Atopic dermatitis: new insights into a common condition

Mark Greener
Freelance writer
markgreener@virginmedia.com

Atopic dermatitis (AD) is one of the most common conditions managed in the community world-wide. The Global Burden of Disease consortium estimates that at least 2.2% of the global population (about 171 million people) lived with AD in 2019 (Faye et al, 2024). In England, eczema prevalence is highest among children (8.0% in those aged younger than 2 years and 14.2% in those aged 2–6 years) and lowest in adults aged 30–39 years (2.8%). Prevalence shows a second peak of 9.9% in people aged 80 years and older (de Lusignan et al, 2021).

AD incidence also shows two peaks. The incidence in England is highest in children aged younger than 1 year old (15.04 per 100 person years) and lowest in people aged 40–49 years (0.35 per 100 person years). Incidence reaches 0.79 per 100 person years in people aged 80 years and older (de Lusignan et al, 2021). AD risk factors also change with age. Recent research suggests, for instance, that antihypertensives may be associated with 43 500 new cases of AD annually among older adults in the UK (Ye et al, 2024).

Most AD cases are mild or moderate and are treated in the community (Faye et al, 2024). However, AD is under intense scrutiny by academic researchers, not to mention drug companies, enabling regular research in the area. For decades, for example, nurses suggested that people with AD and their caregivers should identify and avoid triggers, which may prolong remission (National Institute for Health and Care Excellence (NICE), 2024a). However triggers are in flux. Climate change will alter exposure to pollutants and allergens (Faye et al, 2024) and, as discussed later, recent studies added parental vaping, antihypertensives and salt to a lengthening list of AD triggers (Chiang et al, 2024; Ye et al, 2024; Youn et al, 2024). Dermatologists have a growing appreciation of the complex causes of this common condition.

Abstract

Atopic dermatitis is one of the most common conditions managed in the community world-wide. Atopic dermatitis is under intense scrutiny by academic researchers, not to mention drug companies, enabling regular research in the area. Dermatologists have a growing appreciation of the complex causes of this common condition.

Keywords: Atopic dermatitis • eczema • itching • psoriasis • skin inflammation

What lies beneath

A network of inter-related pathologic strands drives AD, including dysfunction of the skin barrier, marked immune dermatological responses, changes in the skin microbiome, as well as exposure to allergens, other environmental triggers and irritants (eg detergents, pollutants and temperature fluctuation) (Leung, 2024). Based on such insights, researchers devised two main theories to account for AD (Clebak et al, 2024).

According to the 'inside-out hypothesis', inflammation or immune system dysregulation undermines skin barrier function. The 'outside-in' hypothesis suggests that the impaired epidermal barrier provokes immune dysregulation and allergic sensitisation (Clebak et al, 2024). The two hypotheses are not mutually exclusive.

Certainly, skin barrier dysfunction is a major cause of AD (Leung, 2024). An impaired barrier allows allergens, pathogenic bacteria, viruses and fungi to penetrate the skin, triggering inflammation (Clebak et al, 2024; Leung 2024). For instance, 80.0% of people with eczema harbour *Staphylococcus aureus* in areas of skin affected by AD (Nakamura et al, 2020).

Researchers increasingly focus on the mycobiome, the fungal members of the microbiome. Species of the yeast malassezia are the most common fungi on human skin, which feed by breaking down lipids (fats) in skin secretions (Nguyen and Kalan, 2022; Ruchti and LeibundGut-Landmann, 2023).

Usually, the mycobiome is harmless, but malassezia can cause pityriasis versicolor and seborrheic dermatitis (Teufel et al, 2021). Moreover, half of patients with AD show antibodies to malassezia, suggesting that they have been infected with this yeast (Ruchti and LeibundGut-Landmann, 2023). When the barrier function weakens, such as during an exacerbation of AD, malassezia can invade and worsen skin inflammation. However, further studies should be conducted to explore these interactions. The mycobiome is, in general, 'vastly unexplored' (Nguyen and Kalan, 2022).

The genetics of AD

Nothing in clinical medicine, to paraphrase the eminent biologist Theodosius Dobzhansky (1973), makes sense except in the light of genetics. This is certainly true of AD. Filaggrins, for instance, are proteins that bind keratin in epidermal cells and are central to normal skin structure and function (Clebak et al, 2024). Some mutations

encode dysfunctional forms of filaggrin. People who are homozygous (have two copies) for the mutated filaggrin gene are at increased risk of severe AD. Homozygous people also have an earlier onset of AD and more persistent eczema (Anania et al, 2022).

Pathologically, mutated filaggrin results in skin dysfunction, including flattened skin surface cells, decreased levels of natural moisturising factors in the skin and increased skin pH. The increased pH enhances activity of proteases and other enzymes that break down the proteins that maintain epidermal structure (Clebak et al, 2024).

Mutations that encode dysfunctional filaggrin are not the only genetic causes of AD. The largest genome-wide association identified 81 loci (areas of chromosomes that contain a gene linked with AD) associated with eczema in an analysis of people of European ancestry (Budu-Aggrey et al, 2023). Of these, 29 loci had not been reported before. A multi-ancestry analysis (European, Latino or African) associated a further 10 loci with AD, three of which were novel (Budu-Aggrey et al, 2023).

Such insights may help to explain some of the epidemiological patterns of eczema. Eczema is more common in people of Asian and Black ethnic backgrounds than among White children and adults (de Lusignan et al, 2021). However, applying diagnostic criteria to skin of colour can be problematic. For example, discerning skin inflammation in darker skin can be difficult (Faye et al, 2024). NICE (2024b) note that in children of Asian, Black Caribbean and Black African ethnicity, AD can affect extensor surfaces rather than flexures, the typical presentation in White skin. Discoid (circular) or follicular (around hair follicles) patterns may be more common in skin of colour (NICE, 2024b).

New treatment targets

Emollients and topical steroids are the foundation of AD management. NICE (2024c) notes, however, that: 'Emollients are typically under-prescribed and under-used. This results in suboptimal treatment of dry skin and eczema, and may increase the occurrence of flare'. On the other hand, corticosteroids are rather indiscriminate. Corticosteroids directly influence the expression of between 10 and 100 genes depending on the cell and indirectly influence many more (Barnes, 2001).

A new generation of drugs for AD is more precise. Some new treatments inhibit a specific pro-inflammatory cytokine (a chemical that carries signals between cells) (Faye et al, 2024). Several interleukins (IL) and numerous other cytokines contribute to the immune and inflammatory responses in the skin that underlie AD, including IL-4, IL-13, IL-31 and IL-22 (Clebak et al, 2024).

Itching (pruritus) is the hallmark of AD. NICE (2024) notes that AD is unlikely if the patient does not report itch. Among other actions, IL-4 and IL-13 reduce levels of filaggrin and drive the itch-scratch cycle (Leung, 2024). In turn, the itch-scratch cycle worsens AD inflammation by decreasing filaggrin, ceramides and antimicrobial peptides produced by the skin. As a result, the risk of bacterial colonisation and skin infections increases (Clebak et al, 2024). IL-31 is particularly important in pruritus pathogenesis (Clebak et al, 2024). However, itching is a symptom of diseases as diverse as insect bites, contact dermatitis, psoriasis, renal and liver disease, diabetes and depression (Bollemeijer et al, 2024).

Against this background, Dutch researchers (Bollemeijer et al, 2024) interviewed 5246 people aged older than 50 years. Participants median age was 67 years and 56.0% were female. Of these, 33.7% said they experienced itchy skin sometime during their life. A history of AD increased the risk of itching four-fold (odds ratio 4.29). Current AD (odds ratio 1.97), self-reported psoriasis (odds ratio 2.31), current psoriasis (odds ratio 2.11) and self-reported dry skin (odds ratio 1.95) doubled the likelihood of itching. Other factors associated with itching included: female sex (26.0% increased risk), anxiety (36.0%), asthma (40.0%), renal impairment (45.0%) and depression (85.0%). Recall bias may affect the results and the design cannot prove causality. Nevertheless, the findings suggested that the presence of additional factors may contribute to itching in patients with AD, psoriasis, dry skin and other similar conditions(Bollemeijer et al, 2024).

Other new treatments influence pathways controlling important biological processes, such as Janus kinase (JAK) inhibitors (Hou et al, 2002; Xue et al, 2023). JAK, an enzyme, seems to be everywhere in the animalia kingdom, controlling critical pathways in animals as diverse as fish, insects, birds and mammals. In humans, JAK-STAT (signal transducer and activator of transcription) pathways control, among many other actions, blood cell production, metabolism and immune responses, including inflammation. Transducer means the pathway carries the signal, in this case to the DNA in the cell's nucleus. Activator of transcription means that the pathway switches on certain genes, such as those influencing inflammation (Hou et al, 2002; Xue et al, 2023).

Influencing such a highly conserved pathway can cause profound and harmful effects. On the one hand, abnormalities in JAK increase the likelihood of developing, for example, rheumatoid arthritis, blood cancers and AD (Hou et al, 2002; Xue et al, 2023). Therefore, JAK inhibitors treat chronic inflammatory disorders such as several forms of arthritis, spondylarthritis, ulcerative colitis, Crohn's disease, alopecia areata and AD (Medicines and Healthcare products Regulatory Agency, 2023). On the other hand, side-effects can be serious. Oral JAK inhibitors increase the risk of cancer, major adverse cardiovascular events (eg heart attacks and stroke), serious infections, venous thromboembolism (blood clots) and death compared with tumour necrosis factor alpha inhibitors used for the same conditions (Medicines and Healthcare products Regulatory Agency, 2023).

Emerging risk factors

Recent studies link a growing number of risk factors to AD. After adjusting for asthma, allergic rhinitis, respiratory allergies, parental smoking and socio-demographics, children who lived with at least one parent who vaped were 24.0% more likely to have AD than those who did not (Youn et al, 2024).

At the other end of the lifespan, people aged 60 years and older who received an antihypertensive were 29.0% more

likely to develop AD than those who did not, according to an analysis of UK primary care data after adjusting for confounders (Ye et al, 2024). Calcium channel blockers, diuretics and angiotensin receptor blockers show a particularly strong association with eczema (Ye et al, 2024).

Excess salt increases the likelihood of developing hypertension which may at least partly explain why AD increases the risk of cardiovascular disease by 10–20%. Skin appears to store sodium. High sodium levels may increase the risk of autoimmune conditions and chronic inflammation (Chiang et al, 2024). An analysis of 215 832 UK adults, aged 56.3 years on average, found that each gram increase in estimated 24-hour urine sodium excretion increased AD risk by 11.0%, AD severity by 11.0% and active AD by 16.0%. In a group of 13 014 people from the US, the risk of AD rose by 22.0% for each gram increase in dietary sodium (Chiang et al, 2024).

JAK inhibitors exemplify the importance of balancing risks and benefits for each patient when discussing any AD treatment from 'simple' emollients to pharmacologically sophisticated medicines. The therapeutic landscape will undergo further upheaval in the near future, as drugs modulating a plethora of other pathways are being developed (Faye et al, 2024). In the meantime, the growing number of risk factors complicates counselling patients and caregivers about AD. While AD is common and intensively studied, there is still much to learn about eczema. **BJCN**

Accepted for publication: 17 September 2024

Declaration of interest: None

Anania C, Brindisi G, Martinelli I et al. Probiotics function in preventing atopic dermatitis in children. Int J Mol Sci. 2022;23(10):5409. https://doi.org.10.3390/ijms23105409

Barnes PJ. Molecular mechanisms of corticosteroids in allergic diseases. Allergy. 2001;56(10):928–936. https://doi.org.10.1034/j.1398-9995.2001.00001.x

Bollemeijer JF, Zheng KJ, van der Meer AM et al. Lifetime prevalence and associated factors of itch with skin conditions: atopic dermatitis, psoriasis and dry skin in individuals aged > 50 years. Clin Exp Dermatol. 2024;49(9):1036 1043. https://doi.org.10.1093/ced/llae077

Budu-Aggrey A, Kilanowski A, Sobczyk MK et al. European and multi-ancestry genome-wide association meta-analysis of atopic dermatitis highlights importance of systemic immune regulation. Nat Commun. 2023;14(1):6172. https://doi.org.10.1038/s41467-023-41180-2

Chiang BM, Ye M, Chattopadhyay A, Halezeroglu Y, Van Blarigan EL, Abuabara K. Sodium intake and atopic dermatitis. JAMA Dermatology. 2024;160(7):725-731. https://doi.org.10.1001/jamadermatol.2024.1544

Clebak KT, Helm L, Uppal P, Davis CR, Helm MF. Atopic dermatitis. Med Clinic North Am. 2024;108(4):641-653. https://doi.org.10.1016/j.mcna.2023.08.012

de Lusignan S, Alexander H, Broderick C et al. The epidemiology of eczema in children and adults in England: a population-based study using primary care data. Clin Exp Allergy. 2021;51(3):471-482. https://doi.org.10.1111/cea.13784

Dobzhansky T. Nothing in biology makes sense except in the light of evolution. Am Biol Teach. 1973;35(3):125-129. https://doi.org.10.2307/4444260

Faye O, Flohr C, Kabashima K et al. Atopic dermatitis: a global health perspective. J Eur Acad Dermatol Venereol. 2024;38(5):801-811. https://doi.org.10.1111/jdv.19723

Hou SX, Zheng Z, Chen X, Perrimon N. The Jak/STAT pathway in model organisms: emerging roles in cell movement. Dev Cell. 2002;3(6):765-778. https://doi.org.10.1016/s1534-5807(02)00376-3

Leung DYM. Evolving atopic dermatitis toward precision medicine. Ann Allergy Asthma Immunol. 2024;132(2):107-108. https://doi.org.10.1016/j.anai.2023.11.022

Medicines and Healthcare Products Regulatory Agency. Janus kinase (JAK) inhibitors: new measures to reduce risks of major cardiovascular events, malignancy, venous thromboembolism, serious infections and increased mortality. 2023. https://www.gov.uk/drug-safety-update/janus-kinase-jak-inhibitors-new-measures-to-reduce-risks-of-major-cardiovascular-events-malignancy-venous-thromboembolism-serious-infections-and-increased-mortality (accessed 22 September 2024)

Nakamura Y, Takahashi H, Takaya A et al. Staphylococcus agr virulence is critical for epidermal colonization and associates with atopic dermatitis development. Sci Transl Med. 2020;12:eaay4068. https://doi.org.10.1126/scitranslmed.aay4068

Nguyen UT, Kalan LR. Forgotten fungi: the importance of the skin mycobiome. Curr Opin Microbiol. 2022;70:102235. https://doi.org.10.1016/j.mib.2022.102235

NICE. Clinical knowledge summary. How should I diagnose atopic eczema? 2024b. https://cks.nice.org.uk/topics/eczema-atopic/diagnosis/diagnosis/ (accessed 22 September 2024)

NICE. Clinical knowledge summary. Emollients. 2024c. https://cks.nice.org.uk/topics/eczema-atopic/prescribing-information/emollients/ (accessed 22 September 2024)

NICE. Clinical knowledge summary. How should I identify trigger factors for atopic eczema? 2024a. https://cks.nice.org.uk/topics/eczema-atopic/diagnosis/identifying-trigger-factors/ (accessed 22 September 2024)

Ruchti F, LeibundGut-Landmann S. New insights into immunity to skin fungi shape our understanding of health and disease. Parasite Immunol. 2023;45(2):e12948. https://doi.org.10.1111/pim.12948

Teufel A, Howard B, Hu P, Carr AN. Characterization of the microbiome in the infant diapered area: insights from healthy and damaged skin. Exp Dermatol. 2021;30(10):1409–1417. https://doi.org.10.1111/exd.14198

Xue C, Yao Q, Gu X et al. Evolving cognition of the JAK-STAT signaling pathway: autoimmune disorders and cancer. Signal Transduct Target Ther. 2023;8(1):204. https://doi.org.10.1038/s41392-023-01468-7

Ye M, Chan LN, Douglas I, Margolis DJ, Langan SM, Abuabara K. Antihypertensive medications and eczematous dermatitis in older adults. JAMA Dermatol. 2024;160(7): 710–716. https://doi.org.10.1001/jamadermatol.2024.1230

Youn GM, Sarin KY, Chiou AS, Chen JK, Honari G. Parental e-cigarette use and pediatric atopic dermatitis. JAMA Dermatol. 2024;160(7):780–782. https://doi.org.10.1001/jamadermatol.2024.1283