© Pediatr Med Rodz 2023, 19 (2), p. 78–82
DOI: 10.15557/PiMR.2023.0012

Received: 01.06.2023
Accepted: 25.07.2023
Published: 28.08.2023

Agnieszka Gościńska, Agata Będzichowska, Agnieszka Lipińska-Opałka

Atopic dermatitis and the human skin microbiota

Atopowe zapalenie skóry a mikrobiota ludzkiej skóry

Department of Paediatrics, Paediatric Nephrology and Allergology, Military Institute of Medicine – National Research Institute, Warsaw, Poland
Correspondence: Agnieszka Gościńska, Department of Paediatrics, Paediatric Nephrology and Allergology, Military Institute of Medicine – National Research Institute, Szaserów 128, 04-349 Warsaw, Poland, e-mail: aga.goscinska@gmail.com

ORCID iDs

1. Agnieszka Gościńska https://orcid.org/0000-0003-4847-8903
2. Agata Będzichowska https://orcid.org/0000-0002-1756-7316
3. Agnieszka Lipińska-Opałka https://orcid.org/0000-0001-9429-107X

Abstract

The skin microbiota is a complex ecosystem consisting of bacteria, fungi and viruses. The role of the human skin microbiota is to maintain homeostasis in the body. Disruption of the balance of the natural composition of the human microbiome can lead to the development of inflammation and infection. Atopic dermatitis is a chronic and recurrent non-infectious, inflammatory dermatosis characterised by erythematous and exfoliative skin lesions, accompanied by pruritus and a tendency to superinfection. Defect in the epidermal barrier, immune dysfunction and changes in the composition of the skin microbiome underlie the pathogenesis of atopic dermatitis. It has been found that the diversity of atopic skin microbiota is significantly reduced, with a decrease in the number of *Cutibacterium*, *Streptococcus*, *Acinetobacter*, *Corynebacterium* and *Prevotella*, and a concomitant increase in the percentage of *Staphylococcus* bacteria, especially *S. aureus*. It accounts for about 20% of skin microbiome in healthy people, while in patients with atopic dermatitis the percentage of *S. aureus* can increase up to 30–100%. In addition, there is a positive correlation between *S. aureus* skin colonisation and disease severity. *S. aureus* plays a key role in the development of skin inflammation in the course of atopic dermatitis, including through the induction of lymphocyte expansion, release of cytokines, pro-inflammatory lipoproteins, and stimulation of mast cell degranulation. Therefore, properly selected and regular treatment of atopic dermatitis diversifies the skin microflora, often leading to clinical improvement in the patient.

Keywords: atopic dermatitis, AD, skin microbiota, skin microbiome, *Staphylococcus aureus*

Streszczenie

Mikrobiota skóry to złożony ekosystem, składający się z bakterii, grzybów i wirusów. Rolą mikrobioty ludzkiej skóry jest utrzymywanie homeostazy w organizmie, stąd zakłócenie równowagi naturalnego składu mikrobiomu człowieka może prowadzić do rozwoju zapalenia i infekcji. Atopowe zapalenie skóry to nieinfekcyjna, zapalna choroba skóry o przewlekłym i nawrotowym przebiegu, charakteryzująca się występowanie rumieniowo-złuszczeniowych zmian skórnych, z towarzyszącym świądem oraz tendencją do nadkażeń. U podłoża choroby leżą przede wszystkim defekt bariery naskórkowej, zaburzenia funkcjonowania układu odpornościowego oraz zmiana składu mikrobiomu skóry. Obserwuje się wyraźnie zmniejszoną różnorodność mikrobioty skóry atopowej – spadek liczby bakterii z rodzaju *Cutibacterium*, *Streptococcus*, *Acinetobacter*, *Corynebacterium* i *Prevotella*, z równoczesnym wzrostem odsetka bakterii z rodzaju *Staphylococcus*, zwłaszcza *S. aureus*. Na skórze osób zdrowych stanowi on około 20% mikrobiomu, podczas gdy u chorych z atopowym zapaleniem skóry odsetek *S. aureus* potrafi wzrosnąć nawet do 30–100%. Dodatkowo obserwuje się dodatnią korelację kolonizacji skóry *S. aureus* z ciężkością choroby. *S. aureus* odgrywa kluczową rolę w rozwoju stanu zapalnego skóry w przebiegu atopowego zapalenia skóry, między innymi poprzez indukcję ekspansji limfocytów, uwalnianie cytokin, prozapalnych lipoprotein, stymulację degranulacji komórek tucznych. Mikrobiologiczna różnorodność flory bakteryjnej skóry pacjentów z atopowym zapaleniem skóry podczas zaostrzeń choroby jest silnie skorelowana z zastosowanym leczeniem. Wynika z tego, że odpowiednio dobrane i regularnie stosowane leczenie różnicuje florę bakteryjną skóry, niejednokrotnie poprzedzając kliniczną poprawę u chorego.

Słowa kluczowe: atopowe zapalenie skóry, AZS, mikrobiota skóry, mikrobiom skóry, *Staphylococcus aureus*

HUMAN SKIN MICROBIOTA

Skin microbiota is a complex ecosystem consisting of bacteria, fungi and viruses. The term "microbiome" refers to the composition of all genes of microbes that colonise the skin surface[1].

The role of human skin microbiota is to maintain homeostasis in the body by either direct killing or reducing the virulence of pathogens through secreting antimicrobial peptides and other molecules. Additionally, many commensal species that make up the skin microbiome are able to stimulate keratinocytes to generate an immune response[2].

Disruption of the natural composition of the human microbiome can lead to inflammation and infection[3]. Microbial composition of healthy skin has been found to undergo fundamental changes with age. In newborns, it depends on the route of delivery. Infants born vaginally acquire bacteria primarily from maternal vagina, which is mainly colonized by *Lactobacillus*, while those born by caesarean section are colonised mainly by their mothers' skin microbiota[1].

Children under 12 years have their skin mostly colonized by *Streptococcus*, *Granulicatella, Gemella*, *Rothia* and *Haemophilus* bacterial genera, along with fungal genera of *Ascomycota* (*Aspergillus*, *Epicoccum*, *Phoma*), *Cladosporium* and *Cryptococcus.* After the end of puberty, when the production of sebum by the sebaceous glands increases, *Streptococci* are gradually replaced by lipophilic *Cutibacterium* and *Corynebacterium*[4–6].

The human skin microbiota is also shaped by different microenvironmental conditions characteristic for specific skin sites, such as pH, humidity, and sebum content. Sebaceous sites (face, chest, back) are dominated by lipophilic species of the genus *Cutibacterium*, while *Staphylococcus* and *Corynebacterium* are abundant in moist areas (the bends of the elbows and the feet)[6].

Much less data can be found in the literature on the human skin mycobiome. Fungi account for only 1–5% of the skin microbiota[7]. *Malassezia* (*M. dermatis*, *M. furfur*, *M. globosa*, *M. restricta*, *M. sympodialis*) is the most abundant genus in the fungal microflora found on human skin[2]. Only foot sites are colonised by a more diverse combination (*Malassezia* spp., *Aspergillus* spp., *Cryptococcus* spp., *Rhodotorula* spp., *Epicoccum* spp., etc.)[6].

Unlike bacteria and fungi, skin colonisation by eukaryotic viruses is specific to the individual rather than age or anatomical site[6].

ATOPIC DERMATITIS

Atopic dermatitis (AD) is a chronic and recurrent non-infectious, inflammatory dermatosis. It is characterised by erythematous and exfoliative skin lesions, accompanied by pruritus and a tendency to develop bacterial, viral and fungal superinfections[4,8]. Symptom onset is usually observed in the first year of life. Almost 70% of AD patients experience remission or complete resolution by adolescence[5,8], and only 25% of patients develop symptoms after the age of 18 years[8]. The prevalence of AD is estimated at 4.7–9.2% in the paediatric population, and about 0.9–1.4% in adults.

PATHOPHYSIOLOGY OF ATOPIC DERMATITIS

The pathophysiology of AD remains unclear. The underlying causes primarily include epidermal barrier dysfunction, immune dysregulation and altered composition of the skin microbiome[1,4]. Distinguishing between primary events leading to AD and secondary events resulting from the development of atopy remains controversial[3] (Fig. 1).

The skin is the first important line of body's defence against pathogenic microorganisms. The tightly packed cells that make up the stratum corneum form a physical barrier to pathogens, while the peptides and lipids secreted by keratinocytes and glands provide a chemical barrier[9].

Mutations in the *FLG* gene, which encodes the skin protein filaggrin, are the main genetic risk factor[9,10]. Filaggrin is responsible for the aggregation of keratin filaments in corneocytes, and its breakdown products act as natural moisturising factors, maintaining proper skin moisture and pH. Thus, congenital or acquired filaggrin deficiency leads to disruption of both physical and chemical epidermal barrier[10]. Additionally, increased skin pH creates more favourable conditions for colonisation by *Staphylococcus aureus*[11].

Disruption of the mechanical epidermal barrier makes it easier for bacteria to migrate to the deeper layers of the skin[12] and stimulates keratinocytes to release pro-inflammatory chemokines and cytokines. Atopic skin is also characterised by a preferential differentiation of CD4 cells towards the Th2 lineage. Overproduction of Th2 cells in turn leads to increased production of IL-4, IL-5 and IL-13 cytokines, which stimulate IgE synthesis and eosinophilia in peripheral blood and tissues[13]. Cytokines, which are released as part of an inflammatory response, contribute to reduced expression of antimicrobial peptides, such as defensins and cathelicidins, making the skin even more susceptible to increased colonisation by pathogenic bacterial strains[4].

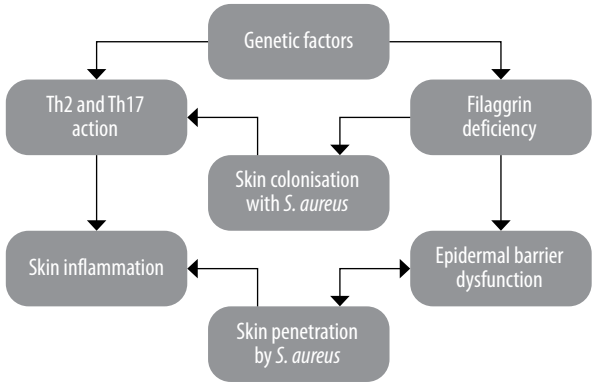

Fig. 1. Interactions between human factors involved in the pathogenesis of atopic dermatitis and S. aureus *colonisation and virulence*[9]

 DOI: 10.15557/PiMR.2023.0012

Numerous publications describe a significantly reduced diversity of atopic skin microbiota – a decrease in the number of bacteria of the genus *Cutibacterium*, *Streptococcus*, *Acinetobacter*, *Corynebacterium* and *Prevotella*, with a simultaneous increase in the percentage of *Staphylococcus*, *S. aureus* in particular[3,4,14]. *S. aureus* accounts for about 20% of skin microbiome in healthy individuals compared to 30–100% in patients with AD[4].

Zheng et al. assessed perioral microbiome in a group of 48 infants with AD symptoms and a control group of 20 healthy children. The skin microbiota was less diverse in AD patients compared to healthy infants. *Streptococcus* was the most common genus on the healthy skin, accounting for even more than 40% of the microbiota. However, in the severe AD patient group, the relative abundances of *Streptococcus* spp. were significantly reduced and replaced with *Staphylococcus* spp., *S. aureus* in particular[15].

On the other hand, Kennedy et al. found lower baseline counts of commensal *Staphylococcus* spp. in 2-month-old infants who later developed AD than in children who did not develop atopic lesions by the age of 1 year, confirming the role of dysbiosis in initiating AD[16].

Furthermore, a positive correlation has been demonstrated between skin colonisation with *S. aureus* and AD severity. *S. aureus* was more common in affected skin regions, especially those with severe inflammation, than non-affected areas. It has also been observed that untreated AD patients have higher counts of *S. aureus* strains on their skin[3,9].

S. aureus plays a key role in the development of skin inflammation in AD, among others by inducing the expansion of T cell-independent B cells, releasing cytokines and pro-inflammatory lipoproteins, and stimulating mast cell degranulation, leading to the release of interleukins such as IL-31 (a cytokine associated with pruritus)[1].

Additionally, *S. aureus* produces a number of proteolytic enzymes and toxins that may disrupt the integrity of the epidermal barrier, facilitating further penetration through the stratum corneum and, as a result, additionally stimulate the inflammatory reaction[4].

The role of chronic, mainly nasal, skin colonisation by *S. aureus* in the development of AD is an interesting issue. Totté et al. conducted a meta-analysis of 19 studies assessing nasal colonization with *S. aureus* (1,051 patients in the study group and 1,263 controls). The study showed that 57% of AD patients were nasal carriers of *S. aureus* compared to only 23% of controls with positive carrier test[17]. On the other hand, Skov et al. showed no statistically significant relationship between *S. aureus* colonisation in the first month of life and the risk of AD in the first 3 years of life in their study in 356 infants[18]. Thus, the possible role of *S. aureus* skin colonisation in the development of AD is still disputable and requires further research.

AD patients have been found to have increased counts of other *Staphylococcus* species, such as S. *epidermidis* and *S. haemolyticus* isolated from their skin[3]. Under normal conditions, *S. epidermidis*, one of the primary human skin commensals, is involved in modulating the innate immune response during skin tissue repair and wound healing. However, the mechanisms utilised by *S. epidermidis* may act against the host under certain conditions. Proteases produced by *S. epidermidis* can degrade the complement factor C5, fibrinogen and antimicrobial peptides in the host, thus avoiding elimination by immune cells[2].

Byrd et al. found that the skin microbiome in patients with less severe symptoms was dominated by heterogeneous *S. epidermidis* strain communities[6]. In their study in a group of 12 children with moderate to severe AD and a group of 11 healthy children, Kong et al. observed significantly more *S. epidermidis* strains on the skin of children with AD during exacerbations than in the period between exacerbations and in the group of healthy patients[14].

Many studies have shown that another skin commensal, *Cutibacterium acnes* (formerly *Propionibacterium acnes*), can also enhance cytolytic activity, promote aggregation and biofilm formation by *S. aureus*[4,6].

Significantly fewer authors focus on the diversity of the fungal skin flora in AD patients. Atopic dermatitis patients show a general increase in skin mycobiome diversity, with increased counts of *Malassezia* strains, especially *M. globosa* and M. *restricta*, as well as *Aspergillus*, *Candida albicans*, *Cryptococcus diffluens* and *Cryptococcus liquefaciens*[3,4,19,20].

TREATMENT OF ATOPIC DERMATITIS BY MODULATING SKIN MICROBIOME

The primary goal of AD treatment is to reduce the severity of disease symptoms and the frequency of exacerbations. The multifactorial nature of the disorder requires a multidirectional approach.

The microbial diversity of AD skin during exacerbations is strongly correlated with the treatment used. This means that the treatment of AD differentiates the skin microflora, often leading to clinical improvement.

Emollients

Atopic dermatitis therapy is currently based on daily topical application of emollients to restore proper epidermal barrier function. The so-called emollients plus, enriched with additional active substances, such as flavonoids, saponins and bacterial lysates from *Aquaphilus dolomiae*, *Vitreoscilla filiformis* are nowadays recommended. They show anti-inflammatory and anti-pruritic effects, as well as inhibit the growth of *S. aureus* and restore homeostasis of skin microbiome in AD[8].

In their study in 6-month-old infants with a positive family history of AD, Glatz et al. showed a greater diversity of skin microflora in the group of children treated with emollients than in controls[21]. A similar clinical study by Seite et al. in a group of 49 AD patients showed an increase in the species diversity of the skin microbiome and a decrease in the number of *Staphylococcus* species[22].

DOI: 10.15557/PiMR.2023.0012

Topical anti-inflammatory treatment

In addition to emollient therapy, topical anti-inflammatory drugs are used as second-line treatment. Topical glucocorticoids (GCs) have been proven to reduce skin colonisation with *S. aureus*. However, it should be remembered that long-term steroid therapy, even topical, may be associated with adverse effects. Therefore, intermittent use of topical corticosteroids every 2–3 days alternating with emollients is recommended[8].

Topical calcineurin inhibitors (tacrolimus, pimecrolimus) show anti-inflammatory effects by inhibiting T-cell activation and release of inflammatory cytokines[8].

Wongpiyabovorn et al., who included a group of 9 AD patients undergoing 4-week monotherapy with tacrolimus in their study, also showed a significant increase in the percentage of commensal species such as *Dermacoccus*, *Pseudomonas*, *Corynebacterium*, *Proteus*, and a lower count of *Actinobacteria* and *Proteobacteria* in the skin microbiota[23].

Antimicrobial treatment

The risk of coexisting bacterial, viral or fungal infections and the need for antimicrobial therapy should be considered in patients with AD, especially during exacerbations. Octenidine, chlorhexidine, mupirocin, fusidic acid and retapamulin as well as antiseptic baths with sodium hypochlorite have been shown to effectively reduce staphylococcal skin colonisation and improve the clinical condition[8]. However, it is important to note the possible development of antibiotic resistance as a result of chronic therapy, as well as the negative impact of prolonged antimicrobial treatment on the natural skin microbiome[4,8]. Oral or intravenous antibiotic therapy is recommended only in patients with systemic symptoms of bacterial superinfection[8].

Probiotics

Currently, many clinical trials suggest the possible involvement of the intestinal microflora in the modulation of systemic inflammatory reaction and immunological processes, and thus in the development of allergic disorders. Probiotics may be a potential preventive measure against AD as they improve the integrity of the epithelial barrier and restore Th1/Th2 balance[24].

In their 2019 meta-analysis of 28 articles, Li et al. found a reduced incidence of AD in children who were supplemented with probiotics both in the prenatal and postnatal period[25].

A study by Wu et al. in a group of AD children aged 4–48 months who were put on 8-week therapy with *Lactobacillus rhamnosus* showed a significant improvement in symptoms assessed with the SCORAD (Scoring of Atopic Dermatitis) index[26]. A similar effect was reported by Niccoli et al. after a 4-week oral therapy *with Lactobacillus salivarius* LS01[27].

Some species of coagulase-negative staphylococci that naturally colonise the skin inhibit the growth of their competitors, such as *S. aureus*, by secreting antimicrobial peptides[2]. The communities of strains producing these lantibiotics are reduced on atopic skin, which is mostly colonised by *S. aureus*. Nakatsuji et al. pointed to the possibility of developing targeted antimicrobial therapy for AD based on the use of specific commensal strains of coagulase-negative staphylococci in the future[28].

CONCLUSIONS

Atopic dermatitis significantly reduces the quality of life of the affected patients. Therefore, it is essential to expand knowledge about the pathophysiology of AD and possible methods of preventing its future exacerbations. Currently, an increasing number of authors focus on the role of abnormal skin microbiota in the pathogenesis of the disorder. The key role in the development of skin dysbiosis in AD is played by *S. aureus*, which is the most prevalent species in the microbiome of atopic skin, especially during exacerbations or after treatment discontinuation. The currently used AD treatment approaches have a proven effect on reducing skin colonization with *S. aureus*. Thus, it can be concluded that therapy based on restoring skin microbiota homeostasis may be the key to treatment with long-lasting effects, and perhaps it may also help prevent the development of AD in the future.

Conflict of interest

The authors report no financial or personal relationships with other individuals or organisations that could adversely affect the content of the publication and claim ownership of this publication.

References

1. Wan P, Chen J: A calm, dispassionate look at skin microbiota in atopic dermatitis: an integrative literature review. Dermatol Ther (Heidelb) 2020; 10: 53–61.
2. Flowers L, Grice EA: The skin microbiota: balancing risk and reward. Cell Host Microbe 2020; 28: 190–200.
3. Bjerre RD, Bandier J, Skov L et al.: The role of the skin microbiome in atopic dermatitis: a systematic review. Br J Dermatol 2017; 177: 1272–1278.
4. Hrestak D, Matijašić M, Čipčić Paljetak H et al.: Skin microbiota in atopic dermatitis. Int J Mol Sci 2022; 23: 3503.
5. Shi B, Bangayan NJ, Curd E et al.: The skin microbiome is different in pediatric versus adult atopic dermatitis. J Allergy Clin Immunol 2016; 138: 1233–1236.
6. Byrd AL, Belkaid Y, Segre JA: The human skin microbiome. Nat Rev Microbiol 2018; 16: 143–155.
7. Oh J, Byrd AL, Deming C et al.: Biogeography and individuality shape function in the human skin metagenome. Nature 2014; 514: 59–64.
8. Nowicki RJ, Trzeciak M, Kaczmarski M et al.: Atopic dermatitis. Interdisciplinary diagnostic and therapeutic recommendations of the Polish Dermatological Society, Polish Society of Allergology, Polish Pediatric Society and Polish Society of Family Medicine. Part I. Prophylaxis, topical treatment and phototherapy. Dermatol Rev/Przegl Dermatol 2019; 106: 354–371.

9. Edslev SM, Agner T, Andersen PS: Skin microbiome in atopic dermatitis. Acta Derm Venereol 2020; 100: adv00164.

10. Cabanillas B, Novak N: Atopic dermatitis and filaggrin. Curr Opin Immunol 2016; 42: 1–8.

11. Miajlovic H, Fallon PG, Irvine AD et al.: Effect of filaggrin breakdown products on growth of and protein expression by *Staphylococcus aureus*. J Allergy Clin Immunol 2010; 126: 1184–1190.e3.

12. Nakatsuji T, Chen TH, Two AM et al.: *Staphylococcus aureus* exploits epidermal barrier defects in atopic dermatitis to trigger cytokine expression. J Invest Dermatol 2016; 136: 2192–2200.

13. Sroka-Tomaszewska J, Trzeciak M: Molecular mechanisms of atopic dermatitis pathogenesis. Int J Mol Sci 2021; 22: 4130.

14. Kong HH, Oh J, Deming C et al.: Temporal shifts in the skin microbiome associated with disease flares and treatment in children with atopic dermatitis. Genome Res 2012; 22: 850–859.

15. Zheng Y, Wang Q, Ma L et al.: Alterations in the skin microbiome are associated with disease severity and treatment in the perioral zone of the skin of infants with atopic dermatitis. Eur J Clin Microbiol Infect Dis 2019; 38: 1677–1685.

16. Kennedy EA, Connolly J, Hourihane JO et al.: Skin microbiome before development of atopic dermatitis: early colonization with commensal staphylococci at 2 months is associated with a lower risk of atopic dermatitis at 1 year. J Allergy Clin Immunol 2017; 139: 166–172.

17. Totté JEE, van der Feltz WT, Hennekam M et al.: Prevalence and odds of *Staphylococcus aureus* carriage in atopic dermatitis: a systematic review and meta-analysis. Br J Dermatol 2016; 175: 687–695.

18. Skov L, Halkjaer LB, Agner T et al.: Neonatal colonization with Staphylococcus aureus is not associated with development of atopic dermatitis. Br J Dermatol 2009; 160: 1286–1291.

19. Han SH, Cheon HI, Hur MS et al.: Analysis of the skin mycobiome in adult patients with atopic dermatitis. Exp Dermatol 2018; 27: 366–373.

20. Zhang E, Tanaka T, Tajima M et al.: Characterization of the skin fungal microbiota in patients with atopic dermatitis and in healthy subjects. Microbiol Immunol 2011; 55: 625–632.

21. Glatz M, Jo JH, Kennedy EA et al.: Emollient use alters skin barrier and microbes in infants at risk for developing atopic dermatitis. PLoS One 2018; 13: e0192443.

22. Seite S, Flores GE, Henley JB et al.: Microbiome of affected and unaffected skin of patients with atopic dermatitis before and after emollient treatment. J Drugs Dermatol 2014; 13: 1365–1372.

23. Wongpiyabovorn J, Soonthornchai W, Wilantho A et al.: Effect of tacrolimus on skin microbiome in atopic dermatitis. Allergy 2019; 74: 1400–1406.

24. Anania C, Brindisi G, Martinelli I et al.: Probiotics function in preventing atopic dermatitis in children. Int J Mol Sci 2022; 23: 5409.

25. Li L, Han Z, Niu X et al: Probiotic supplementation for prevention of atopic dermatitis in infants and children: a systematic review and meta-analysis. Am J Clin Dermatol 2019; 20: 367–377.

26. Wu YJ, Wu WF, Hung CW et al.: Evaluation of efficacy and safety of *Lactobacillus rhamnosus* in children aged 4–48 months with atopic dermatitis: an 8-week, double-blind, randomized, placebo-controlled study. J Microbiol Immunol Infect 2017; 50: 684–692.

27. Niccoli AA, Artesi AL, Candio F et al.: Preliminary results on clinical effects of probiotic *Lactobacillus salivarius* LS01 in children affected by atopic dermatitis. J Clin Gastroenterol 2014; 48 Suppl 1: S34–S36.

28. Nakatsuji T, Chen TH, Narala S et al.: Antimicrobials from human skin commensal bacteria protect against *Staphylococcus aureus* and are deficient in atopic dermatitis. Sci Transl Med 2017; 9: eaah4680.

DOI: 10.15557/PiMR.2023.0012