



Pathophysiology, Diagnosis, and Management of Infections in Atopic Dermatitis

Grace Chan¹ · Peck Y. Ong^{2,3} 

Published online: 11 May 2019

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Abstract

Purpose of Review Atopic dermatitis (AD) is a common and chronic inflammatory skin disease. The purpose of this review article is to assess recent changes in the understanding of pathophysiology, diagnosis, and management of infections in AD.

Recent Findings Recent epidemiological studies have confirmed that AD is not only associated with cutaneous infections, but also extra-cutaneous systemic infections. Basic studies have provided evidence that allergic inflammation contribute to increased infections in AD. Clinical use of diluted bleach to prevent infections in AD remains controversial. On the other hand, progress is being made in the study of microbiome in AD. Commensal bacteria may potentially be used to fight *Staphylococcus aureus* in AD in the future.

Summary AD is a complex disease arising from skin barrier defects that lead to allergen or pathogen invasion and dysfunctional immune responses that promote inflammation. This inflammatory cycle also alters the skin microbiome so that pathogenic organisms, such as *S. aureus*, are more likely to colonize the skin. The skin barrier defects, immune dysregulation, and alteration in the skin microbiome lead to an increased risk for secondary bacterial and viral infections. More targeted therapies and skin probiotics may address inflammation and *S. aureus* in the prevention of infections in AD.

Keywords Atopic dermatitis · Eczema herpeticum · *Staphylococcus aureus*

Introduction

Atopic dermatitis (AD) is a common and chronic inflammatory skin disease. Patients with AD suffer from itch and sleep disruption, which leads to poor school/work performance, low self-esteem, and familial stress. In addition, severe AD patients are at risk for psychiatric disorders including depression

and anxiety disorders. Among these morbidities of AD, another serious complication of AD is infection, which could potentially be life-threatening. It has been shown that adults and children with AD are significantly at risk for serious cutaneous infections as well as extracutaneous infections including systemic and multiorgan infections [1, 2–5]. Infectious complications of AD can also pose a significant financial burden on the healthcare system [3]. This article will review recent advances in the pathophysiology, diagnosis, and management of infections in patients with AD.

This article is part of the Topical Collection on *Infectious Disease and Dermatology*

✉ Peck Y. Ong
pyong@chla.usc.edu

¹ Division of Pediatrics, Children's Hospital Los Angeles, 4650 Sunset Boulevard, MS 75, Los Angeles, CA 90027, USA

² Department of Pediatrics, Keck School of Medicine, University of Southern California, 1975 Zonal Ave, Los Angeles, CA 90033, USA

³ Division of Clinical Immunology and Allergy, Children's Hospital Los Angeles, 4650 Sunset Boulevard, MS 75, Los Angeles, CA 90027, USA

Mechanisms of Infections in AD

Skin Barrier Defects

It has been well-established that skin barrier functions in AD are defective [6]. The skin in AD patients has significantly thinner stratum corneum than healthy controls and increased transepidermal water loss (TEWL) as compared to non-AD

skin. This latter finding has been attributed to a deficiency in various barrier molecules in AD. These molecules include ceramides, fatty acids, cholesterol, involucrin and filaggrin [7]. Deficiency in filaggrin may be partly explained by a loss-of-function mutation in the filaggrin gene, *FLG*. As filaggrin breakdown products, pyrrolidone carboxylic acid and urocanic acid, are natural moisturizing factors which acidify the skin, defects in *FLG* result in dry skin and a rise in pH, which further promotes proliferation and adhesion of *Staphylococcus aureus* (*S. aureus*) [7]. Defects in *FLG* also result in an activation of serine proteases and kallikrein, leading to degradation of tight junctions and corneodesmosomes, and impair the skin barrier [8]. Other barrier gene defects including claudins of tight junction may also contribute to the dysfunction of skin barrier defects in AD [9].

Immune System

Keratinocytes interface between the environment and the cutaneous immune system; they are the primary source of protein and lipid molecules that make up the physical barrier of the skin. They mount many basic immune responses that function in skin defense. Keratinocytes produce IL-33, IL-25, and thymic stromal lymphopoietin (TSLP), which activate innate lymphoid cells 2 (ILC2) to produce type 2 cytokines, IL-4, IL-5, and IL-13, that function in tissue repair [10]. An intrusion of allergens or infectious agents due to skin barrier defects may lead to an overproduction of these cytokines in AD. Keratinocytes also produce chemokines, CCL17 and CCL22, that attract T helper 2 (Th2) cells which further elaborate the production of type 2 cytokines. Th2 cells also produce IL-31, which is a central cytokine in the pathogenesis of itch in AD. Defects in dendritic cells also play a role in increased infections in AD. Plasmacytoid dendritic cells, which produce interferon (IFN)- α that fight viral infections, are absent in AD. On the other hand, AD lesions are predominated by inflammatory myeloid dendritic cells: Langerhans cells (LC) and inflammatory dendritic epidermal cells (IDEC) [11]. Both LC and IDEC overexpress the high-affinity receptor for IgE, Fc ϵ R1, which capture allergens and present them to activate Th2 cells. The overproduction of type 2 cytokines leads to a suppression of both barrier molecules [12•, 13] and antimicrobial peptides (AMPs), which are important in direct killing of pathogenic microbes [14•]. AMPs also function as chemokines that alert the adaptive immunity to fight infections. Defensins attract Th17 cells which are important in fighting cutaneous infections including *S. aureus*.

Environment and Skin Flora

The typical skin microbiome is affected by skin pH, moisture, and keratinocytes. The most commonly detected normal skin flora include *Propionibacterium acnes* (*P. acnes*),

Staphylococcus epidermidis (*S. epidermidis*), and *Corynebacterium* [15]. Skin flora is also found within multiple layers of the skin, suggesting that commensal bacteria may play a greater role in immune modulation than previously thought [16]. *S. epidermidis* interacts with toll-like receptor-2 (TLR-2) to suppress TLR-3-dependent inflammation in the skin. In addition, activation of TLR-2 results in the production of AMPs and leads to an increase in tight junction expression and improvement of skin barrier functions [17]. Both *S. epidermidis* and *P. acnes* produce proteins that inhibit the growth of *S. aureus*. Thus, the normal skin flora is capable of modulating immune activity without initiating a state of chronic inflammation, leading to prevention of pathogenic bacteria over-proliferation [18].

Coagulase-negative staphylococci (CoNS) including *S. epidermidis*, *S. hominis*, and *S. lugdunensis* are known to produce exogenous AMPs (lantibiotics) that have anti-*S. aureus* activities [19]. It has been shown that AD skin has a relative deficiency of protective CoNS, as compared to healthy skin [19]. The strains of gram-negative bacteria, *R. mucosa*, were found to be less bactericidal in AD skin, as compared to those in healthy skin [20]. These factors contribute to increased *S. aureus* colonization in AD.

Diagnosis of Infections in AD

Clinical signs of bacterial infection include weeping, pustules, crusting, or possibly worsening of dermatitis. Bacterial infection in AD skin should be considered in cases where there is failure of response to anti-inflammatory therapy [6, 21]. The majority of bacterial skin and soft tissue infections in AD is caused by *S. aureus*. The rest of bacterial skin infections are caused by *S. pyogenes* or a mixture of both *S. aureus* and *S. pyogenes*. Deeper skin infections such as cellulitis (Fig. 1) and large skin abscesses in AD may lead to more invasive infections including bacteremia, osteomyelitis, septic arthritis, and endocarditis [22]. Systemic signs such as fever and fatigue in AD patients with generalized acute lesions should raise suspicion for bacteremia. Patients with persistent focal tenderness and elevated inflammatory markers such as C-reactive protein or erythrocyte sedimentation rate in spite of ongoing antibiotic treatment for cellulitis should also alert clinicians to the possibility of osteomyelitis. Careful auscultation for new heart murmurs in patients hospitalized for AD, especially those with persistent fever, may prompt further work-up for infectious endocarditis.

A major infectious complication of AD is eczema herpeticum (EH). It consists of nearly one third of children who are hospitalized for infectious complications of AD [22]. Younger age and nonwhite race (Blacks, Asian, and Native Americans) are at increased risk for hospitalization for EH in AD children [2]. In addition, AD patients with more severe

Fig. 1 Erythema and tenderness on the right ankle of and an AD patient, consistent with cellulitis



AD, earlier onset of AD, and other atopic diseases (food allergies and asthma) are also at increased risk for EH [23•]. EH is caused by an infection with herpes simplex virus (HSV). The clinical signs of EH include presence of vesicles, punched-out erosions, or hemorrhagic crusts. The skin may be pruritic or painful, and lesions may be widespread (Fig. 2) [24]. This diagnosis should also be considered in AD patients with vesiculopustular lesions who do not respond to systemic antibiotics [25]. EH may lead to disseminated vesicles with viremia and fever and may result in more serious complications including keratoconjunctivitis and meningitis. HSV exposure is common in general. Nevertheless, EH only affects 3% of AD patients, suggesting that immunological and genetic factors render a subset of AD patients more susceptible to EH [26•].

In addition to EH, AD patients can present with Coxsackievirus infection, known as eczema coxsackium

(EC). This condition can also present with extensive vesicles and skin breakdown. However, EC is not life-threatening and can be managed following standard treatments for AD. EC is clinically significant in that it may be a differential diagnosis of EH. In some EC patients, the signs of hand-foot-mouth disease may be present. In others, a predilection of EC lesions on the buttock areas may be distinct, since these are not common areas for AD.

Management and Therapeutic Approaches

Preventive management of infectious complications in AD primarily involves control of AD flares. To prevent AD flares, patients should avoid irritants and allergens that may trigger AD, including soaps and detergents with fragrances. Wool clothing can also be a significant irritant for AD patients. In

Fig. 2 Widespread vesicular lesions in a child with eczema herpeticum (EH)



young children with AD, food allergens, particularly egg white and cow's milk, can be significant exacerbating factors. There is also increasing evidence that aeroallergens play an important role as a trigger of AD. A double-blind placebo-controlled study has confirmed that aerosolized pollens can aggravate AD [27]. House dust mites and furry pets are also potential triggers for AD. Identifying these allergens and avoiding them can minimize AD flares. There is also evidence that allergen immunotherapy may be beneficial to a subset of sensitized AD patients [28, 29].

In addition to avoiding allergens, patients with AD should maintain skin hydration. AD patients are recommended to shower or bathe daily in warm water [30, 31]. Following the bath, patients should use a fragrance-free moisturizer. It is recommended to use a clean utensil to dispense the product to avoid re-contamination with *S. aureus*. Moisturizers should be applied multiple times a day and as needed when the skin is dry. Moisturizers are the primary therapy for mild AD and adjunctive therapy for moderate-to-severe AD. Maintenance of adequate skin moisture using a daily regimen can improve skin barrier and prevent intrusion by microbial pathogens.

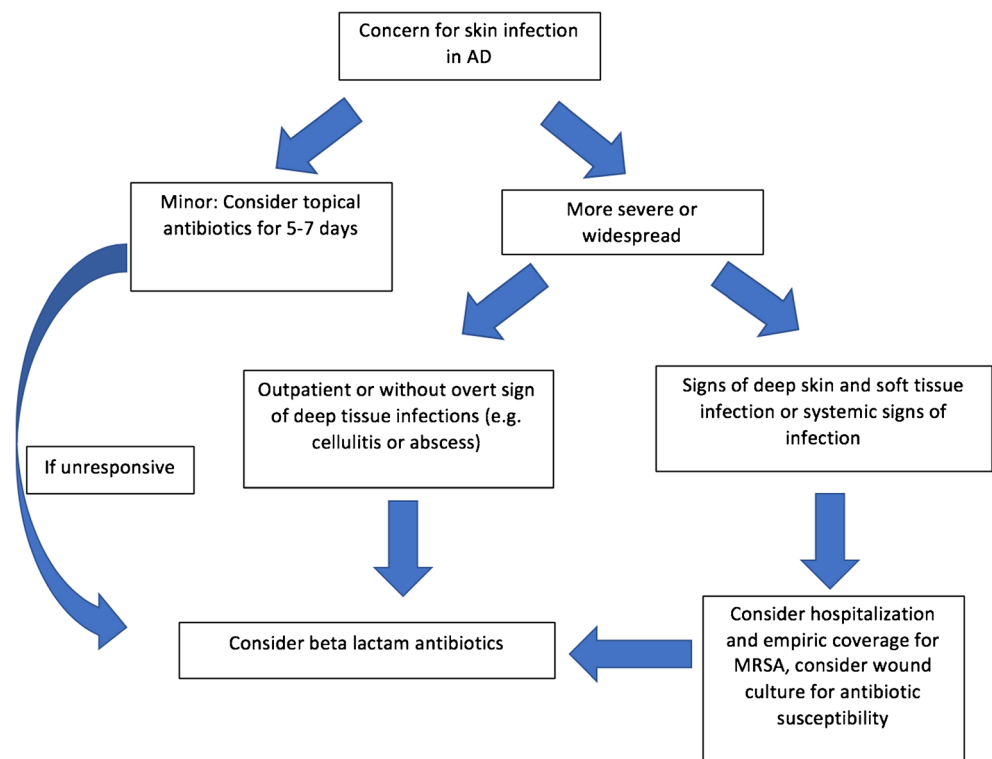
Standard therapy of AD involves the use of topical corticosteroids (TCS). Low-potency TCS is generally suggested for maintenance therapy, but during AD flares, the use of intermediate to mid-potency topical TCS may be necessary. The second-line of topical anti-inflammatory treatment is topical calcineurin inhibitors (TCI), such as tacrolimus and pimecrolimus. Both TCS and TCI have been found to

decrease *S. aureus* colonization [32, 33]. This effect may be due to a reduction of Th2 inflammation and improvement of skin barrier and defense.

Diluted bleach bath is now recommended regularly as part of preventive treatment for AD. The active ingredient, sodium hypochlorite, has activity against *S. aureus* including methicillin-resistant *S. aureus* (MRSA). However, recent studies have been inconsistent regarding the utility of dilute bleach baths [34, 35, 36]. One study found that there was a decrease in *S. aureus* density after both bleach and normal baths. Bleach in conjunction with TCS was also not found to be more effective than TCS alone in reducing skin colonization [37]. More recent meta-analysis showed that dilute bleach bath is not more effective than regular water bath in decreasing AD severity [34]. In addition, the concentration of dilute bleach in clinical use is not sufficient in inhibiting the growth of *S. aureus* and therefore does not explain the efficacy of dilute bleach bath in AD [38]. However, a subgroup of AD patients with recurrent infections may benefit from diluted bleach bath [39]. Further studies on mechanisms are needed.

For AD skin that appears to have a minor infection locally, a topical antibiotic such as mupirocin 2% twice a day for 5 to 7 days may be sufficient. Prolonged use of topical antibiotics is not recommended due to increased risk of cultivating bacterial resistance [40]. In more extensive infections, characterized by painful lesions with mucopurulent discharge, treatment with a beta lactam antibiotic such as cephalexin is recommended (Fig. 3). In AD patients with a recent history of

Fig. 3 Management of bacterial infections in AD



MRSA colonization or infection, clinicians should consider empirical antibiotics that have activity against MRSA. A wound culture with susceptibilities is useful in guiding the choice of antibiotics. AD patients with wide-spread, generalized skin infections, fever, or suspicion for invasive infection may need to be hospitalized for intravenous antibiotics. In patients with systemic signs such as fever and lethargy, a blood culture is recommended to rule out bacteremia. The choice of empirical antibiotics is dependent on regional susceptibility of *S. aureus*. In centers where MRSA infections are prevalent, clindamycin and trimethoprim-sulfamethoxazole are common choices. In AD patients with large drainable abscess, possible osteomyelitis, or septic arthritis, surgical consultation is recommended [41].

If EH is suspected, AD patients who are at high risk for infectious complications, such as those who are young, with wide-spread lesions, or are ill-appearing, should be considered for hospitalization and intravenous acyclovir. Potential complications include viremia, keratoconjunctivitis, and meningitis. Ophthalmic involvement should prompt emergent ophthalmology evaluation to prevent corneal involvement [42]. In patients with mental status change, lumbar puncture should be performed on non-lesional areas. Additional supportive care includes intravenous hydration and pain control. A lesional swab for HSV PCR may help in confirming the diagnosis. Due to frequent bacterial co-infection with EH, a systemic antibiotic is recommended for AD patients who are hospitalized for EH. In less severe EH, patients may be treated outpatient with oral acyclovir for 7–14 days.

Management of EC is based on supportive care and prevention of secondary infections. Patients should continue standard treatments for AD. A lesional swab for enterovirus may be helpful to distinguish EC from EH.

Conclusions

AD is a complex disease arising from skin barrier defects that lead to allergen or pathogen invasion and dysfunctional immune responses that promote inflammation. This inflammatory cycle also alters the skin microbiome so that pathogenic organisms, such as *S. aureus*, are more likely to colonize the skin. The skin barrier defects, immune dysregulation, and alteration in the skin microbiome lead to an increased risk for secondary bacterial and viral infections.

Although conventional treatments for AD have relied upon TCS or TCIs with the use of systemic immunosuppressants in patients with refractory AD, further research into the pathogenesis of AD can lead to more targeted therapies in the host immune response. Dupilumab, which targets the alpha receptor of IL-4 and blocks both IL-4 and IL-13, has been shown to be effective in decreasing the severity of AD in adult patients [43•, 44]. Further studies may evaluate if this monoclonal

antibody could decrease AD inflammation, leading to improved skin defense and fewer skin infections. Other anti-inflammatory therapies for AD in the research pipeline include anti-IL-13, anti-IL-22, and anti-IL-31 monoclonal antibodies [45, 46], as well as topical agents such as phosphodiesterase 4 (PDE4) and Janus kinase (JAK) inhibitors [47, 48]. The effects of these medications on infections in AD will need further studies. The potential use of microbial skin transplant therapy and topical probiotics in controlling *S. aureus* growth may provide a new paradigm in the management of skin infections in AD, particularly in more virulent strains such as MRSA [49].

Compliance with Ethical Standards

Conflict of Interest Grace Chan declares no conflict of interest.

Peck Y. Ong reports personal fees from Pfizer, grants from Regeneron, grants from Incyte, and grants from the Atopic Dermatitis Research Network.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

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