

Reactions to Rituximab in an Outpatient Infusion Center: A 5-Year Review



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What is already known about this topic? Reactions to rituximab occur frequently especially after first exposure and no guidelines exist to manage patients subsequently.

What does this article add to our knowledge? We review current management strategies and discuss an algorithm for managing patients on the basis of the grade of their rituximab infusion reactions.

How does this study impact current management guidelines? This study helps guide management after a rituximab infusion reaction especially for nonallergists and prevents unnecessary avoidance of rituximab.

BACKGROUND: Reactions to rituximab occur frequently, with up to 77% of patients developing a reaction during initial exposure. The safety of rechallenging patients after a reaction is not clear and standard guidelines are lacking.

OBJECTIVE: To better understand clinical decision making surrounding rituximab reactions and subsequent challenge.

METHODS: We performed a 5-year retrospective review of all rituximab reactions at a large academic outpatient infusion center. Patients' demographic characteristics, clinical symptoms, and management of reactions were reviewed. Reaction severity was classified using standard criteria.

RESULTS: Between June 2006 and January 2011, 67 patients (mean age, 58 ± 13 years, 54% men) with at least 1 rituximab reaction were identified. Most reactions occurred during the first exposure to rituximab (63%). Most reactions (n = 59 [88%]) were grade 1 or 2. Fifty-one patients (n = 51 [88%]) were rechallenged with rituximab on the same day as the initial reaction. Most patients with a grade 1 reaction tolerated challenge. Conversely, all 4 patients with a grade 3 reaction had a reaction during challenge. The outcome of same-day challenge after an initial grade 2 reaction was varied; most patients (26 of 31 [84%]) tolerated same-day challenge, but 5 patients had a reaction (all grade 1-2 severity).

CONCLUSIONS: Consistent with previous data, our observations suggest that patients who experience grade 1 reactions to rituximab can be safely rechallenged the same day. A grade 3 or 4 reaction should prompt referral to an allergy specialist for risk assessment before additional rituximab administration. Further research is needed to understand the optimal management of patients with grade 2 reactions. © 2016 American Academy of Allergy, Asthma & Immunology (J Allergy Clin Immunol Pract 2017;5:107-13)

Key words: Rituximab; Monoclonal antibody; Infusion reaction; Desensitization

mAbs are a valuable therapeutic option for patients with many distinct malignancies and rheumatologic conditions. Rituximab is a chimeric murine/human mAb. The antibody is an IgG₁ kappa immunoglobulin containing murine light- and heavy-chain variable regions and human constant regions. It was initially approved in 1997 for the therapy of relapsed indolent non-Hodgkin lymphoma. It is currently approved by the Food and Drug Administration for the hematologic/oncologic treatment of non-Hodgkin lymphoma and chronic lymphocytic leukemia.¹ Rituximab binds the surface antigen CD20 on both normal and malignant B cells and causes cell death via direct cytotoxicity, complement-dependent cytotoxicity, and antibody-dependent cellular cytotoxicity. It has become one of the most widely used biological agents in oncology.²

Rituximab's protean therapeutic benefits must be balanced with a substantial risk of infusional reactions. This risk is especially high during the first infusion, as up to 77% of patients develop a reaction during this initial exposure.¹ Reactions range from mild symptoms (itching, rash, flu-like symptoms, or nausea) to severe anaphylaxis within several hours.³ Interestingly, the risk of development of these infusion reactions decreases with subsequent rituximab infusions; however, the etiology for this has not been clearly elucidated.^{4,5} There are several mechanisms thought to contribute to rituximab infusion reactions. Cytokine release syndrome and mast cell-mediated reactions are

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Grade 1A	Grade 1B	Grade 2	Grade 3	Grade 4	Grade 5
Cutaneous rash Flushing Generalized pruritus	Grade 1A symptoms plus: Back pain and/or Hypertension	Urticaria Nausea/vomiting Throat tightness Asymptomatic bronchospasm Chest tightness	Symptomatic bronchospasm Dyspnea Hypoxia Wheezing	Anaphylaxis Hypotension	Death

FIGURE 1. Modified National Cancer Institute Common Terminology Criteria for Adverse Events Scale. From National Cancer Institute.¹³

associated with acute reactions such as those studied in this article, whereas tumor lysis and serum sickness mechanisms tend to produce delayed reactions.⁶⁻¹⁰ A classification of adverse effects to biologic agents has been proposed, stratifying reactions by etiology (hypersensitivity due to immune reaction against agent, elevated cytokine levels, or cytokine imbalance syndrome, cross-reactivity, and non-immune-mediated reactions).¹¹

Despite the known risks of rituximab, the management of these reactions varies significantly. Common management techniques include avoidance of rituximab, rituximab desensitization, or rechallenge to rituximab using modification of the infusion rate and/or additional premedications. Infusion rate is an especially important variable in this process. Generally, a first infusion of rituximab is started at a rate of 50 mg/h and increased by 50 mg/h every 30 minutes to a maximum of 400 mg/h, whereas subsequent infusions are usually started at 100 mg/h and increased by 100 mg/h every 30 minutes to a maximum of 400 mg/h.¹ If there is a reaction, rituximab should be stopped. However, the safety of rechallenging a patient with rituximab after an infusional reaction is not clear.¹² Complete drug avoidance occurs needlessly in some patients who would benefit from additional rituximab treatment, while other patients are unnecessarily desensitized. *Desensitization* refers to giving a patient increasing doses of a medication at a slow rate until reaching the goal dose. It is important to understand the nature of rituximab reactions and the success (or failure) of current management strategies to propose standardized guidelines that are safe and effective for the management of patients after a rituximab reaction. To better understand these issues, we performed a 5-year review of all patients who developed a rituximab reaction in the outpatient oncology infusion center at a large academic medical center.

METHODS

Adverse events (including drug reactions) are filed as safety reports at our institution, Massachusetts General Hospital, a tertiary care academic medical center. We performed a retrospective chart review of all rituximab-related safety reports at the outpatient oncology infusion center between June 2006 and January 2011. We included only the first documented infusion reaction to rituximab for each patient during this period.

We used clinical notes within the Massachusetts General Hospital electronic health record to gather data including patients' demographic characteristics, history of drug allergies, reason for receiving rituximab treatment, rituximab dose, and cycle number when the reaction occurred. Using problem lists from these notes, we collected data on the following patient comorbidities: eczema, seasonal allergies, asthma, coronary artery disease, hypertension, and diabetes. From both the safety reports and clinical notes, we assessed the nature and frequency of premedication, symptoms of the

rituximab reaction, and treatment of the reactions (with H1 blockers, H2 blockers, steroids, epinephrine, beta-agonists, and/or intravenous fluids).

We classified the grade of the reaction using a modified oncologic version of the National Cancer Institute Common Terminology Criteria for Adverse Events Scale, which scores a reaction from 1 (mild reaction) to 4 (severe reaction) similar to our previous work (Figure 1).¹⁴ In the modified grading scale, grade 1A is defined by cutaneous symptoms only (rash, itching, flushing). Grade 1B includes skin manifestations plus either back pain or hypertension. Grade 2 includes urticaria, nausea, vomiting, throat tightness, asymptomatic bronchospasm, and/or chest tightness. Grade 3 is defined by symptomatic bronchospasm, dyspnea, hypoxia, and/or wheezing. Grade 4 includes anaphylaxis or hypotension. Two allergy/immunology physicians (A.B. and T.L.) independently graded the reactions.

At our institution, first-time infusions of rituximab are administered initially at a rate of 50 mg/h for 1 hour, then increased by 50 mg/h every 30 minutes to a maximum of 400 mg/h. For patients who have tolerated previous infusions, subsequent infusions are given at an initial rate of 20% of the total dose over 30 minutes. The remaining 80% of the total dose is then given over 60 minutes. Standard reduction of the infusion rate to 50% occurs after an infusion reaction at our institution. Our allergy clinic uses a standardized rituximab skin test protocol with published nonirritating skin test concentrations, starting with 10 mg/mL percutaneous skin test and then proceeds to 0.02 mL intradermal skin test (0.1 mg/mL, followed by 1 mg/mL).^{15,16} We also use a standardized desensitization protocol (see Figure E1 in this article's Online Repository at www.jaci-inpractice.org).¹⁶

Data on rechallenge after initial reaction (either same day or another day), subsequent rituximab infusion rates (slowed/administered at 50% standard rate), and referral to allergy were reviewed. Institutional review board approval was obtained before study initiation, and informed consent was waived for this retrospective chart review.

Statistical analysis

Statistical analysis including means $\pm$ SD or percentages was used. Descriptive data are displayed as frequencies or means with SDs.

RESULTS

Among 80 safety reports between June 2006 and January 2011, 67 patients with at least 1 rituximab reaction were identified. To keep our study population consistent and focus on initial rituximab infusion reactions, the 13 additional safety reports (in 9 patients) were excluded from this study because they represented the second or third rituximab reaction within the study period. One patient accounted for 4 of

TABLE I. Patients' demographic characteristics and medical history (N = 67)

Demographic characteristics	Value
Age (y), mean $\pm$ SD	58 $\pm$ 13
Sex: male (%)	54
Race (% of known)	
White	91
Hispanic	6
Black	2
Asian	2
Unknown	
Medical history (%)	
Hypertension	52
Other known drug allergy	46
Asthma	19
Eczema or seasonal allergies	16
Coronary artery disease	12
Diabetes	6

these reports, 1 patient accounted for 2 reports, and the rest each had 1 report. Of these 13 safety reports, most (n = 7 [54%]) reflected patients who had had an initial grade 2 reaction. Five reports (38%) were for patients with initial grade 3 reactions. One report was for a patient with an initial grade 1B reaction.

Patients' characteristics

A slight majority of patients were men (54%), with a mean age of 58 $\pm$ 13 years. Of patients with known race (n = 66), most (91%) were white. Almost all patients (n = 62 [93%]) were receiving treatment for B-cell lymphoma. Other conditions that were treated included T-cell lymphoproliferative disease, autoimmune hemolytic anemia, thrombotic thrombocytopenic purpura, hepatocellular carcinoma, and antimyelin-associated glycoprotein antibody neuropathy with 1 patient for each condition. Hypertension was the most common comorbid condition (52%) (see Table I). Less than half (46%) of the patients had at least 1 other known drug allergy documented. A minority of patients (n = 11 [16%]) had at least 1 atopic condition (eczema or seasonal allergies) or had asthma (n = 13 [19%]).

Characteristics of rituximab reaction and premedication patterns

Most reactions occurred during the first infusion of rituximab (n = 42 [63%]). Six patients (9%) had a reaction during cycle 2. Ten patients (15%) had a reaction during cycles 3 to 10; 5 (7%) had a reaction during cycles 11 to 20; and 4 (6%) had a reaction during cycles 20 to 53 (the highest cycle number). Use of premedications was documented in 52% (n = 35) of the patients, and most (n = 31 [89%]) were premedicated before the infusion with steroids (94%), diphenhydramine (90%), and acetaminophen (87%).

Symptoms and treatment of initial rituximab reaction

Rituximab reactions presented most commonly with cutaneous (n = 42 [63%]) or respiratory (n = 36 [54%]) symptoms. Cutaneous symptoms included generalized pruritus

TABLE II. Symptoms and treatment of initial reaction

Symptoms	(%)
Pruritus	45
Flushing	21
Hives	16
Rash	9
Angioedema	0
Throat itchiness	25
Throat tightness	22
Dyspnea	10
Cough	4
Chills	9
Rigors	6
Diaphoresis	1
Fever	0
Chest pain	9
Hypertension	3
Tachycardia	1
Hypotension	1
Dizziness	0
Nausea	4
Abdominal pain	1
Vomiting	0
Back pain	6
Treatment of initial reaction*	%
H1 blocker	88
Steroids	36
H2 blocker	33
Intravenous fluids	27
Beta-agonist	2
Epinephrine	0

*n = 64, excludes unknown and no treatment.

(n = 30 [45%]), flushing (n = 14 [21%]), and hives (n = 11 [16%]). Respiratory symptoms included throat itchiness (n = 17 [25%]), throat tightness/soreness/scratchiness (n = 15 [22%]), and dyspnea (n = 7 [10%]) (see Table II). Using the modified National Cancer Institute grading, we found that 27% of the patients had a grade 1 reaction (n = 12 [18%] grade 1A; n = 6 [9%] grade 1B). Pruritus was the most common symptom among grade 1 reactions (n = 9), followed by rash (n = 4), flushing (n = 7), and chills (n = 4). Grade 2 reactions presented most frequently (n = 41 [61%]) with respiratory symptoms (n = 29), generalized pruritus (n = 19), hives (n = 11), chest pain (n = 5), and flushing (n = 5). Seven patients (10%) had a grade 3 reaction, with dyspnea in all cases (n = 7 [100%]). One patient had a grade 4 reaction, with hypotension as the only symptom.

Most patients (n = 56 [88%]) were given an H1 blocker after their initial reaction as well as steroids (36%), H2 blockers (33%), and intravenous fluids (27%). Only 2% of the patients received a beta-agonist, and none received epinephrine. Treatment of the reaction in 2 patients was not documented. One patient with a grade 2 reaction (oral pruritus) did not receive any treatment for the initial reaction.

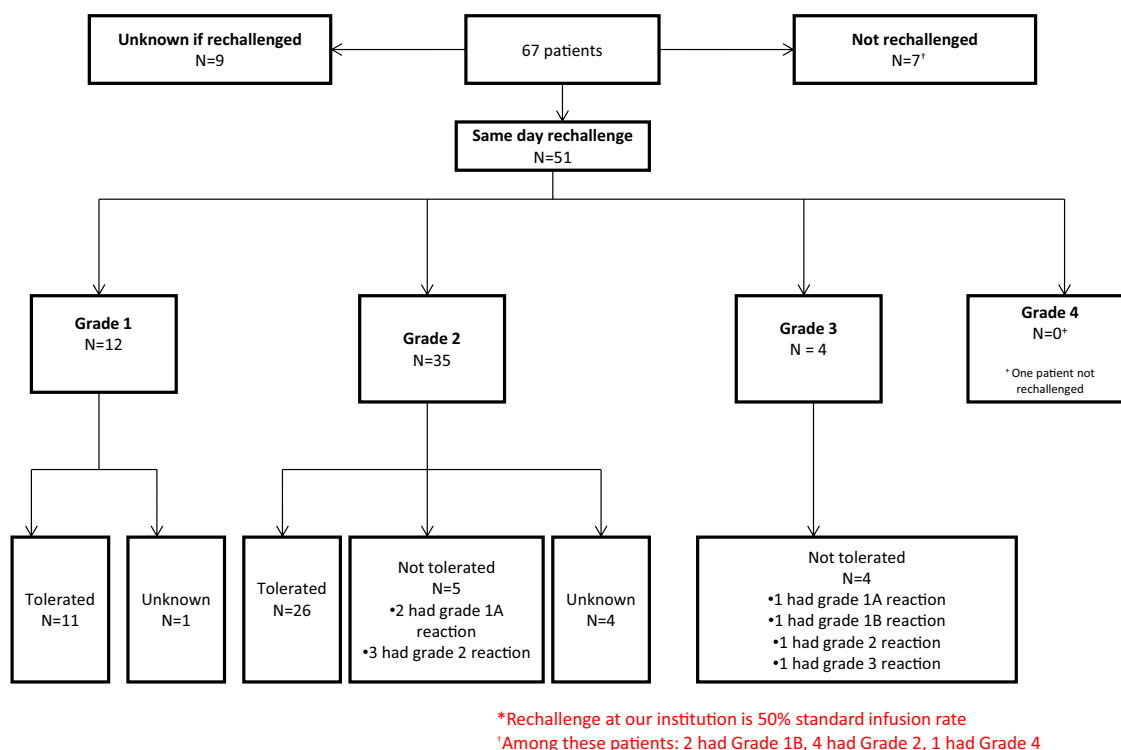


FIGURE 2. Rituximab same-day rechallenge—Grading and outcome. *Rechallenge at our institution is 50% standard infusion rate. †Among these patients, 2 had grade 1B, 4 had grade 2, 1 had grade 4 reactions.

Outcomes of same-day rechallenge after initial rituximab reaction

Out of 67 patients in our study, 51 patients were rechallenged the same day as their initial rituximab reaction. Seven patients were not rechallenged the same day (including 3 patients who were referred to an allergist) and the decision to proceed or defer same-day rechallenge was not documented for 9 patients. The outcome of same-day rechallenge was not documented for 5 of the 51 patients who were rechallenged (see Figure 2).

One grade 1 patient who was rechallenged did not have a recorded outcome. However, all of the remaining 11 patients with grade 1 initial reaction tolerated same-day rechallenge. Most of these patients were treated with H1 antihistamines (N = 10 [83%]), and some were treated with steroids (N = 4 [33%]) or fluids (N = 5 [42%]) after the initial reaction, but all tolerated same-day rechallenge. Slowed (42%) and standard (33%) rituximab infusion rates did not affect the outcome of same-day rechallenge in these patients with grade 1 initial reactions.

The outcome of same-day rechallenge in patients with an initial grade 2 reaction was varied. Although most patients with known outcome (26 of 31 [84%]) with an initial grade 2 reaction tolerated same-day rechallenge, 5 patients (5 of 31 [16%]) had a reaction with grade 1 to 2 severity during same-day rechallenge. There were no notable differences in treatment of initial reaction and infusion rates between patients who tolerated rechallenge and those who did not, with similar proportions of patients who received antihistamines, steroids, and/or a slowed infusion rate between groups. Detailed statistical analysis could not be performed because of the small sample size.

All patients with an initial grade 3 reaction (4 of 4 [100%]) had a reaction during same-day rechallenge. Use of antihistamines (100%), steroids (50%), beta-agonists (25%), intravenous fluids (25%), and/or a slowed infusion protocol (25%) did not prevent a reaction from occurring during same-day rechallenge in this group of patients.

One patient who experienced a grade 4 reaction (with hypotension as the only symptom) was not rechallenged on the same day. The patient's initial blood pressure was 122/68 mm Hg, which dropped to 90s/30s mm Hg. Heart rate remained in the 60s; the patient was on metoprolol. After this patient developed hypotension, the infusion was stopped and the patient received intravenous fluids. The patient received additional rituximab infusions on subsequent days without reported reaction.

Outcome of next treatment for grade 1 patients after same-day rechallenge

Of the 11 patients with initial grade 1 reactions who were rechallenged the same day without further reaction, all received rituximab again within 4 months of the initial reaction. The shortest time to reexposure was 1 day. One patient did not have the next reaction results recorded. Of the remaining 10 patients, only 1 had a reaction. The patient had flushing that resolved on its own, without treatment. Five patients received rituximab at a standard infusion rate, and the rest did not have the rate details in their medical record. Four patients were premedicated, with the most frequent medications including acetaminophen, diphenhydramine, and hydrocortisone. The remaining 7 patients did not have premedication details recorded.

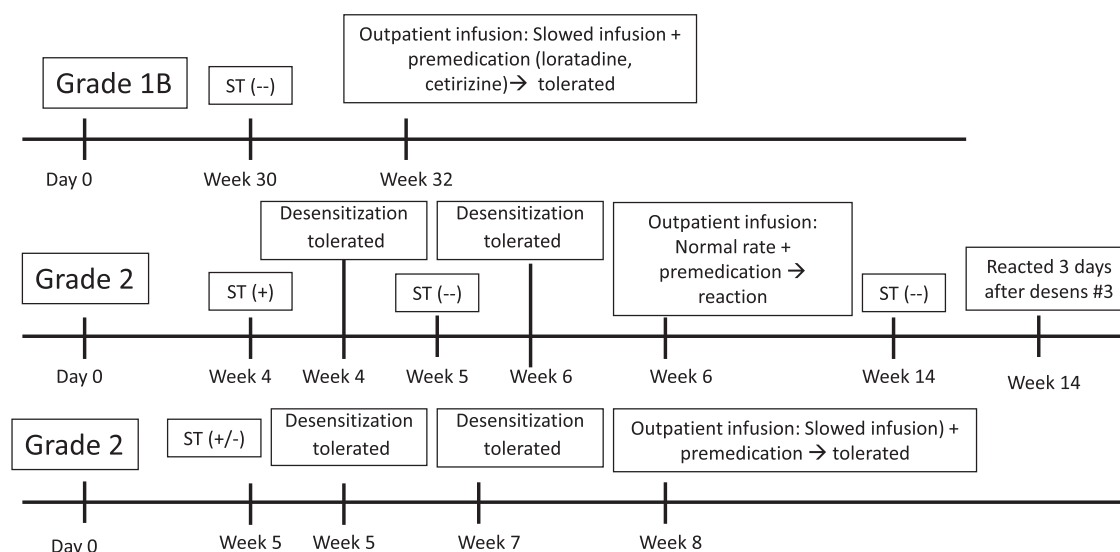


FIGURE 3. Evaluation of patients referred to allergy. *Desens*, Desensitization.

Outcome of next treatment for grade 2 patients after same-day rechallenge

Of the 31 patients with initial grade 2 reactions who were rechallenged the same day with known outcomes (either tolerated or did not tolerate), all 31 received rituximab again. Of the 26 patients with initial grade 2 reactions who tolerated same-day rechallenge, 14 had no reaction upon subsequent rechallenge, 11 had unknown outcome, and 1 had a reaction (grade 3). Of the 5 patients with initial grade 2 reactions who did not tolerate same-day rechallenge, 2 had no reaction upon subsequent rechallenge, 2 had unknown outcome, and 1 had a reaction (grade 2).

Allergy referral

Only 3 patients (4%) in our study were referred to an allergist after their initial reaction. Same-day rechallenge was not performed for any of these patients. Of these 3 patients, 2 had an initial grade 2 reaction and 1 patient had an initial grade 1B reaction (severe back pain, facial flushing, and increased blood pressure).

Skin testing was performed for all 3 patients (results shown in Figure 3). The patient with a grade 1B initial reaction had a negative skin test result, although this was performed more than 6 months after the initial reaction and therefore could represent a false-negative result.¹⁸ This patient tolerated a slowed outpatient infusion (50% standard infusion rate) with premedication (loratadine and cetirizine).

Of the 2 patients with grade 2 reactions, 1 had a positive skin test result and 1 had an indeterminate skin test with poor histamine response. Both skin tests were performed less than 6 weeks after the initial reaction.¹⁸ One patient's skin testing converted to negative 1 week later after the patient received rituximab treatment via a desensitization protocol; the other patient did not undergo repeat skin testing.

The clinical courses of both patients with initial grade 2 reactions are shown in Figure 3. The patient with conversion to negative skin testing tolerated a second desensitization, but then had a reaction (erythema) to an outpatient infusion given at a normal rate with multiple premedication agents (solumedrol,

cetirizine, montelukast, desloratadine, and ranitidine). This patient then had a reaction after a third desensitization. Rituximab was discontinued after the patient developed a delayed reaction (pruritic rash) to rituximab. The patient with indeterminate skin testing tolerated a slowed outpatient infusion after 2 desensitizations, but did not require subsequent rituximab infusions for treatment.

DISCUSSION

This large 5-year retrospective review of rituximab reactions at an academic outpatient infusion center supports previous observations in the literature and provides novel insight into the management of initial rituximab reactions. Patients with initial grade 1 reactions tolerated same-day rechallenge regardless of treatment of initial reaction or subsequent infusion rate. In contrast, grade 3 patients all had a reaction during same-day rechallenge, suggesting that patients with severe (grade 3 or 4) reactions should be referred to an allergist for further risk assessment. Other authors have suggested that for mild or moderate reactions (ie, grade 1 or 2), the infusion should be stopped, then restarted at a slower rate with premedication, whereas for severe reactions the infusion should be discontinued without rechallenge.¹² Our results showing differing reaction rates after same-day rechallenge based on the patient's initial reaction grade support these recommendations. Of note, the rituximab product insert recommends that all patients be premedicated with acetaminophen and an antihistamine, though it acknowledges that there is "insufficient evidence" that premedication reduces the frequency and/or severity of reactions.¹

Various presenting symptoms of infusion reactions are reported in the literature. Our study results diverged from those most frequently cited. We found that the most common clinical reactions were either cutaneous symptoms (itching, flushing, and hives) or respiratory symptoms (dyspnea or throat itching). Previous studies identified that the most common symptoms after initial transfusion were fever, chills, and nausea, with a smaller proportion developing skin manifestations (pruritus, rash, urticaria), hypotension, bronchospasm, or throat swelling.³

It is possible that our results differ in part because our experiences at our outpatient infusion center may be different than those of other populations that have been studied. We are a large academic center, and the referral population might be more severe in terms of tumor burden and/or complexity of comorbid conditions. Tumor burden affects the type of infusion reaction patients have, given that rituximab infusion reaction incidence and severity are associated with B-cell counts.¹⁹ From our diverse study findings, clinicians should be aware that rituximab infusion reactions may present in diverse ways and are not always accompanied by fever or chills.

Further studies on a larger scale are needed to identify predictive characteristics of patients with initial grade 2 reactions who will experience repeat reaction with same-day rechallenge, because grade severity alone did not predict the outcome of rechallenge for patients with grade 2 initial reactions. Among grade 2 patients who were rechallenged the same day with known outcome, 16% experienced repeat reactions. This relatively higher frequency of repeat reactions makes it difficult to create a standardized rechallenge pathway for these patients. In addition, our finding that grade 2 patients were the most likely to have multiple reactions within our time period (as evidenced by safety reports describing subsequent infusion reactions in these patients above) supports the necessity of developing a risk stratification algorithm for these patients. More data are needed to characterize patient characteristics (such as initial symptoms, burden of disease, and comorbidities) that can predict which patients with grade 2 reactions will tolerate same-day rechallenge, which patients will not tolerate rechallenge, and which patients might benefit from allergy referral and/or desensitization. It is somewhat reassuring that repeat reactions were mild or moderate severity (grade 1 or 2), which suggests that these patients can eventually tolerate rituximab therapy.

No patients with grade 3 or 4 reactions were referred to an allergy specialist, which further highlights the importance of establishing a management algorithm for rituximab reactions. Rituximab is likely being unnecessarily avoided in these patients in many places throughout the country. Desensitization can allow patients who require rituximab treatment to tolerate future infusions safely despite severe infusion reactions. Studies have shown that rituximab desensitization, in which patients receive graded drug administration with close monitoring, are successful when performed by trained allergists, though reactions may still occur during this process.^{7,15,17} It is important for clinicians to recognize that patients can have anaphylaxis to rituximab infusions, though it is often underreported.²⁰ If there are suspected symptoms of anaphylaxis, epinephrine should be administered. If patients have a serious reaction and there are reasonable alternatives with similar efficacy, these should be considered by the patient's oncologist.

Of note, the patient who developed a grade 4 reaction during rituximab infusion was able to tolerate subsequent rituximab infusions. This observation can likely be explained by the fact that there are multiple mechanisms contributing to rituximab infusional reactions, including cytokine release syndrome, mast cell-mediated, tumor lysis, and serum sickness.⁶⁻¹⁰ Management differs on the basis of the type of reaction that occurs. Most infusion reactions attributed to cytokine release syndrome can be rechallenged successfully with rituximab, whereas mast cell-mediated hypersensitivity reactions require desensitization.^{7,15} Further research is needed to identify diagnostic tools

that will improve classification and risk assessment of rituximab reactions and help guide management.

On the basis of our data, we propose the following algorithm of management for rituximab infusion reactions. Patients with a grade 1 reaction should receive treatment for the reaction, and then receive same-day rechallenge with normal or reduced infusion rate. Patients with a grade 3 or 4 reaction should be referred to an allergy specialist for skin testing, as well as for evaluation for possible desensitization or monitored rechallenge. However, additional research is required to elucidate the best management approach to patients with a grade 2 reaction. At this time, we recommend that patients with a grade 2 reaction should also be referred to an allergy specialist, given our findings that a significant number still experienced subsequent reaction upon same-day rechallenge and repeated reactions with subsequent infusions.

Limitations of our study include generalizability from a single academic center and from a mostly homogenous population. We suspect there was underreporting of adverse events with rituximab given our low rate of events compared with those seen in other studies. We were also limited by incomplete documentation of rituximab-related events in both the safety reports and in the medical record, leading to a few unknown data points for certain variables that we studied.

In conclusion, our findings highlight the importance of implementing a standardized management algorithm for rituximab reactions to improve safety and quality of care. The National Cancer Institute grading system seems to be an effective initial evaluation tool for triaging patients into those who can safely be rechallenged the same day and those who may benefit from allergy referral and possible desensitization. Consistent with previous data, our study suggests that patients who experience grade 1 reactions to rituximab can be safely rechallenged the same day as their reaction. On the basis of our findings, we suggest that a grade 3 or 4 reaction should prompt referral to an allergy specialist for risk assessment before additional rituximab administration. Further research is needed to understand optimal management of patients who experience grade 2 reactions and to improve risk assessment of patients with grade 2 to 4 reactions. As additional mAbs with diverse targets are used across a number of therapeutic areas including oncologic, neurologic, and rheumatologic clinics, the management of infusion reactions will continue to be a major issue in the care of these complex patients.

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REFERENCES

1. Rituxan (rituximab) label. Available from: http://www.accessdata.fda.gov/drugsatfda_docs/label/2012/103705s5367s53881b1.pdf. Accessed March 27, 2015.
2. Oldham RK, Dillman RO. Monoclonal antibodies in cancer therapy: 25 years of progress. *J Clin Oncol* 2008;26:1774-7.
3. Onrust SV, Lamb HM, Barman Balfour J. Rituximab. *Drugs* 1999;58:79-88.
4. Maloney DG, Grillo-López AJ, White CA, Bodkin D, Schilder RJ, Neidhart JA, et al. IDEC-C2B8 (rituximab) anti-CD20 monoclonal antibody therapy in patients with relapsed low-grade non-Hodgkin's lymphoma. *Blood* 1997;90:2188-95.
5. McLaughlin P, Grillo-López AJ, Link BK, Levy R, Czuczman MS, Williams ME, et al. Rituximab chimeric anti-CD20 monoclonal antibody therapy for relapsed indolent lymphoma: half of patients respond to a four-dose treatment program. *J Clin Oncol* 1998;16:2825-33.

6. Byrd JC, Murphy T, Howard RS, Lucas MS, Goodrich A, Park K, et al. Rituximab using a thrice weekly dosing schedule in B-cell chronic lymphocytic leukemia and small lymphocytic lymphoma demonstrates clinical activity and acceptable toxicity. *J Clin Oncol* 2001;19:2153-64.
7. Castells MC, Tennant NM, Sloane DE, Ida Hsu F, Barrett NA, Hong DI, et al. Hypersensitivity reactions to chemotherapy: outcomes and safety of rapid desensitization in 413 cases. *J Allergy Clin Immunol* 2008;122:574-80.
8. Vultaggio A, Matucci A, Nencini F, Pratesi S, Petroni G, Cammelli D, et al. Drug-specific Th2 cells and IgE antibodies in a patient with anaphylaxis to rituximab. *Int Arch Allergy Immunol* 2012;159:321-6.
9. Dillman R. Infusion reactions associated with the therapeutic use of monoclonal antibodies in the treatment of malignancy. *Cancer Metastasis Rev* 1999;18:465-71.
10. Herishanu Y. Rituximab-induced serum sickness. *Am J Hematol* 2002;70:329.
11. Pichler WJ. Adverse side-effects to biological agents. *Allergy* 2006;61(8):912-20.
12. Lenz H. Management and preparedness for infusion and hypersensitivity reactions. *Oncologist* 2007;12:601-9.
13. National Cancer Institute. Common Terminology Criteria for Adverse Events (CTCAE) Version 4.0. Available from: http://evs.nci.nih.gov/ftp1/CTCAE/CTCAE_4.03_2010-06-14_QuickReference_8.5x11.pdf. Accessed April 12, 2015.
14. Banerji A, Lax T, Guyer A, Hurwitz S, Camargo CA Jr, Long AA. Management of hypersensitivity reactions to carboplatin and paclitaxel in an outpatient oncology infusion center: a 5-year review. *J Allergy Clin Immunol Pract* 2014;2:428-33.
15. 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;124:1259-66.
16. Abadoglu O, Epozurk K, Atayik E, Kaptanoglu E. Successful rapid rituximab desensitization for hypersensitivity reactions to monoclonal antibodies in a patient with rheumatoid arthritis: a remarkable option. *J Investig Allergol Clin Immunol* 2011;21:319-21.
17. Sokol CL, Leung J, Guyer AC, Long A, Wong JT, Wilson MT, et al. Novel rituximab desensitization protocol increases safety of drug desensitization. *J Allergy Clin Immunol* 2012;129:AB371.
18. Patil SU, Long AA, Ling M, Wilson MT, Hesterberg P, Wong JT, et al. A protocol for risk stratification of patients with carboplatin-induced hypersensitivity reactions. *J Allergy Clin Immunol* 2012;129:443-7.
19. Winkler U, Jensen M, Mancke O, Schulz H, Diehl V, Engert A. Cytokine-release syndrome in patients with B-cell chronic lymphocytic leukemia and high lymphocyte counts after treatment with an anti-CD20 monoclonal antibody (rituximab, IDEC-C2B8). *Blood* 1999;94:2217-24.
20. Castells MC. Anaphylaxis to chemotherapy and monoclonal antibodies. *Immunol Allergy Clin North Am* 2015;35:335-48.

Partners HealthCare System

Desensitization Worksheet: Intermediate rituximab desensitization for 1000mg

Med name: **RITUXIMAB** Target dose: 1000 mg

Standard volume per bag: 250 mL

Final rate of infusion: 80 mL/h Time per step: 15 min

Level of severity: Moderate Number of bags: 3 Total number of steps: 13

Bag	Volume per bag (mL)	Concentration (mg/mL)	Total dose per bag (mg)	Amount of bag infused (mL)
1	250	0.04	10	9.38
2	250	0.4	100	18.75
3	300	3.30708267	992.1248	300

Step	Bag	Rate (mL/h)	Time (min)	Cumulative time (min)	Volume infused per step (mL)	Dose administered with this step (mg)	Cumulative dose (mg)
1	1	2.5	15	15	0.63	0.0252	0.0252
2	1	5	15	30	1.25	0.05	0.0752
3	1	10	15	45	2.5	0.1	0.1752
4	1	20	15	60	5	0.2	0.3752
5	2	5	15	75	1.25	0.5	0.8752
6	2	10	15	90	2.5	1	1.8752
7	2	20	15	105	5	2	3.8752
8	2	40	15	120	10	4	7.8752
9	3	10	15	135	2.5	8.2677	16.1429
10	3	20	15	150	5	16.5354	32.6783
11	3	40	15	165	10	33.0708	65.7491
12	3	60	270	435	282.5	934.250854	1000

FIGURE E1. Massachusetts General Hospital Rituximab Desensitization Protocol.

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