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Drug Allergy (MJ Torres Jaén, Section Editor)

Rapid Desensitization in Immediate Hypersensitivity Reaction to Drugs

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Opinion Statement

Adverse drug reactions have increased dramatically worldwide, often preventing the use of first-line therapies. Not infrequently, many patients presenting with drug hypersensitivity reactions are irreversibly labeled as allergic, fact that prevents them to receive the most appropriate treatment for their illnesses. Rapid drug desensitization has become a cornerstone in the management of immediate drug hypersensitivity reactions. It is the only effective procedure for overcoming hypersensitivity reactions to first-line therapy, thus representing an important advance in patients' treatment and prognosis. Continued reports on the safety and efficacy of rapid drug desensitization emerging from different institutions are essential to allow the dissemination of desensitization programs.

Introduction

Adverse drug reactions have increased dramatically worldwide, often preventing the use of first-line therapies. Patients with cancer and chronic inflammatory diseases are increasingly exposed to new chemotherapy drugs and monoclonal antibodies with sensitization potential.

Drug hypersensitivity reactions (DHRs) are a subgroup of unexpected reactions that are characterized by objectively reproducible symptoms and/or signs initiated by exposure to a drug at a dose that is normally tolerated [1••, 2•]. DHRs can be immediate or delayed, depending on the time elapsed between drug

administration and the onset of symptoms. Immediate DHRs occur while the medication is being administered (such as during the infusion of chemotherapy) or within the first hour after administration. Clinical symptoms can be characterized by flushing, urticaria, angioedema, laryngeal edema, gastrointestinal symptoms (nausea, vomiting, diarrhea), respiratory symptoms (rhinoconjunctivitis, bronchospasm), hypotension, and cardiovascular collapse, which can lead to death. Immediate DHRs can further be classified in allergic or non-allergic, depending on the mechanism of the reaction (Fig. 1) [1••, 2•].

Most patients with DHRs are labeled as "allergic" which prevents them from receiving the best treatment for their illnesses. A novel and alternative approach is rapid drug desensitization (RDD), a groundbreaking procedure that allows patients to transiently tolerate the medication that triggered the original reaction, while providing the full treatment dose [3••, 4, 5•].

RDD is a cornerstone in the management of immediate DHRs, including anaphylaxis, and can be applied to the treatment of any immediate hypersensitivity reaction, allergic or non-allergic. RDD induces, in a short period of time, temporary unresponsiveness to a particular drug that had previously induced a hypersensitivity reaction, thereby allowing patients to be safely exposed to the culprit drug. Such temporary unresponsiveness can be achieved by gradual re-introduction of small doses of the involved drug up to full target dose, remarkably reducing the risk of serious and potentially lethal DHRs [3••].

RDD has evolved from empiricism to scientific evidence-based therapy, and its effectiveness has been shown with successful clinical outcomes [6••, 7••, 8]. Despite its clinical success, the mechanisms and molecular targets of RDD are not fully understood. The evidence suggests that the effector cells of anaphylaxis, mast cells and basophils, are rendered hyporesponsive by RDD. Several hypotheses to explain the mechanisms underlying cell hyporesponsiveness were proposed, such as exhaustion of stored mediators caused by repetitive stimulation (taquiphylaxis), Syk and Lyn consumption, FceRI internalization, activation of inhibitory receptors, and suboptimal doses of antigen unable to cross-link FceRI receptors. It has been established that activating signals are counterbalanced by inhibition signals and a number of inhibitory receptors have been identified on mast cells [8–11]. Some of these, such as FcγRII and LILRB4 (GP49), are immunoreceptors signalizing throw tyrosine-based inhibitory motifs (ITIMs) that recruit protein tyrosine phosphatases, which are negative regulators of FceRI-mediated mast cell responses [12]. There are probably several effector mechanisms of RDD.

Clinical tolerance has been described to occur within a few hours in patients undergoing RDD, a time that does not allow induction of tolerance at T cell level. It has yet to be established whether repeated RDD in drug-allergic patients could induce regulatory T cells after multiple desensitizations.

The aim of the present study is to review RDD, addressing its general features, the most important and prevalent procedures, and the future perspectives.

Definition, indications, and contraindications

RDD is the process of induction of a state of unresponsiveness to a drug responsible for a DHR in a short period of time, usually some hours. RDD is a therapeutic procedure indicated for patients with proven or highly suspected hypersensitivity reactions that should be recommended after an individual risk/benefit assessment showing that the benefits outweigh the risks (Fig. 2) [3••, 4, 13•].

The indications of RDD are as follows: (1) There is no alternative drug; (2) The culprit drug is more effective (increased quality of life and/or life expectancy) and/or associated with less side effects than alternative drugs; and (3) The culprit drug has a unique mechanism of action, such as aspirin in "aspirin-exacerbated respiratory disease—AERD." The procedure is indicated with caution in high-risk patients and absolutely contraindicated in delayed severe, life-threatening, reactions such as exfoliative dermatitis syndromes, Stevens-

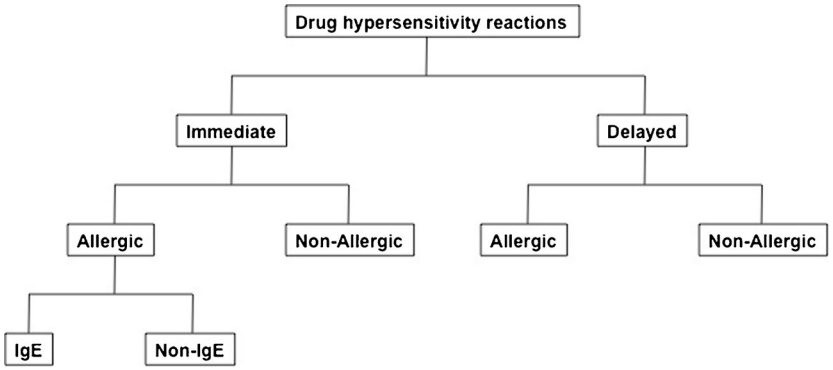

Fig. 1. Classification of drug hypersensitivity reactions (DHRs).

Johnson syndrome (SJS), toxic epidermal necrolysis (TEN), drug reaction with eosinophilia and systemic symptoms/drug-induced hypersensitivity syndrome (DRESS/DIHS), fixed drug eruption, erythema multiforme, bullous dermatitis, acute generalized exanthematous pustulosis (AGEP), severe immunocytotoxic reactions, and vasculitis (Tables 1 and 2).

After confirming the diagnosis of DHR, the allergist must assess the patient risk and evaluate the risk/benefit ratio of RDD (Fig. 2 and Table 2). When RDD is indicated, the patient's consent form must be obtained before the procedure. Although there are general rules, all RDD are drug and dose specific, and the risk stratification has to be individualized for every patient.

General rules

RDD consists in the consecutive administration of small doses of the culprit drug until the full therapeutic dose is reached. The goal of the procedure is to administer suboptimal doses to the patient that will promote "small stimulation" of mast cells/basophils, inducing inhibitory mechanisms and rendering these cells hyporesponsive. The challenge of RDD is to gradually increase the dose of medication without reaching a threshold concentration

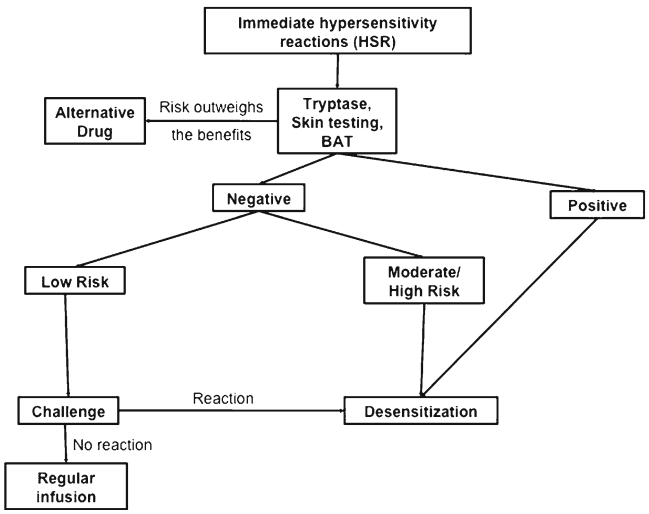

Fig. 2. General algorithm for rapid drug desensitization (Key: *BAT* basophil activation test).

Table 1. Indications and contraindications of rapid drug desensitization (RDD)

Indications	Relative contraindications (high-risk patients)	Absolute contraindications
No alternative drug	Severe anaphylaxis	Severe cutaneous adverse reactions (SJS/TEN, DIHS/DRESS, AGEP)*
Drug is more effective and/or associated with less side effects	Uncontrolled and/or severe respiratory disease (asthma)	Immunocytotoxic reactions (type II reactions)
Drug has a unique mechanism of action	Uncontrolled and/or severe cardiac disease	Vasculitis
		Serum sickness-like (Type III reactions)
	Uncontrolled and/or severe systemic diseases	
	Use of beta-blockers, ACE inhibitors	
	Pregnancy	

**SJS* Stevens-Johnson syndrome, *TEN* toxic epidermal necrolysis, *DIHS* drug-induced hypersensitivity syndrome, *DRESS* drug reaction (rash) with eosinophilia and systemic symptoms, *AGEP* acute generalized exanthematous

that would trigger anaphylaxis, although mast cells/basophils may release some amount of mediators during RDD. Figure 3 illustrates the concept that each administered dose induces more cell inhibition and raises the threshold for clinical symptoms.

Oral and parenteral (IV, IM, and SQ) routes of administration can be used for RDD, presenting similar effectiveness. Some studies suggest that the oral route for penicillin-allergic patients can be safer, easier, and less expensive, although it is not always the most appropriate. There are protocols combining oral and IV RDD for beta-lactams [14•].

RDD starting doses range from 1/10.000 to 1/100 of the full therapeutic dose, but it can be as low as 1/1.000.000 in very high-risk patients. In patients with positive skin test to non-irritating concentration of a drug, the starting dose can be determined on the basis of the endpoint titration. Classical protocols increase doses by doubling them every 15–20 min over the course of several hours until the therapeutic dose is reached [3••, 6••, 7••, 15, 16].

The BWH/DFCI Desensitization Center has established flexible 4- to 16-step protocols that have been used in over 3000 cases, becoming the standard of care at BWH/DFCI [6••, 7••]. The standard RDD protocol has three diluted bags, 12 steps, and is accomplished in 6 h. Patients whose initial hypersensitivity reactions are severe (grade 3, according to Brown's classification [17•]) can be

Table 2. Assessment of risk/benefit ratio

Risk Grade	Features	Protocol	Infusion center
Low-risk	DHR grades 1–2	12 step	Outpatient (day care)
High-risk	DHR grade 3	16–20 step	Intensive care unit
	Severe and/or uncontrolled disease (asthma, cardiac)		
	Beta-blocker use		
	Pregnancy		

DHR drug hypersensitivity reaction

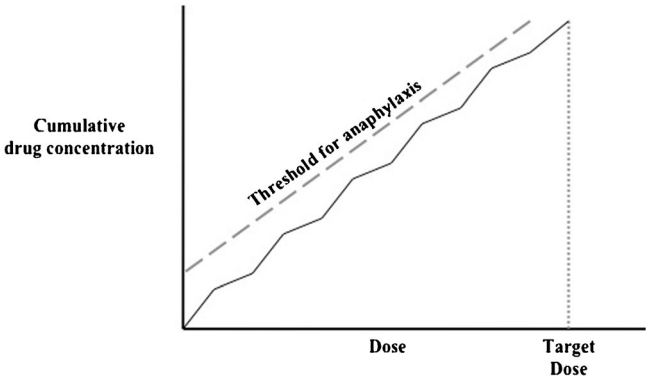

Fig. 3. Hypothetical mechanism of rapid drug desensitization.

desensitized with 4 bags and 16 steps. A 12-step protocol to rituximab and a 16-step protocol to carboplatin are shown in Tables 3 and 4, respectively.

Drug RDD induces a temporary state of tolerance that depends on the drug half-life. Once 2 half lives have spanned after RDD, the patient needs to be redesensitized at the time of next exposure.

Breakthrough reactions during RDD are less severe than the initial DHR, and no deaths have been reported in the last 15 years [18]. The anaphylactic reaction induced by RDD should be treated in the same way of those induced by other agents [7••]. However, a higher level of attention is needed, as patients are premedicated and some symptoms of DHR induced by chemotherapy and monoclonal antibodies are not typical of anaphylactic-like reactions.

Desensitization to platinum compounds

Platinum compounds are mainly used in chemotherapy of ovarian, colorectal, endometrial, and pancreatic cancer. DHR to carboplatin ranges from 9 to 27 %, in most cases corresponding to IgE-mediated allergic reactions [19–21]. In a typical clinical presentation, the patient with ovarian cancer becomes sensitized during the first course of chemotherapy (six carboplatin infusions). When the cancer recurs, the patient is boostered with the seventh exposure and presents anaphylaxis on subsequent exposures.

The characteristics of DHR to platinum compounds are typical of type I reactions, namely most patients develop cutaneous symptoms with palmar or facial flushing. In the report of 413 desensitizations by Castells et al., of the 60 patients who had a DHR to carboplatin, 100 % had cutaneous symptoms, 57 % had cardiovascular symptoms, 40 % had respiratory symptoms, and 42 % had gastrointestinal manifestations [6••]. Other types of heterogeneous and unpredictable reactions, mainly to oxaliplatin, have been reported such as antibody-mediated thrombocytopenia and immune complex-mediated disease with urticaria, joint pain, and proteinuria [22]. Pulmonary fibrosis and cytokine release syndrome with fevers and chills have also been reported [23].

Skin testing and serum-specific IgE to platinum compounds confirmed the involvement of mast cells and IgE in these DHRs [24•]. A recent study showed that platin-specific IgE can be a valuable diagnostic test and that

Table 3. An example of 12-step protocol to rituximab

Name of medication:		**Rituximab**				
Target dose (mg)				637.5		
Standard volume per bag (ml)				250		
Final rate of infusion (ml/h)				80		
Calculated target concentration (mg/ml)				2.55		
Standard time of infusion (minutes)				187.5		
					Total mg per bag	Amount of bag infused (ml)
Solution 1	250	ml of	0.026	mg/ml	6.375	9.25
Solution 2	250	ml of	0.255	mg/ml	63.750	18.75
Solution 3	250	ml of	2.530	mg/ml	632.483	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	0.0128	0.0128
2	1	5.0	15	1.25	0.0319	0.0446
3	1	10.0	15	2.50	0.0638	0.1084
4	1	20.0	15	5.00	0.1275	0.2359
5	2	5.0	15	1.25	0.3188	0.5546
6	2	10.0	15	2.50	0.6375	1.1921
7	2	20.0	15	5.00	1.2750	2.4671
8	2	40.0	15	10.00	2.5500	5.0171
9	3	10.0	15	2.50	6.3248	11.3420
10	3	20.0	15	5.00	12.6497	23.9916
11	3	40.0	15	10.00	25.2993	49.2909
12	3	80.0	174.375	232.50	588.2091	637.5000
Total time (min)=339.375=5.66 h						

oxaliplatin appears to be the most immunogenic platin. Patients sensitized to oxaliplatin are at a higher risk of developing a reaction to carboplatin and cisplatin [24•].

Slow infusion rates and increased premedications have not provided protection against anaphylaxis and severe reactions and even deaths have been reported in heavily premedicated patients [25]. Likewise, attempts to overcome the DHR by switching to another platinum-based agent cannot be recommended due to the high rate of cross-reactions [26]. These patients should undergo skin testing, risk stratification, and if indicated RDD. Desensitization has proven to be a safe and effective way to enable a patient to continue chemotherapy [6••].

Desensitization to taxanes

Taxanes are chemotherapeutic agents that are mainly used in the treatment of ovarian, endometrial, breast, and non-small cell lung cancers. The two main

Table 4. An example of 16-step protocol to carboplatin

Name of medication:		**Carboplatin**				
Target dose (mg)			332.0			
Standard volume per bag (ml)			250			
Final rate of infusion (ml/h)			80			
Calculated target concentration (mg/ml)			1.328			
Standard time of infusion (minutes)			187.5			
					Total mg per bag	Amount of bag infused (ml)
Solution 1	250	ml of	0.001	mg/ml	0.166	9.38
Solution 2	250	ml of	0.013	mg/ml	3.320	9.38
Solution 3	250	ml of	0.133	mg/ml	33.200	18.75
Solution 4	250	ml of	1.318	mg/ml	329.379	250.00
PLEASE NOTE		The total volume and dose dispensed are more than the final dose given to patient because many of the 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	2.5	15	0.625	0.000	0.000
2	1	5	15	1.25	0.001	0.001
3	1	10	15	2.5	0.002	0.003
4	1	20	15	5	0.003	0.006
5	2	2.5	15	0.625	0.008	0.015
6	2	5	15	1.25	0.017	0.031
7	2	10	15	2.5	0.033	0.064
8	2	20	15	5	0.066	0.131
9	3	5	15	1.25	0.166	0.297
10	3	10	15	2.5	0.332	0.629
11	3	20	15	5	0.664	1.293
12	3	40	15	10	1.328	2.621
13	4	10	15	2.5	3.294	5.915
14	4	20	15	5	6.588	12.502
15	4	40	15	10	13.175	25.677
16	4	80	174.375	232.5	306.323	332.000
Total time (min)=399.375=6.66 h						

taxane molecules are paclitaxel and docetaxel. Paclitaxel is a natural molecule that was originally isolated from the bark of the pacific yew tree, and docetaxel is a semi-synthetic molecule derived from a taxoid precursor found in European yew tree needles. The mechanism of DHRs to taxanes remains uncertain and can be more than one. Solvents used to solubilize the taxane molecules (Cremophor for paclitaxel and polysorbate 80 for docetaxel) can cause complement activation leading to anaphylatoxins production and mast cell activation [27]. More recently, IgE-mediated HSR to the taxane molecule itself has been reported, generating interest in providing skin test evaluation for patients with DHR to taxanes [28, 29].

In the initial studies with taxanes, DHR were very frequent and led to the use of premedication with corticosteroids and antihistamine. Even with the use of premedication and with lower infusion rates, hypersensitivity reactions occur in about 10 % of patients, and in 1 % are severe [30, 31]. Most of these reactions occur during the patient first or second lifetime infusion of the drug and present with symptoms such as flushing, dyspnea, throat tightness, and hypotension. However, patients also often report symptoms that are atypical for a DHR such as crushing chest and back and/or pelvis pain [6••].

A recent study showed that risk stratification based on skin testing and the severity of the initial hypersensitivity reaction can safely guide DHR management [29]. In patients that react to taxanes, rapid drug desensitization has been shown to be a safe and effective mean of re-introducing the drug [6••].

Desensitization to monoclonal antibodies

Monoclonal antibodies (mAbs) are drugs with a wide range of applications that include the treatment of neoplastic, inflammatory, and autoimmune diseases [32, 33]. The development of this drug class started in the 1970s, but mAbs' use became widespread in the past decade, leading to an increase in reported DHR secondary to their usage. Some of the main monoclonal antibodies are presented in Table 5, including their targets, incidence of overall injection/infusion site reactions, and severe immediate HSR.

Table 5. Monoclonal antibodies: targets, incidence of adverse and hypersensitivity drug reactions (adapted from Galvão VR [42•])

Rituximab (Rituxan®) IV	CD20	77 % (first infusion)	5–10 %
Ofatumumab (Arzerra®) IV		44 % (first infusion) 67 % (combination therapy)	2 %
Trastuzumab (Herceptin®) IV	Extracellular domain of the HER-2 receptor	40 % (mild; first infusion)	0.6–5 %
Cetuximab (Erbitux®) IV	Extracellular domain of EGFR	15–21 %	1.1–5 %, 14–27 % (Southern USA)
Tocilizumab (Actemra®) IV	IL-6 receptor	7–8 %	0.1–0.7 %
Infliximab (Remicade®) IV	TNF-α	5- 18 %	1 %
Etanercept (Enbrel®) SC		15- 37 %	<2 %
Adalimumab (Humira®) SC		20 %	1 %
Golimumab (Simponi®) SC		4–20 %	n/r
Certolizumab (Cimzia®) SC		0.8–4.5 %	n/r
Brentuximab (Adcetris®) IV	CD30	12 %	**
Omalizumab (Xolair®) SC	IgE	45 %	0.09–0.2 %

**Case reports of anaphylaxis

HSR hypersensitivity reactions, *HER-2* human epidermal growth factor receptor 2, *EGFR* human epidermal growth factor receptor, *TNF-α* tumor necrosis factor alpha, *n/r* not reported, *IgE* immunoglobulin E

Depending on the structure of the monoclonal, it can be more or less immunogenic. What accounts for the difference is the amount of human content present in the antibody, varying from chimeric mouse-human, humanized, to a fully human mAb [34]. Severe DHR can occur even with fully human mAbs such as adalimumab and ofatumumab. DHR to mAbs can occur on the first exposure, as it can be observed with cetuximab and trastuzumab, predominantly in the first three infusions, as with omalizumab, or after multiple exposures [32, 33].

Infusion-related reactions to mAbs can occur in a significant number of patients for certain agents and manifest with chills, fever, nausea, and malaise [7••, 34, 35]. Typical first-time infusion reactions for trastuzumab include chills and/or fever and occur in approximately 40 % of patients [36]. These are thought to be due to the release of proinflammatory cytokines (such as IL-6 and TNF-α) and do not tend to be severe, except for the findings of the of the anti-CD28 monoclonal antibody TGN1412 phase 1 trial in which six volunteers who received the drug developed multiorgan failure as a result of a severe cytokine storm [37].

In addition, there have been reports of types I, III, and IV DHR related to mAb infusion. Patients can present with signs and symptoms typical of type I HSRs, including cutaneous, cardiovascular, respiratory, gastrointestinal, and/or neurological manifestations, while the drug is being infused or within the first hour after administration. Delayed DHR suggestive of type IV reactions have been reported, as well as reactions suggestive of type III reactions (serum sickness-like), with symptoms such as rash, myalgia, fever, polyarthralgias, pruritus, edema, and fatigue [38, 39]. Examples of the latter are DHR induced by infliximab (1 to 14 days after the infusion) and omalizumab (1 to 5 days after infusion) [40, 41].

Monoclonal antibodies whose application is subcutaneous might elicit injection-site reactions. These include local redness, warmth, burning, stinging, itching, urticaria, pain, and induration, varying in frequency from 0.8–4.5 % with certolizumab to up to 45 % with omalizumab. Such reactions can start in the first hour of the injection and tend to resolve in the subsequent days [33].

When managing a DHR related to mAb, the infusion must be immediately stopped and it is strongly advised to obtain a tryptase level within 30 to 120 min of the reaction [42•, 43•, 44]. Increased levels of tryptase will point out to a reaction with an underlying mast cell activation mechanism. Epinephrine is indicated in severe reactions involving hypotension and/or desaturation and should be promptly administered [45•]. Skin testing with the offending agent can be done when an IgE-mediated reaction is suspected, but this specific investigation should wait 2 to 4 weeks to minimize the chances of false-negative results [42•, 46]. The negative predictive value for most mAbs is not known [7••].

RDD is a novel therapeutic option for selected patients who present with DHR to mAbs [3••]. It enables the patient to receive the full treatment dose while protecting from anaphylaxis [7••]. Type I DHR to monoclonals are subject to RDD, and immediate injection-site and systemic reactions elicited by subcutaneous agents (such as adalimumab and etanercept) have also had successful desensitization protocols established (Table 6—desensitization to adalimumab) [47].

Table 6. Desensitization to adalimumab (Time per step: 30 min/ Number of steps: 6/ Total dose: 55mg).

Step	Concentration (mg/ml)	Time (min)	Cumulative time (min)	Volume administered per step (ml)	Dose administered with this step (mg)	Cumulative dose (mg)
1	4	30	30	0.25	1	1
2	4	30	60	0.5	2	3
3	40	30	90	0.1	4	7
4	40	30	120	0.2	8	15
5	40	30	150	0.4	16	31
6	40	30	180	0.6	24	55

Adapted with permission from Galvão VR [42•]

Desensitization to penicillins and other β-lactam antibiotics

Beta-lactams (BLs) are recognized as one of the most frequent causes of immediate and non-immediate drug reactions, being considered the main cause of drug-induced anaphylaxis in developed countries [48]. The prevalence of penicillin hypersensitivity in the general population is unknown. Self-reported BL "allergy" is common (up to 20 % of hospitalized patients), but less than 20 % of patients who report these reactions are really allergic when submitted to skin tests and/or provocation tests [49•].

DHR induced by β-lactams is a classical model of reactions mediated by specific immunological mechanisms, particularly those mediated by IgE antibodies. These antibiotics bind covalently to high-molecular-weight proteins that can later be processed and recognized by the immune system, although the details of how this occurs have not yet been fully determined [50]. BLs continue to be the most common cause of DHRs mediated by specific immunological mechanisms [48, 49•, 50].

Once a patient report a BL-induced hypersensitivity reaction, it is possible to perform skin tests and in vitro tests to confirm the mechanism involved, differentiating IgE or non-IgE-mediated reactions. Most of skin tests are standardized and safe, but once skin tests are negative, provocation tests may be performed to establish the diagnosis [48, 49•].

If BL allergy is confirmed, it is not possible to substitute the antibiotic, and there is no contra-indication to RDD, BL-desensitization (BL-DST) can be indicated. Most case series of BL-DST published have described patients with immediate reactions, using RDD protocols. Since the first report of a BL-DST in 1946, many protocols have been published [48, 49•, 51].

There have been no large comparative studies between oral and IV routes of desensitization, and both have been successfully utilized in RDD to BLs [48, 49•, 52]. Continuous monitoring for adverse reactions is mandatory for both routes. The oral route leads to slower-onset allergic reactions and potential reactions are identified earlier with the IV route [48, 49•]. As it is easier to perform, oral route is most commonly applied to BL-DST.

Even when the antibiotic should be administered intravenously or intramuscularly, as in benzathine penicillin to syphilis treatment, it is

possible to start with the oral route and change to the parenteral route when a high dose is reached. In the Clinical Immunology and Allergy Division of the University of São Paulo, Brazil, the Wendel's protocol has been adapted to treat late latent syphilis, particularly in pregnant patients, who must take three weekly doses of intramuscular benzathine penicillin (Table 7) [53•]. As benzathine penicillin has a long half-life, maintaining high plasma levels even after 3 weeks, patients with DHR successfully desensitized during the first dose administration can take the two subsequent doses as regular infusions.

Although desensitization was originally conceived for type I hypersensitivity reactions, a similar approach has been adopted for patients with delayed non-life-threatening, maculopapular reactions. There is no universal or consensus drug desensitization protocol to date for delayed-type hypersensitivity reactions with BLs [48, 54]. All desensitizations to BLs should be attempted only by experienced staff in the presence of full resuscitation facilities.

Desensitization to aspirin

Hypersensitivity reactions to aspirin (acetylsalicylic acid—ASA) and other non-steroidal anti-inflammatory drugs (NSAIDs) can induce a wide spectrum of hypersensitivity reactions with various timing, clinical manifestations, and severity, involving either immunological (allergic) or non-immunological mechanisms [55•]. NSAIDs are some of the most important drugs imputed in DHRs and are a major cause of drug-induced anaphylaxis in developing countries [56•].

Table 7. Oral rapid penicillin-desensitization protocol to late latent syphilis

Step no.	Penicillin (IU/mL)	Time (min)	Volume administered per step (mL)	Administered dose (IU)	Cumulative dose (IU)
1	1.000	15	0.1	100	100
2	1.000	15	0.3	300	400
3	1.000	15	0.6	600	1.000
4	5.000	15	0.3	1500	2.500
5	5.000	15	0.7	3500	6.000
6	50.000	15	0.1	5.000	11.000
7	50.000	15	0.3	15.000	26.000
8	50.000	15	0.6	30.000	56.000
9	50.000	15	2.0	100.000	156.000
10	50.000	15	4.0	200.000	356.000
11	50.000	15	8.0	400.000	756.000
12	50.000	15	8.0	400.000	1.156.000
Change oral penicillin to intramuscular benzathine penicillin					
13	–	60	–	2.400.000 (i.m.)	3.556.000

RDD protocol of the Clinical Immunology and Allergy Division of the University of São Paulo (adapted from Wendel's protocol [53•]). After taking 1.156.000 IU of oral penicillin, the patients receive the therapeutic dose of benzathine penicillin (2.4 million IU i.m.) and are monitored for at least 60 min

IU International Unit, *mL* milliliter, *min* minute, *i.m.* intramuscularly

DHRs to NSAIDs are classified in five types of hypersensitivity reactions according to clinical features and mechanisms involved: single-NSAID-induced delayed hypersensitivity reactions, single-NSAID-induced urticaria/angioedema or anaphylaxis, aspirin- or NSAID-exacerbated respiratory disease (AERD/NERD), NSAID-exacerbated cutaneous disease, and NSAID-induced urticaria/angioedema [55•]. The first two types involve specific immune responses and patients do not present cross-reactivity between different groups of NSAIDs. On the other side, the three last types are non-allergic and patients are usually cross-intolerant to different groups of NSAIDs.

Since NSAIDs are usually not indicated on a daily basis and can be substituted to other classes of drugs, as corticosteroids or opioids, desensitization is not an option for most hypersensitive patients. Nevertheless, there are specially two clinical pictures in which aspirin is indicated on a daily basis: AERD and cardiovascular or neurovascular disease.

Aspirin desensitization in AERD/NERD

Aspirin-exacerbated respiratory disease (AERD) or non-steroidal anti-inflammatory drug-exacerbated respiratory disease (NERD) has been defined as the clinical tetrad of asthma, chronic rhinosinusitis (CRS), nasal polyposis, and intolerance to non-steroidal anti-inflammatory drugs (NSAIDs), such as aspirin [57]. Ingestion of these medications results in both upper and lower respiratory symptomatology, namely nasal congestion, rhinorrhea, conjunctivitis, laryngospasm, and/or bronchoconstriction. However, other adverse reactions including hypotension, urticaria, and abdominal pain have also been reported.

The first description of an AERD patient desensitized to aspirin was made in 1922 by Widal et al [58]. Since then, many studies have been published showing better outcomes in patients with AERD/NERD who were desensitized to aspirin followed by continuous aspirin therapy [57, 59•]. Aspirin-intolerant asthmatic patients often experience severe and progressive upper and/or lower airway disease despite multiple nasal/sinus surgical procedures and aggressive anti-inflammatory treatment with inhaled and/or systemic corticosteroids and leukotriene-modifying drugs. Patients desensitized with aspirin experience better outcomes, as improvement in numbers of sinus infections, sinus surgeries, sense of smell, nasal and asthma symptoms, decrease in rates of emergency room visits and admission for asthma, and a significant decrease in the use of systemic and topical corticosteroids [59•, 60].

It was recently demonstrated that clinically beneficial effects of aspirin-DST on nasal and bronchial symptoms occur only in patients with aspirin-induced asthma, but not in those who tolerate aspirin [61]. Although most patients with AERD will benefit clinically from desensitization, this treatment is particularly helpful in patients who have suboptimal control of respiratory symptoms with currently available pharmacotherapy, or require multiple operations due to re-growth of nasal polyps, or have intractable sinus disease. Moreover, aspirin-DST is indicated in AERD patients who require aspirin or NSAIDs for concomitant cardiovascular diseases, arthritis, or other medical indications [60, 62].

Many protocols have been performed in aspirin desensitization of AERD/NERD patients, most of them reaching the final dose of 650 mg bid in 2 or 3 days. The actual recommendation is to reach this dose and, if the patient improves and the respiratory disease is controlled, taper the aspirin dose until 325 mg bid [60]. Likewise, there is cross-reaction between NSAIDs in exacerbating AERD, there is cross-desensitization, and patients aspirin-desensitized tolerated other NSAIDs. However, only aspirin is associated with AERD improvement. The general features of aspirin desensitization are summarized in Table 8.

Differently from other drugs, challenge and RDD with aspirin are performed with the same protocol, escalating acetylsalicylic acid (ASA) dose until 325 mg (Table 9). When the aim is to confirm the diagnosis of AERD, the challenge is considered positive if the patient presents a reaction such as naso-ocular symptoms alone or with a decline of 15 % in FEV1, lower respiratory symptoms with a decline of 20 % in FEV1, laryngospasm with any of the signs cited above, or a systemic reaction. If there is any reaction, the test is stopped and the patient is adequately treated [60].

Regarding RDD, if the patient presents a reaction, it has to be rapidly treated and the protocol goes on after the symptoms are resolved. In this case, the ASA provoking dose should be repeated and, if no reaction occurs, the doses continue to be escalated as presented in Table 9. At 325 mg of ASA, DST is completed and it is possible to give 650 mg as first maintenance dose and then continue treating with 650 mg bid [60].

Before starting a challenge or DST with ASA, some important information should be taken carefully. ASA-DST is safe and can be performed in the outpatient clinic, since providers and staff have experience with these procedures. Moreover, outpatient oral ASA-DST are much more cost-effective than inpatient ones. Nevertheless, some rules should be followed. We do not encourage physicians to start ASA challenges if FEV1 values are lower than 60 % of predicted or lower than 1.5 L. Thus, patients should be taking a leukotriene modifier (montelukast, zileuton, or both) prior to aspirin challenge. It has been shown that these drugs protect the lower airways from severe reactions during ASA challenges, without masking a positive reaction [60, 63]. Patients should also continue to take oral and topical corticosteroids and long-acting bronchodilators. However, antihistamines, decongestants, and short-acting inhaled beta-agonists should be discontinued prior to aspirin challenge because they may mask a potential positive reaction [60]. Protocols may start with oral placebo or intranasal ketorolac and then change to ASA.

Table 8. Features of aspirin desensitization for AERD and cardiovascular disease

Disease	AERD	Cardiovascular
Initial dose (mg)	20–40	1–5
Final dose (mg)	325	75–325
Maintenance dose (mg/day)	650–1300	75–325
Cross-desensitization	Yes	Yes/no (dose dependent)
Refractory period (h)	48–72	0–72
Premedication	Leukotriene modifier	Leukotriene modifier (if asthma)

Table 9. Protocol of oral aspirin provocation and rapid desensitization in patients with non-steroidal anti-inflammatory drugs/aspirin-exacerbated respiratory disease suggested by the group of Scripps Clinic, in San Diego, CA, USA (Adapted with permission from Lee RU et al. [60])

Time	Day 0 (or 1)	Day 1 (or 2), mg	Day 2 (or 3), mg
8 AM	Placebo	20–40	100–160
11 AM	Placebo	40–60	160–325
2 PM	Placebo	60–100	325

Aspirin desensitization in cardiovascular and neurovascular diseases

Another possible indication for aspirin-DST is cardiovascular disease (CVD) or neurovascular disease (NVD). Aspirin remains the mainstay of antiplatelet therapy in cardiac patients. Despite the fact that some new drugs have shown efficacy in preventing and treating CVD and NVD, as clopidogrel and ticagrelor, ASA is still the most available and less expensive drug. Moreover, many patients need dual antiplatelet therapy including aspirin, as those undergoing percutaneous coronary intervention (PCI). When patients are hypersensitive, dual antiplatelet combinations without aspirin may be used, but there is only limited evidence supporting this choice [64]. Desensitization is a good alternative for these patients and, differently from NERD/AERD, in CAD and NVD low doses of ASA, as 75 mg per day, have shown efficacy [64].

There are many protocols of RDD to ASA for CVD or NVD, starting from 1 to 5 mg and achieving doses as 75 to 325 mg per day [64–67]. It is important to establish with the patient's physician which dose he desires to achieve before designing the protocol. It is still controversial if ACE inhibitors and beta-blockers should be withheld before the ASA-DST, because of their benefits in vascular diseases. Thus, the use of antihistamines and corticosteroids as premedication is controversial, oppositely to NERD/AERD, for which patients must be treated with leukotriene modifiers and with asthma/rhinosinusitis drugs [66–68]. Finally, once the final therapeutic ASA antiplatelet dose is reached, it should not be interrupted in order to maintain aspirin tolerance.

Final remarks and future perspectives

Rapid drug desensitization (RDD) has become a cornerstone of the management of immediate drug hypersensitivity reactions (DHRs). It is the only effective procedure for overcoming DHRs to first-line therapy, thus representing an important advance in patients' treatment and prognosis. Successful RDD requires categorization of the severity and nature of the initial reaction, skin testing, and risk stratification, leading to the establishment of an initial desensitization protocol, with adjustments based on the patient's response. Understanding the mechanisms involved in RDD will allow improvements in patients' treatment,

overcome unwanted adverse reactions, and identify markers for therapeutic efficacy.

Compliance with Ethics Guidelines

Conflict of Interest

Pedro Giavina-Bianchi declares that he has no conflict of interest.
Marcelo Vivolo Aun declares that he has no conflict of interest.
Violeta Régnier Galvão declares that she has no conflict of interest.
Mariana Castells declares that she has no conflict of interest.

Human and Animal Rights and Informed Consent

This article does not contain any studies with human or animal subjects performed by any of the authors.

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- • Of importance
- •• Of major importance

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