



Drug allergy desensitization is not a unique recipe

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Purpose of review

Drug desensitization is the only therapeutic option for patients with drug allergies who need to receive the drugs they are allergic to, and it is especially critical in patients with an urgent need for chemotherapy, biologics, or antibiotics, where equally effective alternatives might not be available. However, drug desensitization is not a cookbook where anyone with no experience or specific training can find a general recipe. This review article will approach the singularities that make personalized and highly specialized care essential in this field.

Recent findings

Drug desensitization needs to be personalized for each individual patient bearing in mind countless factors. Recent articles have tried to define the optimal resources and the most important factors to account for in personalization. However, drug desensitization is only a tool within the wider management pathway, and we will discuss recent findings in allergy delabelling in chemotherapy, biologics, and antibiotics.

Summary

Risk-assessment, delabelling, and desensitization protocols, as a part of wider management pathways, can be adapted locally along with comprehensive and multifactorial risk-management strategies. These high-complexity and high-risk procedures, such as drug desensitization, need to be managed by expert allergists who can provide personalization, innovation, continuous improvement, research, and teaching in expert centres.

Keywords

anaphylaxis, delabelling, drug allergy, drug desensitization, personalized medicine

INTRODUCTION

Carrying a drug allergy label for an essential medication when no equally effective and well tolerated therapeutical alternatives are available is a critical problem that allergists worldwide need to be ready to address. Of course, any drug allergy label could put anyone in this situation. However, patients with cancer, inflammatory diseases, or recurrent infections who can react to chemotherapy, biologics, or antibiotics are in a far more disadvantageous position as the incidence of their drug hypersensitivity reactions (DHRs) is remarkably high, and the need for urgent treatment is usually imperative, sometimes a matter of life and death [1[¶]].

A significant number of drug allergy labels are usually unnecessary, and a thorough diagnostic allergy workup can help delabel these patients (i.e. rule out an allergy) [1[¶],2,3[¶]]. Fortunately, allergists can provide these patients with cutting edge diagnostic procedures including in-vitro techniques (e.g. total IgE, specific IgE, basophil activation test, serum tryptase, or IL-6), in-vivo techniques

(e.g. skin testing, including endpoint titration, or drug challenge), comprehensive risk assessment tools, multidisciplinary pathways, and more importantly, the appropriate spaces and staff to make this process safe [3[¶]–5[¶]].

Nevertheless, after the assessment by expert allergists, many patients are either confirmed as hypersensitive or cannot be delabeled because of an unfavourable risk assessment [4[¶],5[¶]]. Conse-

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KEY POINTS

- RDD is a valuable technique in the hands of expert allergists with specific resources.
- RDD is not a unique recipe but needs to be personalized for each patient bearing in mind countless factors.
- RDD is part of a broader management pathway that includes diagnostic techniques.
- Delabelling pathways that include drug challenges help identify nonallergic patients and avoid unnecessary RDDs.
- RDD is a high-risk and high-complexity allergy-specific procedure, and it should not be blindly used by healthcare professionals without specific training and experience.

quently, drug desensitization is the only available therapeutic option in these cases [5[•]].

Drug desensitization is a high-risk and high-complexity procedure that takes advantage of the physiology of mast cells and basophils to induce a temporary tolerance in patients with a confirmed DHR [4[•],5[•]]. Effectively, in the hands of expert allergists, even patients with a history of severe DHRs or a high-risk assessment for any reason (e.g. comorbidities, pregnancy, or severe anaphylaxis) can safely receive the drug despite their hypersensitivity [6,7^{••}]. Recent studies show how patients undergoing drug desensitization have similar survival outcomes as their nonallergic counterparts and how this technique is cost-effective, even if it requires expert allergists, experienced staff, and allergy-dedicated spaces to ensure safety [8^{••},9].

Unsurprisingly, despite regional disparities, drug desensitization for cancer, inflammatory diseases, and acute infections has become a standard of care for patients who experience DHRs to chemotherapy, biologics, and antibiotics [1^{••}]. Indeed, recent European guidance summarizes best practice recommendations to try and homogenize management [10^{••},11^{••}].

The heterogeneity and complexity of patients needing drug desensitization to various medications justify centralized care under the allergy department, which can offer the highest safety standards [1^{••}]. Instead, many allergy departments have not yet accepted responsibility for these patients. As a result, nonallergists could be forced to embark on local drug delabelling or desensitization initiatives without the appropriate experience, knowledge, or resources, which can be unsafe, arguably not cost-

effective, and promote disparities in access to drug delabelling and desensitization [1^{••}].

For this reason, the World Allergy Organization (WAO) has recently published a thorough consensus document to support allergists worldwide in offering these essential services [1^{••}]. One of the learning points from this consensus document is that drug desensitization is far more than a way of administering a drug. Instead, excellence and safety in drug desensitization require, at a 'macro' level, redesigning allergy care involving multidisciplinary teams, optimizing spaces, revising pathways, and engaging in continuous professional development and quality improvement [1^{••}]. On the other hand, at a 'micro' level, Precision Medicine and Personalized Medicine make choosing a diagnostic pathway, desensitization protocol, or premedication a rather complex issue, depending on factors like culprit drug, endotypes, or phenotypes [4[•],5[•]].

Drug desensitization is not a 'cookbook' where anyone with no experience or specific training can find a general recipe that will work in any patient or reaction regardless. For this reason, this review article will approach the singularities that make personalized, tailored, and highly specialized care essential in this technique.

PERSONALIZING DEPENDING ON THE ENDOPHENOTYPE

Traditionally, following Gell & Coombs's classification, DHRs can be divided depending on their phenotype and endotype, into type I (typical symptoms of IgE-mediated or non-IgE-mediated release of preformed mediators in mast cells/basophils, such as anaphylaxis), type II (cytotoxic reactions mediated by IgG/IgM bound to the target cell or complement activation, such as drug-induced thrombocytopenia), type III (deposition of immune complexes in tissues and complement activation, such as serum sickness), type IV (mediated by cells rather than antibodies, with a wide range of subtypes of reactions, from benign maculopapular exanthema to the severe Stevens Johnson's syndrome) [12].

However, discoveries in drug allergy have prompted a need to revise this somewhat dated classification [12–16]. Specifically, in the field of chemotherapy and biologics, two further frequently occurring drug hypersensitivity endophenotypes have become relevant in recent years, namely, cytokine release reactions (CRRs, which can feature fever/chills, malaise, erythema, or hypotension, linked to elevations in serum IL-6), and mixed reactions featuring characteristics of both CRRs and type I [17[•]].

Type I DHRs are classically immediate, appearing within 1 h of the exposure to the drug, although

occasionally later (<6 h). Whereas type II, III, and IV DHRs appear mainly after days; however, they might present with earlier onset, especially on reexposure [18,19].

Despite being imperfect, these classifications are helpful to devise the optimal testing strategies [13,14,18]. In addition, they have a significant impact on the therapeutic options as they will influence the indication for drug desensitization and the type of desensitization used [20]. For instance, immediate DHRs (I-DHRs) will benefit from rapid drug desensitization (RDD), where the target dose is reached in hours, and nonimmediate DHRs will benefit from slow desensitizations, where the procedure might take several days [20].

There is a great deal of controversy on whether nonimmediate DHRs benefit from drug desensitization as the mechanisms for drug desensitization have been mainly elucidated in relation to mast cells and basophils [1[■]]. For this reason, this manuscript will focus on RDD.

The consensus amongst the leading groups in RDD is that this procedure is indicated for type I DHRs, CRRs, mixed reactions, and mild benign type IV DHRs [1[■]].

Reportedly, some authors argue that RDD could be an option in types II, III, and nonmild type IV DHRs [21–23]. Nevertheless, reexposing patients who experienced such reactions can be fatal. Therefore, if ever, this kind of ‘off label’ uses of RDD should only be considered in incredibly desperate situations, by highly specialized centres, in a multidisciplinary environment with specific operating procedures, and a research context.

In any case, the patient’s endophenotype is an essential factor in personalization. As we have seen, it will influence the indication of RDD but it might also affect the likelihood of a breakthrough reaction during RDD, and, thus decisions on monitoring and premedication. For example, patients with a CRR endophenotype are more likely to react during RDD and benefit from fluids, COX-1 inhibitors, dose reductions, lower final rates, or even steroids [24,25[■]].

Personalizing depending on desensitization protocols

The most commonly used RDD protocols are intravenous and adhere to basic principles learned from experimental in-vitro data and validation *in vivo* in large cohorts of patients [1[■]]. Namely, the initial dose should be subthreshold for anaphylaxis and around a 1000–10 000th of the target dose (shorter protocols in low-risk patients transitioning from more extended protocols can start at a 100th), there

should be approximately 10–16 steps of 2-to-2.5-fold incremental doses of the drug antigen at fixed 15–30 min time intervals [1[■]].

Three groups encompass the most extensive experience on RDD, and their protocols involve using a standard protocol of three solutions or bags at different concentrations for intravenous administration, which are adaptable to have more bags and steps in higher risk patients or fewer bags and steps in lower risk patients with good tolerance to previous RDDs [4[■]]. The Brigham & Women’s Hospital group (BWH) described 2177 RDDs in 370 patients [9]. The BWH protocols were modeled after prototypes of intravenous penicillin RDD protocols from the 1980s and based on mechanistic in-vitro data published by this group [26]. On the other hand, the Ramon y Cajal University Hospital group (RCUH) studied 515 patients and described 1027 RDDs with a protocol inspired by previous in-vivo and in-vitro data but locally adapted to comply with specific hazardous drug handling measures that involved priming the line with fluids instead of the drug, and thus, made previous RDD protocols unsuitable [6,7[■]]. Of note, the patient/RDD ratio is remarkably different in these studies, and we believe this is because RCUH’s diagnostic pathways, which include drug challenge, are highly effective in delabelling unnecessary allergy labels and optimizing candidates for RDD [2,7[■]]. However, there have been no direct comparisons between groups, and differences between populations’ characteristics could be an alternative explanation. Finally, the Massachusetts General Hospital group (MGH) focused mainly on pathway optimization and personalization of RDD protocols depending on culprit drug and risk stratification by skin testing [27–37]. Interestingly, the MGH RDD protocols are based on previous empiric experience with vanco-mycin RDD [38]. A recent article by Hong *et al.* [4[■]] explored the different approaches of these groups and proposed a diagnostic and management approach combining these experiences.

Interestingly, recent studies explored using single bag protocols to streamline the procedure and avoid the inconveniences and potential errors linked to three bag protocols [39[■],40,41]. However, only one of these single bag studies included a full allergy workup, including drug challenge, to properly characterize and delabel patients, and thus, prevent biased conclusions [39[■]]. Therefore, larger studies with well characterized populations are still needed.

Nevertheless, protocol choice should be personalized and different protocols can coexist within the same institution. For example, RCUH uses their three bag protocol specifically designed for

hazardous drugs, the BWH protocol for nonhazardous drugs like leucovorin, steroids, or antibiotics, and a one bag protocol for cetuximab [7¹¹,42,43].

Personalizing depending on the culprit drug

The inherent characteristics of the culprit drug will have an impact on RDD. There are different models with diverging features depending on the culprit drug: Platins are usually IgE-mediated and need several exposures before triggering a DHR, whereas taxanes are usually non-IgE-mediated and can react on first exposure [1¹¹,10¹¹]. Biologics can behave in both of these ways and not infrequently might induce CRR, or even DHRs mixing features of different types of hypersensitivity (e.g. type I and CRR) [1¹¹,11¹¹]. Finally, all of the above are usually given in intermittent single doses, whereas antibiotics usually involve longer courses [1¹¹]. All these characteristics greatly affect the way we use RDD.

For example, taxanes, known to present better tolerance after each administration, can benefit from transitioning to shorter protocols over time if good tolerance is confirmed [44]. As another example, some authors have attempted to use skin testing preventively to identify patients at risk of sensitization before a DHR appears in patients receiving platins [45,46]. Finally, DHRs to cetuximab, a monoclonal antibody, have been linked to sensitization to alpha-gal, which could trigger IgE-mediated reactions even on first exposure [1¹¹,3¹¹].

The desensitized state might be maintained until the drug is withdrawn, so antibiotics, usually

administered in courses, might only need RDD at the start of a new course. After the patient is desensitized, the next dose can be administered normally, provided the interval as the last dose is not too long for the temporary tolerance to wane. For this reason, the bag volumes and target flow rates of the RDD protocol should ideally mimic those of real-life administration as per local guidelines that will be used after the RDD [47]. A similar situation can happen with courses of corticosteroids [43]. This phenomenon is also observed in other types of drug desensitization, such as oral desensitization, and the literature is substantial for aspirin [48,49].

Personalizing depending on risk assessment

Drug challenge is the criterion standard diagnostic technique to confirm or rule out a drug allergy [12]. Thus, drug challenge in the study of DHRs to chemotherapy and biologics is essential to delabel patients, reduce unnecessary RDDs, reach an accurate diagnosis whenever two drugs are involved, and as a gold standard to validate diagnostic tools [2,3¹¹]. The RCUH has a longstanding experience with over 300 intravenous drug challenges to chemotherapy and biologics [2,7¹¹]. Recently, more centres started including this invaluable technique within their delabelling pathways with promising results (see Fig. 1), calculating that this technique had prevented an estimated increase of 31% in unnecessary RDD procedures [50,51¹¹]. In these studies, drug challenge could exclude hypersensitivity in up to 23–72% (depending on culprit drug) of patients

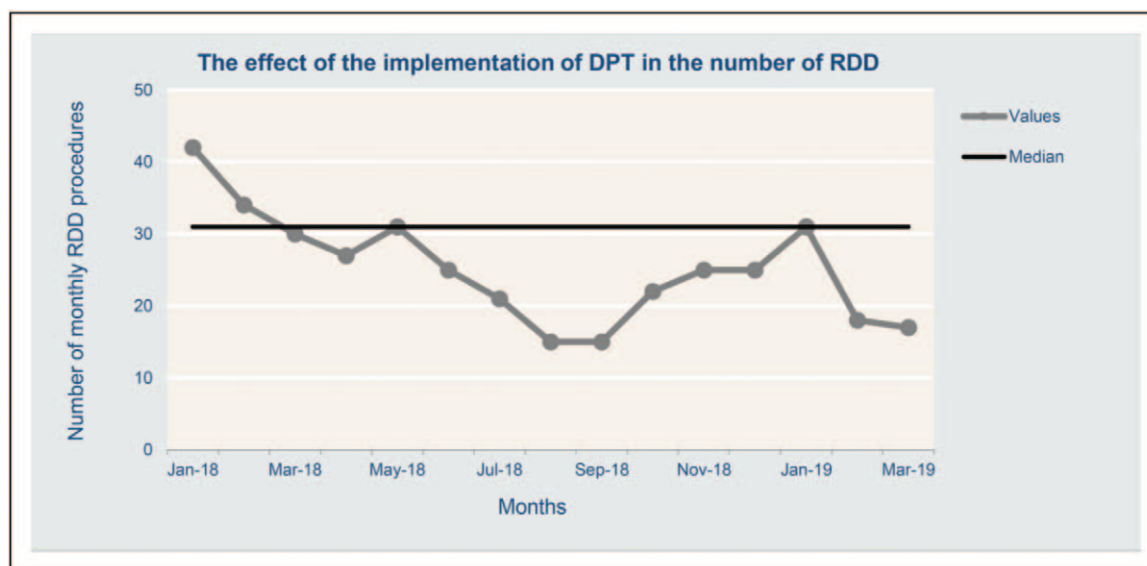


FIGURE 1. Run chart showing a shift in the number of rapid drug desensitization procedures after the implementation of drug provocation testing in our population. Reproduced with permission from Marti-Garrido et al. [50]. DPT, drug provocation testing; RDD, rapid drug desensitization.

sent for allergy assessment after an unequivocal reaction to chemotherapy or biological agent [2,4[■],7[■],50,51[■]].

A good patient selection grants that most drug challenges will be negative (i.e. no reaction). However, intravenous drug challenge with chemotherapy and biologics is an unpredictable procedure that can trigger severe reactions in up to 15% of the challenges that show a positive result, with 4% of patients experiencing haemodynamic changes [2,7[■]]. Indeed, drug challenge is a high-risk and high-complexity procedure that only expert allergists in highly specialized centres should perform, provided access to dedicated spaces and resources can be guaranteed [1[■],10[■],11[■]]. The keys to safety are a comprehensive multifactorial risk assessment and the experience and capabilities to act on it [4[■]].

Therefore, risk assessment is especially relevant when considering patient selection for drug challenges in delabelling pathways [4[■]]. Patients with an unfavourable risk assessment are not ideal candidates for a confirmatory drug challenge, and instead, direct RDD might be a more cautious approach in these patients [5[■]].

Risk stratification involving specific factors can be crucial in management pathways [24,33–36,44,52]. However, a successful risk assessment strategy should not only consider the severity of the reaction or the results in skin testing but it should bear in mind several essential factors that might contribute with different weights to the outcome [4[■],5[■]]. These can involve; namely, endophenotype factors like the different in-vivo and in-vitro biomarkers (STs, specific IgE, tryptase, IL-6, or basophil activation testing); factors related to the drug or the reactions, such as the severity of the reaction, or the type of drug and the number of culprit drugs involved; exceptional situations like pregnancy, acute infections, critically ill patients, the urgency to receive treatment, or clinical trials; factors related to the access to resources, such as appropriate staffing, multidisciplinary team support (including intensive care), standard operating procedures, worst-case scenario recovery plans, or dedicated facilities; factors related to the patient, like comorbidities where exposure might provoke situations beyond medical control; and social factors, such as travel distance to the health centre, level of anxiety, or inclination toward drug challenge vs. RDD [1[■],4[■],5[■]].

Patient-related factors are sometimes overlooked, and yet bearing these in mind is crucial for safety [4[■],5[■]]. For example, two patients could experience a similar DHR with the same drug, and yet their risk assessment could be completely different as one patient is a young and otherwise healthy patient, whereas the other patient has several

comorbidities, such as mastocytosis, uncontrolled asthma, and ischaemic cardiac disease.

Risk assessment can also influence the RDD protocol that might be more suitable for the patient, and in this regard, RCUH and BWH both described a high-risk modification for their standard protocols that adds another bag and further steps to start at a lower dose/time rate [7[■],9].

Personalizing depending on tolerance to the procedure

One of the main controversies in RDD is whether these procedures need specific premedication, as evidence is scarce [1[■],5[■]]. Of note, the manufacturer's instructions of many drugs already involve premedication to a certain degree but there is a discussion about whether additional premedication would be beneficial [1[■]]. Some groups do not add any specific premedication whatsoever and only use this if needed after a breakthrough reaction [50,51[■]]. Other groups recommend routine premedication, especially with antihistamines [9]. In any case, most groups open the door to tailored premedication depending on the initial reaction [1[■],7[■]].

Only two studies attempted a systematic approach to this issue. One explored the superiority of acetylsalicylic acid and montelukast over antihistamines and corticosteroids in reactions to platinum [53]. The other study challenged the need for premedication in RDD to taxanes, arguing that unnecessary premedication could cause adverse effects and affect safety by hiding early signs of anaphylaxis [54].

A recent WAO consensus statement by Alvarez-Cuesta *et al.* [1[■]] summarizes the most common premedication regimes for RDD, including antihistamines for H1 and H2 blockage, leukotriene receptor antagonists to prevent respiratory symptoms, or acetylsalicylic acid to prevent symptoms caused by prostaglandins. Other NSAIDs, opioids, and steroids can be used to avoid CRR symptoms, such as fever/chills or pain, which can also benefit from adding fluids. Benzodiazepines can have a role to relieve the anxiety caused by the procedure.

Regardless of premedication, around 30% of all patients will experience some sort of breakthrough reaction during their first RDD [7[■],9]. Fortunately, several measures can prevent this in subsequent procedures, and virtually all patients will tolerate their RDD by the third/fourth procedure [7[■],25[■]]. Indeed, patients who experience breakthrough reactions should have their following RDD personalized depending on the nature of this breakthrough reaction.

Measures can include adding some of the above premedication regimes (upfront or before reactive steps), intermediate steps to decelerate dose-escalation, longer RDD procedures starting at a lower dose, slower final flow rates, temporary final dose reduction, or omalizumab [1[¶]].

In any case, it is helpful to keep in mind that these reactions could be caused by concomitant drugs, such as leucovorin as patients can become sensitized to more than one drug. As RDD is antigen-specific, these patients will need 'double desensitization' [7[¶],42].

Patients with good tolerance to previous RDD procedures, especially low-risk patients and patients with a non-IgE-mediated endophenotype, have been successfully transitioned to shorter protocols, which becomes very convenient for patients, as they do not need to stay in the centre for so long [5[¶],7[¶],44].

Personalizing depending on resources

Local variations play a major role in the design of the management pathways for these patients [4[¶]]. For example, centres with limited access to intensive care beds might not consider higher risk procedures, such as drug challenge or would consider placing drug challenges later on in the management pathway (for example, after several well tolerated RDD procedures) [4[¶]].

Where local guidelines for managing hazardous drugs require infusion lines to be primed with fluids (as opposed to the actual drug), allergists might need to use the RCUH flexible standard RDD protocol [6,7[¶]]. Or as another example, access to high precision pumps might motivate the use of one bag RDD protocols [39[¶]].

As local variations can significantly affect decision-making and management pathways, informed

consent should be adapted locally in liaison with the local ethics authority. RCUH recommends two types of informed consent. The first one, signed by the allergist and the patient, focused on the different kinds of allergy procedures (e.g. skin testing, drug challenge, or drug desensitization). The second one is an informed consent signed by the referring physician and the patient, in which the referring physician confirms that the culprit drug is indicated as a first-choice drug, and there are no equally effective alternatives, and that the patient understands and agrees to this. The second informed consent is a safety measure to avoid system errors and a helpful tool to ensure that we provide patients with multidisciplinary, coordinated, and empowered decisions.

Regardless of local variations, allergy departments willing to undergo these procedures need to redesign care to make sure they will meet the highest standards. This redesign will involve new spaces, multidisciplinary teams, specially trained staff, involvement of quality improvement and continuous education, teaching, and research [1[¶]].

CONCLUSION

RDD is not a unique recipe that can be found in a 'cookbook' and applied to any given patient. Countless factors will affect the success of the procedure and patient safety (see Fig. 2). Management by experts in RDD and access to specific spaces and resources is essential. Risk management strategies must be adapted locally and must be comprehensive and multifactorial, including risk assessment tools, standard operating procedures, worst-case scenario recovery plans, and constant improvement and training. Multidisciplinary teams led by expert allergists are critical for the sustainability and

Endophenotype	Desensitisation protocols	Culprit drug	Risk assessment	Tolerance to the procedure	Resources
• Affects indication • Affects likelihood of a breakthrough reaction • Affects decisions on monitoring and premedication	• Should adhere to basic principles • Personalized • Flexible • Adaptable to local requirements • Different protocols for different purposes	• Repeated RDDs if the drug is administered intermittently • One-off RDD if the drug is given continuously or in a cycle • Adapt RDD to route, final volume and flow rate • Transitioning to shorter protocols	• Delabelling pathways (drug challenge) • Comprehensive risk management strategies	• Premedication • Adjustments • Transition to shorter protocols • Ex novo DHRs & double RDDs	• Local variations • Redesign of care • Appropriate spaces (safety) • Expert staff • Allergy-led • Multidisciplinary • Quality improvement • Continuous education

FIGURE 2. Factors that affect the personalization of rapid drug desensitization. DHR, drug hypersensitivity reaction; RDD, rapid drug desensitization.

success of RDD. As with any high-complexity and high-risk procedure, personalization in drug desensitization is a fundamental pillar but centres offering this procedure should also pay attention to other fundamental pillars; namely, innovation, continuous improvement, research, and teaching.

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- of special interest
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