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ORIGINAL RESEARCH

Treatment Patterns in Danish Patients with Atopic Dermatitis Before and After Hospital Referral

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ABSTRACT

Introduction: A number of treatments for atopic dermatitis (AD) are available; however, long-term treatment patterns and healthcare consumption in patients with AD are poorly described.

Methods: We conducted a registry-based longitudinal drug utilization study among Danish patients with AD that were referred to their first-ever visit at hospital-based dermatology clinics. Their first visit was in the period between 1 January 2005 and 31 December 2012, and patients were followed up to 5 years after their first visit.

Results: In total, 8213 people with a first-time hospital dermatologist contact for AD were included in the study (3514 aged 0–9 years, 1501 aged 10–19 years, 3198 aged 20 years or older). At first visit, a baseline history of moderately potent topical corticosteroid (TCS) use was seen among 46.6% of children (0–9 years), whereas potent or very potent TCS use was more frequently among older individuals (e.g., 51.1% and 25.6% of people aged 50 years or older had used potent and very potent TCS, respectively). The median (interquartile range) annual number of visits to general practitioners was 4 (2–7) for children and 5 (2–8) for adults, in the 12 months prior to referral. Three years after referral, these numbers had decreased to 2 (1–4) and 3 (1–6), respectively. In the first year after referral, 6% of patients were prescribed systemic corticosteroids, whereas other systemic therapies were used in 5% or less.

Conclusions: After referral, low proportions of patients received systemic treatment, or potent TCS. These findings highlight considerable differences in treatment patterns between general practitioners and private practice dermatologists, compared with hospital-based dermatologists, and emphasize the need for better adherence to evidence-based treatment guidelines.

Keywords: Atopic dermatitis; Atopic eczema; Registry; Treatment patterns

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Key Summary Points

Why carry out this study?

A number of treatments for atopic dermatitis (AD) are available; however, long-term treatment patterns and healthcare consumption in patients with AD are poorly described.

Using nationwide register-data from Denmark, we assessed the use of different treatment patterns and healthcare consumption, before and after referral to specialized hospital-based dermatology clinics, among children and adults with AD in a population-based setting.

What was learned from the study?

Among topical therapies, the most frequently used treatment modalities when presenting to the hospital were potent and moderately potent TCS. Notably, use of topical antibiotics (alone or in combination with TCS) increased in the last 3–6 months prior to the hospital visit, and decreased thereafter, and use of systemic corticosteroids increased dramatically in the months preceding the initial hospital visit.

These findings highlight considerable differences in treatment patterns between general practitioners and private practice dermatologists, compared with hospital-based dermatologists, and emphasize the need for better adherence to evidence-based treatment guidelines.

DIGITAL FEATURES

This article is published with digital features, including a summary slide, to facilitate understanding of the article. To view digital features for this article go to https://doi.org/10.6084/m9.figshare.13604243.

INTRODUCTION

Atopic dermatitis (AD) is an inflammatory skin disease that is characterized by xerosis and intense pruritus [1], and represents a growing burden to healthcare systems worldwide [2, 3], and may considerably impair patients' quality of life [4]. Over the past 30 years, its lifetime prevalence has increased rapidly, namely in the industrialized world, where it has now plateaued at 10–20% [5]. While AD typically begins early in life, it may be present in all ages, and the disease course is often waxing and waning, and may be accompanied by respiratory allergy and recurrent skin infections [6–8]. The majority of patients (approximately 80%) have mild disease [9], but a positive family history, early allergen sensitizations, disease onset before 2 years of age, and severe AD early in life appear to be risk factors for more persistent and severe disease in adulthood [10]. The current standard of care includes education and the use emollients, pharmaceutical interventions (topical and systemic treatments), as well as phototherapy. Topical corticosteroids (TCS) are the mainstay of AD therapy, and even in more severe cases when systemic treatment is needed, TCS are often used in conjunction.

Although many guidelines exist, either local or international, data on real-life treatment patterns over time are lacking. Using nationwide register-data from Denmark, we assessed the use of different treatment patterns and healthcare consumption, before and after referral to specialized hospital-based dermatology clinics, among children and adults with AD in a population-based setting.

Treatment and Referral Patterns in Denmark

As a result of the tax-supported healthcare system in Denmark, all residents have equal and unencumbered access to general practitioners, private practicing specialists, and hospital-based treatment without charge. Upon displaying initial symptoms, patients may consult their general practitioner that may initiate treatment or refer patients to specialists. In the majority of

cases, referrals are sent to private practice dermatologists, but referrals may also be sent directly to hospital-based clinics if deemed appropriate by the general practitioner, or by internal referral, e.g., by a pulmonologist if the patient is already seen in a hospital setting because of asthma. Private practice dermatologists may initiate treatments with topical or systemic treatments (but not biologics as these are reserved for hospital-based clinics) or phototherapy, or may choose to refer patients to a hospital-based dermatology clinic. Data suggest that less than 3% of patients with AD seen in private practice are treated with systemic therapies, including cyclosporine, methotrexate, and azathioprine [11]. While cyclosporine is a key medication of conventional AD treatment in many countries, and widely recommended in international guidelines, historically it is very rarely used for AD in Denmark [12, 13].

According to national Danish guidelines [14], treatment of AD should be done in a stepwise approach, using emollients as baseline therapy. Recommendations are that mild-to-moderate AD is treated with low potency (e.g., hydrocortisone) or moderately potent (e.g., hydrocortisone-17-butyrate) TCS or topical calcineurin inhibitors (TCI). Crisaborole is not marketed in Denmark and thus not recommended. For moderate-to-severe AD, recommendations are treatment with potent (e.g., betamethasone) TCS or TCI, and systemic treatment should be reserved for severe treatment refractory AD cases. Phototherapy is used for mild-to-moderate AD in adults, but only for moderate-to-severe AD in children. Very potent (e.g., clobetasol propionate) TCS are generally not recommended for patients with AD in Denmark. Importantly, systemic corticosteroids are not recommended for treatment of AD in Denmark as standard of care, but may be considered for acute and severe flares in special circumstances. During the current study period, dupilumab was not marketed in Denmark.

METHODS

Data Sources

Denmark has a long tradition of registry-based research due to the availability of nationwide administrative and healthcare registry data [15]. At birth or migration, all Danish residents are assigned a unique, permanent, and unambiguous ten-digit personal identification number that is used across a myriad of registries and databases to enable cross-linkage at individual level. This number serves as the foundation for the Civil Registration System [16], which contains information such as date of birth, sex, migration, and date of death. All inpatient and outpatient hospital diagnoses are recorded according to the Tenth Revision of the International Classification of Diseases (ICD-10) in the National Patient Registry [17]. Hospital-based use of systemic drugs, biologics, and phototherapy treatments (during admission or from outpatient hospital clinics) is also recorded in this registry as treatment procedure codes. Treatments in primary (e.g., general practitioners) and secondary care (e.g., private dermatologists), e.g., phototherapy at private dermatologists, are recorded in the Health Care Statistics Registry [18]. The Danish National Prescription Registry contains complete information from 1 January 1995 and onwards on all prescriptions dispensed to Danish residents at community pharmacies [19]. Registered drugs are categorized according to the Anatomical Therapeutic Chemical classification, a hierarchical classification developed by the World Health Organization for purposes of drug use statistics.

Ethical Approval

Approval from an ethics committee is not required for register studies in Denmark (Danish law: Lov om videnskabsetisk behandling af sundhedsvidenskabelige forskningsprojekter, § 14, stk. 2).

Statistical Analyses

We obtained treatment data for all patients, aged 0–100 years, consulting with a first-time AD diagnosis at a hospital dermatology clinic in Denmark during the period from 1 January 2005 to 31 December 2012. The diagnostic code for AD has previously been validated with a positive predictive value of 95% (98% in children and 92% in adults, respectively) [12]. Data from each patient was used from 1 year prior to the date on which the patient is diagnosed with AD at the dermatology clinic through to 5 years after the time of diagnosis (i.e., up to 31 December 2017 if a patient was enrolled on 31 December 2012). Patients were followed from the date of their first AD hospital diagnosis (the "index" date, i.e., first hospital visit) occurring from 1 January 2005 to 31 December 2012. Data 1 year prior and 5 years after follow-up were displayed graphically and in tables. Data were extracted in 3-month increments during the observation period. Since clinical measurements of AD severity are lacking in large-scale administrative databases such as the ones used in this study, we performed analyses where AD was presumed to be severe if patients received treatment with systemic drugs used for AD. We presented comorbidity burden by use of the Charlson Comorbidity Index, which allows for a comparison of comorbidities between patients with AD and other disease groups on the basis of risk for mortality or resource use as previously described [20]. As this was a descriptive cohort study, we presented results as means with standard deviations (SDs) for normally distributed continuous variables and medians with interquartile ranges (IQRs) for non-normally distributed continuous variables. Count variables were presented as means with percentages and the proportions over time were displayed graphically. All analyses were performed using SAS statistical software version 9.4 (SAS Institute Inc. Cary, NC, USA) and STATA software version 13.0 (StataCorp, College Station, TX, USA).

RESULTS

In total, 8213 people with a first-time hospital dermatologist contact for AD were included in the study between 1 January 2005 and 31 December 2012 (3514 aged 0–9 years, 1501 aged 10–19 years, 3198 aged 20 years or older). The median (IQR) age was 15.5 (3.3–30.7), and there was a female predominance (55.5%; Table 1). The differences in sex distribution were most pronounced among people aged 20–29 (30.5% male), and 30–39 (35.2% male), respectively. The vast majority (88.3%) were of Danish ethnicity; however, among the youngest age group (0–9 years when first presenting at the hospital with AD), 8.6% were of Asian ethnicity, and 4.3% were of African ethnicity (Table 1), which is somewhat higher than the distribution of these ethnicities in the general population in Denmark [12].

At baseline, a history of moderately potent TCS was seen among 46.6% of children (0–-9 years), whereas a history of potent or very potent TCS use was seen more frequently among older individuals. For example, 51.1% and 25.6% of people aged 50 years or older had used potent and very potent TCS, respectively (Table 1). Overall, in the entire population (0–-100 years) the prevalence of comorbidity (from the Charlson Comorbidity Index [21]) at baseline was low (all comorbidities had a prevalence of less than 2%, with the exception of chronic pulmonary disease, 15.1%). This was predominantly driven by the presence of asthma, as also seen in Table 1.

Healthcare consumption was overall highest in the year preceding and the year immediately after first AD hospital diagnosis (Table 2 and Figs. 1, 2). The median (interquartile range) annual number of visits to general practitioners at baseline was 4 (2–7) and 5 (2–8) for children and adults, respectively. Three years later, these numbers had decreased to 2 (1–4) and 3 (1–6), respectively. Among topical therapies, the most frequently used treatment modalities when presenting to the hospital were potent and moderately potent TCS (Fig. 1a). Notably, use of topical antibiotics (alone or in combination with TCS) increased in the last 3–6 months prior

Table 1 Overall characteristics at baseline

	Age 0–9 (*n* = 3514)	**Age 10–19 (*n* = 1501)**	**Age 20–29 (*n* = 1165)**	**Age 30–39 (*n* = 805)**	**Age 40–49 (*n* = 563)**	**Age ≥ 50 (*n* = 665)**	**All (*n* = 8213)**
Age, median (IQR)	2.6 (1.2–5.5)	16.6 (13.9–18.8)	25.3 (22.9–28.3)	35.6 (33.3–38.2)	45.3 (43.2–48.0)	61.0 (55.4–69.6)	15.5 (3.3–30.7)
Male, *n* (%)	1890 (53.8)	585 (39.0)	355 (30.5)	283 (35.2)	230 (40.9)	308 (46.3)	3651 (44.5)
Asthma, *n* (%)							
Hospital diagnosis in past year	183 (5.2)	54 (3.6)	35 (3.0)	25 (3.1)	11 (2.0)	9 (1.4)	317 (3.9)
Hospital diagnosis ever (prior to baseline)	459 (13.1)	301 (20.1)	210 (18.0)	108 (13.4)	77 (13.7)	70 (10.5)	1225 (14.9)
Ethnicity, *n* (%)							
Danish	2937 (83.6)	1376 (91.7)	1053 (90.4)	746 (92.7)	515 (91.5)	625 (94.0)	7252 (88.3)
Asian	302 (8.6)	58 (3.9)	39 (3.4)	17 (2.1)	20 (3.6)	6 (0.9)	442 (5.4)
European (EU-28)	43 (1.2)	13 (0.9)	32 (2.8)	18 (2.2)	13 (2.3)	24 (3.6)	143 (1.7)
European (non EU-28)	75 (2.1)	41 (2.7)	33 (2.8)	14 (1.7)	7 (1.2)	6 (0.9)	176 (2.1)
African	150 (4.3)	9 (0.6)	5 (0.4)	7 (0.9)	6 (1.1)	< 3 (ns)	< 180 (ns)
Highest completed education, *n* (%)							
None or missing	3514 (100.0)	405 (27.0)	< 30 (ns)	< 10 (ns)	< 15 (ns)	< 25 (ns)	~ 4000 (ns)
Primary school	0 (0.0)	946 (63.0)	232 (19.9)	105 (13.0)	97 (17.2)	186 (28.0)	1566 (19.1)
High school diploma	0 (0.0)	135 (9.0)	348 (29.9)	58 (7.2)	33 (5.9)	17 (2.6)	591 (7.2)
Vocational school	0 (0.0)	< 15 (ns)	257 (22.1)	273 (33.9)	201 (35.7)	225 (33.8)	< 1000 (ns)
Access education programs	0 (0.0)	< 3 (ns)	< 3 (ns)	< 3 (ns)	< 3 (ns)	0 (0.0)	< 10 (ns)
Short higher education	0 (0.0)	0 (0.0)	50 (4.3)	54 (6.7)	43 (7.6)	32 (4.8)	179 (ns)
Diploma	0 (0.0)	0 (0.0)	119 (10.2)	162 (20.1)	107 (19.0)	141 (21.2)	529 (6.4)
Bachelor degree	0 (0.0)	0 (0.0)	69 (5.9)	22 (2.7)	7 (1.2)	5 (0.8)	103 (1.3)
Master degree	0 (0.0)	0 (0.0)	60 (5.2)	112 (13.9)	60 (10.7)	38 (5.7)	270 (3.3)

Table 1 continued

	Age 0–9 (*n* = 3514)	Age 10–19 (*n* = 1501)	Age 20–29 (*n* = 1165)	Age 30–39 (*n* = 805)	Age 40–49 (*n* = 563)	Age ≥ 50 (*n* = 665)	All (*n* = 8213)
Ph.D. and research fellowships	0 (0.0)	0 (0.0)	< 3 (ns)	10 (1.2)	3 (0.5)	< 3 (ns)	< 20 (ns)
Medication use, *n* (%)							
TCS, mild	787 (22.4)	196 (13.1)	126 (10.8)	67 (8.3)	66 (11.7)	53 (7.8)	1295 (15.8)
TCS, moderately potent	1638 (46.6)	570 (38.0)	365 (31.3)	223 (27.7)	169 (30.0)	202 (30.4)	3167 (38.6)
TCS, potent	748 (21.3)	586 (42.6)	357 (44.4)	254 (45.1)	357 (44.4)	353 (51.1)	2794 (34.0)
TCS, very potent	67 (1.9)	122 (8.1)	141 (12.1)	118 (14.7)	105 (18.7)	170 (25.6)	723 (8.8)
TCS with antibiotics	981 (27.9)	350 (23.3)	202 (17.3)	138 (17.1)	104 (18.5)	106 (15.9)	1881 (22.9)
Topical antibiotics	612 (17.4)	179 (11.9)	76 (6.5)	80 (9.9)	52 (9.2)	70 (10.5)	1069 (13.0)
Topical antivirals	11 (0.3)	15 (1.0)	9 (0.8)	8 (1.0)	4 (0.7)	7 (1.1)	54 (0.7)
Topical calcineurin inhibitors	596 (17.0)	311 (20.7)	196 (16.8)	130 (16.2)	100 (17.8)	85 (12.8)	1418 (17.3)
Dicloxacillin	291 (8.3)	348 (23.2)	193 (16.6)	148 (18.4)	128 (22.7)	161 (24.2)	1269 (15.5)
Orally administered aciclovir	35 (1.0)	43 (2.9)	58 (5.0)	36 (4.5)	20 (3.6)	20 (3.0)	212 (2.6)
Orally administered valaciclovir	3 (0.1)	3 (0.2)	11 (0.9)	8 (1.0)	3 (0.5)	4 (0.6)	32 (0.4)
Mycophenolate mofetil	0 (0.0)	< 3 (ns)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	< 3 (ns)
Systemic corticosteroids	18 (0.5)	142 (9.5)	164 (14.1)	155 (19.3)	111 (19.7)	170 (25.6)	760 (9.3)
Azathioprine	3 (0.1)	23 (1.5)	27 (2.3)	38 (4.7)	3 (5.3)	40 (6.0)	161 (2.0)
Methotrexate	5 (0.1)	3 (0.2)	4 (0.3)	6 (0.8)	5 (0.9)	18 (2.7)	41 (0.5)
Cyclosporine	< 3 (ns)	5 (0.3)	4 (0.3)	< 3 (ns)	5 (0.9)	8 (1.2)	25 (0.3)

IQR interquartile range, *ns* not shown because of data security requirements, *TCS* topical corticosteroids

Table 2 Healthcare resource use over time

	Baseline (365 to 1 day before index)		1 year (0–365 days after index)		2 years (366–730 days after index)		3 years (731–1095 days after index)	
	Mean (SD)	Median (IQR)	Mean (SD)	Median (IQR)	Mean (SD)	Median (IQR)	Mean (SD)	Median (IQR)
Children								
Visit to general practitioner/family physician	5.1 (4.0)	4 (2–7)	4.2 (3.8)	3 (1–6)	3.4 (3.2)	3 (1–5)	3.0 (2.9)	2 (1–4)
Visit to dermatologist, any								
Hospital dermatology department								
Outpatient	0.0 (0.2)	0 (0–0)	1.1 (0.6)	1 (1–1)	0.1 (0.3)	0 (0–0)	0.1 (0.3)	0 (0–0)
Inpatient	0.0 (0.1)	0 (0–0)	0.1 (0.3)	0 (0–0)	0.0 (0.1)	0 (0–0)	0.0 (0.1)	0 (0–0)
Private practice dermatologists	1.5 (2.5)	0 (0–2)	0.4 (1.3)	0 (0–0)	0.3 (1.3)	0 (0–0)	0.3 (1.1)	0 (0–0)
Valaciclovir prescriptions	0.0 (0.1)	0 (0–0)	0.0 (0.1)	0 (0–0)	0.0 (0.1)	0 (0–0)	0.0 (0.1)	0 (0–0)
Aciclovir prescriptions	0.2 (0.3)	0 (0–0)	0.0 (0.4)	0 (0–0)	0.0 (0.3)	0 (0–0)	0.0 (0.3)	0 (0–0)
Dicloxacillin prescriptions	0.2 (0.6)	0 (0–0)	0.1 (0.5)	0 (0–0)	0.1 (0.3)	0 (0–0)	0.0 (0.3)	0 (0–0)
Potassium permanganate baths	0.1 (0.8)	0 (0–0)	0.0 (0.5)	0 (0–0)	0.0 (0.2)	0 (0–0)	0.0 (0.0)	0 (0–0)
Adults								
Visit to general practitioner/family physician	5.6 (4.6)	5 (2–8)	5.0 (4.9)	4 (2–7)	4.7 (4.6)	3 (1–6)	4.5 (4.6)	3 (1–6)
Visit to dermatologist								
Hospital dermatology department								
Outpatient	0.1 (0.3)	0 (0–0)	1.1 (0.5)	1 (1–1)	0.1 (0.4)	0 (0–0)	0.1 (0.3)	0 (0–0)
Inpatient	0.0 (0.2)	0 (0–0)	0.1 (0.4)	0 (0–0)	0.0 (0.2)	0 (0–0)	0.0 (0.4)	0 (0–0)
Private practice dermatologists	2.8 (5.1)	1 (0–4)	0.8 (2.7)	0 (0–0)	0.6 (2.5)	0 (0–0)	0.6 (2.5)	0 (0–0)
Valaciclovir prescriptions	0.0 (0.4)	0 (0–0)	0.0 (0.6)	0 (0–0)	0.0 (0.5)	0 (0–0)	0.0 (0.4)	0 (0–0)
Aciclovir prescriptions	0.1 (0.6)	0 (0–0)	0.1 (0.7)	0 (0–0)	0.1 (0.6)	0 (0–0)	0.1 (0.8)	0 (0–0)
Dicloxacillin prescriptions	0.4 (0.9)	0 (0–0)	0.3 (1.0)	0 (0–0)	0.2 (0.6)	0 (0–0)	0.1 (0.6)	0 (0–0)

Table 2 continued

	Baseline (365 to 1 day before index)		1 year (0–365 days after index)		2 years (366–730 days after index)		3 years (731–1095 days after index)	
	Mean (SD)	Median (IQR)	Mean (SD)	Median (IQR)	Mean (SD)	Median (IQR)	Mean (SD)	Median (IQR)
Potassium permanganate baths	0.1 (1.3)	0 (0–0)	0.0 (0.4)	0 (0–0)	0.0 (0.2)	0 (0–0)	0.0 (0.4)	0 (0–0)

Visits to general practitioners shown here, may not necessarily be due to AD
SD standard deviation, *IQR* interquartile range

to the hospital visit, and decreased thereafter (Fig. 1a), and use of systemic corticosteroids increased dramatically in the months preceding the initial hospital visit, after which the use decreased considerably (Fig. 1b). Use of systemic dicloxacillin (i.e., the preferred oral antibiotic for treatment *Staphylococcus aureus* in Denmark) increased dramatically in the last months prior to first hospital visit (Fig. 2a) whereas no major change was observed for systemic antiviral therapies (Fig. 2a). Use of other systemic treatments, in particular azathioprine and phototherapy, increased noticeably around the time of first hospital visit (Fig. 1b) albeit the use of these drugs was generally very low.

Most frequently, patients received monotherapy with potent or moderately potent TCS (Fig. 2b), and when stratified by disease severity, patients classified as having mild disease (i.e., those never treated with systemic therapies) most frequently used moderately potent TCS followed by potent TCS (Fig. 2c), whereas patients classified as having severe disease (i.e., those at some point receiving systemic treatment) most frequently used potent TCS followed by moderately potent TCS (Fig. 2d). Data presented in 3-month increments are available from Table 3.

DISCUSSION

In this longitudinal cohort study of patients with AD in Denmark, the most frequently prescribed systemic therapies in the months immediately prior to first hospital dermatologist visit were systemic corticosteroids and dicloxacillin. Approximately one-third of patients were prescribed a potent or moderately potent TCS when referred for hospital-based treatment, and very few patients were treated with systemic therapies. These findings suggest either a considerable undertreatment among patients with AD in Denmark or that patients are mainly referred for treatment of a single severe flare that quickly resolved. Regardless, our findings highlight considerable differences in treatment patterns between general practitioners and private practice dermatologists, compared with hospital-based dermatologists.

The dramatic increase in use of topical or systemic antibiotics and systemic corticosteroids in the last 3–6 months prior to the first hospital referral could suggest that many such hospital referrals are driven in part by uncontrolled disease with frequent skin infections, requiring more intensified or specialized treatment and proper education in how to manage their AD. Notably, however, the spike in use of systemic corticosteroids, followed by a steep decline in such prescriptions after referral, shows a clear divergence from national guidelines which do not recommend use of systemic

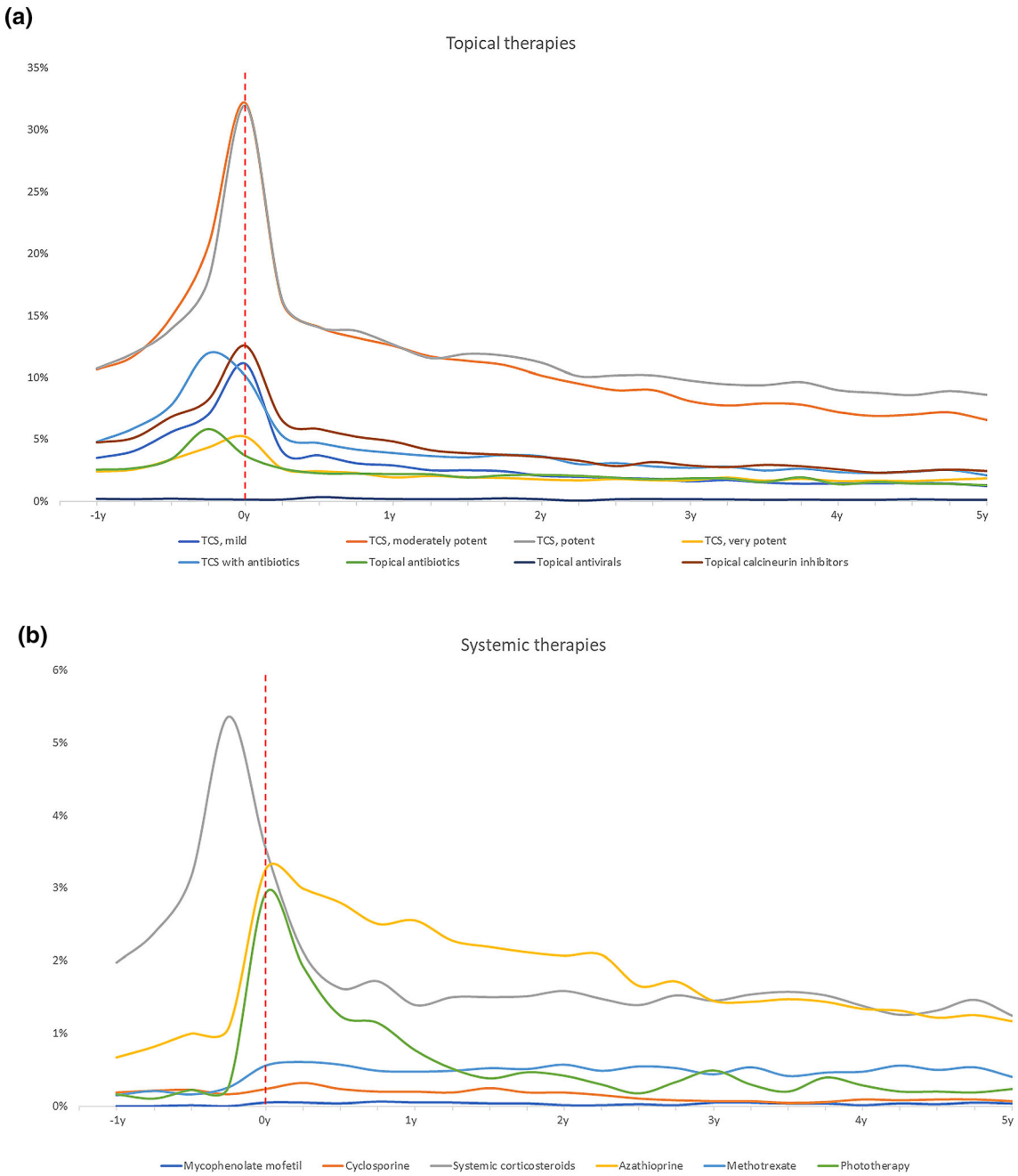

Fig. 1 Use of topical and systemic therapies over time relative to first AD visit. **a** Topical therapies, **b** systemic therapies

corticosteroids as a standard treatment of AD, but recommend that this is reserved for special cases of severe uncontrollable flares [14]. Again, this could also represent a need for further educational efforts of general practitioners and private practice dermatologists to ensure that novel treatment guidelines and recommendations are correctly applied. The overall very low prevalence of systemic therapy in our study is supported by previous studies from Denmark, where only 7% of patients with severe AD received systemic therapy [22, 23]. Notably, the AD diagnosis has been validated in children and adults with very high positive

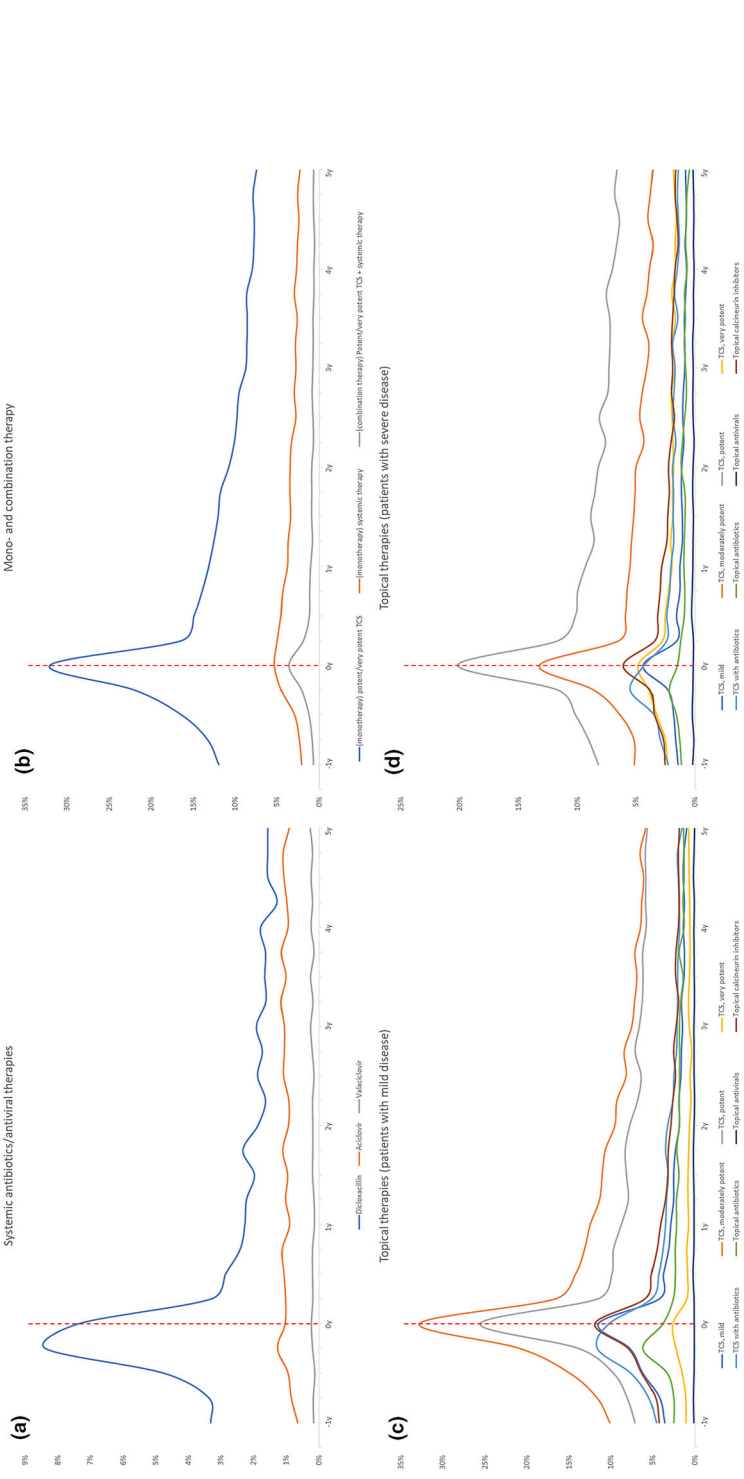

Fig. 2 Treatments over time in patients with atopic dermatitis. Use of treatments relative to first hospital-clinic visit for atopic dermatitis. **a** Use of systemic antibiotics/antiviral therapies. **b** Use of monotherapy and combination therapy. **c** Use of topical therapies among patients with mild disease (i.e., never treated with systemic therapy). **d** Use of topical therapies among patients with severe disease (i.e., those treated with systemic therapy

Table 3 Treatments over time, presented in 3-month increments

	First year, at specific time periods				Second year, at specific time periods				Cumulative	
	0–3 months	3–6 months	6–9 months	9–12 months	12–15 months	15–18 months	18–21 months	21–24 months	First year	Second year
TCS, mild	911 (11.1)	330 (4.0)	305 (3.7)	252 (3.1)	238 (2.9)	206 (2.5)	206(2.5)	199 (2.4)	1338 (16.3)	628 (7.7)
TCS, moderately potent	2646 (32.2)	1324 (16.1)	1156 (14.1)	1086 (13.2)	1032 (12.6)	961 (11.7)	932 (11.3)	904 (11.0)	3666 (44.6)	2264 (27.6)
TCS, potent	2628 (32.0)	1331 (16.2)	1151 (14.0)	1129 (13.7)	1037 (12.6)	948 (11.5)	976 (11.9)	964 (11.7)	3600 (43.8)	2253 (27.4)
TCS, very potent	428 (5.2)	216 (2.6)	198 (2.4)	187 (2.3)	158 (1.9)	168 (2.0)	158 (1.9)	154 (1.9)	671 (8.2)	414 (5.0)
TCS with antibiotics	833 (10.1)	434 (5.3)	385 (0.7)	342 (4.2)	319 (3.9)	299 (3.6)	290 (3.5)	306 (3.7)	1463 (17.8)	869 (10.6)
Topical antibiotics	304 (3.7)	218 (2.7)	187 (2.3)	185 (2.3)	181 (2.2)	180 (2.2)	159 (1.9)	174 (2.1)	787 (9.6)	602 (7.3)
Topical antivirals	12 (0.1)	12 (0.1)	28 (0.3)	19 (0.2)	15 (0.2)	14 (0.2)	15 (0.2)	20 (0.2)	59 (0.7)	48 (0.6)
Topical calcineurin inhibitors	1035 (12.6)	536 (6.5)	480 (5.8)	429 (5.2)	397 (4.8)	339 (4.1)	319 (3.9)	308 (3.8)	1659 (20.2)	899 (11.0)
Dicloxacillin	604 (7.4)	270 (3.3)	235 (2.9)	198 (2.4)	186 (2.3)	182 (2.2)	162 (2.0)	191 (2.3)	1033 (12.6)	584 (7.1)
Aciclovir	85 (1.0)	84 (1.0)	88 (1.1)	92 (1.1)	74 (0.9)	84 (1.0)	79 (1.0)	91 (1.1)	220 (2.7)	219 (2.7)
Valaciclovir	19 (0.2)	15 (0.2)	16 (0.2)	16 (0.2)	11 (0.1)	12 (0.1)	16 (0.2)	15 (0.2)	38 (0.5)	28 (0.3)
Mycophenolate mofetil	4 (0.0)	4 (0.0)	3 (0.0)	5 (0.1)	4 (0.0)	4 (0.0)	3 (0.0)	3 (0.0)	9 (0.1)	9 (0.1)
Cyclosporine	19 (0.2)	26 (0.3)	19 (0.2)	16 (0.2)	16 (0.2)	15 (0.2)	20 (0.2)	15 (0.2)	37 (0.5)	28 (0.3)
Systemic corticosteroids	291 (3.5)	174 (2.1)	133 (1.6)	141 (1.7)	114 (1.4)	123 (1.5)	123 (1.5)	124 (1.5)	493 (6.0)	328 (4.0)
Azathioprine	268 (3.3)	246 (3.0)	230 (2.8)	206 (2.5)	210 (2.6)	187 (2.3)	180 (2.2)	174 (2.1)	413 (5.0)	298 (3.6)
Methotrexate	46 (0.6)	50 (0.6)	47 (0.6)	40 (0.5)	39 (0.5)	40 (0.5)	43 (0.5)	42 (0.5)	96 (1.2)	88 (1.1)
Phototherapy	241 (2.9)	158 (1.9)	102 (1.2)	94 (1.1)	63 (0.8)	42 (0.5)	31 (0.4)	38 (0.5)	388 (4.7)	114 (1.4)

Results are shown as *n* (%)
Columns may not sum to exactly 100% because of multiple therapy use

predictive values in the Danish registries, thus ensuring that patients indeed had AD at the time of their referral [12]. A novel finding, however, is the somewhat low use of potent TCS, which could either be a sign of general undertreatment across therapies or due to steroid-phobia among patients [24]. Nonetheless, the low use of established AD therapies is in stark contrast to the high symptom burden and need for disease resolution that is reported among patients with AD [6, 22]. Notably, the Danish healthcare system provides partial reimbursement of pharmacy-filled prescriptions, including those for topical therapies, and systemic treatments given from hospital clinics (e.g., dupilumab and methotrexate) are provided without the need for co-payment, which therefore should enable a greater access to appropriate therapies to better manage patients' AD. Taken together, these findings suggest that further efforts are needed to heighten the adherence to evidence- and consensus-based treatment guidelines and defined treatment targets, and to provide more optimal care for patients with AD.

Certain limitations apply to the interpretation of the present findings. The study inclusion period was between 2005 and 2012, i.e., before dupilumab was available for treatment of AD. With the advent and introduction of more potent therapies and the subsequent increased disease awareness, it is possible that treatment patterns will change. However, very recent data still suggest that patients with AD in Denmark are markedly undertreated [22]. In the present study we lacked clinical information on disease severity; however, even among patients treated with systemics, i.e., arguably the most severe patients, use of either mono- or combination therapy was very limited, thus highlighting the robustness of our initial findings. Moreover, we lacked data on use of emollients, as such information is not recorded in our data sources. The study was limited to patients that were eventually referred for hospital-based dermatology treatment, and whether the findings also applies to other patient segments such as those only ever seen by private practice dermatologists or general practitioners remains unclear. Lastly, since these data were based on patients seen in the Danish healthcare system, extrapolation to other countries should be done with caution.

In conclusion, we found that a proportion of patients with AD were treated with antibiotics (topical or systemic) and systemic corticosteroids prior to being referred for hospital-based dermatologist treatment. Generally, low proportions of patients received systemic or even potent topical therapy, suggesting that many patients may still be undertreated or that many patients only experience brief flares that quickly resolve. These findings highlight considerable differences in treatment patterns between general practitioners and private practice dermatologists, compared with hospital-based dermatologists, and emphasize the need for better adherence to evidence-based treatment guidelines.

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Compliance with Ethics Guidelines. Approval from an ethics committee is not required for register studies in Denmark (Danish law: Lov om videnskabsetisk behandling af sundhedsvidenskabelige forskningsprojekter, § 14, stk. 2).

Data Availability. The datasets generated during and/or analyzed during the current study are not publicly available due to Danish law. The repository can only be accessed by authorized researchers.

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