Deconstructing adverse reactions to Amoxicillin-Clavulanic Acid: the importance of time of onset

Running title: Amoxicillin-Clavulanic allergy deconstructed

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ABSTRACT

Background: Amoxicillin-clavulanic acid (AX-CL) is the most consumed betalactam antibiotic worldwide. We aimed to establish the different phenotypes of betalactam allergy in those referring a reaction with AX-CL and to investigate the differences between immediate and non-immediate onset.

Methods: Cross-sectional retrospective study performed at Hospital Clínico San Carlos (HCSC) and Hospital Regional Universitario de Málaga (HRUM) in Spain. Patients reporting reactions with AX-CL who completed the allergy workup between 2017 and 2019 were included. Data of reported reaction and allergy workup were collected. Reactions were classified as immediate and non-immediate with 1hour cut-off point.

Results: We included 372 patients (HCSC 208, HRUM 164). There were 90 (24.2%) immediate, 252 (67.7%) non-immediate reactions, and 30 (8.1%) with unknown latency. Allergy to betalactams was ruled-out in 266 (71.5%) and confirmed in 106 patients (28.5%). The final main diagnosis in the overall population were allergy to aminopenicillins (7.3%), to CL (7%), to penicillin (6.5%) and to betalactams (5.9%). Allergy was confirmed in 77.2% and 14.3% of immediate and non-immediate reactions respectively, with a relative risk of 5.06 (95%CI 3.64-7.02) of an allergy diagnosis in those reporting immediate reactions. Only 2/54 patients with late-positive intradermal test (IDT) to CL were diagnosed of CL allergy.

Conclusion: Allergy diagnosis was confirmed in a minority of the whole study population, but 5 times more frequently in those reporting immediate reactions, making this classification useful in risk stratification. Late-positive IDT for CL has no diagnostic value and its late reading could be retrieved from the diagnosis work-up.

Key words: Amoxicillin-Clavulanic acid. Drug allergy. Immediate reaction. Intradermal test. Non-immediate reaction.

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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 alergólogico 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.

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Abbreviations/acronyms

AX, Amoxicillin

AX-CL, Amoxicillin-clavulanic acid

BAT, Basophil activation test

CI, Confidence Interval

CL, Clavulanic acid

DPT, Drug provocation test

HCSC, Hospital Clínico San Carlos

HRUM, Hospital Regional Universitario de Málaga

IDT, Intradermal test

Q1, first quartile

Q3, third quartile

RR, Relative Risk

SD, Standard Deviation

sIgE, Specific IgE

SPT, Skin Prick test

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INTRODUCTION

Betalactam antibiotics are the drugs most frequently involved in drug allergic reactions [1]. In recent years, Amoxicillin-Clavulanic acid (AX-CL) has been widely used to treat a wide spectrum of infections, and it is the most consumed betalactam antibiotic worldwide. CL is a betalactam with betalactamase inhibitor capacity [2]. When AX-CL is involved in allergic reactions, it is crucial to determine which of the two drugs is responsible for the reaction since it has important therapeutic consequences. Those with confirmed allergy only to CL tolerate all other betalactams 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 betalactams. Therefore, it is of utmost importance to perform a comprehensive allergy work-up, not only to "delabel" the non-allergic, but also to correctly classify the allergic patients and provide them with safe guidance of the betalactam drugs to be avoided and those allowed.

Skin prick tests (SPT) and intradermal tests (IDT) followed by drug provocation testing (DPT) are the main diagnostic methods in allergic reactions to betalactams [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, Thermofisher Scientific) is available only for benzylpenicillin, penicillin V, AX, ampicillin, and cefaclor. To date, there is no immunoassay available to detect specific IgE to CL. Basophil activation test (BAT) has been used for investigational purposes. Although it has a suboptimal sensitivity (up to 69%) [1], it can be a useful tool in high-risk patients and potentially replace a DPT in this population [5,6].

Since 2012, the purified CL reagent for skin testing (DAP Clavulanic, Diater, Spain) has been commercially available, making the characterization of CL allergy easier [3]. Immediate responses in SPT or IDT to CL in patients reporting reactions to AX-CL are considered diagnostic [7,8], but 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 up to 71% [9].

We have analysed a large series of patients reporting allergic reactions to AX-CL referred for allergy workup to the Allergy Departments of Hospital Clínico San Carlos (HCSC) in Madrid, and to Hospital Regional Universitario de Málaga (HRUM) in Málaga, both centres in Spain. We aimed to establish the different phenotypes of betalactam allergy in patients with adverse reactions to AX-CL and to investigate differences between those with immediate and non-immediate onset reactions, an aspect that has not been explored previously to the best of our

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knowledge. Additionally, among those with selective allergy to CL we aimed to establish the diagnostic value of late positive IDT.

METHODS

Study design

This is a cross-sectional study with retrospective data recovery. The medical records of patients reporting reactions with AX-CL and referred for study to HCSC and HRUM between 2017 and 2019 were reviewed, and only those who completed the allergy workup were included.

A detailed history of the allergic reactions was obtained, recording 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 non-immediate 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]. Patients with fixed drug eruption, generalized acute exanthematous pustulosis, toxic epidermal necrolysis/Stevens-Johnson Syndrome, drug reactions with eosinophilia and systemic symptoms (DRESS), and drug-mediated organ-specific reactions (i.e. hepatitis) were excluded from study.

Allergy workup

All the diagnostic evaluation was performed following the diagnostic algorithm for betalactams [11] and the recommendations of the ENDA and EAACI drug allergy interest group [4,12,13].

SPT and IDT were performed with benzylpenicilloyl octa-L-lysine (0.04 mg/mL), sodium benzylpenyloate (0.5 mg/mL), AX (20 mg/mL) and CL (20 mg/mL), with histamine and saline solution as positive and negative controls. Additionally, at HCSC SPT and IDT with Penicillin G (10,000 UI/mL), Cefuroxime (2 mg/mL), Ceftazidime (2 mg/mL) and Meropenem (1 mg/mL) were performed. If the index reaction occurred within 2 years to the patients' consultation, specific IgE (sIgE) (ImmunoCAP, Thermofisher Scientific) was obtained for Penicilloyl G, Penicilloyl V, AX, Ampicillin and Cefaclor before drug skin testing.

Depending on how suggestive/severe the history was, and the results of sIgE and skin tests, patients were submitted or not to a DPT with the culprit drug or alternative drugs. In those patients with negative DPT to AX-CL, and a reported index reaction that had occurred over 2

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years before, skin tests were repeated 3 to 6 weeks after the initial study, and if negative a DPT was carried out again. In non-immediate reactions, a negative DPT was followed by the home intake of daily therapeutic doses for 2-3 days to confirm tolerance.

BAT to Penicillin G, AX and CL were performed in patients with immediate reactions at HRUM, and if positive, DPT was not performed.

Variables

Response variable: Final Diagnosis (Allergy to Betalactams, Penicillins, Aminopenicillins, CL, Cephalosporins, Carbapenems, no Allergy).

Variables of Interest: centre, 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 (≤1hour: immediate vs. >1hour: non-immediate), results of SPT, IDT, sIgE, BAT and DPT.

Statistics

Descriptive statistics included frequency and percent for qualitative variables, and median, first and third quartiles (Q1, Q3) or mean and standard deviation (SD) for numerical variables, according to the normality of the distribution. Differences between immediate and non-immediate reactions and between centres were analyzed. Qualitative variables were compared with χ^2or Fisher exact test. Quantitative variables were compared with Student t test or Mann-Whitney test for data with normal and non-normal distributions, respectively. Relative risk (RR) was calculated with its 95% confidence interval (95%CI). Statistical analysis were performed with SPSS version 26 and STATA version 16. Significant level was set at $p<0.05$.

Ethical aspects

The HCSC Ethics Committee and the Provincial Ethics Committee of Málaga reviewed and approved the study protocol (Internal Code: 21/585-O_M and CE PI1800095, respectively). Due to the retrospective character of the study collecting already existing data from medical charts, informed consent exemption was requested and granted. All the subjects included in this study had provided written informed consent for the drug allergy work-up.

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RESULTS

Clinical presentation of AX-CL reactions: differences between immediate and non-immediate reactions and between centres

A total of 372 patients were included, 208 at HCSC, and 164 at HRUM. Mean age at time of study was 45.9 years (SD 19.4), and the interval between the index reaction with AX-CL and the study had a median of 1 year (Q1:0, Q3:3). The majority of patients were female (65.6%). The most common reported symptoms were cutaneous (91.1%), followed by respiratory (15.6%) and gastrointestinal symptoms (11.8%). Anaphylaxis represented 11.3% of the reactions, 4.6% presented syncope and 4.3% hypotension. The most common treatments for the reactions were antihistamines (44.1%) and corticosteroids (41.1%), and only in 2.7% of reactions adrenaline was used (Table I).

There were significant differences between centres for age at time of reaction with older patients at HCSC (46.2 years) compared with HRUM (37.9 years) ($p<0.01$). The interval between the reaction and the allergy work-up was significantly shorter in HCSC (Table I). For the clinical presentation of 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, $p <0.01$), anaphylaxis (14.6% vs 8.7% at HCSC, $p= 0.08$) and hypotension (6.7% vs 2.4% at HCSC, $p=0.048$). However, it did not translate into a higher use of adrenaline, IV fluids or bronchodilators, and only antihistamines were more frequently administered in HRUM (Table I).

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

Overall, as expected, immediate reactions were of a higher severity than non-immediate reactions, with a significantly higher frequency of anaphylaxis, hypotension, syncope, respiratory and gastrointestinal symptoms. Only skin involvement was similarly observed in immediate and non-immediate reactions. Accordingly, there were significant differences in the management of reactions with a higher frequency in administration of adrenaline, IV fluids, bronchodilators and corticosteroids ($p<0.01$ for all drugs) in immediate reactions, whereas antihistamines were similarly used (50% vs 46%, $p=0.05$) (Table I). Similar findings were observed within each center (Table II).

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Immediate reactions were seen more frequently among the patients studied at HRUM (52/164= 31.7%) than at HCSC (38/208= 18.3%) (p<0.01) (Table II). At HRUM patients with non-immediate reactions were significantly younger than those with immediate reactions, a difference that was not found among the patients selected at HCSC (Table II). Among patients with non-immediate reactions the ones selected at HRUM were significantly younger (35.9 years vs 46.6 years, p<0.01) (Table II) which may explain the overall younger age at reaction of the patients from HRUM presented in Table I.

Final diagnosis of AX-CL reactions: differences between immediate and non-immediate reactions and between centres

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

Sixty-five of the 90 patients (72.22%) with immediate reactions were finally diagnosed as allergic, whereas this was only the case in 36 of the 252 (14.29%) with non-immediate reactions, resulting in a RR of having a confirmed allergy of 5.06 (95% CI 3.64-7.02) among patients with immediate reactions (Table IV). There was a high frequency of allergy diagnosis in immediate reactions in patients selected in HRUM (46/52= 88.5% vs HCSC 19/38= 50%, p<0.01) (Table IV). The different diagnosis within immediate and non-immediate reactions did not differ as shown in Table III.

Of the 30 patients with unknown latency, 25 (83.3%) were non-allergic after the allergy workup, and 5 allergic (16.7%), 3 of them to penicillins, 1 to penicillin and cephalosporins, and 1 turned to be allergic to betalactams and CL.

There was a significantly higher frequency of delabeling in HCSC (165/208=79.3%) than in HRUM (101/164= 61.6%) (p<0.01), resulting in a RR of being diagnosed as allergic in HCSC of 0.54 (95% CI 0.39-0.75) compared to HRUM (Table IV). At HRUM there were more patients classified as

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allergic to aminopenicillins (HRUM 28.6% vs. HCSC 20.9%, p=0.01) and to all betalactam drugs (HRUM 30.2% vs. HCSC 7%, p<0.01) than at HCSC (Table III).

Selective allergy to clavulanic acid

Twenty-six patients were diagnosed of being allergic selectively to CL. This represents 7.0% of all patients with adverse reactions with AX-CL, and 24.5% of the allergic ones. No differences were found between centres (Table III). The majority, 57.7% (15/26) of patients allergic to CL 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 V. All of them had a negative DPT with AX.

SPT to CL were performed in 25 patients and 6 (24%) were positive. IDT with CL elicited positive immediate reactions in 14 of the 21 subjects tested (66.7%), and there was one additional positive IDT with AX-CL. Overall, 20 of the 26 patients allergic to CL had a positive immediate SPT or IDT. Only two subjects (2/26=7.7%) had a late positive IDT to CL. They both had a history of non-immediate reactions, and both had a positive DPT with AX-CL, with tolerance to AX in a later DPT.

Six patients (23.1%), including the 2 with late positive IDT to CL, were diagnosed with a positive DPT to AX-CL and a negative DPT to AX. Of the 14 patients diagnosed of selective allergy to CL at HRUM, 9 BAT to CL were done, 7 with a positive result, and 2 negative ones. The latter had an immediate positive SPT or IDT to CL (Table V).

Eleven of the 26 subjects allergic to CL had a non-immediate reaction to AX-CL. Four of them, including the two patients with late positive IDT to CL, presented an allergic reaction during the 3-day home administration of AX-CL after having tolerated a therapeutic dose of AX-CL in the hospital settings. In the remaining 7 subjects, immediate positive cutaneous tests to CL were found in 6, and 1 participant had a positive IDT to AX-CL (Table V).

Late positive IDT to clavulanic acid

Out of the 372 patients with a history of reaction with 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 subjects is presented in Figure 1.

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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 non-allergic to betalactams. The remaining 5 patients had a positive DPT with AX-CL. Of them two had a negative DPT with alternative betalactams (cephalosporins/meropenem) and were diagnosed as allergic to penicillins. One did not accept additional testing and was labeled as allergic to all betalactams. Only 2 patients (4.2% of patients with a DPT with AX-CL with a late positive IDT test to AX-CL) were actually diagnosed as being allergic to CL, as they had a negative DPT with AX.

Six patients did not undergo a DPT with AX-CL (Figure 1). One diagnosed of penicillin allergy had a positive DPT with penicillin with negative DPT to cephalosporins and meropenem. Five were diagnosed of aminopenicillin allergy: 2 had a history of anaphylaxis and tolerated in a DPT; 2 had positive IDT to AX and a negative DPT with penicillin; the fifth one had a positive DPT to AX with a negative DPT to penicillin.

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DISCUSSION

In this retrospective study of reported reactions to AX-CL we analysed the outcome of the allergy workup taking into account the time of onset of reactions, and we have shown for the first time that this approach has important diagnostic consequences. When classifying the reactions into immediate and non-immediate with a 1 hour cut-off point we find that the probability of confirming allergy diagnosis is 5 times higher (RR 5.06, 95% CI 3.64-7.02) among those with immediate onset reactions, and therefore collecting this information is highly relevant in the diagnostic procedure since it contributes to risk stratification.

The 1 hour cut-off point was decided as an approach to collect most of the IgE mediated reactions into the immediate group, although some may arise later, especially when drugs are ingested orally together with foods. The classification of drug allergic reactions considers 1 to 6 hours for the onset of immediate reactions, and after 1 hour for the non-immediate ones, showing that there is an overlap in the onset of reactions [11,14-18].

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

Of all patients studied, the majority (71.5%) proved not to be allergic to betalactams, similar to what has been previously described (5,7, 21). Among those with a confirmed allergy, the most common diagnosis were aminopenicillin allergy (25.5% of allergic subjects), selective CL allergy (24.5%), in line also with previous publications [1,2,5,7], followed by penicillin allergy (22.6%) and betalactam allergy (20.8%). Of note, no differences were found between immediate and non-immediate reactions.

We have found some interesting differences between the 2 centres involved. The frequency of allergy diagnosis was significantly higher (1.8 times) in HRUM (38.4% vs 20.7% in HCSC, Table III) which may be related to a higher proportion (1.7 times) of immediate reactions in their

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population (HRUM 31.7% vs 18.3% in HCSC, Table II) which tended to be of a higher severity (higher rate of respiratory involvement and anaphylaxis) (Table II). This may reflect differences in referral for allergy diagnosis between the two centres. The Allergy Department at HCSC is one of many allergy centres in Madrid with an assigned population of 400,000 inhabitants. Meanwhile, the Allergy Department at HRUM is the only one specialized centre to study 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 referred patients in HRUM. On the other hand more allergy delabeling occurred at HCSC compared to HRUM, probably related to the high frequency of allergy diagnosis in immediate reactions in patients selected in HRUM (Table IV).

There are differences in the proportion of diagnosis of aminopenicillin and betalactam allergies between the two centres (Table III). The higher frequency of aminopenicillin allergy diagnosis in HRUM may be also related to the aforementioned higher proportion of immediate reactions to AX-CL, and of a higher severity, precluding DPT with AX in those with a negative DPT with penicillin and a severe immediate reaction to AX-CL. The lower frequency of betalactams allergy at HCSC is related to the fact that tolerance to cephalosporins and meropenem is usually confirmed, and therefore less patients are classified as allergic to betalactams and more to only penicillins although for the latter the difference was not statistically significant (Table III).

Selective IgE mediated allergy to CL was first described in 1995 with two anaphylaxis cases [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 ended with a diagnosis of CL allergy (26/372), a figure that goes up to 16.7% (15/90) when considering only immediate reactions. Among those patients with a confirmed allergy diagnosis to any betalactam drug, selective CL allergy accounted for 1 out of 4 diagnosis (Table III). Patients selectively allergic to CL were diagnosed with either a positive immediate skin test (prick or IDT), a positive BAT, and/or a positive DPT with AX-CL, in all cases followed by a negative DPT with AX alone (Table IV). Since the purified CL for skin testing was made available, the characterization of CL allergy has become easier [7,8]. Value is always given to immediate positivity of skin tests [5, 9] but the value of a late positivity to IDT is quite doubtful. In our series, 14.5% of the tested patients presented a positive IDT to CL in delayed reading, but CL allergy was only confirmed in 3.7% of them (Table V), indicating that late positivity of CL IDT has no diagnostic value per se and late readings should not be done routinely in the allergy workup of AX-CL reactions.

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Given the great importance of betalactam use, it is of pivotal importance to correctly diagnose those truly allergic. Inappropriate allergy overdiagnosis leads to use of alternative antibiotics, usually not first line, at a higher cost and with greater risk of adverse events and less efficacy, also increasing the risk of antibiotic-resistance [17,24-26], prolonged hospitalizations and increased readmission rates [27]**.** It is well established, and our series also shows it, that the majority of patients reporting adverse reactions to betalactams in general or to AX-CL as in our study are non-allergic. Delabeling these patients and identifying the underlying phenotype in the allergic ones is of great clinical relevance. Patients diagnosed with selective allergy to CL, are barely limited and can safely take all other betalactams including AX alone, although tolerance must be confirmed given that co-sensitization is rare but possible [2,28,29]. Taking the results of the allergy workup of the 372 subjects with AX-CL reactions referred for study who were avoiding all betalactam drugs, 252 (71.5%) could receive any betalactam, 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 betalactams.

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 in immediate and non-immediate with 1 hour cut-off is highly relevant and helps in risk stratification, since those with immediate reactions were 5 times more likely to end up with an allergy diagnosis. Also, 24.5% of patients diagnosed as allergic were found only to be allergic to clavulanic acid. Additionally, we have shown the lack of diagnostic value of the IDT delayed reading to CL, supporting not to do it routinely in the allergy workup.

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Conflicts of Interest

NPFS, MSC, NMP, AGF, ID, GB, ISG, ML and AMHN declare no conflicts of interest.

MFR reports grants for her institution from 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 of them outside the submitted work.

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

Previous Presentation

Partial results of this study were presented as a FLASH TALK "**Deconstructing adverse reactions to amoxicillin-clavulanic acid"** in the EAACI (European Academy of Allergy and Clinical Immunology) Hybrid Congress 2022 organized by the EAACI, Prague – Czech Republic, July 1-3, 2022.

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TABLE 1. Population descriptives

ALL SUBJECTS n=372		HCSC vs HRUM			Latency			
		HCSC (n=208)	HRUM (n=164)	p value	Unknown n=30†	Immediate n=90 (24.2%)	Non immediate n= 252 (67.7%)	Immediate vs non-immediate p value
Age at time of study (years-mean (SD))	45.9 (19.4)	50.1 (19.7)	40.6 (17.7)	<0.01	50.7 (23.8)	46.9 (16.2)	44.9 (19.9)	0.38
Age at time of reaction (years – mean (SD))	42.7 (20.9)	46.2 (21.1)	37.9 (19.6)	<0.01	38.7 (26.9)	44.1 (17.9)	42.6 (21.2)	0.54
Interval between reaction and allergy study (years – median (Q1-Q3))	1 (0-3)	0 (0-3)	1 (0-4)	<0.01	8 (1-24)	1 (0-2)	1 (0-3)	0.75
Sex (n female, %)	244 (65.6%)	146 (70.2%)	98 (59.8%)	0.04	18 (60%)	53 (58.9%)	173 (68.7%)	0.09
CLINICAL PRESENTATION								
Cutaneous	339 (91.1%)	186 (89.4%)	153 (93.3%)	0.30	21 (70%)	82 (91.1%)	236 (93.7%)	0.78
Respiratory *	58 (15.6%)	20 (9.6%)	38 (23.2%)	<0.01	1 (3.3%)	38 (42.2%)	19 (7.5%)	<0.01
Gastrointestinal	44 (11.8%)	20 (9.6%)	24 (14.6%)	0.15	5 (16.7%)	22 (24.4%)	17 (6.7%)	<0.01
Anaphylaxis	42 (11.3%)	18 (8.7%)	24 (14.6%)	0.08	0	34 (37.8%)	8 (3.2%)	<0.01
Syncope	17 (4.6%)	7 (3.4%)	10 (6.1%)	0.23	0	13 (14.4%)	4 (1.6%)	<0.01
Hypotension	16 (4.3%)	5 (2.4%)	11 (6.7%)	0.048	0	13 (14.4%)	3 (1.2%)	<0.01
TREATMENT								
Antihistamines	164 (44.1%)	77 (37%)	87 (53%)	<0.01	3 (10%)	45 (50%)	116 (46%)	0.05
Corticosteroids	153 (41.1%)	75 (36.1%)	78 (47.6%)	0.09	1 (3.3%)	45 (50%)	107 (42.5%)	0.01
Adrenaline	10 (2.7%)	6 (2.9%)	4 (2.4%)	0.76	0	9 (10%)	1 (0.4%)	<0.01
IV fluids	13 (3.5%)	6 (2.9%)	7 (4.3%)	0.59	0	10 (11.1%)	3 (1.2%)	<0.01
Bronchodilator	7 (1.9%)	3 (1.4%)	4 (2.4%)	0.71	0	7 (7.8%)	0 (0%)	<0.01

† Unknown: 19 HCSC, 11 HRUM * Respiratory: upper and/or lower airway involvement.

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TABLE 2. Differences in clinical presentation according to latency and centre

	HCSC N=208			HRUM N=164			HCSC vs HRUM	
	Immediate n=38 (18.3%)	**Non-immediate n= 151 (72.6%)**	**p value**	**Immediate n=52 (31.7%)**	**Non-immediate n= 101 (61.6%)**	**p value**	**Immediate reactions p value**	**Non-immediate reactions p value**
Age at time of study (years-mean (SD))	50.4 (16.8)	49.1 (19.7)	0.69	44.5 (15.5)	38.8 (18.6)	0.047	0.08	<0.01
Age at time of reaction (years – mean (SD))	46.5 (19.4)	46.6 (20.6)	0.98	42.3 (16.7)	35.9 (20.6)	0.05	0.28	<0.01
Interval between reaction and allergy study (years – median (Q1-Q3))	0 (0-2)	0 (0-2)	0.84	1 (0- 2.25)	1 (1-5)	0.11	0.29	<0.01
Sex (female, n %)	26 (68.4%)	108 (71.5%)	0.71	27 (51.9%)	65 (64.4%)	0.14	0.12	0.23
CLINICAL PRESENTATION								
Cutaneous	32 (84.2%)	141 (93.4%)	0.12	50 (96.2%)	95 (94.1%)	0.43	0.08	0.98
Respiratory*	10 (26.3%)	10 (6.6%)	<0.01	28 (53.8%)	9 (8.9%)	<0.01	0.01	0.50
Gastrointestinal	6 (15.8%)	11 (7.3%)	0.09	16 (30.8%)	6 (5.9%)	<0.01	0.11	0.67
Anaphylaxis	10 (26.3%)	8 (5.3%)	<0.01	24 (46.2%)	0	<0.01	0.06	0.02
Syncope	5 (13.2%)	2 (1.3%)	<0.01	8 (15.4%)	2 (2%)	<0.01	0.81	1.00
Hypotension	3 (7.9%)	2 (1.3%)	0.05	10 (19.2%)	1 (1%)	<0.01	0.22	1.00
TREATMENT								
Antihistamines	16 (42.1%)	60 (39.7%)	0.91	29 (55.8%)	56 (55.4%)	0.14	0.01	0.20
Corticosteroids	20 (52.6%)	55 (36.4%)	0.06	25 (48.1%)	52 (51.5%)	0.12	0.70	0.21
Adrenaline	5 (13.2%)	1 (0.7%)	<0.01	4 (7.7%)	0 (0%)	<0.01	0.53	1.00
IV fluids	4 (10.5%)	2 (1.3%)	0.02	6 (11.5%)	1 (1%)	<0.01	0.74	1.00
Bronchodilator	3 (7.9%)	0 (0%)	0.01	4 (7.7%)	0 (0%)	<0.01	1	NE

NE, not estimable * Respiratory: upper and/or lower airway involvement.

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TABLE 3. Final diagnosis of patients with reactions to Amoxicillin-Clavulanic acid

	NO ALLERGY n (%)‡	**ALLERGY**						
		Any drug n (%)‡	**Clavulanic acid** n (%)§	**Aminopenicillin** n (%)§	**Penicillin** n (%)§	**Betalactams*** n (%)§	**Penicillins & Cephalosporins** n (%)§	**Betalactam & Clavulanic*** n (%)§
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%)
Non-Immediate reactions N= 252	216 (85.7%)	36 (14.3%)	11 (30.6%)	9 (25%)	11 (30.6%)	5 (13.9%)	0	0
Immediate vs Non-Immediate p value	**p<0.01**		p = 0.56	p = 0.95	p = 0.12	p = 0.24	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	**p < 0.01**		p = 0.26	**p = 0.01**	p = 0.25	**p < 0.01**	NE	NE

‡ Percent of all subjects; § percent of allergic subjects; NE, not estimable; * these two subgroups of subjects are allergic to betalactams, but only in the subgroup of Betalactam &Clavulanic sensitization to Clavulanic was shown.

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TABLE 4. Relative risk of allergy and non-allergy according to latency and centre

		Allergy	Non allergy	Allergy vs Non allergy p value	Allergy diagnosis RR (95%CI)
All patients N=372	Immediate reactions	65	36	< 0.01	5.06 (3.64-7.02)
	Non-immediate reactions	25	216		0.19 (0.14-0.27)
	HCSC	43	165	<0.01	0.54 (0.39-0.75)
	HRUM	63	101		1.86 (1.34-2.58)
Immediate reactions N=90	HCSC	19	19	<0.01	0.57 (0.41-0.79)
	HRUM	46	6		1.77 (1.27-2.47)
Non-immediate reactions N=252	HCSC	21	130	0.83	0.94 (0.51-1.73)
	HRUM	15	86		1.07 (0.58-1.97)

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TABLE 5. Results of diagnostic tests in the Clavulanic acid allergic patients

Patient ID	Latency		Anaphylaxis	SPT CL 20mg/mL	IDT CL 20mg/mL (immediate reading)	IDT CL 20mg/mL (late reading)	BAT	DPT AX-CL	DPT AX
	≤1h	>1h							
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	N.D.	N.D.	ND	ND	NEG
182		X	NO	NEG	POS	NEG	ND	ND	NEG
183		X	YES	ND	¶AX-CL+	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	N.D.	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	N.D.	N.D.	POS	ND	NEG
P26	X		NO	POS	POS*	N.D.	POS	ND	NEG
P29		X	NO	NEG	POS	NEG	ND	ND	NEG
P31	X		NO	POS	N.D.	N.D.	POS	ND	NEG
P32	X		NO	POS	N.D.	N.D.	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

SPT: Skin Prick Test, IDT: Intradermal Test, BAT: Basophil Activation Test, CL: Clavulanic acid, AX-CL: Amoxicillin-Clavulanic Acid, ND: not done; ¶ 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. *IDT positive at retest.

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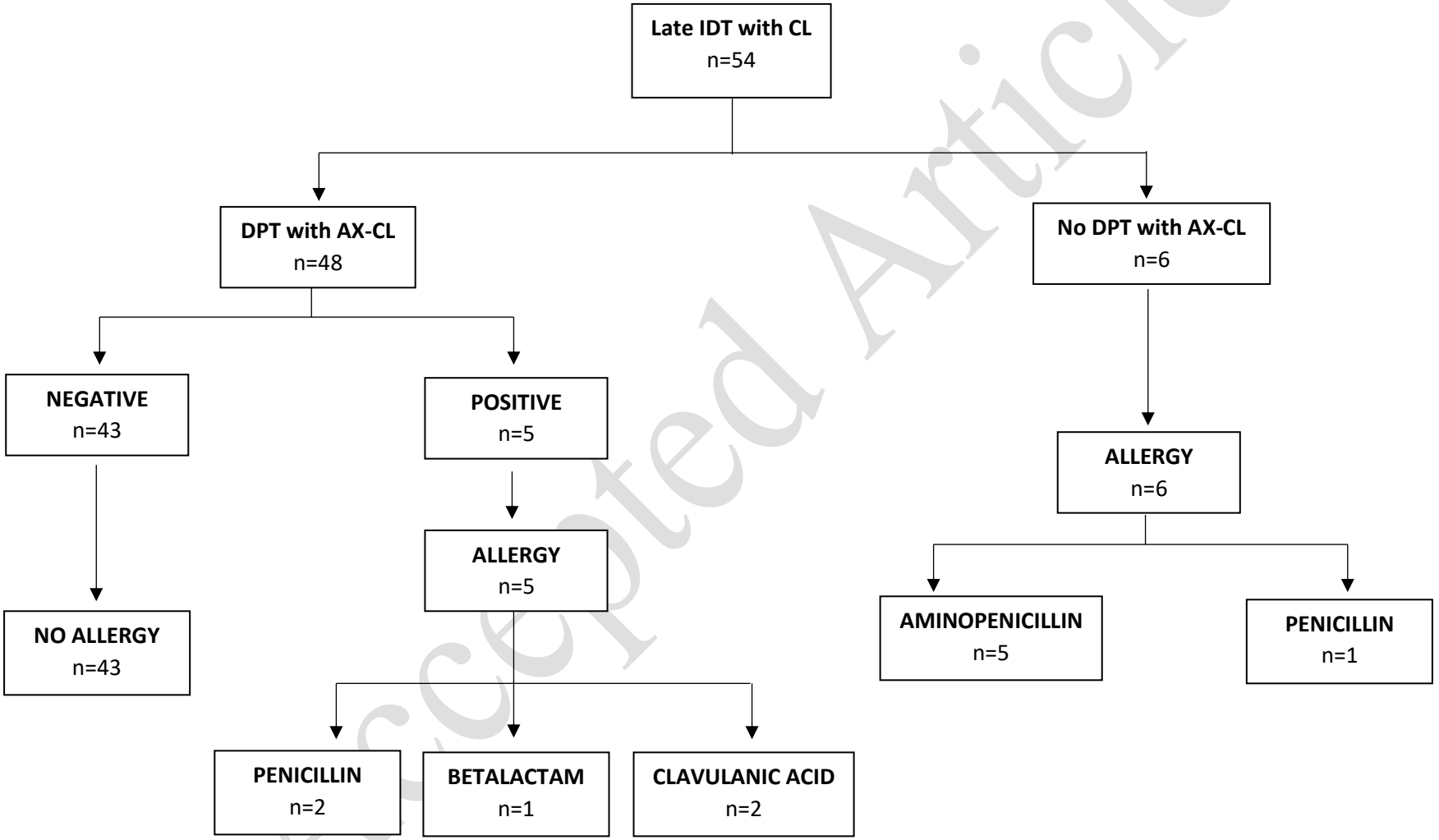
FIGURE 1. Late Positive IDT with Clavulanic Acid



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