

LETTER TO THE EDITOR

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Challenges and preventive strategies in pediatric drug hypersensitivity reactions: where do we stand?

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Abstract

Drug hypersensitivity reactions (DHRs) in pediatric patients present significant clinical challenges due to their potential for severe, life-threatening reactions such as anaphylaxis. Although less common than in adults, DHRs in children are more difficult to diagnose and manage due to limited pediatric-specific research. This study focuses on the role of premedication as a preventive strategy for DHRs, exploring its potential benefits and limitations. While approaches like H1-antihistamines combined with gradual drug dose escalation show promise for reducing mild histamine-mediated reactions, evidence regarding premedication's effectiveness, particularly for non-IgE-mediated mechanisms, remains inconclusive. Rapid drug desensitization (RDD) protocols demonstrate high success rates in certain cases; however, there are no strong recommendations for or against premedication, and controlled studies documenting its real efficacy are lacking. Further research is crucial to establish clear guidelines and improve the safety and outcomes of pediatric drug allergy management.

Keywords Drug hypersensitivity reactions (DHRs), Prevention, Desensitization, Children

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Dear Editor,

Drug allergies in pediatric patients are a significant concern in clinical practice, as they can lead to severe adverse reactions, including life-threatening anaphylaxis. While drug hypersensitivity reactions (DHRs) are less common in children than in adults, they can be more challenging to diagnose and manage due to limited pediatric-specific data. In light of this, finding preventive strategies for drug allergies in pediatric populations is essential to minimize risks and improve patient quality of life. Premedication (PM) is one of the first preventive approach worth considering, though research on its effectiveness in pediatric DHRs remains limited. Most available studies focus on adult populations and show conflicting results, influenced by factors such as the type of drug, the premedication or desensitization protocol used, and individual patient characteristics.



Position papers from the European Network of Drug Allergy (ENDA) and the European Academy for Allergy and Clinical Immunology (EAACI) drug hypersensitivity group indicate that premedication with systemic steroids and antihistamines has limited effectiveness in preventing breakthrough reactions (BRs) [1, 2]. Moreover, premedication may mask early signs of hypersensitivity, creating a false impression of temporary tolerance. However, a recent EAACI position paper suggests that premedication with H1-antihistamines, combined with a slow, gradually increasing dose of certain drugs, may help to mitigate mild reactions due to nonspecific histamine release from mast cells and basophils [3]. This approach could be effective for reactions triggered by agents like opioids, neuromuscular blocking agents (NMBAs), vancomycin, and thiopentone. In this context, taking oral H1-antihistamines 2–3 days before anesthesia may provide effective histamine receptor blockade [3]. Additionally, several factors complicate the use of premedication. Notably, the immunopathological mechanism behind immediate DHRs is not always IgE-mediated. Immediate reactions can also arise through non-IgE pathways, including IgG-mediated mechanisms and complement-mediated responses. For these types of reactions, evidence supporting the efficacy of premedication is even more limited, and few studies have explored its preventive potential. Consequently, understanding and managing both IgE- and non-IgE-mediated reactions remains a challenge in clinical practice. In pediatric patients, the lack of sufficient data has made it impossible to establish recommendations either in favor of or against premedication use.

In this letter, we have reviewed articles on drug adverse reaction prevention in pediatric patients, particularly on the effectiveness of premedication. Most studies focus on premedication in relation to rapid drug desensitization (RDD) procedures, which involve gradually increasing the drug dosage to induce temporary tolerance and prevent hypersensitivity reactions, typically for 2 to 8 h for IgE-mediated reactions; while several days or weeks protocols are necessary for delayed reactions.

In a retrospective study by Enseboga et al. [4], children aged 3 to 13 who experienced HSRs were treated with a modified 12-step RDD protocol, which included premedication with methylprednisolone and hydroxyzine. This approach was used primarily for chemotherapy agents, monoclonal antibodies, and antibiotics, achieving a 90% success rate with no reactions in the majority of desensitization protocols. Positive skin test results were identified as the main risk factor for breakthrough reactions (BRs) [4]. Another study involved 14 pediatric patients who underwent a 12-step desensitization protocol for various drugs, including monoclonal antibodies and antibiotics, with premedication using an antihistamine and

methylprednisolone. Mild to severe reactions occurred in only 13% of cases, with all BRs linked to monoclonal antibody use [5]. Dillman et al. [6] explored premedication with corticosteroids and antihistamines in pediatric and adult patients with previous allergic-like reactions to gadolinium-based contrast agents. BRs were primarily observed in patients with a documented history of contrast media reactions, emphasizing the challenges of managing hypersensitivity in such cases [6]. In the case-control studies by van Wassenae et al. and Szymanska et al. [7, 8], steroid premedication in pediatric IBD patients receiving infliximab was evaluated. Both studies found no significant reduction in infusion reaction rates between groups with and without premedication, suggesting that routine steroid premedication may not be necessary in this population. Yilmaz Topal et al. [9] reviewed records of 211 children receiving biological therapies, finding a 6.64% rate of hypersensitivity reactions, primarily associated with rituximab and infliximab. Some patients required desensitization, which allowed them to safely continue therapy. Premedication with corticosteroids, antihistamines, and additional agents like montelukast was used to mitigate reactions, particularly for those with hematologic-oncologic conditions [9]. These studies collectively highlight the complexity of managing drug allergies in pediatric patients and suggest that while premedication and desensitization protocols can be effective, their success varies depending on the drug type and patient history [10]. However, there are other aspects to consider when discussing drug allergy prevention. Based on the findings in the recent review by the Drug Allergy Commission of the Italian Society of Pediatric Allergy and Immunology (SIAIP), preventive strategies for drug hypersensitivity reactions in children can be developed around key risk factors [11]. Identifying high-risk individuals is essential, with attention to factors such as age, drug history, and any existing comorbidities [11]. Genetic testing is increasingly considered, particularly in children with family histories of DHRs, as certain genetic polymorphisms may increase susceptibility [11]. The approach should prioritize minimizing polypharmacy where possible, as the concurrent use of multiple drugs is a well-known risk factor [11]. Where drug administration is required, the oral route is preferred over intravenous or intramuscular routes to reduce risk [11]. Furthermore, heightened monitoring during periods of viral infections is recommended, as viral co-infections can act as cofactors in triggering drug hypersensitivity [11]. In conclusion, the management of drug allergies in pediatric patients remains complex and requires a comprehensive approach. While premedication and desensitization protocols offer valuable options, their effectiveness varies depending on drug type and individual patient factors. Preventive strategies should be

tailored to address high-risk indicators, such as genetic predispositions, polypharmacy, and patient-specific factors like viral infections. Greater interdisciplinary collaboration and more large-scale studies are essential to validate and optimize drug desensitizations in children. Sharing knowledge across pediatric allergy centers will be crucial for advancing this practice, refining these strategies, and improving safety and outcomes in pediatric drug allergy management [12].

Abbreviations

DHRs	Drug hypersensitivity reactions
PM	Premedication
ENDA	European Network of Drug Allergy
EAACI	European Academy for Allergy and Clinical Immunology
BRs	Breakthrough reactions
H1	Histamine H1 receptor
NMBAs	Neuromuscular blocking agents
IgE	Immunoglobulin E
IgG	Immunoglobulin G
RDD	Rapid drug desensitization
HSRs	Hypersensitivity reactions
IBD	Inflammatory bowel disease
SIAP	Italian Society of Pediatric Allergy and Immunology

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Supplementary Material 1

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References

1. Pagani M, Bavbek S, Alvarez-Cuesta E, et al. Hypersensitivity reactions to chemotherapy: an EAACI position paper. *Allergy*. 2022;77(2):388–403.
2. Bavbek S, Pagani M, Alvarez-Cuesta E, et al. Hypersensitivity reactions to biologicals: an EAACI position paper. *Allergy*. 2022;77(1):39–54. <https://doi.org/10.1111/all.14984>.
3. Garvey LH, Ebo DG, Mertes PM, et al. An EAACI position paper on the investigation of perioperative immediate hypersensitivity reactions. *Allergy*. 2019;74(10):1872–84. <https://doi.org/10.1111/all.13820>.
4. Esenboga S, Akarsu A, Ocak M, et al. Safety and efficacy of rapid drug desensitization in children. *Pediatr Allergy Immunol*. 2022;33(3):e13759. <https://doi.org/10.1111/pai.13759>.
5. Gemici Karaaslan B, Aydemir S, Meric Z, et al. Rapid Drug Desensitization and management of breakthrough reactions in Pediatric patients. *Asthma Allergy Immunol*. 2024;22(3):170–80. <https://doi.org/10.21911/aai.2024.579>.
6. Dillman JR, Ellis JH, Cohan RH, Strouse PJ, Jan SC. Allergic-like breakthrough reactions to gadolinium contrast agents after corticosteroid and antihistamine premedication. *AJR Am J Roentgenol*. 2008;190(1):187–90. <https://doi.org/10.2214/AJR.07.2718>.
7. van Wassenae EA, Meester VL, Kindermann A, Koot BGP, Benninga MA, de Meij TJ. Premedication with intravenous steroids does not influence the incidence of infusion reactions following infliximab infusions in pediatric inflammatory bowel disease patients—a case-control study. *Eur J Clin Pharmacol*. 2019;75(10):1445–50. <https://doi.org/10.1007/s00228-019-02715-z>.
8. Szymanska E, Dadalski M, Sieczkowska-Golub J, et al. Premedication does not influence the incidence of Infliximab Infusion Reactions in Pediatric patients with inflammatory bowel Disease—A single Center Case-Control Study. *J Clin Med*. 2021;10(14):3177. <https://doi.org/10.3390/jcm10143177>. Published 2021 Jul 19.
9. Yilmaz Topal O, Kose V, Acar B, Bayrakci US, Ozyuruk D, Hizal G, Karaatmaca B, Toyran M, Yarali HN, Ozbek NY. Dibe Misirlioğlu E. evaluation of hypersensitivity reactions in Pediatric patients using Biological drugs. *Int Arch Allergy Immunol*. 2021;182(9):844–51. <https://doi.org/10.1159/000515500>.
10. de Las Vecillas L, Caimmi D, Isabwe GAC, Madrigal-Burgaleta R, Soyer O, Tanno L, Vultaggio A, Giovannini M, Mori F. Hypersensitivity reactions to biologics in children. *Expert Opin Biol Ther*. 2023;23(1):61–72.
11. Mori F, Saretta F, Riscassi S, Caimmi S, Bottau P, Liotti L, Franceschini F, Bianchi A, Valluzzi RL, Crisafulli G, Caffarelli C. Risk factors for drug hypersensitivity reactions in children. *Ital J Pediatr*. 2024;50(1):127.
12. Diaferio L, Giovannini M, Clark E, Castagnoli R, Caimmi D. Protocols for drug allergy desensitization in children. *Expert Rev Clin Immunol*. 2020;16(1):91–100.

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