

Controversies in Allergy

Controversies in Allergy: Chemotherapy Reactions, Desensitize, or Delabel?

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DESENSITIZATION WITH RISK STRATIFICATION IS A SAFE AND EFFECTIVE METHOD TO ADDRESS CHEMOTHERAPY HYPERSENSITIVITY" (DRS HONG, BANERJI, AND CASTELLS)

Background

Drug desensitization is the gradual introduction of increasing amounts of a drug over hours to days, leading to temporary tolerance of that drug. Drug desensitization is an extremely useful procedure that enables patients to safely receive a drug to which they previously had an allergic reaction. This is especially important when the offending drug is the treatment of choice or the alternative drugs have a higher chance of treatment failure and/or unacceptable adverse effects. Examples include the treatment of syphilis in pregnant patients with a history of a penicillin allergy or patients with cancer with an allergic reaction to the first-line chemotherapeutic agent. Although various desensitization protocols are described in the literature, the methodology of desensitization is based on *in vitro* mast cell models. These models show that doubling doses of antigen, delivered with at least 10-minute intervals and starting at 1/1000 the target dose, elicit inhibitory mechanisms that prevent mast cell activation and block the release of inflammatory mediators.¹

Drug desensitization is safe and effective

Desensitization was first used in the mid-20th century as a safe and effective method of reintroducing penicillin in patients with type I hypersensitivity to the drug.^{2,3} Extending this technique to other antibiotic families, such as carbapenems, cephalosporins, and quinolones, was similarly safe and effective.⁴⁻⁶ In the late-1990s and early aughts, desensitization was successfully used for chemotherapy drugs such as carboplatin and paclitaxel in patients with ovarian cancer for whom these drugs represented first-line therapy.⁷⁻⁹ In 2008, a large case series of 413 patients showed that 94% of chemotherapy desensitizations were either reaction-free or associated with very mild cutaneous breakthrough reactions requiring minimal intervention such as an additional dose of antihistamine using a standardized 3-bag, 12-step desensitization protocol (see Figure E1 in this article's Online Repository at www.jaci-inpractice.org).¹⁰ Similar drug desensitization success rates are described with other chemotherapeutic agents and biologics. Brennan et al¹¹ described outcomes of 105 desensitizations to biologics in 23 patients using the same 3-bag, 12-step protocol. Breakthrough reactions occurred in 29% of desensitizations, but most of these reactions during drug desensitization were milder than the initial presenting reaction.¹¹ A more recent article by Sloane et al¹² looked at 2177 desensitizations across 370 patients from 2007 to 2010 including both traditional chemotherapy drugs (ie, carboplatin and paclitaxel) and biologics (ie, rituximab, infliximab, and trastuzumab). Nearly 100% of drug desensitizations were completed, and 93% had either no breakthrough reactions or very mild cutaneous symptoms that at most required additional antihistamine treatment. The same study also suggested that patients with ovarian cancer treated with desensitizations showed no trade-off whatsoever in terms of life expectancy as compared with nondesensitized controls.

Drug desensitization requires experience and training

Maintaining a high level of safety and efficacy with drug desensitization requires careful evaluation and good judgment by the allergy specialist when evaluating a potential desensitization candidate. The most important first step is taking a careful history and physical examination and reviewing the details of the reaction. The elements of the history to consider are history of previous exposure to drug of concern, the timing of symptom onset, the symptoms and severity of reaction, and interventions

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*Abbreviations used**RCUH- Ramon y Cajal University Hospital*

the patient did or did not respond to (ie, stopping the infusion, rescue medications, fluids, and epinephrine). If tryptase is obtained during the reaction and is elevated, systemic mast cell activation can be implicated with or without an IgE-related mechanism. This would also be an indication for empiric desensitization. Desensitizations are contraindicated for Stevens-Johnson syndrome, severe exfoliative dermatitis, acute generalized exanthematous pustulosis, and drug reaction with eosinophilia and systemic symptoms syndrome because the mechanisms of these reactions are not fully understood and cannot be modified by desensitization. Certain agents can also cause non-IgE-mediated reactions due to the presence of certain solvents. Taxol, for example, contains polyethoxylated castor oil, aka Cremaphor, which can directly activate mast cells.¹³ Polysorbate 80, a stabilizing agent found in taxotere and a number of biologics, has been found to cause direct mast cell activation, possibly via peroxide formation as a degradation product.¹⁴ Although some of these non-IgE-mediated reactions are amenable to desensitization, the mechanism is less clear.¹⁵ Finally, the newly discovered MRGPRX2 receptor on mast cells, which has been shown to mediate reactions to quinolones and neuromuscular-blocking drugs, highlights the need for continuing research to understand the basic mechanisms of non-IgE-mediated anaphylaxis.¹⁶

Each desensitization requires that the patient and the allergist review the potential risks and benefits including the risk of reaction recurrence and even death. These risks are balanced out however by the likelihood that any recurrent reactions are much less likely to be as severe as the initial reaction due to the highly controlled manner in which drugs are administered in the course of a desensitization, the high degree of monitoring during the infusion, and the immediate availability of intervention medications. The only known report of a desensitization-associated death that we are aware of involved a 47-year-old woman with known diabetes, end-stage renal disease, and newly diagnosed pulmonary hypertension, who died of cardiopulmonary arrest secondary to an anaphylactic reaction during a carboplatin desensitization protocol performed without involvement of an allergy specialist.¹⁷ This tragic occurrence underscores the need for transparency and scrupulous risk stratification when treating patients with significant comorbid conditions.

Role of skin testing and risk stratification

Skin testing and risk stratification are important considerations in the evaluation of patients after a reaction to a chemotherapeutic or biologic agent and before planning desensitization. Risk stratification protocols for different drugs can provide guidance on management of the patient, reduce costs by reducing unnecessary desensitizations, and maintain safety. Skin testing is a very useful diagnostic tool for evaluation and risk stratifying patients who are thought to be candidates for desensitization, but it should be used judiciously and with an understanding of its limitations. Some chemotherapy agents, such as doxorubicin, are irritating to the skin, and skin testing should not be performed. However, for many other agents, published nonirritating concentrations can be used, which reduces the rate of false positives while maintaining

good sensitivity.¹⁸ Skin testing with platinum agents (carboplatin, cisplatin, and oxaliplatin) has been demonstrated to be helpful in confirming the diagnosis of IgE-mediated hypersensitivity.¹⁹⁻²¹ Skin testing for some monoclonals may be prohibitively expensive due to the lack of commercial availability in small aliquots for skin testing, thus necessitating purchase of a full treatment vial for testing. Some of these treatment vials have market prices ranging from US \$1,000 to US \$10,000 per dose.²² It is important to remember though that skin tests represent a snapshot of the patient's allergy status at a moment in time. The data suggest that a time interval of greater than 6 months or potentially less than 4 weeks from the original reaction to the first skin testing can be associated with a false-negative skin test result. However, there is good evidence that repeat skin testing, especially in these patients who are less than 6 weeks or greater than 6 months out from the time of reaction, maintains patient safety and decreases unnecessary desensitizations by distinguishing patients who are truly negative for carboplatin allergy and may tolerate further treatment without desensitization from those who are truly allergic and require repeated desensitization for each future treatment.^{23,24} Costs of repeated skin testing versus continued desensitizations have not been compared, and the true rate of conversion from negative to positive skin testing is not known. Once a patient converts to a positive skin test result, further treatment options would require advancement to a desensitization protocol that would require a level of coordination that could be difficult to achieve on the same day of the skin testing. Protocols using repeat skin testing are termed risk stratification protocols and reduce costs while improving patient care. An algorithm detailing risk stratification as a clinical decision-making tool is outlined in [Figure 1](#).

Desensitization is safer than challenge in specific patients

Given its high degree of efficacy and safety, desensitization gives clinical teams an excellent additional option for patients in need of first-line therapy. Desensitizations are critical when treating severely ill patients who may not be able to give a clear history due to sedation, impaired cognition, or lack of consciousness who urgently need the offending drug under challenging circumstances. These patients should be empirically desensitized. Patients with significant cardiac or pulmonary comorbidity are another group of special concern because they must be assumed to have decreased functional reserve to cope with the stress of an allergic reaction.

Although desensitization is not risk-free, it minimizes as much as possible the risk margin providers must take in these types of situation when the patient urgently needs the drug in question. Another group of difficult-to-treat patients is of those whose memory of their initial reaction is so traumatizing that they are apprehensive to any attempt to readminister the offending drug. By explaining to patients the excellent safety record of desensitization across multiple studies looking at thousands of patients across the world over the past 20 years, they are more likely to have their concerns assuaged and work with providers who recommend the optimal first-line treatment plan.

Desensitization safety can lead to better accessibility

Chemotherapy desensitizations require coordination between multidisciplinary teams (ie, pharmacy, oncology, allergy, nursing, etc), and sometimes an inpatient admission if the patient has a

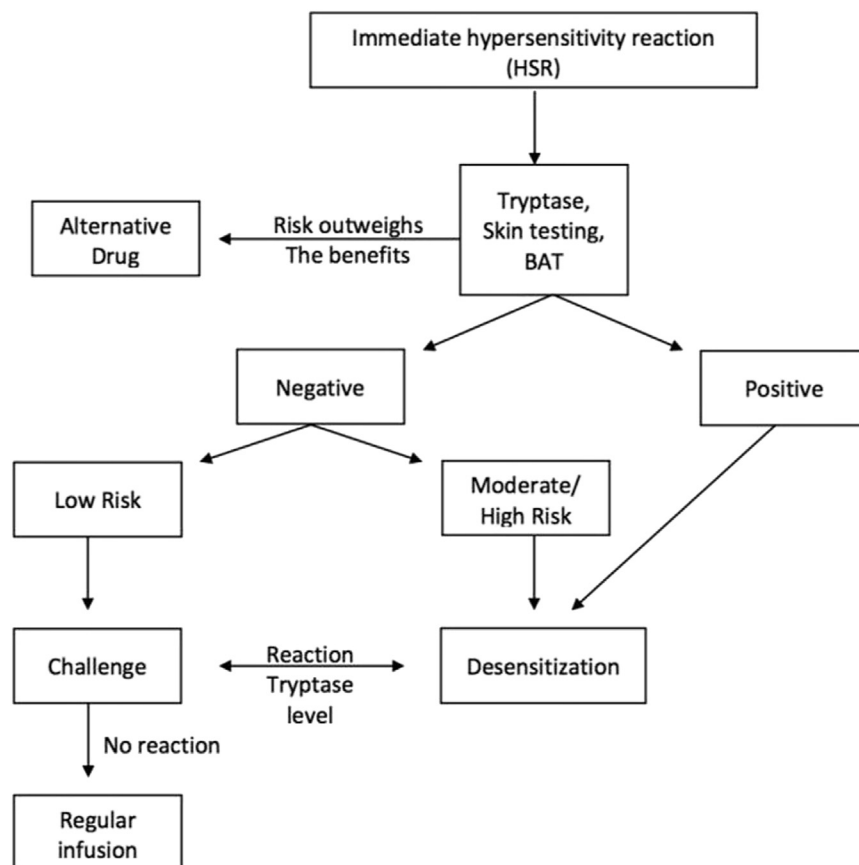


FIGURE 1. Brigham and Women's Hospital clinical risk stratification tool for the management of hypersensitivity reactions to chemotherapeutic agents and biologics. BAT, Basophil activation test.

number of comorbidities that could increase the consequences of a severe breakthrough reaction. However, there are emerging data using process improvement tools that may improve timeliness, efficiency, and satisfaction while maintaining patient safety. Barmettler et al²⁵ implemented 2 dedicated outpatient chemotherapy desensitization chairs, managed by trained staff including oncology and allergy team members. This study demonstrated that chemotherapy outpatient desensitization for oxaliplatin in low-risk patients was associated with more than 3-fold reduction in the mean time to restarting treatment without an increase in hypersensitivity reactions. More importantly, patients reported less disruption, suggesting that this process improvement was also a welcome change from the patient perspective. Similarly, Sloane et al¹² showed that most desensitizations, even in patients with a previous high-grade anaphylactic reaction, could be safely performed in a dedicated outpatient desensitization center with specially trained staff as opposed to the intensive care unit. This allows for improved scheduling, more predictable allocation of nursing resources, and less stress and anxiety for the patient. These findings highlight how the excellent risk profile of desensitization translates into increased access by reducing resource demands and costs for health care centers and patients.

Summary of the desensitization approach

Desensitization is a safe and proven method of offering patients a path to staying on preferred first-line therapy when

they have previously experienced a reaction. Desensitization is based on a basic understanding of hypersensitivity mechanisms, is applicable to a broad array of drugs, and is safer than provocation challenge in patients who are hospitalized and/or critically ill. The safety margin afforded by desensitization is maximized through the taking of a thorough history, physical examination, and proper use of skin testing and risk stratification. With proper risk management, desensitization is highly accessible in the outpatient setting as well and should facilitate wider community use in the future.

"DELABELING REACTIONS TO CHEMOTHERAPY: VALUE AND PRACTICALITIES" (DRS MADRIGAL-BURGALETA AND ALVAREZ-CUESTA) Precision medicine and delabeling

In recent years, we have witnessed worldwide efforts to apply precision medicine to drug allergy.^{26,27} At a practical level, this has resulted in the application of this current knowledge to identify adequate assessment and management pathways.²⁸ The remarkable gaps in knowledge of drug allergy make this endeavor difficult. However, the main groups studying hypersensitivity reactions and desensitization to chemotherapy and biological agents have been pioneers in the practical implementation of precision medicine into drug allergy. Brigham and Women's Hospital,^{10-12,29-34} Massachusetts General Hospital,^{24,25,35-43} and Ramon y Cajal University Hospital (RCUH)⁴⁴⁻⁵⁴ have all

consistently promoted the role of a multidisciplinary framework for advanced clinical practices by taking advantage of the knowledge provided by professionals from different areas. Even if the primary objective remains the same, that is, helping the individual patient, each group has a different approach to diagnosis and management. On that note, various efforts have described endotypes and phenotypes for chemotherapy and biological agents,^{32,36,44} identified risk factors and predictors of a reaction,^{31,33,44,46} explored and validated innovative biomarkers,^{31,32,46} and implemented delabeling for assessment in risk-based pathways.^{11,25,26,32,33,36,44,46,48}

Identifying optimal protocols for delabeling has been a key practical aspect of precision medicine in drug allergy (mainly beta-lactam allergy) during recent years.^{28,55-57} Despite isolated efforts,^{25,36,40,44,46} the role of delabeling and drug challenge before desensitization is frequently overlooked.^{58,59} However, previous experiences with other drugs (including chemotherapy drugs and biologics) have tried to balance safety with delabeling, thus saving patients from unnecessary resource-intensive desensitizations, preventing the use of second-line therapies (which might be less effective, more toxic, and more costly), and improving quality of life.^{25,28,40,44,60,61}

The role of drug challenge in delabeling

Drug provocation testing or drug challenge is the controlled administration of a drug to a patient to rule out or to confirm hypersensitivity, and serves as a criterion standard for drug allergy.^{44,46,50,62-64} As such, it plays a key role in the design of prospective studies exploring optimal delabeling, in the accurate description of phenotypes and endotypes, and in appropriate validation of biomarkers, risk markers, and predictors.^{46,62,63,65} Drug challenge is a long-standing standard of care in drug allergy, although it remains a tool in constant expansion and under active research within the study of drug hypersensitivity.⁶⁶⁻⁷²

The largest and most detailed experience in drug challenges with chemotherapy and biological agents was published by the RCUH.^{44-46,51} This group found that drug challenge had 3 fundamental indications: (1) To rule out hypersensitivity and avoid unnecessary desensitizations, either to drugs that have been involved in a reaction or to drugs with a reported cross-reactivity; (2) to ensure an accurate diagnosis when more than 1 drug is involved in the initial reaction (not an uncommon scenario)⁵¹; and (3) to validate diagnostic tools, because these should be assessed against an optimal criterion standard (ie, drug challenge).^{45,46,62,63,65}

Data of the RCUH cohort's 341 drug challenges show that this technique helped to exclude hypersensitivity in up to 45% of patients sent for allergy assessment after an unequivocal reaction to chemotherapy or biological agents (23% for platins, 49% for biologicals, 52% for taxanes, and 71% for other drugs).⁴⁴ It is indeed quite remarkable that 67% (229 of 341) of all drug challenges were negative; in other words, the number of desensitizations will necessarily be reduced. For example, the RCUH cohort studied 515 patients who needed 1027 desensitizations,⁴⁴ whereas Sloane et al¹² described a cohort of 370 patients, with no data on drug challenge, who needed 2177 desensitizations (although population characteristics could explain some of the differences).

Over the years, other groups have specifically mentioned the use of drug challenge and supported its usefulness with

data,^{25,36,37,40,73} or have at least considered it as a possibility in their pathways.^{11,32,33}

There are currently no data to recommend middle-ground alternatives to drug challenge, such as adding off-label premedication or extending infusion times. Specifically, the latter approach was recently shown to be ineffective.⁴² The RCUH pathway focuses on the dichotomy of drug challenge for diagnosis and rapid drug desensitization for treatment/management of drug hypersensitivity.⁴⁴

Placing the drug challenge within the drug allergy study pathway

Pathways are considerably influenced by local logistic variations and individual experience, although in practical terms there are 2 distinct nonmutually exclusive approaches, namely, drug challenge before desensitization and drug challenge at a later stage. The RCUH reported on challenge before desensitization as an institutional strategy.⁴⁶

The broad experience gained at the RCUH shows that if patient selection and risk-based assessment are favorable, then there is no reason to avoid a drug challenge before desensitization.

Other groups propose first having the patient undergo a short desensitization before considering drug challenge.^{25,36,37,40} The results of this approach are relatively similar, although it is arguably too resource-intensive to subject patients unnecessarily to recurrent desensitizations when their risk assessment would allow for a drug challenge.

There are, of course, gray areas. For example, some centers (depending on staff and resources) might not be willing to challenge patients with a moderate or severe reaction,⁷³ others might consider challenging these patients but only after a first short-desensitization attempt with no reactions,^{40,43} and finally others might consider challenge before desensitization regardless of the severity of the reaction provided the risk assessment is favorable.⁴⁴⁻⁴⁶ As another example, some patients under specific circumstances (long period between reaction to platins and assessment) might need to repeat both skin testing and challenge after an initial uneventful challenge, and might even need further follow-up skin testing.^{36,43-45} Moreover, the time for drug challenge might also vary depending on the type of drug. In fact, some patients who experience recurrent reactions to paclitaxel that are not IgE-mediated might eventually become tolerant to paclitaxel after several administrations.⁴⁰ In such a case, challenge may have a place further down the line after several uneventful desensitizations despite a previous positive challenge. In contrast, an additional confirmatory challenge after several uneventful desensitizations should not be considered in a platin-reactive patient with a confirmed IgE-mediated allergy.

On that note, in a study of 35 paclitaxel-reactive patients, a symptom-based protocol was put into place for patients to be challenged or desensitized.⁴⁰ Mild reactions were challenged successfully, whereas nonmild reactions were moved down the pathway from desensitization to challenge. Eventually, 46% of all referred patients could return to standard infusions, which is similar to the 52% of negative challenges before desensitization in the RCUH study (135 paclitaxel-reactive patients).⁴⁴ However, paclitaxel improves tolerance after repeated administrations,^{33,40} and in its publication, the RCUH team did not consider the possibility of eventually moving down from desensitization to another challenge in patients who initially had

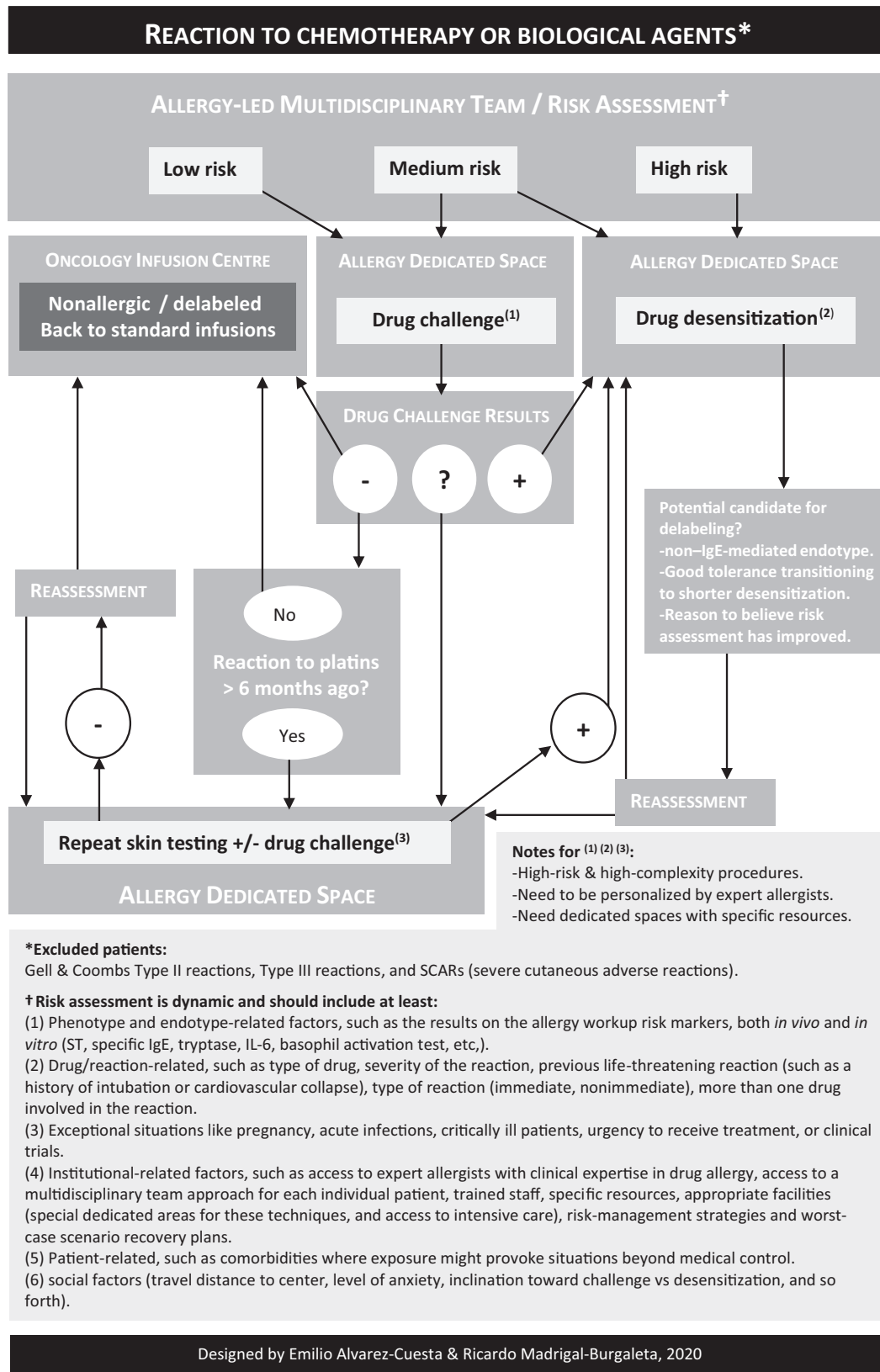


FIGURE 2. Proposed standard protocol for patient delabeling in hypersensitivity to chemotherapy and biological agents (ideally, to be personalized by each individual center depending on resources, population, and other local factors).

TABLE I. Areas of agreement and future route map for the management of allergic reactions to chemotherapy and biologics

Areas of agreement	Areas of controversy	Unmet needs and future research
The role of the allergist as a leading figure	Locally adapted multifactorial risk assessment for each technique Example of controversy, BWH & MGH place a greater focus on the severity of initial reaction	Understanding risk factors in patients who react to RDD and drug challenge
Specific multidisciplinary teams with dedicated spaces	The essential role of endophenotyping: Systematic approach with skin testing whenever possible Example of controversy, RCUH considers end-point titration for ST, whereas BWH warns about the possibly low cost-effectiveness of ST with some drugs. As another example, RCUH performs ST on first attempt before challenge and follows up with ST after a negative challenge, whereas MGH follows a “short RDD and repeat ST” strategy before challenge	Support and promotion by medical and patient societies of the role of the allergist and RDD
RDD with risk stratification is the optimal therapeutic approach (effective, safe, cost-effective, maintains same survival rates as standard administration)	The essential role of endophenotyping: Access to <i>in vitro</i> testing (tryptase, IL-6, total IgE, specific IgE, basophil activation test, etc) BWH, MGH, and RCUH agree on the need for access to these tools, but the exact validation of the tools and their role in the management pathway still needs more data	Better endophenotyping tools and prediction models for risk assessment (wider range of biomarkers, diagnostic score charts, common skin test concentrations, commercial ST products, etc)
Both drug challenge and RDD are high-risk and high-complexity procedures that should be carried out only by expert allergists on adequate settings	The essential role of endophenotyping: Access to drug challenge -To avoid unnecessary desensitizations -To avoid misdiagnosis when many drugs are involved -For internal and external validation of diagnostic procedures and processes in the local population (eg, predictive values) -For research purposes and high-quality publications Example of controversy, RCUH considers that all patients should have access to drug challenge before RDD provided the risk assessment is favorable, whereas MGH tends to put the drug challenge further down the management pathway (after uneventful RDDs)	Including allergy assessment and RDD in official chemotherapy guidelines and manufacturer’s instructions
“Safety-first policy”	Adapting daily practice to local resources and local idiosyncrasies All groups agree on this; however, they inevitably have different local variations; eg, RCUH infusion center is set within the hospital, whereas BWH has outpatient infusion centers. As another example, different groups have different access to ICU beds	Further insight on basic mechanisms, and further multicentric, cost-effectiveness, and survival studies on more populations
Personalized care	Patient empowerment, active involvement on the decision-making process, active involvement on the design of local management pathways All groups agree on this. However, as an example, the RCUH strongly encourages a 3-sided conversation between oncologist, patient, and allergist, to empower the patient to decide on their ideal pathway (eg, whether to go ahead with challenge or not)	The ideal place within the pathway for drug challenge
Constant quality improvement efforts	Locally adapted standard operating procedures For example, RCUH undergoes all first RDDs at the ICU, whereas BWH finds that the ICU might not be systematically needed. Also, RCUH has 2 separate informed consents, one to be signed by oncologist/patient (confirmation of indication of treatment) and another one to be signed by allergist/patient (reaction study/management)	Personalizing and standardizing protocols and pathways for RDD and drug challenge according to endophenotype

BWH, Brigham and women’s Hospital; ICU, intensive care unit; MGH, Massachusetts General Hospital; RDD, rapid drug desensitization; ST, skin testing.

a positive drug challenge (doing so could have potentially improved the percentage of patients tolerating paclitaxel in the RCUH cohort).

On the basis of data from various groups in these scenarios, we propose a universal protocol for delabeling in [Figure 2](#). [Table I](#) presents more data on areas of agreement among these groups and a future route map.

Patient selection and risk assessment

Optimal patient selection and risk assessment are the key to safety. Unfortunately, there is no one way to gain proficiency in

this field, and no one single tool is sufficient. An unequivocal clinical history alone is a poor diagnostic tool (positive predictive value of roughly 63% for oxaliplatin),⁴⁴ skin testing can generate false-negative and false-positive results,⁴⁴⁻⁴⁶ and *in vitro* biomarkers show poor negative predictive values.⁴⁶ Other factors to bear in mind include waiting lists, staff availability, and patient preferences (eg, travel distance to medical center, level of anxiety, and inclination toward challenge vs desensitization).^{40,44}

For these reasons, decisions must be based on a “safety-first policy,” a multidisciplinary discussion, and patient empowerment to actively participate in their care.^{44,49,50} Thus, the

allergist must be aware of all the very complex factors that can affect risk assessment,⁴⁴ as described in Figure 2.

A dynamic, closely monitored approach to risk management is key to safety because of the need to understand that the higher the number of drug challenges performed, the higher the risk of reactions. In the RCUH cohort, 112 challenges were positive, and 34% of positive challenges involved a mild reaction. However, 15% of patients experienced a grade 3 anaphylactic reaction according to Brown's criteria,^{44,74} and even if there were only 4 patients presenting with hemodynamic changes (grade IV anaphylactic shock reaction according to the criteria of RCUH) over a period of 7 years,⁴⁴ drug challenge is undoubtedly a high-risk and unpredictable procedure to be performed only by experts.

Ideally, most reactions should be mild, and there should be virtually no severe reactions. Hence, there is an unmet need for a better understanding of the phenotypes and endotypes of these patients, which will allow for safer protocols and better tools for candidate selection.

A note on the severity of the initial reaction

Several studies use the severity of the initial reaction as a major factor for initial assessment.^{33,40} However, in a prospective cohort study of 135 paclitaxel-reactive patients, severity alone was not found to be significantly associated with the final diagnosis of hypersensitivity.⁴⁴ This can be explained, first, because the severity of the initial reaction might be affected by a series of factors, including suboptimal management,^{35,44} and second, because even if severe reactions are less likely to be challenged,^{33,44,46} mild and moderate reactions are equally likely to be real allergic reactions. The main message from this observation is that severity alone is not necessarily a good predictor, and mild reactors are also at risk of experiencing a positive challenge. Therefore, safety measures must be equally intensive for mild reactors undergoing challenge.

Data seem to show that patients with an initial severe reaction do tend to experience severe reactions during positive challenges even if they are not necessarily at a higher risk of having a positive challenge.^{33,35,44} Therefore, the group of patients who initially experience a severe reaction should be considered a higher-risk group.

Procedure

The actual procedure for drug challenge has been thoroughly described by the RCUH,^{45,46} as have the indications, contraindications, and other considerations.⁴⁵ The key points can be summarized as follows: drug challenge should not delay the patient's treatment; the full dose of treatment should be administered despite the results (patients reacting to challenge show temporary tolerance postreaction, and so the treatment should not be missed); challenge should be decided, designed, and performed by expert allergists with access to *in vivo* and *in vitro* testing and multidisciplinary teams; challenge should be performed in safe dedicated areas (check-lists, anaphylaxis management plans, medication readily available, access to intensive care <1 minute, 1-to-1 nurse, allergist at bedside, worst-case scenario recovery plans); the patient should always be empowered to make the decision and to sign an informed consent document; challenge should only be considered in specialized medical centers and, in the case of a reaction, ideally *in vitro* determinants for further reaction-endotyping should be available

and tailored for the individual patient and for research purposes that could benefit future patients.

Risks of misuse of challenge

The RCUH team previously warned of the risks of "uncontrolled drug challenges" (ie, administering a culprit drug to a reactive patient lacking allergy/risk assessment, in inappropriate environments, by untrained and/or unaware personnel).^{45,46}

A retrospective study by Banerji et al³⁵ shows data on drug challenges being used over a 5-year period by nonallergists with no allergy assessment whatsoever in an outpatient setting. Of the 107 patients who had reacted to paclitaxel, 80 were challenged and 73 did not react. This means 68% of all paclitaxel-reactive patients were not allergic; these data are actually better than the 52% of paclitaxel-reactive patients found to be nonallergic by the RCUH,⁴⁴ or the 46% reported for the Massachusetts General Hospital pathway.⁴⁰ However, we must carefully consider whether the risks assumed by those patients to reach that 68% of patients with a negative challenge outweigh the benefits.

Banerji et al³⁵ highlight how these challenges were led by nonallergists, there was no identifiable systematic allergy workup or risk assessment, the challenge itself did not follow a standard procedure (variable premedication and flow rates, nonsystematic approach depending on the individual oncologist), patients did not receive adrenaline despite clear anaphylaxis, patients were not likely to be individually monitored by an allergist at the bedside with anaphylaxis medication ready, and patients were not challenged in a safe environment (rather in an outpatient infusion center).

Unfortunately, because this is a common scenario in many hospitals, it is necessary to ensure institutional blocking of these practices and train health professionals. Because drug challenge is a high-risk and high-complexity procedure (deaths have been reported from uncontrolled reexposures), it should be performed by expert allergists in dedicated areas with adequate risk assessment and optimal standard operating procedures.⁴⁴⁻⁴⁶

Summary of the delabeling approach

Delabeling patients who have experienced reactions to chemotherapy and biological agents saves a remarkable number of resource-intensive desensitizations and could improve the patients' quality of life when they can go back to standard infusions at their local center. However, delabeling requires a drug challenge, which is a high-risk and complex procedure. Drug challenge and drug desensitizations with chemotherapy and biological agents must be performed only by expert allergists in special centers with a framework of multidisciplinary teams. Ideally, drug challenge should be performed before desensitization if patient selection and the risk-based assessment are favorable; however, drug challenge can be used in different steps of the management pathway depending on patient characteristics and institutional protocols.

JOINT SUMMARY: DESENSITIZE OR DELABEL?

Reactions to chemotherapy pose significant challenges to patients and providers. For patients, such reactions are disconcerting and frightening to experience. For providers, they pose a dilemma to manage because oftentimes the drug in question is the best therapeutic choice. Switching to an alternative agent may represent a significant compromise assuming there is

even an alternative to choose from. This article described 2 approaches, desensitization and allergy delabeling, to best answer this management challenge. Drs Hong, Banerji, and Castells covered the benefits of drug desensitization with or without risk stratification, whereas Drs Madrigal-Burgaleta and Alvarez-Cuesta argued the merits of a standard delabeling protocol that can be flexibly adapted to local resources. Although there are clearly some clinical scenarios in which one approach may be preferred over the other, it is also disingenuous to argue that these 2 approaches are diametrically opposed to one another because they are in fact complementary approaches that take into account our most current understanding of drug hypersensitivity.

The keys to success in the management of these patients are the timely access to a multidisciplinary team led by expert allergists in collaboration with the other specialties involved, and the adequate provision of dedicated resources. Management pathways may vary locally depending on several factors, although the common grounds for an optimal pathway are invariably the high standards of the allergy team in approaching risk assessment. There are clear unmet needs, and future research should focus on biomarkers to better endophenotype these patients, and so allow for an even more personalized and safe management.

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ONLINE REPOSITORY

Name of medication: carboplatin

Target dose (mg)	150
Standard volume per bag (mL)	250
Final rate of infusion (mL/h)	80

Calculated target concentration (mg/mL)	0.6
Standard time of infusion (min)	187.5

				Total mg per bag	Amount of bag infused (mL)
Solution 1	250	mL of	0.006 mg/mL	1.500	9.25
Solution 2	250	mL of	0.060 mg/mL	15.000	18.75
Solution 3	250	mL of	0.595 mg/mL	148.820	250.00

*** PLEASE NOTE *** The total volume and dose dispensed are more than the final dose given to patient
because the initial solutions are *not completely infused*

Step	Solution	Rate (mL/h)	Time (min)	Volume infused per step (mL)	Dose administered with this step (mg)	Cumulative dose (mg)
1	1	2.0	15	0.50	0.0030	0.0030
2	1	5.0	15	1.25	0.0075	0.0105
3	1	10.0	15	2.50	0.0150	0.0255
4	1	20.0	15	5.00	0.0300	0.0555
5	2	5.0	15	1.25	0.0750	0.1305
6	2	10.0	15	2.50	0.1500	0.2805
7	2	20.0	15	5.00	0.3000	0.5805
8	2	40.0	15	10.00	0.6000	1.1805
9	3	10.0	15	2.50	1.4882	2.6687
10	3	20.0	15	5.00	2.9764	5.6451
11	3	40.0	15	10.00	5.9528	11.5979
12	3	80.0	174.375	232.50	138.4021	150.0000
Total time (min) =			339.375	= 5.66 h		

FIGURE E1. Brigham and Women's Hospital's standard 12-step rapid drug desensitization protocol.