

# Prevalence of Hypersensitivity Reactions in Children Associated with Acetaminophen: A Systematic Review and Meta-Analysis

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## Keywords

Acetaminophen · Allergy · Hypersensitivity · Paracetamol · Pediatrics

## Abstract

**Background:** Acetaminophen is the most commonly used antipyretic in children. However, there are limited data assessing hypersensitivity reactions related to acetaminophen usage. **Objectives:** To conduct a systematic review to characterize reported reactions to acetaminophen in adults and children, and perform a meta-analysis to assess the prevalence of acetaminophen hypersensitivity in children with a suspected acetaminophen allergy. **Methods:** We performed a systematic review of studies reporting hypersensitivity reactions to acetaminophen by searching 2 electronic databases. From the selected studies, we included those assessing the prevalence of acetaminophen hypersensitivity by performing oral challenge in our meta-analysis. **Results:** Eighty-five studies were included in the systematic review, assessing a total of 1,030 participants. Immediate (within 1 h of exposure) hypersensitivity reactions were reported in >25% of the articles, while cutaneous nonimmediate reactions were similarly reported in about 25% of the articles. The remaining articles reported Steven-Johnson syndrome/tox-

ic epidermal necrolysis, fixed drug eruptions, and cross-intolerance reactions. Five pediatric studies were included in our meta-analysis. The prevalence of acetaminophen hypersensitivity reaction among children undergoing oral challenge was 10.1% (95% confidence interval 4.5–15.5). **Conclusion:** Future studies assessing the risk of immediate and non-immediate hypersensitivity reactions to acetaminophen and elucidating the mechanism of acetaminophen hypersensitivity reactions are required.

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## Introduction

Acetaminophen is the most commonly used antipyretic medication in children and is also often used to treat pain [1]. Although hepatotoxicity related to acetaminophen overdosing has been well documented [2], acetaminophen hypersensitivity is a rare event [3], and very little is known about the hypersensitivity reactions related to appropriate dosing. Most reported cases of hypersensitivity reactions to acetaminophen involve the skin, in-

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cluding nonimmediate cutaneous eruptions [4], fixed drug eruptions [5], Steven-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN) [6, 7], and anaphylaxis [8]. A type I hypersensitivity reaction, or immediate hypersensitivity reaction, occurs within <1 h after drug exposure, and includes symptoms of urticaria, angioedema, wheezing, hypotension, abdominal pain, and diarrhea [9]. Type IV hypersensitivity reactions are the most common type of nonimmediate reactions, developing 6 h to 10 days after exposure. The reaction is T cell-mediated and usually manifests as a delayed cutaneous reaction, but may have various clinical presentations [9]. Reactions to acetaminophen are reported mostly in association with suspected reactions to nonsteroidal anti-inflammatory drugs (NSAIDs) [3, 4]. Given that there are no validated skin tests, establishing the diagnosis of acetaminophen hypersensitivity relies completely on conducting oral challenges [10, 11].

In studies assessing tolerance for both NSAIDs and acetaminophen, it is reported that the prevalence of acetaminophen hypersensitivity in children reporting allergy to NSAIDs is 4–25% [10, 12]. However, despite the widespread use of acetaminophen in pediatrics, there are limited data regarding the true risk of acetaminophen hypersensitivity in children suspected to have sensitivity to this drug. We aimed to review studies on acetaminophen allergy in adults and children, and to define the prevalence of acetaminophen hypersensitivity in cases with suspected reactions to acetaminophen in children. We will present a pediatric case of an established acetaminophen hypersensitivity, and conduct a systematic review to characterize these reactions in children.

## Case Report

A 6-year-old boy was referred to our allergy clinic for the investigation of a possible hypersensitivity to acetaminophen. At the age of 5 years, the patient was treated at home with acetaminophen for fever, and developed pancorporal urticaria with swelling and pruritus of the eyes 45 min after ingestion. The reaction was treated with oral antihistamines, and resolved completely in 1.5 h. This was not his first exposure to the drug, with at least 1 previous episode of urticaria after acetaminophen exposure reported. The patient has a known allergy to cats. We conducted a graded oral challenge to acetaminophen (Tempra; 50 mg and 20 min later, 500 mg) at the allergy clinic. Three hours after the 500-mg dose, while at home, the patient experienced mild urticaria and angioedema, was treated with oral antihistamines, and returned to the emergency department. At the emergency department, he was prescribed another oral antihistamine (cetirizine) and instructed to avoid acetaminophen. The symptoms resolved after 24 h. The patient returned to our clinic 1 week later for oral challenge with ibuprofen, which was negative.

## Methods

### *Data Sources and Searches*

We conducted a systematic review and meta-analysis of studies that reported the prevalence of hypersensitivity among patients reporting a reaction to acetaminophen. The review was conducted using the PubMed and Embase databases of work published in English and French in the past 10 years, i.e., from January 2007 to January 2017, inclusively.

### *Inclusion and Exclusion Criteria*

We included relevant studies on both children and adults for the systematic review. We focused on studies evaluating both immediate and nonimmediate reactions to acetaminophen. To select the appropriate studies from the search results, the general topic of each article was assessed from the abstract. In certain countries, acetaminophen is best known under the name paracetamol. We therefore included this nomenclature into our research. Studies not pertaining to acetaminophen hypersensitivity were immediately rejected. The articles were then read completely, and were rejected if they were not original articles or had no history consistent with acetaminophen hypersensitivity.

For the meta-analysis, studies were only eligible if the sample size was  $\geq 10$ , and if they had established the prevalence of acetaminophen hypersensitivity by skin testing or oral challenge. Additionally, studies evaluating cross-intolerance to acetaminophen in patients reporting NSAID hypersensitivity were excluded from the meta-analysis.

### *Quality Assessment*

The quality of the remaining articles was then assessed (Table 1). The quality assessment process for each article included methods for identifying sampling biases, testing, and data collection methods, and the population's composition, in compliance with the PRISMA guidelines for systematic reviews. The leading author (S.G.) and two coauthors (M.B.-S. and A.L.) independently evaluated each paper's quality.

### *Statistical Analysis*

Using STATA v12 software, a meta-analysis was conducted to compile the data obtained from the systematic review. The author, year, country, and design of the study, the diagnostic allergy test performed, and the authors' definition of a positive skin test and/or oral challenge were also collected. For each study, the sample size was collected as the total number of patients undergoing an oral challenge to acetaminophen, and the numerator was defined to be the number of patients with a positive result.

## Results

### *Search Results*

The initial PubMed and Embase searches yielded 415 and 407 results, respectively, and 631 records were excluded because they were not relevant. Of the remaining 189 records, 88 were rejected as they were conference abstracts, 11 as they were reviews, 1 as it was a question-and-

**Table 1.** Methodological quality of studies included in the meta-analysis

| First author, year                                                                                                                                                         | External validity                                                |                                 | Internal validity |                                  |                                            |                                            | Detection                                       |                                                                                                                                                                                                                                                                                                        |                                    | type of study |                                            |
|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------|------------------------------------------------------------------|---------------------------------|-------------------|----------------------------------|--------------------------------------------|--------------------------------------------|-------------------------------------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|------------------------------------|---------------|--------------------------------------------|
|                                                                                                                                                                            | patients presented with suspected acetaminophen hypersensitivity | patients presented with NSAID-H | STs conducted     | tested with OC when ST negative? | a positive ST reaction was clearly defined | a positive OC reaction was clearly defined | OC considered positive based on objective signs | OC protocol                                                                                                                                                                                                                                                                                            | differences between sexes assessed |               | assessed NSAID-H to ensure no coreactivity |
| Choi [13], 2016                                                                                                                                                            | ✓                                                                |                                 | n.a.              | ✓ <sup>1</sup>                   | n.a.                                       | ✓                                          | ✓                                               | divided doses every 30–60 min until cumulative dose close to the daily dose was reached                                                                                                                                                                                                                | ✓                                  |               | retrospective                              |
| Topal [14], 2016                                                                                                                                                           | ✓                                                                | ✓                               | ✓                 | ✓                                | ✓                                          | ✓                                          | ✓                                               | 4 or 5 escalating doses administered at 60-min intervals until maximum weight-adjusted single dose was reached                                                                                                                                                                                         | ✓                                  | ✓             | retrospective                              |
| Güvenir [15], 2015                                                                                                                                                         | ✓                                                                | ✓                               | ✓                 | ✓                                | ✓                                          | ✓                                          |                                                 | divided doses every 30 min until cumulative dose close to the age- and weight-adjusted daily dose was reached                                                                                                                                                                                          |                                    | ✓             | prospective                                |
| Loh [16], 2015                                                                                                                                                             | ✓                                                                | ✓                               | n.a.              | ✓ <sup>1</sup>                   | n.a.                                       | ✓                                          | ✓                                               | 4 doses of 25% of the age-appropriate daily dose administered every 60 min                                                                                                                                                                                                                             |                                    | ✓             | retrospective                              |
| Rojas-Perez-Ezquerri [17], 2014                                                                                                                                            | ✓                                                                |                                 | ✓                 | ✓                                | ✓                                          |                                            |                                                 | single-blind placebo step followed by 3 increasing doses (250, 500, and 1,000 mg) at 60-min intervals                                                                                                                                                                                                  |                                    | ✓             | prospective                                |
| Renaudin [18], 2013                                                                                                                                                        | ✓                                                                |                                 | ✓                 | ✓                                | ✓                                          | ✓                                          | ✓                                               | not described                                                                                                                                                                                                                                                                                          |                                    | ✓             | retrospective                              |
| Thalayasingam [19], 2013                                                                                                                                                   | ✓                                                                | ✓                               | ✓                 | ✓                                | ✓                                          | ✓                                          | ✓                                               | administered in incremental doses (1:100, 1:10, and remaining therapeutic dose) at 20-min intervals                                                                                                                                                                                                    |                                    | ✓             | retrospective                              |
| Rutkowski [3], 2012                                                                                                                                                        | ✓                                                                |                                 | ✓                 | ✓                                | ✓                                          | ✓                                          | ✓                                               | starting dose determined by severity of the index reaction (range 50–1,000 mg) was doubled at 60-min intervals until 1,000 mg reached                                                                                                                                                                  |                                    | ✓             | retrospective                              |
| Chalabianloo [20], 2011                                                                                                                                                    | ✓                                                                |                                 | ✓                 | ✓                                | ✓                                          | ✓                                          | ✓                                               | gradually increasing doses (a quarter, a half, and the whole single therapeutic dose) at 30-min intervals                                                                                                                                                                                              | ✓                                  |               | retrospective                              |
| Hassani [21], 2008                                                                                                                                                         | ✓                                                                | ✓                               | n.a.              | ✓ <sup>1</sup>                   | n.a.                                       | ✓                                          | ✓                                               | received a first dose of 1 or 10 mg, depending on the severity of the reaction; gradually increased at 20-min intervals until the appropriate age- and weight-adjusted daily cumulative dose was reached; for the next 2 days, half the therapeutic dose at 9 a.m., half at 12 p.m., and then observed | ✓                                  | ✓             | prospective                                |
| NSAID-H, nonsteroidal anti-inflammatory drug hypersensitivity; ST, skin test; OC, oral challenge; n.a., not applicable.<br><sup>1</sup> OC was performed with no prior ST. |                                                                  |                                 |                   |                                  |                                            |                                            |                                                 |                                                                                                                                                                                                                                                                                                        |                                    |               |                                            |

NSAID-H, nonsteroidal anti-inflammatory drug hypersensitivity; ST, skin test; OC, oral challenge; n.a., not applicable.

<sup>1</sup> OC was performed with no prior ST.

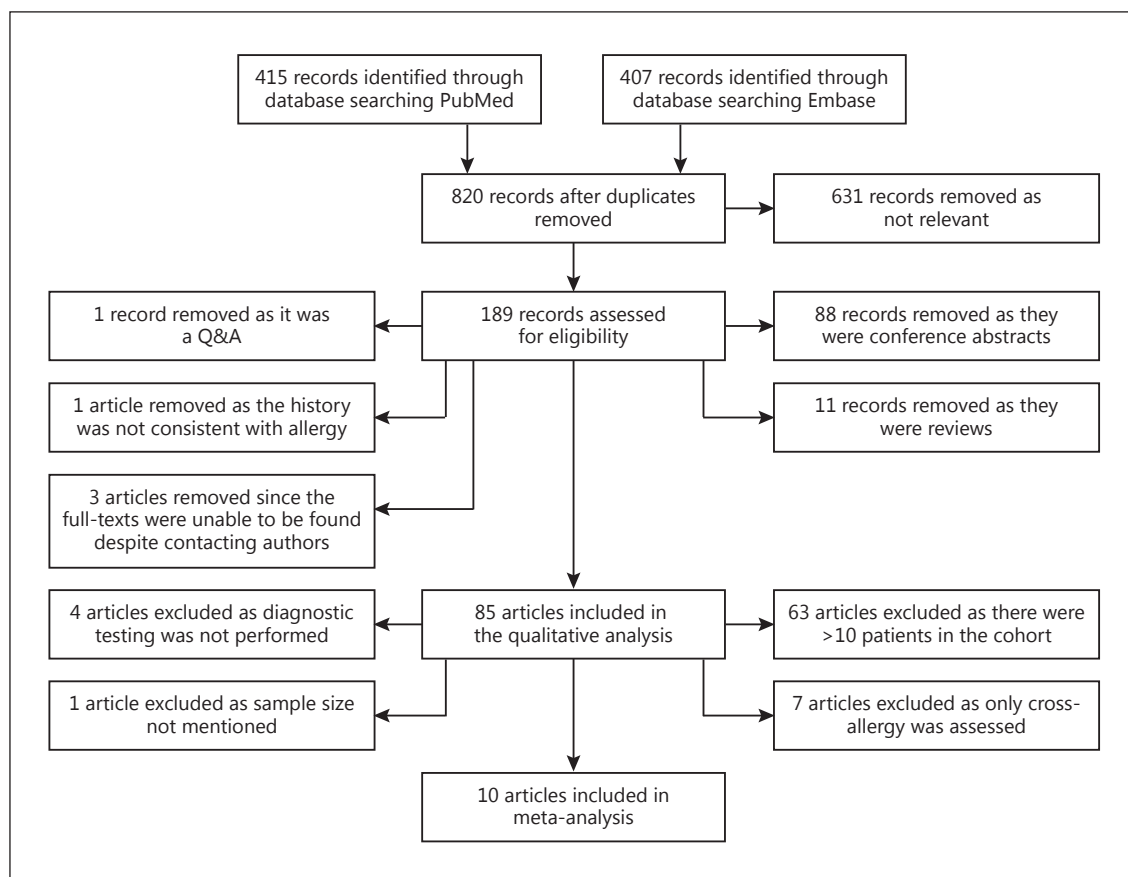


**Fig. 1.** Flow diagram illustrating study selection process.

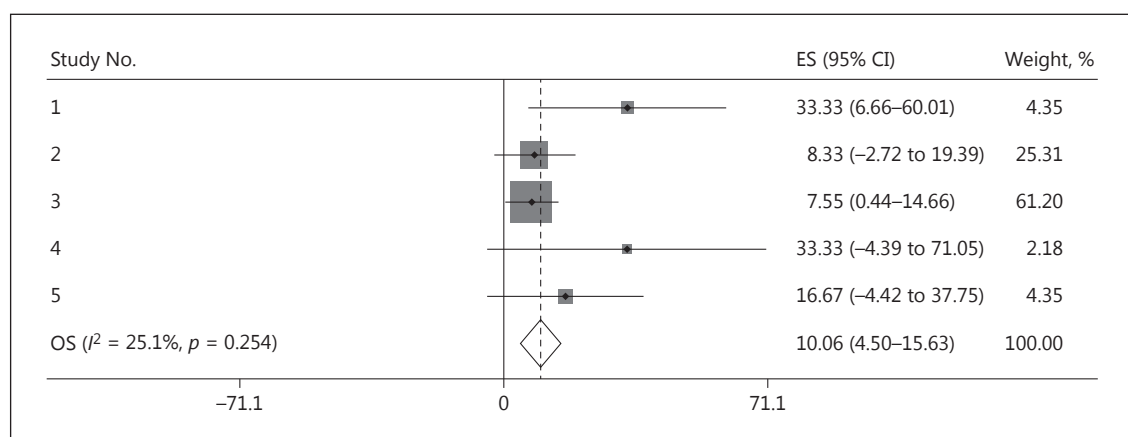


**Fig. 2.** Prevalence of established hypersensitivity to acetaminophen in children among those undergoing oral challenge with the drug. OS, overall survival; ES, effect size.

**Table 2.** Prevalence of acetaminophen hypersensitivity among those undergoing oral challenge to acetaminophen

| First author, year              | Country   | Population      | Hypersensitivity reaction type                          | Patients that underwent OC, <i>n</i> | Confirmed by OC, <i>n</i> | SE    | Prevalence | Confidence interval |
|---------------------------------|-----------|-----------------|---------------------------------------------------------|--------------------------------------|---------------------------|-------|------------|---------------------|
| Choi [13], 2016                 | Korea     | pediatric       | unknown                                                 | 12                                   | 4                         | 13.61 | 33.30%     | 6.66 to 60.01       |
| Topal [14], 2016                | Turkey    | pediatric       | immediate                                               | 24                                   | 2                         | 5.64  | 8.33%      | –2.72 to 19.39      |
| Guenir [15], 2015               | Turkey    | pediatric       | immediate and nonimmediate (fixed drug eruption)        | 53                                   | 4                         | 3.63  | 7.55%      | 0.436 to 14.66      |
| Loh [16], 2015                  | Singapore | pediatric       | immediate                                               | 6                                    | 2                         | 19.25 | 33.33%     | –4.39 to 71.05      |
| Rojas-Perez-Ezquerro [17], 2014 | Spain     | pediatric/adult | immediate and nonimmediate (fixed drug eruption, other) | 10                                   | 10                        | 0.00  | 100.00%    |                     |
| Renaudin [18], 2013             | France    | pediatric/adult | immediate                                               | 10                                   | 5                         | 15.81 | 50.00%     | 19.01 to 80.99      |
| Thalayasingam [19], 2013        | Singapore | adult           | unknown                                                 | 8                                    | 0                         | 0.00  | 0.00%      |                     |
| Rutkowski [3], 2012             | UK        | pediatric/adult | immediate and nonimmediate (other)                      | 31                                   | 15                        | 8.98  | 48.39%     | 32.79 to 65.98      |
| Chalabianloo [20], 2011         | Norway    | pediatric/adult | immediate and nonimmediate (other)                      | 30                                   | 1                         | 3.28  | 3.33%      | –3.09 to 9.76       |
| Hassani [21], 2008              | France    | pediatric       | immediate                                               | 12                                   | 2                         | 10.76 | 16.67%     | –4.42 to 37.75      |

OC, oral challenge; SE, standard error.

answer article, 3 since the full-text articles could not be found despite contacting the authors, and 1 because the history was not consistent with acetaminophen hypersensitivity (Fig. 1). The 85 remaining articles [3, 9, 13–21, 24–97] were included in the qualitative analysis (online suppl. Table S1; for all online suppl. material, see [www.karger.com/doi/10.1159/000487556](http://www.karger.com/doi/10.1159/000487556)).

### Systematic Review

The 85 articles included in the systematic review represented 1,030 adult and pediatric patients with both immediately and nonimmediately reported hypersensitivity reactions to acetaminophen. Over one-quarter of the articles reported immediate reactions, including anaphylaxis. Almost 25% of the articles reported nonimmediate, cutaneous reactions, which excluded SJS/TEN and fixed drug eruption reactions. The other 50% of articles described SJS/TEN, fixed drug eruptions, cross-intolerance reactions, and unknown reactions.

### Meta-Analysis

For the meta-analysis, 63 of the 85 articles were excluded, as they did not have a sample size  $\geq 10$ . Of the remaining articles, 7 were excluded as they only assessed patients reporting NSAID hypersensitivity, 4 because diagnostic allergy testing was not performed, and 1 as the sample size was not reported (Fig. 1). The remaining 10

articles were included in the meta-analysis since they had acceptable methods and they were assessed for their quality (Table 1). This represents a total of 259 patients evaluated for a suspicion of acetaminophen hypersensitivity.

### Prevalence of Hypersensitivity to Acetaminophen in Patients with a Positive Oral Challenge Result

For both adult and pediatric patients, the meta-analysis of patients positive on oral challenge to acetaminophen resulted in a pooled estimate for the prevalence of hypersensitivity to acetaminophen of 10.1% (95% confidence interval [CI] 6.0–14.2; Table 2; online suppl. Fig. S1). The pooled estimate for the prevalence of hypersensitivity to acetaminophen for only the pediatric patients was 10.1% (95% CI 4.5–15.6; Fig. 2).

### Discussion

This is the first study to provide a pooled estimate of acetaminophen hypersensitivity among children with suspected reactions. Our findings revealed that 10% of the children who underwent an oral challenge to acetaminophen had a true hypersensitivity. Due to its widespread use in children, pediatricians should be made aware of the potential for hypersensitivity to acetaminophen in children. By conducting a systematic review of 85 articles, our

results suggest that the percentage of reported reactions were similar for immediate and nonimmediate hypersensitivity reactions to acetaminophen. The majority of the articles about pediatric patients included in our meta-analysis report immediate-type reactions (Table 2), consistent with other studies reporting that acetaminophen and ibuprofen are the most common elicitors of immediate-type reactions in children [22]. While the mechanism underlying acetaminophen allergy is not yet fully understood, we can hypothesize that immediate reactions are likely IgE-mediated, as described by de Paramo et al. [23]. Studies also report a high risk of hypersensitivity to acetaminophen in patients who experience ibuprofen-induced anaphylaxis [24], so it is important to assess cross-intolerance to acetaminophen in such patients.

Our systematic review revealed that in almost half of the articles, an oral challenge to acetaminophen was used, rather than skin tests, to evaluate and diagnose a confirmed hypersensitivity reaction. Due to the absence of standardized skin tests for acetaminophen [12], it is not surprising that the diagnostic approach relies mainly on oral challenge. Our data reinforce the safety of oral challenge to determine acetaminophen hypersensitivity [25], given that the reactions reported were all mild (online suppl. Table S1) and that skin tests are not standardized. Given that the majority of those suspected have negative challenges, all reported cases should be appropriately evaluated in order to correctly establish the diagnosis of acetaminophen hypersensitivity.

Given the overlap in 95% CIs of prevalence in adult and pediatric patients and in pediatric patients only, our analysis did not actually establish a higher risk of acetaminophen hypersensitivity in the pediatric population. Upon analysis of the 5 articles assessing pediatric patients only, the pooled estimate for the prevalence of acetaminophen hypersensitivity did not change significantly; however, the  $I^2$  value fell to <50% indicating less variation across the studies (Fig. 2). Factors such as the age of patients, failing to control for gender effect, and the different definitions of the term “hypersensitivity reactions” could account for the high heterogeneity found when conducting a meta-analysis of all patients (online suppl. Fig. S1). The managing physicians should, appropriately, assess all cases of suspected hypersensitivity to acetaminophen in order to avoid mislabeling of patients as allergic to acetaminophen.

Our study has potential limitations. A selection bias could be found in studies included in our systematic review, i.e., some reports assessed acetaminophen hypersensitivity in patients reporting hypersensitivity reactions

to both acetaminophen and NSAIDs. However, in our meta-analysis, we included only studies in which acetaminophen hypersensitivity reactions were reported and assessed by oral challenge. To ensure no cross-intolerance, the majority of these studies also assessed hypersensitivity to NSAIDs. A potential within-study bias could have been introduced because some reports in our meta-analysis did not clearly indicate the number of patients undergoing oral challenge to acetaminophen, and not all patients underwent the oral challenge. Another limitation of this study is that articles reporting positive oral challenge did not distinguish between immediate and nonimmediate hypersensitivity reactions. Hence, at this point, we are unable to report the risk of immediate versus nonimmediate hypersensitivity reactions to acetaminophen. Another potential limitation relates to the fact that the studies reviewed did not mention the brand of acetaminophen used for oral challenge or assess hypersensitivity to acetaminophen versus other active and inactive ingredients in the acetaminophen preparation, e.g., mannitol.

Future studies are required to develop biomarkers to diagnose true acetaminophen hypersensitivity and develop safe and appropriate oral challenge protocols. Genetic markers associated with an increased risk of acetaminophen hypersensitivity could provide screening tools for individuals suspected to be at an increased risk, e.g., those with previous reactions to NSAIDs.

## Disclosure Statement

The authors have no conflicts of interest to declare.

## Funding Sources

There was no funding.

## Author Contributions

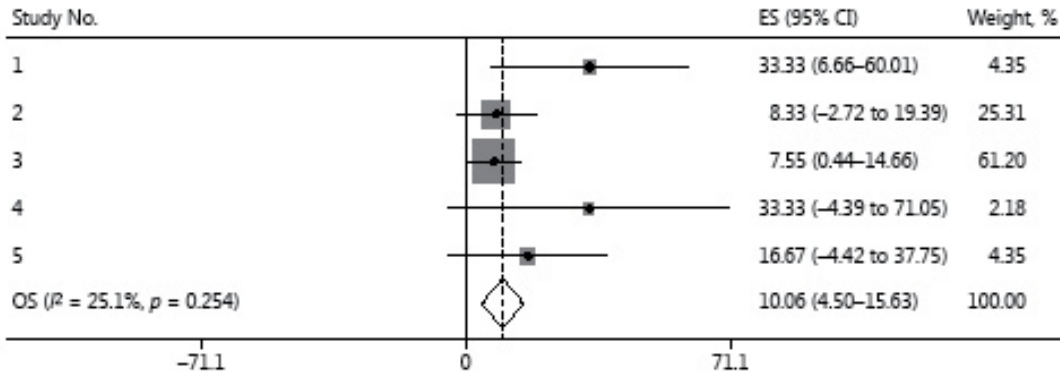
Sofianne Gabrielli contributed to the conceptualization, methodology, and investigation. She curated the data, performed formal analysis, wrote the initial manuscript, and edited the manuscript. Moshe Ben-Shoshan was involved in the supervision and oversight, and contributed to the methodology, data curation, and formal analysis. He was involved in reviewing and editing the manuscript. Alexandra Langlois contributed to data curation and formal analysis. She was involved in editing and reviewing the manuscript.

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| First author, year              | Country   | Population      | Hypersensitivity reaction type                          | Patients that underwent OC, n | Confirmed by OC, n | SE    | Prevalence | Confidence interval |
|---------------------------------|-----------|-----------------|---------------------------------------------------------|-------------------------------|--------------------|-------|------------|---------------------|
| Choi [13], 2016                 | Korea     | pediatric       | unknown                                                 | 12                            | 4                  | 13.61 | 33.30%     | 6.66 to 60.01       |
| Topal [14], 2016                | Turkey    | pediatric       | immediate                                               | 24                            | 2                  | 5.64  | 8.33%      | -2.72 to 19.39      |
| Güvenir [15], 2015              | Turkey    | pediatric       | immediate and nonimmediate (fixed drug eruption)        | 53                            | 4                  | 3.63  | 7.55%      | 0.436 to 14.66      |
| Loh [16], 2015                  | Singapore | pediatric       | immediate                                               | 6                             | 2                  | 19.25 | 33.33%     | -4.39 to 71.05      |
| Rojas-Perez-Ezquerro [17], 2014 | Spain     | pediatric/adult | immediate and nonimmediate (fixed drug eruption, other) | 10                            | 10                 | 0.00  | 100.00%    |                     |
| Renaudin [18], 2013             | France    | pediatric/adult | immediate                                               | 10                            | 5                  | 15.81 | 50.00%     | 19.01 to 80.99      |
| Thalayasingam [19], 2013        | Singapore | adult           | unknown                                                 | 8                             | 0                  | 0.00  | 0.00%      |                     |
| Rutkowski [3], 2012             | UK        | pediatric/adult | immediate and nonimmediate (other)                      | 31                            | 15                 | 8.98  | 48.39%     | 32.79 to 65.98      |
| Chalabianloo [20], 2011         | Norway    | pediatric/adult | immediate and nonimmediate (other)                      | 30                            | 1                  | 3.28  | 3.33%      | -3.09 to 9.76       |
| Hassani [21], 2008              | France    | pediatric       | immediate                                               | 12                            | 2                  | 10.76 | 16.67%     | -4.42 to 37.75      |

OC, oral challenge; SE, standard error.