

ORIGINAL

Appropriateness of antibiotic prescription at a Pediatric Emergency department

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Abstract

Objectives: To determine the appropriateness of antibiotic prescribing in the pediatric emergency department.

Material and methods: An observational, descriptive, and cross-sectional study was conducted including all patients aged 0-14 years who visited the pediatric emergency department in January 2020. Patients who were diagnosed with an infectious disease and who received an antibiotic prescription at discharge were identified. Appropriateness of antibiotic prescribing was evaluated based on the Spanish antibiotics guideline (ABE) and other consensus documents published in the literature.

Results: The prescription was considered inappropriate in 57.7% of the cases (n=60). The reasons were: antibiotics not indicated in 40% (n=24), inappropriate active ingredient in 30% (n=18), and incorrect dosage in 30% (n=18). The indications that accounted for the highest number of prescription errors were acute otitis media and acute pharyngotonsillitis, whereas the condition with the highest rate of inappropriate prescriptions were skin and soft tissue infections (85.7% of inappropriate prescriptions), mainly due to incorrect dosage. Overall, 68.3% of inappropriate prescriptions were in patients aged 0-4 years.

Conclusions: More than half of the prescriptions analyzed in this study were not appropriate. This finding as well as the underlying reasons provide insight into the practice of antibiotics prescribing in our setting and the relevance of implementing improvement interventions, such as an antimicrobial stewardship program, and may be a starting point for prospective or multicenter studies with a larger sample size.

ADECUACIÓN DE LA PRESCRIPCIÓN ANTIBIÓTICA EN LAS URGENCIAS PEDIÁTRICAS

Resumen

Objetivos: Determinar la adecuación de la prescripción de antibióticos en el servicio de Urgencias Pediátricas.

Material y métodos: Estudio observacional, descriptivo y transversal en pacientes de 0-14 años atendidos en urgencias pediátricas durante enero de 2020. Se analizó la adecuación de la prescripción en aquellos niños con patología infecciosa y con antibioterapia al alta, utilizando como referencia la guía ABE y otros documentos de consenso publicados en revistas científicas.

Resultados: Se consideró la prescripción inadecuada en el 57,7% de los casos (n= 60). Los motivos fueron: antibioterapia no indicada en el 40% (n= 24), principio activo no

adecuado en el 30% (n= 18) y posología incorrecta en el 30% (n= 18). Las enfermedades que mayor número de errores de prescripción aportaron fueron la otitis media aguda y la faringoamigdalitis aguda, y siendo la patología con mayor tasa de inadecuación las infecciones de piel y partes blandas (85,7% de prescripciones inadecuadas), principalmente por prescripción de una posología incorrecta. El 68,3% de prescripciones inadecuadas se dieron en pacientes de 0-4 años.

Conclusiones: Más de la mitad de las prescripciones analizadas en este estudio fueron no adecuadas. Este dato junto con los motivos que subyacen ofrece una visión sobre la situación en nuestro entorno y la pertinencia de implantar intervenciones de mejora tales como un programa de optimización de uso de antibióticos, así como servir de punto de partida para realizar estudios prospectivos o multicéntricos con mayor tamaño muestral.

INTRODUCTION

Currently, antibiotic use and the development of antimicrobial resistance are among the greatest threats to public health⁽¹⁻³⁾. With regard to the situation in Spain, a 2018 report by the European Centre for Disease Prevention and Control (ECDC) concluded that both in- and outpatient antibiotics use in Spain are among the highest in the EU⁽²⁾.

In the pediatric setting, infectious diseases account for around two-thirds of the pediatric emergency department visits⁽⁴⁾. In addition, antibiotics are the most commonly prescribed drugs (20-23% of the total) and are used for the treatment of respiratory tract infections, many of which are predominantly viral in etiology^(4,5). Therefore, judicious prescribing of antibiotic therapy in this patient group is particularly important.

Several studies conducted in Spain have addressed the appropriateness of antimicrobial prescribing in children, and, although the methodological differences are significant, estimates of inappropriate use range from 15.2% to 51.9% of the total number of antibiotic prescriptions in this age group^(4,6-8).

In children, inappropriate prescribing of antibiotics has consequences in terms of direct effects at the patient level (allergic and idiosyncratic reactions, toxicity, and intolerance), the potential development of chronic diseases and long-term effects, as well as consequences for the community⁽⁹⁾.

Furthermore, as childhood is a critical period for metabolic and immunological development and considering that the highest prescription rates are observed at younger ages, frequent use of antibiotic therapy may alter the microbiome and lead to a disruption of these systems^(9,10).

Because of the above, the ECDC report proposes recommendations for Spain, which include enhancing antibiotic stewardship, developing national guidelines and training activities, and the implementation of prevention programs with defined goals and indicators⁽²⁾. Similarly, the National Antibiotic Resistance Plan (PRAN) addresses different issues, such as the need to strengthen the resistance surveillance and monitoring system, implement antibiotic stewardship programs (PROA) both in hospitals and primary care settings, and encourage research studies focusing on areas such as the antibiotic use and the emergence of resistance⁽³⁾. Hence, conducting studies to assess the antibiotic prescribing patterns in different areas and settings of the National Health System can prove extremely valuable.

The primary objective of our study was to assess the appropriateness of antibiotic prescribing in the pediatric emergency department of Hospital Universitari Sant Joan d'Alacant. In addition, we aimed to identify diseases in which inappropriate use most commonly occurred as well as the reasons why, including aspects such as indication, antibiotic selection, dose, dosing interval, duration, and formulation.

The secondary objectives included the evaluation of other patient variables, such as sex, age, comorbidities, allergy to antibiotics, previous antimicrobial therapy, clinical diagnosis at discharge, and antibiotic prescribed.

MATERIAL AND METHODS

An observational, descriptive, cross-sectional study was conducted to assess antibiotic prescribing in pediatric patients that visited the emergency department of the Hospital Universitari Sant Joan d'Alacant during the month of January 2020. Our hospital is a tertiary-care academic center located in a predominantly urban area. The emergency department receives an annual volume of approximately 15,500 to 17,000 pediatric emergencies, with 750 to 800 emergency admissions.

Pediatric care at the emergency department is provided by pediatricians, pediatric residents, and family and community physicians with experience in pediatric care.

Inclusion criteria: Children aged 0 to 14 years seen at the pediatric emergency department in January 2020 who had infectious diseases and received oral antibiotic therapy at discharge.

Patients who required admission or transfer to another hospital, those who received antimicrobial therapy by topical, otic or ophthalmic routes, and those in whom treatment previously prescribed by the pediatrician at the primary care center or by another specialist was prolonged were excluded from the study.

The primary outcome was the assessment of the percentage of patients receiving inappropriate antibiotic treatment. The treatment was defined as inappropriate if it was prescribed for a disease for which it was not indicated, if the antibiotic chosen was not the drug of choice, or if the dose, timing, duration, or formulation were incorrect. Similarly, secondary variables, including sex, age, comorbidities, antibiotic allergy, previous antimicrobial treatment, clinical diagnosis at discharge, and antibiotic prescribed, were collected and analyzed.

The criteria for appropriateness were established based on the Spanish antibiotics guideline (ABE)⁽¹¹⁾, as well as consensus recommendations from the Spanish Association of Pediatrics and the Spanish Society of Pediatric Infectious Diseases⁽¹²⁻¹⁵⁾, the Spanish Association of Primary Care Pediatrics⁽¹⁶⁾, and others^(17,18). Additional information on the established criteria can be found in [Annex I](#).

Descriptive statistics were employed to summarize the study variables. Frequencies and percentages were calculated for qualitative variables, while means and standard deviations were computed for quantitative variables. For quantitative variables with an asymmetric distribution, the median and interquartile range (IQR) were determined. The correlation between qualitative variables was analyzed using the Chi-square test, with a statistical significance level set at $p < 0.05$. Data analysis was performed using Microsoft Excel 365.

The data were retrospectively analyzed, preserving patient confidentiality and anonymity at all times. This study was approved by the Research Ethics Committee of Hospital Universitari Sant Joan d'Alacant ([Annex 1](#)), committee code: 20/055, on 26/1/21, in accordance with the standards of good clinical practice. Furthermore, it is hereby declared that there is no conflict of interest associated with the execution of this study. The writing of the manuscript adhered to the recommendations of the STROBE statement for observational studies⁽¹⁹⁾.

RESULTS

As shown in [Figure 1](#), we reviewed the discharge records of 1095 patients who presented at the pediatric emergency department during the study period. Among these patients, 76.3% ($n = 836$) received a diagnosis classified as an infectious event, and 12.4% ($n = 104$) of them were prescribed antibiotic treatment upon discharge.

Of the final sample ($n = 104$), the median age was 4 years (IQR, 2-6 years). The male-female ratio was 1.42:1. Only two

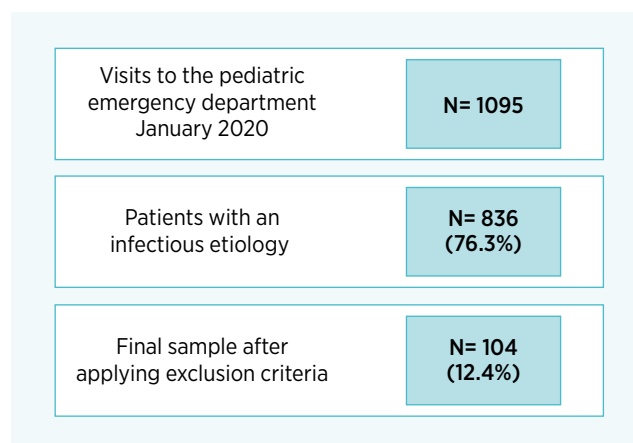


FIGURE 1. Flow diagram showing how the final sample was achieved. After applying the exclusion criteria, of 836 patients with an infectious disease, 665 were not prescribed antibiotic treatment at discharge, three were prescribed either topical, otic, or ophthalmic antibiotics, 51 patients were admitted to our center or referred to another hospital, and in 13 patients the treatment prescribed by the primary-care physician or another specialist was prolonged.

patients (1.9%) had a history of relevant comorbidity: one with cystic fibrosis and the other with recurrent acute otitis media (AOM). None of the patients had a history of antibiotic allergies. A total of 8.7% ($n = 9$) were already receiving antibiotic therapy before seeking emergency care.

The antibiotic therapy prescribed was considered inappropriate in 57.7% ($n = 60$). [Table 1](#) presents the total numbers and percentages of antibiotic prescription appropriateness and inappropriateness, categorized by clinical entities. The reasons for classifying prescriptions as inappropriate were antibiotic therapy not indicated in 40% ($n = 24$), inappropriate active ingredient in 30% ($n = 18$), and incorrect dosage in 30% ($n = 18$) of the cases. [Table 2](#) provides a detailed breakdown of the main reasons for inappropriate prescriptions, both overall and according to specific clinical entities.

Incorrect dosage included errors in dosing, duration, timing, and formulation. It is worth mentioning that there

TABLE 1. Appropriate and inappropriate antibiotic prescription by diagnosis.

Prescription by diagnosis	Appropriate		Inappropriate		TOTAL
	N	%	N	%	N
AOM	20	44.4	25	55.6	45
APT	11	55	9	45	20
LRTI	5	45.5	6	54.5	11
UTI	3	37.5	5	62.5	8
Skin and soft tissue infection	1	14.3	6	85.7	7
Typical pneumonia	3	50	3	50	6
URTI	0	0	3	100	3
Acute cervical lymphadenitis	1	50	1	50	2
Sinusitis	0	0	2	100	2
TOTAL	44	42.3	60	57.7	104

AOM: acute otitis media; APT: acute pharyngitis and tonsillitis; LRTI: lower respiratory tract infections; UTI: urinary tract infections; URTI: upper respiratory tract infections

TABLE 2. Reasons of inappropriate antibiotic prescription by clinical entity and overall.

Diagnosis	Antibiotic not indicated N (%)	Inappropriate active ingredient N (%)	Incorrect dosing N (%)	Total N (%)
AOM	9 (36%)	8 (32%)	8 (32%)	25 (41.7%)
APT	7 (77.8%)	2 (22.2%)	0 (0%)	9 (15%)
Skin and soft tissue infection	1 (16.7%)	1 (16.7%)	4 (66.7%)	6 (10%)
LRTI	3 (50%)	0 (0%)	3 (50%)	6 (10%)
UTI	0 (0%)	3 (60%)	2 (40%)	5 (8.3%)
Typical pneumonia	0 (0%)	2 (66.7%)	1 (33.3%)	3 (5%)
URTI	3 (100%)	0 (0%)	0 (0%)	3 (5%)
Sinusitis	1 (50%)	1 (50%)	0 (0%)	2 (3.3%)
Acute cervical lymphadenitis	0 (0%)	1 (100%)	0 (0%)	1 (1.7%)
TOTAL	24 (40%)	18 (30%)	18 (30%)	60 (100%)

AOM: acute otitis media; APT: acute pharyngitis and tonsillitis; LRTI: lower respiratory tract infections; UTI: urinary tract infections; URTI: upper respiratory tract infections.

were 3 patients in whom 2 errors occurred simultaneously. Thus, incorrect dosage was identified in seven patients, incorrect duration in 10 patients, and incorrect formulation in four patients.

Antibiotics prescribed, in order of frequency were amoxicillin in 54.8% (n= 57), amoxicillin-clavulanic acid in 19.2% (n=20), azithromycin in 11.5% (n= 12), cefixime in 6.7% (n= 7), cefuroxime in 2.9% (n= 3), josamycin and fosfomicin both in 1.9% each (n= 2), and penicillin V in 1% (n= 1). [Figure 2](#) lists the antibiotics prescribed by frequency in each of the clinical entities.

The appropriateness of antibiotic prescribing was analyzed across different age groups, but no statistically significant differences were observed. [Figure 3](#) shows the rates of inappropriate prescription in each age group.

DISCUSSION

After evaluating the prescribed antibiotic therapy and analyzing the data, an inappropriate prescription rate of 57.7% (n= 60) was observed. Comparing these results with

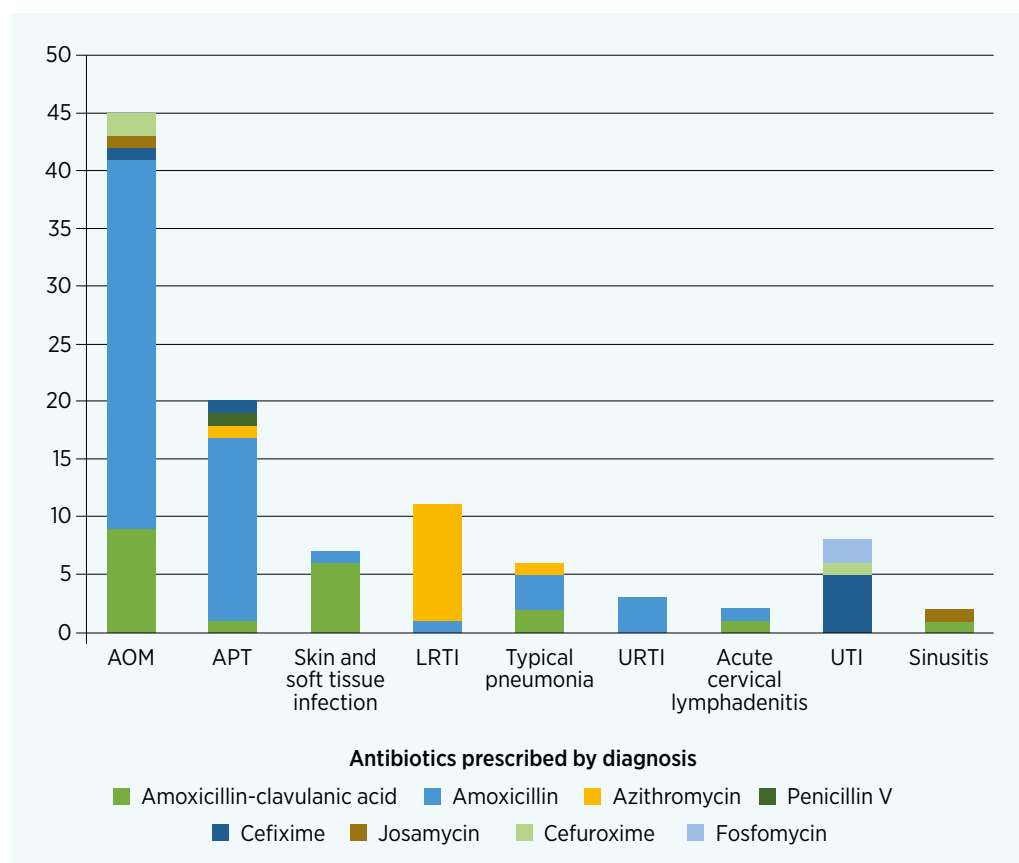


FIGURE 2. Bar graph showing antibiotics prescribed according to frequency for each diagnosis.

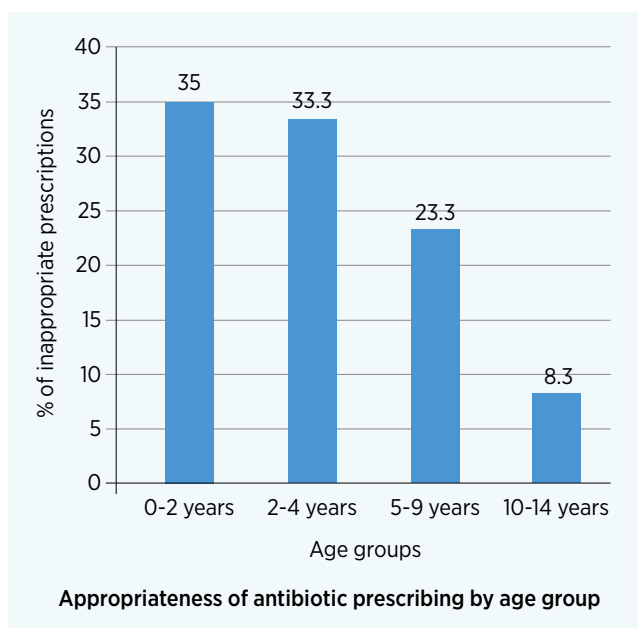


FIGURE 3. Bar graph showing the rates of inappropriate prescribing by age.

those of other studies conducted in Spain is challenging due to the methodological differences between them and the limited number of studies evaluating antibiotic prescribing in pediatric emergency departments.

The study conducted by Croche-Santander et al.⁽⁴⁾ evaluated the inappropriate use of antibiotic therapy in pediatric emergency departments and identified a 51.9% rate of inappropriate prescriptions. In our study, a similar methodology was followed, although some differences should be noted: the duration of that study was longer (one year), the sample was randomly selected (while in our study a sample of consecutive cases was used), and the guidelines and documents used as a reference to assess the appropriateness of the prescription were specific to that hospital (whereas in our study, national guidelines and consensus documents were used).

The study conducted by Durán-Fernández-Feijóo et al.⁽⁷⁾ assessed antibiotic prescribing in children under 18 years of age diagnosed with AOM, acute pharyngitis and tonsillitis (APT), and community-acquired pneumonia (CAP) in pediatric emergency departments over a one-year period. Inappropriate prescribing was found in 22.3% of the cases. In that study, the study period was longer, the sample was selected through randomization, and only three clinical entities were studied as diagnoses. In addition, the discharge records were reviewed by two investigators, with consultation of a third in case of discrepancies, and the guidelines and documents used as references were also specific to the center itself.

The study by Vallano-Ferraz et al.⁽⁸⁾ evaluated antibiotic therapy prescribed in children aged 0-18 years with a diagnosis of acute bronchitis and bronchiolitis at pediatric emergency departments of different Spanish hospitals. Inappropriate prescribing was found in 26% of cases. However, this was a multicenter study, the study period was longer (5 months), the sample was randomly selected, only two diseases were studied, and patients who were admitted to the hospital were not excluded.

Regarding the reasons for inappropriate prescribing in our study, the most frequent cause was the prescription of antibiotics when not indicated for the particular case, followed by the use of an inappropriate active ingredient and incorrect dosage, both occurring at the same rate.

In terms of the most common reasons for inappropriate prescribing and diseases involved in the errors, the following should be highlighted:

Prescription of antibiotic therapy that was not indicated mainly occurred in:

- Cases of AOM that did not meet criteria for immediate treatment.
- Cases of APT that did not meet ≥ 2 McIsaac criteria or did meet the criteria but did not undergo a *Streptococcus pyogenes* or group A *Streptococcus* (GAS) rapid antigen detection test (RADT) or culture to confirm suspicion. It is noteworthy that treatment based solely on symptoms and signs of APT would be inappropriate in at least 30% of cases⁽¹²⁾.
- Cases of upper respiratory tract infections (URTI), in which antibiotic treatment was not indicated as the first-line choice.
- Cases of lower respiratory tract infections (LRTI) that did not require treatment.

Regarding the prescription of an inappropriate active ingredient, the following was observed:

- In cases of AOM, the most frequent reason for this error was the prescription of amoxicillin-clavulanic acid in patients who met the criteria for treatment with amoxicillin.
- Cases of APT in which azithromycin and amoxicillin-clavulanic acid were prescribed due to vomiting, whereas the penicillin G benzathine is the treatment of choice in this situation or in case of poor compliance⁽¹⁶⁾.
- Cases of typical CAP in which amoxicillin-clavulanic acid and azithromycin were erroneously prescribed, while amoxicillin is the treatment of choice.
- Cases of lower urinary tract infection (UTI) in which third generation cephalosporins (cefixime) were prescribed but are not the treatment of choice.

Regarding dosage errors:

- The most frequent was the incorrect duration of treatment, which is consistent with the findings of other studies^(4,7).
- Regarding dosing, the most important cases were those of AOM in which an inadequate dose was prescribed, mainly consisting of an insufficient dose of amoxicillin, which did not reach a minimum of 75 mg/kg/day.

In our series, the most frequently used antibiotics were broad-spectrum penicillin's, accounting for 74% of the total prescriptions (54.8% for amoxicillin and 19.2% for amoxicillin-clavulanic acid). These findings are consistent with those observed in other studies, which reported 57.7%⁽⁴⁾ and 94%⁽⁷⁾. The next most frequently prescribed antibiotics were macrolides (azithromycin) in 11.5% of the cases, a proportion that aligns with frequencies found in other studies ranging from 5% to 10%⁽⁴⁾.

The diseases associated with the highest rate of inappropriate prescriptions in absolute numbers were AOM (41.7%), APT (15%), skin and soft tissue infections and LRTI (10% each). Again, the former two accounted for the highest rates of

inappropriate prescriptions in other studies^(4,7). It should be noted, however, that the clinical entities in which inappropriate antibiotics were most commonly prescribed were skin and soft tissue infections (85.7%) and UTIs (62.5%).

Interestingly, 68.3% of inappropriate prescriptions occurred in the 0-4 age group (35% in the 0-2 age sub-group and 33.3% in the 2-4 age sub-group), while the 5-9 age group accounted for 23.3% of inappropriate prescriptions and the 10-14 age group for 8.3%. This trend in antibiotic prescribing by age group has also been reported in other studies conducted in outpatient settings^(9,10).

Our study has limitations related to the cross-sectional observational design and the retrospective data collection. Information bias may have been present during data collection due to inaccuracies or omissions in patients' discharge reports concerning clinical aspects, diagnosis, antibiotic therapy, dosage, allergies, previous treatment, or comorbidities. In addition, the challenge of identifying the infectious etiology of various clinical processes should be acknowledged. Other possible limitations are that we did not take into account aspects of treatment adherence or self-medication, which could provide a more comprehensive view of the actual use of antibiotics. Further limitations that need to be considered when interpreting the results are the inability to assess a possible seasonal pattern as the analysis was restricted to a period of one month only and the small sample size. It should also be noted that the antibiotic prescribing was analyzed in outpatients, i.e., those who were discharged from the hospital. This factor should be taken into account when interpreting the results in terms of the overall diseases, since the appropriateness of prescriptions in patients who were admitted to the hospital was not assessed.

One of the strengths of the study was that all the patients seen at the emergency department during the study period were reviewed, together with an analysis of the main variable by disease and age group. This approach allows for a high degree of representativeness of the study population and its easy reproducibility. Similar to the study of Croche Santander et al.⁽⁴⁾, which inspired our work, the study design may be helpful to conduct studies with similar characteristics enabling the collection and comparison of prescription data related to antibiotic use to evaluate the quality of antibiotic prescribing. Consequently, this study may serve as a foundation to initiate prospective or multicenter studies with larger sample sizes⁽³⁾.

Regarding the implications for clinical practice, this type of study provides valuable information to evaluate the current state of antibiotic prescribing in a pediatric emergency department. It therefore serves as a first step in identifying strengths and good practices as well as shortcomings and weaknesses and may pave the way for the implementation of strategies including the creation of PROA teams and the conduction of follow-up studies, as mentioned above. It should also be taken into account that at the time of the study the center did not have either an established PROA team or specific clinical practice guidelines in place.

In conclusion, it is noteworthy that more than half of the analyzed prescriptions were found to be inappropriate. The understanding of the extent of inappropriate prescriptions and the underlying reasons offers an opportunity to improve

the quality of care by identifying the shortcomings or weaknesses, which is the starting point for implementing corrective strategies, including PROA teams and training courses.

The study was conducted at the Department of Pediatrics, Hospital Universitari Sant Joan d'Alacant, Alicante, Spain, and the Departments of Pharmacology, Pediatrics, and Organic Chemistry, Universidad Miguel Hernández de Elche, Alicante, Spain.

The authors declare that they have no conflicts of interest and that the study received no public or private funding.

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ANNEX 1.

The following observations were taken into account to establish the criteria for appropriate antibiotic prescribing in different diseases:

- In general, the doses were considered not appropriate in terms of quantity if they did not coincide with the doses established in the guidelines and documents consulted. However, it is worth mentioning the specific case of high doses of amoxicillin: As the standard is 80 mg/kg/day, the dose prescribed was inappropriate if it was less than 75 mg/kg/day.
- Regarding formulation, the main aspect taken into account was the adequate concentration or proportion of the active ingredient.
- For AOM, the criteria for immediate initiation of antibiotic therapy were: children under 2 years of age, especially under 6 months; children with bilateral AOM, severe symptoms (defined as fever > 39°, intense otalgia of more than 48 hours of evolution, general condition) or otorrhea (not due to otitis externa); children with a history of recurrent/persistent AOM or a family history of AOM sequelae; any age at which good follow-up cannot be guaranteed. In the remaining cases, a watch-and-wait approach or deferred antibiotic treatment was considered correct⁽¹⁶⁾. The criteria for the administration of amoxicillin-clavulanic acid or cefuroxime-axetil were the following: children under 6 months of age, severe AOM in children under 2 years of age, family history of AOM sequelae, recurrent AOM, history of failure of previous treatment with amoxicillin, AOM with purulent conjunctivitis (since the most frequent etiology is *H. influenzae*), and previous antibiotic treatment with amoxicillin in the past 30 days.

- To evaluate antibiotic prescribing in patients with APT, we evaluated the clinical findings in the discharge report using the McIsaac criteria to estimate the probability of pre-test streptococcal tonsillitis, and the relevance of performing a GAS RADT or culture in those who met two or more criteria^(12,16).

The following criteria have been approved for antibiotic prescription: GAS APT confirmed by RADT or culture, APT with high suspicion of GAS with a negative RADT and a pending culture result, APT coinciding with cases of confirmed streptococcal infection within the family environment, and a history of acute rheumatic fever in either the child or a cohabiting relative^(12,16). Patients who did not meet these criteria, for example, with clinical suspicion without RADT or culture confirmation, the prescription was considered inappropriate. Although the recommended dosage regimen is every 12 hours, the 8-hour regimen was considered appropriate if the antibiotic and dose were the first-line choice.

- In skin and soft tissue infections, the formulation of amoxicillin-clavulanic acid was taken into account for the appropriate prescription. In several patients an 8:1 formulation was prescribed, while for the pathogens that mostly cause these infections (gram-positive cocci) the appropriate formulation is 4:1; As a result, in those instances, a higher absolute amount of clavulanic acid was administered than required to achieve adequate doses of amoxicillin⁽¹⁶⁾.