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INVITED REVIEW

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How to manage drug-virus interplay underlying skin eruptions in children

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ABSTRACT

The majority of viral rashes occurring during an antibiotic therapy are considered as a drug hypersensitivity reaction (DHR). Differentiating a viral rash versus a DHR is difficult or even impossible. In delayed DHRs the interplay between viruses and drugs is summarized according to the recent literature. The question is if the same reaction will again occur in case of drug re-exposure in absence of the concomitant viral infection because of persistent immune reactivity. Epstein Barr Virus (EBV) and Human Herpes virus 6 (HHV-6) models are analyzed in case of maculopapular exanthemas (MPEs) and drug reaction with eosinophilia and systemic symptoms (DRESS) over a course of drug therapy. MPEs are the most common skin manifestation during a viral infection and a concomitant drug therapy. In type IVb reactions to drugs a hapten/pro-hapten mechanism and a pharmacological interaction (p-i mechanism) are described as the 2 major ways to make T cells response functional. Rarely the altered repertoire model is involved. The Human Leukocyte Antigen (HLA) predisposition is an additional essential factor that can facilitate DHR. In MPEs rarely a DHR is confirmed by allergy testing. Severity and duration of MPEs, the presence of eosinophilia and systemic symptoms make more reliable the persistent nature of the reaction. Research on this topic is needed in order to provide the clinicians with instruments to decide when to suspect future reactions upon drug re-exposure even in the absence of a viral infection, because those patients should be investigated by a complete drug allergy work up.

Keywords: Drug hypersensitivity, Skin eruption, Viral exanthema, Maculopapular exanthema, Children, Pediatrics

INTRODUCTION

Skin eruptions are the most frequent cause of pediatrician consultation, and up to 17% of pediatric emergency admissions are due to the occurrence of a skin eruption.[1,2] So far, despite the high frequency of this problem, epidemiologic data are scarce. The major cause of skin eruptions are infections, in particular viruses are able to induce skin rashes by themselves.[3] Viruses in contrast to bacteria have the ability to infiltrate tissue cells by fixating to cellular receptors or by intracellular penetration and to grow in dermal and epidermal cells.[4] Moreover, viruses may have a direct cytopathic effect, disrupting skin cells, discharging pro-

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inflammatory signals, cytokines and chemokines and activating immunologic responses.[3] The objective manifestations are the occurrence of skin lesions such as maculopapular or urticarial rashes, especially in children.[4]

On the counterpart, commonly children take antimicrobials in the setting of a viral infection. Most antibiotics are improperly used to treat upper airways diseases in the first years of life, but in this age range the causative agents are more frequently viruses than bacteria.[5]

The frequency of children developing an exanthema or delayed appearing urticaria while taking concomitantly a drug is 10%, but while viral infections are frequently detected when investigated, allergy to the drug taken can be rarely confirmed (7–20%).[6–11]

The estimated incidence of maculopapular viral exanthemas is 158.3/10.000 (C.I. 142.3–174.4)[12] and when occurring during a drug course treatment it makes the diagnosis of drug hypersensitivity challenging. Clinically is very difficult or even impossible to differentiate a rash of viral origin from a drug reaction. This difficulty is exacerbated by the fact that viral infections may increase the risk of morbilliform drug reaction by acting as co-factors for immune stimulation. Numerous clinical observations suggest that viral infections promote or aggravate drug-related skin rashes.

Viruses and drugs act in the same way: tissue cells are modified upon virus binding uptake and the same happens among drug binding. The modified tissue cells act as antigen presenting cells (APC) and present viruses or drugs modified peptides or the drug itself to T cells and thanks to their cytotoxic virus or drug specific activity work against tissue cells.[13] The similarity of drug- and/or virus-activity on tissue cells possibly explain also the similarity of drug- and/or virus-induced skin rashes.

Morbilliform drug eruptions are among the most common cutaneous adverse drug reactions (CADRs) representing 35% in children.[14]

They are characterized by small pink to red macules and papules that start from the trunk rapidly spreading to the arms with symmetrical distribution (Fig. 1).

Drugs often associated with morbilliform or maculopapular lesions include most commonly antibiotics, antiepileptics and non-steroidal anti-inflammatory drugs (NSAIDs) in children.

The term "morbilliform" skin rash was initially used to describe the cutaneous manifestation of the measles infection and now, together with the

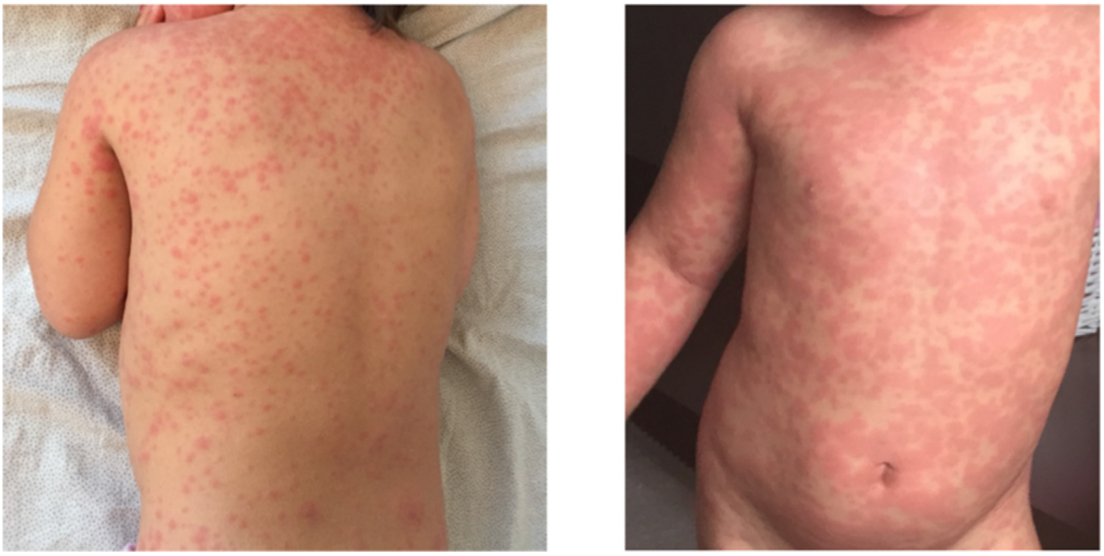

Fig. 1 Maculopapular exanthemas (MPEs)

terms maculopapular, it is widely used to describe skin eruptions with similar morphology.[15]

The underlying pathomechanism of drug maculopapular exanthemas (MPEs) is not well known, though a delayed T cell immune-mediated reaction is suspected.[16]

Along this paper, the mechanisms by which viruses and drugs may interact in the setting of delayed MPEs are summarized, assuming that the 2 triggers have to be analyzed together. The question to be answered is not if the skin eruption is due to the virus or to the drug separately, but rather if the same reaction will again occur in case of drug re-exposure in the absence of the concomitant viral infection because of persistent immune reactivity.

ADVERSE DRUG REACTIONS

Adverse drug reactions (ADRs) are defined as noxious and unintended response to a drug that occurs at usual doses used for diagnosis, prevention and treatment.[17]

ADRs can be target or off target effects of a pharmaceutical compound and drug allergy with immunomediated humoral or cellular reactions is classified in the off target reactions group.[18,19]

A huge proportion of Drug Hypersensitivity reactions (DHRs) is consistent with the involvement of the adaptative immunity (T cells or specific IgE).

According to the classification proposed by Gell and Coombs, T cell mediated reactions can be classified from Type IVa to Type IVd, based on the different cells involved and the different patterns of clinical manifestations.[20]

In particular Type IVa reactions are defined as contact dermatitis, Type IVb reactions include MPE and drug reaction with eosinophilia and systemic symptoms (DRESS), Type IVc reactions include Steven Johnson Syndrome/Toxic epidermal necrolysis (SJS/TEN) and Type IVd reactions consists of acute generalized exathematous pustulosis (AGEP). In this context DHRs vary from benign skin rashes to more severe exanthemas up to severe cutaneous adverse reactions (SCARS) associated with acute and long-term morbidity and mortality.[21]

Among the group of delayed DHRs, Type IVb reactions to drugs and in particular MPE are most frequently reported as already said. Most of them are mild, self-resolving, commonly transient and limited in extension. Skin rashes usually appear during the first weeks of exposure (4–21 days) to a new drug and fade within few weeks of drug discontinuation.

However, 2–6.7% of cutaneous reactions can develop into severe and potentially life-threatening reactions as in case of DRESS.[15,22] In DRESS, the skin rash becomes generalized, confluent, itchy, purpuric and associated to face angioedema, fever (>38.5 °C), lymphadenopathy and internal organ involvement (Fig. 1).[23]

Gell and Coombs classification is useful to distinguish clinically different DHRs, but it does not explain the specific immunological mechanisms underlying the activation of T cells by different drugs.

In this paper we will focus on Type IVb reactions in particular on MPE being the major diagnostic challenge.

DRUG-VIRUS INTERPLAY

Several specific viruses, more commonly belonging to the herpes virus family such as Epstein Barr Virus (EBV) or Human Herpes virus 6 (HHV6) take part in the immune phenomena underlying DHRs such as MPE and DRESS.[5]

The interplay between viruses and drugs is complex and in most of the cases DHRs depend on the way through which T cells are stimulated by the drugs. Commonly, the viral infection comes first priming the reactivity to drugs in 2 ways (Fig. 2).[13]

In the first way, drugs such as beta-lactams with a low molecular weight, or drug metabolites, become new antigens after a covalent binding to endogenous protein (ie, serum albumin) or peptides. New antigens are presented by APC on Human Leukocyte Antigen (HLA) molecules with subsequent activation of T cells.[24] T cells react via specific T cell receptors to drug modified proteins or drug modified peptides, when the homeostatic conditions are disrupted by danger signals.[25]

In the presence of a concomitant viral infection, which acts as a second signal, an immune stimulatory

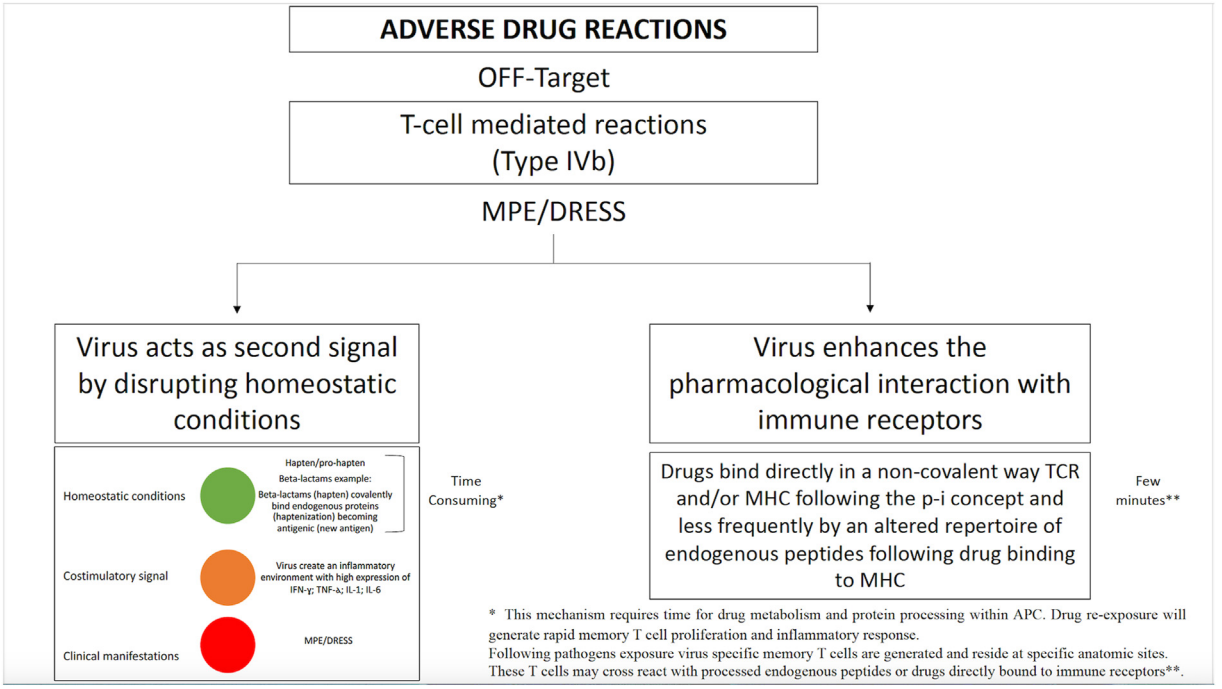

Fig. 2 The interplay between viruses and drugs. IFN = interferon, TNF = Tumor necrosis factor, IL = interleukin, MPE = maculopapular exanthemas, DRESS = drug reaction with eosinophilia and systemic symptoms, MHC = major histocompatibility complex, TCR = T cell receptor

environment is made by the release of pro-inflammatory cytokines and co-stimulatory molecules.

In the second way drugs directly interact with immune receptors, but those bindings are labile and not sufficient to trigger an immune reaction. This is a direct pharmacological stimulation (p-i concept) not requiring antigen processing. In particular the offending drug through a non-covalent interaction with T cell receptors (TCR) or HLA in less than 10 min may be able to stimulate T cells. This stimulation is effective only during a concomitant viral infection because viruses increase the expression of immune receptors so thanks to numerous p-i interactions the avidity is increased becoming functional for DHRs.

A very rare third way of interaction between T cells and drugs is called the altered repertoire model: drugs occupy a position in the HLA peptide binding groove modifying the binding cleft and the specificity of self-peptides binding to the HLA molecules.[26]

EBV MODEL: THE INFECTION ACTS AS CO-FACTOR AND IT COMES FIRST

EBV infection enhances the $CD8^+$ T cell population and provokes a systemic inflammation with increased expression of adhesion molecules and presence of cytokines (IFN-gamma; TNF-alfa, IL-1, IL-6, IL-2) which significantly increase hapten-specific immunity.[27] For example, amoxicillin acts as an hapten and in the presence of co-stimulatory molecules such as CD80, CD86, CD40 on APC, and of an increased expression immune receptors induced by viruses, both viral and drug specific T cells are activated.[13] A subsequent suppression of TH2 response (IL-4, IL-5, IL-9, IL-13) takes place.[28,29] In particular the reduction of IL-10 which is considered a tolerogenic cytokine, may led to a reversible loss of drug tolerance for example in case of beta-lactams intake during an EBV infection, with subsequent development of a DHRs such as MPE.[30,31] In addition, the increased virus-induced expression of immune receptors enhances the probability of low affine p-i interactions and the overall avidity.

The altered HLA-drug-TCR interaction may became sufficiently stable and results in T cells stimulation and clinical symptoms. The HLA predisposition is an additional essential factor that can facilitate DHR including beta-lactams.[32]

The HLA is important in the p-i mechanism, in contrast haptens bind to various peptide sequences presented by various HLA alleles.[33]

The initial incidence of combined EBV and aminopenicillins induced exanthemas was higher compared to the percentages more recently reported (80% vs 10–30%).[34-36]

Up to now, a rash occurring during an EBV infection and antibiotic treatment was considered a transient loss of tolerance due to a virus-mediated immune alteration (mainly p-i mechanism) and many patients tolerate aminopenicillins upon later re-exposure showing negative skin tests results.[37]

Conversely recent studies demonstrated that a true long-lasting antibiotic hypersensitivity (mainly hapten/pro-hapten mechanism) might be a lot more prevalent than previously thought during EBV infection and concomitant amoxicillin therapy. Specific T lymphocytes (lymphocyte transformation test: LTT), positive delayed intradermal tests (IDTs) or Patch Tests (PTS) with beta-lactams have been demonstrated with even positive drug provocation test (DPT) or severe DHR upon re-exposure to the beta-lactam at distance from the initial reaction.[30,38-41]

HHV-6 MODEL: VIREMIA IS THE EXPRESSION OF DHR AND COMES LATER

HHV-6 was the first chronic persistent virus incriminated in the pathology of DRESS.[42] However the role of HHV replication remains controversial because several studies reported that HHV replication does not occur early in the clinical course of DRESS and generally viremia is observed greater than 2 weeks following symptoms onset (Fig. 3).[18]

The hypothesis that DHR come first and viremia is a consequence of a massive immune stimulation (mainly p-i) by the drug is supported by the fact that the youngest reported patient developed DRESS at 38 days of life suggesting a non-HHV-6 related pathogenesis.[43]

The pathophysiology of DRESS is not fully elucidated. Three mechanisms seem to interact: 1) genetic predisposition such as HLA type or cytochrome p450 polymorphism[44]; 2) viral infection (first infection or replication) inducing B cell suppression, hypogammaglobulinemia and an immune-state of pre-activation; 3) drugs and metabolites as trigger of immune reaction.

DRESS occurs after 2–6 week after starting a new medication and is characterized by prodromal

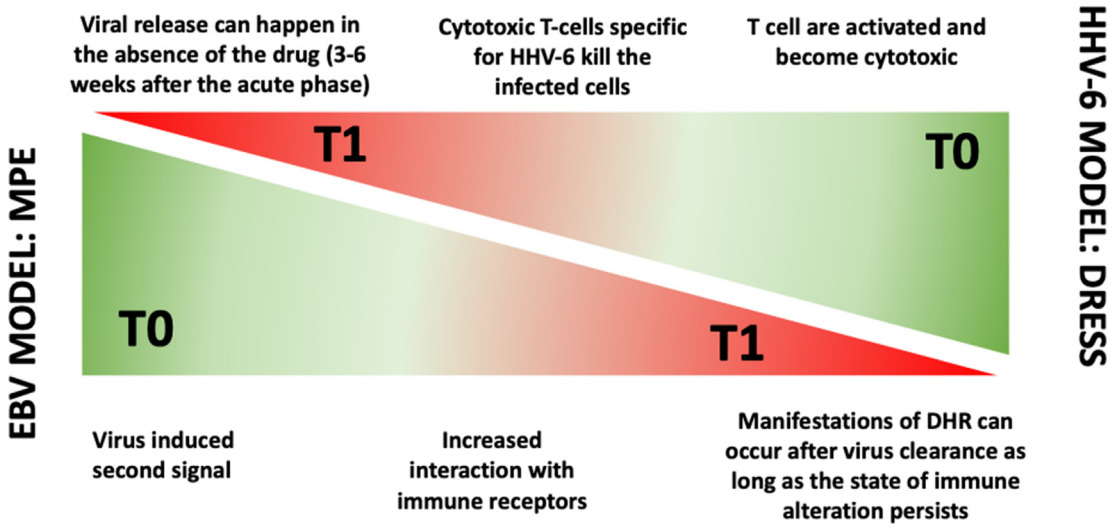

Fig. 3 EBV and DRESS models. T0 = Time 0, T1 = Time 1, DHR = druh Hypersensitivity reaction, DRESS = Drug reaction with eosinophilia and systemic symptoms, HHV-6 Human Herpes virus 6, EBV = Epstein Barr Virus, MPE = Maculopapular exanthema

symptoms such as fever. Subsequent skin manifestations consist of MPE in 85% of patients.[45]

MPE may progress on occasion to more severe skin involvement causing suspicion of DRESS (Fig. 1). Eosinophilia is 1 criterion for DRESS diagnosis on the counterpart it is an unusual finding in viral exanthemas. Eosinophilia is described in DHRs as the consequence of high production of IL-5 by drug specific T cells from patients with MPE.[46]

The drug by a p-i mechanism can activate specific T cells controlling viral replication by IFN-gamma release. Both naïve and memory T cells go through a polyclonal, polyspecific, cytotoxic expansion. Among them, there are also herpes virus specific T cells who become cytotoxic and when encounter their target stimulus (HHV-6, Citomegalovirus, EBV) in the peripheral tissue kill the herpes infected cells with a secondary release of viruses.[47–49]

Before the viremia there is a release of cytokines such as TNF-alfa and IL-6.[13,50]

In this context the event sequence is inverted: the viremia is not the expression of viral replication with active infection and subsequent symptoms, but it is the result of viral particles release by killed cells.

In contrast some authors include viremia in the criteria for DRESS diagnosis, assuming that the drug induced immunosuppression makes one more susceptible to virus reactivation, including HHV-6 which anyway is most consistently reactivated in adults than in children.[31]

MANAGEMENT

The follow up management of DHRs needs a complete drug allergy work up. Up to now several risk models have been proposed to identify those who are more at risk of being truly allergic to a specific drug.[51–53] Several factors depending on the host, on the infective agents and on the drugs are involved and interact in the development of DHRs (Fig. 4).

In case of delayed DHRs, the IDTs at delayed reading and the PTs should be performed as in vivo tests. PTs should be preferred at first in case of severe delayed DHRs. DPT should be performed to reach a confident diagnosis, but not in case of severe reactions.

Among the *in vitro* tests LTT and ELIspot assay are used as research tools and are not ready for routinely use. Moreover, HLA-typing could be used in known drug phenotypes.[21]

Today biomarkers are missing to predict the severity of Type IV b reactions in the acute phase and to identify those with history of MPE who are more at risk for future reactions in case of drug re-exposure.

In the acute phase of DRESS for example, those with HHV-6 positivity showed significantly more severe forms and longer hospitalization compared

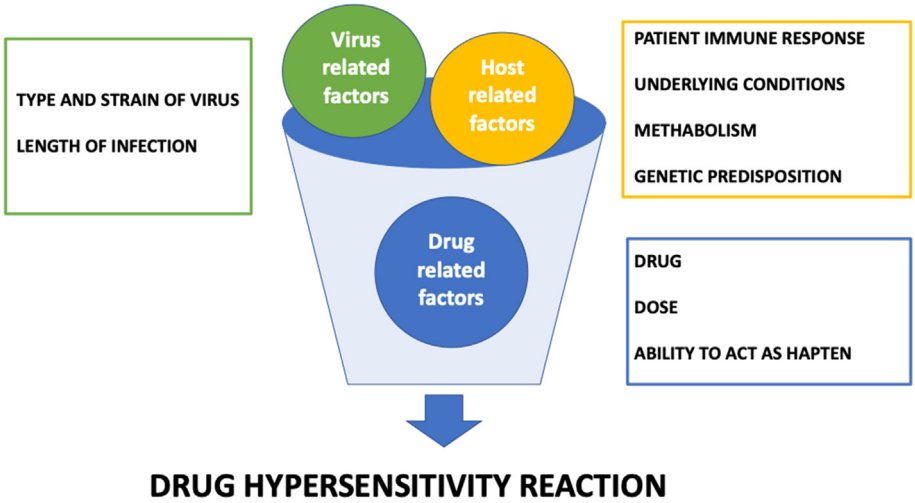

Fig. 4 Risk factors associated with DHR

Delayed DHRs	Virus induced exanthemas
Activated $CD4^+CD8^+$ T cells HLA predisposition/hapten; pro-hapten nature Time of appearance >3 days from the first drug intake More severe exanthemas Eosinophilia IL-5; granzyme B; perforin	Only activated $CD4^+$ T cells No HLA predisposition (p-I concept) Time of appearance <3 days from the first drug intake Mild exanthemas No Eosinophilia IFN-gamma
Long Duration of skin manifestations	Short Duration of skin manifestations
Persistent nature (Memory T cells)	Transient nature (No memory T cells)
Allergy Work up (IDTs; PTs; LTT)	Allergy work up not required or not complete

Table 1. Delayed DHRs vs Virus induced exanthema. *DHR = Drug Hypersensitivity reaction, IL = interleukin, IDT = intradermal tests, PT = patch tests, LTT = lymphocyte transformation test, IFN = interferon, HLA = Human Leukocyte Antigen*

to HHV-6 negative subjects in a retrospective case series of 29 children with DRESS.[54]

Moreover, in DRESS cases, genetic predisposition plays a central role in predicting the risk of reactions to specific drugs (ie, HLA A 31:01 and Carbamazepine).

Some cytokines profiles are more associated to viral rashes (ie, IFN-gamma) and some others to drug rashes (ie, IL-5; granzyme B; perforin).[13]

Anyway, so far viral infections represent the major differential diagnosis in patients with suspicion of DHRs (Table 1).

Possibly the combination of viral infection facilitating the drug reaction is transient and the single drug may be tolerated in the future. This is the reason why a complete drug allergy work up results frequently negative in children with history of delayed MPE while on a course of drug therapy.[55]

Exanthemas occurring less than 72 h after starting a new medication are more likely to be due to viruses because drug induced MPEs are thought to be a delayed DHRs not occurring within the first 3 days of drug assumption unless there is a history of previous exposure and sensitization.[16]

Identifying those children with a reproducible and a persistent nature of drug induced MPE not only in the context of a viral infection is challenging. MPEs can be mild or more severe.[56] Cytotoxic $CD4^+$ T cells seems to be involved in milder forms, $CD4^+$ and $CD8^+$ T cells seems to be involved in more extensive and maculopapular forms.[57] A concomitant viral infection may boost CD8+T cells in different tissues, explaining the mechanism underlying more severe MPEs as these described for example during EBV infection and beta-lactams treatment as already mentioned.[40] In particular the duration and the extent of skin manifestations, facial swelling and clinical severity of the reaction may indicate a prolonged drug reactivity. The reason of this persistency is not completely understood, but it is important to discriminate because if the original exanthema is mild and with a short-term course probably it is due to the virus and will not reappear on drug re-exposure. Consequently, to answer the question if the child can tolerate again the drug, clinicians have to correctly identify if the DHR is transient or persistent, in summary if drug specific memory T cells have been developed and can be activated in the absence of a viral infection by the drug itself in the future. This possibility is mainly described in the hapten/pro-hapten mechanism. In the p-i interaction, co-stimulatory signals are not necessary and the immune stimulation is provoked by the higher expression of TCR and HLA during a viral infection. This mechanism could explain why this type of DHR is transient and not confirmed by drug allergy testing. This scenario can explain low affine p-i interaction, because in case of HLA predisposition the p-i inter-

action is strong and DHR is more severe not requiring viral enhancement. Indeed, long lasting reactivity is well documented in DRESS.[58]

CONCLUSIONS

Investigation for drug allergy in children is time consuming because of the high prevalence of viral illness in children and the low percentage of confirmed DHR particularly when testing MPEs.

Differentiating between a viral exanthema and a DHR is often not possible in the acute phase. The severity and duration of skin symptoms as well as the presence of systemic symptoms may impact whether a DHR can re-occur without viral infection.[39]

For example, eosinophilia is suggestive for a drug specific T cell activation by a p-i or a hapten/pro-hapten mechanism of reaction. Memory drug specific T cells may persist and provoke DHR in the future, even in the absence of concomitant viral infection.

Caubet et al[7] did not find a relationship between the severity of the index reaction and the risk for positive DPT with the culprit, but up to now an agreement on the definition of more severe exanthemas has not been reached and the number of children with more severe exanthema included in the study was low. In delayed so called "benign" MPE recent agreement has been reached on skipping skin testing to directly provoke the patient with the culprit drug. This conclusion has been reached because of the low sensitivity of skin tests 31.5% with a specificity of 96% and the low positivity of DPT [for example with the culprit beta-lactams it varies between 0 and 15% (mean value 5.9)]. Only 25% of patients who reacted to DPT had positive skin tests with the culprit drug.[55,59] Among delayed MPEs there are different mechanisms of interplay between virus and drug. Adaptative immune system (IgE and T cells) is involved in DHR. Antibodies and drug reactive T cells stimulated by hapten or p-i mechanism have been identified. To make even more complicated the scenario, a drug does not act in a mutually exclusive way, but for example in case of beta-lactams these can act as antigen or can stimulate the immune system by p-i mechanism.

The aim is to differentiate those children at risk for future reactions because of the development of memory T cells from those with transient virus-dependent loss of drug tolerance.

In case of mild reactions, according to the recent evidences, the drug could be safely used again without recurrence of DHR in the absence of a concomitant viral infection. Tonson la Tour[60] demonstrated that 11 out of 18 children with DHR during viral infections did not react upon re-exposure.

The underlying mechanisms even not fully elucidated should be known, because with few clinical and laboratory elements the clinician has to make the choice to prescribe again safely the drug or to refer the patient to an allergy specialist for investigation before prescribing again the same drug. In the review paper by Tsabouri et al about skin eruptions in pediatric population, it is reported an algorithm of how to approach children with an exanthema.[61]

With regard to the treatment of DRESS, antiviral therapy has been reported as a treatment option alongside anti-inflammatory corticosteroids, to prevent complications related to herpes virus reactivation, but no consensus has been reached, especially in children so far. Publications focusing on this topic are reported in literature but they refer mainly to adult patients. There is 1 report including a 3-month-old infant treated with ganciclovir after DRESS by antiepileptic drugs, complicated by viremia by Citomegalovirus.[62] However, the decision to start an antiviral therapy should be always shared with the infectious disease specialist.

Research on this topic is needed in order to provide clinicians with more elements to avoid false labeling, unnecessary and time-consuming allergy tests and drug avoidances in a period in which antibiotic resistances, health costs and mortality risks due to ineffective therapies are increasing.

Abbreviations
DHR, drug hypersensitivity reaction; EBV, Epstein Barr Virus; HHV-6, Human Herpes virus 6; MPEs, maculopapular exanthemas; DRESS, drug reaction with eosinophilia and systemic symptoms; APC, antigen presenting cells; CADRs, cutaneous adverse drug reactions; SCARS, severe cutaneous adverse reactions; NSAIDs, non-steroidal anti-inflammatory drugs; SJS/TEN, Steven Johnson Syndrome/ Toxic epidermal necrolysis; AGEP, acute generalized exathematous pustulosis; HLA, Human Leukocyte Antigen; TCR, T cell receptors; LTT, lymphocyte transformation test; IDTs, intradermal tests; PTS, Patch Tests; DPT, drug provocation test.

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Data sharing and data accessibility
No datasets were used for the current study.

Author contributions
All authors declare that they have made substantial contributions to the conception and design, literature review, drafting the article and revising it critically for important intellectual content.
All authors approved the final manuscript as submitted, gave their consent for publication and agreed to be accountable for all aspects of the work.

Ethics approval
Ethics approval does not apply to this work given that this is a literature review, and no patient information is disclosed.

Declaration of competing interest
Authors declare no conflicts of interest in relation to this work.

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