A Retrospective Review of the Frequency and Nature of Acute Hypersensitivity Reactions at a Medium-Sized Infusion Center: Comparison to Reported Values and Inconsistencies Found in Literature

Patricia A. DeMoor¹, Yuri Matusov², Colleen Kelly³, Shobha Kolan⁴, Linda Barnachea⁴, Lyudmila A. Bazhenova⁵

1. Infusion Center, University of California, San Diego Moores Comprehensive Cancer Center
2. Department of Clinical Investigations, University of California, San Diego Moores Comprehensive Cancer Center
3. Department of Biostatistics, University of California, San Diego Moores Comprehensive Cancer Center
4. Department of Pharmacy, University of California, San Diego Moores Comprehensive Cancer Center
5. Department of Medicine, Division of Hematology and Oncology, University of California, San Diego School of Medicine and Medical Center

* These authors contributed equally to this work.

Corresponding author: Yuri Matusov, Clinical Trials Office, University of California, San Diego Moores Cancer Center, 3855 Health Sciences Drive, MC 0698, La Jolla, California 92093-0698. Tel: (858) 246-0357; Fax: (858) 822-5380; Email: matusov@ucsd.edu

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Abstract

Purpose: To evaluate acute hypersensitivity reactions at the UCSD Moores Cancer Center in San Diego, compare our findings to those reported previously in the literature, and examine the effectiveness of the objective grading scale as represented by the Common Terminology Criteria for Adverse Events (CTCAE).

Patients and Methods: Using the available pharmacy and electronic medical record data from 2006-2010, we examined our reported hypersensitivity reactions (HSRs) using the CTCAE v.3.0 and v.4.0. A thorough literature review was also performed to compare our findings with those previously reported.

Results: We found 222 cases of HSRs, of which 50% were due to immunotherapeutics. Most were grade 1 or 2 by any CTCAE criteria. The clinical presentation of HSRs varied between drug classes. Using different versions of grading schema led to inconsistencies in ~50% of all HSRs. Fifty-two percent of all cases not due to blood products were rechallenged on the same day. The reported literature HSR frequencies for each causative agent showed a striking variability, possibly indicating that previous studies used a wide variety of grading and reporting systems for adverse events.

Conclusion: HSRs are common in clinical practice, and most are mild or moderate. There are inconsistencies in reporting HSRs between studies. The existence of several grading schema and subjective definitions of hypersensitivity could be contributing to poor clinical generalizability. Along with an improved system of reporting HSRs to minimize underreporting, a standard system of objectively assessing HSRs is necessary for purposes of research and clinical practice.

Key words: hypersensitivity reactions, immunotherapeutics, literature review
Introduction

Acute hypersensitivity reactions (HSRs) are a known source of great stress to patients, their families, nurses, other patients, and physicians. In past assessments, 52% of a nursing staff has reported that infusion reactions are draining and frightening to them, and 42% of nurses feel that physicians do not adequately inform patients about the risk associated with an intravenous infusion. Around 88% of outpatient and 62% of inpatient nurses consider infusion reactions frightening to other patients, with the potential to cause anxiety and confusion. Since the opening of the Rebecca and John Moores UCSD Cancer Center (MCC) in San Diego, California in 1978, it was anecdotally believed that no patient had ever experienced a respiratory arrest-level HSR in the Infusion Center until May 2007, which prompted our clinical team to elucidate our adverse event profile, compare it to reports published previously, and review our practices regarding intravenous infusion of drugs with increased risk of hypersensitivity. The development of a variety of assessment tools, of novel therapies, and of evolving premedication schema in the past decade has made standardization of assessment challenging; this has resulted in substantial misrepresentation of HSR incidence and severity, both to patients and providers. To improve care for patients receiving these therapies, and to improve the safety and efficacy of outpatient administration for these therapies, we felt it necessary to evaluate the HSR environment; specifically, what should be addressed is the true frequency and incidence in the modern setting, the factors which providers take into account when assessing and treating HSRs, and the scientific soundness of certain treatment methods. Given the amount and variety of therapies administered at our center, it was felt to be an appropriate environment for such an initial evaluation.

Materials and Methods

The retrospective review was approved by the University of California, San Diego Institutional Review Board. HSRs taking place from June 2006 until January 2010 in the MCC were reported by clinical staff as part of the Infusion Center Standard Operating Procedure using the electronic Quality Variance Reporting (eQVR, Incident Reporting 2.0, University of California) system, a web-based event tracking system for collecting and analyzing data regarding patient care service quality. During this time the MCC administered over 30,850 infusions to about 4,000 patients. All HSRs reported by eQVR were reviewed twice, independently, by PAD and YM. Baseline data, including patient demographics, history of known allergies, premedications administered (and the adherence to this institution’s existing standard premedication protocols), agent suspected of causing the HSR, signs and symptoms, reaction management, and the decision to same-day rechallenge were collected, using the PCIS (Siemens Invision Clinicals, Siemens Medical Solutions, Malvern, PA) and Hyperspace Clinical EMR (Epic Systems, Verona, WI) electronic medical record system. Since the eQVR links each HSR to a unique medical record number, the team verified that there were no duplicate HSR reports. Each HSR was graded retrospectively (not at time of event) using three separate grading systems – the Common Terminology Criteria for Adverse Events (CTCAE) version 3.0 Allergic Reaction/Hypersensitivity (AR), CTCAE v.3.0 Cytokine-Release Syndrome/Acute Infusion Reaction (CRS), and CTCAE v.4.0 Infusion-Related Reaction. Reaction attribution to an agent was ascertained from practitioners’ notes of the event in question. ADRs were analyzed for various characteristics using Microsoft Excel 2003 (Microsoft, Redmond, Washington). Total drug administration at the MCC was determined by utilizing three pharmacy drug database systems (PCIS, Siemens, Epic) used during the time period. A thorough literature review of package inserts, prospective and retrospective studies, and anecdotal case reports (dating from the time of the registrational clinical trials for each agent until 2010) was then performed in the interest of determining HSR frequency and incidence at other locations. This was done during 2010 by performing searches of the combinations of the terms “adverse effect,” “hypersensitivity,” “adverse reaction,” “adverse drug reaction” with the names of therapeutic agents in PubMed and MedLine, with 280 reports found. The selected 100 unique reports were in English with a primary focus on acute adverse effects of chemotherapeutic and biotherapeutic agent or experiences with acute hypersensitivity events in oncology outpatient settings. These reports were analyzed for the method of HSR assessment, HSR frequency and incidence, changes in administration practice, differences in perceived and actual HSR risk on the part of patients and providers, pharmacological HSR mechanisms, and, where applicable, impact on the institution.

Statistical Analysis

Cohen's weighted kappa was calculated to assess the consistency between CTCAE v.3.0 AR and CTCAE v.3.0 CRS, where large discrepancies between
HSR grades are weighted more heavily than similar grades. The weighted kappa statistic was assessed using the Landis and Koch scale (1977), which translates the numerical score into categories of poor, slight, fair, moderate, substantial, or almost perfect. The average HSR grades were compared between subjects rechallenged and those that were not, overall and by drug category, using the Mantel-Haenszel chi-square test of a linear association.

Results

We found a total of 222 documented HSRs in our Infusion Center from June 2006 until January 2010. The median age of female and male patients was 47 and 69 years old, respectively; 59% of patients evaluated were women (Table 1). Patients were evaluated for average exposure to the causative agent at the time of the reaction, defined as the number of previous times that a patient received the therapy plus the one causing the HSR. Of medications, platinums were most likely to cause an HSR with extensive exposure. In 12 cases, HSRs took place on secondary exposure to a medication (i.e., re-treatment with the agent following disease recurrence for patients who had been treated with it after the initial diagnosis). For those, the average exposure to the agent was as follows: platinums, 2.3; immunotherapy, 1; iron products, 1.

Approximately 60% of patients had no known allergies and 18% were known to have a single allergen. There was no correlation between the number of known allergens and the likelihood of having a reaction to a particular agent or drug class.

Frequency and incidence of reactions

The total number of reactions by therapeutic agent, administrations of the HSR-causing agent, patients receiving the agent during the specified time period, rate of HSRs per administration (‘administration frequency’) and per patient (‘incidence’), and values found in the literature are summarized in Table 2. When compared to individual agents, rituxumab caused the majority of HSRs (27%), followed by paclitaxel (10%). It should be noted that all iron agents (responsible for 5.9% of all HSRs) were classified together; because of the low HSR incidence to iron agents, they were not separated into low- and high-molecular weight preparations.

Table 1. Patient demographics and prior allergy history.

|                         | Average age | % (n)          |
|-------------------------|-------------|----------------|
| Female                  | 54.75 years (SD 15.37) | 59 (131)      |
| Male                    | 41 (91)     |                |

| Average exposure causing HSR: | % (n)          |
|------------------------------|----------------|
| Taxanes                      |                |
| NKDA                         | 46.2 (12)      |
| 1 allergy                    | 11.3 (3)       |
| 2 allergies                  | 15.4 (4)       |
| 3+ allergies                 | 26.9 (7)       |
| Platinum                     |                |
| NKDA                         | 56 (14)        |
| 1 allergy                    | 28 (7)         |
| 2 allergies                  | 12 (3)         |
| 3+ allergies                 | 4 (1)          |
| Immunotherapy                |                |
| NKDA                         | 68.2 (75)      |
| 1 allergy                    | 17.3 (19)      |
| 2 allergies                  | 5.5 (6)        |
| 3+ allergies                 | 9.1 (10)       |
| Blood products               |                |
| NKDA                         | 54.5 (18)      |
| 1 allergy                    | 18.2 (6)       |
| 2 allergies                  | 12.1 (4)       |
| 3+ allergies                 | 15.2 (5)       |
| Iron Products                |                |
| NKDA                         | 38.5 (5)       |
| 1 allergy                    | 30.8 (4)       |
| 2 allergies                  | 0 (0)          |
| 3+ allergies                 | 30.8 (4)       |
| Other                        |                |
| NKDA                         | 60 (9)         |
| 1 allergy                    | 6.7 (1)        |
| 2 allergies                  | 0 (0)          |
| 3+ allergies                 | 6.7 (1)        |

Non Known Drug Allergies total | 39.9 (133) |
1 allergy total                | 18 (40)    |
2 allergies total              | 9.5 (21)   |
3+ allergies total             | 12.7 (28)  

*Exposure* is defined as the average number of previous times that a patient received the therapy, plus one causing the HSR. Includes only the main classes of drugs causing HSR (as indicated). *Some patients in these classes had an HSR on secondary exposure to the drug (i.e., following recurrence).
### Table 2. Total HSRs with drugs suspected of their causality, June 2006-January 2010.

| Agent Suspected of Causality | Total Administrations of Agent | Total Patients Receiving Agent | HSR (n) | % of HSRs per Administration (Frequency) | % of HSRs per Patient (Incidence) | % Incidence Reported | % Incidence of “severe” reactions reported |
|-----------------------------|--------------------------------|--------------------------------|---------|------------------------------------------|-----------------------------------|---------------------|-------------------------------------------|
| Rituxumab                   | 3213                           | 600                            | 60      | 1.9                                      | 10                               | 50-87<sup>6,8</sup> | 3-10<sup>6,8</sup>                  |
| Paclitaxel                  | 2927                           | 520                            | 23      | 0.8                                      | 4.4                              | 0.7<sup>1,3,6,12</sup> | 1.3<sup>1,3,11-18</sup>              |
| Platelets                   | Not Available                   | Not Available                   | 19      | N/A                                      | N/A                              | Not Available        | Not Available                           |
| Carboplatin                 | 1395                           | 345                            | 16      | 1.1                                      | 1.6                              | 0.8<sup>1,3,4,19-28</sup> | 2<sup>2,9,13,24,25</sup>            |
| Alemtuzumab                 | 689                            | 35                             | 15      | 2.2                                      | 42.9                             | 26-96<sup>2,9</sup>      | 9-16<sup>2,9</sup>                  |
| Infliximab                  | 1361                           | 210                            | 13      | 1                                        | 6.2                              | 9.7<sup>1,3,10,21</sup>   | <1-4<sup>3,20,21</sup>              |
| Packed red blood cells      | Not Available                   | Not Available                   | 13      | N/A                                      | N/A                              | Not Available        | Not Available                           |
| Iron products (all)         | 673                            | 152                            | 13      | 1.9                                      | 8.6                              | Not Compared         | Not Compared                           |
| Intravenous immunoglobulin  | 3717                           | 363                            | 12      | 0.3                                      | 3.3                              | 0.8-6<sup>2,3,13</sup> | <0.007<sup>3,34</sup>               |
| Oxaliplatin                 | 66                             | 142                            | 7       | 10.6                                     | 4.9                              | 0.7<sup>2,3,17,28,36,43</sup> | 0.5-3<sup>3,20,38,37,39,44</sup> |
| Doxorubicin liposomal       | 1331                           | 202                            | 4       | 0.3                                      | 2                                | 1.74<sup>3,4,5,7</sup>   | 0.5<sup>3,4,5,7</sup>               |
| Docetaxel                   | 825                            | 215                            | 3       | 0.4                                      | 1.4                              | 0.8-25<sup>1,3,17,20,35</sup> | 1<sup>1,3,17,20</sup>              |
| Vancomycin                  | 207                            | 62                             | 3       | 1.4                                      | 4.8                              | Not Examined         | Not Examined                           |
| Bevacizumab                 | 2074                           | 272                            | 2       | 0.1                                      | 0.7                              | Not Examined         | Not Examined                           |
| Trastuzumab                 | 2723                           | 267                            | 2       | 0.1                                      | 0.7                              | 4<sup>1,3,10,21</sup>   | Not Available                           |
| Investigational antibody    | Not Available                   | Not Available                   | 2       | N/A                                      | N/A                              | Not Available        | Not Available                           |
| Ofatumumab                  | 41                             | 7                              | 2       | 4.9                                      | 28.6                             | 38-64<sup>5,57</sup>   | 1-7<sup>5,57</sup>                  |
| Cisplatin                   | 1925                           | 451                            | 1       | 0.1                                      | 0.2                              | 0<sup>2,3,8,12,15,58-76</sup> | 1.7-5<sup>8,71</sup>              |
| Cetuximab                   | 790                            | 99                             | 1       | 0.1                                      | 1                                | 10.9<sup>7,57</sup>     | 3-8<sup>9,7,57</sup>                |
| Gemtuzumab                  | 7                              | 5                              | 1       | 14.3                                     | 20                               | 20-82<sup>1,10,43</sup> | 4-11<sup>1,10,43</sup>             |
| Autologous stem cells       | Not Available                   | Not Available                   | 1       | N/A                                      | N/A                              | Not Available        | Not Available                           |
| Pemetrexed                  | 636                            | 170                            | 1       | 0.2                                      | 0.6                              | 2<sup>3,8,12,15,58-76</sup> | 0<sup>1,4,8</sup>                 |
| Epothilone                  | 61                             | 22                             | 1       | 1.6                                      | 4.5                              | Not Examined         | Not Examined                           |
| Amphotericin                | 268                            | 24                             | 1       | 0.4                                      | 4.2                              | Not Examined         | Not Examined                           |
| Lidocaine                   | Not Available                   | Not Available                   | 1       | N/A                                      | N/A                              | Not Available        | Not Available                           |
| Etoposide                   | 1409                           | 142                            | 1       | 0.1                                      | 0.7                              | Not Examined         | Not Examined                           |
| Prochlorperazine            | Not Available                   | Not Available                   | 1       | N/A                                      | N/A                              | Not Available        | Not Available                           |
| Gemcitabine                 | 3249                           | 446                            | 1       | 0.03                                     | 0.2                              | Not Examined         | Not Examined                           |
| Interferon                  | 105                            | 4                              | 1       | 1                                         | 25                               | Not Examined         | Not Examined                           |
| Irinotecan                  | Not Available                   | Not available                  | 1       | N/A                                      | N/A                              | Not Available        | Not Available                           |

Summary of total HSR-causative agent administrations and total patients receiving the drug, with HSR totals, HSR frequency and incidence, and incidence as found in literature. Experimental drugs are unnamed if there is no published data as of yet and are certain to be causative. There was no data on total administrations for blood products and certain common premedications which were thought to be causative of HSR. Only the most common agents were evaluated in the literature review.
Total administration of certain agents could not be ascertained, either because they were too frequently used (as with reactions to premedications), experimental with yet-unpublished data, or otherwise unavailable to the study team (as with blood products). Values reported in the literature are noted in terms of general HSR incidence and incidence of severe HSR. Only the most common agents were evaluated in this literature review.

The most commonly-administered drug at our center, of available data, was intravenous immunoglobulin (given 3,717 times), followed by gemcitabine (given 3,249 times) and rituxumab (given 3,213 times). However, rituxumab was given to the greatest number of patients (n=600), followed by paclitaxel (n=520) and cisplatin (n=451).

Figure 1 outlines the breakdown of causative agents into specific drug classes. Immunotherapeutics, as a class, accounted for half of the HSRs, with rituxumab accounting for 54% of the cases within the immunotherapeutic class. When blood products, accounting for 33 cases, are excluded, HSRs to immunotherapeutics account for 58% of all HSRs, taxanes 14%, platinum agents 13%, and iron products 7%. An investigational monoclonal antibody (still in clinical trials, with safety data unpublished) was felt to be responsible for 2 of the HSRs.

**Reaction Severity**

All sign, symptom and rechallenge data reported is provided on a per-HSR case, rather than per-patient, basis. Since only 8 patients experienced more than one HSR, the rates per HSR case should be similar to the rates per patient. The profile of the most commonly reported signs and symptoms per drug class is shown in Figure 2. The distribution of signs and symptoms reported at below 20% was more varied. Patients experiencing HSRs to taxanes reported the following signs or symptoms in more than 50% of cases: thoracic symptoms (chest pain, tightness, and pressure – 61.5%), respiratory symptoms (dyspnea, wheezing, and desaturation – 53.8%), and dermatological symptoms (46.1%). For platinum agents, these were respiratory symptoms (68%) and dermatological symptoms (64%). In regard to immunotherapeutic agents, blood products, and iron products, the most common findings were chills and rigors (46.4%), dermatological symptoms (36.4%), and both dermatological and respiratory symptoms (38.5%), respectively. The treatment methods for HSRs to each drug class were very similar, utilizing mainly diphenhydramine (>60% of all cases), and intravenous hydrocortisone and oxygen (>20% of cases each). There was no deviation from this institution’s standard premedication protocol in the case of any HSR.

HSRs graded with the 3 different criteria of the CTCAE demonstrated an evident difference depending on which criterion of the CTCAE v.3.0 (AR or

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**Figure 1.** HSR-causative agents, as a percentage of the total number of HSRs, separated by drug class, June 2006-January 2010. The upper chart includes blood products. ‘Other treatment’ comprises all agents with a single HSR case. The lower chart is a breakdown of causative agents within the class of immunotherapeutic agents.

There were substantial differences between HSR administration frequency and incidence for several common HSR-causing agents; specifically, rituxumab had a 1.9% administration frequency and a 10% incidence, paclitaxel had a 0.8% administration frequency and a 4.4% incidence, and alemtuzumab had a 2.2% administration frequency and 42.9% incidence at our center.
CRS) was utilized (Figure 3). Using the CTCAE v.3.0 CRS and CTCAE v.4.0 Infusion-Related Reaction schema led to identical grade values. The HSR grades were consistent across all schemas in approximately 50% of cases, though this frequency was slightly lower among taxanes (34.6% consistency) and iron products (30.8% consistency). Overall, Cohen’s weighted kappa was 0.487, a value representing “moderate agreement” by Landis and Koch’s scale. Weighted kappa was lowest for iron products (0.255) and taxanes (0.287), and highest for blood products (0.562).

Figure 4 illustrates both the relative totals of each grade as well as the differences in these totals as a result of different grading systems. The majority of HSRs were moderate-to-severe (CTCAE grade 2-3), with two HSRs resulting in death (one to carboplatin and one to gemtuzumab).

**Rechallenge**

There were 98 (52% of HSRs not due to blood products) attempts to rechallenge patients on the same day following HSR. Nearly all (n=92) were successful. Only 3 HSRs due to blood products were followed by rechallenge, and all were successful. Immunotherapeutics were rechallenged most often (69% of all rechallenged agents), with generally good success (only 5 cases could not be rechallenged successfully). Regardless of the grading method used, the overall HSR grade distribution was significantly lower for those reactions that were rechallenged than for those that were not (p-value<0.05). There was a larger difference in the HSR grade distributions between these groups when the CTCAE AR grading system was used. However, when restricted to immunotherapy reactions, the HSR grades distributions were essentially the same in these groups. Twenty-one cases were rechallenged following reactions that were grade 3-4 by both criteria.

![Figure 2](http://www.jcancer.org)
Figure 3. Breakdown of HSRs, June 2006-January 2010, as graded by CTCAE v3.0

Figure 4. Differences in breakdown of HSRs of a particular grade when using CTCAE v.3. Cytokine Release Syndrome / Acute Infusion Reaction (C.R.S.) and CTCAE v.3 Allergic Reaction / Hypersensitivity (A.R.). There were no grade 1 reactions as per CTCAE v.3 Acute Hypersensitivity / Infusion Reaction.
Discussion

Severe HSRs are reported in ≤ 5% of all chemotherapy infusions, with platinum compounds and taxanes accounting for the greatest risk, but milder HSRs are certainly no rarity in any infusion center\textsuperscript{13}. HSR risk is quoted by physicians when presenting treatment options to their patient and is utilized in appropriate infusion center staffing, so there is no question that the study of HSRs is one which will remain relevant.

Our review of the literature, while covering only major agents, revealed that there are enormous disparities in HSR risk not only between our data and published reports, but also among the reports themselves. There are substantial confounding factors which must be remembered when quoting reaction risk, including inconsistencies in the CTCAE v.3.0, the most commonly-used HSR assessment tool in oncology today\textsuperscript{88}. The terminology currently used to describe an HSR is by no means standard.

The commonplace term ‘allergic reaction’ fell under criticism as scientifically inaccurate as early as 1979\textsuperscript{73}. An allergy – that is, a type I, IgE-mediated immune response – is facilitated by a sensitization period of repeat exposure to the allergen. HSRs to carboplatin and oxaliplatin support this feature; the incidence of HSRs per patient population increases with the number of doses given and in cases of documented occupational exposure to platinum salts. However, a longer platinum-free interval between courses of carboplatin has been correlated to an increased incidence of HSRs\textsuperscript{1,3,19,20,22,28,37,40,49}. The IgE-mediated mechanism is thus not wholly accurate, and has led researchers to question the validity of the reaction as an allergic one, to consider the possibility of a non-immunological histamine release, and to even view the nature of a HSR as idiosyncratic\textsuperscript{19,23}.

Similarly, there is a lack of consensus regarding mechanisms of HSRs to monoclonal antibodies. Frequent initial-exposure reactions to cetuximab, alemtuzumab, and rituxumab counter IgE-mediated hypersensitivity\textsuperscript{5,7,29}; infliximab, however, is known to cause reactions after multiple rounds of therapy\textsuperscript{40,91}.

There is a great deal of conviction, however, that taxane HSRs are non-IgE-mediated. These HSRs are most frequent at first or second exposure, are severe only during these administrations, nearly all patients rechallenged after the first administration are able to tolerate subsequent cycles, and they are dose- and rate-dependent\textsuperscript{12,17,49,92}. Nonetheless, the majority of studies reviewed here used the CTCAE AR grading criteria.

Today’s premedication protocols do not always reflect those environments in which trials were initially conducted. Many early cisplatin trials did not utilize glucocorticoids and antihistamines, as is commonly done today\textsuperscript{9,58,59,61,62,64,68,69,73}, which may account for the decreased incidence in more recent studies. There are, additionally, documented decreases of over 50% in HSR incidence (general and severe) in trials where premedication for docetaxel and paclitaxel was standard\textsuperscript{11,14-16,48,49,51,93-98}. Citation errors remain; as Weiss and colleagues have noted, citation of older publications with a different premedication protocol as references in modern reports has led to significant discrepancies.

In clinical trials, investigators continue to employ a wide variety of grading scales. The CTCAE itself has undergone several revisions (v.4 released May 2009), but as late as 2003, teams have used early versions of the CTCAE for assessing severity of HSRs\textsuperscript{81,82}. The World Health Organization, Eastern Cooperative Oncology Group, and Radiation Therapy Oncology Group sometimes use their own scales for grading allergic reactions. Furthermore, the majority of trials reviewed here used a subjective variety of terms to define a reaction; the definitions of each of these terms, where provided, infrequently corresponded to those in the CTCAE. Some studies graded each sign and symptom of a HSR separately using the CTCAE, rather than as general condition. At least one team has proposed a completely new, 3-grade, system for anaphylaxis whereas another has suggested elimination of the anaphylaxis category altogether\textsuperscript{99-102}.

The CTCAE v.3.0 itself poses another problem. In using AR and CRS scales, the same hypersensitivity reaction can be graded as moderate (grade 2), severe (grade 3), or life-threatening (grade 4); this was evident at our center. Moreover, the CTCAE v.3.0 indicates parenteral rescue medications in grade ≥3 allergic reactions, whereas these are given at the first, mildest, sign of a HSR in most infusion centers\textsuperscript{88}, including ours. Many inconsistencies have been removed in the CTCAE v.4.0, which provides nearly identical gradations of allergic reactions and infusion-related reactions, and features a new category, anaphylaxis, which is consistent with the other relevant categories.

Some reports provide a risk of HSR per number of infusions and others per number of patients, which adds an additional layer of inconsistency. This is not irrelevant; as our data indicates, the difference in reported percentages can be hundredfold (Table 2 subselects for those reports which provided incidence figures in the same manner as do we). Often, the calculation method is not specified in published reports, establishing a potential for misquoting. Our review
showed at least three published articles citing previous research erroneously.

The importance of consistent grading is not trivial; reported differences in percentages can lead to misconceptions about HSRs and their management, misinformation given to patients as they prepare to initiate treatment, and inappropriate staffing in infusion centers. Only with a variety of prospective evaluations of therapies using a standardized grading scheme will we understand the true reaction frequencies, an exact profile, and an evidence-based method for the decision to rechallenge.

While the most obvious use of a standard grading system is in data reporting for clinical research, the grade for a HSR can have bearing on the physician’s clinical judgment. Another past literature review indicated that patients who had a mild-to-moderate (grade 1-2) reaction on first exposure are likely to tolerate rechallenge with a drug; this is contraindicated in patients having a grade 3-4 reaction. However, some reports asserted that mild-to-moderate reactions to monoclonal antibodies only require a decrease of rate, rather than cessation altogether. Immediate re-treatment, particularly on the same day with the same preparation, is especially important for outpatient treatment centers and their patients. If performed properly, it can result in the minimizing of treatment time and costs without adversely affecting patient safety.

This topic should also continue to be explored for educational purposes. At our institution, the full-time staffing of the Infusion Center with dedicated Physician Assistants experienced in the medical management of patients experiencing HSRs has resulted in high rechallenge success rates and comprehensive management of HSRs. However, we found that the likelihood of the decision to rechallenge taxanes (a drug class with an unclear rechallenge indication) increased over time, with no similar trend in average grade of the reaction; coincidentally, the timeline of this study paralleled the initiation of a mid-level practitioner in the Infusion Center. This suggests that the deciding practitioner’s knowledge of HSR management increases with time and is the key factor in making such a decision.

Finally, the study of HSR mechanism remains significant. Although IgE-mediated and non-IgE-mediated reactions can be similar in clinical presentation, they are vastly disparate in mode of development, and this may have bearing on the pharmacological interaction of rescue medication. Whether the mechanism of a reaction is relevant to clinical management remains under debate. Specifically, one report pointed out that treatment of a docetaxel HSR with antihistamines may be detrimental, as doing so inhibits cytochrome P450, which is responsible for docetaxel elimination. Since many sites, including ours, have a standing protocol for HSRs which includes antihistamines, an intravenous steroid, and possibly epinephrine, it is worthwhile to extend research in this area.

In this study, HSR frequency and incidence was based solely on eQVR reporting, and there is a strong suspicion of underreporting or erroneous reporting of HSR frequency by eQVR; thus, there may be an underestimation of true reaction frequency and incidence (particularly among milder HSRs). In addition, this study was a retrospective analysis of a single-center experience at an academic medical center; thus, extrapolation of the findings to other institutions must be done with care. We have implemented a comprehensive, prospective, multi-year study of HSRs at the MCC Infusion Center which bypasses use of the eQVR system; however, continued study of HSRs at other institutions is necessary to validate the conclusions.

**Conclusion**

The findings presented here indicate an inadequacy in the systematic reporting of acute hypersensitivity reactions to non-oral medications. HSR incidence tends to vary widely between reports, and thus the incidence and characteristics at MCC tend to reflect some, while strongly conflicting with others. A variety of CTCAE criteria and interpretations, difference in reporting rates as administration frequency versus incidence, an evolution of premedication, and citation errors all contribute to this issue. Since a multitude of clinical decisions is based upon the conclusions of reported literature, it is necessary to devise or formally adopt a system used universally for reporting HSRs. Finally, modern word processing software should be utilized to minimize referencing errors. The findings must be validated in larger, multi-center settings with special emphasis on preventing underreporting or erroneous reporting.

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**Conflict of Interest**

The authors have declared that no conflict of interest exists.
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