ORAL DRUG CHALLENGE IN DRUG HYPERSENSIVITY REACTIONS AND ITS SAFETY

Lorena Stella∗,1, Joana Soares∗∗, Adriana Ferreira∗∗, Fátima Praça∗∗, Jorge Romariz∗∗∗, Herculano Costa∗∗∗ and Claudia Pedrosa∗∗∗

∗Pediatrics Department, Centro Hospitalar de Vila Nova de Gaia/Espinho, EPE., ∗∗Pediatrics Department, Centro Hospitalar do Tmega e Sousa, EPE., ∗∗∗Immunoallergology and Pediatric Pulmonology Unit, Pediatrics Department, Centro Hospitalar Vila Nova de Gaia/Espinho, EPE.

ABSTRACT

Introduction: Drug allergy is a common suspicion in the pediatric age, although rarely confirmed. Considering its relevance in therapeutic decisions, the definitive diagnosis is important. The oral drug challenge has a significant role in confirming the diagnosis and finding safe alternative treatment options. Objectives: Characterize a pediatric population submitted to oral drug challenge in a level III hospital and evaluate the safety and need of a venous catheter. Materials and methods: A retrospective study includes all oral drug challenges performed between January 2018 and December 2020 in patients younger than 18 years. Results: 186 oral drug challenges were performed during the study period, 85.5% were performed either to confirm or exclude the diagnosis, and the remaining 14.5% were designed to choose a safe alternative regimen. The median age was 5 years. Personal history of atopy was positive in 24.3% of patients. Amoxicillin was the tested drug in 42.5% of the sample, and amoxicillin was associated with clavulanic acid in 22%. In 38% of cases, the manifestations appeared within the first 24 hours. There were 2.1% (n=4) positive oral drug challenges, and the drugs were amoxicillin (2 cases), paracetamol and ibuprofen. Conclusions: Allergy to drugs is rare in pediatric age, but its suspicion is common. Considering its relevance in therapeutic decisions, referring all suspected cases to diagnostic clarification is important. There was no record of any serious reaction in our sample, namely anaphylaxis, requiring iv medication. The oral drug challenge is essential in confirming or excluding hy-persensitivity and is a safe procedure.

KEYWORDS Allergy drugs, oral challenge, safety

Abbreviations:

• IDT: intradermal tests
• NSAIDs: non-sterooidal anti-inflammatories
• ODC: oral drug challenge
• STP: skin prick test

SSLR: serum sickness-like reactions

Introduction

Suspected drug allergy is a frequent cause for consultation in the pediatric age. The majority of the reactions in children are attributed to beta-lactams (BL), followed by non-steroidal anti-inflammatories (NSAIDs) and non-β-lactam antibiotics.[1]

Hypersensitivity reactions are divided into immediate or non-immediate. The former usually occurs within an hour after the drug administration and are mediated by specific IgE antibodies. The latter manifest more than one hour after taking the drug and can be mediated by T cells.[2]

A definitive diagnosis is important to establish the proper treatment and correct preventive measures. The diagnostic approach involves taking a thorough clinical history and detailed
Objective exam in cases of suspected hypersensitivity. When an IgE-mediated reaction is suspected, it is useful to perform skin prick test (STP) and intradermal tests (IDT), specific immunoglobulin E (IgE) test or basophil activation test (BAT). [3,4] If a T-cell-mediated reaction is suspected, lymphocyte transformation test (LTT) or delayed-read ing intradermal/epicutaneous tests can be useful. [3-5] Epicutaneous tests are especially useful for non-immediate hypersensitivity to anticonvulsants and NSAIDs. Skin prick tests have low sensitivity, and intradermal tests are painful and hardly tolerated by young children.[1]

The oral drug challenge (ODC) has an essential role in diagnosing these situations, allowing to confirm or exclude drug allergy and find safe alternative treatment options.[6] Although controversy subsists between different protocols, it is consensual that this test should always be carried out in a hospital setting, under clinical surveillance. Increasing doses should be used, with varying time intervals, from 30 minutes to a week.

Objectives
This study aimed to characterize the pediatric population submitted to oral drug challenge, with thorough analyses of the positive cases and to evaluate the safety and need of a venous catheter.

Material and Methods
We carried out a retrospective analysis of the clinical files of patients submitted to ODC from January 1st 2018, to December 31st 2020. The following variables were included: gender, age, referral provenance, personal and family history of atopy, suspected drug(s), clinical manifestations, the time interval between drug administration and the onset of symptoms, drug-specific IgE, skin prick test (STP) and intradermal tests (IDT), the result of the ODC. For descriptive analysis of the data, the software Statistical Package for the Social Sciences® (SPSS), version 22.0, was used.

Results
The study comprised 173 patients, 54.3% male (n=94). The median age was 5 years (3 months - 17 years). Personal history of atopy was positive in 24.3% (n=42) of patients. During the study period, 186 ODC were performed, 66 in 2018, 77 in 2019 and 43 in 2020, related to the pandemic context.

The average number of years between the episode and the completion of the ODC was 2.7 years. Regarding the ODC performed, 85.5% (n = 159) were used to reach a diagnosis (confirmation or exclusion) whereas the remaining 14.4% (n = 27) were conducted to test alternative drugs (ce-furoxime in 85% cases) The majority of the tests involved amoxicillin (79 tests - 42.5%) and the association of amoxicillin-lin and clavulanic acid (41 tests - 22%). The remaining drugs were ibuprofen (n = 16 - 0.6%), ce-furoxime (n = 9 - 4.8%); paracetamol (n = 4 - 2.1%); azithromycin (n = 2 - 1.1%); fluoxacillin (n = 2 - 1.1%); and others (n= 6 - 3.2%) (Figure 1).

The main clinical manifestations were mucocutaneous (n= 143 - 92.8%). Serum sickness-like re-actions (SSLRs) were found in 7.1% of cases (n = 11). Two cases of anaphylaxis were reported, both treated with adrenalin. In 38% of cases (n=60), the manifestations appeared within the first 24 hours, with 17% of cases (n=27) occurring in the first hour. The average number of days between drug administration and clinical manifestations was 3.5 days. Measurements of specific IgE for penicillin G, penicillin V and Amoxycillin were performed in 43.5% of cases (n=81).

In 39.8% (n=74), STP and IDT were performed, with 6 positive tests for clavulanic acid (the child subsequently tolerated amoxicillin in ODC). Oral drug challenge was negative in 97.8% of patients (n = 182) and positive in 2.1% (n = 4), and the drugs were amoxicillin (in 2 cases), paracetamol and ibuprofen (Table 1).

Discussion
Clinical manifestations of drug allergy can be diverse and often similar to other common pediatric pathologies, like a bacterial or viral rash [1] Diagnosis can be challenging, especially at younger ages, where cutaneous manifestations of infectious diseases are more frequent.

The most common suspected drugs were antibiotics, namely beta-lactams, which agrees with the literature.[1] Mucocutane ous manifestations were the commonest, most of these with late-onset, consistent with the literature. Most children were not submitted to prior STP or IDT or specific serum IgE testing, supported by the literature.[1]

Of the 186 suspected drug allergy cases that underwent ODC, the diagnosis was excluded in 182 cases. This study aimed to assess the safety of drug provocation tests, a fundamental tool in diagnosing hypersensitivity. However, the low positivity (< 5%) we observed using this technique further highlights the need to carry out provocation tests further. ODC did not confirm the 2 cases of anaphylaxis described, and from the 11 patients who had sus-pectected serum sickness-like reactions, only 1 had positive ODC. This is a safe approach when performed in a hospital setting. There was no record of any serious reaction, namely anaphylaxis, and no patient required iv medication in our study. In the particular case of patients with penicillin allergy, there is an increased risk of adverse reactions to cephalo-sporins, so their tolerance must also be tested, as performed in the presented cases. [7]

Conclusion
True drug allergy is rare in the pediatric age. Nevertheless, although rare, its suspicion is com-mon, especially with beta-lactams. Clinical manifestations are diverse, with the most common reactions being non-immune maculopapular rashes and urticaria. Thus, the main differential diagnosis is a viral infection. Considering its relevance in therapeutic decisions, it is important to refer to all the suspected cases in order to clarify the diagnosis. Therefore, the oral drug challenge is the gold standard in diag-nosing hypersensitivity. Furthermore, these allow unnecessary antibiotic evictions to be done away with and contribute to an important cost reduction [8]. It should be noted that in the case of antibiotics, unnecessary evictions lead to increased consumption of second-line drugs, which could lead to microbial resistance, with a visible impact on pub-lic health [9]. The reduced rate of adverse reactions in the tests, their easy control and the absence of hospital admissions allow us to conclude that provocation tests are suitable and safe. Therefore, this study supports the unnecessity of venous catheters in children submitted to ODC. It can be used only in high-risk patients. As reflected in the present series, its implementation is acceptable even without previous skin tests in children with non-severe maculopapular exanthemas or non-immediate urticaria.
### Table 1: Description of cases whose oral drug challenge was positive.

<table>
<thead>
<tr>
<th>Case</th>
<th>Age</th>
<th>PH of atopy</th>
<th>FH of atopy</th>
<th>Suspected drug</th>
<th>Reaction</th>
<th>Specific IgE</th>
<th>STP and IDT</th>
<th>ODC</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>7y</td>
<td>yes</td>
<td>no</td>
<td>amoxicillin</td>
<td>9 days after, SSLR</td>
<td>negative</td>
<td>negative</td>
<td>positive (9 days after, urticaria)</td>
</tr>
<tr>
<td>2</td>
<td>16y</td>
<td>no</td>
<td>yes</td>
<td>paracetamol</td>
<td>immediate, urticaria</td>
<td>unrealized</td>
<td>negative</td>
<td>positive (20 minutes after, swollen lips)</td>
</tr>
<tr>
<td>3</td>
<td>3y</td>
<td>no</td>
<td>yes</td>
<td>amoxicillin</td>
<td>10 days after, maculopapular exanthema</td>
<td>negative</td>
<td>unrealized</td>
<td>positive (1 hour after, urticaria)</td>
</tr>
<tr>
<td>4</td>
<td>6y</td>
<td>yes</td>
<td>yes</td>
<td>ibuprofen</td>
<td>immediate, urticaria</td>
<td>unrealized</td>
<td>unrealized</td>
<td>positive (1 hour after, eyelid edema)</td>
</tr>
</tbody>
</table>

PH: personal history; FH: family history; SSLR: serum sickness-like reactions; STP: skin prick test; IDT: intradermal tests; ODC: oral drug challenge

### Author contributions

All authors have contributed to this work: Lorena Stella was a major contributor in collecting data and writing the manuscript. Joana Soares and Adriana Ferreira had an important role in collecting data and formal analysis; Cláudia Pedrosa critically reviewed the study proposal; Fátima Praça, Jorge Romariz and Herculano Costa reviewed and edited the manuscript. All authors read and approved the final manuscript.

### Funding

This work did not receive any grant from funding agencies in the public, commercial, or not-for-profit sectors.

### Conflict of Interest

There are no conflicts of interest to declare by any of the authors of this study.

### References


