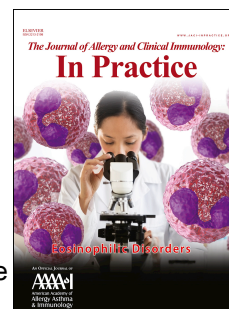


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Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS) : Series of 49 French pediatric cases

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Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS) :

Series of 49 French pediatric cases

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Abstract

Background: Drug reaction with eosinophilia and systemic symptoms (DRESS) is a rare and potentially fatal adverse drug reaction. It can be difficult to diagnose, even more so among children, since symptoms may mimic other commonly encountered pediatric conditions.

Objective: To describe clinical and laboratory features of DRESS syndrome in the pediatric population (≤ 18 years of age), establish causative agents and treatment modalities.

Methods: Multicenter retrospective study of probable and definite DRESS cases (RegiSCAR ≥ 4) in children hospitalized in 15 French University Hospitals between 2000 and 2020.

Results: We included 49 cases. All children had fever and rash, 69.4% had lymphadenopathy and 65.3% had facial edema. The most common organ affected was the liver (83.7%). Treatment consisted in topical corticosteroid only for 30.6%, systemic corticosteroid for 55.1%; 12.2 % received IVIg. Among culprit drugs of probable and certain probability, 65% were antibiotics and 27.5% antiepileptics, with a median time to DRESS symptom onset after initiation of 15 days (13 days with antibiotics and 21 days with antiepileptics). Twenty-seven children had allergy assessment for causative agents: 65.4% had positive tests.

Conclusions: The culprit drugs are frequently antibiotics and antiepileptic drugs and onset is often less than two weeks after the treatment starts, especially with antibiotics. Treatment with topical corticosteroids appears sufficient in the least severe cases. Treatment by systemic corticosteroid therapy remains the reference treatment in case of severe organ damage.

Highlights box

1. What is already known : Drug reaction with eosinophilia and systemic symptoms (DRESS) is a rare and potentially fatal adverse drug reaction. It can be difficult to diagnose, even more so among children, since symptoms may mimic other commonly encountered pediatric conditions.

2. What does this article add to our knowledge : This case series shows that clinical and biological characteristics of DRESS syndrome in the pediatric population are similar to those of adults. The onset of firsts symptoms can be less than two weeks after the treatment starts, especially with antibiotics.

3. How does this study impact current management guidelines : Treatment with topical corticosteroids appears sufficient in the least severe cases. Patch tests allow to confirm the imputability of the molecule in the majority of tested cases.

Key words

Drug Reaction with Eosinophilia and Systemic Symptoms; DRESS; pediatric, children; antibiotics, antiepileptic drugs

79 Abbreviations

- 80 APS: Naranjo Adverse Reaction Probability Scale
- 81 CMV: Cytomegalovirus
- 82 DRESS: Drug Reaction with Eosinophilia and Systemic Symptoms
- 83 EBV: Epstein Barr Virus
- 84 FISARD: French Investigators for Skin Adverse Reactions to Drugs group
- 85 GNEDS: Groupe Nantais d'Ethique dans le Domaine de la Santé (Nantes Health Ethics Group)
- 86 GRC-SFDP: Groupe de Recherche Clinique de la Société Française de Dermatologie
- 87 Pédiatrique (Clinical Research Unit of the French Society of Pediatric Dermatology)
- 88 HH : Human Herpes Virus
- 89 HLH : Haemophagocytic lymphohistiocytosis
- 90 IDR: Intra Dermo Reaction
- 91 IVIg: Intravenous Immunoglobulin
- 92 PCR: Polymerase Chain Reaction
- 93 PTs: Patch Tests
- 94 SC: Systemic Corticosteroid
- 95 TS: Topical corticosteroids

Introduction

Drug reaction with eosinophilia and systemic symptoms (DRESS) is a rare and potentially fatal adverse drug reaction classified among severe cutaneous adverse reactions (SCARs) (1). It is classified under delayed drug-induced hypersensitivity reaction characterized by fever, rash, lymphocyte activation (lymph node enlargement, 'atypical' activated lymphocytes), eosinophilia and various visceral dysfunctions with a risk of multi-organ failure. The physiopathological mechanisms of DRESS syndrome result from the interaction between one (or more) drug(s) or their metabolites and an immune receptor (Human Leukocyte Antigen or T cell receptors) leading to a T cell-mediated response (2–4). Reactivations of herpes virus, especially HHV-6, are frequently observed but it remains unclear whether the viral reactivation (or a primary viral infection) is the trigger event of the DRESS syndrome or whether viral reactivation is a consequence of the DRESS (5–8). Diagnosis can be delayed because of the variable clinical presentation, and the similarities with infection or lymphoproliferative diseases. Its incidence among the pediatric population is unknown and its knowledge has for a long time been based on case reports and small cases series. In 2019, Metterle et al. (9) published a review of the literature collating 130 pediatric cases. The most common clinical presentations included fever, a morbilliform rash and lymphadenopathy. The liver was the most frequently involved organ (80%). Time from treatment initiation to first symptoms was three to 60 days (average 24 days), and DRESS syndrome was secondary to antiepileptics in 50% and antibiotics in 30.8% of cases. Our study aims to analyze the epidemiology, clinical and laboratory features, identify drugs associated with the reaction and the therapeutic management of DRESS syndrome among children.

Materials and methods

We performed a retrospective study of DRESS syndrome diagnosed between 2000 and 2020 among pediatric population in 15 French hospitals. The clinical study was conducted in accordance with the relevant versions of the French Public Health Code, national and international good clinical practice (GCP) guidelines, and the Declaration of Helsinki, each in the applicable version. Our study was submitted to and approved by the local Research Ethics Committee (GNEDS) of Loire-Atlantique on Septembre 1, 2020. The Regiscar score (10) was used to establish the diagnosis of DRESS (Table E1, available in Online Repository Text). The inclusion criteria were: (i) diagnosis of DRESS, (ii) RegiSCAR score ≥ 4 , (iii) age ≤ 18 years and (iv) at least one suspected drug. Standardized questionnaires (available in Online Repository Text) were used to collect data from the patient's medical record. Investigators were members of Clinical Research Unit of the French Society of Pediatric Dermatology (GRC-SFDP)) or the French Investigators for Skin Adverse Reactions to Drugs group (FISARD) of the French Society of Dermatology. In each centre, cases were identified by dermatologists, allergologists, pediatricians and the pharmacovigilance centre. We collected data about demographics, suspected culprit drugs, clinical and laboratory data, treatment of DRESS and testing suspect drugs. Liver involvement was defined by a twofold or greater increase of transaminases compared to normal values. Kidney involvement was defined by elevated creatinine, proteinuria, anuria or electrolyte disturbance. The different drugs, dates of introduction and discontinuation were documented. Suspected drugs were defined as all drugs started within 12 weeks before the onset of the rash and still administered or stopped less than five half-lives before rash onset. We determined the causality of drugs according to the Naranjo Adverse Reaction Probability Scale (APS) (11). In the case of a confirmed reaction to a drug, other drugs with compatible timelines were not excluded from the list of

142 suspect drugs. All the data were collected using Microsoft Excel. Analyses was performed
143 using SAS statistical software (SAS Institute Inc., Cary, North Carolina, USA). Quantitative
144 data are expressed as median $\pm$ range and qualitative data in percentage (%).

Results

We identified 64 potential DRESS cases from the medical records of 15 French hospitals. Of these, a total of 15 cases were excluded : one case was a DRESS-like rash (12,13) during viral infection and lacked a causative agent, 11 cases had a RegiSCAR scores <4 and three cases had insufficient data. Finally 49 cases were included in the study.

Characteristics

Patient's and DRESS syndrome's characteristics are summarized in Table 1. The median age was eight years (range: 5 weeks - 18 years) and 44.9% were male. Three children (6.1%) had previously experienced a drug-induced skin reaction (two with unspecified rash, one with urticaria), two of them to the same drug as the DRESS syndrome (one with sulfamethoxazole-trimethoprim and one with penicillin). Eight children (16.3%) were immunocompromised. The DRESS occurred during a hospital stay in 24.5%. According to the RegiSCAR score, 55.1% were definite and 44.9% were probable DRESS syndrome (characteristics of each group are available in Table E2 in Online Repository Text). The diagnosis of DRESS syndrome was made in a median time of six days after rash onset (range: 0-28). A differential diagnosis was presumed for 22 children (44.9%) (viral infection in 63.6%, Kawasaki disease in 22.7%). The majority of diagnoses were made by dermatologists (57.1% of cases), while pediatricians provided the diagnosis in 12.1% of cases (Table 1).

As described in Table 2, fever and rash were documented in all children. In 95.4% of cases, the rash covered more than 50% of the body surface area. A morbilliform exanthema was described in 67.3% (monomorphic in 66.7% (Figure 1), polymorphic in 33.3%, including purpura, target-like lesions, eczema-like lesions, blisters and pustules). Erythroderma was

described in 14.3%. Pruritus was reported in 67.3% and facial edema in 65.3% (Figure 1). Lymphadenopathy was observed in 69.4%. Mucosal involvement was described in 40.8% (associated cheilitis in 30.6% (Figure 2), mouth $\pm$ throat involvement in 16.3% and conjunctivitis in 10.2%). The most commonly affected organs were the liver (41 children, 83.7%), kidneys (13 children, 26.5%; associated with isolated proteinuria in 54% of cases and moderate creatinine elevation in 38% of cases), lungs (11 children, 22.4%) and gastrointestinal tract (five children, 10.2%). Myocarditis was described in one case and meningitis in one. Biological abnormalities are detailed in Table 3. Eosinophilia (absolute count $> 500/\text{mm}^3$) was present in 85.7% and atypical lymphocytes were observed in 49%. An investigation for viral reactivation or primary infection was conducted for 42 children (18 by serology and polymerase chain reaction [PCR], 16 PCR only and eight serology only). Among the 34 children who were investigated by PCR, 17 (50%) were positive. Among them, 32 were tested for HHV-6 : seven were positive (21.9%); four were positive for Parvovirus B19, four for Epstein-Barr virus (EBV), two for HHV-7 and two for cytomegalovirus (CMV), including two children with co-infection EBV and CMV. Twelve children (24.5%) had biological criteria for haemophagocytic lymphohistiocytosis (HLH) (14).

A skin biopsy was performed in 29 cases (59.2%). The analysis of histopathology was available for 27 biopsies (Table E3, available in Online Repository Text): the most common pattern included an epidermis with cytoid bodies and lymphocytic exocytosis, sometimes spongiosis. The dermis was classically the place of a perivascular lympho-histiocytic inflammatory infiltrate. The presence of eosinophils was not a consistent finding (33.3% of biopsies).

Course and treatment

Median duration of eruption was 20.5 days (range: 4-90), this persisted more than 15 days in 72.5%. Median time from the beginning of the rash to maximal count of eosinophils was 10 days (range: 0-35), and to maximal rate of transaminase elevation 11 days (1-35). Median time of resolution of transaminase was 28 days (7-68) after onset of rash (Figure 2). Seventeen (34.7%) children were transferred to an intensive care unit (median duration stay five days, range: 1-26). One child died from cardiopulmonary arrest due to myocarditis and one child died from septic and hypovolemic shock complicated by multivisceral failure syndrome in a context of erythroderma. Median duration of hospitalization was 13 days (range: 3-60): 10 days (range: 3-39) for community cases and 22 days (range: 12-60) for hospital cases. Specific treatments of DRESS syndrome are summarized in Table 1; 51% received topical corticosteroid (TS) and 55.1% systemic corticosteroids (SC) (median duration for SC: 42.5 days (range: 1-546), introduced at a dose of 2mg/kg in 36.4% of cases, 1mg/kg in 54.5% and 0.5 mg/kg in 9.1% of cases). Children treated with TS only appeared to have less severe presentation than those who received SC therapy with a shorter duration of rash (16 days versus 23.5 days, respectively) and 13% of hospitalization in intensive care versus 48%, respectively. Six cases (12.2%) received intravenous immunoglobulin (IVIg) (for three patients, this was due to the initial hypothesis of Kawasaki disease) and two cases (4.1%) received ciclosporin. Thirty-six patients (73.5%) were followed after discharge : the median number of consultations was three (range: 1-10) and the median follow-up was 8.8 months (range: 3 days - 5.8 years). A relapse was noted in 11 cases (22.4%), within a delay of six weeks to six months after the resolution of eruption for six cases (54.5%). Relapse was attributed to the decrease or cessation of corticosteroid therapy in three cases (27.3%). Long-term sequelae were observed in five patients (10.2%): one with vitiligo, one with hyperpigmentation and one systemic lupus revealed a year after resolution of DRESS (with

anti-SSA and anti-SSB antibodies). Two children presented complications of steroids : the first child presented with corticoid-induced hypertension; he received 46 days of corticosteroids for the management of a severe DRESS syndrome with liver involvement (resolution 36 days after the onset of the rash), HLH and bronchial syndrome. He was receiving long-term treatment with inhaled fluticasone. The second child presented with corticotropic insufficiency and diabetes mellitus; he received one year and six months of corticosteroids for a chronic DRESS (multiple episodes of recurrence on attempts to decrease the corticosteroids) with lung (alveolar infiltrate) and liver involvement.

Causative drugs

Among the 85 medications suspected of inducing DRESS, 49 (57.6%) were antibiotics and 17 (20%) antiepileptics. The median time of DRESS onset after introduction was 13 days (range: 0-70) (antibiotics: 12, range: 0-44; antiepileptics: 21, range : 4-52). If one calculates this for drugs of definite or probable imputability only according to the APS (11) (40 drugs): 26 (65%) were antibiotics and 11 (27.5%) antiepileptics. The delay of onset was 15 days (range: 1-44) (antibiotics: 13, antiepileptics: 21) and 47.5% of the drugs have a delay < 15 days (13 antibiotics and five antiepileptics).

Suspect drugs were continued after the onset of rash for a median duration of four days (range: 0-88), although when considering the drug classes separately, this is three days for antibiotics rising to 10 days for antiepileptics. A table summarizing all the culprit drugs (Table E4) is available in Online Repository Text.

Tests

Allergy assessment was performed for 26 children (53%) in a median time of seven months (range: 2-39 months) after hospital discharge and was conducted according to The European Network on Drug Allergy (ENDA) and European Academy of Allergy and Clinical Immunology (EAACI) guidelines (15,16). 23 had patch tests (PTs), nine had intradermal test (IDR), three had prick test, two had lymphocyte transformation test (LTT) and two had oral provocation. Tests were positive for 17 children (65.4%): PTs were positive for 15 children (61.5%), among them a child had a LTT positive for another drug (co-sensitization for vancomycin and sulfamethoxazole-trimetoprim) and both children subjected to oral provocations were positive (one of these provocation tests resulted in a recurrence of the DRESS syndrome). Two children had positive immediate but not delayed IDR (oxacillin and capsofugin, the latter also positive for prick test) while the patch tests were negative. These two children were not included in the positive tests due to the absence of a delayed reaction.

Discussion

Although the frequency cannot be specified through this descriptive cohort, we have identified 49 cases of probable or definite DRESS syndromes among pediatric population over the last twenty years in France. This diagnosis, which was rarely mentioned in children, seems to be better known (75% of the cases in our cohort have been described in the last five years). This cohort provides a detailed description of the clinical and biological presentation, the course and the causative agents of pediatric DRESS and allows us to illustrate the similarities and differences between children and adults (Table E5, available in Online Repository Text).

The most frequent clinical manifestations in our study were fever, rash, lymphadenopathy and facial edema and the most common affected organ was the liver (83.7%) – confirming

observations made in previous adults (17,18) and pediatric (9,19–23) series. The percentage of lung involvement (22.4%) is comparable to the adult cohorts described by Lee et al. (24) and Kardaun et al. (18) (20% and 32% respectively); the most common manifestations were interstitial infiltrates (27%) and acute respiratory distress syndrome (27%) as described in the systematic review by Taweessedt and al. (25). Five children presented with diarrhea (10%), one of them with vomiting. None of them had histological investigations. Digestive tract involvement is poorly described in the different cohorts of adults or children. When described, the symptoms are non-specific and are not investigated. In the study by Newell et al (19), 44% of children presented with digestive involvement, including 57% with vomiting, 29% with diarrhea and 29% with bloody diarrhea. A few cases of oesophagitis and/or inflammatory colitis up to and including ulcerative colitis have been reported (26,27). The number of HHV-6 reactivations (22%) was lower than in previous studies (43% and 36%) (9,18).

The diagnosis of DRESS was essentially made by dermatologist and median diagnostic delay after onset of rash was six days resulting in a frequent delay in the discontinuation of the culprit drug(s). We highlight that the biological picture worsens after apparition of skin symptoms, in spite of stopping the culprit drug (Figure 2).

We report a high prevalence of antibiotic-related cases with the penicillin class, sulfamethoxazole-trimethoprim and vancomycin at the top of the list. Among antiepileptics, carbamazepine was the main drug responsible, as found in previous studies (9,17–19).

It has long been accepted that DRESS occurs within two to eight weeks after the introduction of medication (27,28). In our study the latency period is shorter and 47.5% of the drugs of definite or probable imputability have a latency period < 15 days. Our study suggests that

DRESS syndrome among pediatric population can occur less than 15 days after drug introduction. These results are consistent with those reported in other series (9,16,19,22) and the study by Soria et al.(30).

There is currently no consensus on the therapeutic management of DRESS, as there are no randomized controlled trials evaluating the efficacy of the different treatments. Topical corticosteroids (TS) are proposed for non-severe DRESS, whilst in the case of internal organ involvement, treatment with a systemic corticosteroid (SC) is recommended (31,32). In our study, 31% received only TS. These cases appeared to be less severe than those who received SC therapy (13% of hospitalization in intensive care versus 48%). Furthermore, the rash appears to resolve more rapidly (16 days versus 23.5 days). These results are consistent with those of Funck-Brentano et al.(33) and Uhara et al.(34) who suggested that TS can be used in patients with non-severe DRESS. Treatment with SC might favor relapse (30) and is often prolonged and carries an infection risk (35,36). In the various observational studies and literature reviews, SC have been used in 43-100% of cases in both adults and children (9,17,19, 21, 23), while the use of TS is rarely mentioned (9% of children in the cohort by Newell et al. (19) and 21% in the cohort by Bessmertny et al. (21)).

In our study, six children received IVIg, with a median duration of the rash of 15 days (versus 21 days for the other cases in the cohort). Treatment with IVIg has been described in a few severe cases with variable results (37–39). A recent series of seven pediatric cases showed that a treatment combining IVIg and SC led to a rapid improvement of the children's general condition (40). On another hand, in a series of six adult cases treated with IVIg alone, five patients had severe adverse events, suggesting that IVIg must not be used as stand-alone treatment in DRESS (37). Ciclosporin has been proposed when SC are contraindicated or in

cases of corticosteroid resistance. It has been reported in a few cases as a successful alternative (41–43). Ciclosporin was received by two children in our case series. In the first case, this was because of a non-response to SC and IVIg treatment, with resolution of the rash one month after starting ciclosporin. For second child, ciclosporin was started after 9 months of chronic evolution of the DRESS syndrome, but the introduction of ciclosporin combined with continued corticosteroid therapy did not control the disease, and the child died from septic and hypovolemic shock complicated by multivisceral failure syndrome in a context of erythroderma 18 months after onset of DRESS.

In a study that retrospectively examined 43 cases of DRESS syndrome, Chen et al. (44) reported 11.5% of long-term sequelae and found that autoimmune sequelae were more common in younger patients. In our study, five patients developed long-term sequelae, including two related to the prolonged use of corticosteroids and two autoimmune complications: one vitiligo and one systemic lupus, which has already been reported in the literature (44–47).

Allergy assessment, which consisted of patch tests for the majority of children, were positive in 65.4% of cases, data comparable to the literature (48, 49). No delayed IDR was positive in our cohort.

The most important limitation of this study is the retrospective analysis of medical records in which data may be missing. In addition, since the recruitment of the included cases was based on volunteered by members of the SFDP and the FISARD group, this approach will have missed cases (recruitment bias). Finally, investigators were mainly dermatologists and

it is possible that some rare cases of DRESS with visceral manifestations but minimal or absent cutaneous symptoms were not recruited.

Conclusion:

Due to the diversity of its clinical and biological presentation, the diagnosis of DRESS syndrome is difficult. This often leads to a delay in diagnosis and cessation of culprit drugs. This series shows that the onset of DRESS syndrome in the pediatric population is often less than two weeks after the treatment starts, especially when it involves antibiotics. The initial management will consist of stopping suspected culprit drug(s), i.e. those introduced in the last three months. Clinical and biological signs of DRESS should be closely monitored over a long period of time, as the condition may worsen despite the cessation of the drug(s). Treatment with topical corticosteroids appears sufficient in the least severe cases. Treatment by systemic corticosteroid therapy remains the reference treatment in case of severe organ damage, and the place of IVIg remains to be determined.

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Figure and Table Legends

Figure 1. 3 years old child with diffuse maculopapular rash, facial edema and cheilitis.

Figure 2. Culprit drug initiation, Clinical & Biological Events Timeline in relation to onset of rash (defined as Day 0).

This box-plot reports the time between drug initiation (drugs of probable and definite probability according to Naranjo criteria (11)) in relation to the onset of the rash (left side) and time between diagnosis of DRESS syndrome, biological parameters (eosinophil and transaminase peak, transaminase resolution) and rash resolution in relation to the onset of the rash (right side).

Table 1. Demographics and characteristics of patients and DRESS syndrome

Table 2. Clinical features

Table 3. Biological characteristics

Table 1: Demographics and characteristics of patients and DRESS syndrome

			n = 49	%	
Age, median (range)			8 (5 weeks -18 years)		
Sex	Male		22	44.9	
	Female		27	55.1	
History of cutaneous drug reaction			3	6.1	
Comorbidity	Allergy (other than drug reaction)		5	10.2	
	Atopy		3	6.1	
	Epilepsy		16	32.7	
	Immunodepression ^a		8	16.3	
RegiSCAR score	Probable (4-5)		22	44.9	
	Definite (≥ 6)		27	55.1	
Time from onset of rash to diagnosis of DRESS (days), median (range)			6 (0-28)		
Specialist establishing the diagnosis of DRESS	Dermatologist		28	57.1	
	Pediatrician		6	12.2	
	Allergologist		4	8.2	
	Intensive care anesthetist		2	4.1	
	Infectious disease specialist		1	2	
	Pharmacovigilance system		1	2	
	Differential diagnosis [n = 22 children]	Viral infection		14	28.6 [63.6]
Kawasaki disease		5	10.2 [22.7]		
Others		Exanthem following amoxicillin during mononucleosis		7	14.3 [31.8]
		Scarlet fever			
		Toxic shock syndrome			
		Erythema multiforme			
		Pseudolymphoma			
		Malignant hemopathy or Juvenile idiopathic arthritis			
		Acute generalized exanthematous pustulosis			
Treatment of DRESS syndrome	None		3	6.1	
	Topical corticosteroid	Total	25	51	
		Topical corticosteroids only	15	30.6	
	Systemic therapy	Systemic corticosteroid (median duration)		27	55.1
		IV then oral		14 (42.5 days)	24.5
		IV only		3 (2 days)	10.2
		Oral only		10 (44.5 days)	20.4
		Intravenous Immunoglobulin		6	12.2
		Cyclosporin		2	4.1
Hospitalization in intensive care unit			17	34.7	
Duration of stay in intensive care unit (days), median (range)			5 (1-26)		
Duration of hospitalization (days), median (range) : all			13 (3-60)		
Community cases			10 (3-39)		
Hospital cases (n = 12) ^b			22 (12-60)		
Relapse ^c			11	22.4	
Death			2	4.1	

^a Immunodepression : dialysis chronic kidney disease; IgG4 deficiency; cystic fibrosis, acute lymphocytic leukemia under chemotherapy; vasculitis under corticosteroids and cyclophosphamide; hydrocephalus under corticosteroids; 2 autoinflammatory diseases under IL-1-blocking agent. ^b Duration of stay after onset of rash. ^c Relapse: recurrence of clinical or biological signs after their normalisation in the absence of reintroduction of culprit drug

RegiSCAR: Registry of Sever Cutaneous Adverse Reaction; IV: Intravenous

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Table 2: Clinical features

		n = 49	%
Fever (temperature > 38.5°C)		49	100
Rash		49	100
Morbilliform (maculopapular)		33	67.3
	Monomorphic	22 ^a	44.9
	Polymorphic	11	22.4
Macular		3	6.1
Nonspecified		7	14.3
Erythroderma		7 ^a	14.3
Associated skin lesions	Purpura	9	18.4
	Pustules	5	10.2
	Target-like lesions	3	6.1
	Urticaria	2	4.1
	Eczema-like lesions	1	2
	Blisters	1	2
Body surface area	<i>[Case where answer is available n = 43]</i>		
	< 50 %	2	4.1 [4.6]
	50 - 90 %	31	63.3 [72.1]
	> 90 %	10	20.4 [23.3]
Rash duration (days), median (range) <i>[Case where answer is available n = 40]</i>		20.5 (4-90)	
< 15 days		11	22.4 [27.5]
15 - 29 days		18	36.7 [45]
≥ 30 days		11	22.4 [27.5]
Pruritus <i>[Case where answer is available n = 39]</i>		33	67.3 [84.6]
Edema (total) <i>[Case where answer is available n = 42]</i>		34	69.4 [81]
Facial		32	65.3 [76.2]
Extremities		11	22.4
Generalized		3	6.1
Lymphadenopathy <i>[Case where answer is available n = 44]</i>		34	69.4 [77.3]
Hepatomegaly <i>[Case where answer is available n = 37]</i>		12	24.5 [32.4]
Splenomegaly <i>[Case where answer is available n = 33]</i>		7	14.3 [21.1]
Mucosal involvement <i>[Case where answer is available n = 41]</i>		20	40.8 [48.8]
Lips		15	30.6
Mouth/throat		8	16.3
Eyes		5	10.2
Internal organ involvement	Liver (<i>elevated transaminases</i>)	41	83.7
	Kidney (<i>Table 3</i>)	13	26.5
	Lung (<i>3 interstitial infiltrate, 3 ARDS (2 with orotracheal intubation), 2 broncho-obstructive syndrome, 1 alveolar infiltrate, 1 pleural effusion, 1 nocturnal desaturation</i>)	11	22.4
	Gastrointestinal tract (<i>5 diarrhea, 1 with vomiting</i>)	5	10.2
	Heart (<i>myocarditis</i>)	1	2
	Central nervous system (<i>meningitis</i>)	1	2
^a A child with initial morbilliform exanthema presented with erythroderma when relapsing ARDS : Acute Respiratory Distress Syndrome			

Table 3: Biological characteristics

	n = 49	%
Eosinophilia	42	85.7
500 - 749/mm ³ or < 10%	3	6.1
750 - 1500 x10 ⁹ /mm ³ or 10-20%	8	16.3
> 1500 x10 ⁹ /mm ³ or > 20%	31	63.3
Eosinophils peak (days after onset of rash) , median (range)	10 (0-35)	
Absolute count (/mm ³), median (range)	2585 (610-10 000)	
Atypical lymphocytes [Cases where response is available n = 33]	24	49 [72.7]
Elevated transaminases > 2 limit of normal	41	83.7
Transaminases peak (days after onset of rash) , median (range)	11 (1-35)	
Transaminases resolution (days after onset of rash), median (range)	28 (7-68)	
Kidney	13	26.5
Proteinuria	7	14.3
Creatinine elevation (1.2 ULN; 1.35 ULN; 1.9 ULN; 2.8 ULN; 4.5 ULN)	5	10.2
Electrolyte disturbance	2	4.1
Hematuria	1	2
<i>Patients profiles:</i>	<i>n=13</i>	
Proteinuria only	7	53.8
Creatinine elevation only	4	30.8
Creatinine elevation + Electrolyte disturbance + anuria	1	7.7
Hematuria + Electrolyte disturbance+ polyuria	1	7.7
TSH elevation (8.6 UI/L)	1	2
Lipase elevation (1025 UI/L)	1	2
Biological criteria for Haemophagocytic lymphohistiocytosis ^a	12	24.5
Viral reactivation or infection		
Total positive PCR and/or Serology [Tested cases n = 42]	17	34.7 [40.5]
Positive viral PCR ^b [Tested cases n = 34]	17	34.7 [50]
HHV-6 [Tested cases n = 32]	7	14.3 [21.9]
HHV-7 [Tested cases n = 12]	2	4.1 [16.7]
Parvovirus B19 [Tested cases n = 21]	4	8.2 [19]
EBV [Tested cases n = 29]	4	8.2 [13.8]
CMV [Tested cases n = 31]	2	4.1 [6.5]
Positive serology for IgM [Tested cases n = 26]	3	6.1 [11.5]
EBV ^c [Tested cases n = 24]	2	4.1 [8.3]
VZV ^d	1	2
^a 3 or more of the following criteria: elevated transaminases, bicytopenia, hyperferritinemia >500 ng/ml, lactate dehydrogenase elevation, hypertriglyceridemia >3 mmol/L or hypofibrinemia <1.5g		
^b 34 children were investigated by polymerase chain reaction (PCR) : 17 (44.7%) were positive, including two children with EBV + CMV.		
^c Among the 26 children who had viral serology, 2 had results compatible with EBV primary infection (VCA-IgM positive and no IgG): first case had also a positive parvovirus B19 PCR, and second case had also a positive EBV PCR.		
^d One child had results compatible with VZV primary infection, who is also one of child with the EBV + CMV co-reactivation.		
CE: Creatinine elevation, CMV: Cytomegalovirus, EBV: Epstein-Barr virus, HHV: Human Herpes Virus, PCR: Polymerase Chain Reaction, TSH: thyroid-stimulating hormone; ULN: upper limit of normal; VZV: Varicella-zoster virus		

Table E1: Scoring System for Classifying DRESS Cases as Definite, Probable, Possible, or No Case, from Kardaun et al¹⁰

Score	-1	0	1	2	Minimum	Maximum
Fever $\geq 38.5^{\circ}\text{C}$	No/U	Yes			-1	0
Enlarged lymph nodes		No/U	Yes		0	1
Eosinophilia		No/U			0	2
Eosinophils ($\times 10^9/\text{L}$)			0.7 - 1.499	≥ 1.5		
Eosinophils %, if leukocytes $< 4\text{G/L}$			10 - 19.9	≥ 20		
Atypical lymphocytes		No/U	Yes		0	1
Skin involvement					-2	2
Rash extent (% body surface area)		No/U	$> 50\%$			
Rash suggesting DRESS ¹	No	U	Yes			
Biopsy suggesting DRESS	No	Yes /U				
Organ involvement ²					0	2
Liver		No/U				
Kidney		No/U				
Muscle/heart		No/U				
Pancreas		No/U				
Other organ		No/U				
Resolution ≥ 15 days	No/U	Yes			-1	0
Evaluation of other potential causes						
Antinuclear antibody						
Blood culture						
Serology for HAV/HBV/HCV						
Chlamydia/mycoplasma						
If none positive and ≥ 3 of above negative			Yes		0	1
TOTAL					-4	9

DRESS: Drug Reaction with Eosinophilia and Systemic Symptoms; U: unknown/unclassifiable; HAV: hepatitis A virus; HBV: hepatitis B virus; HCV: hepatitis C virus.

¹Rash suggesting DRESS: ≥ 2 of the following symptoms: purpura, infiltration, facial oedema, scaling

²After exclusion of other explanation: 1, one organ; 2, two or more organs.

Final score: < 2 , no case; 2-3, possible case; 4-5, probable case > 5 , definite case..

Table E2: Patients' and DRESS syndrome characteristics: substratification of possible and probable cases

	TOTAL		Definite cases		Probable Cases	
	n = 49	%	n=27	%	n= 22	%
Age , median (range)	8		7		10.5	
Sex (male)	22	44.9	14	52	8	36.4
Treatment of DRESS syndrome						
None	3	6.1	1	3.7	2	9.1
Topical corticosteroid	25	51	10	37	15	68.2
Systemic corticosteroid	27	55.1	19	70.4	8	36.4
Intravenous Immunoglobulin	6	12.2	4	14.8	2	9.1
Cyclosporin	2	4.1	2	7.4	0	0
Hospitalization in intensive care unit	17	34.7	12	44.4	5	22.7
Duration of stay (days), median (range)	5 (1-26)		5 (1-26)		12 (2-20)	
Duration of hospitalization (days), median (range)	13 (3-60)		15 (3-41)		12.5 (4-60)	
Relapse	11	22.4	7	25.9	4	18.2
Death	2	4.1	2	7.4	0	0
Rash duration* (days), median (range)	20.5 (4-90)		23 (7-90)		14 (4-84)	
< 15 days	11	27.5	2	8.7	9	52.9
15 - 29 days	18	45	12	52.2	6	35.3
≥ 30 days	11	27.5	9	39.1	2	11.8
Internal organ involvement						
Liver (<i>elevated transaminases</i>)	41	83.7	27	100	14	63.6
Kidney	13	26.5	7	25.9	6	27.3
Lung	11	22.4	10	37	1	4.5
Gastrointestinal tract	5	10.2	4	14.8	1	4.5
Heart	1	2	1	3.7	0	0
Central nervous system (meningitis)	1	2	0	0	1	4.5
Eosinophilia > 750 x10 ⁹ /mm ³	39	79.6	24	88.9	15	68.2
Atypical lymphocytes*	24	72.7	19	95	5	38.5
Viral reactivation or infection (<i>Percentage of tested cases for PCR or serology</i>)	17	40.5	11	44	6	35.3
Positive HHV-6 PCR (<i>Percentage of tested cases</i>)	7	21.9	4	20	3	25
Culprit drugs of probable and definite probability according to Naranjo criteria (11)	n = 36 children		n = 21 children		n = 15 children	
Antibiotics	22	61.1	12	57.1	10	66.7
Antiepileptics	11	30.6	8	38.1	3	20

RegiSCAR: Registry of Severe Cutaneous Adverse Reaction; HHV: Human Herpes Virus, PCR: Polymerase Chain Reaction

*percentage of case where answer is available

Table E3: Skin biopsies' results		
Histological findings	n = 27	%
Inflammatory infiltrate	23	85.2
Perivascular inflammatory infiltrate	20	74.1
Civatte's bodies (cytoid bodies)	17	63
Exocytosis	14	51.9
Vacuolization	9	33.3
Presence of eosinophils	9	33.3
Spongiotic dermatitis	7	25.9
Hyperplasic epidermis	6	22.2
Orthokeratosis	4	14.8
Pustules	2	7.4

Table E4: Culprit drugs												
	n	%	Latency ^a (days), mediane (range)	Naranjo ^b (n)			Allergy assessment					
TOTAL	85	100	13 (0-70)	Definite	Probable	Possible	Patch Test			Other		
							Done	+	-	IDR	OPT	LTT
Antibiotics (32 cases)	49	57.6	12 (0-44)	2	24	23						
Penicillins	18	21.2	7 (0-22)									
Piperacillin-Tazobactam	8	9.4	12.5 (2-22)	0	6	2	4	3	1	2-	1+	
Amoxicillin	6	7	3.5 (0-8)	1	3	2	4	1	3	2-		
Oxacillin	2	2.4	19; 21	0	2	0	2	2	0	1-/1+*		
Amoxicillin + Clavulanic Acid	1	1.2	1	0	1	0	1	1	0			
Ampicillin	1	1.2	3	0	0	1						
Trimethoprim- Sulfamethoxazole	5	5.9	17 (5-27)	1	4	0	4	2	2	2-	1+	1+
Sulfadiazine	1	1.2	24	0	0	1						
Vancomycin	7	8.2	11 (3-17)	0	2	5	4	1	3	3-		
Cefadroxil	2	2.4	22; 22	0	2	0	2	2	0			
Cefotaxime	2	2.4	13; 19	0	1	1	1	0	1	1-		
Cefepime	1	1.2	13	0	1	0	1	1	0	1-		
Ciprofloxacin	3	3.5	5; 12; 13	0	0	3	3	0	3			
Levofloxacin	1	1.2	12	0	0	1						
Metronidazole	3	3.5	2; 12; 19	0	0	3	2	0	2	1-		
Rifampicin	2	2.4	1; 44	0	1	1	2	0	2			
Clindamycin	1	1.2	25	0	0	1	1	0	1			
Minocycline	1	1.2	16	0	1	0						
Gentamicin	1	1.2	17	0	0	1	1	0	1	1-		
Imipenem	1	1.2	9	0	0	1						
Antiepileptics (16 cases)	17	20	21 (4-52)	0	11	6						
Carbamazepine	9	10.6	12 (4-38)	0	8	1	2	2	0			
Oxcarbazepine	2	2.4	12; 43	0	1	1	1	1	0			
Levetiracetam	2	2.4	15; 52	0	0	2						
Lamotrigine	2	2.4	7; 40	0	1	1						
Phenobarbital	1	1.2	21	0	1	0						
Stiripentol	1	1.2	47	0	0	1						
Antiinflammatories	4	4.7		0	0	4						
Hydroxychloroquine	1	1.2	4	0	0	1						
Mesalazine (Pentasa)	1		39	0	0	1						
Ibuprofen	1		4	0	0	1	1	0	1	1-		
Colchicine	1		25	0	0	1	1	0	1			
Biologics	2	2.4		0	2	0						
Anakinra (anti-IL1)	1	1.2	7	0	1	0						
Canakinumab (anti-IL1)	1	1.2	70	0	1	0						
Others	13	15.3			1	12						
Esomeprazole	2	2.4	4; 46	0	0	2				1-		
Liposomal Amphotericin B	1		9	0	0	1	1	0	1	1-		1-
Caspofungin	1		19	0	0	1				1+*		
Pyrimethamine	1		24	0	0	1						
Enoxaparin	1		46	0	0	1						
Amisulpride	1	1.2	43	0	0	1						
Clobazam	1		23	0	0	1						
Clozapine	1		35	0	1	0						
Sodium feredetate	1		15	0	0	1	1	0	1			
Nifedipine	1		63	0	0	1						
Ondansetron	1		13	0	0	1	1	0	1	1-		
Furosemide	1		18	0	0	1	1	0	1	1-		

^aDelay between initiation of culprit druag and onset of rash; ^bNaranjo Adverse Reaction Probability Scale (11) (≥9: definite; 5-8: probable; 1-4:

^aDelay between initiation of culprit drug and onset of rash; ^bNaranjo Adverse Reaction Probability Scale (11) (≥9: definite; 5-8: probable; 1-4:

*possible; 0:doubtful); LTT: Lymphocyte transformation test; OPT: Oral provocation test; *Immediate IDR positive only*

Journal Pre-proof

Table E5: Comparison with previous studies

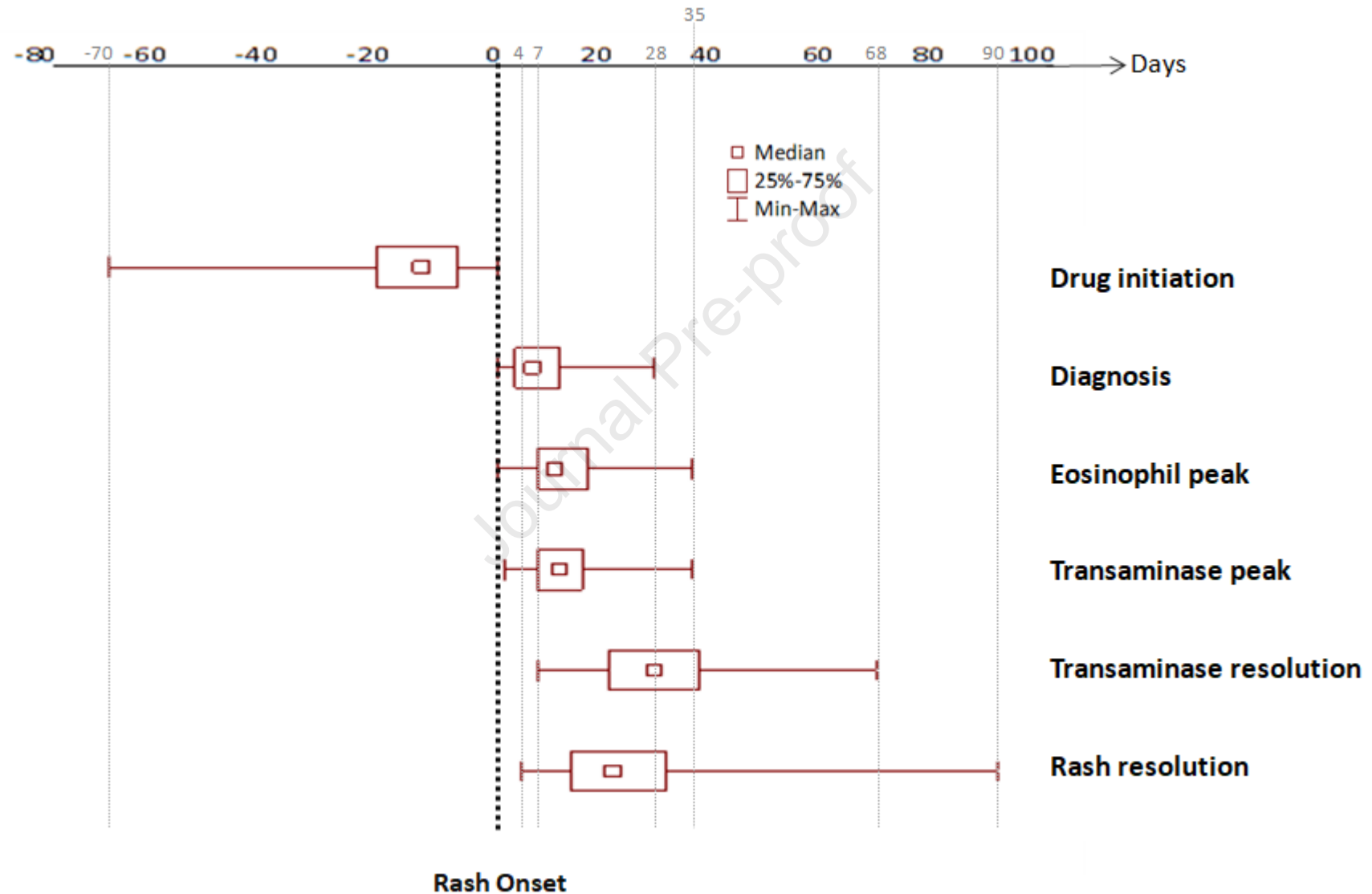
Data	Metterle ^a Pediatric	Newell ^b Pediatric	Our study Pediatric	Kardaun ^c Adult	Cacoub ^d Adult (and pediatric)
Total number of patients	130	32	49	117	124
Age (year)	8.7	9	8	48	40.7
Fever (%)	96.2	100	100	90	71
Skin rash (%)	99.2	100	100	99.2	99
Morbilliform (%)	89.2	U	67.3	15	60
Erythroderma (%)	5.4	43.6	14.3	U	-
Lymphadenopathy (%)	74.6	84.4	69.4	54	65
Facial edema (%)	51.5	71.8	65.3	76	39
Liver (%)	80	90.6	83.7	75	90
Spleen (%)	21.5	U	14.3	15	U
Kidney (%)	15.4	15.6	26.5	37	9
Lung (%)	7.7	15.6	22.4	32	5
Gastrointestinal tract (%)	U	U	10.2	5	U
Eosinophilia > 0.750 x 10 ⁹ L ⁻¹ (%)	90	56	79.6	90	82
Atypical lymphocytes (%)	40.8	71.9	49	40.8	35
HHV6 (% positive of tested cases)	42.9	U	21.9	36	84
Delay between initiation of the culprit drug and onset of rash (days), median (range)	23.8 (3-60)	21(6 - 49)	15 [1-70]*	22 (U)	28(4-112)
Implicated drugs					
Antibiotics (%)	30.8	0	65*	11	14.5
Antiepileptics (%)	50	100	27.5*	35	39.5
Systemic corticosteroids (%)	88.5	59.4	55.1	-	77
IgIV (%)	12.3	15.6	12.2	-	9
Hospital stay (days)	U	10.9	13	17	U
Long term sequelae (%)	10.8	9.4	10.2	U	U
Mortality (%)	5.4	0	4.1	1.7	5.2
^a Metterle et al. (9) Literature Review (1997-2019), "probable" and "definite" cases ^b Newell et al. (19) Retrospective study, antiepileptics (1997-2003); Gastrointestinal tract: percentage of 44% (14 children) but including 2 with pancreatitis ^c Kardaun et al. (18) Prospective study (2003-2009), "probable" and "definite" cases ^d Cacoub et al. (17) Literature Review (1997-2009), (results from the "probable" and "definite" cases group) * Culprit drugs of probable and definite probability according to Naranjo criteria (11), n = 40 drugs for 36 children U = Unspecified, IVIg: Intravenous immunoglobulin					

Figure 1 : 3 years old child with diffuse maculopapular rash, facial edema and cheilitis.



Figure 2. Culprit drug initiation, Clinical & Biological Events Timeline in relation to onset of rash (defined as Day 0)

Drugs of probable and definite probability according to Naranjo criteria (11)



Pediatric DRESS

Investigator :

email address :

City :

Date:

PATIENT : Initial (Last name-First name):..... Sex : M ☐ F ☐ Date of birth :/...../.....

Comorbidities (medical and surgical history) :.....

Known allergies (specify if documented or suspected):.....

Regular treatment :

HISTORY OF DISEASECurrent infectious context: YES ☐ NO ☐ Unknown ☐

Date of onset of rash:/...../..... Date of hospitalization :/...../.....

Date of diagnosis of DRESS:/...../..... Specialist establishing the diagnosis:

Other suggested diagnosis(es):

CULPRIT DRUGS :

1) Posology : Indication :

Date of introduction :/...../..... Date of discontinuation :/...../.....

If long-standing treatment: was it at any time discontinued? YES ☐ NO ☐ Unknown ☐

[specify dates/reason:]

If recent treatment: has it been received before? YES ☐ [year :] NO ☐ Unknown ☐

2) Posology : Indication :

Date of introduction :/...../..... Date of discontinuation :/...../.....

If long-standing treatment: was it at any time discontinued? YES ☐ NO ☐ Unknown ☐

[specify dates/reason:]

If recent treatment: has it been received before? YES ☐ [year :] NO ☐ Unknown ☐

3) Posology : Indication :

Date of introduction :/...../..... Date of discontinuation :/...../.....

If long-standing treatment: was it at any time discontinued? YES ☐ NO ☐ Unknown ☐

[specify dates/reason:]

If recent treatment: has it been received before? YES ☐ [year :] NO ☐ Unknown ☐

4)...

CLINICAL FEATURES :Fever ($T^{\circ} > 38.5$) : YES ☐ NO ☐ Unknown ☐Rash : Erythema ☐ Papules ☐ Purpura ☐ Eczema-like ☐ Pustules ☐Erythroderma ☐ No rash ☐ Other : Body surface area : % [Unknown ☐]Pruritus : YES ☐ NO ☐ Unknown ☐ Pain : YES ☐ NO ☐ Unknown ☐Œdema : YES ☐ NO ☐ Unknown ☐ location : Mucosal involvement : YES ☐ NO ☐ Unknown ☐ Location : Lymphadenopathy : YES ☐ NO ☐ Unknown ☐ Location :**BIOLOGICAL CHARACTERISTICS :** For biological values, **max rate** = the highest rate reached during the follow-up.Atypical lymphocytes : YES ☐ [max rate, date :] NO ☐ Unknown ☐Éosinophilie : YES ☐ [max rate, date :] NO ☐ Unknown ☐

Others blood count abnormalities:

Elevated transaminases : YES ☐ NO ☐ Unknown ☐

[max rate, date AST :, max rate, date ALT :]

Kidney involvement: YES ☐ [creatinine max rate, date:] NO ☐ Unknown ☐Proteinuria : YES ☐ [max rate, date:] NO ☐ Unknown ☐Haemophagocytic lymphohistiocytosis: YES ☐ [date:] NO ☐ Unknown ☐☐ hyperferritinemia:, ☐ hypertriglyceridemia:, ☐ LDH elevation:**Virus :** for each item, tick if tested, circle PCR result, specify serology result:

Virus	PCR	Serology	Virus	PCR	Serology
☐ HHV6	☐ + / -	☐	☐ CMV	☐ + / -	☐
☐ HHV7	☐ + / -	☐	☐ Parvovirus B19	☐ + / -	☐
☐ HHV8	☐ + / -	☐	other :	☐ + / -	☐
☐ EBV	☐ + / -	☐	other :	☐ + / -	☐

OTHER INTERNAL ORGAN INVOLVEMENT :Hepatomegaly : YES ☐ NO ☐ Unknown ☐ Splenomegaly : YES ☐ NO ☐ Unknown ☐Pancreas : YES ☐ NO ☐ Unknown ☐ specify: Heart : YES ☐ NO ☐ Unknown ☐ specify: Lung : YES ☐ NO ☐ Unknown ☐ specify:

Others :

SPECIFIC TREATMENT OF DRESS (topical and/or systemic) : YES ☐ NO ☐ Unknown ☐

- 1) Posology : Date of introduction : .../.../... Date of discontinuation : .../.../...
 2) Posology : Date of introduction : .../.../... Date of discontinuation : .../.../...
 3) Posology : Date of introduction : .../.../... Date of discontinuation : .../.../...
 4) ...

EVOLUTION :

Hospitalization in intensive care unit : YES ☐ NO ☐ Unknown ☐ [duration of stay.....]

Date of hospital discharge:/...../..... **Death** ☐ [Cause :]

Number of follow-up consultations: [Unknown ☐

Date of last consultation:/...../..... [Unknown ☐] **Loss to follow-up** ☐

Date of resolution of symptoms:

Skin :/...../..... [Unknown ☐]

Others : •/...../..... •/...../.....
 •/...../..... •/...../.....

Date of resolution of biological disturbances: •/...../.....

•/...../..... •/...../..... •/...../.....

Relaps (without reintroduction of the culprit drug) : YES ☐ NO ☐ Unknown ☐

Specify : date/duration/treatment :

Sequelae : No ☐ Hypothyroidism ☐ Diabetes ☐ Cushing's syndrome (iatrogenic) ☐

Cutaneous abnormalities ☐

Others (specify) :

ALLERGY ASSESSMENT: YES ☐ [date :/...../.....] NO ☐ Unknown ☐

Results :

REINTRODUCTION OF CULPRIT DRUG(S): YES ☐ NO ☐ Unknown ☐

Date :/...../..... Drug(s) :

Protocole :

Reaction : YES ☐ NO ☐ Unknown ☐ [Specify :]

SKIN BIOPSY : YES ☐ NO ☐ *Please provide the pathology report*