What is new in drug hypersensitivity in children?

Marina Atanaskovic-Markovic[1]

[1]University of Belgrade Faculty of Medicine

May 15, 2020

Abstract

This review highlights the novelties in understanding the underlying immunological mechanisms of drug hypersensitivity reactions (DHRs) as well as tiny changes in clinical classification and diagnosis of DHRs with special reference to beta-lactams (BLs) in the pediatric population, in the last couple of years. Viral infections are very often in children and they can provoke skin rashes which is difficult to differentiate from DHRs. Because of that allergy to BLs in children is overdiagnosed. The correct diagnosis of BLs allergy in children is still an important and hot topic. In this review has been outlined the need for correct diagnosis of BLs allergy in children as well as needed to change the paradigm.

New understanding of drug hypersensitivity mechanism

In the last few years, we came to a better understanding of the underlying immunological mechanisms of drug hypersensitivity reactions (DHRs). Therefore, DHRs have been classified into allergic, pharmacological interaction (p-i concept) and pseudoallergic. In allergic reaction the drug act as hapten and specific immune response is directed against a hapten-carrier complex (the hapten hypothesis). This can be mediated by IgE and IgG antibodies or by T cells. According to the type of reactions these reactions can be immediate or nonimmediate. Elicitors are: beta-lactactams- BLs, sulphanilamides, quinolones, metamizol, radiocontrast media- RCM, neuromuscular blocking agent- NMBA and antineoplastics. In p-i concept the drug can bind directly to HLA or TCR. p-i reactions are considered nonimmediate. The most frequent elicitors are: BLs, sulphanilamides, quinolones, metamizol, RCM, vancomycin, antineoplastics, anticonvulsants, local anaesthetics and abacavir. In pseudoallergic reaction the drug binds directly to the receptor or interact with enzymes of effector cells. These reactions are considered immediate. Type of drugs eliciting DHRs by pseudoallergic mechanism are: nonsteroidal anti-inflammatory drugs- NSAIDs, quinolones, RCM, NMBA and vancomycin.[1,2]

Clinical classification of DHRs

Tiny changes were made through clinical classification of DHRs, but controversies still exist. Immediate reactions (IRs) appear within 1 hour up to 6 hours, after the first dose of the last therapeutic course. In general IRs are mediated by IgE antibodies. The clinical manifestation of those reactions ranges from benign urticaria with or without angioedema, up to potentially life-threatening anaphylaxis. Two clinical entities of IRs have been proposed: mild IRs (urticaria /angioedema), and severe IRs (anaphylaxis/anaphylactic shock). IRs can also be mediated by COX-1 inhibition or by MRGPRX2 (Mas-related G-protein-coupled receptor member X2). Clinical entities are: urticaria, angioedema, anaphylaxis and respiratory symptoms. Nonimmediate reactions (NIRs) occur more than 6 hours after the first dose of the last therapeutic course, which often start 2 to 5 days later. NIRs are mediated by T cells. Clinical manifestations of those reactions ranges from benign rashes (maculopapular exanthema-MPE or fixed drug eruption- FDE or serum sickness like reactions SSLR) to potentially life-threatening severe cutaneous adverse reactions (SCARs) such as Stevens-Johnson syndrome-SJS and toxic epidermal necrolysis-TEN, drug reaction with eosinophilia and systemic symptoms-DRESS, acute generalized exanthematous pustulosis-AGEP or single organ reaction

such as drug induced liver disease (DILI). Also two clinical entities of NIRs have been proposed: mild NIRs (MPE, SSLR) and severe NIRs (SCARs).[1-3]

Diagnosis

BLs still are the most commonly prescribed and used antibiotics in children. Viral infection can provoke skin rashes such as MPE or urticaria, therefore it is difficult to differentiate DHRs from skin symptoms due to infections.[4,5] There must be at least one exposure before the index reaction, but we have to keep in mind that a previous sensitization can be unsuspected and due to cross-reactivity.[3] About 10% of parents report suspected allergy to at least one BLs in their children.[6] So the most of children are labeled as 'drug allergic'. But, after a proper evaluation, allergy will be confirmed only in a small percentage of children, indicating that true allergy to BLs is rare and overdiagnosed.[7-9] Because of that, the diagnosis of BLs hypersensitivity in children is still an important and hot topic.[10]

Most information about approach and management on BLs hypersensitivity in children is applied from available guidelines and consensus statement for adults.[6,11]

The first step in the diagnostic work up is complete and precise clinical history. It is essential to differentiate between an adverse reaction and a real DHR, as well as, whether is an IR and NIR. The following steps will vary depending on type of reaction (IR or NIR).

IRs

For IR there are agreement that the skin (prick and intradermal) tests with culprit BL, should be performed before confirmatory oral drug provocation test- DPT.[3,5, 6, 9,12] Skin tests have a relatively high diagnostic value in IRs [6,13], but more pediatric studies need to confirm these data. The DPT is still the gold standard for the diagnosis of IRs, [3, 6, 11, 13] but there is no consensus on the best protocol for performing DPT. It is still necessary to establish the optimal step doses and the optimal duration of provocation.[3] General recommendation for DPT, including indications and contraindications, also apply for children.[14]

In vitro testing is a part of a diagnostic algorithm for IRs to BLs along with other tests. Quantification of serum drug-specific IgE (sIgE) measurements and direct/indirect basophil activation tests (BATs) are frequently not performed. At the present time, there is controversy regarding sIgE immunoassay. sIgE immunoassay in some European countries is recommended for evaluating IRs to BLs, but in United States, it is not used because of its suboptimal sensitivity and low concordance with skin tests and DPTs.[2,15]

NIRs

The biggest changes were made throughout the diagnosis of NIR to BLs. In the last couple of years, lots of papers have been published which have shown that direct oral DPTs without prior skin testing are safe and effective in confirming or excluding hypersensitivity to BLs in children with benign rashes.[16 -26] Some authors still think that a skin test with the culprit BL is safe and that it should be performed (as an extra security step) in children with NIR, to avoid exposing them directly to higher doses of suspected BLs, by DPT.[8,25, 27, 28] Another disagreement is the protocol for performing DPT. The optimal (incremental or full) doses and intervals between the doses are controversial. The length of DPT varies among the different studies, going from as short as 1[16,20,29,30] day to 5 [18, 23, 26, 31]or more days,[6, 24] or the same length of the index reaction.[24,30]

There is general agreement that diagnostic work up should be performed for a minimum of 4 to 6 weeks after reaction to avoid both false-positive, false negative and flare-ups of systemic reactions.[32]

In the last few years there haven't been major changes in the diagnosis SCARs induced by BLs. Patch tests are useful in diagnosis AGEP and DRESS, but they have low sensitivity (<30%) in diagnosis SJS/TEN. Intradermal tests are potentially useful in AGEP, their safety is unknown in DRESS, and contraindicated in SJS/TEN. DPTs are contraindicated in SCARs.[32, 33]

In vitro test, such as IFN-gamma producing cells determination by enzyme-linked immunospot assay

(ELISpot), in combination with patch tests has demonstrated a potential utility in BLs induced SCARs. The sensitivity and specificity of the lymphocyte transformation test (LTT) is still unsatisfactory.[2,15]

Conclusions

There are similarities and differences between Europe and America in the approach to the diagnosis of BLs hypersensitivity in children. The diagnosis of BLs hypersensitivity in children is still an important and hot topic, and continues to be a challenge. It is necessary to educate the public and health workers about the differences in adverse reactions to drugs and real drug hypersensitivity reactions "drug allergies". Thus, it could reduce overdiagnosis and promote appropriate procedures, that will prevent the overlabeling of drug allergy. There is a need to make a recommendation in pediatric guidelines, but for this, it is required further studies to validate this.

Reference:

1. Pichler WJ. Immune pathomechanism and classification of drug hypersensitivity. Allergy. 2019;74:1457-1471.

2. Mayorga C, Fernandez TD, Montanez MI, Moreno E, Torres MJ. Recent development and highlights in drug hypersensitivity. Allergy 2019;74:2368-2381.

3. Torres MJ, Adkinson NF, Caubet JC, et al; for the AAAAI/WAO 2018 Symposium Penicillin and Cephalosporin Allergy Testing Working Group. Controversies in Drug Allergy: Beta-Lactam Hypersensitivity Testing. J Allergy Clin Immunol Pract 2019;7:40-5.

4. Brockow K, Ardern-Jones MR, Mockenhaupt M, et al. EAACI position paper on how to classify cutaneous manifestations of drug hypersensitivity. Allergy 2019;74(1):14-27.

5. Calamelli E, Caffarelli C, Franceschini F, et al. A practical management of children with antibiotic allergy. Acta Biomed 2019;90 (Supll 3):11-19.

6. Gomes E, Brockow K, Kuyucu S, et al, on behalf of the ENDA/EAACI Drug Allergy Interst Group. Drug hypersensitivity in children: report from the pediatric task force of the EAACI Drug Allergy Interest Group. Allergy 2016; 71(2):149-61.

7. Caubet JC, Kaiser L, Lemaitre B, Fellay B, Gervaix A, Eigenmann PA. The role of penicillin in bening skin rashes in childhood: a prospective study based on drug rechallenge. J Allergy Clin Immunol 2011;127(1):218-222.

8. Atanaskovic-Markovic M, Gaeta F, Medjo B, et al. Non-immediate hypersensitivity reactions to beta-lactam antibiotics in children-our 10-year experience in allergy work-up. Pediatr Allergy immunol 2016;27(5):533-538.

9. Norton AE, Konvinse K, Phillips EJ, Broyles AD. Antibiotic allergy in pediatrics. Pediatrics 2018;141(5):e20172497.

10. Eigenmann PA, Akdis C, Bousquet J, et al. Highlights and recent development in food and drug allergy, and anaphylaxis in EAACI Journals (2017). Pediatr Allergy Immunol 2018;29:801-807.

11. Demoly P, Adkinson NF, Brockow K et al. International Consensus on drug allergy. Allergy 2014; 69(4):420-437.

12. Atanaskovic-Markovic M, Caubet JC. Management of drug hypersensitivity in pediatric population. Expert Rev Clin Pharmacol 2016;9(10):1341-1349.

13. Saretta F, Mori F, Cardinale F, et al. Pediatric drug hypersensitivity:which diagnostic tests? Acta Biomed 2019;90 (Supll 3):94-107.

14. Aberer W, Bitcher A, Romano A, et al. Drug provocation testing in the diagnosis of drug hypersensitivity reactions: general consideration. Allergy 2003;58:854-863.

15. Mayorga C, Didier EG, Lang D, et al. Controversies in drug allergy:*In vitro* testing. J Allergy Clin Immunol 2019;143:56-65.

16. Mill C, Primeau MN, Medoff E, et al. Assessing the Diagnostic Properties of a Graded Oral Provocation Challenge for the Diagnosis of Immediate and Nonimmediate Reactions to Amoxicillin in Children. JAMA Pediatr 2016;170(6):e160033.

17. 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.

18. Confino-Cohen R, Rosman Y, Meir-Shafrir K, et al. Oral Challenge without Skin Testing Safely Excludes Clinically Significant Delayed-Onset Penicillin Hypersensitivity. J Allergy Clin Immunol Pract 2017;5:669-675.

19. Vyles D, Adams J, Chiu A, Simpson P, Nimmer M, Brousseau DC. Allergy Testing in Children With Low-Risk Penicillin Allergy Symptoms. Pediatrics 2017;140(2):e20170471.

20. Kuruvilla M, Thomas J. Direct oral amoxicillin challenge without antecedent penicillin skin testing in low-riak patients. Ann Allergy Asthma Immunol 2018;121(5):627-628.

21. Macy E, Vyles D. Who needs penicillin testing? Ann Allergy Asthma Immunol 2018;121:523-529.

22. Ibanez MD, del Rio PR, Lasa EM, et al. Prospective assesment of diagnostic tests for pediatric penicillin allergy,from clinical history to challenge tests. Ann Allergy Asthma Immunol 2018;121(2):235-244.e3.

23. Iammatteo M, Arango SA, Ferastraoaru D, et al. Safety and Outcommes of Oral Graded Challenges to Amoxicillin without Prior Skin Testing. J Allergy Clin Immunol Pract 2019;7:236-243.

24. Vila L, Garcia V, Azcona OM, Pineiro L, Meijide A, Balboa V. Mild to moderate hypersensitivity reactions to beta-lactams in children: a single-centre retrospective review. BMJ Paediatrics Open 2019;3:e000435.

25. Macy E, Ensina LF. Is Skin testing Required Prior to Drug Challenges? J Allergy Clin immunol Pract 2019;7(2):412-417.

26. Celik IK, Guvenir H, Hurmuzlu S, et al. The negative predictive value of 5-day drug provocation test in nonimmediate beta-lactam allergy in children. Ann Allergy Asthma Immunol 2020;124:494-499.

27. Manuyakorn W, Singvijarn P, Benjaponpitak S, et al. Skin testing with β-lactam antibiotics for diagnosis of β-lactam hypersensitivity in children. Asian Pac J Allergy Immunol 2016;34:242-247.

28. Diaferio L, Chiriac AM, Leoni MC, et al. Skin tests are important in children with β-lactam hypersensitivity, but may be reduced in number. Pediatr Allergy Immunol 2019;30(4):462-468.

29. Chiriac AM, Rerkpattanapipt T, Bousquet PJ, Molinari N, Demoly P. Optimal step doses for drug provocation tests to prove beta-lactam hypersensitivity. Allergy 2017;72(4):552-561.

30. Rodriguez RG, Lozano LM, Ortega AE, Segade JB, Bonilla PG, Torrijos EG. Provocation Tests in Nonimmediate Hypersensitivity Reactions to β-Lactam Antibiotics in Children: Are Extended Challenges Needed? J Allergy Clin Immunol Pract 2019;7:265-269.

31. Labrosse R, Paradis L, Lacombe-Barrios J, et al. Efficacy and Safety of 5-Day Challenge for the Evaluation of Nonsevere Amoxicillin Allergy in Children. J allergy Clin Immunol pract 2018;6(5):1673-1680.

32. Phillips EJ, Bigliardi P, Bircher AJ, et al. Controversies in drug allergy: Testing for delayed reactions. J Allergy Clin Immunol 2019;143:66-73.

33. Dibek Misirlioglu E, Guvenir H, Bahceci S, et al. Severe Cutaneous Adverse Drug Reactions in Pediatric Patients: A Multicenter Study. J Allergy Clin Immunol Parct 2017;5(3):757-763.