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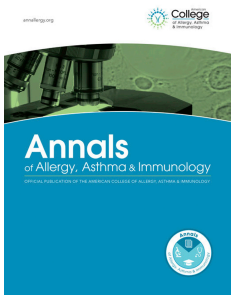


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# The Infectious Complications of Atopic Dermatitis

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Objective : Atopic dermatitis (AD) is a chronic inflammatory skin disease that is complicated by an increased risk for skin and systemic infections. Preventive therapy for AD is based on skin barrier improvement and anti-inflammatory treatments, whereas overt skin and systemic infections require antibiotics or anti-viral treatments. This review updates the pathophysiology, diagnosis, management, controversy of antibiotic use, and potential treatments of AD infectious complications.

Data Sources : Published literature obtained through PubMed searches and clinical pictures.

Study Selections : Studies relevant to the mechanisms, diagnosis, management and potential therapy of AD infectious complications.

Results : Skin barrier defects, type 2 inflammation, S. aureus colonization and cutaneous dysbiosis are the major predisposing factors for the increased infections in AD. While overt infections require antibiotics, the use of antibiotics in AD exacerbation remains controversial.

Conclusion : Infectious complications are a co-morbidity of AD. Although not common, systemic bacterial infections and eczema herpeticum can be life-threatening. Preventive therapy of infections in AD emphasizes skin barrier improvement and anti- inflammatory therapy. The use of antibiotics in AD exacerbation requires further studies.

## Introduction

Atopic dermatitis (AD) is the most common chronic inflammatory skin disease that affects both children and adults, with a prevalence of up to 18% and 7%, respectively. Patients with AD and their caregivers suffer from decreased quality of life, including disruption in daily activities at school and work, sleep disturbance, depression, and anxiety.[1] In addition to these complications, AD patients are at increased risk for infections.[2] The prevalence of cutaneous and systemic infections in patients with AD is significantly higher than those without AD.[3] Infectious complications of AD include skin and soft tissue infections (SSTI), eczema herpeticum (EH), bacteremia, osteomyelitis, septic arthritis, and endocarditis.[4] These complications lead to significant financial burden on the healthcare system.[5] In this review, we will summarize advances in the mechanisms, clinical complications, and management of infections in AD.

## What causes an increase in infections in AD?

### *Skin barrier defects*

AD is inherently associated with skin barrier defects as measured by transepidermal water loss (TEWL).[6] AD patients have a significantly thinner stratum corneum due to a lack of terminal keratinocyte differentiation. As a result of skin barrier abnormalities, AD is associated with increased TEWL, which is greatest in the most severe AD patients.[2] The molecular basis for skin barrier defects is due to a deficiency in proteins and lipids with barrier functions including filaggrin, involucrin, claudins, ceramides, cholesterol, and free fatty acids.[7] Filaggrin gene loss-of-function (*FLG* LoF) was the first evidence for the genetic basis of skin barrier defects in AD.[2]

*FLG* LoF leads to decreased skin hydration and renders AD susceptible to environmental insults including allergens and pathogens.[2] In healthy skin, filaggrin is broken down into hygroscopic amino acids including urocanic acid (UCA) and pyrrolidone carboxylic acid (PCA), which maintain the acidic pH of the stratum corneum. The acidic environment in healthy skin decreases the expression of two staphylococcal surface proteins, clumping factor B and fibronectin binding protein, which bind to host protein cytokeratin 10 and fibronectin, respectively.[2] Defects in filaggrin expression leads to decreased UCA and PCA levels, as well as a rise in pH, which favors *Staphylococcus aureus* (*S. aureus*) proliferation.[8] *FLG* LoF is associated with early-onset AD, and is present in about 25 to 30% of AD patients of European and Asian descent.[9] A more recent study using newer sequencing method (massively parallel sequencing) also found a relatively high prevalence (15.3%) of *FLG* LoF among African American children with AD.[10] This prevalence is significantly higher than the 5.8% that was previously found.[10] AD patients with *FLG* LoF had a seven times higher risk of having four or more episodes of skin infections requiring antibiotics within one year compared to AD patients without *FLG* LoF.[2] *FLG* LoF also confers significant higher risk for EH in patients with AD.[2] Lipids in the stratum corneum of AD patients have been found to differ substantially in composition from those of healthy individuals. Patients with AD have decreased expression of fatty acid elongases that contribute to observed changes in skin lipids and IL-4 and IL-13 having an inhibitory effect on these enzymes.[11] In addition to physical barrier defects, AD is also known to have a deficient chemical barrier which comprises of innate defense molecules including β defensin-2 and cathelicidin.[2]

*Immune dysregulation*

Keratinocytes are skin epithelial cells that contribute to the barrier functions and immune response. In AD patients, keratinocytes produce an increased amount of thymic lymphopoietin (TSLP), IL-33 and IL-25,[2] which activates innate lymphoid cells 2 (ILC2) to produce type 2 cytokines including IL-4, IL-5 and IL-13.[12] IL-4 and IL-13 have been shown to suppress keratinocyte expression of antimicrobial peptides and skin barrier functions,[11,13] thus predisposing AD patients to have increased skin infections. In addition to keratinocytes, endothelial cells, macrophages, mast cells and basophils are other cellular sources of IL-33.[12,14] IL-33 is stored preformed in the nucleus of these cells and produced readily to exert its inflammatory effects.[12] It attaches to its receptor, ST2, on ILC2 to activate the production of IL-5 and IL-13.[2] IL-25 acts on both ILC2 and T cells by attaching to its receptor, IL-17RB.[12,15] In combination with IL-33 and TSLP, it enhances the proliferation and cytokine expression by ILC2.[12] Both IL-33 and IL-25 are highly expressed in AD lesions.[2]

Defects in dendritic cells (DC) also contribute to increased infections in AD. Both myeloid and plasmacytoid DC in AD patients produced significantly less interferon (IFN)-α.[2] Toll-like receptor-2 (TLR-2)-sensing of *S. aureus* by Langerhans cells (LC) and inflammatory dendritic epidermal cells (IDEC) has also been found to be impaired in AD patients.[16] NK cells have recently been found to be deficient in AD patients.[17] This deficiency may also contribute to increased type 2 inflammation due to a potential counter-regulatory mechanism between NK cells and type 2 inflammation.[17]

*S. aureus colonization*

Up to 90% of AD patients are colonized with *S. aureus*.[2] This predominance of *S. aureus* is unique to AD, as compared to healthy subjects and patients with another chronic inflammatory skin disease, psoriasis.[18] The predominance of *S. aureus* in AD may be attributed to the virulence factors of this bacteria and its ability in evading the cutaneous immunity of AD patients. *S. aureus* fibronectin has a special affinity for type 2 inflammation.[19] In addition, *S. aureus* produces enterotoxins (superantigens), which are known to break down the skin barrier and enhance type 2 inflammation.[19] Superantigens also down-regulate cutaneous production IFN-γ and TNF-α, both of which are important mediators of cellular immunity against bacterial and viral infections.[20] Methicillin-resistant *S. aureus* (MRSA) has been found to produce significantly more superantigens than methicillin-sensitive *S. aureus* (MSSA).[2] Both superantigens and another staphylococcal toxin, α toxin, may contribute to keratinocyte apoptosis and barrier defects in AD.[2,21] Staphylococcal δ toxin may also contribute to AD inflammation by inducing mast cell degranulation.[19]

*Dysbiosis of skin flora*

The maintenance of healthy skin also depends on its commensal microbiome. Normal skin flora is found beyond the surface of the epithelium, which highlights the protective role in immune defense and regulation.[22] The most abundant microbes consists of *Cutibacterium acnes* (formerly known as *Propionibacterium acnes*), *Cornyebacterium,* and coagulase-negative *Staphylococcus* (CoNS).[22] AD patients are deficient in commensal bacteria,[22] this facilitates the

virulence *S. aureus* in lesional skin (Fig. 1). The roles of commensal bacteria are two-fold: 1. their ability in modulating the host immune system in order to minimize inflammation and to increase protection against microbial pathogens; 2. their ability to directly outcompete microbial pathogens such as *S. aureus*. CoNS *S. epidermidis* was found to produce a lipoitechoic acid that is capable of preventing injury-induced TLR-3-mediated cutaneous inflammation via TLR-2 interaction.[22] *S. epidermidis* also modulates host cytotoxic and regulatory T cells in wound repair and immune tolerance, respectively.[22] In addition to its anti-inflammatory role, *S. epidermidis* may also up-regulate antimicrobial peptide production by keratinocytes to protect against microbial pathogens.[22] CoNS including *S. epidermidis*, *S. lugdunensis*, and *S. hominis* are capable of producing proteases or antimicrobial factors that either prevent biofilm formation by *S. aureus* or are bactericidal against it.[22]

**Bacterial Infections**

Impetigo, cellulitis, and skin abscesses are common SSTI in AD. The most common cause of these infections is *S. aureus*. Impetigo typically presents with oozing serum that has dried up, giving it a honey-crusted appearance surrounded by an erythematous base (Fig. 2). Impetigenous lesions may also present with fluid-filled blisters (bullous impetigo), which may be mistaken for EH. Non-purulent SSTIs include erysipelas and cellulitis. These infections usually start in a focal skin area but may spread rapidly to cover the major parts of the body such as the arms, legs, trunk or face.[23] Focal erythema, swelling, warmth, and tenderness are signs of these infections. These patients may develop fever and bacteremia. Purulent SSTI presents as skin abscesses which may be fluctuant or non-fluctuant nodules or pustules surrounded by

erythematous swelling. The lesion(s) may be tender and warm. MRSA is a common cause of these lesions. SSTI in AD patients may lead to systemic complications which include bacteremia, osteomyelitis, septic arthritis/bursitis, and more rarely endocarditis and staphylococcal scalded skin syndrome (SSSS), which is mediated by staphylococcal toxins. Persistent fever and specific signs including ill-appearing, lethargy (bacteremia), focal point tenderness of bone (osteomyelitis), joint swelling (septic arthritis/bursitis), heart murmur (endocarditis), and widespread desquamation (SSSS) should raise suspicion for these infections. Persistent elevated inflammatory markers such as C-reactive protein (CRP) or erythrocyte sedimentation rate (ESR) further increase the index of suspicion for these infections. MSSA and MRSA cause an equal proportion of infectious complications (40% each) in hospitalized children with AD.[4] These infection rates are consistent with that of general pediatric inpatient populations across United States.[24] The second most common cause of SSTI and systemic infections in AD is *Streptococcus pyogenes* (*S. pyogenes*). *S. pyogenes* may cause infections in AD patients by itself or in combination with *S. aureus*. These skin infections typically present with pustules or impetigo. The lesions may appear as punched-out erosions with scalloped borders that mimic EH.[25] While SSTI and systemic infections in AD present with overt signs that facilitate diagnosis and antibiotic treatment, the so-called “infected eczema” associated AD exacerbation is not as clearly defined.[26] Patients with severe AD exacerbation tend to have more generalized cutaneous signs and symptoms. These include erythema, swelling, oozing, and tenderness, all of which may also be signs of skin infections. However, Cochrane analysis shows that antibiotics do not improve the severity of AD in these patients.[27] The main concern with the overuse of antibiotics in AD exacerbation is the potential development of bacterial resistance and dysbiosis.[28] However, apart from the outcome of AD severity, there may be a subset of patients

with severe AD exacerbation who may benefit from antibiotics in terms of infections or prevention of infectious complications.[4,28,29] It has been proposed that these patients may be differentiated by a higher density of *S. aureus* and amount of tissue damage caused by *S. aureus*-host interaction.[29] Children with severe AD exacerbation were found to have elevated CRP and ESR, although these levels were significantly less than that of patients with infectious complications.[4] There may be potential use in these inflammatory markers in identifying AD patients who are at risk for severe infectious complications.

**Viral Infections**

EH is caused by infection with herpes simplex virus (HSV)-1, which is a potentially life-threatening infectious complication in AD patients. Nearly a third of children who are hospitalized for AD infectious complications were related to EH.[4] Younger age and non-white race (African Americans, Asians, and Native Americans) are at increased risk for hospitalization with EH.[30] EH can manifest with skin pruritus or pain and presence of vesicles, punched-out erosions (Fig. 3), or hemorrhagic crusts that can become more extensive. Local skin infection may progress to disseminated vesicles with skin breakdown. Systemic EH infection may present with fever, malaise, viremia, and complications including keratoconjunctivitis, encephalitis, and septic shock.

HSV exposure is common in the general population and is present in 60% of adults and 20% of children.[31] Immunologic and genetic elements likely contribute to the vulnerability of a subset of AD patients, as EH only affects 3% of AD patients.[31] AD patients with EH have been shown to have IFN-γ receptor-1 single nucleotide polymorphisms and reduced IFN-γ production

that may contribute to an impaired immune response to HSV.[2] AD patients who develop EH tend to have more severe AD, earlier-onset AD, high total serum IgE/peripheral eosinophils, presence of other atopic diseases such as food allergies and asthma, as compared to their AD counterparts without EH.[2] AD patients with a history of *S. aureus* skin infections are also at higher risk for developing EH.[2] This is consistent with the clinical observation that EH frequently occurs concurrently with secondary *S. aureus* skin infection in AD patients.[2]

Eczema coxsackium (EC) should be considered a differential diagnosis for EH as it can present with extensive vesicles and skin erosion.[2] EC is a viral infection caused by coxsackie viruses in the enterovirus family. Some EC patients may also have symptoms of hand-foot-mouth disease such as oral sores and papules involving hands and feet (Fig. 4). Other possible symptoms include fever, sore throat and poor appetite. In contrast to EH, EC is not life-threatening and can be managed with standard AD treatments.[2] If the diagnosis between EH and EC is unclear, a lesional PCR for enterovirus can be obtained to differentiate between the two etiologies. Though more common in children, EC has also been described in adults.[32]

Molluscum contagiosum (MC) is a poxvirus that belongs to the Molluscipoxvirus subfamily, but it is distinct from vaccinia, variola, and cowpox viruses in the Orthopoxvirinae genus.[33] MC infection in AD patients may be diffuse or along the AD distribution (Fig. 5). Skin barrier defects predispose AD patients to MC and chronic scratching leads to the spread by auto-inoculation. MC infection in AD has been associated with *FLG* LoF.[34]

Eczema vaccinatum (EV) is a life-threatening infection in AD patients that is caused by live vaccinia virus (VV) in smallpox vaccines.[2] EV is rare since the discontinuation of routine smallpox vaccination in 1971. In 2002, due to the concern that smallpox virus may be used as a bioterrorism weapon, a national program began to vaccinate U. S. military members, select

laboratory researchers, and first responders with smallpox vaccine.[2] Pre-outbreak smallpox vaccine is contra-indicated in persons with a history of AD or persons who are in close contact with AD patients. With careful screening, there have been only few cases of disseminated EV or EV by auto-inoculation since 2002.[35] Most of the affected patients have been either military members or close contacts of military members who had a recent history of smallpox vaccination. Although rare, an acute presentation of vesiculo-pustular/nodular rash in an AD patient with a military background or who has close contact with military personnel, along with a recent history of smallpox vaccination, should raise an index of suspicion for EV.

**Prevention of Infections in AD**

The approach in preventing infections in AD is based on addressing the predisposing factors for infections. Daily skin hydration and moisturization is recommended for AD patients to maintain skin barrier functions.[36] AD patients should take a daily warm shower or bath, followed by gentle drying and application of a moisturizer or a prescribed topical medication. The choice of moisturizer should be based on the patient's or parent's preference and experience. In general, a thick or ointment-based moisturizer (e.g. petrolatum) is better than cream in retaining moisture in the skin. Application of petrolatum has been shown to upregulate antimicrobial peptides and induce key barrier differentiation markers such as filaggrin and involucrin in patients with AD.[37] The use of standard topical anti-inflammatory medications including topical corticosteroids (TCS) and topical calcineurin inhibitors (TCI) have been shown to improve skin barrier functions based on TEWL.[30-40] TCS and TCI have also been shown to decrease *S. aureus* colonization in AD lesions.[41-44] Topical anti-inflammatory treatments have been associated with increased microbial diversity in AD lesions.[45,46] Although multiple case

reports have found an association between EH and the use of anti-inflammatory medications in AD, this was not supported by a recent multicenter study which reviewed over 200 cases of EH.[47] The authors found that the use of TCS, TCI, systemic corticosteroid, or cyclosporine was not associated with the onset of EH. Uncontrolled AD inflammation is likely the primary risk factor for EH (or bacterial infections), rather than the anti-inflammatory treatment. Therefore, in the absence of an active infection, anti-inflammatory treatment should confer protection against infections in AD patients (Fig. 6). Dupilumab, a monoclonal antibody that targets the IL-4 α receptor to neutralize the effects of IL-4 and IL-13, was found to decrease *S. aureus* colonization and increase microbial diversity.[48] Pooled analysis of dupilumab clinical trials showed significant improvement in SSTI and EH, as compared to placebo.[49,50] These observations are consistent with the suppressive effects of IL-4 and IL-13 on skin barrier functions and endogenous antimicrobial peptide expression in AD lesions, predisposing AD patients to increased infections. Due to the current unprecedented global pandemic of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2 or COVID-19), there has been some concern whether systemic anti-inflammatory medications for AD including dupilumab may increase the risk of AD patients for this viral infection. Case series, mainly from Italy, have thus far not supported an increased risk of COVID-19 infection in AD patients who are treated with dupilumab. A global web-based registry has been set up for clinicians to monitor the risk and outcome of COVID-19 in AD patients receiving systemic agents including dupilumab (www.covidderm.org).

Attempt to decolonize *S. aureus* is largely experimental. There is insufficient evidence that dilute bleach bath and antibiotics result in sustained decolonization of *S. aureus* in AD.[27] Dilute bleach at 0.005% was not suppressive of *S. aureus* growth or toxin production.[51] Acetic

acid (apple cider vinegar) has been used as a antimicrobial bathing additive for AD,[52] although its efficacy in *S. aureus* clearance in AD has not been established. Another study showed that 0.5% acetic acid daily bath for 14 days did not improve skin barrier function or acidity in AD patients, as compared to plain water baths.[53] On the other hand, skin irritation was reported in some patients treated with dilute acetic acid. Chlorhexidine bath has been used in the decolonization of MRSA in the general population, but it has not been studied adequately in AD. A potential side effect of this antimicrobial agent is allergic contact dermatitis.[54] The Infectious Diseases Society of America published guidelines for the management of recurrent SSTI due to MRSA in 2011.[55] Similar principles apply to the management of recurrent SSTI in AD. Based on these guidelines and findings of more recent studies/expert opinion, a suggested approach to decolonization of *S. aureus* in AD patients with recurrent SSTIs is outlined in Table 1.[55-57]

**Management of Infectious Complications in AD**

About 20% of AD children hospitalized for infectious complications had invasive bacterial infections.[4] AD patients with signs and symptoms of systemic illness, hospitalization and empiric intravenous antibiotics are recommended. The empiric antibiotic regimen should provide coverage against *S. aureus* as this is the most commonly identified bacterial pathogen in AD. For critically ill patients, coverage for both MRSA and MSSA with vancomycin and an anti-staphylococcal β-lactam is appropriate as vancomycin is inferior to nafcillin or first-generation cephalosporins for the treatment of serious MSSA infections.[55] For severe but non-life-threatening infections, vancomycin may be used alone as empiric therapy, pending culture results. Clindamycin can also be considered if there is not concern for an endovascular infection and local prevalence of clindamycin resistance is <15%.[58] Bacteremia due to *S. aureus* requires

use of a bactericidal intravenous agent initially. For MRSA, vancomycin is the drug of choice. For MSSA, cefazolin and nafcillin are both acceptable first-line agents, though nafcillin can cause venous irritation and phlebitis when administered peripherally. As long as there are no concerns for ongoing bacteremia or an endovascular focus, completion of therapy with an oral agent to which the isolate is susceptible is appropriate in children with *S. aureus* bacteremia.[55] Duration of therapy should be determined by clinical response but typically 7 to 14 days is recommended. Infective endocarditis is a rare complication of AD.[4] Careful auscultation for heart murmur is recommended.

For AD patients with uncomplicated, non-purulent skin infection, a β-lactam antibiotic that covers both *S. aureus* and β-hemolytic streptococci (e.g. cefazolin or cephalexin) may be sufficient pending clinical response or culture, taking into account local epidemiology and resistance patterns.[4,55] On the other hand, in AD patients with skin abscess, history of MRSA colonization, close contacts with history of skin infections or recent hospitalization, coverage for MRSA should be considered. Clindamycin, doxycycline, trimethoprim-sulfamethoxazole and linezolid are all acceptable oral options for MRSA skin infections in both children and adults assuming the isolate is susceptible *in-vitro*.[55] Of note, the rates of clindamycin resistance have been rising amongst both MRSA and MSSA nationally, though there is regional variation.[59] AD patients with minor, localized skin infections such as impetigo may be treated with topical mupirocin ointment. Duration of therapy typically ranges from 5 to 10 days depending on clinical response.[55]

Lesional HSV PCR should be sent on suspicion of EH. However, treatment with systemic antiviral should not be withheld pending the results of HSV testing. Co-infection of EH with *S. aureus* is also common, concurrent treatment with an anti-*S. aureus* antibiotic should be

considered. Table 2 provides antiviral treatment options for EH as well as suggested dosing in adults and children. There are no formal guidelines regarding the preferred route of administration of antivirals or indications for hospitalization in patients with EH. For patients with extensive skin involvement, signs of systemic illness and those <1 year of age, parenteral acyclovir should be considered initially. Fever and mild systemic symptoms often accompany mucocutaneous HSV infections, particularly with the initial episode. Once clinical improvement is demonstrated, transition to an oral agent to complete the course of therapy is appropriate. For mild cases, oral acyclovir can be considered and was associated with faster healing and resolution of pain in a randomized, placebo-controlled trial of 60 adults and adolescents with EH.[60] Valacyclovir, the L-valyl ester prodrug of acyclovir, has 3 to 5-fold greater bioavailability than oral acyclovir, can be dosed less frequently and plasma concentrations are comparable to parenteral acyclovir.[58] Topical antivirals do not have an appreciable benefit in HSV mucocutaneous disease and do not have a role in the treatment of EH.[58] Patients with herpetic lesions on or around the eye should be emergently evaluated by an ophthalmologist.[33] Rarely, EH can be complicated by HSV meningoencephalitis which should be treated with a prolonged course of intravenous acyclovir and managed in conjunction with a neurologist and infectious disease specialist.

AD patients with recurrent EH may benefit from long-term suppressive therapy, though this has not been studied. Suggested oral suppressive dosages are shown in Table 2. The need for ongoing therapy should be reassessed after 6 to 12 months. Development of resistance to acyclovir is rare in EH but may be suspected in cases of recalcitrant EH or frequent recurrences of EH despite suppressive therapy and good adherence to chronic therapy.[33,61] Forscarnet is the

recommended therapy for acyclovir-resistant HSV infections since acyclovir-resistant HSV isolates are also resistant to valacyclovir.

Treatment for EC is supportive with continuation of routine skin care and AD treatments including TCS. MC is benign, and observation is recommended in most cases. Attempt is made to minimize scratching that spreads the lesions. This includes daily skin care and topical anti-inflammatory treatments. Sedating fast-acting anti-histamines may be helpful in decreasing scratch during sleep. Treatments such as curettage, cryotherapy, salicylic acid, imiquimod, and cantharidin ("beetle juice") are associated with either pain, a risk for scarring, or mixed results of efficacy.[62] However, a more recent randomized placebo-controlled trial has shown efficacy in the use of cantharidin for the treatment of pediatric MC.[63] When evaluating pustule-vesicular rash in AD patients with a military background or a history of close contact with a military personnel who had recent vaccination, an index of suspicion for EV should be raised. Suspected cases should be reported to CDC Emergency Operation Center for assistance in diagnosis and management. EV patients with systemic symptoms may require treatment with vaccinia immune globulin (VIG).

**Potential Therapy in the Pipeline**

A number of agents currently in the pipeline that may help in the prevention of infections in AD include anti-inflammatory treatments that target type 2 inflammation.[64] These include monoclonal antibodies that target IL-13, IL-33, TSLP and OX40. Janus Kinase (JAK) inhibition has also been shown to reduce inflammation and improve skin barrier in AD. Both topical and oral JAK inhibitors are in various phases of clinical trials. Topical delgocitinib has been

approved for AD in Japan.[65] Pruritus and associated scratching in AD can contribute to significant damage of the skin barrier and new therapeutic options are needed. A long-term trial with nemolizumab (anti-IL-31 receptor A monoclonal antibody) showed improvement in pruritus and AD severity.[64] Other anti-itch treatments under investigation include transient receptor potential melastatin agonists (TRPM) and vanilloid antagonists (TRPV).[66] Improvement of skin barrier function and cutaneous innate immunity in AD is of interest, as it may prevent external triggers and skin infections.[67] While the attempt to prevent AD in healthy infants with daily emollient application has been disappointing,[68] whether or not skin barrier functions may be modified in established AD remains to be investigated. Aryl hydrocarbon receptor (AHR) agonists, which increase filaggrin expression, were found to improve AD and endogenous antimicrobial production in preliminary studies.[69,70] Directly targeting *S. aureus* is also an active area of investigation. These treatments include natural products with anti-*S. aureus* activity,[71] synthetic antimicrobial peptides,[72] and *S. aureus* lytic agents.[73] There is currently no approved *S. aureus* vaccine. However, approaches that target *S. aureus* toxins are in development.[74] There is increasing evidence that topically applied probiotics may be a viable approach against *S. aureus* in AD. In a small study, a gram negative bacteria, *R.mucosa*, was found to improve AD and decrease *S. aureus* burden in adults and children with AD.[75] *S. hominis* strains were found to produce an autoinducing peptide that is capable of inhibiting *S. aureus* accessory gene regulatory quorum sensing system and prevent biofilm formation by *S. aureus*.[76]

## Conclusions

AD is a complex disease associated with skin barrier defects that results in allergen or pathogen invasion and dysfunctional immune responses, causing a vicious cycle of

inflammation. The skin microbiome is altered because of this dysregulation, and pathogenic organisms such as *S. aureus* are more likely to colonize the skin. The combination of skin barrier defects, immune dysregulation, and alteration in the skin microbiome results in an increased risk for skin infections.

The prevention of infection in AD should emphasize skin barrier repair and maintenance anti-inflammatory medications without relying on antibiotics. The need for antibiotics in patients with severe AD exacerbations remains controversial. This is because some of the signs and symptoms associated with severe AD exacerbation resemble that of bacterial skin infections. It is possible that there is a threshold at which *S. aureus* levels and the extent of host tissue damage evolve into an infection. Studies are needed to investigate biomarkers that assist in determining this threshold. Acute-phase response markers such as CRP and ESR may be helpful in determining the need for antibiotics in patients with severe AD exacerbation who are suspected to have infections. Future studies should also address whether anti-inflammatory treatments, especially those that specifically target type 2 inflammation, may benefit AD patients with active infection. This is based on the premise that suppressing type 2 inflammation may lead to improvement of immunity against microbial pathogens.

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Table 1: Suggested decolonization regimen to eradicate *S. aureus* carriage among AD patients and their household contacts

| **Decolonization strategy** |
|---|
| **1. Optimize underlying condition** |
| Daily skin care:<br>Topical corticosteroid or calcineurin inhibitor for eczema areas<br>Emollients for unaffected areas<br>Basic wound care measures for severe eczema lesions (e.g. covering open or weeping wounds to prevent spread and secondary infection)<br>Avoidance of triggers for eczema flares |
| **2. Education on best personal hygiene practices** |
| Mechanisms of *S. aureus* transmission (e.g. skin-to-skin contact, fomites)<br>Emphasize personal hygiene practices:<br>Frequent hand washing with soap and water or alcohol-based sanitizer<br>Daily bathing or showering<br>Avoid reusing or sharing personal hygiene items that contact the skin (e.g. towels, loofas, razors, cosmetics, brushes, etc.)<br>Avoid contamination of topical medications and moisturizers (use pump or pour containers)<br>Keep fingernails clean and trimmed, avoid scratching |
| **3. Environmental hygiene measures** |
| Regularly clean high-touch surfaces (e.g. counters, door knobs, appliances, etc.) with commercially available disinfectants<br>Use a barrier between exposed skin and high-touch surfaces touched by multiple people (e.g. exercise equipment)<br>Wash clothing, towels and washcloths with hot water and detergent before reuse<br>Wash bedding at onset and completion of decolonization regimen<br>Wash hands before and after touching pets |
| **4. Personal and household decolonization** |
| Nasal decolonization with intranasal mupirocin 2% ointment twice daily for 5-10 days<br>AND<br>Topical decolonization with either one of the following:<br>Dilute bleach baths[a] for 15 minutes twice weekly (1 tsp of bleach per gallon of water or ¼ cup of bleach per ¼ standard tub or 13 gallons of water) for 3 months<br>Chlorhexidine gluconate 4% solution[b] once daily for 5-14 days<br>Dilute bleach baths for 15 minutes twice weekly with chlorhexidine washes daily on days bleach baths not given for 3 months |
| **5. IF recurrent infections despite decolonization** |
| Optimize underlying condition, personal and environmental hygiene<br>Assess level of adherence with above regimen<br>Repeat decolonization of patient and all household contacts with:<br>Intranasal mupirocin 2% ointment twice daily for 5 days once or twice a month for 6 months<br>AND<br>Topical decolonization with dilute bleach baths as above twice weekly OR chlorhexidine gluconate solution as above for 5 days every 2 weeks for 6 months[c]<br>May consider concomitant use of oral antibiotic therapy on a case-by-case basis with rifampin and another oral agent to which the isolate is susceptible to for 5-10 days |

[a] Dilute bleach baths may be preferable to chlorhexidine solutions in AD patients as chlorhexidine can cause skin irritation, repeat exposure can lead to resistance and it is more costly.
[b] Chlorhexidine can be applied as a wash or disposable wipe, care should be taken to avoid the contact with the face and the 4% solution should be thoroughly rinsed off with water after application.
[c] Can consider changing decolonizing agents.

**Table 2:** Antiviral drugs for treatment of eczema herpeticum due to herpes simplex virus

| Drug | Suggested Adult/Adolescent Dose | Suggested Pediatric Dose | Comments |
|---|---|---|---|
| **Acute treatment** | | | |
| Acyclovir | IV: 5-10 mg/kg/dose every 8 hours<br><br>Oral: 200-400 mg/dose five times daily | IV: 5-10 mg/kg/dose every 8 hours<br><br>≥2 years: Oral 20 mg/kg/dose 4 times daily (max 800 mg/dose) | • Typical duration 7-14 days<br>• Needs to be adjusted for abnormal renal function<br>• Monitor renal function, electrolytes, CBC while on therapy |
| Valacyclovir | Oral (typical): 1 g twice daily<br><br>Oral (alternative): 500 mg three times daily | ≥3 months: Oral: 20 mg/kg/dose twice daily (max 1,000 mg/dose) | • Off-label<br>• Typical duration 5-7 days<br>• Limited pediatric data<br>• Compounded liquid form can be prepared with instructions on drug package insert |
| Famciclovir | Oral: 500 mg/dose twice daily | Insufficient data to recommend dosing | • Off-label<br>• Limited data<br>• Typical duration 5-14 days<br>• May be able to use higher doses for shorter duration |
| Foscarnet | IV: 80-120 mg/kg/day in divided doses every 8-12 hours | IV (limited data): 120 mg/kg/day in divided doses every 8-12 hours | • Off-label, for acyclovir-resistant HSV infections<br>• Continue until clinical response<br>• Monitor renal function closely, ensure adequate hydration |
| **Chronic suppressive therapy** | | | |
| Acyclovir | ≥12 years: Oral: 400 mg/dose twice daily | Oral: 20 mg/kg/dose twice daily (max 400 mg/dose) | • Up to 12 months duration<br>• Limited data available<br>• Monitor electrolytes, renal function, CBC while on therapy |
| Valacyclovir | Oral: 1 g once daily | Insufficient data to recommend dosing | • Off-label<br>• Limited data for non-genital infections |

Abbreviations: CBC (complete blood count); HSV (herpes simplex virus)

**Fig. 1** Dysbiosis and immune dysregulation of AD.

**Fig. 2** Impetigo in a child with AD.

**Fig. 3** Eczema herpticum.

**Fig. 4** Eczema coxsakium with palm lesions.

**Fig. 5** Molluscum contagiosum along the flexural areas of an AD patient.

**Fig. 6** Principles of infection prevention and treatment in AD.

**Fig. 1**

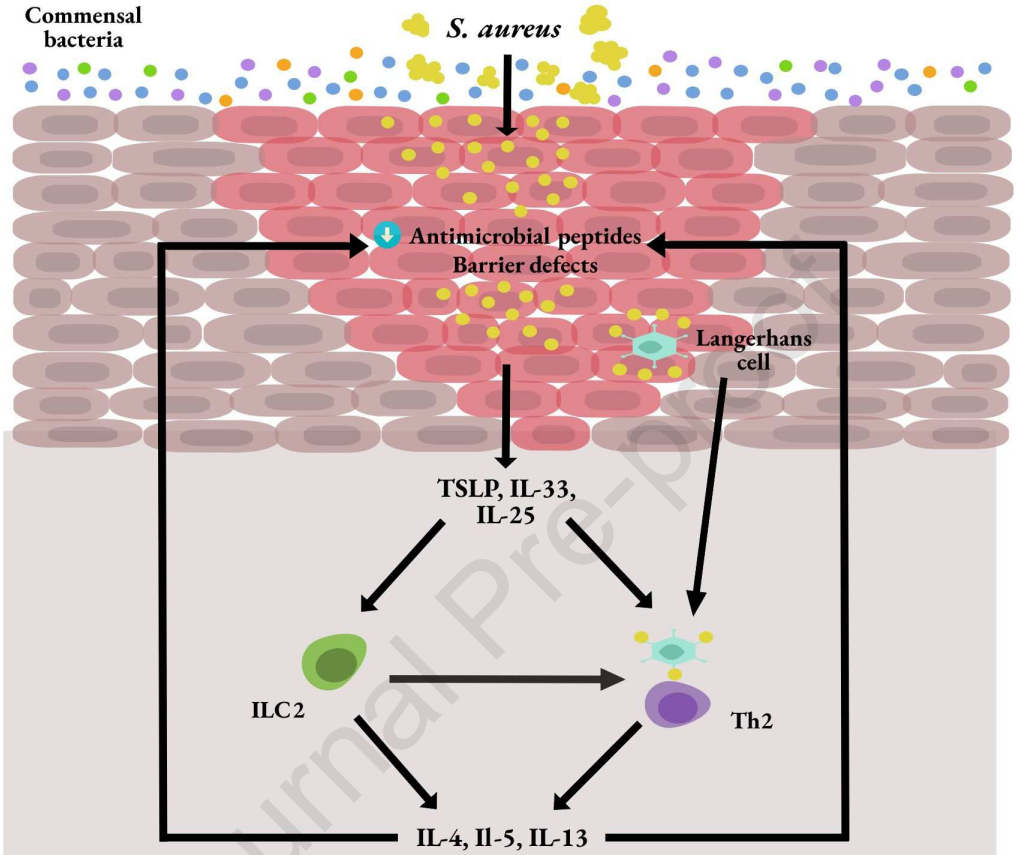

**Fig. 2**

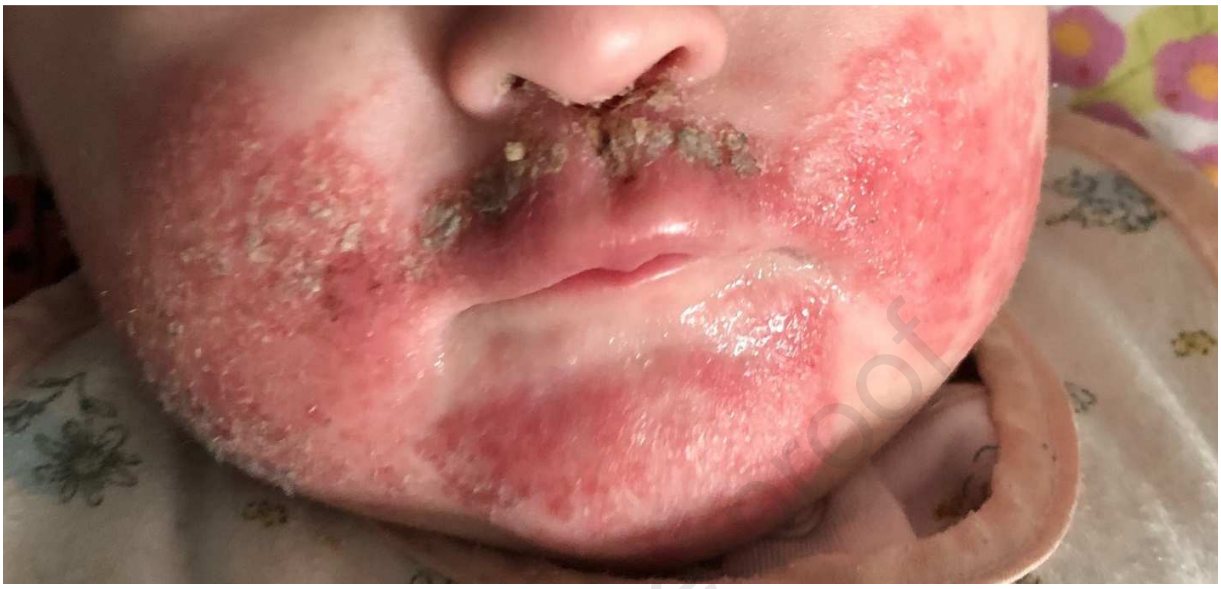

**Fig. 3**

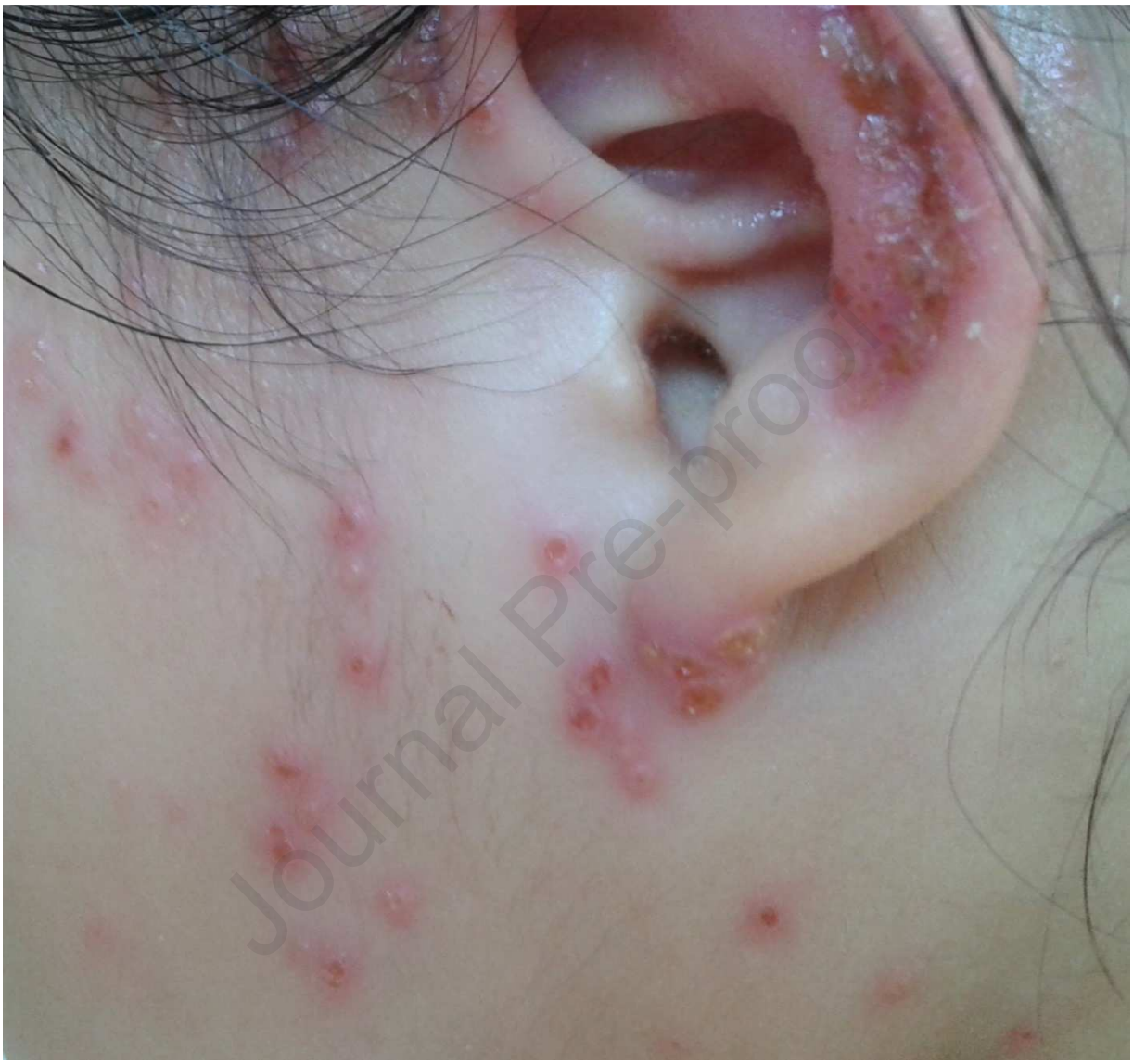

**Fig. 4**

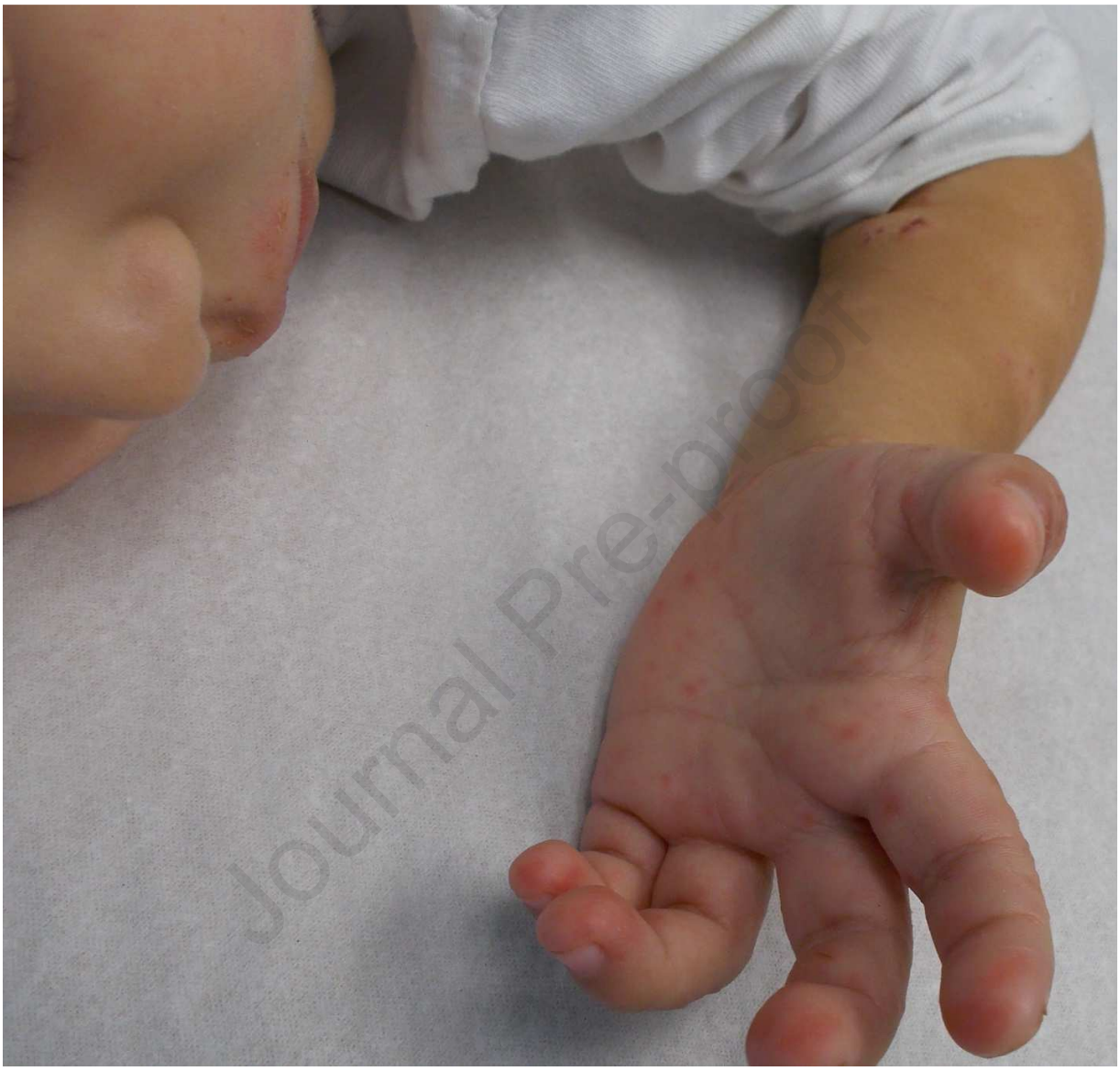

**Fig. 5**

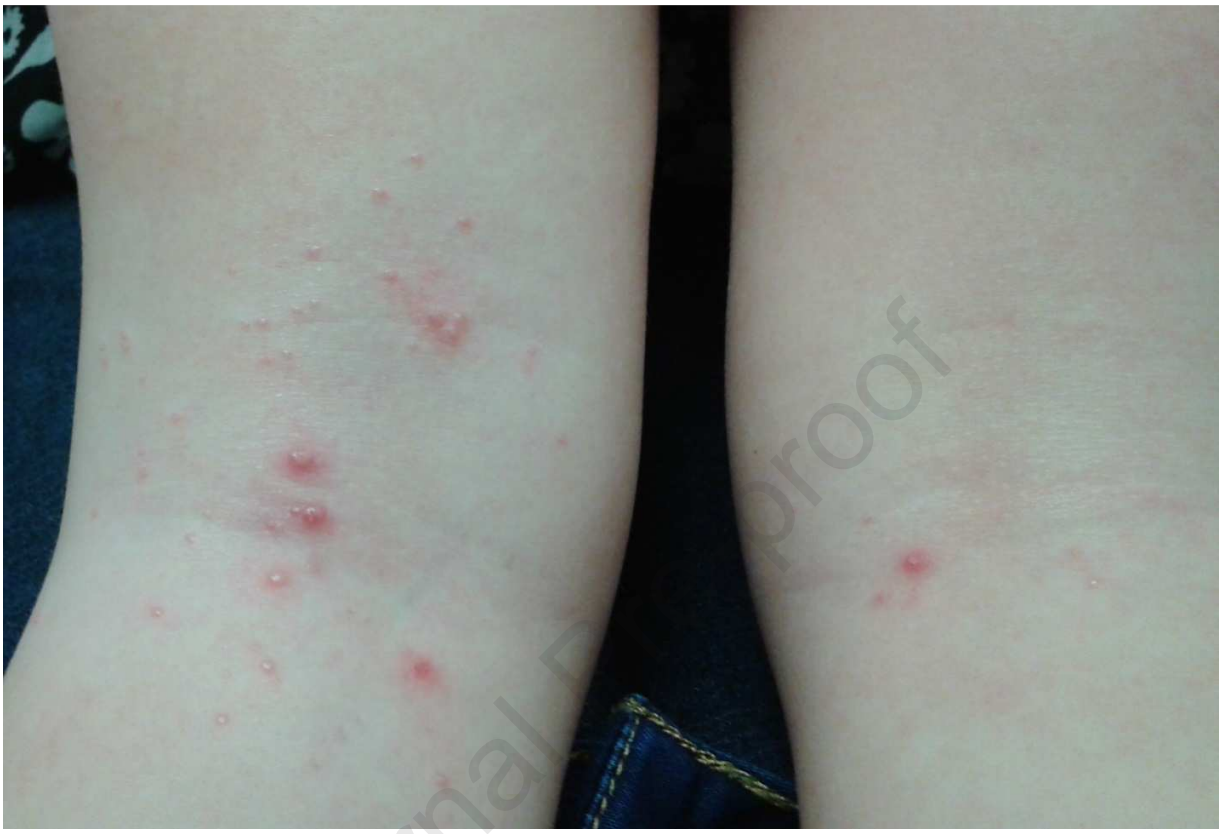

**Fig. 6**