

# Multiple Drug Hypersensitivity

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## Keywords

Drug hypersensitivity · Multiple drug hypersensitivity · Drug rash with eosinophilia and systemic symptoms · Maculopapular exanthema · p-i concept

## Abstract

Multiple drug hypersensitivity (MDH) is a syndrome that develops as a consequence of massive T-cell stimulations and is characterized by long-lasting drug hypersensitivity reactions (DHR) to different drugs. The initial symptoms are mostly severe exanthems or drug rash with eosinophilia and systemic symptoms (DRESS). Subsequent symptoms due to another drug often appear in the following weeks, overlapping with the first DHR, or months to years later after resolution of the initial presentation. The second DHR includes exanthema, erythroderma, DRESS, Stevens-Johnson syndrome/toxic epidermal necrolysis (SJS/TEN), hepatitis, and agranulocytosis. The eliciting drugs can be identified by positive skin or in vitro tests. The drugs involved in starting the MDH are the same as for DRESS, and they are usually given in rather high doses. Fixed drug combination therapies like sulfamethoxazole/trimethoprim or piperacillin/tazobactam are frequently involved in MDH, and 30–40% of patients with severe DHR to combination therapy show T-cell reactions to both components. The drug-induced T-cell stimulation appears to be due to the p-i mechanism. Importantly, a perma-

nent T-cell activation characterized by PD-1+/CD38+ expression on CD4+/CD25<sup>low</sup> T cells can be found in the circulation of patients with MDH for many years. In conclusion, MDH is a drug-elicited syndrome characterized by a long-lasting hyperresponsiveness to multiple, structurally unrelated drugs with clinically diverse symptoms.

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## Introduction

The term multiple drug hypersensitivity (MDH) was coined by Sullivan et al. [1], who described in 1986 some patients with reactions to chemically distinct antibiotics. They noted that 13% of penicillin-allergic patients developed a drug reaction to nonpenicillin antibiotics like sulfonamides, tetracyclines, erythromycin, vancomycin, and aminoglycosides, with rash, anaphylaxis, drug fever, Stevens-Johnson syndrome/toxic epidermal necrolysis (SJS/TEN), and serum sickness, while only 1.4% reacted if no drug allergy history existed. Later it was found that patients with a history of a previous drug allergy had a 9.4-fold increased risk of developing a drug allergy to a distinct antibiotic compared to patients without a drug allergy [2]. In addition, 10% of the family members of drug-allergic patients developed a drug allergy [3].

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**Table 1.** Distinction between DRESS, flare-up reactions, MDH, and intolerance reactions

	DRESS <sup>a</sup>	Flare-up <sup>b</sup>	MDH	NSAID intolerance
Drug: the reactions occur to	first	second	second or third	various NSAID
Drug exposure before the symptoms	>10 days	2–4 h to 2 days	>3 days	<1 h
Expansion of drug-induced T cells	days or weeks	only activation, no expansion	days or weeks	T cells are not involved
Symptoms	DRESS/ exanthema	identical to the first DHR	similar to or different from the first DHR	urticaria, anaphylaxis, bronchospasm
Sensitization (skin tests/LTT)	yes	no	yes (to 2 or more drugs)	no
Persistence	no <sup>a</sup>	no	yes	yes <sup>c</sup>

DHR, drug hypersensitivity reaction; DRESS, drug rash with eosinophilia and systemic symptoms; MDH, multiple drug hypersensitivity; NSAID, nonsteroidal anti-inflammatory drugs; LTT, lymphocyte transformation tests. <sup>a</sup> Most patients with DRESS do not develop MDH. <sup>b</sup> In flare-up reactions, similar symptoms reappear upon a short exposure to a new drug days to weeks after the acute DHR but, after a while (i.e., weeks to months), the hypersensitivity disappears and the drugs are able to be tolerated. Hence the reactivity is not persistent. Some flare-up reactions may be due to viral reactivations. <sup>c</sup> Persistence is not related to an immune reaction.

Later, the term MDH was also used for reactions observed in patients suffering from intolerance presenting with urticaria, angioedema, and/or anaphylaxis to structurally distinct, but functionally related, nonsteroidal anti-inflammatory drugs [4, 5]. However, intolerance reactions to nonsteroidal anti-inflammatory drugs are not immune mediated but rather they are related to the pharmacological properties of all nonsteroidal anti-inflammatory drugs (i.e., inhibition of cyclooxygenase). To differentiate MDH from intolerance reactions, it was proposed that the term MDH should be used only for clinically well-defined drug hypersensitivity reactions (DHR) elicited by 2 or more chemically distinct drugs, where their involvement has been proven by skin tests or in vitro tests [6, 7] (Table 1).

The T-cell activations in MDH are not due to cross-reactivity. Cloning of drug-reactive T cells of a patient with DHR to 4 different drugs revealed that each T-cell clone was highly specific for a single drug, and no cross-reactive T-cell clones were found [8]. Moreover, drug-reactive T cells of a patient with MDH were found to have a distinct function with a distinct cytokine production upon drug-specific stimulation [9]. This is consistent with the observation that patients with MDH to different drugs develop diverse clinical manifestations [6, 7, 10].

Here we summarize the clinical and immunological aspects of MDH based on clinical data of 31 patients with MDH and our database of lymphocyte transformation tests (LTT). MDH is a syndrome that persists long after the drug treatment has been stopped and can result in highly different clinical manifestations. It is distinct from flare-up reactions, drug rash with eosinophilia and systemic symptoms (DRESS), and intolerance reactions (Ta-

ble 1). Here we review this syndrome with the aim of raising awareness and stimulating research on this still widely unknown syndrome.

### MDH, DRESS, and Flare-Up Reactions

Reports on MDH are rare. Gex-Collet et al. [6] proposed that MDH should be proven by positive skin and/or in vitro tests to distinct drugs. We observed previously that about 10% of patients with severe drug hypersensitivity have additional reactivity to structurally unrelated drugs in vivo and/or in vitro [7]. This is similar to the incidence of MDH of 13% described by Sullivan et al. [1]. Studer et al. [11] used cutaneous symptoms and skin test reactivity to at least 2 chemically distinct substances as criteria for MDH. The incidence of MDH was much lower in that study (0.6%), probably because most of the patients selected from their database might have had just mild cutaneous symptoms. Importantly, clinical studies of MDH [6–8, 10, 11] have shown that the initial manifestation can be exclusive severe exanthema or erythroderma rather than DRESS; for example, in the series of Studer et al. [11], only 4 out of 11 patients with MDH had DRESS as the initial manifestation, and in the study of Daubner et al. [8] the number was only 4 out of 7.

A large collection of recurrent drug reactions was published recently by Picard et al. [10]. They found that 15 out of 60 (25%) patients with prior DRESS experienced relapses with rash, eosinophilia, and/or elevated liver function tests to new drugs 2–240 days after the acute DRESS. Regrettably, sensitizations to the involved drugs were not documented and thus their data do not differentiate between real MDH and “flare-up” reactions.

**Table 2.** Clinical manifestations of first and follow-up manifestations of MDH

Clinical manifestation of DHR (first episode) ( <i>n</i> = 31)	Clinical manifestation of DHR (second/third episode)
Severe exanthema/erythroderma ( <i>n</i> = 13)	– Exanthema/erythrodermia
DRESS ( <i>n</i> = 12)	– DRESS (often with different organ involvements including hepatitis, nephritis, carditis, and/or pancreatitis)
Erythema multiforme major ( <i>n</i> = 3)	– Arthralgia, exanthema, and urethritis
Bullous IgA dermatosis ( <i>n</i> = 1)	– Agranulocytosis
SDRIFE ( <i>n</i> = 1)	– SDRIFE
Vasculitis (after SMX/TRM) ( <i>n</i> = 1)	– malaise and swelling

SDRIFE, symmetrical drug-related intertriginous and flexural exanthema; SMX/TRM, sulfamethoxazole/trimethoprim; MDH, multiple drug hypersensitivity; DHR, drug hypersensitivity reaction; DRESS, drug rash with eosinophilia and systemic symptoms.

Flare-up reactions describe the transient and rapid re-appearance of identical DHR symptoms when another drug is given while the immune system is still activated by the first DHR (Table 1) [12]. Typically within a few hours after taking a new drug, the preexisting DHR-related skin symptoms become aggravated, with a transient increase in the number of circulating eosinophils and/or liver enzymes. As such rapid flare-up reactions frequently occur days to weeks after the initial manifestation in DRESS, it is not easy to differentiate flare-up reactions from viral reactivations or other complications [10, 13]. Indeed, viral reactivations themselves may contribute to the clinical symptoms of flare-up reactions [14]. As flare-up reactions normally prompt immediate cessation of the new therapy, the second drug is given only briefly. It is assumed that the second drug does not stimulate the immune system long enough to cause T-cell expansion and permanent sensitization to the new drug. Skin tests to the second drug and drug-induced proliferation as assessed via *in vitro* LTT remain negative. Importantly, the second drug is tolerated again when the activation of T cells caused by the initial DHR has resolved. Common elicitors of flare-up reactions are antipyretics such as acetaminophen or antibiotics/antiviral medications.

Some of the cases described by Picard et al. [10] might have been flare-up reactions but others that appeared many days after the acute DRESS and occurred after a longer treatment period may correspond to a true second DHR in the frame of MDH. A careful assessment of the described DRESS cases in the literature revealed that the appearance of new symptoms is common in DRESS [10–17]. However, these were often labeled relapses linked to infectious complications and they were seldom recognized as new drug-elicited events. Some of the second reactions were even fatal [18, 19].

### Clinical Characteristics of MDH

We previously described the clinical characteristics of patients with MDH in 2 case series comprising altogether 14 patients [6, 7]. Here we have extended the number of patients to altogether 31 (see online suppl. Table 1S; see [www.karger.com/doi/10.1159/000458725](http://www.karger.com/doi/10.1159/000458725) for all online suppl. material) and summarized the clinical aspects in Table 2. The initial manifestation of MDH is mostly severe exanthema (*n* = 13, including 1 case of erythroderma) often with some eosinophilia and a moderate elevation of transaminases (ALT and/or AST 2–5 times the upper limit of normal) but not enough to meet the diagnostic criteria for DRESS [20, 21]. Twelve out of 31 patients with MDH met the diagnostic criteria for DRESS. A further 3 patients had erythema multiforme major. One patient had initially a bullous IgA dermatosis after metronidazole and ceftriaxone, another had symmetrical drug-related intertriginous and flexural exanthema after allopurinol, and finally one patient had vasculitis after sulfamethoxazole/trimethoprim (Table 2). The eliciting drugs of the first and follow-up DHR of MDH are listed in Table 3.

Severe DHR are accompanied by lymphocytosis with massive lymphocyte activation (lymphoblasts) and this is also one of the main diagnostic criteria for DRESS [20, 21]. This strong lymphocyte activation can persist for weeks or months after drug withdrawal, and it is still present even when the clinical symptoms have disappeared. Our clinical experiences suggest that the presence of these lymphoblasts in the circulation correlates with the ongoing predisposition to react to other drugs, resulting in either short flare-up reactions or further DHR to new drugs [14]. Indeed, 12 out of 31 patients with MDH reacted immediately to the combination therapy (6 of the 12 reacted

**Table 3.** Drugs involved in MDH

<i>First drug (n = 31)</i>	
5×	amoxicillin
3×	amoxicillin/clavulanic acid, sulfasalazine (sulfapyridine/5-aminosalicylic acid), sulfamethoxazole/trimethoprim, phenytoin, carbamazepine, and rifampicin
2×	lidocaine
1×	vancomycin, allopurinol, escitalopram, metronidazole/ceftriaxone, cefepime, cefuroxime, piperacillin/tazobactam, and isoniazid
<i>Follow-up drugs (second or third DHR)</i>	
2×	amoxicillin, sulfamethoxazole/trimethoprim, and budesonide
1×	phenytoin, lamotrigine, carbamazepine, triamzolam, amitriptyline, pantoprazole, rifampicin, metronidazole, sulfamethoxazole <sup>a</sup> , ceftobiprole, ceftriaxone, ertapenem, penicillin G, piperacillin/tazobactam, vancomycin, clindamycin, levofloxacin, and ciprofloxacin

Other drugs known to induce MDH are: antituberculous drugs like pyrazinamide and ethambutol; radiocontrast media, torasemide, furosemide, flucloxacillin, imipenem (and possibly other drugs; the list is not complete). MDH, multiple drug hypersensitivity; DHR, drug hypersensitivity reactions. <sup>a</sup> Only single sensitization (not to trimethoprim).

also later) and 13 out of 31 patients reacted within the first 2–6 weeks to 2 or more drugs. On the other hand, 12 out of 31 patients developed a second DHR years after the first DHR; the longest time interval was reported from a 14-year-old boy with carbamazepine-induced DRESS who developed clindamycin-induced exanthema 20 years later. This was also the youngest patient of our case series (online suppl. Table 1S).

The follow-up symptoms can be identical to or different from the first DHR (Table 2). Identical symptoms to the second drug were observed in 8 patients, among whom 5 patients had DRESS again. Two of these had an additional organ involvement, one with pancreatitis and the other with fulminant liver failure [18]. One patient reacted twice with symmetrical drug-related intertriginous and flexural exanthema, first to allopurinol and then to amoxicillin, with a 2-year interval in between. Four patients had repeatedly exanthema.

Most subsequent symptoms in the context of MDH differed from the first presentation; they changed from DRESS to exanthema or to an isolated drug-induced liver injury. Others developed acute generalized exanthema-

tous pustulosis ( $n = 1$ ), erythroderma ( $n = 2$ ), and exanthema with arthralgia or other organ involvements with nephritis, pancreatitis, or agranulocytosis [22] (Table 2). Thus, either fewer or more dangerous symptoms could appear in follow-up DHR manifestations.

The 2 cases of lidocaine-initiated MDH were similar; they reacted initially to lidocaine-containing hemorrhoidal cream with contact dermatitis. They both developed a massive systemic skin reaction with erythema multiforme after subcutaneous application of lidocaine. Strangely enough, both developed as a second DHR a contact allergy to budesonide 9–10 years later, which manifested as localized facial rash/swelling upon inhalation of budesonide and contact dermatitis to cross-reactive corticosteroid-containing creams.

SJS/TEN does not appear as a first manifestation of MDH, but it may occur as a second or third manifestation (3 out of 31 patients). This is also in agreement with the report by Picard et al. [10], which showed that only 1 out of 60 patients with SJS/TEN developed symptoms upon exposure to a second drug. Of note, SJS/TEN differs from DRESS in that no lymphocytosis and no evidence of massive cell activation in the circulation is found in most SJS/TEN patients [23]. Identification of the culprit drug(s) of SJS/TEN is often difficult [24]. One patient even developed first maculopapular exanthema, then DRESS, then acute generalized exanthematous pustulosis, and lastly a fatal TEN to different drugs within a span of 2 months [25].

A controversial issue is the role of herpes viruses in DRESS and MDH. HHV6, Epstein-Barr virus, and cytomegalovirus reactivations can be found in many patients 2–4 weeks after the onset of DRESS [17, 20, 26, 27], but these have not been described in patients with severe exanthema alone, who account for many of the patients with MDH. This, as well as the delayed appearance of herpes virus reactivations in DRESS, suggests that these viral reactivations are not necessary to start an MDH syndrome. Nevertheless, they may play a role in some individual cases in which recurrent relapses, flare-up reactions, and even new DHR occur [10, 17, 26, 27]. Importantly, the activation of T cells in MDH, which are found years after the acute DHR, cannot be linked to an ongoing cytomegalovirus or HHV6 infection [8].

We observed MDH almost exclusively in patients with T-cell-mediated drug reactions and our explanation of MDH is based on this T-cell concept. However, there exist cases of IgE-mediated anaphylaxis to structurally distinct drugs. For example, some patients with perioperative anaphylaxis react, on skin tests and in vitro, to biva-

**Table 4.** LTT results of patients who had DHR to a combination therapy

Total positive LTT	Positive LTT	Positive LTT	Positive LTT
Amoxicillin/clavulanic acid <i>n</i> = 115	amoxicillin 64 (56)	clavulanic acid 12 (10)	amoxicillin and clavulanic acid 39 (34)
Cotrimoxazole <sup>a</sup> <i>n</i> = 37	sulfamethoxazole 16 (43)	trimethoprim 4 (11)	sulfamethoxazole and trimethoprim 17 (46)
Piperacillin/tazobactam <sup>b</sup> <i>n</i> = 21	piperacillin 7 (33)	tazobactam 7 (33)	piperacillin and tazobactam 7 (33)
Sulfasalazine <sup>b</sup> <i>n</i> = 10	sulfapyridine 6 (60)	5-ASA 0 (0)	sulfapyridine and 5-ASA 4 (40)
Total ( <i>n</i> = 183)	93 (33–60%)	23 (0–33%)	67 (33–46%)

Values are presented as numbers (%) unless otherwise stated. LTT, lymphocyte transformation tests; DHR, drug hypersensitivity reaction; 5-ASA, 5-aminosalicylic acid; DRESS, drug rash with eosinophilia and systemic symptoms. Thirty-three to forty-six percent of patients had double sensitizations. The frequency of single and double sensitizations in drug-allergic patients during 4 commonly used drug combination therapies is shown. Positive LTT (stimulation index >3) to the combination therapy were selected from >2,000 LTT analyzed over 6 years. Patients with DRESS to the above-mentioned combination therapy were positive in 65–85% of LTT. <sup>a</sup> Mostly severe exanthema. <sup>b</sup> Mostly DRESS.

lent drugs like chlorhexidine and to neuromuscular blocking agents like rocuronium. While these cases fulfill the formal criteria for MDH, they clearly have a different mechanism and are not linked to severe T-cell reactions. These solely IgE-mediated cases are not discussed in this review.

### Simultaneous, Sequential, and Distant Forms of MDH

Gex-Collet et al. [6] differentiated 2 forms of MDH based on simultaneous or sequential sensitizations leading to DHR. Studer et al. [11] proposed a similar approach; they distinguished MDH patients who developed a sensitization to different substances during the same episode of cutaneous DHR (mostly lasting 2–6 weeks) from MDH patients in whom different substances caused a second DHR in separate episodes. In addition, they differentiated MDH based on DRESS from that which was possibly related to viral replication. Although it is difficult to delineate different triggers in the first episode of DHR, it makes logical sense to differentiate simultaneous from sequential forms of MDH as the simultaneous forms are often due to therapy with fixed drug combinations (Table 4). In some cases, DHR may occur years later, representing a distant form of MDH.

#### Simultaneous

MDH syndrome may start with sensitizations to more than one drug at the start of therapy. This simultaneous sensitization occurs if drugs are given in a combination therapy. Examples include sulfamethoxazole combined with trimethoprim (cotrimoxazole), amoxicillin combined with clavulanic acid, and piperacillin combined with tazobactam. The concurrent use of vancomycin with rifampicin, of metronidazole with ceftriaxone, and of antituberculous therapy (e.g., rifampicin and isoniazid) also resulted in simultaneous MDH. Twelve out of 31 patients belonged to this simultaneous subgroup (see online suppl. Table 1S).

When the LTT data of patients with DHR due to combination therapy with at least one positive LTT (stimulation index >3) over 6 years were analyzed, the frequency of double sensitizations was found to be rather high (33–46%; Table 4). Some of these patients developed a further DHR to another drug later. Occasionally (4 out of 31 patients), a combination therapy was responsible for the second manifestation of MDH (see online suppl. Table 1S).

#### Sequential

An initial severe DHR is a risk factor for a flare-up reaction or a second DHR. The first therapy is stopped because of a DHR and the second therapy may be started, often within days, while T cells are still activated. Not infrequent-

ly, the new drug may just elicit a flare-up reaction. However, when the treatment lasts longer, a second, true DHR directed against the alternative drug may develop, resulting in MDH. This was observed in 13 out of 31 MDH patients.

It is not uncommon that more than 2 drugs are involved in MDH [25]. We repeatedly observed both simultaneous and sequential appearances of DHR occurring in the same patient who reacted to 3–4 different drugs (see online suppl. Table 1S and 2S).

#### *Distant (Long-Interval) MDH*

The distant, long-interval form of MDH occurs when the DHR symptoms appear after the initial DHR has already disappeared. It occurred in 12 out of 31 patients. The interval between the first and second DHR ranged from 2 to 20 years. This implies that a patient with a severe DHR like DRESS may be at risk for developing a second DHR for many years. Whether this represents a preexisting predisposition for the development of MDH even before the onset of the first DHR or this risk is acquired after the initial DHR is unknown at this stage.

### **Risk Factors for the Development of MDH**

The majority of MDH develop in patients with DRESS. Consequently, the risk factors involved in eliciting DRESS are also relevant for the development of MDH.

#### *Type of Drug*

Use of a drug that is able to cause a severe T-cell-mediated DHR is a main risk factor. As most MDH start with DRESS, the same drugs involved in DRESS are also involved in MDH. Antiepilepsy medications, sulfonamide antibiotics, and allopurinol are the main causes of DRESS and, not surprisingly, these drugs were also involved in our MDH patients who had DRESS (Table 3). However, drugs that are uncommon causes of DRESS can still be the starting drugs for MDH if the first reaction was severe.

#### *High Drug Concentration*

Most of the drugs eliciting DRESS are given at relative high daily doses, often exceeding 1 g/day. The frequent occurrence of MDH to combination therapy may also be due to the high individual drug doses used in these combinations (see online suppl. Table 3S).

#### *Combination Therapy*

DHR to both components of a fixed combination therapy like amoxicillin/clavulanic acid, cotrimoxazole (sul-

famethoxazole/trimethoprim), and piperacillin/tazobactam is rather common. Table 4 summarizes the LTT results extracted from our database covering 6 years (2,000 LTT; Table 4). While sulfasalazine is not a combination drug per se, it is metabolized to sulfapyridine and 5-aminosalicylic acid and double sensitizations to both components occur (Table 4). All of these medications are also given in gram quantities (see online suppl. Table 3S). The frequency of double sensitizations is higher than the frequency of sensitization to the less “immunogenic” compounds (33–46 vs. 0–33%; Table 4). This suggests that the reactivity to the less immunogenic compound (e.g. clavulanic acid in amoxicillin/clavulanic acid) is enhanced if an immune reaction to the more immunogenic compound (i.e., amoxicillin) occurs simultaneously.

Similar to fixed combination therapy is the situation with antituberculous therapy, where treatment schemes also rely on a high dose of isoniazid, rifampicin, pyrazinamide, and either ethambutol or streptomycin together. In this instance, a simultaneous reactivity to 2 or more compounds can develop (see online suppl. Table 1S).

#### *Longer-Lasting Treatment*

Many of the therapies causing DRESS/MDH are given for more than 10–20 days. This prolonged treatment seems to increase T-cell reactions to the drug in general and it is also a risk factor for DRESS/MDH, especially if given in high doses. Therefore, MDH syndrome appears in patients on long-term, high-dose therapy for conditions such as complicated infections (e.g., for prosthetic joint infection) or epilepsy. On the other hand, many drugs used for hypertension or hypercholesterolemia are not linked to DRESS/MDH in spite of continuous treatment. Most of these drugs are given at lower doses (typically <50 mg/day) and are not known or infrequent causes of DHR.

#### *No Human Leukocyte Antigen Linkage to MDH Syndrome*

Severe reactions (SJS/TEN/DRESS) to some drugs are linked to certain human leukocyte antigen (HLA) alleles [28, 31]. These linkages can be explained by an off-target activity of a particular drug to a certain HLA protein [32]. For example, carbamazepine binds with a rather high affinity to HLA-B\*15:02, oxypurinol binds to HLA-B\*58:01, and abacavir binds to HLA-B\*57:01 [28–31]. The starting DHR of an MDH syndrome can consequently be linked to a drug that has an HLA linkage. However, the MDH itself, presenting as a syndrome with multiple DHR, is not linked to a certain HLA. An exception is if

the HLA-protein involved in the first DHR also binds to drugs involved in the follow-up DHR. For example, an individual who develops carbamazepine-induced DHR due to the drug binding to HLA-B\*15:02 may also develop subsequent DHR to lamotrigine or phenytoin which may also bind to HLA-B\*15:02 [33]. Further analysis of HLA and of other genetic predispositions is needed as some data have indicated a familiar predisposition [3].

### Patho-Mechanism of MDH

As there is no animal model for MDH, in vitro data rely on analysis of blood samples and biopsies of affected patients. In a few cases analyzed, lymphocytosis and the presence of activated T cells in the circulation (CD3+, CD4+ and/or CD8+, and HLA-DR+) or tissue (liver) have been found [18, 34]. The study of Daubner et al. [8] investigated the question of whether T regulatory cells (CD4+/CD25<sup>bright</sup>/foxp3+) are deficient in patients with MDH or not. Seven MDH patients in remission, 6 patients with a prior monoallergy, and 6 healthy controls were recruited and analyzed. Their in vitro reactivity to tetanus toxoid and various drugs (mainly antibiotics and antiepileptics) was analyzed by depleting and selectively readding CD4+, CD25<sup>bright</sup>, foxp3+ T regulatory cells in proliferation assays. All 7 MDH patients showed a drug-specific reactivity in in vitro proliferation assays years after the acute event. Interestingly, no functional deficiency of T regulatory cells was observed either in the drug-specific assays or in the control cultures with tetanus toxoid as the antigen.

The surprising result of this study is that patients with MDH still showed signs of permanent cell activation in the circulation years after the acute event. While the massive T-cell stimulation with circulating lymphoblasts disappeared within weeks to months after the acute DHR, some signs of T-cell activation detectable by flow cytometry persisted longer. This persistent T-cell activation of MDH patients was characterized by CD4+, CD25<sup>dim</sup> (the study focused on CD4 cell reactions only), which contained an activated T-cell subset (PD-1+/CD38+) and this PD-1+/CD38+ subset contained the drug-reactive T cells. Patients with a monoallergy did not have these CD4+, CD25<sup>dim</sup>, CD38+, and PD-1+ T cells [8]. Initially it was speculated that the continued CD38+ and PD-1+ expression within the CD4+, CD25<sup>dim</sup> cell fraction might be due to an ongoing infection by endogenous herpes viruses, as the PD1+/CD38+ phenotype was also ob-

served in chronic herpes virus infections [35, 36]. However, a viral analysis of the patients failed to document an ongoing herpes virus (cytomegalovirus and HHV6) infection.

### Unresolved Questions

MDH is a new syndrome, and many clinical and immunological questions are unsolved.

How do drugs stimulate T cells in MDH? The initial DHR – a DRESS or severe exanthema – appears to be initiated by p-i-mediated T-cell stimulations where the drug directly binds noncovalently to a particular HLA protein itself with a substantial affinity (p-i HLA) [37–41]. Classical hapten-dependent reactions with covalent binding of the drug to the HLA-presented peptide were repeatedly excluded [31, 37–42]. In sulfamethoxazole-induced DHR, the drug may bind to the TCR (p-i-TCR) [43, 44]. Thus the initial manifestation of MDH appears to be mostly p-i mediated.

A second feature of MDH is the strengths of the reaction – both in vivo (e.g., DRESS) and – if tested – also in vitro. The T-cell proliferations to a single drug as assessed by LTT revealed a polyclonal stimulation with stimulation indices >50 (normally <2) (see online suppl. Table 2S), which was stronger than the stimulation by a large protein antigen like tetanus toxoid and sometimes even exceeded the mitogen stimulation with phytohemagglutinin or pokeweed mitogen. This massive, drug-induced proliferation in a 6- to 7-day culture is reminiscent of proliferations observed in mixed leukocyte reactions. This would be consistent with the allo-immune hypothesis of DHR which postulates that severe DHR are due to p-i stimulations resulting in allo-like immune stimulations [32, 45]. It hypothesizes that drug binding to HLA modifies the HLA-peptide complex and makes it look like an allo-HLA structure, which then elicits a strong, polyclonal T-cell stimulation. This has been documented in the abacavir model, where the peptide-abacavir-HLA-B\*57:01 complex acquires the conformation of the {peptide-HLA-B\*58:01} complex [32]. If one applies this concept to severe DHR in general, MDH may start with a massive, graft-versus-host disease-like immune stimulation, which in the case of MDH somehow persists for years (elevated PD-1/CD38+ T cells). Follow-up reactions in MDH appear to be mostly p-i stimulations as well, but hapten-dependent immune stimulations may also occur. Further studies on the patho-mechanism of MDH and its long-lasting T-cell reactivity are needed.

**Table 5.** Possible measures to avoid flare-up reactions and further DHR

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Restrict the use of drugs in patients with ongoing severe DHR (mainly DRESS) as much as possible.
If new drugs are needed, choose drugs that are effective at low doses (<50 mg/day).
Replace antipyretics with physical measures (e.g., wet compresses instead of acetaminophen).
Use antibiotics only for therapy, not for prophylaxis.
Suppress the immune stimulation by corticosteroid therapy (oral or i.v. prednisolone is normally tolerated). For example, 0.3–0.5 mg/kg/day of prednisolone equivalent for 2–7 days, followed by a stepwise reduction, dependent on the amount of circulating lymphoblasts.
Alternatively, attempt to create a therapy-free interval for days to weeks. Keep these measures as long as the proportion of massively activated lymphocytes (lymphoblasts) in the circulation is elevated <sup>a</sup> .

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DHR, drug hypersensitivity reaction; DRESS, drug rash with eosinophilia and systemic symptoms. These measures are based on clinical experience and the risk factors described in the text. <sup>a</sup> Standard values of lymphoblasts differ from lab to lab. A substantial decrease should be noted.

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It is difficult to comprehend why stimulation by one drug would pave the way for an additional reaction to other drugs. This is the case in simultaneous MDH to both components of a fixed combination therapy (Table 4). As already mentioned, the drug-reactive T cells of MDH patients are specific to the particular drug and they are not cross-reactive. One explanation might be that an ongoing T-cell activation is a risk factor for a second DHR; similar to the costimulatory effect of viral infections (Epstein-Barr virus and HIV) on the manifestation of a DHR, the T-cell activation of the first DHR may lower the threshold of reactivity to a second drug [8].

What keeps the T cells of MDH patients in “alarm mode” for years and what facilitates a second sensitization? According to the allo-immune model of DHR, the initial allo-like immune reaction (e.g., DRESS) might also include T cells cross-reactive for autoantigens, which remain stimulated, even when the drug has been removed. The MDH might thus correspond to a chronic graft-versus-host disease-like stimulation. Indeed, the CD4+, CD-25<sup>dim</sup>, CD38+, and PD-1+ T cells found in MDH are also found in chronic graft-versus-host disease [45].

## Conclusion

MDH is a rather novel syndrome which is characterized by DHR to various structurally different drugs. It is initiated by severe T-cell reactions (mostly severe exanthema and DRESS), which appear to have a long-lasting effect on the patient’s immune system.

MDH is often seen as a complication of an ongoing DRESS with recurrence of some of the DRESS symptoms over time [10, 11]. However, clinical data has shown that MDH can start outside of DRESS [8, 10] and the clinical course of the second and third DHR is often different to DRESS (Table 3). Thus, not the disease DRESS itself but rather the strengths of the T-cell stimulation seems to be the decisive factor for development of a MDH. Since SJS/TEN is not a risk factor for developing MDH, the type of immune stimulation (probably a more CD4-biased stimulation with strong T-cell expansion and thus lymphocytosis and circulating lymphoblasts) might be crucial as well.

The chronicity of the MDH syndrome is documented by the long time interval between DHR manifestations (up to >20 years) and the presence of permanently activated T cells expressing PD-1+, CD38+ in the circulation for years. These activated T cells were found in MDH with simultaneous, sequential, or distant DHR appearances. MDH thus challenges the conventional concept of DHR as an acute, drug-dependent reaction; an initial severe DHR may alter the immune system permanently and switch it to a chronic immune disorder.

Whether the presence of permanently activated T cells is detrimental to health is not known. A high percentage of PD1+, CD38+ circulating T cells has also been found in other chronic diseases such as graft-versus-host disease [45] and chronic herpes virus infections [35, 36]. In the latter it was linked to a reduced life span of the affected persons [46].

We did not use provocation tests to define MDH. Provocation tests are contraindicated in severe DHR and potentially problematic in patients with a tendency to react to more drugs. Nevertheless, they would be helpful in MDH due to a combination therapy such as cotrimoxazole, as the conclusion that both drugs (e.g., sulfamethoxazole and trimethoprim) are involved in eliciting DHR is only based on positive skin and/or in vitro tests to both drugs of the combination therapy (Table 4).

Patients with MDH present a diagnostic and therapeutic dilemma for the treating physician. The symptoms are often similar to infectious complications and may not be linked to a new DHR [13]. It is difficult to know which

antibiotic can be given safely to a patient with active DRESS, given that up to 25% of patients may develop an MDH [10]. It is possible that there are some drugs or antibiotics that pose a lower risk for the development of new DHR. Indeed, not every drug to which the patient was exposed was positive on LTT (see example in online suppl. Table 2S). Such data need to be collected and evaluated.

Based on our clinical experience, and the risk factors described above, we propose the following actions to lower the risk of the development of MDH in patients with severe T-cell-mediated reactions: (1) minimize the use of further drugs; (2) omit antipyretics; (3) avoid antibiotics unless they are absolutely indicated; (4) if needed, choose drugs that can be given at a lower dose (such as possibly <50 mg/day); (5) dampen the hyperactivation of the immune system by steroids (e.g., 0.3–0.5 mg/kg/day of a prednisolone equivalent for 2 to >7 days with a slow dose reduction – the amount of immunosuppression required might be monitored by evaluating the amount of circulating lymphoblasts; and (6) try to create a therapy-free interval for days to weeks (Table 5).

Research on drug hypersensitivity relies on clinical and in vitro analysis of patients, as animal models are not available. The study of a new drug hypersensitivity-relat-

ed syndrome like MDH is therefore difficult, in particular if it is rare. The description of MDH as an own syndrome is in its infancy, and many of the data presented in this review are still clinical observations that need to be verified, most likely in multicenter studies. Both clinical and immunological studies might be done in patients with DRESS, as these represent a high-risk group for MDH [10]. However, also the double sensitization in combination therapy appears to be frequent enough to allow a systematic analysis (Table 4). The value of determining CD4+, CD25<sup>dim</sup>, PD-1+, CD38+ as a marker for MDH patients needs to be confirmed, as does the role of activated CD8+ T cells, which was not addressed in the study by Daubner et al. [8]. An important question is whether activated T cells can already be found in potential MDH patients, i.e., before the second (or third) DHR takes place. Finally, how long these T cells remain in the circulation and whether the permanent presence of these activated T cells in the circulation has a deleterious effect on general health needs to be clarified [46].

## Disclosure Statement

The authors declare no conflict of interests.

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