipid during therapy of atopic dermatitis. *Microbial Ecology in Health & Disease* 1993;6:181-184.

'The normal bacterial skin flora in humans is composed of three major groups of Gram-positive bacteria, the coryneform bacteria, the micrococci and the staphylococci, with only a minor component of Gram-negative bacilli. This is chiefly because the skin is a comparatively dry habitat, with available water as the chief factor controlling growth; occlusion of skin is a potent way to increase the number of bacteria on the skin. Gram-negative bacilli require more available water than Gram-positive bacteria and this probably controls their population density.'

'The factors that permit skin colonization in eczema, or conversely prevent colonization in normal individuals, are not known, but since the essential fatty acids are more toxic to *S. aureus* than to the coagulase-negative species, and since a deficit of essential fatty acids may result in a poor skin structure, this may form part of the equation.'

Noble W.C. Skin bacteriology and the role of *Staphylococcus aureus* in infection. *British Journal of Dermatology* 1998;139:9-12.

'*Staphylococcus aureus* was abundant on AD skin compared with control skin, and correlated positively to disease severity. Affected skin sites were dominated more by *S. aureus* than unaffected sites, especially inflamed areas (vs. xerotic) – and during a flare the abundance increased dramatically in untreated patients. Besides *S. aureus*, other species from the *Staphylococcus* genus were increased on involved sites. These included *S. epidermidis* and *S. haemolyticus*.'

'The bacterial diversity on AD skin was low compared with control skin, and reduced during a flare. Reductions in species from the genera *Streptococcus*, *Propionibacterium*, *Acinetobacter*, *Corynebacterium* and *Prevotella* were found – not solely attributed to an increase in *S. aureus*. *Propionibacterium acnes* was also found less frequently on facial AD skin than on control skin, and was inversely correlated to disease severity.'

'While the microbiome is increasingly drawing attention as a possible target in the prevention and treatment of AD, new methodological approaches have not yet brought us far in understanding the impact of dysbiosis in AD. Staphylococcal species are key players in worsening of AD, and may also be important in the establishment of the disease. Other microbes such as *Propionibacterium*, *Streptococcus*, *Acinetobacter* and *Malassezia* have been found to be implicated in AD dysbiosis. However, robust data are missing on the influence of methodological procedures, characteristics of the microbiome structure related to temporal dynamics, clinical measures and factors altering the microbiome.'

Bjerre R. D. et al. The role of the skin microbiome in atopic dermatitis: a systematic review. *British Journal of Dermatology* 2017;177:1272-1278.

'*S. aureus* can be isolated from lesional skin, especially from intertriginous regions, the nose ('nasal carriage'), as well as unaffected atopic skin. Next to mechanical triggers (scratching), predominantly alkaline pH and decreased IgA secretion through sweat production, there are several important pathophysiological features leading to the disruption of the primary skin defence system. Various factors contributing to increased numbers of *S. aureus* in atopic skin and the perpetuation of inflammation have recently been discovered: altered lipid composition within the stratum corneum; exposed extracellular matrix adhesins; changes in immune response; bacterial superantigens and increased specific IgE production.'

Roll A. et al. Microbial colonization and atopic dermatitis. *Current Opinion in Allergy and Clinical Immunology* 2004;4(5):373-378.

Host factors affecting colonisation

Increased colonisation of atopic eczema patients with *S. aureus* may be due to increased adherence of the bacteria to the stratum corneum. *S. aureus* can adhere to and colonise damaged skin more easily than healthy skin, partly due to the increased expression of microbial binding sites, adhesins, on eczematous skin and also proteases produced by the host which allow the bacteria to penetrate into the deeper layers of the skin. Alkaline skin pH, skin surface lipid deficiency (e.g. decreased fatty acids and ceramides), decreased microbial diversity, reduced production of endogenous antimicrobial peptides (AMP's) and filaggrin deficiency in atopic eczema patients may also play a critical role in *S. aureus* colonisation. Collectively, this skin barrier dysfunction enhances *S. aureus* colonisation.

'Various factors are involved in the altered skin colonization by *S. aureus* in AD including an altered epidermal barrier, increased bacterial adhesion, defective bacterial clearance, and decreased innate immune responses.'

'*S. aureus* are tightly attached to the uppermost corneocytes, and can penetrate the epidermis via the intercellular spaces probably as a result of lipid deficiencies in AD skin. In AD, the average pH of the skin is slightly more alkaline, and sphingosine levels are decreased in both lesional and nonlesional stratum corneum. In addition, the dryness and cracking of AD skin, as a result of transepidermal water loss caused by altered lipid content, may facilitate bacterial colonization. Furthermore, Th-2 cytokines such as IL-4 in atopic skin increase expression of fibronectin and fibrinogen, receptors that mediate the adhesion of *S. aureus* to stratum corneum.'

Baker B.S. The role of microorganisms in atopic dermatitis. *Clinical and Experimental Immunology* 2006;144:1-9.

'The susceptibility of the atopic skin to colonization with *S. aureus* may be for several reasons: *S. aureus* cell walls exhibit receptors, the so-called adhesins, for epidermal and dermal fibronectin and fibrinogen. As the skin of patients with AD lacks an intact stratum corneum, dermal fibronectin might be uncovered and increase the adherence of *S. aureus*. Fibrillar and amorphous structures have been traced between *S. aureus* cells and corneocytes and may result in a bacterial biofilm that contributes to the adherence of *S. aureus*. Skin surface lipids such as free fatty acids and polar lipids have been shown to exhibit antibacterial activity. The observation that *S. aureus* penetrates into intracellular spaces of the epidermis suggests that skin surface lipids are deteriorated in patients with AD. Furthermore, immunological factors might also enhance susceptibility to *S. aureus*.'

Breuer K. et al. *Staphylococcus aureus*: colonizing features and influence of an antibacterial treatment in adults with atopic dermatitis. *British Journal of Dermatology* 2002;147:55-61.

'In AD, the pH of the skin shifts toward alkalinity, in part due to low sweat secretion and decreased levels of fatty acids.'

'Since low pH is detrimental to *S. aureus*, the bacteria must neutralize the acidity in order to colonize the skin.'

'*S. aureus* adhesion is also influenced by changes in the *stratum corneum* cell composition and morphology that occur in AD. Corneocytes expose ligands such as fibronectin, loricrin, and cytokeratin that interact with bacterial proteins as fibronectin-binding proteins A and B (FnBPA, FnBPB), clumping factor B (ClfB), and the iron-regulated surface determinant A protein (IsdA), promoting adhesion of *S. aureus* and providing resistance to antimicrobial lipids.'

Gehrke A. E. et al. *Staphylococcus aureus* adaptation to the skin in health and persistent/recurrent infections. *Antibiotics* 2023;12(10):1520.

'In contrast to healthy skin, AD skin is permissive for *S. aureus* colonization. The antimicrobial peptides LL-37, β -defensins, and dermicidin are present at reduced levels in AD skin. One mechanism underlying this effect is the known inhibition of IL-4 and IL-13 on human β -defensin 2 and 3 gene expression. *S. aureus* species grow poorly in acidic conditions, as seen in healthy stratum corneum, but grow much better in higher pH conditions, which are often seen in patients with AD. *S. aureus* isolated from patients with AD binds more strongly to intact AD skin and in standard binding assays than *S. aureus* isolated from unaffected carriers, an effect that is modulated by levels of filaggrin breakdown products (natural moisturizing factor) in human corneocytes. In patients with established AD, filaggrin deficiency, either genetic or acquired from T_H2 skewing, leads to irregular or deformed corneocytes. *S. aureus* isolates from patients with AD also bind more strongly to these corneocytes compared with isolates from unaffected control subjects in a clumping factor B-dependent fashion.'

Paller A. S. et al. The microbiome in patients with atopic dermatitis. *Journal of Allergy and Clinical Immunology* 2019;143(1):26-35.

C. The pathophysiological role of *Staphylococcus aureus*

A number of studies investigating the pathogenic role of *S. aureus* in atopic eczema have been published. Findings show that *S. aureus* releases exotoxins that act as superantigens and are potent immunostimulators. Additional toxins, such as the staphylococcal phenol soluble modulins (PSMs), including δ -toxin and α -toxin, may enhance the virulence, as may the production of proteases. The exact role of these factors in promoting colonisation and virulence are being more widely investigated and reported.

'There are numerous ways in which *S. aureus* may potentially contribute to the pathogenesis of eczema, including via production of various proteins such as superantigens and proteases. Superantigens penetrate the skin barrier and cause chronic inflammation through a variety of mechanisms, including:

1. stimulation of cytokine (a type of protein used for signalling in the immune system) release from T-cells;
2. acting as an allergen by induction of IgE antibodies, which cause release of inflammatory mediators from mast cells (cells that release histamine during inflammatory or allergic reactions) and basophils (a type of white blood cell);
3. stimulation of antigen-presenting cells and keratinocytes (a type of skin cell) to release pro-inflammatory cytokines, thereby increasing T-cell infiltration;
4. increasing cutaneous lymphocyte-associated antigen receptor (a skin-homing receptor) on T-cells, causing migration to the skin and increasing inflammation; and
5. increasing skin inflammation caused by other allergens.

Superantigens also increase adherence of *S. aureus* to the skin by exposing extracellular matrix adhesins (a type of protein) and cause corticosteroid resistance.'

'*S. aureus* also produces proteases, which cause skin barrier breakdown, allowing penetration of allergens and irritants. *S. aureus*-derived proteases cleave endogenous protease inhibitors (proteins produced by the body that prevent the breakdown of proteins by enzymes called proteases), induce pro-inflammatory and pro-allergic responses, promote Th2 immune response and result in IgE production.

Other *S. aureus*-derived proteins may also contribute to skin inflammation in eczema. Phenol-soluble modulins (a type of bacterial toxin) attract and lyse (break up) neutrophils (a type of white blood cell), making *S. aureus* more likely to cause harm. Fibronectin-binding protein, a type of protein produced by *S. aureus* that enables it to stick to and enter cells of the host organism, activates T-cells (a type of cell from the immune system, that plays a key role in skin inflammation). This activation results in the release of chemical messengers called cytokines that also promote skin inflammation.'

George S. M. C. *et al.* Interventions to reduce *Staphylococcus aureus* in the management of eczema. *Cochrane Database of Systematic Reviews* 2019, Issue 10. Art No.:CD003871.

'The underlying pathogenic mechanisms of *S. aureus* in relation to AD have still not been fully elucidated. However, recent studies suggest a causal role in the complex pathogenesis of AD by showing that *S. aureus* colonization precedes (flares of) the disease. *S. aureus* can facilitate skin barrier defects and inflammation in AD using different mechanisms. Examples of this include the stimulation of mast-cell degranulation by staphylococcal delta toxin, the induction of keratinocyte apoptosis by alpha toxin, the stimulation of T cells by enterotoxins that act as superantigens and the modulation of inflammation by staphylococcal surface proteins, protein A and lipoteichoic acid.'

Totté J. E. E. *et al.* Prevalence and odds of *Staphylococcus aureus* carriage in atopic dermatitis: a systematic review and meta-analysis. *British Journal of Dermatology* 2016;175(4):687-695.

'It has been documented that *S. aureus* is able not only to colonize the surface of the skin, but it also penetrates the dermis, where the bacterium can come into direct contact with immune cells and stimulate the production of proinflammatory cytokines. *S. aureus* produces a range of potent virulence factors that appeared to play a crucial role in the inflammation process driven by the bacterium, e.g., PSMs (phenol soluble modulins), proteases (aureolysin, V8 protease, SspA serine protease, ScpA cysteine protease), superantigens (staphylococcal enterotoxin A, B, TSST-1).'

Ogonowska P. et al. Colonization with *Staphylococcus aureus* in atopic dermatitis patients: attempts to reveal the unknown. *Frontiers in Microbiology* 2021;11:567090.

'To study the mechanisms by which *S. aureus* might exacerbate AD, Leung et al characterized the toxins produced by *S. aureus* isolates from the skin of AD patients. More than half of the AD patients had *S. aureus* that secreted identifiable toxins, primarily the superantigenic toxins SEA, SEB and TSST-1. As a proof of concept, Strange et al studied the effects of SEB applied to intact normal skin and the uninvolved skin of patients with AD. They reported significant erythema and induration following application of SEB to uninvolved normal-appearing AD skin. Three of the six AD subjects studied experienced a flare of their disease in the elbow flexure ipsilaterally to where the SEB patch was applied. These authors concluded that superantigens can exacerbate and sustain the inflammation associated with AD.'

'...These findings raise the possibility that epicutaneous superantigenic toxins induce specific IgE in AD patients, leading to mast-cell degranulation *in vivo* when the toxins penetrate the disrupted epidermal barrier, thereby promoting the scratch-itch cycle prominent in atopic patients. In addition, recent studies indicate that staphylococcal superantigens can trigger B cells to produce allergen-specific IgE, providing a novel mechanism by which microbial superantigens could aggravate allergic responses.'

Leung D.Y.M. et al. The role of superantigens in human diseases: therapeutic implications for the treatment of skin diseases. *British Journal of Dermatology* 1998;139:17-29.

'There is also an understanding that individuals with skin disease may be genetically predisposed to microscopic structural changes in the skin barrier, including increased synthesis of extracellular matrix adhesins, fibronectin and fibrinogen for SA, reduced skin lipid content, an alkaline skin surface pH and reduced production of endogenous antimicrobial peptides due to defective innate immune responses. Collectively, this skin barrier dysfunction enhances SA colonization. It also allows the entry of SA superantigens (SSAGs), as well as allergens and irritants, thus contributing to exacerbation of skin disease.'

'SSAGs are exotoxins produced by SA which play a key role in the chronic inflammatory nature of AD. They have the ability to trigger an enhanced inflammatory response through the stimulation of a variety of T-cell clones and cytokine secretions. Over 70% of SA strains isolated from the skin of AD patients produce superantigens such as alpha-toxin, toxic shock syndrome toxin-1 and staphylococcal enterotoxins and their role has been established in several immunohistological studies based on SA strains isolated from the lesional skin of patients with AD. Increased levels of antistaphylococcal superantigen specific IgE and IgM antibodies, in addition to cytokines such as interleukin (IL) 4 and interferon- γ , have also been quantified in the sera of most patients with AD compared to normal controls and have been shown to decrease with treatment. There is also a positive correlation between colonization with superantigen producing strains of SA and clinical severity of AD. SSAGs can also induce corticosteroid resistance, which may increase the severity of skin disease. This has led to the hypothesis that eradication of SA may lead to a steroid sparing effect, which is an incentive to management as long term topical corticosteroid use may lead to adverse effects such as local irritation, skin atrophy and skin depigmentation.'

Lee M. and Van Bever H. The role of antiseptic agents in atopic dermatitis. *Asia Pacific Allergy* 2014;4(4):230-240.

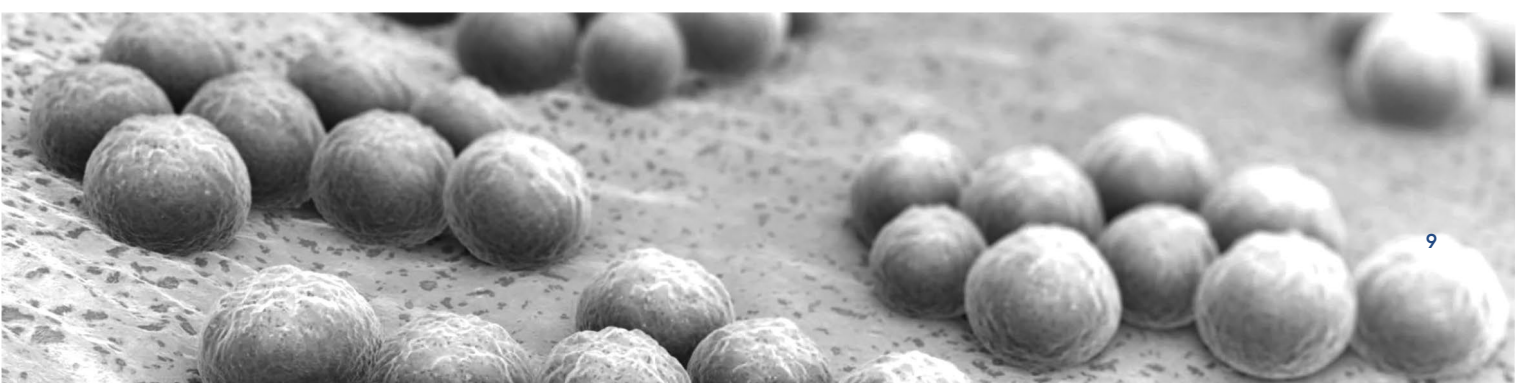
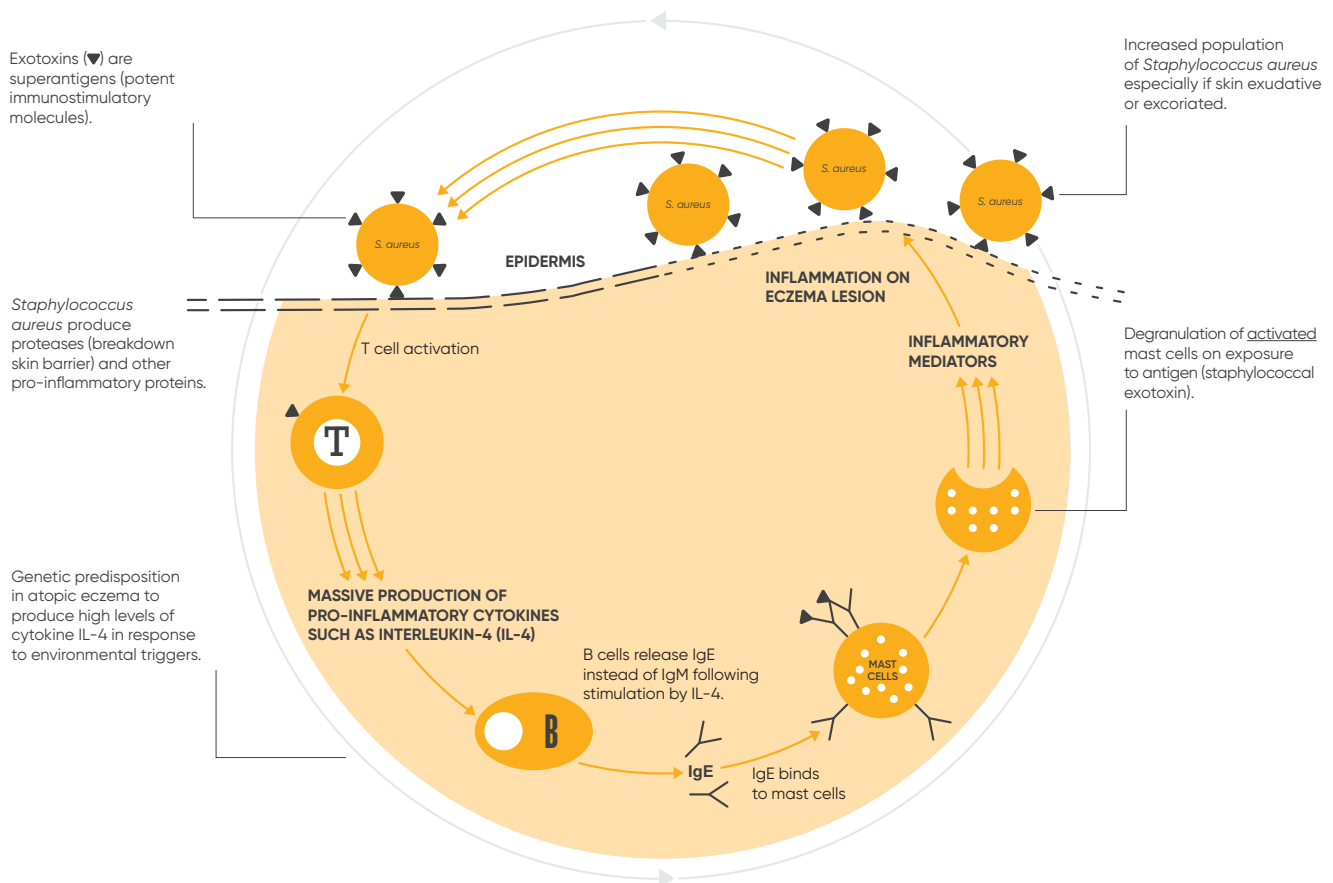
'These findings suggest the possibility that local production of exotoxin at the skin surface could cause IgE-dependent mast cell degranulation. This could have several important consequences. First, the acute release of histamine and other mediators could trigger the itch-scratch cycle which can exacerbate AD. More important, mast cell degranulation results in the local release of mediators, cytokines, and leukocyte chemotactic factors that result in late-phase inflammatory reactions. Since patients with AD are colonized with *S. aureus*, the continuous release of exotoxins into the skin may promote the chronic inflammation found in AD.'

'These data may also explain the clinical observation that many flares of eczema correlate with high colonization counts of *S. aureus* on the skin and that the skin rash frequently resolves when *S. aureus* is eradicated or drastically reduced following antibiotic therapy.'

Leung D.Y.M. et al. Presence of IgE antibodies to staphylococcal exotoxins on the skin of patients with atopic dermatitis: Evidence for a new group of allergens. *Journal of Clinical Investigation* 1993;92(3):1374-1380.

It is known that *S. aureus* causes a 'vicious circle' in atopic eczema. Release of superantigenic exotoxins activates large populations of T cells, resulting in release of pro-inflammatory cytokines, IgE and inflammatory mediators. *S. aureus* also produce proteases, which help to breakdown the skin barrier, allowing penetration of allergens and irritants. These proteases and other *S. aureus* derived proteins, such as the phenol-soluble modulins (a type of bacterial toxin) and staphylococcal surface proteins (e.g. protein A and lipoteichoic acid), all have pro-inflammatory effects which exacerbate this cycle. This contributes to the exacerbation and maintenance of skin inflammation in atopic eczema patients. This also permits more *S. aureus* to infiltrate the inflamed and disrupted epidermal barrier thus reinforcing the cycle.

The vicious circle caused by *Staphylococcus aureus* in atopic eczema



D. Clinical implications of *Staphylococcus aureus* colonisation on the skin

Severity of eczema

Colonisation of atopic eczema patients with *S. aureus* has been well documented, as has the role of *S. aureus* derived superantigens in atopic eczema. In this section the clinical implications of *S. aureus* colonisation and the effects this may have on disease severity are reported.

'The bacterial flora of the skin was assessed quantitatively in 50 children with eczema, aged 6 months to 14 years, referred to the hospital for the first time. Twenty non-atopic controls with an unrelated non-infective disorder were also studied.'

'Bacterial colonization of the skin was consistently more common and greater in amount from patients compared with controls. *Staphylococcus aureus* was the most common pathogen isolated from patients only; from the worst affected area of eczema in 74% of patients and from an uninvolved skin site in 30% of patients. Quantitative assessment showed that the density of colonization was proportional to the severity of eczema.'

Goodyear H. M. et al. Skin microflora of atopic eczema in first time hospital attenders. *Clinical and Experimental Dermatology* 1993;18:300-304.

'In lesional skin, meta-regression showed that the prevalence of colonization increased with disease severity.'

'A meta-regression for the variables AD severity, NOS score [Newcastle-Ottawa Scale]* and age was performed to identify possible sources of heterogeneity. The prevalence of lesional skin colonization was independent of the NOS score but increased with AD severity (1.02, 95% CI 0.21-1.82) and age (0.64, 95% CI 0.15-1.14). A subgroup analysis of the studies that included patients with mild AD showed colonization of the skin in 43% of the patients (95% CI 31-57; $I^2 = 79.15$), whereas the pooled prevalence for severe AD was 83% (95% CI 74-89; $I^2 = 65.78$).'

*Newcastle-Ottawa Scale is used to assess the quality of nonrandomised studies in meta-analyses.

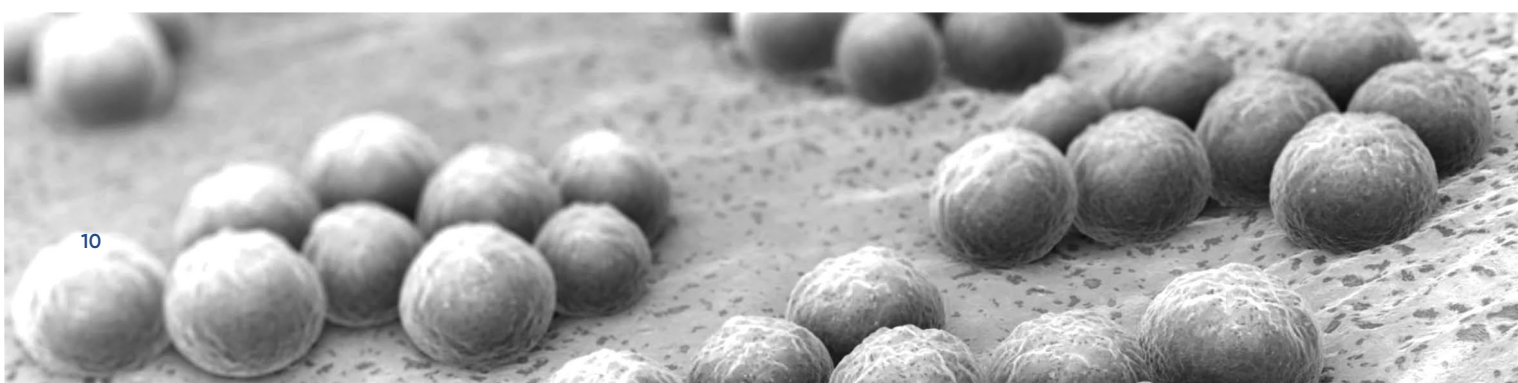
Totté J. E. E. et al. Prevalence and odds of *Staphylococcus aureus* carriage in atopic dermatitis: a systematic review and meta-analysis. *British Journal of Dermatology* 2016;175(4):687-695.

'It is likely that the density of *S. aureus* is more relevant than simply the presence of the bacteria. The density of *S. aureus* colonization correlates with the severity of AD.'

'Similarly, microbiome studies of paediatric patients with AD show that the relative abundance of *S. aureus* is associated with disease flares and correlates with severity.'

'*Staphylococcus aureus* colonisation can be associated with three main clinical scenarios in AD: (i) stable or baseline AD without clinical evidence of overt infection; (ii) AD flare without clinical evidence of overt infection; and (iii) overtly infected AD with the classical symptoms...'

Alexander H. et al. The role of bacterial skin infections in atopic dermatitis: expert statement and review from the International Eczema Council Skin Infection Group. *British Journal of Dermatology* 2020;182(6):1331-1342.



'A total of 78 adult patients with AD were included...'

'Lesional and nonlesional skin of patients with AD showed lower HI [hydration index] and higher pH and TEWL compared with nonlesional skin and with healthy controls. PCA [pyrrolidone carboxylic acid] content was lower on lesional skin but similar on nonlesional and control skin. Staphylococcal density was significantly higher on lesional and nonlesional patient skin compared with control skin, with a 2.6 and 2.3 log ratio, respectively. It was higher on lesional than on nonlesional patient skin.'

'A significant association was found between high staphylococcal density on lesional or nonlesional skin and severe AD. The sensitivity analysis was consistent with the primary analysis: considering lesional skin, the variables associated with severe AD as defined by a SCORAD index of more than 40 were *S. aureus* density (odds ratio [OR], 5.4; 95% CI, 1.85-15.9) and TEWL (OR, 3.4; 95% CI, 1.17-10). When considering nonlesional skin, only *S. aureus* density was significantly associated with severe AD (OR, 4.2; 95% CI, 1.6-11.3). A significant association was found between high staphylococcal density on lesional or nonlesional skin and AD course severity (P = .007 and .003, respectively).'

Tauber M. et al. *Staphylococcus aureus* density on lesional and nonlesional skin is strongly associated with disease severity in atopic dermatitis. *Journal of Allergy and Clinical Immunology* 2016;137(4):1272-1274.

'The goal of this study was to evaluate the frequency and role of *Staphylococcus aureus* infection in patients with atopic dermatitis (AD). In 81 children, ages 2 months to 9 years, affected with moderate to severe AD, 308 samples from the cutaneous lesions were obtained and analyzed. *S. aureus* was isolated in 52 children (64.2%).'

'Our data demonstrate the importance of *S. aureus* in the clinical manifestation of AD and, in particular, its role in worsening the eczematous lesions of the face, neck, and perineum in children less than 1 year of age.'

'*S. aureus* colonization and infection of the skin are thought to play an important role in the pathogenesis of AD. Many studies show that the extent of *S. aureus* colonization of the skin of AD patients correlates with disease severity, and in our study the infection rate of AD was higher in patients with severe AD (SCORAD > 40, 70.2% of infected patients) than in patients with moderate AD (55.8%).'

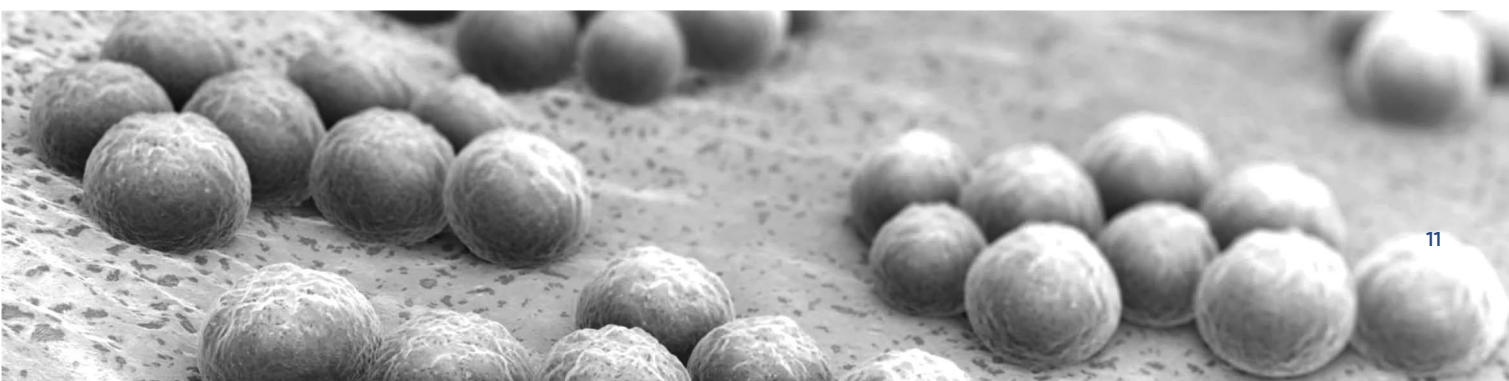
Ricci G. et al. Frequency and clinical role of *Staphylococcus aureus* overinfection in atopic dermatitis in children. *Pediatric Dermatology* 2003;20(5):389-392.

'The skin of patients with atopic dermatitis exhibits a striking susceptibility to colonization and infection with *Staphylococcus aureus*. In this context it has been previously shown that *S. aureus*-derived superantigens could function as classic allergens, inducing production of functionally relevant specific IgE antibodies.'

'Twenty of 58 children (34%) were sensitized to superantigens (45% to SEB, 10% to SEA, 45% to SEA and SEB). In this group, severity of atopic dermatitis and levels of specific IgE to food and air allergens were significantly higher. The degree of disease severity correlated to a higher extent with the presence of SEA/SEB-specific antibodies than with total serum IgE levels. Density of colonization with superantigen-secreting *S. aureus* strains was higher in the superantigen IgE-positive group. Sixty-three percent of these children experienced repeated episodes of superficial *S. aureus* skin infections.'

'Sensitization to *S. aureus*-derived superantigens may be involved in disease exacerbation. The presence of SEA/SEB-specific antibodies had additional explanatory value for disease severity and therefore may be helpful in the characterization of children with severe atopic dermatitis.'

Bunikowski R. et al. Prevalence and role of serum IgE antibodies to the *Staphylococcus aureus*-derived superantigens SEA and SEB in children with atopic dermatitis. *Journal of Allergy and Clinical Immunology* 1999;103:119-124.



Transmission and recolonisation

Atopic eczema patients colonised with *S. aureus* may act as carriers or 'reservoirs,' leading to transmission of the bacteria and possible infection to other subjects. Similarly, these *S. aureus* 'reservoirs' may lead to recolonisation of patients following *S. aureus* eradication therapy.

'Our results confirm the possible role of colonization with *S. aureus* as an aggravating factor in AD. *S. aureus* was isolated from the majority (94%) of our patients, either from the skin (11%) or the anterior nares (6%) or, as in most cases (77%) from both sites, suggesting the nose may act as a reservoir of *S. aureus* strains, which are spread over the skin surface by autotransmission. The fact that the nasal and cutaneous strains produced the same toxins in most cases supports this hypothesis. Of our patients, 50% carried *S. aureus* on both clinically affected and unaffected skin, and cultures could be grown from both acute and chronic lesions, which is in keeping with the data reported by other groups.'

Breuer K. et al. *Staphylococcus aureus*: colonizing features and influence of an antibacterial treatment in adults with atopic dermatitis. *British Journal of Dermatology* 2002;147:55-61.

'*Staphylococcus aureus* colonization is common in atopic dermatitis (AD) and can exacerbate the disease. Additionally, some evidence shows that patients with AD may act as reservoirs for *S. aureus* transmission to others. This study compared *S. aureus* colonization in AD patients and their caregivers with control patients and their caregivers... AD patients had a significantly greater carriage of *S. aureus* from lesional and clinically normal skin as well as the hand. Significant increases in carriage of *S. aureus* were found in the anterior nares and hands of caregivers to AD patients compared with control caregivers. Topical corticosteroid use did not affect recovery of *S. aureus*. There was a significant correlation between recovery of *S. aureus* from lesional skin and recovery from the anterior nares ($p=.002$) and hands ($p<.0001$). These findings suggest that the anterior nares and the hands may be important reservoirs and vectors for the transmission of *S. aureus* to lesional skin and to close contacts of these patients.'

Williams J.V. et al. *S. aureus* isolation from the lesions, the hands, and the anterior nares of patients with atopic dermatitis. *Paediatric Dermatology* 1998;15:194-198.

'Patients with atopic dermatitis (AD) are often heavily colonized by *Staphylococcus aureus*, which adversely affects eczema severity. Strategies to control *S. aureus* in AD include antibiotic and or antiseptics. However long-term efficacy is unclear.'

'In this study we consider extra-cutaneous factors that may cause *S. aureus* re-colonization in adult AD. Twenty-one patients with AD were recruited and were assessed for: duration of AD, use of topical or oral antibiotic within the preceding 3 months, the number of hospital admissions during the preceding year and current treatment. The types of topical treatments used, vehicle, container and the expiry dates were also recorded. The severity of AD was assessed by SCORAD index. Microbiological assessment for *S. aureus* carriage from affected skin, anterior nares, emollient and topical steroid was undertaken using culture, Staphaurex test and antibiotic resistance. Of the patients 86% had *S. aureus* colonization. The median SCORAD score were greater in those colonized with *S. aureus* ($P=0.02$) and those with contaminated treatments ($P=0.05$). Prior antibiotic treatment, prior hospital admission and nasal carriage did not influence the median SCORAD. Three extra-cutaneous mechanisms by which *S. aureus* can re-colonize the skin were identified: antibiotic resistance, nasal carriage and treatment contamination.'

Gilani S.J.K. et al. *Staphylococcus aureus* re-colonization in atopic dermatitis: beyond the skin. *Clinical and Experimental Dermatology* 2005;30:10-13.

'Nasal carriage of *S. aureus* is common among the general population (up to 35% carriage rate) and is higher among patients with atopic eczema (39-82% colonized). Of the 17 patients with nasal *S. aureus* carriage in this study, only two did not have *S. aureus* on skin swab culture; one of these had previously been treated with antibiotics. A further possible explanation for the persistence of *S. aureus* despite prior antibiotic treatment is colonization of the parent leading to re-colonization of the child. Only 6 of the 46 parents had nasal carriage of *S. aureus* however, in all these cases the children were also colonized with *S. aureus*. It seems likely that parental *S. aureus* carriage influences *S. aureus* colonization in the child.'

Patel G.K. et al. *Staphylococcus aureus* colonization of children with atopic eczema and their parents. *Acta Dermato-venereologica* 2001;81:366-367.



E. Rationale for using Dermal antimicrobial emollients

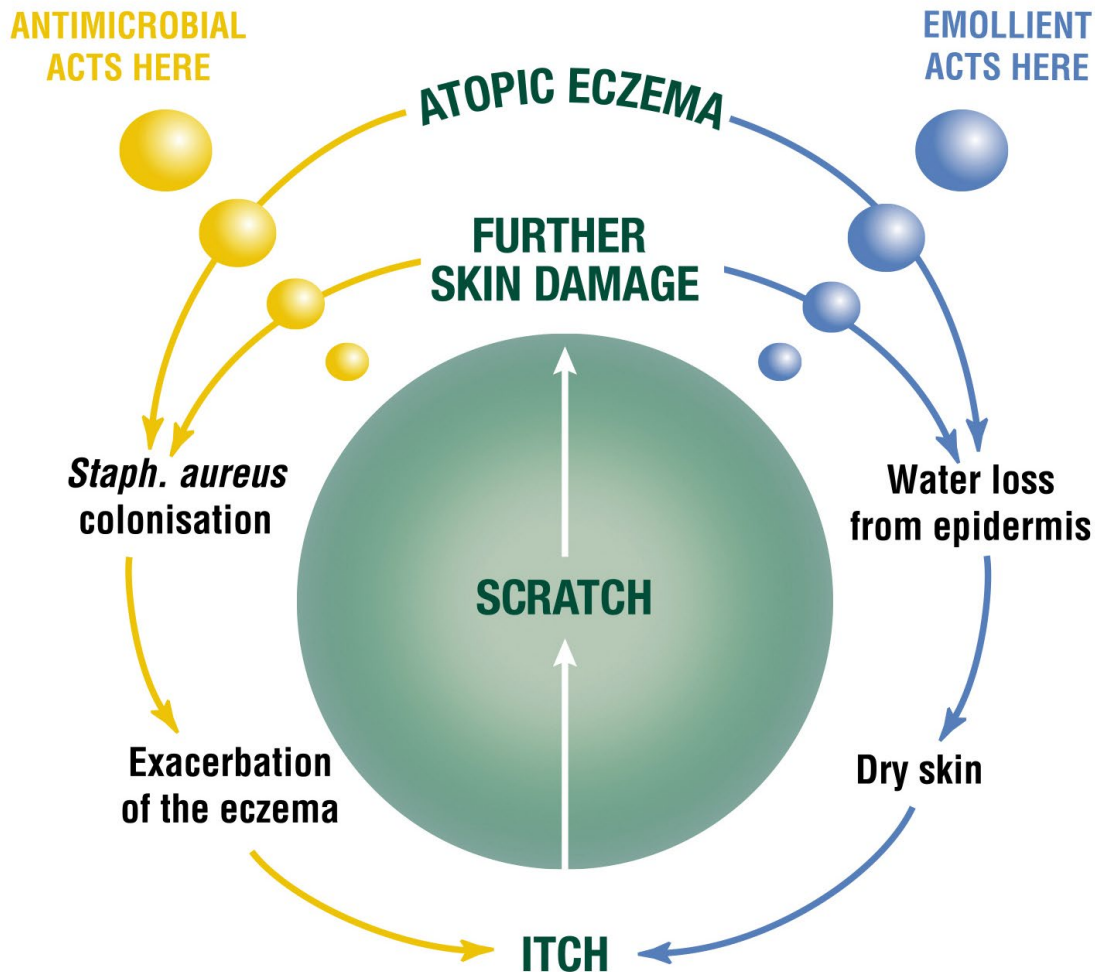
Atopic eczema is a common skin condition which can be exacerbated by the presence of the bacteria *Staphylococcus aureus* (*S. aureus*). This bacteria plays an important role in the pathogenesis of atopic eczema and is known to colonise atopic skin and release chemical mediators which cause an inflammatory reaction in the skin, leading to itching and scratching. This process is known as the itch-scratch cycle.

When treating atopic eczema, it is important to ensure that both the dry skin condition and the presence of *S. aureus* bacteria are considered when selecting an appropriate therapy. Antiseptics are used to lower bacterial load. They include solutions of chlorhexidine salts, triclosan, and potassium permanganate, and antiseptics incorporated into emollients.⁸

The Dermal range of products has been designed not only to provide effective emollient characteristics but also, importantly, antimicrobial activity to help reduce the viability and proliferation of *S. aureus*, and thereby improve the outcome of treatment.

When used for dry and itchy skin conditions, Dermal breaks the itch-scratch cycle in two ways:

- The antimicrobials combat *Staphylococcus aureus*, including resistant strains such as methicillin resistant *S. aureus* (MRSA) and fusidic acid resistant *S. aureus* (FRSA) and consequently reduce the itchy inflammatory reaction to the bacterial superantigenic exotoxins.
- The two emollient ingredients soothe and rehydrate dry skin, relieving the irritation caused by dryness and helping to restore a normal skin barrier function.



Dermol Lotion, Dermol Cream, Dermol Wash and Dermol Shower contain emollient oils to help rehydrate dry skin and two low strength antimicrobial agents, benzalkonium chloride 0.1% and chlorhexidine dihydrochloride 0.1%. Together they provide effective and synergistic antimicrobial activity when applied directly to the skin, or used as a soap substitute, and with both at low concentration, the risk of skin irritation is minimised. These Dermol products also contain cetomacrogol, a non-ionic soap substitute for cleansing, whilst avoiding the drying and irritant effect of conventional soaps and detergents.

Dermol Bath Emollient contains benzalkonium chloride 0.5%, which is powerfully antibacterial in its own right, particularly against Gram-positive organisms. Its activity resides in the large,

positively charged cation, which is mobilised in the bath water towards the negatively charged surface of the skin and bacterial cell walls as soon as the patient immerses in the bath. This affinity helps to concentrate the antibacterial agent precisely where it is needed, to provide effective antimicrobial activity. Dermol Bath Emollient is formulated as a true emulsion, to fully disperse in the bath water and evenly coat the whole body.

The Dermol range of antimicrobial emollients has been especially formulated to offer significant convenience and ease of use – advantages designed to maximise patient compliance. Dermol products are suitable for all ages and sensitive skin, they do not contain sodium lauryl sulfate (SLS), parabens or perfumes.

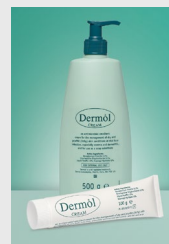
The Dermol Range



Dermol Lotion 5% oils

Dermol Lotion is specially formulated to be absorbed into dry skin and is non-greasy. It helps maintain the moisture content of the skin and is a cosmetically acceptable soap substitute.

Dermol Lotion - For dry skin.



Dermol Cream 20% oils

Dermol Cream is a rich, hydrating emollient cream, with a high oil content and humectant (glycerol) to hydrate dry, sensitive skin. It also works well as a soap substitute.

Dermol Cream - For very dry skin.



Dermol Shower 5% oils

Dermol Shower Emollient contains a non-ionic soap substitute for skin cleansing and washing and avoids the drying and irritant effects of ordinary shower gels and soap. It can also be reapplied as a leave-on moisturiser after showering.

Dermol Shower - In the shower to avoid soap.



Dermol Bath 50% oils

Dermol Bath provides antimicrobial emollient protection when bathing. It is specially formulated to disperse throughout the bath water to efficiently cover the body and help avoid leaving messy tide marks.

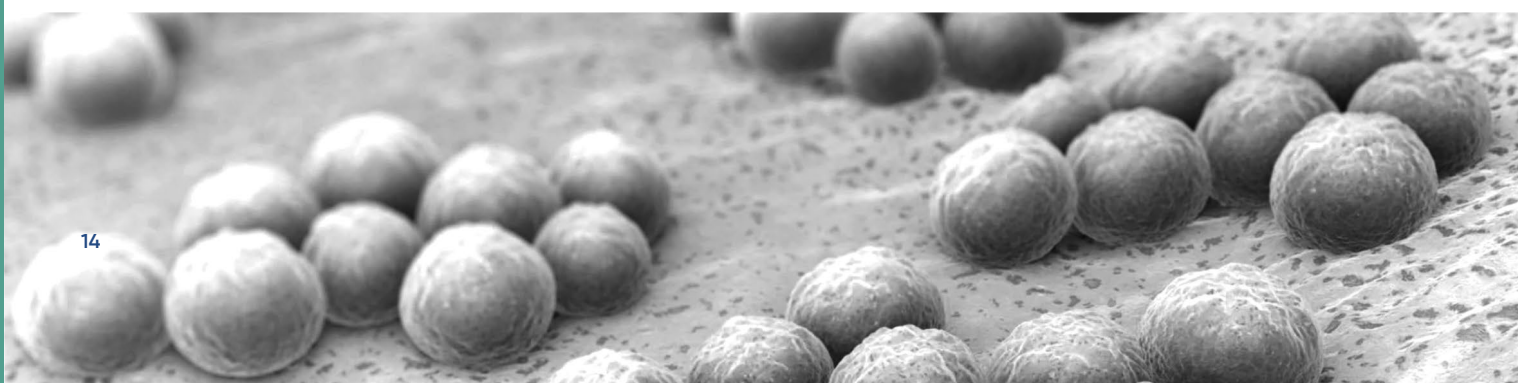
Dermol Bath - In the bath water.



Dermol Wash 5% oils

Dermol Wash contains a non-ionic soap substitute for skin cleansing and washing and avoids the drying and irritant effects of ordinary soaps. It can also be reapplied as a leave-on moisturiser after washing.

Dermol Wash - At the sink to avoid soap.



a) Clinical evaluation of the Dermol Range

i) Evaluation of Dermol Lotion

An open study to evaluate patient acceptability/ tolerability and effectiveness of Dermol Lotion in the management of chronic dry and pruritic skin conditions, especially eczema and dermatitis, in infants and young children.⁹

- 40 children (average age 6 years) receiving emollients for eczema/dermatitis were enrolled in a single centre GP study.
- Patients substituted their previous emollient for Dermol Lotion for two weeks.

Results after 14 days

Clinical effectiveness	Itching limbs/trunk	Itching face/neck	Dryness limbs/trunk	Dryness face/neck
Absent	2	18	0	18
Completely better	7	6	5	6
Much better	13	8	18	7
Better	11	4	11	4
No change	6	3	4	4
Worse	0	0	1	0
Much worse	0	0	0	0

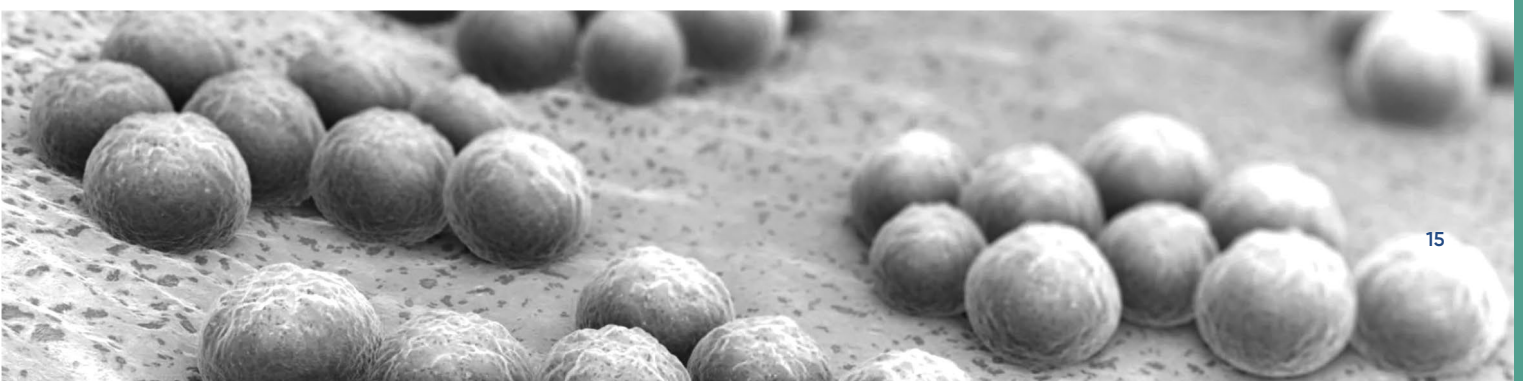
- 72% of users (or parents) ranked Dermol Lotion as more effective, 23% equivalent and 5% as less effective than their previous emollient treatment.
- In the opinion of the investigator, 9 of the 17 patients receiving adjunctive treatment were able to reduce its potency and/or frequency of application.

Cosmetic acceptability	As a skin lotion	As a soap substitute*	Overall effectiveness
Excellent	8	1	2
Very good	14	4	15
Good	12	17	20
Satisfactory	3	5	0
Poor	2	0	2

*12 patients did not use as a soap substitute

Conclusions

- These results confirm the effectiveness and ease-of-use/acceptability of Dermol Lotion in the management of these skin conditions.
- Dermol Lotion provided significant relief of itching and dryness in over 75% of cases where these symptoms were present.
- Dermol Lotion was generally well liked by patients in terms of effectiveness and ease-of-use, when compared with those they had used previously.
- Dermol Lotion was also found to be satisfactory by all patients who used it as a soap substitute.



ii) Evaluation of Dermol Cream

A study to evaluate hydration, acceptability and clinical efficacy of Dermol Cream in patients with dry skin conditions such as eczema/dermatitis.¹⁰

- 100 patients (adult, elderly or children ≥ 2 years) receiving prescribed emollients for dry/pruritic skin conditions were enrolled in this four centre GP study.
- Patients substituted their previous emollient for Dermol Cream for two weeks.

Results after 14 days

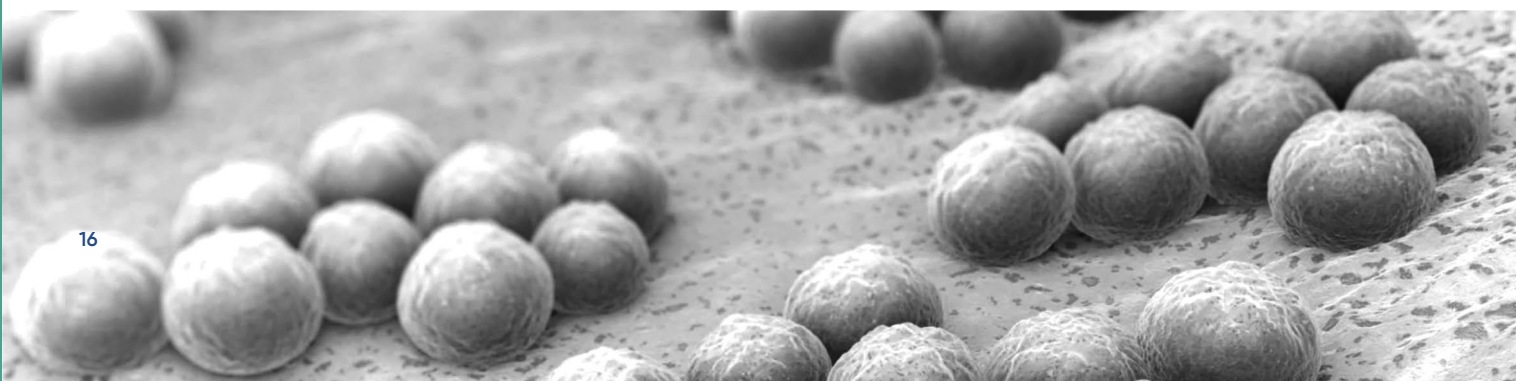
	Dryness	Itching
Excellent	36	30
Good	44	33
Satisfactory	18	30
Poor	2	6

Characteristic	Excellent	Good	Satisfactory	Poor
Odour	33	38	27	1
Consistency	25	51	23	1
Ease-of-use	30	50	19	1
Time to absorb	25	49	22	4
Soothing	36	44	17	3
Smoothing	39	42	18	1
Moisturising	39	41	19	1

- **For relief of dry skin** – 66% of patients preferred Dermol Cream compared to 12% who preferred their previous emollient ($p < 0.001$).
- **For relief of itching** – 60% of patients preferred Dermol Cream compared to 13% who preferred their previous emollient ($p < 0.001$).
- **Use as a soap substitute** – 66% of patients rate Dermol Cream as 'excellent' or 'good' as a soap substitute.

Conclusions

- Dermol Cream was generally well liked by patients.
- A statistically significant number of patients preferred Dermol Cream to their previous emollient for the relief of itching, dryness and in terms of cosmetic acceptability.
- It performed well as a soap substitute.



iii) Evaluation of Dermal Bath Emollient*

An open clinical study to evaluate Dermal Bath Emollient as an adjunct in the treatment of dry skin conditions.¹¹

- 54 patients (aged 1-88 years) attending a hospital out-patient clinic with dry skin conditions e.g. eczema, ichthyosis or psoriasis were recruited.
- Patients added 30ml of the bath emollient to their baths and continued using regular adjunctive topical therapy for up to 12 weeks.

Results

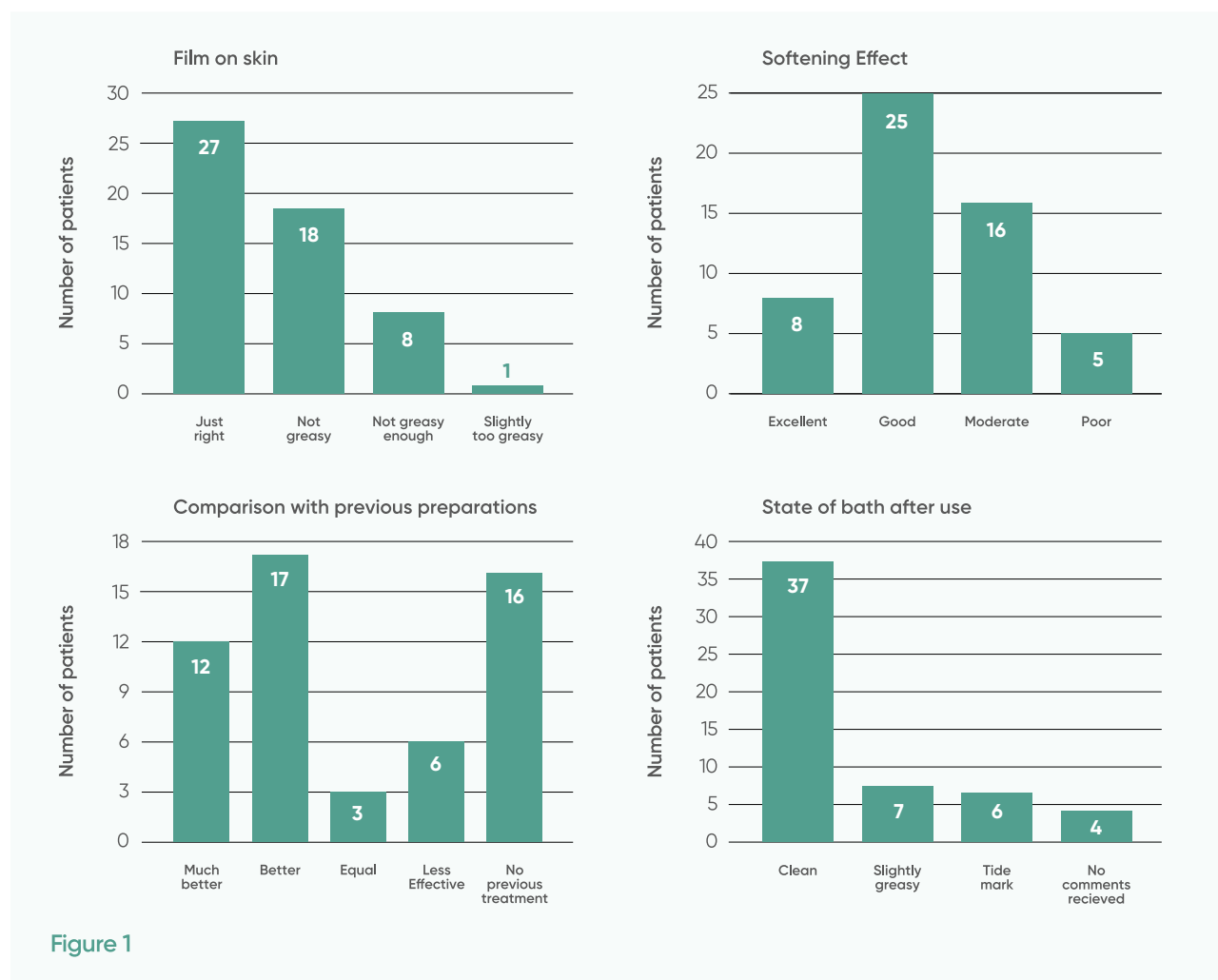


Figure 1

- Patients found the bath emollient convenient and easy to use and 76% of patients rated the bath emollient as 'much better' or 'better' than previously used preparations.
- 70% of patients reported that they were 'pleased' or 'very pleased' with the effectiveness of the product.
- 98% of patients found the bath emollient to have 'good' or 'very good' dispersal in water.
- 87% of patients experienced satisfactory cleansing with the product.

Conclusions

- In the opinion of the supervising Consultant Dermatologist, enhanced patient compliance helped to reduce the quantity and potency of adjunctive topical steroid use.
- The bath emollient was found to have a useful role to play in the management of patients with dry skin conditions.

* Dermal Bath Emollient formulation is based on the Emulsiderm formulation.

b) Antimicrobial efficacy of the Dermol Range

i) Antimicrobial efficacy studies on Dermol Lotion against *S. aureus* both *in vitro* and *in vivo*

In vitro antimicrobial activity of Dermol Lotion compared with a bland emollient cream (containing a preservative).⁹

- Test samples of each emollient were inoculated with *S. aureus*.
- Samples were taken at regular intervals over a 30-minute period.

Results

Table 5 - *In vitro* antimicrobial activity of Dermol Lotion and bland emollient cream (containing a preservative) against *S. aureus*. Values are log reductions in viable counts (>5 is equivalent to 100% mortality).

Preparation	Sampling time (min)				
	0	5	10	20	30
Dermol Lotion	1	>5	>5	>5	>5
Bland emollient cream	1	3	4	>5	>5

Conclusions

- The study confirmed the rapid bactericidal effect of Dermol Lotion, important in order to combat the colonising bacteria known to be implicated in conditions such as atopic eczema.
- By contrast, the reduction in viable bacterial count obtained with the bland emollient was much slower, and likely attributable to the preservative ingredient necessarily present in all such water-containing emulsified preparations.

In vivo cutaneous antimicrobial activity of Dermol Lotion compared with a bland emollient cream (containing a preservative).⁹

- This *in vivo* test used direct application of Dermol Lotion or a bland emollient cream, to the toe webs of each foot of healthy volunteers – as a recognised model for *S. aureus* colonisation in atopic patients.
- Bacterial cell counts were estimated from microbial samples taken immediately before and 6 hours after application.

Results

Table 6 - Determination of antimicrobial activity of Dermol Lotion *in vivo*. Values are median counts $\times 10^{-3}$.

	Total count		<i>S. aureus</i> count	
	Initial	After 6h contact	Initial	After 6h contact
Phase 1				
Dermol Lotion (right foot)	2000	25.2	204	7.2
Bland emollient cream (left foot)	1260	1600	360	360
Phase 2				
Dermol Lotion (left foot)	3000	76	184	8.8
Bland emollient cream (right foot)	2160	1040	640	460

Conclusions

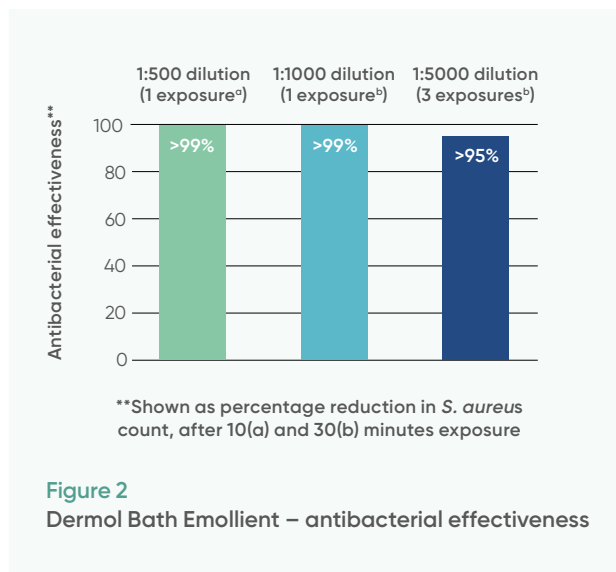
- Dermol Lotion produced a significant reduction in the indigenous population of viable colony-forming bacteria, including staphylococci, which was sustained even 6 hours after application.
- In contrast, bacterial overgrowth actually increased after treatment with the bland emollient cream (containing only a preservative).
- Given that bacteria proliferate rapidly on the skin and would be expected to recover over such a 6 hour period, the observed reductions in viable counts confirm the bactericidal activity of Dermol Lotion.

ii) Antimicrobial efficacy studies on Dermal Bath Emollient* both *in vitro* and *in vivo*

In vitro antimicrobial activity.¹²

- *S. aureus* inoculum was added to various aqueous dilutions of the bath emollient thus simulating use in the bath.
- Bacterial kill rates were determined at 10 and 30 minutes.

Results



- A 1 in 500 dilution achieved complete bactericidal activity against *S. aureus* within 10 minutes.
- A higher dilution of 1 in 1000 achieved a reduction in viable count in excess of 97% within 10 minutes and greater than 99% within 30 minutes.

Conclusions

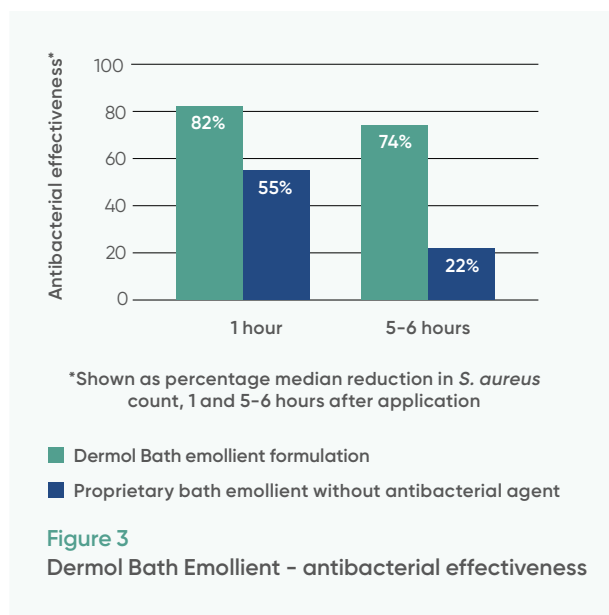
- Even at extended dilution in the patient's bath water, the bath emollient achieved substantial bactericidal activity against *S. aureus*, the microorganism implicated in atopic dermatitis.
- In normal clinical usage, the bactericidal activity might be even greater, because a proportion of the antimicrobial remains on the patient's skin after bathing.

* Dermal Bath Emollient formulation is based on the Emulsiderm formulation.

In vivo cutaneous antimicrobial activity of Dermal Bath Emollient compared with a non-antimicrobial proprietary bath emollient.¹³

- Dermal Bath Emollient was applied to the toe webs of one foot and a non-antimicrobial bath emollient applied to the other foot in 18 healthy volunteers.
- Swabs were taken immediately before, at 1 hour and 6 hours post application.

Results



Conclusions

- After 6 hours, Dermal Bath Emollient significantly reduced the population of viable colony-forming bacteria, compared to the bland emollient ($p=0.007$).
- The bactericidal activity is sustained for at least 6 hours.

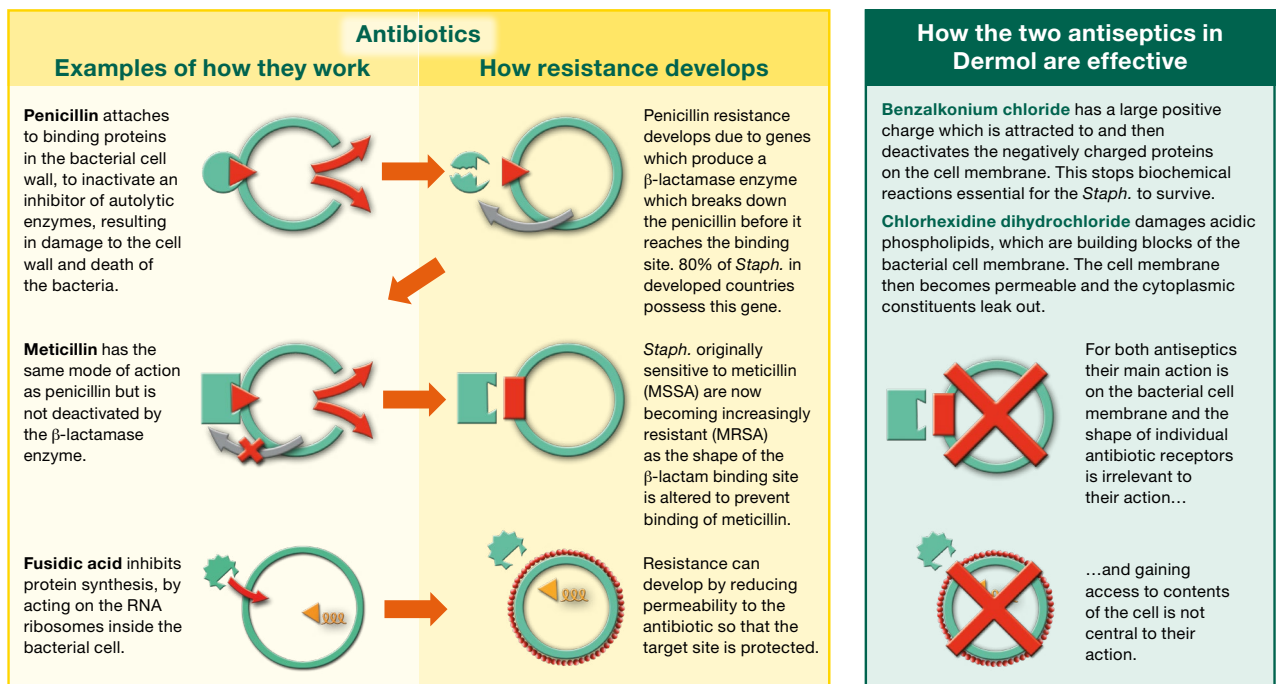
c) Avoiding antimicrobial resistance

Concerns have been raised about the injudicious use of antimicrobial agents, particularly topical antibiotic preparations, and the development of bacterial resistance for many years now. A number of published studies have reported increased incidences of bacterial resistance to antibiotics, such as meticillin and fusidic acid.

Antiseptics are effective antimicrobial agents, which can minimise bacterial resistance and continue to be effective against antibiotic resistant strains by virtue of their non-specific bactericidal mechanisms of action, as illustrated in the diagram below.

Minimising antimicrobial resistance

As the Dermol antimicrobial emollients contain antiseptics and not antibiotics, the risk of antibiotic resistance developing is minimised.



The antimicrobial agents in Dermol Lotion, Cream, Wash and Shower Emollient are benzalkonium chloride and chlorhexidine dihydrochloride, both present at a low but clinically effective concentration of 0.1%. These are known to act synergistically to enhance their activity, while minimising the risk of skin irritation, which is concentration dependent. The antimicrobials in Dermol are antiseptics which have a different mode of action to antibiotics. Because of this, the risk of antibiotic resistance is minimised.

The Dermol range of products has been widely used, helping eczema patients for more than 25 years. Based on extensive clinical usage, irritant or allergic adverse reactions to the Dermol products are very rare (<1/10,000 based on spontaneous reporting).¹⁴ Because of the synergism and enhanced activity, the two antiseptics in Dermol are clinically effective at a low concentration of just 0.1% each.

To summarise, the Dermol range contains antiseptics at a low concentration to avoid irritation and as they are very unlikely to induce resistance to antibiotics, they can be considered a very useful choice for routine use.

d) Activity of the Dermal range against resistant strains of *S. aureus in vitro*

i) Routine infection control using a proprietary range of combined antiseptic emollients and soap substitutes – their effectiveness against MRSA and FRSA.¹⁵

- The Dermal range was tested against methicillin resistant *Staph aureus* (MRSA) and fusidic acid resistant *Staph aureus* (FRSA) according to the rigorous European Standard (EN1276:1997) normally applied to disinfectants and antiseptics used in non-clinically sensitive circumstances.
- Neat samples of Dermal Lotion, Shower and Cream and 1% dilution of Dermal Bath were inoculated with MRSA or FRSA either in the presence of bovine serum albumin (BSA) to mimic clinically 'dirty' conditions or without BSA to mimic 'clean' conditions.
- Samples were taken at specified intervals over a 30-minute period.

Results

Table 7 - Activity of Dermal Cream, Dermal Lotion and Dermal Shower against FRSA and MRSA

	Contact time (min)	FRSA		MRSA	
		Log Kill (Clean)	Log Kill (Dirty)	Log Kill (Clean)	Log Kill (Dirty)
Dermal Cream (undiluted)	0	<4.6*	<3.5*	<3.6	<3.6
	5	>6.4*	4.2*	5.7	4.8
	10	>6.4*	5.6*	6.0	6.0
	20	>6.4*	5.6*	>6.0	>6.0
	30	>6.4*	>6.5*	>6.0	>6.0
Dermal Lotion/ Dermal Shower (undiluted)	0	<2.9	<2.9	<3.6	<3.6
	5	>6.4	>6.4	5.3	3.9
	10	>6.4	>6.4	>6.0	>6.0
	20	>6.4	>6.4	>6.0	>6.0
	30	>6.4	>6.4	>6.0	>6.0

Key: ■ = ≥ 99.999% (5 log) reduction ■ = ≥ 99.99% (4 log) reduction
*mean result of two tests

Dermal Cream, Lotion and Shower met the standard criteria of ≥5 log reduction (99.999% reduction) in microbial counts within 5 minutes against both FRSA and MRSA under 'clean' conditions and within 10 minutes under 'dirty' conditions against MRSA.

Table 8 - Activity of Dermal Bath (1% dilution) against FRSA and MRSA

	Contact time (min)	FRSA		MRSA	
		Log Kill (Clean)	Log Kill (Dirty)	Log Kill (Clean)	Log Kill (Dirty)
Dermal Bath (1% diluted)	0	<4.1	<4.1	<3.6	<3.6
	5	4.8	<4.1	<3.6	<3.6
	10	4.8	<4.1	4.1	<3.6
	20	5.0	4.4	4.3	3.7
	30	5.3	4.6	4.4	3.8

Key: ■ = ≥ 99.999% (5 log) reduction ■ = ≥ 99.99% (4 log) reduction

Dermal Bath even at 1% dilution achieved ≥5 log reduction against FRSA (and greater than 4 log reduction against MRSA) after 20 minutes under 'clean' conditions and a reasonable kill of close to 4 log reduction (99.99%) by 20 minutes under 'dirty' conditions.

Conclusions

- The Dermal range exhibited significant antimicrobial activity against FRSA and MRSA.
- The Dermal range of antiseptic emollients are designed for use on sensitive skins and can be used in a variety of ways as soap substitutes, body washes, leave-on preparations and even for bathing.
- The Dermal range are a useful addition to the infection control armamentarium (even against FRSA and MRSA) and being antiseptic rather than antibiotic, they are unlikely to induce bacterial resistance.

ii) Antimicrobial activity against mupirocin-resistant *Staphylococcus aureus* *in vitro*.¹⁶

- The activity of Dermol Lotion and Dermol Cream against a mupirocin resistant strain of *S. aureus* was assessed in accordance with Eu Ph 9.2 5.1.11 test method.
- In summary, antimicrobial activity was determined by adding test suspension of *S. aureus* NC13616 to the samples of antiseptic products.
- Samples were taken at specified intervals over a 30-minute period.
- A disinfectant is considered to meet the efficacy required for bactericidal activity when able to produce a reduction in viability of $\geq 5 \text{ Log}_{10}$.

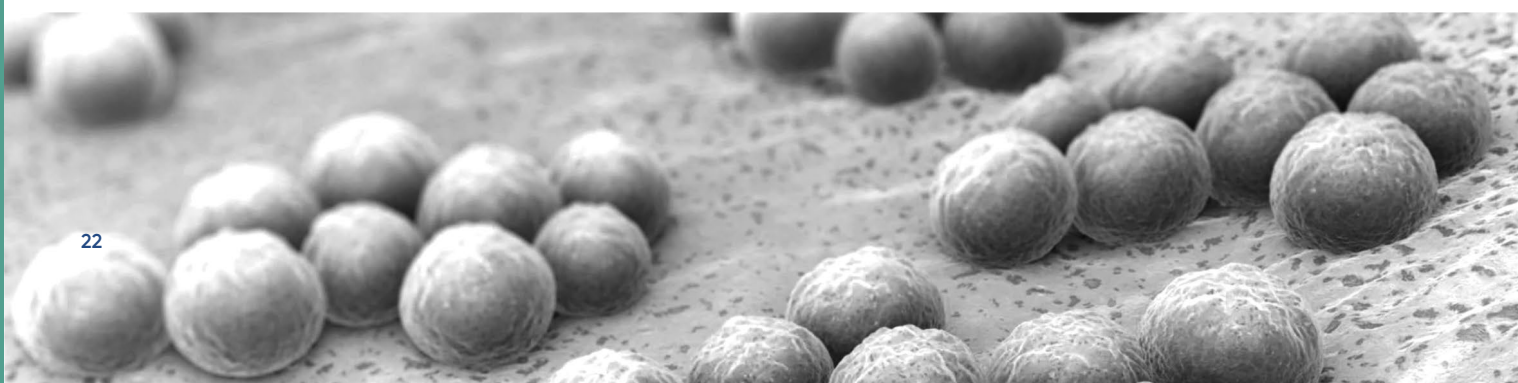
Results

Table 9 - Activity of Dermol Lotion and Dermol Cream against mupirocin resistant <i>Staphylococcus aureus</i>			
Dermol Lotion and Dermol Cream			
Organism (contact time)	Log Kill	Pass Criteria	Pass/Fail
<i>S. aureus</i> (5 min)	>6.51	≥ 5.0	Pass
<i>S. aureus</i> (10 min)	>6.51	≥ 5.0	Pass
<i>S. aureus</i> (20 min)	>6.51	≥ 5.0	Pass
<i>S. aureus</i> (30 min)	>6.51	≥ 5.0	Pass

- The control count of test microorganisms was 3.2×10^8 cfu/ml.
- Both Dermol Lotion and Dermol Cream achieved $> 6.51 \text{ Log}_{10}$ kill at all tested time points (5 min, 10 min, 20 min and 30 min).
- The procedure was also successfully validated.

Conclusion

- Tested *in vitro*, topical antiseptic formulations Dermol Lotion and Dermol Cream exhibit rapid bactericidal activity against *S. aureus* NC13616 (EMRSA-15 mupA +ve), a strain that has been reported to be mupirocin resistant.



e) Atopic eczema exacerbation

Biofilms comprise of surface-associated, highly structured communities of microorganisms enclosed within a protective extracellular matrix. *Staphylococcus* biofilms have been associated with atopic dermatitis and by harbouring staphylococcal bacteria, this may leave dry, itchy, damaged skin prone to ongoing irritation by the microorganisms.

i) *Staphylococcus* biofilm inhibition, *in vitro*, using an antiseptic emollient containing chlorhexidine and benzalkonium chloride.¹⁷

- Biofilms of MRSA and MSSA (from clinical isolates) and *Staphylococcus aureus* and *Staphylococcus epidermidis* (reference strains) were formed *in vitro*.
- After removal of planktonic bacteria, Dermol Lotion (at different dilutions) was added to the biofilms. The Sessile Minimum Inhibitory Concentration (SMIC) was assessed (the MIC associated with microorganisms present in the protective biofilm).

Results

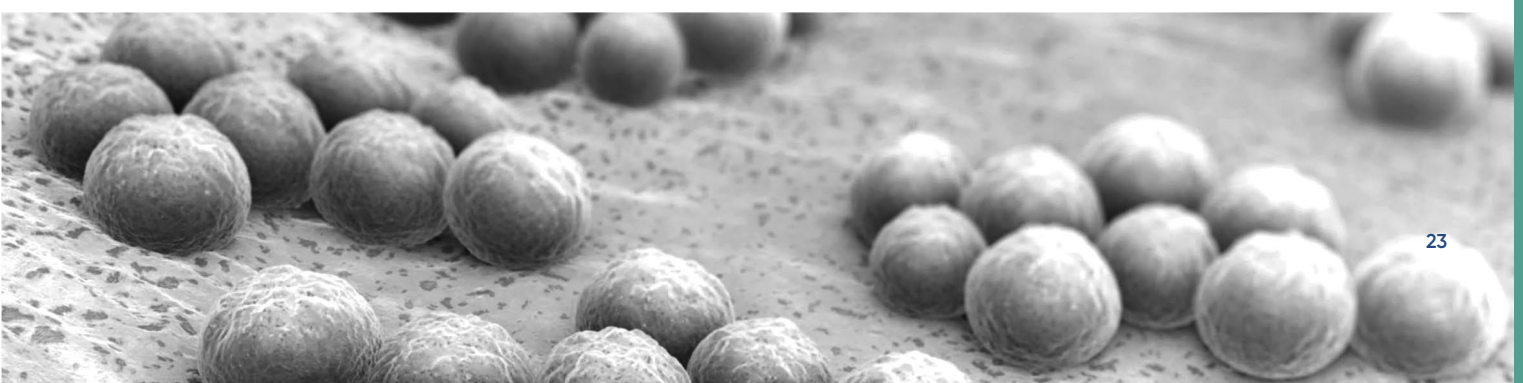
Microorganism	Dermol Lotion SMIC
<i>S. aureus</i> (NCTC 6751)	1 in 16 dilution
<i>S. epidermidis</i> (RP62A)	1 in 8 dilution
MRSA (EMRSA 100)	1 in 8 dilution
MSSA (Newman)	1 in 16 dilution

Microorganism	% dispersal at SMIC
<i>S. aureus</i> (NCTC 6751)	67%
<i>S. epidermidis</i> (RP62A)	32%
MRSA (EMRSA 100)	12%
MSSA (Newman)	0%

The percentage dispersal of the biofilm, at the SMICs, is presented in Table 11.

Conclusion

- When tested *in vitro*, Dermol Lotion significantly inhibited *Staphylococcus* biofilms, and this was not generally associated with high levels of biofilm dispersal, indicating that the antimicrobial agents penetrated inside the biofilm matrix.



f) Skin cleansing with soap substitutes in the Dermol Range

Most ordinary soaps, foaming shower gels and bubble baths contain harsh cleansing agents that can have a detrimental effect on the integrity of the skin. Ordinary soaps and detergents, which are anionic, can act as primary irritants. One example, sodium lauryl sulfate, is actually used as a positive marker for skin susceptibility to irritancy.¹⁸

A non-ionic surface active agent avoids these problems and is therefore more acceptable as a soap substitute for repeat usage on sensitive skin such as found in atopic eczema. Using an antimicrobial emollient soap substitute for skin cleansing and washing avoids the drying and often irritant effects of ordinary soaps and cleansers whilst helping to reduce bacterial load on the skin.

The Dermol range, which contains a non-ionic cleansing agent, can be used as antimicrobial emollient soap substitutes with 'skin-friendly' benefits to avoid the skin-drying effects of ordinary soaps. Dermol Cream, Dermol Lotion, Dermol Shower and Dermol Wash can also be reapplied as a leave-on moisturiser after patting the skin dry.

Development of antibiotic resistant strains of *S. aureus* such as methicillin resistant (MRSA) and fusidic acid resistant (FRSA) can be a problem in Dermatology. As referenced earlier, the Dermol range has been shown to exhibit significant antimicrobial activity against MRSA and FRSA.

Dermol Lotion has been shown to be as effective against methicillin resistant *S. aureus* (MRSA) as it is against methicillin sensitive *S. aureus* (MSSA) as shown below.¹⁸

i) *In vitro* antimicrobial activity of Dermol Lotion against MSSA and MRSA.¹⁸

Exposure to both the neat lotion and a 10 x dilution produced no viable counts of either MRSA or MSSA after as little as 5 minutes contact.

Table 12 – Antimicrobial activity of Dermol Lotion against methicillin sensitive (MSSA) and methicillin resistant (MRSA) *Staphylococcus aureus*

Strain of <i>S. aureus</i>	Dilution of Dermol Lotion	Control	Total viable count		
			Contact time (mins)		
			0	5	10
MSSA	Undiluted	120 million	5.6 million	0	0
	x10 dilution	120 million	0.7 million	0	0
MRSA	Undiluted	83 million	1.3 million	0	0
	x10 dilution	83 million	0.13 million	0	0

In addition, Dermol Wash has shown bactericidal activity against strains of *S. aureus* that carry the virulence factor Panton-Valentine Leukocidin (PVL-SA) irrespective of methicillin susceptibility status (i.e. MSSA or MRSA).¹⁹ PVL-producing strains are more virulent and tend to result in more severe skin and soft tissue infections than non-PVL producing *Staphylococcus*. Circulating strains may be methicillin-sensitive or resistant: PVL-MSSA or PVL-MRSA.

PVL-SA infections are highly transmissible. The broken, scratched (and often abraded) skin resulting from dermatitis may be prone to this infection. This is especially the case when the patient either lives communally (for example, in military barracks or university halls of residence) or takes part in close contact sports such as rugby or judo.

ii) Evaluation of the bactericidal activity of an antiseptic emollient wash formulation against Panton-Valentine Leukocidin producing *Staphylococcus aureus* (in vitro).¹⁹

- In vitro study (BS EN 1276:2009) tested the bactericidal activity of Dermal Wash against 3 strains of PVL – *S. aureus* (from clinical isolates) and a reference strain
 - 2 PVL-MSSA
 - 1 PVL-MRSA
 - 1 PVL negative MSSA (reference)
- Bovine serum albumin was used as an interfering substance, at 0.03% w/v to simulate 'clean' conditions and at 0.30% w/v for 'dirty' conditions.

Results

Table 13 – Bactericidal activity of Dermal Wash

Contact time (min)	ATCC 6538 (MSSA)		ARL-11-046 (PVL-MRSA)		ARL-12-016 (PVL-MSSA)		ARL-12-098 (PVL-MSSA)	
	Log Reduction (Clean)	Log Reduction (Dirty)	Log Reduction (Clean)	Log Reduction (Dirty)	Log Reduction (Clean)	Log Reduction (Dirty)	Log Reduction (Clean)	Log Reduction (Dirty)
5	>5.23	>5.23	5.12	>5.36	>5.23	>5.23	>5.28	>5.28
10	>5.23	>5.23	>5.36	>5.36	>5.23	>5.23	>5.28	>5.28
20	>5.23	>5.23	>5.36	>5.36	>5.23	>5.23	>5.28	>5.28
30	>5.23	>5.23	>5.36	>5.36	>5.23	>5.23	>5.28	>5.28

Dermal Wash met the stringent test criteria of ≥ 5 log reduction within 5, 10, 20 and 30 minutes contact time under both 'clean' and 'dirty' conditions against the reference strain and all three PVL-positive clinical isolates of *S. aureus* irrespective of meticillin susceptibility status.

Conclusion

- Dermal Wash can be described as bactericidal (as defined by BS EN 1276:2009) against PVL-SA. Within the limitations of the test protocol, the presence of PVL genes in the MRSA and MSSA test strains did not affect sensitivity to the active substances in the antiseptic emollient wash.

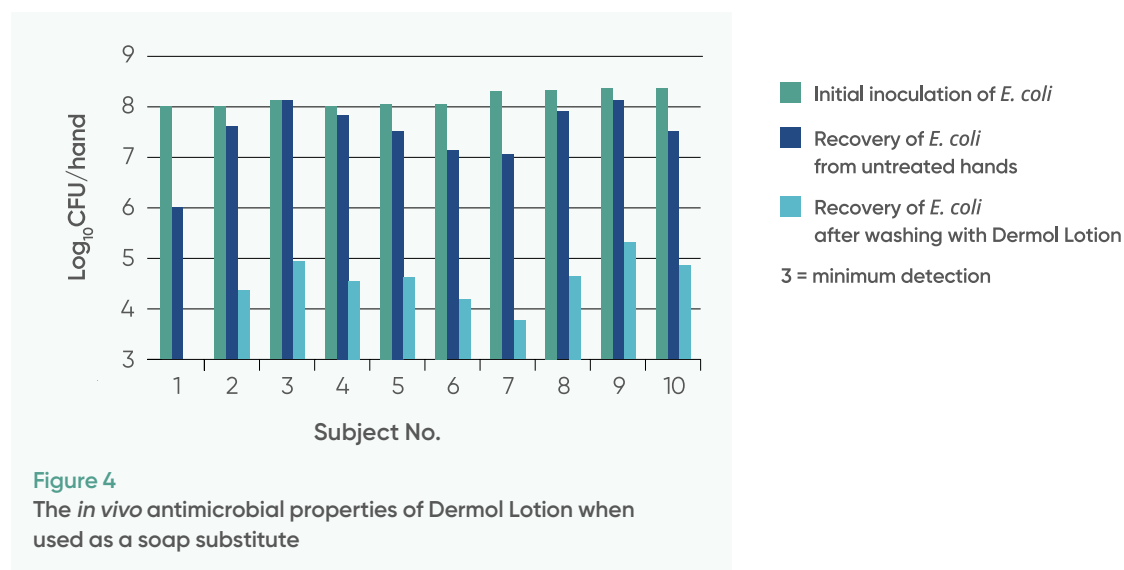
The studies below against *E.coli* further demonstrate the effectiveness of Dermol Lotion and Dermol Wash when used as antimicrobial emollient soap substitutes.

iii) Antimicrobial activity of Dermol Lotion and Dermol Wash against transient microorganisms such as *Escherichia coli* (*E. coli*) (*in vivo*).¹⁸

Microorganisms found on the hands and other parts of the body may be classified as 'transients' and 'residents'. Transients, e.g. *E. coli*, do not usually grow on the skin and are acquired by day-to-day contact with contaminated surfaces. 'Residents' are the normal stable microflora of the skin and are more difficult to remove by washing or disinfection. They consist mainly of *S. epidermidis*, other staphylococci, micrococci and corynebacteria. In circumstances where elimination of 'transient' organisms is desired, a model involving artificial contamination can be used to assess the effectiveness of an antibacterial agent.

- The hands of 10 healthy volunteers were inoculated with *E. coli*.
- Dermol Lotion was used as a wash and emollient on the hands.
- Recovery of viable organisms was determined using ethanol as a negative control, after inoculation with *E. coli* (positive control) and after application of *E. coli* and Dermol Lotion.
- The efficacy of Dermol Lotion was evaluated as a \log_{10} reduction factor (RF) when compared to the positive control.

Results



- No viable counts of *E. coli* were detected in the negative controls.
- The average RF value was 3.02 for Dermol Lotion.
- Dermol Lotion killed between 99.8 and 100% of microorganisms.

Conclusions

- The FDA recommendation for removal of bacteria is a 2 \log_{10} reduction after 1 wash and 3 \log_{10} reduction after 10 washes with a medicated soap. A 3 \log_{10} reduction represents an activity rate of 99.9%.
- Dermol Lotion showed an average of 3 \log_{10} reduction after just one wash and therefore far exceeds the FDA requirements for a medicated soap.
- This demonstrates that Dermol Lotion used as an antimicrobial soap is highly effective as a hand wash to remove transient organisms.

Similarly, Dermol Wash has proven antimicrobial activity meeting Standard BS EN1499 (modified) against *E. coli*.²⁰

iv) Bactericidal activity of a 'skin friendly' combined handwash and leave-on skin conditioner (*in vivo*).²⁰

- Dermol Wash used as a combined handwash and leave-on skin conditioner, complies with Standard EN 1499 (modified), the evaluation test for suitability of a hygienic handwash where disinfection is medically needed.
- The test comprises assessment of the number of test organisms (*E.coli*) released from the fingertips of artificially contaminated hands before and after hygienic handwash with Dermol Wash or standard soft soap (as a reference product).

Results

	Reference Product			Test Product		
	Log ₁₀ pre values	Log ₁₀ post values	Log ₁₀ reduction	Log ₁₀ pre values	Log ₁₀ post values	Log ₁₀ reduction
1	6.44	3.15	3.29	7.20	2.99	4.21
2	7.47	3.54	3.93	7.06	3.56	3.50
3	7.29	4.28	3.01	7.36	3.18	4.18
4	7.05	3.67	3.38	6.64	3.05	3.59
5	7.15	4.07	3.08	7.17	3.72	3.45
6	7.07	4.11	2.96	7.35	3.59	3.76
7	7.10	3.76	3.34	7.20	2.76	4.44
8	7.17	3.98	3.19	7.28	3.16	4.12
9	7.41	3.89	3.52	7.24	3.63	3.61
10	7.40	3.16	4.24	7.36	2.78	4.58
11	7.44	3.69	3.75	7.34	2.57	4.77
12	7.31	3.88	3.43	7.07	3.14	3.93
13	7.34	3.95	3.39	7.24	3.06	4.18
14	6.99	4.22	2.77	7.08	3.10	3.98
15	7.38	3.32	4.06	7.52	2.89	4.63
Mean	7.20	3.78	3.42	7.21	3.15	4.06
Standard deviation	0.262	0.358	0.419	0.202	0.344	0.424

Conclusion

- It was concluded that Dermol Wash used as a hygienic handwash and leave-on skin conditioner, was significantly more effective than the reference soap with a mean Reduction Factor [in microbial counts] of 4.06 compared to 3.42 ($p=0.01$).

v) The *in vivo* effects on stratum corneum of an antimicrobial hand wash used to supplement alcohol rub in professional hand cleansing.²¹

Dermol Wash has also demonstrated protective effects on skin condition when used in conjunction with alcohol rubs in semi-intensive hand washing regimes. This study was a single-centre assessor-blind, parallel-group comparison in 40 healthy, adult volunteers: 20 subjects received Dermol Wash after alcohol rub and 20 subjects received Hibiscrub. Subjects had to assess changes in their skin condition over 5 days and by the end of day 5, scores of 'much worse' were recorded by 70% in the comparator group and in 15% of the Dermol Wash group ($p < 0.001$).

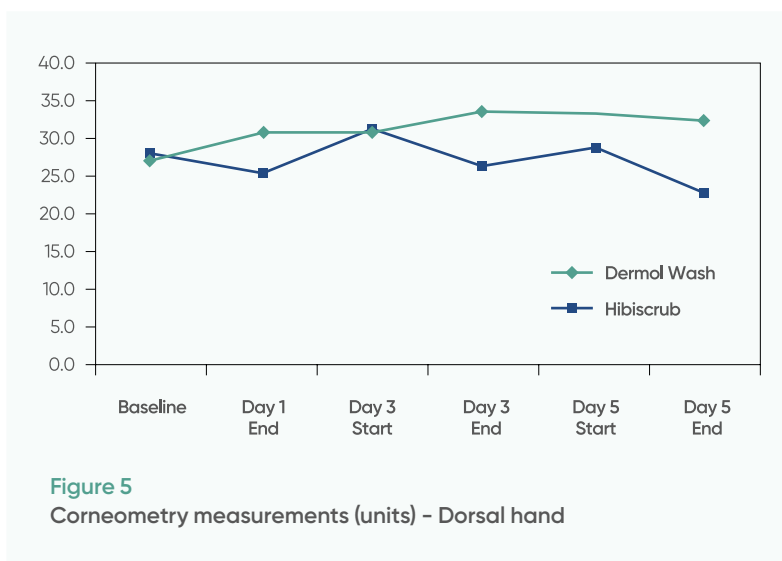
Results

Table 15 - Subjects' assessment of how skin felt. Parentheses indicate cumulative numbers of withdrawn subjects.

Category	End day 1		End Day 3		End Day 5	
	Alcohol rub/ Dermol Wash	Alcohol rub/ Marketed comp	Alcohol rub/ Dermol Wash	Alcohol rub/ Marketed comp	Alcohol rub/ Dermol Wash	Alcohol rub/ Marketed comp
-2: Skin feels much worse than before study	1	4	2 (1)	8 (2)	3 (1)	14 (4)
-1: Skin feels slightly worse than before study	8	11	13	11	10	4 (1)
0: Skin feels the same as before study	9	5	5	1	7	2
1: Skin feels slightly better than before study	1	0	0	0	0	0
2: Skin feels much better than before study	1	0	0	0	0	0

Dermol Wash also performed better when assessed by corneometry:

- Dermol Wash - 19% increase in skin hydration at the end of day 5 in comparison to baseline
- Hibiscrub - 18% decrease in skin hydration at the end of day 5 in comparison to baseline
- Dermol Wash better than Hibiscrub at all time points except for the start of day 3



Conclusion

It was concluded that the use of an appropriate hand wash product, such as Dermol Wash, even in conjunction with ubiquitous alcohol rubs which are notoriously problematic, can achieve significant benefits – assessed in terms of subjects' own assessments of how their skin feels, and measured by corneometry.

g) Helping to prevent secondary infection in compromised skin

A compromised skin barrier is a route of ingress for microbes, which leaves the skin susceptible to secondary infection. The Dermal range helps to combat bacteria on the skin and rehydrate dry skin by helping to restore the skin barrier function and helping to prevent secondary infection in compromised skin. When tested *in vitro*, products in the Dermal range have proven antimicrobial activity against several microbes that can cause secondary infection. These include:

- *Pseudomonas aeruginosa*²²
- *Streptococcus pyogenes*²³
- *Malassezia furfur*²⁴

For further study details please visit the website below or scan the QR code:

Visit www.dermal.co.uk/Dermal then select the button:
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h) Further uses of Dermal antiseptic emollients

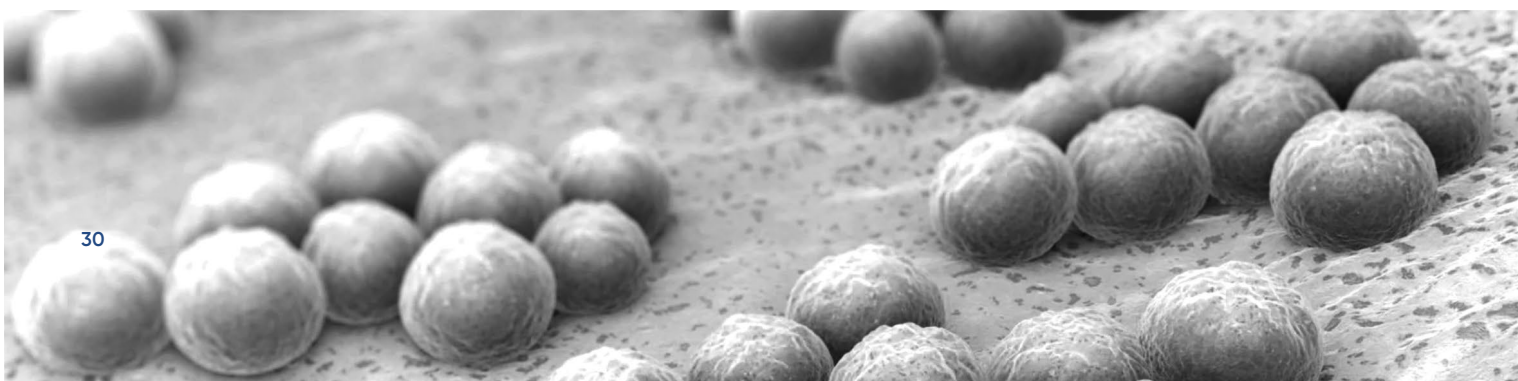
Potential problems arise in those patients going into hospital for elective surgery or routine procedures who show a positive result for carriage of MRSA following pre-hospital admission screening. In this situation, patients will not be able to undergo surgery until the MRSA has been eradicated. In such cases, the Dermal range may offer a useful therapeutic option in people with skin conditions or delicate skin due to its antimicrobial activity against MRSA as shown previously.²⁵

Secondly, doctors and nurses working in Occupational Health Departments within hospitals often find Dermal Lotion or Dermal Cream useful for treating the hands of medical personnel that have become very dry, sore and even fissured as a result of contact dermatitis from the constant use of soap and/or alcoholic hand rubs and scrubs. In this situation, Dermal Lotion or Dermal Cream can be used as an antibacterial soap substitute, with the added benefit of emollient properties to soothe and rehydrate dry, sore and chapped hands, thus enabling the healthcare staff to continue at work.

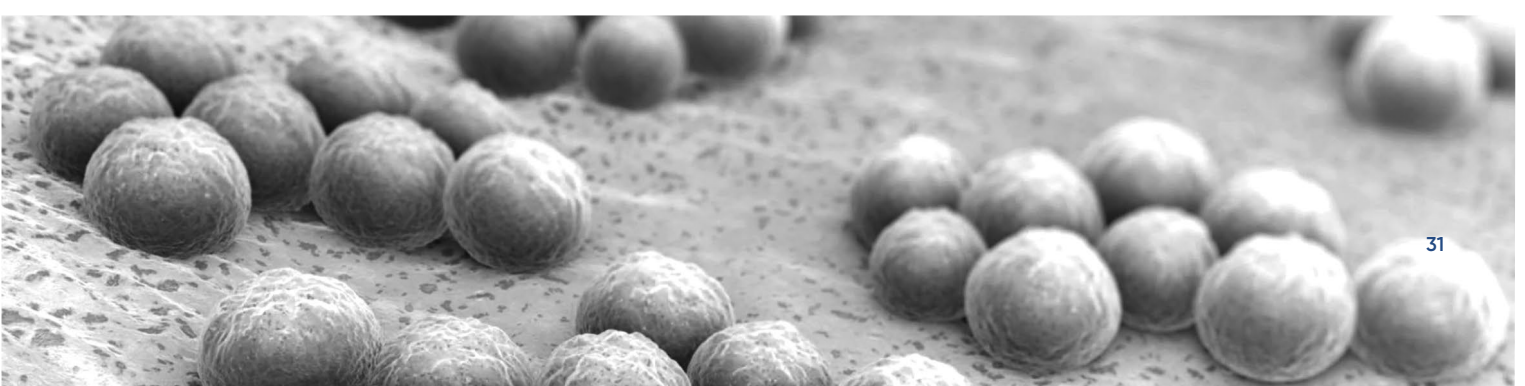
To summarise, Dermal Lotion can be considered an effective, well tolerated hand wash to control bacterial contamination. It has been shown to be effective even in the presence of resistant bacteria i.e. MRSA and FRSA. With its emollient properties and low irritancy potential, Dermal Lotion provides a useful alternative to soap for routine hand washing, particularly for those with soap or detergent induced hand dermatitis.

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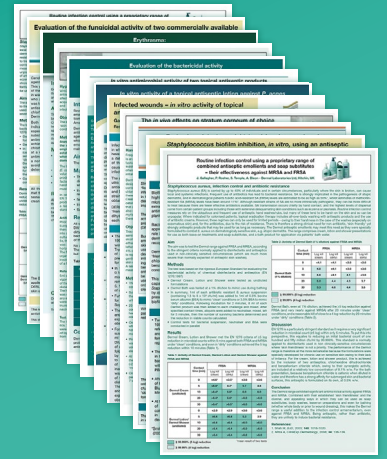
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Dermol antimicrobial emollients Backed by clinical evidence¹⁻¹⁵



- Specially formulated for use on dry and itchy skin conditions, including eczema and elderly pruritus.
- Antimicrobials and emollients working together to help:
 - maintain the moisture content of the skin and prevent exacerbation of eczema
 - repair compromised skin and prevent secondary infection.
- Dermol can be used for as long as required to maintain the moisture content of the skin and help combat potentially pathogenic microbes.
- Versatile, well tolerated, suitable for all ages and sensitive skin.

Helping patients
for nearly 30 years
Only available
from pharmacies



To find out more about the Dermol range, including clinical evidence, scan the QR code or visit www.dermal.co.uk/Dermol then select the button: "VIEW DERMOL DOSSIER"

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Dermol® Wash Cutaneous Emulsion, Dermol® 200 Shower Emollient and Dermol® 500 Lotion

Benzalkonium chloride 0.1% w/w, chlorhexidine dihydrochloride 0.1% w/w, liquid paraffin 2.5% w/w, isopropyl myristate 2.5% w/w.

Dermol® Cream

Benzalkonium chloride 0.1% w/w, chlorhexidine dihydrochloride 0.1% w/w, liquid paraffin 10% w/w, isopropyl myristate 10% w/w.

Uses: Antimicrobial emollients for the management of dry and pruritic skin conditions, especially eczema and dermatitis, and for use as soap substitutes.

Dermol® 600 Bath Emollient

Benzalkonium chloride 0.5% w/w, liquid paraffin 25% w/w, isopropyl myristate 25% w/w.

Uses: Antimicrobial bath emollient for the management of dry, scaly and/or pruritic skin conditions, especially eczema and dermatitis.

Package quantities: Dermol Wash: 200ml pump dispenser. Dermol 200 Shower Emollient: 200ml shower pack. Dermol 500 Lotion: 500ml pump dispenser. Dermol Cream: 100g tube, 500g pump dispenser. Dermol 600 Bath Emollient: 600ml bottle. **Legal category:** Dermol Cream and Dermol Wash Cutaneous Emulsion [P], Dermol 200 Shower Emollient, Dermol 500 Lotion and Dermol 600 Bath Emollient GSL/[P]. **MA holder:** Dermal Laboratories, Tatmore Place, Gosmore, Hitchin, Herts, SG4 7QR, UK. 'Dermol' is a registered trademark.

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