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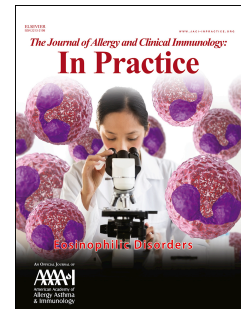
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Establishing amoxicillin allergy in children through direct graded oral challenge (GOC): evaluating risk factors for positive challenges, safety, and risk of cross reactivity to cephalosporines

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Abstract

Background

Data on the diagnostic properties of direct oral challenges without the use of skin tests in children with suspected amoxicillin allergy is sparse.

Objective

Assess the use of direct oral challenges.

Methods

A cohort study was conducted between March 2013 and March 2020, in Montreal and Winnipeg. All children referred with reported history of benign reactions (i.e., limited to the skin with no mucosal lesions and no vesicles) to amoxicillin were recruited and a two-step graded oral challenge (GOC) was conducted. Data were collected on demographics, clinical characteristics, and comorbidities. Eligible children were followed to assess reactions to subsequent use of amoxicillin and to assess the safety of cephalexin use in children with a positive GOC.

Results

Among 1914 children recruited, 1811 (94.6%) tolerated the GOC, 42 (2.2%) developed mild immediate reactions, and 61 (3.2%) developed mild nonimmediate reactions. Among 265 participants who had a negative GOC and reused amoxicillin; 226 (85.3%) reported tolerance, and 39 (14.7%) had mild cutaneous reactions. Chronic urticaria (adjusted Odds Ratio [aOR = 1.16; 95%CI, 1.09-1.23]) and an index reaction occurring within 5 minutes of exposure [aOR = 1.09; 95%CI, 1.04-1.14] were associated with immediate reactions during the GOC. Symptoms lasting longer than 7 days [aOR = 1.05; 95%CI, 1.02-1.09] and parental drug hypersensitivity [aOR = 1.04; 95%CI, 1.03-1.06] were associated with nonimmediate reactions. Among those reacting to the GOC 12.5% reacted with mild cutaneous reactions to cephalexin challenge.

Conclusions

Direct GOCs are an accurate and safe confirmatory to establish true hypersensitivity among children reporting benign reactions to amoxicillin.

Highlights Box

What is already known about this topic?

The diagnosis of true amoxicillin allergy in children is challenging and previous studies suggest poor sensitivity and high rate of false positive skin tests.

What does this article add to our knowledge?

Our study establishes that a direct graded oral challenge (GOC) with no prior skin tests can be used accurately and safely to diagnose amoxicillin allergy in children reporting cutaneous non-vesicular rashes developing during amoxicillin treatment.

How does this study impact current management guidelines?

In children reporting benign skin rashes in the course of amoxicillin treatment direct challenge is an appropriate confirmatory test. Cephalexin induced reactions can occur in just over 10% of children with confirmed amoxicillin allergy. However, reactions are mild and limited to the skin.

Key Words

Hypersensitivity; pediatric; safe; diagnosis; Amoxicillin; beta lactam; oral challenge; cephalosporines; cross reactivity; associated factors

Abbreviations

aOR: adjusted odds ratio

CI: confidence interval

CU: chronic urticaria

DRESS: drug reaction with eosinophilia and systemic symptoms

GOC: graded oral challenge

MCH: Montreal Children's Hospital

SJS: Stevens-Johnson syndrome

TEN: toxic epidermal necrolysis

HLA: human leukocyte antigen

TCR: T-cell receptor

VRE: Vancomycin Resistant Enterococcus

Introduction

Penicillin derivatives, mainly amoxicillin and cephalosporins, are the major class of antibiotics used to treat common pediatric bacterial infections such as acute otitis media.¹⁻³ Up to 10% of children in North America and Europe are labelled as allergic to amoxicillin/cephalosporins due to the development of adverse reactions (mostly rashes) during or following, antibiotic treatment. These reactions are often not appropriately investigated.¹⁻³ There is controversy regarding the best diagnostic algorithm to accurately evaluate these children in the clinical setting. Currently, most children are labeled as allergic to the antibiotic without confirmatory testing and are treated with less effective second line antibiotics associated with co-morbidities [e.g., Vancomycin Resistant Enterococcus (VRE)], anti-microbial resistance, and increased healthcare costs.⁶

The diagnosis of immune-mediated reactions is challenging, as available skin tests have a limited role in the diagnosis of immediate reactions (defined as the occurrence of objective symptoms such as rash, wheezing, rhinitis, or severe and repetitive vomiting within one hour of exposure or of a graded oral challenge (GOC)⁷ and no role in the diagnosis of mild nonimmediate reactions in children (cutaneous symptoms which occur more than one hour after exposure/challenge).⁸ Recently studies on the validity of skin tests to detect amoxicillin allergy in children based on challenges of all participants suggest that the sensitivity of skin tests is less than 10%^{4,5} and that specificity is almost 98%⁵.

Although a drug-specific oral provocation testing is considered the gold standard for diagnosis, it is rarely used in practice, owing to lack of data regarding its safety and accuracy in children.⁹ Moreover, the approach to the diagnosis and management of patients with suspected hypersensitivity is complicated by concerns of cross-reactivity between penicillin derivatives and cephalosporins, which is reported to range between 1.6 and 30%.^{10, 11}

We aimed to assess the safety and accuracy of a direct GOC (i.e., with no prior skin tests) in a large sample of children, to evaluate factors associated with a positive GOC, and to determine the percentage of children with a positive amoxicillin GOC who could tolerate a structurally similar cephalosporin.

Methods

Patients

Children were recruited from 3 main sources: the Montreal Children's Hospital (MCH), an outpatient allergy clinic affiliated with the Montreal Children's Hospital and the Meadowood Medical Centre in Winnipeg. Patients were grouped into three groups, according to outcome of the GOC: tolerance to GOC (Group A), immediate reaction (< 1 hour after GOC, Group B) or nonimmediate reaction (>1 hour and up to 1 week after GOC, Group C) (*Figure 3*). We included only reactions considered benign. Reactions were considered benign if limited to the skin with no mucosal lesions and no vesicles. We excluded children with history of drug reaction with eosinophilia and systemic symptoms (DRESS), Stevens-Johnson syndrome (SJS), toxic epidermal necrolysis (TEN) or anaphylaxis (reactions affecting 2 systems or more or resulting in hypotension). Anaphylaxis was excluded based on the patient's physician and the attending allergist's clinical assessment based on index reaction symptoms and the aforementioned definition. To participate, parents/legal guardian(s) signed the consent form on the behalf of children (<7 years-old), while older children and adolescents co-signed with their parents/legal guardian. For assessment of cross-reactivity between amoxicillin and cephalexin (1st generation cephalosporin), we approached patients who had an adverse reaction to the amoxicillin GOC and offered a cephalexin GOC to consenting families.

Allergy testing

Participants were offered a two-step non-blinded GOC with 10% of the weight-adjusted therapeutic dose, 20 minutes of observation, 90% of the weight-adjusted therapeutic dose, and additional observation for 1 hour after the last dose. The dose ranged from 500 mg to a maximum of 1.5g of amoxicillin and cephalexin.¹⁴ The dose range was determined according to the standard dose recommended in Canada.⁴

Data collection

This observational study features both retrospective and prospective arms. The index reaction was retrospectively characterized through a standardized questionnaire that capturing clinical characteristics, co-morbidities (including history of atopy and use of medications regularly and in association with antibiotic treatment), suspected antibiotic exposure and management of the reaction. This data was coded and stored anonymously in our REDCap database at the Research Institute of the McGill University Health Centre for Innovative Medicine. Outcomes of the GOC and subsequent use of amoxicillin were investigated prospectively. GOC outcomes were obtained from the attending allergist (immediate reactions) or reported by parents (nonimmediate reactions) by phone or through our study email. In addition, trained members of our team contacted families by phone within 3 months of the GOC to verify that no immediate reactions occurred. Subsequent use of amoxicillin was tracked via a five-year follow up, whereby families were contacted annually by phone beginning one year after the GOC. The study was approved by the McGill University Ethics Committee and the Research Ethics Board at the University of Manitoba.

Statistical analysis

Descriptive statistics were used to summarize demographic and clinical characteristics of reactions through averages, medians, and interquartile ranges. Univariable and multivariable logistic regression analyses were performed to assess potential confounders and evaluate the effects of sociodemographic factors (age, sex, ethnicity), presence of comorbidities (e.g., asthma, food hypersensitivity, chronic urticaria), parental history of drug hypersensitivity and atopy in biological parents, and clinical characteristics of reactions to GOC. Model selection was performed by including medically relevant variables, by following the general rule of ~10 events per variable and based on the Akaike Information Criterion. P-values of 0.05 or lower were considered to indicate statistical significance. All statistical analyses were conducted using RStudio version 1.1.456 – © 2009-2018 RStudio, Inc.

Results

Demographics and Clinical Characteristics

From March 2013 to March 2020, 1844 children from Montreal (both outpatient allergy clinic and MCH) and 70 children from Winnipeg with suspected amoxicillin hypersensitivity were recruited by trained members of each center. The median age was 1.7 years [interquartile range, 1.0-3.6 years] and approximately half [53.8%] were males. The median time from the patient's antibiotic reaction to their GOC was 1.1 years [IQR, 0.4-3.6] (*Figure 3*). Among all participants, 257 reported immediate (non-anaphylactic) reactions, 1352 children reported non immediate reactions, and in 305 children this information was unknown. Group A included most of the participants, with 1811 patients (94.6%) who tolerated the provocation test. Group B had 42 (2.2%) participants who developed mild immediate reactions and three of these patients (7%) reacted to their first dose of the GOC. Group C contained 61 (3.2%) individuals who developed mild to moderate nonimmediate reactions (*Figure 1 & 2*).

No participant who reacted to the challenge, whether immediate or nonimmediate, had anaphylaxis (*Figure 2*). Reactions with symptoms limited to the skin were classified as mild.⁶ All immediate reactions to GOC were mild (*Figure 2*). Nonimmediate reactions were not observed on site and were reported by the participants or guardians to our team. All nonimmediate reactions were mild and limited to the skin (*Figure 2*). Among all participants, 58.5% of patients with tolerance to GOC, 54.8% of patients with mild immediate reactions, and 67.2% of patients with mild reactions to GOC reported that index reaction occurred upon first exposure to amoxicillin (*Figure 3*).

Factors associated with positive GOC

Details of the index reaction were collected from parental report and, when available, use of photos taken during the reaction. Patients who were reported to have reacted within 5 minutes after taking a dose of amoxicillin were more likely to have an immediate positive GOC [aOR = 1.09; 95%CI, 1.05-1.14] compared to patients whose index reaction occurred more than 5 minutes after their last dose taken. A history of chronic urticaria (CU) [aOR = 1.16; 95%CI, 1.09-1.23] $p < 0.001$ was also associated with an immediate positive GOC. CU was defined by the occurrence of urticaria and/or angioedema almost daily for at least 6 weeks.²⁶ These odds were obtained after adjusting for age at reaction, sex, comorbidity, and time to initial reaction.

Patients whose index reactions were reported to have lasted for more than 7 days were more likely to experience a nonimmediate reaction to the GOC compared to participants whose symptoms lasted 7 days or less [aOR = 1.05; 95%CI, 1.02-1.09] $p < 0.001$. Parental report on drug hypersensitivity drugs [aOR = 1.04; 95%CI, 1.03-1.06] $P < 0.001$ was also associated with nonimmediate reactions. The logistic model included duration of symptoms, age at reaction, sex, drug-naïve state, and parental drug hypersensitivity.

Follow-up

In order to detect false negative results of the GOC, patients who tolerated the GOC (Group A) were contacted annually to assess tolerance to amoxicillin during subsequent use. Among 1420 individuals eligible for follow up, 890 (62.7%) responded to our telephone follow up questionnaire. Among responders, 265 (29.8%) participants had reused amoxicillin at least one year after their challenge (*Figure 1*). Among those patients, 226 participants (85.3%) reported

tolerance, while 39 (14.7%) had subsequent mild reactions. Patients whose index reactions had lasted more than 7 days were more likely [aOR = 1.28; 95%CI, 1.12-1.46] $p < 0.001$ to have a subsequent reaction, compared to patients whose symptoms lasted 7 days or less. Patients whose parents reported a drug hypersensitivity [aOR = 1.14; 95%CI, 1.04-1.25] $p < 0.01$ were also more likely to have a reaction to a subsequent use of amoxicillin. Those estimates were obtained while adjusting for age at reaction, sex, parental drug hypersensitivity, and duration of symptoms.

Cross reactivity

In order to assess the potential for cross-reactivity among amoxicillin and cephalixin participants from Groups B and C were offered a GOC with cephalixin, with a total of 32 consenting participants (*Figure 1*). Among the 17 patients from Group B, three (3/17; 17.6%) reacted immediately to the cephalixin GOC and among the 15 from Group C one (1/15; 6.7%) had a nonimmediate reaction to the cephalixin GOC. These were the only four reactions (4/32; 12.5%) to the cephalixin GOC. All reactions were mild and limited to the skin. Among those reacting to cephalixin, the one patient who consented to a cefixime challenge did not have a reaction to cefixime.

Discussion

We have conducted the largest study to date assessing true amoxicillin hypersensitivity based on direct GOC with no prior use of skin tests. Our results reveal that the vast majority (94.6%) of children in this referral population were tolerant to amoxicillin, with only 5.4% of patients reacting to the GOC (2.2% immediate and 3.2% nonimmediate) with mild symptoms. Patients who react during GOC are labelled allergic, as it is considered the gold standard in diagnosis of drug allergy.¹⁶ These results are consistent with recently published reports by our group and others^{12, 17} suggesting that fewer than 10% of apparent reactions occurring during β -lactam treatment have a true amoxicillin hypersensitivity.^{15, 18-21} Disparity in the prevalence between suspected and true reactions may be due to virus induced urticaria and delayed exanthems, both of which are often mislabelled as allergic reactions.²²

More than half of the participants (Group A, B, and C) reacted to amoxicillin on their first exposure. Our results indicate that a history of previous exposure to the antibiotic was not associated with a positive amoxicillin challenge (immediate or nonimmediate). It is possible that mechanisms such as off-target activity of drugs on immune receptors like HLA and T cell receptors or interaction with receptors or enzymes of inflammatory cells (pseudo-allergy) account for this observation.^{7,8} Recall bias could account for this high prevalence of reactions in penicillin-naïve children, as the traditional Gell-Coombs classification of drug hypersensitivity which suggest that exposure is warranted to generate sensitization. However, this bias was minimized by requesting parents to provide drug records to the clinic visit. The role of prenatal exposure has been suggested, as almost one third of pregnancies may include use of commonly prescribed antibiotics.²³ It is also possible that other mechanism may explain reaction upon first exposure such as direct interaction between drugs and immune receptors (HLA or TCR), resulting in alloimmune-like stimulation of T cells and hypersensitivity reactions, even upon first exposure.²⁴

One of the objectives of this study was to determine factors associated with a positive GOC. We found higher odds of immediate reaction to the GOC among patients with a reported history of a reaction occurring within five minutes of exposure to amoxicillin. This observation is likely reflecting the possibility that reactions occurring in such a short time interval were more likely due to Type I (IgE mediated) hypersensitivity.²⁵ The association of immediate reactions with CU could be explained by the pivotal role played by mast cells in both conditions. In most cases, CU is spontaneous and related to mast cell activation by an autoantigen²⁶. Active mast cells may be also more prone to react to antibiotics. Indeed, it has been reported that penicillin can play a role in CU flares (frequency = 0.2%).²⁷ Although statistically significant, our results on the association of chronic urticaria and immediate reactions to the GOC could be enhanced with a larger population.

Patients whose index reactions lasted for more than 7 days and reported parental drug hypersensitivity were both associated with nonimmediate reactions, after adjusting for age at reaction, sex, race, parental drug hypersensitivity, and duration of symptoms. Most common viral rashes in children last up to 7 days²⁸, thus cutaneous symptoms with longer duration may reflect a true amoxicillin hypersensitivity. The association between nonimmediate reactions and reported family history of drug hypersensitivity is supported by previous reports on the association between specific genetic loci and other nonimmediate drug allergies, suggesting a familial effect.^{29, 30}

Based on our annual follow-up findings, a rate of only 14.7% (39 patients) of false negative was established for the GOC (*Figure1*). This rate applies to our dose range (500mg to 1500mg) and it is worth noting that the false negative rate could be higher if the dose were lower. This arm of the study allowed us to calculate a negative predictive value of 85.3%, demonstrating the usefulness of the GOC for tolerant patients. The presence of any false negatives, although low, can be explained by coincidental events at the time of antibiotic use, as recalled by parents. An interaction between a virus^{31, 32} and antibiotic, or the underlying infection itself, can cause cutaneous reactions.^{1, 3} Moreover, exanthems are overall most likely to be secondary to underlying infection, especially in children less than 5 years of age.^{33, 34} Therefore, it is safe to assume that the follow-up has likely captured amoxicillin-related hypersensitivity reactions that would have been missed even when conducting prolonged challenges in a child that is not sick. Assuming that tolerance upon subsequent use is the ultimate reflection of the absence of hypersensitivity, the GOC had a negative predictive value of 85.3%. This measure could be an upper bound while the true percentage of true hypersensitivity may be lower.

Although it is reported that skin tests have high negative predictive values⁹, it is noteworthy that negative predictive values are affected by the prevalence of disease and are expected to be high in children reporting amoxicillin reaction given the low prevalence of true amoxicillin hypersensitivity in this population.^{4, 5} Therefore, to validate tests, it is crucial to assess the sensitivity of the test compared to the gold standard, i.e. drug challenge.

Cross-reactivity among antibiotics is reported to be related to the resemblance of their R side chain groups.²⁹ Our findings suggest 17.6% and 6.7% cross-reactivity in immediate and nonimmediate reactors, respectively, in antibiotics with similar side chains. Cross-reactivity is reported to be less than 2% for cephalosporins and penicillins with different side chains.³⁵ Indeed, in a previous study by our group, cefixime (that does not share a similar R1 chain with amoxicillin) was well tolerated in all cases with positive GOC to amoxicillin.¹⁵ Our higher rate of cross-reactivity could be attributed to the higher level of similarity of the R1 side chains of amoxicillin and cephalexin.³⁵ There is also a potential sampling bias. Indeed, we only had 4 reactions out of 32 patients thus with a larger sample, we would probably see a decrease in cross-reactivity rate. Of note, our findings are still reassuring given that all reactions were mild.

Conclusion

Our results establish the safety, efficacy, and accuracy of performing a direct GOC to diagnose true amoxicillin hypersensitivity without prior skin testing in children reporting immediate or nonimmediate benign cutaneous reactions to amoxicillin. We were able to identify factors associated with immediate and nonimmediate reactions to a two-step GOC with amoxicillin. For immediate reactions to the GOC, these risk factors include a history of index reaction occurring within 5 minutes of drug administration, and a history of CU. For nonimmediate reactions to the GOC, parental drug hypersensitivity is a risk factor. The negative predictive value of the GOC was 85.3% which was determined by five year follow up of potentially false negative patients. Cross-reactivity between cephalexin and amoxicillin was calculated to be 12.5%. Future large studies are required to establish the risk of cross-reactivity between other cephalosporins and amoxicillin. Based on these findings, new guidelines should be developed to evolve towards a safe and appropriate diagnostic algorithm of true amoxicillin hypersensitivity in children, a rare and over diagnosed condition.

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Figure 1 Legend

Flow diagram of participants with a graded oral challenge (GOC) for amoxicillin and cephalexin. This figure illustrates the breakdown of participants into groups based on their reaction to the GOC and their subsequent reactions to amoxicillin or other cephalosporins.

Figure 2 Legend

9, Gastrointestinal symptoms include abdominal pain, vomiting, or diarrhea; *21 = Involvement of mucosal membranes ;22 = Other (lethargy, ecchymosis, sneezing, convulsions, headache, sore throat, irritability, dysphagia, cough, anorexia, ulcers, insomnia, chest pain, confusion, hemorrhagic skin lesions, telangiectasia, epiphora, myalgia, mouth sore, erythema, xeroderma). Error bars indicate standard error. Immediate reaction (≤ 1 hour after ingestion of amoxicillin); nonimmediate reaction (>1 hour and up to 1 week after ingestion of amoxicillin)

Figure 3 Legend

$N_{\text{total}} = 1914$ participants. All frequencies are presented in percentage.
^a missing data = 26 in group A. ^b missing data = 10 in group B. ^c missing data = 26 in group A. ^d missing data = 40 in group A, 1 in group C. ^e ibuprofen (Motrin, Advil). ^f paracetamol/acetaminophen (Tempra, Tylenol) ^g fluticasone (Avamys), fluticasone/salmeterol (Advair), ciprofloxacin/dexamethasone (Ciprodex), mometasone (Nasonex), fluticasone propionate (Flovent), dexamethasone, beclometasone (Qvar), prednisolone, ciclesonide (Alvesco), Biphentin, Loratadine (Claritin), diphenhydramine (Benadryl), salbutamol (Ventolin), fluticasone/salmeterol (Advair), montelukast (Singulair), morphine bacitracin/polymyxin B (Polysporin), mupirocine (Bactroban), oseltamivir (Tamiflu), ketoconazole (Ketoderm), ADHD medication, rectal anti-pyretic (1), eye drops (2), natural products (1), and ear drop (1); acetaminophen or ibuprofen (5).

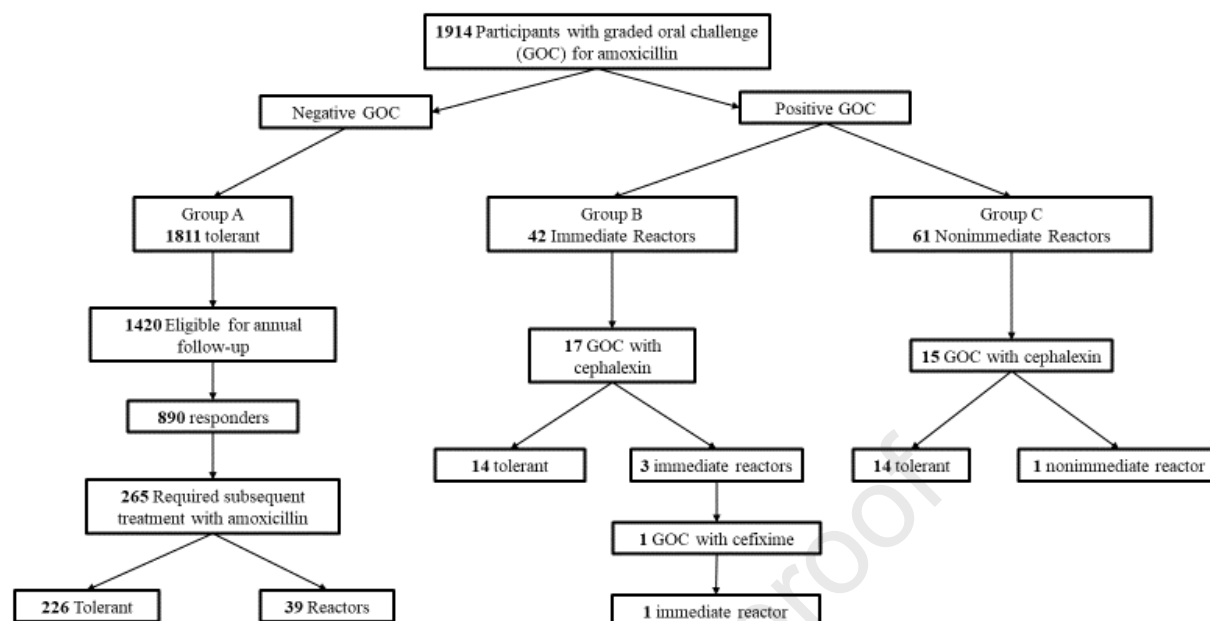


Figure 1. Flow diagram of participants with a graded oral challenge (GOC) for amoxicillin and cephalixin

Figure 2. Frequencies of the Symptoms Experienced during Immediate and Nonimmediate Index Reaction

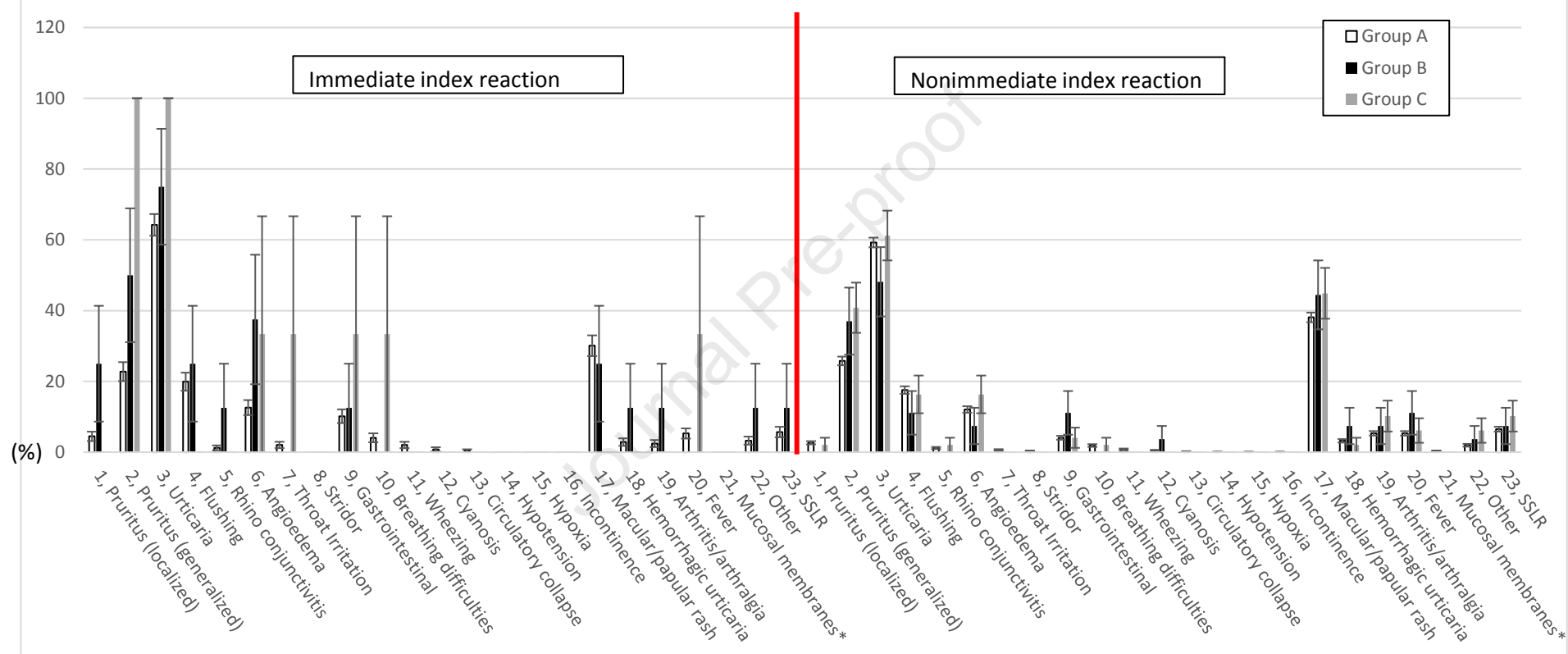


Figure 3. Sociodemographic and Clinical Characteristics of Patients Receiving a GOC for Amoxicillin

	Group A n = 1811	Group B n = 42	Group C n = 61
Participants	94.6	2.2	3.2
Male	53.8	54.8	52.5
Median age at initial suspected reaction (IQR), years ^a	1.8 (1.0-3.6)	2.1 (1.2-6.1)	3.0 (1.0-2.9)
Median age at GOC (IQR), years ^b	4.1 (2.1-7.7)	4.9 (1.7-9.6)	3.5 (1.8-8)
Time between initial suspected reaction and GOC, median (IQR), years ^c	1.1 (0.4-3.7)	0.5 (0.3-3.2)	1.2 (0.3-2.7)
Antibiotic given for acute otitis media	66.3	61.9	68.9
First exposure	58.5	54.8	67.2
Concurrent drug use			
NSAID ^e	21.0	11.9	24.6
Acetaminophen ^f	30.0	14.3	36.1
Other ^g	10.7	4.8	1.6
No treatment	48.2	69.0	41.0
Time to initial suspected reaction			
<5min	2.3	12.5	1.6
5-60 min	11.7	7.5	3.3
1-8h	31.9	37.5	36.1
>8h	41.1	30.0	44.3
Unknown	13.0	12.5	14.8
Duration of symptoms in initial suspected reaction			
1-3 days	63.5	70.0	54.1
4-7 days	25.3	15.0	26.2
More than 7 days	7.4	12.5	19.7
I do not know	3.9	2.5	0.0
Reaction occurred after how many days of treatment			
1-3d	52.0	61.9	42.6
4-7d	25.4	21.4	31.1
>7d	16.4	7.1	21.3
post treatment	3.5	7.1	4.9
Do not know	3.2	2.4	1.6
Used other antibiotic since the reaction			

Yes	58.2	47.6	59.3
No	29.9	42.9	33.3
Do not know	11.9	9.5	6.7
Comorbidities			
Allergy	13.4	16.7	9.8
Asthma	14.0	19.0	13.1
Eczema	25.6	26.2	26.2
Chronic urticaria (CU)	1.1	9.5	1.6
None	49.0	38.1	59.0
Other	7.8	17.1	3.3
Do not know	4.2	2.4	0.0
Parental drug allergy	26.7	31.0	54.1