

# A Case of a Child With Several Anaphylactic Reactions to Drugs

Global Pediatric Health  
Volume 6: 1–4  
© The Author(s) 2019  
Article reuse guidelines:  
sagepub.com/journals-permissions  
DOI: 10.1177/2333794X19855287  
journals.sagepub.com/home/gph



Daniela Podlecka, MD, PhD<sup>1</sup>, Joanna Jerzynska, MD, PhD<sup>1</sup>,  
Kamila Malewska-Kaczmarek, MD<sup>1</sup>, and Iwona Stelmach, MD, PhD<sup>1</sup> 

## Abstract

Adverse drug reaction is defined as any harmful, unintended, and undesired effect of a drug that occurs at doses used for treatment, prevention, or diagnoses. Most of these reactions are classified as type A reactions, which by definition are predictable, common, dose-dependent, and caused by known pharmacological actions of the drug, drug toxicity, and side effects. Allergic reactions are qualified as type B reactions independent of dose, affecting a small population, suggesting that individual patient host factors are important. In pediatric population,  $\beta$ -lactam antibiotics are the most common reason for adverse drug reactions, followed by nonsteroidal anti-inflammatory drugs. In this article, we report the case of a child with several anaphylactic reactions to several drugs, including cefuroxime, amoxicillin/clavulanate, clarithromycin, ibuprofen, and budesonide, in a context of suspected *Helicobacter pylori* infection.

## Keywords

Anaphylactic shock,  $\beta$ -lactam antibiotics, allergy, children

Received August 16, 2018. Received revised April 30, 2019. Accepted for publication May 10, 2019.

## Introduction

According to the statement of the World Health Organization, an adverse drug reaction (ADR) is defined as any harmful, unintended, and undesired effect of a drug that occurs at doses used for treatment, prevention, or diagnoses.<sup>1</sup> Most of these reaction are classified as type A reactions, which by definition are predictable, common, dose-dependent, and caused by known pharmacological actions of the drug, drug toxicity, and side effects.<sup>1</sup> Allergic reactions are qualified as type B reactions independent of dose, affecting a small population, suggesting that individual patient host factors are important.<sup>1</sup> In the pediatric population,  $\beta$ -lactam (BL) antibiotics are the most common reason for ADRs, followed by nonsteroidal anti-inflammatory drugs (NSAIDs).<sup>1</sup> As viral infections are very common in children, it is considered that these infections may also act like cofactors in susceptible individuals, resulting in skin rashes occurring during BL treatment.<sup>1</sup>

Beta-lactams are the most common prescribed antibiotics and are responsible for the majority of hypersensitivity reactions to drugs.<sup>1,2</sup> Cross-reactivity is important in hypersensitivity to BL because these drugs have a similar structure and side chains.<sup>3</sup> Acute reactions are a consequence of previous exposure to penicillin, resulting

in release of histamine and other mediators from mast cells. The signs and symptoms are typical for anaphylactic reaction.

## Ethical Approval and Informed Consent

Written consent on the case report was obtained from the parents (institutional review board: RNN/147/18/KE; dated May 15, 2018).

## Case Report and Hospital Course

We present a case of a 7.5-year-old boy admitted to our Pediatric and Allergology Clinic due to allergy to BL antibiotics for full diagnostics. The patient was born G1P1 with a birth weight of 3450 g and Apgar score of 9/10 points. His neonatal period was uncomplicated. The patient had a history of frequent respiratory tract

<sup>1</sup>N. Copernicus Memorial Hospital, Lodz, Poland, Medical University of Lodz, Poland

### Corresponding Author:

Iwona Stelmach, Pilsudskiego 71 Street, Łódź 90-328, Poland.  
Email: alergol@kopernik.lodz.pl



infections (average once a month) since the beginning of preschool, usually requiring antibiotics. He was vaccinated according to the schedule. A family history of atopic diseases was negative. The boy was diagnosed with asthma and allergic rhinitis due to house dust allergy, and since 2016, he went under subcutaneous immunotherapy. Previously, he had been hospitalized several times due to pneumonia and asthma exacerbation (at the age of 5 and 6 years) and one time for orchitis (at the age of 2 years). According to the interview collected from his mother, due to infection in May 2017, the child had been given oral cefuroxime. About 15 minutes after the first dose of this antibiotic, a disseminated urticaria appeared, followed by edema of the face tissues. He was seen by a medical doctor and had been given intramuscular corticosteroids and antihistamines, achieving improvement of symptoms; the antibiotic had been changed to clarithromycin. After a course of 5 days of treatment, a similar situation developed—disseminated urticaria and difficulties in breathing. The boy had been hospitalized, and he had been treated with intravenous corticosteroids and antihistamines. Up to the date of first hospitalization for anaphylaxis, the patient had been treated with different BL antibiotics without any adverse reactions. The child was referred to our Allergic Department for drug allergy diagnostics. We performed this diagnostic in 3 months after the adverse event, according to the European Academy of Allergology and Clinical Immunology (EAACI) guidelines.<sup>1</sup> Medical examination and laboratory findings confirmed no current infection. Skin prick tests were performed with amoxicillin, amoxicillin/clavulanate, and cefuroxime in concentrations as recommended in previous studies<sup>4,6</sup>; skin prick test was strongly positive only for cefuroxime (wheal 6 mm + pseudopodium). Because of the boy's medical history of severe anaphylactic reaction and a positive skin prick test for cefuroxime, we decided to abandon the oral drug provocation test (DPT) with cefuroxime, defining it as a culprit drug. We performed a provocation test with the alternative BL drug—amoxicillin. According to the EAACI guidelines,<sup>1,2</sup> it was a 2-day blinded provocation test (placebo and the drug given in titrated doses up to the dispensable dose) performed under the control of spirometry parameters and vital signs (heart rate, respiratory rate). During the whole provocation test with amoxicillin, we did not notice any adverse reaction; thus, the parents were informed that oral amoxicillin may be used safely in case of infections needing therapy with antibiotics.

The parents were advised to come back to our department in 2 months for another diagnosis of clarithromycin sensitivity. In October 2017 (2 months after the first provocation), skin prick test performed with

clarithromycin was negative. Intradermal test was not performed, because it is painful, time consuming, and its role has been widely debated in children.<sup>7</sup> DPT with clarithromycin was performed as described previously (blinded and placebo-controlled oral provocation with titrated doses up to the dispensable dose) without any adverse events. The patient was discharged and referred to the Allergy Outpatient Clinic for further observation and immunotherapy continuation.

Between October 2017 and April 2018, the boy had been treated twice with amoxicillin and azithromycin (for pharyngitis and pneumonia); no adverse events were noticed. At the end of April 2018, the child was admitted to our department because of asthma exacerbation due to pneumonia. Treatment with amoxicillin/clavulanic acid was administered. Fifteen minutes after the first intravenous dose, the boy declared feet itching, followed by disseminated urticaria, face edema, bronchospasm, and drop in blood pressure. An immediate treatment with epinephrine, antihistamines,  $\beta$ 2 agonists, and oxygen were given with rapid improvement in the boy's general condition. The treatment was continued with intravenous aminoglycoside (biodacine) administered in a slow drip infusion for 5 more days. During the hospitalization, the boy developed a rota viral infection manifested by diarrhea, fever, vomiting, and general malaise. Because of the fever, our patient was treated with paracetamol followed by ibuprofen. About 5 minutes after an oral dose of ibuprofen, the patient developed an anaphylaxis; 2 doses of epinephrine were needed to achieve stabilization of vital signs. The patient was given drip infusions, dexamethasone, and inhaled budesonide. After 2 days, the patient presented disseminated urticaria and bronchoconstriction during the inhalation with budesonide. Several measurements of tryptase level were normal. A positive test for stool antigen *Helicobacter pylori* was found.

## Final Diagnosis

The patient was diagnosed as allergic to BL antibiotics.

## Discussion

Beta-lactams are the most frequent cause of antibiotic hypersensitivity in children, more specifically amoxicillin alone or with clavulanic acid. According to EAACI guidelines for drug allergy diagnosis, only the oral DPT is a gold standard for identification of the culprit drug in patients with drug hypersensitivity reactions.<sup>1,2,8</sup> In the presented patient, with immediate reaction after cefuroxime in the past and positive skin prick test with this drug, we performed the prick test and the DPT with

amoxicillin, both of which were negative. We did not perform intradermal test with amoxicillin, since the patient was treated with this drug several times, with no adverse reactions. The anaphylaxis appeared after an intravenous dose of amoxicillin/clavulanate. In some reports, clavulanic acid has been associated with very few allergic reactions, suggesting a low allergenic potential.<sup>3,9,10</sup> Others state that selective reactions to clavulanate account for around 30% of allergic reactions to the combination amoxicillin/clavulanate.<sup>11</sup> However, our patient was not suspected for hypersensitivity to clavulanic acid because he was treated with amoxicillin/clavulanate several times in the past without adverse reactions and had negative skin prick test with amoxicillin/clavulanate.

The second anaphylaxis appeared after administering an oral ibuprofen. The questions to be addressed is whether this was an immunoglobulin E-mediated allergy or other mechanism are involved. In the future, diagnosis of hypersensitivity to ibuprofen or alternate NSAIDs as well as with cephalosporins of first, second, and third generations should be performed. However, our patient had several severe reactions and DPT should be done with caution. Until full diagnostics are performed, the patient was recommended to use antihistamine drugs and lower the high temperature naturally during infection. In the case of infections requiring the treatment with antibiotics, the hospitalization was recommended.

According to the National Institute of Allergy and Infectious Diseases (NIAID) and the Food Allergy and Anaphylaxis Network (FAAN), anaphylaxis is a serious reaction that has a rapid onset and may cause death.<sup>12,13</sup> It is a systemic immunoglobulin E-mediated reaction resulting from the sudden release of multiple mediators from mast cells and basophils. If the NIAID/FAAN criteria are met and anaphylaxis is diagnosed, epinephrine administration is mandatory. All patients with anaphylaxis, regardless the age, require immediate treatment. The administration of epinephrine at a dose of 0.01 mg/kg (1:1000) is the first-line treatment for anaphylaxis. There are no absolute contraindications to this treatment.<sup>12-14</sup> Second-line interventions include removal of the trigger, proper posture to diminish the respiratory distress, oxygen supply, fluid support, inhaled short-acting  $\beta_2$ -agonists and H1 and H2 antihistamines, and glucocorticosteroids.<sup>12-14</sup>

## Conclusion

In conclusion, in our patient, we cannot rule out the hypersensitivity to clavulanate or presence of nonspecific factors, for example, *Helicobacter pylori*, as the

direct cause of immediate allergic reaction to amoxicillin treatment.

Clavulanic acid is inherently unstable in solution, requiring the use of excipients; therefore, hypersensitivity diagnostics is very difficult. We should also be aware that many factors, for example, infections, other diseases, or genetic factors, may affect the development of ADRs. Some of these factors are patient-related, drug-related, or socially related factors. Age, for instance, has a very critical impact on the occurrence of ADRs; very young patients are more vulnerable to these reactions than other age groups. Other factors are gender, race, kidney problems, liver function, drug dose, and frequency.<sup>15</sup>

Further studies and in vitro tests of subject groups of children suspected for drug hypersensitivity are needed to provide important knowledge to this critical process. Pharmacogenomics is a very recent science, which emphasizes the genetic predisposition of ADRs.

As the administration of epinephrine is first-line treatment for anaphylaxis, parents and patients should be educated on how to recognize the symptoms of anaphylaxis and on how to use adrenaline auto-injectors. An individualized emergency action plan should be developed for each patient at risk for anaphylaxis.<sup>12-14</sup>

According to the guidelines of the EAACI, the absolute indications for adrenaline auto-injector are previous anaphylaxis with food, latex, animal allergens or unavoidable triggers, previous exercise-induced anaphylaxis or idiopathic anaphylaxis, coexistent moderate to severe unstable asthma with food allergy, untreated venom allergy, and mast cell disorder.<sup>13</sup>

## Author Contributions

DP: Contributed to conception and design.

JJ: Contributed to acquisition; agrees to be accountable for all aspects of work ensuring integrity and accuracy.

KMK: Drafted manuscript.

IS: Critically revised manuscript; gave final approval.

## Declaration of Conflicting Interests

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

## Funding

The author(s) received no financial support for the research, authorship, and/or publication of this article.

## Informed Consent

We obtained written permission from the parents for the publication of this case history.

**ORCID iD**

Iwona Stelmach  <https://orcid.org/0000-0002-1475-8221>

**References**

1. Gomes ER, Brockow K, Kuyucu S, et al; ENDA/EAACI Drug Allergy Interest Group. Drug hypersensitivity in children: report from the pediatric task force of the EAACI Drug Allergy Interest Group. *Allergy*. 2016;71:149-161.
2. Demoly P, Adkinson NF, Brockow K, et al. International consensus on drug allergy. *Allergy*. 2014;69:420-437.
3. Ponvert C, Perrin Y, Bados-Albiero A, et al. Allergy to betalactam antibiotics in children: results of a 20-year study based on clinical history, skin and challenge tests. *Pediatr Allergy Immunol*. 2011;22:411-418.
4. Co Minh HB, Bousquet PJ, Fontaine C, Kvedariene V, Demoly P. Systemic reactions during skin tests with beta-lactams: a risk factor analysis. *J Allergy Clin Immunol*. 2006;117:466-468.
5. Bousquet PJ, Pipet A, Bousquet-Rouanet L, Demoly P. Oral challenges are needed in the diagnosis of beta-lactam hypersensitivity. *Clin Exp Allergy*. 2008;38:185-190.
6. Manuyakorn W, Singvijarn P, Benjaponpitak S, et al. Skin testing with  $\beta$ -lactam antibiotics for diagnosis of  $\beta$ -lactam hypersensitivity in children. *Asian Pac J Allergy Immunol*. 2016;34:242-247.
7. Moral L, Caubet JC. Oral challenge without skin tests in children with non-severe beta-lactam hypersensitivity: time to change the paradigm? *Pediatr Allergy Immunol*. 2017;28:724-727.
8. Torres MJ, Romano A, Celik G, et al. Approach to the diagnosis of drug hypersensitivity reactions: similarities and differences between Europe and North America. *Clin Transl Allergy*. 2017;7:7.
9. Zambonino MA, Corzo JL, Muñoz C, et al. Diagnostic evaluation of hyper-sensitivity reactions to beta-lactam antibiotics in a large population of children. *Pediatr Allergy Immunol*. 2014;25:80-87.
10. Sánchez-Morillas L, Pérez-Ezquerro PR, Reaño-Martos M, Laguna-Martínez JJ, Sanz ML, Martínez LM. Selective allergic reactions to clavulanic acid: a report of 9 cases. *J Allergy Clin Immunol*. 2010;126:177-179.
11. Torres MJ, Montañez MI, Ariza A, et al. The role of IgE recognition in allergic reactions to amoxicillin and clavulanic acid. *Clin Exp Allergy*. 2016;46:264-274.
12. Anagnostou K. Anaphylaxis in children: epidemiology, risk factors and management. *Curr Pediatr Rev*. 2018;14:180-186.
13. Muraro A, Roberts G, Worm M, et al; EAACI Food Allergy and Anaphylaxis Guidelines Group. Anaphylaxis: guidelines from the European Academy of Allergy and Clinical Immunology. *Allergy*. 2014;69:1026-1045.
14. Azevedo J, Gaspar Â, Mota I, et al. Anaphylaxis to beta-lactam antibiotics at pediatric age: six-year survey. *Allergol Immunopathol (Madr)*. 2019;47:128-132.
15. Alomar MJ. Factors affecting the development of adverse drug reactions (Review article). *Saudi Pharm J*. 2014;22:83-94.