PEER REVIEW HISTORY

BMJ Paediatrics Open publishes all reviews undertaken for accepted manuscripts. Reviewers are asked to complete a checklist review form and are provided with free text boxes to elaborate on their assessment. These free text comments are reproduced below.

ARTICLE DETAILS

TITLE (PROVISIONAL)	Mild to moderate hypersensitivity reactions to beta-lactams in children, a single centre retrospective review
AUTHORS	Vila, Leticia; Garcia, Vanesa; Martinez Azcona, Oihana; Pineiro, Loreley; Meijide, Angela; Balboa, Vanesa

VERSION 1 – REVIEW

REVIEWER	Reviewer name: Michael Rieder Institution and Country: Children's Hospital, London Health Sciences Centre, Western University. London, Ontario, Canada Competing interests: None
REVIEW RETURNED	04-Feb-2019

GENERAL COMMENTS	The authors report a study evaluating the diagnostic approach to purported penicillin allergy in children with mild to moderate reactions and describe the success of an aggressive approach to oral challenge (which they refer to as drug provocation test - DPT) in these children. The authors conclude that proceeding directly to oral challenge/DPT without skin testing is children with histories of possible mild to moderate allergic/adverse reactions to beta-lactams is appropriate and timely. Study design is straightforward and easy to follow. The authors have selected children with a retrospective history of beta-lactam allergy, which has been shown in many publications to over-estimate the incidence of allergy (Ann Allergy Asthma Immunol 2016; 117: 273-9). However, this is a major clinical problem as false classification of beta-lactam allergy has significant real world consequences for both patients and the health care system and thus this question is important (Ann Allergy Asthma Immunol 218; 120: 190-4). The author's conclusion is clear and supported by data. A word of caution as to this approach for children with more serious adverse events (DRESS, SJS, etc.) is warranted. As well, some thought should go into the use of this approach for putative serum sickness like reactions, as it would appear that most of these children would have had a 3 - 5 day DPT. Given that there is some literature that suggests that serum sickness like reactions to cefaclor develop after 7 to 8 days of therapy, and given that one child actually developed a serum sickness like reaction requiring corticosteroid therapy, this suggests that perhaps a more conservative approach is required for possible serum sickness like reactions (Clin Pharmacol Ther 1988; 63: 686-93). A question that is raised is how this manuscript adds to the literature in this area given that there are other studies calling for this overall approach, i.e. directly moving to drug challenge without use of skin tests, for example Moral and Caubet (Pediatr Allergy Immunol 2017; 28: 724-7) which the authors cite among other studies on line 276 as well as other large studies not cited (J Allergy Clin Immunol Pract

	2017; 6: 669-75). The authors need to expand this part of their discussion to place their work in context to the literature in what is after years of stagnation becoming a rapidly evolving field. As a minor point on line 92 I think "de" should be "the". On line 263 "cols" should be capitalized. As well, "et al." is an abbreviation, i.e. there is a "." after "al."

VERSION 1 – AUTHOR RESPONSE

Reviewer: 1

Comments to the Author:

1. The authors report a study evaluating the diagnostic approach to purported penicillin allergy in children with mild to moderate reactions and describe the success of an aggressive approach to oral challenge (which they refer to as drug provocation test - DPT) in these children. The authors conclude that proceeding directly to oral challenge/DPT without skin testing is children with histories of possible mild to moderate allergic/adverse reactions to beta-lactams is appropriate and timely.

Response: I agree with Dr Rieder that it would be great to have an alternative diagnostic tool to DPT. Unfortunately up to date, there is no skin test or laboratory test reliable enough to support the diagnosis of delayed hypersensitivity reactions to drugs. This is the reason why the diagnosis of non-immediate reactions to beta-lactams relies on DPT.

2. Study design is straightforward and easy to follow. The authors have selected children with a retrospective history of beta-lactam allergy, which has been shown in many publications to over-estimate the incidence of allergy (Ann Allergy Asthma Immunol 2016; 117: 273-9).

Response: We have added a sentence in the discussion indicating this limitation of the study. We have included the reference suggested by Dr Rieder.

From the moment we finished the study we follow this protocol on our daily practice. Patients have not experienced severe reactions during DPT, mainly because these patients reported mild and moderate adverse reactions.

After finishing the present retrospective study sent, we followed 64 patients with adverse reactions to beta-lactams. They underwent DPT without previous skin testing. We found a similar incidence of drug allergy (7%) in this sample (data not shown). The incidence of the retrospective analysis seems to be close to the “real” incidence of beta-lactam allergy, at least in our population. Also, our results agreed with others reported in the literature, as mentioned in the introduction.

3. However, this is a major clinical problem as false classification of beta-lactam allergy has significant real world consequences for both patients and the health care system and thus this question is important (Ann Allergy Asthma Immunol 2018; 120: 190-4).

Response: We agree. As we mention in the discussion, establishing an accurate diagnosis of beta-lactam allergy is associated not only with a more rationale use of antibiotics but also with lower rates of health care utilization

4. The author's conclusion is clear and supported by data. A word of caution as to this approach for children with more serious adverse events (DRESS, SJS, etc.) is warranted. As well, some thought should go into the use of this approach for putative serum sickness like reactions, as it would appear that most of these children would have had a 3 - 5 day DPT.

Given that there is some literature that suggests that serum sickness like reactions to cefaclor develop after 7 to 8 days of therapy, and given that one child actually developed a serum sickness like reaction requiring corticosteroid therapy, this suggests that perhaps a more conservative approach is required for possible serum sickness like reactions (Clin Pharmacol Ther 1988; 63: 686-93).

Response: This approach is not recommended for severe adverse drug reactions as DRESS or Steven-Jonhsons. In these cases, skin tests should be performed. Since they are usually negative, diagnosis relies most of the times on the clinical history.

Serum sickness-like reactions could be considered moderate.

We always explain to the patients and to their parents, the risks of performing DPT since there is the possibility of reproducing the same reaction at home during the procedure.

Parents then decide if they want to perform DPT with the culprit drug or with an alternative antibiotic (for example, if the reaction was reported with amoxicillin, they may prefer to perform DPT with cefuroxime). Most times they decide to try the suspected drug again at home. In our experience, the majority of patients with serum sickness-like reactions tolerate de antibiotic on DPT, highlighting the relevance of the infectious agent in the etiopathogenesis of this type of reactions.

5. A question that is raised is how this manuscript adds to the literature in this area given that there are other studies calling for this overall approach, i.e. directly moving to drug challenge without use of skin tests, for example Moral and Caubet (Pediatr Allergy Immunol 2017; 28: 724-7) which the authors cite among other studies on line 276 as well as other large studies not cited (J Allergy Clin Immunol Pract 2017; 6: 669-75). The authors need to expand this part of their discussion to place their work in context to the literature in what is after years of stagnation becoming a rapidly evolving field.

Response: With this study we support previous recommendations and propose a new protocol for DPT. The DPT protocol is thought to identify the major number of truly allergic children trying to minimize the adverse effects of the antibiotic (as diarrhea).

We emphasize this in the discussion (lines: 275-278 and 302-305).

6. As a minor point on line 92 I think "de" should be "the". On line 263 "cols" should be capitalized. As well, "et al." is an abbreviation, i.e. there is a "." after "al."

Response: Changes had been made. We replaced and “cols” by “et al”.