

The European treatment of severe atopic eczema in children taskforce (TREAT) survey

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Summary

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Background There is a paucity of evidence for the use of systemic agents in children with atopic eczema refractory to conventional therapy, resulting in considerable variation in patient management.

Objectives The European TREATment of severe Atopic eczema in children Taskforce (TREAT) survey was established to collect data on current prescribing practice, to identify factors influencing the use of specific systemic agents, and to inform the design of a clinically relevant intervention study.

Methods Consultant physician members of the paediatric dermatology societies and interest groups of eight European countries were invited to participate in a web-based survey. The multiple-response format questionnaire collated data on clinical practice in general, as well as detailed information on the use of systemic agents in refractory paediatric atopic eczema.

Results In total, 343/765 members (44.8%) responded to the invitational emails; 89.2% were dermatologists and 71% initiate systemic immunosuppression for children with severe atopic eczema. The first-line drugs of choice were ciclosporin (43.0%), oral corticosteroids (30.7%) and azathioprine (21.7%). Ciclosporin was also the most commonly used second-line medication (33.6%), with methotrexate ranked as most popular third choice (26.2%). Around half of the respondents (53.7%) replied that they routinely test and treat reservoirs of cutaneous infection prior to starting systemic treatment. Across the eight countries, penicillins were the first-line antibiotic of choice (78.3%).

Conclusions In the absence of a clear evidence base, the European TREAT survey confirms the wide variation in prescribing practice of systemic immunosuppression in refractory paediatric atopic eczema. The results will be used to inform the design of a randomized controlled trial relevant to patient management across Europe.

What's already known about this topic?

- There is a paucity of evidence for the use of systemic agents in children with atopic eczema refractory to conventional therapy, resulting in considerable variation in patient management.

What does this study add?

- The TREAT survey is the first European venture investigating current practice in the use of systemic agents in severe childhood atopic eczema.
- The survey confirms significant variability in therapeutic approaches, although there are strong trends favouring a small number of agents, namely ciclosporin, oral corticosteroids and azathioprine.

Atopic eczema (AE; synonymous with 'eczema', 'childhood eczema' and 'atopic dermatitis') is the most common cutaneous disease of childhood, affecting 10–15% of those under the age of 5 years in developed countries.¹ In general, AE can be adequately controlled with topical therapies. However, a small subset of children with severe or recalcitrant disease requires systemic agents to induce and maintain disease control.² In children, there is a paucity of published evidence to guide such practice, anecdotally resulting in wide variation in treatment approaches among clinicians across Europe, although no survey has previously been conducted to confirm this impression.

The European TREATment of severe Atopic eczema in children Taskforce (TREAT) was launched in 2010 with three main objectives: (i) to collate detailed data on current practice in the management of severe childhood AE; (ii) to identify factors influencing the use of specific systemic agents; and (iii) to inform the design of a clinically relevant intervention study.

Patients and methods

Study design and population

An anonymous, online, multiple-response-format survey was conducted among consultant members of the paediatric dermatology societies and special interest groups of eight European countries: the U.K. (British Society for Paediatric Dermatology), France (Société Française de Dermatologie Pédiatrique), Germany (Paediatric Dermatology Interest Group, German Dermatological Society), Italy (Società Italiana di Dermatologia Pediatrica), the Netherlands (The Society for Paediatric Dermatology, Dutch Paediatric Dermatology Domain group), Denmark (Danish Society of Dermatology), Sweden (Paediatric Dermatology Interest Group, Swedish Society for Dermatology and Venereology) and Spain (Grupo Español de Dermatología Pediátrica). Between June and December 2011, all current consultant members received a

letter announcing the survey, a unique anonymized survey link embedded within an invitation email, and five staggered reminder emails in the case of nonresponders. Participants were able to conduct the survey in English, German, Italian or Spanish.

The survey was conceived and coordinated by the Paediatric Dermatology Department of St John's Institute of Dermatology, Guy's and St Thomas' NHS Foundation Trust, London, U.K. (L.E.P., A.M.P. and C.F.) and conducted in collaboration with the European Dermato-Epidemiology Network (EDEN), who helped to establish contact with a number of European study centres. C.F., Å.S. and J.S. are EDEN steering committee members. The survey was approved by the ethics committee of Guy's and St Thomas' NHS Foundation Trust.

Survey content

The survey consisted of 48 questions, divided into five sections, initially collating the demographic and professional characteristics of the respondents, including age, sex, specialty, proportion of paediatric patients seen and use of standardized measures to determine childhood AE severity, quality of life and response to treatment. Participants were given the option to select from the following objective measures: Eczema Area and Severity Index (EASI),³ Scoring Atopic Dermatitis index (SCORAD),⁴ Patient-oriented Scoring Atopic Dermatitis index (Po-SCORAD),⁵ Nottingham Eczema Severity Score (NESS),⁶ Six Area Six Sign Atopic Dermatitis score (SASSAD),⁷ Patient-Oriented Eczema Measure (POEM),⁸ Children's Dermatology Life Quality Index (CDLQI),⁹ Infants' Dermatitis Quality of Life Index (IDQoL),¹⁰ Dermatitis Family Impact score (DFI),¹¹ SKINDEX-29,¹² Patient Global Assessment and Physician's Global Assessment.

Participants were asked whether they use systemic agents to treat severe paediatric AE. Those answering 'no' took no further part in the survey. Physicians responding 'yes' were presented with a clinical scenario accompanied by clinical images to standardize responses (Fig. 1). Participants were

asked to select the first-, second- and third-line systemic medications they would employ in such a case, outside the context of an acute flare, given a selection of oral corticosteroids, ciclosporin, azathioprine, methotrexate, mycophenolate mofetil (MMF) or 'other drug', with space for free-format entry. For each drug selected, participants then detailed their initial and maximum dosing schedule, the average and maximum duration of treatment and the discontinuation regimen.

Furthermore, the testing for and treatment of skin infection in children on systemic agents for severe AE was explored. Participants were asked whether they regularly test and treat reservoirs of infection and were asked to indicate their use of topical antibiotics, antiseptic washes, bath additives and bleach baths, both prophylactically and in those clinically infected. Physicians were able to select the oral antibiotics they most frequently use to treat skin infection, given a choice of penicillins, macrolides, cephalosporins or 'other', again with space for free-format entry.

Finally, the survey explored the use of treatment guidelines to direct systemic treatment of severe childhood AE, followed by questions determining the availability of eczema education, nursing and other support services and perceived barriers to the use of systemic agents.

Statistical analysis

We present primarily descriptive analyses. Odds ratios (ORs) and corresponding 95% confidence intervals (CIs) were calculated in relation to systemic-medication-prescribing behaviour. Following univariate analysis, significant risk estimates were mutually adjusted in logistic regression. The following variables were evaluated as potential confounders: sex, age, primary specialty (dermatology vs. paediatrics vs. other), number of years working in the specialty, patient caseload (children only vs. adults and children) and place of practice (university teaching hospital vs. other locations). The statistical analyses

were conducted by C.F. and S.A. using SPSS software version 19.0 (IBM, Armonk, NY, U.S.A.).

Results

Study population, place of practice and use of validated measures

In total 765 invitation emails were distributed; 46 were undeliverable. Twenty-four participants replied that the survey was not relevant to their practice, and three were excluded as they were not seeing paediatric patients. Of the remaining 692 invitees, 343 (49.6%) completed the full survey. The response rates by country were as follows: Denmark 26/33 (78.8%), France 33/221 (14.9%), Germany 32/91 (35.2%), Italy 32/36 (88.9%), the Netherlands 43/74 (58.1%), Spain 62/104 (59.6%), Sweden 20/25 (80.0%), and U.K. 95/181 (52.5%). The per country proportion of the overall survey response rate was as follows: Denmark 7.6%, France 9.6%, Germany 9.3%, Italy 9.3%, the Netherlands 12.5%, Spain 18.1%, Sweden 5.8% and the U.K. 27.7%.

The demographic and professional characteristics of the 343 respondents are reported in Table 1. In total 55.4% were female and the majority were dermatologists (89.2%); the remaining 10.8% were paediatricians. Some 38.8% had been working in their specialty for > 20 years and 36.4% for 10–20 years.

Almost half of the study group (49.6%) worked in a university teaching hospital, 32.9% in other hospital locations and 17.5% in community settings. Only 19% pursue a purely paediatric practice while 81% reported a clinical caseload incorporating both adults and children. The proportions of paediatric patients making up their caseloads were: 100% children (18.9%), 75–99% (3.5%), 50–75% (9.6%), 25–50% (29.2%) and < 25% (38.8%). Most physicians (66.5%) replied that they typically reviewed fewer than two newly



Fig 1. This 12-year-old girl has had severe atopic eczema since the age of 4-months. She is being maximally treated with antiseptic soap substitutes, emollients, potent topical corticosteroids and antihistamines and failed to respond to a course of narrowband UVB phototherapy.

Table 1 Participants' demographic and professional characteristics

Characteristic	n (%)
Sex	
Male	153 (44.6)
Female	190 (55.4)
Age (years)	
20–30	7 (2.0)
31–40	71 (20.7)
41–50	142 (41.4)
51–60	81 (23.6)
> 60	42 (12.2)
Country of work	
U.K./Ireland	95 (27.7)
Spain	62 (18.1)
The Netherlands	43 (12.5)
France	33 (9.6)
Germany	32 (9.3)
Italy	32 (9.3)
Denmark	26 (7.6)
Sweden	20 (5.8)
Primary specialty	
Dermatology	306 (89.2)
Paediatrics	37 (10.8)
Practice location	
University teaching hospital	170 (49.6)
Other hospital	113 (32.9)
Community	60 (17.5)
Caseload	
Paediatrics only	65 (19.0)
Adults and children	278 (81.0)

referred children with severe AE resistant to standard topical therapy in an average 3-month period; 16.9% saw between three and five such patients and 16.6% saw more than five patients. Over half (56%) utilize standardized measures to determine childhood AE severity, quality of life and response to treatment in their routine practice. The three most commonly cited measures were SCORAD (35.1%), Physician's Global Assessment (19.0%) and CDLQI (13.1%).

Systemic prescribing behaviour

Use of systemic agents

In total, 244 respondents (71.1%) answered that they initiate systemic therapy for children with severe AE. The following variables were found to be nonsignificant confounders for prescribing behaviour in univariate analysis (95% CI in brackets): sex [male vs. female, OR 0.80 (0.50–1.28), $P = 0.36$], age [< 50 vs. ≥ 50 years, OR 0.97 (0.60–1.58), $P = 0.40$] and number of years working in specialty [< 20 vs. ≥ 20 years, OR 0.72 (0.44–1.18), $P = 0.19$]. The two significant factors emerging from the multivariate analysis were place of work [university teaching hospital vs. other setting, mutually adjusted OR 3.89 (2.29–6.60), $P < 0.001$] and primary specialty [dermatology vs. paediatrics, mutually adjusted OR 2.81

(1.35–5.84), $P = 0.006$]. In total, 201 of these participants (82.4%) indicated that their choice of systemic therapies and dosing regimens would not differ for younger children, i.e. those under the age of 12 years.

Drug selection

Across the eight European Union countries, the first-line systemic agents of choice were ciclosporin (43.0%), oral corticosteroids (30.7%) and azathioprine (21.7%) (Table 2, Fig. 2a). Methotrexate and MMF were selected first by only 0.8% and 0.5% of participants, respectively. Ciclosporin was also the most commonly selected second-line medication (33.6%), followed by azathioprine (28.7%), methotrexate (17.2%) and oral corticosteroids (12.3%). Methotrexate ranked as the most popular third-choice drug (26.2%), followed by azathioprine (20.5%), MMF (17.2%) and ciclosporin (10.7%). These results were not significantly altered when the countries with the lowest response rates, France and Germany, were excluded from the analysis. Seven doctors revealed their use of alternative systemic agents in recalcitrant cases: long-term, low-dose antibiotics ($n = 1$, UK, selected first-line), efalizumab ($n = 1$, Spain, selected third-line), TNF- α inhibitors ($n = 1$, Netherlands, selected second-line), omalizumab ($n = 2$, Spain, selected second-line and third-line) and oral tacrolimus ($n = 2$, Spain, third-line and France, first-line).

Regional variation

A detailed analysis of drug choice by country for the most commonly selected medications is given in Table 2 and Figure 2b. Azathioprine was the most commonly selected first-line agent in the U.K. (39%) and Denmark (65%) but, in contrast, it was selected most frequently as 'not used' in Sweden (64%). Corticosteroids are commonly utilized as a first-line therapy in Spain (47%), the Netherlands (45%) and Sweden (64%), but are reserved as the second-line therapy in Italy (41%). Furthermore, methotrexate ranked as the most popular second-line therapy in France (59%) and Denmark (47%), but was the most common third-line choice in the U.K. (36%), Germany (47%) and Sweden (36%).

Dosing schedules

Respondents recorded detailed dosing schedules, duration of treatment and discontinuation regimens for their selected drugs. Ciclosporin was generally started at a dose of 2–3 mg kg⁻¹ per day (45.1%) up to a maximum dose of 3–5 mg kg⁻¹ per day (76.1%). The average duration of treatment was 2–4 months (45.4%), with a maximum duration of 12 months in over half of the respondents (56.8%). Therapy was most commonly discontinued by means of slow titration over a 1-month period (38.5%). Azathioprine was commonly commenced at 1 mg kg⁻¹ per day (54.3%), titrated up to a maximum dose of 3 mg kg⁻¹ per day (60.7%) for 4–12-month treatment courses (49.7%), and was frequently

Table 2 First-, second- and third-line systemic drug selection across all countries and by country

Drug selection in all countries, n (%)									
	Ciclosporin	Azathioprine	Methotrexate	Corticosteroids	Mycophenolate mofetil				
First line	105 (43.0)	53 (21.7)	2 (0.8)	75 (30.7)	1 (0.4)				
Second line	82 (33.6)	70 (28.7)	42 (17.2)	30 (12.3)	10 (4.1)				
Third line	26 (10.7)	50 (20.5)	64 (26.2)	20 (8.2)	42 (17.2)				
Not used	31 (12.7)	71 (29.1)	136 (55.7)	119 (48.8)	191 (78.3)				
Drug choice by country for ciclosporin, azathioprine, methotrexate and ciclosporin, n (%)									
	U.K. (n = 84)	France (n = 17)	Germany (n = 15)	Italy (n = 22)	Spain (n = 58)	Netherlands (n = 20)	Sweden (n = 11)	Denmark (n = 17)	Total (n = 244)
Ciclosporin									
First line	29 (35)	11 (65)	13 (87)	14 (64)	25 (43)	8 (40)	3 (27)	2 (12)	105 (43.0)
Second line	32 (38)	4 (24)	2 (13)	6 (27)	23 (40)	7 (35)	5 (45)	3 (18)	82 (33.6)
Third line	11 (13)	2 (12)	0 (0)	1 (5)	5 (9)	2 (10)	0 (0)	5 (29)	26 (10.7)
Not used	12 (14)	0 (0)	0 (0)	1 (5)	5 (9)	3 (15)	3 (27)	7 (41)	31 (12.7)
Azathioprine									
First line	33 (39)	1 (6)	0 (0)	0 (0)	5 (9)	2 (10)	1 (9)	11 (65)	53 (21.7)
Second line	35 (42)	2 (12)	7 (47)	1 (5)	16 (28)	5 (25)	1 (9)	3 (18)	70 (28.7)
Third line	9 (11)	5 (29)	1 (7)	7 (32)	16 (28)	8 (40)	2 (18)	2 (12)	50 (20.5)
Not used	7 (8)	9 (53)	7 (47)	14 (64)	21 (36)	5 (25)	7 (64)	1 (6)	71 (29.1)
Methotrexate									
First line	2 (2)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	2 (0.8)
Second line	10 (12)	10 (59)	1 (7)	3 (14)	7 (12)	1 (5)	2 (18)	8 (47)	42 (17.2)
Third line	30 (36)	1 (6)	7 (47)	3 (14)	12 (21)	4 (20)	4 (36)	3 (18)	64 (26.2)
Not used	42 (50)	6 (35)	7 (47)	16 (73)	39 (67)	15 (75)	5 (46)	6 (35)	136 (55.7)
Corticosteroids									
First line	16 (19)	3 (18)	2 (13)	8 (36)	27 (47)	9 (45)	7 (64)	3 (18)	75 (30.7)
Second line	6 (7)	0 (0)	3 (20)	9 (41)	5 (9)	4 (20)	2 (18)	1 (6)	30 (12.3)
Third line	7 (8)	1 (6)	2 (13)	1 (5)	4 (7)	3 (15)	1 (9)	1 (6)	20 (8.2)
Not used	55 (65)	13 (76)	8 (53)	4 (18)	22 (38)	4 (20)	1 (9)	12 (71)	119 (48.8)

extended beyond 12 months, if required (60.7%). One-third of respondents (32.9%) titrate azathioprine over 1 month to suspend therapy, while 31.2% simply discontinue the drug. The most commonly selected starting dose for methotrexate was 200 $\mu\text{g kg}^{-1}$ per week (49.1%), with a maximum dose of 400 $\mu\text{g kg}^{-1}$ per week (39.8%). The average duration of treatment was 4–12 months (57.4% of use), although this was frequently extended beyond 12 months (62.0%) in severe cases.

Skin infection

Over half of the physicians (53.7%) replied that they routinely test and treat reservoirs of infection, for example using nasal swabs, to detect carriage of *Staphylococcus aureus*, before starting systemic treatment. One-third (34.4%) test and treat the child alone and 19.3% test and treat both the child and their family members. In clinically infected patients, the majority employ topical antibiotics for the nose (53.7%), topical antiseptics for the skin (68.9%) and oral antibiotics (88.5%) in addition to standard AE topical or oral treatments. In those with no clinical signs of secondary infection, some physicians use the fol-

lowing prophylactically: nasal antibiotics (15.6%), topical antibiotics (7.0%) and oral antibiotics (6.6%). Antiseptic washes and bath additives are used by nearly half (49.2%) as a preventative measure against skin infection. In contrast, bleach baths were selected as rarely or never used by 82.8% of physicians. Across the eight countries, penicillins were the first-line antibiotic of choice (78.3%) to treat skin infections. Macrolides and cephalosporins were most commonly selected second (61.9%) or third-line (31.1%), respectively.

Guidelines, support services and barriers to prescribing

Local, national or international guidelines were cited as being used by 15.7%, 29.2% or 15.5% of participants, respectively, to direct the use of systemic agents. Those most commonly quoted were guidelines from the British Association of Dermatologists, the American Academy of Dermatology, the U.K. National Institute for Health and Care Excellence, the Acad mia Espa ola de Dermatolog a y Venereolog a and the European Academy of Dermatology and Venereology.

Almost three-quarters of respondents (73.3%) have access to inpatient facilities for children on systemic therapy for AE.

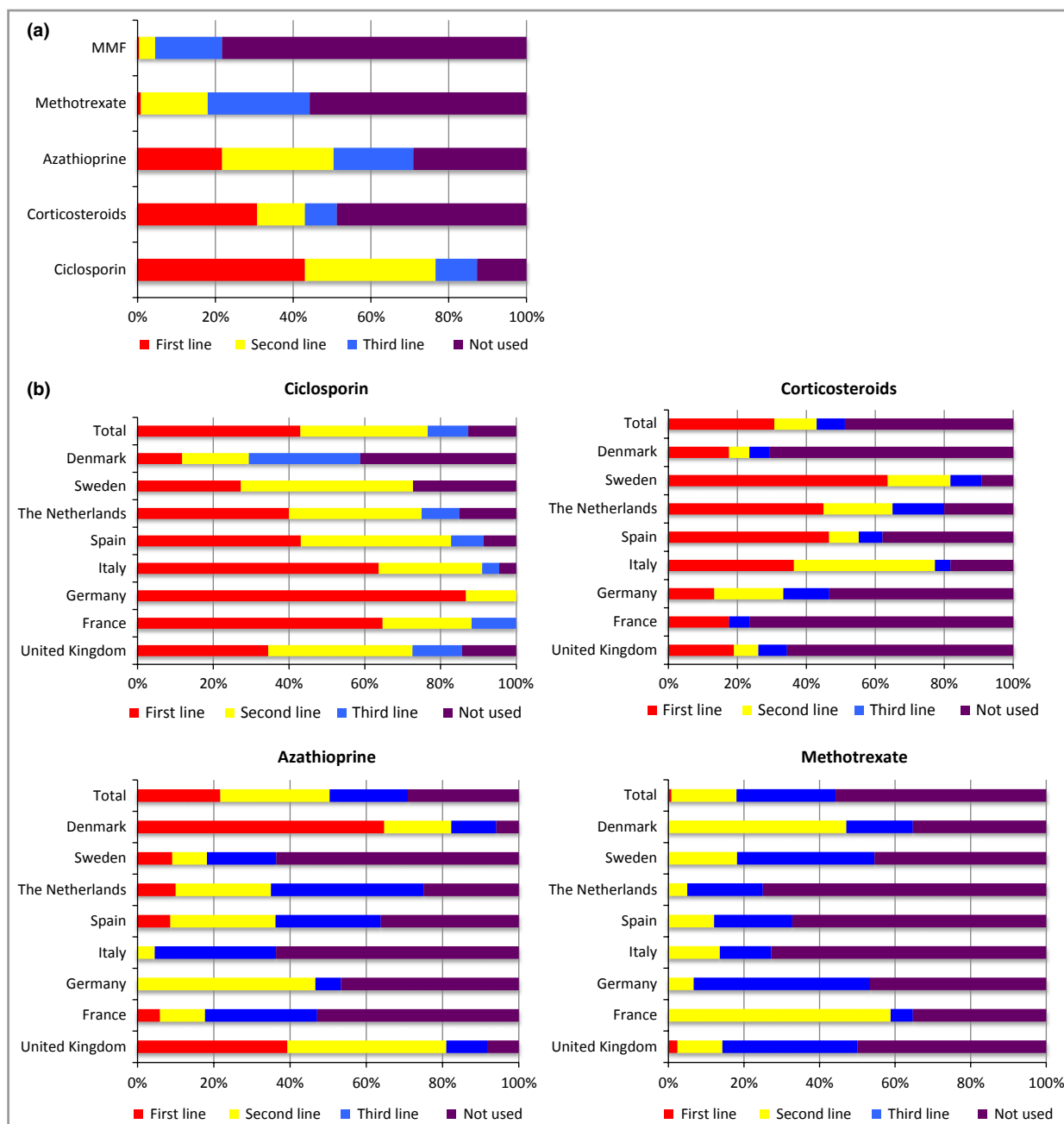


Fig 2. First-, second- and third-line systemic drug selection (a) across all countries and (b) by country. MMF, mycophenolate mofetil.

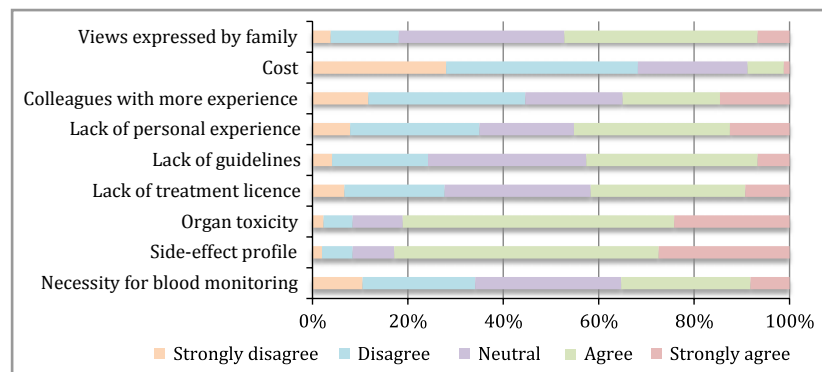
More than half (58.6%) have nursing support services and a smaller proportion (31.1%) have access to a dedicated eczema education programme for patients and their families. A small number (6.6%) have access to nurses qualified to prescribe systemic agents within their practice ($n = 14$ U.K., $n = 1$ Netherlands, $n = 1$ Denmark).

The major factors quoted as discouraging use of systemic agents in the treatment of severe childhood AE were potential side-effects (82.8% either strongly agreed or agreed) and long-term organ toxicity (81.1% either strongly agreed or agreed; Fig. 3).

Discussion

This is the first European survey investigating the use of systemic therapy in children with severe, recalcitrant AE. Among those physicians initiating systemic therapy, ciclosporin was selected as the most commonly utilized agent overall, for treatment periods of up to 12 months' duration. Azathioprine and methotrexate were instituted less frequently, but for longer treatment courses. However, there were significant country-specific variations. For example, azathioprine was the first-choice systemic in the U.K. (39%)

Fig 3. Likert scale depicting perceived barriers to the use of systemic agents in children with severe atopic eczema.



and Denmark (65%), and methotrexate ranked as the most popular second-line therapy in France (59%) and Denmark (47%). Furthermore, the two main factors determining prescribing behaviour were place of work (university hospital vs. other settings) and primary specialty, with dermatologists significantly more likely to initiate systemic agents compared with paediatricians.

Variation between countries in the prescribing patterns of systemic agents in paediatric AE is unsurprising given the lack of controlled trials in this age group. By means of a comprehensive systematic literature review, we identified only six randomized controlled trials conducted in children under the age of 16 years, comprising 158 patients in total. The study interventions tested include ciclosporin vs. intravenous immunoglobulin,¹³ short-course ciclosporin vs. continuous ciclosporin,¹⁴ orally and nasally administered beclomethasone dipropionate vs. placebo,¹⁵ intravenous immunoglobulin vs. placebo,¹⁶ flunisolide steroid analogue vs. placebo¹⁷ and montelukast vs. placebo.¹⁸ Notably, The TREAT survey results demonstrate that aside from the studies investigating ciclosporin therapy, these trials do not reflect current systemic prescribing practice for paediatric AE in Europe. Beyond the lack of drug licensing and trial evidence to guide clinical management, another potential reason for diversity in the management of severe AE across Europe is divergent healthcare systems (e.g. access to secondary care, and referral routes, thus the likelihood of being treated by a dermatologist or paediatrician). Although they are of interest, the TREAT survey was not designed to examine these factors.

Ciclosporin, the most studied systemic agent for AE, has been shown to be effective in children with severe AE^{14,19,20} and was the drug most commonly selected for use by TREAT respondents. In both France and Germany, it is the only systemic agent licensed for use in AE in adults and children over 16 years of age, which may, in part, explain its prevalent use across Europe. However, patients often relapse quickly upon discontinuation,²¹ and given its potential for cumulative, long-term side-effects,²² ciclosporin is generally recommended for short-term use to gain initial control or as a bridge between other steroid-sparing agents.^{23,24} Dosing regimens ranged between 2 and 5 mg kg⁻¹ per day, although studies suggest that in children low-dose ciclosporin might achieve

comparable results with higher dosing schedules,^{25,26} and this warrants further research.

Systemic corticosteroids are typically used for short-course flare control in AE, as unacceptable long-term side-effects limit their prolonged use in children. Study evidence comes from adult trials, and further investigation in children is merited.

There have been two randomized controlled trials of azathioprine vs. placebo in adult AE,^{27,28} but there is limited published evidence for its use in the paediatric population.^{29,30} It takes 8–12 weeks for azathioprine to reach its full therapeutic potential, which, along with adverse effects in those with low-activity thiopurine methyltransferase polymorphism, and the potential long-term risk of lymphoma,² may explain why the TREAT survey found azathioprine to be a less popular first-line medication.

Schram *et al.*³¹ compared the efficacy and safety of azathioprine vs. methotrexate in a randomized controlled trial in adults with severe AE and found no significant differences between the two treatments, although the authors concluded that methotrexate might have a slightly more favourable side-effect profile. Others claim that the therapeutic benefits of methotrexate are less dramatic in AE than with ciclosporin and azathioprine, although the potential long-term toxicity is lower.³² While methotrexate was less commonly selected as a first-line drug by TREAT survey respondents, treatment courses were often extended beyond 12 months, and its use as an effective, longer-term agent in paediatric AE warrants further study.

In 2007, Heller *et al.*³³ reported a series of children with AE successfully treated with MMF. A promising alternative for severe, recalcitrant AE, it appears little used by the European physicians responding to the TREAT survey. Its use in adult AE has been documented,²⁴ and additional, prospective randomized controlled trials are warranted in children.

Patients with AE have high rates of cutaneous colonization with *S. aureus*, and the use of oral antibiotics in those with overt secondary infection is a well-established clinical practice among TREAT physicians. However, a significant number also use antibiotics and other antistaphylococcal interventions prophylactically, despite a 2008 Cochrane review finding no benefit for their prophylactic use in noninfected patients with AE.³⁴

Only one-third of respondents have access to a dedicated eczema education programme within their service. Staab *et al.*³⁵ found education to be an effective means of improving both clinical symptoms and treatment compliance, and further investigation into the benefits of such support services and their delivery modalities is merited.

There are several limitations to this study. Although the response rate was high for an online survey, there remains a risk of selection and response bias, most notable in those countries with a low response rate (France and Germany). However, a sensitivity analysis excluding these two countries did not appreciably alter the results. In order to achieve a representative sample of current prescribing practice, all members of the paediatric dermatology societies and interest groups of eight European countries were approached. Furthermore, six reminder emails were distributed to enhance the response rate, the survey was translated from English into three other languages to encourage participation, and a case scenario with clinical images was incorporated to aid standardization of responses.

In summary, the TREAT survey is the first pan-European venture to investigate the current use of systemic agents in severe childhood AE. As anticipated, there was significant variation in therapeutic approaches, although there were strong trends favouring a small number of agents. While the information derived from this study does not constitute guidelines, it may help to define current 'best practice', and the TREAT survey results are currently being used to design a randomized controlled trial in children that will directly inform current clinical practice.

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