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Atopic dermatitis and *Staphylococcus aureus* secondary skin infections

Antibiotic stewardship should guide treatment

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Introduction

Atopic dermatitis (AD) is a chronic pruritic inflammatory skin disease that occurs most frequently in children but can also affect adults.[1] A characteristic feature of patients with AD is the abundant presence of *Staphylococcus aureus* relative to healthy individuals.[2] Generally, the human skin microbial population (often referred to as the microbiome) consists of a variety of staphylococci, *Propionibacterium acnes* and yeasts. All of these microorganisms are present on the skin surface and in skin folds, as well as in hair follicles.[2] The opportunistic pathogen, *S. aureus*, can be isolated from more than 90% of AD skin lesions; in fact, one study isolated *S. aureus* from 100% of lesional skin and 79% of normal skin in patients with AD.[2,3] *S. aureus* is commonly implicated as the causative pathogen in secondary skin infections in people with AD.[3]

LEARNING OBJECTIVES

You will learn:

- *Staphylococcus aureus* is commonly implicated as the causative pathogen in secondary skin infections in people with atopic dermatitis (AD), with *S. aureus* antibiotic resistance of increasing concern worldwide
- Understanding of the pathogenesis and recognising clinical features of *S. aureus* infection in AD forms the basis of guiding treatment choices that support the principles of antibiotic stewardship
- Maintaining skin barrier function and considered use of anti-inflammatory and antibiotic therapy is recommended as best practice for treatment of AD with secondary infection.

Secondary bacterial infections in AD

Patients with AD are strongly predisposed to the development of secondary staphylococcal infections as a result of colonisation of the stratum corneum by *S. aureus*, damage to the skin barrier and a defective immune response. The number of *S. aureus* organisms in AD patients is 100-fold higher than in healthy individuals.[2]

Pathogenesis of *S. aureus* infection

The mechanism for increased *S. aureus* colonisation on AD skin is unknown, but it is likely to be the result of a number of complex processes, including disruption of skin barrier function due to scratching, exposure of inflamed underlying skin and loss of certain innate antibacterial activities consequent on changes in lipid composition or β-defensin levels. Lipid deficiencies in AD skin contribute to dry, cracked and brittle skin that is predisposed to *S. aureus* colonisation.[4]

S. aureus as an allergen

The immune system over-responds to skin colonisation by *S. aureus* in those with AD. The infection has a toxic effect on keratinocytes and stimulates lymphocytes to secrete proinflammatory cytokines, which leads to the development of the chronic form of AD. The bacteria themselves, as well as their excreted metabolites, induce the activation of T lymphocytes, macrophages and antigen-presenting cells with consequent increased

This report was made possible by an unrestricted educational grant from **Adcock Ingram**. *The content of the report is independent of the sponsor.*

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production of immunoglobulin E (IgE). Anti-staphylococcal IgE has been identified and measured in patients with AD and these levels correlate with the severity of the disease.[2]

S. aureus has been known to produce superantigens that exacerbate the inflammatory response in AD and induce corticosteroid insensitivity.[3] The *S. aureus* strains isolated from the skin of patients with AD release toxins such as staphylococcal enterotoxins A, B and C, and the toxic shock syndrome toxin-1 (TSST-1), which penetrate the epidermis and interact with various immune cells; this leads to an inflammatory response orchestrated by T cells. These virulence factors act as superantigens and are produced by almost 70% of *S. aureus* strains.

Staphylococcal superantigens (SSAgs) trigger T cell activation by binding non-specifically to the T cell receptors without the need for antigen presentation, thereby stimulating the lymphocytes to excessively produce cytokines.[2,5] Additionally, SSAgs promote the production of IgE, which activates mast cells and basophils to release inflammatory mediators (Figure 1). When SSAgs penetrate the skin barrier, they not only contribute to the development of chronic inflammation in the atopic skin lesions, but also make T cells unresponsive to topical corticosteroids; so patients with AD may be insensitive to this treatment.[2,4]

Clinical features of AD and secondary infection

Since *S. aureus* colonises nearly 100% of AD patients, impetiginisation of AD lesions is frequent and is associated with disease exacerbation.[1] The infected plaques become crusted, honey-coloured and weeping as a result of secondary infection. The surrounding tissues often show features of cellulitis and, occasionally, blisters and pustules may also be seen (Figure 2). The infection may also be more subtle, however, presenting as excoriations, increased erythema or fissuring of the skin.[3]

Distinction between simple colonisation and infection may be difficult. Clinical features that are more indicative of infection rather than colonisation include:[2,6]

- Painful, oozing or crusted honey-coloured lesions
- Pustules and blisters
- An asymmetrical distribution
- Rapid exacerbation
- Systemic disease.

Colonisation by *S. aureus* also increases the Eczema Area and Severity Index (EASI) and the number of doctor's appointments required because of AD exacerbation. One study has shown that during a one-year period, there was an average of six appointments per patient related to exacerbations of AD.[7]

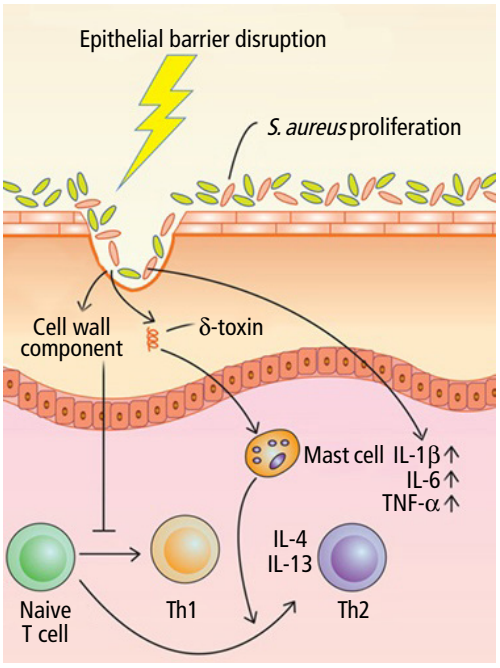

Figure 1. Dysbiosis – effects of *S. aureus* on the immune system

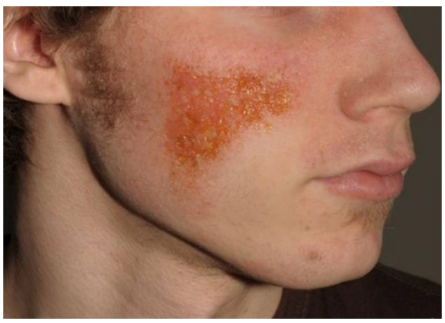

Image source: https://www.researchgate.net/figure/Secondarily-infectedatopic-dermatitis-on-the-face-of-an-adolescent_fig2_275359278

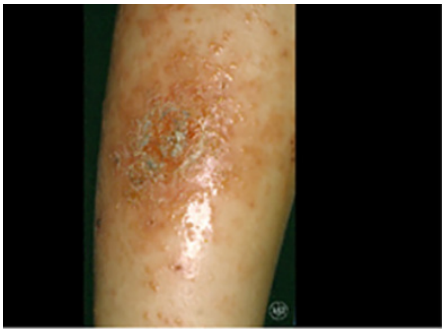

Image source: https://www.aad.org/diseases/eczema/child-eczema-infection

Figure 2. Presentation of secondary infection in AD

Treatment of AD and infected dermatitis

Antibiotic resistance is one of the major challenges when treating *S. aureus* infection. MRSA is a growing problem in patients with AD, and some studies have shown that up to 30% of the colonising strains in patients with AD are MRSA.[6,8]

Cleansing

The treatment of AD is always based on the use of the correct emollients and the correct 'bath routine'.[9] It is advised that the amount of time spent in the water be limited to 5-10 minutes. Washing in hot water is discouraged. The use of soap that foams and bubble baths, as well as the shampooing of hair in the bath, are also advised against. The aim of this washing routine should be to gently remove crusts and debris without further damaging the already impaired barrier function. This process will start to address any secondary infection or bacterial colonisation. In the event of recurrent staphylococcal infection of the skin, the addition of bleach baths once to twice a week is recommended. This requires adding half a cup of 6% bleach to a full bathtub. Guard against a solution that is too strong, as this may cause irritation.

Pharmacological treatments

Glucocorticoids (corticosteroids) or calcineurin inhibitors are the mainstay of anti-inflammatory therapy in the management of chronic AD.[4] It is prudent to note that topical steroids alone are effective against skin colonisation with *S. aureus*.[10] However, it is evident that not all patients have significant improvement in skin disease following low- or moderate-potency topical corticosteroid therapy. Use of high-potency topical corticosteroids or systemic corticosteroids for prolonged periods also places patients at risk for adverse effects.[4]

It is well established that topical and systemic antibiotics can be effective in the patient with AD, reducing clinical severity of skin disease when secondarily infected by *S. aureus*. This is due to the reduction or elimination of pathogenic bacteria, which secrete superantigens and other toxins known to trigger skin inflammation.[4] The major advantage of using topical antibiotics is the ability to achieve a high concentration of the antibiotic in the skin where it is needed, without the side effects inherently associated with the use of systemic antibiotics.[3]

Several studies have demonstrated that the combination of a topical corticosteroid with a topical antibiotic is significantly more effective at reducing skin inflammation caused by secondarily infected AD than using either the topical corticosteroid or topical antibiotic alone.[11] Since inflamed skin expresses increased attachment sites for *S. aureus*, the enhanced effectiveness of combined treatment may be due to the ability of corticosteroids to reduce skin inflammation in combination with the antibacterial activity of antibiotics that eliminate the pro-inflammatory effects of *S. aureus*. Antibiotics have anti-inflammatory actions which could have effects on bacterial attachment. By eliminating superantigens and augmenting corticosteroid sensitivity, combination topical antibiotic/corticosteroid therapy may allow doctors to use low- to medium-potency topical corticosteroids to achieve the same clinical effects as high-potency corticosteroids when used alone.[4]

Take note that the treatment of AD uncomplicated by infection with antimicrobials and antiseptics is not beneficial. This was confirmed by a Cochrane review in 2010.[12]

Two topical antibiotic products commonly used in South Africa are mupirocin and fusidic acid. The scheduling of fusidic acid cream was recently downgraded to schedule 2 and therefore this product is now available over the counter. Other antibiotics such as neomycin, gentamicin, β-lactams and macrolides are rarely used and are not recommended as first line therapy.

A useful product, available in South Africa, is a combination of fusidic acid and 0.1% betamethasone (a potent corticosteroid). This highly beneficial combination has been shown to achieve a 98% bacteriological response (eradication of bacteria) in patients with infected AD.[5]

Fusidic acid/corticosteroid combinations work quickly with observable improvement within the first week.[3] In addition, studies have shown that short-term use (two weeks) of fusidic acid/corticosteroid combinations do not increase the development of resistance.[3]

Conclusion

Colonisation of AD skin by *S. aureus* is the norm. Distinguishing colonisation from infection may be tricky. Even in cases of clinically evident secondary bacterial infections, the treatment will always start with the general measures of emollients and bath habits because improvement of the barrier function will reduce invasion of surface bacteria. Anti-inflammatory medications such as topical corticosteroids or calcineurin inhibitors are the second pillar of treatment. If clinically indicated, short courses of topical antibiotics should be added not only to treat the secondary bacterial infection, but also to eradicate bacteria-secreting superantigens. In very severe and widespread cases the use of systemic medications may be indicated. Always keep the development of antibiotic resistance in mind and therefore be judicious in the prescription of antibiotics – topical and systemic alike.

KEY LEARNINGS

- The extent of *S. aureus* colonisation correlates with the severity of AD
- Treatment of AD aims to address the defective epidermal barrier, dryness of skin, inflammation and secondary infection
- It is important to maintain skin barrier function by using intensive skin hydration and emollient regimens
- *S. aureus* antibiotic resistance, e.g. methicillin-resistant *S. aureus* (MRSA), is a growing problem worldwide and demands careful selection of topical antimicrobial agents
- Combinations of a topical antibacterial with a topical corticosteroid in short-term treatment is effective, without inducing resistant strains of *S. aureus*, and is indicated when there is clinical suspicion of infection.

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Published by

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Reg: 2012/216456/07

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