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DRESS and AGEF Reactions to Iodinated Contrast Media: A French Case Series

Angèle Soria, Emmanuelle Amsler, Claire Bernier, Brigitte Milpied, Florence Tétart, Cécile Morice, Frédéric Dezoteux, Marie-Christine Ferrier-Le Bouedec, Annick Barbaud, Delphine Staumont-Sallé, et al.

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6

7 Angèle Soria* (1) MD, PhD, Emmanuelle Amsler* (2) MD, Claire Bernier (3) MD, Brigitte Milpied
8 (4) MD, Florence Tétart (5) MD, Cécile Morice (6) MD, Frédéric Dezoteux (7) MD, Marie-Christine
9 Ferrier-Le Bouedec (8) MD, Annick Barbaud (2) MD, PhD, Delphine Staumont-Sallé (7), MD, PhD,
10 Haudrey Assier (9) MD, on behalf of the FISARD group.

11 (1) Sorbonne Universités, Paris, Service de Dermatologie et d'Allergologie, Hôpital Tenon, Paris
12 HUEP, APHP, Paris, France. Centre d'Immunologie et des Maladies Infectieuses – Paris
13 (Cimi-Paris), INSERM U1135, Paris, France

14 (2) Sorbonne Universités, Paris, Service de Dermatologie et d'Allergologie, Hôpital Tenon, Paris
15 HUEP, APHP, Paris, France.

16 (3) Service de Dermatologie, Hôpital Hôtel Dieu, CHU Nantes

17 (4) Service de Dermatologie, Hôpital Saint André, Bordeaux

18 (5) Clinique dermatologique CHU de Rouen et Centre Erik Satie, Allergologie CHU Rouen

19 (6) Service de Dermatologie, Caen

20 (7) Service de Dermatologie, Hôpital Claude Huriez, CHU Lille

21 (8) Service de Dermatologie, CHU Estaing, Clermont-Ferrand

22 (9) Service de Dermatologie, Hôpital Henri Mondor, APHP, Créteil

23 **Corresponding author:**

24 Pr Angèle Soria, Service de Dermatologie-Allergologie, Hôpital Tenon, Assistance Publique-Hôpitaux
25 de Paris 4, rue de la Chine 75020 Paris. Email: angele.soria@aphp.fr. Tel: +33 156017220

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39 **Abstract**

40

41 **Background**

42 Drug reactions with eosinophilia and systemic symptoms (DRESSs) and acute generalized
43 exanthematous pustulosis (AGEP) are potentially severe cutaneous adverse drug reactions.

44 **Objective**

45 To describe the clinical findings and sensitization profiles of DRESS and AGEP patients who
46 had been administered iodinated contrast media (ICMs).

47 **Methods**

48 All adult patients in the dermatologist's FISARD network diagnosed with a DRESS or AGEP
49 highly suspected to have been caused by an ICM were included retrospectively.

50 **Results**

51 Thirteen DRESSs and 19 AGEPS who had been administered ICMs were included, and the
52 median delay in DRESS and AGEP occurrence after ICM administration was short, 4 and 1
53 days, respectively. Five AGEP had systemic involvement. A high cosensitization rate (46%)
54 was observed among the DRESS, mainly with beta-lactam antibiotics.

55 Overall, 77% of our patients were sensitized to several ICMs. Patch tests (PT) identified the
56 suspected ICM for 21 cases (72%).

57 The retrospective nature, the limited number of subjects, the absence of a control group of
58 healthy individuals and the lack of detailed information on previous exposure to sensitizing
59 drugs are limitations of this study.

60 **Conclusion**

61 We report a large series of DRESSs and AGEP related to ICM administration. Skin tests
62 appear useful for diagnosis and potentially to identify alternative ICMs.

63

64

65

66 **Highlights box**

67 **1. What is already known about this topic? (18/35 words)**

68 Delayed hypersensitivity reactions to ICMs are well known mostly maculopapular exanths
69 but AGEP and DRESS are rarely reported.

70 **2. What does this article add to our knowledge? (29/35 words)**

71 Iodinated contrast media should be considered as a potential culprit drug in severe cutaneous
72 adverse drug reactions. Skin testing to ICM demonstrates frequent cross-reactivity in DRESS
73 and AGEP reactions.

74 **3. How does this study impact current management guidelines (18/35 words)**

75 Skin testing appears useful for diagnosis and possibly identification of cross-reactive ICM
76 agents in DRESS and AGEP reactions.

77

78 **Keywords:** Acute generalized exanthematous pustulosis, Cutaneous adverse drug reaction
79 Drug reaction with eosinophilia and systemic symptoms, Iodinated contrast media, Skin tests.

80

81

82 **Abbreviations**

83 AGEP: Acute generalized exanthematous pustulosis

84 CADR: Cutaneous adverse drug reaction

85 DRESS: Drug reaction with eosinophilia and systemic symptoms

86 ICM: Iodinated contrast media

87 IDT: Intradermal test

88 PT: Patch test

89 SCAR: Severe cutaneous adverse drug reaction

90

91 **Text**

92 **Introduction**

93 Drug reaction with eosinophilia and systemic symptoms syndrome (DRESS) is characterized
94 by widespread skin involvement, fever, and lymphadenopathy with at least one instance of
95 visceral involvement associated with biological abnormalities (eosinophilia, mononucleosis-
96 like atypical lymphocytes) ^{1,2}. Acute generalized exanthematous pustulosis (AGEP) is
97 characterized by a rash with sterile nonfollicular pustules, high fever and elevated circulating
98 neutrophil counts ^{3,4}. AGEP and DRESS syndrome, two potentially life-threatening severe
99 cutaneous adverse drug reactions (SCARs), are rarely reported caused by iodinated contrast
100 media (ICM) ⁵.

101 Aromatic amines, lamotrigine, allopurinol, sulfonamides and some antibiotics are the most
102 common culprit drugs responsible for DRESS ^{6,7}, whereas those most responsible for AGEP
103 include pristinamycin, ampicillin, fluoroquinolones, sulfonamides, hydroxychloroquine and
104 diltiazem ^{8,9}.

105 Delayed hypersensitivity reactions to ICMs have been reported in 0.5 to 23% of recipients
106 ^{10,11}. Maculopapular exanthems and delayed urticarias of unclear mechanism are the most
107 frequent delayed cutaneous adverse drug reactions (CADRs) reported following ICM
108 administration ^{5,12}.

109 We retrospectively analyzed a series of patients with a diagnosis of DRESS or AGEP highly
110 suspected to have been caused by an ICM, among the French dermatologist network FISARD.

111 The aim of the study was to describe the clinical presentations and sensitization profiles of
112 DRESS and AGEP patients who had been administered ICM.

113

114 **Materials and methods**

115 *Case selection*

116 We retrospectively included all patients highly suspected of having a DRESS or AGEP to
117 ICM recorded between 2010 and 2020 within the French dermatologists' FISARD network.

118 The inclusion criteria were adult patients (≥ 18 years) with a diagnosis of DRESS or AGEP
119 made by a dermatologist^{2,4} highly suspected to have been caused by an ICM according to
120 either a positive skin test or challenge test. In accordance with French legislation, institutional
121 review board approval was waived owing to the retrospective review of patient data for the
122 study.

123 *Data collection*

124 All patient medical records were retrospectively analyzed. The epidemiological (*i.e.*, age, sex)
125 and clinical characteristics were recorded, and the diagnosis scores were calculated using the
126 RegiSCAR² and EuroSCAR criteria⁸. We recorded information on all possibly incriminated
127 drugs as well as possible new exposures.

128

129 *Allergological work-up*

130 Patch tests (PTs) were performed on the back or external sides of the arms with commercial
131 ICM solutions either diluted between 10 and 30% in saline or as is. If the PT was negative, an
132 intradermal test (IDT) using commercial ICM solutions diluted 10% in saline and/or as is
133 were performed, as recently recommended for delayed hypersensitivity to ICMs^{13,14}. The PT
134 and IDT readings were performed between 2 and 5 days later. Readministration of an ICM
135 after the allergological work-up was also recorded.

136 Other suspected drugs were assessed with PTs (active ingredient diluted to 10% pet. or
137 commercialized drug form diluted to 30% pet.). If the PT was negative and injectable

138 commercial solutions were available, an IDT with a diluted drug solution according to the
139 previous ENDA/EAACI¹⁵ recommendations was performed.

140 A PT was considered positive if it met the ICDRG criteria¹⁶. A delayed IDT was considered
141 positive in the case of infiltrated erythema, and a provocation test was considered positive in
142 the case of relapse of any eruption.

143 Lerondeau *et al.* proposed an allergological classification into ICM subgroups A
144 (ioxitalamate, iopamidol, iodixanol, iomeprol, ioversol and iohexol), B (iobidridol and
145 ioxaglate), and C (amidotrizoate) with a higher frequency of cross-reactions between ICMs
146 belonging to the same subgroup than between ICMs of different subgroups¹⁷. More recently,
147 Schrijvers *et al.* proposed revising this classification by including iopromide in group A due
148 to the presence of the N-(2,3-dihydroxypropyl) carbamoyl side chain and excluding iopamidol
149 and ioxitalamate, which lack this carbamoyl¹⁸.

150 For this study, we decided to classify iopromide into group A because of the suggestion of
151 several publications^{17,19-21}; we did not remove iopamidol and ioxitalamate from group A
152 because only the Schrijvers *et al.* study suggests removing them from this group.

153 We evaluated the cross-reactivity profile within class A and between class A and the other
154 classes in patients with AGEP or a DRESS due to ICM administration. Indeed, the majority of
155 commercialized ICMs belong to class A, while others (i.e., amidotrizoate) are the only
156 representatives of their classes.

157

158 *Statistical analysis*

159 Quantitative data are described with the mean or median. Categorical data are described with
160 numbers (%) and were compared with the chi-square test. $p < 0.05$ was considered statistically
161 significant.

162

163 **Results**

164 *Patients, clinical findings and suspected ICM*

165 Thirteen ICM-DRESS patients, mainly after a CT scan (12 cases), were finally enrolled,
166 including 8 women, with a median age of 58 years (Table 1). All patients had at least one
167 organ involved. Ten had a definite diagnosis of DRESS with a RegiSCAR score ^{2,22} strictly
168 above 5. Four out of 12 patients tested for Herpesvirus, 3 tested for Epstein-bar virus and 1
169 tested for cytomegalovirus demonstrated replication. The delay in DRESS occurrence after
170 ICM administration ranged from 12 hours to 21 days with a median of 4 days. Notably, for 7
171 patients, the time to onset of DRESS after the administration of the ICM was very short, less
172 than or equal to 3 days.

173 Nineteen AGEP patients were finally enrolled, including 11 women, with an average age of
174 63 years (Table 2). Six of the patients were included without details in a monocentric study
175 focusing on iobitridol in different types of ICM-induced CADR ²³. The median EuroSCAR
176 score, assessed for 18 of the 19 patients, was 8, and 17 had a certain or probable diagnosis of
177 AGEP (score ≥ 5). All patients were hospitalized, and mild liver and renal involvement were
178 present in 4 and 1 patients, respectively. The delay in AGEP occurrence after ICM
179 administration ranged from a few hours to 8 days with a median of 1 day.

180 The suspected ICMs were iomeprol in 10 cases, iohexol in 8 cases, ioversol in 6 cases,
181 iodixanol in 5 cases, iobitridiol in 3 cases, and iopromide in 2 cases (Table 3). These results
182 include 2 patients for whom 2 ICMs were administered concomitantly and/or closely together
183 (ioversol and iobitridol for patient No. 1 and iodixanol and iomeprol for patient No. 20).

184 ICM was administered intravenously for a CT scan for 25 patients by an arterial route for
185 coronary angiography for 5, and via an unknown route for 2.

186 Previous ICM administrations were unknown for 19 patients; 10 patients had at least one ICM
187 injection before, and 3 patients had never had one. Two patients who never previously
188 received any ICM presented with DRESS with short delays of occurrence of 1 (patient No. 1)
189 and 5 days (patient No. 5). Twelve AGEP patients had short delays of occurrence of ≤ 1 day
190 each.

191 *Allergological work-up*

192 The allergological work-up (skin tests and/or re-exposure) was performed with a median
193 known delay of 175 days (45-1825 days) after recovery for 28 patients (Table 3). One DRESS
194 patient (No. 13) did not undergo a skin test but had accidental positive ICM re-exposure.

195 Overall, ICM skin tests were performed for 29 and 22 patients with PT and IDT, respectively.
196 Nine patients only underwent PT; for 5 patients (Nos. 5, 8, 12, 28, and 30), this was because
197 all or at least 2 ICM classes available for testing were positive, while for 4 patients (Nos. 2, 4,
198 11 and 15), this was because their teams were not in the habit of performing the IDT for
199 severe CADR_s (Table 3). Conversely, 2 patients (Nos. 25 and 32) directly underwent an IDT
200 without a previous PT, as this was the typical procedure for the patients' teams.

201 Allergological work-up was positive for the suspected ICM in 32 evaluated patients: 31 with
202 skin tests and 1 with a positive challenge (patient No. 13 refused the skin test after positive
203 accidental readministration of the suspected ICM). Of the 31 patients investigated with skin
204 tests, the PT identified the suspected ICM for 21 (72%) (out of 29 PTs).

205 The PTs were also positive for another ICM in 16 patients (55%) (Table 3). Finally, additional
206 IDTs performed for 20 patients to enhance the sensitivity of a negative PT, to diagnose or to
207 find alternative ICMs detected the suspected ICMs in 9 cases (Nos. 1, 7, 10, 14, 16, 18, 20,
208 29; with 2 suspected ICMs for patient No. 20) and other positive ICMs in 13 patients (Nos. 1,
209 3, 10, 16, 17, 18, 20, 21, 22, 23, 24, 26, 31).

210 The patients were also investigated for several ICMs (3 to 10, median: 6 ICMs): 28 for at least
211 2 ICM classes and 3 only for ICM class A (Nos. 5, 20 and 24).

212 For 9 patients, the ICM was the only drug suspected to have caused the CADR. For the 23
213 remaining cases, other concomitant treatments with a comparable delay were also suspected
214 (11/13 DRESS patients and 12/19 AGEP patients). These concomitant treatments were
215 explored by an allergological work-up (skin tests +/- challenge) for 21 patients (9 DRESS and
216 12 AGEP). For 6 DRESS patients, the skin tests were positive for other molecules in addition
217 to the positive ICM (Table 3). This reflected a cosensitization rate of 46% among the DRESS
218 patients. The molecules that tested positive were amoxicillin in 3 patients and
219 imipenem/cilastatin, ceftriaxone and omeprazole in 1 patient each. Among the AGEP patients,
220 the skin tests for the concomitant drugs were positive for several molecules (atovaquone,
221 aciclovir and valaciclovir) only for 1 patient with hairy cell leukemia (No. 28); (Table 3).

222 ICMs were readministered following a negative ICM test (PT and IDT) for 4 AGEP patients
223 who needed CT scans, none of whom showed any relapse (Nos. 14, 20, 27, 29). One patient
224 experienced a recurrence of DRESS upon accidental re-exposure with the same ICM (No. 13).

225

226 *ICM cross-reactivity profile during the occurrence of DRESS and AGEP*

227 The suspected ICM belonged to classes A and B for 31 and 3 cases, respectively (Table 3),
228 according to previously published classifications^{17,18}. No patient had a suspected ICM
229 belonging to class C, probably due to the limited indications for amidotrizoate (licensed only
230 for urinary explorations in our country).

231 Among the 31 patients explored, 24 (77%) were sensitized to several ICMs, and when
232 evaluable, 14/28 (50%) were sensitized to 2 or more different classes of ICMs (Table 3).

233 Among the 30 patients with a class A suspected ICM, including patient N°1 with class A and
234 B suspected ICMs, cross-reactivity with another class was observed in 14 (54%) of the 26

235 evaluable patients. Based on the results from all tests performed, either as suspected or for
236 alternatives, the cross-reactivity within class A was higher (81%) than that between class A
237 and other classes (41%, $p=0.02$) (Table 4).

238 Discussion

239 We report here a large retrospective series of patients with severe cutaneous adverse drug
240 reactions to ICMs, 13 patients with DRESS and 19 with AGEP, and no patients with Stevens-
241 Johnson Syndrome and Toxic Epidermal Necrolysis.

242 The epidemiological and clinical characteristics of the DRESS patients in this series are
243 similar to those of other previously published studies or literature reviews^{6,22,24,25}. Twenty-
244 two cases of DRESS to ICM are currently reported in the literature^{5,18,21,23} with delays of
245 occurrence generally of less than 2 or 3 days after administration of the ICM. ICM was the
246 suspected for patients with rapid-onset DRESS occurring less than 2 days after the initial
247 exposure, as already described²¹. In this series, we observed a short-delay occurrence of
248 DRESS after ICM administration, with a median of 4 days. The short delay of onset, unusual
249 for DRESS, and the ad hoc administration of ICM could be responsible for the omission of
250 ICMs in the investigation of DRESS.

251 Eighteen detailed cases of AGEP to ICM were previously reported, with skin tests performed
252 for 9 patients^{19,26-36}. The AGEP patients in the published studies were all hospitalized, in line
253 with those of our series. Systemic involvement is possible in AGEP but was not reported in
254 previous ICM cases⁹. In this series, 5 patients experienced mild-intensity systemic
255 involvement that did not require specific treatment or prolonged hospitalization. The delay in
256 AGEP occurrence observed in this series ranged from a few hours to a maximum of 3 days,
257 with most patients having a delay less than or equal to 1 day, in line with published cases.

258 The ICM skin tests were very useful for establishing the responsibility of the ICM in the
259 patients' SCARs. In fact, 72% of patients had a positive PT for the suspected ICM. When
260 performed, the IDT enhanced the sensitivity of the skin tests by positively identifying 9
261 patients with a negative PT for the suspected ICM and 13 cases for another ICM. This
262 retrospective study had no control group. Undiluted ICM skin tests with delayed readings are

263 recommended and interpretable in several recent publications, and negative controls have
264 been reported by these teams and in our experience^{13,14}.

265 In this series, no recurrence of DRESS or AGEP was reported during the ICM skin tests, even
266 during IDT explorations, but for all patients, allergological exploration was performed some
267 months after SCAR recovery as recommended³⁷.

268 Cross-reactivity between ICMs is high during AGEPs and DRESSs to ICMs; 77% of the
269 patients were sensitized to several ICMs. As expected, the cross-reactivity within the class A
270 ICMs was significantly ($p=0,02$) higher (81%) than that between class A and other classes,
271 which reached 41%.

272 These results show the interest in the use of a wide allergological work-up that includes ICMs
273 of different classes in addition to the incriminated ICM in particular after a severe CADR.
274 Indeed, the determination of a safe alternative ICM cannot be based only on the
275 recommendation of the use of an ICM from another class.

276 Furthermore, we report here a high rate of multiple-drug cosensitization during DRESS to
277 ICM (46%), which is higher than that already reported in the literature—between 0.3³⁸ and
278 18%³⁹—but is in accordance (45.4%) with a recent study that employed skin tests and gradual
279 challenges⁴⁰. Moreover, this rate was possibly underestimated since not all other suspected
280 treatments were completely explored and a negative PT was not always followed by an IDT.
281 Positive skin tests for beta-lactam antibiotics were obtained 5 of the 6 patients investigated
282 and should be implicated in the same way as the ICMs. Beta-lactam could be a
283 worsening/triggering cofactor of the DRESS to the ICM, or conversely, the ICM could be a
284 contributing factor to the DRESS. Only one AGEP patient (No. 28) had concomitant
285 cosensitization to other drugs, but he suffered from hairy cell leukemia.

286 Overall, the risk of cross-reactivity between classes during a DRESS or AGEP to ICM
287 remains high. Skin tests are very useful for this indication prior to the administration of a new
288 ICM.

289 Our study suffers from some limitations, notably its retrospective nature, the restriction of the
290 inclusion of only patient confirmed to have a DRESS or AGEP to ICM, the absence of a
291 control group of healthy individuals and the nature of the allergological explorations varying
292 between teams (number of ICMs tested, IDT dilutions, etc.).

293 Some studies report variable negative predictive values for skin tests in delayed
294 hypersensitivity to ICMs¹³; but the predictive values of skin tests in SCAR and especially in
295 DRESS and AGEP are not known.

296 Nonetheless, the data collection was particularly thorough, as all participating centers were
297 specifically interested in studying DRESSs and AGEP.

298 **Conclusion**

299 This large retrospective series of 13 DRESS and 19 AGEP patients suggests that ICMs are not
300 rare suspected drugs for severe cutaneous adverse drug reactions. Faced with patients
301 presenting with a DRESS or AGEP, dermatologists and allergologists must ask for
302 information regarding ICM administration, which is not always spontaneously provided
303 during the patient inquiry. Skin tests performed in expert centers with a large panel of ICMs
304 seem to be particularly powerful.

305

306

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308

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427 **Table 1.** Clinical and biological characteristics of the DRESS patients.

N°	Age(y)/Sex	Eosinophilia, / μ L (Mean: 2648)	Organ involvement	Fever	Lymphadenopathy	RegiSCAR scoring ^a	Viral positive PCR	Delay of DRESS occurrence, d	ICM administration	Culprit ICM
1	58/F	1110	L	Yes	Yes	7	EBV	21	scan	loversol/iobitridol
2	68/M	1660	L	Yes	no	5	-	1	scan	lohexol
3	60/F	1400	L	Yes	no	4	-	6	coro	loversol
4	16/F	1050	L	Yes	no	8	-	1	scan	lobitridol
5	58/M	470	L	U	Yes	4	-	5	scan	lohexol
6	58/F	2440	L, R	Yes	Yes	9	CMV	3	scan	iobitridol
7	70/F	1060	L, R	Yes	no	6	EBV	2	scan	lomeprol
8	67/M	2670	L	Yes	no	6	-	7	scan	loversol
9	44/F	6000	L, R	Yes	no	6	U	6	scan	loversol
10	56/F	4000	L, P	U	U	6	-	2	scan	lohexol
11	53/M	2400	L	Yes	U	7	-	2	scan	lohexol
12	67/F	1060	L, R	Yes	no	6	EBV	0.5	scan	lomeprol
13	39/M	2900	L, R	Yes	Yes	7	-	6	scan	lohexol

428

429 ICM: iodinated contrast media, M: male, F: female, L: liver involvement, R: renal involvement, P: pancreatic involvement, U: unknown, scan: CT scan; coro: coronary
 430 angiography, EBV: Epstein-barr virus, CMV: cytomegalovirus, PCR: polymerase chain reaction. ^a: according Kardaun et al (2).

431

432 **Table 2.** Clinical and biological characteristics of the AGEP patients.

N°	Age(y) /sex	Fever	AGEP evocative histology	Neutrophilia/mm ³	Hospitalization	Organ involvement	Euroscar scoring ^b	Delay of AGEP occurrence, d	ICM administration	Culprit ICM
14	64/F	U	Yes	17070	Yes	L	8	8	scan	lomeprol
15	79/M	-	Yes	13960	Yes	-	9	1	scan	lohexol
16	36/F	U	Yes	no	Yes	-	5	1	scan	lohexol
17	49/F	-	Yes	U	Yes	-	5	2	U	lomeprol
18	60/F	U	U	21000	Yes	-	8	Few hours	scan	iopromide ^c
19	82/M	Yes	Yes	14780	Yes	L	10	1	scan	lodixanol
20	74/M	Yes	Yes	18800	Yes	L	12	1	coro	lodixanol/iomeprol
21	86/F	Yes	Yes	17800	Yes	-	5	4	scan	loversol
22	93/M	Yes	Yes	13000	Yes	-	6	3	scan	lomeprol
23	39/F	Yes	Yes	19500	Yes	-	10	1	scan	lomeprol
24	67/F	Yes	ND	16300	Yes	R	8	2	coro	lodixanol
25	64/F	-	ND	U	Yes	L	2	1	scan	loversol
26	64/F	Yes	ND	U	Yes	-	8	1	scan	lomeprol
27	63/F	Yes	Yes	23000	Yes	-	9	Few hours	scan	lomeprol
28	47/M	Yes	U	U	Yes	-	NE	U	U	lopromide
29	49/M	-	+/- ^a	20000	Yes	-	8	5	coro	lodixanol
30	35/M	Yes	Yes	14090	Yes	-	10	1	scan	lomeprol
31	61/F	Yes	ND	No	Yes	-	6	1	scan	lodixanol
32	47/M	-	ND	No	Yes	-	6	1	coro	lohexol

433 ICM: iodinated contrast media, M: male, F: female, U: unknown, L: liver involvement, R: renal involvement, ND: not done, NE: not evaluable; scan: CT scan; coro: coronary
434 angiography. ^a histology compatible with AGEP, ^b according to Sidoroff et al. (8), ^c several AGEP episodes after many ICM, one due to iopromide.

435 **Table 3. Allergological work-up for iodinated contrast media.**

N°	Culprit ICM (class ^a)	Delay skin reaction and skin tests, d	Other drugs concomitantly administered, skin tests results/challenge results	Allergological work-up according ICM cross reactivity classification ^a			
				Patch tests, results: +/-	Intradermal skin tests, results: +/-	ICM re-exposure results (+/-)	Cross-reactivity ^d
DRESS							
1	loversol/lobitridol (A+B)	270	Amoxicillin + Ceftriaxone - Gentamicin - Trimethoprim/sulfamethoxazole -	A: <u>loversol</u> + lomeprol - lopamidol - lodixanol -loxitalamate - B: lobitridol -	A: lomeprol + lopamidol + lodixanol + loxitalamate + B: <u>lobitridol</u> +	ND	A+B ^f
2	lohexol (A)	730	Piperacillin/tazobactam Levetiracetam	A: <u>lohexol</u> + lodixanol+ B: lobitridol-	ND	ND	A
3	loversol (A)	210	None	A: lohexol+ lodixanol+ <u>loversol</u> + lomeprol + loxitalamate + lopamidol - lopromide + B : lobitridol - loxaglate -	A: lopamidol + B: lobitridol - loxaglate -	ND	A
4	lobitridol (B)	180	Amoxicilline - Ceftriaxone ^b -/- Cefpodoxime ^b -/-	A: lohexol - lodixanol - lomeprol - lopamidol - B: <u>lobitridol</u> +	ND	ND	B
5	lohexol (A)	120	None	A: <u>lohexol</u> + lodixanol+ lopromide +	ND	ND	na
6	lobitridol (B)	55	Bictégravir - Emtricitabine -/- Tenofovir -/- Pyrimethamin - Sulfadiazine - Dolutegravir ^b -/-	A: lodixanol - lomeprol -lopamidol - B: <u>lobitridol</u> +	A: lodixanol - lomeprol - lopamidol -	ND	B
7	lomeprol (A)	180	Paracetamol -/- Aciclovir -/-	A: lodixanol - lomeprol - B: lobitridol -	A: lodixanol - <u>lomeprol</u> + B: lobitridol -	ND	A
8	loversol (A)	720	Amoxicillin +	A: lohexol+ lodixanol+ <u>loversol</u> + lomeprol + lopamidol + B: lobitridol + loxaglate + C: Amidotrizoate -	ND	ND	A+B
9	loversol (A)	NA	Amoxicillin + Cefpodoxime -/- Ceftriaxone ^b -/- Cefuroxime - Cefotaxime -/- Piperacillin/tazobactam - Imipenem/cilastatine -/- Omeprazole - Pantoprazole ^b - Lansoprazole ^b - Rabeprazole ^b -	A: lohexol+ lodixanol+ <u>loversol</u> + lomeprol + lopamidol + B: lobitridol + loxaglate + C: Amidotrizoate -	C: Amidotrizoate -	ND	A+B

10	lohexol (A)	135	Imipenem/cilastatine +	A: lohexol – Iodixanol -Iopamidol - lomeprol - Iopromide - B: Ioxaglate -	A: <u>lohexol</u> + Iodixanol + Iopamidol + lomeprol + Iopromide - B: Ioxaglate -	ND	A
11	lohexol (A)	360	Ceftriaxone + Extencillin ^b + Amoxicillin ^b + Cefotaxim ^b - Cefazoline ^b - Cefuroxime ^b -	A: <u>lohexol</u> + Iodixanol+ Ioversol + lomeprol + Iopromide + Iopamidol - B: Iobitridol + Ioxaglate - C: Amidotrizoate +	ND	ND	A+B +C
12	lomeprol (A)	180	Omeprazole + Pantoprazole ^b + Lansoprazole ^b - Rabeprazole ^b - Esomeprazole ^b -	A: lohexol+ Iodixanol+ <u>lomeprol</u> + Ioxitalamate + B: Iobitridol + C: Amidotrizoate +	ND	ND	A+B +C
13	lohexol ^c (A)	ND	Carbamazepine	ND	ND	lohexol ^c +	na
AGEP							
14	lomeprol (A)	180	Amiodarone - Apixaban -	A: lomeprol - Iodixanol - B: Iobitridol -	A: <u>lomeprol</u> + Iodixanol - B: Iobitridol -	Iobitridol -	A
15	lohexol (A)	90	None	A: <u>lohexol</u> + Iodixanol + Iopamidol + lomeprol + B: Iobitridol - Ioxaglate + C: Amidotrizoate -	ND	ND	A+B
16	lohexol (A)	105	None	A: lohexol - Iodixanol - Iopamidol - lomeprol - Iopromide - B: Iobitridol -	A: <u>lohexol</u> + Iodixanol + Iopamidol + lomeprol + Iopromide + B: Iobitridol -	ND	A
17	lomeprol (A)	1825	Amoxicilin/clavulanic acid - Tramadol -	A: lohexol + Iodixanol + Iopamidol - <u>lomeprol</u> + Ioxitalamate + Ioversol - Iopromide - B: Iobitridol + Ioxaglate - C: Amidotrizoate -	A: Iopamidol +Ioversol + Iopromide + C: Amidotrizoate -	ND	A +B
18	Iopromide (A)	NA	None	A: lohexol + Iodixanol -lomeprol + Ioxitalamate + Iopromide - B: Iobitridol - C: Amidotrizoate -	A: Iodixanol + <u>Iopromide</u> + B: Iobitridol + C: Amidotrizoate -	ND	A+B
19	Iodixanol (A)	120	Cotrimoxazole -	A: lohexol - Iodixanol - lomeprol – Ioxitalamate - B: Iobitridol – Ioxaglate -	A: lohexol - <u>Iodixanol</u> + lomeprol - Ioxitalamate - B: Iobitridol - Ioxaglate -	ND	A
20	Iodixanol/ lomeprol (A+A)	120	Verapamil - Isosorbide dinitrate -	A: lohexol - Iodixanol - lomeprol - Iopamidol -	A: lohexol + <u>Iodixanol</u> + <u>lomeprol</u> + Iopamidol -	Iobitridol -	na
21	Ioversol (A)	120	Pristinamycine -	A: <u>Ioversol</u> + lohexol + Iodixanol -lomeprol -Ioxitalamate - B: Iobitridol – Ioxaglate -	A: Iodixanol + lomeprol + Ioxitalamate - B: Iobitridol - Ioxaglate -	ND	A
22	lomeprol (A)	45	Speciafoldine -	A: lohexol - Iodixanol - <u>lomeprol</u> + Iopamidol + B: Iobitridol - C: Amidotrizoate -	A: lohexol + Iodixanol - B: Iobitridol - C: Amidotrizoate -	ND	A

23	lomeprol (A)	730	None	A: lohexol + Iodixanol + Iopamidol + <u>lomeprol</u> + Ioxitalamate + Ioversol + Iopromide + B: Iobitridol - Ioxaglate + C: Amidotrizoate -	B: Iobitridol + C: Amidotrizoate -	ND	A+B
24	Iodixanol (A)	30	Omeprazole - Enapranil - Isosorbide dinitrate -	A: <u>Iodixanol</u> + lohexol -Ioxitalamate -	A: lohexol + Ioxitalamate -	ND	na
25	Ioversol ^e (A)	150	None	ND	A: lohexol + Iodixanol + lomeprol + Ioxitalamate + B: Ioxaglate +	ND	A+B
26	lomeprol (A)	180	Amoxicilin/clavulinic acid -/-	A: lohexol + Iodixanol + Iopamidol - <u>lomeprol</u> + Ioxitalamate - B: Iobitridol - Ioxaglate -	A: Iopamidol + Ioxitalamate - B: Iobitridol - Ioxaglate +	ND	A+B
27	lomeprol (A)	60	Ciclosporine -/-	A: <u>lomeprol</u> + Iodixanol - B: Iobitridol -	A : Iodixanol - B: Iobitridol -	Iobitridol -	A
28	Iopromide (A)	912	Ceftriaxone – Atovaquone + Aciclovir + Valaciclovir +	A: lohexol + Ioversol + Iodixanol + Iopamidol + lomeprol + <u>Iopromide</u> + B: Iobitridol +	ND	ND	A+B
29	Iodixanol (A)	150	None	A: Iodixanol - Iopamidol -lomeprol - Iopromide - B: Iobitridol -	A: <u>Iodixanol</u> + Iopamidol -lomeprol - Iopromide - B: Iobitridol -	Iopromide -	A
30	lomeprol (A)	155	None	A: Iodixanol + Iopamidol + <u>lomeprol</u> + Iopromide + B: Iobitridol +	ND	ND	A+B
31	Iodixanol (A)	175	Hydroxyzin - Tramadol -	A: lohexol - <u>Iodixanol</u> + B: Iobitridol -	A: lohexol - B: Iobitridol +	ND	A+B
32	Iohexol (A)	877	Ramipril -	ND	A: Iodixanol + <u>Iohexol</u> + B: Iobitridol -	ND	A

436

437 ICM: iodinated contrast media, d: days, ND: not done, NA: not available. ^a ICM group of cross reactivity, ^b substitutive drug with negative skin tests and challenge, ^c Iohexol
438 was inadvertently re-administered with recurrence of the DRESS in a few hours, ^d cross-reactivity evaluated with skin tests, na: not established and not applicable when skin
439 tests explored only one ICM class, ^e Ioversol was not available for testing, ^f for this patient cross-reactivity and/or co-sensitization are not evaluable, due to suspected ICM of
440 two different classes (A and B). Underlining: suspected ICMs.

441

442

443 **Table 4.** Positive skin test results and cross-reactivity for explored DRESS and AGEP patients.

444

			A						B		C	
			IOMEPROL	IODIXANOL	IOHEXOL	IOPAMIDOL	IOVERSOL	IOXITALAMATE	IOPROMIDE	IOBITRIDOL	IOXAGLATE	AMIDOTRIZOATE
Suspected ICM	A	IOMEPROL ^a n=10	10/10	6/10	6/6	5/6	2/2	3/4	3/3	4/9	2/3	1/4
		IODIXANOL ^a n=5	0/2	5/5	2/4	0/2	-	0/2	0/1	1/3	0/1	-
		IOHEXOL n=7	4/4	7/7	7/7 ^b	3/4	1/1	-	3/4	1/5	1/3	1/2
		IOPAMIDOL n=0	-	-	-	-	-	-	-	-	-	-
		IOVERSOL ^c n=6	6/6	6/6	5/5	4/4	5/5 ^d	3/4	1/1	3/5	3/5	0/2
		IOXITALAMATE n=0	-	-	-	-	-	-	-	-	-	-
		IOPROMIDE n=2	2/2	2/2	2/2	1/1	1/1	1/1	2/2	2/2	-	0/1
	B	IOBITRIDOL ^e n= 3	1/3	1/3	0/1	1/3	-	1/1	-	3/3	-	-
		IOXAGLATE n=0	-	-	-	-	-	-	-	-	-	-
	C	AMIDOTRIZOATE n=0	-	-	-	-	-	-	-	-	-	-
n positive/n tested			23/27	27/33	14/20	14/20	9/9	8/12	9/11	14/27	6/12	2/9
Cross-reactivity within the class A n positive/n tested (%) (suspected excluded)			79/97 (81%)						NA		NA	
Cross-reactivity between class A (suspected or not) and other classes n positive/n tested (%)			23/56 (41%; p=0.02 ^f)									

445

446

447

448

ICM: iodinated contrast media, ^a 1 patient had iodixanol and iomeprol suspected, ^b 1/8 patient had no iohexol skin-tests, ^c 1 patient had ioversol and iobidridiol suspected, ^d 1 patient (No. 25) was not tested with ioversol (the culprit ICM), ^f using chi-squared test.