Original Article

Differentiating Between β-Lactam-Induced Serum Sickness–Like Reactions and Viral Exanthem in Children Using a Graded Oral Challenge

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What is already known about this topic? Diagnosing serum sickness–like reactions (SSLRs) is challenging given that the exact pathogenic mechanisms is unknown. It is thought to occur due to a non–IgE-mediated response to medication or viral infection.

What does this article add to our knowledge? This study shows that a graded oral challenge is an appropriate and safe method to diagnose to SSLR.

How does this study impact current management guidelines? A graded oral challenge should be incorporated as a confirmatory test for SSLR given that the reaction is benign. Negative challenge patients should not avoid β-lactam antibiotics.

BACKGROUND: Serum sickness–like reactions (SSLRs) are defined by the presence of rash (primarily urticaria) and joint complaints (arthralgia/arthritis) that are believed to occur due to a non–IgE-mediated response to medications. However, similar reactions can occur due to viral infections, and it can be difficult to distinguish between the two. This may lead to unnecessary avoidance of the culprit antibiotic.

OBJECTIVE: We aimed to evaluate children presenting with suspected SSLRs through a graded oral challenge (GOC).

METHODS: All children referred to the Montreal Children's Hospital for potential antibiotic allergy (β-lactam or other antibiotics) and a clinical presentation compatible with SSLR were recruited for the study between March 2013 and February 2020. A standardized survey with questions on treatment, symptoms, and associated factors was completed, and a GOC (10% and subsequently 90% of the oral antibiotic dose) was conducted. Patients with a negative GOC were contacted annually to query on subsequent antibiotic use.

RESULTS: Among 75 patients presenting with suspected SSLRs, the median age was 2.0 years and 46.7% were males. Most reactions were attributed to amoxicillin. Among the 75 patients, 2.7% reacted immediately (within 1 hour) to a GOC and 4.0% had a nonimmediate reaction. Of the 43 patients successfully contacted, 20 reported subsequent culprit antibiotic use of

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Abbreviations used
CI- Confidence interval
GOC- Graded oral challenge
IQR- Interquartile range
SSLR- Serum sickness–like reaction

whom 25.0% had a subsequent mild reaction (macular/papular rash).
CONCLUSIONS: This is the first and largest pediatric study to assess SSLR using a GOC. Our findings suggest that using a GOC is safe and appropriate for differentiating between β-lactam-induced SSLR and viral exanthem in this population. **© 2020 American Academy of Allergy, Asthma & Immunology** **(J Allergy Clin Immunol Pract 2021;9:916-21)**

Key words: *Serum sickness–like reaction; SSLR; Antibiotic reaction; Amoxicillin; Graded oral challenge; GOC; Urticaria; Joint complaints; Safety*

β-Lactam antibiotics are some of the most commonly used medications among children due to their safety, efficacy, and relatively low cost.[1] However, they are also often associated with adverse reactions such as anaphylaxis, angioedema, urticaria, macular/papular rash, serum sickness–like reactions (SSLRs), Stevens-Johnson syndrome, and toxic epidermal necrolysis. Amoxicillin is reported to account for the majority of β-lactam adverse reactions, followed by cephalosporins.[2,3] The current confirmatory tests used to establish drug-related adverse reactions include corroboration of a suggestive clinical history, use of skin tests, measurements of specific IgE levels and basophil activation tests in research settings, and drug challenge tests.[1] The validity of these tests for diagnosing antibiotic-related adverse reactions is questionable due to reported high false-negative and false-positive rates. Recently, studies have suggested that a graded oral challenge (GOC) without prior use of skin tests is a safe and accurate strategy for the diagnosis of skin limited reactions (including macular, papular, and urticarial rash) in the pediatric population.[1,4,5] However, confirming the diagnosis of a subgroup of children presenting with SSLRs that are nonimmediate in nature is still challenging.[1]

SSLR is defined as an immunological condition characterized by skin rash and arthralgia, with or without fever (Figures 1 and 2). These symptoms can present several days to several weeks after exposure of the trigger.[6] In addition to the characteristic cutaneous manifestations, patients with SSLRs are reported to have malaise, lymphadenopathy, abdominal pain, nausea, vomiting, diarrhea, myalgias, headaches, and self-limited symmetric arthritis.[7] Similarly, in rare cases, viral infections can be associated with a similar rash called "urticaria multiforme."[8] Although SSLRs have the important property of benignity, an appropriate diagnosis remains imperative as its impact will often dictate the course of subsequent antibiotic treatments. Misdiagnosing such a reaction will often lead to the avoidance of first-line antibacterial therapy for other broader spectrum, less safe, and more expensive agents.

It is important to distinguish the more common SSLR from true serum sickness. Serum sickness is a type III immune complex–mediated hypersensitivity reaction that is usually caused by the administration of foreign serum or protein, usually horse serum.[9,10] This reaction is characterized by the deposition of circulating immune complexes in blood vessels and tissue, complement system activation, and subsequent inflammatory response.[10] True serum sickness patients usually have renal and hepatic involvement.[1] SSLRs typically occur 1 to 2 weeks after the administration of a culprit nonprotein drug and are characterized by fever, rash, and joint involvement. However, unlike true serum sickness, SSLRs rarely affect the liver and kidneys and the prognosis is excellent. The most frequent cutaneous manifestations were macular/papular rash, urticaria occasionally having dusky to ecchymotic centers, and outbreak resembling urticaria multiforme.[1,10,11] Although cutaneous manifestations are present in both SSLRs and typical delayed-onset T-cell-mediated β-lactam associated rashes, these can be unambiguously differentiated by the presence of arthralgia with or without fever in the case of SSLR.[6] SSLRs are currently treated with antihistamines and the discontinuation of the culprit antibiotic, an appropriate treatment for a reaction known to be benign and self-limiting. The pathogenesis of SSLRs is unknown; however, it is not associated with circulating immune complexes, hypocomplementemia, or vasculitis.[1,12]

We aimed to assess the use of a GOC to diagnose the presence of SSLRs among pediatric patients with a suspected allergy to β-lactam antibiotics. To our knowledge, this is the first study assessing the diagnostic properties of a GOC for SSLRs.

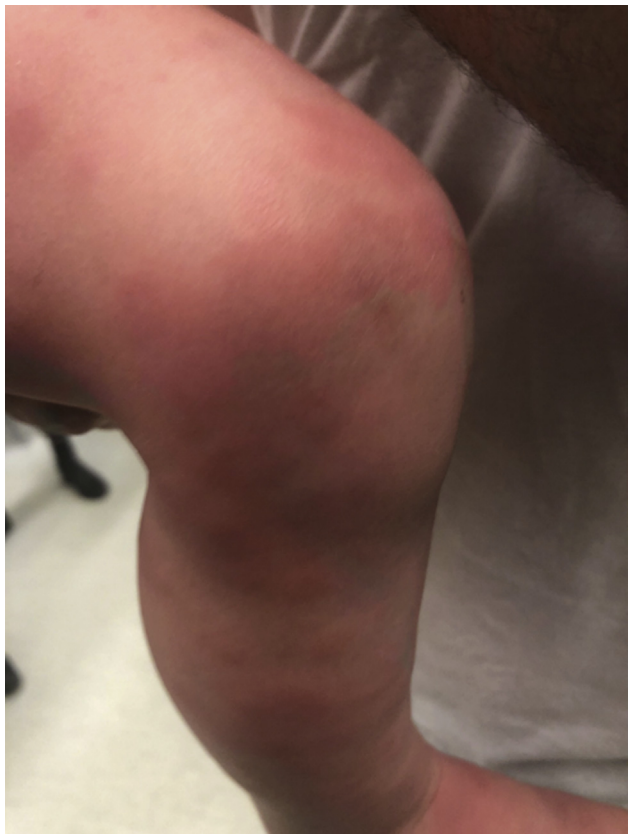

FIGURE 1. Joint inflammation associated with serum sickness–like reactions.

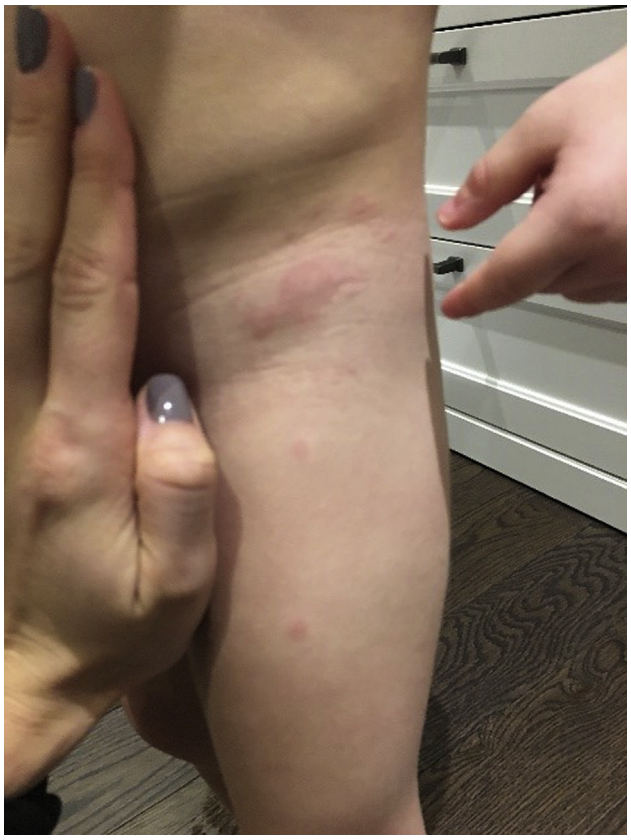

FIGURE 2. Cutaneous reaction to subsequent antibiotic use.

METHODS

Setting

All children referred to the Montreal Children's Hospital allergy clinic, Montreal, Quebec, Canada, for potential antibiotic allergy (β-lactam or other antibiotics) and a clinical presentation compatible with SSLR (defined by the presence of rash, primarily hives, and joint complaints [arthralgia/arthritis]) were approached for participation. Patients with reactions compatible with anaphylaxis, Stevens-Johnson syndrome, toxic epidermal necrosis, drug reaction with eosinophilia and systematic symptoms, and acute generalized exanthematous pustulosis were excluded.[1]

Design

This study is made up of 2 arms: 1 retrospective branch, in which suspected antibiotic reactions were explored and then categorized, and 1 prospective branch, which examined GOC outcomes and future antibiotic use. The diagnostic properties of the GOC were evaluated in accordance with the Standards for Reporting Diagnostic Accuracy reporting guidelines.[13] This study was approved by the McGill Research Ethics Board, and all participants provided written informed consent.

Source of data

After obtaining consent, a previously validated standardized survey was completed by a trained member of our research team and the family.[1] This survey consisted of questions concerning clinical manifestations as well as their onset (time from the first dose of the last course of treatment to onset of SSLR), comorbidities, suspected antibiotic exposure, treatment of the adverse drug reaction, and family history. Comorbidities included history of atopy, regularly used medications, and other medications used at the time of the reaction. All children were offered a GOC constituting 10% of the therapeutic dose of the culprit antibiotic. For amoxicillin challenges, the remaining 90% of the therapeutic dose (ie, 50 mg/kg/dose up to a maximum of 1.5 g) was administered 20 minutes later. For cephalosporins, doses were based on the age-appropriate doses as previously published. Patients were observed for a minimum of 1 hour after their last dose. Challenge doses were based on the child's weight with doses ranging from 500 to 1500 mg. All patients with negative GOC results were given a study e-mail and telephone contact to report any adverse reaction in the following weeks, month, or on subsequent treatment. In addition, trained members from our research team contacted all participants 1 month after the GOC (by phone or e-mail according to the patient's discretion) to assess any development of reactions occurring within 1 month of the GOC. Patients were asked to contact the research team (through phone or study e-mail) if an adverse reaction occurred.

Positive challenge outcomes occurring within 1 hour of the last dose were classified as being immediate. Such a diagnosis was made solely based on the presence of objective symptoms including but not limited to urticaria, angioedema, wheezing, rhinitis, severe and repetitive vomiting, diarrhea, protracted abdominal pain, or shock.[1,2] Nonimmediate reactions encompassed all reactions manifesting more than 1 hour from the last dose of the GOC and up to 1 week afterward. Such reactions were defined as parents' report of arthritis or arthralgia along with the previously mentioned objective symptoms. Reactions with the presence of skin symptoms and/or mild fever were classified as grade 1; all reactions with measurable but non−life-threatening symptoms were classified as grade 2; all life-threatening reactions were classified as grade 3; and all reaction with cardiac arrest and/or respiratory arrest were classified as grade 4.[14,15]

Participants who had immediate and nonimmediate reactions were invited for reassessment and offered a GOC with a third-generation oral cephalosporin such as cefixime, as it can be used as antibiotic treatment in place of amoxicillin to treat similar pathogens. The same protocol was followed for this challenge, where 10% of the therapeutic dose of cefixime was administered, followed by 90% of the therapeutic dose (ie, 8 mg/kg/dose). Patients were observed for a minimum of 1 hour after their last dose. In addition, participants with a negative GOC were followed annually to query on the subsequent use of the antibiotic for which they were challenged, and on the development of any reaction on subsequent use. We attempted to contact patients up to twice per day in different days of the week before categorizing them as nonresponders.

Statistical analysis

Patients' demographics and initial reaction clinical characteristics were summarized as percentages for categorical data and by median (interquartile range [IQR]) for continuous data. Relationships between categorical GOC outcomes and clinical characteristics of the initial reaction were examined by logistic regression. All statistical analyses were performed using R version 3.6.2 statistical software (R Core Team [2019]; R Foundation for Statistical Computing, Vienna, Austria).

Ethics approval

The study was granted ethical clearance by the McGill University Health Center Research Ethics Board (REB# 12-084 PED). All

TABLE I. Demographic and initial reaction information collected at clinic visit

Variable	Patients (n = 75)
Age at index reaction, median (IQR)	2.00 (1.20, 4.00)
Sex, n (% males)	35 (46.7)
Symptoms of index reaction, n (%)	
Pruritus (generalized)	31 (41.3)
Urticaria	48 (65.3)
Angioedema	26 (34.7)
Macular/papular rash	33 (44.0)
Gastrointestinal	8 (10.7)
Throat tightness	2 (2.7)
Breathing difficulties	3 (4.0)
Arthritis/arthralgia	75 (100)
Fever	30 (40.0)
Antibiotic type, n (%)	
Amoxicillin	66 (88.0)
Clavulin	5 (6.7)
Cefprozil	2 (2.7)
Cephalexin	2 (2.7)
Exposure route, n (%)	
Ingestion	75 (100.0)
Contact	0 (0.0)
Inhaled	0 (0.0)
Parenteral administration	0 (0.0)
Infection treated, n (%)	
Otitis media	51 (68.0)
Pneumonia	4 (5.5)
Upper respiratory tract infection*	14 (18.7)
Other†	5 (6.7)
Unknown viral infection	2 (2.7)
Time interval of index reaction after most recent dose, n (%)	
<5 min	2 (2.7)
<1 h	8 (10.7)
<8 h	17 (22.7)
>8 h	40 (53.3)
Unknown	8 (10.7)
Index reaction after how many days from the first dose of the last course of treatment, n (%)	
1-3 d	17 (22.7)
4-7 d	24 (32.0)
>7 d	25 (33.3)
After treatment ended	8 (10.7)
Unknown	1 (1.3)
Duration of symptoms related to index reaction, n (%)	
1-3 d	14 (18.7)
4-7 d	35 (46.7)
>7 d	26 (34.7)
Unknown	0 (0.0)
Known allergy, n (%)	11 (14.7)
Known asthma, n (%)	10 (13.3)
Known eczema, n (%)	17 (22.7)
History of parental drug hypersensitivity, n (%)	19 (25.3)
History of other parental allergies, n (%)	27 (36.0)
History of parental asthma, n (%)	8 (10.7)

IQR, Interquartile range; *SSLR*, serum sickness–like reaction.
All index reactions fit the SSLR definition.[6]
*Upper respiratory tract infection treated include 4 cases of streptococcal pharyngitis, 4 cases of undiagnosed throat infections, 1 case of pharyngitis, 2 cases of bronchitis, 1 case of tonsillitis, and 2 cases of sinusitis.
†Other infections include 1 case of scarlet fever, 1 case of osteomyelitis, 1 case of dental abscess, 1 case of cellulitis, and 1 post–nose surgery patient.

participants prospectively included provided a written informed consent although it was deemed unnecessary for retrospective data collection.

RESULTS

Between March 2013 and February 2020, 75 patients with suspected SSLRs were recruited into the LAACTAM study at the Montreal Children's Hospital. The median age was 2.00 years (IQR, 1.20, 4.00) with 46.7% of patients being male. The majority of patients were treated for otitis media with amoxicillin being the culprit antibiotic (Table I). All 75 patients underwent a GOC, to which 3 outcomes were identified: positive immediate reaction to the GOC (2.7%), positive nonimmediate reaction to the GOC (4.0%), and negative challenge (93.3%) (Table II). All challenge reactions were classified as self-limiting mild grade 1 reactions limited to the skin, none satisfying the SSLR definition.[14,15]

Annual follow-ups included all consenting patients except children who had positive challenge outcomes (2.7% immediate and 4.0% nonimmediate) as they are considered true reactors and instructed to avoid the culprit antibiotic. Of the 43 negative challenge patients successfully contacted (67.1%), 20 patients had subsequent culprit antibiotic use with 25.0% having subsequent reactions (Figure 3). All disclosed subsequent reactions were classified as grade 1, and were mild, self-resolving, and limited to the skin, none fitting the criteria for SSLR.[14,15]

SSLRs occurring within 4 to 7 days of antibiotic treatment were associated with increased likelihood of positive GOC outcome along with positive subsequent reaction to the culprit antibiotic (adjusted odds ratio, 1.20; 95% confidence interval [CI], 1.01, 1.42), when adjusting for age at index reaction, male sex, antibiotic type, and history of parental drug hypersensitivity (Table III). Age, male sex, antibiotic type, and history of parental drug hypersensitivities were all not associated with a positive GOC outcome and positive subsequent reaction to the culprit antibiotic.

DISCUSSION

We have conducted the first and largest study to assess the safety and efficiency of a GOC in all children presenting with SSLR. Given the benign outcome of the GOC and of subsequent use of antibiotics in those with negative challenge, we believe that the GOC is a safe and useful strategy to diagnose antibiotic allergy in children presenting with suspected SSLR.[1] Similar to other large cohorts not assessing specifically patients with SSLR, positive GOCs were mild and limited to the skin.[1] The low risk of reaction to a GOC and the benign nature of this reaction as

TABLE II. Graded oral challenge outcome

Variable	n (%)
Challenge outcome	
Positive (immediate)	2 (2.7)
Positive (nonimmediate)	3 (4.0)
Negative	70 (93.3)

All positive challenge reactions were grade 1 reactions.[14,15]

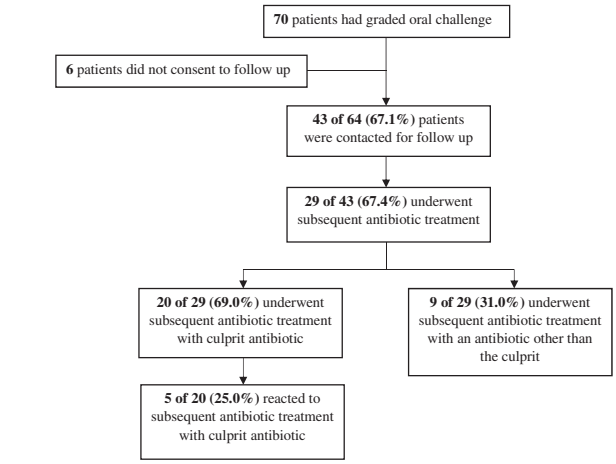

FIGURE 3. Subsequent antibiotic use and reaction from annual follow-up.

TABLE III. Factors associated with positive graded oral challenge outcome or positive subsequent reaction in pediatric patients

Variable	Univariate	Multivariate
Characteristics	OR (95% CI)	OR (95% CI)
Age at index reaction	1.00 (0.98, 1.02)	1.00 (0.97, 1.02)
Sex (male)	0.96 (0.82, 1.12)	0.97 (0.83, 1.14)
Antibiotic type—amoxicillin	1.05 (0.84, 1.30)	1.09 (0.87, 1.37)
Reaction within 4-7 d of treatment	1.18 (1.00, 1.39)*	1.20 (1.01, 1.42)*
History of parental drug allergy	1.03 (0.86, 1.23)	1.04 (0.87, 1.25)

CI, Confidence interval; *OR*, odds ratio.
*Indicates statistical significance ($P < .05$).

well as subsequent reactions are consistent with previous reports published by our group[1] and others.[4,16]

Given the benign nature of these reactions, the safety profile of GOCs, and the lack of other confirmatory tests, we believe that GOCs should be incorporated in the diagnostic algorithm of suspected SSLR. However, we believe that cases with reactions occurring within 4 to 7 days should be challenged in hospital setting given the higher likelihood of reaction. Furthermore, the increased use of GOCs would contribute to the appropriate use of first-line antibiotic treatment in cases that are related to viral infection rather than true amoxicillin allergy.

Our results show that index reactions occurring within 4 to 7 days of antibiotic treatment are associated with positive GOC outcome and reaction after the subsequent use of the culprit antibiotic (Table III). Previous studies reveal heterogeneity regarding the time intervals between exposure to the culprit drug and the development of SSLRs ranging from 2 to 21 days.[17] Such inconsistencies could be explained by poor identification of true reactors due to misclassification bias given that challenges and long-term follow-up are rarely done.

In contrast to other studies in which cases of rash and joint involvement are rarely challenged, we have consistently challenged all children presenting with these symptoms. Hence, our sample represents an unbiased and accurate assessment through challenge of these cases. Our study has some potential limitations. Our sample size is limited to 75 cases. However, SSLR is substantially less common than other types of drug-associated reactions.[1] Although only 6.7% of patients had positive challenge outcomes (either immediate or non-immediate), we found a rate of reaction of 25.0% on subsequent use. The rate of recurrent reactions with therapeutic antibiotic use in this paper is similar to the 10.9% risk of recurrent reactions previously reported by our group (25% vs 10.9%, difference in proportions of 14.1% [95% CI, −10%, 38%]).[1] All subsequent reactions were grade 1, mild, and limited to the skin.[14,15] The high rate of subsequent reactions missed with GOC may be due to immune reactions that develop over the course of a few days to weeks of treatment. A potential solution would be to consider a GOC over a larger time interval, such as 5 to 7 days.[18] However, a lengthier challenge also exposes patients to the risk of bacterial antibiotic resistance development, making the subsequent use of antibiotics ineffective.[19] Furthermore, recent studies suggest a lack of value for prolonged challenge in cases with suspected antibiotic allergy.[20] Drug-virus interactions are also a known cause of adverse drug reaction and can be potentially reproduced only in cases that use the culprit antibiotic during subsequent infection.[1,10,12] Nevertheless, it has not yet established what are the exact pathogenic mechanisms accounting for SSLRs in the presence of medication use. However, given that rashes at least were reproduced on challenge with antibiotics in healthy children, it is likely that the drug has a major role in the development of SSLR.

In conclusion, we conducted the first and largest study to assess the use of a GOC as a diagnostic strategy in children presenting with suspected SSLR. Our findings suggest that using a GOC is safe for differentiating between β-lactam-induced SSLR and viral exanthem in this population. Future large-scale studies are required to identify risk factors associated with true SSLRs in children and to predict the probability of outgrowing these reactions over time.

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