ORIGINAL ARTICLE DOI: 10.20515/otd. 1970044

Osmangazi Journal of Med, 2026;48(5):939-949

Osmangazi Journal of Medicine

e-ISSN: 2587-1579

Rituximab-Associated Hypersensitivity Reactions in Pediatric Patients: A Real-World Analysis of Risk Profile and Desensitization Outcomes

Pediatrik Hastalarda Rituksimab İlişkili Aşırı Duyarlılık Reaksiyonları: Risk Profili ve İlaç Desensitizasyonu Sonuçlarının Gerçek Yaşam Analizi

L.Tuba Karakurt[1], Rüveyda Gülmez[2], İrem Kunter[3], Hatice Kübra Dursun[4], Salih Türkmen[3], Şeyma Sönmez Şahin[5], Onur Çandır[6], Fatma Betül Çakır[6], Elif Yüksel Karatoprak[5], Kübra Öztürk[4], Nilüfer Göknar[2], Mustafa Arga[1]

[1] Department of Pediatric Allergy and Immunology, Göztepe Prof Dr Süleyman Yalçın City Hospital, Istanbul, Türkiye
[2] Department of Pediatric Nephrology, Göztepe Prof Dr Süleyman Yalçın City Hospital, Istanbul, Türkiye
[3] Department of Pediatrics, Göztepe Prof Dr Süleyman Yalçın City Hospital, Istanbul, Türkiye
[4] Department of Pediatric Rheumatology, Göztepe Prof Dr Süleyman Yalçın City Hospital, Istanbul, Türkiye
[5] Department of Pediatric Neurology, Göztepe Prof Dr Süleyman Yalçın City Hospital, Istanbul, Türkiye
[6] Department of Pediatric Hematology Oncology, Göztepe Prof Dr Süleyman Yalçın City Hospital, Istanbul, Türkiye

Correspondence / Sorumlu yazar
Leman Tuba KARAKURT

Department of Pediatric Allergy and Immunology, Göztepe Prof Dr Süleyman Yalçın City Hospital, Istanbul, Türkiye

e-mail: tuuubakaya@yahoo.com

Received : 18.06..2026

Accepted : 24.07. 2026

Ethics Committee Approval: The study was approved by Göztepe Prof. Dr. Süleyman Yalçın City Hospital Non-Interventional Clinical Research Ethics Committee (Decision No: 2026/0377, Date:25.05.2026).

Informed Consent: The authors declared that it was not considered necessary to get consent from the patients because the study was a retrospective data analysis.

Authorship Contributions: Study conception and design: TK and RG. Data collection: TK, RG, İK, and HD. Statistical analysis: TK. Clinical management of patients and interpretation of data: ŞŞ, OÇ, FBÇ, EK, KÖ, NG, and MA. The first draft of the manuscript was written by TK, and all authors critically reviewed and commented on previous versions. All authors read and approved the final manuscript.

Copyright Transfer Form: Copyright Transfer Form was signed by author.

Peer-review: Externally peer-reviewed.

Conflict of Interest: No conflict of interest was declared by the authors.

Financial Disclosure: The author declared that this study received no financial support

Abstract: Data regarding the incidence, clinical phenotype, and risk factors of hypersensitivity reactions (HSRs) associated with rituximab in pediatric populations remain limited. This study aimed to evaluate the frequency, clinical phenotype, severity, timing, and management outcomes of rituximab-associated HSRs and to investigate the factors for HSR development in children. This single-center retrospective cohort study included all patients aged 0–18 years who received rituximab between March 2019 and April 2026. Demographic characteristics, atopic comorbidities, concomitant immunosuppressive therapies, pre-infusion laboratory parameters, and HSR details were recorded. Reactions were classified according to Brown's anaphylaxis grading system and phenotyped as Type I, cytokine release syndrome (CRS), or infusion-related reaction (IRR). A total of 30 patients (56.7% female; median age 12.6 years) received 129 rituximab infusions. The per-patient HSR rate was 13.3% (n=4), and the per-infusion rate was 3.1%. Two patients experienced Type I reactions (anaphylaxis), one had CRS, and one had an IRR. All HSRs occurred within the first two treatment courses, with a significantly lower median dose number in the HSR group (2 vs. 4; p=0.044). No demographic, clinical, or laboratory parameter was significantly associated with HSR development. Rapid drug desensitization (RDD) was successfully performed in three patients (11 procedures), enabling uninterrupted treatment continuation. Immediate HSRs to rituximab occur at a notable frequency in pediatric patients, predominantly during early treatment courses. RDD under pediatric allergy guidance allows safe treatment continuation even in children with a history of anaphylaxis. These findings underscore the importance of enhanced clinical vigilance during initial infusions and the integration of a multidisciplinary risk management approach.

Keywords: anaphylaxis, hypersensitivity, pediatric, rapid drug desensitization, rituximab

Özet: Pediatrik popülasyonda rituksimaba bağlı aşırı duyarlılık reaksiyonlarının (ADR) sıklığı, klinik fenotipi ve risk faktörlerine ilişkin veriler sınırlıdır. Bu çalışmada, rituksimab ilişkili ADR'lerin sıklığı, klinik fenotipi, şiddeti, ortaya çıkış zamanı ve yönetim sonuçlarının değerlendirilmesi ile çocuklarda ADR gelişimi ile ilişkili faktörlerin araştırılması amaçlandı. Bu tek merkezli retrospektif kohort çalışmasına, Mart 2019 ile Nisan 2026 arasında rituksimab tedavisi alan 0-18 yaş arası tüm hastalar dahil edildi. Demografik özellikler, atopik komorbiditeler, eş zamanlı immünosüpresif tedaviler, infüzyon öncesi laboratuvar parametreleri ve ADR ayrıntıları kaydedildi. Reaksiyonlar Brown anafilaksi derecelendirme sistemine göre sınıflandırıldı ve Tip I, sitokin salınım sendromu (SSS) ya da infüzyonla ilişkili reaksiyon (İİR) olarak fenotiplendirildi. Toplam 30 hastaya (%56,7 kız; medyan yaş 12,6 yıl) 129 rituksimab infüzyonu uygulandı. Hasta başına ADR oranı %13,3 (n=4), infüzyon başına oran ise %3,1 idi. İki hastada Tip I reaksiyon (anafilaksi), bir hastada SSS ve bir hastada İİR gelişti. Tüm ADR'ler ilk iki tedavi kürü içinde ortaya çıktı ve ADR gelişen grupta medyan doz sayısı anlamlı olarak daha düşüktü (2vs4; p=0,044). Hiçbir demografik, klinik veya laboratuvar parametresi ADR gelişimi ile anlamlı ilişki göstermedi. Üç hastada (11 işlem) hızlı ilaç desensitizasyonu (HİD) başarıyla uygulanarak tedavinin kesintisiz sürdürülmesi sağlandı.Rituksimaba bağlı erken tip ADR'ler pediatrik hastalarda dikkate değer bir sıklıkta ve ağırlıklı olarak erken tedavi kürleri sırasında görülmektedir. Pediatrik alerji rehberliğinde uygulanan HİD, anafilaksi öyküsü olan çocuklarda dahi tedavinin güvenle sürdürülmesine olanak tanımaktadır. Bu bulgular, ilk infüzyonlar sırasında klinik dikkatin artırılmasının ve multidisipliner bir risk yönetimi yaklaşımının benimsenmesinin önemini vurgulamaktadır.

Anahtar Kelimeler: anaphylaxis, hypersensitivity, pediatric, rapid drug desensitization, rituximab

How to cite/ Atıf için: Karakurt LT , Gülmez R , Kunter İ , Dursun HK , Türkmen S , Sönmez ŞahinŞ , Çandır O , Çakır FB , Yüksel Karatoprak E , Öztürk K , Göknar N , Arga M , Rituximab-Associated Hypersensitivity Reactions in Pediatric Patients: A Real-World Analysis of Risk Profile and Desensitization Outcomes, Osmangazi Journal of Medicine, 2026;48(5):939-949

1. Introduction

Rituximab is a chimeric IgG1 monoclonal antibody targeting the CD20 transmembrane antigen expressed on the surface of B lymphocytes (1). Following binding to the CD20 antigen, it induces selective depletion of CD20-positive B cells through complement-dependent cytotoxicity, antibody-dependent cellular cytotoxicity, and direct apoptosis induction mechanisms (2).

In recent years, rituximab use in the pediatric population has progressively increased in parallel with adult indications (3). It has become an important therapeutic option, particularly in patients with inadequate response to conventional immunosuppressive therapies, owing to its efficacy in reducing steroid burden, maintaining remission, and controlling disease activity (3). However, it has been reported that the safety profile in pediatric patients may differ from that of adults due to the developing immune system, concomitant immunosuppressive therapy use, and disease-specific pathophysiological differences (4, 5). Therefore, real-world data specific to the pediatric age group are needed.

Rituximab-associated hypersensitivity reactions (HSRs) constitute a heterogeneous spectrum in terms of clinical phenotype and underlying immunological mechanisms (6). Clinical manifestations range from mild-to-moderate symptoms such as flushing, urticaria, angioedema, bronchospasm, laryngeal edema, hypotension, fever, and rigors to, rarely, anaphylaxis and cardiovascular collapse (7). Among anti-CD20 monoclonal antibodies, rituximab is considered one of the agents with the highest hypersensitivity risk, with acute infusion reaction rates reaching up to 77%, particularly during the first infusion (8). In adult studies, the frequency of IgE-mediated reactions has been reported as 5–10%, and the rate of Grade ≥3 severe reactions as 2–19% (9). Pediatric studies have demonstrated that the HSR frequency is approximately 15%, anaphylaxis frequency is 3–4%, the majority of reactions are mild-to-moderate in severity, and they can be successfully managed with standard premedication and infusion rate adjustment (3,10). Late-onset severe reactions such as Stevens–Johnson syndrome, toxic epidermal necrolysis, and serum sickness are extremely rare (6).

Age, sex, underlying disease, cumulative rituximab dose, concomitant immunosuppressive therapy use, atopic comorbidities, and pre-infusion laboratory parameters have been evaluated as potential risk factors for HSR development. However, conflicting results exist among current studies, and it has been reported that reliable risk prediction with standard clinical variables cannot be achieved in pediatric populations (11).

Our aim was to evaluate the frequency, clinical phenotype, severity, timing, and management outcomes of HSRs developing in patients receiving rituximab therapy and to investigate factors that may influence HSR development.

2. Material and Methods

2.1. Study Design and Patient Selection

This retrospective cohort study was conducted by reviewing the electronic medical records of all patients aged 0–18 years who received rituximab in the pediatric nephrology, rheumatology, neurology, and hematology-oncology units at a single center between March 2019 and April 2026. Patients who were initiated on rituximab therapy and had complete follow-up data were included. As this was a retrospective study including all eligible patients treated during the study period (a consecutive convenience sample), sample size or power calculation was not performed. The study protocol was approved by the institutional local Ethics Committee (No:2026/0377) and was conducted in accordance with the principles of the Declaration of Helsinki.

2.2 Data Collection

Data obtained from patient records and the hospital information management system were compiled using a standardized data collection form, encompassing demographic characteristics (age, gender, anthropometric measurements), primary diagnosis, atopic comorbidities (asthma, allergic rhinitis, atopic dermatitis, food allergy), family history of atopy, previous drug allergy history,

concomitant immunosuppressive therapies (cyclosporine, tacrolimus, mycophenolate mofetil, corticosteroids, azathioprine, hydroxychloroquine, methotrexate, cyclophosphamide), and exposure to intravenous immunoglobulin (IVIG) and other biological agents. Treatment-related variables included rituximab dose (a standard dose of 375 mg/m² was administered, although in two cases the dose was capped at a maximum of 500 mg), infusion number, cumulative course number, infusion rate at the time of reaction, and premedication protocol. All patients received standard premedication (antihistaminic, methylprednisolone, and paracetamol) prior to each infusion.

2.3. Definition and Classification of Reactions

All symptomatic events occurring within the first six hours following the initiation of infusion were classified as immediate-type hypersensitivity reactions. Severity grading of reactions was performed according to Brown's anaphylaxis classification: Grade 1 (mild reaction confined to the skin and subcutaneous tissue), Grade 2 (moderate reaction involving at least two organ systems without significant hypotension or hypoxemia), and Grade 3 (severe reaction characterized by systolic blood pressure <90 mmHg or syncope and/or oxygen saturation <92%) (12). Reaction phenotypes were categorized as Type I (IgE/non-IgE-mediated), cytokine release syndrome (CRS), infusion-related reaction (IRR), mixed type, and delayed Type IV (13). Classification was based on the timing of symptom onset relative to the infusion, the predominant clinical manifestations (including fever, chills/rigors, flushing, urticaria, bronchospasm, hypotension, oxygen desaturation, and gastrointestinal symptoms), and the response to interruption of infusion and supportive treatment. CRS was considered when systemic inflammatory manifestations, particularly fever and chills/rigors, predominated, whereas IRR was diagnosed in patients with infusion-associated symptoms that did not fulfill criteria for Type I hypersensitivity or CRS. The diagnosis of anaphylaxis was established according to international consensus criteria (14).

2.4. Laboratory Assessment

Pre-infusion laboratory data recorded included complete blood count (white blood cell count, hemoglobin, platelet count, absolute neutrophil, lymphocyte, and eosinophil counts, eosinophil percentage), C-reactive protein, erythrocyte sedimentation rate, serum total IgE, complement C3 and C4, albumin, uric acid, lactate dehydrogenase, blood urea nitrogen, creatinine (with estimated glomerular filtration rate calculated using the Schwartz formula), electrolytes, and urine protein-to-creatinine ratio. In patients who developed reactions, baseline and reaction-time serum tryptase levels were assessed when feasible.

2.5. Reaction Management and Rapid Drug Desensitization

Upon reaction development, the infusion was immediately discontinued; epinephrine, systemic corticosteroids, antihistamines, and fluid resuscitation were administered according to the reaction type and severity. In patients with severe initial reactions for whom continuation of treatment was considered clinically indispensable and no equally effective alternative options were available, rapid drug desensitization (RDD) protocols were implemented. RDD is a temporary tolerance-inducing procedure in which the culprit drug is administered in a stepwise and strictly time-controlled manner, beginning with ultra-low doses, typically ranging between 1/10,000 and 1/100,000 of the target therapeutic dose, followed by gradual dose escalation at predefined intervals until the full cumulative dose is reached. This controlled incremental exposure results in a transient state of immune tolerance, allowing safe administration of the required drug despite a documented or highly suspected hypersensitivity reaction (15). All RDD procedures were performed under the supervision of a pediatric allergist, in a monitored clinical setting, with one-to-one nursing care.

2.6. Statistical Analysis

Statistical analyses were performed using IBM SPSS Statistics v25 (IBM Corp., Armonk, NY). The normality of continuous variables was assessed using the Shapiro–Wilk test. Non-normally distributed variables were presented as median (interquartile range, IQR);

categorical variables were expressed as frequency (%). The Mann–Whitney U test was used for comparison of continuous variables between two independent groups, and the Pearson chi-square or Fisher's exact test was used for categorical variable comparisons. The odds ratio (OR) was calculated as the effect size measure for Fisher's exact test. A p-value of <0.05 was considered statistically significant for all tests.

3. Results

30 patients aged 0–18 years who received rituximab were identified through electronic medical records and included in the analysis, as complete clinical data were available for all participants. Overall, a total of 129 rituximab infusions were administered to these patients. Of the patients, 56.7% (n=17) were female, and the median age was 12.6 (IQR 8.0–14.4) years. Twenty-eight patients received the standard rituximab dose of 375 mg/m², while two received a dose capped at a maximum of 500 mg. The most common indications were nephrotic syndrome spectrum (steroid-dependent/resistant nephrotic syndrome, focal segmental glomerulosclerosis) at 40.0% (n=12), ANCA-associated vasculitis at 23.3% (n=7), connective tissue diseases at 13.3% (n=4), and neurological diseases (MOGAD, autoimmune encephalitis, optic neuritis) at 13.3% (n=4) (Table 1). Atopic comorbidities were present in 23.3% (n=7) of patients. Ten patients (33.3%) had been exposed to IVIG or another biological agent prior to rituximab. Standard premedication was administered to all patients. Detailed demographic and clinical characteristics of the study population are presented in Table 1.

3.3. Hypersensitivity Reactions and Clinical Features

The per-patient HSR rate was 13.3% (n=4), while the per-infusion HSR rate was 3.1%; these comprised Type I (IgE/non-IgE-mediated) reactions (anaphylaxis) (n=2), cytokine release syndrome (n=1), and infusion-related reaction (n=1). Paired baseline and reaction-time serum tryptase levels were available in both anaphylaxis patients, rising from 3.26 to 7.13 µg/L (Case 1) and from 2.31 to 5.04 µg/L (Case 4); both increases met the consensus criterion for mast cell activation (≥20% plus 2 µg/L above baseline). The median onset time of reactions was 30 (range 20–110) minutes after infusion initiation. Mixed-type reactions, delayed-type reactions, and serum sickness were not observed in any patient. No mortality occurred. Detailed clinical characteristics of patients who developed reactions are presented in Table 2.

3.4. Analysis of Factors Associated with Hypersensitivity Reactions

Patients who developed reactions and those who did not were compared in terms of demographic characteristics, concomitant therapies, and pre-infusion laboratory parameters (Table 3). No significant differences were found between the HSR and non-HSR groups regarding age, sex, atopic comorbidities, family history of atopy, drug allergy history, or prior biological agent exposure (Table 3).

When pre-infusion laboratory values were compared, no statistically significant differences were demonstrated between the two groups for CRP, total IgE, absolute eosinophil count, C3–C4, albumin, lactate dehydrogenase, white blood cell count, and platelet levels (Table 3).

When reaction timing was examined, all HSRs (4/4; 100%) occurred during the first two treatment courses. The median dose number at the time of reaction was 2 (IQR 1–2) in the HSR group, compared with 4 (IQR 2–5) in the non-HSR group (*p=0.044*). The highest HSR rate was observed in nephrotic syndrome patients (3/12; 25.0%), followed by ANCA-associated vasculitis (1/7; 14.3%); no HSRs were observed in the SLE, neurological, hematological, or rheumatological disease groups during the study period (Table 3).

In three of the four patients who developed reactions, RDD was performed because treatment continuation was clinically imperative. A total of eleven desensitization procedures were performed in the three RDD-treated patients. A representative rituximab desensitization protocol applied in our cohort is presented in Table 4. All RDD processes were completed successfully; rituximab therapy was not permanently discontinued in any of the patients who developed reactions.

Table 1. Demographic and clinical characteristics of patients received rituximab (n=30)

	n (%)
Age (year) [median (IQR)]	12.6 (8.0–14.4)
Gender (F/M)	17 (56.7) / 13 (43.3)
Primary diagnosis	
Nephrotic syndrome (SSNS/SRNS/FSGS/FRNS)	12 (40.0)
ANCA-related vasculitis	7 (23.3)
SLE/connective tissue diseases	4 (13.3)
Neurological diseases (MOGAD/encephalitis/ON)	4 (13.3)
Hematological diseases (DLBCL, thalassemia)	2 (6.7)
Juvenile idiopathic arthritis	1 (3.3)
Atopic comorbidity	7 (23.3)
Family history of atopy	2 (6.7)
Previous drug allergy history	3 (10.0)
Previous IVIG/biologic agent exposure	10 (33.3)

ANCA: *antineutrophil cytoplasmic antibody;* ***DLBCL:*** *diffuse large B-cell lymphoma;* ***FRNS:*** *frequently relapsing nephrotic syndrome;* ***FSGS:*** *focal segmental glomerulosclerosis;* ***IQR:****interquartile range;* ***IVIG:*** *intravenous immunoglobulin;* ***MOGAD:*** *myelin oligodendrocyte glycoprotein antibody-associated disease;* ***ON:*** *optic neuritis;* ***SLE:*** *systemic lupus erythematosus;* ***SRNS:*** *steroid-resistant nephrotic syndrome;* ***SSNS:*** *steroid-sensitive nephrotic syndrome*

Table 2. Clinical characteristics and management outcomes of patients who developed HSRs

Case	Gender	Age (year)	Diagnosis	Dose	HSR type	Grade	Time to onset (min)	Symptoms	Management	Outcome
C1	M	2.4	SRNS	2	Type I	3	20	Bronchospasm, urticaria, angioedema	RDD was performed in subsequent four treatment courses	Urticaria occurred during the final step of the first RDD. The procedure successfully managed by dose escalation adjustment
C2	F	6.2	ANCA-related vasculitis	1	IRR	1	30	Dyspnea	Infusion rate was reduced	Subsequent infusions were completed without complications
C3	M	16.3	FSGS	1	CRS	2	110	Hives, itching in the throat	RDD was performed in subsequent four treatment courses	Subsequent infusions were completed without complications
C4	F	12.6	FRNS	2	Type I	3	30	Bronchospasm, urticaria	RDD was performed in subsequent three treatment courses	Anaphylaxis occurred during the final step of the first RDD. The procedure successfully managed with a modified protocol

ANCA:*antineutrophil cytoplasmic antibody;* ***CRS:*** *cytokine release syndrome;* ***F:*** *female;* ***FRNS:*** *frequently relapsing nephrotic syndrome;* ***FSGS:*** *focal segmental glomerulosclerosis;* ***HSR:*** *hypersensitivity reaction****;*** ***IRR:*** *infusion-related reaction;* ***M:*** *male;* ***RDD:*** *rapid drug desensitization;* ***SRNS:*** *steroid-resistant nephrotic syndrome*

Table 3. Comparison of patients with and without HSR

	HSR (+) (n=4)	**HSR (−) (n=26)**	**p**
Characteristics			
Age (year) [median (IQR)]	9.4 (5.2–13.5)	13.1 (8.9–14.4)	0.234
Gender [n (%)]			
Female	2 (11.7)	15 (88.3)	0.982
Male	2 (15.3)	11 (84.7)	
Course number at the HSR [median (IQR)]	2 (1–2)	4 (2–5)	0.044
Primary diagnosis [n (%)]			
Nephrotic syndrome (SSNS/SRNS/FSGS/FRNS)	3 (25.0)	9 (75.0)	
ANCA-related vasculitis	1 (14.3)	6 (85.7)	
SLE/connective tissue diseases	0 (0)	4 (100)	0.268
Neurological diseases (MOGAD/encephalitis/ON)	0 (0)	4 (100)	
Hematological diseases (DLBCL, thalassemia)	0 (0)	2 (100)	
Juvenile idiopathic arthritis	0 (0)	1 (100)	
Atopic comorbidity [n (%)]	1 (25.0)	6 (23.1)	0.946
Previous IVIG/biologic agent exposure [n (%)]	0 (0)	10 (38.5)	0.272
CRP (mg/L) [median (IQR)]	0.61 (0.60–0.78)	1.33 (0.60–3.79)	0.253
Total IgE (IU/mL) [median (IQR)]	63 (39–230)	53 (15–107)	0.738
Absolute eosinophil count (/μL) [median (IQR)]	225 (120–302)	90 (25–167)	0.343
C3 (g/L) [median (IQR)]	1.56 (1.28–1.96)	1.28 (1.05–1.57)	0.351
C4 (g/L) [median (IQR)]	0.36 (0.32–0.38)	0.23 (0.19–0.28)	0.096
Albumin (g/dL) [median (IQR)]	3.14 (2.43–4.02)	4.06 (3.66–4.36)	0.258
LDH (U/L) [median (IQR)]	235 (196–273)	234 (211–271)	0.879

***C:** complement; **CRP:** C-reactive protein; **DLBCL:** diffuse large B-cell lymphoma; **F:** female; **FRNS:** frequently relapsing nephrotic syndrome; **FSGS:** focal segmental glomerulosclerosis; **g,** gram; **HSR:** hypersensitivity reaction; **IgE:** immunglobulin E; **IQR:** interquartile range; **IU:** International unit; **IVIG:** intravenous immunoglobulin; **L:** liter; **LDH:** lactate dehydrogenase; **mL:** milliliter; **M:** male. **MOGAD:** myelin oligodendrocyte glycoprotein antibody-associated disease; **ON:** optic neuritis; **SLE:** systemic lupus erythematosus; **SRNS:** steroid-resistant nephrotic syndrome; **SSNS:** steroid-sensitive nephrotic syndrome*

Table 4. Rapid drug desensitization protocol for rituximab hypersensitivity

Premedication (before the procedure);

13 h before: cetirizine 10 mg orally.

7 h before: methylprednisolone 50 mg orally.

1 h before: cetirizine 10 mg orally + paracetamol 500 mg orally + methylprednisolone 50 mg orally.

Solution preparation

(target dose 500 mg rituximab = 50 mL)

Solution 1: 10 mL withdrawn from Solution 2 + 90 mL saline = 0.02 mg/mL (total 100 mL)

Solution 2: 1 mL (10 mg) of undiluted drug + 49 mL saline = 0.2 mg/mL (total 50 mL)

Solution 3: 49 mL (490 mg) of undiluted drug + 201 mL saline = 1.96 mg/mL (total 250 mL)

Step	Solution	Rate (mL/h)	Time (min)	Volume infused (mL)	Dose administered (mg)	Cumulative dose (mg)
1	1	2	15	0.5	0.01	0.01
2	1	5	15	1.25	0.025	0.035
3	1	10	15	2.5	0.05	0.085
4	1	20	15	5	0.1	0.185
5	2	5	15	1.25	0.25	0.435
6	2	10	15	2.5	0.5	0.935
7	2	20	15	5	1	1.935
8	2	40	15	10	2	3.935
9	2	80	15	20	4	7.935
10	3	10	15	2.5	4.9	12.835
11	3	20	15	5	9.8	22.635
12	3	40	15	10	19.6	42.235
13	3	80	174	232	454.72	**497**

A three-bag, 13-step protocol was used, beginning with the most dilute solution (Solution 1) and progressing to the least dilute (Solution 3). Each step was administered over 15 minutes except for the final step. The total cumulative dose delivered was 497 mg.

h: *hour;* ***min:*** *minute;* ***mg:*** *milligram;* ***mL:*** *milliliter.*

4. Discussion

Data regarding the incidence, clinical phenotype, and risk markers of rituximab-associated HSRs in the pediatric age group are considerably limited compared with the adult literature. Our study holds clinical significance as it systematically presents the HSR frequency, phenotypic distribution, timing, and risk profile under real-world conditions in a multidisciplinary pediatric cohort, while also providing contemporary data encompassing RDD management outcomes.

The frequency of severe HSRs to biological agents, including rituximab, in childhood rheumatic diseases has been shown to be 3–5% (5). Although rituximab-specific data are limited, the frequency of immediate HSRs to biological agents in pediatric inflammatory bowel disease has been reported as 9.8% (4). Among anti-CD20 monoclonal antibodies, rituximab has been reported to cause acute reactions in up to 77% of first infusions, and the first infusion has therefore been defined as a high-risk window (8). The per-patient HSR rate of 13.3% in our cohort is broadly in line with previous pediatric reports. The anaphylaxis frequency of 6.7%, however, is higher than the 2–4% generally described in pediatric studies. Given that this estimate is based on only two events in 30 patients, it carries a wide confidence interval and should be interpreted with caution; it may also reflect the relatively high proportion of high-risk indications, particularly

nephrotic syndrome, in our cohort rather than a true difference in reaction risk.

In adults, it has been reported that 63% of HSRs occur during the first course, with a marked decrease in frequency in subsequent courses (8,16). Similarly, the majority of rituximab-associated reactions in adults have been observed to develop during the initial infusions, with tolerance developing in subsequent courses (6). A similar pattern of reaction clustering during early courses has been reported in children (4, 5). One of the most striking findings in our study was that all HSRs developed within the first two treatment courses and that the median dose number at the time of reaction was significantly lower in the HSR group (median dose 2 vs. 4, *p=0.044*). These results, consistent with the adult literature, demonstrate that rituximab-associated HSRs in the pediatric population also concentrate within the first two-course window and that this period requires close clinical surveillance.

In the cohort by Isabwe et al. examining HSRs following rituximab use in adults, the reactions were reported as 63% Type I, 13% cytokine release, and 21% mixed-type HSRs (13). In a single-centered study involving 24 patients, the Type I rate was reported as 46% and mixed-type as 42% (17). In our study, two of the four reactions were classified as Type I, one as CRS, and one as IRR; mixed-type and delayed-type reactions were not observed. The absence of mixed-type and delayed-type reactions in our population may be attributable to the relatively short cumulative exposure duration compared with adults and the fact that sufficient repeated doses for sensitization had not yet been reached.

In our study, no significant association was identified between HSR development risk and age, sex, atopic comorbidities, family history, previous drug allergy, or prior biological/IVIG exposure. This finding is consistent with that of Bavbek et al., who demonstrated no significant association between breakthrough reactions and age, gender, skin test positivity, course number, or atopy in an adult biological agent cohort (18). In another study, no significant association was found between skin test positivity and breakthrough reaction risk in a rituximab series of 25 patients (10). In a study the presence of concomitant allergic disease identified as an independent risk factor for immediate HSR development to biological agents in children with inflammatory bowel disease (4). Furthermore, Soyer et al. demonstrated an association between reaction risk and renal involvement, multiple biological exposure, and frequent hospitalization history in pediatric rheumatic diseases (5). The absence of a significant risk factor in our study may be related to the limited sample size, low event frequency, and more homogeneous clinical characteristics of the study population compared with those in the literature.

In adults with hematological malignancies, elevated pre-infusion CRP has been reported to be associated with IRR (8). In our data, CRP, IgE, eosinophils, C3–C4, and other inflammatory markers were not found to be associated with HSRs. These findings suggest that standard clinical and laboratory variables may not be sufficient alone to predict HSR risk in a pediatric nephrological/rheumatological population. This result supports the view that the role of atopy in reaction risk cannot be consistently demonstrated in small samples and that the disease-specific context shapes the risk profile.

In nephrotic syndrome, hypoalbuminemia, massive proteinuria, intravascular volume disturbances, and concomitant multiple immunosuppressive therapy may lower the reaction threshold through indirect effects on mast cell stability and cytokine homeostasis (4). In adult follicular lymphoma patients, a significantly higher reaction rate was identified compared with diffuse large B-cell lymphoma patients, which was attributed to disease-specific tumor burden and CD20 expression patterns (16). In children, Grade ≥2 reaction rates reaching up to 45% have been reported in acute lymphoblastic leukemia patients (3). Adult inflammatory bowel disease data have shown that concomitant immunomodulator use reduces HSR risk (4, 19). In our cohort, three of the four HSRs occurred in patients with nephrotic syndrome, in whom the highest reaction rate was observed (3/12; 25.0%), which may suggest a disease-specific predisposition; however, given the small number of events and the lack of statistical significance, this observation should be regarded as hypothesis-generating and warrants investigation in larger cohorts.

Rapid drug desensitization (RDD) constitutes an effective and safe therapeutic bridge in patients who develop immediate-type HSRs and in whom treatment continuation is clinically imperative. Görgülü et al. successfully completed 98.5% of 141 RDD procedures in 24 adult patients, reporting a breakthrough reaction rate of 17% (17). In another study, all 53 desensitization procedures were completed, with only three cases experiencing Grade 1 breakthrough reactions (20). Furthermore, in the large series by Madrigal-Burgaleta et al. using

antineoplastic and biological agents, structured RDD protocols achieved success rates exceeding 95% (21). In our study, treatment was maintained without interruption in all three patients who underwent RDD; mild breakthrough reactions were observed at the final step in two cases, and rituximab was successfully administered by increasing the number of steps and adding supplemental premedication. Our results are consistent with these high success rates and support the safe applicability of RDD in the pediatric population, even in children with a history of severe anaphylaxis. This finding strongly demonstrates that children who develop severe reactions to rituximab in clinical practice can be maintained on therapy with RDD under pediatric allergy specialist guidance rather than being directly redirected to alternative agents, and is consistent with international guidelines (7, 22).

The strengths of our study include the limited availability of real-world data on rituximab hypersensitivity reactions in the pediatric population, the systematic classification of reactions according to current international phenotyping criteria, evaluation of comprehensive pre-infusion laboratory parameters alongside demographic characteristics, the assessment of paired baseline and reaction-time serum tryptase levels in patients with anaphylaxis, and the provision of a homogeneous comparison framework through the use of a standardized premedication protocol in all patients. Furthermore, the management of all patients by a pediatric allergy specialist and the successful implementation of RDD in all indicated cases, enabling uninterrupted continuation of rituximab therapy, constitute a reference model for treatment sustainability in clinical practice.

Our study has several limitations. First, the retrospective single-center design carries risks of selection bias and data incompleteness. Second, the limited sample size and low event number reduced statistical power, precluded multivariable analysis, and may have left some relevant associations undetected. Third, multiple variables were compared without correction for multiple testing; the single significant finding (course number) should therefore be regarded as hypothesis-generating, particularly as the two groups were not indexed at a comparable time point. Fourth, although paired serum tryptase measurements were available in patients with anaphylaxis, systematic biomarker assessment for all reaction phenotypes was not feasible because IL-6, rituximab skin testing, and anti-rituximab antibodies were not routinely evaluated. Therefore, phenotyping relied primarily on clinical criteria, and some overlap between CRS and IRR cannot be completely excluded. Fifth, the reaction frequency reported here reflects the residual risk under premedication rather than the intrinsic reactogenicity of rituximab, and the independent contribution of premedication to risk reduction could not be assessed in this design. Finally, the non-standardized follow-up for delayed-type reactions and serum sickness may have led to underestimation of their true prevalence. Multicenter, prospective, biomarker-supported pediatric studies are needed to overcome these limitations.

5. Conclusion

Immediate HSRs to rituximab occur at a notable frequency in the pediatric population; however, severe reactions are rare, and all reactions tend to emerge during early courses (first two doses). RDD performed under pediatric allergy guidance enables safe and effective treatment continuation even in children with a history of anaphylaxis. These findings underscore the importance of a comprehensive risk management model integrating standard premedication, stepwise infusion rate escalation, multidisciplinary monitoring, and RDD when indicated in pediatric patients planned for rituximab therapy, and demonstrate that larger, multicenter, and prospective studies will facilitate the development of biomarker-based risk stratification tools.

REFERENCES

1. Pierpont TM, Limper CB, Richards KL. Past, present, and future of rituximab—the world's first oncology monoclonal antibody therapy. Front Oncol. 2018;8:163.

2. Salles G, Barrett M, Foà R, Maurer J, O'Brien S, Valente N, et al. Rituximab in B-cell hematologic malignancies: a review of 20 years of clinical experience. Adv Ther. 2017;34(10):2232-73.

3. Mori F, Saretta F, Bianchi A, Crisafulli G, Caimmi S, Liotti L, et al. Hypersensitivity reactions to monoclonal antibodies in children. Medicina (Kaunas). 2020;56(5):232.

4. Polat Terece S, Ertoy Karagol HI, Teker Duztas D, Koken G, Ozturk H, Yapar D, et al. Immediate hypersensitivity reactions to biologic drugs in children with inflammatory bowel diseases. Int Arch Allergy Immunol. 2025;186(2):142-9.

5. Soyer O, Demir S, Bilginer Y, Batu ED, Sonmez HE, Arıcı ZS, et al. Severe hypersensitivity reactions to biological drugs in children with

rheumatic diseases. Pediatr Allergy Immunol. 2019;30(8):833-40.

6. Fouda GE, Bavbek S. Rituximab hypersensitivity: from clinical presentation to management. Front Pharmacol. 2020;11:572863.

7. Bavbek S, Pagani M, Alvarez-Cuesta E, Castells M, Dursun AB, Hamadi S, et al. Hypersensitivity reactions to biologicals: an EAACI position paper. Allergy. 2022;77(1):39-54.

8. Levin AS, Otani IM, Lax T, Hochberg E, Banerji A. Reactions to rituximab in an outpatient infusion center: a 5-year review. J Allergy Clin Immunol Pract. 2017;5(1):107-13.e1.

9. Brennan PJ, Rodriguez Bouza T, Hsu FI, Sloane DE, Castells MC. Hypersensitivity reactions to mAbs: 105 desensitizations in 23 patients, from evaluation to treatment. J Allergy Clin Immunol. 2009;124(6):1259-66.

10. Wong JT, Long A. Rituximab hypersensitivity: evaluation, desensitization, and potential mechanisms. J Allergy Clin Immunol Pract. 2017;5(6):1564-71.

11. Karmacharya P, Poudel DR, Pathak R, Donato AA, Ghimire S, Giri S, et al. Rituximab-induced serum sickness: a systematic review. Semin Arthritis Rheum. 2015;45(3):334-40.

12. Brown SG. Clinical features and severity grading of anaphylaxis. J Allergy Clin Immunol. 2004;114(2):371-6.

13. Isabwe GAC, Garcia Neuer M, de Las Vecillas Sanchez L, Lynch DM, Marquis K, Castells M. Hypersensitivity reactions to therapeutic monoclonal antibodies: phenotypes and endotypes. J Allergy Clin Immunol. 2018;142(1):159-70.e2.

14. Cardona V, Ansotegui IJ, Ebisawa M, El-Gamal Y, Fernandez Rivas M, Fineman S, et al. World Allergy Organization anaphylaxis guidance 2020. World Allergy Organ J. 2020;13(10):100472.

15. Castells M. Rapid desensitization for hypersensitivity reactions to medications. Immunol Allergy Clin North Am. 2009;29(3):585-606.

16. Hou CH, Chang H, Ong YC, Kuo MC, Kao HW, Lee HL. Risk factors and clinical consequences of rituximab infusion-related reactions. Medicine (Baltimore). 2025;104(26):e42972.

17. Görgülü B, Seval GC, Kendirlinan R, Toprak SK, Özcan M, Bavbek S. Rapid drug desensitization with rituximab in 24 cases: a single-center experience. J Investig Allergol Clin Immunol. 2019;29(6):468-70.

18. Unutmaz Erkaya DG, Bayrak Durmaz MS, Görgülü Akın B, Bavbek S. Retrospective analysis of rapid drug desensitization with biologic agents: a single center experience. Clin Transl Allergy. 2024;14(10):e12397.

19. Galvão VR, Castells MC. Hypersensitivity to biological agents—updated diagnosis, management, and treatment. J Allergy Clin Immunol Pract. 2015;3(2):175-85.

20. Lebel E, Ben-Yehuda D, Bohbot E, Dranitzki Z, Shalit M, Tal Y. Hypersensitivity reactions to rituximab: 53 successful desensitizations in 7 patients with severe, near-fatal reactions. J Allergy Clin Immunol Pract. 2016;4(5):1000-2.

21. Madrigal-Burgaleta R, Bernal-Rubio L, Berges-Gimeno MP, Carpio-Escalona LV, Gehlhaar P, Alvarez-Cuesta E. A large single-hospital experience using drug provocation testing and rapid drug desensitization in hypersensitivity to antineoplastic and biological agents. J Allergy Clin Immunol Pract. 2019;7(2):618-32.

22. Picard M, Galvão VR. Current knowledge and management of hypersensitivity reactions to monoclonal antibodies. J Allergy Clin Immunol Pract. 2017;5(3):600-9.

©Copyright 2026 by Osmangazi Tıp Dergisi - Available online at tip.ogu.edu.tr©Telif Hakkı 2026ESOGÜ Tıp Fakültesi - Makale metnine dergipark.org.tr/otdweb sayfasından ulaşılabilir.