

Skin Testing and Drug Provocation Tests in Epidermal Necrolysis: A French Experience



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What is already known about this topic? Allergological workup may be useful in epidermal necrolysis (EN), but outcomes are rarely reported. Intradermal tests and provocation tests have been historically contraindicated after EN.

What does this article add to our knowledge? Allergological workup can be performed by specialized teams without causing adverse reactions and constitute a useful tool to identify some culprit or safe drugs.

How does this study impact current management guidelines? Hypersensitivity testing in EN, although of limited sensitivity, may be useful to limit further drug avoidance. We propose an algorithm to standardize the practices of allergological workup in EN.

BACKGROUND: There are limited data on the use of skin testing, other than patch testing, and challenges in the evaluation of epidermal necrolysis (EN), including Stevens-Johnson syndrome and toxic epidermal necrolysis.

OBJECTIVE: To report a French multicenter experience in skin testing and challenges in EN, and investigate the factors associated with tests' positivity.

METHODS: All patients who were evaluated by patch tests (PTs), skin prick tests, intradermal tests (IDTs), or drug provocation tests (DPTs) for EN between 2010 and 2020 were retrospectively included through 2 French drug reaction networks.

RESULTS: In total, 113 patients were included from 8 centers. Median (interquartile range) time from EN to hypersensitivity

workup was 7.9 months (5.1–15 months). All patients had PTs, 17 (15%) had skin prick tests or IDTs with delayed readings and 32 (28.3%) had DPTs. One mild reaction occurred after a DPT. Overall, 22 patients (19.5%) had positive PTs, and the only factors associated with positivity were Algorithm of Drug Causality for Epidermal Necrolysis (ALDEN) score and drug class. Only 1 IDT was positive but considered irrelevant. The DPTs were never performed to prove responsibility of a highly suspected drug but were used to confirm current tolerance of needed medications.

CONCLUSIONS: Allergological workup in EN, performed by specialists involved in EN, seems safe. Skin tests, although of limited sensitivity, can be helpful for considering the reintroduction of essential drugs according to a benefit-to-risk

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Abbreviations used

ALDEN-Algorithm of Drug Causality for Epidermal Necrolysis

CADR-Cutaneous adverse drug reaction

DPT-Drug provocation test

EN-Epidermal necrolysis

IDT-Intradermal test

IQR-Interquartile range

NSAIDs-Nonsteroidal anti-inflammatory drugs

PT-Patch test

SJS-Stevens-Johnson syndrome

SPT-Skin prick test

TEN-Toxic epidermal necrolysis

decision. We propose an algorithm for approaching hypersensitivity testing in patients with EN, to be adapted to each patient. © 2022 American Academy of Allergy, Asthma & Immunology (J Allergy Clin Immunol Pract 2022;10:3252-61)

Key words: Epidermal necrolysis; Stevens-Johnson syndrome; Lyell syndrome; Toxic epidermal necrolysis; Patch tests; Intradermal tests; Drug provocation tests; Cutaneous adverse drug reaction; Skin tests

INTRODUCTION

Epidermal necrolysis (EN; including Stevens-Johnson syndrome [SJS] and toxic epidermal necrolysis [TEN]) is a rare and severe delayed mucocutaneous hypersensitivity reaction.^{1,2} The mortality rate at the acute phase is estimated at 14% to 23%, and long-term sequelae can affect quality of life.^{3,4} Epidermal necrolysis is drug induced in 85% to 90% of cases and occurs 4 to 28 days, on average, after the initiation of the causal drug.^{2,3,5} Given its severity, EN can generate multiple drug contraindications and pharmacophobia, especially when several drugs are initially suspected.²

Drugs at high risk of EN are sulfonamide antibiotics, including cotrimoxazole, sulfasalazine, dapsone, allopurinol, antiepileptic agents, oximam-type nonsteroidal anti-inflammatory drugs (NSAIDs), and nevirapine.^{6,7} Other reported drugs include proton pump inhibitors, other classes of antibiotics or NSAIDs, and as recently reported, some new immunotherapies and targeted therapies.^{6,7} The Algorithm of Drug Causality for Epidermal Necrolysis (ALDEN) assesses a drug causality specifically in EN.⁵ It classifies drug causality as very unlikely (<0), unlikely (0–1), possible (2–3), probable (4–5), or very probable (≥6).

In other cutaneous adverse drug reactions (CADRs), skin testing (patch tests [PTs], skin prick tests [SPTs], and intradermal tests [IDTs]) helps identify the causal drug to avoid recurrence and limit further drug avoidance.⁸ However, tests must be safe, and their sensitivity and positive and negative predictive values depend on the drug tested and the type of CADR.⁹ In EN, allergological workup is poorly reported.

Three previous small series evaluated the value of PTs to investigate EN.^{10–12} Delayed, not immediate, positive reactions on IDTs were reported in 7 patients.^{13–16} Recurrence or elicitation of EN owing to skin testing has not been described in the literature, but 1 study reported diffuse non–life-threatening rashes after PTs in 2 patients investigated for EN.¹⁷

Although PTs are recommended in guidelines, SPTs and IDTs are still considered potentially unsafe in EN, with a risk of relapse of the CADR.^{9,11,18–21}

Drug provocation tests (DPTs) are considered the best tools to delabel drug hypersensitivity.²² Drug provocation tests in EN, not preceded by skin testing, were described in 2 series.^{23,24} Because of the severity of the disease, DPTs in EN are contraindicated by all guidelines.^{9,19,21,22}

Consequently, owing to the paucity of data on allergological workup and the low sensitivity of PTs in EN, patients or their practitioners avoid the suspected drugs, potentially cross-reactive drugs, and sometimes many unrelated drugs.

With this French multicenter study, we report the modalities, results, and tolerance of skin testing and challenges in a large series of EN patients.

METHODS

Case selection

This retrospective multicenter study included all patients who were evaluated by at least 1 test among PTs, SPTs, IDTs, and DPTs for EN between January 1, 2010, and December 31, 2020. Cases were selected from databases of dermatology departments affiliated with 2 French networks involved in the management of severe CADRs, the Reference Center for Toxic Bullous Dermatoses and Severe Drug Reactions (TOXIBUL) and the French Investigators for Skin Adverse Reactions to Drugs (FISARD) group. Epidermal necrolysis was diagnosed according to published clinical and histological criteria.^{1,2,25} We excluded patients with other CADRs such as generalized bullous fixed drug eruption or erythema multiforme or with medical records with missing data.^{1,2,6}

Data collection and outcomes

The following clinical data were extracted from medical charts: inclusion center, sex, age at onset of EN, clinical form of EN (SJS, SJS/TEN overlap, or TEN according to the body surface area involved), suspect drugs and their ALDEN score, time from the acute phase of EN to allergological workup, and type of tests performed and their results. Detailed testing procedures were collected for each patient.

The primary outcome was the proportion of patients who were evaluated by PTs, SPTs, IDTs, and/or DPTs. The other variables analyzed were the habits of testing methods per center, rate of adverse test reactions and test positivity (for PTs, SPTs, IDTs, DPTs), description of drugs involved (suspected and their respective ALDEN score, tested, positivity of tests, resumed or not). Adverse test reactions could range from a locoregional skin reaction beyond the test area for skin tests to a diffuse rash or a relapse of EN for skin tests or DPTs. We studied factors associated with positive PTs among age, sex, type of EN (SJS, SJS/TEN overlap, TEN), time to the test after EN onset, centers, pharmacological class, and ALDEN score for the corresponding suspect drug.

Statistical analysis

We describe quantitative data with median and interquartile range (IQR) and categorical data with number (%). Factors associated with positive PTs were investigated by univariate analyses with χ^2 test, Fisher exact test, or logistic regression models. Tests were considered significant at P less than .05.

Ethics statement

The study was approved by the Institutional Review Board of Henri Mondor Hospital (00011558-2021-120).

TABLE I. Baseline characteristics of patients included for allergological testing to explore EN (n = 113)

Characteristics	Values
Sex (M/F)	47 (41.6%)/66 (58.4%)
Age at onset of drug reaction (y), median (range)	38.6 (2.2–84.7)
Time from the acute phase of EN to testing (mo)	
Median (IQR)	7.9 (5.1–15.0)
≤4	13 (11.5%)
≤2	2 (1.8%)
Clinical forms of EN	
SJS	61 (54.0%)
TEN	46 (40.7%)
SJS/TEN overlap	6 (5.3%)
Total number of suspect drugs	217
Number of suspect drugs per patient, median (IQR)	2 (1–2)
Number of ALDEN scores available (ALDEN rate, %)	196 (90.3%)

RESULTS

Patient characteristics

From 8 centers, we selected 187 patients; 74 cases were excluded because of a diagnosis other than EN (n = 56) or for missing data (n = 18). Finally, 113 patients were included (66 women [58.4%]; median [range] age at onset of EN 38.6 years [2.2–84.7 years]; median [IQR] time from EN to tests 7.9 months [5.1–15 months]) (Table I). The main suspected drugs were antibiotics (n = 71 patients), including beta-lactams (n = 39; amoxicillin and amoxicillin-potassium clavulanate (n = 20) and cotrimoxazole (n = 9); NSAIDs (n = 36); anti-convulsants (n = 25), including lamotrigine (n = 12) and carbamazepine (n = 3); acetaminophen (n = 10); proton pump inhibitors (n = 7); tetrazepam (n = 6); and allopurinol (n = 6). A total of 217 drugs were suspect (median [IQR] per patient 2 [1–2]). The ALDEN score was available for 196 of 217 suspect drugs (90.3%).

Allergological workup

All patients were evaluated by PTs (n = 113), 17 (15%) by SPTs and/or IDTs with delayed reading, and 32 (28.3%) by DPTs (Table II). Centers followed the guidelines of the European Society of Contact Dermatitis (ESCD) for drug PTs: active ingredient diluted at 10% in petrolatum or marketed pharmaceutical form diluted at 30% in petrolatum (Table II).²⁷ The specificity of PTs was controlled with data from the literature.²⁸ The SPTs involved the undiluted drug in its commercialized form. For IDTs, only injectable forms of the drugs were used, diluted to previously recommended maximal concentrations or with lower concentrations (10^{-4} from the used concentration, up to the recommended concentration) (Table II).²⁹ The IDTs followed ESCD guidelines from 2010 to 2018 then guidelines for performing IDTs since 2018.^{27,30} The PTs were applied on the skin of the back for 2 days, then assessed at days 2 and 4.³¹ In 14 cases, in addition to testing on the back, PTs were also applied on a previously injured skin area.

The SPTs and IDTs were only performed if the previous PT was negative for the drug tested. The SPTs preceded IDTs in 8

patients, but 6 patients had IDTs without SPTs and 3 had SPTs only. The SPTs and IDTs had an immediate assessment at 20 minutes and a delayed assessment at 48 to 72 hours.

The tests performed by center are presented in Table III.

Skin testing always involved the drugs suspected of causing the EN, but nonsuspected drugs could also be tested, representing alternatives, either structurally related drugs with a risk of cross-reaction (eg, another beta-lactam) or structurally unrelated drugs (eg, another class of NSAIDs) only to reassure the patient or the practitioner before a drug introduction (Table II).

Overall, 26 of the 32 patients (81.3%) who had DPTs were from the same center (Table III). The DPTs were never performed to prove responsibility of a highly suspected drug but rather to confirm current tolerance of needed drugs (Table IV). The DPTs were preceded only by PTs without SPTs/IDTs in 25 of 32 patients (78.1%), whereas 7 of 32 patients (21.9%) had PTs and SPTs/IDTs before DPTs. The escalating doses used for some DPTs were for precautionary reasons and not for tolerance induction.

Test results

In all, 22 of 113 patients (19.5%) had at least 1 positive PT, 2 only on previously injured skin, both with cotrimoxazole (Table II). The results of PTs performed with suspected drugs (n = 239) for the EN episode are detailed in Table V. Details of all PTs (with suspected drugs [n = 239] and nonsuspected drugs [n = 221] structurally related [n = 190] or nonstructurally related [n = 31]) are presented in Tables E1 and E2 (available in this article's Online Repository at www.jaci-inpractice.org). The PTs were positive on day 2 for 7 patients (31.8%) and negative on day 2 but positive on day 4 for 15 patients (68.2%). The PTs were more frequently positive with suspected than nonsuspected drugs (n = 28 of 39, 11.7% vs n = 3 of 221, 1.4%; $P < .001$). Two patients had positive PTs with different drugs, the only 3 positive PTs for nonsuspected drugs. In 1 case, cefotaxime, ceftazidime, and amoxicillin were suspected and PTs were positive with ceftriaxone, cefepime, and ceftazidime, by probable cross-reactions between cephalosporins.¹⁶ A second patient had an EN due to cotrimoxazole and had positive PTs to cotrimoxazole and gliclazide, which are sulfonylurea and non-sulfonylurea sulfonamides, respectively.³² The median (IQR) ALDEN score was higher for suspected drugs with positive than negative PTs (6 [3–6] vs 2 [0–5]; $P < .001$). Patch test positivity also varied significantly by drug class ($P < .001$) (Table V). Univariate analysis did not identify other factors associated with PT positivity among age, sex, type of EN, time to test after the onset of EN, and centers (Table E3; available in this article's Online Repository at www.jaci-inpractice.org).

No SPT was positive. One 10^{-1} diluted IDT was positive on day 2 for bortezomib (6-mm erythematous papule). However, the patient had also developed large erythematous papules at all subcutaneous injection sites during his former treatment with undiluted bortezomib, so the test may have been a false positive and was considered irrelevant. Main drugs tested by IDTs were beta-lactams (n = 11), macrolides (n = 3), NSAIDs (n = 10), acetaminophen (n = 4), and iodinated contrast media (n = 3) (Table E4; available in this article's Online Repository at www.jaci-inpractice.org).

No adverse reactions were reported after skin testing: neither rash beyond the test area nor relapse of EN. A patient experienced a mild reaction without relapse of EN after a DPT: 20

TABLE II. Allergological tests performed for EN: modalities and results

Variables	PTs	SPTs	IDTs	DPTs
Patients tested, n (%)	113 (100)	11 (9.7)	14 (12.4)	32 (28.3)
Total number of tests performed	460	-	36	51
Number of tests per patient, median (IQR)	3 (1–5)	-	3 (1–4)	1 (1–2)
Tested drugs				
Tests of suspected drugs for EN	239	-	16	25
Tests of nonsuspected drugs for EN:	221	-	20	26
Structurally related drugs with potential cross-reactivity with the suspected drug	190		14	17
Nonstructurally related drugs	31		6	9
Skin test modalities, n (%)				
Usual dilutions*	111 (98.2)	-	5 (35.7)	
Higher dilutions	2 (1.8)	-	9 (64.3)	
Additional PT on previously injured skin by the EN	14 (12.4)			
Patients with at least 1 positive test, n	22	0	1†	1†
Positivity rate, %	19.5	0	7.1	3.1

*For PTs: according to the guidelines of the European Society of Contact Dermatitis (ESCD) of 2001. For IDTs: according to ESCD guidelines from 2010 to 2018, then since 2018 according to the 2020 guidelines for performing IDTs of Barbaud et al.³⁰

†See description in the text.

TABLE III. Inclusions and allergological workup per center

Inclusion center no.	Included patients (n = 113)	Allergological workup for EN (patients, n)					Positivity rate of PTs for suspect drugs, %
		PTs only	PTs, IDTs only	PTs, IDTs, and DPTs	PTs and DPTs without IDTs	DPTs/tested	
1	51 (45.1%)	22	3	2	24	26/51 (51.0%)	7.2
2	35 (31%)	31	2	1	1	2/31 (5.7%)	10.5
3	10 (8.8%)	9	1	0	0	0/10 (0%)	29.6
4	8 (7.1%)	6	1	0	1	1/8 (12.5%)	10.5
5	3 (2.7%)	2	0	1	0	1/3 (33%)	20
6	1 (0.9%)	1	0	0	0	0/1 (50%)	25
7	4 (3.5%)	2	0	2	0	2/4 (50%)	0
8	1 (0.9%)	0	1	0	0	0/1 (0%)	0
Total	113 (100%)	73	8	6	26	32/113 (28.3%)	11.7

P = .10

minutes after resuming full-dose acetaminophen (500 mg), a patient developed urticaria without angioedema, with mild transitory desaturation (oximetry 93%), but without any other clinical changes, including no respiratory distress, no auscultatory abnormalities, and no dyspnea. Other vital parameters were normal. The evolution was favorable within 30 minutes under oxygen therapy and 1 dose of dexchlorpheniramine without relapse (Table IV). Contraindication to acetaminophen was maintained after the reaction.

Overall, patients had 217 suspected drugs for the EN episode (Table I), and for 53 of these medications (24.4%), allergological workup excluded them from the suspects or verified tolerance to an alternative.

DISCUSSION

We report a large series about skin testing and challenges in EN. In this study, all patients were evaluated by PTs, 15% by SPTs and/or IDTs, and 28.3% by DPTs. The absence of adverse reaction to the tests highlights that allergological workup for EN is safe if performed in specialized centers. The utility of these tests for EN is also suggested because they helped find a solution

for almost a quarter of suspected drugs, by either ruling out drug hypersensitivity or confirming tolerance to alternatives.

In our series, the drugs tested were different from high-risk drugs for EN assessed in the literature.^{6,7} Allergological recruitment explains this discrepancy. Not all EN patients are tested: according to local databases, the mean number of EN cases seen over the study period in the 2 main recruiting departments was 25 and 20 per year, so only about one-fifth of EN patients were tested in these centers. Patients with only 1 suspected drug with strong notoriety (eg, allopurinol, carbamazepine, lamotrigine, cotrimoxazole) or nonessential suspected drugs often do not benefit from testing. However, patients with several essential suspected drugs should benefit from skin testing to identify the responsible drug. For this reason, antibiotics such as beta-lactams were more frequently tested than were high-risk drugs with strong notoriety. Moreover, certain drugs such as acetaminophen or beta-lactams had been frequently initiated in response to early symptoms of the EN, undiagnosed at that stage, and were erroneously considered among the suspected drugs and stopped (protopathic bias).³³ These drugs were then tested and rechallenged.

The ENs were mainly evaluated by PTs, performed with the same modalities as for other delayed CADRs.^{18,27,31} In total,

TABLE IV. Motives and modalities of DPTs

Patients with DPT(s)	Suspect drug(s) (ALDEN score)	DPT: drug(s) resumed	Reasons for DPTs (sometimes several reasons for 1 patient)	DPT modalities (time from the acute phase of the EN to DPT, mo)	Reaction
			(1)* (2)† (3)‡ (4)§		
1	Allopurinol (6), colchicine (2)	Colchicine	(3)	Full dose, day care hospitalization (14)	No
2	Amoxicillin (1)	Ceftriaxone	(1)(2)	Full dose, day care hospitalization (247)	No
		Cefpodoxime		Full dose, day care hospitalization (248)	No
3	Vancomycin (2), acetaminophen (0)	Acetaminophen	(3) PT positive for vancomycin, PT and IDT negative for acetaminophen	Full dose, day care hospitalization (7)	Yes
4	Amidotrizoate (NA)	Iobitridol	(2)	Escalating dose, outpatient setting (643)	No
5	Piroxicam (NA)	Ketoprofen	(4)(2)	Escalating dose, outpatient setting (121)	No
6	Acetaminophen (1), cefpodoxime (−5), amoxicillin (3)	Acetaminophen	(1)	Escalating dose, outpatient setting (12)	No
7	Ibuprofen (2)	Ibuprofen	(1)	Full dose, short inpatient hospitalization (10)	No
8	Amoxicillin potassium clavulanate (7), levofloxacin (4)	Ceftriaxone	(1)(2)	Full dose, short inpatient hospitalization (8)	No
9	Acetaminophen (−1), ibuprofen (0)	Ibuprofen	(1)	Full dose, short inpatient hospitalization (7)	No
10	Lamotrigine (6)	Phenobarbital	(4)(2)	Full dose, short inpatient hospitalization (7)	No
11	Phenylbutazone (6)	Acetylsalicylic acid	(4)(2)	Full dose, outpatient setting (368)	No
		Ibuprofen		Full dose, outpatient setting (369)	No
12	Ibuprofen (0), acetylsalicylic acid (−4), acetaminophen (0)	Acetaminophen	(1)	Escalating dose, short inpatient hospitalization (3)	No
13	Josamycin (−1)	Azithromycin	(1)(2)	Full dose, short inpatient hospitalization (405)	No
14	Amoxicillin (1)	Ceftriaxone	(1)	Full dose, short inpatient hospitalization (17)	No
		Amoxicillin		Full dose, short inpatient hospitalization (18)	No
15	Lamotrigine (6), domperidone (2)	Domperidone	(3) PT positive for lamotrigine	Full dose, short inpatient hospitalization (9)	No
16	Oxyphenbutazone (6)	Ibuprofen	(4)(2)	Full dose, short inpatient hospitalization (345)	No
17	Pristinamycin (3), alprazolam (2)	Alprazolam	(3)(2) PT positive for pristinamycin	Full dose, short inpatient hospitalization (16)	No
		Spiramycin		Full dose, short inpatient hospitalization (17)	No
18	Cefpodoxime (1), ibuprofen (−2)	Amoxicillin	(1)(2)	Full dose, outpatient setting (39)	No
19	Cotrimoxazole (6), ketoprofen (1)	Paroxetin	(4)	Full dose, short inpatient hospitalization (163)	No
		Pantoprazole		Full dose, short inpatient hospitalization (164)	No
20	Cotrimoxazole (6), amoxicillin (0), furosemide (2)	Cefpodoxime	(3)(2) PT positive for cotrimoxazole and gliclazide	Full dose, short inpatient hospitalization (5)	No
		Amoxicillin		Full dose, short inpatient hospitalization (6)	No
		Furosemide		Full dose, short inpatient hospitalization (7)	No
		Clarithromycin		Full dose, short inpatient hospitalization (8)	No
21	Acetaminophen (2), ibuprofen (2), amoxicillin (3)	Amoxicillin	(1) Positive PCR for <i>Mycoplasma pneumoniae</i> on nasopharyngeal swab and in skin blister fluid	Full dose, short inpatient hospitalization (3)	No

22	Cefpodoxime (−3)	Cefpodoxime	(1)	Full dose, short inpatient hospitalization (4)	No
23	Piroxicam (5)	Nimesulide	(4)(2)	Full dose, short inpatient hospitalization (312)	No
		Ketoprofen		Full dose, short inpatient hospitalization (313)	No
		Acetylsalicylic acid		Full dose, short inpatient hospitalization (314)	No
24	Amoxicillin potassium clavulanate (5), valaciclovir (3), fluconazole (4), esomeprazole (2), phenoxymethyl penicillin (−1)	Ceftriaxone	(3)(2) PT positive for amoxicillin and amoxicillin potassium clavulanate	Full dose, short inpatient hospitalization (11)	No
		Phenoxymethyl penicillin		Full dose, short inpatient hospitalization (12)	No
		Fluconazole		Full dose, short inpatient hospitalization (13)	No
		Voriconazole		Full dose, short inpatient hospitalization (14)	No
		Esomeprazole		Full dose, short inpatient hospitalization (15)	No
		Cefpodoxime		Full dose, short inpatient hospitalization (16)	No
25	Amoxicillin potassium clavulanate (−1)	Amoxicillin potassium clavulanate	(1)	Full dose, short inpatient hospitalization (5)	No
26	Diltiazem (0), digoxin (0)	Digoxin	(3)(2) PT positive for diltiazem	Full dose, short inpatient hospitalization (9)	No
		Verapamil		Full dose, short inpatient hospitalization (10)	No
27	Amoxicillin potassium clavulanate (−1), cefpodoxime (−1), ibuprofen (−4), acetylcysteine (−2)	Amoxicillin potassium clavulanate	(1)	Full dose, short inpatient hospitalization (6)	No
		Cefpodoxime		Full dose, short inpatient hospitalization (7)	No
		Ibuprofen		Full dose, short inpatient hospitalization (8)	No
28	Ibuprofen (−4), acetaminophen (−2)	Ibuprofen	(1)	Full dose, short inpatient hospitalization (51)	No
29	Amoxicillin (5)	Ceftriaxone	(2)	Full dose, short inpatient hospitalization (5)	No
30	Ibuprofen (1), levonorgestrel (2)	Ibuprofen	(1)	Full dose, short inpatient hospitalization (5)	No
31	Amoxicillin (−1), ibuprofen (−4), acetaminophen (−4)	Amoxicillin	(1)	Full dose, short inpatient hospitalization (10)	No
		Ibuprofen		Full dose, short inpatient hospitalization (11)	No
32	Amoxicillin (−1), carbocysteine (−2)	Cefpodoxime	(1)(2)	Full dose, short inpatient hospitalization (7)	No

NA, Not available.

*(1) One of the suspected drugs or a structurally related drug because EN was considered postinfectious, of questionable diagnosis, or non–drug-induced (essential drugs with low ALDEN scores).

†(2) Drug belonging to the same class to limit further drug avoidance.

‡(3) One of the least suspected drugs because of the presence of drugs with higher liability (proven by allergy tests or not).

§(4) Nonsuspected and nonstructurally related drug for patient or practitioner reassurance.

||See description in the text.

TABLE V. Details of the suspected drugs tested by PTs and their results

	PTs	Positive PTs, positivity rate (%)
PTs of suspected drugs for the EN	239	28 (11.7)
Suspected drugs tested in PTs		
Antibiotics	84	10 (11.9)
Beta-lactams	42	5 (11.9)
Ceftriaxone	3	2 (66.7)
Ceftazidime	1	1 (100)
Amoxicillin	19	1 (5.3)
Amoxicillin potassium clavulanate	6	1 (16.7)
Others	13	0
Macrolides and related	11	1 (9.1)
Pristinamycin	3	1 (33.3)
Others	8	0
Fluoroquinolones	7	0
Other antibiotics	23	4 (17.4)
Cotrimoxazole	17	3 (17.6)
Vancomycin	2	1 (50.0)
Others	4	0
Antivirals	5	0
Antifungals	2	0
NSAIDs	35	1 (2.9)
Ibuprofen	17	1 (5.9)
Piroxicam	4	0
Others	14	0
Analgesics	12	0
Anticonvulsants	28	6 (21.4)
Lamotrigine	14	5 (35.7)
Phenobarbital	5	1 (20.0)
Carbamazepine	3	0
Oxcarbazepine	0	0
Phenytoin	2	0
Others	4	0
Benzodiazepines	14	8 (57.1)
Tetrazepam	10	8 (80.0)
Others	4	0
Neuroleptics	2	0
Antidepressants	1	0
Proton pump inhibitors	8	1 (12.5)
Esomeprazole	5	1 (20.0)
Others	3	0
Allopurinol	7	0
Colchicine	5	0
Antihypertensive drugs	6	2 (33.3)
Ramipril	1	1 (100)
Diltiazem	1	1 (100)
Others	4	0
Anticoagulants	2	0
Iodinated contrast media	3	0
Others	26	0

19.5% of patients had at least 1 positive PT, similar to published series.^{10,11} The percentage of positive PTs was associated with the ALDEN score for the suspected drugs tested ($P < .001$), which might suggest good PT specificity.

The percentage of PT positivity for suspected drugs differed by the drug: the most frequent positive results were with tetrazepam, lamotrigine, cotrimoxazole, and ceftriaxone. Of note, tetrazepam was withdrawn from the European market in 2013 owing to excess risk of EN.³⁴ In contrast, although often suspected and tested, drugs such as amoxicillin or ibuprofen induced only a few positive PTs (Table V). The negative predictive value of PTs in EN is unknown.¹¹ A difference of sensitivity according to the drug has been reported. Lin et al¹² reported 62.5% ($n=10/16$) positive PTs with carbamazepine, which is a much higher positivity than 9.1% ($n=2/22$) and 23.5% ($n=4/17$) in the other 2 series of EN PTs with miscellaneous drugs in European populations.^{10,11}

Two PTs were positive on only previously injured skin and not uninjured skin on the back. In EN, 1 case of a positive PT on only previously injured skin was reported.³⁵ Adding PTs on previously injured skin may be useful for EN if no dorsal skin lesion had occurred during the acute phase (which is unusual in our clinical experience) or if there is any doubt with a generalized bullous fixed drug eruption.

Time from EN to PTs did not affect their positivity. There is no recommendation on the time frame for testing after EN.¹¹ A loss of detectable drug sensitivity over time has been described. In the series by Kauppinen,²³ 8 patients with SJS had DPTs: the 5 patients challenged within 4 months after SJS had reactions, whereas the 3 patients challenged after 4 months had a negative DPT. Lymphocyte transformation tests also yield higher positive results if performed within 8 weeks of the acute phase.³⁶ Patients in our study were tested mostly after 4 months (Table I). Larger series are needed to find the optimal time between the acute phase of EN and skin tests. Although our study definitely cannot answer this question, we suggest that testing within 4 months might be necessary to increase test sensitivity in EN.

In our series, SPTs/IDTs, performed in 15% of patients, with higher dilutions than in other CADR in two-thirds of cases, were not sensitive but did not reactivate any EN. The absence of adverse reactions to SPTs/IDTs in this study and the literature may suggest that they could be performed safely in EN.¹³⁻¹⁶ However, the low number of SPTs/IDTs performed in our series does not allow for strongly asserting their usefulness and their tolerance in EN. The tests must be performed in larger series to conclude, especially for drugs with sensitive SPTs/IDTs in other CADR such as beta-lactams.^{19,30} In the literature, 6 of the 7 positive IDTs in EN were with beta-lactams.¹³⁻¹⁶

For DPTs, Kauppinen²³ reported diagnostic DPTs in 18 EN cases; 6 of 18 were positive: 5 mild eruptions without mucosal involvement or epidermal detachment and 1 with mucosal involvement and blisters healed in 2 weeks. In the latter patient, the causal drug had been reintroduced only 3 days after the initial episode of SJS. A later study reported rechallenges of antituberculosis drugs involved in 24 EN cases with human immunodeficiency virus–tuberculosis coinfection; 11 reacted with a rash without mucosal involvement or epidermal detachment.²⁴ Two relapses of EN have also been reported after prescription of anticonvulsants of different classes.³⁷ Moreover, relapses after accidental rechallenges have been described.³⁸ In our study, DPTs, performed essentially in 1 center, were promising because they confirmed current tolerance of needed drugs without serious reactions. Of note, most of the DPTs were performed directly after PTs, without SPTs/IDTs. The only reaction observed after DPT with acetaminophen was mild, as were most of those

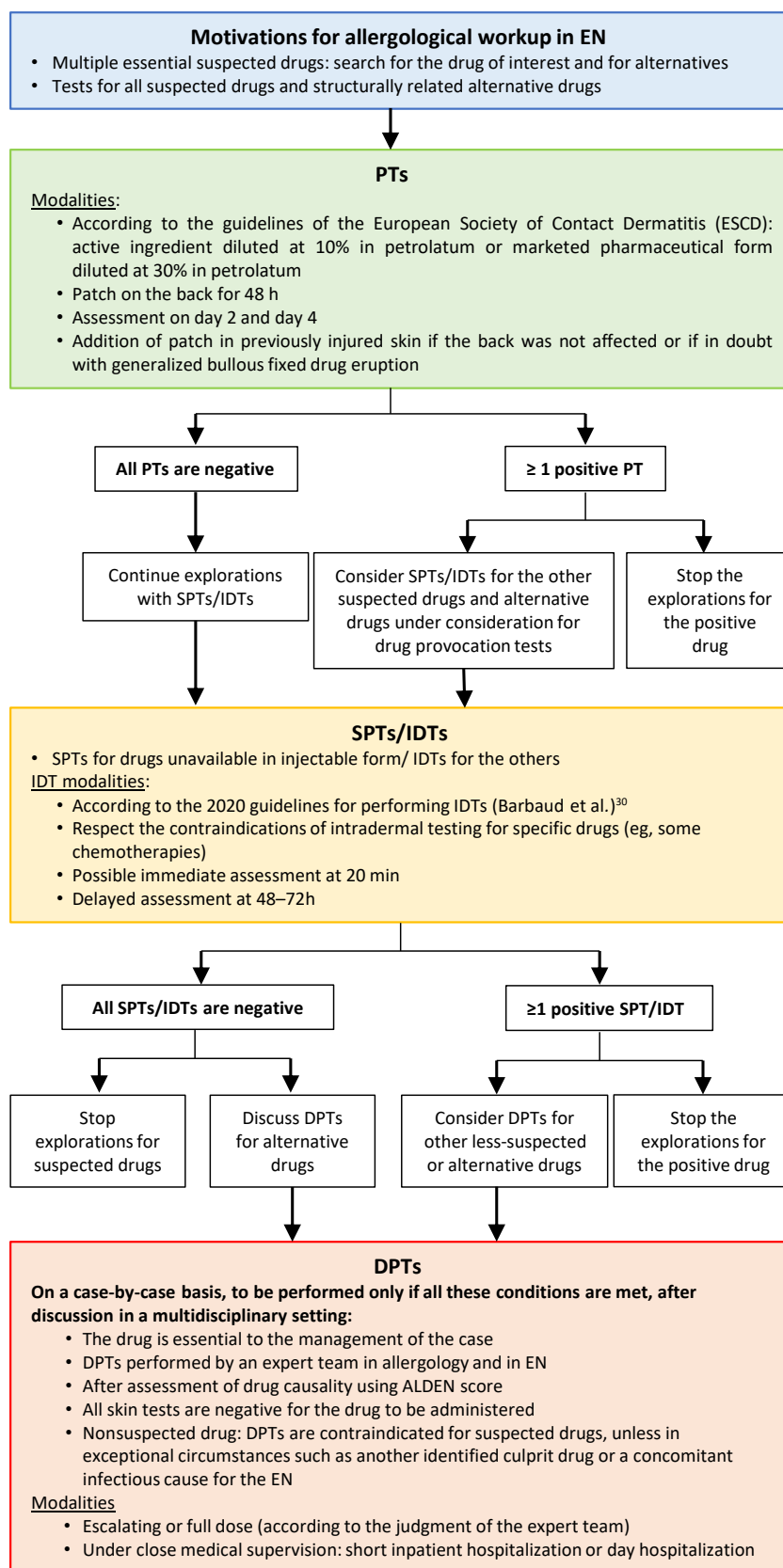


FIGURE 1. Proposed algorithm for allergological workup in EN.

reported in previous studies, and early (20 minutes after resumption), which is unexpected in a delayed hypersensitivity.^{23,24} However, the reactions of the 6 positive DPTs in the Kauppinen series²³ occurred within 6 hours, including 1 immediate-type eruption with urticaria and facial edema.²³ Although in our case the relevance of acetaminophen as suspect for the initial episode of EN was questionable (ALDEN score was 0), early or mild reaction to a resumed drug does not seem to rule out its causality for EN.^{23,24} Given the early onset of reactions in the literature and in our case, short-term hospital monitoring seems appropriate for DPTs: daycare or short inpatient hospitalization.

The explanation of the low sensitivity of skin tests and the only reaction observed after DPTs is challenging. The main trigger for keratinocyte necrosis in EN is the release of granzyme, perforin, and granzyme B by cytotoxic T lymphocytes and natural killer cells.³⁹ The tests do not seem to reproduce this mechanism, perhaps because of a lack of memory T cells persisting after the acute episode, the absence of a danger signal (eg, concomitant infection), or the absence in the tests of a metabolite of the drug causing the EN.

Limitations of this study are its retrospective design and the small sample of patients evaluated by SPTs/IDTs and DPTs. The DPTs were mainly performed in 1 center, which may limit their interpretation. The variation in testing between centers reinforces the need to standardize allergological practices in EN.

We propose an algorithm for the workup of EN to be adapted to each patient (Figure 1). Allergological testing should be done if any of the suspected drugs are essential for the patient to find alternatives to be resumed by DPTs. All suspected drugs (started within 4 weeks prior and still in use or stopped less than 5 half-lives at the time of EN) should be tested by skin testing as should structurally related alternative drugs with a risk of cross-reaction. Although this testing was sometimes performed in our study for reassurance, nonstructurally related drugs with no risk of cross-reaction should not be tested or they may induce adverse sensitization. The PTs should be performed first, followed, if negative, by delayed-reading SPTs/IDTs. The SPTs can be performed for drugs unavailable in injectable form. The IDTs are possible for injectable drugs, with no strong argument for performing higher dilutions than in other CADRs. Then negative skin tests for the less-suspected drugs with low ALDEN score (≤ 1) or their structurally related drugs may allow DPTs to be considered in some cases. The DPTs for essential drugs may be discussed within a multidisciplinary setting with experts in EN, allergology, and pharmacovigilance, after assessment of drug causality, using at best ALDEN scores for each drug, if all skin tests for that drug were negative and even more if another suspected drug had a positive test or if an infectious cause was identified. The benefit-to-risk ratio of DPTs in EN should be carefully considered. The DPTs are used to reassure and confirm current tolerance to essential drugs but, of course, never for diagnostic purposes to prove the EN and its causal drug.

Skin tests and DPTs can complement *in vitro* tests such as human leukocyte antigen allele screening or lymphocyte transformation tests, but these latter are often not available in routine practice.^{36,40}

Allergological workup seems safe in EN. Skin tests, although of limited sensitivity, are useful. The DPTs are reserved for special cases. They should be considered only to confirm current tolerance to essential drugs and if the strict conditions for their

performance are respected. We propose an algorithm to harmonize hypersensitivity testing of patients with EN.

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TABLE E1. Details of all drugs tested by PTs and their results

Drugs tested by PTs	PTs	Positive PTs, positivity rate (%)
All PTs	460	31 (6.7)
Antibiotics	204	12 (5.9)
Beta-lactams	147	7 (4.8)
Ceftriaxone	12	3 (25)
Ceftazidime	4	1 (25)
Amoxicillin	26	1 (3.8)
Amoxicillin potassium clavulanate	7	1 (14.3)
Others	98	1 (1.1) (cefepime)
Macrolides and related	18	1 (5.6)
Pristinamycin	4	1 (25)
Others	14	0
Fluoroquinolones	14	0
Other antibiotics	25	4 (16)
Cotrimoxazole	17	3 (17.6)
Vancomycin	2	1 (50.0)
Others	6	0
Antivirals	5	0
Antifungals	3	0
NSAIDs	78	1 (1.3)
Ibuprofen	23	1 (4.4)
Piroxicam	8	0
Others	47	0
Analgesics	13	0
Anticonvulsants	51	6 (11.8)
Lamotrigine	15	5 (33.3)
Phenobarbital	10	1 (10)
Carbamazepine	8	0
Oxcarbazepine	3	0
Phenytoin	5	0
Others	10	0
Benzodiazepines	16	8 (50)
Tetrazepam	10	8 (80)
Others	6	0
Neuroleptics	2	0
Antidepressants	1	0
Proton pump inhibitors	21	1 (4.8)
Esomeprazole	9	1 (11.1)
Others	12	0
Allopurinol	7	0
Colchicine	5	0
Antihypertensive drugs	15	2 (13.3)
Ramipril	1	1 (100)
Diltiazem	1	1 (100)
Others	13	0
Anticoagulants	2	0
Iodinated contrast media	5	0
Others	32	1 (3.1) (gliclazide)

NSAIDs, Nonsteroidal anti-inflammatory drugs; PTs, patch tests.

TABLE E2. Details of nonsuspected and nonstructurally related drugs tested by PTs and their results

Nonsuspected and nonstructurally related drugs tested by PTs	PTs (n)	Positive PTs (n)
PTs of nonsuspected and nonstructurally related drugs	31	0
NSAIDs	25	0
Ibuprofen	4	0
Piroxicam	4	0
Diclofenac	4	0
Ketoprofen	3	0
Acetylsalicylic acid	3	0
Celecoxib	2	0
Nimesulide	2	0
Naproxen	1	0
Niflumic acid	1	0
Phenylbutazone	1	0
Analgesics: acetaminophen	1	0
Benzodiazepines	2	0
Clonazepam	1	0
Diazepam	1	0
Proton pump inhibitors: pantoprazole	1	0
Others	2	0
Artemether-lumefantrine	1	0
Dihydroartemisinin-piperazine	1	0

TABLE E3. Univariate analysis of characteristics associated with positive PTs

Characteristics (PTs performed; n = 239)	Positive PTs (n)	P value
Sex		.4
Female	18	
Male	10	
Clinical forms of EN		.7
SJS	13	
TEN	13	
SJS/TEN overlap	2	
Age at onset of drug reaction (y) (Mann-Whitney test)		.1
Positive PTs: median (IQR) = 49.5 (31–65.2)		
Negative PTs: median (IQR) = 40 (19–56)		
Time from the acute phase of EN to testing (mo)		
≤6	10	.4
>6	16	
≤12	22	.3
>12	4	
Time from the acute phase of EN to testing (mo) (Mann-Whitney test)		.97
Positive PTs: median (IQR) = 8 (4–10)		
Negative PTs: median (IQR) = 7 (4–12)		
Main pharmacological class of suspected drugs		<.001
Antibiotics	10	
NSAIDs	1	
Anticonvulsants	6	
Tetrazepam	8	
Proton pump inhibitors	1	
Antihypertensive drugs	2	
Others	0	
ALDEN score (Mann-Whitney test)		<.001
Positive PTs: median (IQR) = 6 (3–6)		
Negative PTs: median (IQR) = 2 (0–5)		
Centers		.1
1	10	
2	8	
3	1	
4	0	
5	0	
6	1	
7	2	
8	6	

ALDEN, Algorithm of Drug Causality for Epidermal Necrolysis; EN, epidermal necrolysis; IQR, interquartile range; SJS, Stevens-Johnson syndrome; TEN, toxic epidermal necrolysis.

TABLE E4. Details of all drugs tested by IDTs

Drugs tested by IDTs	IDTs (n)	Positive IDTs (n)
All IDTs	37	1*
Antibiotics	15	0
Beta-lactams	11	0
Amoxicillin	4	0
Ceftriaxone	4	0
Cefixime	1	0
Cefuroxime	1	0
Penicillin G	1	0
Macrolides and related	3	0
Clarithromycin	2	0
Clindamycin	1	0
Fluoroquinolones: levofloxacin	1	0
NSAIDs	10	0
Ibuprofen	3	0
Nimesulide	2	0
Phenylbutazone	2	0
Diclofenac	1	0
Ketoprofen	1	0
Piroxicam	1	0
Analgesics: acetaminophen	4	0
Benzodiazepines: clonazepam	1	0
Iodinated contrast media: iobitridol	3	0
Others: bortezomib	4	1*

IDTs, Intradermal tests.

*Considered irrelevant.