Viral infections and drug hypersensitivity

Marie-Charlotte Brüggen¹ and Werner Pichler²

¹UniversitätsSpital Zurich Dermatologische Klinik
²ADR-AC GmbH Holligenstr 91 3008 Bern

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Abstract

Virus infections and T cell-mediated drug hypersensitivity reactions (DHR) can influence each other. In most instances, systemic virus infections appear first. They may prime the reactivity to drugs in two ways: First, by virus-induced second signals: certain drugs like β-lactam antibiotics are haptens and covalently bind to various soluble and tissue proteins, thereby forming novel antigens. Under homeostatic conditions, these neo-antigens do not induce an immune reaction, probably because co-stimulation is missing. During a virus infection, the hapten-modified peptides are presented in an immune-stimulatory environment with co-stimulation. A drug-specific immune reaction may develop and manifest as exanthema. Second, by increased pharmacological interactions with immune receptors (p-i): drugs tend to bind to proteins and may even bind to immune receptors. In the absence of viral infections, this low affine binding may be insufficient to elicit T cell activation. During a viral infection immune receptors are more abundantly expressed and allow more interactions to occur. This increases the overall avidity of p-i reactions and may even be sufficient for T cell activation and symptoms. There is a situation, where the virus-DHR sequence of events is inverted: in drug reaction with eosinophilia and systemic symptoms (DRESS), a severe DHR can precede reactivation and viremia of various herpes viruses. One could explain this phenomenon by the massive p-i mediated immune stimulation during acute DRESS, which coincidentally activates many herpes virus-specific T cells. Through p-i stimulation, they develop a cytotoxic activity with killing of herpes peptide-expressing cells and release of herpes viruses. These concepts could explain the often transient nature of DHR occurring during viral infections and the often asymptomatic herpes-virus viraemia after DRESS.

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Werner J. Pichler ¹ & Marie-Charlotte Brüggen², ³, ⁴

¹ ADR-AC GmbH, Holligenstr 91, 3008 Bern
² Allergy Unit, Department of Dermatology, University Hospital Zürich
³ Faculty of Medicine, University Zürich
⁴ Christine Kühne – Center for Allergy Research and Education (CK-CARE)

ORCID IDs: Werner Pichler: 0000-0002-8117-359X Marie-Charlotte Brüggen: 0000-0003-3215-3370

Corresponding author: Werner J Pichler, MD ADR-AC GmbH Holligenstr 91 CH 3008 Bern Switzerland
e-mail: werner.pichler@adr-ac.ch

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Abstract:
Virus infections and T cell-mediated drug hypersensitivity reactions (DHR) can influence each other. In most instances, systemic virus infections appear first. They may prime the reactivity to drugs in two ways: First, by virus-induced second signals: certain drugs like β-lactam antibiotics are haptens and covalently bind to various soluble and tissue proteins, thereby forming novel antigens. Under homeostatic conditions, these neo-antigens do not induce an immune reaction, probably because co-stimulation is missing. During a virus infection, the hapten-modified peptides are presented in an immune-stimulatory environment with co-stimulation. A drug-specific immune reaction may develop and manifest as exanthema. Second, by increased pharmacological interactions with immune receptors (p-i): drugs tend to bind to proteins and may even bind to immune receptors. In the absence of viral infections, this low affine binding may be insufficient to elicit T cell activation. During a viral infection immune receptors are more abundantly expressed and allow more interactions to occur. This increases the overall avidity of p-i reactions and may even be sufficient for T cell activation and symptoms. There is a situation, where the virus-DHR sequence of events is inversed: in drug reaction with eosinophilia and systemic symptoms (DRESS), a severe DHR can precede reactivation and viremia of various herpes viruses. One could explain this phenomenon by the massive p-i mediated immune stimulation during acute DRESS, which coincidentally activates many herpes virus-specific T cells. Through p-i stimulation, they develop a cytotoxic activity with killing of herpes peptide-expressing cells and release of herpes viruses. These concepts could explain the often transient nature of DHR occurring during viral infections and the often asymptomatic herpes-virus viraemia after DRESS.

Keywords: exanthems, virus infection, drug hypersensitivity, hapten, p-i concept, DRESS, herpes virus, viraemia, SARS-Cov2

Abbreviations: antigen-presenting cell: APC; drug hypersensitivity reactions: DHR; p-i: pharmacological interactions with immune receptors; human leukocyte antigens: HLA; T cell receptor: TCR; maculopapular exanthema: MPE, Stevens-Johnson syndrome and toxic epidermal necrolysis: SJS/TEN; drug reaction with eosinophilia and systemic symptoms: DRESS; Epstein-Barr virus: EBV; human herpes virus 6: HHV6; cytomegalovirus: CMV;

Introduction

Viral infections are common and can cause a multitude of symptoms. The most frequently observed are respiratory, fever, and exanthems. Due to the similarities between the symptoms presented during the early stages of viral and bacterial infections (e.g., fever and tonsillitis) and/or because a bacterial superinfection is considered, many patients with viral infections are treated with antibiotics and antipyretics. Shortly after these drugs were used in practice, a high incidence of exanthems was observed, which was later attributed to viral infection. Such connections between viral infections and drug hypersensitivity (DH) were particularly apparent in young children experiencing their first encounter with various respiratory viruses, and in adult patients with Epstein-Barr virus (EBV) and human immunodeficiency virus (HIV) infections [1-5].

While the clinical manifestation of the interplay between viral infections and DH has been widely acknowledged for many years, an explanation for this increased incidence is missing. Indeed, the topic is complex due to virus diversity, the number of causative drugs, and the varied clinical manifestations involved.

The mechanisms underlying DH have been explored intensively in the last 25 years. A substantial fraction of DHR involves the adaptive immune system (IgE, T cells), and drug-reactive T cells and antibodies have been identified. Regarding T cell stimulations, two predominant mechanisms have been elaborated: the hapten and p-i concepts.

Some beta-lactams are haptens, which means that they bind by covalent bonds to proteins, and thus form a new and stable antigen [6]. But mostly they do not elicit immune reactions, presumably because no co-stimulation (second signal) is provided by the drug itself [7]. The second mechanism postulates a non-covalent (pharmacological, off-target) binding to immune receptors like human leukocyte antigen (HLA) or T cell receptors (TCR) [7, 8]. This binding to crucial components of the cellular immune system, can result in an unorthodox, sometimes severe immune stimulation in the absence of co-stimulation (pharmacological interaction with immune receptors, p-i concept). This concept has been summarized in previous review...
articles emphasizing the similarity to an allo-and partly superantigen stimulation [9-11].

Here we try to incorporate these two concepts of drug-induced T cell stimulation to explain the association between viral infections and T cell-mediated DHR. We highlight that DHRs during viral infections are driven by co-stimulation of T cells, or simply by the increased expression of TCR/HLA on T cells. We believe, these concepts explain the transient nature and low reproducibility of most drug-induced exanthems originally appearing in the context of (transient) virus infections.

Exanthems in DH

The typical manifestations of virus-related DHR are so-called “rashes”. These are macular or maculopapular exanthems (MPE), some have vesicles. They are often mild in nature, and transient. However, some virus-linked DHRs which affect a large proportion of the body surface area, can last much longer, are more maculopapular, and can be associated with signs of liver involvement (transient elevation of ALAT/ASAT) [12, 13].

Systemic MPE itself represents a rather strong immune stimulation [14, 15]. Patients display an expansion of activated lymphocytes in peripheral blood, upregulation of HLA class II expression on CD8+ lymphocytes, expression of CD25 and CD69 on CD4+ cells, and increased concentrations of IFN-γ, TNFα, IL-5, IL-6, etc in the serum [16]. Histological analysis of MPE reveals CD4+, and, to a lesser extent, CD8+ T cells infiltrating the dermis and epidermis [17, 18]. This response has been demonstrated to be, in part, drug-specific [19]. Notably, in MPE, both the infiltrating CD8+ and CD4+ T cells are cytotoxic [17, 18, 20]. The target of this cytotoxic reaction are activated keratinocytes expressing HLA class II- and adhesion molecules (e.g. ICAM) [17, 18].

The extent of CD8+ cell infiltration seems to be variable [14, 15]. In most drug-induced MPE, CD4+ T cells predominate in the skin and CD8+ T cells predominate in the circulation. Milder exanthems are mediated by cytotoxic CD4+ T cells, while the more extensive and maculopapular forms are due to both CD4+ and CD8+ cell-mediated cytotoxicity. Bullous forms appear to be mediated mainly by CD8+ T cells [21]. A concomitant virus infection may also boost the CD8+ T cell involvement in the tissue. The recently described MPE during COVID-19 displayed massive polyclonal T cell activation in the circulation and a rather high percentage of infiltrating CD8+ T cells (CD8:CD4 ratio of 3:1) into the cutis/epidermis [22]. A similar but more severe response was also observed in some exanthemas following beta-lactam use during EBV infection [12]. The most powerful example of how a concomitant virus infection can impact DHR is seen during HIV infections. The incidence of SJS/TEN, which is a predominantly CD8+/NK cell-mediated reaction [21, 23, 24], is about 100-fold increased in HIV patients compared to non-infected individuals [25].

In normal MPE without virus involvement, around 50% of patients present with substantial eosinophilia [26, 27]. In contrast, eosinophilia is an unusual finding in viral exanthemas [27]. Indeed, some drug-specific T cells from patients with MPE excrete high amounts of IL-5, which may explain the typical eosinophilia in various forms of DHR [28][22].

Why some viral infections exacerbate DHR more frequently than other microorganisms is currently unknown. A partial explanation may lay in the similarly complex immune responses stimulated by viruses and drugs. They can provide soluble and cell-bound antigens, engage in peptide presentation via HLA class I and II and manipulate various components of the cellular immune system. This similarity is also reflected by the similar clinical and histological appearance of virus- or drug-induced exanthemas. Some drug-induced exanthemas are so similar to viral exanthems, that they were named accordingly (morbilliform or rubeola-like exanthems). Similar exanthems are also seen in graft-versus-host disease, where eosinophilia is also observed [29]. There are clinical similarities between virus, allo-allele and drug-induced exanthems and, as discussed previously, there may also be mechanistic similarities [9].

Viral infections enhance T cell hypersensitivity to drugs

A clue to better understanding the interplay between virus infection and DH lies in the two different ways, by which drugs can stimulate T cells. First by forming a new antigen (hapten -protein complex)[6] and
second by the p-i mechanism, which results in an unorthodox, mostly cytotoxic T-cell stimulation [8, 9].

**Hapten reactions:**

Hapten stimulations of T cells occur due to the formation of a new antigen, which is based on stable bonds between drugs and proteins. The new antigen is processed and presented as a haptenized peptide to T cells. Such antigen stimulations are common in contact dermatitis. Importantly, co-stimulation (e.g., engagement of adhesion molecules between APCs and T cells) is required to initiate an immune response. Contact dermatitis however is an incomplete model for systemic DHR, as orally or parentally administered drugs are unable to provide a co-stimulatory signal [10]. Thus, even if the drug can act as hapten and hapten-protein complexes are formed, the missing co-stimulation may prevent an immune reaction and DHR [7].

The most frequent elicitors of DHR are β-lactams, which are also often involved in virus-exacerbated DHR. Treatment with β-lactams (e.g., amoxicillin) results in ubiquitous haptenization of both soluble and cell-bound proteins [7]. Thus, one condition for a conventional immune response – formation of an antigen – is already fulfilled upon simple administration. This formation of new antigens, however, is clearly insufficient for developing a clinically apparent immune response/DHR, as only <8% of β-lactam-treated patients develop symptoms of DH [31]. If β-lactams are administered during a viral infection, the ongoing systemic inflammation with high expression of adhesion molecules and presence of cytokines (IFN-γ, TNF, IL-1, IL-6, etc) significantly increases hapten-specific immunity. [32] (Fig 1).

**p-i reactions:** When drugs elicit systemic T cell responses, this reaction relies predominantly on the non-covalent binding of drugs to certain parts of TCR or HLA molecules (p-i stimulations) [10]. This binding to immune receptors is unique, as it can induce unorthodox T cell activation in the absence of co-stimulation. This type of T cell activation has been shown to share some features of an allo-reaction [9] and drug binding to the HLA-peptide-TCR complex makes it look like an allo-HLA-peptide-TCR complex [33]. As such, allo-reactions are characterized by high levels of cytotoxicity, a feature also observed in T cell-mediated DHR [17, 18, 20].

P-i stimulations may happen with all drugs, including drugs that have hapten-like characteristics, as covalent bonds are always preceded by non-covalent drug binding to a suitable site in the protein [10, 34]. Even when the drug binds directly to immune receptors, no functional consequence may be observed, as the interaction is of low affinity and is only transient. Such low affinity binding remains unnoticed and does not stimulate immune activation and clinical symptoms.

Under certain circumstances, this low affinity binding may become relevant (Fig 2). Viral infections can induce systemic immune reactions [32]. This may increase the expression of HLA and adhesion molecules on APC and tissue-resident cells, while the broad T cell activation results in increased expression of TCR and of other adhesion molecules. This increase in immune receptor expression enhances the probability of low affine p-i interactions, and the overall avidity (i.e., the sum of low affine drug/immune receptor interactions) increases. The interaction of altered HLA-drug-TCR may also become sufficiently stable and result in T cell activation and clinical symptoms (Fig 2). Whether the increased expression of costimulatory molecules (T-cells, APC) does also contribute to the stability of the labile TCR-drug-HLA complex and thus symptomatic DH is unknown, but possible (see Sars-Cov2 infection and DH).

Examples of viral infections, which prime for DHR:

**Viral infections in childhood:**

In children suffering from acute upper respiratory airway viral infections, the incidence of exanthems after therapy with antibiotics (mostly β-lactams) is high [35]. This phenomenon can be observed following infections with a wide range of different viruses such as picornavirus, coronaviruses, hMPV, influenza A-B, parainfluenza, and RSV. These observed exanthems are mostly mild and transitory, but they can have lasting consequences. For example, infected children can be labeled as drug (“penicillin”)-allergic, but later no sensitization to drugs is observed in skin tests and the eliciting drug is again well tolerated [36].
**EBV infection and aminopenicillin exanthema:**

The use of aminopenicillins in young adults with an EBV infection has long been considered an almost mandatory cause of exanthema, with an initially reported incidence of over 80% [37]. However, current data report a much lower incidence of aminopenicillin-induced exanthema (10-30%) [3, 13]. Moreover, many patients tolerate aminopenicillins upon later re-exposure and skin tests show negative results. Some patients with EBV infection and DHR however retain their reactivity to aminopenicillins and may react to the drug (alone) again with rather severe reactions for many years [12, 38]. The reason for this distinct persistence of drug reactivity is unclear. The duration and extent of the initial reaction, the presence of facial swelling, and clinical severity of extracutaneous manifestations may indicate prolonged drug reactivity and should prompt the decision to perform a diagnostic workup [39].

**SARS-Cov2 infection and DH:**

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) patients have also begun to display DH. It is difficult to determine whether DH occurs more frequently following SARS-CoV-2 infections by looking at case reports/series alone. The latter, however, suggests that the clinical presentation of DH in SARS-CoV-2 patients is more extensive/severe [22, 40, 41]. Strikingly, according to the observations of others [42, 43] and ourselves, most of these DHRs were observed during the first wave of infections in 2020, and mostly in patients with a severe disease course. These DHRs were characterized by an extensive cutaneous involvement, prominent eosinophilia, a slow clinical resolution, and, in DRESS patients, a lack of responsiveness to high-dose systemic corticosteroids.

Although it is tempting to hypothesize that SARS-CoV-2 itself could act as a warning signal and impact DH, our experimental findings suggest an indirect rather than direct effect in promoting DH via triggering cytokine storm. This, in turn, leads to the hyperactivation and enhanced expression of co-stimulatory molecules on APCs/monocytes [44] and primes a T1 cell response to drugs. This is in line with the clinical observations that 1) these DHR seem to occur at the later stages of SARS-CoV-2 infections when the virus is barely still detected in the blood, and 2) that only patients with severe SARS-CoV-2 infections are affected.

**HIV infection and DH**

**HIV and sulfonamide allergy:**

Aromatic sulfonamides are an important group of antibiotics. Up to 3% of patients treated with sulfonamides present with exanthema and sometimes with fever and mild elevation of liver enzymes [45, 46]. In patients, these reactions give rise to numerous T cell clones, many of which have been investigated in great detail [47, 48]. One of the sulfamethoxazole reactive T cell clones (“H13”) was analyzed for reactivity to 11 other sulfanilamides and patients were found to react to half of these. Molecular docking and computational analysis revealed that the reactive sulfanilamides were bound to TCR Vβ20.1, while the non-reactive sulfanilamides failed to bind [48]-[50]. Interestingly, the binding site was a common site on this TCRVβ chain, which is present in all individuals (in 1-3% of all T cells).

These data may explain two questions concerning DH to sulfonamides:

a) The incidence of DHR to sulfonamides rises from 3 to 33 % in HIV+ patients receiving sulfamethoxazole/trimethoprim, either as prophylaxis [4, 49], or as a treatment for pneumocystis pneumonia [50]. One possible explanation could be that such HIV+ patients are undergoing a massive immune stimulation and that under these conditions the binding of sulfamethoxazole to TCR Vβ20.1 becomes more functionally and clinically relevant. b) “Sulfa-allergy” is a term mostly used in the USA and may describe a rash appearing after exposure to various sulfonamide-containing drugs [5]. This ominous “sulfa-allergy” may be the result of sulfamethoxazole binding to the common site on TCRVβ20-1, which, in those people where this T cell subset is already activated may result in symptoms [9].

**HIV and SJS/TEN**
Enhanced expression of immune receptors may also be responsible for the highly elevated incidence of SJS/TEN in HIV-infected patients. Indeed, the mechanism underlying SJS has been found to be due to p-i, where investigated [21, 23, 24]. HIV infection increases HLA expression, and, although there are reduced T cells present, these circulating T cells are highly activated. Thus, the opportunity for T cells to react to drugs and stimulate p-i reactions is dramatically increased. This could explain that the incidence of SJS/TEN (in response to various drugs) is around 100-fold increased in HIV-infected compared to non-infected individuals [25]. Some authors have proposed additional factors such as HIV-induced depletion of immunoregulatory cells and increased oxidative stress as favoring the development of DH [5, 51], but this remains controversial [50].

First DH, then virus release

In the above-mentioned examples, the viral infection primes the immune system for enhanced reactivity to drugs and thus clearly precedes the first manifestations of DH. However, there is an important exception to this sequence of events. In DRESS, DH develops first, and viraemia of endogenous herpes viruses (e.g. human herpes virus 6 (HHV6), cytomegalovirus (CMV), Epstein-Barr virus (EBV)) is subsequently detected. This viraemia can be detected already in the acute stage, but most commonly it is found 3-6 weeks later [52-54]. That means the viraemia develops, at least in the vast majority of cases, after cessation of the drugs which induce DRESS (Fig 3). Herpes virus reactivation is a rather common event, and HHV6 is even included in the Japanese definition of DRESS [54, 55]. Some of the herpes viruses are regularly present simultaneously [56], and often the viraemia remains asymptomatic. Severe complications as a result of this viral reactivation appear to be rare and are described mainly during CMV infections (colitis, myocarditis) [57, 58]. Whether the high systemic cytokine levels (e.g., TNFα and G-CSF) in the acute phase of DRESS play a role in CMV reactivation and related complications [58], is doubtful, as CMV reactivation and these complications usually appear much later [59].

An intense p-i stimulation, which involves the activation and expansion of many (polyclonal) CD4+ and CD8+ T cells, underlies DRESS [9, 10, 60]. This stimulation develops over weeks and is mirrored by lymphocytosis with many lymphoblasts in the peripheral blood (part of DRESS definition). These p-i-activated T cells are cytotoxic and infiltrate various tissues [61]. Additionally, DRESS is characterized by a massive activation and expansion of eosinophils in the peripheral blood and target organs.

The p-i stimulation affects both naïve and memory T cells and causes an activation and expansion of various T cells (polyclonal, polyspecific, cytotoxic) [9, 10]. Within this p-i activated T lymphocyte pool, are also T cells that are specific for endogenous herpes viruses. Up to 10% of all CD8+ T cells may be herpes virus-specific [62] and they control viral replication, likely via local IFN-γ release [63][64]. The p-i activation of these T cells may also have a dramatic effect on their effector function. Virus-specific T cells become cytotoxic due to the drug-induced p-i stimulation, and when they encounter their target stimulus (i.e., HHV6, CMV, EBV) in the peripheral tissue, these T cells kill the herpes-infected cells. In fact, an increase in TNFα and IL-6 was observed before HHV6 reactivation in DRESS, which was found to occur 3-4 weeks following the initial diagnosis [65][66]. As a consequence, the endogenous intracellular herpesviruses are released. The release of viral particles results in blood viraemia, most often in the absence of actual viral replication. In many cases, the viraemia remains asymptomatic.

Other authors have linked systemic cytokine storm, as detected in some acute DRESS cases, to viral replication (as shown for TNFα and HHV6) [67, 68], and, as in the case of CMV, serious, potentially fatal complications. However, most viraemia is observed weeks after the cytokine storm.

Beyond viral reactivations, the p-i-activation of T cells in DRESS may also be linked to the occurrence of late autoimmune complications. Instead of virus-specific T cells, the activation and subsequent functional switch to a cytotoxic effector mode may happen in autoreactive T cells [10].

Clinical impact and conclusion

Many factors influence the clinical manifestation of DH in the context of viral infections. These can be
virus-, drug- and/or patient-related. Among the virus-related factors are the type and strain of the virus and the length of infection. The drug itself, the dose, its ability to act as a hapten, the patient’s underlying condition, antiviral/antidrug immune response, and potential state of immunosuppression also contribute in this setting. It is challenging, but important for a better understanding of DHR in viral infections, to dissect the respective contribution of these virus-, drug- and/or patient-related factors.

The models proposed can be generalized to various virus infections, and are not dependent on a specific type of virus: The analysis of the timing of symptoms and therapy, as well as the careful monitoring of virus load in SARS-CoV-2-infected patients, has emphasized that DH manifestations are not linked to the presence of viruses, nor that viraemia after DRESS is linked to the presence of a drug. They are due to the virus- or drug-triggered immune stimulations, but are not dependent on the presence of its elicitor (drug or virus). The manifestations of DH can therefore occur after virus clearance – as long as the state of immune activation persists. Vice versa, viral release can occur in the absence of a drug, as illustrated in the late complications of DRESS (Fig 3).

For the clinician, the following questions are important:

1) *Is re-exposure to the incriminated drug possible after the viral infection has disappeared?*

This refers to the importance that the viral infection has played in the DHR, and questions whether the drug-directed T cell response would be potent enough to occur in the absence of viral infection. This may critically differ depending on the type of T cell response involved, i.e., whether it is hapten- or p-i-induced.

So far, it is unclear whether hapten- or p-i-induced DHR are longer lasting. In hapten responses, the co-stimulation is mainly required for initiation of a classical T cell response [30]. A certain memory T cell response, which is less dependent on co-stimulation, might develop [64]. Thus, the re-exposure to the drug/hapten alone might be sufficient for the reactivation of memory T cells, suggesting that at least some classical hapten-reactive T cells may be restimulated even in the absence of virus co-stimulation.

In p-i reactions, co-stimulation is of less importance [9, 10]. The viral infection increases the frequency of p-i interactions and results in a higher affinity of p-i, which is limited to the time of virus infection. After the elimination of viruses, the *in vivo* conditions return to normal. This reduces the frequency of drug-immune receptor interactions and may be insufficient to cause clinically-important T cell stimulation. This dependence on higher expression of TCR/HLA would also explain why sensitization during skin tests is often absent. However, this scenario may only apply to low affine p-i interactions. During high affine p-i stimulations, the DHR is more severe (SJS/TEN, DRESS) and less dependent on viral enhancement. Thus, they may occur without viral co-stimulation. Indeed, a long-lasting reactivity is well documented for DRESS [66].

The severity and duration of cutaneous symptoms, as well as the presence of systemic symptoms, may impact whether a DHR can re-occur without viral infection [38]. An extensive exanthem and prominent blood eosinophilia may be indicative of a substantial drug-specific T cell expansion due to high affine (strong) p-i or extensive hapten reactions and potent downstream IL-5 production. The pool of drug-specific T cells may persist and the DHR reappears upon drug re-exposure, even in the absence of virus co-stimulation. On the other hand, Caubet JC did not find a relationship between the severity of exanthems to positive provocation tests, but the number of positive provocation used in this study was small [2]. Alternatively, if the DHR symptoms were mild even in the presence of viral infection, they might not re-appear upon re-exposure to the drug without virus infection. Therefore, there would be no reason to withhold beta-lactams (or related drugs) in the future.

To add further complexity, p-i- and hapten-induced T cell responses in the context of viral infections are not mutually exclusive. β-lactams, for instance, can stimulate the immune system not only by forming an antigen, but also by stimulating via p-i [68]. Viral infections enhance both classical antigen stimulation and unorthodox p-i stimulation by β-lactams, which may explain the high incidence of β-lactams in virus enhanced DHR.
II) Viraemia after DRESS: induced replication or mostly release of endogenous viruses?

It is still a matter of debate whether viraemia of herpes viruses is a causative or reactive factor in DRESS and to which extent the viraemia is clinically relevant.

In the Japanese definition of DRESS/DiHS, herpes virus infection (mainly CMV) is considered an important cause of DRESS morbidity and mortality and HHV6 viraemia even figures as a diagnostic criterium [54]. Consequently, they recommend antiviral therapy in DRESS/DiHS [69].

The virus-release hypothesis, presented here, sees viraemia as a secondary phenomenon. Viraemia in this case would not precede, or even induce, the drug-directed T cell response. The virus-release hypothesis is compatible with the potential simultaneous increase of various herpes viruses (HHV6, CMV, EBV) in the blood [59]. Since most patients do not exhibit viraemia-associated symptoms, antiviral treatment in these asymptomatic patients would not be warranted. Indeed, antivirals and other new medications should be avoided in DRESS patients since they tend to develop “multiple drug hypersensitivity” [70][71]. However, multiple drug hypersensitivity symptoms due to antiviral medication have not been reported in Japan.

In summary, viral infections might prime the immune system for DHR by enhancing immune reactivity to drugs (p-i) and hapten-protein complexes. Consequently, severe DHR may cause viral particle release/viraemia due to the actions of cytotoxic T cells. However, these conclusions are still hypothetical and need further substantiation. In particular, we need more clinical and immunological data on the type and duration of drug-induced immune reactions. However, such data are difficult to obtain with an iatrogenic disease like DHR and even more difficult to obtain for a combination of viral infection and DHR.

Nevertheless, one should start with a more precise clinical evaluation of DHR. We should aim at substituting the term “rash” with a more exact description of the exanthema, especially the extent and severity of the reaction and its duration – a picture is always helpful. Furthermore, signs of even mild systemic involvement/severity, as evidenced by eosinophilia, lymphocytosis and elevation of liver enzymes, should be more carefully considered in DHR. We should not forget that it is an iatrogenic disease, which needs particular attention. Such a more in-depth approach and the resulting data may help us further dissect and understand DHR in viral infections. In consequence, this may help to avoid the obvious mislabelling of often very young patients with mostly harmless, transient exanthema as permanently penicillin-allergic, which may cause much confusion in daily clinical practice. Finally, the question arises if one should not consider virus-enhanced reactions in the risk assessment of certain drugs-like antibiotics.

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Figure Legends

Fig 1. Viral enhancement of hapten drugs (amoxicillin):

Hapten drugs like amoxicillin bind by covalent bonds to many proteins in the peripheral blood/tissue, and drug-modified peptides enter the HLA-class I and class II antigen presentation pathway. Nevertheless, no immune response to the modified proteins is developed, probably because co-stimulatory signals, necessary for mounting an immune response, are missing.
A viral infection enhances the expression of immune receptors (TCR, HLA) and costimulatory molecules (e.g., CD80, CD86, CD40).

When the patient is treated with a hapten drug like amoxicillin during such a viral stimulation, the same cell presenting viral peptides may also present amoxicillin-modified peptides in the context of costimulatory molecules. Thus, not only viral-specific T cells are activated, but also amoxicillin-specific T cells, as the costimulation serves both virus and amoxicillin reactions. Immunity to virus and amoxicillin means DH can develop.

**Fig 2. Viral enhancement of p-i acting drugs**

Drugs bind to proteins (non-covalently, reversibly, low affinity), including immune receptor proteins. Such low-affinity binding is mostly clinically irrelevant, as it is insufficient to elicit T cell stimulation. However, during viral infections, immune receptors are expressed in much higher density, the chances for increased low affine interactions increases and the p-i binding may become functionally relevant. T cells are activated by the drug, as long as the virus-induced immune stimulation lasts. When the virus-induced immune activation is over, the patient no longer shows any drug reactivity.

**Fig 3. Virus release due to massive p-i activation (DRESS)**

A high affine p-i activation can lead to strong T cell activation, T cell expansion, and the acute symptoms of DRESS such as cytotoxicity in various organs. Such p-i activated T cells can also contain herpes virus peptide-specific T cells (reactive towards HHV6, CMV, EBV), which usually control the replication of the virus in the tissue via IFN-γ release. Through p-i activation, such T cells switch from a controller (IFNγ) to a cytotoxic phenotype. When they encounter herpes peptide-expressing cells, they attack them, the prefabricated viruses are released, and viraemia of various herpes viruses occurs.

**References**


Immune reactivity to

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p-i-mechanism of T-cell activation

Immune reactivity to

<table>
<thead>
<tr>
<th></th>
<th>drugs</th>
<th>virus</th>
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<tbody>
<tr>
<td>low affinity</td>
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<td>expression of HLA I, II, TCR</td>
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<td>T-cell activation (virus)</td>
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<td>virus infection and many p-i interactions</td>
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<tr>
<td>T-cell activation (drug + virus)</td>
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</tbody>
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Tables.docx available at https://authorea.com/users/332013/articles/576160-viral-infections-and-drug-hypersensitivity