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Atopic Dermatitis

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SYSTEMATIC REVIEW

Prevalence and Incidence of Atopic Dermatitis: A Systematic Review

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The primary objective of this study was to systematically review and analyse epidemiological studies of the prevalence and incidence of atopic dermatitis (AD) during childhood and adulthood, focusing on data from the 21st century. A systematic search of PubMed, EMBASE and Google (manual search) was performed in June 2019, followed by data abstraction and study quality assessment (Newcastle–Ottawa Scale). Cross-sectional and longitudinal epidemiological studies of individuals with AD (doctor-diagnosed or standardized definition) were included. Of 7,207 references reviewed, 378 moderate/good-quality studies were included: 352 on prevalence of AD and 26 on incidence of AD. In the 21st century, the 1-year prevalence of doctor-diagnosed AD ranged from 1.2% in Asia to 17.1% in Europe in adults, and 0.96% to 22.6% in children in Asia. The 1-year incidence ranged from 10.2 (95% confidence interval (95% CI) 9.9–10.6) in Italy to 95.6 (95% CI 93.4–97.9) per 1,000 person-years in children in Scotland. There were few recent studies on incidence of AD in the 21st century and no studies on adults only; most studies were conducted in Europe and the USA. Epidemiological studies on childhood and adulthood AD in different continents are still needed, especially on the incidence of AD during adulthood.

Key words: systematic review; atopic dermatitis; prevalence; incidence.

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SIGNIFICANCE

Atopic dermatitis is common, and is often burdensome for the individual. An overview of how often AD occurs is therefore necessary. A systematic review was performed, which included more than 7,000 articles with data from all continents, on children and adults. Each year, up to 17.1% of adults and 22.6% of children were diagnosed with AD; with as many as 9.6% new cases of AD in children. Surprisingly, in adults, studies on new cases were from the 20th century. The results will be useful for patient organizations, physicians, scientists and healthcare planning, especially as new therapies are emerging.

Atopic dermatitis (AD) is a common inflammatory skin disease. AD causes an itchy rash and dry skin and has a substantial impact on quality of life (1, 2). In Europe and the USA, recent data suggests that the prevalence of AD among children is approximately 20% and, among adults, it ranges between 7% and 14%, with substantial variation between countries (1, 3–8).

AD leads to substantial social and financial costs and accounts for the largest global burden of disability owing to skin diseases (9).

The onset of AD occurs during the first years of life in approximately 80% of individuals (10), and that approximately 60% experience remission in adolescence (11). Recent studies indicate evidence of adult-onset AD, but the incidence across different age groups and countries remains unclear (12–14).

Differences in study design and definition of AD contribute to the heterogeneity in reported prevalence and incidence data (15). Differences across studies in factors such as study design, research teams, location, and methods, result in heterogeneity in estimates of the prevalence and incidence of AD, which may underestimate or overestimate the "true" prevalence and incidence of AD in children and adults. Furthermore, AD often features intermittent disease symptoms and signs, which can differ across age groups and skin types.

Knowledge of the prevalence and incidence of AD across different age groups and countries is essential for healthcare planning and patient counselling. Diagnosis based on validated diagnostic criteria, especially physician diagnosis, is often the preferred method. The United Kingdom Working Party diagnostic criteria (UK criteria) are a validated measure for physician assessment of AD and are thus useful (16). Epidemiological data from the 21st century could increase our understanding of the burden of AD.

The primary objective of this study was to systematically review and analyse epidemiological studies of the prevalence and incidence of AD during childhood and adulthood, with a particular focus on publications

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from 2000 through 2019. Secondary outcomes were the prevalence and incidence across age, sex, decade, and country/region.

MATERIALS AND METHODS

A systematic search of PubMed, EMBASE, and Google (manual search) was performed in June 2019. Pre-defined search terms and MeSH (Medical Subject Heading) headings and keywords were developed in collaboration with a medical librarian. The searches are described in **Appendix 1**. Reference lists of included studies and conference abstracts were also screened and Google was searched manually for potential additional studies.

Study selection, data abstraction, and quality assessment

The study included cross-sectional and longitudinal epidemiological studies of individuals with AD, diagnosed by a doctor or using a standardized definition, such as the UK criteria for AD or the International Study of Asthma and Allergies in Children (ISAAC) criteria (17). We primarily searched for studies in English and German. Following a manual search, relevant articles in other languages were also included; specifically, one article in Dutch, 8 in French, and one in Spanish. Exclusion criteria were: intervention studies, clinic-based studies, studies on specific exposed populations (e.g. occupations), and studies of patients with hand eczema only. Title, abstract, and full-text screening was performed independently by two authors in order to assess whether the predefined eligibility criteria were met.

Predefined data extraction sheets and quality assessment sheets were used, which included the Newcastle–Ottawa Scale (NOS) for cohort studies and a modified version of the NOS for cross-sectional studies (18). Screening, data extraction, and quality assessment were performed by two authors (LvK, SB), and discrepancies were resolved by author consensus. Corresponding authors of studies were contacted via e-mail when possible to obtain information about prevalence or incidence by sex.

The primary outcome was prevalence (point prevalence, 1-year (y) prevalence, and/or lifetime prevalence) and incidence of AD. Secondary outcomes included the prevalence and incidence of AD across age, sex, decade, and country/region and quality assessment using the NOS. A particular focus was on publications using data from 2000 through 2019.

This review is reported according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) (19). When numbers were provided in the original articles but not percentages, then percentages were calculated.

RESULTS

Study selection

The search identified 7,207 abstracts. Of these, 966 articles were selected for full-text review. A manual search and article reference list search identified another 21 studies. Of the articles reviewed, 378 fulfilled the inclusion criteria. In total, 115 of the included studies used data from 2000 onwards. A total of 20 of the studies with data from, and including, 2000 onwards reported 1-year prevalence for doctor-diagnosed AD, and 6 reported incidence for doctor-diagnosed AD. Of the papers included, 337 reported on children and 54 on adults or on both children and adults.

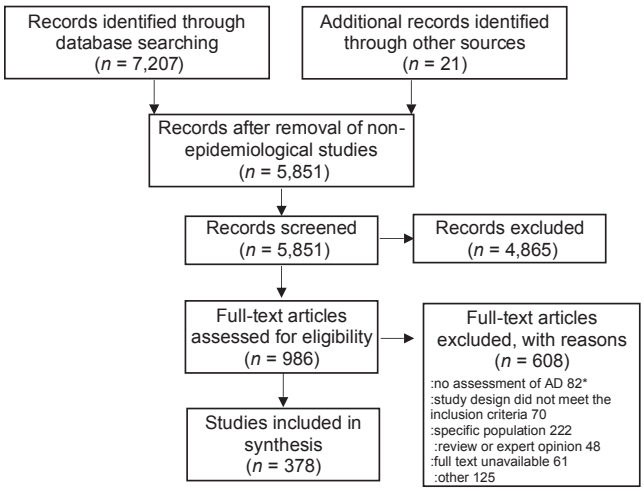

Fig. 1. Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) flow diagram. Results of search strategy. *No assessment of atopic dermatitis (AD): data on asthma, allergic rhinitis or allergy and not specifically on AD.

The study flow diagram (**Fig. 1**) reports article numbers and reasons for exclusion.

Study characteristics

The studies identified in the search in June 2019 included data from 1958 to 2017. Of these studies, 200 were conducted in Europe, 122 in Asia, 20 in North America, 20 in South America, 23 in Africa, and 14 in Australia; several articles reported on data from several countries. Study samples were between 108 to more than 30 million individuals. Some studies were conducted on several continents and on both children and adults. For study characteristics, see Supplement 1 (http://lup.lub.lu.se/record/e240247d-7664-4263-9918-3b38e704fd06).

There were 342 cross-sectional studies and 36 longitudinal studies. Twenty-eight studies used a doctor diagnosis drawn from study records or patient records and 2 studies relied on a doctor diagnosis based on both physical examination and questionnaire data.The longitudinal studies often used birth cohorts; the earliest of these started in 1958.

The definition of AD varied, and often the ISAAC criteria were used; only 10 studies used the UK criteria and 11 used the Hanifin & Rajka criteria (20), as described in Supplements 1–7 (available from http://lup.lub.lu.se/record/e240247d-7664-4263-9918-3b38e704fd06).

Prevalence of atopic dermatitis

The results for prevalence are presented in **Tables I** and **II** and Supplements 2–7 (available from http://lup.lub.lu.se/record/e240247d-7664-4263-9918-3b38e704fd06).

Studies on children and on both children and adults: all data (1958–2018). The overall point prevalence of AD symptoms in children ranged from 1.7% to 32.8% (21–25). The 1-year prevalence of AD symptoms varied

Table I. Doctor-diagnosed 1-year prevalence of atopic dermatitis (AD) in children assessed in the year 2000 or later by continents

Study	Study type	*n*	Age, years (if not otherwise stated)	One-year prevalence of doctor-diagnosed AD					
				Europe %	Africa %	North America %	South America %	Asia %	Australia %
Aberle et al. 2018 (193)	Cross-sectional study	1,687	10–11	10.1					
Abuabara et al. 2019 (34)	UK primary care cohort study	8,604,333	0–17	12.3					
Civelek et al. 2011 (35)	Cross-sectional study	6,755	10–11					0.94	
Dell et al. 2010 (235)	Cross-sectional study	5,493	5–9			21.4			
Dogruel, et al. 2016 (79)	Birth cohort study	1,377	0–12 months					4.3	
Harangi et al. 2007 (50)	Cross-sectional study	1,454 (2002) 1,454 (2005)	7–14	15.1 16.1					
Horak et al. 2014 (252)	Cross-sectional study	16,019	Mean ± SD age 8.4 ± 1.2	13.9					
Hwang et al. 2010 (255)	Cohort study	277,934	<20					2.0	
Lee et al. 2016 (274)	Cross-sectional study	8,947	1–18					14.3	
Mohn et al. 2018 (378)	Cohort study	373,954	<6	17.0					
Oak et al. 2012 (36)	Cross-sectional study	37,570	Middle-school students					22.6	
Shaw et al. 2011 (306)	National health survey	102,353	Children	10.7					
Simpson et al. 2002 (379)	GP health records	252,538	0–4	9.5					
Wijga et al. 2011 (156)	Survey based on general practitioner records, population surveys and a literature search	79,272	0–9 10–17	5.5 1.8					

SD: standard deviation.

from 0.7% in children and adults in Ethiopia (26), to 2.0% in children in Urumqi (27), and 22.7% in Kuwait (28). The 1-year prevalence in children based on doctor diagnosis of AD ranged from 0.96% to 22.6% (21–25).

The lifetime prevalence of AD varied from 1.2% in Turkey in children aged 7–12 years (132), the same lifetime prevalence of 1.2% was reported in Ethiopia (26) in children and adults with a mean age of approximately 22–23 years, and 36.2% in Beijing (27); the age at assessment of lifetime prevalence was 6–7 years. Lifetime prevalence of doctor-diagnosed AD assessed at age 6–7 years was 1.4% in Lithuania and 36.2% in Beijing (27, 29).

Studies on adults: all data (1958–2018). In adults, the overall point prevalence of AD symptoms ranged from 1.2% to 9.7% (1, 30). The 1-year prevalence of AD symptoms varied from 1.3% in Germany to 22.7% in Kuwait (28, 31), and the 1-year prevalence based on doctor diagnosis ranged from 1.2% to 17.1% (1, 32).

The lifetime prevalence of AD ranged from 1.7% to 17.7% in Kuwait; the age at assessment of lifetime prevalence was 18–26 years. The prevalence of AD in Scandinavia between ages 0–29 years was 34.1%; the lifetime prevalence of doctor-diagnosed AD was 14.6% to 20.2% in Kuwait; the age at assessment of lifetime prevalence was 18–26 years (1, 28, 31, 33).

Studies of 21st century data for children and adults. For children, the point prevalence ranged from 0% in Nigeria to 18.2% in Turkey (39, 40). For adults, it varied from 0.64%–0.9% in Israel to 9.7% in Denmark in 2010 (1, 41). For children, the 1-year symptom prevalence ranged from 4.1% to 22.7% and for adults from 7.3% to 22.7% (28, 42, 43). The 1-year prevalence of doctor-diagnosed AD ranged from 1.2% in Asia to 17.1% in Europe in adults, and from 0.96% to 22.6% in children in Asia (1, 32, 34–36). For children, the lifetime symptom prevalence ranged from 4.4% to 17.7% assessed at age 7–15 years, and for adults ranged from 3.0% to 17.7% (28, 31, 44).

Table II. Doctor-diagnosed 1-year prevalence of atopic dermatitis (AD) in adults assessed in the year 2000 or later by continents

Study	Study type	*n*	Age, years	One-year prevalence of doctor-diagnosed AD					
				Europe (%)	Africa (%)	North America (%)	South America (%)	Asia (%)	Australia (%)
Abuabara et al. 2018 (195)	GP health records	848,435	18–74	5.1					
Abuabara et al. 2019 (34)	Health improvement network	8,604,333	75–99	8.7					
Barbarot et al. 2018 (210)	Multinational cross-sectional survey study	US (*n* = 19,986) Canada (*n* = 10,004) France (*n* = 9,964) Germany (*n* = 9,971) Italy (*n* = 9,897) Spain (*n* = 9,924) UK (*n* = 10,001) Japan (*n* = 10,911)	18–64	Overall 4.9 2.2 for Germany to 8.1 for Italy		US 3.5 Canada 4.4		2.1 Japan	
Hwang et al. 2010 (255)	National health insurance register	997,729	All ages, mean ± SD 33.8 ± 20.70					1.2	
Latvala et al. 2005 (32)	Military services assessment	1.4 million	18–19	1.2 1.2					
Werfel et al. 2018 (374)	Cross-sectional survey	9,971	18–65	2.23					
Zietze et al. 2018 (373)	Health insurance data	3.3 million	18+	1.6–1.9					

SD: standard deviation; GP: general practitioner.

For children, the lifetime prevalence of doctor-diagnosed AD ranged from 4.7% to 20.2% assessed at age 7–15 years and for adults ranged from 17.6% to 20.2% (28, 31, 45).

Trends by continent: 21st century data. In Asia, studies reporting repeated measures indicated higher proportions of AD in the 21st century. For example, Liao et al. (46) assessed the prevalence of parent-reported AD symptoms in 2002 and 2007 in 6–8-year-olds in Taiwan and reported an increase from 5.8% to 7.7%, and an increase in lifetime prevalence of doctor-diagnosed AD from 18.0% to 23.9%. In the 21st century in Europe and North America there was no specific trend and data seemed stable for studies that reported repeated measures (46–53).

Trends by continent: all data (1958–2018). As shown in Supplements 2–4 (available from http://lup.lub.lu.se/record/e240247d-7664-4263-9918-3b38e704fd06), in Africa, prevalence of AD has generally increased; some studies that reported repeated measures of AD across different years confirm this trend (54–56), although one study from Nigeria reported the opposite trend (57). In Asia, some studies suggest an increasing prevalence (46, 58–60), but the results are mixed (61–63) and prevalence of AD was generally lower compared with other regions such as Europe. In the USA, the prevalence reported was somewhat higher in the 21st century compared with the 20th century; however, the few studies reporting repeated measures suggested no clear trend (64–66). In Europe, most studies reported an increasing incidence and prevalence in the 21st century compared with the 20th century and studies reporting repeated measures also suggest an increase in AD (67–74), although other studies found no increase (53, 75). In Australia, most studies suggested a higher prevalence in recent years compared with the 20th century, and this was confirmed in most of the repeated measures studies (76, 77).

Prevalence by sex: all data (1958–2018). Of all studies, 54 reported on the prevalence or incidence of AD by sex. The 1-year prevalence of AD and lifetime prevalence of doctor-diagnosed AD was higher in females (range 0.6–24.3%; 1.0–35.5%, respectively) than in males (range 0.8–17.6%; 1.4–37.3%, respectively) in most studies (Supplements 5–7; http://lup.lub.lu.se/record/e240247d-7664-4263-9918-3b38e704fd06), and this was consistent across different continents, although a higher prevalence in males was also reported (72).

The point prevalence in children assessed in good-quality studies was 24% in females compared with 35% in males at age up to 1 year; in schoolchildren the proportions were 11.1% and 8.1%, respectively (78, 79). One good-quality study that used the NOS assessment in adolescents aged 12–14 years showed a 1-year symptom prevalence for girls of 9.64% and for boys of 17.10% (80). In adults, the point prevalence was 10.2% in females and 5.8% in males (28). The 1-year symptom prevalence in female adults was 13.1% (95% confidence intervals [CI] 12.4–13.8) and in males 10.8% (95% CI 2.4–13.8).

Prevalence by age and continent: all data (1958–2018). The prevalence of AD was stable across age groups and across populations. There were no differences in prevalence across continents; for example, prevalence of AD was high in both Sweden and Africa. However, lower prevalence was observed in China, central Asia, and eastern Europe. There was no clear trend regarding age groups. For example, Burr et al. (82) reported a 1-year prevalence lower than 10% for children, similar to Nissen et al. (83), but higher prevalences were also reported and similar numbers reported for adults by Williams & Strachan (84). However, when considering the range of reported 1-year prevalence in the 21st century, children showed the highest prevalence (22.6%) (28, 36, 81–84).

Study design and assessment methods

There was heterogeneity across study designs and study populations and therefore a meta-analysis was not performed. Studies using signs of AD (ISAAC) reported a higher prevalence of AD than those using physician diagnosis. The number of times AD was measured per study period did not significantly affect the reported prevalence of AD.

Incidence of atopic dermatitis

Atopic dermatitis incidence for 21st century data. The incidence of AD was reported in 17 studies; of these, 6 studies were conducted in the 21st century (**Table III**). The 1-year incidence ranged from 10.2 (95% confidence interval (CI) 9.9–10.6) in Italy to 95.6 (CI 93.4–97.9) per 1,000 person-years in children in Scotland. The incidence of AD in adults was 7.41 (6.27–8.74) per 1,000 person years in 1968 (85).

Atopic dermatitis incidence for all data (1958–2018). In all included studies, the highest incidence of AD occurred during infancy and the incidence was also high in early childhood. For example, Nissen et al. (83) reported the highest incidence of AD during the first 18 months of life, von Kobyletzki et al. (11) reported that approximately 80% of children with AD had disease onset during infancy, and Williams et al. (84) reported that 66% had disease onset by the age of 7 years. Ballardini et al. (81) found that, between age 0–12 years, the proportion of "new" incident cases in the last 12 months in Stockholm, Sweden, was 53% of all prevalent cases. However, a considerable incidence was also reported during adolescence and adulthood. The reported proportion of adult-onset AD was 8.0% in Germany at age 28–30 years (1, 52, 86–90).

Study quality

The study quality ranged from moderate to good, as shown in Supplement 2 (http://lup.lub.lu.se/record/e240247d-7664-4263-9918-3b38e704fd06). One study

Table III. Summary of study results regarding incidence of atopic dermatitis in children and adults from the year 2000 and onwards

Author, year and reference	Study type	Year of enrollment/ study start	Study size (participants, *n*)	Females (%)	Country	Age, (range) at enrollment	Age, years at study end	Follow-up	Definition of eczema	Incidence definition	One-year incidence baseline (if applicable)	One-year incidence (95% CI)	Male incidence	Female incidence
Anandan C et al., 2009 (87)	Cohort	1995	unclear	nr	Scotland	All ages	All ages	8	Doctor diagnose and symptoms	Incidence rate of eczema per 1,000 patients per year	nr	10.2 (9.9–10.6)	8.8 (8.4–9.2)	11.6 (11.1–12.1)
Cantarutti et al., 2015 (37)	Cohort	2006–12	145,233	47.9	Italy	0–13	0–13	6	Doctor diagnose	Incidence per 1,000 person-years	14.1 (13.4–14.7)	16.5 (15.6–17.5)	nr	nr
Halkjaer LB et al., 2006 (344)	Birth cohort	2001	411	50.6	Denmark	At age 1 month	1–2	Scheduled visits every 6 months. Age at last follow-up 3 years	Doctor diagnose and symptoms	Incidence of atopic dermatitis per year	At 1 year 31%	10% from age 1 to age 2 years	nr	nr
Mebrahtu et al. 2016 (38)	Cohort	2012–14	13,734	nr	UK	0	3–7	Median 5.55; range, 0–7.6	Doctor diagnose or treatment-based algorithm	Incidence rate per 1,000 person-years	nr	95.6 (93.4–97.9)	96.5 (93.4–99.7)	94.8 (91.7–98)
Mebrahtu et al., 2016 (38)	Cohort	2012–14	13,734	nr	UK	0	3–7	Median 5.55; range, 0–7.6	Doctor diagnose or treatment-based algorithm	One year incidence, %		52.4 (51.5–53.2)	nr	nr
Mohn et al., 2018 (378)	Cohort	2009–15	357,451 (2009) 373,954 (2014)	nr	Norway	<6	6–12	6	Doctor diagnose or treatment-based algorithm	Incidence rate per patient-years.	2009: 0.028 (0.028–0.029) 2014: 0.073 (0.071–0.075)	2014: 0.034 (0.033–0.035)	nr	nr
Simpson et al. 2008 (52)	Cohort	2001–05	>30 million	nr	UK	All ages	nr	4	Doctor diagnose	Age and sex standardized one-year incidence per 1,000 patient-years	9.6 (9.5–9.7)	13.6 (13.5–13.7)	nr	nr

nr: not reported; SD: standard deviation.

reported on infant-onset AD and this may have excluded prevalent AD diagnosed during later childhood or adulthood.

Some studies, such as the COPSAC study, included high-risk infants in addition to the "general population", thus potentially overestimating the prevalence and incidence of AD (91).

DISCUSSION

This was a systematic review of 378 cross-sectional and birth cohort studies of several million individuals from all continents. The findings indicate a high prevalence of AD across continents.

The studies were heterogeneous, which made it difficult to compare the epidemiology of AD in different settings. Several different diagnostic criteria were used and the study designs differed. Furthermore, the appearance, knowledge of, and definition of AD may differ across continents, cultures, and time periods. This makes comparisons between geographical regions and time periods difficult. The study size also varied considerably. However, with this in mind, the results suggest that there are steady prevalence estimates across different age groups.

There were more studies on children, and doctor-diagnosed 1-year prevalence of AD was seldom assessed in Africa, South America, and Australia. This may be partly explained by differences in healthcare, as the European studies often used general practitioner datasets or insurance data.

The reported prevalence of AD was usually higher during the 21st century than the 20th century, especially in Africa and even in Europe. The data for Asia were more heterogeneous. There was a high prevalence of AD in children and adults. The high prevalence of AD in adults could be explained by high persistence or adult onset of AD. Some studies suggested a higher prevalence of AD for females than for males across all ages; however, there were conflicting results regarding sex differences. A higher prevalence of AD in males may be a result of surveillance bias in some settings (72). Interestingly, the incidence was high in all age groups, and more studies are needed on the definition and associated factors of adult incident AD.

Strengths and limitations

No articles were excluded from the review because of language restrictions, and the search strategy was designed to detect all relevant studies. However, it is possible that some relevant

studies were missed. The definitions of AD may have changed over the decades; however, the trends in data using doctor-diagnosed AD, self-reported AD using ISAAC criteria, and otherwise-reported AD were quite stable.

Some diagnostic criteria included infant onset of disease and thus some cases of AD with onset later than infancy might have been missed (92). As the symptoms and signs of AD may vary across age groups and skin types, using the same diagnostic criteria for different groups of patients may overestimate or underestimate AD in some groups. However, comparison of data using similar diagnostic criteria is very useful, and validated self-report measures to diagnose AD are needed.

Although similar diagnostic criteria were used in some studies, like the ISAAC or adapted ISAAC criteria, differences in study design and slight differences in the questionnaires used made it difficult to summarize the data. In contrast, the study by Williams et al. compared the prevalence of AD symptoms in 56 countries using a similar study design and method (93).

This systematic review included a comprehensive search and a critical assessment of the reviewed studies. The findings report data from representative population-based epidemiological studies, including those with large representative cohorts, data from several decades, and data from all continents. The study thus reports on findings in highly diverse settings and populations.

However, some included studies were designed to assess the prevalence and incidence of AD, whereas others reported on AD as a secondary outcome. The definition of AD is important, as it affects the reported proportions; it is possible that other forms of dermatitis were included. Most epidemiological studies had no information on treatment, which might have influenced disease symptoms and reported prevalence of AD symptoms.

Many studies lacked data on participation rate, and only a few studies reported data on socioeconomic position. It is possible that individuals with AD who had higher socioeconomic status were more likely to participate.

The studies in this review included data from 1958 until 2017. The changes in prevalence and incidence may reflect changes in disease patterns and prevalence of risk factors; however, the fact that studies used different methods of AD assessment should be kept in mind. This review reports point prevalence, 1-year prevalence, and lifetime prevalence. This comprehensive reporting may be useful, as prevalence of AD can show seasonal variations.

Comparison with other studies

The results of this study compare well with results from a systematic review using ISAAC data with a mean 12-month prevalence of 7.9% at age 6–7 years and 7.3% at age 13–14 years. The present data are also in accord with data from ISAAC studies suggesting that there is no clear pattern of prevalence of AD across continents (17). The results are in line with studies suggesting a lower prevalence in the 20th century than in the 21st century (94, 95). In a systematic review by Abuabara et al. (96), a prevalence of AD for adolescents/young adults and children was similar to our findings. A review by Pols et al. (95) reported that the assessed prevalence of AD may vary according to diagnostic methods. More studies are needed using the same validated diagnostic tools and a similar study design. There are more studies on the epidemiology of AD in Europe and the USA; a comprehensive worldwide assessment is needed.

There is also a lack of incidence studies. An understanding of incidence is important for the understanding of disease mechanisms (97). Changes in incidence can even suggest risk factors that need targeting. Most studies use questionnaire data to assess the prevalence of AD, and validated diagnostic criteria are important. The ISAAC criteria and the UK criteria are validated and used worldwide, which permits data comparisons. Further standardization and validation for self-reported assessment of AD may be useful. The results of this study have relevance for healthcare planning and patient counselling.

Below, the 14 references appearing in Tables I–III of this papers are numbered in accordance with the complete list of references also appearing in the supplements shown at: http://lup.lub.lu.se/record/e240247d-7664-4263-9918-3b38e704fd06.

Conclusion

As assessed by both patients and physicians, AD is a common disorder that has increased in most continents and reached a stable plateau in Europe and North America. There are only a few recent studies on the incidence of AD in the 21st century and no studies on adults only; most studies have been conducted in Europe and the USA. More epidemiological studies on childhood and adulthood AD in different continents are needed, especially on the incidence of AD during adulthood. However, assessment of AD must be more standardized across cultures in order to improve future epidemiological studies.

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Appendix 1

Search strategy

Database: Ovid MEDLINE(R) ALL <1946 to June 07, 2019>

Search Strategy:

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1 Dermatitis, Atopic/ or exp Eczema/ or "atopic dermatit*".mp. or eczem*.mp. (42116)

2 Epidemiology/ or exp Epidemiologic Methods/ or epidemiolog*.mp. (6379163)

3 Remission, Spontaneous/ or Remission Induction/ or incidence/ or prevalence/ or remission.mp. or incidence*.mp. or prevalen*.mp. or persisten*.mp. (1891461)

4 1 and 2 and 3 (5085)

5 "population based".mp. (119262)

6 2 or 3 (7138602)

7 1 and 5 and 6 (603)

8 4 or 7 (5321)

9 exp Animals/ not Humans/ (4587438)

10 8 not 9 (5256)

11 limit 10 to (english or german) (4876)

12 remove duplicates from 11 (4869)

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Embase

Session Results Date 10 Jun 2019

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No.	Query Results	Results
#11.	#8 NOT #9 AND ([english]/lim OR [german]/lim)	4,752
#10.	#8 NOT #9	5,274
#9.	'animal'/exp NOT 'human'/exp	5,257,153
#8.	#4 OR #7	5,323
#7.	#1 AND #5 AND #6	867
#6.	#2 OR #3	4,049,189
#5.	'population based'	167,518
#4.	#1 AND #2 AND #3	4,862
#3.	'remission'/exp OR 'incidence'/exp OR 'prevalence'/exp OR remission OR incidence OR prevalen* OR persisten*	2,704,826
#2.	'epidemiology'/de OR epidemiolog*	2,011,417
#1.	'atopic dermatitis'/exp OR 'eczema'/exp OR 'atopic dematit*' OR eczem*	75,678

REVIEW ARTICLE

Counting the Burden: Atopic Dermatitis and Health-related Quality of Life

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Atopic dermatitis is the most prevalent chronic inflammatory skin condition globally. The burden of atopic dermatitis on children and adults is extensive and there is also significant impact on the lives of patient caregivers and family members. It is important to be able to measure this impact to inform clinical decisions and to plan appropriate patient and carer support. The current impact of atopic dermatitis on children and adults can be measured using several different quality of life questionnaires: the most frequently used are the Dermatology Quality of Life (DLQI), Children's Dermatology Quality of Life and Infants Dermatology Quality of Life. The impact on partners and family can be measured using several atopic dermatitis specific questionnaires or the Family DLQI or the generic Family Reported Outcome Measure, FROM-16.

Key words: eczema; atopic dermatitis; quality of life; dermatitis.

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The dry, itchy, eczematous skin of atopic dermatitis (AD) has a profound impact on quality of life (QoL). The pathophysiology of AD is postulated to be a combination of epithelial barrier defects, (1) immune system dysfunction (2) and psycho-neurogenic inflammation (3). The characteristics of AD are heterogenous with varying clinical presentations according to age or anatomical region (4). AD has also been described as a systemic disorder given its wide-ranging associations from malignancies to cardiovascular effects (5). It is the most prevalent chronic inflammatory skin condition globally (6), but there are challenges in collating the extensive epidemiological data. Worldwide, up to 50% of cases labelled as AD are not in fact truly 'atopic' i.e. phenotypic eczema that is associated with circulating allergen-specific IgE. A phase two study of the largest AD sample in the world demonstrated a weak association between flexural eczema and atopy (7, 8) and therefore it cannot be assumed this presentation is always attributable to atopy. Furthermore *ad hoc* prevalence studies are often diverse and based on different diagnostic and sampling methods making true data comparison difficult.

SIGNIFICANCE

Atopic dermatitis is the most common inflammatory skin condition globally that affects both children and adults. The symptoms of atopic dermatitis as well as the demands of treatment often contribute to a significant impact on patient quality of life (QoL). This QoL impairment may also extend to caregivers, partners and close family members of atopic dermatitis sufferers. This review aims to evaluate the impact of atopic dermatitis on the QoL of patients and close relatives. A myriad of tools are available for measuring QoL; a brief description of the most relevant instruments is also presented in this article.

The burden of disease of AD on children is extensive and there is also significant impact on the lives of patient caregivers and family members (9). In affected adults, this effect is multi-dimensional with implications for mental health, work productivity and QoL. This review focusses on the measurement of QoL in AD patients, in particular on the QoL measures recommended by Harmonising Outcome Measures for Eczema (HOME), and the implications of the wider impact that AD has across different ages, social groups and countries.

Health-related quality of life (HRQoL) is a specific aspect of the wider concept of "quality of life". Throughout this manuscript "quality of life" refers to HRQoL.

EPIDEMIOLOGY OF ATOPIC DERMATITIS

The determination of accurate prevalence data for any disease depends on there being clear agreed diagnostic criteria and the ability to gather data from subjects that represent the general population. However, there are several differing diagnostic criteria that may be used in surveys of AD prevalence, contributing to confusion, and the methodology of many surveys leads to selection bias, for example if data from a clinic is measured rather than from a population cross-section. The various prevalence figures quoted in this review relate to the population described in the corresponding reference and may not be generalised to other populations.

Most AD epidemiological data have focussed on the paediatric population (9). The advent of the International Study of Asthma and Allergies in Children (ISAAC) has provided a standardised platform to identify over a

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million children suffering with AD worldwide (10). The prevalence ranged from 0.9% (India) to 22.5% (Ecuador) in a sample of 380,000 children aged 6–7 years from 60 countries (11). For teenagers (ages 13–14, 660,000 subjects) the prevalence values range from 0.2% (China) to 24.6% (Columbia) with generally higher values seen in Latin America and Africa. In the European Union the point prevalence is 4.4% (12).

There have been several studies examining the adult population. The European Community Respiratory Health Survey (ECRHS) study collated data from US and European subjects and identified prevalence rates ranging from 0.3% (Switzerland) to 6.2% (Estonia) (13). Recently, Barbarot et al. (12) conducted an international survey on representative samples of adults (ages 18–64) worldwide using standardised methods and diagnostic criteria. Prevalence values ranged from 2.1% (Japan) to 8.1% (Italy), and there were further variations within countries and regions. Generally, there was a higher prevalence in females, but in the UK and the USA there was no significant difference in prevalence between females and males. Peak prevalence was from age 25 to 45 years, with AD then becoming less prevalent with increasing age ($p < 0.05$). However, a study limitation was that subjects self-diagnosed using modified UK Working Party criteria, with under 10% having a physician diagnosis. Regardless of which measure was used, USA subjects reported having the most severe AD, whereas in southern Europe the prevalence of mild disease was higher than in northern countries such as in the UK (12).

A systematic review of 13 studies conducted in the Netherlands and the UK demonstrated that the prevalence of AD assessed by general practitioners (1.8–9.5%) was lower than when self-reported (11.4–24.2%) (14). This may be because milder cases do not present to general practitioners, or self-reporting may over-diagnose. Kim et al. (15) analysed 110,000 cases and reported that the mean age of AD diagnosis was 1.6 years, with < 5% cases experiencing persistent disease at 20 years follow-up. Disease severity, duration, later onset and female sex were all associated with persistent disease.

As the above studies demonstrate, there is a large burden of disease from AD. It is imperative to measure the impact of this condition in those who are affected by it, because this information is essential to inform the clinician concerning choice of therapy. This data is also useful in the assessment of novel therapies, and in monitoring response to therapy.

PATIENT REPORTED OUTCOME MEASURES

A Patient Reported Outcome (PRO) is any report that comes directly from a patient about a health condition or its treatment, without interpretation by a clinician or anyone else (16). The initial drive for PROs was led by the pharmaceutical industry. In the US during the late 1980s there was an increased awareness of the importance of patient input in assessing treatment. The seminal Rand Health Insurance experiment collected patients' self-report of health status to understand the impact of health insurance plans on health outcomes (17). Following this, Tarlov et al. (18) conducted an observational study to ascertain how outcomes of care were affected by specific components of the health care system. This landmark Medical Outcomes Study concluded that tools should be developed for "monitoring the patient wellbeing in office practice and clinical research." The Food and Drug Administration (FDA) initiated the requirement for QoL assessments in oncology trials (19). However, a report of a PRO measure used as an endpoint in a clinical trial involved anti-hypertensives: when the results were published by the press, although the endpoint measured tolerability rather than efficacy, the stock market value of the pharmaceutical company rose resulting in an economic impact of a health related outcome (20). The term "patient reported outcome" was coined in the year 2000 and the plethora of outcome measures subsequently developed led to the development of a PRO harmonisation group (21).

PROs may include evaluation of symptoms, functional status, or general or HRQoL.

THE IMPACT OF ATOPIC DERMATITIS ON QUALITY OF LIFE

QoL measurement has become an integral aspect of monitoring disease and intervention efficacy across dermatology. Three dimensions in particular have been proposed that are key to QoL evaluation: 'now', 'long-term' and 'family' (22). The 'now' is important for current assessment, but the long-term effects as well as wider implications for family should also influence treatment and health-economic decisions. It is vital to understand the various aspects of QoL impairment across the range of AD sufferers.

The impact of AD on children is comparable to other childhood chronic diseases such as cerebral palsy, epilepsy and cystic fibrosis (23). A review by Olsen et al. (24) identified data from 37 studies on 4082 children with AD and found that AD had, on average, a moderate effect on health-related QoL. However in each study there was a wide range of reported impacts of AD. Children with AD are often affected on a daily basis including problems when feeding, changing clothes and playing, thus depriving them of a 'normal childhood'(25). The chronicity of AD is often not a focus in studies: QoL scores may differ between primary and secondary care settings as the latter are likely to include more severe cases.

There are similar concerns for teens and adolescents. Parents fear that their children may be unable to make friends when older (26). Growing up, they develop a sense of being different due to alienating comments and having to explain several misconceptions (27), eventually

leading to a feeling of isolation and the need to be 'different' (28). Despite the debilitating nature of AD and the wider effect on school-work, AD does not impact academic performance in adolescents (29) and compliance with topical treatment in this group was reported in one study to be as high as 96% (30). Nevertheless, AD may influence career pathways. Advice to adolescents about work where having AD may involve risk is important to help them decide appropriate careers (31). The transition from paediatric to adult clinics is often a challenging period and the Department of Health in England has identified a specialised need in this area (32). A trial of 'young adult' clinics for AD patients with open access psychological support demonstrated significant improvement in QoL with high satisfaction rates.

AD has long been considered mainly a childhood problem, but the prevalence in adults ranges between 3–5% (33). In a review of two cohorts, 38% of adults with AD had symptom onset in childhood. (34). Over half of adult patients report that AD has a moderate to extremely large effect on their QoL. Many describe pain, stinging and embarrassment from their AD impacting their choice of clothing. The burden increases with increasing severity of disease (35): 57% of adults miss at least one day of work in the preceding year and describe problems with intimacy and feelings of guilt due to AD. Over 10% of 1189 people with moderate to severe AD demonstrated depressive symptoms (35). Of those subjects suffering from severe AD, 88% felt their ability to tackle life was at least partly compromised (35).

Whether the patient is a child, teenager or adult, AD impacts on the extended family as well as on caregivers, a concept described as 'The Greater Patient' (36). This effect may be experienced by anyone with a close relationship with the patient (37). This broader impact of disease is increasingly being recognised as another dimension of healthcare, with the advent of several new questionnaires to ascertain this impact. AD, being a common childhood condition, is a particularly relevant field of research given the 'web of relationships' involved from an early stage (38).

Several major life changing decisions, such as choice of education, choice of career, choice of partner or decisions about whether to have children may be influenced by having a chronic skin disease such as AD (39). The impact of the disease on such decisions can therefore alter the life course of people affected, with the impact of the disease echoing through the decades.

A BRIEF HISTORY OF QOL IN ATOPIC DERMATITIS

A plethora of QoL measures have been developed within dermatology, especially in psoriasis and AD. A systematic review by Rehal & Armstrong (40) in 2011 attempted to identify trends in outcome instruments used in AD trials. Of the 382 studies included, only 67 studies incorporated QoL measurements. Eleven instruments were identified for measuring QoL, of which the Children's Dermatology Quality of Life (CDLQI) was the most frequently used followed by Dermatitis Family Index (DFI), Dermatology Life Quality Index (DLQI) and Infant Dermatology Quality of Life questionnaire (IDQoL). Three tools measured the QoL of family members of patients with AD: DFI, Parents Index of Quality of Life in Atopic Dermatitis (PIQol-AD) and Parents of Children with Atopic Dermatitis (PQol-AD). The authors surmised that an overall increase in use of QoL instruments from 1985 to 2010 indicated the emerging importance of QoL measures for patient evaluation and management.

HARMONISING OUTCOME MEASURES FOR ATOPIC DERMATITIS

Noting the myriad of outcome assessments for AD, the first International Conference on HOME was held in 2010 (41) and a decision was made for a core outcome set (COS) to be developed for AD. All scales had to pass the OMERACT filter of truth, discrimination and feasibility (42). The studies assessing the validity of different instruments were required to pass the COSMIN checklist (43). In 2011, 4 outcome domains were agreed on: symptoms, clinical signs, long-term control of flares and QoL (44). At the HOME III meeting Eczema Area and Severity Index (EASI) was recommended as the instrument for the outcome disease severity (45), HOME IV recommended Patient Oriented Eczema Measure (POEM) as the PRO for measuring symptoms (46). Heinl et al. (47) in 2016 conducted a study on QoL instruments used in eczema trials using the Global Resource of Eczema Trials (GREAT) database. In the 303 studies included from 2002–2014, approximately 90% of studies used a PRO, however only 63 used QoL measures. Eighteen named and 4 unnamed QOL instruments were found. Unlike the study by Rehal et al. mentioned above, (40), Heinl et al. (47) did not find evidence of increasing use of QOL measures, however confirming Rehal et al's finding, the DLQI, CDLQI, IDQol and DFI were the most frequently used instruments. Four instruments measured the impact of AD on carers of patients of which two were named (DFI, PIQoL-AD).

Around the same time Hill et al. (48) conducted a systematic review looking at trends in disease severity and QoL instruments for patients with AD. Only 45 of the 135 identified studies measured QoL. Again, the DLQI, CDLQI, IDQoL and DFI were the most commonly used instruments. Hill et al. found 28 QoL measures in contrast to the 22 reported by Heinl and colleagues (47), possibly due to the different databases searched. Hill et al. (48) also found that the number of articles reporting on QoL peaked in 2012. Three instruments (DFI, FDLQI and PIQoL-AD) measured impact of QoL on caregivers.

HOME V concentrated on the definition core outcome for long-term control and its measurement as well as future areas of research for a tool to measure children's QoL (49). It was agreed that a new instrument should be developed for long-term control and that further research on itch intensity was necessary. It was also decided that none of the QoL instruments could be recommended at that point in time due to concerns with validation in certain areas.

However, the sheer number of QoL instruments in the above studies, with some instruments used only in single studies, highlighted the importance of standardised methods for measuring QoL in AD in order to compare various intervention measures. Therefore, at the 2019 HOME VII meeting (50) it was agreed to recommend DLQI and CDLQI to measure the QoL of adults and children and the proxy measure IDQoL to measure the QoL of infants. Two new instruments which had been developed in response to the recommendations from HOME V, Atopic Dermatitis Control Test (ADAPT) and Recap of Atopic Eczema (RECAP) were recommended for measuring long-term control. In addition, the Numerical Rating Scale (NRS-11) (51) to measure the intensity of itch was recommended in addition to POEM as the PRO to measure symptoms. It was also agreed that the COS for AD should be measured at baseline and end of the primary endpoint to ensure comparability in trial results.

QUALITY OF LIFE INSTRUMENTS FOR ATOPIC DERMATITIS CHOSEN BY THE HOME INITIATIVE

Historically, the value of clinical research has been reduced by different outcome measures being used in individual studies, making comparison impossible. The HOME initiative, by identifying a set of core measures provides the potential for improved assessment, comparison and combination of data.

Dermatology Life Quality Index

The DLQI is a dermatology-specific questionnaire developed in 1994 (52). There are over 110 translations, used in over 80 countries (53). The DLQI is quick and easy to perform and score in routine clinical practice. During the initial development, 120 patients answered the open-ended question "list all the ways your skin disease affects you". The questionnaire was developed from the answers.

The DLQI is a 10-item questionnaire with a one week recall period. It is completed, on average, in two minutes. The DLQI assesses the impact of skin disease on symptoms and feelings, daily activities, leisure, work and school, personal relationships and the impact of treatment. The ten question scores (each 0–3) are added to give the DLQI score (maximum 30).

The DLQI has been extensively validated in numerous studies with regards to its psychometric properties as well as its use in clinical research (54–56). The DLQI structure has been examined with respects to dimensionality indicating one to 4 factors across various studies (54). It is responsive to change (57, 58) with high test–retest reliability (59, 60).

The DLQI validated score banding (61) allows meaningful score interpretation. For example, score band 0–1 indicates no effect on a patient's life and 11–20 a large effect. This banding can help inform clinical decisions. The DLQI has been significantly correlated with numerous other measures highlighting its construct validity (54), and used as the standard comparator in the validation of many novel QoL questionnaires. The DLQI has been mapped to the EQ-5D using ordinal logistic regression allowing the prediction of dermatology-specific utility values from generic EQ-5D scores (62). The model allows the capture of disease-specific data that generic measures are often unable to capture, thereby generating more precise health economic data without the need for utilising multiple questionnaires. However, though the model is validated for large groups of data, it requires further testing at an individual subject level. An electronic format has been developed and validated against the paper format demonstrating equivalence (63).

Although the DLQI is the most commonly used measure across dermatology (55, 64), several limitations have been described including concerns regarding under-representation of emotional aspects and its uni-dimensionality (65). Furthermore, there are concerns over score interpretation when "not relevant" options are chosen. In the DLQI, for 8 of the 10 items it is possible for the respondent to choose "Not relevant". If the subject does this for one question, because the life aspect enquired about is not part of the respondent's usual life pattern, then the overall maximum score is reduced. The more questions that are answered "not relevant" the greater the impact on the maximum possible score. Some subjects might therefore not reach a critical level that is used to help inform a clinician concerning the use of some therapy, even though the reason that a question may be "not relevant" may be that the skin disease has severely impacted that aspect of the respondent's life. It has therefore been suggested that the final score should be adjusted depending on the number of "Not relevant" answers given (66).

However, introducing an additional more complicated scoring system may not be appropriate (67) and would be impractical in busy clinics, require a wide range of revalidation studies to be performed and introduce confusion into the interpretation of DLQI scores (68). Whatever method is used to calculate them, DLQI scores should be used to help the clinician take the most appropriate decision for individual patients, and not used to restrict clinical judgement. A simple approach would be for any clinician reviewing a completed DLQI, or indeed any QoL questionnaire, to note whether or not there were any "Not relevant" answers, to enquire further and to take this into account as part of the information informing their clinical decisions.

Although many properties of the DLQI have been extensively validated, the DLQI has been criticised for not having been subject to Rasch analysis (69, 70), a method for the refinement of items and to convert the ordinal scale to a fundamental measure. However, the high face validity of the questions, the simplicity of its use and the easy interpretability of its scores have led to the DLQI being the first QoL measure with which dermatologists worldwide have become familiar (71), contributing to a cultural shift towards patient-centred medicine. Many clinicians have embedded the use of the DLQI in their routine practice because of their experience of its usefulness in routine clinical care, and the DLQI is incorporated in national guidelines or registries in at least 40 countries.

The DLQI has been recommended by the HOME initiative as the core instrument for measuring the impact of AD on the QoL of adult patients with AD (50).

Minimal Clinically Important Difference

The minimal clinically important difference (MCID) is the minimal change in score considered clinically significant by clinicians and patients (72). This provides additional meaning to QoL score changes. The DLQI MCID value is 4 points (73). We have proposed a 'multiple-MCID' concept has (74) to allow a more distinguishing analysis of interventional studies. However, this requires extensive further validation.

Children's Dermatology Life Quality Index

The CDLQI measures the impact of skin conditions on the QoL of children aged 4–16 years (75). A 10-item questionnaire was developed, based on 169 replies from children, asking how their skin condition affected their life. The CDLQI measures impact over the last week on symptoms and feelings, leisure, school or holidays, personal relationships, sleep and treatment. One question has a choice of two options dependent on whether or not within the last week the child was in school or on holiday. Each question has 4 possible answers. A cartoon version appeals to younger children (76). The CDLQI has been validated extensively (77–79). It is completed in mean in 2 min and has score bands to give meaning to the scores (80). There is no published minimal clinically important difference (MCID) for CDLQI described for use across all skin diseases. However, for use in children with AD it has been suggested that the MCID for the CDLQI is between 6–8 points (81).

The CDLQI has been recommended by HOME as the core QoL instrument for measuring the impact of AD on the QoL of children (50).

Infants' Dermatitis Quality of Life index

The IDQoL is a dermatitis specific parent/caregiver proxy measure of the QoL of children under the age of 4 years (82). It is a 10-item questionnaire with a one week recall period. The items measure the perceived impact on QoL of itch and scratch, mood, time to sleep, playing or swimming, family activities, mealtimes, treatment, dressing and undressing, and bath time. An additional question records the severity of dermatitis as perceived by the parent/caregiver. The IDQoL had been translated into several languages and is frequently used in AD trials and validation aspects have been described (83). The IDQoL has been recommended by HOME as the core QoL instrument for measuring the impact of AD on the QoL of infants (50).

The core measures chosen may change in the future if more appropriate measures are developed, but there is huge strength to be gained by always using the same set. The minimal clinically important difference and descriptive score meaning bands have not been described for the IDQoL.

Disability adjusted life years

Whereas Quality Adjusted Life Years (QALYs) are years of healthy life lived, Disability Adjusted Life Years (DALYs) are years of healthy life lost. To calculate the burden of a certain disease, the disability weighting is multiplied by the number of years lived in that health state and is added to the number of years lost due to that disease (84). Using DALYs, the global burden of skin disease survey revealed that eczema causes the highest burden of all skin diseases worldwide (85). Eczema is one of top 50 most common causes of disease, with a global prevalence estimated at 229 million people affected. However, it must be remembered that AD affects the QoL of not only those directly affected but also their close family members.

FAMILY IMPACT OF ATOPIC DERMATITIS

Impact on parents

AD is a chronic disease so the symptoms require constant attention. Treatment for AD includes regular use of emollients along with various topical and systemic measures. The treatment process can have an adverse impact on the QoL of the patient (86) and also the main caregivers, especially when young children are affected. Inevitably parents are affected too. A meta-ethnography study (87) collated parental and childhood/adolescent experiences of AD. It is postulated that parent and child bonding is affected as skin irritation may limit physical interactions (88). Furthermore, the associated behavioural difficulties such as restlessness and hyperactivity may be demanding for parents, resulting in frustration and exhaustion (89). Parents may choose not to have further children because of the current burden on the wider family. Dedicating time for treatment application and extra housework also directly impacts parental work responsibilities and therefore has financial implications (90). The symptoms experienced by children e.g. sleep disturbance, restlessness, psychological strain and embarrassment may all be experienced

second hand by parents and therefore their QoL is a key determinant of the child's well-being (26, 91).

Parents report having to apply creams that children dislike, often resulting in the need for coercion (92). Cultural issues may play an important role in parental attitudes to their affected child. Mothers may feel they did something wrong during pregnancy, or develop a sense of guilt for neglecting other children because of their focus on the child with AD (91). Anxiety may be exacerbated by conflicting advice on management, including the long-term sequelae of topical corticosteroids being inadequately explained by health professionals (93).

Loss of sleep is another familiar theme in parents of children with AD. Angelhoff et al. (94) conducted a study into the perceptions of sleep in such parents. Eleven mothers and one father, with children aged 0–2 years with SCORing Atopic Dermatitis (SCORADs) of >15 were interviewed. All but one parent experienced fragmented sleep. Most parents accepted the sleep loss but expressed a desire for longer uninterrupted sleep. Sleep loss led to fatigue with parents perceiving this had a negative effect on the whole family. The participants felt that the sleep loss was normalised by other family members and ignored by health professionals. The participants also felt that dynamics between parents and other siblings had changed, leading to feelings of guilt and sadness.

Moore et al. (95) reported that parents of children with eczema suffered sleep loss, with the mothers losing a median of 39 min and fathers a median of 45 min of sleep. In contrast, parents of children with asthma lost no sleep. While both parents of children with AD had increased anxiety scores, the mothers had two-fold higher scores of depression than mothers of children with asthma. This was related more to the sleep loss than to a direct effect of the eczema.

In contrast, in an ongoing large prospective, longitudinal, population-based cohort study 11,649 mother–child pairs in the UK were followed up by Ramirez et al. (96) from birth to 10 years. Children were classified as having AD on the basis of the presence of flexural dermatitis on two occasions. After adjusting for confounders, sleep duration and early morning awakening were similar in mothers of children with active AD and mothers with children never having reported AD. However, difficulty in falling asleep, subjectively insufficient sleep and day-time exhaustion were more frequently reported in mothers of children with active AD. The authors also reported larger effects in mothers of children with more severe AD. Adjusting for child sleep disturbances did not change the conclusions, and other factors such as anxiety and stress related to caring for children with AD may have been contributory.

Pustisek et al. (97) studied the QoL of 171 parents (mean age 32 years) of children with AD in Croatia. The mean FDLQI score (range 0–30) was 13.6 ± 6.0. indicating a major effect on the QoL of parents. The most frequently recorded problems were time spent looking after the child, household expenditure and emotional distress, as in a Ukraine study (98). The mean Perceived Stress Scale score was 20.0 ± 5.8, 7 points higher than the average person aged 30–40 years, indicating higher stress levels in parents of children with AD and a correlation with QoL.

The impact of a child's eczema on the QoL of mothers and fathers may vary. Marciniak et al. (99) assessing parents QoL with the FDLQI, found that children's AD had a greater impact on the QoL of mothers than of fathers. Whilst the impact on the social life, spare time and daily expenditure was similar, mothers' relationships with other people were more affected than fathers' relationships with others, however the greatest impact on fathers was on their work or education. This was in contrast to the study by Pustisek et al. (97) where work or education were the lowest scoring items on the FDLQI: this could be because most participants in Pustisek's study were female with over half on maternity leave or unemployed.

Counter-intuitively, there may be positive outcomes resulting from a child suffering with AD. Parents may develop a strengthened bond with their children through the extra time spent treating and supervising them (100). To stop children from scratching, parents spend more time holding children closer, and balanced with the discomfort of physical symptoms, this overall creates a deeper emotional closeness (26). Parents also feel empowered by learning about AD and educating others about this debilitating condition (87).

Impact on siblings

Basra & Finlay proposed the term "Greater Patient' to encompass the interdependence of patients with their close relations (36). In childhood AD this includes the parents, who are generally the caregivers, however, in childhood siblings usually live together and their lives may also be affected. Whilst there are many studies on the QoL of siblings of children affected with other medical conditions, notably cancers (101–106), there is a lack of information on the impact of QoL on siblings of children affected with skin conditions, including AD. It is difficult to compare from the literature the effect on the QoL of siblings of skin disease compared to other diseases, due to the wide variety of instruments that have been used. Siblings of children with chronic conditions may have the same QoL as their peers (107), but it has also been suggested that siblings may have increased levels of distress (102). The parent child relationship and the sibling bond may also be affected when a child in the family has a chronic condition (108).

These negative interactions with family members (94, 99) coupled with sleep deprivation can leave patients, and their carers, feeling exhausted, stressed and depressed (96, 97). There may therefore be repercussions on siblings of patients affected with AD: this area needs further investigation.

The above findings illustrate the importance of assessing the QoL of family members. Several dermatology specific and AD specific validated instruments exist for measuring the impact of QoL on family members of patients with AD. The HOME initiative has not yet addressed this. However, the TREatment of ATopic eczema (TREAT) Registry Taskforce has recommended that for research registries for paediatric and adult patients with AD, if family impact is measured, the Family Dermatology Life Quality Index (FDLQI) should be used (109).

QUALITY OF LIFE INSTRUMENTS FOR FAMILY MEMBERS

Family Dermatology Life Quality Index

The FDLQI is a 10-item questionnaire, with a recall period of one month, assessing the impact on the QoL of adult family members of people of any age with any skin condition (110). The questionnaire includes the domains of emotional and physical wellbeing, relationships, leisure activities, social life, burden of care, impact on job/study, housework and expenditure. Each question is scored on a 4-point scale (0–3). The FDLQI has been translated into several languages (111) and has been used in various studies involving AD and other dermatological conditions (97, 99, 112–116).

Dermatitis Family Index

The DFI, the first family QoL questionnaire in dermatology measures the impact of having a child with AD on the QoL on their adult family members (117). This 10-item dermatitis specific questionnaire measures the impact over the last week on QoL in the domains of housework, food preparation and feeding, sleep of others in the family, family leisure activities, time spent on shopping, expenditure, tiredness, emotional distress, relationships and impact of child's treatment. Each question is scored from 0–3 points. There are no validated banding descriptors for the DFI, but some studies have used non-validated scoring descriptors (118, 119). The DFI has the advantage of being eczema specific and its measurement properties have been reviewed (120). The DFI, along with DLQI, CDLQI and IDQoL is one of the most frequently used instruments for measuring QoL in eczema studies (40, 47, 121).

Parents Index of QoL in Atopic Dermatitis

The PIQoL-AD is another AD specific measure to assess the impact of the child's AD on the QoL of parents (122). Developed on the basis of multinational qualitative interviews with parents of children up to age 8 years with AD, this is a 28-item unidimensional questionnaire (123). The lower the score, the better the QoL, a change of 2–3 PIQoL-AD points over time is considered meaningful.

Childhood Atopic Dermatitis Impact Scale (CADIS)

CADIS is a QoL measure for parents of children with AD combined with a proxy measure for children under the age of 6 years (124). It measures the impact on QoL of the domains of symptoms, activity limitations and behaviour, family and social function, parent sleep and parent emotion. This 45-item questionnaire uses 5-point Likert Scales giving a maximum score of 180. The recall period is the last 4 weeks and the questionnaire can be completed in approximately 6 min (125). Whilst it does not have score band descriptors, the MCID is considered to be a 12% change from the total score or a 12% change from any of the individual domains (126).

Family Reported Outcome Measure

Speciality and condition specific questionnaires cannot compare the impact on QoL of family members between different specialities. Golics et al. (127) developed the Family Reported Outcome Measure (FROM-16), based on relatives of patients from 26 medical specialties.

FROM-16 has 16 questions and can be used to assess the QoL of any adult member of the family of a patient of any age with any disease. The average completion time is 2 min. FROM-16 consists of the Emotional domain with 6 questions and the Personal and Social Life domain with 10 questions. Each question has three possible answers: 'Not at all', 'A little' and 'A lot' scoring 0, 1 and 2, respectively. Validation studies have been completed in Germany and Thailand and further validation characteristics are being studied. FROM-16 can be used to compare the QoL of family members across different disciplines in medicine, thus making it easier to make meaningful comparisons in QoL trials involving different medical conditions.

The Impact on Family Scale (IOF) (128, 129) has been validated to measure the impact of QoL on the adult family members of children suffering with chronic illness or disability. However, unlike the FROM-16, which can be used in the family members of patients of any age, the IOF should only be used for family members of affected children

DISCUSSION

In any scientific endeavour, it is essential to be able to measure some characteristic of what is being studied. Without measurement, it may be possible to describe, but impossible to make meaningful comparisons or detect change. It could almost be said that if you can't measure something, it doesn't really exist, at least to a scientist. The same applies in medicine, a field of science that coexists as an 'art'. Advances have followed the ability to measure: measuring blood pressure has enabled identification and control of hypertension, measuring visual fields has allowed diagnosis of ophthalmic and neurolo-

gical conditions and measuring frequency of micturition is used as an alert to diabetes and prostatic hypertrophy. Perhaps because of the visual nature of dermatology, a focus on measurement came late to our subject. But this delayed focus has coincided with a realisation that, as part of delivering the highest quality of care, we need to better understand what our patients are experiencing (130). In addition, qualitative studies should be used more often in combination with quantitative studies to gain more insight into the real burden of diseases such as AD.

This review has focussed on questionnaires specifically designed to measure the impact on QoL of skin diseases in general or of AD in particular. However, there are also a wide range of questionnaires that are designed to be used across all diseases. Examples of such measures include the Short-Form 36, the WHOQOL and EuroQoL (EQ-5D). Utility information giving QALY information is typically calculated from EQ-5D data, and this is sometimes used by national or international drug regulation agencies to inform decisions concerning resource allocation. However, use of QoL data in this way may overlook critical aspects of the reality of the impacts of skin diseases, such as the psychological impact that understanding the risk of mortality, say of a malignant melanoma, may have. And having a basal cell carcinoma that is treated appropriately may have a low impact on QoL, but if untreated the long-term consequences can be extremely serious. Therefore, when QoL measures are used to inform resource allocation, wider aspects of the conditions must also be considered.

This review has described some of the many ways in which the lives of people with AD are affected by their condition. Large multicentre studies in Europe and the USA determined that patients with psoriasis felt that their dermatologists were not aggressive enough with therapy: it is likely that the same applies at least to adult AD. By having insight into the individual patient's experience, more appropriate therapeutic decisions may be made, especially over the coming decade with the advent of many novel powerful systemic therapies for AD.

The Greater Patient, the close family members, may all experience impact on their QoL through having a family member with AD. But the "Greater Patient" also acts as the "Greater Therapist", as family members support the patient with practical therapeutic help, such as application of topical emollients and drugs, and giving encouragement to persist with therapy. The role of the family in promoting adherence to agreed treatment plans should not be underestimated. Therefore, understanding the experiences of family members, and identifying their needs may make a crucial contribution to the success of therapy.

Being able to measure the QoL impact of AD provides stark challenges to the health care team. Of course, the over-riding aim must be to effectively suppress the disease. Having identified the QoL problems we can no longer ignore them and we are obliged to creatively develop methods to address these issues. We now have the tools to assess prospectively the impact of AD on QoL.

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Centenary theme section: ATOPIC DERMATITIS

REVIEW ARTICLE

Disease Mechanisms in Atopic Dermatitis: A Review of Aetiological Factors

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Atopic dermatitis is a prevalent inflammatory skin condition characterized by itch and dry skin, which affects 15–20% of children and 3–5% of adults. This article reviews epidemiological, clinical and experimental data to provide an overview of the most important disease mechanisms in atopic dermatitis. Genetic predisposition, environmental insults, atopic triggers, complex host immune response and skin barrier changes, and altered skin microbiota are discussed. Whilst our understanding of atopic dermatitis has improved dramatically in recent years, many basic aspects are still not understood. Further research is needed to fully understand this complex skin disease.

Key words: atopic dermatitis; aetiology; pathophysiology; pathomechanism; risk.

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SIGNIFICANCE

The aetiology of atopic dermatitis is poorly understood, but studies have provided insight into the pathomechanism, which may improve the prediction of onset of atopic dermatitis and its prophylaxis. This review provides an overview of the pathogenesis and pathomechanism of atopic dermatitis.

Atopic dermatitis (AD) is a prevalent inflammatory skin condition characterized by itch and dry skin, which affects 15–20% of children and 3–5% of adults. In large proportions of affected patients AD is chronic or remitting, as shown by epidemiological studies (1).

The pathogenesis of AD is complex and poorly understood. However, in recent years, there has been major advancements in our understanding of the disease mechanism of AD, e.g. through the discovery of common filaggrin gene (*FLG*) mutations as a strong risk factor for AD, as well as the significant clinical effects of antagonistic therapy against interleukins (IL) 4, 13, 22 and 31.

This review provides a holistic overview of the most important disease mechanisms in AD.

INCIDENCE OF ATOPIC DERMATITIS PEAKS IN EARLY CHILDHOOD

AD predominately begins in early childhood, as indicated by a recent prospective Danish study, which showed that nearly all cases of AD are diagnosed before the age of 7 years (2). It is currently unclear to what degree "late-onset AD" is important in absolute numbers, as studies have shown that patients who present with AD in adulthood may have forgotten about their childhood AD, and that the disease may therefore represent re-activation of previous disease. This notion is strongly emphasized by the finding that approximately 29% of Swedish adults aged 31–42 years with a school health record of AD in childhood did not recall this when asked as adults (3). In asthma, patients with adult onset seem to have different disease mechanisms, and it is possible that this may also be the case for AD. Moreover, the epidemiology of AD may change over time, in concert with new causative exposures. As an example, use of cosmetic products in adolescence has been associated with new onset of AD or recurrence of previous disease (4). Nonetheless, AD normally begins in early childhood; a time where the skin barrier is vulnerable to stress (5–7). This will lead to a decrease in the threshold level against common triggers. As discussed in this review, the skin barrier defect is central to the risk of developing AD.

GENETIC PREDISPOSITION

AD is a clinical syndrome, as indicated by the Hanifin & Rajka criteria for AD (8). These criteria dictate that a certain number of major and minor criteria need to be fulfilled in order to make a diagnosis of AD, including a list of phenotypic and heritable characteristics, such as xerosis, palmar hyperlinearity, keratosis pilaris (all associated with *FLG* mutations), infra-orbital folds or darkening, as well as facial pallor. Importantly, family predisposition to atopic disease is a major criterion of the Hanifin & Rajka criteria, and twin studies have shown that the heritability of AD is very high (9). The Hanifin & Rajka criteria were unintentionally developed for use in patients with predominately European ancestry, and it is clear that the phenotypic characteristics observed in other ethnic groups are under-represented, and that the

criteria may fail when used in these populations (10). An example is the recent observation that pigmentation on the lips is associated with AD in Asian subjects (11).

FLG mutations lead to dry skin, characterized by elevated pH, increased colonization with staphylococci, enhanced penetration and reactivity to chemicals and allergens, and therefore, expectedly, a strongly increased risk of AD (12). Nearly all carriers of *FLG* mutations with AD develop their skin disease within their first 2 years of life (13), whereas children with later onset do not have these mutations (14). The discovery of *FLG* mutations provided a new, and much needed, basis for the study of paediatric AD, and led to a strong re-emphasis on primary skin barrier impairment as a crucial factor for the development of AD. Since then, it has been shown that dry skin at birth and at 2 months of age, independent of *FLG* mutations, can predict AD at 12 months of age, and that daily application of emollients in high-risk infants may reduce the risk of AD (15). Importantly, the normal skin barrier in the 2 first years of infancy is very different from that of adult skin; for example, the levels of natural moisturizing factors (NMF), a degradation product of filaggrin, are much reduced (16). The tendency for AD to begin on the cheeks is also explained by a local, very pronounced, reduction in NMF, which may last until 3 years of age (6). The down-regulation of filaggrin on exposed skin areas, as well as the increased prevalence of *FLG* mutations in populations that have migrated far from the Equator, is probably explained by evolutionary benefits due to increased synthesis of vitamin D following facilitated penetration of ultraviolet (UV) (17). Importantly, a deficiency of filaggrin, whether primary or secondary, results in increased penetration of allergens and risk of sensitization, which, in turn, may explain the increased risk of allergic asthma, rhinitis and food allergy in carriers of FLG mutations who have AD (18).

ENVIRONMENTAL EXPOSURE

The crucial role of environmental exposure and skin stressors cannot be overemphasized when explaining the aetiology of the AD epidemic. Modern society has resulted in dramatic changes in human exposure, with increased use of, or exposure to, household products, cosmetics, tobacco, processed food, and air pollution, but at the same time reduced exposure to microorganisms and solar irradiation, as a result of increased hygiene, fewer people living together in the same household, and less time spent outside. Epigenetic changes due to environmental changes or insults could explain a large part of the endemic proportions of AD. In support of this theory, large genome-wide association studies have identified only a small proportion of genetic factors associated with AD (19). However, how the environmental changes have influenced the risk of AD at a mechanistic level is largely unknown.

Being born in the autumn or winter in the Northern hemisphere, or being exposed to a dry and cold climate, has been strongly associated with AD (20, 21). This is probably explained by skin exposure to low temperatures, as well as low ambient humidity due to indoor heating, which can negatively affect the skin barrier and result in dermatitis (22). Similarly, bathing infants in hard water may increase the risk of AD, possibly due to increased pH, which, among other aspects, results in premature cleavage of cornedesmosomes (20). Exposure to air pollution and being born in a newly built home have also been associated with AD (23, 24), perhaps because chemicals negatively affect the epidermal barrier. For example, short-term exposure to airborne formaldehyde results in increased water loss from the skin surface (25) in patients with AD, and toluene, a common air pollutant, can directly down-regulate synthesis of filaggrin (26). Interestingly, exposure to solar irradiation, which is normally avoided in infancy, to reduce the risk of skin malignancy, seems to protect against AD (27, 28). This could be explained by the positive effects of sub-erythemogenic doses of UVB irradiation on the skin barrier, which, among other aspects, reduces *Staphylococcus aureus* colonization, itch, and T-cell invasion.

EARLY ALTERATIONS IN THE IMMUNE SYSTEM

The crucial role of early-age alterations in immune activity on the development of AD is emphasized by the significantly reduced risk of AD in premature infants (29). Moreover, thymectomy in infancy reduces the risk of AD by 20%, suggesting that removal of the thymus decreases the number of circulating T cells that can act to develop AD (30). In indirect support of this assumption, a study found significantly larger thymus sizes in children with AD compared with controls, although this may also be a consequence of the increased demand for T cells in patients with AD (31). The farm theory suggests that microbial exposure may reduce the risk of diseases mediated by T-helper (Th) cell 2, including AD (32), but it is probably more important for allergic diseases than for AD per se. The finding that neonate exposure to dogs can strongly reduce the risk of AD could be confounded, but it is also possible that changes in the host gut microbiome can affect the tolerance-reactivity balance (33). It is unclear how nutrients and alcohol use in mothers can affect the risk of AD, but is has been suggested that the Th2 skew induced by alcohol intake may lead to a higher prevalence of AD in infants (34). Similarly, nutrients may affect the child's immune response, but this area is complex, and little evidence exists. Collectively, AD occurs mainly in genetically predisposed individuals who have significant skin barrier impairment and who are exposed to AD triggers (or who are overly protected against the crucial microorganisms that could prevent excessive Th2 skew in childhood) (**Fig. 1**).

VICIOUS CYCLE IN ATOPIC DERMATITIS

AD is a skin condition in which primary (or secondary) skin barrier impairment leads to (further) skin inflammation, and in which *S. aureus* colonization may increase, and in turn may drive both eczema severity and the relentless sensation of itch (35). This leads to scratching and additional barrier impairment, thus creating a vicious cycle. Clinicians attempt to stop this cycle by restoring the skin barrier with emollients, reducing inflammation and itch with use of topical/oral immune suppressants or immune modulating drugs, as well light therapy, and, finally, decreasing the burden of *S. aureus* by use of disinfectants and antibiotics. Evidence supporting the benefits of emollient use to treat AD is the strongly increased time to subsequent flares in emollient users, and the reduced need for topical corticosteroids (36). However, barrier restoration without simultaneous control of inflammation seems to be inadequate in the treatment of AD (37). Prophylactic use of topical anti-inflammatory agents, e.g. with application twice weekly, works to reduce the risk of new flares (38).

PATHOGENIC ROLE OF *STAPHYLOCOCCUS AUREUS*

While the exact role of bacteria in the pathogenesis of AD is unclear, colonization with *S. aureus* is very common in lesional and non-lesional AD skin. Antimicrobial peptides, which work as broad-spectrum antibiotics to kill Gram-negative and Gram-positive bacteria, are reduced in patients with AD, which, in turn, allows bacteria to colonize the skin (39). *S. aureus* can induce serine protease activity, which will destroy corneodesmosomes, and allow invasion (40). Moreover, the expression of Th2 cytokines is activated by proteases released by *S. aureus* (41), and *S. aureus* toxin increases the allergic response by activating mast cells (42), and induces up-regulation of T cells via a superantigen-mediated mechanism (43). *S. aureus* also release α-toxins, which forms pores in keratinocyte membranes leading to cellular damage (44). Individuals with AD and *FLG* mutations have a 7-fold higher risk of *S. aureus* skin infections, in part due to increased pH, but also due to the lack of the direct growth inhibition of the filaggrin proteins (45, 46). The levels of filaggrin degradation products, i.e. NMF, seem to regulate the strength of *S. aureus* corneocyte adhesion, the first step in skin colonization (47).

SKIN MICROBIOME AND DISEASE CONTROL

While the skin hosts the most diverse commensal community of humans, with over 1,000 different bacterial species, the role of the skin microbiome in AD is poorly understood (48, 49). An animal study showed that

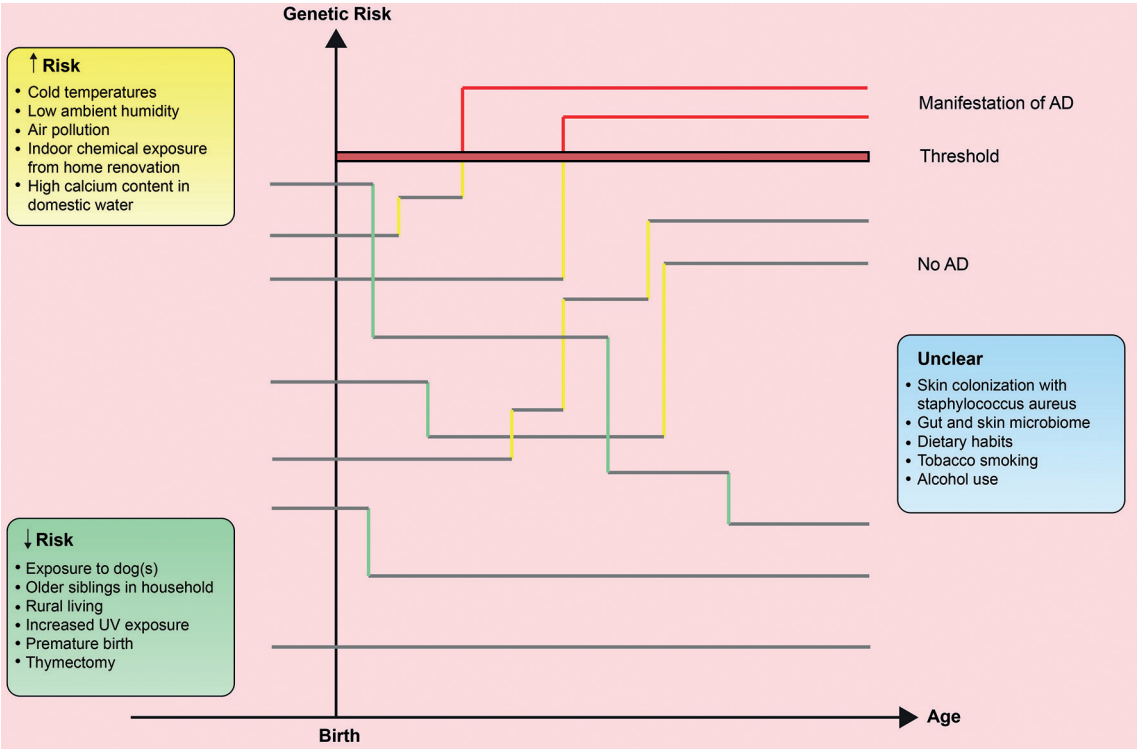

Fig. 1. Theoretical outline of how genetic risk genes and environmental risk exposures interact and may impact the risk of atopic dermatitis (AD). If a child reaches the threshold bar for AD, the disease will manifest. Factors that increase the risk of AD are represented by *yellow vertical lines*, whereas factors that decrease the risk are represented by *green vertical lines*. Once AD has manifested, the lines are shown in *red*.

filaggrin deficiency and microbial dysbiosis triggered intracellular IL-1α secretion and drove chronic inflammation, hence indicating an important pathogenic role (50). Moreover, following successful treatment of AD, *Streptococcus*, *Propionibacterium*, and *Corynebacterium* species increase in numbers along with microbial diversity (51).

DYSFUNCTIONAL LESIONAL AND NON-LESIONAL SKIN

It is important to understand that non-lesional AD skin is also different from the skin of normal controls (**Fig. 2**). It shows decreased or altered synthesis of important epidermal proteins, e.g. filaggrin, filaggrin 2, involucrin, loricrin, hornerin, and tight junctions, but also decreased synthesis of antimicrobial peptides and lipids, (52–58) as well as increased expression of high-affinity IgE receptor on dendritic CD1a, along with increased numbers of T cells and their cytokines. Children with AD and food allergy have stratum corneum abnormalities in non-lesional skin that are not found in children with AD and controls without food allergy. Thus, filaggrin and ω-hydroxy fatty acid sphingosine are reduced, and there are important changes in the epidermal lamellar bilayer architecture (59). Thus, skin measurements in non-lesional AD skin show elevated pH, increased water loss from the skin surface, and increased penetration of chemicals (60). Moreover, AD skin displays a reduced reactivity threshold to exogenous stressors, such as skin irritants, allergens and *S. aureus*, in part due to the creation of resident T-cell populations (61–63). The changes in non-lesional skin are largely determined by disease extent and severity (53), probably reinforcing the impression of AD as a generalized skin disease.

HETEROGENEOUS INFLAMMATORY RESPONSE, DEFICIENT SKIN BARRIER AND EXOGENOUS STRESSORS

Type 2 immunity-associated cytokines, such as IL-4 and IL-13, as well as other cytokines, including, but not limited to, IL-1, IL-17, IL-22, IL-31 IL-33, and thymic stromal lymphopoietin (TSLP) have important roles in AD. It is presently unclear whether significant differences exist between AD skin of children and adults, as well as between different ethnic groups, and to what degree this should affect treatment strategy (64, 65). While certain endotypes of AD are suspected to exist, the heterogeneous cytokine landscape could also, in part, be explained by the crucial pathogenic role of the sustained skin barrier impairment in lesional and non-lesional AD skin. Thus, the continuous bombardment and penetration of microorganisms, chemicals, irritants and allergens into the primary and sustained skin barrier impairment in AD could lead to secretion of various cytokines, and as discussed below, activate the Th1 and Th17 axis in addition to the Th2 axis. The exact immune response would be expected to depend on genetics, age, sites of skin exposure, possible co-infection, climatic effects, and type of elicitor. Interestingly, use of monoclonal antibodies against the IL-4 and IL-13 receptors seems to be slightly less effective in facial skin; an anatomical area which is exposed to environmental pollutants and climatic factors (66).

ATOPIC TRIGGERS

To date, there has been little research into the reactivity to various stressors. A survey in children with AD showed that sweating from exercise was a common exacerbator

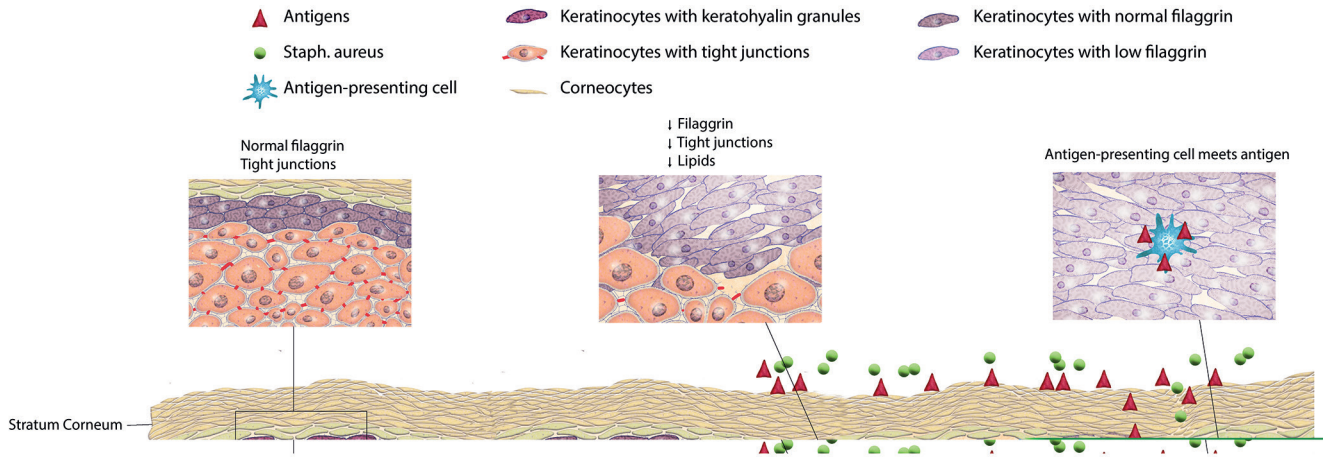

Fig. 2. Important skin barrier changes in atopic dermatitis (AD). Innate and acquired inflammation in AD leads to downregulation and degradation of filaggrin and tight junction proteins, in turn leading to a dry and leaky skin barrier with elevated pH, which allows bacteria to colonize and allergens, irritants and microorganisms to invade. Tight junction reduction further allows antigen presenting cells to move upwards and meet the antigens. Lipid synthesis is compromised at several levels, which acts in concert with protein dysfunction to allow increased loss of water from the skin surface. In an attempt to restore the skin barrier and prevent excessive water loss, acanthosis occurs, often in conjunction with mild spongiosis.

of AD (67). While the exact mechanisms is unknown (68) and, at least in part, could be explained by the direct effects of heating (69), leaking of sweat into the epidermis due to dysfunctional tight junction function could be relevant (70), as well as obstruction of sweat ducts due to filaggrin deficiency (71). Other well-established triggers for AD include exposure to wool, hot weather, psychological stress and sleep deprivation. Induction of stress leads to scratching behaviour in patients with AD, but not in controls (72). The dysfunctional and partly unresponsive peripheral hypothalamic-pituitary-adrenal axis in AD skin could also be important (73). Moreover, psychological stress reduces the recovery time of the stratum corneum, decreases lipid synthesis, and increases the risk of skin infections (74). Exposure to grass allergens may cause worsening of AD in grass-allergic AD individuals through IL-4 release (75). Contact allergens, e.g. fragrances and certain rubber chemicals, have been shown to elicit Th2 immune activity in patch test reactions, as opposed to many other allergens that elicit Th1 immune response (76, 77). Furthermore, exposure to experimental and environmental contact allergens in patients with AD causes Th2 immune response activity, but Th1 immune response in non-atopic skin (78). How this translates into clinical relevance is currently unclear. A recent study examined the skin immune response to various atopic triggers in individuals with normal skin and found that exposure to hard water is associated with IL-4 secretion in the epidermis (79).

CYTOKINE ANTAGONISM AND THE IMMUNE RESPONSE

The most important knowledge about the immune response in AD has been derived from clinical trials using antagonists against specific cytokines. To date, mainly IL-4, but also IL-13, antagonisms have proven to reduce the severity of AD, whereas IL-22 inhibition mostly worked in patients with severe AD (80). While IL-31 inhibition significantly reduced itch in patients with AD, the effects on AD have not been appropriately examined (81). Clinical studies into the development of antibodies against TSLP, IL-33 and IL-17C are ongoing. These published data clearly indicate the relative importance of the above-mentioned cytokines, but other chemokines and cytokines will be targeted in the future.

COMPLEX IMMUNE RESPONSE

It is beyond the scope of this review to describe the immunopathophysiology of AD in detail. Briefly, predominately Th2 (IL-4, IL-5, IL-13, IL-31) and Th22 (IL-22) deviation is observed in acute and chronic AD lesions, which, in turn, down-regulate expression of important skin barrier proteins, such as filaggrin. Innate lymphoid cells also release Th2 cytokines, now increasingly referred to as type 2 immunity. In chronic AD lesions, a parallel activation of the Th1 axis is observed, and in both acute and chronic AD, IL-17 activation can be found (82). Yet, even in healthy skin from patients with AD, there is increased expression of inflammatory cytokines and chemokines, as well as of their receptors, and an increased number of lymphocytes compared with healthy controls, suggesting increased immuno-surveillance in the skin and risk of acute inflammation (53).

Apart from the negative influence on the skin barrier, Th2 inflammation inhibits antimicrobial peptide synthesis and increases *S. aureus* colonization. The Th2 cells may, in many patients, lead to antibody isotype switching to IgE and recruit mast cells, eosinophils, basophils and dendritic cells. Elevated levels of IgE correlate with AD and atopic co-morbidities, including asthma and food allergies (83). Previously, this has been used to subtype AD into extrinsic AD, where allergic sensitization has taken place, and intrinsic AD, in which patients have normal levels of IgE. However, patients with normal IgE levels may also be sensitized and vice versa. It has even been suggested to use the terms intrinsic factors to describe inborn factors e.g. *FLG* mutations, Th2 skewing, etc., which affect the skin barrier function or the immune response in terms of AD and extrinsic factors to describe exogenous factors, e.g. *S. aureus*, detergents, allergens, etc. (82). Interestingly, IgE may target keratinocytes in up to 25% of patients with AD, indicating that IgE may play an important role in impairment of the skin barrier (84).

Regulatory T cells can suppress the Th2 response, and the balance between these 2 cell types is central to development of tolerance. It is not known whether a primary immune-deficiency/imbalance might be the prime cause of AD. Single nucleotide polymorphisms (SNPs) in, for example, ST2 (a member of the interleukin 1 family), IL-13, IL-12, have been reported to be associated with AD, and a huge work in developing a taxonomy for AD subtypes based on serum levels of cytokines has been undertaken (85). A recent work was able to distinguish at least 3 different subtypes of AD, based on analysis of 147 different soluble factors, yet this does not, in itself, show that the immune response is the prime cause of the disease (86). Rather, it indicates that patients with AD have different propensity to react to exogenous stimuli and that, even within the group of patients with AD, this differs slightly and gives rise to different subtypes. The result of this may be the development of personalized medicine for patients with AD (87).

ROLE OF SYSTEMIC INFLAMMATION

Adult patients with AD have significantly elevated levels of circulating cytokines and chemokines (87). While it is intriguing to consider that the systemic inflammation in AD can negatively affect the function of other organs, such as the central nervous system and vascular system,

there is currently no convincing evidence to support this. Nonetheless, AD has been associated with anxiety, depression, autism and attention deficit disorders, and it is possible that cytokines may cause a leaky blood–brain barrier and become absorbed into the cerebrospinal compartments and negatively affect cognitive development, by affecting the glia cells and neurogenesis. Decreased sleep quality due to itch is, however, also a major risk factor for ADD and depressive symptoms. The link between asthma and AD is not fully understood, but the shared type 2 immunity and effect of dupilumab on severity of both AD and asthma support that systemic inflammation could play an important role. While some patients with AD experience worsening of their AD during or after asthma attacks, it is unclear whether this is explained by psychological stress or by cytokines reaching the skin.

CONCLUSION

This review highlights some important disease mechanisms of AD. While understanding of AD has improved in recent years, many basic aspects are still not understood. For example, why do AD lesions outside the flexural areas tend to clear once flexural eczema is controlled? Why is AD a flexural disease? What triggers an AD flare? What explains the resolution of AD in the majority of children? What is the role of foods as triggers for AD? Why do AD children have fewer naevi than controls? These are just some of many unanswered questions. In conclusion, more research is needed into this complex skin disease.

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Centenary theme section: ATOPIC DERMATITIS

REVIEW ARTICLE

Genetics in Atopic Dermatitis: Historical Perspective and Future Prospects

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Atopic dermatitis (AD) is a common, complex trait, arising from the interplay of multiple genetic and environmental factors. This review provides an overview of developments in the field of AD genetics. AD shows high heritability; strategies to investigate genetic risk include linkage, candidate gene studies, genome-wide association and animal modelling. Loss-of-function mutations in *FLG*, encoding the skin barrier protein filaggrin, remain the strongest genetic risk factor identified for AD, but variants influencing skin and systemic immune function are also important. AD is at the forefront of genetic research, from large-scale population studies to *in vitro* models and detailed molecular analyses. An understanding of genetic risk factors has considerably improved knowledge of mechanisms leading to atopic skin inflammation. Together this work has identified avenues for therapeutic intervention, but further research is needed to fully realise the opportunities of personalised medicine for this complex disease, to optimise patient benefit.

Key words: atopic dermatitis; eczema; filaggrin; genetic; genome-wide; risk; phenotype; transcriptome.

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SIGNIFICANCE

Atopic dermatitis (also called eczema) often runs in families, showing that this disease occurs partly because of inherited genetic risk. Research to understand the genetic variation that contributes to an individual's risk of atopic dermatitis has improved our understanding of mechanisms in the skin that can lead to a leaky barrier and inflammation. Already this knowledge has been applied to treatment and eventually it is hoped that these insights will lead to personalised medicine, in which treatment is tailored to a patient's genetic make-up and their individual type of atopic dermatitis.

Atopic dermatitis (AD), synonymous with atopic eczema, is a common chronic inflammatory skin disorder with a lifetime prevalence of 10–20% in developed countries (1, 2). AD is considered to be a genetically "complex disease", with interactions of multiple genetic, biological and environmental factors leading to skin barrier dysfunction and altered immunological response. Having AD has a severely negative impact on health-related quality of life, including self-confidence and sleep; it also implies a socioeconomic burden (3).

AD has been known from ancient times. According to the Roman biographer Suetonius, the Emperor Augustus suffered from symptoms and signs of atopic diseases "…noting a number of hard, dry patches suggesting ringworm, caused by an itching of his skin" as well as "seasonal disorders," noticing that he experienced in the early spring "a tightness of the diaphragm; and when the sirocco blew, catarrh" (4).

This review aims to provide readers with a historical perspective on the progression of genetic studies in AD over recent decades, the rapid escalation of molecular techniques and a view to future opportunities in the field.

WHAT HAVE WE LEARNED ABOUT ATOPIC DERMATITIS GENETICS OVER THE PAST 100 YEARS?

Heritability of AD: family and twin studies

It can clearly be observed that atopic diseases show a familial aggregation, with clustering of affected individuals within families, demonstrating the importance of genetic heritability. The term 'heritability' refers to the proportion of variation within a clinical feature that is attributable to genetic factors (5). A family history of atopic diseases, in particular AD, is the strongest of all risk factors. The presence of any atopic disease in one parent is estimated to increase a child's risk of developing AD 1.5-fold, whereas the risk is increased ~3-fold and ~5-fold, respectively, if one or both parents have AD (6, 7). Familial aggregation can be due to shared environment and/or shared genes and a way to address the genetic component is to study twins. These studies have shown a concordance rate of 72–86% in monozygotic twins and 21–23% in dizygotic twins (8, 9). These data demonstrate that the genetic contribution to the development of AD is substantial and this heri-

tability has been estimated at 70–80% (10, 11) – a high heritability for a complex trait (12). For comparison, psoriasis heritability is approximately 68% (13) whilst other inflammatory barrier diseases show heritability of 7–38% for periodontitis (14) and approximately 67% in ulcerative colitis (15).

Strategies for the investigation of genetic risk

Various different strategies have been used to study genetic components in complex diseases such as AD. In broad genomic analyses (genome-wide linkage, genome-wide association studies) a pre-existing knowledge of the function of genes is not required, nor the biology of the trait in question; it is a 'hypothesis-free' approach. In contrast, directed genetic analysis such as a candidate gene approach is a strategy in which certain loci or genes considered to be of interest for the phenotype are selected for study. The selection can be based on earlier studies, "educated guesses" or knowledge of the pathogenesis and function of previously identified genes or loci; this is a 'hypothesis-driven' approach. Each of these strategies has been used to provide insight into AD.

Linkage studies

Genetic linkage is a method for mapping genes. It exploits the fact that a marker (often a microsatellite marker such as repeated DNA sequences, mostly di-, tri-, and tetra-nucleotide repeats) show variation between individuals. Informative markers have many alleles and are distributed at known locations throughout the genome. The first genome-wide study in AD identified a major susceptibility locus on chromosome 3q21 (16). During the following years, additional genome-wide studies in AD were performed and several more loci were identified including 1q21,3p,17q, 18q,11.13q. However, these loci were often too wide and they required labour intensive fine-mapping. Genome-wide association studies (GWAS) have subsequently replaced genome-wide linkage (17). The technique of GWAS is described in more detail below.

Candidate genes

Filaggrin (FLG). Using a candidate gene approach, and the link between ichthyosis vulgaris and AD, the *FLG* gene was identified as a susceptibility gene for AD in 2006 (18). This was a major breakthrough and also established the impaired skin barrier function as having a key role in the development of AD. Filaggrin is involved in the development of keratinocytes to maintain epidermal integrity and it is an important marker of keratinocyte differentiation. During keratinocyte differentiation, profilaggrin is dephosphorylated and degraded into monomers, which condense in the cytoskeleton of keratin to form an intensive protein-lipid matrix. Consequently, these filaggrin monomers are degraded into amino acids, which contribute to the natural moisturising factors, maintaining skin hydration, a low pH and other aspect of the barrier function of the stratum corneum (**Fig. 1**).

Loss-of-function mutations in *FLG* are present in up to 10% in the Northern European population. They cause the common monogenetic dry skin disorder ichthyosis vulgaris. The most common loss-of-function mutations in Europe are R501X, 2282del4, R2447X and S3247X. Together these 4 null mutations account for >90% of null mutations in the population (21). Among European patients with moderate to severe AD up to 40% of the patients carry a *FLG* null mutation. In meta-analysis the risk of getting AD in a mutation carrier is increased 3-fold

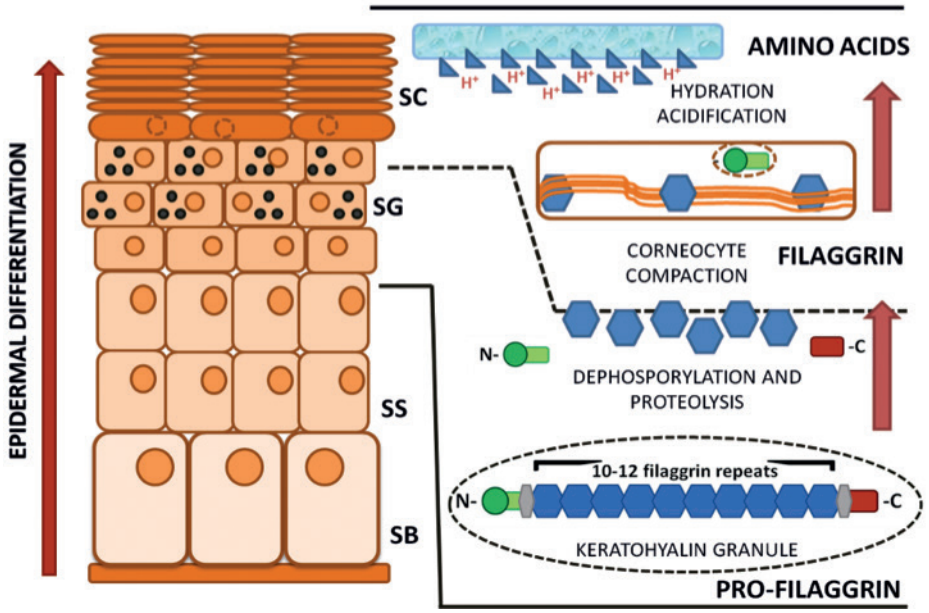

Fig. 1. Filaggrin expression and processing in the epidermis. The pro-protein profilaggrin is cleaved in a stepwise process into filaggrin monomers which are then degraded to release amino acids, contributing to 'natural moisturising factors' in the stratum corneum (19, 20). Filaggrin is an important marker of keratinocyte differentiation. SC: stratum corneum; SG: stratum granulosum; SS: stratum spinosum; SB: stratum basale.

(odds ratio 3.12) (22, 23). However, among Europeans only ~20% of patients with mild-to-moderate AD carry *FLG* null mutations and >50% of individuals carrying *FLG* mutations do not develop any atopic disease and this indicates that *FLG* mutations are neither necessary nor sufficient to cause AD (24).

The frequency of *FLG* null mutations diverges in different populations and >50 have been characterized worldwide (25, 26). In Asian countries, the prevalence of mutation varies from 3% to over 50%, and many mutations are family-specific (25, 27–30). Research in people of African ancestry has been relatively limited to date and the prevalence of *FLG* null mutations appears to be less than 1% (31–33). Studies on African Americans have shown a slightly higher frequency of *FLG* mutations and *FLG2* has also been identified as a possible susceptibility gene (34, 35).

To address the question of why *FLG* mutations are so prevalent in the white European population, it has been hypothesized that this is due to an evolutionary advantage. The increased skin barrier permeability in filaggrin-deficient skin may enhance immunity to infections, conferring 'natural vaccination' to individuals with *FLG* mutations during European pandemics (36). Additionally, filaggrin deficiency may confer an evolutionary advantage in higher latitudes (i.e. Northern Europe) through its role in increasing vitamin D biosynthesis. Vitamin D3 levels are 10% higher in German and Danish individuals with *FLG* null mutations, which may be due to a reduction in filaggrin's role as an endogenous UVB filter in the skin (37).

Besides mutations there are intragenic repetitive gene sequences or 'copy number variations' in *FLG* that determine the amount of filaggrin monomer expressed in the skin. Having more repeats (12 compared to 10 on each allele) is associated with reduced risk of AD (38) by a dose-dependent effect within this repetitive gene sequence. The effects of cytokines, such as IL-4, IL-13, IL-17A, IL- 22, IL-25, IL-31, and TNF-α have also been shown to suppress filaggrin expression in the skin, resulting in additional barrier impairment (39, 40).

Even though *FLG* mutations and the filaggrin protein are extremely important in AD pathogenesis, there must be yet unknown, additional factors/genes or functions of gene involved in AD development that still are to be found.

Some other candidate genes in atopic dermatitis. Other genes that has been detected through a candidate gene approach, supported by knowledge of AD biology, and replicated by GWAS are genes involved in the Th2 immune response, for instance IL-4 located on chromosome 5q31.1, the IL-4 receptor located on chromosome 16p12.1-p11.2 and IL-13 on chromosome 5q31.1 (24, 41).

More candidate genes have been detected through the study of monogenic diseases that have features that resemble AD. Netherton syndrome (OMIM #256500) is a rare monogenic disease with AD-like lesions in the skin and increased IgE levels. The gene mutation underlying Netherton is in the Serine Protease Inhibitor Kazal-Type 5 gene (*SPINK5*) located on chromosome 5q32. *SPINK5* encodes a 15-domain protease inhibitor Lymphoepithelial Kazal-Type-Related Inhibitor (LEKTI) which is expressed in epithelial and mucosal surfaces and in the thymus. In several studies, there has been an association between *SPINK5* variants and AD, also in different populations (42–45). Other candidate genes will be studied as a result of new approaches to assessing monogenic disorders and extreme phenotypes, as discussed below.

Animal models

Animal models have the advantages that one can more easily control the environment and create genetic homogeneity. Apart from humans, dogs have spontaneous AD that has been studied and documented (46).

There are also several AD mouse models that have been described and generated over the years, each focusing on one or more aspects of human AD. The mouse models can be divided into 3 main categories: (*i*) Inbred strains of mice that develop AD-like phenotypes. The most well-known of these are the flaky tail mouse and the NC/Nga mouse (47, 48). The Flaky tail (ft) recessive mouse mutation arose spontaneously on the background of a recessive matted (*ma*) trait (49). The *ft* mutation has been identified as a 1-bp deletion in the *Flg* gene resulting in a premature stop codon (50), analogous to the human *FLG* mutations. More recently the *ma* trait has been separated from the flaky tail mouse and identified as a nonsense mutation in the novel gene *Matt* encoding the protein mattrin which is also postulated to have a role in skin barrier biology (51). (*ii*) Genetically engineered models, in which genes can be silenced or be overexpressed, for example the claudin-1 (52) and *Flg* knockout mice (53). (*iii*) Models that can be induced by exogenous agents with for example the allergens ovalbumin and house dust mite (as recently reviewed (54)).

ATOPIC DERMATITIS IS AT THE FOREFRONT OF CURRENT GENETIC TECHNOLOGY AND ITS APPLICATION

The prevalence of AD and the accessibility of disease-relevant tissues – both skin and blood – has allowed AD research to be at the forefront of applying new technologies. This has been powerfully facilitated by the active collaboration of large consortia across Europe and throughout the world. The advance of genetic and genomic analysis techniques has occurred at a rapid pace over recent decades. Large-scale and more focused molecular analysis techniques provide complimentary information; an overview of these approaches is given in **Fig. 2** and each is described below.

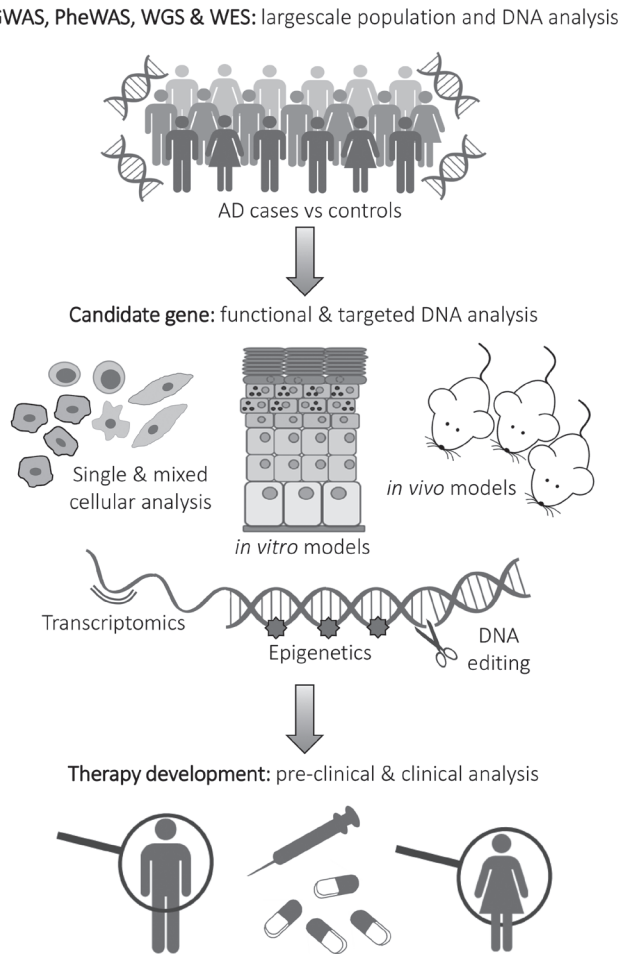

Fig. 2. Complimentary strategies for genetic analysis leading to therapy development. GWAS, genome-wide association study; PheWAS, phenome-wide association study; WGS, whole genome sequencing; WES, whole exome sequencing; AD: atopic dermatitis.

Genome-wide association studies

GWAS is a technique in which very large numbers of single nucleotide polymorphisms across the genome are compared between large numbers of cases and controls, to identify differences that are associated with disease status. GWAS have been conducted in several different populations worldwide, and a recent meta-analysis has synthesized these studies (55). Over 30 loci (regions of DNA) have been identified as showing association with AD risk. Some loci include well established genetic effects, such as the epidermal differentiation complex on chromosome 1q21.3 (which includes *FLG*) and the cytokine cluster on chromosome 5. Many of the other regions are between genes, meaning that their functions require detailed follow-up work to ascertain a functional mechanism. One example is the region on chromosome 11q13.5 which interacts with a gene, *EMSY*, >30 kilobases away; *EMSY* has recently been shown to have an effect on skin barrier formation and function of relevance to AD (56). Another gene, *LRRC32*, >60 kilobases away from the same locus on chromosome 11q13.5, may also play a role in AD pathogenesis (57), demonstrating the pleiotropic effects that arise from genetic variation.

Further, larger, meta-GWAS studies are on-going, because larger sample sizes allow the detection of additional risk loci, although their effect sizes are likely to be smaller.

Phenome-wide association studies

Phenome-wide association (PheWAS) is a technique in which large numbers of phenotypic traits are tested for association with single genetic variants. For example, a loss of function variant in *FLG* shows strong association with atopic phenotypes including AD, asthma, allergic rhinitis and food allergy in a PheWAS study, as expected (58). Unexpected or previously unknown associations with genotypes may be revealed using PheWAS and the technique may also be applied to drug repositioning (59).

Whole exome sequencing and whole genome sequencing

Whole exome sequencing (WES) is a technique that studies the genetic sequence of the DNA in exons that code for proteins, and also exonic regions in non-coding RNAs. WES focuses on exons because they are most likely to have a direct functional effect; however, each variant requires careful assessment to define which may lead to loss-of-function or other functional effect.

WES in 22 Ethiopian people with AD and ichthyosis vulgaris has revealed rare variants in *FLG* and several other genes within the epidermal differentiation complex, as well as nonsense and missense mutations in previously unreported candidate genes including *GTF2H5, ADAM33, EVPL* and *NLRP1* (60). Some of these findings indicate population-specific variation rather than disease-associated variants. There was no evidence of recurrently-mutated causal genes in this population and AD appears to show considerable heterogeneity in genetic susceptibility (60).

Whole genome sequencing (WGS) sequences intergenic regions as well as exons, because many of the regulatory mechanisms are situated in intergenic DNA. WGS generates more data and is potentially more powerful than WES, but the interpretation of non-coding variants on a large scale remains very challenging as their functional effects are not well defined. The cost of WGS is also a limiting factor to sample size and to date no large WGS have been reported in AD.

Epigenetic studies

'Epigenetic' refers to heritable changes in gene expression that occur without alteration to the DNA sequence. In the context of AD, there are multiple environmental and pathophysiological effects which could impact on skin cells via epigenetic mechanisms, ranging from ma-

ternal factors *in utero*, to early life exposures, irritant and allergic effects. Two important epigenetic mechanisms are histone modifications and DNA methylation. These regulate chromatin structure and DNA accessibility to transcription factors and polymerases (61). Specific histone modifications can be used to predict and delineate regulatory features such as promotors and enhancers in the genome. Epigenetic mechanisms are central to the precise control of skin development and homeostasis (reviewed (62)). A number of studies have linked abnormal epigenetic control of the immune system and skin barrier to AD pathogenesis (63). Key differences in DNA methylation are observed between lesional and non-lesional AD epidermis and these correlate with changes in the expression of skin barrier and innate immune genes (64). Non-coding RNA including micro RNAs (miRNAs) confer an additional level of epigenetic control by regulating mRNA translation or degradation. Differential expression of number of miRNAs has been reported in lesional AD skin (63). Considerable further work is needed to fully understand epigenetic control in AD.

Three-dimensional DNA analyses

DNA may be represented diagrammatically as if it were a straight linear molecule, but in vivo it is extensively folded and wrapped around protein structures in three-dimensional space. Due to this folding, genomic regions that are far from each other in the linear DNA are brought in close proximity in the 3D genome (65). This complex and dynamic process facilitates long range control of gene expression by bringing distant promotor and enhancer elements together (66). Recent technological advances including chromosomal conformation capture (5C) and Hi-C or Hi-Cap, have allowed these interacting regions to be delineated. The techniques crosslink DNA with formaldehyde prior to digestion and sequencing so that interacting regions are sequenced together (65, 67). HiCap uses probes to capture promoters across the genome and regions important in gene regulation such as enhancers. Then, selected promoter–enhancer interactions can be sequenced. This analysis is performed in different cell lines and at different timepoints to reveal the dynamic process and identify candidate genes (68). Importantly, since the 3D interactions are cell-type as well as cell-state-specific, Hi-C analysis has been applied to differentiating keratinocytes, to characterise spacial control of promotor-enhancer interactions likely to be of relevance to AD (56, 67).

Transcriptome analysis

Transcriptomic analysis describes the study of RNA molecules that are present in a cell or tissue, having recently been transcribed from DNA. These molecules include protein-coding messenger RNA (mRNA), ribosomal RNA, transfer RNA, long non-coding RNA (lncRNA), micro RNA (miRNA) and others; their half-lives range from seconds to minutes. The transcriptome is a highly dynamic system and it is cell-type and cell state-dependent; differentiated cells show different gene expression compared to undifferentiated cells. Transcriptome analysis performed on skin itself is most relevant for dermatological conditions, but transcriptomics of serum or blood may also provide valuable insight into skin-related inflammatory conditions, including AD. Transcriptomic analyses are very sensitive; skin biopsy samples from so-called 'non-lesional' (clinically uninflamed) skin from an AD patient show profound abnormalities in the transcriptome, including barrier impairment, dysregulation of lipid metabolism and an activated stress response (69). The AD lesional skin transcriptome shows a disease signature (70) that improves after treatment (71).

Single cell analysis

Most of the molecular analyses on skin to date have been carried out using whole skin biopsies, or epidermal samples. However single cell analysis is now feasible, for DNA and RNA sequencing, as well as protein analysis (72). These techniques offer the prospect to study individual cells, define new cell types and gain insight into the functional and structural heterogeneity of skin as a complex organ. The Human Cell Atlas is an international collaboration to make single cell analytical data available to researchers (73) and the skin component of this atlas is eagerly awaited. Several research laboratories have already released published data and tools to allow the interrogation of skin transcriptome analysis, for example murine data from the Kasper lab (74).

CRISPR-cas9 gene editing

CRISPR (clustered regularly interspaced palindromic repeat) sequences are found in bacterial DNA and form part of their immune response to phage infection. Cas9 (CRISPR-associated protein 9) is an enzyme that cleaves DNA selectively at sequences containing the CRISPR motif. In 2012 it was reported that this mechanism can be exploited for genetic engineering; guide-RNAs are used to direct the cas9 enzyme to cleave DNA in precisely-targeted editing. Application of CRISPR-cas9 allows the effects of genetic variation to be tested directly and the technique has revolutionised molecular biology. This cost-effective and relatively easy-to-use technology has allowed researchers to precisely and efficiently target, edit, modify and mark genomic loci in a wide range of cells and organisms (75). Within dermatology, CRISPR-cas9 editing has been used to correct the genetic defects in several forms of epidermolysis bullosa and of relevance to AD, the technique can be used to investigate candidate genes *in vitro* (see below).

Functional analyses in vivo

Clinical observation followed-up with genetic analysis has increased our understanding of severe phenotypes which include features of AD. Following on from Netherton syndrome, these 'human knock-out' models include *CARD11* mutations (causing systemic atopic inflammation), *DSG1* and *DSP* mutations (causing severe dermatitis, multiple allergies and metabolic wasting) and various immunodeficiency syndromes with AD-like skin inflammation (such as Wiskott-Aldrich, caused by mutations in *WAS*) (76).

Functional analysis of the skin of AD patients *in vivo* also offers opportunities to gain understanding of the pathophysiology. Transepidermal water loss (TEWL) (77) measures the 'inside-to-outside' barrier function and *in vivo* it is proportional to skin inflammation; capacitance or conductance of the stratum corneum give a quantitative measure of water content; and tape-stripping can be used as a relatively non-invasive methods for sampling the skin transcriptome, proteome and lipids of relevance to AD (78).

Organotypic models of atopic dermatitis

Three-dimensional organotypic models of human skin bridge the gap between cultured cells in monolayer and animal models. Multi-layered organotypic models recapitulate many features of human epidermis including: morphology, spatiotemporal expression of terminal differentiation/proliferative markers and an appropriate complement of epidermal lipids (79, 80). Several organotypic models of AD have been described which generally use one of two basic approaches: the first involves the treatment of organotypic models derived from normal healthy cells with AD-relevant cytokines and the second models *FLG* deficient AD through gene silencing or the use of *FLG*-mutant keratinocytes (81). Th2 cytokines (IL-4 and IL-13) stimulate a spongiotic epidermal morphology, similar to that observed in AD (82). Organotypic models deficient in filaggrin expression broadly recapitulate many of the structural, molecular and functional defects observed in AD skin. These include a lack of keratohyalin granules, increased paracellular permeability (83, 84) and protein expression signatures consistent with AD skin (85, 86). Filaggrin deficient organotypic skin, therefore, mirrors many changes observed in the AD skin and thus represents a useful model for the study of AD disease mechanisms and therapeutic options.

Organotypic models allow the investigation of tissue-specific genetic effects and the opportunity for testing other AD candidate genes, by knockdown, over-expression, or CRISPR-cas9 editing of genes of interest.

Functional analyses in vitro

Organotypic skin models grown at the air liquid interface develop a competent bidirectional epidermal barrier with similar biophysical properties to human skin. They offer the advantage over monolayer cell cultures, that they are tractable for physiologically relevant functional analysis (87). The outside-in barrier can be quantified in organotypic models using topically applied hydrophilic dye such as Lucifer yellow. This is naturally excluded from the epidermis by the lipid-rich stratum corneum but can permeate into the deeper epidermal and dermal layers if the skin barrier is immature or impaired (83). Analogous to the *in vivo* situation described above, the inside-outside barrier of organotypic cultures can also be determined by measuring the rate of TEWL (56). These techniques have been used successfully to investigate both the effect of previously uncharacterized genes and the *FLG* deficiency on skin barrier function (56, 83, 85).

OUTSTANDING QUESTIONS AND FUTURE WORK

The rapid progress made in recent years still leaves a large amount of work to fully capitalize on novel understanding for the benefit of patients.

More detailed genetic studies

The majority of heritability in AD remains unexplained. Improvements in technology have allowed more and more detailed interrogation of the coding and non-coding regions of the genome which are likely to hold important mechanistic information. Outstanding questions involve tissue-specific effects in skin; the relative accessibility of this tissue allows dermatological studies to take advantage of direct sampling for epigenetic studies and more detailed transcriptome analyses. Copy number variation within *FLG* has a dose-dependent effect on AD (38) and more detailed analyses are required to assess CNV in other risk loci. On a genome-wide level, even larger numbers of cases and controls will be required to achieve the statistical power to detect gene-gene interactions and gene-environment interactions of relevance to AD. These studies remain challenging in their financial cost and computational requirements.

More inclusive genetic research

As described above, the majority of genetic research to date in AD has been conducted in people of white European ancestry. However, the clinical phenotype of AD is different in different ethnicities and studies of genetic risk in African (35) and Asian (88) populations have provided valuable complimentary insight (89). There has been a call in the field to prioritise diversity in human genomics research because this will increase the accuracy, utility and acceptability of using genomic information for clinical care (90). The International Symposium on Atopic Dermatitis (ISAD) has recently

published a position statement calling for more research on AD in Africa (91).

Integration of -omics for personalised medicine

Genetic studies have given important information for understanding AD mechanisms, particularly the initial or 'root cause' of atopic skin inflammation. However, the combination and integration of information provided by the full complement of techniques described above will be required to increase our understanding of AD pathophysiology sufficiently to allow translation for clinical impact. Furthermore, given the complexity and diversity of this trait, further developments in machine learning and more powerful *in silico* analyses (76) are likely to be required to gain full benefit from the wealth of molecular data.

Application of genetic discoveries to drug development

The quest for understanding genetic mechanisms in AD is not merely an academic exercise. Genetic studies can provide a causative link between a sequence variant and a phenotype and drugs developed to target a pathway informed by human genetic studies have above-average chances of clinical success (92). Filaggrin deficiency remains a challenging therapeutic target, even though the genetic discovery was made more than a decade ago, but genetic studies continue to identify causal pathways for AD in increasingly precise and personalised detail. The era of 'personalised medicine' is expected to bring a new relationship between genomics and drug development, testing the physiological and molecular bases for disease, but success in this endeavour would ultimately transform drug development and clinical use (93).

CONCLUSION: THE FUTURE LOOKS BRIGHT

In 1952, Rosalind Franklin was the first to crystallise DNA fibres to study their structure using X-ray diffraction; in 1953 James Watson and Francis Crick reported the double helix structure of DNA; in 1990 the Human Genome Project began and in 2003 the Human Genome Project was completed, providing a sequence of the entire human genome – approximately 3 billion base pairs in length.

Since this time, we have progressed a long way in understanding more of the detail of how DNA sequence variation contributes to human health and disease. There has been a particularly rapid explosion of knowledge in the last 20 years, brought about by increased technical capacity for sequencing DNA and RNA. Whilst it is unlikely that another single gene exists with the impact of *FLG* upon AD risk, the future appears bright for AD patients: New techniques will refine understanding of genetic risk, with a multi-ethnic perspective, providing powerful insight to drive the development of new pharmacological interventions. These will increasingly be targeted to specific disease mechanisms for each individual patient with AD. The next 100 years is likely to see a step-change in the management of this challenging disease.

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REVIEW ARTICLE

Skin Microbiome in Atopic Dermatitis

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Atopic dermatitis is a common inflammatory skin disease with a complex pathogenesis that includes imbalanced immune system signalling, impaired skin barrier and enhanced *Staphylococcus aureus* skin colonization. The skin bacterial communities are characterized by increasing abundance of *S. aureus*, leading to reduced diversity compared with the bacterial communities on healthy skin, and increasing disease severity. In contrast, fungal communities are richer and more diverse on the skin of patients with atopic dermatitis, although distribution of the most common species is similar in patients and controls. Filaggrin deficiency in atopic dermatitis skin might be related to the enhanced skin colonization by *S. aureus*. In addition, *S. aureus* expressing variant virulence factors have been shown to elicit atopic dermatitis-like phenotypes in mice, indicating that specific *S. aureus* strains can induce flare-ups. This review aims to provide an overview of the recent literature on the skin microbiome in atopic dermatitis.

Key words: atopic dermatitis; skin microbiome; *Staphylococcus aureus*; filaggrin.

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SIGNIFICANCE

Atopic dermatitis is a common skin disease characterized by dry and itchy skin with eczema flares. The disease is associated with changes in the skin microbiota, which constitutes all microorganisms present on the skin surface. The greatest difference is due to increased abundance of *Staphylococcus aureus*, a bacterium that can cause skin infections and probably contributes to aggravation of the disease. This review aims to provide an overview of recently published literature regarding changes in the skin microflora in atopic dermatitis and its association with disease severity and exacerbation.

Atopic dermatitis (AD) is a common inflammatory skin disease that affects 10–20% of children and 2–10% of adults in developed countries (1, 2). The pathogenesis of the disease is complex and includes impaired skin barrier function and an imbalanced immune system with enhanced Th2, Th17, and Th22 signalling (3). Furthermore, patients with AD have an increased burden of *Staphylococcus aureus* skin colonization, which is associated with disease severity and exacerbation (4–8). Within recent years, where it has become possible to examine complete microbial communities using advanced DNA sequencing technologies, it is evident that cutaneous *S. aureus* is associated with decreased bacterial diversity on AD skin (8–13). The aim of this review is to provide an overview of the recent literature on the skin microbiome as well as microbe-host interactions in AD.

There is no single established accepted definition of the term "microbiome" in the scientific community. Often, this term is defined as the composition of all microbial genes in a community (14), but it has been argued that this definition rather describes the "metagenome" and that the word "microbiome" should be defined as all microorganisms in a habitat (the "microbiota"), their genomes, and the surrounding environmental conditions (15). In this review, the latter definition is used.

Skin microorganisms can be identified using culture-based assays, and complete microbial communities can be examined by DNA sequencing (**Box 1**) followed by diversity and taxonomy analysis (**Box 2**). Recently, Grogan et al. (16) have summarized the techniques used for studying the skin microbiome, and the methods are therefore not described in detail in this review.

HEALTHY SKIN MICROBIOME

The skin is an important first-line defence against pathogenic microbial invasion. Tight connections between corneocytes in the stratum corneum form a physical barrier, and antimicrobial peptides and lipids secreted from keratinocytes and glands provide a chemical barrier (17). In addition, commensal skin microorganisms can impede growth of pathogens, either directly by secreting antimicrobial molecules, or indirectly by occupying space and competing for nutritional resources (18, 19).

The skin microbiota consists of diverse organisms, including bacteria and fungi. In adults, the microbial community composition is rather stable over time, despite of the constant exposure to external microorganisms from other humans and the surrounding environment (20). However, the composition of the microbiota changes during puberty, with children having a more diverse microbiota compared with adults (21–23).

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Box 1. Assays for examination of microbial organisms and communities

- Culture assays: Plating and culturing of samples in order to detect and isolate specific viable microorganisms of interest. Advantages of this method are the possibility to use isolated strains for additional analysis, e.g. testing for antimicrobial resistance and examine the gene content using molecular methods. Also, it is known that the detected microbes are alive and viable. Disadvantages are that it is difficult to detect microorganisms that do not grow easily under standard laboratory conditions and that it is not possible to examine the microbial community as a whole.
- Whole genome sequencing: Sequencing genomes of specific microorganism of interest allows to examine the genetic content and thus properties of the single strain. This method is especially useful for comparing strains and their relatedness, e.g. to examine the similarity of strains isolated from distinct skin sites within individuals. A disadvantage of this method is that only selected strains are examined.
- Targeted amplicon sequencing: Sequencing of selected variable regions of the 16S rRNA gene can be used to identify most bacteria in a sample, making it possible to examine the composition of the bacterial community. The transcriptional spacer regions ITS1/2 and variable regions of the 18S rRNA gene can be used to study eukaryotic microbial communities, such as fungal communities. An advantage of targeted amplicon sequencing is thus the ability to examine whole microbial communities, though this method has its limitations as it often is impossible to differentiate between related species. Another disadvantage of this method is that all available target DNA is sequenced, including DNA from microbial contaminants and human skin cells, which especially constitutes a problem for low biomass samples, such as skin samples.
- Metagenomic shot-gun sequencing: Shot-gun sequencing is used to examine the complete genomes of the microbiota. This allows to detect all species constituting the microbiota at the strain level as well as examining specific properties of the community, e.g. metabolic pathway genes. A disadvantage of shot-gun sequencing is that deep-sequencing is required in order to obtain a high resolution making the method very expensive. As a consequence, most metagenomic studies are based on minor sample sets. Another disadvantage, which also applies to the amplicon DNA sequencing method, is the lack of discrimination between live and dead organisms.

Bacteria constitute the greatest proportion of the microbiota, representing more than 70% of species in most skin areas (24). 16S rRNA gene sequence analysis has shown that *Corynebacterium, Cutibacterium* (formerly *Propionibacterium* (25)), *Micrococcus, Staphylococcus, Streptococcus*, Betaproteobacteria, and Gammaproteobacteria are common skin-colonizing bacteria (9, 21, 23, 24, 26). Microbial richness and Shannon-diversity are influenced by the microenvironmental conditions on the skin, including pH, moisture, sebum content, and topography (24, 26, 27). Sebaceous skin sites (e.g. facial areas and the upper part of the chest and back) are dominated by *Cutibacterium acnes* and are less diverse and rich compared with moist skin (e.g. nares, axillary vault, antecubital fossa, and popliteal fossa) and dry skin (e.g. volar forearm) (24, 26). *C. acnes* is also the most abundant species in dry skin, whereas no single bacterial species is over-represented in moist skin, although *Corynebacterium* spp. and *Staphylococcus* spp. relative abundances are greatest (24). Fungi constitute 1–5% of the skin microbiota (24), with *Malassezia* being the most common and abundant habitant (27, 28).

Box 2. Diversity and taxonomy analysis

- Alpha-diversity: Diversity within samples.
  - Richness: the total number of species or unique sequences in a sample.
  - Shannon Index: a diversity measure that takes into account both species richness and evenness.
- Beta-diversity: Diversity between samples.
  - Pairwise comparison of community structures can be measured using distance-based methods, e.g.:
    - Weighted UniFrac: Dissimilarity measure based on species presence/absence data. Takes into account the phylogenetic relatedness of species.
    - Unweighted UniFrac: Dissimilarity measure based on the relative abundances of species. Takes into account the phylogenetic relatedness of species.
    - Jaccard: Dissimilarity measure based on species presence/absence data. Does not take into account the phylogenetic relatedness of species.
    - Bray-Curtis: Dissimilarity measure based on the relative abundances of species. Does not take into account the phylogenetic relatedness of species.
  - Ordination plots: Visualization of beta-diversity based on the pairwise distance measures. Samples with similar community structures are clustered together. The axes determine the degree of variance between samples.
  - Hierarchical clustering: Samples are clustered in a dendrogram based on the pairwise distance measures.
- Taxonomy analysis: Analysis of species distributions in a community/sample.

SKIN MICROBIOME IN ATOPIC DERMATITIS

AD is clinically characterized by red, dry, and itchy skin, with eczema flares and disease exacerbation. Interestingly, the clinical presentation of AD changes with age (29). Infants (< 1 year) are primarily affected by acute lesions of the cheeks, scalp, neck, trunk, and extensor parts of the extremities. Children (2–12 years of age) are mostly affected by eczema at the antecubital and popliteal fossa, and adolescents and adults by chronic lesions comprising the head, neck, hands, and flexural areas (and sometimes widespread disease). Consequently, published studies on the skin microbiome in AD have focussed on distinct skin areas depending on the age group investigated. A major genetic risk factor of AD in Asian and Caucasian populations is loss-of-function mutations in the *FLG* gene encoding the skin protein filaggrin (30). Filaggrin is essential for the alignment of keratin in the corneocytes, and filaggrin breakdown products act as natural moisturizing factors (NMFs) important for proper skin hydration. Thus, filaggrin is important for maintaining a functional skin-barrier. Th2 and Th22 cytokines can down-regulate *FLG* expression, and thus lead to filaggrin deficiency in AD independently of loss-of-function mutations in *FLG* (3). Filaggrin deficiency and reduced levels of NMFs and free fatty acids, followed by an increase in skin pH, lead to an altered skin ecology in AD (31–34). Also, microbial communities are altered on AD skin compared with normal healthy skin, as described below.

Bacterial community on atopic dermatitis skin during infancy

As in healthy control skin, the skin microbial composition in AD differs between age groups, with distinct bacteria being over-represented at different ages (10, 21). Two case-control studies have compared the bacterial community composition on skin from infants with and without AD (35, 36). Zheng et al. (35) examined the bacterial community composition in perioral skin in infants with clinical signs of AD at the sample site and in age-matched healthy controls. The microbial diversity was lower on AD skin compared with healthy control skin, with the largest difference observed between patients with severe AD and healthy controls. *Streptococcus* was the most common bacterial genus at the perioral skin, with mean relative abundances exceeding 40% in both healthy

control skin and lesional skin from patients with mild/moderate AD. However, in the severe AD patient group, relative abundances of *Streptococcus* spp. were significantly reduced and replaced with *Staphylococcus* spp, primarily *S. aureus*. In contrast, bacterial communities on skin from the cheeks, nose tip, antecubital fossa, and popliteal fossa were generally similar in infants with or without AD (36). Importantly, the AD group consisted of infants who not necessarily had developed AD or had active disease at the sampling time-points, which very well can influence the results. *S. aureus* was not identified in any of the skin samples (36), despite the fact that *S. aureus* is frequently detected on antecubital and popliteal fossa skin regions in older children and adults with AD (8, 10). Although this could indicate that *S. aureus* colonization at the antecubital and popliteal fossa is not an essential marker for AD during disease development in the first year of life, culture-based analysis has indicated the opposite (37). Thus, Meylan et al. (37) found that frequencies of *S. aureus* colonization at axillary and antecubital fossa skin were significantly higher at the time of diagnosis among infants and toddlers (0–2 years of age) developing AD compared with non-AD age-matched controls. However, frequencies of *S. aureus* colonization were less than 15% and thus remarkably lower compared with the prevalence in older children and adults with AD (6). In addition, *S. aureus* colonization of the anterior nares, which is a major habitat for *S. aureus* in both healthy and AD individuals (6, 38), was not considered to be a risk factor for AD development among infants with familial predisposition (39). Thus, a possible role of cutaneous *S. aureus* colonization during development of AD still needs further investigation.

Bacterial community on atopic dermatitis skin during childhood and adulthood

Several studies have shown that bacterial communities on skin of children and adults with established AD are less diverse, and are dominated by increased proportions of *S. aureus* compared with communities on healthy skin (8–13, 21, 35). Quantification of cutaneous *S. aureus* abundances has shown that the proportional increase of *S. aureus* is due to a significant greater absolute abundance of *S. aureus* on AD lesional and non-lesional skin compared with healthy control skin (40–42). No difference in absolute abundances of the 3 common skin bacteria *Corynebacterium*, *Cutibacterium*, and *Streptococcus* were observed between AD and healthy control skin in children (40). Thus, the increased relative abundance of *S. aureus* on AD skin is probably not due to decreased colonization with these bacteria, but mainly a result of an enhanced burden of *S. aureus* on the skin. This could also explain that the total bacterial load is significantly greater on AD skin compared with healthy control skin (**Fig. 1**) (40, 43).

Kong and colleagues (8) were the first to examine the temporal bacterial variation on antecubital and popliteal fossa skin in children during and after an AD flare episode (8, 12). Bacterial diversity was significantly reduced during flares at both skin sites, compared with baseline and post-flare samples. The decreased diversity during AD flares was associated with increased relative abundances of *S. aureus*, which exceeded 40% in many of the samples. The increase in relative abundances of *S. aureus* was accompanied by a decrease in the relative abundance of *Streptococcus salivarius* (8, 44), a commensal bacteria of the oral cavity, intestines and skin that has been shown to possess anti-inflammatory potentials *in vitro* (45). In addition, higher proportions of *S. salivarius* contributed to greater bacterial diversity on the skin of the cheek, volar- and dorsal forearm in healthy infants with a family history of atopic diseases and thus at higher risk of developing AD (44). The proportional abundances of *S. aureus* decreased significantly at the post-flare sample time-point, but were still slightly higher compared with *S. aureus* proportional abundances in the healthy control samples (8, 12). Yet, no significant difference in alpha-diversity was observed between baseline, post-flare, and healthy control skin, which could indicate that skin bacterial diversity is only reduced during flare-ups. Several studies have compared alpha-diversity on lesional and non-lesional AD skin, but with different conclusions. Three studies found that the bacterial diversity was lower on lesional skin compared with non-lesional skin (13, 21, 46), whereas 2 other studies found that the diversity was equally reduced on affected and un-affected AD skin compared with healthy control skin (9, 10). Neither age nor sampling sites can explain the

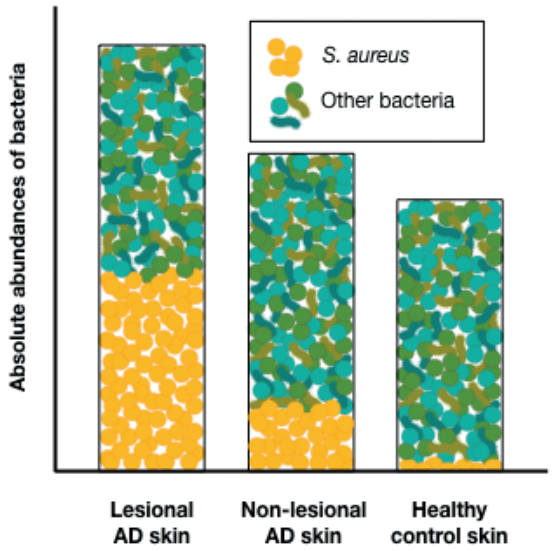

Fig. 1. Absolute abundances of bacteria in atopic dermatitis (AD) skin and healthy skin. Bacterial densities are significantly greater on AD lesional skin compared with healthy control skin, which mainly is due to significantly increased abundances of *S. aureus* in AD lesional skin. *S. aureus* absolute abundances are also increased in AD non-lesional skin, but not as much as in lesional skin.

conflicting results. These studies might indicate that it is not the eczema itself that drives the changes in diversity, but other AD-related factors in or on the skin that not only are associated with lesional skin areas (e.g. *S. aureus* colonization, lipid composition or pH).

Clausen et al. (9) discovered that the bacterial community composition (beta-diversity) varied significantly between lesional and non-lesional skin areas in adult AD patients, with the greatest variance being due to a different distribution of Staphylococcal species. One-third of the lesional skin samples were dominated by *S. aureus* (relative abundances greater than 50%), whereas only a few non-lesional skin samples were characterized by high proportions of *S. aureus*. Instead, coagulase-negative staphylococcal species (CoNS), such as *S. epidermidis* and *S. hominis*, dominated the bacterial community on non-lesional skin in a majority of patients. In accordance, Baurecht et al. have shown that relative abundances of CoNS are reduced and *S. aureus* abundances increased in acute and chronic lesional skin compared with non-lesional AD skin (46). Though the identified CoNS are common colonizers of moist skin, their abundances were lower on healthy control skin compared with non-lesional AD skin at the antecubital fossa (9, 46). It could thus be hypothesized that the skin ecology in AD supports enhanced staphylococcal growth on both lesional and non-lesional skin, and that changes in the distribution among the staphylococcal species towards greater abundances of *S. aureus* can contribute to the development of eczema locally on the skin. However, no changes in the proportion of either *S. epidermidis*, *S. hominis* or *S. capitis* at the antecubital- and popliteal fossa during or after a flare-up episode was identified among paediatric AD patients (12), suggesting that a potential role for the CoNS spp. in AD still needs to be clarified. Furthermore, species level analysis might not be sufficient, as distinct strains within a species can have distinct phenotypes. For example, Nakatsuji et al. have shown that CoNS strains isolated from the skin of healthy individuals more often are capable of killing *S. aureus* compared with CoNS strains isolated from AD skin (42). Also, colonization of specific subspecies of *S. aureus* seems to be favoured in AD, as *S. aureus* clonal complex 1 (CC1) strains are more often detected on skin and in nares from AD patients compared with healthy controls (47). The increased prevalence of CC1 *S. aureus* colonization might be due to intrinsic factors in AD, e.g. CC1 *S. aureus* colonization have been associated with carriage of loss-of-function mutations in *FLG* (7), or due to extrinsic factors, such as treatment practice leading to selection of antibiotic resistance (48, 49).

Eukaryotic microbial community on atopic dermatitis skin

Few studies have examined the eukaryotic microbial community on AD skin, and only in adults and Asian populations (50–52). Focus has been on fungal communities, which was found to be richer and more diverse on AD lesional skin compared with healthy control skin (50, 51). *Malassezia*, especially *M. globosa* and *M. restricta*, was the dominant fungus in both AD lesional skin and healthy control skin (50, 51). An increase in the proportional abundance of *M. dermatitis* and *M. sympodialis* was identified on the skin of individuals with a history of AD (no active disease) compared with individuals without AD (52). However, no differences in the proportions of these 2 species were found between lesional skin of AD patients with active disease and healthy control skin (51, 53). Another fungal species, *Candida albicans*, was found to be over-represented on AD lesional skin on the cheeks (presence in 100% of samples), compared with healthy control skin from the same area (presence in 10% of samples) (51). The literature regarding skin eukaryotic microbial communities in AD is limited, and thus, additional studies with more attendees are needed in order to validate the presented results.

Atopic dermatitis disease severity is associated with changes in skin microbial communities

Significant differences in alpha- and beta-diversity across AD severity scores have been identified in both lesional and non-lesional skin sites, with patients with more severe disease having the lowest bacterial diversity on the skin (9, 10, 13, 54). Brandwein et al. (10) found that the bacterial community composition in antecubital- and popliteal fossa in patients with mild/moderate AD was more similar to the community composition of healthy control skin than to skin areas in patients with severe AD, regardless of whether samples were collected from lesional or non-lesional skin. This finding supports the hypothesis that the AD phenotype, such as an overall impaired skin barrier and skin inflammation, has a widespread effect on the skin microbial community and not only on lesional skin areas.

S. aureus skin and nasal colonization is significantly more prevalent among patients with more severe disease (6, 7, 55, 56), and increased relative abundances of *S. aureus*, at least at the antecubital fossa, have been associated with increasing AD severity scores (10–13). However, conflicting results regarding total *S. aureus* densities on skin in relation to AD severity have been published. Thus, *S. aureus* absolute abundances have been associated with increasing severity scores among adult patients (13, 57), whereas no association was detected in a paediatric AD population (54).

Studies investigating eukaryotic microbial communities on AD skin are sparse, but one study implies that there is an association between AD severity scores and the fungal community on skin, as beta-diversity analysis showed distinct community compositions in samples from patients with severe AD compared with samples from those with mild/moderate AD (51).

MICROBE-HOST INTERACTIONS IN ATOPIC DERMATITIS

Microbiome studies have made it evident that microbial communities on AD skin differ from those of healthy skin, and that the greatest difference is due to an over-representation and greater abundance of *S. aureus* on AD skin. What are the mechanisms behind these differences? Functional analysis studies suggest that the AD phenotype, including impaired skin barrier function, increased pH, and skin inflammation, can promote changes in the skin microbial communities (43, 58, 59). Moreover, *S. aureus* can induce skin inflammation and aggravate AD (12, 60–62). Thus, a vicious circle might exist, with filaggrin deficiency in skin leading to enhanced colonization of *S. aureus*, which through the expression of virulence factors then can induce skin inflammation and contribute to further skin barrier impairment, and, in turn, can facilitate the maintenance of an imbalanced skin microbial community (**Fig. 2**). The mechanism behind these connections is elaborated below.

Atopic dermatitis pathogenesis facilitates changes in skin microbial communities

In AD, loss-of-function mutations in the *FLG* gene have been associated with changes in the overall bacterial community composition on non-lesional AD skin (9, 46), as well as with an increased risk of *S. aureus* colonization on lesional skin and in anterior nares (7). These studies indicate that filaggrin can influence bacterial growth and colonization on the skin. In accordance, presence of the filaggrin breakdown products urocanic acid (UCA) and pyrrolidone carboxylic acid (PCA), which contribute to skin acidification, have been shown to reduce *S. aureus* growth *in vitro* (58). More neutral pH, reflecting the skin pH in AD, has been associated with increased expression of *S. aureus* genes involved in colonization, including the gene encoding clumping factor B, which mediates adherence to keratinocytes (58, 59). Thus, increased *S. aureus* colonization among AD patients with *FLG* loss-of-function mutations (7) might be due to changes in skin pH caused by UCA and PCA deficiency. In addition to increased *S. aureus* adherence in epidermis, filaggrin deficiency is also associated with enhanced migration of *S. aureus* into the dermis skin layer. Nakatsuji et al. (43) showed that skin barrier impairment in mice, induced by genetic predisposition (*FLG* loss-of-function mutations) and physical skin disruptions (tape stripping), led to enhanced penetration of *S. aureus* into the dermis where it could activate the host immune system. In humans, the absolute abundance of *S. aureus* was significantly greater in dermis of AD lesional skin compared with healthy control skin, indicating that *S. aureus* can migrate more easily into the deeper skin layers of patients with AD with a disrupted skin barrier (43). Disrupted AD skin is also more permeable to allergens, which can trigger type I allergic responses in sensitized individuals. To corroborate this, patients with AD are also more often hypersensitive to a wide range of microbial allergens, including allergens from *S. aureus* and the skin colonizing fungal species *Malassezia furfur* and *Candida albicans*, compared with the general population (63–65).

AD skin might not only be more susceptible to *S. aureus* colonization, but also more vulnerable to *S. aureus* virulence. Alpha-haemolysin (also known as alpha-toxin), a virulence factor secreted by *S. aureus*, has thus been shown to adhere more easily to keratinocytes in AD skin compared with keratinocytes in healthy skin (66, 67). Alpha-haemolysin adheres to sphingomyelin lipids in the membranes of keratinocytes, leading to cell lysis and contribution to skin barrier disruptions (68). The density of sphingomyelin lipids, and thus the amount of free adherence sites for alpha-haemolysin, is regulated by the enzyme acid sphingomyelinase. Filaggrin deficiency as well as Th2 cytokines promote down-regulation of acid sphingomyelinase, thus enhancing alpha-haemolysin binding efficiency (66, 67). Thus, filaggrin deficiency in AD probably both favours *S. aureus* colonization and enhanced *S. aureus* mediated cytotoxicity and immune activation (**Table I**).

S. aureus *as an inducer of clinical atopic dermatitis*

Byrd et al. (12) have shown that *S. aureus* isolated from AD skin, but not *S. aureus* from normal healthy skin, was able to induce skin inflammation in wild-type mice with no genetic predisposition. Skin inflammation, assessed by epidermal thickening and cutaneous infiltration of immune cells, including Th2 and Th17 cells, was more pronounced in mice inoculated with *S. aureus* from patients with more severe AD. This study highly suggests

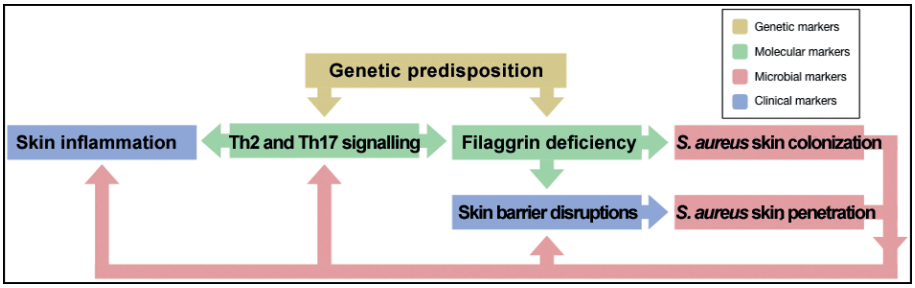

Fig. 2. Proposed connections between human factors involved in AD pathogenesis and *S. aureus* colonization and virulence.

Table I. The effect of filaggrin deficiency on *S. aureus* skin colonization and virulence

Effect of filaggrin deficiency		
Primary outcomes	Secondary outcomes	Refs
Increased skin pH	Enhanced *S. aureus* growth and colonization	(58, 59)
Impaired skin barrier	Enhanced *S. aureus* migration through the epidermal barrier and into dermis	(43)
Increased density of sphingomyelin lipids in keratinocyte membranes	Enhanced binding of alpha-haemolysin (cytotoxic *S. aureus* virulence factor)	(67)

that certain strains of *S. aureus* are able to elicit lesions similar to those observed in AD. The detected effect of *S. aureus* is probably mediated by the production of virulence factors, such as phenol-soluble modulins (PSM) and enterotoxins.

Several studies indicate that *S. aureus* induced skin inflammation and barrier disruption in mice are dependent on secretion of PSM-alpha, which promotes interleukin (IL)-17A mediated pro-inflammatory responses *in vitro* (human keratinocytes) and *in vivo* (mice) (60, 69, 70). Another PSM, known as delta-toxin, was also able to mediate *S. aureus* induced skin inflammation in mice, an effect that probably is mediated by delta-toxin induced mast cell degranulation, IgE production and enhanced IL-4 expression (62, 71). Interestingly, PSM-alpha transcripts are significantly more abundant in *S. aureus* isolated from AD skin compared with those from *S. aureus* isolated from healthy control skin (60), and delta-toxin production has been found to be considerably higher among *S. aureus* from lesional skin compared with non-lesional skin on patients with AD (62). These findings might explain why *S. aureus* strains isolated from AD lesional skin were better at eliciting skin inflammation compared with *S. aureus* from healthy skin (12).

S. aureus enterotoxins have also been proposed to be important mediators of *S. aureus* induced skin inflammation. Thus, topical application of staphylococcal enterotoxin B (SEB) to skin have been shown to cause erythema and epidermal thickening in both healthy volunteers and patients with AD (72), an effect which likely is mediated by enhanced T-cell signalling (72, 73). Studies indicates that *S. aureus* from AD skin more often carry genes encoding enterotoxins (*sea*, *seb*, *sec*, and *sed*) and more often produce these toxins compared with *S. aureus* isolated from non-AD individuals (73, 74). Furthermore, carriage of enterotoxin producing *S. aureus* has been associated with increased AD severity (assessed by SCORAD) (73, 75).

In one study, alpha-haemolysin was also found to be produced more frequently by AD *S. aureus* (91% of isolates) compared with production rates among *S. aureus* from healthy volunteers (33% of isolates) (61), which in combination with AD genetic predisposition for enhanced binding efficiency of the toxin (66, 67) could make alpha-haemolysin a potent inducer of skin barrier disruptions in AD (61). However, two other studies found lower proportions of *S. aureus* producing alpha-haemolysin on AD skin (30–63% of isolates) (76, 77) and a third study reported an alpha-haemolysin gene (*hla*) expression frequency of 59% among *S. aureus* nasal isolates from healthy carriers (78), highlighting that population-based differences and use of distinct assays can influence the results. Thus, future studies need to elucidate whether alpha-haemolysin, and other *S. aureus* toxins, is upregulated in *S. aureus* colonizing AD skin.

The above-mentioned studies support the hypothesis that *S. aureus* virulence is a major driver of AD disease exacerbation and might even be a direct cause of flare-ups. In order to cause disease, *S. aureus* must first colonize the skin. *S. aureus* isolated from AD skin has an enhanced binding activity of clumping factor B, leading to increased adhering to corneocytes, compared with *S. aureus* from healthy skin (79). In addition, CC1 *S. aureus*, which is a dominant clone in AD (7, 79, 80), had a slightly higher binding affinity compared with other *S. aureus* lineages (79). Thus, the increased prevalence of *S. aureus* skin colonization in AD might both be due to host factors and *S. aureus* factors (58, 59, 79). A summary of the described *S. aureus* virulence factors shown to be involved in AD is given in **Table II**.

EFFECT OF ATOPIC DERMATITIS TREATMENTS ON SKIN MICROBIAL COMMUNITIES

Topical application of corticosteroid (glucocorticoids) based creams is a common treatment of AD lesions. Prospective studies examining the effect of topical corticosteroid treatment on skin microbial communities in AD, have shown that 4–6 weeks of treatment led to significant increases in bacterial Shannon-diversity and richness (40, 81), whereas 7–10 days of treatment had no influence on alpha-diversity, though an clinical improvement was observed (35). Thus, a possible effect of topical corticosteroid on skin microbial communities is dependent of several weeks of continuous treatment. Comparative studies also imply that topical corticosteroid

Table II. Virulence factors upregulated in *S. aureus* isolated from atopic dermatitis skin compared with *S. aureus* from healthy control skin

Virulence factors	Clinical outcomes	Mediators	Refs
PSM-alpha	Skin inflammation Skin barrier disruptions	IL-17A signalling Protease activity	(60, 70)
Delta-toxin	Skin inflammation	IL-4 signalling Mast cell degranulation IgE release	(62, 71)
Alpha-haemolysin	Skin barrier disruptions	Keratinocyte lysis	(61)
Enterotoxin B	Skin inflammation	T-cell signalling	(72)
Clumping factor B	*S. aureus* colonization	Cell adherence	(79)

PSM: phenol-soluble modulin; IL: interleukin.

treatments have an effect on the skin microbial community, as AD patients undergoing topical corticosteroid treatments prior to sample collections often have a more diverse bacterial population with lower relative abundances of *S. aureus* compared with non-treated patients (8, 9, 81). This effect might be due to direct inhibition of *S. aureus* as well as to a general improvement on skin conditions due to the anti-inflammatory properties of corticosteroids (82).

A keystone treatment practice in AD is application of emollients and moisturizers, which restore skin barrier integrity and prevents flare-ups. Despite extensive use, little is known about what effect this treatment approach has on skin microbial communities, but one study indicates that emollient application leads to decreased proportions of *Staphylococcus* spp. on AD lesional skin (83). Although it indeed would be interesting to examine the long-term effect of emollient usage on the skin microbiome, it might be challenging and ethically unjustifiable to set up such study, as it would include an AD patient group that will be denied treatment with emollients and moisturizers for a longer period.

One study has examined the effect of dupilumab treatment, an anti-inflammatory systemic therapy offered to adults with severe and chronic AD, on the skin bacterial community (13). Sixteen weeks of treatment led to increased alpha-diversity and a decrease in relative and absolute *S. aureus* abundances on lesional as well as non-lesional AD skin. However, this effect was lost 18 weeks after treatment termination. Dupilumab inhibits IL-4/IL-13 signalling, and the study thus shows that reduction of Th2-mediated signalling may influence *S. aureus* skin colonization.

Another common treatment practice, at least in some countries, is topical application of fusidic acid, which is a narrow-spectrum antibiotic used against *S. aureus*. Unfortunately, bacterial growth of other common bacterial species on skin, including CoNS, are also inhibited by fusidic acid (84), and recent studies have shown a high prevalence of fusidic acid resistant *S. aureus* on AD skin and nares (48, 49), signifying that alternative treatment regimens are needed for the control of *S. aureus* colonization. Future treatment approaches could include *S. aureus* anti-virulence therapy (71) or application of commensal skin bacteria with anti-*S. aureus* properties (42). Oral administered antibiotics might also impact the cutaneous bacterial community composition and select for antibiotic resistance among skin bacteria (85–87).

CONCLUSION

Multiple studies have shown that increased abundance of *S. aureus* and loss of bacterial diversity on skin are associated with disease severity and flares in children and adults with AD. The enhanced burden of *S. aureus* skin colonization is probably facilitated by AD-related changes in the skin, including reduced levels of filaggrin and NMFs leading to increased skin pH and skin barrier impairment. In addition, deficiency of commensal bacterial strains with *S. aureus* inhibitory properties may contribute to the increased density of *S. aureus* on AD skin. Functional assays indicate that cutaneous *S. aureus* can exacerbate AD by expressing virulence factors that can induce skin inflammation and skin barrier disruption. Thus, changes in the composition of the skin bacterial community may be an important inducer of the clinical manifestations in AD patients with established disease. Whether bacterial community dysbiosis is also considered to be present prior to AD development is still unclear, and needs further investigation. Increasing knowledge regarding *S. aureus* as a potent promoter of AD exacerbation, has highlighted the skin microbial community as a potential target for future treatment strategies, and is a research field of great interest. Future studies are needed to explore the potentials, efficiency and safety of these novel anti-bacterial treatment approaches.

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REVIEW ARTICLE

A Therapeutic Renaissance – Emerging Treatments for Atopic Dermatitis

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Atopic dermatitis (AD) is a chronic, inflammatory cutaneous disease that is characterized by complex immune dysregulation and skin barrier dysfunction with a wide variety of clinical phenotypes. Until recently, conventional therapeutic modalities for AD remained rather non-specific despite AD's complex etiology. Failing to take into account the underlying inflammatory pathways led to treatments with inadequate efficacy or unacceptable long-term toxicities. We are currently in the midst of a therapeutic renaissance in AD. Recent progress in molecular medicine provides us a better understanding of the AD pathogenesis, suggesting a dominant helper T cell (Th) 2/Th22 response with a varying degree of Th1/Th17 overexpression. Targeted therapeutic agents including biologics and small molecule inhibitors in development hold promises for more effective and safer therapeutic approaches for AD. A better understanding of individual differences amongst AD patients will allow for a more tailored approach in the future. This review aims to cover the most promising emerging therapies in the field of atopic dermatitis utilizing recently published manuscripts and up-to-date conference abstracts and presentations.

Key words: atopic dermatitis; targeted therapeutic agents; biologics; small molecule inhibitors.

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SIGNIFICANCE

Effective treatment of atopic dermatitis is complicated due to its chronic nature, multifaceted pathophysiology, and variable clinical manifestations. The success of dupilumab confirms the importance of type 2 cytokines in the pathophysiology of atopic dermatitis. Besides type 2 cytokines, certain phenotypes of atopic dermatitis may be driven by additional cytokine pathways. However, data to date attempting to target specific cytokines outside of the type 2 axis have been largely unsuccessful. Further data using large-scale and long-term clinical trials are needed in order to create tailored and personalized treatments for atopic dermatitis.

With an increasing prevalence worldwide, atopic dermatitis (AD) is a chronic, pruritic inflammatory skin disease that often presents in infancy and may persist or re-emerge in adulthood (1). The pathophysiology of AD is complex and involves genetic predispositions, environmental factors, skin barrier dysfunction, immune dysregulation, and disruptions in the skin microbiota (2, 3). Approximately one third of all AD patients have moderate-to-severe disease with symptoms including pruritus, increased risk of sleep disturbances, mental health comorbidities, and suicidal ideation, all of which contribute to a poor quality of life (QoL) (4, 5). Selecting treatments for AD in the clinical setting is often challenging due to a variety of AD phenotypes, which may be due to the various cytokine profiles of AD (6). Conventional systemic immunosuppressive agents including corticosteroids, cyclosporine, methotrexate, azathioprine, and mycophenolate mofetil provide inadequate long-term control in many patients who require systemic therapy due to inadequate efficacy or adverse drug reactions. Thus, there remains a large unmet need for an effective and safe long-term systemic treatment for AD. Considering the multifactorial etiology of AD, the ideal therapeutic treatment should target the specific molecular defect or defects underlying the particular patient's disease. Over the past few years, our increasing knowledge of the immunopathogenesis and heterogeneity of AD has initiated an era of targeted therapeutics, such as biologics and small molecule inhibitors. We can expect to see a more personalized therapeutic treatment approach for AD in the future.

PATHOPHYSIOLOGY OF ATOPIC DERMATITIS

Analysis of the skin and blood of patients with AD reveal an array of adaptive and innate immune derangements. For many years, AD pathophysiology was thought to be driven by a predominant helper T (Th) 2 response in the acute phase of the disease, and a skewed Th1 response in the chronic phase (7). This acute (Th2) and chronic (Th1) paradigm emerged from studies involving inhalant allergen patch tests – an artificial model system with questionable relevance to AD. In this model, Th2 cells and interleukin (IL)-4 messenger RNA (mRNA) were predominantly observed in acute lesions, while Th1 cells and recombinant interferon (IFN)-γ mRNA were prima-

rily seen in chronic lesions (8). Recent findings using patients with AD, not patch tests, have suggested that AD has a stronger association with a Th2/Th22 response and a much more variable Th1/Th17 response throughout both the acute and chronic stages of the disease (9–11). In the acute phase, lesions display overactivation of Th2/Th22 related signals and to a lesser degree Th17 related signals (12, 13). Intensification of these axes, along with an upregulation of Th1 cells, recruit and coordinate the chronic phase of the disease (9).

In AD skin, disruption of the epidermal barrier by irritants, allergens, and pathogens give rise to the activation of nonlymphoid cells like Langerhans cells (LC) and keratinocytes. Epidermal disruption may also occur via genetically driven alterations in skin barrier function such as loss-of-function mutations in the *FLG* gene that encodes for the skin barrier protein filaggrin (14). Disrupted keratinocytes initiate or potentiate inflammation via the release of cytokines and chemokines, including thymus- and activation-regulated chemokine (TARC), thymic stromal lymphopoietin (TSLP), IL-25, and IL-33. These cytokines drive local tissue inflammation and activate a series of Th2-mediated events such as immunoglobulin (Ig) E class switching and recruitment of IL-5 dependent eosinophils into the skin (**Fig. 1**) (15, 16). Th2 cells release IL-4, IL-5, IL-13, and IL-31, which mediate the activation of additional inflammatory cells like mast cells and eosinophils. They also inhibit the expression of barrier proteins such as filaggrin, and barrier lipids such as ceramides (17, 18). Notably, IL-4 and IL-13 induce keratinocytes to secrete additional TSLP, which results in Th2 polarization and a positive feedback loop (19). IL-31, an interleukin that induces itching via sensory nerves, is upregulated in AD lesions and triggers scratching behavior, which may further drive inflammation (20). Group 2 innate lymphoid cells (ILC2s), which are activated by keratinocyte mediators, release both IL-5 and IL-13 that perpetuates Th2 immunity (21, 22). In conjunction with IL-17 released by Th17 cells, IL-22 released by Th22 cells promotes epidermal hyperplasia and aberrant epidermal differentiation (9).

By identifying a growing number of immune pathways underlying AD, numerous targeted and broad-acting drugs are currently in the therapeutic pipeline. Given the critical role of the Th2 axis in AD, anti-Th2 agents like dupilumab, which represents the first biologic drug approved for AD, have been developed (23, 24). Multiple targeted drugs involving the Th22 and Th17 pathways, as well as broader T cell inhibitors, are also currently under investigation. The aim of this review is to provide up to date information regarding this unique and promising era of innovation and novel therapeutic development.

CLINICAL AND MOLECULAR HETEROGENEITY OF ATOPIC DERMATITIS

Recent research reveals several AD subtypes classified by different endotypes and phenotypes including age, chronicity, ethnicity, filaggrin gene mutational status, IgE status, *S. aureus* colonization status, and underlying molecular signaling abnormalities (25–28). Subtypes of various ethnic backgrounds such as European American decent, African American decent, and Asian origin have also been identified. Other AD classifications include pediatric patients versus adult patients, subjects with acute versus chronic disease, and patients exhibiting intrinsic versus extrinsic type. In spite of a similarity in clinical presentation and response to therapy, extrinsic AD was historically defined as patients with high serum IgE levels, personal and family atopic background, while the intrinsic phenotype having normal IgE levels shows female predominance and lack any other atopic diathesis (25).

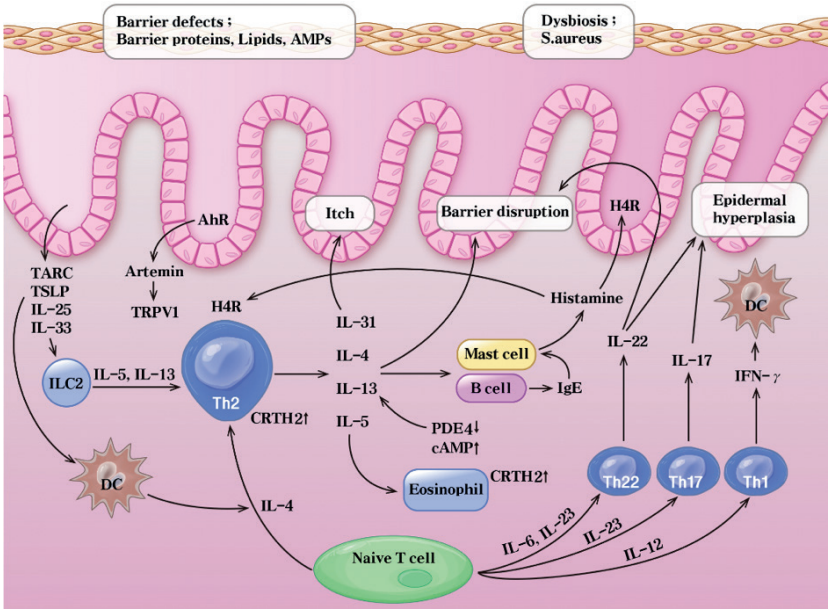

Fig. 1. Immune pathophysiology of atopic dermatitis (AD). In AD skin, epidermal disruption initiates or potentiates inflammation through the release of cytokines and chemokines, including thymus- and activation-regulated chemokine (TARC), thymic stromal lymphopoietin (TSLP), interleukin (IL) -25, and IL-33. These cytokines drive local tissue inflammation and activate a series of Th2 cytokines such as IL-4, IL-5, IL-13, and IL-31, thereby leading to immunoglobulin (Ig) E class switching and accumulation of inflammatory cells into the skin. Together with IL-17 released by Th17 cells and IL-22 released by Th22 cells, epidermal hyperplasia and barrier disruption are intensified throughout the acute and chronic stages of AD. AD: atopic dermatitis; Th: helper T; AMPs: antimicrobial peptides; AhR: aryl hydrocarbon receptor; ILC2: group 2 innate lymphoid cells; TRPV1: transient receptor potential cation channel subfamily V member 1; H4R: histamine receptor type 4; DC: dendritic cell; CRTH2: chemoattractant receptor-homologous molecules expressed on Th2 lymphocytes; PDE4: phosphodiesterase4; cAMP: cyclic adenosine monophosphate; IFN-γ: interferon-γ.

Despite a strong polarization of Th2/Th22 identified in the general AD population, there appears to be a relatively dominant Th17 subtype in pediatric patients, patients of Asian descent, and patients with intrinsic AD. African-American patients with AD and pediatric patients with AD also appear to lack any Th1 activation (25). A Dutch study based on the analysis of serum biomarkers of 193 adult patients with moderate-to-severe AD identified 4 endotype clusters of AD (29). Clusters 1 and 4 show higher levels of Th2 cytokine expression in "erythematous" phenotypes, while clusters 2 and 3 show lower levels of Th2 cytokine expression in "lichenified" phenotypes. Although further studies are needed to confirm the reliability of these subtypes, these findings and others can serve as useful tools in developing targeted treatments for AD. The clinical relevance of emerging endotypes will be deemed clinically relevant if they identify patients that respond better to a particular therapeutic (i.e., precision medicine) or help predict the natural course.

TOPICAL THERAPIES

Despite the advent of new systemic agents, topical therapies are still an essential component in the management of AD. Topical anti-inflammatory therapies for AD include the use of topical corticosteroids (TCS) as first-line therapy with topical calcineurin inhibitors (TCI) as an alternative to TCS in areas where TCS use is not recommended. Moderate-to-severe patients with AD, however, are often inadequately controlled with these agents. Additionally, the prolonged use of TCS may cause telangiectasia, skin atrophy, dyschromia, and adverse events. The use of TCI is often limited by burning and stinging (30). Given these limitations in traditional topical therapies, there remains a significant unmet need for patients. New topical agents are now being studied to modulate phosphodiesterase (PDE) 4, Janus kinase (JAK)-signal transducer and activator of transcription (STAT) signaling pathway, aryl hydrocarbon receptor (AhR), and the skin microbiome (**Table I**).

PDE4 inhibitors

Hanifin and colleagues (31) first made the observation that AD monocytes display overactive phosphodiesterase enzyme activity. Inhibition of PDE4 leads to an increase in cyclic adenosine monophosphate (cAMP), resulting in the down-regulation of inflammatory cytokines in chronic inflammatory skin diseases such as psoriasis and AD (32). Crisaborole, a topical PDE4 inhibitor was first approved in 2016 by the US Food and Drug Administration (FDA) for patients with mild-to-moderate AD over the age of 2 years. Two phase III trials showed

Table I. Novel topical targeted therapies of AD (in or beyond phase II trial)

Target	Agent	Mechanism	Phase status	Clinical trials
Phosphodiesterase 4 (PDE4)	Crisaborole/AN2728	PDE4 inhibitor	I/II completed	NCT01652885
			II completed	NCT03233529
				NCT01602341
			II completed	NCT03954158
			III completed	NCT02118766
				NCT02118792
			III ongoing	NCT04040192
			IV ongoing	NCT03868098
				NCT03539601
	MM36/OPA-15406	PDE4 inhibitor	II completed	NCT02945657
				NCT02068352
				NCT02914548
				NCT03018691
			III ongoing	NCT03961529
			III completed	NCT03911401
				NCT03908970
	Roflumilast	PDE4 inhibitor	II completed	NCT01856764
				NCT03916081
	AN2898	PDE4 inhibitor	II completed	NCT01301508
	Lotamilast/RVT-501/E6005	PDE4 inhibitor	I/II completed	NCT01179880
				NCT02094235
			II completed	NCT01461941
				NCT02950922
				NCT03394677
	DRM02	PDE4 inhibitor	II completed	NCT01993420
	LEO29102	PDE4 inhibitor	II completed	NCT01037881
Janus kinase (JAK)	Tofacitinib	JAK 1/3 inhibitor	II completed	NCT02001181
	Delgocitinib/JTE-052/LEO124249	JAK 1/3 inhibitor	IIa completed	NCT01037881
	Ruxolitinib/INCB18424	JAK 1/2 inhibitor	II completed	NCT03011892
			III ongoing	NCT03745651
				NCT03745638
Aryl hydrocarbon receptor (AhR)	Tapinarof/ WBI-1001/benvitimod/ GSK2894512	AhR agonist	I/II completed	NCT00837551
			II completed	NCT02564055
				NCT01098734
S. aureus	Roseomonas mucosa bacteria	Commensal interaction	I/II completed	NCT03018275
	Coagulase-negative Staphylococcus	Commensal interaction	I/II completed	NCT03151148
			II ongoing	NCT02144142

significant efficacy with 51% clear and 48% almost clear in the Investigator's Static Global Assessment (ISGA) score (33). A large vehicle effect, however, leads to a relatively large number needed to treat (NNT), ranging between 8 and 14. (34). This translates to between 8 and 14 patients are needed to be treated before one person achieves success over vehicle treatment (35). Improved signs of pruritus and good drug tolerability were reported amongst patients. Limited adverse events included pain, burning, and stinging. However, the clinical prevalence of these events are seemingly more common in clinical practice than that reported in trials. A study of crisaborole over 48 weeks confirmed its safety for longer-term use (36) but comparative efficacy data with other topical agents is currently lacking. A new study has been initiated to evaluate the efficacy of crisaborole compared to other topical agents like TCS and TCI (NCT03539601). MM36 (OPA-15406), another PDE4 inhibitor with high selectivity for PDE4B, at higher concentration showed significant improvement in Eczema Area and Severity Index (EASI) score at week 1 compared to placebo and persisted for 8 weeks (37). Various PDE4 inhibitors including roflumilast, AN2898, lotamilast, DRM02, and LEO29102 are currently undergoing phase II and phase III trials. Overall, topical PDE4 inhibitors appear to be a safe approach to long-term management of selected mild-to-moderate AD without the potential for significant systemic absorption or cutaneous atrophy.

JAK and other kinase inhibitors

JAK inhibitors are small molecules that inhibit the JAK-STAT signaling pathway. Although they have been mostly studied as systemic therapeutics for AD, topical applications have also shown promise in clinical trials. The JAK -STAT pathway has been implicated in the signaling of multiple AD-related cytokines such as IL-4, IL-5, IL-6, IL-12, IL-13, IL-22, IL-23, IL-31, IL-33, and IFN-γ (38–40). A JAK family of 4 receptor associated kinases (JAK1, JAK2, JAK3, and tyrosine kinase (TYK) 2) phosphorylate intracellular receptors and increase the production of a group of STATs, leading to the activation of targeted gene expression (**Fig. 2**). JAK inhibitors target different combinations of kinases with variable selectivity, resulting in overlapping but distinct inhibitory effects on various cytokine pathways. Spleen tyrosine kinase (SYK) is a non-receptor tyrosine kinase involved in the release of pro-inflammatory cytokines including IL-17, B cell activation, and keratinocyte differentiation (40). The SYK pathway plays an important role in Th17 signaling by recruiting Th17 cells to the skin along with inducing the production of CCL (C-C motif chemokine ligand) 20 (41). Consequently, targeting the JAK-STAT and SYK pathways downregulates multiple immune axes involved in the pathogenesis of AD (Th1, Th2, Th17, and Th22). The broader immune modulation of JAK inhibition holds the potential to bring greater efficacy. However, this theoretically results in an increase in potential adverse events as well.

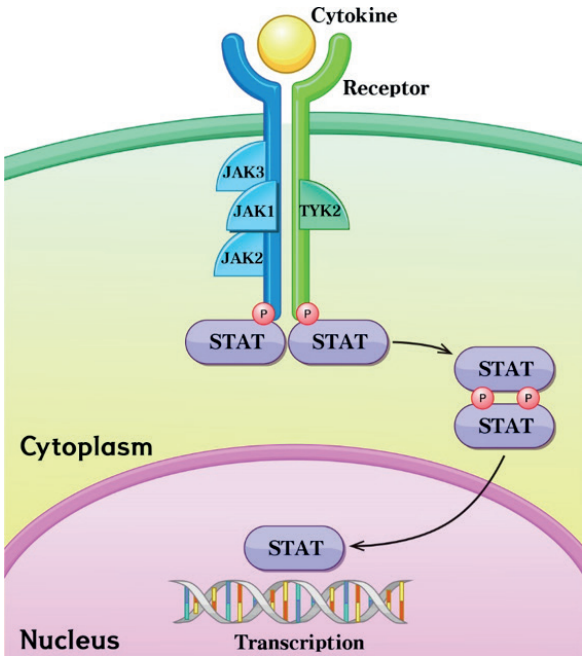

Fig. 2. JAK-STAT pathway. A cytokine binds to its cell surface receptor. A Janus kinase (JAK) family of four receptor associated kinases (JAK1, JAK2, JAK3, and tyrosine kinase (TYK) 2) phosphorylate intracellular receptors and increase the production of a group of signal transducer and activator of transcription (STAT). Phosphorylated STATs dimerize and translocate to the nucleus, leading to the activation of targeted gene expression.

Topical JAK inhibitors decrease IL-4 and IL-13 signaling pathways and enhance skin barrier functions in mouse AD models (42). A phase IIa trial investigating tofacitinib, a potent JAK1/JAK3 inhibitor, for patients with mild-to-moderate AD showed significant reduction of pruritus by day 2 and a large reduction in EASI score by week 4 (81% vs. 29% (placebo), $p<0.001$) (43). The application site reactions reported in two subjects were mild pain or mild pruritus. A controlled study of delgocitinib (JTE-052/LEO 124249), a pan JAK (JAK1-3,TYK2) inhibitor, showed significant improvement in the overall symptoms of AD by week 4, and low modified EASI (mEASI) and Investigator's Global Assessment (IGA) scores with a favorable safety profile (44). Improvements in pruritus were also observed by day 1, which was likely due to the inhibition of IL-31 signaling mediated by the JAK-STAT pathway (20) or possibly via direct effect of JAK inhibition on itch transmission by neurons (45). Improvements in mEASI score with the higher doses of delgocitinib were similar to the tacrolimus 0.1% ointment active control arm, although there was no statistical comparison (44). In an ongoing phase II trial, topical ruxolitinib (INCB018424), a potent JAK1/JAK2 inhibitor, showed significant efficacy in EASI score at week 4 in the cream 0.5% and 1.5% arms versus vehicle (46). Topical ruxolitinib at higher doses (1.5%) showed greater improvements in EASI score at week 4 than triamcinolone cream 0.1%. Other JAK inhibitors such as cerdulatinib (RVT-502), a

dual JAK and SYK inhibitor, and SNA-125, a JAK 3 and tropomyosin receptor kinase A (TrkA) inhibitor, are currently being evaluated in phase I/II trials of AD, however no data are available for review at this time.

AhR agonist

The AhR is a cytosolic ligand-activated transcription factor that is involved in both pro- and anti-inflammatory signaling pathways (47). It has the potential to impact the balance of Th17 and regulatory T (Treg) cell production and can restore epidermal barrier function (48, 49). Tapinarof (benvitimod/GSK2894512/WBI-1001), an AhR agonist, is a naturally derived molecule produced by the bacterial symbionts of entomopathogenic nematodes (50). In two phase II trials, significant improvements in EASI and IGA scores were seen at week 4 in patients with mild-to-moderate AD and significant efficacy in IGA scores of both 0.5% and 1% dosing groups at week 6 in patients with mild-to-severe AD (51, 52). In earlier studies of higher dose tapinarof at 2%, headache, diarrhea, nausea and/or vomiting were observed. This suggests the potential for systemic absorption at higher concentrations (53). Phase 3 studies are anticipated.

Commensal organisms

Cutaneous dysbiosis, characterized by a reduction in microbial diversity and an increase in colonization of *S. aureus,* has been shown to initiate and worsen the flare of AD (54). Recent research suggests a unique phenotype and endotype for patients colonized with *S. aureus*. Characteristics of *S. aureus*-colonized patients include more severe skin disease, reduced barrier function, increased serum lactate dehydrogenase (LDH) levels, increased allergen sensitization, elevated IgE levels, elevated eosinophil counts, and increased levels of various Th2 biomarkers such as TARC, periostin, and CCL26 (55). Increased *S. aureus* colonization has been proposed as a potential mechanism for disease progression and flare-up of AD. A recent open-label trial with topical application of *Roseomonas mucosa* for patients with AD found that the commensal bacterium provided patients with clinical improvement in AD severity and pruritus, and a reduction of TCS use (56). Another study reported that autologous transplantation of coagulase-negative *Staphylococci* enriched with novel anti-*S. aureus* peptides leads to a decrease in *S. aureus* colonization and clinical improvements in AD (57). Currently, a phase I/II trial using *Roseomonas mucosa* and a phase II trial testing coagulase-negative *Staphylococcus* are underway. These studies will help elucidate whether the dysbiosis in AD is a primary driver of the disease or merely a consequence of barrier dysfunction or type 2 inflammation. Should this approach provide efficacy, it is intriguing to speculate that transplanting beneficial live commensals could theoretically yield a remittive effect on the disease.

SYSTEMIC THERAPIES

Systemic treatments may be appropriate for pediatric and adult patients with moderate-to-severe AD whose disease is inadequately controlled with appropriate amounts of topical therapies. According to an International Eczema Council (IEC) consensus paper, the decision to commence or offer systemic treatments should involve an assessment of disease severity, an understanding of the impact on QoL, and include individual factors such as patient preferences, prior treatment history, financial considerations, and comorbidities (58). Traditionally, systemic therapies include phototherapy or systemic immunomodulators such as corticosteroids, cyclosporine, methotrexate, azathioprine, and mycophenolate mofetil. Given the risk of potential toxicities with traditional immunosuppressant long-term treatments, there is still an unmet need for safe and effective long-term therapies. Dupilumab, the first biologic drug approved for AD, has filled this large void for a safe and effective therapy for long-term use. Since the advent of dupilumab, a number of biologics and small molecule inhibitors are now being developed and investigated to provide alternatives to dupilumab (**Table II**).

Targeting Th2 pathway

IL-4 and/or IL-13 antagonists. IL-4 and IL-13 are the key mediators of Th2 inflammatory responses and are responsible for the production of IgE. Cell culture studies reveal increased IL-4/IL-13 levels that not only lead to the recruitment of additional inflammatory cells, but also disturb skin barrier function by inhibiting the production of barrier structural proteins like filaggrin, lipids and antimicrobial peptides, and encourage *S. aureus* colonization (57, 59). IL-13 is overexpressed in both lesional and non-lesional AD, and correlates with disease severity (10, 60). Dupilumab, a fully human monoclonal antibody (mAb), inhibits both the IL-4 and IL-13 signaling pathway by blocking their shared IL-4Rα receptor subunit (61). Dupilumab was approved to treat moderate-to-severe AD in adults in the US and Europe in 2017, and its approval was extended to patients with moderate-to-severe AD over the age of 12 years in the US in 2019 (62). In a phase III trial of identical design (SOLO1 and SOLO2), adult patients with moderate-to-severe AD who received dupilumab every other week showed improvement in disease at week 16, with the proportion of patients achieving a 75% reduction in EASI score (EASI-75) ranging between 44–51% versus placebo (12–15%) (24). Patients also reported improvements in their symptoms including pruritus, anxiety, and depression. They also reported an overall improvement in QoL. In another phase III study (LIBERTY AD CHRONOS), a year-long trial of dupilumab showed an improved disease activity with a good safety profile when combined with TCS exhibiting only local injection reactions and conjunctivitis as adverse events (63). A LIBERTY AD CAFÉ study with concomi-

Table II. Novel systemic targeted therapies of atopic dermatitis (AD) (in or beyond phase II trial)

Target	Agent	Mechanism	Route	Phase status	Clinical trials
Biologics					
T-helper 2	Dupilumab	Anti-IL-4Rα mAb	Subcutaneous	IV ongoing	NCT03411837
					NCT03293030
					NCT03389893
					NCT03667014
	Pitrakinra/Aeroderm	Anti-IL-4 mAb	Subcutaneous	IIa completed	NCT00676884
	Lebrikizumab	Anti-IL-13 mAb	Subcutaneous	II completed	NCT02340234
					NCT03443024
					NCT02465606
					NCT04178967
				III ongoing	NCT04146363
	Tralokinumab	Anti-IL-13 mAb	Subcutaneous	II completed	NCT02347176
					NCT03562377
				III completed	NCT03363854
					NCT03160885
					NCT03131648
				III ongoing	NCT03587805
					NCT03761537
					NCT03526861
	Tezepelumab/AMG157/ MEDI9929	Anti-TSLP mAb	Subcutaneous	IIa completed	NCT02525094
				II ongoing	NCT03809663
	GBR830	Anti-TSLP mAb	Subcutaneous	II completed	NCT02683928
				IIb ongoing	NCT03568162
	KHK4083	Anti-OX40 mAb	Subcutaneous	II ongoing	NCT03703102
	Nemolizumab/CIM331	Anti-IL-31RA mAb	Subcutaneous	II completed	NCT01986933
					NCT03100344
				II ongoing	NCT03921411
				III ongoing	NCT03989206
					NCT03985943
					NCT03989349
	Mepolizumab	Anti-IL-5 mAb	Intravenous	II terminated	NCT03055195
T-helper22	Fezakinumab/ILV-094	Anti-IL-22 mAb	Subcutaneous	II completed	NCT01941537
T-helper 1/ T-helper 17	Ustekinumab	Anti-IL-12/23p40 mAb	Subcutaneous	II completed	NCT01806662
					NCT01945086
	Secukinumab	Anti-IL-17A mAb	Subcutaneous	II completed	NCT02594098
					NCT03568136
	MOR106	Anti-IL-17C mAb	Subcutaneous	II terminated	NCT03568071
					NCT03864627
IgE	Omalizumab	Anti-IgE mAb	Subcutaneous	II completed	NCT01179529
				IV completed	NCT02300701
					NCT00822783
	Ligelizumab/QGE031	Anti-IgE mAb	Subcutaneous	II completed	NCT01552629
Interleukin (IL)-1α	Bermekimab/MABp1	Anti-IL-1α mAb	Subcutaneous	II completed	NCT03496974
				II ongoing	NCT04021862
Small molecules					
Janus kinase (JAK)	Barcitinib	JAK1/2 inhibitor	Oral	II completed	NCT02576938
				III completed	NCT03334422
					NCT03733301
					NCT03334396
				III ongoing	NCT03559270
					NCT03435081
					NCT03334435
					NCT03428100
					NCT03952559
	Upadacitinib/ABT494	JAK1 inhibitor	Oral	II completed	NCT02925117
				III ongoing	NCT03607422
					NCT03569293
					NCT03568318
					NCT03738397
					NCT03661138
	Abrocitinib/PF-04965842	JAK1 inhibitor	Oral	II completed	NCT02780167
				II ongoing	NCT03915496
				III completed	NCT03349060
					NCT03575871
					NCT03627767
					NCT03422822
				III ongoing	NCT03720470
					NCT03796676
	ASN002/Gusacitinib	JAK/spleen tyrosine kinase inhibitor	Oral	II completed	NCT03531957
				II terminated	NCT03654755
Phosphodiesterase (PDE) 4	Apremilast	PDE4 inhibitor	Oral	II completed	NCT02087943
					NCT00931242
Chemoattractant receptor-homologous molecules expressed on Th2 lymphocytes (CRTH2)	OC000459/ODC-9101	CRTH2 mAb	Oral	IIa completed	NCT02002208
	Fevipiprant/QAW039	CRTH2 mAb	Oral	IIb completed	NCT01785602
Histamine receptor	ZPL-389	H4R inhibitor	Oral	II completed	NCT02424253
				II ongoing	NCT03948334
					NCT03517566
Neuropeptide substance P and neurokinin 1 receptor (NK1R)	Tradipitant/VLY-686	NK1R inhibitor	Oral	II completed	NCT02651714
				III completed	NCT03568331
				III ongoing	NCT04140695
	Serlopitant/VPD-737	NK1R inhibitor	Oral	II completed	NCT02975206
				III ongoing	NCT03540160

tant use of TCS exhibited an EASI-75 of 63% at week 16 in moderate-to-severe adult AD who were refractory or intolerant to cyclosporine (64). Translational studies reveal that dupilumab reduces expression of Th2 immunity markers, Th17/Th22-related epidermal hyperplasia, and inflammatory cell infiltrates. It also enhances the expression of genes that control epidermal differentiation and barrier function, including genes for loricrin and filaggrin (65). Two meta-analyses demonstrated statistically significant increased efficacy and a well-tolerated safety profile for patients with moderate-to-severe AD on dupilumab compared to placebo (66, 67).

Dupilumab-induced conjunctivitis, or ocular surface disease, is a common (5–28% of patients) but poorly understood side effect (68). The conjunctivitis is usually mild to moderate in severity and can be treated with various topical anti-inflammatory approaches. For unknown reasons, the conjunctivitis associated with dupilumab therapy only occurs in patients with AD. This side effect was not observed in studies of asthma or chronic sinusitis (24). Ongoing mechanistic studies will hopefully shed light onto the etiology of this adverse effect.

Overall, dupilumab appears to be a safe therapy suitable for long-term use. Dupilumab does not appear to be immunosuppressive and has not been associated with increased overall infection rates. Studies reveal significantly reduced risk of serious or severe infections and bacterial non-herpetic skin infections compared to placebo (69). Dupilumab appears to correct AD skin dysbiosis – perhaps the mechanism that explains the observed protection against skin infections (65). Vaccination responses are also not affected by dupilumab therapy (70). No laboratory monitoring is required as no end-organ damage has been observed (70, 71). Dupilumab was also recently approved by the FDA for moderate-to-severe asthma with eosinophilic phenotype or oral corticosteroid-dependent asthma and chronic rhinosinusitis with nasal polyposis that are also driven by type 2 cytokines (62). Pitrakinra (Aeroderm), a biologic that targets only IL-4, has been tested in a phase IIa trial. However, no results have been reported and the status of further development is unknown.

IL-13 antagonists. IL-13 plays an important role in allergic inflammation and is expressed in both acute and chronic lesions of AD (72). Like IL-4, IL-13 induces keratinocyte to produce CCL26, thereby causing an accumulation of eosinophil at the inflammatory lesion (73). Lebrikizumab, an anti-IL-13 mAb, at 125 mg dose every 4 weeks achieved an 50% reduction in EASI score (EASI-50) of 82% at week 12 as compared to a placebo group response of EASI-50 of 62% at week 12 for patients with moderate-to-severe AD with concomitant mandatory TCS use twice daily ($p = 0.026$) (74) in a placebo-controlled phase II trial (TREBLE). In a recent press release from a phase IIb trial, patients treated with lebrikizumab at the 125 mg dose every 4 weeks and at the 250 mg dose every 2 or 4 weeks showed significantly dose- and frequency-dependent improvements in EASI scores compared to placebo at 16 weeks (75). Tralokinumab, another anti-IL-13 mAb, showed significant improvement in EASI and IGA scores in a phase II study, particularly in patients with high serum biomarker levels of IL-13 activity (76). Heavy use of concomitant TCS likely diminished the effect size when compared to placebo. Patients reported improvement in QoL and pruritus, and there were no significant adverse effects. A phase III trial (NCT03131648) using tralokinumab monotherapy without TCS is underway to better evaluate its efficacy. Overall, IL-13 inhibitors appear to be well tolerated and show an acceptable safety profile with limited adverse events, including upper respiratory infections (URIs), nasopharyngitis, and headaches that are common but mild and self-limited (74, 76). Phase III data will be important to reveal whether conjunctivitis is an IL-13 class effect or is limited to only certain biologics targeting the pathway.

Inhibitors of the TSLP-OX40 axis. The TSLP-OX40 axis is also known to play an important role in initiating the Th2 allergic inflammatory response (77). Keratinocyte-derived TSLP activates dendritic cells to induce the production of Th2 immunity cytokines such as IL-4, IL-5, IL-13, and tumor necrosis factor (TNF)-α (19). IL-33 appears to amplify TSLP's effect of inducing expression of OX40 ligand on dendritic cells (78, 79). Tezepelumab (AMG157/MEDI9929), an anti-TSLP mAb, is regarded to be a potential suppressor of the Th2 pathway. In a phase IIa trial (NCT02525094), however, it did not show a significant EASI-50 response compared to placebo at week 12 in patients with moderate-to-severe AD, presumably due to heavy concomitant TCS use in the placebo group (80). In a phase IIa trial, GBR 830, an anti-OX40 mAb, was well tolerated and showed an acceptable safety profile, decreased inflammatory serum biomarkers, and significant improvement in EASI-50 versus placebo (81). In a phase I trial (NCT03096223), patients treated with KHK4083, an anti-OX40 mAb, every 2 weeks for 6 weeks showed a continuous reduction in EASI score even at week 22 suggesting a long-lasting response (82). An additional phase II trial (NCT03703102) is underway. Currently, there have been several proof-of-concept (PoC) trials testing various TSLP-OX40 axis-related inhibitors including a TSLP receptor antagonist MK-8226 (NCT01732510), an anti-IL33 mAb Etokimab (ANB020) (NCT03533751).

IL-31 receptor antagonists. Interruption of the itch-scratch cycle is one of the main goals in managing AD. IL-31, dubbed the "itch cytokine" is predominantly produced by activated Th2 cells and mast cells. The IL-31 receptor (IL-31R) is expressed on C-fibers of peripheral neurons (83). IL-31 is significantly increased in acute and chronic AD and plays a critical role in pruritus and disease activity (84). Nemolizumab, an anti-IL-31RA

mAb, showed a significant reduction in visual analogue scale (VAS) scores for pruritus in patients with moderate-to-severe AD in a 12-week phase II trial (85). In another long-term phase II trial, it showed significant and continued itch suppression and was well-tolerated over the 64 weeks trial with limited adverse events, including nasopharyngitis, AD exacerbations, and URIs (86). A recent phase IIb trial revealed that nemolizumab significantly improved EASI, IGA and itch scores at week 24 versus placebo and was well tolerated, with the 30 mg dose being most effective (87). BMS-981164, an anti-IL-31 mAb, was completed as a phase Ib trial (NCT01614756), but results have not yet been published. KPL-716 is an anti-oncostatin M receptor beta mAb (anti-OSMRβ) inhibiting both IL-31 and oncostatin M, an inflammatory signal implicated in pruritus, Th2 inflammation, and fibrosis. KPL-716 showed good safety and tolerability as well as an anti-pruritic effect in patients with moderate-to-severe AD in a phase Ia/Ib study (88). Additional phase II studies (NCT03858634, NCT03816891) for chronic pruritic diseases and prurigo nodularis are currently underway.

IL-5 antagonist. Eosinophils are speculated to play a large role in the pathogenesis of AD due to their high prevalence in tissue and blood found throughout the course of the disease. IL-5 induces the migration of eosinophils within inflamed tissue of patients with Th2 allergic inflammatory diseases like asthma and eosinophilic esophagitis (89). Mepolizumab, an anti-IL-5 mAb recently approved for severe eosinophilic asthma, was tested in a pilot study for AD but did not reach statistical significance in SCORing Atopic Dermatitis (SCORAD) score, pruritus scoring, and TARC levels despite decreasing the peripheral blood eosinophilic count (90). Given its efficacy in treating eosinophilic asthma, a phase II trial for moderate-to-severe AD had been implemented to test the effectiveness in the AD subtype with eosinophilia but was terminated early, as this study reached pre-determined futility criteria following interim analysis.

Targeting Th22 pathway

IL-22 promotes epidermal hyperplasia and disrupts barrier function by inhibiting keratinocyte differentiation and tight junction production (91). IL-22 is significantly increased in AD lesions and expression levels correlate with disease severity (60). In a phase II trial funded by the National Institutes of Health, fezakinumab, an anti-IL-22 mAb, did not reach significance in reducing the SCORAD score compared to placebo, but a sub-analysis of severe AD (SCORAD score >50) showed significant improvement with fezakinumab versus placebo (92). It was overall well-tolerated with a limited safety profile, including URIs as adverse events. A recent study revealed fezakinumab had a better efficacy in patients with a higher IL-22 baseline, suggesting an effect of IL-22 blockade on multiple inflammatory pathways encompassing Th1, Th2, Th17, and Th22 axis (93). Treatment antagonizing IL-22 could be a promising option amongst African American, Asian, intrinsic, and pediatric AD subtype patients showing dominant Th22 polarization and/or psoriasiform Th17/Th22 endotypes (25).

Targeting Th17 pathway

Some phenotypes such as Asian, intrinsic, pediatric, and elderly AD show higher expression of Th17-related markers like those found in psoriasis (25). Thus, these patients may be potential candidates for IL-17/IL-23 targeting therapies. IL-23 initiates both Th17 and Th22 pathways and is significantly decreased after AD treatments (94). The IL-17 family consists of 6 members of interleukins, IL-17A-F. Among them, IL-17A and IL-17C show complementary cooperation between keratinocytes and T cells, leading to the amplification of cell immune responses (95). Unlike IL-17A which is produced by Th17 cells and innate immune cells, IL-17C appears to be a keratinocyte-derived cytokine (96). Despite showing promise in several reports of AD (97, 98), ustekinumab, a mAb antagonizing IL-12/IL-23p40 with efficacy in psoriasis, did not demonstrate significant improvements over placebo with concomitant TCS use in a phase II trial for AD (99). In another phase II trial in Japan, patients with severe AD treated with ustekinumab 45 mg and 90 mg did not show meaningful efficacy versus placebo, although it was generally well-tolerated (100). MOR106, an anti-IL-17C mAb, exhibited an EASI-50 of 83% at week 4 at the higher dose and the treatment response maintained over 2 months after stopping treatment in a phase I trial (NCT02739009) (101). MOR106 and secukinumab, an anti-IL-17A mAb, are being tested for AD in phase II trials.

IgE antagonists

IgE is a hallmark for atopic diseases and is a downstream product of the Th2 axis. It is implicated in basophilic activation and the initiation of sensitization in allergic inflammatory cascades. IgE is also present on the cell surface of inflammatory dendritic cells (IDECs) characteristic of AD (102). Extrinsic AD subtypes defined by high levels of IgE and pediatric AD subtype with a tendency for atopic march early on in life may be good targeted candidates for anti-IgE drugs (25). However anti-IgE treatments in AD have shown largely negative results. Omalizumab is a recombinant humanized monoclonal IgG1κ antibody used in chronic spontaneous urticaria and asthma. Despite some case series demonstrating favorable efficacy for AD, omalizumab did not show improved efficacy over placebo in an RCT (103). A phase IV trial for severe pediatric AD was completed, but results have not yet been posted. In a phase II trial, patients treated with ligelizumab (QGE031), a high affinity anti-IgE Ab,

every 2 weeks for 12 weeks did not show a significant reduction in the severity for AD compared to placebo (104). The phase I trials using other anti-IgE agents, such as MEDI4212 (NCT01544348) and XmAb7195 (NCT02148744) have been completed, but show limited potential (105, 106). To date, anti-IgE approaches do not appear to have significant clinical activity in AD.

IL-1α antagonist

IL-1α, a prototypical pro-inflammatory cytokine, is an attractive target as its major reservoir appears to be keratinocytes, which may play a key role in the initiation of the inflammatory cascade found in AD (107). IL-1α also enhances matrix metalloproteinases activity, thereby leading to epithelial barrier breakdown (108). Bermekimab (MABp1) is a naturally derived human mAb that shows immunomodulating activity by blocking IL-1α activity. The drug failed in a phase III for colorectal cancer, but is now being evaluated for inflammatory skin diseases like hidradenitis suppurativa and AD. A phase II trial of 38 patients with moderate-to-severe AD revealed significant improvements at all clinical endpoints (109). Controlled studies are needed to better assess the potential of this novel therapy in AD.

JAK inhibitors

JAK inhibitors potentially have a wide application in inflammatory skin diseases including AD. JAK is a key mediator in signaling numerous cytokines involved in the pathogenesis of AD, including IL-4 and IL-13. Notably, IL-4 requires signaling through JAK1/3 while IL-13 signals through JAK1/TYK2 (110). The JAK-STAT pathway may play an important role in mediating both inflammation and pruritus in AD (40). Baricitinib is a potent oral JAK1/JAK2 inhibitor approved in the EU and the US for the treatment of rheumatoid arthritis. In a phase II trial, patients with moderate-to-severe AD showed significant improvements in EASI-50 at week 16, 61% (4mg) versus 37% (placebo) when treated with baricitinib in combination with TCS (111). Patients also reported tolerating the medication well with improvements in pruritus and sleep. Dose-dependent adverse events including headache, increased creatine phosphokinase, and nasopharyngitis were reported. Two phase III trials BREEZE-AD1 and BREEZE-AD2 confirmed significant clinical efficacy in both baricitinib doses of 2 mg and 4 mg with a good safety profile for patients with moderate-to-severe AD (112). A number of phase III trials for baricitinib that include combination therapy with TCS and longer-term endpoints are still being recruited. Upadacitinib (ABT-494), a selective oral JAK1 inhibitor, is currently underway in clinical trials for rheumatoid arthritis, Crohn's disease, ankylosing spondylitis and psoriatic arthritis. In a phase IIb trial, upadacitinib showed reduction in pruritus as early as week 1 and a significant dose-dependent improvement in EASI score at week 2 in patients with moderate-to-severe AD (113). Adverse events included URIs and AD exacerbations. Further phase III trials including younger patients with moderate-to-severe AD are also currently underway. In a phase IIb trial, abrocitinib (PF-04965842), a selective oral JAK1 inhibitor, showed dose-dependent improvement in EASI and IGA scores at week 12 versus placebo (40). The top-line results detailed in a press release of a phase III trial of abrocitinib showed statistically significant results with good tolerability and no unexpected safety events (114). Other phase III trials with long-term treatment periods are now being investigated. In a short-term clinical I trial (NCT03139981), ASN002 (Gusacitinib), a dual inhibitor of pan-JAK (JAK1-3, TYK2) and SYK, showed improvement in clinical severity at week 4 with a reduction in Th2/Th22 biomarkers (115). Another phase II trial with longer duration is still ongoing. Oral tofacitinib in a small open-label study showed impressive reductions in SCORAD with no adverse events (116).

PDE4 inhibitor

PDE4 inhibitor increases intracellular cAMP levels, leading to a down regulation of a number of cytokines involved in AD including IL-2, IL-5, IL-13 IL-17, IL-22, IL-31, and IL-33 (117). PDE inhibitor also upregulates the anti-inflammatory cytokine IL-10. Apremilast, an oral PDE4 inhibitor approved for psoriasis and psoriatic arthritis, showed promising results in an AD pilot study (118). However, in a phase II trial, apremilast showed no significant change in EASI score at week 12 at a dose of 30 mg compared to placebo. Although apremilast at a dose of 40 mg showed clinical efficacy and decreased Th17/Th22 related biomarkers, it was discontinued due to serious adverse event like cellulitis (119).

Chemoattractant receptor-homologous molecules expressed on Th2 lymphocytes antagonists

Chemoattractant receptor-homologous molecules expressed on Th2 lymphocytes (CRTH2) is a prostaglandin D2 receptor that is expressed on Th2 cells, eosinophils, and basophils. It stimulates the initiation of Th2 cell migration in the skin (120). Two PoC phase II trials for two CRTH2 antagonists, OC000459 (ODC-9101) and fevipiprant (QAW039) had been completed, but results did not demonstrate efficacy (121, 122).

Histamine receptor type 4 antagonists

Histamine (H) is a known itch-inducing mediator. Yet, the roles of H1 and H2 blockade in AD and AD-associated itching has been rather disappointing (123). Histamine receptor type 4 (H4R) is expressed on Th2 cells, Th17 cells, keratinocytes, and sensory neural cells. H4 stimulation also stimulates IL-31 production (124). JNJ-

39758979, an H4R antagonist, was terminated early in a phase IIa trial due to serious adverse events including agranulocytosis (NCT01497119) although it did show significant reduction in pruritus compared to placebo (125). In a phase II trial testing ZPL-389, another H4R antagonist, significant reductions in EASI and SCORAD scores were found at week 8 compared to placebo for patients with moderate-to-severe AD with concomitant use of TCS. However, there was no significant reduction in pruritus (126). Additional phase II trials of ZPL-389 are still ongoing.

Neuropeptide substance P and neurokinin 1 receptor antagonists

Neuropeptide substance P and neurokinin 1 receptor (NK1R), the receptor for substance P, is associated with AD disease activity (127). The NK1R antagonist prompts decreased scratching behavior in AD mouse models (128). In a PoC phase II trial for patients with AD and chronic pruritus, patients treated with oral tradipitant (VLY-686) for 4 weeks experienced a significant reduction in pruritus VAS from baseline ($p < 0.0001$) (129). A phase III trial for tradipitant is currently underway. In a phase II trial involving AD patients with severe pruritus, subjects taking oral serlopitant (VPD-737) for 6 weeks revealed numeric differences in pruritus scores compared to placebo. However, the differences were not statistically significant (130).

CONCLUSION

Despite its high prevalence worldwide, effective management of AD is complicated due to its multifaceted pathophysiology, variable clinical manifestations, and chronic course of the disease. The success of dupilumab in AD confirms the central importance of type 2 cytokines in the pathophysiology of AD. In addition to type 2 cytokines, certain phenotypes of AD may be driven by additional cytokine pathways. However, data to date attempting to specifically target cytokines outside of the type 2 axis have largely been unsuccessful. Broad acting JAK inhibition may help patients with AD that are driven by more complex cytokine endotypes. Further data using large-scale and longer-term clinical trials with proper outcome measures that assess signs, symptoms, quality-of life and long-term control as recommended by the HOME initiative (www.homeforeczema.org) are needed in order to create tailored and personalized treatments for AD. The results of studies for several other promising approaches targeting inflammation, the microbiome, itch, and PDE4 are eagerly awaited.

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REVIEW ARTICLE

Prevention of Atopic Dermatitis

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Despite advances in atopic dermatitis (AD) treatments, research into AD prevention has been slow. Systematic reviews of prevention strategies promoting exclusive and prolonged breastfeeding, or interventions that reduce ingested or airborne allergens during pregnancy and after birth have generally not shown convincing benefit. Maternal/infant supplements such as Vitamin D have also not shown any benefit with the possible exception of omega-3 fatty acids. Systematic reviews suggest that probiotics could reduce AD incidence by around 20%, although the studies are quite variable and might benefit from individual patient data meta-analysis. Skin barrier enhancement from birth to prevent AD and food allergy has received recent interest, and results from national trials are awaited. It is possible that trying to influence major immunological changes that characterise AD at birth through infant-directed interventions may be too late, and more attention might be directed at fetal programming *in utero*.

Key words: atopic dermatitis; atopic eczema; eczema; prevention.

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SIGNIFICANCE

Just like we can prevent infectious diseases like polio, it should be possible to prevent eczema (atopic dermatitis), food allergy and asthma. Most things that have been tried so far to prevent eczema including exclusive breastfeeding, timing of starting solids, supplements like Vitamin D and reducing house dust mite do not seem to work. Taking probiotics (friendly gut bacteria) during pregnancy probably reduces the risk of eczema by around 20%, although we are still not sure what combination is best. New research is trying to find out if special creams that make a baby's skin barrier stronger can prevent eczema.

Despite the familiar adage that "prevention is better than cure", prevention of atopic dermatitis (AD) has been a relatively neglected topic of research until recently. A PubMed search (using the terms [atopic dermatitis OR eczema] AND treatment (August 14th 2019) revealed 19,755 hits, compared with just 3,150 when disease terms were combined with "prevention". Reasons for lack of research could include a lack of interest in population-based research in favour of basic science (**Fig. 1**), lack of research skill capacity in prevention research, lack of funding and a limited choice of identifiable risk factors that are amenable to public health manipulation. However, the number of AD prevention studies has increased over the last 10 years, especially in the field of probiotics and interventions to enhance the skin barrier. Basic science discoveries into the human microbiome and genetics of AD may have played a part in contributing to this recent trend (1, 2). Whilst identifying risk factors that can be manipulated is an essential part of prevention research, understanding the mechanisms by which the effects of prevention are mediated is interesting but not essential. For example, the benefits of stopping smoking to prevent lung cancer became apparent from simple epidemiological research long before the mechanisms and precise carcinogens were discovered (3). Prevention of disease is arguably a much more logical and cost-effective way to manage the burden of a disease such as AD than focussing solely on drug treatment of sick individuals who seek medical help after a long chain of irreversible pathological events (**Fig. 2**). Whilst some drugs such as

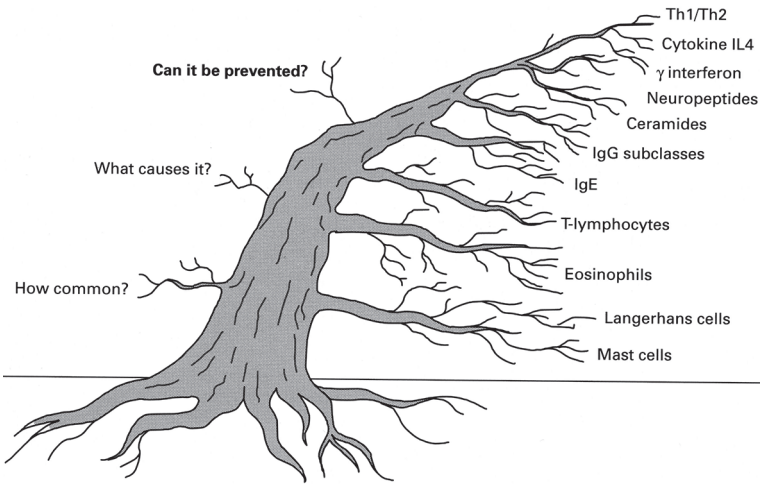

Fig. 1. A skewed interest toward cellular and molecular atopic dermatitis (AD) mechanisms relative to research into AD populations. Research into AD over the last 50 years has been dominated by interest in cells rather than broader questions such as whether disease prevention is possible.

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penicillin for streptococcal infection can be curative, most only modify rather than cure chronic diseases like AD, they are often expensive, and all are associated with potential adverse effects.

This article attempts to critically review the current state of science on the prevention of atopic dermatitis. Throughout this article, we will refer to the disease of interest as AD, which is synonymous with atopic eczema or just "eczema" (4). We use the term atopic dermatitis to describe the clinical phenotype, rather than the scientific definition of clinical phenotype plus evidence of IgE sensitisation to environmental allergens. We start by introducing the reader to key considerations when designing or critically appraising studies of AD prevention, using our direct experience in designing and running a randomised controlled trial (RCT) of emollients to prevent AD. We then explore the main interventions that have been used to try and prevent AD such as maternal and infant dietary restrictions or supplements, aeroallergen avoidance and approaches designed to enhance the external skin barrier. The authors have chosen to use systematic reviews of evidence and RCTs as the evidence source where possible. Systematic reviews were harvested from the Centre of Evidence-Based Dermatology international collection of systematic reviews which is updated monthly by a senior information scientist (Dr. Douglas Grindlay) (5). Rather than summarise all 102 systematic reviews on AD prevention in this collection, we instead refer to overviews of systematic reviews or the most recent and comprehensive systematic reviews where possible (6, 7). We used the Global Resource for Eczema Trials (GREAT) database for RCTs that might not yet be included in systematic reviews (8).

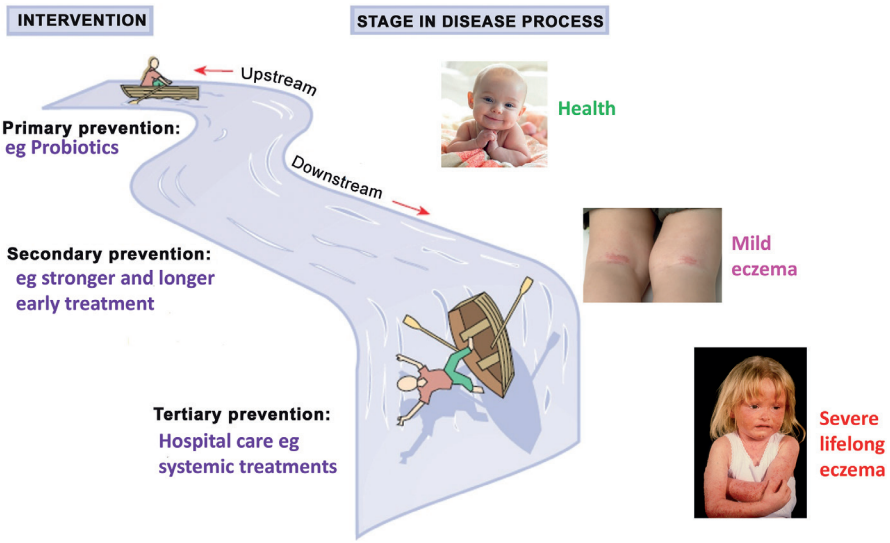

Fig. 2. Where is intervention most effective? Although the concept of prevention of atopic dermatitis is rarely discussed at international meetings, an upstream approach is a far more logical approach to reduce the burden of disease at a population level than the current approach of treating sick individuals with expensive drugs who present to secondary care after a long chain of pathological events.

SOME KEY BASIC CONSIDERATIONS

The power of prevention

Because prevention strategies act at a population level, their power is often not appreciated by individuals compared with treatments for a disease. Yet the power of prevention is potentially huge. In his article entitled "The power of prevention and what it requires" Woolf draws our attention to the fact that whereas new diabetes drugs that reduce glycohemoglobin levels by 0.5% often make the headlines, exercise, that can lower the incidence of diabetes by 50%, rarely achieves such publicity (9). The conquest of many infectious diseases such as diphtheria, smallpox, polio and measles are testament to the power of prevention, yet individuals who would have contracted these diseases are seldom "grateful" to those developing and implementing vaccines as it is unclear who would have contracted the disease in the first place. The recent re-emergence of measles due to misguided beliefs about vaccine safety, termed "vaccine hesitancy", are timely reminders of the "invisible" and powerful effects of population-based interventions (10).

Primary, secondary and tertiary prevention

Primary prevention typically refers to intervening before health effects occur. Secondary prevention implies detecting a disease at an early stage to prevent worsening, whereas tertiary prevention is the reduction of symptoms or improvement in quality of life of those with established disease – i.e. where health care professionals normally operate (11).

Application of the Participant, Intervention, Comparator and Outcomes framework to atopic dermatitis prevention studies

Participant, Intervention, Comparator and Outcomes (PICO) is a framework used in evidence-based medicine to understand the structure of RCTs and is useful when considering the design and critical appraisal of AD prevention trials (12).

Participants. Most AD prevention studies target a high-risk population e.g. babies born to families with a first-degree relative with AD or associated allergic diseases such as asthma, hay-fever or food allergy. The advantage of this approach is that parents who have experienced AD themselves or witnessed it in family members are often highly motivated (during pregnancy or soon after) to undertake interventions that could prevent AD in their new

baby. The disadvantage is that if the selected population is too narrow, the intervention may have a limited overall population impact. However, tackling an entire population such as all newborns is challenging, especially if the behaviour change modification is substantial, as parents will be less motivated to act on something that will be of little perceived benefit to their child. This phenomenon is known as the prevention paradox – a term coined by Rose to denote "a measure that brings large benefits to the community offers little to each participating individual" (13). **Fig. 3** illustrates the possible trade-off between high and low risk approaches to AD prevention suggested previously (14).

Intervention. An essential step in the prevention of any disease is a thorough knowledge of risk factors that can be manipulated. For example, filaggrin gene mutations cannot be directly manipulated *in utero* at present (although it may be possible in time) whilst a reduction in house dust mite in the home environment is achievable. Another key consideration is the acceptability of interventions given that healthy people are being asked to undergo elaborate changes to their lives in order to prevent disease in a proportion of people – the identity whom will remain unknown to them. Here, there is often a trade-off between intensity of intervention which might achieve a larger effect (such as applying emollient twice a day to their child for 2 years, wash only in soft water and use no soap) versus those that are likely to have wider population reach (such as advice to use emollients once daily for the first year of life as in the BEEP trial) (15). Testing acceptability of interventions is essential before proceeding to full scale evaluation (16). Assessing safety is paramount in prevention studies. Whilst individuals with severe AD might accept the risk of nausea and liver disease from methotrexate therapy, healthy individuals will have a low threshold for rejecting interventions with even small risks, such as the slipping on emollients spilt on a bathroom floor. Furthermore, minor adverse effects such as transient stinging after emollient application can reduce adherence to an intervention.

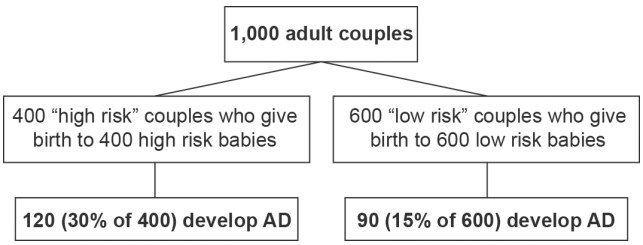

Fig. 3. Hypothetical example of the prevention yield from a high risk vs low risk prevention approach for atopic dermatitis. Depicts an average Western population where 40% of 1,000 adult couples have a strong family history of atopy and 60% do not. If 30% of the high risk babies develop AD compared with 15% without such a family history, a high risk approach would only prevent 57% (120/120+90) of AD cases at a population level. Adapted from Williams HC. Atopic Dermatitis. In: Williams HC, Strachan DP (eds). The Challenge of Dermato-Epidemiology. Boca Raton, CRC Press Inc., 1997.

Comparator. In the absence of a clear reference standard of an effective active treatment, control interventions for AD prevention trials are typically "standard care" (which is often not defined), an attention control, or some form of placebo (e.g. inactive probiotics). Convincing parents with a family history of AD to take part in a study with a 50:50 chance that their new baby will be allocated to the "no treatment" group can be challenging, and unless equipoise is carefully explained, parents may drop out if they don't get the "new active" intervention. Feasibility studies that test randomisation and retention are essential and offer the opportunity to develop patient information materials with patients that imply active monitoring and altruistic rewards to overcome the notion of "control neglect" that can result in resentful demoralisation (17).

Outcomes. Whereas clinical trials of people with AD (prevalent cases) seek to reduce disease severity, one is trying to prevent new (incident) cases from developing in a prevention study. There is a lack of research on defining an incident case of AD. Simpson et al. (18) undertook a systematic review of definitions of an incident case of AD used in prevention studies. Of 102 included studies, 27 did not define an incident case, 28 used the Hanifin & Rajka criteria (19), and 21 used definitions unique to that study without referencing the source. It is important to note that "chronic relapsing course" (a major criterion for the Hanifin & Rajka criteria), whilst acceptable for measuring cumulative incidence, is problematic when defining a new case which, by definition, has not yet become chronic. Yet diagnosing AD confidently in a baby on the first day they develop an eczematous rash is also fraught with problems as transient irritant eczematous dermatoses (which are probably not true AD) are common in infancy. Simpson et al. (20) suggested a compromise whereby the UK refinement of the Hanifin & Rajka criteria are used to denote a continuous or intermittent itchy skin condition lasting at least 4 weeks.

Ideally outcome assessment should be separated from the intervention period by a clear margin to separate treatment effects from prevention effects. For example, in the two small preliminary studies that suggested emollients might prevent AD, outcomes were assessed at the end of the intervention period, making it difficult to assess whether the apparent benefit was due to emollients preventing AD or actively treating new mild AD (16, 21). This is why the main BEEP trial of emollients used during the first year is assessing the primary outcome of AD (those fulfilling the UK refinement of the Hanifin & Rajka criteria in the last year) at the age of 2 years (15). Whilst complete prevention of disease is the ultimate goal, prevention of more severe forms of the disease (which cause the most morbidity and result in most healthcare usage) is also an important goal in AD prevention trials. Because the shape of AD prevalence in any population is skewed to the left (**Fig. 4**), even small shifts in the reduction of population severity can result in large gains in absolute terms for the number switching from severe to moderate or mild to very

mild/subclinical disease. Time to onset of AD is another outcome that can be considered although it is debatable whether simply delaying onset of a miserable disease to an older age is really a bonus. Given that AD is closely related to other "atopic" diseases such as food allergy, asthma and hay fever, AD prevention studies also need to evaluate whether benefits are seen in these diseases too. Measuring other atopic diseases present their own challenges, e.g. true food allergy has a low incidence making it unlikely that beneficial effects will be precisely measured even in large studies, and conditions like asthma have a later age of onset adding to the cost of following up individuals from RCTs that start at birth to older ages.

Reducing bias. In addition to standard approaches to reduce RCT biases such as registration of study protocols before recruitment starts and ensuring randomisation is truly random and concealed, two biases require special consideration in AD prevention trials. The first is performance bias which results from treating intervention and control groups differently. More attention given to the intervention group can result in different ancillary behaviours that can affect AD risk, so it is important that both groups are treated in the same way in terms of regularity of contact and incentives from the research team, and any post-randomisation behaviours that could confound the study result are recorded. Sometimes such behaviours can include contamination of the intervention in the control group (because they think they are missing out on something beneficial), which can be a particular problem if the intervention is something that can be easily accessed by participants without the need for healthcare professionals, such as reduction of house dust mites in the home. Contamination should therefore be measured and explored in the analysis. A second challenge lies in the fact that because many interventions such as emollient application or installing a water softener cannot be blinded, it is essential to include some form of objective outcome assessment (e.g. visible eczema recorded by investigators blinded to intervention status) to mitigate the risk of information bias. Studies should present findings as absolute risk reductions as well as the more impressive sounding relative risk reductions in order to provide a more realistic indicator of population benefit.

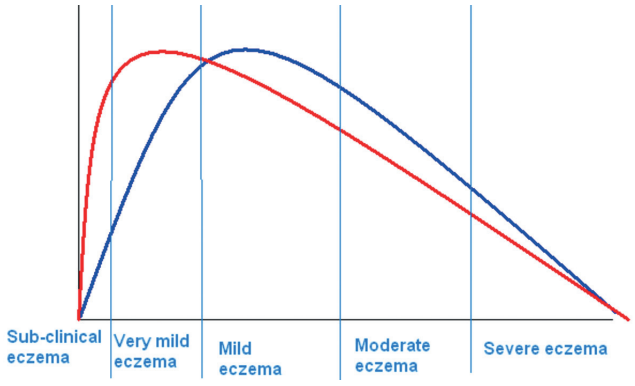

Fig. 4. Schematic representation of atopic dermatitis severity (x-axis) versus number with atopic dermatitis in two hypothesized populations. Even if atopic dermatitis cannot be prevented completely, shifting the population severity distribution of disease to the left (red curve) could have a huge impact on pushing more into subclinical disease and reducing the absolute proportion with severe disease who suffer the most and who consume most health resources.

THE EVIDENCE

Primary prevention

The 2011 overview of systematic reviews of primary prevention. In an attempt to reconcile the increasing number of Cochrane and non-Cochrane systematic reviews on AD prevention, a group (including the two authors) undertook an overview of all such systematic reviews in 2011 (search date up to August 2010). Quantitative and qualitative methods were used to collate and combine data where possible using Cochrane methods. Included reviews had to include some quantitative data that could be combined, search date within the last 5 years, and included participants between the ages of zero and 18 years. Seven systematic reviews containing 39 RCTs and 11,897 participants met the inclusion criteria. All 7 reviews were considered methodologically sound, although the data from the review on probiotics had to be re-analysed as data from one trial had been included more than once in the same meta-analysis. Interventions included use of hydrolysed formula milk (extensive and partial), extended duration of exclusive breastfeeding, dietary supplementation with omega-3 and omega-6 oils, maternal dietary antigen avoidance during pregnancy, lactation or both, soy formula milks, along with prebiotics and probiotics. Participants were from a mixture of high and lower risk families, although risk was rarely adequately defined. None of the pooled interventions showed clear evidence of benefit for AD prevention. A subgroup analysis of those at high risk of developing AD based on just one RCT found that prebiotics (ingested substances that favour the growth of beneficial bacteria in the gut) decreased AD incidence by 58% (RR: 0.42; 95% CI: 0.21, 0.84) compared with no prebiotics. Data on whether those developing AD were truly atopic was missing from most of the studies, and in those that did, there was no evidence that the interventions decreased atopy. One non-randomised study suggested that prolonged exclusive breastfeeding (at least 6 months) reduced AD incidence by 60% (RR 0.40, 95% CI 0.21 to 0.78). Despite the lack of any convincing signals for any of the interventions tested, the risk estimates for most interventions had low precision, indicating that some interventions with no evidence of benefit could still be useful.

The post 2011 overview era

Interventions that are ingested by mothers and/or infants. Also known as the "inside out" approach, ingested maternal/infant interventions include exclusive breastfeeding,

delay or early introduction of foods other than milk, dietary restrictions, and dietary supplements. Although breastfeeding (exclusive or prolonged) has clear benefits for infants, a systematic review of 16 moderate quality observational studies suggests that it does not appear to be protective of AD (22). One large cluster RCT (the PROBIT trial in Belarus) that promoted breastfeeding found a reduction in self-reported flexural eczema but not lung function, a finding that needs to be replicated (23). Around a half of milk feeding studies have been judged to be at high risk of bias (24). A Cochrane review of 5 trials failed to show any benefit of maternal avoidance of allergenic foods for AD prevention (25). A 2019 systematic review of mainly observational studies of complementary feeding (whereby other foods and drinks complement human or formula milk) found no clear evidence between the age at which complementary feedings is started and the risk of AD, food allergy or asthma (moderate evidence) (26). The same review found limited to strong evidence that introducing allergenic foods in year one of life to try and induce tolerance does not increase AD or food allergy risk, but may prevent egg and peanut allergy. The one well-conducted RCT included in the review found no benefit for AD prevention from early introduction of allergenic foods (27).

Interest in vitamin D supplementation as a possible preventative intervention stems from the association between low vitamin D levels and increased incidence and severity of AD. Vitamin D is also known to have a regulatory influence on skin barrier function and the immune system and skin barrier function, both of which are involved in AD development (28). A 2017 systematic review (search date January 2016) found one RCT and 3 non-RCTs that addressed vitamin D supplementation in women and children as a means of preventing allergic diseases found no clear evidence of benefit but with low certainty of evidence (29). A more recent and well conducted RCT found no clear benefit of infant vitamin D supplementation in the primary prevention of AD (30). A systematic review of omega-3 long-chain polyunsaturated fatty acids (such as from fish) intake during pregnancy found mixed results for AD prevention from observational studies, but a possible protective effect in the 3 included RCTs for early onset AD (31).

The evidence that ingested probiotics (non-pathogenic live bacteria or yeasts that can restore a dysfunctional pro-inflammatory gut microbiome) or prebiotics (non-digestible food ingredients that encourage beneficial bacteria to thrive) or both (synbiotics) can prevent AD is gathering momentum (32). The field is complicated as probiotics and prebiotics refer to a very wide range of ingredients, and they can be given to the mother during pregnancy, during lactation, to the infant after birth and various combinations of these and for different periods, leading to considerable heterogeneity which impacts on the ability to combine studies. One systematic review exploring the possible health benefits of yoghurt consumption among infants and toddlers that included two older cohort studies suggested a possible benefit for AD prevention, and called for new studies that evaluated such foods in a more contemporary setting (33). A systematic review in 2019 of 22 pooled trials published between January 2008 and May 2018 showed a reduction in AD incidence (RR 0.81, 95% CI: 0.70–0.93) for those receiving probiotic supplementation during pregnancy and/or infancy. Subgroup analysis suggested that benefits were strongest for those receiving *Lactobacillus* and *Bifidobacterium*, for those in whom probiotic supplementation occurred during pregnancy and infancy and in preventing AD developing in the first two years of life rather than later (34). Sources of study heterogeneity was also assessed and found to be mainly accounted by follow-up time (I^2 62.7%) and length of probiotic supplementation (I^2 53.5%). A more extensive systematic review that pooled 28 studies (27 good quality RCTs and one high quality cohort study, search date from inception to March 2018) showed a beneficial effect on AD prevention for probiotics compared with controls (OR 0.69; 95% CI 0.58–0.82, **Fig. 5**) (35). Analysis of studies whereby probiotics were provided only prenatally or postnatally did not show such benefit, prompting the authors to conclude that benefits are only realised when probiotics are started during pregnancy and continued in the infant for the first 6 months of life. A broader and high-quality systematic review of diet during pregnancy and infancy arrived at similar conclusions regarding a protective effect of probiotics on AD development from 19 probiotic trials (risk ratio 0.78; 95% CI 0.68–0.90; I^2 61% and an absolute risk reduction of 44 cases per 1,000; 95% CI 20–64) (24). Subgroup analysis suggested that it was maternal rather than infant probiotic supplementation that was important for realising a protective benefit. The evidence of prebiotics alone was weak due to high risk of bias, inconsistency, imprecision, and indirectness of study results.

Although the World Allergy Organisation guideline panel has determined that there is a net benefit of probiotics for AD prevention, concerns regarding the heterogeneity of studies remains (36). A comprehensive review of probiotics across all human diseases concluded that the evidence for benefit in allergic diseases was still uncertain and a stimulus for further studies rather than firm clinical recommendations (37). A high-quality individual patient data (IPD) meta-analysis – a type of systematic review that gathers and combines data belonging to individual patient who take part in clinical trials rather than aggregate data – would better identify who benefits most from probiotics, when and why (38).

Interventions directed at the external skin surface. The main "outside in" approaches for preventing AD, sensitisation and food allergy have included attempts to reduce airborne allergens such as house dust mite at the time of birth, increasing exposure to an anthroposophic environment and measures to enhance the skin barrier. A systematic review of house dust mite avoidance strategies (alone or

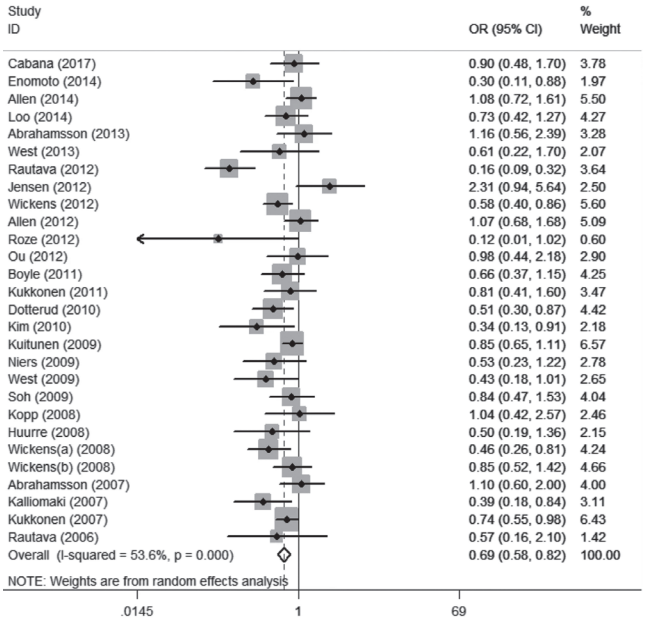

Fig. 5. The preventive effect of probiotics in atopic dermatitis. Forest plot depicting a meta-analysis that used a random effects model combining 28 evaluated studies. Although the summary odds ratio (OR) suggests clear benefit (OR 0.69; 95% confidence interval (CI) 0.58–0.82; $p < 0.0001$), there was considerable heterogeneity between the studies ($I^2 = 53.6\%$) (33). Reproduced with kind permission from the American Journal of Clinical Dermatology.

with allergen avoidance) that included 7 RCTs (search date October 2014) concluded such modalities do not decrease the risk of developing AD. Studies that have found strong associations between early exposures to anthroposophic environments such as farm animals have been limited to observational studies so far, but are a fruitful source of ideas for new possible primary interventions (39). Since the discovery of a strong association between AD and loss-of-function mutations in *FLG*, the gene encoding filaggrin – an essential protein for healthy skin barrier function, interest has increased on the potential benefits of skin barrier enhancement as a means of preventing AD and food allergy (40). Impaired skin barrier may precede eczema development and may be the route by which sensitisation to food allergens occurs (41, 42). Stimulated by the results of two small pilot RCTs that suggested a large benefit from using emollients on the skin of infants born to families with atopy, two large prevention RCTs have been set up to test the hypothesis that emollients from birth can prevent AD (15, 16, 21, 43). The first of these studies (Barrier Enhancement for Eczema Prevention (BEEP) trial) is investigating daily emollient for the first year of life in babies born to atopic families. The second, the Preventing Atopic Dermatitis and Allergies in children study (PreventADALL), is a factorial trial – a trial whereby two or more interventions are carried out and assessed simultaneously. The PreventADALL trial compares (*i*) no intervention with (*ii*) skin care (oil-bath at least 5 days/week to age 9 months) and (*iii*) consecutive introduction of allergenic foods (peanut, milk, wheat, and egg) between 3 and 4 months of age and (*iv*) both skin and complementary feeding strategies. Results of BEEP and PreventADALL are not available at the time of writing. Two trials were published in 2019, both of which used complex emollients containing ingredients such as ceramide designed to enhance the skin barrier (44, 45). The first study suggested that emollient therapy may reduce AD incidence, but this was not statistically significant, and there was no effect of emollient on barrier measurements (46). The second larger study was a factorial trial of emollient and synbiotics and found no evidence of a protective effect of either intervention (44). At least 10 other similar prevention trials that explore the potential of different skin barrier products to prevent AD in high and low risk populations (46). Together, most of these studies now form part of a prospectively-planned meta-analysis consortium called SCiPAD (Skin care intervention for prevention of atopic disease) (47, 48). Other direct to skin approaches such as "probiotic creams" that serve to influence the early skin microbiome towards one that is less favourable for the development of AD are also worthy of further research (49).

Combined approaches. Whilst it might be easier to implement one simple intervention to prevent AD, it might be possible to combine multiple interventions each of which has a small beneficial effect, especially if they interact to produce more than the sum of the whole. The hazard of a "throw in everything that might work" strategy is that they can become black boxes that are not amenable to replication, unless the components are separated using designs such as factorial trials as currently being done in the PreventADALL study (50).

Secondary prevention

Treating AD more aggressively when it first appears in an attempt to alter the subsequent course of disease in terms of remission or decreasing severity is an attractive notion. One such study of aggressive early treatment is underway in Japan, in which 650 infants who develop AD between the ages of 7–13 weeks old will be randomly assigned to enhanced topical anti-inflammatory treatment or conventional treatment with the aim of preventing food allergy and reducing AD severity (51). Poorly controlled disease resulting in skin damage from scratching can lead to a cascade that results in individuals developing autoimmunity towards their own skin components, a phenomenon that might be key to driving disease chronicity (52). Other non-pharmacological approaches such as behavioural methods to limit skin damage from scratching when AD first appears are also worth considering in this context (53). Like primary prevention, secondary prevention should not be taken lightly, especially with regards to safety. If for example, only 10% of those given early aggressive treatment with prolonged topical corticosteroids benefit from such therapy, then 90% arguably undergo "overtreatment" and incur side effects in order to benefit the few.

So far, prevention of related diseases such as food allergy and asthma have only been considered in the context of early interventions that primarily aim to prevent AD, but another important question to consider in relation to secondary prevention of AD is whether interventions that are initiated when AD is first identified can prevent the development of conditions such as asthma. Such a concept was the basis of the Early Treatment of the Atopic Child study (ETAC) whereby 795 children with new onset AD between 1 and 2 years of age were randomised to cetirizine or placebo for 18 months. Cetirizine was chosen because it might inhibit eosinophil tracking to the lungs as well as its anti-histamine effect. The ETAC study did not show that asthma could be prevented by such an approach (54). Although urticaria rates were less in the intervention group, severity of AD was not reduced in the cetirizine group either, throwing doubt on the value of anti-histamines in the treatment of AD – an observation that has been confirmed in a subsequent Cochrane review (55, 56). A follow-up RCT from ETAC called the EPAAC study explored the use of levocetirizine for the prevention of asthma in children with AD who were sensitised to grass and/or house dust mite was stopped due to lack of benefit (57).

Tertiary prevention

In its broadest sense tertiary prevention refers to disease treatment, prevention of deterioration, disease complications and sequelae. In relation to AD, one of the most important advances in disease treatment over the last 30 years has been the concept of proactive treatment (two consecutive days per week) for those who have been stabilised. This has been shown to dramatically reduce the number of subsequent flares (58). A meta-analysis by Schmitt et al. showed that topical fluticasone reduced the risk of further flares by around half (relative risk 0.46, 95% CI 0.38–0.55) with more modest reductions in flares with weekly topical tacrolimus (RR 0.78, 95% CI 0.60–1.00) (59). When considering prevention of flares, it is equally important to consider induction of remission before proactive therapy is initiated – the concept of "get control then keep control" as illustrated schematically in **Fig. 6** (60). Another review suggested that Vitamin D supplementation for early disease may have a small beneficial effect in reducing later disease severity (61). Given that AD is a chronic relapsing condition, prevention of flares and embracing the concept of overall disease control have become key considerations in improving quality of life of AD sufferers (62). Better prediction of flares in what often appears a random process offers exciting prospects for personalised medicine.

What about adult-onset atopic dermatitis?

Most of the evidence discussed relates to early life. This is with good reason as AD typically starts in the first few years of life. Recent studies have drawn attention to the importance of AD in adults, pointing out that around one in 4 of those with adult AD appear to develop it for the first time in adulthood (63). Less is known about the risk factors for adult-onset AD in order to identify candidates for prevention studies (64). One study of 67,643 US women postulated that niacin intake might protect against adult AD since niacin has been found to decrease transepidermal water loss. Instead, it found that adult AD was paradoxically increased with niacin intake, a finding that needs to be replicated (65).

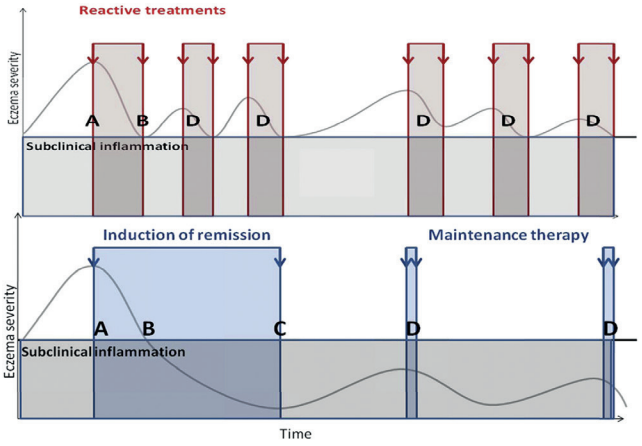

Fig. 6. The concept of getting control then keeping control in atopic dermatitis. A more subtle interpretation of tertiary prevention is the principle of inducing remission of atopic dermatitis with an initial blast of topical treatment followed by prevention of disease flares with weekly pulses of two consecutive days of topical treatment (also known as the Centre of Evidence-Based Dermatology "get control and keep control" approach). When contrasted against more traditional reactive approaches, the proactive approach results in more disease being pushed into a subclinical state and hence better overall disease control. Reproduced with kind permission from the Journal of Allergy and Clinical Immunology.

CONCLUSIONS

The last few decades of research into the prevention of AD have thrown up very few signals of simple, safe interventions that are likely to be effective at a population level. Errors in the design and reporting of studies tend to be repeated rather than learned, and the same old interventions are often tested again and again with little new insight. Past research has also been concerned with a rather fruitless obsession with allergic factors despite the fact that around half of people with "atopic" dermatitis are not atopic in the scientific sense (66). The main exception to the lack of positive findings for AD prevention has been the use of probiotics. Probiotic use has consistently shown modest benefit and good safety when tested in different populations around the world, prompting the World Allergy Organisation guideline panel to determine that there is a likely net benefit from using probiotics resulting primarily from prevention of eczema. The WAO guideline panel suggests using probiotics in: (*i*) pregnant women at high risk of having an allergic child; (*ii*) women who are breastfeeding infants at high risk of developing allergy; and (*iii*) infants at high risk of developing allergy. New evidence is likely to emerge on barrier enhancement as a strategy for AD

prevention over the next 5 years, especially through the SCiPAD prospectively planned meta-analysis.

In terms of future research, it is worth exploring new risk factors rather than doing more studies on the same interventions that do not look promising. The comprehensive overview of systematic reviews of epidemiology of allergic diseases conducted by Genuniet et al. (67) is a good place to start and by reconsidering the host of non-specific, specific and internal factors that make up the "exposome" for AD (67, 68). Rather than considering reduction of harmful exposures, exploration of increasing potentially beneficial substances might be considered. Given the inverse relationship between helminth exposure and allergic sensitisation, derivative products that switch off the dysfunctional immune response could be explored further (69). The foetal environment may be a better place to focus than the infant environment. Rather than conducting more probiotic trials, stopping and conducting a more refined analysis of the 28 or so existing studies using individual patient data meta-analysis may help to bridge the gap between cautious recommendation and implementation in order to benefit future generations of children who might otherwise be destined to a life with AD.

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