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Review Article

Microbes and atopic dermatitis: The Yin and Yang of barrier and immune dysfunction

微生物與異位性皮膚炎：皮膚屏障和免疫功能障礙的陰陽律

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Atopic dermatitis (AD) is a chronic, inflammatory skin condition caused by a complex interaction of genetic and environment factors. Inherited defects within the stratum corneum are increasingly recognised as a key causative factor in the development of AD. Patients with AD also demonstrate a high rate of colonisation by microbes, notably *Staphylococcus aureus*. Controversy exists regarding the use of antimicrobial agents in the management of AD. We briefly review the role of stratum corneum dysfunction in AD, the influence of cutaneous colonisation and infections, and provide an update on the utility of anti-staphylococcal treatment in AD.

異位性皮膚炎是由遺傳和環境因素兩者複雜相互作用而引致的一種慢性皮膚炎症。皮膚角質層內的遺傳缺陷被逐漸認定爲此病的重要致病因素；同時，患者身上的微生物定植量亦偏高，特別是金黃色葡萄球菌。因此，在異位性皮膚炎的治理中應否使用抗菌劑亦一直存在爭議。在本文中，我們會簡要回顧角質層功能障礙在異位性皮膚炎中所扮演的角色和皮膚定植及感染累及的影響，並提供最新的抗葡萄球菌治療在異位性皮膚炎中的應用資訊。

Keywords: Anti-bacterial agents, atopic dermatitis, epidermis, *Staphylococcus*

關鍵詞：抗菌劑、異位性皮膚炎、表皮、葡萄球菌

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Introduction

Atopic dermatitis (AD) is a chronic, inflammatory skin condition that typically presents in childhood and often occurs in individuals with a personal or family history of other atopic diseases, including asthma and allergic rhinitis.[1,2] The lifetime prevalence of AD is estimated to be 10-20% in children and 1-3% in adults and it increased significantly over the latter half of the 20th century.[1,2] The pathogenesis of AD is complex and

continues to be elucidated. AD is known to have a significant genetic component, as demonstrated by genetic and epidemiological twin studies,[3,4] as well as an environmental component, given the propensity of AD to occur more frequently in urban, rather than rural, regions.[2]

Theories of the pathophysiology of AD traditionally focused on the "atopic" component of the disease and the immunological basis of cutaneous hypersensitivity. However, recent evidence has shifted towards the central role of inherited defects within the epidermal barrier. This "outside-in" theory maintains that defective stratum corneum function is the primary pathophysiological factor in AD and precedes the development of inflammation.[2,5]

AD is associated with a high rate of cutaneous bacterial, viral and fungal infections. Distinct from infection, a significant percentage of AD patients are colonised by *Staphylococcus aureus,* with the majority of reports estimating a prevalence of 60-80%,[6,7] but with reports of greater than 90% prevalence in some studies.[8] The high rate of *S. aureus* colonisation is attributed to a combination of decreased barrier function, reduced production of anti-microbial peptides, and increased expression of adherence molecules.[1,2] Several studies suggest the presence of *S. aureus* may itself exacerbate barrier dysfunction and inflammation and may be associated with disease flares.[6] However, the utility of specific anti-microbial treatment in patients without signs of overt superinfection continues to be debated.

In this article we review briefly recent perspectives on the pathogenesis of AD, including the role of stratum corneum dysfunction and the influence of cutaneous colonisation and infections, and assess the evidence regarding anti-staphylococcal treatment in the management of AD.

Barrier and immune dysfunction

The stratum corneum plays a vital role in the barrier function of the skin and acts to prevent the entry of harmful or immunogenic materials, while also preventing water loss. Compromised stratum corneum structure and function is increasingly recognised as a key causative factor in AD. In immunologically susceptible individuals, greater exposure to allergens through a damaged epidermal barrier may result in immune hyperreactivity and inflammation.[9] Similarly, increased water loss through the damaged stratum corneum accounts for the xerosis observed clinically in AD patients.

The association between epidermal dysfunction and AD is supported by gene expression studies, which demonstrate an array of stratum corneum differentiation abnormalities.[3] Genomic profiling of mRNA from AD skin lesions by Guttman-Yassky and colleagues demonstrated significant deficiencies in a number of genes involved in maintaining stratum corneum structure.[3] These findings were confirmed by electron microscopy of AD lesions, which demonstrated thinning and regional absence of the stratum corneum, decreased corneocyte compaction, and loss of intracellular lipids.[3]

The central role of stratum corneum dysfunction in AD is further supported by recent evidence revealing a significant association between AD and the filaggrin protein, encoded by the *FLG* gene.[10-12] Filaggrin is involved in the differentiation of the epidermis and acts to maintain the skin barrier.[11] Inherited *FLG* loss-of-function mutations are responsible for the development of ichthyosis vulgaris[13] and confer increased risk of AD.[14] *FLG* mutations are reported to be present in 20-50% individuals with AD and greater than 50% when considering those with moderate to severe disease.[3] In comparison, the prevalence of filaggrin mutations in the general population is 5-10%.[10] In one cross-sectional study examining a cohort of 3,099 German children, the presence of a *FLG* mutation was associated with greater than three-fold increased odds of developing AD.[14] In a case-control study of Irish children with moderate-severe AD, an odds ratio of 7.44 was

reported when examining the relationship between AD and the five most prevalent mutations in *FLG* among Europeans.[12] The significant causative association between filaggrin and AD is striking given the complexity of AD pathogenesis, and is illustrative of the central role of the stratum corneum.

FLG mutations are not universally present in AD.[5,12] Other factors contributing to stratum corneum dysfunction have been identified.[4,5] The cutaneous lipid barrier, composed primarily of cholesterol, free fatty acids, and ceramide, is vital in maintaining the skin barrier and preventing transepidermal water loss. Dysfunction of this lipid barrier, notably loss of ceramide, is also thought to contribute to the cutaneous dehydration and increased exposure to extrinsic factors.[1,2] AD is associated with abnormally high expression of degrading enzymes, such as sphingomyelin deacylase, resulting in ceramide degradation and deficiency. Hara et al demonstrated that the activity of sphingomyelin deacylase is fivefold greater in AD lesions, compared to the skin of healthy controls.[15]

The role of ceramide destruction in AD is supported by studies demonstrating improvements in AD status after topically administered ceramide. In one such study, Chamlin and colleagues added a topical ceramide-based moisturiser to the treatment regimen of 24 children with refractory AD.[16] After six weeks, all patients demonstrated improvements in the Severity Score for Atopic Dermatitis (SCORAD) scores, along with reductions in measured transepidermal water loss.[16]

Inherited deficiencies in the skin barrier may be exacerbated by exposure to environmental proteases, as well as proteolytic and lipolytic substances produced by microbes colonising AD lesions.[17] For example, some common allergens, such as dust mite proteins, possess cysteine or serine protease activity.[17] Moreover, the presence of inflammation in AD lesions can, in turn, further damage the epidermal barrier. There is evidence suggesting that increased cytokine expression in AD stimulates production of a variety of endogenous proteases.[2,17] Furthermore, IL-25 has been shown to be elevated in AD and may inhibit filaggrin synthesis, resulting in further barrier damage.[18]

Microbes associated with atopic dermatitis

AD is associated with a significantly elevated rate of cutaneous viral, fungal, and bacterial infections. Among viral infections, patients with AD are vulnerable to recurrent, prolonged or severe infections with herpes simplex virus[2,19] (HSV) and molluscum contagiosum.[20] The presence of immune dysfunction is highlighted by the fact that the smallpox vaccine is contraindicated in AD patients due to risk of eczema vaccinatum, which is characterised by disseminated cutaneous infection after virus exposure.[21]

In a subset of AD patients, HSV infection can result in eczema herpeticum (EH), a condition characterised by an extensive, disseminated HSV infection.[19] One study examined the risk factors for the development of EH in individuals with AD and reported that the incidence of EH is higher in those with more severe and widespread disease, higher serum IgE levels, and in those with concurrent asthma and food allergies.[19] A history of EH was also associated with a higher risk of *S. aureus* and molluscum contagiosum infections, suggesting those with worse barrier or immune function may be at greater risk for multiple types of cutaneous infections.[19] In another study, AD patients with a history of EH were shown to be more likely to have a filaggrin mutation than AD patients without EH.[22] The R501X filaggrin mutation conferred a 3.4 times greater odds of developing EH among European individuals with AD. These findings were replicated among a group of patients of African American ancestry.[22]

Patients with AD are also at increased risk of cutaneous fungal infections. Most notably, high rates of colonisation with *Malassezia* species have

been demonstrated, especially in adults with head and neck involvement.[23,24] Adults with AD of the head and neck have *Malassezia*-specific IgE more frequently than those without. Patients with AD may also have greater immune reactivity to allergens associated with colonisation by *Malassezia* species. In one study, 67% of patients with AD showed reactivity to *Malassezia* antigens, compared to 7% of patients with seborrhoeic dermatitis.[25] Several trials have demonstrated clinical improvement in AD associated with treatment with systemic anti-fungal medications.[26,27] For example, Ikezawa et al treated 40 patients with AD refractory to conventional treatments with 100 mg of itraconazole daily for eight weeks and reported clinical improvement and reduced need for topical steroids in all patients.[26]

Cutaneous and nasal colonisation with *Staphylococcus aureus* is ubiquitous among patients with AD. The prevalence of *S. aureus* colonisation in AD is estimated to be between 60-94% overall, compared to 2-25% in unaffected individuals.[1,6,8,28] Even in clinically unaffected areas of skin in those with AD, colonisation rates as high as 42-78% have been reported.[29,30] Perhaps surprisingly, while the rates of *S. aureus* colonisation are high in AD, the rate of methicillin-resistant staphylococcal aureus (MRSA) infection does not appear to be particularly elevated.[6,7]

Defects in the immune barrier are likely not the sole factor for the high prevalence of staphylococcal colonisation, as the rate of bacterial colonisation in AD is significantly higher than in other conditions demonstrating compromised barrier function. For example, the risk of cutaneous infection was shown to be four times higher in AD patients compared to those with psoriasis, despite defective barrier function in that condition as well.[31] One explanation is that the TH_2 inflammatory state may facilitate cutaneous adherence of *S. aureus*. IL-4 has been shown to induce the expression of fibronectin and promote bacterial colonisation in animal models.[1] Another mechanism involves reduced expression of anti-microbial peptides, such as cathelicidins (LL-37) and beta-defensins.[2,32] TH_2 cytokines, namely IL-4 and IL-13, have been shown to decrease production of beta-defensin gene expression.[32] It has also been suggested that increased expression of IL-10 associated with AD reduces both LL-37 and beta-defensin expression.[28] Accordingly, the reduction in inflammation by topical corticosteroids and calcineurin inhibitors has consistently been shown to be associated with decreased *S. aureus* content in AD lesions.[1]

Much debated is whether the presence of *S. aureus* may contribute to AD pathogenesis. There is little controversy that *S. aureus* colonisation correlates with greater AD disease severity.[6] Kong and colleagues demonstrated that an overall decrease in microbial diversity and overgrowth of *S. aureus* is temporally correlated with AD flares.[33] Conversely, AD treatment and subsequent improvement was shown to correlate with greater cutaneous microbial diversity.[33] *S. aureus* may also sustain and exacerbate inflammation through the production of superantigens, which non-specifically interact with the T-cell receptor and produce a robust inflammatory response.[2,6,34,35] It has been demonstrated that levels of IgE against the staphylococcal superantigen correlate with disease severity.[35] Furthermore, virulence factors released by *S. aureus,* such as sphingomyelin deacylase, may in turn further damage the stratum corneum.[9]

Antibiotic treatment and atopic dermatitis

In the case of clinically evident bacterial superinfection of AD lesions, antibiotic treatment is warranted.[1,36] Huang et al conducted a prospective, randomised controlled trial (RCT) demonstrating improvements in AD status after antimicrobial treatments in paediatric patients with signs of overt bacterial infection.[37] All 31 children were first treated with 50 mg/kg of oral cephalexin daily for two weeks, and then continued on topical anti-inflammatory and emollient treatments. The

investigators assigned patients to receive either dilute sodium hypochlorite bleach baths for 5-10 minutes biweekly and intranasal mupirocin, or water baths and intranasal petroleum. Patients in the bleach bath/mupirocin group demonstrated significant reductions in Eczema Area and Severity Index (EASI) scores at both one- and three-month follow up. The investigators independently assessed EASI scores for the head and neck region and found no difference compared to placebo. This finding was attributed to the fact that only the trunk was submerged during bleach baths.[37]

However, controversy exists regarding the clinical utility of antimicrobial treatments in AD in the context of colonisation. Hung et al evaluated 60 patients with AD and *S. aureus* colonisation treated with 0.05% fluticasone propionate cream or 0.03% tacrolimus ointment, with or without the addition of 2% fusidic acid antibiotic cream.[38] After eight weeks, patients treated with fluticasone or tacrolimus demonstrated significant improvements in SCORAD scores, as well as decreases in *S. aureus* colonisation. Fluticasone treatment, however, resulted in more rapid reduction of *S. aureus* compared to treatment with tacrolimus. The addition of fusidic acid was associated with a higher rate of staphylococcal eradication, but did not improve AD severity scores when added to either regimen and resulted in two cases of novel fusidic acid resistance. The authors concluded that anti-inflammatory treatment with topical corticosteroids or tacrolimus, without specific antibiotic treatment, is sufficient to reduce *S. aureus* burden and AD severity.[38]

Gong and colleagues performed a multicentre RCT comparing treatment of AD with hydrocortisone butyrate, along with mupirocin or a vehicle ointment in 337 Chinese patients.[39] At seven-day follow-up, patients with severe disease demonstrated significant benefit in EASI scores from combination treatment. However, there was no difference detected between groups beyond seven days. Further, no difference was observed among patients with mild or moderate disease at any time point during the study.[39]

Travers and colleagues treated 49 paediatric patients with AD and evidence of *S. aureus* colonisation with a regimen consisting of oral antihistamines, desonide ointment on the face and intertriginous areas, and 0.1% triamcinolone ointment on the rest of the body.[40] Patients were also given a two-week course of oral cephalexin (25-50 mg/kg day). In this cohort, 15% of patients were colonised with MRSA. All patients, including those with MRSA, demonstrated improvements in EASI scores, as well as decreases in bacterial products and reductions in inflammatory cytokine expression. This also correlated with an increase in beta-defensin expression. Given the expected resistance of MRSA to cephalexin, it was concluded that the observed clinical benefit was due to the reduction of inflammation and disinhibition of anti-microbial peptide production. Therefore, the authors conclude that oral antibiotics did not provide additional benefit over topical anti-inflammatory medications.[40]

A recent systematic Cochrane review examined the utility of anti-staphylococcal interventions in AD.[36] After reviewing 26 trials, involving 1,229 patients, it was concluded that, while antibiotic treatment reduced *S. aureus* load, there is no evidence to suggest it improves clinical outcomes. The authors concluded that, in accordance with the above studies, there was no evidence to support the use of anti-microbial interventions in AD patients in the absence of overt clinical superinfection.[36]

Conclusion

In AD, stratum corneum dysfunction results in greater exposure to extrinsic antigens and subsequent immune activation and inflammation. Impaired skin barrier and innate immune defenses also result in colonisation by specific microbes, especially *S. aureus*. Despite evidence that empirical antibiotic treatment in AD is of marginal utility, antibiotic therapy is over utilised, resulting in microbial resistance without major clinical benefit. Specific treatments against pathogens,

particularly *S. aureus*, should generally be reserved for instances of overt infection. Continued efforts into understanding the pathophysiology underlying AD are vital to the development of more effective and appropriate treatment strategies.

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