

POSITION PAPER

Desensitization in delayed drug hypersensitivity reactions – an EAACI position paper of the Drug Allergy Interest Group

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Abstract

Drug hypersensitivity may deprive patients of drug therapy, and occasionally no effective alternative treatment is available. Successful desensitization has been well documented in delayed drug hypersensitivity reactions. In certain situations, such as sulfonamide hypersensitivity in HIV-positive patients or hypersensitivity to antibiotics in patients with cystic fibrosis, published success rates reach 80%, and this procedure appears helpful for the patient management. A state of clinical tolerance may be achieved by the administration of increasing doses of the previously offending drug. However, in most cases, a pre-existent sensitization has not been proven by positive skin tests. Successful re-administration may have occurred in nonsensitized patients. A better understanding of the underlying mechanisms of desensitization is needed. Currently, desensitization in delayed hypersensitivity reactions is restricted to mild, uncomplicated exanthems and fixed drug eruptions. The published success rates vary depending on clinical manifestations, drugs, and applied protocols. Slower protocols tend to be more effective than rush protocols; however, underreporting of unsuccessful procedures is very probable. The decision to desensitize a patient must always be made on an individual basis, balancing risks and benefits. This paper reviews the literature and presents the expert experience of the Drug Hypersensitivity Interest Group of the European Academy of Allergy and Clinical Immunology.

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Drug hypersensitivity reactions account for more than 15% of all adverse drug reactions and are an important problem in clinical medicine. Drug hypersensitivity reactions may be allergic or nonallergic. Allergic reactions are IgE- or non-IgE-mediated (1). They have also been classified into

immediate and nonimmediate (2). Immediate drug hypersensitivity reactions occur within 1 h after drug exposure and can be IgE-mediated or linked to a nonspecific histamine release. Nonimmediate or delayed reactions manifest after more than 1 h. In some of these reactions, a T-cell-mediated

mechanism has been demonstrated (3). Here, the delay is typically 12–24 h.

For the purpose of this paper, the focus lies only on typical uncomplicated and nonserious, mild delayed reactions with different clinical presentations (Table 1), primarily maculopapular exanthems and fixed drug eruptions (FDE).

Exanthematous drug eruptions are the most common delayed hypersensitivity reactions and have been reported to occur in approximately 2% of hospitalized patients and complicate 3 per 1000 courses of drug therapy (4). The majority of exanthematous drug eruptions consist of uncomplicated maculopapular exanthems without clinically detectable systemic involvement. The usual practice is to permanently avoid the culprit drug and to use a structurally different, non-cross-reacting compound for future treatment. However, there are situations where there is no alternative to using the causative drug. In such situations, drug desensitization has been shown to be safe and successful in certain cases, for example, the use of sulfamethoxazole in HIV patients or antibiotics in patients with cystic fibrosis.

In a recent position paper, an expert panel under the auspices of EAACI reviewed available desensitization procedures for immediate drug hypersensitivity and gave recommendations (5). For delayed hypersensitivity reactions, the literature on desensitization is less extensive and more controversial. This consensus paper aims to clarify the many uncertain and controversial issues including the definitions, indications, and

contraindications, as well as the protocols and recommend guidelines with regard to the management of such patients.

In the literature, there are no controlled studies. Regarding the case reports or case series published, a formal evidence-based review is impossible. Therefore, the expert panel considered literature data collected by searching Medline database using the keywords: drug hypersensitivity, drug allergy, desensitization, tolerance induction, graded challenge. The panel also considered the experience of some European centers. This document represents the collective opinion of the expert panel concerning desensitization in delayed drug hypersensitivity as a consensus statement.

Definitions

In the context of diagnostic and therapeutic procedures in hypersensitivity reactions to drugs, many different terms and definitions have been used in the literature, which are sometimes overlapping. In this paper, we use the following definitions for the terms:

1 Drug tolerance

This term defines a state in which a patient with drug hypersensitivity will tolerate a drug without an adverse reaction. The exact duration of the tolerance after desensitization in delayed drug hypersensitivity is unknown and may depend on the type of reaction, the drug, and on patient-related factors. Drug tolerance does neither indicate a permanent state nor that the mechanism involved is immunologic tolerance (6).

2 Treating through

'Treating through' is the continuation of a drug treatment in the presence of a developing or established drug hypersensitivity reaction. In some situations, patients have been treated through, for example, a mild exanthem, sometimes under cover of anti-allergic medication such as corticosteroids and antihistamines (7–12), with or without dose reduction.

3 Provocation, Re-exposure, Graded drug challenge, Incremental test dosing, Dechallenge/Rechallenge

These terms have sometimes been used in the context of desensitization procedures. However, we consider them as diagnostic procedures, which are applied to confirm or exclude drug hypersensitivity (13, 14), and not to induce tolerance to the drug (5, 15).

4 Desensitization, Hyposensitization, Tolerance induction, Adaptive deactivation

These terms are used for procedures describing the induction of a clinical tolerance to a drug responsible for a previous hypersensitivity reaction. Here, the term 'tolerance' is used more in the sense of pharmacological tolerance, because there is little knowledge on a putative induction of an immunological mechanism during the procedure and should not be confused with the same term used in immunology. In contrast to de-/hyposensitization with peptide allergens such as aeroallergens or hymenoptera venoms, in drug desensitization with xenobiotics, there is usually only a state of temporary tolerance as long as the patient is treated with the pharmacologically active substance (5). After the cessation or interruption of the treatment, drug hypersensitivity may recur within some days, requiring a new course of desensitization.

Table 1 Clinical presentations of delayed drug hypersensitivity reactions

Exanthematic manifestations
Macular/maculopapular/papular exanthem
Symmetrical drug-related intertriginous flexural exanthema (SDRIFE, former Baboon syndrome)
Acute generalized exanthematous pustulosis (AGEP)
Drug rash with eosinophilia and systemic symptoms (DRESS)/drug hypersensitivity syndrome (DHS)
Severe cutaneous adverse reactions (SCAR)
Erythema multiforme (EM)
Stevens–Johnson Syndrome (SJS)
Toxic epidermal necrolysis (TEN)
Dermatitis
Fixed drug eruption
Others
Cutaneous vasculitis
Autoimmune skin disorders, for example drug-induced pemphigus or pemphigoid
Stomatitis
Internal organ manifestations (isolated or in the context of complex exanthems)
General symptoms: malaise, eosinophilia, fever, arthritis, lymphadenopathy
Organ involvement: hepatitis, pneumonitis, nephritis, nephrotic syndrome, myocarditis
Blood cell dyscrasias: neutropenia, thrombocytopenia, anemia
Systemic vasculitis
Systemic autoimmune disorders, for example drug-induced lupus erythematosus

Pathomechanism of delayed drug reactions and mechanism of desensitization

Cutaneous hypersensitivity reactions to drugs may be caused by different pathogenic mechanisms (Table 2). The specific involvement of T cells in this context is suggested by positive responses to delayed-reading intradermal tests and/or patch tests and lymphocyte transformation or activation tests (LTT). In nonbullous maculopapular exanthema, perforin-positive and granzyme B-positive CD4⁺ T cells kill activated keratinocytes, whereas a large number of cytotoxic CD8⁺ T cells in the epidermis are associated with formation of vesicles and bullae. Drug-specific T cells also orchestrate inflammatory skin reactions through the release of various cytokines. It has been proposed to subcategorize T-cell-mediated delayed hypersensitivity reactions into type IVa–d (Table 2). The release of certain cytokines and chemokines preferentially activates and recruits monocytes (type IVa), eosinophils (type IVb), or neutrophils (type IVd). Cytotoxic functions by either CD4⁺ or CD8⁺ T cells are predominant in type IVc reactions, but also seem to participate in other type IV reactions (16).

Other hypersensitivity reactions to drugs with late onset include drug-induced immune thrombocytopenia, drug-induced immune hemolytic, and aplastic anemia, as well as drug-induced neutropenia (Gell-Coombs type II). The pathophysiology of those blood cell dyscrasias is for the most part mediated by drug-induced antibodies, capable of causing cytopenia by complement activation, but also the formation of immune complexes (17).

With regard to desensitization in type I drug-induced hypersensitivity, some pathophysiological understanding exists on the mechanism of tolerance induction (5). In type II or type III reactions, desensitization is contraindicated, and in type IV reactions, there is only little literature data concerning the mechanism of desensitization. So far, only Teraki et al. demonstrated in FDE caused by allopurinol that the number of lesional CD25⁺ CD4⁺ T cells increased significantly after desensitization, whereas the number of lesional CD8⁺ T cells decreased from 94% of CD3⁺ cells to only 35% during desensitization. The authors suggest that the CD25⁺ CD4⁺ T regulatory cells migrating into the FDE lesion during desensitization might have a suppressive effect on the effector function of CD8⁺ T cells in FDE lesions. (18).

Indications and criteria for desensitization

Based on the literature, obligatory requirements for drug desensitization are (Table 3) as follows:

- 1 The urgent need for therapy or prophylaxis of a disease.
- 2 The drug concerned is irreplaceable or more effective than the potential alternatives.
- 3 The unavailability of a non-cross-reacting pharmaceutical agent for treatment.
- 4 The previous delayed drug reaction was not severe or life-threatening.
- 5 The potential benefit outweighs the potential risks.

Table 2 Classification of drug hypersensitivity (adapted from Refs 3 and 53)

	Antibody mediated				Cell mediated			
	Type I	Type II	Type III		Type IVa	Type IVb	Type IVc	Type IVd
Immune reactant	IgE	IgG	IgG		IFN- γ , TNF- α (T _H 1 cells)	IL-5, IL-4/IL-13 (T _H 2 cells)	Perforin/granzyme B (CTL)	CXCL8, IL-17 (?), GM-CSF (T cells)
Antigen	Soluble antigen	Cell- or matrix-associated antigen	Soluble antigen		Antigen presented by cells or direct T-cell stimulation		Cell-associated antigen or direct T-cell stimulation	Soluble antigen presented by cells or direct T-cell stimulation
Effector	Mast cell activation	FcR ⁺ cells (phagocytes, NK cells)	FcR ⁺ cells, Complement		Macrophage activation	Eosinophils	T cells	Neutrophils
Example of hypersensitivity reaction	Anaphylaxis, bronchoconstriction	Hemolytic anemia, thrombocytopenia	Serum sickness, Arthus reaction		Tuberculin reaction, allergic contact dermatitis (with IVc)	Maculopapular exanthema with eosinophilia	Contact dermatitis, maculopapular and bullous exanthema, hepatitis	Acute generalized exanthematous pustulosis (AGEP)

Table 3 Criteria and contraindications for desensitization in delayed hypersensitivity

Criteria for desensitization	
●	Drug therapy is essential
●	Drug is irreplaceable, more effective than alternatives, or it has a unique mechanism
●	Unavailability of a non-cross-reacting drug
●	Previous reaction is well documented and not severe, for example maculopapular exanthem or fixed drug eruption; preferably, the mechanism is known after allergologic workup
●	Potential benefits outweigh the potential risks
Contraindications	
Absolute	
●	Severe or life-threatening drug-induced diseases like SJS/TEN, DHS/DIHS/DRESS, cutaneous or systemic vasculitis, severe mucosal ulcerations
●	Drug-induced autoimmune disorders
●	Drug-induced severe general symptoms, such as drug fever, arthritis, generalized lymphadenopathy
●	Drug-induced organ involvement, such as hepatitis, nephritis, pneumonitis, or cytopenias, or severe eosinophilia
Relative (only after careful consideration)	
●	AGEP
●	Underlying autoimmune disorders
●	Pre-existing severe renal or hepatic impairment
●	Severe cardiac disease/hemodynamically unstable patient
●	Simultaneous treatment with potentially interfering drugs

The drug to be desensitized should present an optimal treatment for the disease in question. Any previous adverse drug reaction should be well documented, at least on a clinical level. It is highly preferable/recommended to also have some information on the underlying pathophysiology attained by adequate diagnostic means such as, where applicable, intradermal tests with delayed reading, patch tests and/or adequate validated *in vitro* assays. In situations, in which a causal relationship with the incriminated drug is not easy to investigate and prove, a direct tolerance induction by incremental dosing may be a pragmatic approach. The patient has to be informed about the risk and alternatives and should give his/her written informed consent for the procedure.

An attempt on desensitization to a drug that has previously caused a nonimmediate hypersensitivity reaction can only be undertaken if the previous reaction was not severe, for example an uncomplicated exanthem or FDE. It is also possible to desensitize critically ill patients, for example with acute infections, if the above-mentioned requirements for this specific situation are complied with.

There are some particular conditions where desensitization procedures following delayed-type hypersensitivity reactions have been applied with particular success. Numerous reports on successful desensitization in some mild, delayed-type T-cell-mediated reactions have been published. These include HIV-positive patients treated with trimethoprim/sulfamethoxazole for *Pneumocystis jirovecii* pneumonia (10) or *Pneumocystis*

prophylaxis, and *Toxoplasma* infection and tuberculostatic treatment in patients with tuberculosis. Whitaker (19) reports on 275 desensitization procedures in 42 adult patients with cystic fibrosis and recurrent bronchial infections with an overall success rate of 91% (piperacillin + tazobactam, ceftazidime, meropenem, aztreonam, tobramycin, polymyxin E).

A second group of disorders includes therapy-resistant epilepsy, inflammatory bowel diseases (ulcerative colitis and Crohn's disease), rheumatic disorders (rheumatoid arthritis), and patients with severe gout. In addition, many individual patients with different drugs have been successfully desensitized. For detailed success rates, see Table S1. It has to be pointed out, however, that in most cases, sensitization has not been documented (e.g. by a positive skin test). Thus, many cases of a successful 'desensitization' may correspond only to an unproblematic re-exposure of patients who were not sensitized previously.

Contraindications

In our opinion, desensitization with the culprit drug is absolutely contraindicated (Table 3) in severe or life-threatening delayed drug hypersensitivity reactions, such as Stevens–Johnson syndrome (SJS), toxic epidermal necrolysis (TEN), drug hypersensitivity syndrome (DHS), also called drug reaction/rash with eosinophilia and systemic symptoms (DRESS), or drug-induced hypersensitivity syndrome (DIHS) (20). In acute generalized exanthematous pustulosis (AGEP), careful consideration is needed, even though there is a report of a successful desensitization with epoetin- α in a patient with severe renal insufficiency (21). Patients with extensive mucosal ulcerations, cutaneous or systemic vasculitis, drug-induced autoimmune disorders, and severe general symptoms, for example drug fever, arthritis, or generalized lymphadenopathy, should not be desensitized. Desensitization in patients with drug-induced internal organ involvement such as hepatitis, nephritis, pneumonitis, cytopenias (agranulocytosis, thrombocytopenia, anemia), or severe eosinophilia is not recommended (Table 3), because the evolution of these conditions is unpredictable and may get beyond medical control.

Severe underlying disorders, such as renal or hepatic insufficiency and indicated therapy with potentially interfering drugs, as well as unstable cardiac disease or uncontrolled autoimmune disorders, are relative contraindications (13, 22).

There are some cases where exceptions due to the severity of the situation have been made. We are aware that there have been reports in the literature on successful desensitizations in patients with sulfamethoxazole-induced SJS (23) and drug-induced hepatitis (24–26). However, we are convinced that currently the risks outweigh by far the benefit.

Procedures

Published protocols

There are, so far, no controlled studies available on desensitization in delayed-type hypersensitivity reactions to drugs.

Publications vary in number of patients assessed from single case reports to patient series of less than five patients to several dozens of patients per individual drug, as listed on the EAACI website (Table S1). The reports vary greatly in terminology, characterization of patients, and the practical aspects concerning desensitization, for example dose increment, route of administration, time interval between incremental doses, number of days needed to reach a full therapeutic dose, and use of premedication.

The most extensive literature exists on patients who have been desensitized with co-trimoxazole, particularly HIV-positive patients (10). Other successfully desensitized sulfonamides include diaminodiphenylsulfone (dapsone), sulfadiazine, sulfasalazine, and mesalazine. Desensitization with antibiotics, especially in patients with cystic fibrosis, includes beta-lactams and few cases each with ciprofloxacin, clindamycin, tetracyclines, and others (Table S1).

There are a few reported cases on one or several tuberculo-static drugs, such as ethambutol, isoniazid, rifampicin, streptomycin, and p-amino salicylic acid, but also with antimycotics, such as fluconazole and itraconazole, as well as virostatics (amprenavir, efavirenz, nevirapine, zidovudine) (27–30). Other medications such as pentamidine and pyrimethamine were used in protozoal infections. Some patients have been successfully brought to a state of clinical tolerance with the antiepileptics carbamazepine, oxcarbazepine, and phenobarbital.

Miscellaneous drugs include allopurinol, clopidogrel bisulfate, methylphenidate, mesalazine (5-amino salicylic acid), nitrogen mustard, penicillamine, leflunomide, and epoetin- α .

For recommendations on how to proceed when considering a desensitization procedure, see Table 4. When planning a desensitization procedure, we recommend using published protocols detailing success rates based on more than 10 patients, if available, for example with drugs with a large body of evidence (e.g. SMZ-TMP). Again, it has to be stressed that frequently the presence of hypersensitivity has not been documented in the published cases. Therefore, the published success rates may suggest a far too optimistic situation for real hypersensitivity reactions as compared to unproblematic re-exposures of patients who were never sensitized.

If following published studies, we advise to consider the quality and scientific soundness of the paper with regard to detailed information on the previous reaction, indication, and procedure. Unfortunately, most protocols lack a sound description of the previous clinical reaction; many do not give any information on the underlying pathomechanism or details of the procedures, such as dose increments or time intervals between incremental doses.

Unlike in immediate hypersensitivity reactions, problems or complications in delayed-type hypersensitivity reactions may occur with a delay of many hours or even days and therefore may only be recognized at a later stage. Patients who have experienced a previous delayed hypersensitivity reaction do not normally develop another type of adverse reaction, for example an immediate-type reaction upon re-exposure. However, such phenomena have been observed

Table 4 Recommendations

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- Things to consider before start
 - Characterize patient
 - Check criteria and contraindications (Table 3)
 - Assess clinical manifestation of previous reaction as detailed as possible
 - Possibly on the basis of allergological tests
 - Possibly confirm diagnosis by provocation tests
 - Affirm comorbidities, comedications, and risk factors
 - Obtain written informed consent
 - Choose appropriate protocol
 - Check whether protocol for the culprit drug exists
 - Check for clinical description of patients, soundness of the protocol, and success rate/outcome
 - If there exists, no appropriate protocol check below
 - Prior to starting the procedure
 - Assess complete clinical status
 - Document skin, mucous membranes, internal organs, lymph nodes
 - Laboratory as appropriate, but at least full blood count, hepatic and renal parameters, CRP
 - Decide on starting dose, dose increments, and dose intervals
 - During and after desensitization
 - Apply chosen protocol, modify according to criteria below
 - Check skin and mucous membranes, lymph nodes, body temperature, at regular intervals, recommended at least daily
 - Laboratory parameters as appropriate (e.g. blood cell counts)
 - Monitor the underlying disease appropriately
 - In case of an adverse event, adjust the protocol or stop the procedure, administer symptomatic treatment
 - Please report outcome of your patients to EAACI/Drug Allergy Interest Group DAIG, also in case of failure.
(e-mail to the Secretary of the Interest Group: <http://www.eaaci.net/sections-a-igs/ig-on-drug-allergy.html>)
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exceptionally, both in the literature and by members of our expert panel (31) (cf complications and risks).

The hypersensitivity reactions should be completely resolved or at least stable before beginning a desensitization procedure. There are situations where desensitization has to be done despite an ongoing reaction.

Preparation of the patient

Before beginning any desensitization procedure, a complete clinical status including examination of the skin, mucosal membranes, internal organs, and documentation of lymph nodes is mandatory. Laboratory analysis includes at least a full blood count, hepatic and renal parameters, and markers for inflammation (e.g. C-reactive protein, CRP). Skin and mucous membranes, body temperature, heart rate, and blood pressure should be monitored before and at regular intervals during any drug desensitization with the aim to detect any incipient hypersensitivity reaction.

Route of administration

Although in immediate-type reactions, the intravenous administration is a common and preferred option if possible, and in delayed-type reactions, usually the oral route can also be chosen, depending on the drug formulation. There is no evidence that a change in the administration route during desensitization is problematic. There are no data to show that for safety reasons, the intravenous route is to be preferred over the oral route. However, the different pharmacokinetics has to be taken into account.

Dose interval and cumulative dose

The dosing interval has to be chosen according to the drug and the previous reaction of the patient. The pharmacokinetics of both the drugs, especially the influence of metabolites, should be considered and be particularly observed. In patients with exanthems, most often slow protocols with gradually increasing doses have been used, which last from hours (32, 33) (Table 5) to days (34, 35) (Table 6) to several weeks (36, 37). Whereas rush protocols have the clear advantage over slow protocols because full therapeutic doses of the drug in question can be reached within a few hours or 1 to 2 days, they also exhibit higher risks and failure rates. Some

patients who initially failed a rush protocol were successfully desensitized with a modified and slower protocol (38, 39).

The occurrence of the first clinical symptoms of a potential renewed hypersensitivity reaction may be delayed by 2–3 days. For this reason, in patients with delayed-type reactions, mostly long protocols with repetitive, slowly increasing doses have been recommended and used. In infectious diseases, such as patients with HIV infection or tuberculosis, there is an inherent risk of induction of resistance. The cumulative daily dose should not exceed the recommended upper daily dose, especially in drugs with a narrow therapeutic window. In patients with underlying diseases that could influence the metabolism or elimination of a drug, such as liver or renal disorders, the single and cumulative doses, as well as the time interval between administrations of the doses, need to be adapted. In children, weight-adjusted dosing is necessary.

Setting

Desensitization in delayed-type hypersensitivity is mostly done in a hospital setting for practicability and optimal surveillance (especially with drugs administered intravenously), but this is not obligatory. However, this decision needs to be based on the quality of the previous reaction, the patient's condition, and the availability of a 'safe' protocol for the specific situation. Nevertheless, still a close monitoring of the patient by experienced physicians is strongly recommended with regular controls of the skin and for systemic symptoms. In case of a suspicion of incipient hypersensitivity reaction, laboratory analyses including at least a full blood count, hepatic and renal parameters, and markers for inflammation (e.g. CRP) are mandatory to detect internal involvement. Intensive care unit surveillance may be required in severely ill patients.

Complications and risks

Any reintroduction of a drug in a patient who has experienced a hypersensitivity reaction has an inherent risk that the same reaction might occur again. Although rarely experienced and described in the literature, more severe symptoms or more extensive manifestations may be elicited (40, 41). In HIV patients with exanthems to sulfonamides, the develop-

Table 5 Protocol for intravenous ceftazidime desensitization performed on 23 patients with 83 procedures in the Leeds Adult Cystic Fibrosis Unit (19)

Dose no.	Time [min] at start of infusion; continuous infusion over 20 min	[mg] Ceftazidime in 45 ml 0.9% NaCl
1	0	0.0036
2	20	0.036
3	40	0.36
4	60	3.6
5	80	36
6	100	360
7	120	3600

The protocol is analogously used for other antibiotics (total of 192 procedures on 42 patients between 2004 and 2008). For detailed success rates and information on premedication, see Table S1 (Supporting information).

Table 6 Protocol for oral desensitization with trimethoprim/sulfamethoxazole in HIV-positive patients over 6–13 days (42)

Dosing level	Portion of single-strength TMP-SMZ [%]	Amount (frequency) of TMP (40 mg)/SMZ (200 mg) suspension [ml]	Total dose TMP [mg]	Total dose SMZ [mg]
1	12.5	1.25 (q.d.)	10	50
2	25	1.25 (b.i.d.)	20	100
3	37.5	1.25 (t.i.d.)	30	150
4	50	2.5 (b.i.d.)	40	200
5	75	2.5 (b.i.d.)	60	300
6	100	1 single-strength tablet (TMP 80 mg/SMZ 400 mg)	80	400

Each dosing level is a daily dose; dosing levels could be repeated once (q.d., once daily; b.i.d., twice daily; t.i.d., 3 times daily).

ment of high fever in addition to the recurrence of the maculopapular exanthem forced to interrupt the desensitization (42). Also more severe reactions, for example bullous exanthems, could occur upon reintroduction of the drug, even under premedication and use of a slower protocol. Fégueux et al. (43) reported an HIV-positive female patient with cerebral toxoplasmosis who underwent a desensitization procedure with sulfadiazine over 6 days under premedication with prednisolone and antihistamines. After having reached the therapeutic dose of sulfadiazine, the corticosteroid was slowly tapered until day 18. Two days after withdrawal of prednisolone, she developed fatal TEN.

There are also adverse reactions that are not similar or identical to the initial hypersensitivity reaction; however, these appear coincidental and the relation to the original reaction remains unclear. Although the occurrence of anaphylaxis in a patient with an initial febrile maculopapular rash is exceptional, such diverse adverse reactions have been observed particularly in HIV-positive patients (44). A HIV-positive child was challenged with TMP-SMX after having developed a generalized erythema and glossitis and reacted with an anaphylactic reaction to the challenge (45).

Leukopenia and pancytopenia several weeks after a primarily successful desensitization have rarely been reported. This has been subsumed under the acronym CODS (co-trimoxazole desensitization syndrome) (46).

Controversies, unsolved problems, and need for future research

Desensitization in delayed-type drug hypersensitivity may be possible and may enable to continue an effective and safe treatment. However, there have been no controlled clinical trials, very few well-documented cases and the underlying pathophysiology is largely unknown (18). In addition, published desensitization success rates are questionable, because in many patient series, the diagnosis of drug hypersensitivity has not been confirmed by prior allergological testing including provocation tests. There are a number of issues that warrant further examination and research.

Protocols

There is no universal or consensus drug desensitization protocol to date for delayed-type hypersensitivity reactions. Protocols vary in the duration taken to achieve therapeutic dose, ranging from a few hours to several weeks. It is highly desirable to reach the therapeutic dose as quickly as possible but rush protocols frequently have a higher failure rate (Table S1).

Other protocol-related questions include the *mode of drug administration*, *intervals* between doses and *dose increment*. While the drug preparation may determine the route of administration, there seems to be no clear advantage of intravenous over oral routes or *vice versa*. With the intravenous route, it is possible to administer the drug by slow infusion, stepwise increase the rate of infusion, or infuse boluses of increasing dose. Oral administration is more convenient, but blood levels could be affected by gastric pH and absorption.

The starting dose may vary from one-millionth (19) to one-eighth (28) of the therapeutic dose. Protocols may also differ in the time interval between doses or optimal timing of dose increases. They need to be based on the pharmacokinetics of the specific drug as well as on the pathophysiology of the drug hypersensitivity reaction, the clinical history, and comorbidities of the patient. Many protocols are in fact 'tailor-made' for each patient and each drug.

Premedication

There is no consensus on the value of premedication prior to, and comedication during desensitization, the type and dose of pre-/comedication. Antihistamines and corticosteroids have often been used (Table S1), but there are also reports on more immunosuppressive approaches (47). Premedication may not prevent break-through reactions (47–49), which in some cases are more severe than the initial reaction in spite of high doses of steroid premedication over several days.

The controversies in our expert panel center around the following questions: early break-through reactions may be masked by premedication, but mild reactions might be prevented by premedication, and therefore, premedication might also be associated with higher success rates. It is yet unclear whether premedication influences the effectiveness of desensitization, a point that is being debated in the context of antihistamine premedication for desensitization in immediate-type reactions. Currently, there are no sufficient data for recommendations on this topic.

Antibiotic resistance

The risk of developing antibiotic resistance by administering subtherapeutic doses over days or even weeks, depending on the protocol, has not been conclusively investigated. In a historic paper, Horne and Grant report two cases of resistance of tubercle bacilli (*Mycobacterium tuberculosis*) to isoniazid under subtherapeutic doses of para-aminosalicylic acid during a desensitization procedure with para-aminosalicylic acid, although the organisms remained sensitive to para-aminosalicylic acid (50).

Patients with positive skin tests

Very few cases ($2 \times$ penicillin, $2 \times$ colchicine, $1 \times$ co-trimoxazole, $1 \times$ rivastigmine) with positive skin tests with late reading to the drug to be desensitized were found (Table S1). Drira et al. (51) reported one patient with tuberculosis with positive patch tests to isoniazid, rifampicin, and pyrazinamide and positive oral challenge to all three drugs, who was later successfully desensitized over the course of 22 days to all three drugs. Another patient with familial Mediterranean fever and positive skin tests with late reading to colchicine was successfully desensitized within 13 days [Bircher AJ, pers. communication] (Table S1). In the study by Gompels et al. (41), 4 HIV-positive patients who had reacted to co-trimoxazole after/during desensitization were patch tested, all with negative result. As positive skin tests may represent

cellular activation to a very low concentration of the drug in question, desensitization in skin test-positive patients is likely to be more dangerous than in skin test-negative patients. However, it has to be noted that skin tests in delayed drug hypersensitivity often have a low sensitivity and specificity (52) and are therefore in any case not a very reliable predictive diagnostic tool.

Future needs

To improve the body of evidence in some central questions, special effort and studies are needed on the following issues:

Patient related

- Registry of trials and outcome of special cases.
- Prognostic markers for successful/unsuccessful desensitization.
- Genetic studies on factors influencing outcome.
- Investigations on the duration of the tolerance and the mode of action.
- Characterization of differences in patients with immune-mediated (positive skin tests) vs non-immune-mediated hypersensitivity reactions (1) with regard to protocols and successful outcome.

Protocol related

- Multicenter clinical trials with standardized and well-characterized patients.

- Comparison of different protocols in one well-characterized patient group and comparison of one protocol in various, well-characterized patient groups.
- Case reports with appropriate investigation and documentation of the causal relationship of the hypersensitivity reaction with the incriminated drug and the outcome of a well-documented attempt on desensitization.
- Route of administration.
- Significance of premedication.

Lastly, a case needs to be made for publication of unsuccessful attempts on desensitization. We suspect a significant bias in the published literature toward successful cases, but at least as much can be learnt from those with a negative outcome.

Conflict of interest

The authors declare no conflict of interest.

Supporting Information

Additional Supporting Information may be found in the online version of this article:

Table S1. Extensive table on published drugs/protocols for desensitization including information on: Drug, Route of administration, Target dose, Number of increments, Duration of the protocol, Information on previous (skin) test results, Premedication and Outcome.

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Preamble:

Table 4: This table contains detailed information on desensitization procedures in delayed type hypersensitivity extracted from publications in journals listed in PubMed and the personal experience of some of the authors. The table is meant to give orientation for physicians in search of a protocol for desensitization with regard to the drug in question, indications, details on dosing, dose intervals, premedication and successrates. Many more publications with this topic have been screened but were excluded due to lack of details in the description of the original hypersensitivity reaction or of the protocol or outcome. Sometimes, only parts of the published experience were used for the table, e.g. in cases where patients with immediate and delayed type hypersensitivity and desensitization were published in the same paper. The original publication should be consulted before starting the procedure. The information has been extracted with care, however no guarantee can be taken for the correctness of the data. Any comments or additional experience is wellcome.

Table legend:

ADR	adverse drug reaction
n.i.	no information
n.t.	not tested
s	successful
f	failure
D	Desensitization procedure
P	patient
IDT	intradermal tests
PT	patch test
Prick	prick test
sIgE	specific IgE
LTT	lymphocyte transformation test
p.o.	per oral
i.v.	intravenously
i.c.	intracutaneously
AH	any antihistamin
steroids	corticosteroids
MPE	maculopapular exanthem
SJS	Stevens-Johnson syndrome
TEN	toxic epidermal necrolysis
EMM	erythema multiforme majus
FDE	fixed drug eruption
pos	positive
neg	negative

bid	twice daily
tid	three times daily
qid	four times daily
qd	daily

*	recommended reading
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drug	indication	Number of patients	prior clinical reaction	diagnostic test	route	target dose	number of increments and doses	total duration of protocol	Premedication	outcome	Literature		comment
beta-lactams													
aztreonam *	cystic fibrosis	10	one of the following: MPE, urticarial rash, FDE, arthralgia		i.v.		7 increments	2.5 hrs	steroids+AH in 3D, AH in 3D, none in 8D	14D/10P; 4f	Whitaker P et al, J Cyst Fibros 2011, doi: 10.1016/j.jcf.2011.02.002		
cefotaxime	bacterial spondylitis	1	MPE, eosinophilia	Dechallenge/Rechallenge	i.v.	2 x 2g/d	14	1 day	none	1sD/1P	Papakonstantinou G et al. Clin Invest 1993;71:165-7		Type I or Type IV?
ceftazidime *	cystic fibrosis	23	one of the following: MPE, urticarial rash, FDE, arthralgia	n.d.	i.v.		7 increments	2.5 hrs	steroids+AH in 28D, AH in 10D, none in 45D	83D/23P, 8f	Whitaker P et al, J Cyst Fibros 2011, doi: 10.1016/j.jcf.2011.02.002		
ceftazidime	cystic fibrosis	7	MPE, a.o.	n.d.	i.v.	1 g/d	25	2 days	none	9sD/7P, 1f	Ghosal J et al. J Antimicrob Chemother 1997; 29:556-7		no clear distinction btw. MPE and urticaria
imipenem/cilastatin	ventilator associated pneumonia	1	MPE, pruritus	IDT neg, but i.v. provocation pos	i.v.	1008 mg/d (impaired renal function)	9 increments	4 hrs	none	1sD/1P	Gorman SK et al. Ann Pharmacother 2003; 37:513-6		
meropenem *	cystic fibrosis	13	one of the following: MPE, urticarial rash, FDE, arthralgia		i.v.		7 increments	2.5 hrs	steroids+AH in 18D, AH in 13D, none in 11D	42sD/13P, 4f	Whitaker P et al, J Cyst Fibros 2011, doi: 10.1016/j.jcf.2011.02.002		

[illegible]

ciprofloxacin *	cystic fibrosis, pseudomonas infection	2	MPE	Prick, PT negative in 1P, oral challenge positive in 2P	p.o.	2x500mg/d	6 increments with 26 doses	6 days	none	>4sD/2P	Bircher AJ et al. Allergy 1997;52:124-6-48	
ciprofloxacin	cystic fibrosis	1	FDE	graded challenge with levofloxacin pos;	p.o.	2x750 mg/d		3 days	n.i.	1sD/1P, but initially recurrence of lesions. "treat through" procedure lead to disappearance of lesions within 14 days	Garcia Rodriguez R et al. J Invest Allergol Clin Immunol 2011; 21(1):76-80	also tolerance of pipemidic acid (1st generation quinolone), adapted protocol of cotrimoxazole in Patriarca et al. J Invest Allergol Immunol 2008; 18(4); 309-11
clindamycin	HIV, toxoplasmosis	1	MPE	oral provocation test	p.o.	4x600mg/d	3/day	7 days	none	1s	Marcos C et al. AIDS 1995; 9(10):1201-2	
clindamycine	HIV, toxoplasmosis	1	generalized rash	none	p.o.	4x600mg/d		1 day	dexamethasone, hydroxyzine	1s	Sanwo MC et al. Ann Allergy 1995; 74:84	
clindamycine	HIV, toxoplasmosis	3	cutaneous rash	n.i.	n.i.	n.i.	n.i.	n.i.	n.i.	3sD/3P	Antinori A et al. Ital J Neurol Sci 1992; 13:475-9	no specification on the nature of the rash
ethambutol	mycobacteriosis	3	MPE, pruritus, fever	oral challenge pos	p.o.	400 mg tid	13 increments	2 days	none	3sD/3P; 2/3 had recurrent rash that was "treated through"	Matz J et al. Am J Respir Crit Care Med 1994; 149:815-7	

isoniazid	TBC	12	several diverse reactions	Dechallenge/ Rechallenge	p.o.	3x100mg/d	1-3/d	50 days	n.i.	12s, 0f	Berté SJ et al. Am Rev Respir Dis 1964;90:598- 606	no clear distinction btw. MPE and urticaria
isoniazid	TBC	n.i.	several diverse reactions	Dechallenge/ Rechallenge	i.m., then p.o.	3x100mg/d	1-3/d	40 days	n.i.	n.i.	Berté SJ et al. Am Rev Respir Dis 1964;90:598- 606	no clear distinction btw. MPE and urticaria
isoniazid	Quantiferon -TB test pos; Tuberculin test pos	1	acute hepatitis	Dechallenge	p.o.	300 mg/d	5 increments, 14 doses	14 days	n.i.	initially 1sD/1P, but interstitial pneumoni a 2 weeks after desensitiz ation	Migita K et al. Rheumatol Int 2010; DOI 10.1007/s002 96-010-1441- 2	
isoniazid	pleural TBC	1	acute hepatitis	LTT pos	p.o.	300 mg/d	5 increments, 13 doses	13 days	n.i.	1sD/1P	Ikegame S et al. J Infect Chemother DOI 10.1007/s101 56-010-0189- 7	
isoniazid, ethambutol, rifampicin, pyrazinamide	TBC, AIDS	8	SJS/TEN	history	n.i.	INH 300mg, EMB 800mg, RMP 600mg, PZA 1500mg	16 increments (4 increments per drug), dose increase every 2nd day	31 days	none	7sD/7P, 1f/1P	Kura MM et al. Int J Dermatol 2001; 40:481-484	

isoniazide, rifampicin, pyrazinamide (Rifater ®)	TBC	1	MPE, enanthem, fever	oral challenge pos, Patch test positive to all three		4250mg Rifater ®	22 increments	22 days	AH	1sD/1P	Drira I et al. Rev Pneumol Clin 1997; 53:104-6	
metronidazole	vaginal trichomoniasis	1	FDE	topical application pos.	i.v.	2g/d	14 increments	approx. 6hrs	none	1sD/1P	Pearlman MD et al, Am J Obstet Gynecol 1996; 174:934-6	CAVE: weal after topical applicaton of metronidazole gel to vagina
p-amino salicylic acid	TBC	99	several diverse reactions	Dechallenge/ Rechallenge	p.o.	3x4g/d	1-3/d	34 days	n.i.	87s, 12f	Berté SJ et al. Am Rev Respir Dis 1964;90:598- 606	no clear distinction btw. MPE and urticaria
p-amino salicylic acid	inflammatory bowel disease	1	MPE, fever, fatigue, weakness	oral challenge positive	p.o.	2 g/d	6 increments	6 days	co-medication with prednisone 15 mg	1sD/1P	Butchey J et al. J Allergy Clin Immunol 1997; 99:S431	
polymyxin E *	cystic fibrosis	9	one of the following: MPE, urticarial rash, fever, arthralgia	n.d.	i.v.		7 increments	2.5 hrs	Steroids+AH in 26, AH in 24, none in 15	65sD/9P, 3f	Whitaker P et al, J Cyst Fibros 2011, doi: 10.1016/j.jcf. 2011.02.002	
streptomycin	TBC	6	several diverse reactions	Dechallenge/ Rechallenge	i.m.	1 gm/d	1-3/d	40 days	n.i.	2s, 4f	Berté SJ et al. Am Rev Respir Dis 1964;90:598- 606	no clear distinction btw. MPE and urticaria
rifampicin	mycobacteriosis	1	MPE, pruritus	oral challenge pos	p.o.	300 mg bid	13 increments	2 days	none	1sD/1P	Matz J et al. Am J Respir Crit Care Med 1994; 149:815-7	
rifampicin	TBC	1	MPE	oral challenge pos	p.o.	300 mg bid	13 increments	2 days	none	1sD/1P	Pech O et al. Dtsch Med Wschr 2001; 126:16	

rifampicin	infected hip prosthesis	1	MPE, mild interstitial nephritis	positive challenge	p.o.	3 x 300mg/d	7 increments with 39 doses	7 days	none	1sD/1P	Bircher AJ., pers. Communication
rifampicin	Pulmonary tuberculosis in HIV+	6	Generalized exanthem-between 5th and 14th day	clinical evolution	p.o.	600mg/d	14	3days	none	success	Josefina R. Cernadas*, Carmen Botelho*, António Sarmento** Poster at DHM4-2010
rifampicin	Tuberculous meningitis no HIV+	2	Generalized exanthema-between 6th and 10th day	clinical evolution	p.o.	600mg/d	7	1day	none	1sD/1P, 1f	Josefina R. Cernadas*, Carmen Botelho*, António Sarmento** Poster at DHM4-2010
rifampicin	Pulmonary tuberculosis and sepsis	1	Generalized exanthema-between 6th and 10th day	clinical evolution	p.o.	600mg/d	7	1 day	none	1f	Josefina R. Cernadas*, Carmen Botelho*, António Sarmento** Poster at DHM4-2010
rifampicin + isoniazid	urogenital tuberculosis	1	generalized exanthem with bullae on the legs	n.t.	p.o.	4 x 150 mg/d of Rimactazid®	6 increments in 27 doses	6 days	none	1sD/1P	Bircher AJ, pers. Communication
tobramycine *	cystic fibrosis	7	one of the following: MPE, urticarial rash, fever, arthralgia		i.v.		7 increments	2.5 hrs	steroids+AH in 13D, none in 26D	39D/8P, 1f	Whitaker P et al, J Cyst Fibros 2011, doi: 10.1016/j.jcf.2011.02.002
sulfanilamides											
TMP-SMX	HIV, PCP	9	pruritic rash, MPE	Rechallenge in 2P pos	p.o.	80/400mg b.i.d.	34 increments	24 hrs	1P with prednisone	9s/9P	Kalanadhabhatta V et al. Ann Allergy Asthma Immunol 1996; 77:394-400

TMP-SMX *	HIV, prophylactic	44	MPE, fever	Rechallenge pos	p.o.	80/400mg/d	12 increments	6 hrs	none	40sD/44P	Demoly P et al. JACI 1998; 102:1033-6; Demoly et al. JACI 2000;105:588-9 Wacker P et al; J Ped Haematol Oncol 2000; 22(4):340-3	
TMP-SMX	Listeriosis, ALL	1 child	rash	n.i.	i.v.	n.i.	7 increments	n.i.	n.i.	1s/1P		Protocol like in Kletzel et al 1991
TMP-SMX	hemophiliacs with HIV	7 children and young adults	multiform erythema, edema, respiratory difficulty	n.i.	p.o.	n.i.	7 increments	n.i.	n.i.	6sD, 1f	Kletzel M, et al. Am J Dis Child 1991; 145:1428-9	at least 2 patients with urticarial reactions to the protocol
TMP-SMX	HIV	45	fever, urticarial or macupapular rash, erythroderma	n.t.	p.o.	160/800 mg/d	40 doses	36 hrs	n.i.	37sD/45P, 8f, but 10 late hypersensitivity reactions, finally 27sD/45P	Nguyen M et al. AIDS 1995; 9:573-5	also urticarial rash included! Protocol also used by Bonfanti et al, Biomed & Pharmacother 2000; 54:45-9 on 34 HIV+patients with rash, urticaria, fever, 27sD/34P, 7f
TMP-SMX	HIV, PCP prophylaxis	22	rash	n.i.	p.o.	1400mg SMX/d	3 doses/d	8 days	n.i.	22sD/22P	Warren E et al. Pharmacotherapy 1997; 17(5):900-916	
TMP-SMX	HIV, PCP prophylaxis	30	MPE, fever	n.i.	p.o.	mostly 80/400 mg/d	8 increments	5 or 9 days	n.i.	32sD/29P, 1f	Piketty C et al. Ann Med Interne 1996; 147(5):327-330	
TMP-SMX	HIV, prophylaxis	20	MPE, fever		p.o.	80/400 mg/d		20 days		13sD/20P	Bissuel FF et al. AIDS 1995; 9:407-8	
TMP-SMX	AIDS, PCP	1	MPE, fever, hepatitis	n.t.	p.o.	160/800mg bid	12 increments	18 days	none	1sD/1P	MacLean Smith R et al. Ann Int Med 1987; 106:335	

TMP-SMX	HIV, PCP	3	MPE, fever, leukopenia, eosinophila	Prick and IDT done in 1 Pat	p.o.	320/1600mg/d	8 increments with 30 doses	26 days	hydroxyzine 50 mg every 8 hrs	2sD/3P, 1f	White MV, Ann Allergy 1989; 62(3):177-9	IDT pos immediately in 1 Pat
TMP-SMX	HIV, PCP	2	SJS/EMM	none	p.o.	160/800mg/d	32 increments	8 days	n.i.	2sD/2P	Douglas et al. Clin Infect Dis 1997; 25:1480	
TMP-SMX	HIV, toxoplasmosis or PCP	18	MPE, fever	none	p.o. and/or i.v.	160-800mg/d	varying	1 to 5 days	none	17sD/16P in 22 attempted desensitizations	Augello Carregal V et al. J Allergy clin Immunol 1997; 99:S431	
TMP-SMX	HIV	28	erythematous skin rash±fever	n.i.	p.o.	160/800mg/d	10 increments	10 days	none	23sD/28P initially, 5 f, but 5 late failures	Absar N et al. JACI 1994; 93:1001-5	protocol also used for treatment of spino-cerebellar atrophy type 3 Machado-Joseph in: Ablin J et al. N Z J Med 2004; 117(1191):U819 no skin tests in affected area; protocol adapted for ciprofloxacin in Garcia Rodriguez R et al. J Invest Allergol Clin Immunol 2011; 21(1):76-89
TMP-SMX	infected hip prosthesis	1	FDE	PrickT and PT neg	p.o.	320/1600mg/d	37 increments	10 days	n.i.	1s/1P	Patriarca G et al. J Invest Allergol Clin Immunol 2008; 18(4):309-11	
TMP-SMX	toxoplasmosis during pregnancy	1 pregnant woman (25 weeks)	MPE	dechallenge/rechallenge, Prick neg, IDT neg	p.o.	320/1600mg/d	34 increments, 35 doses	4 days	cetirizine upon reaching full dose	1sD/1P	Nucera E et al; Allergy 2000; 55:681-2	birth of healthy child

TMP-SMX	HIV, prophylaxis	22	morbilliform rash, fever, abnormal liver function, vomiting, dysesthesias	n.t.	p.o.	160/800 mg/d	6 increments	5 hrs	none	18sD/22P ; 3 late failures	Gluckstein D et al. Clin Infect Dis 1995;20:849-53	upon oral challenge before desensitization: anaphylactic reactions in 8 pat
TMP-SMX	AIDS, PCP	3	MPE, thrombopenia, neutropenia, elevated liver enzymes, fever,	n.i.	p.o.	160/800mg bid	10 increments	16 days	n.i.	2sD/2P, 1 f	Papakonstantinou G et al. Klin Wochenschr 1989; 67:316; Papakonstantinou G et al. Klin Wochenschr 1988; 66:351-3	1P tolerated TMP-SMX in therapeutic dose after interruption of treatment for 8 weeks
TMP-SMX	HIV, PCP	97	rash, fever	n.t.	p.o.	80/400mg/d	6 increments	6 days	none	73sD/97P	Leoung GS et al. J Infect Dis 2001; 184:922-7	
TMP-SMX	HIV, prophylaxis	22	rash, fever	negative prick and IDT with immediate reading, IgG ELISA inhibition	p.o.	160/800mg /d	24 increments	8 days	none	19sD/19P , 3 f; 5 patients with intermittent ADR treated with prednisone and AH	Rich JD et al. Ann Allergy Asthma Immunol 1997; 79:409-14	skin tests with immediate reading, no late reading!
TMP-SMX	HIV, prophylaxis	33	adverse cutaneous reaction	Prick and IDT neg with late reading	p.o.	160/800 mg three times weekly	11 increments with 21 doses	11 days	none	27sD/27P , 6 f; 11 P with intermittent cutaneous ADR, treated with AH	Belchí-Hernández J et al. Ann Allergy Asthma Immunol 1996; 76:355-8	

TMP-SMX *	HIV, AIDS	48	rash 1/- fever, pruritus; involvement of 1 mucous membrane in 7 patients	n.t.	p.o.	80/400 mg/d	8 increments, 8 doses	3 days	AH until day 10, no steroids	37sD/48P, 11f	Caumes E et al. Arch Dermatol 1997; 133:465-9	1 Patient with non-fatal myocardial infarction during failed desensitization procedure
TMP-SMX	HIV, prophylaxis	1	MPE, fever	PT questionable	p.o.	80/400 mg/d	8 increments	3 days	none	1sD/1P, but transient fever, flare-up of PT-sites and eosinophilia after last dose	Kardaun SH et al. Contact Dem 2009; 61(1):50-1	
TMP-SMX	HIV, prophylaxis	>50	mild generalized cutaneous reactions	n.t.	p.o.	80/400 mg/d	8 increments	1 day	none	sucess	Rodrigues J. et al, Abstract Book, p 29 Poster 2nd Int. Drug Hypersensitivity Meeting, Liverpool 2006.	
TMP-SMX	HIV, prophylaxis	30	moderate generalized eczanthematous reaction with clinical symptoms	n.t.	p.o.	80/400 mg/d	11 increments	4 days	AH, oral steroids	sucess	Rodrigues J, et al. Abstract Book, p 29 Poster 2nd Int. Drug Hypersensitivity Meeting, Liverpool 2006.	
sulphadiazine *	AIDS, cerebral toxoplasmosis	16	MPE, pruritus	n.t.	p.o.	2-4g/d	25 increments in 31 doses	5 days	steroids in some patients	10sD/10P in 22 desensitization attempts, 6 f	Tenant-Flowers M et al. AIDS 1991; 5(3):311-5	

sulphadiazine	AIDS, cerebral toxoplasmosis	3	MPE, fever, leucopenia	n.t.	p.o.	2-4g/d	7-11 increments	7-11 days	dexamethasone 9-16mg/d, tapering	3sD/3P	Bell ET et al. Lancet 1985; 1(8421):163	
sulfadiazine	AIDS, opportunistic infection	4	macular or morbilliform rash, fever, pruritus	oral challenge pos	p.o.	100mg/kg/d	24 increments	10days	none	4sD/4P	de la Hoz Caballer B et al. J Allergy Clin Immunol 1991; 88(1):137-8 Antinori A et al. Ital J Neurol Sci 1992; 13:475-9	possibly immediate type reaction??
sulfadiazine	HIV, toxoplasmosis	23	cutaneous rash	n.i.	n.i.	n.i.	n.i.	n.i.	n.i.	23s		no specification on the nature of the rash
sulfadiazine	AIDS, toxoplasma chorioretinitis	1	cutaneous eruption	n.i.	p.o.	3 g/d	6 increments	24 hrs	none	1sD/1P, MPE after 10d, suppressed by prednisone	Greenberger PA et al. J Allergy Clin Immunol 1987; 79:484-8	
sulfadiazine	nocardia brain abscess	1	MPE, fever to TMX-SMX	n.i.	n.i.	n.i.	n.i.	n.i.	Prednisone 60 mg qd, hydroxyzine 25 mg qid	1P, initially successful, relapse after tapering of Prednisone, tolerance with increase of prednisone	Boxer MB et al. NER Allergy Proc 1988; 9(3):219-223	
sulphasalazine	rheumatoid arthritis	6	MPE	n.t.	p.o.	2 g/d	n.i.	24 days	n.i.	4sD/4P, 1f, 1sD with reduced dose	Bax DE et al. Ann Rheum Dis 1986; 45:139-40	
sulphasalazine	spondylarthropathy	1 child	scaly erythematous eruption	Dechallenge/Rechallenge	p.o.	500 mg b.i.d	12 increments	24 days	prednisolone 2.5 mg every other day	1sD/1P	Kümmerle-Deschner J et al. Acta Paediatr 1995; 84:952-4	

sulphasalazine	rheumatoid arthritis (6), psoriatic arthritis (2), juvenile chronic arthritis (1)	9	rash	Rechallenge in 4 patients positive	p.o.	2g/d	no details, start with 1 mg and increase to 800 mg until day 24, then add 500 mg every week	39 days	n.i.	3sD/9P, 6f	McCarthy C et al. Ir J Med Sci 1994; 163(5):238-9	protocol on the basis of Holdsworth CD. Br Med J 1981; 282:110
sulphasalazine	ulcerative colitis	8	rash +/- fever	n.i.	p.ol.	2-3 g/d	few details, start with 1 mg, increase to 100 mg in at least 14 days, 500 mg after 23 days at the earliest	varying	n.i.	7sD/8P, 1f	Holdsworth CD. Br Med J 1981; 282:110	few details on prior clinical reaction, at least 4 patients could possibly suffer from immediate type hypersensitivity; protocol also used in Farr M et al. Br Med J 1982 (284):118 in 1 patient with "rash" to sulphasalazine; protocol also used in Koski JM Clin Exp Rheumatol 1993;11:169-70 in 21 patients with rheumatologic disorders and "pruritic erythematous eruptions"; 16sD/21P, 5f
sulfasalazine	ulcerative colitis	1	MPE	n.i.	p.o.	500mg qid	n.i.	1 month	none	1sD/1P	Boxer MB et al. NER Allergy Proc 1988; 9(3):219-223	as in Prudy et al 1984
sulfasalazine	inflammatory bowel disease	12	rash±fever	n.i.	p.o.	500mg qid	n.i.	1 month	none	11s/1f	Purdy BH et al. An Intern Med 1984; 100:512-514	similar protocol in Fardy JM et al. J Clin Gastroenterol 1988; 10(6):635-7

sulfasalazine	ulcerative colitis, sclerosing cholangitis	1	interstitial pneumonitis, eosinophilia, fever, malaise	Dechallenge/Rechallenge	p.o.	1g tid	6 increments	6 weeks	continued medication with 30 mg of prednison for primary disease	initially 1sD/1P, but late failure after 3 months (recurrence of interstitial pneumonia)	Sullivan SN J Clin Gastroenterol 1987; 9(4):461-3	eosinophilia also with 5-ASA, tolerance of disodium azodisalicylate
sulfasalazine	ulcerative colitis	1	pulmonary infiltration and eosinophilia (PIE-syndrome)	dechallenge	p.o.	500 mg tid	10 increments	10 weeks	n.i.	1sD/1P	Yamakado S et al. Int Med 1992; 31(1):108-113	
sulfasalazine	ulcerative colitis	2	moderate generalized exanthem	clinical	p.o.	3 g/d	12	5 days	none	sucess	Rodrigues J et al. DHM2 Liverpool, 2006 DHM4 Rome, 2010	
sulfasalazine	ulcerative colitis	1	moderate generalized exanthem, GI-symptoms and -cramps		p.o.	3 g/d	22	10 days	No, but DZT only after recover	success	Rodrigues J et al. DHM2 Liverpool, 2006 DHM4 Rome, 2010	
mesalazine	ulcerative colitis	1	Severe Systemic symptoms without cutaneous involvement	Rechallenge pos several times	p.o.	2500mg/d	43	66days	none	success - still on 2500mg	Rodrigues J et al. Allergy 2009; 64 (S90): 295.	
mesalamine	ulcerative colitis	1	generalized MPE to olsalazine	dechallenge	p.o.	2g/d	>18 increments	>21 days	none	1sD/1P	Stelzle RC et al. Ann Allergy Asthma Immunol 1999; 83:23-24	

dapsone	HIV, PCP	14	fever, MPE, pruritus,	n.t.	p.o.	50mg bid	13increments with 23 doses	42 days	n.i.	13sD/13P, 1f	Metroka CE et al. JAMA 1992; 267(4):512		
antivirals													
amprenavir	HIV	1	MPE	Dechallenge / Rechallenge, IDT pos ?	p.o.	600mg b.i.d	12 increments	5.5 hrs	none	1s	Kohli-Pamnani A et al. Ann Allergy Asthma Immunol 2006; 96:620-23		possibly irritant immediate positivity in IDT!
efavirenz	HIV	1	generalized pruritic rash	Dechallenge/ Rechallenge	p.o.	600 mg/d	18 increments	18 doses	initially none, but after development of rash on day 12 AH were given prior to each new dose	1sD/1P	Philipps EJ et al. Ann Pharmacother 2002; 36:430-2		no distinction possible between type I or IV, but therapy of rash was more appropriate for type IV reaction
nevirapine	HIV	6	MPE, fever, edema	Prick neg	p.o.	n.i.	12 increments	5.5 hrs	none	6s/6P, but 1P with hepatitis after 1 mo	Messaad D et al. Clin Exp Allergy 2002; 32:733-35		Type I or type IV?, target dose?
nevirapine	HIV	2	MPE, fever, myalgia	Prick neg	p.o.	n.i.	12 increments	5.5 hrs	none	2s	Demoly P et al. JACI 1999; 104:504-5 Duque S et al. J Allergy Clin Immunol 1996; 98:234-5		
zidovudine	HIV, cerebral toxoplasmosis	1	MPE, fever, malaise	n.t.	p.o.	500 mg/d	10 increments	10 days	methylprednisolone 24mg/d, AH	1sD/1P			
zidovudine	HIV	1	lichenoid drug eruption, elevated liver parameters	dechallenge	p.o.	1200 mg/d	37 increments	37 days	none	1sD/1P, co-medication with prednisone from day 11-18 for other reasons	Carr A et al. J Allergy Clin Immunol 1993; 91(2): 683-5		

others													
penicillamine	Mb. Wilson	1	MPE, fever	n.t.	p.o.	1000 mg/d	6, increment every 3 d	16 days	Prednisone 20-30mg/d	1D/1P	Chan CY et al. AJG 1994;89:442-3		
penicillamine	Mb. Wilson	6	MPE or urticarial rash, fever, lymphadenopathy, slight eosinophilia, cytopenia	dechallenge, rechallenge positive in 3/6	p.o.	1000 mg/d	starting dose 50 mg/d or 250 mg/d		Prednisone 30-40 mg	6sD/6P	Sternlieb I et al. JAMA 1964;189:748-54		
allopurinol *	tophaceous gout with/w/o renal impairment, CLL (2)	9 and 23	MPE, pruritus, fever, some with eosinophilia and facial swelling, one patient with stomatitis	rechallenge/reexposure in 4 patients pos.	p.o.	50-100 mg/d, more in some patients	9 (-11) increments, increase every 3 d (5-10 d in high-risk patients)	28 days	2 pat. with renal transplants + immunosuppressive therapy, concomittant corticosteroids in 18 pat.	21sD/32P, 7 sD with alteration of protocol, 4f; 7 with late adverse reaction, 3 late discontinuations	Fam AG et al. Am J Med 1992; 93:299-302 and Fam AG et al. Arthritis Rheum 2001; 44 (1):231-8	same protocol used for FD E by: Teraki Y et al. Clin Lab Invest 2004; 209:29-32	

allopurinol	severe gout, renal failure	1	erythema multiforme with eosinophilia	n.t.	p.o.	100 mg/d	increments according to clinical situation every 1 to 7 days	47 days to 50 mg, another 7 days to 100mg/d	hydroxyzine 50 mg/d, prednisone 7.5-30mg/d	using protocol of Fam AG et al.: failure with MPE, exfoliative dermatitis, fever, eosinophilia 23%, 1sD/1P with protocol as written	Tanna SB et al. Ann Pharmacother 1999; 33:1180-3
allopurinol	gout	1	MPE, pruritus	Dechallenge/Rechallenge	p.o.	300 mg/d	29 increments	30 days	none	1sD/1P	Webster E et al. Arthritis Rheum 1985; 28(6):707-9
allopurinol *	gout	1	severe rash, fever	Rechallenge	p.o.	300mg/d	29 increments	30 days	none	1sD/1P	Meyrier A. Br Med J 1976; 2:458
allopurinol *	hyperuricemia	1	FDE	rechallenge	p.o.	200 mg/d	11 increments, increase every second day	6 weeks	10 mg prednisone/d	initially failure, 1sD/1P with dose increase every 7 days	Teraki et al. Clin Lab Invest 2004; 209:29-32

according to Webster et al 1985; Fam et al. 2001;

allopurinol	gout	1	MPE, conjunctivitis, nephritis, eosinophilia, leukocytosis	n.t.	p.o.	300mg/d	17 increments, increase every 3 d	46 days, with further doubling of dose after 270 d	co-medication with low-dose prednisone	1D/1P	Vázquez-Mellado J et al. J Clin Rheumatol 2000; 6(5):266-8	
allopurinol	tophaceous gout	1	erythematous rash, oral ulceration	n.t.	p.o.	100 mg/d	9 increments	60 days	none	initial failure on dose increment every 3 d, 1sD/1P with increments every 6 d	Gillott TJ et al. Rheumatology 1999; 38:	
allopurinol	gout	1	FDE	Rechallenge pos	p.o.	300 mg/d	30 increments	16 days	none	1sD/1P	Umpiérrez A et al. JACI 1998; 101:286-7	modified protocol of Meyrier A. Br Med J 1976; 2:458
allopurinol	gout	1	FDE	Rechallenge pos	p.o.	100 mg/d	9 increments	28 days	prednisone 10 mg/d	1sD/1P	Kelso JM et al. JACI 1996; 97:1171-2	
allopurinol	gout, SLE, Klinefelter syndrome	1	MPE, fever, eosinophilia	dechallenge	p.o.	200 mg/d	8 increments	30 days	n.i.	1sD/1P, died from aplastic anemia 6 months later	McDonald J et al. J Rheumatol 1988; 15:865-8	
allopurinol	hyperuricemia	4	FDE	PT	p.o.	100 mg/d	11 increments	4 days	none	success	Cernadas J pers. Communication in- DHM2 and DHM4	Solution of 50 mg allopurinol powder in 500 ml of H2O + 14% sodium-bicarbonate, later

												tablets
allopurinol	gout	1	FDE	PT	p.o.	first 300 mg/d, later 200 mg/d	first 11 increments, then 23 increments	4 days, later 10 days	none	2f/1P, then 1sD/1P	Cernadas J, pers. Communicato in	Solution of 50 mg allopurinol powder in 500 ml of H2O + 14% sodium-bicarbonate, later tablets
allopurinol	severe gout	1	generalized exanthema	PT	p.o.	300 mg/d	63 increments	30 days	none	1f (10 day protocol)/1P, later 1sD/1P	Cernadas J, pers. Communicato in	Solution of 50 mg allopurinol powder in 500 ml of H2O + 14% sodium-bicarbonate, later tablets
allopurinol	hyperurice mia	1	FDE	PT	p.o.	200 mg/d	11 increments	4 days	none	1sD/1P	Cernadas J, pers. Communicato in	Solution of 50 mg allopurinol powder in 500 ml of H2O + 14% sodium-bicarbonate, later tablets
anastrozole	breast cancer	2	macular exanthem, with burning facial edema, progression to the neck and upper thorax; conjunctival hyperemia	PT neg	p.o.	1 mg/d	7 increments, 12 doses	3 days	none	2sD/2P	Rodrigues J et al. Allergol Immunopathol (Madr). 2009;37(1):50-1.	
carbamazepine	epilepsy	1	erythroderma, elevated liver enzymes, eosinophilia, lymphadenopathy, fever	rechallenge	p.o.	200mg b.i.d.	dose doubling every two days	approx. 6 weeks	none	1sD/1P	Smith H et al. The Lancet 1985;325:753	

carbamazepine	epilepsy	7	whole-body rash	n.t.	p.o.	200mg b.i.d.	dose doubling every two days	6 weeks	none	7sD/7P	Earmes P. The Lancet 1989; 333:509	same protocol as Smith et al, The Lancet 1985
carbamazepine	schizoaffective disorder	1	MPE	n.t.	p.o.	300mg b.i.d.	11 increments with 21 doses	6 weeks	none	1sD/1P	Hermle L et al. Nervenarzt 1993; 64:208-210	
carbamazepine	partial complex seizures	5	diffuse dermatitis	n.t.	p.o.	400-600mg/d	approx. 9 increments	24 days	AH daily	5sD/5P	Purves SJ et al. Can J Neurol Sci 1988; 15:237	
colchicine	familial mediterranean fever, Behcet's disease	1	MPE	oral challenge pos	p.o.	1mg/d	12 increments	12 days	none	1sD/1P	Levinger U et al. Clin Exp Rheumatol 2001;19(5 Suppl1):S79 Bircher AJ, pers. Communication, analogous to: Cabili S et al. Rheumatologie 1982; 12:207-8	
colchicine	familial mediterranean fever	1	MPE	skin test with late reading positive	p.o.	2mg/d	13 increments	13 days	none	1sD/1P	Josefina Rodrigues, Carmen Botelho as a clinical case on "Non immediate desensitization protocols"-DHM4-2010	
colchicine	familial mediterranean fever	1	FDE	PT pos, oral challenge positive	p.o.	1mg/d	13	24 days	none	1sD/1P		
epoetin-alpha	renal failure	1	AGEP	Rechallenge pos. 2x; IDT and PT neg	s.c.	2000 IU (16.8ug)	6 increments	2 days	cetirizine, ranitidine, prednisone	1s	Ruano FJ et al. Allergy 2009; 64: 1795-98	
												oral -solution prepared by H.pharmacysts with crushed pills until day16

hydroxychloroquine	seronegative polyarthritis, SLE, Sjögren's syndrome	3	MPE	n.t.	p.o.	2 x 200 mg/d	15 increments	36 days	none	3sD/3P, 1 patient with transient itch treated with AH	Mates et al. J Rheumatol 2006; 33(4):814-816	
imatinib	CML	4	MPE, erythematous rash, macular exanthem, bullous rash	n.t.	p.o.	400 mg/d	16 increments	4 hours	none	3sD/3P, 1f	Nelson RP et al. Ann Allergy Asthma Immunol 2006; 97:216-222	total of 10 patients, others without clearly identifiable clinical diagnosis, e.g. "rash" or urticaria
methylphenidate	ADHS	1	MPE	Rechallenge pos; PrichT, PT neg	p.o.	10mg/d	24 increments	10 days	none	1s	Confino-Cohen R et al. J Child Adol Psychopharmacol 2005; 15:703-5	
methylphenidate	ADHS	1	erythema, pruritus, fever	De-& Rechallenge pos; PT neg	p.o.	20mg/d	16 increments	6 days	none	2sD/1P	Rodrigues J et al. Allergol Immunopathol 2008; 36:303-5	
methylphenidate	ADHS	1	MPE	n.t.	p.o.					1sD/1P	Bircher AJ, pers. Communication	
nitrogen mustard	mycosis fungoides/cutaneous T-cell lymphoma	19	contact dermatitis	titrated open application test	i.v.	200ug/d	6 increments	4 days	varying	17sD/2 partially successful desensitizations/19P	Van Scott EJ et al. Cancer 1973; 32:18-30	
oxcarbazine	epilepsy	1	fever, generalized erythematous rash, lymphadenopathy, eosinophilia	none	p.o.	1200 mg/d	started with 0.1 mg, dose doubling every 2nd day	63 days	none	1sD/1P	Watts D et al. J Neurol Neurosurg Psych 1991; 54:376	

phenobarbital	complex partial seizures	1	generalized papulous exanthem	rechallenge positive, PT neg	p.o.	150 mg/d	7 increments, 41 doses	initially 15 days, total of 9 weeks	none	1sD/1P	Fröscher W et al. Nervenarzt 1998; 69:158-61	
pyrimethamine	AIDS, cerebral toxoplasmosis	2	rash	n.t.	p.o.	25 mg t.i.d	6 steps	18 days	n.i.	2sD/2P	Gonzalez GE et al. J Allergy Clin Immunol 1992; 89 (1 pt2):177	unspecified rash
pyrimethamine	HIV, toxoplasmosis	1	MPE	n.t.	p.o.	100mg/d	16 steps	6 hrs	none	1s	Bouboulis DA et al. Ann Allergy Asthma Immunol 1995; 74:491-4	
rivastigmine	Alzheimer's dementia	1	generalized MPE	Prick and IDT with late reading neg; PT pos	p.o.	3mg/d; ater stepwise increase to 9mg/d	18 increments		n.i.	1sD/1P	Makris M et al. Allergy 2010; 65:925-6	
thalidomide	plasmocytoma	1	morbilliform rash	Rechallenge pos, LTT neg	p.o.	400mg/twice a week	2 steps	4 weeks	methyl-prednisolone 1mg/kg/d	1s	Nijsten T et al. Dermatology 2002; 204:365-7	