ORIGINAL ARTICLE

Deconstructing Adverse Reactions to Amoxicillin-Clavulanic Acid: The Importance of Time of Onset

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Abstract

Background: Amoxicillin-clavulanic acid (AX-CL) is the most consumed ß-lactam antibiotic worldwide. We aimed to establish the different phenotypes of ß-lactam allergy in patients reporting a reaction to AX-CL and to investigate the differences between immediate and nonimmediate onset.
Methods: We performed a cross-sectional retrospective study at Hospital Clínico San Carlos (HCSC), Madrid and Hospital Regional Universitario de Málaga (HRUM), Málaga, Spain. We included patients reporting reactions with AX-CL who underwent the allergy work-up between 2017 and 2019. Data on the reported reaction and allergy work-up were collected. Reactions were classified as immediate and nonimmediate with a 1-hour cut-off.
Results: The study population comprised 372 patients (HCSC 208, HRUM 164). There were 90 immediate reactions (24.2%), 252 nonimmediate reactions (67.7%), and 30 reactions with unknown latency (8.1%). Allergy to ß-lactams was ruled out in 266 patients (71.5%) and confirmed in 106 patients (28.5%). The final main diagnosis in the overall population was allergy to aminopenicillins (7.3%), to CL (7%), to penicillin (6.5%), and to ß-lactams (5.9%). Allergy was confirmed in 77.2% and 14.3% of immediate and nonimmediate reactions, respectively, with a relative risk of 5.06 (95%CI, 3.64-7.02) for an allergy diagnosis in those reporting immediate reactions. Only 2/54 patients with a late-positive intradermal test (IDT) result for CL were diagnosed with CL allergy.
Conclusion: Allergy was diagnosed in a minority of the study population. However, given that it was diagnosed 5 times more frequently in patients reporting immediate reactions, this classification proved useful for risk stratification. Late-positive IDT results for CL have no diagnostic value. Therefore, the late IDT reading for CL could be removed from the diagnostic work-up.

Key words: Amoxicillin-clavulanic acid. Drug allergy. Immediate reaction. Intradermal test. Nonimmediate reaction.

Resumen

Antecedentes: La amoxicilina-ácido clavulánico (AX-CL) es el antibiótico betalactámico más consumido en el mundo. En este trabajo nos propusimos establecer los distintos fenotipos de alergia a betalactámicos en pacientes que referían una reacción con AX-CL, e investigar las diferencias entre las reacciones de aparición inmediata y no inmediata.
Métodos: Estudio retrospectivo transversal realizado en el Hospital Clínico San Carlos (HCSC) y en el Hospital Regional Universitario de Málaga (HRUM) en España. Se incluyeron pacientes que referían reacciones con AX-CL que completaron el estudio alergológico entre 2017 y 2019. Las reacciones se clasificaron como inmediatas y no inmediatas con el punto de corte de 1 hora.
Resultados: Se incluyeron 372 pacientes (HCSC 208, HRUM 164). Hubo 90 (24,2%) reacciones inmediatas, 252 (67,7%) no inmediatas y 30 (8,1%) de latencia desconocida. La alergia a betalactámicos se descartó en 266 (71,5%) y se confirmó en 106 pacientes (28,5%). Los principales diagnósticos fueron alergia a aminopenicilinas (7,3%), a CL (7%), a penicilina (6,5%) y a betalactámicos (5,9%). La alergia se

confirmó en el 77,2% y el 14,3% de las reacciones inmediatas y no inmediatas, respectivamente, con un riesgo relativo de 5,06 (IC 95%: 3,64-7,02) de ser diagnosticado de alergia en los que referían reacciones inmediatas. Sólo 2 de 54 pacientes con una prueba intradérmica (IDT) tardía positiva a CL fueron diagnosticados de alergia a CL.
Conclusiones: El diagnóstico de alergia se confirmó en una minoría de los sujetos que referían reacciones a AX-CL, aunque fue 5 veces más frecuente en los que notificaron reacciones inmediatas, lo que hace que esta clasificación sea útil en la estratificación del riesgo. La IDT positiva tardía para CL no tiene valor diagnóstico y su lectura tardía es innecesaria para establecer el diagnóstico.

Palabras clave: Amoxicilina-ácido clavulánico. Alergia a medicamentos. Reacción inmediata. Prueba intradérmica. Reacción no inmediata.

Summary box

- **What do we know about this topic?**
  Amoxicillin-clavulanic acid (AX-CL) is the most consumed ß-lactam antibiotic worldwide. The different phenotypes of ß-lactam allergy in patients with adverse reactions to AX-CL and the differences between those with immediate and nonimmediate reactions have not been previosuly investigated.
- **How does this study impact our current understanding and/or clinical management of this topic?**
  Allergy diagnosis was 5 times more frequent in patients reporting immediate reactions, making this a useful tool for risk stratification. We also found that 7% of patients reporting adverse reactions to AX-CL and 24.5% of patients with proven allergy had selective CL allergy.

Introduction

ß-Lactam antibiotics are the drugs most frequently involved in allergic reactions [1]. In recent years, amoxicillin-clavulanic acid (AX-CL) has been widely used to treat a wide spectrum of infections, becoming the most consumed ß-lactam antibiotic worldwide. The ß-lactam CL inhibits ß-lactamase [2]. When AX-CL is involved in allergic reactions, it is crucial to determine which of the 2 drugs is responsible, since the difference has important consequences for therapy. Patients with confirmed allergy only to CL tolerate all other ß-lactams including AX [1], and those with a confirmed allergy to AX may be allergic to either aminopenicillins alone, to all penicillins, to penicillins and cephalosporins, or to all ß-lactams. Therefore, it is of the utmost importance to perform a comprehensive allergy work-up, not only to delabel the nonallergic patient, but also to correctly classify allergic patients and provide them with safe guidance on the ß-lactam drugs to be avoided and those allowed.

Skin prick tests (SPTs) and intradermal tests (IDTs) followed by drug provocation testing (DPT) are the main diagnostic methods in allergic reactions to ß-lactams [3,4]. In vitro tests are usually recommended in high-risk patients before skin testing in order to reduce the risk of systemic reactions. Serum-specific IgE assay (ImmunoCAP, Thermo Fisher Scientific) is available only for benzylpenicillin, penicillin V, AX, ampicillin, and cefaclor. No immunoassays to detect specific IgE to CL have been developed to date. The basophil activation test (BAT) has been used for investigational purposes. Despite its suboptimal sensitivity (up to 69%) [1], the BAT can be a useful tool in high-risk patients and potentially replace DPT in this population [5,6].

The purified CL reagent for skin testing (DAP Clavulanic, Diater) has been commercially available since 2012, thus making characterization of CL allergy easier [3]. Immediate responses in SPTs or IDTs to CL in patients reporting reactions to AX-CL are considered diagnostic [7,8], although the diagnostic value of a late positive IDT has not been established. By combining skin test results to both AX and CL, the sensitivity in finding selective responders to CL increases to 71% [9].

We analyzed a large series of patients reporting allergic reactions to AX-CL referred for an allergy work-up to the Allergy Departments of Hospital Clínico San Carlos (HCSC) in Madrid, Spain and Hospital Regional Universitario de Málaga (HRUM) in Málaga, Spain. We aimed to establish the different phenotypes of ß-lactam allergy in patients with adverse reactions to AX-CL and to investigate differences between those with immediate and nonimmediate reactions, an aspect that has not been explored previously to our knowledge. Additionally, among those with selective allergy to CL, we aimed to establish the diagnostic value of late positive IDT results.

Methods

Study Design

We performed a cross-sectional study with retrospective data recovery. We reviewed the medical records of patients reporting reactions to AX-CL and referred for study to HCSC and HRUM between 2017 and 2019 and included only those who underwent a complete allergy work-up.

A detailed history of the allergic reactions was obtained, and the variables recorded included culprit drug, dose, form of administration, latency between drug administration and onset of reaction, symptoms presented, and treatment required.

Reactions were classified as immediate and nonimmediate when the latency between drug intake or administration and

the onset of allergy symptoms was up to 1 hour or longer than 1 hour, respectively [10]. We excluded patients with fixed drug eruption, generalized acute exanthematous pustulosis, toxic epidermal necrolysis/Stevens-Johnson syndrome, drug reactions with eosinophilia and systemic symptoms (DRESS) syndrome, and drug-mediated organ-specific reactions (ie, hepatitis).

Allergy Work-up

The evaluation was performed following the diagnostic algorithm for ß-lactams [11] and the recommendations of the ENDA and EAACI Drug Allergy Interest Group [4,12,13].

SPTs and IDTs were performed with benzylpenicilloyl octa-L-lysine (0.04 mg/mL), sodium benzylpenicilloate (0.5 mg/mL), AX (20 mg/mL), and CL (20 mg/mL). Histamine and saline solution were used as positive and negative controls. Additionally, at HCSC, SPTs and IDTs were performed with penicillin G (10 000 IU/mL), cefuroxime (2 mg/mL), ceftazidime (2 mg/mL), and meropenem (1 mg/mL). If the index reaction occurred within 2 years of the patients' consultation, specific IgE (sIgE) (ImmunoCAP, Thermo Fisher Scientific) was obtained for penicilloyl G, penicilloyl V, AX, ampicillin, and cefaclor before skin testing.

Depending on how suggestive/severe the history was and the results of sIgE and skin tests, patients underwent DPT with the culprit drug or with alternative drugs. In patients with a negative DPT result to AX-CL and a reported index reaction that had occurred over 2 years previously, skin tests were repeated 3 to 6 weeks after the initial study. If negative, a new DPT was performed. In nonimmediate reactions, a negative DPT was followed by home intake of daily therapeutic doses for 2-3 days to confirm tolerance.

BATs were performed with penicillin G, AX, and CL in patients with immediate reactions at HRUM. If the BAT was positive, DPT was not performed.

Variables

Response variable: Final diagnosis (allergy to ß-lactams, penicillins, aminopenicillins, CL, cephalosporins, carbapenems, no allergy).

Variables of interest: center, sex, age at time of study and at time of reaction, time interval between reaction and study, clinical presentation and treatment of initial reaction, latency between drug administration and onset of reaction (≤1 hour [immediate] vs >1 hour [nonimmediate]), and the results of SPT, IDT, sIgE, BAT, and DPT.

Statistical Analysis

Descriptive statistics included frequency and percentage for qualitative variables and median (IQR) or mean (SD) for numerical variables, according to the normality of the distribution. Differences between immediate and nonimmediate reactions and between centers were analyzed. Qualitative variables were compared using the χ^2 or Fisher exact test. Quantitative variables were compared using the *t* test or Mann-Whitney test for normally and nonnormally distributed data, respectively. Relative risk (RR) was calculated with its 95%CI. The statistical analysis was performed with IBM SPSS Statistics for Windows, Version 26.0 (IBM Corp.) and STATA version 16. Statistical significance was set at $P<.05$.

Ethical Aspects

The HCSC Ethics Committee and the Provincial Ethics Committee of Málaga reviewed and approved the study protocol (Internal Codes: 21/585-O_M and CE PI1800095, respectively). Given the retrospective character of the study, where data were collected from medical charts, an exemption from the need for informed consent was requested and granted. All the patients included in this study had provided their written informed consent for the drug allergy work-up.

Results

Clinical Presentation of AX-CL Reactions: Differences Between Immediate and Nonimmediate Reactions and Between Centers

A total of 372 patients were included (208 at HCSC and 164 at HRUM). Mean age was 45.9 (19.4) years, and the median interval between the index reaction with AX-CL and the study was 1 (0-3) year. Most patients were female (65.6%). The most common symptoms were cutaneous (91.1%), followed by respiratory symptoms (15.6%) and gastrointestinal symptoms (11.8%). Anaphylaxis accounted for 11.3% of the reactions, syncope 4.6%, and hypotension 4.3%. The most common treatments for the reactions were antihistamines (44.1%) and corticosteroids (41.1%); adrenaline was used in only 2.7% of reactions (Table 1).

There were significant differences between centers for age at the time of the reaction, with patients being older at HCSC (46.2 years) than at HRUM (37.9 years) ($P<.01$). The interval between the reaction and the allergy work-up was significantly shorter in HCSC (Table 1). As for the clinical presentation of the reactions, patients recruited in HRUM appeared to have more severe reactions, with a significantly higher frequency of respiratory involvement (23.2% vs 9.6% at HCSC, $P<.01$), anaphylaxis (14.6% vs 8.7% at HCSC, $P=.08$), and hypotension (6.7% vs 2.4% at HCSC, $P=.048$). However, this did not translate into a higher use of adrenaline, IV fluids, or bronchodilators, and only antihistamines were more frequently administered in HRUM (Table 1).

There were 90 immediate reactions (24.2%) and 252 nonimmediate reactions (67.7%). In 30 patients (8.1%), it was not possible to establish the latency period, with the result that they were not included in the subsequent analysis that took latency into account. However, their characteristics are presented in Table 1.

Overall, as expected, immediate reactions were more severe than nonimmediate reactions, with a significantly higher frequency of anaphylaxis, hypotension, syncope, and respiratory and gastrointestinal symptoms. Only skin involvement was observed in both immediate and nonimmediate reactions. Accordingly, there were significant differences in the management of reactions, with a higher frequency in administration of adrenaline, IV fluids, bronchodilators, and corticosteroids ($P<.01$ for all drugs) in

Table 1. Study Population.

All patients n=372		HCSC vs HRUM			Latency			
		HCSC (n=208)	HRUM (n=164)	*P* Value	Unknown n=30[a]	Immediate n=90 (24.2%)	Nonimmediate n=252 (67.7%)	Immediate vs nonimmediate *P* value
Mean (SD) age at time of study, y	45.9 (19.4)	50.1 (19.7)	40.6 (17.7)	<.01	50.7 (23.8)	46.9 (16.2)	44.9 (19.9)	.38
Mean (SD) age at time of reaction, y	42.7 (20.9)	46.2 (21.1)	37.9 (19.6)	<.01	38.7 (26.9)	44.1 (17.9)	42.6 (21.2)	.54
Median (IQR) interval between reaction and allergy work-up, y	1 (0-3)	0 (0-3)	1 (0-4)	<.01	8 (1-24)	1 (0-2)	1 (0-3)	.75
Female sex, No. (%)	244 (65.6%)	146 (70.2%)	98 (59.8%)	.04	18 (60%)	53 (58.9%)	173 (68.7%)	.09
Clinical presentation								
Cutaneous	339 (91.1%)	186 (89.4%)	153 (93.3%)	.30	21 (70%)	82 (91.1%)	236 (93.7%)	.78
Respiratory[b]	58 (15.6%)	20 (9.6%)	38 (23.2%)	<.01	1 (3.3%)	38 (42.2%)	19 (7.5%)	<.01
Gastrointestinal	44 (11.8%)	20 (9.6%)	24 (14.6%)	.15	5 (16.7%)	22 (24.4%)	17 (6.7%)	<.01
Anaphylaxis	42 (11.3%)	18 (8.7%)	24 (14.6%)	.08	0	34 (37.8%)	8 (3.2%)	<.01
Syncope	17 (4.6%)	7 (3.4%)	10 (6.1%)	.23	0	13 (14.4%)	4 (1.6%)	<.01
Hypotension	16 (4.3%)	5 (2.4%)	11 (6.7%)	.048	0	13 (14.4%)	3 (1.2%)	<.01
Treatment								
Antihistamines	164 (44.1%)	77 (37%)	87 (53%)	<.01	3 (10%)	45 (50%)	116 (46%)	.05
Corticosteroids	153 (41.1%)	75 (36.1%)	78 (47.6%)	.09	1 (3.3%)	45 (50%)	107 (42.5%)	.01
Adrenaline	10 (2.7%)	6 (2.9%)	4 (2.4%)	.76	0	9 (10%)	1 (0.4%)	<.01
IV fluids	13 (3.5%)	6 (2.9%)	7 (4.3%)	.59	0	10 (11.1%)	3 (1.2%)	<.01
Bronchodilator	7 (1.9%)	3 (1.4%)	4 (2.4%)	.71	0	7 (7.8%)	0 (0%)	<.01

Abbreviations: HCSC, Hospital Clínico San Carlos; HRUM, Hospital Regional Universitario de Málaga.
[a]Unknown: 19 HCSC, 11 HRUM.
[b]Respiratory: upper and/or lower airway involvement.

immediate reactions, whereas antihistamines were used with a similar frequency in both (50% vs 46%, *P*=.05) (Table 1). Similar findings were observed within each center (Table 2).

Immediate reactions were more frequent among the patients studied at HRUM (52/164 [31.7%]) than at HCSC (38/208 [18.3%]) (*P*<.01) (Table 2). At HRUM, patients with nonimmediate reactions were significantly younger than those with immediate reactions; this difference was not observed among the patients selected at HCSC (Table 2). Among patients with nonimmediate reactions, those selected at HRUM were significantly younger (35.9 years vs 46.6 years, *P*<.01) (Table 2), thus potentially explaining the overall younger age at the time of the reaction among patients from HRUM in Table 1.

Final Diagnosis of Reactions to AX-CL: Differences Between Immediate and Nonimmediate Reactions and Between Centers

The final diagnosis is detailed in Table 3. Of note, 71.5% of patients (266/372) were finally diagnosed as nonallergic to ß-lactams after having tolerated the culprit drug in a DPT. Of the 106 patients (28.5%) finally classified as allergic, 26 (24.5%) were allergic to CL, 27 (25.5%) to aminopenicillins, 24 (22.6%) to penicillins, 26 (24.6%) to all ß-lactams, and 3 (2.8%) to penicillins and cephalosporins. The 26 patients who were allergic to ß-lactams comprise 22 who were allergic to ß-lactams (20.8%) and 4 who were allergic to ß-lactams and to CL (3.8%) (only the latter were sensitized to CL).

Table 2. Differences in Clinical Presentation According to Latency and Center.

	HCSC N=208			Latency			HCSC vs HRUM	
	Immediate n=38 (18.3%)	Nonimmediate n=151 (72.6%)	*P* Value	Immediate n=52 (31.7%)	Nonimmediate n= 101 (61.6%)	*P* Value	Immediate *P* value	Nonimmediate *P* value
Mean (SD) age at time of study, y	50.4 (16.8)	49.1 (19.7)	44.5 (15.5)	38.8 (18.6)	.047	44.5 (15.5)	.08	<.01
Mean (SD) age at time of reaction, y	46.5 (19.4)	46.6 (20.6)	42.3 (16.7)	35.9 (20.6)	.05	42.3 (16.7)	.28	<.01
Median (IQR) interval between reaction and allergy work-up, y	0 (0-2)	0 (0-2)	1 (0- 2.25)	1 (1-5)	.11	1 (0- 2.25)	.29	<.01
Female sex, No. (%)	26 (68.4%)	108 (71.5%)	27 (51.9%)	65 (64.4%)	.14	27 (51.9%)	.12	.23
Clinical presentation								
Cutaneous	32 (84.2%)	141 (93.4%)	.12	50 (96.2%)	95 (94.1%)	.43	.08	.98
Respiratory[a]	10 (26.3%)	10 (6.6%)	<.01	28 (53.8%)	9 (8.9%)	<.01	.01	.50
Gastrointestinal	6 (15.8%)	11 (7.3%)	.09	16 (30.8%)	6 (5.9%)	<.01	.11	.67
Anaphylaxis	10 (26.3%)	8 (5.3%)	<.01	24 (46.2%)	0	<.01	.06	.02
Syncope	5 (13.2%)	2 (1.3%)	<.01	8 (15.4%)	2 (2%)	<.01	.81	1.00
Hypotension	3 (7.9%)	2 (1.3%)	.05	10 (19.2%)	1 (1%)	<.01	.22	1.00
Treatment								
Antihistamines	16 (42.1%)	60 (39.7%)	.91	29 (55.8%)	56 (55.4%)	.14	.01	.20
Corticosteroids	20 (52.6%)	55 (36.4%)	.06	25 (48.1%)	52 (51.5%)	.12	.70	.21
Adrenaline	5 (13.2%)	1 (0.7%)	<.01	4 (7.7%)	0 (0%)	<.01	.53	1.00
IV fluids	4 (10.5%)	2 (1.3%)	.02	6 (11.5%)	1 (1%)	<.01	.74	1.00
Bronchodilator	3 (7.9%)	0 (0%)	.01	4 (7.7%)	0 (0%)	<.01	1	NE

Abbreviation: HCSC, Hospital Clínico San Carlos; HRUM, Hospital Regional Universitario de Málaga; NE, not estimated.
[a]Respiratory: upper and/or lower airway involvement.

Sixty-five of the 90 patients with immediate reactions (72.22%) were finally diagnosed as allergic, whereas this was only the case in 36 of the 252 with nonimmediate reactions (14.29%), resulting in an RR of 5.06 (95%CI, 3.64-7.02) for a confirmed allergy among patients with immediate reactions (Table 4). Allergy was very frequently diagnosed in immediate reactions in patients selected in HRUM (46/52 [88.5%] vs HCSC 19/38 [50%], *P*<.01) (Table 4). No differences in diagnosis were observed within immediate and nonimmediate reactions (Table 3).

Of the 30 patients with unknown latency, 25 (83.3%) were nonallergic after the allergy work-up, and 5 were allergic (16.7%), 3 of them to penicillins, 1 to penicillin and cephalosporins, and 1 to ß-lactams and CL.

There was a significantly higher frequency of delabeling in HCSC (165/208 [79.3%]) than in HRUM (101/164 [61.6%]) (*P*<.01), resulting in an RR of 0.54 (95%CI, 0.39-0.75) for being diagnosed as allergic in HCSC compared to HRUM (Table 4). At HRUM, more patients were classified as allergic to aminopenicillins (HRUM 28.6% vs HCSC 20.9%, *P*=.01) and to all ß-lactam drugs (HRUM 30.2% vs HCSC 7%, *P*<.01) than at HCSC (Table 3).

Selective Allergy to Clavulanic Acid

Twenty-six patients were diagnosed as being selectively allergic to CL, ie, 7.0% of all patients with adverse reactions to AX-CL and 24.5% of allergic patients. No differences were found between centers (Table 3). Most patients who were allergic to CL (57.7% [15/26]) had immediate reactions, and 38.5% (10/26) had anaphylaxis.

The results of the diagnostic tests performed in the patients with a confirmed CL allergy are shown in Table 5. All of them had a negative DPT result with AX.

SPTs to CL were performed in 25 patients, and 6 (24%) were positive. IDT with CL elicited positive immediate reactions in 14 of the 21 patients tested (66.7%); IDT with AX-CL was positive in 1 case. SPT or IDT revealed a positive immediate result in 20 of the 26 CL-allergic patients. Only 2 patients (2/26 [7.7%]) had a late positive IDT result with CL. Both had a history of nonimmediate reactions, and both had a positive DPT result for AX-CL, with tolerance to AX in a subsequent DPT.

Six patients (23.1%), including the 2 with late positive IDT results for CL, had a positive DPT result for AX-CL and

Table 3. Final Diagnosis of Patients With Reactions to Amoxicillin-Clavulanic Acid.

		Allergy						
	No allergy No. (%)[a]	Any drug, No. (%)[a]	Clavulanic acid, No. (%)[b]	Aminopenicillin, No. (%)[b]	Penicillin, No. (%)[b]	ß-Lactams[c], No. (%)[b]	Penicillins and cephalosporins No. (%)[b]	ß-Lactams and clavulanic acid[c], No. (%)[b]
All patients N=372	266 (71.5%)	106 (28.5%)	26 (24.5%)	27 (25.5%)	24 (22.6%)	22 (20.8%)	3 (2.8%)	4 (3.8%)
Immediate reactions n=90	25 (27.8%)	65 (72.2%)	15 (23.1%)	18 (27.7%)	10 (15.4%)	17 (26.1%)	2 (3.1%)	3 (4.6%)
Nonimmediate reactions n=252	216 (85.7%)	36 (14.3%)	11 (30.6%)	9 (25%)	11 (30.6%)	5 (13.9%)	0	0
Immediate vs nonimmediate *P* value	<.01		.56	.95	.12	.24	NE	NE
HCSC n=208	165 (79.3%)	43 (20.7%)	12 (27.9%)	9 (20.9%)	16 (37.2%)	3 (7%)	3 (7%)	0
HRUM n=164	101 (61.6%)	63 (38.4%)	14 (22.2%)	18 (28.6%)	8 (12.7%)	19 (30.2%)	0	4 (6.3%)
HCSC vs HRUM *P* value	.01		.26	.01	.25	.01	NE	NE

Abbreviations: HCSC, Hospital Clínico San Carlos; HRUM, Hospital Regional Universitario de Málaga.
[a]Percentage of all patients.
[b]Percentage of allergic patients.
[c]These 2 subgroups of patients are allergic to ß-lactams. However, sensitization to clavulanic acid was only shown in the subgroup of ß-lactam and clavulanic acid.

Table 4. Relative Risk of Allergy and Not Having Allergy According to Latency and Center.

		Allergy	No allergy	Allergy vs no allergy, *P* value	Allergy diagnosis RR (95%CI)
All patients N=372	Immediate reactions	65	36	<.01	5.06 (3.64-7.02)
	Nonimmediate reactions	25	216		0.19 (0.14-0.27)
	HCSC	43	165	<.01	0.54 (0.39-0.75)
	HRUM	63	101		1.86 (1.34-2.58)
Immediate reactions n=90	HCSC	19	19	<.01	0.57 (0.41-0.79)
	HRUM	46	6		1.77 (1.27-2.47)
Nonimmediate reactions	HCSC	21	130	.83	0.94 (0.51-1.73)
	n=252	15	86		1.07 (0.58-1.97)

a negative DPT for AX. In the 14 patients diagnosed with selective allergy to CL at HRUM, 9 BATs were performed for CL: 7 with a positive result and 2 with a negative result. The latter had an immediate positive SPT or IDT result for CL (Table 5).

Eleven of the 26 patients who were allergic to CL experienced a nonimmediate reaction to AX-CL. Of these, 4, including the 2 patients with late positive IDT results for CL, presented an allergic reaction during the 3-day home administration of AX-CL after tolerating a therapeutic dose of AX-CL in the hospital. In the remaining 7 patients, immediate positive skin test results with CL were recorded in 6 patients, and 1 participant had a positive IDT result with AX-CL (Table 5).

Late Positive IDT to Clavulanic Acid

Of the 372 patients with a history of reaction to AX-CL, 54 (14.5%) had a late positive response in the IDT to CL but only 2 had a final diagnosis of selective CL allergy (3.7%). The final diagnosis of these patients is presented in the Figure.

Table 5. Results of Diagnostic Tests in Clavulanic Acid–Allergic Patients.

Patient ID	Latency ≤1 h	Latency >1 h	Anaphylaxis	SPT CL 20 mg/mL	IDT CL 20 mg/mL (immediate reading)	IDT CL 20 mg/mL (late reading)	BAT	DPT AX-CL	DPT AX
8	X		Yes	Neg	Pos	Neg	ND	ND	Neg
9	X		No	Neg	Pos	Neg	ND	ND	Neg
27		X	Yes	Neg	Pos	Neg	ND	ND	Neg
97		X	No	Neg	Pos	Neg	ND	ND	Neg
103	X		No	Neg	Pos	Neg	ND	Pos	Neg
169		X	Yes	Pos	ND	ND	ND	ND	Neg
182		X	No	Neg	Pos	Neg	ND	ND	Neg
183		X	Yes	ND	AX-CL+[a]	Neg	ND	ND	Neg
186	X		Yes	Neg	Pos	Neg	ND	ND	Neg
232	X		No	Neg	Pos	Neg	ND	ND	Neg
243		X	No	Neg	Pos	Neg	ND	ND	Neg
201		X	No	Neg	Neg	Pos	ND	Pos	Neg
P34		X	No	Neg	Pos	Neg	ND	Pos	Neg
P16	X		No	Pos	ND	Neg	Pos	ND	Neg
P21	X		Yes	Neg	Pos	Neg	Pos	ND	Neg
P23	X		Yes	Neg	Pos	Neg	Neg	ND	Neg
P25	X		Yes	Pos	ND	ND	Pos	ND	Neg
P26	X		No	Pos	Posb	ND	Pos	ND	Neg
P29		X	No	Neg	Pos	Neg	ND	ND	Neg
P31	X		No	Pos	ND	ND	Pos	ND	Neg
P32	X		No	Pos	ND	ND	Neg	ND	Neg
P48		X	No	Neg	Neg	Neg	ND	Pos	Neg
P273	X		No	Neg	Neg	Neg	ND	Pos	Neg
P275	X		Yes	Neg	Neg	Neg	Pos	ND	Neg
P276	X		Yes	Neg	Neg	Neg	Pos	ND	Neg
P30		X	No	Neg	Neg	Pos	ND	Pos	Neg

Abbreviations: AX-CL, amoxicillin-clavulanic acid; BAT, basophil activation test; CL, clavulanic acid; DPT, drug provocation test; IDT, intradermal test; ND, not determined; SPT, skin prick test.

[a]IDT performed with a commercial preparation of AX-CL at concentrations of 20 mg/mL AX and 4 mg/ml CL; SPT and IDT with AX alone were negative.

[b]IDT positive at retest.

Of these 54 patients, 48 underwent DPT with AX-CL, and 43 (79.6% of the 54 patients) tolerated the culprit drug and were therefore diagnosed as being nonallergic to ß-lactams. The remaining 5 patients had a positive DPT result with AX-CL. Of these, 2 had a negative DPT with alternative ß-lactams (cephalosporins/meropenem) and were diagnosed as allergic to penicillins. One did not accept additional testing and was labeled as allergic to all ß-lactams. Only 2 patients (4.2% of patients with a DPT with AX-CL and a late positive IDT test to AX-CL) were eventually diagnosed as being allergic to CL, as they had a negative DPT result with AX.

Six patients did not undergo a DPT with AX-CL (Figure). One diagnosed with penicillin allergy had a positive DPT result with penicillin and a negative DPT result with cephalosporins and meropenem. Five were diagnosed with aminopenicillin allergy: 2 had a history of anaphylaxis and tolerated DPT with penicillin; 2 had a positive IDT result with AX and a negative DPT result with penicillin; the fifth had a positive DPT result for AX with a negative DPT result for penicillin.

Discussion

In this retrospective study of reported reactions to AX-CL, we analyzed the outcome of the allergy work-up taking into account the time of onset of reactions and showed for

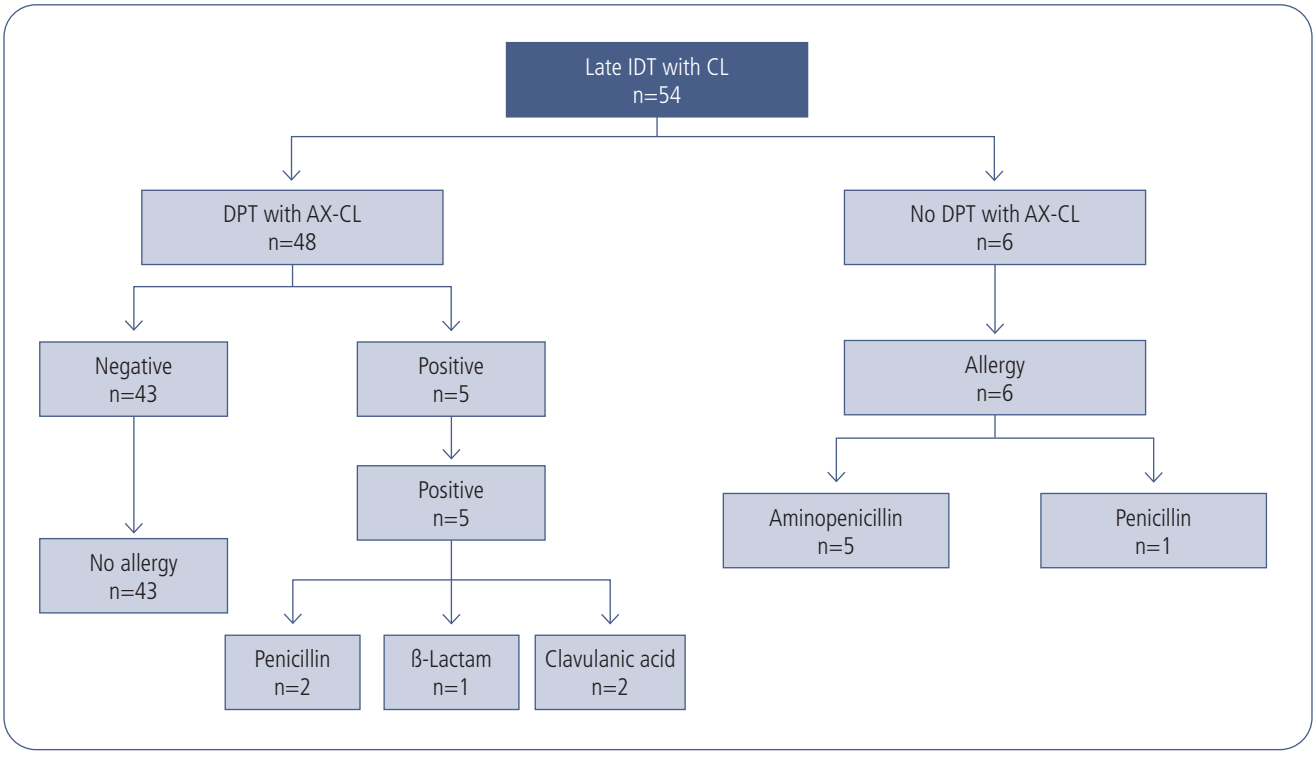

Figure. Late positive IDT with clavulanic acid. IDT indicates intradermal test; CL, clavulanic acid; AX, amoxicillin.

the first time that this approach has important diagnostic consequences. When classifying the reactions into immediate and nonimmediate based on a 1-hour cut-off point, we found that the probability of confirming a diagnosis of allergy is 5 times higher (RR, 5.06 [95%CI, 3.64-7.02]) among those with immediate reactions and, therefore, that collecting this information is highly relevant in the diagnostic work-up, since it contributes to risk stratification.

The 1-hour cut-off point was chosen to ensure that most of the IgE-mediated reactions were in the immediate group, even though some may occur later, especially when drugs are ingested orally together with foods. The classification of drug-induced allergic reactions allows 1 to 6 hours for the onset of immediate reactions and any time after 1 hour for the nonimmediate ones, showing that there is an overlap in onset [11,14-18].

With the 1-hour cut-off point selected, we showed that immediate reactions were of greater severity, with a significantly higher frequency of anaphylaxis, hypotension, syncope, and respiratory and gastrointestinal symptoms, which translated into a higher frequency of treatment with adrenaline, IV fluids, bronchodilators, and corticosteroids. Skin involvement was frequently similar in both immediate and nonimmediate reactions and was the dominant clinical presentation in the latter. These findings are consistent with the literature, where urticaria/angioedema, upper/lower airways and gastrointestinal symptoms, and anaphylaxis are the common presentations in immediate reactions and skin involvement the most common in nonimmediate reactions. Furthermore, a subset of the nonimmediate reactions may be viral exanthemas incorrectly treated with antibiotics [10,17,19,20].

Of all the patients studied, most (71.5%) proved not to be allergic to ß-lactams, as reported elsewhere [5,7,21]. Among those with a confirmed allergy, the most common diagnosis was aminopenicillin allergy (25.5% of allergic patients), selective CL allergy (24.5%, in line with previous publications [1,2,5,7]), followed by penicillin allergy (22.6%) and ß-lactam allergy (20.8%). Of note, no differences were found between immediate and nonimmediate reactions.

We found interesting differences between the 2 centers involved. Allergy was significantly more frequent (1.8 times) in HRUM (38.4% vs 20.7% in HCSC, Table 3), probably because of the higher proportion (1.7 times) of immediate reactions in their population (HRUM 31.7% vs 18.3% in HCSC, Table 2), which tended to be more severe (higher rate of respiratory involvement and anaphylaxis) (Table 2). This may reflect differences in referral for diagnosis of allergy between the 2 centers. The Allergy Department at HCSC is one of many allergy centers in Madrid, with a catchment population of 400 000 inhabitants. Meanwhile, the Allergy Department at HRUM is the only specialized center for assessment of drug allergy in Málaga, covering a population of more than 1.6 million inhabitants. This can explain the higher proportion of immediate/severe allergic reactions within the patients referred to HRUM. On the other hand, allergy delabeling was more common at HCSC than at HRUM, probably owing to the high frequency of allergy diagnosis in immediate reactions in patients selected in HRUM (Table 4).

We found differences in the frequency of diagnosis of aminopenicillin and ß-lactam allergies between the 2 centers (Table 3). The higher frequency of aminopenicillin allergy

diagnosed in HRUM may be also related to the aforementioned higher proportion of immediate reactions to AX-CL. The reactions were also more severe, precluding DPT with AX in those with a negative DPT for penicillin and a severe immediate reaction to AX-CL. The lower frequency of ß-lactam allergy at HCSC is related to the fact that tolerance to cephalosporins and meropenem is usually confirmed, and, therefore, fewer patients are classified as allergic to ß-lactams and more to penicillins only, although for the latter, the difference was not statistically significant (Table 3).

Selective IgE-mediated allergy to CL was first described in 1995, with 2 cases of anaphylaxis [22]. Since then, many more cases have been reported [3,7,8,9,23], and it is currently estimated that about 30% of immediate allergic reactions to AX-CL correspond to selective CL allergy [1]. In our series, 7% of all the reported adverse reactions to AX-CL were eventually diagnosed as CL allergy (26/372), a figure that reaches 16.7% (15/90) when only immediate reactions are considered. Among those patients with a confirmed diagnosis of allergy to any ß-lactam drug, selective CL allergy accounted for 1 out of 4 diagnoses (Table 3). Patients selectively allergic to CL were diagnosed with either a positive immediate skin test result (prick or IDT), a positive BAT result, and/or a positive DPT result with AX-CL, in all cases followed by a negative DPT result with AX alone (Table 4). Since purified CL was made available for skin testing, characterization of CL allergy has become easier [7,8]. Value is always given to immediate positivity of skin tests [5,9], although the value of late positivity to IDT remains doubtful. In our series, 14.5% of the patients tested had a positive IDT result to CL in the delayed reading, although CL allergy was only confirmed in 3.7% of them (Table 5), indicating that late positivity of IDT with CL has no diagnostic value per se and that late readings should not be taken routinely in the allergy work-up for AX-CL reactions.

Given the widespread use of ß-lactams, it is of pivotal importance to correctly diagnose patients who are truly allergic. Inappropriate overdiagnosis of allergy leads to use of alternative—usually not first-line—antibiotics, which are more expensive, carry a greater risk of adverse events, are less efficacious, and increase the risk of antibiotic resistance [17,24-26], prolonged hospitalizations, and increased readmission rates [27]. It is well established—and demonstrated in our series—that most patients reporting adverse reactions to ß-lactams in general or to AX-CL in particular (as in our study) are nonallergic. Delabeling these patients and identifying the underlying phenotype in the allergic ones is of considerable clinical relevance. Patients diagnosed with selective allergy to CL are barely limited and can safely take all other ß-lactams, including AX alone, although tolerance must be confirmed, given that cosensitization is rare but possible [2,28,29]. Taking the results of the allergy work-up of the 372 patients with reactions to AX-CL referred for study who were avoiding all ß-lactam drugs, 252 (71.5%) could receive any ß-lactam, 26 (7%) only had to avoid CL, 27 (7.2%) had to avoid aminopenicillins, 24 (6.4%) penicillins, 3 (0.8%) penicillins and cephalosporins, and only 26 (7%) really needed to avoid all ß-lactams.

In summary, our study highlights the importance of a comprehensive allergy work-up in patients reporting reactions with AX-CL and shows that the classification of reported reactions as immediate and nonimmediate according to a 1-hour cut-off is highly relevant and helps in risk stratification, since those with immediate reactions were 5 times more likely to be eventually diagnosed with allergy. Moreover, 24.5% of patients diagnosed as allergic were found to be allergic only to CL. Additionally, we showed the lack of diagnostic value of the delayed reading in IDT with CL, thus supporting not performing it routinely in the allergy work-up.

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Conflicts of Interest

MFR reports the following: grants for her institution from the Spanish government, Aimmune Therapeutics, and Diater; consultancy fees from Aimmune Therapeutics, DBV, Novartis, Reacta Healthcare, and SPRIM; and lecture fees from Aimmune Therapeutics, Ediciones Mayo S.A, Diater, GSK, GA2LEN, HAL Allergy, MEDSCAPE, Novartis, and EPG Health, all outside the submitted work.

MJTJ reports grants/contracts and payment/honoraria for lectures from Diater Laboratories.

The remaining authors declare that they have no conflicts of interest.

Previous Presentations

Partial results of this study were presented as a FLASH TALK "Deconstructing adverse reactions to amoxicillin-clavulanic acid" at the European Academy of Allergy and

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