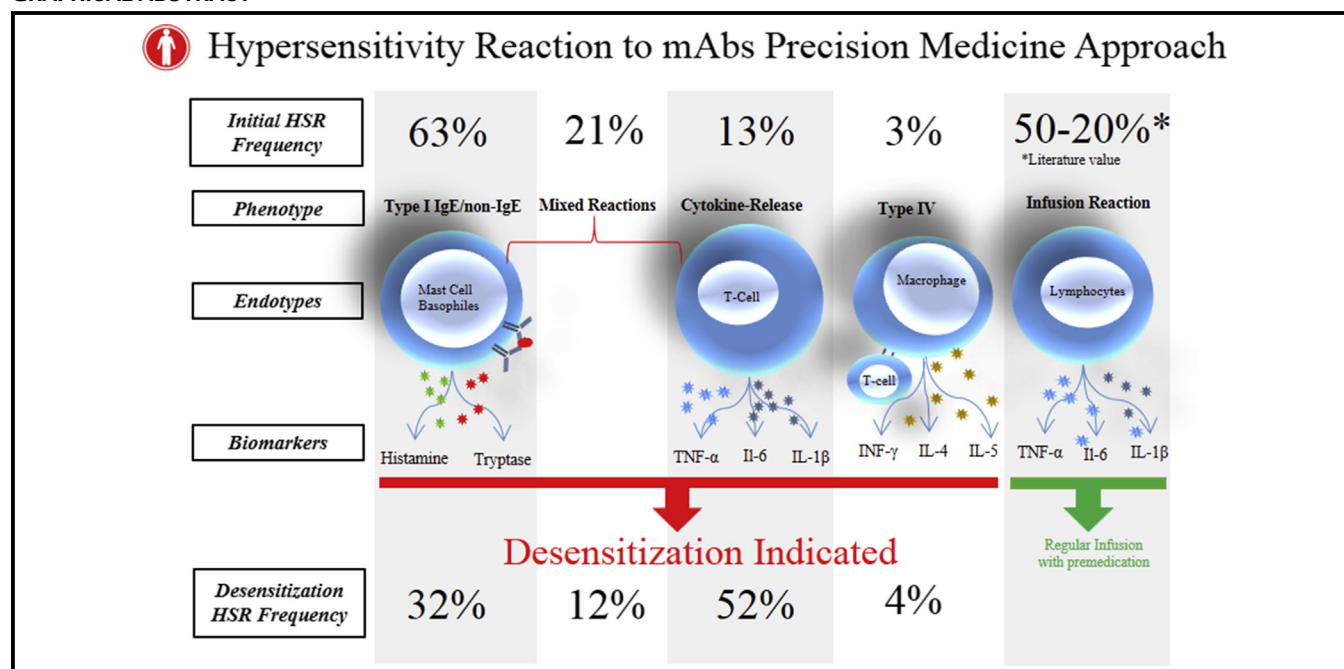


# Hypersensitivity reactions to therapeutic monoclonal antibodies: Phenotypes and endotypes



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## GRAPHICAL ABSTRACT



**Background:** The increasing use of mAbs has led to a rise in hypersensitivity reactions (HSRs), which prevent their use as first-line therapy. HSRs' symptoms, diagnostic tools, and directed management approaches have not been standardized. **Objective:** We propose a novel evidence-based classification of HSRs to mAbs, based on the clinical phenotypes, underlying endotypes and biomarkers, as well as their management with desensitization.

**Methods:** Phenotypes, endotypes, and biomarkers of HSRs to 16 mAbs for 104 patients were described and compared with the outcomes of 526 subcutaneous and intravenous desensitizations.

**Results:** Initial reactions presented with 4 patterns: type I-like reactions (63%), cytokine-release reactions (13%), mixed reactions (21%), and delayed type IV reactions (3%). In contrast, of the 23% breakthrough HSRs during desensitization, 52% were cytokine-release reactions, 32% were type 1, 12% were mixed, and 4% were type I with delayed type IV. Skin testing to 10 mAbs in 58 patients was positive in 41% of patients. Serum tryptase was elevated in 1 patient and IL-6 was elevated in 8 patients during desensitization and was associated with a cytokine-release phenotype.

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**Conclusions:** HSRs to mAbs can be defined as type I, cytokine-release, mixed (type I/cytokine-release), and type IV reactions, which are identified by biomarkers such as skin test, tryptase, and IL-6. These phenotypes can be used to improve personalized and precision medicine when diagnosing HSRs to mAbs and providing management recommendations with desensitization. Desensitization provides a safe and effective retreatment option to remain on culprit mAbs as first-line therapy. (J Allergy Clin Immunol 2018;142:159-70.)

**Key words:** Monoclonal antibody, hypersensitivity reaction, phenotype, endotype, biomarkers, tryptase, IL-6, skin testing, desensitization, precision medicine

The use of mAbs has increased dramatically and is currently the cornerstone of targeted therapies for cancer and inflammatory diseases. Parallel to the increased use of mAbs, an increase in hypersensitivity reactions (HSRs) have been observed. This often prevents continued use of first-line therapies for fear of inducing severe HSRs, anaphylaxis, and death.<sup>1,2</sup>

Although the Gell and Coombs classification has been useful to provide mechanistic understanding of HSRs, the classification and diagnosis of reactions to mAbs have provided a challenge. New approaches for better understanding drug hypersensitivity involve characterization of reactions by phenotype, endotype, and biomarkers.<sup>3</sup> Phenotypes are defined by the clinical presentation, and endotypes refer to the cellular and molecular mechanisms of the HSRs defined by the biomarkers, such as skin testing, tryptase, and others.<sup>4</sup> Critically, the clinical presentation for mAb HSRs may overlap several mechanisms, and diagnosis and management protocols have not been standardized.

Hypersensitivity reactions to mAb include infusion-related reactions, cytokine-release reactions, type I (IgE/non-IgE), type III, and delayed type IV reactions. Infusion-related reactions and cytokine-release reactions to mAbs can occur at first infusion and may typically present with mild to severe symptoms including flushing, chills, fever, tachycardia, hypertension, dyspnea, nausea, vomiting, and syncope.<sup>5-8</sup> The difference between infusion-related reactions and cytokine-release reactions is the self-limiting nature of infusion-related reactions on repeat exposure and the response to premedication.<sup>5-10</sup> Type I reactions to mAbs such as those seen with rituximab and cetuximab, can manifest with flushing, pruritus, urticaria, shortness of breath, hypotension, and life-threatening anaphylaxis. These symptoms are associated with the release of mast cells/basophils mediators, including tryptase, histamine, leukotrienes, and prostaglandins, whose actions affect cutaneous, respiratory, gastrointestinal, and cardiovascular organ systems.<sup>11,12</sup> Type III HSRs arise when soluble antigens aggregate with IgG/IgM (immune complexes) that deposit in tissues and may cause injury either locally (arthus reaction with mAb injection) or systemically and have been described with infliximab, etanercept, and adalimumab.<sup>13-15</sup> Delayed type IV HSRs to mAbs, including rituximab, may range from nonsevere maculopapular rash to severe reactions (Stevens-Johnson syndrome, toxic epidermal necrolysis). They typically arise from 12 hours to several weeks after exposure to the offending mAb and are thought to be T-cell mediated but other mechanisms may be involved.<sup>16-19</sup>

Desensitization has emerged as a powerful tool that is safe and effective to maintain patients on first-line therapy and patients

#### Abbreviations used

HSR: Hypersensitivity reaction  
IV: Intravenous

presenting with type I and cytokine-release reactions to mAbs are thought to be candidates for desensitization.<sup>20</sup> However, data on widespread mAb desensitization is limited. Brennan et al described HSRs to rituximab, infliximab, and trastuzumab in 23 patients with 105 desensitizations; they concluded that desensitization is a promising method for mAb reexposure after a HSR, but the possibility of a reaction remains with each desensitization.<sup>9</sup>

Herein we provide the largest description of HSRs to mAbs and define the phenotypic and endotypic expression of these HSRs as well as their management with 526 subcutaneous and intravenous (IV) desensitizations to 16 mAbs in 104 patients, with paramount safety and no deaths. In particular, we report new high impact mAbs to programmed cell death-1 and human epidermal growth factor receptor-2 blockade (pembrolizumab, nivolumab, pertuzumab, and trastuzumab) and provide new guidelines in the management and treatment of reactions, creating a new standard of care for mAb desensitization.

## METHODS

### Patient selection

This study is a retrospective review of patients who received desensitization as part of standard of care at the Drug Hypersensitivity and Desensitization Center at Brigham and Women's Hospital and Dana Farber Cancer Institute. All patients who received desensitization to any mAb from January 1, 2014 to December 31, 2016 were included and desensitizations were performed in both outpatient and medical intensive care unit settings. We also included 1 patient who received desensitization to cetuximab in 2011. The study was approved by the Brigham and Women's Hospital institutional review board (protocol 2016P001276). Desensitization was offered to patients who presented with reactions during or shortly after drug administration that were consistent with immediate-type HSRs or with delayed reactions without severe rash and required mAb therapy as first-line treatment.

Patients with severe cutaneous adverse reactions—drug eruption with eosinophilia and systemic symptoms, acute generalized exanthematous pustulosis, Stevens-Johnson syndrome, or toxic epidermal necrolysis—were excluded, because of the high risk of recurrence that could lead to fatality on reexposure.<sup>21,22</sup> Patients with chemical hepatitis, bone marrow suppression, and renal complications were also excluded from desensitization.

### Classification and severity of HSRs

Symptoms of allergic reactions were characterized into cutaneous (flushing, erythema, pruritus, hives, angioedema, delayed maculopapular rash), respiratory (dyspnea, chest tightness, wheezing, cough, oxygen desaturation), throat (itchy, tickle, lump in throat, tightness, swelling, hoarse voice, difficulty swallowing, stridor), cardiovascular (chest pain, tachycardia, bradycardia, electrocardiogram changes, hypotension, hypertension, presyncope/syncope), gastrointestinal (nausea, vomiting, diarrhea, abdominal pain), neuromuscular (chest pain, back pain, headache, tingling, vision problem, sense of impending doom, seizure, loss of consciousness), and general symptoms (fever, chills/rigors). HSRs severity was graded by the modified Brown classification. Grade I (mild) reactions were limited to 1 organ system typically skin; grade II (moderate) reactions involved 2 or more organ systems without change in vital signs; grade III (severe) reactions included 1 or more organs systems with vital signs changes such as hypotension, oxygen desaturation, throat closure, seizure, or loss of consciousness.<sup>23</sup>

**TABLE I.** Monoclonal desensitization protocols: Pembrolizumab intravenous desensitization protocol (target dose 200 mg)

| Bag | Volume per bag (mL) | Concentration (mg/mL) | Total dose per bag (mg) | Amount of bag infused (mL) |
|-----|---------------------|-----------------------|-------------------------|----------------------------|
| 1   | 100                 | 0.02                  | 2                       | 9.38                       |
| 2   | 100                 | 0.2                   | 20                      | 18.75                      |
| 3   | 100                 | 1.96063               | 196.063                 | 100                        |

| Step        | Bag | Rate (mL/h) | Time (min) | Cumulative time (min) | Volume infused per step (mL) | Dose administered with this step (mg) | Cumulative dose (mg) | Fold increase per step |
|-------------|-----|-------------|------------|-----------------------|------------------------------|---------------------------------------|----------------------|------------------------|
| 1           | 1   | 2.5         | 15         | 15                    | 0.63                         | 0.0125                                | 0.0125               | 0                      |
| 2           | 1   | 5           | 15         | 30                    | 1.25                         | 0.025                                 | 0.0375               | 2                      |
| 3           | 1   | 10          | 15         | 45                    | 2.5                          | 0.05                                  | 0.0875               | 2                      |
| 4           | 1   | 20          | 15         | 60                    | 5                            | 0.1                                   | 0.1875               | 2                      |
| 5           | 2   | 5           | 15         | 75                    | 1.25                         | 0.25                                  | 0.4375               | 2.5                    |
| 6           | 2   | 10          | 15         | 90                    | 2.5                          | 0.5                                   | 0.9375               | 2                      |
| 7           | 2   | 20          | 15         | 105                   | 5                            | 1                                     | 1.9375               | 2                      |
| 8           | 2   | 40          | 15         | 120                   | 10                           | 2                                     | 3.9375               | 2                      |
| 9           | 3   | 10          | 15         | 135                   | 2.5                          | 4.9016                                | 8.8391               | 2.45                   |
| 10          | 3   | 20          | 15         | 150                   | 5                            | 9.8031                                | 18.6422              | 2                      |
| 11          | 3   | 40          | 15         | 165                   | 10                           | 19.6063                               | 38.2484              | 2                      |
| 12          | 3   | 80          | 61.875     | 226.88                | 82.5                         | 161.7516                              | 200                  |                        |
| Total time: |     |             |            | 3.78 h                |                              |                                       |                      |                        |

## Skin testing

The commercial solution was obtained or reconstituted per the manufacturer's instructions and further diluted in normal saline for intradermal testing. For epicutaneous skin testing, a drop of the full strength mAb was applied to the volar surface of the forearm, followed by pricking with a Quintest device (Bayer, Spokane, Wash). For intradermal injections, dilutions for skin testing were based on published nonirritating concentrations<sup>24,25</sup> or 0.02 mL of a 1:1000 dilution, followed by 1:100 and 1:10 dilutions if the result was negative. Skin tests were performed at least 2 weeks after the initial HSR to minimize false-negative results. A positive reaction was defined as a wheal with a diameter at least 3 mm larger than produced by a negative control (normal saline). Histamine prick (10 mg/mL) was used as a positive control.<sup>9,26</sup> Skin testing to certain mAbs was not performed due to cost considerations.

## Desensitization protocols and treatment of reactions

Intravenous mAbs desensitization protocols consist of 1 to 4 solutions (each in 100 to 500 mL of saline depending on mAb and manufacturer's recommendations). The first bag contains a solution with 1/100 dilution, the second a 1/10 dilution, and the third dilution (full concentration) is calculated by subtracting the cumulative dose administered in steps 1 to 8 from the total target dose.<sup>1,9</sup> These solutions are administered in 4, 8, 12, or 16 steps with 2- to 2.5-fold dose increments, along with increasing infusion rate each 15 minutes, except the final step, which is maintained until the complete targeted dose is achieved. For the subcutaneous mAbs, a 7-step protocol was used starting with a 1/10 dilution of the original concentration in the first 4 steps followed by the original dilution in the remaining 3 steps. The time interval between steps is 30 minutes with doubling dose each step until the target dose is reached. Examples of desensitization protocols are shown in [Tables I and II](#).

Based on the symptoms during initial HSRs, premedications were administered 30 minutes prior to the desensitization. Cetirizine (10 mg orally) and famotidine (20 to 40 mg orally or intravenously) were standard of care for all protocols. Additional premedication included aspirin (for flushing) and montelukast (for bronchospasm). COX-1 inhibitors, acetaminophen, steroids, and opioids were used to prevent chills, rigors, fever, and pain.

Other premedications including IV fluids, hydroxyzine, doxepin, fexofenadine, diphenhydramine, loratadine, albuterol, zileuton, ondansetron, gabapentin, and lorazepam were added as necessary or per patient preference.

Patients were asked to hold  $\beta$ -adrenergic blocking medications for 24 hours prior to desensitization.

If a mild reaction occurred during desensitization, the infusion was paused and medications were administered based on the type of symptom. Once the reaction resolved, the infusion was resumed at the step where it was suspended. If a severe reaction developed, desensitization was stopped and the patient was treated appropriately with proper rescue medications.

## Statistical analysis

The primary goal of the study was to identify characteristics that contributed to successful desensitization including age, sex, underlying disease, atopy, previous lifetime exposures, skin testing, protocol, phenotype, endotype, and biomarkers of reaction. To test statistical differences between the 2 groups, a 2-sided Welch *t* test with a 95% confidence interval was used for the continuous variables and a chi-squared test was used for the categorical variables. The mean  $\pm$  SD for each variable and the number and the percentage for each categorical variable were calculated and reported. All statistical analysis was performed in R statistical software (R Consortium, Vienna, Austria).

## RESULTS

### Patient characteristics

One hundred and four patients had 526 desensitizations with 16 different mAbs. Thirty-seven percent of these patients were atopic (history of asthma, allergic rhinitis, food allergy, urticaria, and/or hymenoptera venom allergy) and 27% experienced adverse drug reactions to other medications ([Table III](#)). The most common indications for treatment were hematologic malignancies (47 of 104), connective tissue diseases, and other autoimmune diseases (32 of 104) ([Table IV](#)).

**Initial reaction symptoms and phenotypes.** Cutaneous symptoms (flushing/warmth/erythema 32%, pruritis 29%, urticaria 19%) were the most common initial symptoms followed by respiratory (dyspnea 21%) and throat (tightness/swelling 14%) symptoms. Vital sign changes such as hypotension and oxygen desaturation were found in 11% and 7%, respectively ([Fig 1](#)). Initial reactions presented with 4 phenotypes: type I (63%),

**TABLE II.** Monoclonal desensitization protocols: Omalizumab subcutaneous desensitization (target dose 150 mg)

| Step | Time (min) | Concentration (mg/mL) | Volume (mL) | Dose (mg) | Cumulative dose (mg) |
|------|------------|-----------------------|-------------|-----------|----------------------|
| 1    | 0          | 12.5                  | 0.12        | 1.5       | 1                    |
| 2    | 30         | 12.5                  | 0.24        | 3         | 4.5                  |
| 3    | 60         | 12.5                  | 0.48        | 6         | 10.5                 |
| 4    | 90         | 12.5                  | 0.96        | 12        | 22.5                 |
| 5    | 120        | 125                   | 0.19        | 23.75     | 46.25                |
| 6    | 150        | 125                   | 0.39        | 48.75     | 95                   |
| 7    | 180        | 125                   | 0.44        | 55        | 150                  |

Vial concentration 125 mg/mL (150 mg/1.2 mL).

**TABLE III.** Demographics and patient characteristics

| Demographics (n = 104)     |        |                     |             |           |              |                           |           |                             |             |
|----------------------------|--------|---------------------|-------------|-----------|--------------|---------------------------|-----------|-----------------------------|-------------|
| Sex                        |        | Age (y)             | Atopy       |           |              | ADR                       | Diagnosis |                             |             |
| Male                       | Female | 21-82 (mean 54)     | Asthma + AR | Urticaria | Food allergy | Hymenoptera venom allergy | 27%       | Oncology                    | Nononcology |
| 33                         | 71     |                     | 27%         | 7%        | 2%           | 1%                        |           | 58                          | 46          |
| Desensitizations (n = 526) |        |                     |             |           |              |                           |           |                             |             |
|                            |        |                     |             |           |              | Location                  |           |                             |             |
| Range                      |        | Average per patient |             | Median    |              | Outpatient                |           | Medical intensive care unit |             |
| 1-75                       |        | 5.06                |             | 8         |              | 455 (86.5%)               |           | 71 (13.5%)                  |             |

ADR, Adverse drug reaction; AR, allergic rhinitis.

cytokine-release reactions (13%), mixed (21%), and delayed type IV reactions (3%) (Fig 2, A).

**Severity of initial reactions.** Most initial reactions were grade II (48%), and 29% of patients had a grade III reaction (Fig 2, B). Rituximab had a higher percentage of grade II reactions 31 of 52 (60%) and infliximab had higher number of grade I reactions 7 of 18 (39%). Tocilizumab and brentuximab had higher numbers of grade III reactions but had sample sizes of only 3 and 8, respectively (Table IV).

**Desensitization protocols.** Of the 526 desensitizations performed, 425 (80%) used a 3 bag–12 step protocol. Other protocols including 1 bag–3 steps, 2 bag–8 steps, and 4 bag–16 steps were used in 6%, 3%, and 9%, respectively. Nine 7-steps and 1-challenge protocols were performed for 3 subcutaneous mAbs. Intravenous fluid as premedication was used in 81 desensitizations; patients who received fluids as part of standard premedication (without having a breakthrough reaction during desensitization) had a reaction rate of 18% with only grade I reactions. Similarly, patients who received fluids after a breakthrough reaction during desensitization had lower grade of reaction in subsequent desensitizations (1.3 to 0.35).

**Reaction during desensitization.** During desensitization, the predominant symptoms were rigors 24%, chills 23%, and back pain 18% (Fig 1) with cytokine-release reactions as the major HSR phenotype (52%) (Fig 2, B and C). Of 526 desensitizations, 404 (77%) were completed without a reaction. Reactions were most likely to occur at step 12 (53 of 122). Of all the desensitizations, 15% (78) had mild (grade I), 8% (42) moderate (grade II), and 0.4% (2) severe reactions (grade III) with 1 patient treated with epinephrine (Fig 2, D). There were no grade III reactions during the first desensitization (Fig 2, E). Out of 18 desensitizations with multiple reactions (at different steps), 3 (16%) had worsening severity of the reaction over time (2 from grades I to II

and 1 from grades I to III). All subcutaneous desensitizations were done successfully in 4 patients (Table IV).

The severity of the reaction during first desensitization when compared with the initial reaction was significantly lower ( $P = 1.3 \times 10^{-13}$ ) (Fig 2, E). Greater lifetime exposure to the culprit drug significantly lowered the average desensitization grade reaction ( $P = .003$ ) (see Fig E1 in this article's Online Repository at [www.jacionline.org](http://www.jacionline.org)), concurrently, the frequency and severity of reactions during desensitization decreased with multiple desensitizations (Fig 2, G). A dose reduction of 25%, 50%, or 75% was recommended when patients failed protocols despite modifications such as rate decrease and increase in premedication. The dose was decided depending on the severity of HSR (the more severe HSR, the lower the dose) and in agreement with the treating physician. Dose reduction was used for 6 patients during 21 desensitizations; there were no reactions in 15 desensitizations. Patients who continued to have breakthrough reactions had less severe grade of reaction from  $1.9 \pm 1.3$  to  $0.6 \pm 1.2$ . Three patients achieved desensitization at 100% of targeted dose; 2 patients did not need any more desensitizations per provider choice; and 1 patient did not continue desensitization because of persistent grade 2 reactions despite a 50% dose reduction during 2 desensitizations.

**Skin testing and correlation with severity of reaction.** Skin testing was performed for 10 mAbs in 58 patients, with 24 positive (9 prick, 15 intradermal) (41%) and 34 negative results (59%) (Table V). Skin testing was positive in 44% of type I phenotype and in 11% of cytokine-release reactions phenotype during initial reaction (Fig 3, A) and in 69% of type I during desensitization (Fig 3, B). There was a significant drop in reaction grade for both skin test results (Fig 3, C). A positive skin test was associated with greater severity of initial reaction ( $P$  value of .0088) (Fig 3, C).

**TABLE IV.** Characteristics of biological drugs, indications, severity of initial reaction, and number of patients and desensitizations by agent

| Agent/route                 | Target        | Type      | Indication                  |    | Grade of initial reaction |    |     | Patients/<br>desensitizations |
|-----------------------------|---------------|-----------|-----------------------------|----|---------------------------|----|-----|-------------------------------|
|                             |               |           |                             |    | I                         | II | III |                               |
| Rituximab IV (Rituxan)      | CD20          | Chimeric  | Hematological malignancies* | 35 | 7                         | 31 | 15  | 52/234                        |
|                             |               |           | Connective tissue diseases† | 8  |                           |    |     |                               |
|                             |               |           | Autoimmune diseases‡        | 7  |                           |    |     |                               |
|                             |               |           | Inflammatory diseases§      | 2  |                           |    |     |                               |
| Infliximab IV (Remicade)    | TNF-α         | Chimeric  | Uveitis                     | 5  | 7                         | 8  | 3   | 18/86                         |
|                             |               |           | Ulcerative colitis          | 4  |                           |    |     |                               |
|                             |               |           | Crohn disease               | 3  |                           |    |     |                               |
|                             |               |           | Psoriatic arthritis         | 2  |                           |    |     |                               |
|                             |               |           | Sarcoidosis/arthritis       | 1  |                           |    |     |                               |
|                             |               |           | MCTD                        | 3  |                           |    |     |                               |
|                             |               |           |                             |    |                           |    |     |                               |
| Tocilizumab IV (Actemra)    | IL-6 receptor | Humanized | RA                          | 2  | 0                         | 0  | 3   | 3/48                          |
|                             |               |           | JRA                         | 1  |                           |    |     |                               |
| Brentuximab IV (Vedotin)    | CD30          | Chimeric  | Hodgkin lymphoma            | 4  | 2                         | 2  | 4   | 8/42                          |
|                             |               |           | CTCL                        | 3  |                           |    |     |                               |
|                             |               |           | CLL                         | 1  |                           |    |     |                               |
| Trastuzumab IV (Herceptin)  | HER2          | Humanized | Breast cancer               | 7  | 1                         | 4  | 2   | 7/30                          |
| Obinutuzumab IV (Gazyva)    | CD20          | Humanized | CLL                         | 2  | 0                         | 1  | 1   | 2/22                          |
| Abatacept IV (Orencia)      | CD80/86       | Human     | RA                          | 2  | 2                         | 0  | 0   | 2/13                          |
| Ofatumumab IV (Arzerra)     | CD20          | Humanized | CLL                         | 2  | 1                         | 1  | 0   | 2/12                          |
| Bevacizumab IV (Avastin)    | VEGF          | Humanized | Ovarian cancer              | 1  | 1                         | 0  | 0   | 1/11                          |
| Pertuzumab IV (Perjeta)     | HER2          | Humanized | Breast cancer               | 2  | 0                         | 2  | 0   | 2/7                           |
| Omalizumab SC (Xolair)      | IgE           | Humanized | Asthma                      | 2  | 0                         | 1  | 0   | 2/5                           |
| Adalimumab SC (Humira)      | TNF-α         | Human     | Ankylosing spondylitis      | 1  | 1                         | 0  | 0   | 1/4                           |
| Nivolumab IV (Opdivo)       | PD-1          | Human     | Melanoma                    | 1  | 1                         | 0  | 0   | 1/2                           |
| Pembrolizumab IV (Keytruda) | PD-1          | Humanized | Ovarian cancer              | 1  | 1                         | 0  | 0   | 1/1                           |
| Golimumab SC (Simponi)      | TNF-α         | Human     | Ankylosing spondylitis      | 1  | 0                         | 0  | 1   | 1/1                           |
| Cetuximab IV (Erbix)        | EGFR          | Chimeric  | Colon cancer                | 1  | 0                         | 0  | 1   | 1/8                           |
| Total                       |               |           |                             |    | 24                        | 50 | 30  | 104/526                       |

CLL, Chronic lymphocytic leukemia; CTCL, cutaneous T-cell lymphoma; EGFR, epidermal growth factor receptor; HER2, human epidermal growth factor receptor-2; JRA, juvenile rheumatoid arthritis; MCTD, mixed connective tissue disease; PD-1, programmed cell death 1; RA, rheumatoid arthritis; VEGF, vascular endothelial growth factor.

\*Non-Hodgkin lymphoma, CLL, Waldenstrom macroglobulinemia.

†RA, systemic lupus erythematosus, MCTD.

‡Vasculitis, scleroderma, dermatomyositis, myositis, antisynthetase syndrome, immune thrombocytopenic purpura, IgG4 disease.

§Chronic inflammatory demyelinating polyneuropathy, focal segmental Glomerulosclerosis.

**Biomarkers.** Tryptase was performed in 45 patients and was elevated in 1 patient during 2 desensitizations (21.4 ng/mL and 23.6 ng/mL with a baseline of 14.3 ng/mL). IL-6 was tested in 13 patients and was elevated in 8 of them (Table VI).

## DISCUSSION

We provide a new evidence-based description of phenotypes and endotypes to HSRs in 104 patients who reacted to 16 mAbs (34% of available mAbs) and were successfully treated with desensitization. This description should facilitate the diagnosis and management of HSRs to mAbs.

Our most common mAbs were rituximab, infliximab, tocilizumab, brentuximab, and trastuzumab, with fewer new humanized mAbs such as pertuzumab, nivolumab, and pembrolizumab. Reactions are less common with humanized mAbs due to their lack of mouse antibody parts, however immunogenicity persists likely due to the use of transgenic mouse cell lines, which cannot generate human carbohydrate side chains<sup>27-29</sup> (Fig 4).

We classified the HSRs into 4 phenotypes: type I (IgE/non-IgE), cytokine-release reactions, mixed (type I/cytokine-release), and type IV reactions. Type I (63%) was the most common initial

HSR presentation (Figs 1 and 3). The incidence of urticaria was higher than in any other reported drug HSRs and may be a unique signature of mAb HSR. Interestingly, during desensitization, we observed a change from type I to cytokine-release reactions (Fig 2, A and C). The mechanism of this conversion is unclear; however, 1 possibility is that the desensitization and standard premedication blocks type I HSRs, but not symptoms of cytokine-release reactions. This does not explain HSRs during the initial reactions and why patients do not have equal number of cytokine-release and type I reactions initially (or mixed reactions) and highlights the possibility of HSR phenotype switching during subsequent reactions.

Establishing biomarkers for the identification of the endotype underlying HSRs to drugs is critical to identifying, grading, and managing reactions and currently biomarkers are only available for types I, III, and IV but not II. Tryptase has been shown to be elevated during type I HSRs; in our report, tryptase was elevated during rituximab desensitization on 2 occasions (same patient). The elevation was associated with symptoms compatible with type I and may show a subclinical reaction that was asymptomatic due to H1/H2 blockade. In the patients sampled, elevated IL-6 was consistently associated with cytokine-release symptoms

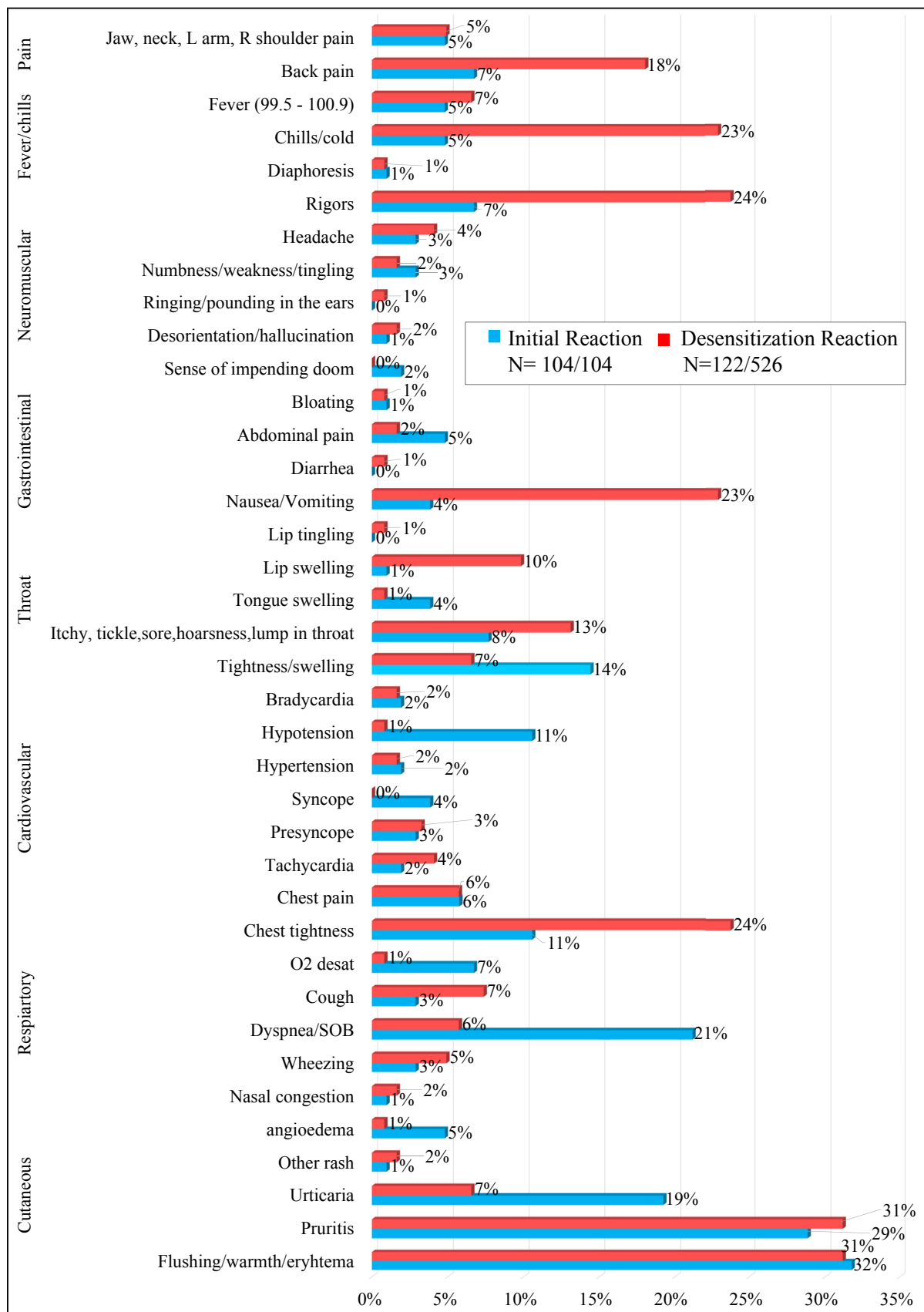


**FIG 1.** Symptoms during initial versus desensitization reactions. Percentage of patients who reacted with specific symptoms categorized by organ system. The initial reaction included all patients (n = 104) and the desensitization reactions included all patients who had a breakthrough reaction during desensitization (n = 122 of 526). *SOB*, Shortness of breath.

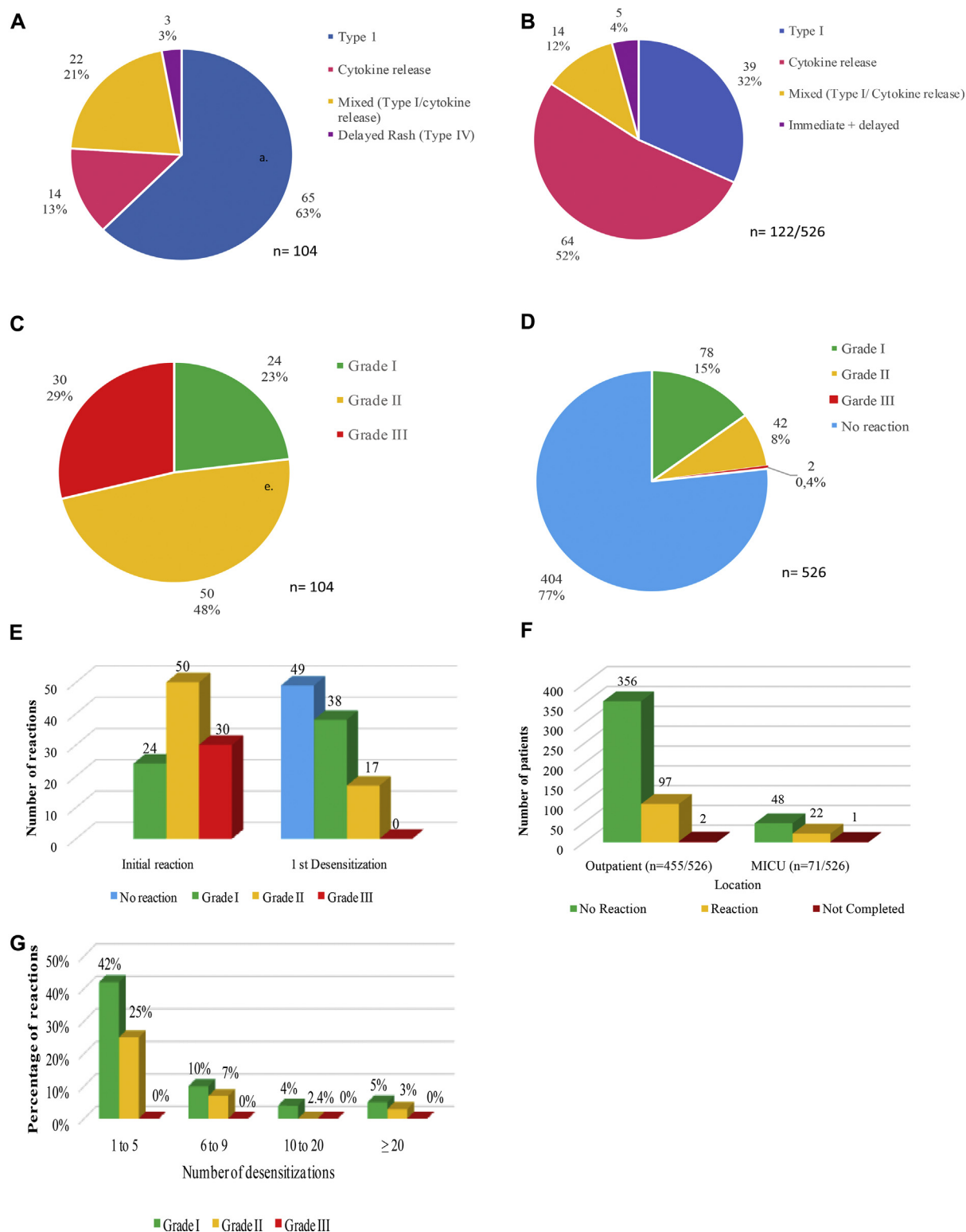


**FIG 2.** Characteristics of initial versus desensitization reactions. **A** and **B**, Phenotypes and severity of initial reactions. **C** and **D**, Phenotypes and severity of desensitization reactions. **E**, Severity of initial reaction versus reaction during first desensitization. **F**, Reactions during desensitizations and outcomes based on the location of desensitization. **G**, Severity of reaction based on number of desensitizations. *MICU*, Medical intensive care unit.

**TABLE V.** Skin test results and skin test concentrations

| Agents*                            |          | Rituximab | Infliximab | Brentuximab | Adalimumab | Cetuximab | Tocilizumab | Trastuzumab | Abatacept | Bevacizumab | Pertuzumab | Total patients |
|------------------------------------|----------|-----------|------------|-------------|------------|-----------|-------------|-------------|-----------|-------------|------------|----------------|
| Skin test results                  | Positive | 18 (52)   | 3 (23)     | 1 (33)      | 1 (100)    | 1 (100)   | 0           | 0           | 0         | 0           | 0          | 24 (41)        |
| Number of patients (%)             | Negative | 17 (48)   | 10 (77)    | 2 (67)      | 0          | 0         | 1 (100)     | 1 (100)     | 1 (100)   | 1 (100)     | 1 (100)    | 34 (59)        |
| Skin testing concentration (mg/mL) | Prick    | 10        | 10         | 1.8         | 50         | 2         | 20          | 21          | 25        | 25          | 30         | 9 (37.5)       |
| Patients with positive results     |          |           |            |             |            |           |             |             |           |             |            |                |
|                                    | 1st ID   | 0.01      | 0.1        | 0.0018      | 0.05       | 0.002     | 0.02        | 0.21        | 0.025     | 0.25        | 0.3        | 4 (16.7)       |
|                                    |          | 2 (6)     | 1 (8)      | 1 (33)      |            |           |             |             |           |             |            |                |
|                                    | 2nd ID   | 0.1       | 1          | 0.018       | 0.5        | 0.02      | 0.2         | 2.1         | 0.25      | 2.5         | 3          | 8 (33.3)       |
|                                    |          | 7 (20)    |            |             | 1 (100)    |           |             |             |           |             |            |                |
|                                    | 3rd ID   | 1         | —          | 0.18        | 5          | 0.2       | 2           | —           | 2.5       | —           | —          | 3 (12.5)       |
|                                    |          | 2 (6)     |            |             |            | 1 (100)   |             |             |           |             |            |                |

Values are n or n (%). Results from patient skin testing and skin testing concentrations used. Skin testing to certain mAbs was not performed due to cost considerations. ID, Intradermal.

\*Skin test concentration dilutions have not been validated and the possibility that the positive test is due to irritant effect cannot be ruled out. These dilutions are based on Hong et al.<sup>25</sup>

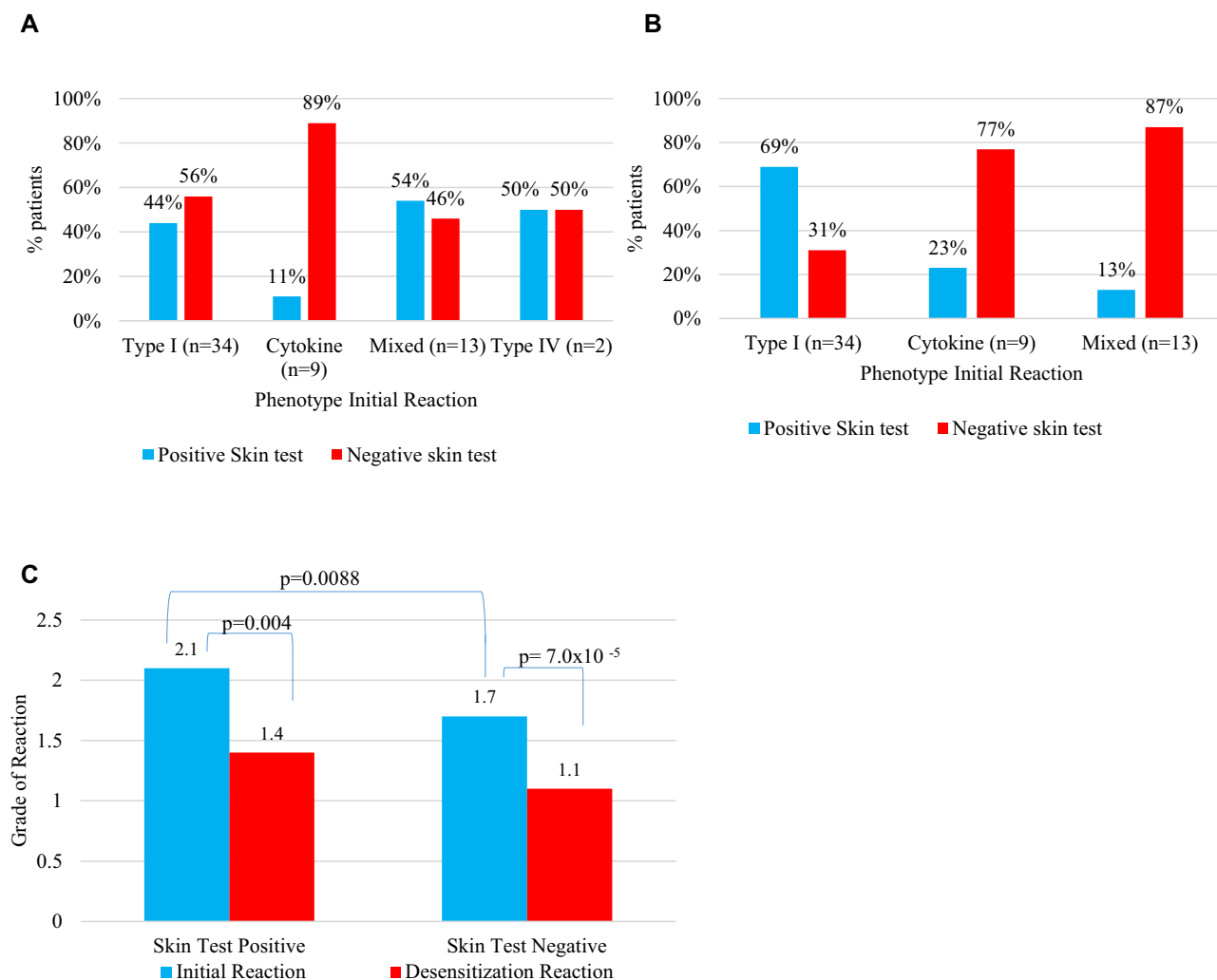


**FIG 3.** Phenotypes and severity of HSRs with skin testing. **A**, Initial phenotype with percentage of skin test results. **B**, Desensitization phenotype with percentage of skin test results. **C**, Grade of reaction during initial and desensitization reactions based on skin testing.

**TABLE VI.** Biomarkers during desensitization

| Patient | Drug         | Tryptase (ng/mL)<br>Levels > 11.5 ng/mL or > 1.2 times<br>baseline + 2 ng/mL are considered<br>elevated |                    | IL-6 (pg/mL)<br>Normal value < 17.4 pg/mL |                    | Symptoms                                               |
|---------|--------------|---------------------------------------------------------------------------------------------------------|--------------------|-------------------------------------------|--------------------|--------------------------------------------------------|
|         |              | Baseline                                                                                                | During DS reaction | Baseline                                  | During DS reaction |                                                        |
| 1       | Rituximab    | 14.3                                                                                                    | 23.6               | N/A                                       | N/A                | Nausea, vomiting, chills,<br>dry heaves                |
| 2       | Rituximab    | N/A                                                                                                     | 21.4<br>4.8        | N/A                                       | 26.2               | Throat and chest<br>tightness, chills, back<br>pain    |
| 3       | Rituximab    | N/A                                                                                                     | 4.1                | 21.4                                      | 947.5              | Itchy throat, rigors,<br>hypertension,<br>tachycardia  |
|         |              |                                                                                                         | 3.9                |                                           | 92.8               | Rigors, chills, fever,<br>tachycardia,<br>hypertension |
| 4       | Rituximab    | 9.7                                                                                                     | 8.4                | N/A                                       | 165                | Fever, chills                                          |
| 5       | Rituximab    | 6.1                                                                                                     | 10.2               | <2.9                                      | <3000              | Rigors, chills, nausea,<br>fever                       |
| 6       | Brentuximab  |                                                                                                         | 4.2 3.1            | 5.2                                       | 94.6*              | Delayed fever                                          |
| 7       | Obinutuzumab | 9.1                                                                                                     | 7.9                | 8.8                                       | 4053               | Rigors, fever                                          |
| 8       | Obinutuzumab |                                                                                                         | N/A 7.1            | N/A                                       | 938.3              | Chills, back pain, chest<br>pain, rigors, fever        |
| 9       | Tozilizumab  | 4.1                                                                                                     | 5.6                | <4.1                                      | 103.2              | Rigors, fever, nausea,<br>tachycardia                  |

Biomarkers, including tryptase and IL-6, for patients drawn at baseline, during reaction, compared with the symptoms, specific mAb. No data on initial reaction biomarkers was available.

DS, Desensitization; N/A, not available.

\*The patient presented fever 12 hours after the DS was completed and the IL-6 was drawn 24 hours.

(Table VI). IL-6 is an important biomarker for identifying and managing cytokine-release reactions.

Other biomarkers, such as skin tests, have not been standardized for mAbs HSRs, but they have been shown to be useful in risk stratification in chemotherapy algorithms.<sup>4</sup> We provided skin testing in 58 patients (56%), the remaining 46 were deferred due to the high cost of mAbs (Table V). Negative skin test results occurred in 5 mAbs, and 4 of these patients had phenotypes consistent with mixed, cytokine-release, and type IV reactions, indicating that the negative skin test reflected the underlying endotype. The other patient had a mild type I reaction to tocilizumab. Type IV reactions may predispose the development of IgE-mediated type I reactions; therefore desensitization was recommended for patients with delayed reactions and positive skin testing results. The utility of skin testing for mAbs still needs to be validated given the few patients tested. Even though a small number of initial type I reactions (44%) was linked to a positive skin test (Fig 3, A), during desensitization, a higher percentage of type I phenotypes (69%) was likely to occur in patients with positive skin test (Fig 3, B). These findings suggest that skin testing may be valuable in predicting the phenotype for breakthrough reactions. There was a significant increase in the initial grade of reaction for patients with positive skin testing ( $P = .0088$ ) and, though not statistically significant, the grade of reaction during desensitization was lower for patients with negative skin testing (Fig 3, C). This confirms the relevance and importance of skin testing for mAbs and is described in the mAb algorithm (Fig 5).

Demographically, our patients had higher rates of atopy than did the general population (37% vs 25%) and significantly higher rates of adverse drug reactions (27% vs <1%), but rates were lower in our patients compared with patients with chemotherapy HSRs (47% for atopy and 50% for adverse drug reactions) (Table III).<sup>20,30</sup>

The grade of reaction decreased significantly with increased lifetime exposures to mAb (more exposures to mAb at time of initial reaction). A high reaction grade and frequency of reaction occurred most often during first and second lifetime exposures and later decreases in reaction grade and severity with greater exposure to mAb at initial reaction.

Reactions occurring during desensitization were significantly less severe than were the initial HSRs, notably on the first desensitization there were no severe grade III symptoms such as hypotension, syncope, and/or oxygen desaturation (Fig 2 and see Fig E2 in this article's Online Repository at [www.jacionline.org](http://www.jacionline.org)). HSRs during desensitization occurred in only 23% of patients with the majority having mild (grade I) reactions. As previously reported, most reactions occur at the final step of desensitization,<sup>9,30</sup> and we show that reactions during the first bag of the protocol were rare. This may indicate that the first bag is not necessary for mAbs desensitization. Although, as it has been shown in *in vitro* models, early desensitization steps are necessary to prevent reactions to larger doses encountered in later steps of desensitization.<sup>31-33</sup> Further evidence is required before the role of the first bag is established.

Patients who were given prophylactic fluids (normal saline) had less severe reactions (1 vs 1.4), and patients who received

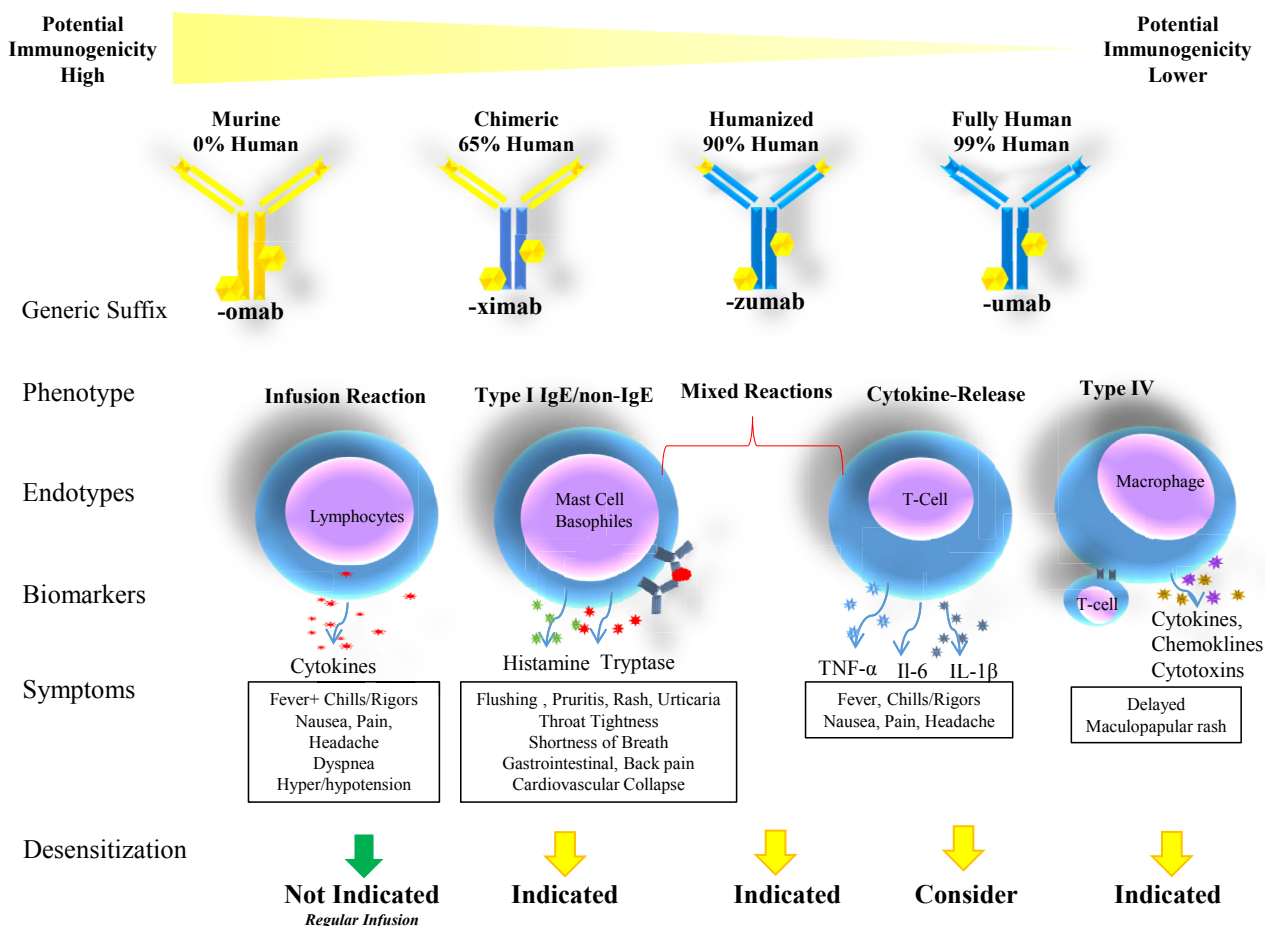
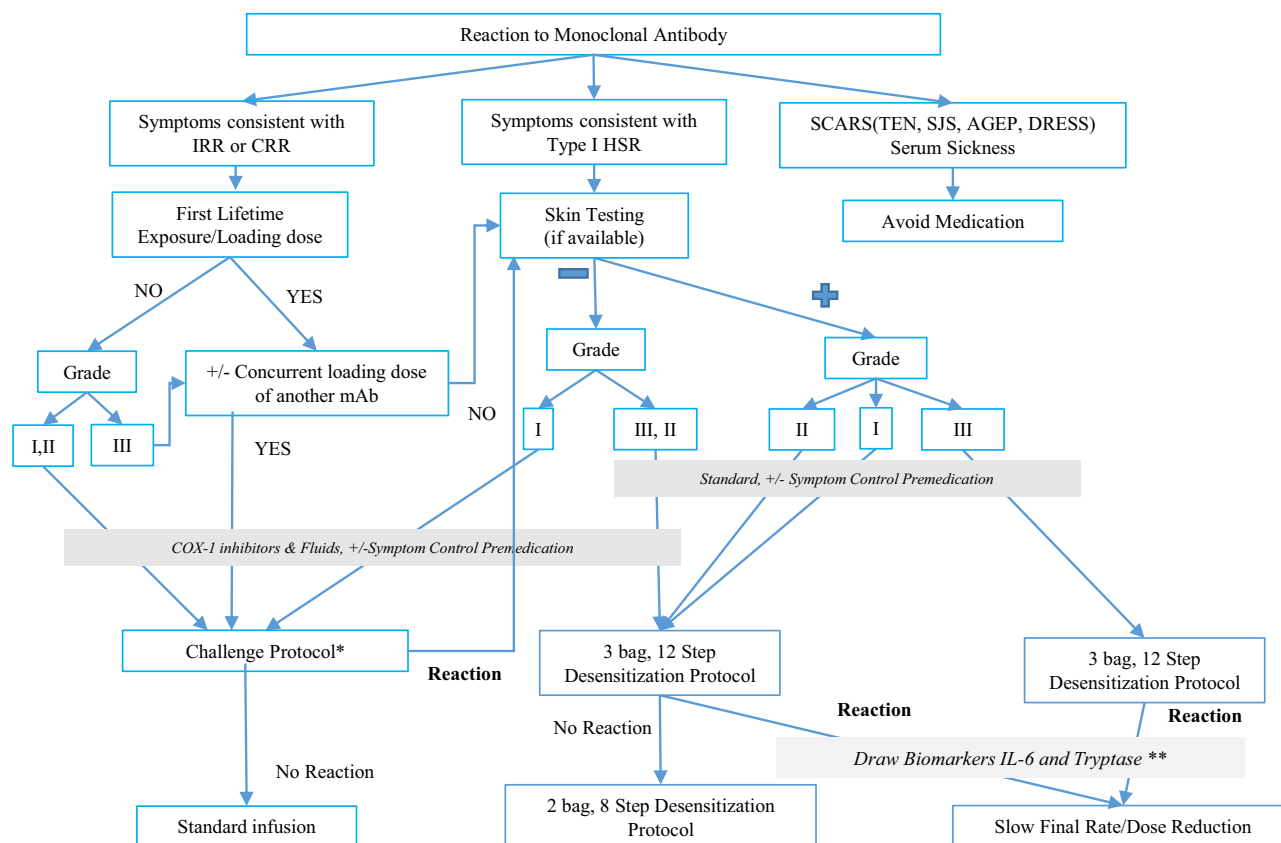


**FIG 4.** Proposed new classification and new management recommendations for precision medicine for HSR to mAbs. Diagram outlining the immunogenicity of mAbs, the proposed underlying mechanisms, endotypes, and biomarkers of mAb HSRs and indications for desensitization.

fluids after breakthrough reactions had a decrease in reaction severity. The proposed mechanism underlying the effectiveness of fluids is the dilution of both antigens and mast-cell mediators, decreasing their concentration and allowing for the rapid clearance of immunogenic substances. For patients with cytokine-release reactions, 100 cc/hour is recommended throughout the first 11 steps with an increase to 250 cc/hour after step 12 (for a 3 bag–12 step protocol when the drug is at peak concentration and rate). During a reaction, the rate of fluid can be increased to 500 cc/hour until symptoms resolve. These recommendations are outlined in an algorithm that is provided to facilitate risk stratification based on phenotypes, clinical presentation, and biomarkers (Fig 5).<sup>20</sup>

Based on prior data that showed long-term tolerization after multiple desensitizations, dose reduction was used to tolerize patients to their target dose when initial desensitizations were not successful.<sup>9</sup> Dose reduction and subsequent dose escalation over multiple desensitizations (ie, 50% to 75% to 100%) had a tolerizing effect in 3 of 6 patients. These long-term tolerizing mechanisms are not well understood and need clarification. These mechanisms also do not create a true desensitized state and reexposure to the offending biological is not recommended without desensitization. As seen in previous reports, repetitive desensitization conferred a decreased risk of reaction during the procedure with a plateau after 20 desensitizations.<sup>9</sup>

Limitations of this study include the retrospective nature that meant only associations could be made in regard to biomarkers (including skin testing) and medication used during desensitization (such as IV fluids). Because our patients came from many different disease groups, collection of biomarkers at initial HSR was extremely limited. Further evaluation of biomarkers at baseline, during initial reaction, desensitization, and postdesensitization are needed to provide clinically relevant tools that correlate with the clinical phenotype. In addition to IL-6 and tryptase, other biomarkers should be investigated to strengthen the understanding the underlying endotypes of types II, III, IV, and cytokine-release reactions. A limitation for the skin test procedures is that they have not been validated. The skin test reagents are expensive and not accessible in most cases. Special skin testing solutions containing all the component epitopes in high concentration may be necessary to create an effective diagnostic tool. In addition, confirming nonirritating concentrations (including controls), predictive values (positive or negative), and economic landscape/reimbursement concerns are important considerations for mAb skin testing. Justification of mAb skin testing depends in part on the ability to leverage the substantial costs associated with these medications to the potential prognostic utility in risk stratification and management of these patients. Given that a small amount of



#### Premedication:

Standard (H1/H2 blockers) cetirizine/ famotidine

Symptom Control: montelukast, aspirin, gabapentin

COX-2 Inhibitors: ibuprofen, toradol

Fluids: CRR reactions: 100 cc/hr. until step 12 w/ increase to 250cc/hr. 500cc/hr during reaction.

Slow Final Rate: 60 or 40 cc/hr f

Dose Reduction: 75%, 50% or 25% of target dose.

\*Challenge Protocol: 1 bag 2 step – 1/10<sup>th</sup> total dose over 15 min, wait 15 min if no reaction, 9/10<sup>th</sup> the total dose give based on specific medication hospital policy.

\*\* Tryptase should be drawn at 30 min post reaction

\* Standard Infusion +/- premedication

**FIG 5.** Proposed algorithm for the management of HSRs to mAbs. Severe cutaneous adverse reactions (SCARs): drug eruption with eosinophilia and systemic symptoms (DRESS), acute generalized exanthematous pustulosis (AGEP), Stevens-Johnson syndrome (SJS), or toxic epidermal necrolysis (TEN). \*Challenge/regular infusion given with appropriate premedication. CRR, Cytokine-release reaction; IRR, infusion-related reaction.

mAb is used to prepare skin tests (0.1 mL of full strength solution), perhaps the availability of small aliquots or biosimilars can be an option in the future. Specific IgE and basophil activation tests should also be paired with skin testing to create a triumvirate diagnostic test that provides clear identification of the HSR phenotype.<sup>12,34-36</sup>

## Conclusion

A new proposed classification for HSRs to biologicals is provided based on the presentation and includes 4 phenotypes: type I, cytokine-release, mixed, and type IV reactions. The predominant initial HSR phenotype changes from predominantly type I to cytokine-release during desensitization. Desensitizations to

526 IV and subcutaneous biologicals, 523 (99.4%) were successfully completed. IV fluids and dose reduction are useful strategies in cases of difficult desensitizations. Our results show efficacy and safety of desensitization to mAbs. Correlation of HSR phenotypes with endotypes (IgE, non-IgE) as well as biological markers such as skin test, tryptase, and IL-6 and will help direct the management of HSRs to mAbs. Precision and personalized medicine should be applied to patients with HSR to biologicals.

**Clinical implications: This article provides novel evidence-based phenotypes and endotypes of HSRs to 16 mAbs and provides tools for diagnosis and management to improve personalized and precision medicine for HSRs to mAbs.**

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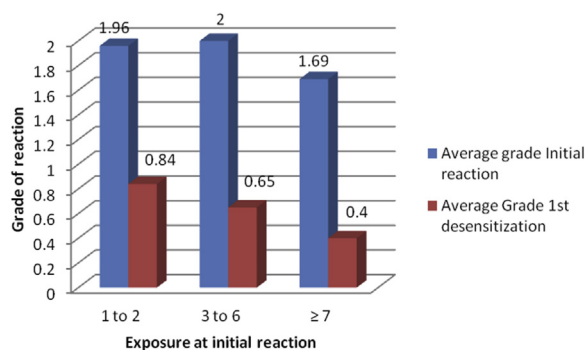


**FIG E1.** Severity of reaction based on exposures to mAbs. *Blue bars* represent the average grade of initial reaction based on previous exposure to mAbs (1-2, 3-6, 7 and greater). *Red* represents grade of reaction on first desensitization based on the same exposure.

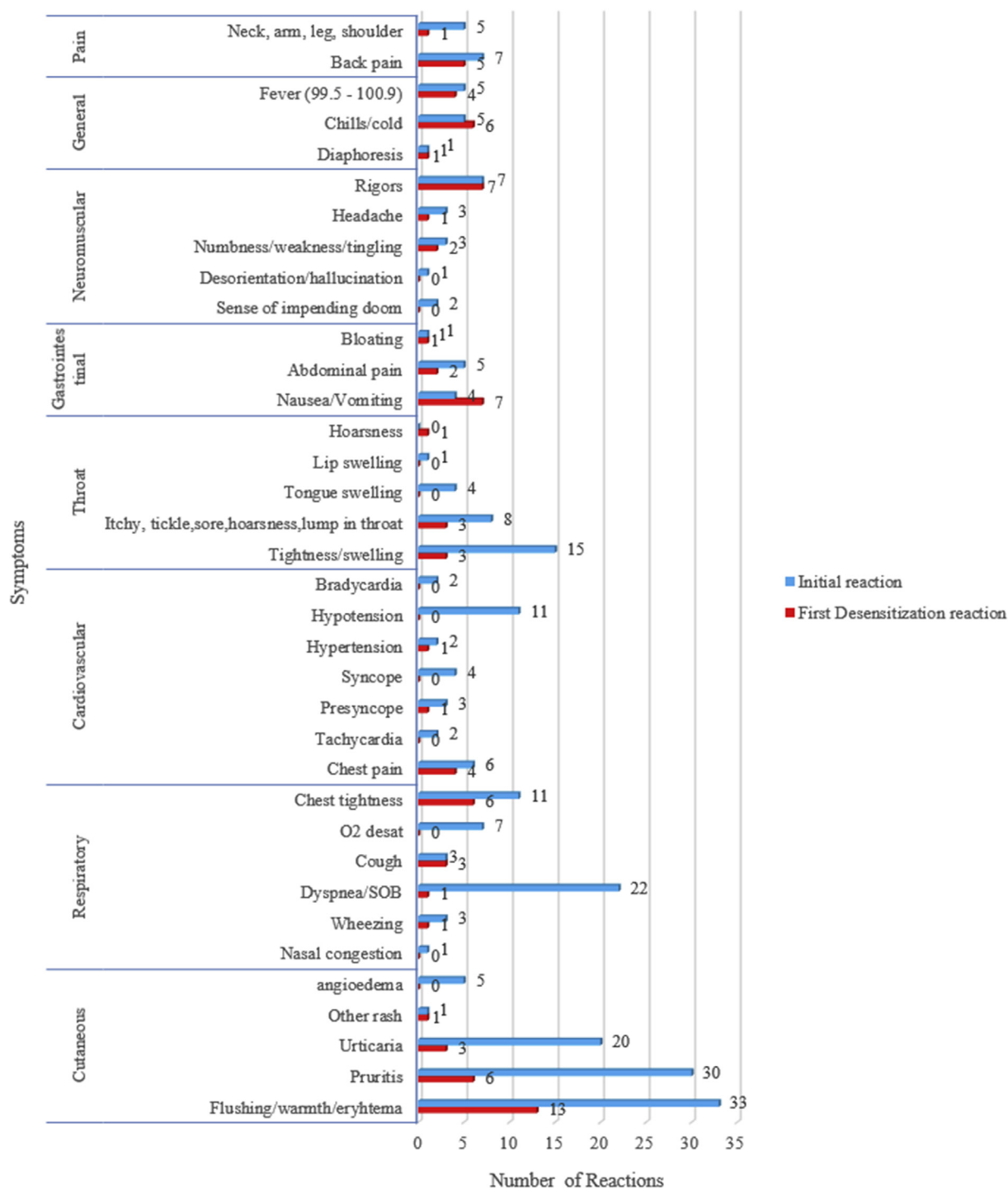


**FIG E2.** Symptoms of initial reaction versus first desensitization. Percentage of patients who reacted with specific symptoms categorized by organ system. The initial reaction included all patients (n = 104) and the desensitization reactions included all patients who had a breakthrough reaction during first desensitization.