

ORIGINAL ARTICLE

CONTACT
DERMATITIS

WILEY

Hypersensitivity to antibiotics in drug reaction with eosinophilia and systemic symptoms (DRESS) from other culprits

Luis G. Santiago¹  | Francisca J. Morgado¹  | Mariana S. Baptista¹  |
Margarida Gonalo^{1,2} 

¹Department of Dermatology, Coimbra University Hospital, Coimbra, Portugal

²Faculty of Medicine, University of Coimbra, Coimbra, Portugal

Correspondence

Dr Luis G. Santiago, Department of Dermatology, Centro Hospitalar e Universit rio de Coimbra, Praceta Prof. Mota Pinto, Coimbra 3000-075, Portugal.
Email: luisgsantiago2@gmail.com

Abstract

Background: Antibiotics have been implicated in the reactivation of exanthema and systemic involvement in drug reaction with eosinophilia and systemic symptoms (DRESS); however, it is not clear whether these patients become sensitized to the antibiotic.

Objective: To evaluate if, after DRESS, patients become sensitized to antibiotics.

Methods: We retrospectively reviewed the patch test (PT) data and clinical files of DRESS patients who were administered antibiotics during DRESS from other culprits.

Results: Nine patients out of 17 (53%) were positive to antibiotics in PT: six to the penicillin group and three to cephalosporins (including one patient with additional positivity to vancomycin). Considering the eight patients who were negative to antibiotics in PT, seven were exposed to a fluoroquinolone. Four cases were patch tested again and three remained positive to antibiotics 2 to 5 years thereafter. Two patients with positive PT results had an accidental re-exposure to antibiotics and developed a maculopapular exanthema without systemic symptoms.

Conclusion: Exposure to antibiotics during DRESS or its prodromal phase could enhance sensitization to antibiotics, as confirmed by a positive PT. Reproducibility of positive PTs to antibiotics after several years and reactivation after re-exposure support that T-cell-mediated hypersensitivity to antibiotics in the setting of DRESS is a specific reaction.

KEYWORDS

antibiotics, cutaneous adverse drug reactions, DRESS, hypersensitivity, neosensitization, patch test

1 | INTRODUCTION

Drug reaction with eosinophilia and systemic symptoms (DRESS) is a severe cutaneous adverse drug reaction (CADR) resulting from a complex interplay between drugs and a virus in a susceptible host. Drug-

specific immune response is a key factor, with aromatic anticonvulsants and allopurinol as the most frequently reported culprits.^{1,2} Multiple drug hypersensitivity (MDH), a concept described by Sullivan et al in 1989 after the report of drug reactions to non-beta-lactam antimicrobial drugs in 13% of penicillin-allergic patients,³ may also play a role in the

persistence of clinical manifestations and longer duration of drug hypersensitivity reactions.^{4,5} MDH is more prevalent in severe drug reactions (mostly DRESS, but also severe exanthema or erythroderma) than expected, compared with mild drug reactions.⁶

The clinical presentation of DRESS is heterogeneous and includes cutaneous manifestations (exanthema or erythroderma) and systemic involvement (hematological, hepatic, renal and/or cardiac, among others), but pathognomonic clinical, laboratorial, or histopathologic features are lacking.^{1,2} Owing to the initial prodromal presentation with fever, malaise, and a widespread rash that may mimic an infectious disease, antibiotics are frequently administered,⁷ and they may aggravate the course of the disease, namely, with reactivation of the exanthema and systemic involvement, but it is not clear whether these individuals actually become sensitized to the antibiotic.

The present study aims to evaluate if patients with DRESS from other culprits developed aggravation because of sensitization to antibiotics administered during the course of the disease, or during its prodromal phase, using the positive patch test (PT) as the evidence of a delayed hypersensitivity reaction to the antibiotic.

2 | METHODS

In a retrospective study, we reviewed PT data and clinical files of DRESS patients (probable or definite cases based on the RegiSCAR diagnostic criteria⁸) from our institution who were patch tested between January 2010 and December 2018. Only patients with a history of concomitant antibiotic administration and a highly probable nonantibiotic culprit (according to the French pharmacovigilance criteria defined by Bégaud et al⁹) were included. Patients had no previous history of antibiotic hypersensitivity and denied previous drug reactions. We looked also for positive accidental reintroduction and cutaneous drug reactions since the first PT. Patients who had positive PT reactions to antibiotics more than 2 years ago were invited, by telephone, to perform new PTs. In cases with clinical imputability to allopurinol, testing for HLA-B*58:01 was performed after 2013.

All PTs were performed, following the patient's informed consent, between 6 weeks and 6 months after resolution of the initial reaction and at least 1 month after discontinuation of systemic corticosteroids. Culprit drugs and a whole series of systemic antibiotics were tested 10% petrolatum (pet.; Chemotechnique Diagnostics, Vellinge, Sweden) with some additional antibiotics prepared locally 10% pet. using the intravenous powder or capsules/tablets (Table 1). As controls for the allergens prepared at our laboratory, we tested all other patients who were exposed, or reacted, to other culprit antibiotics. Allergens were applied on the upper back for 48 hours with Finn chambers on Scanpor tape. PT readings were performed on day (D) 2 or D3 and D4 or D7, according to ESCD guidelines.¹⁰ Only + (erythema and infiltration of the whole PT area) or more intense reactions were considered positive. Reproducibility of positive PT results was defined as the persistence of a positive reaction over time, regardless of its intensity.

We used the IBM SPSS software, version 21.0 (Armonk, New York) to perform the chi-square test, the Mann-Whitney *U* test,

and the independent sample *t* test to compare categorical, nonparametric, and parametric data, respectively. Statistical significance was considered for a *P*-value < .05.

3 | RESULTS

We included 17 patients (eight females/nine males; age range, 10 to 89 years [mean 47.4 ± 24.6]) with DRESS from a nonantibiotic culprit drug who were given antibiotics at the onset or later during the course of the reaction, namely, penicillin derivatives in seven, cephalosporins in three, and fluoroquinolones in seven patients (Table 2). In addition, two patients received more than one class of antibiotics (vancomycin in patient 7 and piperacillin/tazobactam in patient 15). No flare-up of CADRs occurred during patch testing and no unexplained positive reactions were observed within the entire series of antibiotics tested.

The number of patients tested with the same antibiotic series at our institution during the same period was 242 (179 females and 63 males), ranging from 9 to 93 years (mean 50.8 ± 18.9 years). Patients suffered mainly from maculopapular exanthema (*n* = 183), followed by DRESS (*n* = 19), acute generalized exanthematous pustulosis (*n* = 10), photosensitive eruptions (*n* = 9), delayed urticaria (*n* = 8), fixed drug eruption (*n* = 7), and Stevens-Johnson syndrome/toxic epidermal necrolysis (*n* = 6). Two patients had DRESS from cotrimoxazole without any other suspected drug and, therefore, were

TABLE 1 Allergens included in our patch testing series of antibiotics

Allergens supplied by Chemotechnique Diagnostics	Allergens prepared in-house
Amoxicillin trihydrate	Amoxicillin-clavulanic acid ^a
Benzylpenicillin potassium salt	Ampicillin ^b
Cefalexin	Cefazolin ^b
Cefradine	Cefoxitin ^b
Cefotaxime sodium salt	Ceftizoxime ^a
Cefuroxime sodium	Ceftriaxone ^c
Ciprofloxacin hydrochloride	Cefuroxime ^c
Clarithromycin	Cotrimoxazole ^a
Clindamycin phosphate	Imipenem-cilastatin ^c
Cotrimoxazole	Levofloxacin ^a
Dicloxacillin sodium salt hydrate	Lomefloxacin ^a
Doxycycline monohydrate	Meropenem ^c
Erythromycin base	Metronidazole ^b
Minocycline hydrochloride	Piperacillin-tazobactam ^c
Norfloxacin	Teicoplanin ^c
Spiramycin base	Vancomycin ^c

^aAllergen prepared from tablet or capsules obtained from the hospital pharmacy.

^bAllergen prepared from the pure drug supplied by a pharmaceutical company.

^cAllergen prepared from powder from the hospital pharmacy for intravenous injection.

not included in this study. PT reactivity was higher for penicillins ($n = 29$, 25.9% of suspected cases), mainly for amoxicillin ($n = 23$, 25.1%), followed by the lincosamides (clindamycin) ($n = 12$, 19.7%), cephalosporins ($n = 7$, 7.6%), and fluoroquinolones ($n = 5$, 11.9%).

3.1 | Characteristics of the population

Among the 17 DRESS cases included (Table 2), cutaneous manifestations developed within 25.5 ± 6.0 days (range 13 to 36) after drug administration and consisted of a generalized maculopapular rash involving more than 50% of the body surface in 14 patients (82%) or erythroderma in three (18%), and facial edema in 12 (71%). Systemic manifestations included pyrexia in 14 patients (82%), lymphadenopathy in 11 (65%), and liver and/or renal involvement in 17 (100%). Atypical circulating lymphocytes were found in 10 patients (59%) and eosinophilia (>700 eosinophils/ μL) in 16 (94%). Antibiotics were administered for a median of 6 days, in five cases before the development of skin manifestations. Five patients started antibiotics during hospitalization, two due to misdiagnosis (cases 3 and 7) and three due

to concomitant infectious disease (case 15 cholecystitis; case 16 urinary tract infection; and case 17 pneumonia).

The mechanisms underlying DRESS development were not investigated in the majority of cases: human herpesvirus 6 (HHV-6) infection was detected by quantitative polymerase chain reaction (PCR) assay after 2012 in less than half of cases and was positive in 75% (Table 2). Other potential causes of symptoms besides drugs were ruled out in all cases based on the following criteria: absence of anti-nuclear antibody $>1:80$ and antidouble-stranded DNA; negative blood culture; and negative serology for hepatitis B, hepatitis C, and human immunodeficiency virus.

3.2 | Culprit drug and PT reactivity

Based on the clinical data, chronology, and rechallenge, antiepileptic agents were the triggers in 10 patients (carbamazepine 6, phenytoin 2, hydantoin 1, topiramate 1) and allopurinol in seven patients (Tables 3 and 4). PT to the culprit anticonvulsant was positive in 90%, particularly to carbamazepine, but no reactivity was observed with

TABLE 2 Clinical characteristics of the patients

Case	Year	Age	Sex	Positive PT to AB	DRESS duration (d) ^a	Duration of AB (d)	AB administration ^b	RegiSCAR criteria ^d	Flare-up reported ^e	HHV6	Resolution (wk)
1	2010	12	M	+	31	10	D-15 to D-6 ^c	6		n.t.	3
2	2010	25	F		24	7	D-4 to D2	6		n.t.	3
3	2010	70	M	+	23	4	D0 to D3	7	Yes	n.t.	5
4	2011	51	M	+	33	5	D-4 to D0 ^c	5		n.t.	3
5	2012	52	F		18	7	D-8 to D-2 ^c	6		n.t.	4
6	2012	53	M		24	5	D-10 to D-4	8		n.t.	5
7	2012	69	F	+	30	9	Cefoxitin D0 to D1; Ceftazidime and vancomycin D2 to D8	7	Yes	n.t.	6
8	2012	70	F	+	29	7	D-7 to D-1	5		+	4
9	2013	22	M		13	4	D-3 to D0	5		-	3
10	2013	25	M	+	20	4	D-3 to D0 ^c	5		+	4
11	2013	62	F		26	7	D-8 to D-2	6		+	4
12	2015	16	M	+	20	5	D-4 to D0 ^c	6		n.t.	3
13	2015	89	F		31	7	D-11 to D-5	7		+	4
14	2016	55	M		23	5	D-4 to D0	5		+	3
15	2017	49	M	+	30	7	D0 cefoxitin; D1 to D6 piperacillin/tazobactam	8	Yes	+	7
16	2018	10	F		22	2	D0 to D1	7		n.t.	4
17	2018	76	F	+	36	7	D0 to D6	7		-	4

^aTime between first culprit drug intake and first manifestations of DRESS.

^bPositive and negative days are in relation with the day of hospitalization (D0).

^cStarted antibiotic therapy before the development of skin manifestations.

^dRef. 8.

^eFlare is characterized by a rapid elevation of hepatic and renal panel, eosinophilia and/or progression to erythroderma following onset of symptoms when another drug is given.

TABLE 3 Characteristics of patients with positive PT to antibiotics used concomitantly during DRESS from a nonantibiotic culprit

Case	Culprit drug	Antibiotic used during DRESS	PT reactions ^a	Repeated PT reactions ^b	HLA-B*58:01
1 ^c	Carbamazepine	Amoxicillin	Carbamazepine +++ Amoxicillin +++ Ampicillin +++	Carbamazepine + Amoxicillin +++ Ampicillin ++	n.t.
3	Carbamazepine	Amoxicillin	Carbamazepine ++ Amoxicillin + Ampicillin +	n.t.	n.t.
4	Carbamazepine	Amoxicillin	Carbamazepine ++ Amoxicillin + Ampicillin ++	Carbamazepine + Amoxicillin Neg Ampicillin Neg	n.t.
7 ^c	Phenytoin	Cefoxitin Ceftazidime Vancomycin	Phenytoin ++ Cefazolin +++ Cefoxitin +++ Cefotaxime n.t. Vancomycin +++ Acyclovir ++	Phenytoin Neg Cefazolin ++ Cefoxitin ++ Cefotaxime ++ Vancomycin ++ Acyclovir ++	n.t.
8	Carbamazepine	Amoxicillin	Carbamazepine ++ Amoxicillin ++ Ampicillin ++	n.t.	n.t.
10	Allopurinol	Amoxicillin	Allopurinol Neg Amoxicillin ++ Ampicillin ++	n.t.	Pos
12	Carbamazepine	Amoxicillin	Carbamazepine ++ Amoxicillin +	Carbamazepine ++ Amoxicillin +	n.t.
15	Allopurinol	Cefoxitin Piperacillin/tazobactam	Allopurinol Neg Cefoxitin ++ Piperacillin/tazobactam Neg	n.t.	Pos
17	Allopurinol	Ceftriaxone	Allopurinol Neg Ceftriaxone ++ Cefotaxime +	n.t.	Pos

Abbreviations: DRESS, drug reaction with eosinophilia and systemic symptoms; Neg, no reaction; n.t., not tested; Pos, positive; PT, patch test.

^aReadings on day (D) 2 or D3 and D4-D7.

^bPT repeated in 2015 for cases 1 and 4; in 2017 for cases 7 and 12.

^cPatients with accidental re-exposure to antibiotics (amoxicillin in case 1 and cefotaxime in case 7).

allopurinol. HLA-B*58:01 was positive in five of seven patients reacting to allopurinol.

3.3 | Antibiotics and PT reactivity

Nine patients (53%) developed positive PT to antibiotics (Table 3): six to penicillins, three to the cephalosporins (including one patient with additional positivity to vancomycin), and none to ciprofloxacin or levofloxacin. A positive reaction to a single antibiotic was observed in two of the nine patients, whereas the majority (77.8%) had more than one positivity that could be attributed to cross-reaction, namely, between amoxicillin and ampicillin in five cases and between different cephalosporins in two cases. Patient 6 was additionally positive to acyclovir.

Considering the eight patients (47%) with negative PT, seven (88%) had a history of fluoroquinolone administration during DRESS and one had used amoxicillin (Table 4). Oral rechallenge was not performed in these patients; however, none were advised to avoid these antibiotics that tested negative. The only patient with a negative PT

to amoxicillin had a small latency between administration of the two drugs, negative PCR for HHV-6 and did not report a flare.

When comparing these subgroups, flare-up reactions during DRESS were more prevalent in the positive PT group ($P = .008$). No association was found between PT positivity and age, sex, time between first culprit drug intake and first manifestations of DRESS, duration of antibiotic usage, RegiSCAR criteria, HHV-6, and time to resolution.

3.4 | Evolution during the DRESS episode

Three cases reported a flare characterized by an elevation of hepatic and renal panel, eosinophilia, and/or progression to erythroderma after taking the antibiotic (Table 2; case 3 after ceftriaxone; case 7 after cefoxitin and, for this reason, antibiotic therapy was changed to vancomycin and ceftazidime, respectively; case 15 after use of cefoxitin before cholecystectomy). PTs to antibiotics were positive in these cases (Table 3). All patients recovered with systemic steroids and early withdrawal of the culprit drug (median 4 weeks). As expected, patients that reported a flare presented a slower resolution of skin and systemic symptoms.

TABLE 4 Characteristics of patients with negative PT to antibiotics used concomitantly during DRESS by a nonantibiotic culprit

Case	Imputable drug	Antibiotic introduction	PT reactions ^a	HLA-B*58:01
2	Topiramate	Ciprofloxacin	Topiramate + Ciprofloxacin Neg	n.t.
5	Allopurinol	Ciprofloxacin	Allopurinol Neg Ciprofloxacin Neg	n.t.
6	Phenytoin	Ciprofloxacin	Phenytoin ++ Ciprofloxacin Neg	n.t.
9	Carbamazepine	Amoxicillin	Carbamazepine ++ Amoxicillin Neg	n.t.
11	Allopurinol	Levofloxacin	Allopurinol Neg Levofloxacin Neg	Pos
13	Allopurinol	Ciprofloxacin	Allopurinol Neg Levofloxacin Neg	Neg
14	Allopurinol	Levofloxacin	Allopurinol Neg Levofloxacin Neg	Pos
16	Hydantoin	Ciprofloxacin	Hydantoin Neg Ciprofloxacin Neg	n.t.

Abbreviations: DRESS, drug reaction with eosinophilia and systemic symptoms; Neg, no reaction; n.t., not tested; Pos, positive; PT, patch test.

^aReadings on day (D) 2 or D3 and D4-D7.

3.5 | Repeat patch test and accidental re-exposure

Four patients accepted the invitation and were patch tested again 2 to 5 years after the first episode and three of these four patients had again the same positive reaction to antibiotics. Two patients, during accidental systemic re-exposure to antibiotics (amoxicillin in case 1 and cefotaxime in case 7), developed maculopapular exanthema with no systemic symptoms, therefore with no reactivation of DRESS.

4 | DISCUSSION

Multiple drug hypersensitivity (MDH) has been reported in the literature with incidence rates between 10% and 18% when considering severe drug reactions proven by positive skin or *in vitro* tests.^{3,4,11,12} Our case series suggests that hypersensitivity to antibiotics in DRESS from a nonantibiotic culprit is much more common. We confirmed this reactivity in 53% of positive patch tested patients, with four patients (patients 1, 4, 7, and 12) having similar PT reactions years later and two cases by accidental reintroduction (patients 1 and 7). In six patients the antibiotic was maintained after the diagnosis, mainly because a concomitant infectious disease could not be disregarded: three patients reported a flare-up reaction and had positive PT to these antibiotics, supporting the possibility of a new sensitization. Patient 6 supports this concept: he had positive PT to all the drugs administered during the episode (three antibiotics, acyclovir, and the culprit).

The pathogenesis of DRESS is complex and mechanistic explanations are multiple and not mutually exclusive^{1,2,13-15}: disturbance in the delicate balance between circulating and dermal-infiltrating effector T cells and regulatory T cells; genetic deficiency of detoxifying enzymes such as epoxide hydrolase; association with human leukocyte antigen (HLA) haplotypes, such as HLA-B*57:01 for abacavir,

HLA-A*31:01 for carbamazepine, and HLA-B*58:01 for allopurinol; reactivation of HHVs, in particular HHV-6, Epstein-Barr virus (EBV), HHV-7, and cytomegalovirus (correlating with immune dysregulation); drug-induced immunosuppression followed by an inflammatory immune recovery syndrome; drug-specific T cells, suggesting a T-cell-mediated reaction. Our findings suggest that T-cell-mediated hypersensitivity to antibiotics in the setting of DRESS is a specific reaction, very probably a “neosenitization,” and not a transient reactivity during the strong immunostimulation as previously implied. Possibly, during the massive activation of the immune system induced by other culprits,^{4,16,17} presentation of these drugs to the immune system is enhanced and individuals indeed become sensitized. Furthermore, the enhanced *in vitro* viral replication after exposure of patient's lymphocytes to aminopenicillin has been demonstrated for HHV-6 and implicated as a possible mechanism to induce a flare-up reaction.¹⁸

Flare-up reactions are described as the transient and rapid reappearance of identical symptoms when another drug is given while the immune system is still activated by the first drug reaction.¹⁹ They start hours after taking a new drug with an elevation of hepatic and renal laboratory markers, eosinophilia, and/or progression of pre-existing skin symptoms; prompt withdrawal of the new therapy is indicated. It was previously assumed that the second drug does not stimulate the immune system long enough to cause T-cell expansion and permanent sensitization.⁴ However, we observed that even 1 to 2 days of drug administration could be sufficient to elicit a positive reaction (cases 7 and 15). Patient 15 was admitted with a cholecystitis-like acute abdomen in the context of a DRESS syndrome to allopurinol. After one administration of cefoxitin as a perioperative antimicrobial prophylaxis, the patient developed a massive systemic reaction with erythroderma and the PT was positive only to cefoxitin.

Reactivity to the antibiotics in the PT was variable according to the class of antibiotics, with no positive PT observed with fluoroquinolones. Generally, when patch testing antibiotics in nonimmediate CADR,

reactivity to penicillins (3%–25.4%) is more frequent than reactivity to fluoroquinolones, namely, to ciprofloxacin or levofloxacin (0%–17.5%).^{20,21} Nevertheless, quinolone skin tests are considered a useful tool for diagnosing hypersensitivity. A negative PT predicted a negative challenge result in 94% and only 5% of patients with a negative skin test had a positive challenge test.²² No other statistically significant differences were found that could explain the between different classes in patch testing.

This study confirms the long-term high reproducibility of PT to some antibiotics described previously.²³ Daubner et al demonstrated that while the massive T-cell stimulation with circulating lymphoblasts disappeared within weeks to months after the acute MDH, some signs of T-cell activation persisted for longer.²⁴ Among four patients, there was 75% persistence of PT to the antibiotic 2 to 5 years after the initial onset of DRESS, including one case in which the PT positivity to the culprit became negative (case 6). In two cases with accidental re-exposure to the antibiotic, patients developed a maculopapular exanthema different from the initial DRESS episode. This is consistent with the observation that in DRESS each T-cell clone was highly specific for a single drug with a distinct cytokine production upon drug-specific stimulation.²⁵ Chemical structural differences between penicillins/cephalosporins and allopurinol/anticonvulsants and different pathways of drug metabolism suggest that a possible cross-reaction is unlikely.

A curious finding was that although these patients already had signs of drug hypersensitivity (fever, lymphadenopathy, and organ involvement), five patients only developed a skin rash after starting the antibiotic. This resembles EBV infection, when few individuals develop exanthema during the acute infection, but when given antibiotics (aminopenicillins are by far the most common culprit) almost all develop exanthema and some also become newly sensitized to the antibiotic and may develop a specific drug reaction following later re-exposure.^{26,27}

5 | CONCLUSION

Additional sensitization to an antibiotic during DRESS could explain some cases of prolonged clinical symptoms and exacerbations following discontinuation of the culprit. Approximately 50% of patients may develop an multidrug resistance to antibiotics, particularly penicillins. It is possible that fluoroquinolones have a lower risk for the development of an MDH. We therefore reinforce the need to avoid new drug exposure during DRESS, due to the higher risk of a new and lifelong sensitization.

CONFLICT OF INTERESTS

The authors declare no conflicts of interest.

ORCID

Luis G. Santiago  <https://orcid.org/0000-0003-2587-5535>

Francisca J. Morgado  <https://orcid.org/0000-0001-5006-4334>

Mariana S. Baptista  <https://orcid.org/0000-0003-3442-615X>

Margarida Gonalo  <https://orcid.org/0000-0001-6842-1360>

REFERENCES

1. Santiago F, Gonalo M, Vieira R, Coelho S, Figueiredo A. Epicutaneous patch testing in drug hypersensitivity syndrome (DRESS). *Contact Dermatitis*. 2010;62(1):47–53.
2. Cacoub P, Musette P, Decamps V, et al. The DRESS syndrome: a literature review. *Am J Med*. 2011;124(7):588–597.
3. Sullivan TJ, Remedios C, Ong MD, Gilliam LK. Studies of the multiple drug allergy syndrome. *J Allergy Clin Immunol*. 1989;83:270.
4. Pichler WJ, Srinoulprasert Y, Yun J, Hausmann O. Multiple drug hypersensitivity. *Int Arch Allergy Immunol*. 2017;172(3):129–138.
5. Gex-Collet C, Helbling A, Pichler WJ. Multiple drug hypersensitivity—proof of multiple drug hypersensitivity by patch and lymphocyte transformation tests. *J Investig Allergol Clin Immunol*. 2005;15(4):293–296.
6. Studer M, Waton J, Bursztejn AC, Aimone-Gastin I, Schmutz JL, Barbaud A. Does hypersensitivity to multiple drugs really exist? *Ann Dermatol Venerol*. 2012;139(5):375–380.
7. Lee HY, Walsh S, Creamer D. Initial presentation of DRESS: often misdiagnosed as infections. *Arch Dermatol*. 2012;148(9):1085–1087.
8. Kardaun SH, Sidoroff A, Valeyrie-Allanore L, et al. Variability in the clinical pattern of cutaneous side-effects of drugs with systemic symptoms: does a DRESS syndrome really exist? *Br J Dermatol*. 2006;155(2):422–428.
9. Miremont-Salamé G, Théophile H, Haramburu F, Bégaud B. Causality assessment in pharmacovigilance: the French method and its successive updates. *Therapie*. 2016;71(2):179–186.
10. Johansen JD, Aalto-Korte K, Agner T, et al. European Society of Contact Dermatitis guideline for diagnostic patch testing - recommendations on best practice. *Contact Dermatitis*. 2015;73(4):195–221.
11. Barbaud A, Collet E, Milpied B, et al. A multicentre study to determine the value and safety of drug patch tests for the three main classes of severe cutaneous adverse drug reactions. *Br J Dermatol*. 2013;168(3):555–562.
12. Liippo J, Pummi K, Hohenthal U, Lammintausta K. Patch testing and sensitization to multiple drugs. *Contact Dermatitis*. 2013;69(5):296–302.
13. Cho YT, Yang CW, Chu CY. Drug reaction with eosinophilia and systemic symptoms (DRESS): an interplay among drugs, viruses, and immune system. *Int J Mol Sci*. 2017;18(6):1243.
14. Morito H, Ogawa K, Fukumoto T, et al. Increased ratio of FoxP3+ regulatory T cells/CD3+ T cells in skin lesions in drug-induced hypersensitivity syndrome/drug rash with eosinophilia and systemic symptoms. *Clin Exp Dermatol*. 2014;39(3):284–291.
15. Shiohara T, Mizukawa Y. Drug-induced hypersensitivity syndrome (DiHS)/drug reaction with eosinophilia and systemic symptoms (DRESS): an update in 2019. *Allergol Int*. 2019;68(3):301–308.
16. Gaig P, García-Ortega P, Baltasar M, Bartra J. Drug neosensitization during anticonvulsant hypersensitivity syndrome. *J Investig Allergol Clin Immunol*. 2006;16(5):321–326.
17. Hari Y, Frutig-Schnyder K, Hurni M, et al. T cell involvement in cutaneous drug eruptions. *Clin Exp Allergy*. 2001;31(9):1398–1408.
18. Mardivirin L, Valeyrie-Allanore L, Branlant-Redon E, et al. Amoxicillin-induced flare in patients with DRESS (drug reaction with eosinophilia and systemic symptoms): report of seven cases and demonstration of a direct effect of amoxicillin on Human Herpesvirus 6 replication in vitro. *Eur J Dermatol*. 2010;20(1):68–73.
19. Pichler WJ, Daubner B, Kawabata T. Drug hypersensitivity: flare-up reactions, cross-reactivity and multiple drug hypersensitivity. *J Dermatol*. 2011;38(3):216–221.
20. Pinho A, Coutinho I, Gameiro A, Gouveia M, Gonalo M. Patch testing - a valuable tool for investigating non-immediate cutaneous adverse drug reactions to antibiotics. *J Eur Acad Dermatol Venerol*. 2017;31(2):280–287.

21. Lammintausta K, Kortekangas-Savolainen O. The usefulness of skin tests to prove drug hypersensitivity. *Br J Dermatol*. 2005;152(5): 968-974.
22. Venturini Díaz M, Lobera Labairu T, del Pozo Gil MD, Blasco Sarramián A, González Mahave I. In vivo diagnostic tests in adverse reactions to quinolones. *J Investig Allergol Clin Immunol*. 2007;17(6): 393-398.
23. Pinho A, Marta A, Coutinho I, Gonçalo M. Long-term reproducibility of positive patch test reactions in patients with non-immediate cutaneous adverse drug reactions to antibiotics. *Contact Dermatitis*. 2017; 76(4):204-209.
24. Daubner B, Groux-Keller M, Hausmann OV, et al. Multiple drug hypersensitivity: normal Treg cell function but enhanced in vivo activation of drug-specific T cells. *Allergy*. 2012;67(1):58-66.
25. Beeler A, Engler O, Gerber BO, Pichler WJ. Long-lasting reactivity and high frequency of drug-specific T cells after severe systemic drug hypersensitivity reactions. *J Allergy Clin Immunol*. 2006;117(2): 455-462.
26. Renn CN, Straff W, Dorfmueller A, Al-Masaoudi T, Merk HF, Sachs B. Amoxicillin-induced exanthema in young adults with infectious mononucleosis: demonstration of drug-specific lymphocyte reactivity. *Br J Dermatol*. 2002;147(6):1166-1170.
27. Ónodi-Nagy K, Kinyó Á, Meszes A, Garaczi E, Kemény L, Bata-Csörgő Z. Amoxicillin rash in patients with infectious mononucleosis: evidence of true drug sensitization. *Allergy Asthma Clin Immunol*. 2015;11(1):1.

How to cite this article: Santiago LG, Morgado FJ, Baptista MS, Gonçalo M. Hypersensitivity to antibiotics in drug reaction with eosinophilia and systemic symptoms (DRESS) from other culprits. *Contact Dermatitis*. 2020;1-7. <https://doi.org/10.1111/cod.13462>