



## **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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**Title: DRESS and AGEP reactions to iodinated contrast media: a French case series**

**Short running title:** DRESSs and AGEPS to iodinated contrast media

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

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

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

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

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

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

(6) Service de Dermatologie, Caen

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

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

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

**Corresponding author:**

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

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## **Abstract**

### **Background**

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

### **Objective**

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

### **Methods**

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

### **Results**

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

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

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

### **Conclusion**

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

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 exanthems  
69 but AGEF 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 AGEF 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 AGEF 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

## Text

### Introduction

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

Aromatic amines, lamotrigine, allopurinol, sulfonamides and some antibiotics are the most common culprit drugs responsible for DRESS <sup>6,7</sup>, whereas those most responsible for AGEP include pristinamycin, ampicillin, fluoroquinolones, sulfonamides, hydroxychloroquine and diltiazem <sup>8,9</sup>.

Delayed hypersensitivity reactions to ICMs have been reported in 0.5 to 23% of recipients <sup>10,11</sup>. Maculopapular exanthems and delayed urticarias of unclear mechanism are the most frequent delayed cutaneous adverse drug reactions (CADRs) reported following ICM administration <sup>5,12</sup>.

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

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

## **Materials and methods**

### *Case selection*

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

The inclusion criteria were adult patients ( $\geq 18$  years) with a diagnosis of DRESS or AGEF made by a dermatologist<sup>2,4</sup> highly suspected to have been caused by an ICM according to either a positive skin test or challenge test. In accordance with French legislation, institutional review board approval was waived owing to the retrospective review of patient data for the study.

### *Data collection*

All patient medical records were retrospectively analyzed. The epidemiological (*i.e.*, age, sex) and clinical characteristics were recorded, and the diagnosis scores were calculated using the RegiSCAR<sup>2</sup> and EuroSCAR criteria<sup>8</sup>. We recorded information on all possibly incriminated drugs as well as possible new exposures.

### *Allergological work-up*

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

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

commercial solutions were available, an IDT with a diluted drug solution according to the previous ENDA/EAACI<sup>15</sup> recommendations was performed.

A PT was considered positive if it met the ICDRG criteria<sup>16</sup>. A delayed IDT was considered positive in the case of infiltrated erythema, and a provocation test was considered positive in the case of relapse of any eruption.

Lerondeau *et al.* proposed an allergological classification into ICM subgroups A (ioxitalamate, iopamidol, iodixanol, iomeprol, ioversol and iohexol), B (iobidridol and ioxaglate), and C (amidotrizoate) with a higher frequency of cross-reactions between ICMs belonging to the same subgroup than between ICMs of different subgroups<sup>17</sup>. More recently, Schrijvers *et al.* proposed revising this classification by including iopromide in group A due to the presence of the N-(2,3-dihydroxypropyl) carbamoyl side chain and excluding iopamidol and ioxitalamate, which lack this carbamoyl<sup>18</sup>.

For this study, we decided to classify iopromide into group A because of the suggestion of several publications<sup>17,19–21</sup>; we did not remove iopamidol and ioxitalamate from group A because only the Schrijvers *et al.* study suggests removing them from this group.

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

### *Statistical analysis*

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



## **Results**

### *Patients, clinical findings and suspected ICM*

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

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

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

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

Previous ICM administrations were unknown for 19 patients; 10 patients had at least one ICM injection before, and 3 patients had never had one. Two patients who never previously received any ICM presented with DRESS with short delays of occurrence of 1 (patient No. 1) and 5 days (patient No. 5). Twelve AGEF patients had short delays of occurrence of  $\leq 1$  day each.

#### *Allergological work-up*

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

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

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

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

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

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

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

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

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

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

Among the 30 patients with a class A suspected ICM, including patient N°1 with class A and 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).

## **Discussion**

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

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

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

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

recommended and interpretable in several recent publications, and negative controls have been reported by these teams and in our experience<sup>13,14</sup>.

In this series, no recurrence of DRESS or AGEP was reported during the ICM skin tests, even during IDT explorations, but for all patients, allergological exploration was performed some months after SCAR recovery as recommended<sup>37</sup>.

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

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

Furthermore, we report here a high rate of multiple-drug cosensitization during DRESS to ICM (46%), which is higher than that already reported in the literature—between 0.3<sup>38</sup> and 18%<sup>39</sup>—but is in accordance (45.4%) with a recent study that employed skin tests and gradual challenges<sup>40</sup>. Moreover, this rate was possibly underestimated since not all other suspected treatments were completely explored and a negative PT was not always followed by an IDT. Positive skin tests for beta-lactam antibiotics were obtained 5 of the 6 patients investigated and should be implicated in the same way as the ICMs. Beta-lactam could be a worsening/triggering cofactor of the DRESS to the ICM, or conversely, the ICM could be a contributing factor to the DRESS. Only one AGEP patient (No. 28) had concomitant cosensitization to other drugs, but he suffered from hairy cell leukemia.

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

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

Some studies report variable negative predictive values for skin tests in delayed hypersensitivity to ICMs<sup>13</sup>; but the predictive values of skin tests in SCAR and especially in DRESS and AGEP are not known.

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

## **Conclusion**

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

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

N°	Age(y)/Sex	Eosinophilia, / $\mu$ L (Mean: 2648)	Organ involvement	Fever	Lymphadeno pathy	RegiSCAR scoring <sup>a</sup>	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. <sup>a</sup>: 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 <sup>3</sup>	Hospitalization	Organ involvement	Euroscar scoring <sup>b</sup>	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 <sup>c</sup>
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	iopromide
29	49/M	-	+/- <sup>a</sup>	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. <sup>a</sup> histology compatible with AGEp, <sup>b</sup> according to Sidoroff et al. (8), <sup>c</sup> several AGEp episodes after many ICM, one due to iopromide.

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

N°	Culprit ICM (class <sup>a</sup> )	Delay skin reaction and skin tests, d	Other drugs concomitantly administered, skin tests results/challenge results	Allergological work-up according ICM cross reactivity classification <sup>a</sup>			Cross-reactivity <sup>d</sup>
				Patch tests, results: +/-	Intradermal skin tests, results: +/-	ICM re-exposure results (+/-)	
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 <sup>f</sup>
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 - Cetrixaxone <sup>b</sup> -/- Cefpodoxime <sup>b</sup> -/-	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 <sup>b</sup> -/-	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 <sup>b</sup> -/- Cefuroxime - Cefotaxime -/- Piperacillin/tazobactam - Imipenem/cilastatine -/- Omeprazole - Pantoprazole <sup>b</sup> - Lansoprazole <sup>b</sup> - Rabeprazole <sup>b</sup> -	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 – lodixanol -lopamidol - lomeprol - lopromide - B: loxaglate -	A: <u>lohexol</u> + lodixanol + lopamidol + lomeprol + lopromide - B: loxaglate -	ND	A
11	lohexol (A)	360	Ceftriaxone + Extencillin <sup>b</sup> + Amoxicillin <sup>b</sup> + Cefotaxim <sup>b</sup> - Cefazoline <sup>b</sup> - Cefuroxime <sup>b</sup> -	A: <u>lohexol</u> + lodixanol+ loversol + lomeprol + lopromide + lopamidol - B: lobitridol + loxaglate - C: Amidotrizoate +	ND	ND	A+B +C
12	lomeprol (A)	180	Omeprazole + Pantoprazole <sup>b</sup> + Lansoprazole <sup>b</sup> - Rabeprazole <sup>b</sup> - Esomeprazole <sup>b</sup> -	A: lohexol+ lodixanol+ <u>lomeprol</u> + loxitalamate + B: lobitridol + C: Amidotrizoate +	ND	ND	A+B +C
13	lohexol <sup>c</sup> (A)	ND	Carbamazepine	ND	ND	lohexol <sup>c</sup> +	na
AGEP							
14	lomeprol (A)	180	Amiodarone - Apixaban -	A: lomeprol - lodixanol - B: lobitridol -	A: <u>lomeprol</u> + lodixanol - B: lobitridol -	lobitridol -	A
15	lohexol (A)	90	None	A: <u>lohexol</u> + lodixanol + lopamidol + lomeprol + B: lobitridol - loxaglate + C: Amidotrizoate -	ND	ND	A+B
16	lohexol (A)	105	None	A: lohexol - lodixanol - lopamidol - lomeprol - lopromide - B: lobitridol -	A: <u>lohexol</u> + lodixanol + lopamidol + lomeprol + lopromide + B: lobitridol -	ND	A
17	lomeprol (A)	1825	Amoxicilin/clavulanic acid - Tramadol -	A: lohexol + lodixanol + lopamidol - <u>lomeprol</u> + loxitalamate + loversol - lopromide - B: lobitridol + loxaglate - C: Amidotrizoate -	A: lopamidol +loversol + lopromide + C: Amidotrizoate -	ND	A +B
18	lopromide (A)	NA	None	A: lohexol + lodixanol -lomeprol + loxitalamate + lopromide - B: lobitridol - C: Amidotrizoate -	A: lodixanol + <u>lopromide</u> + B: lobitridol + C: Amidotrizoate -	ND	A+B
19	lodixanol (A)	120	Cotrimoxazole -	A: lohexol - lodixanol - lomeprol – loxitalamate - B: lobitridol – loxaglate -	A: lohexol - <u>lodixanol</u> + lomeprol - loxitalamate - B: lobitridol - loxaglate -	ND	A
20	lodixanol/ lomeprol (A+A)	120	Verapamil - Isosorbide dinitrate -	A: lohexol - lodixanol - lomeprol - lopamidol -	A: lohexol + <u>lodixanol</u> + <u>lomeprol</u> + lopamidol -	lobitridol -	na
21	loversol (A)	120	Pristinamycine -	A: <u>loversol</u> + lohexol + lodixanol -lomeprol -loxitalamate - B: lobitridol – loxaglate -	A: lodixanol + lomeprol + loxitalamate - B: lobitridol - loxaglate -	ND	A
22	lomeprol (A)	45	Speciafoldine -	A: lohexol - lodixanol - <u>lomeprol</u> + lopamidol + B: lobitridol - C: Amidotrizoate -	A: lohexol + lodixanol - B: lobitridol - 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 <sup>e</sup> (A)	150	None	ND	A: lohexol + Iodixanol + lomeprol + Ioxitalamate + B: Ioxaglate +	ND	A+B
26	lomeprol (A)	180	Amoxicilin/clavulanic 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. <sup>a</sup> ICM group of cross reactivity, <sup>b</sup> substitutive drug with negative skin tests and challenge, <sup>c</sup> Iohexol  
438 was inadvertently re-administered with recurrence of the DRESS in a few hours, <sup>d</sup> cross-reactivity evaluated with skin tests, na: not established and not applicable when skin  
439 tests explored only one ICM class, <sup>e</sup> Ioversol was not available for testing, <sup>f</sup> 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



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

			A							B		C
			IOMEPROL	IODIXANOL	IOHEXOL	IOPAMIDOL	IOVERSOL	IOXITALAMATE	IOPROMIDE	IOBITRIDOL	IOXAGLATE	AMIDOTRIZOATE
Suspected ICM	A	IOMEPROL <sup>a</sup> n=10	10/10	6/10	6/6	5/6	2/2	3/4	3/3	4/9	2/3	1/4
		IODIXANOL <sup>a</sup> 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 <sup>b</sup>	3/4	1/1	-	3/4	1/5	1/3	1/2
		IOPAMIDOL n=0	-	-	-	-	-	-	-	-	-	-
		IOVERSOL <sup>c</sup> n=6	6/6	6/6	5/5	4/4	5/5 <sup>d</sup>	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 <sup>c</sup> 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 <sup>f</sup> )									

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