

REVIEW

Atopic dermatitis in schoolchildren and adolescents: a critical review of Italian epidemiological data and systemic treatments

May EL HACHEM¹, Luigi NALDI², Iria NERI³, Maria P. PEDONE⁴,
Francesca FANELLI⁴, Carlotta GALEONE⁵ *

¹Dermatology Unit, Bambino Gesù Children's Hospital, IRCCS, Rome, Italy; ² Department of Dermatology, San Bortolo Hospital, Vicenza, Italy; ³Division of Dermatology, Department of Experimental, Diagnostic and Specialty Medicine, Sant'Orsola-Malpighi Hospital, University of Bologna, Bologna, Italy; ⁴Sanofi S.p.A, Milan, Italy; ⁵Outcome Research Unit, Statinfo, Renate, Monza e Brianza, Italy

*Corresponding author: Carlotta Galeone, Outcome Research Unit, Statinfo, Renate, Monza e Brianza, Italy. E-mail: carlotta.galeone@gmail.com

ABSTRACT

INTRODUCTION: The epidemiology of atopic dermatitis (AD) is largely different in pre-school and schoolchildren. We summarized the available epidemiological data on schoolchildren (6-11 years) and adolescents (12-17 years) in Italy and reviewed information on systemic treatments for moderate-to-severe AD in adolescents.

EVIDENCE ACQUISITION: In January 2019, we searched for data on prevalence and/or incidence of AD and on the efficacy, effectiveness and safety of systemic AD therapies. Papers were evaluated and selected, and relevant information was extracted. Twenty papers from 17 studies reported original epidemiological information on AD in Italy.

EVIDENCE SYNTHESIS: Most studies were conducted before 2005. Though variations emerged between studies, the lifetime prevalence of AD was estimated between 15-17% in schoolchildren and between 8-13% in adolescents. The (12-months) period prevalence of AD was estimated between 8-10% in children and between 8-11% in adolescents. Up-to-date information on the prevalence of severe AD is not available. Cyclosporine A may be used in pediatric age patients (children and adolescents) with persistent or severe AD refractory to topical treatments, but its use has several limitations, and is not recommended in patients younger than 16 years. The treatment paradigm of AD is still far from being satisfactory.

CONCLUSIONS: We provided a quantitative synthesis of AD epidemiology in Italian schoolchildren and adolescents. Recent data are needed, as most information dates back to the 1990s or early 2000s, and data on the incidence of AD, the proportion of severe cases, and treatment of severe cases in the real-world setting are scanty.

(Cite this article as: El Hachem M, Naldi L, Neri I, Pedone MP, Fanelli F, Galeone C. Atopic dermatitis in schoolchildren and adolescents: a critical review of Italian epidemiological data and systemic treatments. Ital J Dermatol Venereol 2021;156:650-8. DOI: 10.23736/S2784-8671.20.06669-9)

KEY WORDS: Adolescent; Child; Atopic dermatitis; Epidemiology; Incidence; Prevalence.

Introduction

Atopic dermatitis (AD), a multi-factorial, chronic relapsing inflammatory skin disease, is one of the most common conditions at the pediatric age. The prevalence of AD has been increasing over the last 40-50 years in several high-income countries and other selected world areas.¹⁻³

Most subjects develop AD during the first years of life, experience AD symptoms for a few years and improve by adolescent age.⁴ Still, given the relapsing, intermittent nature of AD, epidemiological assessment of the disease is

difficult and would need a protracted follow-up period. In fact, there are some indications that the prevalence of AD might remain similar throughout childhood and adolescent age.⁵ In the International Study of Asthma and Allergies in Childhood (ISAAC), one of the largest epidemiological investigations on AD, disease prevalence in year 2002-2003 varied widely, ranging between 1% and 22% worldwide.¹ In Western European countries, AD prevalence was 6-16% in children aged 6-7 years and 4-11% in adolescents aged 13-14 years. In another large study from the USA, the overall prevalence of 10% and 8.5% were

reported in year 2003 in the 9-12 and 13-17 age groups, respectively.⁶

A minority of patients develop severe disease,³ with a relevant impact on the quality of life of both children and parents. In mild and moderate AD, adequate topical treatments often allow a satisfactory control of the disease,⁷ while in patients with moderate-to-severe AD, various systemic treatment options are available in addition to topical therapy, but their long-term efficacy and safety profile are questionable.^{8,9}

The main aims of this investigation are to review Italian data on the prevalence and incidence of AD in schoolchildren and adolescents and to assess, in the same population groups, the epidemiology of moderate/severe AD. We also reviewed and discussed the literature on the use of systemic treatments for moderate/severe AD in adolescents.

Evidence acquisition

Review of Italian epidemiological data of AD

We searched for data on prevalence and/or incidence of AD in children and adolescents aged 6-17 years in Italy through the use of different databases and/or search browsers. Figure 1 shows the details of the identification of scientific articles and their selection process. In January 2019, we searched for quantitative epidemiological AD data using PubMed/Medline and EMBASE. The search string used in PubMed/Medline was structured as follows: “(allergic dermatitis OR atopic dermatitis OR atopic eczema OR infantile eczema OR allergic eczema) AND Italy AND (incidence OR prevalence OR epidemiology OR frequency OR occurrence).” The same combination of terms was used in the EMBASE search (in the latter, the search was restricted to the “school age and adolescent” study group). No publication date restrictions were applied.

Study selection was performed by two independent reviewers. In a first step, we excluded papers that were clearly not relevant on the basis of their title and abstract (e.g., those focused on adults >18 years or on infants or young children <6 years old, those conducted in countries other than Italy, those examining contact dermatitis or other diseases, etc.). In a second step, the remaining papers were evaluated in-depth based on the full manuscript, examining whether epidemiological information on AD in Italy was available. In order to check the accuracy of bibliography searches and thus the completeness of the articles included, we performed additional cross-validation searches as follows: we examined the reference lists of

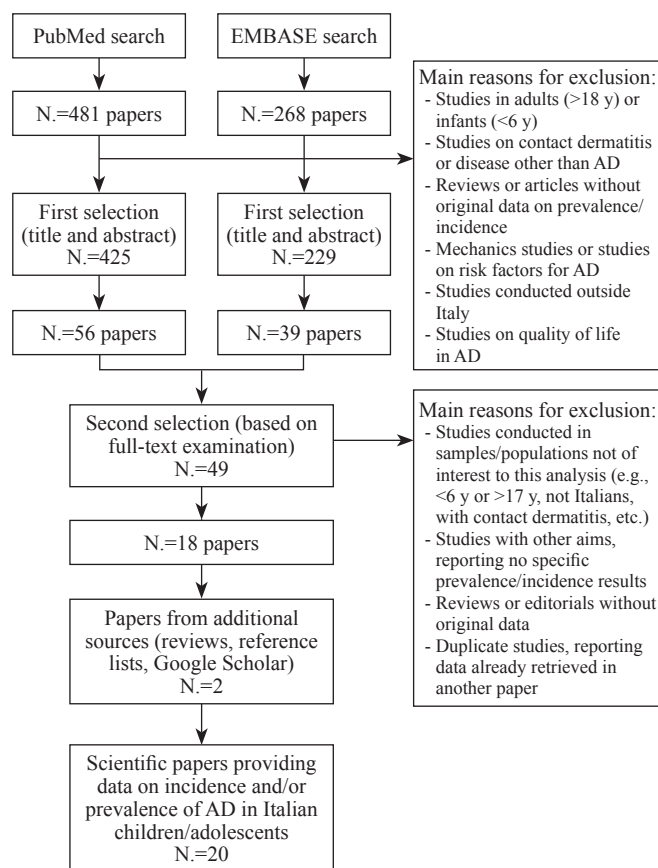


Figure 1.—Flow chart for search and selection of publications on the epidemiology of AD in schoolchildren and adolescents in Italy.

the publications that had been selected and of relevant reviews on AD epidemiology; we explored Google Scholar by entering together the main keywords of this investigation (e.g., “atopic dermatitis,” “incidence,” “prevalence,” “Italy”), ordering results by relevance and then reviewing the publications retrieved. No study was excluded a-priori for weakness of design or data quality.

Relevant information included in the publications selected were extracted and organized in summary Tables to facilitate the synthesis and interpretation of the findings. We separated data according to age group examined in each paper, *i.e.*, schoolchildren (defined, in this analysis, as those aged 6-11 years), adolescents (defined as age 12-17 years) and mixed schoolchildren/adolescent (for overlapping age groups, *e.g.*, we included in this group those studies reporting results for subjects aged 10-13 years¹⁰ or 7-14 years¹¹). We extracted identification data of each publication (*i.e.*, first author, year of publication), as well as information on the period of investigation, geographic area, study design,

age, sample size, source of data, type of diagnosis of AD, epidemiological measures and main results.

We also conducted searches on selected web resources that could supply additional data from the “grey literature.” Thus, we explored websites of a number of agencies, institutions, associations of patients and specialized press, including the World Health Organization (WHO), Italian Ministry of Health, Italian Institute of Statistics (ISTAT), Italian National Institute of Health (ISS), Statistical Office of the European Communities (EUROSTAT), UK National Institute for Health and Care Excellence (NICE), European Network for Health Technology Assessment (EUnetHTA), Scuola dell’Atopia (www.fondation-dermatite-atopique.org), etc.

Review on systemic treatments for AD in adolescents

A similar strategy was used to identify articles focused on systemic treatments for AD in adolescents. We conducted

literature searches through PubMed/Medline, EMBASE and the Cochrane Library. Differently from the epidemiological data review methods, however, the literature search was not restricted to Italy. Given the changing scenario of treatments for severe AD, articles published during the period 2000-2019 were mainly considered, though no formal search restriction according to the time period was applied. Searches were performed for the following systemic therapies: corticosteroids, cyclosporine A, methotrexate, azathioprine, biologics, antihistamines.

Evidence synthesis

Results on prevalence and incidence of disease in Italian schoolchildren and adolescents

A total of 20 papers from 17 studies reporting original information on the prevalence and/or incidence of AD in subjects aged 6-17 years in Italy were identified.^{1, 3, 10-27}

TABLE I.—Main characteristics of studies with information on atopic dermatitis in Italian schoolchildren and adolescents.^{1, 3, 10-27}

Study	Study period	Area	Design	Age (years)	Sample size	Notes
Astarita 1988 ¹⁴	NR	Province of Naples	Cross-sectional	9-15	930	
Angioni 1989 ¹³	1986	Alghero, Sardinia	Cross-sectional	6-12	1691	
Businco 1998 ¹⁶	NR	Italy	Survey	6-12 >12	NR	Data from an editorial. The full paper is unpublished
Williams 1999 ³	1994-95	14 centers throughout Italy	Cross-sectional	1) 6-7y 2) 13-14	1) 20,815 2) 26,477	ISAAC study Phase I / SIDRIA I
Agosti 2003 ¹²	Children born in 94-95, followed for 6 y	Milan	Cohort	6	98	Children with very low birth weight were not included here due to potential selection bias
Di Domenicantonio 2003, Weinmayr 2014 ^{19, 27}	2000-01	Rome	Cross-sectional	10	1307-1760	ISAAC study Phase II. Sample size was 1760 in the first and 1307 in the second report
Girolomoni 2003 ²²	2000	7 cities in Italy	Cross-sectional	9	1369	
Asher 2006, Galassi 2006 ^{1, 21}	2002	9 centers throughout Italy	Cross-sectional	1) 6-7 2) 13-14	1) 11,287 2) 10,267-11,192	ISAAC study Phase III / SIDRIA 2. Sample size was 11,192 in the first and 10,267 in the second report
Macucci 2007 ¹¹	2004	Province of Siena	Cross-sectional	7-14	460	Study in young athletes
Mattei 2007 ²⁴	2004	Province of L'Aquila	Cross-sectional	13-14	1100	
Brescianini 2009 ¹⁵	2003-04	2 towns near Rome	Cross-sectional	11-15	481	
Naldi 2009 ²⁵	1997	13 provinces throughout Italy	Cross-sectional	13-14	3179	
Ventura 2009 ²⁶	NR	Bari	Cross-sectional	8-20	330	194 young athletes and 136 controls
Cibella 2011 ¹⁷	2005-06	Palermo	Cross-sectional	10-17	2150	
Marcon 2011, De Marco 2012 ^{18, 23}	2006	Viadana (Mantua)	Cross-sectional	3-14	3854	
Cantarutti 2015 ¹⁰	2006-12	Italy	Retrospective cohort	1) 5-9 2) 10-13	1) ≈50,000 2) ≈30,000	
Fuiano 2015 ²⁰	2009-10	S. Marco in Lamis (Foggia)	Cross-sectional	7-13	459	

The main characteristics of each study are outlined in Table I.^{1, 3, 10-27} Of 17 studies, six were conducted on a national basis and 11 were local investigations conducted in Northern, Central or Southern Italy. Most studies were surveys or cross-sectional analyses. Only four of 17 studies were recent, *i.e.*, conducted from 2005 onwards. By examining the characteristics of each study, a few ones were identified as particularly relevant due to their methods, sample size, international framework (reporting, however, specific data for the Italian context) and/or recency.^{1, 3, 10, 19, 21, 27}

A total of 10 papers from eight studies reported specific Italian data on children aged between 6 and 11 years, whereas six papers from five studies reported data on adolescents aged between 12 and 17 years. Nine papers from eight studies provided data on mixed schoolchildren/adolescent populations (Supplementary Digital Material 1: Supplementary Table I).^{1, 3, 10-27} Scanty data are available for AD incidence across all age groups.

The results of 20 papers, according to age group and with three study categories: all studies, only national-level studies, best source (evaluated based on sample size, study design, recency and geographic area covered), are summarized in Table II.^{3, 10, 20, 21} Heterogeneity between study results was elevated, as the prevalence/incidence ranges were generally large. In children aged 6-11 years, the median lifetime prevalence of AD among six studies was 15% and the median period prevalence (12-months) of AD was 8%. The best source estimates showed slightly higher figures, *i.e.*, 17% and 10%, respectively. In adolescents aged 12-17 years, both the median lifetime prevalence (among four studies) and the median period prevalence (among

four studies) of AD were 8%. The best source estimates reported a prevalence of 13% and 11%, respectively. Information on severe disease and on incidence of AD was limited (only one study each).

Interpretation of epidemiological findings

We conducted an extensive review of epidemiological data on AD in Italy, in subjects aged between 6 and 17 years. Our findings on schoolchildren are consistent with previous indications²⁸ and show a lifetime prevalence of AD around 15-17% and a period prevalence between 8% and 10%, though in presence of large variation between studies. Adolescents have a similar 12-months prevalence of disease as schoolchildren, supporting the observation that the disease — after a decrease from the first years of life to schoolchildren age — tend to stabilize at subsequent ages.⁵ One study provided information on AD incidence in Italy at different pediatric ages, though the age ranges examined did not cover the whole school and adolescent age.¹⁰ In that study, Italian incidence rates of AD decrease from about 6.5/1000 in children aged 5-9 years to 3/1000 at age 10-13 years. These estimates are slightly lower than those reported in other European studies conducted at a northern latitude than Italy,²⁹ consistently with a North-South gradient of allergic and autoimmune diseases.³⁰ Italian data on the incidence of AD in the age group considered are, however, limited to one single report that does not consider the full range of pediatrics.

Regarding trends of AD, the ISAAC phases I-III and the PEDIANET studies allowed comparison over time of epidemiological measures of AD in Italy. The first study measured prevalence in year 1994-95 and, later, in year

TABLE II.—*Synthesis of the main results of Italian studies investigating the epidemiology of AD, according to age.*^{3, 10, 20, 21}

Parameters	All studies			National studies only			Best source ^a	
Age/measure	N. studies	Range	Median	N. studies	Range	Median	Study	Estimate
Children, age 6-11 years								
Lifetime prevalence	6	2-34%	15%	3	14-17%	15%	Galassi ²¹	17%
Period prevalence ^b	6	4-10%	8%	5	4-10%	6%	Cantarutti ¹⁰	10%
Period prevalence, severe AD ^c	1	0.1%	0.1%	1	0.1%	0.1%	Williams ³	0.1%
Incidence rate (/1000 p-y)	1	≈6.5	≈6.5	1	≈6.5	≈6.5	Cantarutti ¹⁰	≈6.5
Adolescents, age 12-17 years								
Lifetime prevalence	4	7-13%	8%	3	7-13%	9%	Galassi ²¹	13%
Period prevalence ^b	4	1-11%	8%	3	1-11%	6%	Galassi ²¹	11%
Period prevalence, severe AD ^c	1	0.4%	0.4%	1	0.4%	0.4%	Williams ³	0.4%
Mixed, age 6-17 years								
Lifetime prevalence	6	4-22%	13%	0	-	-	Fuiano ²⁰	14%
Period prevalence ^b	5	0.2-12%	4%	1	4%	4%	Cantarutti ¹⁰	4%
Incidence rate (/1000 p-y)	2	≈3-26	14	1	≈3	≈3	Cantarutti ¹⁰	≈3

p-y: person-years.

^a The best source was evaluated based on sample size, study design, recency and geographic area covered; ^b in most studies, current prevalence refers to prevalence in the last 12 months; ^c in the only study providing data, severe AD was defined as itchy rash and sleep loss at least one night per week.

2002.²¹ The prevalence of AD increased significantly during that period, particularly in children aged 6-7 years. The second study found that the prevalence of AD increased in children between 2006 and 2012, while the incidence of new AD cases remained almost unchanged during the same period.¹⁰ This is consistent with the findings of a worldwide systematic review of time trends in the prevalence and incidence of AD, which showed an increasing prevalence of disease between 1990 and 2010 in several areas of the World, including Western Europe.²

One of our aims was to examine severe AD, but the issue has been rarely considered in schoolchildren and adolescents in Italy. In fact, only one study — the large ISAAC-I study conducted in 1994-95 — provided information on this topic using, however, a simplified definition of severe AD, *i.e.* presence of itchy rash and sleep loss at least one night per week.³ In that study, the prevalence of severe AD was low (*i.e.*, below 0.5%) in both schoolchildren and adolescents. In an Italian survey of 437 family pediatricians, the average percentage of severe cases among AD patients aged <18 years (thus, including also infants and pre-school children) was reported around 8%.³¹ This corresponds, on a population basis, to an approximated prevalence of 1%. Still, data on the issue are scanty and, moreover, relatively outdated, likely reflecting the rarity of severe disease in children. An early report from an international cross-sectional study, presented after our systematic search was conducted and thus not examined in this investigation, included data of 1698 Italian adolescent (12-17 years) patients. Among 286 patients receiving prescription treatment for AD (17% of the Italian subjects), the prevalence of severe AD was 6.6% according to Patient-Oriented Eczema Measure and 5.1% according to patient global assessment of disease severity.³²

Among the limitations of this analysis, the clinical definition or — more often — the question used in the survey to assess the presence of AD varied across different studies (*e.g.*, «Has your child ever had AD?», «Has your child ever had an itchy rash?»). Such differences may have an impact on the prevalence or incidence measured in each study. In most studies, the presence of AD was, in any case, self-reported by the adolescent surveyed or — for children — by a parent. The lifetime prevalence of AD was lower in adolescents than in children aged 6-11, while a higher prevalence would reasonably be expected (*i.e.*, lifetime prevalence should generally increase with age). This may be at least in part explained by information bias in adolescents and their parents. The symptoms of AD are often limited to infancy and early childhood, and recall of

AD may decline as subjects get older. Since the disease tends to increase over time,² a cohort effect is another potential (partial) explanation for this finding. Finally, recent information on AD prevalence and incidence in Italian school children and adolescents is limited, underlining the need for new, up-to-date studies on the issue.

Review on systemic treatments in adolescents

We hereby provide a critical review of the available evidence on the efficacy, effectiveness and safety of systemic treatments for AD in adolescence. This section is structured in separate paragraphs for each systemic therapy. Overall, quantitative data in adolescents are few, particularly from the real-world setting.

Systemic oral corticosteroids

Evidence on the role of systemic corticosteroids to manage moderate/severe AD during the pediatric age — and specifically adolescence — is limited. A randomized controlled trial of patients aged 3-14 years with moderate/severe AD reported an improvement in clinical characteristics of eczema in children receiving oral and nasal beclomethasone dipropionate for 4 weeks as compared to placebo, in the presence of limited adverse effects as compared to other corticosteroids.³³

Consensus documents and guidelines^{9, 34-36} consistently concluded that, although systemic corticosteroids are still commonly prescribed in Europe to manage severe AD, their use should be avoided or at least limited to special situations (*e.g.*, during an acute flare) and short-term use. Long-term treatment should be avoided, in adults and particularly at the pediatric age, as it may lead to many and potentially severe adverse effects, including adrenal suppression, weight gain, growth suppression, and increased susceptibility to infection.^{37, 38}

Cyclosporine A

Cyclosporine A efficacy has been showed in a few randomized controlled studies, conducted in patients of all ages, that reported improvements in various AD severity and quality of life scores and established that the efficacy increases with higher drug dosages.^{39, 40}

Cyclosporine A may be used in pediatric age patients (children and adolescents) with a persistent or severe disease.⁹ Still, cyclosporine A use has several limitations: adverse events, ranging from mild to severe, are relatively common and therefore cyclosporine A should generally be used in the short-term (*i.e.*, 3 to a maximum of 6-12

months); some effects, although minor, may be psychologically troublesome in patients of adolescent age (e.g., hypertrichosis); AD relapse is frequent after the end of treatment; a few weeks after treatment discontinuation, AD severity returns similar to the scores measured before starting cyclosporine A treatment.⁴¹ Due to common side effects, renal and hepatic functions, blood pressure and hematic levels of cyclosporine should be monitored during treatment.

According to the “European TReatment of severe Atopic eczema in children Taskforce” (TREAT) survey,⁴² a multi-country web-based investigation conducted in year 2011 involving 343 physicians of various European pediatric dermatology societies and interest groups, systemic treatment has been initiated in 71.1% of severe cases and cyclosporine A was the most frequently prescribed first-line therapy for severe AD (43%), followed by oral corticosteroids (31%), azathioprine (22%) and other infrequently used drugs. In Italy as well, cyclosporine A was by far the most frequently prescribed first-line therapy (64%), followed by corticosteroids (36%).

Severe AD is among the indications of the use of cyclosporine A in Italy, according to the National Drug Agency (*Agenzia Italiana del Farmaco*, AIFA). However, cyclosporine A use is not recommended in patients <16 years, except for transplants and nephrotic syndrome. With reference to the use of cyclosporine A in adolescent/young women, cyclosporine increases the catabolism of hormones of oral contraceptives and thus may decrease the contraceptive potential. Further, their concomitant use may lead to increased hematic levels of cyclosporine due to potential interactions between drugs.⁴³

Other immunosuppressive treatments

Information on the efficacy and safety of other immunosuppressant agents (*i.e.*, azathioprine and methotrexate) to treat AD is generally restricted to adults. Data from studies conducted in children or adolescents are limited and their findings are often hampered by small study sample size. Their (off-label) use in real-life clinical practice is also infrequent.

A first analysis of the therapeutic response and safety of azathioprine in a pediatric population with severe AD was conducted between 1997 and 2000 in 48 children aged 6-16 years.⁴⁴ Patients had been evaluated, before starting treatment, for their levels of thiopurine methyltransferase (TPMT), to identify patients at high risk of myelosuppression. Most patients (41 of 48, 85.4%) had a good or excellent response after 3 months of treatment and short-term

adverse events profile was acceptable, with no patient developing neutropenia.

Two subsequent analyses based on very small groups of pediatric patients with severe AD treated with azathioprine are available. The first one is a prospective study including 12 children aged 2-18 years with recalcitrant AD,⁴⁵ that reported clinical improvement in 11 of them (91.7%) and mild adverse events. The study also showed that repeated measurement of TPMT activity was clinically useful to predict absence of response or change in response to azathioprine. The second one is a retrospective investigation including 11 patients aged 8-18 years, treated between 2007 and 2017.⁴⁶ After 6 months of treatment, azathioprine was highly effective (*i.e.*, complete or almost complete clearance of AD) in 7 out of 11 patients, while in 2 cases treatment was stopped due to adverse events.

Regarding methotrexate, a head-to-head short term (12 weeks) randomized study compared the efficacy of methotrexate and cyclosporine A in 40 children aged 7-14 years with severe AD.⁴⁷ At week 12, both treatments showed similar efficacy to significantly reduce the SCORAD of AD patients (around 50% reduction). In the same study, several mild and temporary adverse events were reported in both treatment groups: those in methotrexate treated children included anemia (30%), fatigue (30%), abnormal liver functions (25%), nausea and vomiting (20%), and glossitis with oral ulceration (20%); those in cyclosporine treated children included fatigue (45%), leukopenia (35%), headache (25%), anemia (20%), and flu-like symptoms (20%).

In a retrospective review conducted in New Zealand in 43 patients aged 2-16 years, methotrexate improved AD in 25 of 30 (83%) children with follow-up data.⁴⁸ In particular, parents of 23 (77%) children reported that AD was “a lot better” while on methotrexate treatment and two (7%) that AD was “slightly better”, whereas five (17%) reported “no change” in AD. Methotrexate was well tolerated, with a few adverse events. One child was diagnosed with posterior subcapsular cataracts, considered related to previous treatment with corticosteroids (oral and topical). Long-term information (*i.e.*, median follow-up of 2 years after methotrexate cessation) was also collected. Of the 25 patients who responded to methotrexate, 15 (60%) had no AD relapse and 10 (40%) relapsed at a median of 24 (interquartile range: 10.5-28.5) months post-methotrexate. More specifically, six (24%) patients reported relapses as bad as before methotrexate treatment, with no further systemic treatment, and 4 (16%) restarted methotrexate.

In recent guidelines of AD management, both azathioprine and methotrexate are considered as potential off-

label treatment options for severe AD not only in adults but also in pediatric populations.^{9, 35, 49} For azathioprine, however, screening for TPMT activity before starting treatment and subsequent monitoring of blood cell counts are recommended.

Biologics

In year 2017, dupilumab was the first biological agent approved for first-line treatment of moderate/severe AD in adults in the USA and Europe. The USA FDA and EMA have recently approved dupilumab for moderate/severe AD treatment in adolescents eligible, too.

Various large randomized controlled trials supported the efficacy and safety of dupilumab in adults.⁵⁰⁻⁵² A consensus-based European guideline on AD treatment recommended using dupilumab as a disease-modifying, long-term drug in patients with moderate to severe disease, when topical treatment is not sufficient and other systemic therapies are not advisable.⁹

Data on younger populations have been published recently in a randomized, placebo-controlled phase 3 trial of adolescents with uncontrolled moderate-to-severe AD.^{53, 54} This found results similar to those reported in adults, with a clear improvement in signs, symptoms and quality of life in patients treated with dupilumab, in presence of an acceptable safety profile. In particular, several outcome measures related to disease severity, body surface affected, pruritus, sleep loss and quality of life (including Patient-Oriented Eczema Measure and Children's Dermatology Life Quality Index) were significantly improved over 16 weeks in both dupilumab groups (*i.e.*, 300 mg every 4 weeks; 200 or 300 mg — according to patient baseline body weight — every 2 weeks) as compared to placebo.^{54, 55} An early confirmation of the efficacy and safety findings of the trial in the clinical practice setting comes from a Real-World analysis of 111 pediatric AD patients, in which dupilumab was used off-label.⁵⁶ Additional data on dupilumab efficacy and safety in the long-term (1-year) come from a recent phase III open-label extension study based on 36 adolescents.⁵⁷ This showed long-term improvement in Eczema Area and Severity Index (EASI) scores during follow-up, with 78% of patients in the 2 mg/kg group and 88% in the 4 mg/kg group achieving EASI-75 at week 52, and no new safety signals as compared to the safety profile reported in adults. Overall, these results may be particularly relevant in consideration of the major unmet need for effective treatment of moderate-to-severe AD in adolescent patients.

Other biological drugs such as nemolizumab and lebrikizumab showed some promising results for moderate to severe AD.⁵⁸ Nemolizumab is currently being tested in a phase 3 study of patients aged 12 years and older.⁵⁹ Lebrikizumab was granted fast-track designation by the USA Food and Drug Administration for the treatment of moderate-to-severe AD in late 2019. Traditional biologics such as rituximab and omalizumab have been used off-label and tested in small case-series or trials of severe AD in children.⁶⁰ Their efficacy in AD is unclear but appears, in any case, limited and their use is not recommended, also in consideration of potential adverse effects.

Antihistamines

The evidence on a potential beneficial role of antihistamines use in AD is weak. This notwithstanding, according to an analysis of the USA National Ambulatory Medical Care Survey based on physician (including pediatrician) visits conducted in 2003-2012, antihistamines are used frequently for AD.⁶¹ Sedating antihistamines may be used in the short-term in children with AD and comorbidities such as allergic asthma or rhinitis, while long-term use is not recommended as it may affect sleep quality.^{9, 35}

Conclusions

We provided a critical review of Italian epidemiological data and systemic treatments for AD, focusing on the pediatric age and particularly on adolescents. Though the prevalence of active AD in Italy in subjects aged 6-17 years appears to be lower than in pre-school children, the disease remains relatively frequent. On the other hand, severe AD is infrequent in schoolchildren and adolescents, and this might explain the paucity of epidemiological data on severe disease. Information of this review is aimed to advance knowledge of the disease and may be useful at a public health level.

References

1. Asher MI, Montefort S, Björkstén B, Lai CK, Strachan DP, Weiland SK, *et al.*; ISAAC Phase Three Study Group. Worldwide time trends in the prevalence of symptoms of asthma, allergic rhinoconjunctivitis, and eczema in childhood: ISAAC Phases One and Three repeat multicountry cross-sectional surveys. *Lancet* 2006;368:733-43.
2. Deckers IA, McLean S, Linssen S, Mommers M, van Schayck CP, Sheikh A. Investigating international time trends in the incidence and prevalence of atopic eczema 1990-2010: a systematic review of epidemiological studies. *PLoS One* 2012;7:e39803.
3. Williams H, Robertson C, Stewart A, Ait-Khaled N, Anabwani G, Anderson R, *et al.* Worldwide variations in the prevalence of symptoms of

atopic eczema in the International Study of Asthma and Allergies in Childhood. *J Allergy Clin Immunol* 1999;103:125–38.

4. Bieber T. Atopic dermatitis. *N Engl J Med* 2008;358:1483–94.

5. Abuabara K, Yu AM, Okhovat JP, Allen IE, Langan SM. The prevalence of atopic dermatitis beyond childhood: A systematic review and meta-analysis of longitudinal studies. *Allergy* 2018;73:696–704.

6. Shaw TE, Currie GP, Koudelka CW, Simpson EL. Eczema prevalence in the United States: data from the 2003 National Survey of Children's Health. *J Invest Dermatol* 2011;131:67–73.

7. Williams HC. Clinical practice. Atopic dermatitis. *N Engl J Med* 2005;352:2314–24.

8. Schmitt J, Schäkel K, Schmitt N, Meurer M. Systemic treatment of severe atopic eczema: a systematic review. *Acta Derm Venereol* 2007;87:100–11.

9. Wollenberg A, Barbarot S, Bieber T, Christen-Zaech S, Deleuran M, Fink-Wagner A, *et al.*; European Dermatology Forum (EDF), the European Academy of Dermatology and Venereology (EADV), the European Academy of Allergy and Clinical Immunology (EAACI), the European Task Force on Atopic Dermatitis (ETFAD), European Federation of Allergy and Airways Diseases Patients' Associations (EFA), the European Society for Dermatology and Psychiatry (ESDaP), the European Society of Pediatric Dermatology (ESPD), Global Allergy and Asthma European Network (GA2LEN) and the European Union of Medical Specialists (UEMS). Consensus-based European guidelines for treatment of atopic eczema (atopic dermatitis) in adults and children: part II. *J Eur Acad Dermatol Venereol* 2018;32:850–78.

10. Cantarutti A, Donà D, Visentin F, Borgia E, Scamarcia A, Cantarutti L, *et al.*; Peditanet. Epidemiology of Frequently Occurring Skin Diseases in Italian Children from 2006 to 2012: A Retrospective, Population-Based Study. *Pediatr Dermatol* 2015;32:668–78.

11. Macucci F, Guerrini L, Strambi M. Asthma and allergy in young athletes in Siena Province. Preliminary results. *J Sports Med Phys Fitness* 2007;47:351–5.

12. Agosti M, Vegni C, Gangi S, Benedetti V, Marini A. Allergic manifestations in very low-birthweight infants: a 6-year follow-up. *Acta Paediatr Suppl* 2003;91:44–7.

13. Angioni AM, Fanciulli G, Corchia C. Frequency of and risk factors for allergy in primary school children: results of a population survey. *Paediatr Perinat Epidemiol* 1989;3:248–55.

14. Astarita C, Harris RI, de Fusco R, Franzese A, Biscardi D, Mazzacca FR, *et al.* An epidemiological study of atopy in children. *Clin Allergy* 1988;18:341–50.

15. Brescianini S, Brunetto B, Iacovacci P, D'Ippolito C, Alberti G, Schirru MA, *et al.* Prevalence of self-perceived allergic diseases and risk factors in Italian adolescents. *Pediatr Allergy Immunol* 2009;20:578–84.

16. Businco L, Bartolucci M. Atopic dermatitis and food allergy in Europe—prevalence and risk factors. *Allergy* 1998;53(Suppl):136–8.

17. Cibella F, Cuttitta G, La Grutta S, Melis MR, Lospalluti ML, Uasuf CG, *et al.* Proportional Venn diagram and determinants of allergic respiratory diseases in Italian adolescents. *Pediatr Allergy Immunol* 2011;22:60–8.

18. de Marco R, Pesce G, Girardi P, Marchetti P, Rava M, Ricci P, *et al.* Foetal exposure to maternal stressful events increases the risk of having asthma and atopic diseases in childhood. *Pediatr Allergy Immunol* 2012;23:724–9.

19. Di Domenicantonio R, De Sario M, Sammarro S, Compagnucci P, Forastiere F, Pistelli R, *et al.* [Asthma and allergies in childhood in Rome: Italian contribution to the ISAAC II]. *Epidemiol Prev* 2003;27:226–33. Italian.

20. Fuiano N, Diddi G, Delvecchio M, C CI. Prevalence of positive atopy patch test in an unselected pediatric population. *Clin Mol Allergy* 2015;13:2.

21. Galassi C, De Sario M, Biggeri A, Bisanti L, Chellini E, Ciccone G, *et al.* Changes in prevalence of asthma and allergies among children and adolescents in Italy: 1994-2002. *Pediatrics* 2006;117:34–42.

22. Girolomoni G, Abeni D, Masini C, Sera F, Ayala F, Belloni-Fortina A, *et al.* The epidemiology of atopic dermatitis in Italian schoolchildren. *Allergy* 2003;58:420–5.

23. Marcon A, Cazzoletti L, Rava M, Gisondi P, Pironi V, Ricci P, *et al.* Incidence of respiratory and allergic symptoms in Italian and immigrant children. *Respir Med* 2011;105:204–10.

24. Mattei A, Angelone AM, Di Stefano R, Sbarbati M, Cialfi D, di Orio F. [Prevalence of asthma, respiratory symptoms and allergic disorders among adolescents in the province of Aquila]. *Epidemiol Prev* 2007;31:247–52. Italian.

25. Naldi L, Parazzini F, Gallus S; GISED Study Centres. Prevalence of atopic dermatitis in Italian schoolchildren: factors affecting its variation. *Acta Derm Venereol* 2009;89:122–5.

26. Ventura MT, Cannone A, Sinesi D, Buquicchio R, Carbonara M, Di Leo E, *et al.* Sensitization, asthma and allergic disease in young soccer players. *Allergy* 2009;64:556–9.

27. Weinmayr G, Forastiere F, Büchele G, Jaensch A, Strachan DP, Nagel G; ISAAC Phase Two Study Group. Overweight/obesity and respiratory and allergic disease in children: international study of asthma and allergies in childhood (ISAAC) phase two. *PLoS One* 2014;9:e113996.

28. Naldi L. Dermatite atopica: epidemiologia. La scuola dell'atopia. Springer; 2007. p. 23–35.

29. Henriksen L, Simonsen J, Haerskjold A, Linder M, Kieler H, Thomsen SF, *et al.* Incidence rates of atopic dermatitis, asthma, and allergic rhinoconjunctivitis in Danish and Swedish children. *J Allergy Clin Immunol* 2015;136:360–6.e2.

30. Okada H, Kuhn C, Feillet H, Bach JF. The 'hygiene hypothesis' for autoimmune and allergic diseases: an update. *Clin Exp Immunol* 2010;160:1–9.

31. Ruggiero G, Gelmetti C, Adamo MC, Baldessari D, Bonfanti R, Brero P, *et al.* Atopic dermatitis (AD) management in an Italian pediatric clinic. *G Ital Dermatol Venereol* 2012;147:71–81.

32. Silverberg JI, Barbarot S, Gadkari A, Simpson EL, Weidinger S, Mina-Osorio P, *et al.* Epidemiology of atopic dermatitis in the adolescent population: a cross-sectional study in the United States and Europe. *Ann Allergy Asthma Immunol* 2021;126:1458.

33. Heddle RJ, Soothill JF, Bulpitt CJ, Atherton DJ. Combined oral and nasal beclomethasone dipropionate in children with atopic eczema: a randomised controlled trial. *Br Med J (Clin Res Ed)* 1984;289:651–4.

34. Drucker AM, Eyerich K, de Bruin-Weller MS, Thyssen JP, Spuls PI, Irvine AD, *et al.* Use of systemic corticosteroids for atopic dermatitis: international Eczema Council consensus statement. *Br J Dermatol* 2018;178:768–75.

35. Galli E, Neri I, Ricci G, Baldo E, Barone M, Belloni Fortina A, *et al.* Consensus Conference on Clinical Management of pediatric Atopic Dermatitis. *Ital J Pediatr* 2016;42:26.

36. Eichenfield LF, Hanifin JM, Luger TA, Stevens SR, Pride HB. Consensus conference on pediatric atopic dermatitis. *J Am Acad Dermatol* 2003;49:1088–95.

37. Aljabab F, Choonara I, Conroy S. Systematic Review of the Toxicity of Long-Course Oral Corticosteroids in Children. *PLoS One* 2017;12:e0170259.

38. Caplan A, Fett N, Rosenbach M, Werth VP, Micheletti RG. Prevention and management of glucocorticoid-induced side effects: A comprehensive review: Ocular, cardiovascular, muscular, and psychiatric side effects and issues unique to pediatric patients. *J Am Acad Dermatol* 2017;76:201–7.

39. Roekvisch E, Spuls PI, Kuester D, Limpens J, Schmitt J. Efficacy and safety of systemic treatments for moderate-to-severe atopic dermatitis: a systematic review. *J Allergy Clin Immunol* 2014;133:429–38.

40. Schmitt J, Schmitt N, Meurer M. Cyclosporin in the treatment of patients with atopic eczema - a systematic review and meta-analysis. *J Eur Acad Dermatol Venereol* 2007;21:606–19.

41. McAleer MA, Flohr C, Irvine AD. Management of difficult and severe eczema in childhood. *BMJ* 2012;345:e4770.

42. Proudfoot LE, Powell AM, Ayis S, Barbarot S, Baselga Torres E, Deleuran M, *et al.*; European Dermato-Epidemiology Network (EDEN). The European TREATment of severe Atopic eczema in children Taskforce (TREAT) survey. *Br J Dermatol* 2013;169:901–9.
43. Agenzia Italiana del Farmaco. Ciqorin. Riassunto delle caratteristiche del prodotto; 2016 [Internet]. Available from: https://farmaci.agenziafarmaco.gov.it/aifa/servlet/PdfDownloadServlet?pdfFileName=foot er_000813_042787_RCP.pdf&sys=m0b113 [cited 2021, Sep 24].
44. Murphy LA, Atherton D. A retrospective evaluation of azathioprine in severe childhood atopic eczema, using thiopurine methyltransferase levels to exclude patients at high risk of myelosuppression. *Br J Dermatol* 2002;147:308–15.
45. Caufield M, Tom WL. Oral azathioprine for recalcitrant pediatric atopic dermatitis: clinical response and thiopurine monitoring. *J Am Acad Dermatol* 2013;68:29–35.
46. Noguera-Morel L, Knöpfel N, Torrelo A, Hernández-Martín A. A Retrospective Study of Systemic Treatment of Severe Atopic Dermatitis With Azathioprine: Effectiveness and Tolerance in 11 Pediatric Patients. *Actas Dermosifiliogr (Engl Ed)* 2019;110:227–31.
47. El-Khalawany MA, Hassan H, Shaaban D, Ghonaim N, Eassa B. Methotrexate versus cyclosporine in the treatment of severe atopic dermatitis in children: a multicenter experience from Egypt. *Eur J Pediatr* 2013;172:351–6.
48. Purvis D, Lee M, Agnew K, Birchall N, Dalziel SR. Long-term effect of methotrexate for childhood atopic dermatitis. *J Paediatr Child Health* 2019;55:1487–91.
49. Chiricozzi A, Belloni Fortina A, Galli E, Girolomoni G, Neri I, Ricci G, *et al.* Current therapeutic paradigm in pediatric atopic dermatitis: practical guidance from a national expert panel. *Allergol Immunopathol (Madr)* 2019;47:194–206.
50. Beck LA, Thaçi D, Hamilton JD, Graham NM, Bieber T, Rocklin R, *et al.* Dupilumab treatment in adults with moderate-to-severe atopic dermatitis. *N Engl J Med* 2014;371:130–9.
51. Blauvelt A, de Bruin-Weller M, Gooderham M, Cather JC, Weisman J, Pariser D, *et al.* Long-term management of moderate-to-severe atopic dermatitis with dupilumab and concomitant topical corticosteroids (LIBERTY AD CHRONOS): a 1-year, randomised, double-blinded, placebo-controlled, phase 3 trial. *Lancet* 2017;389:2287–303.
52. Simpson EL, Bieber T, Guttman-Yassky E, Beck LA, Blauvelt A, Cork MJ, *et al.*; SOLO 1 and SOLO 2 Investigators. Two Phase 3 Trials of Dupilumab versus Placebo in Atopic Dermatitis. *N Engl J Med* 2016;375:2335–48.
53. Simpson E. Dupilumab Efficacy and Safety in Adolescents with Moderate-to-Severe Atopic Dermatitis: Results from a Multicenter, Randomized, Placebo-Controlled, Double-Blind, Parallel-Group, Phase 3 Study. 27th European Academy of Dermatology and Venereology (EADV) Congress Paris, 2018.
54. Simpson EL, Paller AS, Siegfried EC, Boguniewicz M, Sher L, Gooderham MJ, *et al.* Efficacy and Safety of Dupilumab in Adolescents With Uncontrolled Moderate to Severe Atopic Dermatitis: A Phase 3 Randomized Clinical Trial. *JAMA Dermatol* 2020;156:44–56.
55. Paller AS, Bansal A, Simpson EL, Boguniewicz M, Blauvelt A, Siegfried EC, *et al.* Clinically Meaningful Responses to Dupilumab in Adolescents with Uncontrolled Moderate-to-Severe Atopic Dermatitis: Post-hoc Analyses from a Randomized Clinical Trial. *Am J Clin Dermatol* 2020;21:119–31.
56. Igelman S, Kurta AO, Sheikh U, McWilliams A, Armbricht E, Jackson Cullison SR, *et al.* Off-label use of dupilumab for pediatric patients with atopic dermatitis: A multicenter retrospective review. *J Am Acad Dermatol* 2020;82:407–11.
57. Cork MJ, Thaçi D, Eichenfield LF, Arkwright PD, Hultsch T, Davis JD, *et al.* Dupilumab in adolescents with uncontrolled moderate-to-severe atopic dermatitis: results from a phase IIa open-label trial and subsequent phase III open-label extension. *Br J Dermatol* 2020;182:85–96.
58. Snast I, Reiter O, Hodak E, Friedland R, Mimouni D, Leshem YA. Are Biologics Efficacious in Atopic Dermatitis? A Systematic Review and Meta-Analysis. *Am J Clin Dermatol* 2018;19:145–65.
59. ClinicalTrials.gov. Efficacy and Safety of Nemolizumab in Subjects With Moderate-to-Severe Atopic Dermatitis - NCT03985943; 2021 [Internet]. Available from: <https://clinicaltrials.gov/ct2/show/NCT03985943> [cited 2021, Sep 24].
60. Andrae DA, Wang J. Immunologic effects of omalizumab in children with severe refractory atopic dermatitis: a randomized, placebo-controlled clinical trial. *Pediatrics* 2014;134(Suppl 3):S160.
61. He A, Feldman SR, Fleischer AB Jr. An assessment of the use of antihistamines in the management of atopic dermatitis. *J Am Acad Dermatol* 2018;79:92–6.

Conflicts of interest.—Maria P. Pedone and Francesca Fanelli are employees of Sanofi S.p.A. Carlotta Galeone is a researcher at Statinfo. All other authors declare no conflicts of interest.

Funding.—The study was supported by a research grant from Sanofi S.p.A. to Statinfo.

Authors' contributions.—All authors read and approved the final version of the manuscript.

History.—Article first published online: October 16, 2020. - Manuscript accepted: June 3, 2020. - Manuscript revised: May 26, 2020. - Manuscript received: April 14, 2020.

Supplementary data.—For supplementary materials, please see the HTML version of this article at www.minervamedica.it