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Author contributions: JD contributed to the investigation by analysing and interpreting the burden associated to atopic dermatitis in Spain and was a major contribution in the intellectual content revision. AM analysed the current situation of atopic dermatitis in Spain, interpreted the statistical data and was a major contributor in writing the manuscript. All authors read and approved the final manuscript.

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Abstract

Background: Atopic dermatitis is a chronic inflammatory skin disease that has substantial effects on patients’ quality of life, with a prevalence between 2.2% and 17.6% worldwide. This study aimed to evaluate the use of specialised care resources generated by children and adults with atopic dermatitis, and the associated direct medical costs.

Methods: Admission details from patients admitted in specialised healthcare centres (inpatient and outpatient care) in Spain between 1 Jan 2000 and 31 Dec 2017 were analysed in a retrospective multicentre study.

Results: Records corresponded to 3036 patients, 1266 aged 5 years or younger. Comorbid conditions corresponded to skin infections and respiratory difficulties (asthma, bronchiectasis). Hospital incidence of atopic dermatitis was 5.8 per 100,000 persons, stable over the study period, and 30.0 per 100,000 in those aged 5 years and younger. Mean annual direct medical cost per patient was €2469. Overall, direct medical costs per patient increased significantly over the study period (p<0.0001).

Conclusion: Hospital incidence of atopic dermatitis remained stable over the study period, which is in contrast with the increasing incidence reported by the Spanish government in primary care centres. The increase in direct medical costs of specialised care responded to the increase in treatment costs.

Keywords: atopic dermatitis; incidence; comorbidity; specialised care; direct medical costs.
1. Introduction

Atopic dermatitis is a chronic inflammatory skin disease characterised by pruritus, dry skin and eczematous lesions [1,2]. Disease onset is usually in early childhood, before 3-5 years of age, and it often persists during adulthood, having substantial effects on patients’ quality of life [2-4]. Treatment is focused on improving the skin condition, alleviating pruritus and inflammation in order to improve life quality [5]. Mild atopic dermatitis is generally managed with topical steroids or calcineurin inhibitors, while more severe cases may be treated with phototherapy and systemic immunomodulators, or the recently developed antibody-based treatments [6,7].

The prevalence of atopic dermatitis is variable among different populations and for its different severity levels; its general prevalence is estimated to be between 2.2% and 17.6%, with the highest self-reported prevalence found in Spain [8]. Atopic dermatitis represents a significant burden for patients and healthcare systems in direct medical costs and social, academic and indirect costs, especially when considering the paediatric population [9]. Admissions into specialised care centres could contribute significantly to this burden; in fact, a study developed in the United States analysing paediatric dermatology inpatient services indicated that 86% of all admissions were for atopic dermatitis in 2009-2010 [10]. Thus, the interest in understanding the profile and needs of the patients with atopic dermatitis treated in specialised care centres.

The Spanish healthcare system consists of an extended network of primary healthcare centres, the first contact point with the patient, and a secondary care setting that includes outpatient specialised care, inpatient care and emergency care. The analysis of real-world evidence provides a clear image of current practice, which can assist resource allocation decisions in public health [11,12].
This study aimed to evaluate the use of specialised care resources generated by children and adults with atopic dermatitis and the associated direct medical costs. In addition, patient characteristics and hospital incidence were analysed.

2. Methods

2.1 Study setting

Admission records of patients that were admitted in specialised healthcare centres (inpatient and outpatient care) between 1 Jan 2000 and 31 Dec 2017 were analysed in a retrospective multicentre study. Records were extracted from a Spanish National discharge database including public and private hospitals, which covers 90% of hospitals in Spain and is representative of all Spanish regions. Data is codified at the hospital level by means of the International Statistical Classification of Diseases and Related Health Problems, 9th version (ICD-9) prior to 2016 and 10th version (ICD-10) after the year 2016 [13,14]. The database is validated internally and subjected to periodic audits; in this process, errors and unreliable data are eliminated. Equally, the Spanish Ministry of Health registers admission data from primary care centres, used to obtain data on pharmaceutical consumption; this database is codified using the International Classification of Primary Care, Second edition (ICPC-2).

2.2 Data extraction

Records of admissions in which atopic dermatitis was registered as the admission motive were identified from the database using the ICD-9 and ICD-10 codes: 691.8 and L20. The medication prescribed to these patients was obtained for the year 2017, and categorized according to the Anatomical Therapeutic Chemical (ATC) classification, identifying the patients with the ICPC-2 code S87 [15,16].
All parameters identifying healthcare centres or medical history were re-coded within healthcare centres to maintain records anonymised, in accordance with the principles of Good Clinical Practice and the Declaration of Helsinki. This research did not involve human participants and there was no access to identifying information; in this context the Spanish legislation does not require patient consent and ethics committee approval [17].

### 2.3 Study variables

The variables extracted for analysis were: patients’ sex and age, date of admission, type of admission, date of discharge, type of discharge (including death), readmission rate (defined as a subsequent readmission for the same cause within 30-days after discharge), admission motive, secondary diagnoses registered during the admission and admission costs. Pharmaceutical prescription data was obtained from primary care records.

### 2.4 Data analysis

Patient characteristics were analysed in the first admission registered per patient. All the admission files were used to analyse the nature of admission, length of stay, readmission rate, medical procedures and admission costs. An independent analysis was performed considering the patients aged 5 years and younger, considering the typical age of disease onset, comparing in all cases to patients older than 5 years of age. Hospital incidence was calculated as the number of cases of atopic dermatitis registered in the specialised care database within the total number of patients. Direct medical cost of specialised care was calculated based on the admission costs that are registered in the database; these are assigned according to the standardised average expenses of admissions and medical procedures determined by the Spanish Ministry of Health.
(include all expenses related to the admission: examination, medication, surgery, diet, costs associated to personnel, medical equipment and resources). The costs of prescribed medication were not available.

Frequencies are presented for dichotomous variables and mean and range were calculated for quantitative variables. Normality was tested with the Kolmogorov-Smirnov test. A Cochran-Armitage trend test was performed to assess temporal trends in the incidence of atopic dermatitis and the Mann-Kendall trend test was used to assess temporal trends in the length of stay and direct medical costs. Two-tailed T-student or one-way analysis of variance were used as appropriate to compare characteristics between patient groups, with null hypothesis “patient characteristics are independent from age”. Two-sample Z tests were used to test for differences in sample proportions between age groups. In all cases, a p<0.05 was considered statistically significant.

Statistical analyses were performed using Microsoft Excel© Professional Plus 2016 (Microsoft Corporation, Redmond, WA, USA) and StataSE 12 for Windows (StataCorp LP. 2011. Stata Statistical Software: Release 12. College Station, TX, USA).

3. Results

Admission records corresponded to 3,036 patients, admitted in specialised care centres in Spain between 2000 and 2017; 1266 of the patients were aged 5 years or younger (Table 1). A history of allergies was registered in 22.4% of all admissions and 16.8% of admissions of patients aged 5 years and younger. Overall, 15.7% of admissions of all patients registered chronic obstructive pulmonary disease, namely asthma and bronchiectasis. In addition, skin infections and other bacterial infections were found in a number of admissions. The frequency of diagnosis of all relevant comorbidities varied significantly between age groups (p<0.0001).
The hospital incidence of atopic dermatitis was 5.8 per 100,000 persons over the study period, 30.0 per 100,000 in those aged 5 years and younger. The incidence registered in specialised care centres decreased significantly over the study period for the patients aged 5 years and younger (p<0.0001), while in the total patient population it was stable (Figure 1a).

Patients aged 5 years and younger registered a higher percentage of urgent admissions (84.3% in patients age 5 years and younger vs. 61.2% in those over 5 years; p<0.0001) (Table 2). Up to 99.6% of all admissions were inpatient admissions and mean length of hospital stay (LOHS) was of 5.7 days. Patients aged 5 years or younger required shorter stays, with a mean of 4.3 days (vs. 6.5 days in patients over 5 years; p<0.0001) and the LOHS decreased significantly over time in both age groups (p<0.0001) (Figure 1b).

The most common medical procedures registered on admission included blood microscopic examination, which included the examination of IgE levels, the injection of steroids and antibiotics and skin biopsies. Additionally, pharmacological interventions registered in primary care centres showed a majority of antibiotics, non-steroid anti-inflammatory products, antihistamines and corticosteroids (Table 2).

Total annual direct medical costs were €465,565 for the patients registered in the database (N=3036). Mean annual direct medical cost per patient was €2469. No differences were observed per age groups in this cost: €2310 in patients aged 5 years and younger, and €2549 in patients older than 5 years of age (p=0.3724). Significant shifts appeared in the costs per patient over time: a major increase is observed between the years 2009 and 2010 (p<0.0001) (Figure 2a). Mean admission cost reached the €3052 between 2010 and 2013.
Subsequently, the diagnosis of comorbid conditions over time was analysed. An increase in the diagnosis of asthma and bronchiectasis, and skin infections was observed between 2009 and 2010 (p<0.0001) (Figure 2b). The registry of allergy history peaked the year 2008 and after 2012 (p<0.0001); other relevant comorbidities did not exhibit any major trends.

4. Discussion

This study evaluated the burden of atopic dermatitis in specialised care centres in Spain over a large time period (2000-2017) aiming to provide a description of patients’ needs in terms of specialised healthcare and the associated medical costs. The 3036 patients included in the study had a mean age of 18.8 years; in addition, 41.7% (1266) of the patients hospitalised due to atopic dermatitis were aged 5 years or younger. Hospital incidence of atopic dermatitis was 5.8 per 100,000 persons between 2000 and 2017, increasing to 30.0 per 100,000 in those aged 5 years and younger. Prevalence studies show significantly higher figures in children, a population group in which atopic dermatitis is often present preceding the diagnosis of other allergic disorders later in life [18].

Overall, the prevalence of atopic dermatitis continues to increase, especially in low-income countries [18]. In this study, hospital incidence of atopic dermatitis remained stable over time, while the portion of patients aged 5 years and younger decreased over the study period; this trend was likely to respond to differences in the treatment of this condition. The Spanish Ministry of Health registered an increasing incidence of atopic dermatitis in primary care centres between 2011 and 2017 (223 per 10,000 persons in 2011 to 464 per 10,000 persons in 2017) [15].
A history of allergies was registered in 22.4% of all patients; in addition, patients were diagnosed with skin infections and respiratory conditions. The association with cutaneous infections has been previously analysed in patients with atopic dermatitis, often colonised with \textit{Staphylococcus aureus} [19]. Asthma was identified in 12.1% of patients with atopic dermatitis in a previous study in Spain, in which it was associated with a more intensive use of medical resources [20]. Anxiety disorders were present in patients with atopic dermatitis in previous studies, registered in up to 31.9% when self-reported [21].

Most of the admissions analysed were inpatient admissions, with a LOHS that decreased over the study period. The injection of steroids appeared underrepresented in this patient group; however, drugs registered herein did not necessarily coincide with acute manifestations of this condition. A previous study in Spain indicated that cyclosporine was the most frequent immunosuppressant [22].

The mean direct medical cost of specialised care of atopic dermatitis was €2469. A significant increase was registered in patient costs between 2009 and 2010. The diagnosis of several comorbid conditions increased between 2010 and 2013; however, a causal relation cannot be confirmed since this raise could respond to an increased registration rate of such conditions. In addition, mean unit costs of medical procedures and for the treatment of conditions as declared by the Spanish Ministry of Health increased over the study period: major and minor skin disorders had a mean cost of €4164, €3997, €7829 and €5549 the years 2002, 2008, 2011 and 2015, respectively; similarly, the treatment of bronchitis and asthma had a mean cost of €3913, €3799, €4785 and €4240 the same years [23].
Overall, public expenditure on specialised care in Spain increased at least a 10% over the past 20 years [24]. However, the direct medical cost of specialised care of atopic dermatitis displayed a decreasing tendency between 2011 and 2017.

A number of limitations may have influenced the results of this study. The characteristics of patients and comorbid conditions were limited to those registered in the database. The analysis was limited by the ICD-9 and ICD-10 codification; for instance, all blood examination procedures were clustered in a single code. The revision of pharmaceutical interventions included all drugs in primary care registries, which impeded the evaluation of interventions specific for acute or severe manifestations of atopic dermatitis; in addition, medication was only available for the year 2017. Further studies will be required to evaluate the indirect costs of this condition at the Spanish level.

5. Conclusions

The incidence of atopic dermatitis measured in specialised care centres was stable over the study period, contrarily to the incidence reported by the Spanish Ministry of Health in primary care centres. Direct medical costs of specialised care increased considerably over the study period as a result of the increase of treatment costs of asthma and skin disorders.

6. Declarations

Ethics approval and consent to participate

Ethics committee approval and consent were not required for this study.

Data Availability Statement

The data that support the findings of this study is available from the Spanish Ministry of Health via the Unit of Health Care Information and Statistics (Spanish Institute of Health...
Information) for researchers who meet the criteria for access to confidential data at https://www.mscbs.gob.es/estadEstudios/sanidadDatos/home.htm

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**Declaration of financial and other interest**

The authors declare that they have no competing interests.

### 7. References


Papers of special note have been highlighted as:

* of interest

** of considerable interest
8. Figures

Figure 1 (a) Hospital incidence of atopic dermatitis in Spain and (b) length of hospital stay (2000-2017).
Figure 2 (a) Direct medical cost per patient over time and (b) percentage of admissions in which relevant comorbid conditions were diagnosed over time (2000-2017).
## 9. Tables

### Table 1 Patient characteristics registered upon admission (2000-2017).

|                                | All patients (N=3036) | ≤ 5 years of age (N=1266) | > 5 years of age (N=1770) | p-value *  
|--------------------------------|-----------------------|---------------------------|---------------------------|-------------------------  
| Admission number               | 3790                  | 1412                      | 2378                      | -                         
| Males, %                       | 56.6                  | 59.5                      | 54.6                      | 0.0075                   
| Mean age, years (range)        | 18.8 (0-99)           | 1.5 (0-5)                 | 31.2 (6-99)               | <0.0001                 
| History of allergies (excluding medication), % | 22.4                  | 16.8                      | 26.0                      | <0.0001                 
| Asthma and bronchiectasis, %   | 15.7                  | 2.6                       | 24.3                      | <0.0001                 
| Infections of skin and subcutaneous tissue, % | 11.9                  | 16.8                      | 8.8                       | <0.0001                 
| Bacterial infection, %         | 11.1                  | 13.5                      | 9.5                       | <0.0001                 
| Other diseases of the upper respiratory tract, % | 4.4                   | 1.4                       | 6.3                       | <0.0001                 
| Essential hypertension, %      | 3.7                   | 0.0                       | 6.1                       | <0.0001                 
| Anxiety disorders, %           | 2.3                   | 0.1                       | 3.8                       | <0.0001                 
| Overweight and obesity, %      | 1.4                   | 0.3                       | 2.1                       | <0.0001                 

* ≤ 5 years of age vs. > 5 years of age.

### Table 2 Medical procedures and pharmaceutical interventions registered in patients with atopic dermatitis (2000-2017).

<table>
<thead>
<tr>
<th></th>
<th>All patients, %</th>
<th>Patients ≤ 5 years of age, %</th>
<th>Patients &gt; 5 years of age, %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Urgent admissions</td>
<td>69.8</td>
<td>84.3</td>
<td>61.2</td>
</tr>
<tr>
<td>Mean length of hospital stay, days (range)</td>
<td>5.7 (0-74)</td>
<td>4.3 (0-37)</td>
<td>6.5 (0-74)</td>
</tr>
<tr>
<td>Readmission rate</td>
<td>6.4</td>
<td>5.9</td>
<td>6.7</td>
</tr>
<tr>
<td><strong>Medical procedures</strong></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Microscopic examination of blood</td>
<td>20.6</td>
<td>30.6</td>
<td>13.1</td>
</tr>
<tr>
<td>Steroid injection</td>
<td>11.1</td>
<td>18.6</td>
<td>5.8</td>
</tr>
<tr>
<td>Antibiotic injection</td>
<td>10.8</td>
<td>12.1</td>
<td>9.6</td>
</tr>
<tr>
<td>Skin biopsies</td>
<td>6.8</td>
<td>14.3</td>
<td>1.6</td>
</tr>
<tr>
<td>Injection or infusion of other therapeutic or prophylactic substance</td>
<td>6.7</td>
<td>12.5</td>
<td>2.5</td>
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<tr>
<td>Diagnostic ultrasound of abdomen...</td>
<td>6.0</td>
<td>9.0</td>
<td>3.9</td>
</tr>
<tr>
<td>Routine chest x-ray, so described</td>
<td>5.8</td>
<td>11.3</td>
<td>1.7</td>
</tr>
<tr>
<td>Anatomic and physiologic measurements and manual examinations</td>
<td>4.8</td>
<td>5.1</td>
<td>4.5</td>
</tr>
<tr>
<td>Injection or infusion of immunoglobulin</td>
<td>4.1</td>
<td>9.8</td>
<td>0.2</td>
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<tr>
<td>Electrocardiogram</td>
<td>2.6</td>
<td>5.6</td>
<td>0.4</td>
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<tr>
<td><strong>Pharmacological interventions</strong></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>D06A – Antibiotics for topical use</td>
<td>4.9</td>
<td>8.7</td>
<td>4.2</td>
</tr>
<tr>
<td>Code</td>
<td>Description</td>
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<td>2020 Sales</td>
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