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1 **Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS) :**

2 **Series of 49 French pediatric cases**

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43 **Abstract**

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

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

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

51 **Results:** We included 49 cases. All children had fever and rash, 69.4% had lymphadenopathy
52 and 65.3% had facial edema. The most common organ affected was the liver (83.7%).
53 Treatment consisted in topical corticosteroid only for 30.6%, systemic corticosteroid for
54 55.1%; 12.2 % received IVIg. Among culprit drugs of probable and certain probability, 65%
55 were antibiotics and 27.5% antiepileptics, with a median time to DRESS symptom onset after
56 initiation of 15 days (13 days with antibiotics and 21 days with antiepileptics). Twenty-seven
57 children had allergy assessment for causative agents: 65.4% had positive tests.

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

63 **Highlights box**

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

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

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

75

76 **Key words**

77 Drug Reaction with Eosinophilia and Systemic Symptoms; DRESS; pediatric, children; antibiotics,
78 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
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

96 Introduction

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

118 **Materials and methods**

119 We performed a retrospective study of DRESS syndrome diagnosed between 2000 and 2020
120 among pediatric population in 15 French hospitals. The clinical study was conducted in
121 accordance with the relevant versions of the French Public Health Code, national and
122 international good clinical practice (GCP) guidelines, and the Declaration of Helsinki, each in
123 the applicable version. Our study was submitted to and approved by the local Research
124 Ethics Committee (GNEDS) of Loire-Atlantique on Septembre 1, 2020. The Regiscar score
125 (10) was used to establish the diagnosis of DRESS (Table E1, available in Online Repository
126 Text). The inclusion criteria were: (i) diagnosis of DRESS, (ii) RegiSCAR score ≥ 4 , (iii) age ≤ 18
127 years and (iv) at least one suspected drug. Standardized questionnaires (available in Online
128 Repository Text) were used to collect data from the patient's medical record. Investigators
129 were members of Clinical Research Unit of the French Society of Pediatric Dermatology
130 (GRC-SFDP)) or the French Investigators for Skin Adverse Reactions to Drugs group (FISARD)
131 of the French Society of Dermatology. In each centre, cases were identified by
132 dermatologists, allergologists, pediatricians and the pharmacovigilance centre. We collected
133 data about demographics, suspected culprit drugs, clinical and laboratory data, treatment of
134 DRESS and testing suspect drugs. Liver involvement was defined by a twofold or greater
135 increase of transaminases compared to normal values. Kidney involvement was defined by
136 elevated creatinine, proteinuria, anuria or electrolyte disturbance. The different drugs, dates
137 of introduction and discontinuation were documented. Suspected drugs were defined as all
138 drugs started within 12 weeks before the onset of the rash and still administered or stopped
139 less than five half-lives before rash onset. We determined the causality of drugs according to
140 the Naranjo Adverse Reaction Probability Scale (APS) (11). In the case of a confirmed
141 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 (%).

145 **Results**

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

150

151 **Characteristics**

152 Patient's and DRESS syndrome's characteristics are summarized in Table 1. The median age
153 was eight years (range: 5 weeks - 18 years) and 44.9% were male. Three children (6.1%) had
154 previously experienced a drug-induced skin reaction (two with unspecified rash, one with
155 urticaria), two of them to the same drug as the DRESS syndrome (one with
156 sulfamethoxazole-trimethoprim and one with penicillin). Eight children (16.3%) were
157 immunocompromised. The DRESS occurred during a hospital stay in 24.5%. According to the
158 RegiSCAR score, 55.1% were definite and 44.9% were probable DRESS syndrome
159 (characteristics of each group are available in Table E2 in Online Repository Text). The
160 diagnosis of DRESS syndrome was made in a median time of six days after rash onset (range:
161 0-28). A differential diagnosis was presumed for 22 children (44.9%) (viral infection in
162 63.6%, Kawasaki disease in 22.7%). The majority of diagnoses were made by dermatologists
163 (57.1% of cases), while pediatricians provided the diagnosis in 12.1% of cases (Table 1).

164

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

169 described in 14.3%. Pruritus was reported in 67.3% and facial edema in 65.3% (Figure 1).
170 Lymphadenopathy was observed in 69.4%. Mucosal involvement was described in 40.8%
171 (associated cheilitis in 30.6% (Figure 2), mouth ± throat involvement in 16.3% and
172 conjunctivitis in 10.2%). The most commonly affected organs were the liver (41 children,
173 83.7%), kidneys (13 children, 26.5%; associated with isolated proteinuria in 54% of cases and
174 moderate creatinine elevation in 38% of cases), lungs (11 children, 22.4%) and
175 gastrointestinal tract (five children, 10.2%). Myocarditis was described in one case and
176 meningitis in one. Biological abnormalities are detailed in Table 3. Eosinophilia (absolute
177 count > 500/mm³) was present in 85.7% and atypical lymphocytes were observed in 49%. An
178 investigation for viral reactivation or primary infection was conducted for 42 children (18 by
179 serology and polymerase chain reaction [PCR], 16 PCR only and eight serology only). Among
180 the 34 children who were investigated by PCR, 17 (50%) were positive. Among them, 32
181 were tested for HHV-6 : seven were positive (21.9%); four were positive for Parvovirus B19,
182 four for Epstein-Barr virus (EBV), two for HHV-7 and two for cytomegalovirus (CMV),
183 including two children with co-infection EBV and CMV. Twelve children (24.5%) had
184 biological criteria for haemophagocytic lymphohistiocytosis (HLH) (14).

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

191

192 **Course and treatment**

193 Median duration of eruption was 20.5 days (range: 4-90), this persisted more than 15 days in
194 72.5%. Median time from the beginning of the rash to maximal count of eosinophils was 10
195 days (range: 0-35), and to maximal rate of transaminase elevation 11 days (1-35). Median
196 time of resolution of transaminase was 28 days (7-68) after onset of rash (Figure 2).
197 Seventeen (34.7%) children were transferred to an intensive care unit (median duration stay
198 five days, range: 1-26). One child died from cardiopulmonary arrest due to myocarditis and
199 one child died from septic and hypovolemic shock complicated by multivisceral failure
200 syndrome in a context of erythroderma. Median duration of hospitalization was 13 days
201 (range: 3-60): 10 days (range: 3-39) for community cases and 22 days (range: 12-60) for
202 hospital cases. Specific treatments of DRESS syndrome are summarized in Table 1; 51%
203 received topical corticosteroid (TS) and 55.1% systemic corticosteroids (SC) (median duration
204 for SC: 42.5 days (range: 1-546), introduced at a dose of 2mg/kg in 36.4% of cases, 1mg/kg in
205 54.5% and 0.5 mg/kg in 9.1% of cases). Children treated with TS only appeared to have less
206 severe presentation than those who received SC therapy with a shorter duration of rash (16
207 days versus 23.5 days, respectively) and 13% of hospitalization in intensive care versus 48%,
208 respectively. Six cases (12.2%) received intravenous immunoglobulin (IVIg) (for three
209 patients, this was due to the initial hypothesis of Kawasaki disease) and two cases (4.1%)
210 received ciclosporin. Thirty-six patients (73.5%) were followed after discharge : the median
211 number of consultations was three (range: 1-10) and the median follow-up was 8.8 months
212 (range: 3 days - 5.8 years). A relapse was noted in 11 cases (22.4%), within a delay of six
213 weeks to six months after the resolution of eruption for six cases (54.5%). Relapse was
214 attributed to the decrease or cessation of corticosteroid therapy in three cases (27.3%).
215 Long-term sequelae were observed in five patients (10.2%): one with vitiligo, one with
216 hyperpigmentation and one systemic lupus revealed a year after resolution of DRESS (with

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

225

226 **Causative drugs**

227 Among the 85 medications suspected of inducing DRESS, 49 (57.6%) were antibiotics and 17
228 (20%) antiepileptics. The median time of DRESS onset after introduction was 13 days (range:
229 0-70) (antibiotics: 12, range: 0-44; antiepileptics: 21, range : 4-52). If one calculates this for
230 drugs of definite or probable imputability only according to the APS (11) (40 drugs): 26 (65%)
231 were antibiotics and 11 (27.5%) antiepileptics. The delay of onset was 15 days (range: 1-44)
232 (antibiotics: 13, antiepileptics: 21) and 47.5% of the drugs have a delay < 15 days (13
233 antibiotics and five antiepileptics).

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

238

239 **Tests**

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

252

253 Discussion

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

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

264 observations made in previous adults (17,18) and pediatric (9,19–23) series. The percentage
265 of lung involvement (22.4%) is comparable to the adult cohorts described by Lee et al. (24)
266 and Kardaun et al. (18) (20% and 32% respectively); the most common manifestations were
267 interstitial infiltrates (27%) and acute respiratory distress syndrome (27%) as described in
268 the systematic review by Taweeseedt and al. (25). Five children presented with diarrhea
269 (10%), one of them with vomiting. None of them had histological investigations. Digestive
270 tract involvement is poorly described in the different cohorts of adults or children. When
271 described, the symptoms are non-specific and are not investigated. In the study by Newell et
272 al (19), 44% of children presented with digestive involvement, including 57% with vomiting,
273 29% with diarrhea and 29% with bloody diarrhea. A few cases of oesophagitis and/or
274 inflammatory colitis up to and including ulcerative colitis have been reported (26,27). The
275 number of HHV-6 reactivations (22%) was lower than in previous studies (43% and 36%)
276 (9,18).

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

281

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

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

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

291

292 There is currently no consensus on the therapeutic management of DRESS, as there are no
293 randomized controlled trials evaluating the efficacy of the different treatments. Topical
294 corticosteroids (TS) are proposed for non-severe DRESS, whilst in the case of internal organ
295 involvement, treatment with a systemic corticosteroid (SC) is recommended (31,32). In our
296 study, 31% received only TS. These cases appeared to be less severe than those who
297 received SC therapy (13% of hospitalization in intensive care versus 48%). Furthermore, the
298 rash appears to resolve more rapidly (16 days versus 23.5 days). These results are consistent
299 with those of Funck-Brentano et al.(33) and Uhara et al.(34) who suggested that TS can be
300 used in patients with non-severe DRESS. Treatment with SC might favor relapse (30) and is
301 often prolonged and carries an infection risk (35,36). In the various observational studies and
302 literature reviews, SC have been used in 43-100% of cases in both adults and children
303 (9,17,19, 21, 23), while the use of TS is rarely mentioned (9% of children in the cohort by
304 Newell et al. (19) and 21% in the cohort by Bessmertny et al. (21)).

305 In our study, six children received IVIg, with a median duration of the rash of 15 days (versus
306 21 days for the other cases in the cohort). Treatment with IVIg has been described in a few
307 severe cases with variable results (37–39). A recent series of seven pediatric cases showed
308 that a treatment combining IVIg and SC led to a rapid improvement of the children's general
309 condition (40). On another hand, in a series of six adult cases treated with IVIg alone, five
310 patients had severe adverse events, suggesting that IVIg must not be used as stand-alone
311 treatment in DRESS (37). Ciclosporin has been proposed when SC are contraindicated or in

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

320

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

327

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

331

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

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

338

339 **Conclusion:**

340 Due to the diversity of its clinical and biological presentation, the diagnosis of DRESS
341 syndrome is difficult. This often leads to a delay in diagnosis and cessation of culprit drugs.

342 This series shows that the onset of DRESS syndrome in the pediatric population is often less
343 than two weeks after the treatment starts, especially when it involves antibiotics. The initial

344 management will consist of stopping suspected culprit drug(s), i.e. those introduced in the
345 last three months. Clinical and biological signs of DRESS should be closely monitored over a

346 long period of time, as the condition may worsen despite the cessation of the drug(s).

347 Treatment with topical corticosteroids appears sufficient in the least severe cases.

348 Treatment by systemic corticosteroid therapy remains the reference treatment in case of
349 severe organ damage, and the place of IVIg remains to be determined.

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353 **References**

- 354 1. Cho Y-T, Yang C-W, Chu C-Y. Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS):
355 An Interplay among Drugs, Viruses, and Immune System. *Int J Mol Sci*. 2017 Jun 9;18(6):1243.
- 356 2. White KD, Chung W-H, Hung S-I, Mallal S, Phillips EJ. Evolving models of the
357 immunopathogenesis of T-cell mediated drug allergy: the role of host, pathogens, and drug
358 response. *J Allergy Clin Immunol*. 2015 Aug;136(2):219–34.
- 359 3. Bharadwaj M, Illing P, Theodossis A, Purcell AW, Rossjohn J, McCluskey J. Drug Hypersensitivity
360 and Human Leukocyte Antigens of the Major Histocompatibility Complex. *Annu Rev Pharmacol*
361 *Toxicol*. 2012 Feb 10;52(1):401–31.
- 362 4. Redwood AJ, Pavlos RK, White KD, Phillips EJ. HLAs: Key regulators of T-cell-mediated drug
363 hypersensitivity. *HLA*. 2018;91(1):3–16.
- 364 5. Picard D, Janela B, Descamps V, D’Incan M, Courville P, Jacquot S, et al. Drug reaction with
365 eosinophilia and systemic symptoms (DRESS): a multiorgan antiviral T cell response. *Sci Transl*
366 *Med*. 2010 Aug 25;2(46):46ra62.
- 367 6. Criado PR, Criado RFJ, Avancini J de M, Santi CG. Drug reaction with Eosinophilia and Systemic
368 Symptoms (DRESS) / Drug-induced Hypersensitivity Syndrome (DIHS): a review of current
369 concepts. *An Bras Dermatol*. 2012 Jun;87(3):435–49.
- 370 7. Shiohara T, Ushigome Y, Kano Y, Takahashi R. Crucial Role of Viral Reactivation in the
371 Development of Severe Drug Eruptions: a Comprehensive Review. *Clin Rev Allergy Immunol*.
372 2015 Oct;49(2):192–202.
- 373 8. Descamps V, Ranger-Rogez S, Musette P, Barbaud A. Le DRESS (drug reaction with eosinophilia
374 and systemic symptoms): une synergie médicaments-virus qui peut conduire en réanimation.
375 *Réanimation*. 2011 May;20(3):223–7.
- 376 9. Metterle L, Hatch L, Seminario-Vidal L. Pediatric drug reaction with eosinophilia and systemic
377 symptoms: A systematic review of the literature. *Pediatr Dermatol*. 2020 Jan;37(1):124-129.
- 378 10. Kardaun SH, Sidoroff A, Valeyrie-Allanore L, Halevy S, Davidovici BB, Mockenhaupt M, et al.
379 Variability in the clinical pattern of cutaneous side-effects of drugs with systemic symptoms:
380 does a DRESS syndrome really exist? *Br J Dermatol*. 2007;156(3):609-611.

- 381 11. Naranjo CA, Busto U, Sellers EM, Sandor P, Ruiz I, Roberts EA, Janecek E, Domecq C, Greenblatt
382 DJ. A method for estimating the probability of adverse drug reactions. *Clin Pharmacol Ther.*
383 1981 Aug;30(2):239-45.
- 384 12. Descamps V, Brunet-Possenti F. Drug Reaction with Eosinophilia and Systemic Symptoms or
385 Virus Reactivation with Eosinophilia and Systemic Symptoms. *Pediatr Dermatol.* 2016
386 Sep;33(5):562.
- 387 13. Dondi A, Parladori R, Mori F, Liccioli G, Bassi A, Lanari M et al. Viral rashes mimicking drug
388 reaction with eosinophilia and systemic symptoms syndrome in children after β -lactams intake:
389 a diagnostic challenge. *Eur J Pediatr.* 2021 Mar 9.
- 390 14. Risma KA, Marsh RA. Hemophagocytic Lymphohistiocytosis: Clinical Presentations and
391 Diagnosis. *J Allergy Clin Immunol Pract.* 2019 Mar;7(3):824-832.
- 392 15. Brockow K, Romano A, Blanca M, Ring J, Pichler W, Demoly P. General considerations for skin
393 test procedures in the diagnosis of drug hypersensitivity. *Allergy.* 2002 Jan;57(1):45-51.
- 394 16. Brockow K, Garvey LH, Aberer W, Atanaskovic-Markovic M, Barbaud A, Bilo MB et al.;
395 ENDA/EAACI Drug Allergy Interest Group. Skin test concentrations for systemically
396 administered drugs -- an ENDA/EAACI Drug Allergy Interest Group position paper. *Allergy.* 2013
397 Jun;68(6):702-12.
- 398 17. Cacoub P, Musette P, Descamps V, Meyer O, Speirs C, Finzi L, et al. The DRESS Syndrome: A
399 Literature Review. *Am J Med.* 2011 Jul;124(7):588–97.
- 400 18. Kardaun SH, Sekula P, Valeyrie-Allanore L, Liss Y, Chu CY, Creamer D, et al. Drug reaction with
401 eosinophilia and systemic symptoms (DRESS): an original multisystem adverse drug reaction.
402 Results from the prospective RegiSCAR study. *Br J Dermatol.* 2013 Nov;169(5):1071–80.
- 403 19. Newell BD, Moinfar M, Mancini AJ, Nopper AJ. Retrospective Analysis of 32 Pediatric Patients
404 with Anticonvulsant Hypersensitivity Syndrome (ACHSS). *Pediatr Dermatol.* 2009;26(5):536–46.
- 405 20. Ahluwalia J, Abuabara K, Perman MJ, Yan AC. Human herpesvirus 6 involvement in paediatric
406 drug hypersensitivity syndrome. *Br J Dermatol.* 2015;172(4):1090–5.
- 407 21. Bessmertny O, Hatton RC, Gonzalez-Peralta RP. Antiepileptic hypersensitivity syndrome in
408 children. *Ann Pharmacother.* 2001 May;35(5):533-8.

- 409 22. Sasidharanpillai S, Sabitha S, Riyaz N, Binitha MP, Muhammed K, Riyaz A, et al. Drug Reaction
410 with Eosinophilia and Systemic Symptoms in Children: A Prospective Study. *Pediatr Dermatol.*
411 2016 Mar;33(2):e162–5.
- 412 23. Han XD, Koh MJ -A., Wong SMY. Drug reaction with eosinophilia and systemic symptoms in a
413 cohort of Asian children. *Pediatr Dermatol.* 2019 May;36(3):324–9.
- 414 24. Lee JY, Lee SY, Hahm JE, Ha JW, Kim CW, Kim SS. Clinical features of drug reaction with
415 eosinophilia and systemic symptoms (DRESS) syndrome: a study of 25 patients in Korea. *Int J*
416 *Dermatol.* 2017 Sep;56(9):944-951.
- 417 25. Taweeseedt PT, Nordstrom CW, Stoeckel J, Dumic I. Pulmonary Manifestations of Drug Reaction
418 with Eosinophilia and Systemic Symptoms (DRESS) Syndrome: A Systematic Review. *Biomed Res*
419 *Int.* 2019 Sep 24;2019:7863815.
- 420 26. Do-Pham G, Charachon A, Duong TA, Thille AW, Benhaïem N, Bagot M, Chosidow O, Roujeau JC,
421 Wolkenstein P, Valeyrie-Allanore L. Drug reaction with eosinophilia and systemic symptoms and
422 severe involvement of digestive tract: description of two cases. *Br J Dermatol.* 2011
423 Jul;165(1):207-9.
- 424 27. Eland IA, Dofferhoff AS, Vink R, Zondervan PE, Stricker BH. Colitis may be part of the
425 antiepileptic drug hypersensitivity syndrome. *Epilepsia.* 1999 Dec;40(12):1780-3.
- 426 28. Bocquet H, Bagot M, Roujeau JC. Drug-induced pseudolymphoma and drug hypersensitivity
427 syndrome (Drug Rash with Eosinophilia and Systemic Symptoms: DRESS). *Semin Cutan Med*
428 *Surg.* 1996 Dec;15(4):250–7.
- 429 29. Shiohara T, Inaoka M, Kano Y. Drug-induced Hypersensitivity Syndrome(DIHS): A Reaction
430 Induced by a Complex Interplay among Herpesviruses and Antiviral and Antidrug Immune
431 Responses. *Allergol Int.* 2006 Jan 1;55(1):1–8.
- 432 30. Soria A, Bernier C, Veyrac G, Barbaud A, Puymirat E, Milpied B. Drug reaction with eosinophilia
433 and systemic symptoms may occur within 2 weeks of drug exposure: A retrospective study. *J*
434 *Am Acad Dermatol.* 2020 Mar;82(3):606-611.
- 435 31. Descamps V, Ben Saïd B, Sassolas B, Truchetet F, Avenel-Audran M, Girardin P, et al. Prise en
436 charge du drug reaction with eosinophilia and systemic symptoms (DRESS). *Ann Dermatol*
437 *Vénérologie.* 2010 Nov;137(11):703–8.

- 438 32. Husain Z, Reddy BY, Schwartz RA. DRESS syndrome. *J Am Acad Dermatol*. 2013
439 May;68(5):709.e1-709.e9.
- 440 33. Funck-Brentano E, Duong T-A, Bouvresse S, Bagot M, Wolkenstein P, Roujeau J-C, et al.
441 Therapeutic management of DRESS: A retrospective study of 38 cases. *J Am Acad Dermatol*.
442 2015 Feb;72(2):246–52.
- 443 34. Uhara H, Saiki M, Kawachi S, Ashida A, Oguchi S, Okuyama R. Clinical course of drug-induced
444 hypersensitivity syndrome treated without systemic corticosteroids: DIHS treated without
445 systemic corticosteroids. *J Eur Acad Dermatol Venereol*. 2013 Jun;27(6):722–6.
- 446 35. Kano Y, Horie C, Inaoka M, Ishida T, Mizukawa Y, Shiohara T. Herpes Zoster in Patients with
447 Drug-induced Hypersensitivity Syndrome/DRESS. *Acta Derm Venereol*. 2012;92(2):206–7.
- 448 36. Ushigome Y, Kano Y, Ishida T, Hirahara K, Shiohara T. Short- and long-term outcomes of 34
449 patients with drug-induced hypersensitivity syndrome in a single institution. *J Am Acad*
450 *Dermatol*. 2013 May;68(5):721–8.
- 451 37. Joly P, Janela B, Tetart F, Rogez S, Picard D, D’Incan M, et al. Poor Benefit/Risk Balance of
452 Intravenous Immunoglobulins in DRESS. *Arch Dermatol*. 2012 Apr 1;148(4):543–4.
- 453 38. Kito Y, Ito T, Tokura Y, Hashizume H. High-dose Intravenous Immunoglobulin Monotherapy for
454 Drug-induced Hypersensitivity Syndrome. *Acta Derm Venereol*. 2012;92(1):100–1.
- 455 39. Comfere NI, Sartori-Valinotti JC, Bruce AJ, Drage LA. Successful treatment of lamotrigine-
456 associated drug hypersensitivity syndrome with intravenous IgG. *J Am Acad Dermatol*. 2012
457 Jun;66(6):e249–50.
- 458 40. Marcus N, Smuel K, Almog M, Prais D, Straussberg R, Landau D, et al. Successful Intravenous
459 Immunoglobulin Treatment in Pediatric Severe DRESS Syndrome. *J Allergy Clin Immunol Pract*.
460 2018 Jul;6(4):1238–42.
- 461 41. Kuschel SL, Reedy MS. Cyclosporine treatment of drug reaction with eosinophilia and systemic
462 symptoms (DRESS) syndrome: a case report and brief review of the literature. *Pract Dermatol*.
463 2018 Oct;2018:41-43.
- 464 42. Ton A, Kassab L, Patel A, Dawson N. Severe acute hepatitis in drug reaction with eosinophilia
465 and systemic symptoms (DRESS) syndrome resolved following cyclosporine. *J Allergy Clin*
466 *Immunol Pract*. 2020 Jan 1;8(1):398–400.

- 467 43. Harman KE, Morris SD, Higgins EM. Persistent anticonvulsant hypersensitivity syndrome
468 responding to ciclosporin. *Clin Exp Dermatol.* 2003;28(4):364–5.
- 469 44. Chen Y-C, Chang C-Y, Cho Y-T, Chiu H-C, Chu C-Y. Long-term sequelae of drug reaction with
470 eosinophilia and systemic symptoms: A retrospective cohort study from Taiwan. *J Am Acad*
471 *Dermatol.* 2013 Mar 1;68(3):459–65.
- 472 45. Lonowski S, Hau J, Worswick S. Vitiligo: a potential autoimmune sequela of DRESS syndrome. *Br*
473 *J Dermatol.* 2016;175(3):642–4.
- 474 46. Kano Y, Tohyama M, Aihara M, Matsukura S, Watanabe H, Sueki H, et al. Sequelae in 145
475 patients with drug-induced hypersensitivity syndrome/drug reaction with eosinophilia and
476 systemic symptoms: Survey conducted by the Asian Research Committee on Severe Cutaneous
477 Adverse Reactions (ASCAR). *J Dermatol.* 2015;42(3):276–82.
- 478 47. Aota N, Hirahara K, Kano Y, Fukuoka T, Yamada A, Shiohara T. Systemic Lupus Erythematosus
479 Presenting with Kikuchi-Fujimoto’s Disease as a Long-Term Sequela of Drug-Induced
480 Hypersensitivity Syndrome. *Dermatology.* 2009;218(3):275–7.
- 481 48. Lehloenya RJ, Peter JG, Copascu A, Trubiano JA, Phillips EJ. Delabeling Delayed Drug
482 Hypersensitivity: How Far Can You Safely Go? *J Allergy Clin Immunol Pract.* 2020 Oct;8(9):2878-
483 2895.e6.
- 484 49. Barbaud A, Collet E, Milpied B, Assier H, Staumont D, Avenel-Audran M, et al. A multicentre
485 study to determine the value and safety of drug patch tests for the three main classes of severe
486 cutaneous adverse drug reactions. *Br J Dermatol.* 2013;168(3):555–62.

487 **Figure and Table Legends**

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

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

491
492 This box-plot reports the time between drug initiation (drugs of probable and definite
493 probability according to Naranjo criteria (11)) in relation to the onset of the rash (left side)
494 and time between diagnosis of DRESS syndrome, biological parameters (eosinophil and
495 transaminase peak, transaminase resolution) and rash resolution in relation to the onset of
496 the rash (right side).

497 **Table 1. Demographics and characteristics of patients and DRESS syndrome**

498

499 **Table 2. Clinical features**

500 **Table 3. Biological characteristics**

501

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)

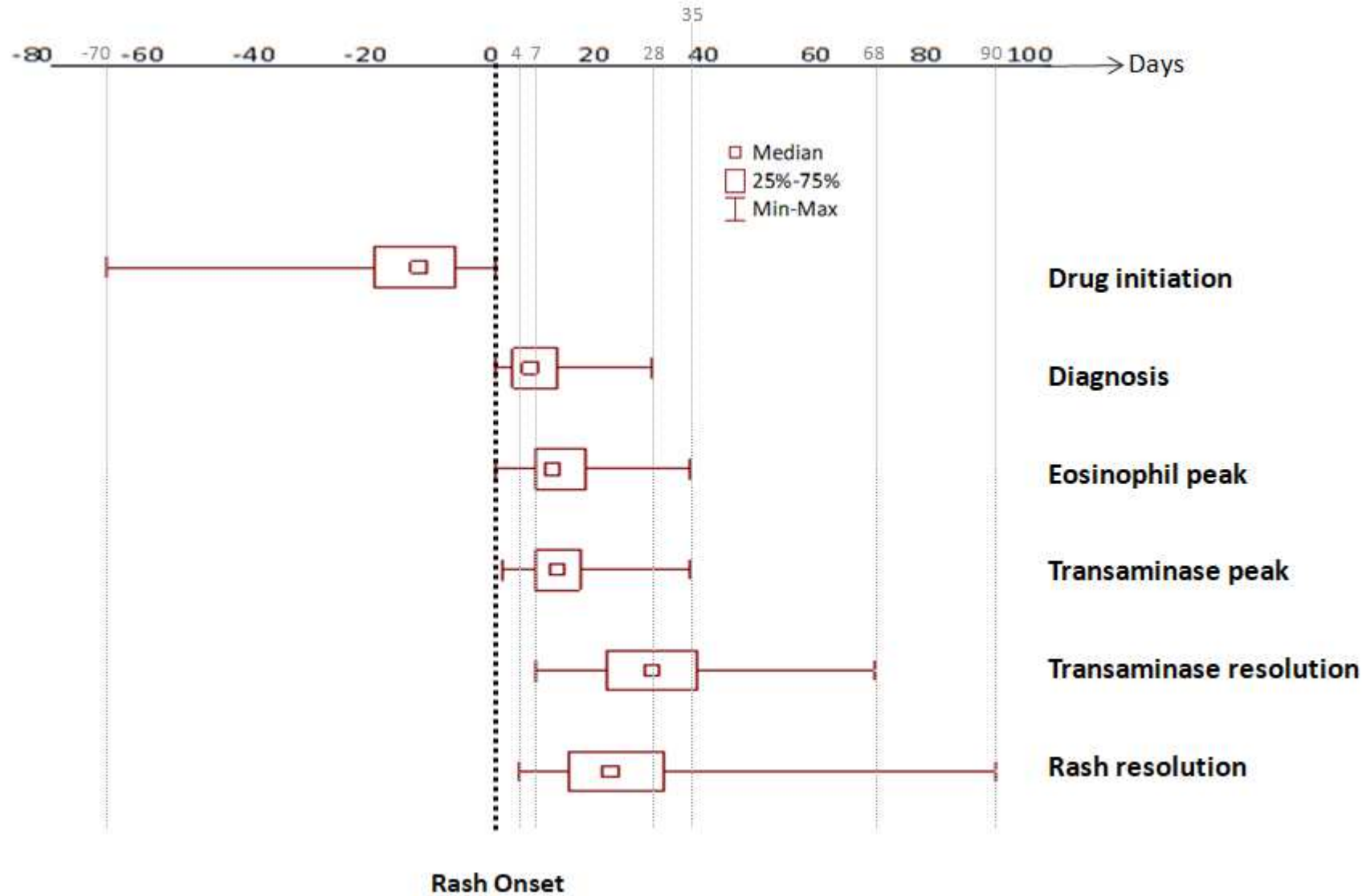


Table 1: Demographics and characteristics of patients and DRESS syndrome

		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	
				28.6
Differential diagnosis [n = 22 children]	Viral infection	14	[63.6]	
	Kawasaki disease	5	10.2	
				[22.7]
	Others	7	14.3	
	Exanthem following amoxicillin during mononucleosis			
	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
			27	
	Systemic therapy	Systemic corticosteroid (median duration)	14 (42.5 days)	55.1
		IV then oral	3 (2 days)	24.5
		IV only		10.2
		Oral only	10 (44.5 days)	20.4
		Intravenous Immunoglobulin		
		Cyclosporin	6	12.2
		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		

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 profils:</i>	<i>n=13</i>	
<i>Proteinuria only</i>	7	53.8
<i>Creatinine elevation only</i>	4	30.8
<i>Creatinine elevation + Electrolyte disturbance + anuria</i>	1	7.7
<i>Hematuria + Electrolyte disturbance+ polyuria</i>	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 deshydrogease 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		