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The role of drug, dose and the tolerance/intolerance of new drugs in multiple drug hypersensitivity syndrome (MDH)

Short title: Multiple drug hypersensitivity: The role of new drugs

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Abstract:

Background: Multiple drug hypersensitivity syndrome (MDH) is used to describe persons with a drug hypersensitivity reaction (DHR) to at least two chemically unrelated drugs, confirmed by skin test or in vitro assay.

Methods: Medical records of 25 patients with MDH, tested and confirmed at our allergy division were retrospectively evaluated in terms of clinical course, involved drugs, daily drug dose, latency periods, test results of skin test and cellular assays and tolerated drugs in subsequent pharmacological treatments.

Results: MDH almost exclusively appeared as a delayed, often severe DHR and started in 14/25 with a drug reaction with eosinophilia and systemic symptoms (DRESS). Penicillins (13/25, 52.0%) and cephalosporins (6/25, 24.0%), typical high dose drugs, were most often identified as elicitors of MDH, especially at the first DHR, followed by aromatic antiepileptics (7/25, 28.0%), vancomycin (4/25, 16.0%) and antibiotic sulfonamides (4/25, 16.0%). Cephalosporins, clindamycine and radio contrast media (RCM) were mainly involved in subsequent DHR. The median daily drug dose of all drug trigger was 1875.0 mg (662.5; 2100.0) at the first DHR and 600.0 mg (300.0; 1300.0) at subsequent DHR, p=0.0420.

Conclusion. High dose drugs, especially betalactam antibiotics, RCM and clindamycin are common elicitors of subsequent DHR in patients with MDH. Macrolides, quinolones, doxycycline, non-aromatic antiepileptics and paracetamol were often tolerated. As the same drugs elicited both flare-up reactions and real DHR, drug induced flare-up reactions may be precursors of a possible second DHR and MDH. The administration of highly dosed drugs should be avoided in patients at risk for MDH.

Introduction

Multiple drug hypersensitivity syndrome (MDH) was originally described in case reports by Sullivan et al. [1] and was based on clinical criteria and some skin tests. This syndrome was "revived" by analyzing T cell reactivity of patients with drug hypersensitivity [2]: it was noted that some patients with a T cell reaction to drugs (exanthema, DRESS) had a strong reactivity to more than one drug in vitro (lymphocyte transformation test (LTT)) and in vivo (mainly patch tests (PT)) [2]. These observations were summarized in case series [2, 3, 4, 5, 6, 7, 8] and defined as a drug hypersensitivity reaction (DHR) to at least 2 chemically and pharmacologically unrelated drugs [2, 7]. Three subforms of MDH were described according to the sequence of symptoms onset: (1) the simultaneous form, based on the appearance of symptoms to two drugs or more simultaneously (in the case of combination therapy for instance), (2) the sequential form in which subsequent reactions occur during the acute stage, and (3) the distant form when reactions occur to drugs given months to years apart [2, 7]. To distinguish this syndrome from other drug reactions, it was recommended to prove the double or triple reactivity by skin or in vitro tests to two or more drugs [2, 7]. The proof of an immune mediated mechanism allows to exclude any drug intolerance or pseudoallergic reactions, where e.g. various chemically distinct non-steroidal anti-inflammatory drugs (NSAID) may be responsible for repeated reactions as well [9].

The pathophysiology of MDH is under investigation. In the initial descriptions by Sullivan [1], no distinction of immediate and delayed reactions were made. In the later more detailed studies on MDH, the initial clinical symptoms and drug specific T cell reactivity in vitro and in vivo suggested that this syndrome starts with a strong T cell reactivity [10]. A step forward in analyzing the mechanism of MDH was the study of Daubner B et al. [11]. T cell reactivity of seven MDH patients has been compared with 6 mono-allergic patients with maculopapular exanthema (MPE). They could show that the multiple reactivity was not due to cross-reactivity. No deficiency of T reg cells in reactions to drugs or the control antigen tetanus toxoid could be observed in MDH or in the control MPE patients [11]. A puzzling finding was the observation that patients with a prior MDH carried, months to years after the acute symptoms, still a population of activated T cells in the circulation, although no infection and no clinical sign of auto-immune disease were evident. These cells were CD4+, CD25dim, CD38+, PD1+ and could be found only in MDH patients and not in mono-allergic patients with prior MPE [11]. Interestingly, the same activated T cells were also described in patients with chronic viral disease or graft versus host disease [12]. Based on new studies on immune stimulations of T cells by drugs, which emphasized the similarity of drug and allo-stimulations [12, 13], the clinical characteristics of patients with MDH symptoms and the

study of Daubner et al. [11] it was hypothesized that MDH represents a kind of chronic graft versus host disease like condition, developing from an acute DHR, which ends up in a chronic stimulation.

The aim of this study was to highlight certain clinical hallmarks of MDH and to elaborate clinical recommendations how to diagnose and treat patients with MDH or patients at risk for developing MDH. Only patients with proven immune mediated mechanism of MDH were included. We focused on the eliciting drugs, especially on drugs responsible for subsequent reactions, on the timing and dose of the drugs and on the role of comorbidities. We also provide a list of drugs, which were tolerated in subsequent pharmacological treatments. Together these clinical findings result in recommendations how one could manage patients with MDH or at risk for MDH.

Methods

Study design

Patients with a diagnosis of MDH, tested and confirmed at our allergy division were retrospectively identified in February 2019 with a search tool from the hospital record database. Search terms included "multiple drug hypersensitivity", "MDH" and we screened for patients with sensitization to two or more drugs. All patients gave informed consent to the evaluation of their drug allergy history. The study was approved of the local ethics committee (Kantonale Ethikkommission Bern). The project was conducted in accordance with the protocol, the Declaration of Helsinki, the principles of Good Clinical Practice and locally relevant regulations.

Study population

Patients with a visit at our allergy division between January 2011 and December 2018 were included in the study. We defined MDH as a immunologically mediated DHR to two or more unrelated drugs and defined therefore the following inclusion criteria: one or more clinically well documented DHR with detection of at least 2 or more structurally different drug triggers either by skin or in vitro tests (table 1). Skin tests were performed and read according to the EAACI/ENDA guidelines [14]. Exclusion criteria were reactions with subjective symptoms (only pruritus, discomfort, pain etc.), drug reactions suggestive for pharmacologic side effects, reactions to pharmacologically related drugs, possible cross reactivity between causative drugs, doubtful test results (irritative, repeated negative tests), and patients with chronic spontaneous urticaria or urticarial dermographism. Patients with DHR diagnosed by drug provocation test (DPT) only were excluded too, as DPT cannot distinguish between immunological and non-immunological DHR.

Assessment of clinical data

We evaluated the medical records of each MDH case for numbers and the type of DHR (DRESS, MPE, acute generalized exanthematous pustulosis (AGEP), Stevens Johnson syndrome (SJS), toxic epidermal necrolysis (TEN), symmetrical drug related intertriginous and flexural exanthema (SDRIFE), anaphylaxis (ANA) etc.). It was determined whether a patient developed only a single DHR with sensitization to combination therapies or sequentially given drugs within the same DHR episode or MDH with two or more DHR. The initial manifestation of MDH was defined as first DHR, all following DHR defined as subsequent DHR. Drug-induced flare-up reactions were distinguished from DHR and defined as a rebound of clinical symptoms such as exanthema, elevation of liver enzymes and eosinophilia to a new given drug without eliciting sensitization. Drug induced flare-ups occur usually during or after an acute DHR-phase [15, 16], resulting in the withdrawal of this drug. According to the skin and the in vitro tests (lymphocyte transformation test), drug triggers for each DHR were recorded. In addition, age, gender, latency period (start of therapy until symptoms occur), daily drug dose and trigger of drug induced flare-up reactions were extracted from the medical records. Any comorbidity present at the first DHR was investigated.

For each case we evaluated which new drugs were used and whether they were well tolerated (no subsequent DHR, no drug induced flare-up reaction). We focused on antibiotics, antiepileptics, analgesics, contrast agents and proton pump inhibitors. We analyzed the relationship of patients who were exposed to a particular drug after the first DHR and how many of them tolerated it (tolerated/exposed). We classified drugs that were tolerated in 75% of cases administered as mostly tolerable.

Statistical analysis

Results were evaluated by descriptive statistics. Analysis were performed using Graphpad Prism 8 (GraphPad Software, Inc, La Jolla, Calif). Categorical variables (e.g., gender, type of hypersensitivity reaction, culprit drug, etc.) are expressed in percentage. Continuous variables (e. g. age, drug dose, latency period etc.) are reported as median and interquartile ranges. The Man-Whitney U test was used to compare drug dose and latency period between the first and all subsequent DHR.

Results

Patient characteristics

Out of 39 patients screened, we analyzed the data of 25 cases (14 patients were excluded, 7 not fulfilling the inclusion criteria, 2 for incomplete data, 3 could not be contacted and 2 patients

declined to participate). 15/25 (60.0%) patients were female, the median age at the first DHR was 50 years (range 5-73). Only one child was identified with MDH (5 years old). An IgE mediated mechanism was found in one patient who had a combination of an immediate and delayed type DHR (table 4, patient number 8). Most patients developed a severe delayed DHR as first DHR: 14/25 (56.0%) fulfilled the criteria of a DRESS (Regiscar score of 5 or more) [17], 5/25 patients (20.0%) had a generalized MPE (of which 3 with fever and facial swelling), two patients each developed a SJS/TEN (8.0%) and AGEP (8.0%), one patient a bullous exanthema (table 2). 15/25 had 2 or more DHR, of which 11 subjects developed a different manifestation of DHR. The most frequent subsequent DHR was an MPE (11/15, 73.3%), followed by AGEP (3/15, 20.0%), DRESS (2/15, 13.3%) and SDRIFE (1/15, 6.7%). Epilepsy was the most frequent concomitant diseases (8/25, 32.0%), followed by renal insufficiency (7/25, 28.0%) and autoimmune disorders (7/25, 28.0%). We found most frequently a distant form of MDH (11/25, 44%), followed by sequential (6/25, 24%) and simultaneous (5/25, 20%), 3 patients had an overlap (3/25, 12%).

Trigger of MDH and drug induced flare-up reactions

Findings of all MDH trigger are summarized in figure 1. Betalactam antibiotics, especially penicillins (13/25, 52.0%) were most often identified as trigger, followed by cephalosporins (6/25, 24.0%). Penicillins were primarily involved in the first DHR (12/25), aromatic antiepileptics (7/25, 28.0%) caused only first DHR. On the other hand vancomycin (4/25, 16.0%) and sulfonamide antibiotics (4/25, 16.0%) were involved in both first and subsequent DHR. Clindamycin (4/25, 16.0%), non-aromatic antiepileptics (2/25, 8.0%) and radio contrast agents (4/25, 16.0%) almost never caused a first DHR. Two patients had an immune mediated DHR to a non steroidal anti-inflammatory drug (metamizole, diclofenac).

Drug-induced flare-up reactions occurred in 13 patients (13/25, 52.0%), of which 8 had a DRESS as a first DHR. Cephalosporins (5/25, 20.0%) were at the top of the ranking as trigger for drug induced flare-up reactions, followed by clindamycin and metamizole (each 2/25, 8.0%).

Tolerated drugs

In 22 out of 25 patients we had information on the medication administered after the first DHR (table 3). Although betalactam antibiotics have been often involved in first DHR, they seem to be tolerated later at least partially: 4 out of 6 tolerated penicillins and 4 out of 12 tolerated cephalosporins. The classic DRESS triggers vancomycin (0/2), antibiotic sulfonamides (0/2) and aromatic antiepileptics (0/1) were never tolerated. One patient (table 4, number 8) tolerated lamotrigine if administered below a daily dose of 100mg. Clindamycin was often used, but never tolerated (0/5). Macrolides (2/2), quinolones (7/9), linezolid (2/2) and doxycycline (4/4) were better

tolerated antibiotics. Regarding antiepileptic drugs, non-aromatic antiepileptic drugs (8/10) (especially valproate, levetiracetam and topiramat) and benzodiazepines (4/4) usually seem to be well tolerated. Paracetamol (11/12) and opiates (9/9) were successfully used as analgesic drugs, ibuprofen was tolerated in 4 patients (4/4). Metamizole seemed to be tolerated only partially (4/7).

The role of drug dose

Drug dose was evaluated in patients with delayed DHR (n=24). At the first DHR the daily dose of all drug trigger exceeded 1000mg (median 1875.0 mg (662.5; 2100.0)). Interestingly, the daily drug dose in subsequent DHR was significantly lower than at the first DHR, (600.0 mg (300.0; 1300.0)), p=0.0420. (figure 2a).

Latency period

The median latency period for the first DHR was 19.0 days (19.0 (9.0; 28.0)), and 3 days for subsequent DHR (3.0 (2.0; 7.0), p<0.0001 (figure 2b). The shortest latency time overall (table 4, patient number 12) was 2 hours in a subsequent DHR. Although resembling anaphylaxis, the mechanism was T cell mediated.

The median time interval between the first and the second DHR was 26 (6.0; 71.0) months.

Discussion

MDH is a chronic condition developing from an acute and severe T cell mediated DHR [11]. Why only some patients with DRESS or severe MPE develop symptoms of MDH, and others not, is unclear. The aim of this study was to describe the clinical aspects of patients with MDH, namely of the first and subsequent DHR of MDH, the type of drugs and the role of dosing.

1. Analysis of the first DHR

As previously described in MDH case series [2, 3, 4, 5, 6, 7, 8], classical DRESS triggers, especially antiepileptics, sulfonamides and vancomycin were often the responsible drugs for the first DHR. This observation is not different from severe DHR not linked to MDH [18]. However, betalactam antibiotics, in particular penicillins and cephalosporins were often responsible for first DHR with more than half of our MDH cohort reacting

2. Analysis of subsequent DHR

Of particular interest was the analysis of the subsequent DHR. The following differences compared to the first DHR were found:

a) Drugs causing subsequent DHR were different from the ones causing first DHR. This may be explained with the fact that reserve drugs (like clindamycin) have been used. Three drugs

appearing repeatedly in subsequent DHR but rarely found as elicitors of a first DHR, are 1. clindamycin, which is a rare cause of DHR [19], but was responsible in 3 patients for subsequent DHR and in 2 for a flare up reaction, 2. the analgesic drug metamizole was found in subsequent DHR and flare-up reactions, mainly with MPE and 3. radio contrast media (RCM) were involved in 3 subsequent DHR. T-cell reactions to RCM in the normal population is usually mild [20]. Based on our study, it seems that triggering DHR enhances the subsequent reactivity to RCM (seen in 3/25).

b) The dose of drug trigger in subsequent DHR was substantially lower than in the first DHR. It is striking that most drug trigger, especially at the first DHR, were high dose drugs. In fact, we noticed that first DHR primarily occured with drugs used at daily doses above 1g. Especially betalactam antibiotics are often administered in doses well over 2g per day. Another observation is that a dose increase causes a delayed DHR (table 4, patient number 2). The doses for causative drugs in subsequent DHR were significantly lower (Fig. 2). An explanation might be, that T cells were already activated [11], and were able to react to lower doses. That could explain why in subsequent DHR a larger variety of drugs was able to react.

c) The time interval between drug exposure and symptoms was substantially shorter in subsequent DHR. As already mentioned under point b, this would suggest that a lower cumulative drug dose is required to trigger further DHR.

d) Some drugs induced flare up reactions or a subsequent DHR. We assume that both phenomena are related. Drug induced flare up reactions have been observed in more than half of our patients (52.0%) of which 8 had DRESS and 2 a severe MPE. This suggests that drug induced flare up reactions may represent a milder/beginning DHR, whereby the immune stimulus is too weak to result in a permanent sensitization. Reoccurrence of cutaneous symptoms without sensitization as an aftereffect of a severe delayed DHR is not rare and -according to Picard - occurs in up to 25% [21]. Therefore, patients with drug induced flare-up reactions after a DHR may be at risk of developing MDH, when the exposure lasts longer.

3. Tolerated drugs

For clinicians facing a patient with MDH it is important to offer a medication with a low probability to cause another DHR or flare-up reaction. In our MDH cohort macrolides, quinolones, doxycycline and linezolid have mostly been tolerated. Clindamycin on the other hand caused a subsequent DHR in 3 and a flare-up reaction in 2 subjects! Good tolerance was also seen to non-aromatic antiepileptics, especially administered in low doses. Although severe DHR have been described, valproic acid, but also levetiracetam, were particularly frequently tolerated [22, 23].

Why some drugs cause DHR and others not, is unclear. Although the drug dose at subsequent DHR is lower, it might still be important. DHR to RCM, which are given only once, but in very high concentrations, indicate this. Two examples may illustrate the relevance of drug dose: We could observe a second DHR (DRESS) after increasing the dose of valproic acid (table 4, patient number 2). A second patient had several flare-up reactions, namely each time lamotrigine was increased to over 100mg (table 4, patient number 8).

It is interesting to note that ibuprofen and paracetamol are often well tolerated. Although this contradicts our hypothesis about the influence of drug dose, many other factors, particularly metabolism, may play a role in terms of tolerability. In this respect it may be relevant that these drugs are frequently used only demand and not given continuously.

4. How can MDH courses be prevented concretely?

A severe delayed DHR is a risk factor for subsequent DHR. This risk is highest in patients with DRESS (ca. 20%, own data). Therefore, a second DHR/MDH should be considered in every patient with DRESS or with severe exanthema, which do not fulfill the criteria for DRESS. Based on our experience, we propose the following approach in patients with severe delayed DHR or MDH:

Use of low concentrations/drugs with high affinity for the original target: Since T cell mediated DHR are often off target activities on immune receptors, we would recommend drugs which have a high affinity for their target protein, and thus are effective in low concentrations (probably 2-digit mg range [7]). The concentration of such drugs may be too low for an off-target activity on immune receptors (pharmacological interaction of drugs with immune receptors), which seem to play a role in most of these T-cell reactions [12].

To avoid: Vancomycin and antibiotic sulfonamides should be avoided. Beta-lactam antibiotics should be administered when clearly indicated and introduced then likewise at the lowest effective dose. The same consideration applies for all new drugs, especially in patients with comorbidities such as renal insufficiency, autoimmune diseases or epilepsy.

Probably allowed: Macrolides, quinolone antibiotics, doxycyclin and linezolid seem to be tolerated. Of the antiepileptic drugs, primarily non-aromatic variants and benzodiazepines should be chosen. The use of RCM and magnetic resonance contrast media needs to be limited. Metamizole and diclofenac should be avoided. Paracetamol and Ibuprofen seem to be a good alternative. Drugs to be avoided and often tolerated drugs in MDH are summarized in table 3.

This study is limited by the retrospective design. However, this was necessary to assess enough patients for an initial analysis. The number of MDH patients is probably underestimated in our

study as a) we used quite stringent inclusion criteria; b) some patients with drug allergies to structurally unrelated drugs were probably not labeled as such and c) we assume that up to 25% of patients with DRESS develop a relapse [21]. The evaluation of drug dose is limited, as the number of cases is rather small and different drugs were compared. It must be taken into account that the drug dose at the subsequent DHR was influenced by the first DHR (increased use of reserve drugs). For further studies, our hypothesis of the relevance of the drug dose would have to be investigated within the same drug class and a higher number of study participants.

MDH is rare but for a patient with MDH a highly problematic iatrogenic disease. Prospective multicenter studies on DRESS/MDH with clinical and laboratory analysis should be envisaged. Studies using T-cell phenotyping of DRESS patients with and without MDH should be performed and address the question why only a part of DRESS patients develop a MDH course.

Conclusion

Our study describes clinical characteristics of patients with MDH with the aim to better understand how MDH progressions are favored. Patients with severe delayed DHR are at risk for MDH wherein betalactam antibiotics are often involved in inducing MDH. With regard to drugs, it seems advisable to avoid typical DRESS triggers, and to choose drugs which are effective in a low dose range. Some highly-dosed drugs as beta-lactam antibiotics, RCM and clindamycin should be avoided in further treatments, when alternatives are available.

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Tables

Table 1 Inclusion criteria to diagnose multiple drug hypersensitivity syndrome.

Main criteria
Well documented drug hypersensitivity reaction: ≥1
Sensitization to ≥2 structurally different drug trigger in skin test
Sensitization to ≥2 structurally different drug trigger in cellular assay (ec. LTT)

Main criteria 1+2 or 1+3 should be fulfilled to diagnose MDH

Table 2 Patient characteristics

	MDH (total)	MDH with single DHR	MDH with 2 or more DHR
	N=25	N=10	N=15
Demographics			
Age at first reaction	50.0 (39.0; 65.0)	48.0 (35.5; 63.5)	60.0 (41.0; 65.0)
Gender (female)	15 (60.0%)	5 (60.0%)	10 (60.0%)
Preexisting conditions			
Atopic disposition	4 (16.0%)	1 (10.0%)	3 (20.0%)
Epilepsy	8 (32.0%)	3 (30.0%)	5 (33.3%)
Autoimmune disorder	7 (28.0%)	2 (20.0%)	5 (33.3%)
Renal insufficiency	7 (28.0%)	3 (30.0%)	4 (26.7%)

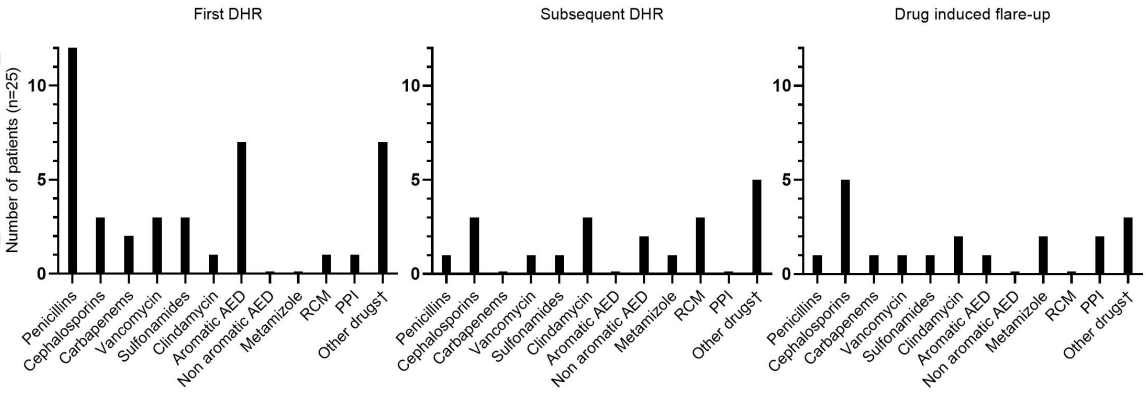
Type of first DHR			
IgE mediated (anaphylaxis)	1 (4.0%)	-	1 (6.7%)
DRESS	14 (56.0%)	6 (60.0%)	8 (53.3%)
MPE	5 (25.0%)	2 (20.0%)	3 (20.0%)
SJS / TEN	2 (8.0%)	1 (10.0%)	1 (6.7%)
AGEP	2 (8.0%)	1 (10.0%)	1 (6.7%)
Bullous exanthema	1 (4.0%)	-	1 (6.7%)
Drug induced flare-up reactions	13 (52.0%)	3 (30.0%)	10 (66.7%)
Type of MDH recurrence			
DRESS	-	-	2 (13.3%)
MPE	-	-	11 (73.3%)
SDRIFE	-	-	1 (6.7%)
AGEP	-	-	3 (20.0%)
Months to second DHR	-	-	26 (6.0; 71.0)
Type of MDH			
simultaneous	5 (20.0%)	5 (50.0%)	-
sequential	6 (24.0%)	4 (40.0%)	2 (56.0%)
distant	11 (44.0%)	-	11 (25.0%)
overlap	3 (12.0%)	1 (10.0%)	2 (8.0%)

In MDH with single DHR, drug trigger were given in combination therapies or sequentially within the same drug hypersensitivity (DHR) episode. Values are median and interquartile ranges (IQR) for continuous variables. Categorical variables reported as n (%).

Multiple drug hypersensitivity syndrome (MDH), drug reaction with eosinophilia and systemic symptoms (DRESS), maculopapular exanthema (MPE), anaphylaxis (ANA), acute generalized exanthematous pustulosis (AGEP), symmetrical drug related flexural and intertriginous exanthema (SDRIFE), stevens johnson syndrome (SJS), toxic epidermal necrolysis (TEN)

Figure 1

Summary of all MDH triggers, separated for the first DHR, subsequent DHR and drug induced flare-up reactions.



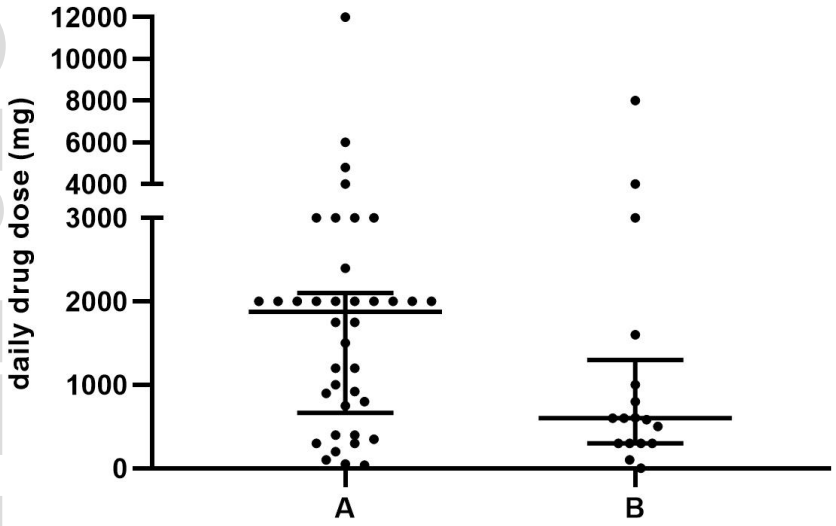
All values are reported as n. Multiple drug hypersensitivity syndrome (MDH), drug hypersensitivity reaction (DHR), antiepileptic drugs (AED), radio contrast media (RCM), proton pump inhibitors (PPI).

† see table 4 for details

Figure 2

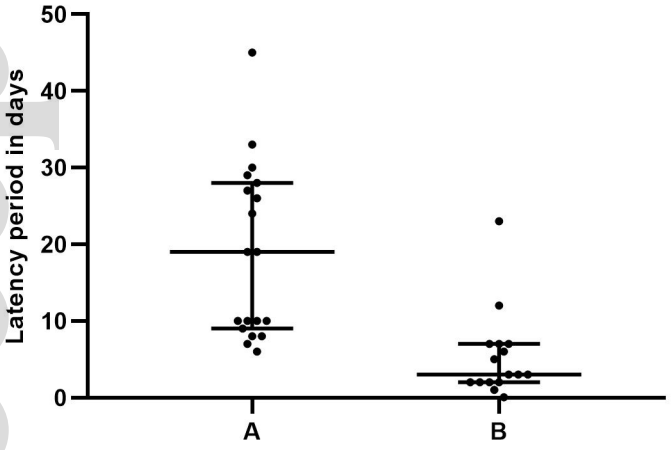
Comparison of daily doses of drug trigger (2a) and latency period (2b) in MDH patients with delayed drug hypersensitivity reactions (DHR) (n=24)

Figure 2a



Daily doses (mg) of MDH trigger between the first (A: 1875.0 mg (662.5; 2100.0)) and subsequent DHR (B: 600.0 mg (300.0; 1300.0)) were compared, using the Man-Whitney U test (p=0.0420). Values are median and interquartile ranges (IQR).

Figure 2b



The latency period between the first (A: 19.0 days (9.0; 28.0)) and subsequent DHR was compared (B: 3.0 days (2.0; 7.0 of MDH), using the Man-Whitney U test ($p<0.0001$). Values are median and interquartile ranges (IQR).

Table 3

List of drugs that can promote subsequent DHR or drug induced flare-up reactions in MDH and drugs which were mostly tolerated in subsequent pharmacological treatments.

Drugs often involved in subsequent reactions	**Drugs, which are mostly well tolerated**
Antibiotics	
Penicillins (esp. Piperacillin, Amoxicillin) (4/6)	Macrolides (2/2)
Cephalosporins (esp. Cefuroxim, Ceftriaxon, Cefepime) (4/12)	Quinolones (7/9)
Vancomycin (0/2)	Linezolid (2/2)
Sulfonamide antibiotics (esp. Sulfamethoxazol) (0/2)	Doxycyclin (4/4)
Clindamycin (0/5)	
Anticonvulsants	
Aromatic anticonvulsants (0/1)†	Non aromatic anticonvulsants (esp. levetiracetam, valproic acid, topiramat) (8/10)
	Benzodiazepines (4/4)
Analgesics	
Metamizole (4/7)	Paracetamol (11/12)
Diclofenac (1/2)	Ibuprofen (4/4)
	Aspirin (5/5)
	Opiates (9/9)
Radio contrast media	
All radio contrast media (2/5)	

† Lamotrigin over 100mg daily dose

The values indicate the relationship of patients who were exposed to a particular drug after the first DHR and how many of them tolerated it (tolerated/exposed). Drugs were classified as mostly tolerable, if tolerated in 75% of cases administered.

Table 4

Characteristics of the MDH hypersensitivity reactions and allergy workup in 25 participating subjects

Patient	Type of initial reaction	Trigger of first DHR	Skin test	LTT	Type of MDH relapse	Trigger of subsequent DHR	Skin test	LTT	Drug induced flare-up reaction (no sensitization)	Tolerated drugs after first DHR
1	DRESS	Sulfamethoxazol	PT +	+	MPE	Diclofenac	PT +	+		Amoxicillin/clavulanic acid, azithromycin, cefpodoxim, ceftriaxon, cefuroxim, omeprazole, opiates, paracetamol
2	DRESS	Phenytoin Carbamazepin Amoxicillin	n/a PT + PT +	+ + +	DRESS	Valproic acid	PT +	+	Clindamycin Ceftriaxon	Brivaracetam, clarithromycin clonazepam, diazepam, levetiracetam, moxifloxacin, opiates, pantoprazole, zonisamid
3	DRESS	Sulfamethoxazol	PT +	+	DRESS	Vancomycin	PT +	+	Ceftriaxon	Aspirin, doxycyclin, linezolid, opiates, pantoprazole, paracetamol, pregabalin, tigecyclin
4	DRESS	Ceftriaxon	PT +	+	MPE	Iomeprol	PT +	+	Meropenem Vancomycin	Aspirin, metamizole, pantoprazole, paracetamol, piperacillin/tazobactam
5	MPE	Amoxicillin	PT +	n/a	MPE	Sulfamethoxazole	PT -	+	Cefuroxim	Doxycyclin, linezolid,

										moxifloxacin
6	DRESS	Meropenem Vancomycin	PT + PT -	- +	n/a	n/a	n/a	n/a	Ciprofloxacin Daptomycin Pantoprazol Fluconazol	Amoxicillin, cefpodoxim, ceftriaxon, opiates, pantoprazole, paracetamol
7	DRESS	Vancomycin Rifampicin	PT - PT -	+ +	MPE	Iobitridol	PT +	+	Clindamycin	Aspirin, paracetamol, cefuroxim
8	ANA	Erythromycin	IDT +	n/a	MPE MPE MPE MPE AGEP	Valproat Gabapentin Mirtazapin Pregabalin Cefuroxim	PT + PT + PT + PT + PT +	n/a	Lamotrigin (in daily dose over 100mg)	Aspirin, clonazepam, metamizole, midazolam, omeprazole, opiates, paracetamol
9	Bullous exanthema	Cefepime	IDT +	+	MPE	Metamizol	PT +	n/a	Amoxicillin	No drugs
10	DRESS	Phenytoin Pantoprazol	PT – PT +	+ -	n/a	n/a	n/a	n/a		Amoxicillin/clavulanic acid, ciprofloxacin, clobazam, clonazepam, doxycyclin, gabapentin, iobitridole, lansoprazol, metamizole, opiates, paracetamole, valproic acid
11	AGEP	Hydoxychloroquin	n/a	+	MPE	Budesonid	PT +	n/a		Aspirin, levetiracetam
12	DRESS	Phenytoin	PT -	+	MPE	Cefuroxim	PT +	+	Metamizole	Ciprofloxacin, clobazam,

					MPE	Iomeron	PT +	+	Paracetamol	doxycyclin, opiates, topimarat
					MPE	Iopromid	PT +	+		
					AGEP	Clindamycin	PT +	-		
		Phenytoin	PT -	+						
		Lamotrigin	PT -	+						
		Ceftriaxon	PT +, IDT +	+						
		Flucloxacillin	PT +, IDT +	+						
13	DRESS	Iobitridol	PT +, IDT +	+	n/a	n/a	n/a	n/a		No data
					MPE	Flucloxacillin	PT +	-		
					MPE	Cefuroxim	PT +	-		
14	DRESS	Carbamazepin	PT +	+	MPE	Ceftriaxon	PT +	-		Diclofenac, valproic acid
15	Severe MPE	Amoxicillin	PT +	n/a	SDRIFE	Clindamycin	PT +	n/a		Ibuprofen, paracetamol
		Amoxicillin	PT +	+						
16	SJS	Clindamycin	PT +	+	n/a	n/a	n/a	n/a		No data
17	Severe MPE	Flucloxacillin	PT +	-	MPE	Norfloxacin	PT +	+	Cefepime	No drugs
18	TEN	Amoxicillin	PT +	-	AGEP	Clindamycin	PT +	-		No data
		Phenytoin	PT -	+					Metamizole	Ciprofloxacin, levetiracetam,
19	Severe MPE	Amoxicillin	PT +	+	n/a	n/a	n/a	n/a	Metronidazol	valproic acid
		Amoxicillin	PT -	+						
20	MPE	Metronidazol	PT -	+	n/a	n/a	n/a	n/a		No drugs
		Piperacillin	PT +	+						Aztreonam, daptomycin,
		Meropenem	PT -	+						ibuprofen, moxifloxacin,
21	DRESS	Vancomycin	PT -	+	n/a	n/a	n/a	n/a	Sulfamethoxazole	omeprazole, opiates,

										paracetamol, tigecyclin
22	DRESS	Amoxicillin Carbamazepin	n/a n/a	+ +	n/a	n/a	n/a	n/a		Pregabalin
23	AGEP	Amoxicillin Prednisolon	PT + PT +	+ +	n/a	n/a	n/a	n/a		No drugs
24	DRESS	Sulfapyridine 5-amino salicylic acid	n/a n/a	+ +	n/a	n/a	n/a	n/a		Cefuroxim, ibuprofen, iobitridole, metamizole, opiates, pantoprazole, paracetamol
25	DRESS	Clarithromycin	PT +	-	MPE	Gadobutrol	PT +	n/a	Omeprazole Ceftriaxon	Ciprofloxacin, ibuprofen, paracetamol

Patch test (PT), intradermal test (IDT), lymphocyte transformation test (LTT), drug provocation test (DPT), drug reaction with eosinophilia and systemic symptoms (DRESS), maculopapular exanthema (MPE), anaphylaxis (ANA), acute generalized exanthematous pustulosis (AGEP), symmetrical drug related flexural and intertriginous exanthema (SDRIFE), stevens johnson syndrome (SJS), toxic epidermal necrolysis (TEN), not applicable (n/a)