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BMJ Paediatrics Open

Mild to moderate hypersensitivity reactions to beta-lactams in children

Journal:	<i>BMJ Paediatrics Open</i>
Manuscript ID	bmjpo-2019-000435
Article Type:	Original article
Date Submitted by the Author:	08-Jan-2019
Complete List of Authors:	Vila, Leticia; Complejo Hospitalario Universitario A Coruña, Pediatrics Garcia, Vanesa; CHUAC, Allergy Martinez Azcona, Oihana; Complejo Hospitalario Universitario A Coruna, Pediatrics Pineiro, Loreley; Complejo Hospitalario Universitario A Coruna, Pediatrics Meijide, Angela; Complejo Hospitalario Universitario A Coruna, Allergy Balboa, Vanesa; Complejo Hospitalario Universitario A Coruna, Epidemiology and Biostatistics
Keywords:	Allergy, Paediatric Practice

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Manuscripts

TITLE PAGE

Title: Mild to moderate hypersensitivity reactions to beta-lactams in children.

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Word count for the text: 2364

Word count for the abstract:236

Number of Tables: 3

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4 30
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6 31
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8
9 32 The authors declare that they have no conflicts of interest related to the
10
11 33 manuscript contents.
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15 35 All authors declare that there were no sources of funding for the research
16
17 36 reported in the manuscript.
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22 38 ABSTRACT

23
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25 39 Objective

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27 40 Beta-lactam (BL) antibiotics are the most reported drugs in hypersensitivity
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29 41 reactions in children. More than 90% of these children tolerate the suspected
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31 42 drug after diagnostic work up.
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34 43 Skin tests (ST) show low sensitivity. Our aim was to assess the performance of
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36 44 DPT without previous ST in mild and moderate delayed reactions and to
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38 45 propose a new DPT protocol.
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41 46 Design of the study

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43 47 Charts from 213 children under 15 years of age referred for suspected BL-
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45 48 allergy from 2011 to 2013, were reviewed.
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48 49 Prick, intradermal and patch tests were performed with major determinant
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50 50 penicilloyl-polylysine, minor determinant mixture, AMX, cefuroxime, penicillin G
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52 51 and AMX-clavulamate.
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55 52 Children with negative skin tests underwent DPT. After an initial full dose of
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57 53 antibiotic, DPT was carried on for 3 days at home in patients reacting within the
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4 54 first 3 days of treatment. If the reaction took place from day 4 on of treatment,
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6 55 patients took the antibiotic for 5 days.
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9 56 Results

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11 57 We included 108 girls and 105 boys. Mean age at the time of reaction was 3.66
12
13 58 \pm 3.06 years. 195 patients (91,5%) reacted to one BL. 154 reactions (67.2%)
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15 59 were non-immediate. Mild to moderate skin manifestations were most frequently
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17 60 reported. AMX-clavulanate was the most frequently involved (63.4,4%). DPT
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19 61 confirmed the diagnosis of drug hypersensitivity in 17 (7.3%) cases. These 17
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21 62 patients had negative ST.
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24 63 Conclusion

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27 64 In mild and moderate cases of BL hypersensitivity, diagnosis can be performed
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29 65 by DPT without previous ST
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34 67 Key words: beta-lactam allergy, delayed hypersensitivity, amoxicillin, drug
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36 68 provocation test
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9 7310
11 74 MAIN TEXT12
13 7514
15
16 76 TITLE: Mild to moderate hypersensitivity reactions to beta-lactams in children17
18 7719
20 78 INTRODUCTION21
22 7923
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25 80 Although around 10% of parents report drug hypersensitivity in their children (1,
26
27 81 2), after a careful evaluation, more than 90% of these children are able to tolerate
28
29 82 the suspected drug (1, 3-5).30
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32 83 In the pediatric population, antibiotics, mainly beta-lactam (BL) and specially
33
34 84 amoxicillin (AMX) (6, 7) are the most commonly involved drugs, followed by
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36 85 nonsteroidal anti-inflammatory drugs (1, 3). Unlike adults, children usually
37
38 86 experience mild nonimmediate skin reactions, as maculopapular exanthema and
39
40 87 nonimmediate urticarial rash (8). Most of these benign skin reactions are not truly
41
42 88 allergic but related to the underlying infectious disease or due to the interaction
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44 89 between the antibiotic and the infectious agent (5, 9).45
46
47 90 An accurate diagnosis of antibiotic hypersensitivity not based only on clinical
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49 91 history is mandatory since antibiotic allergy labels imply the use alternative
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51 92 antibiotics which may be more expensive, less effective and may contribute to an
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53 93 increase in antibiotic-resistant bacteria (10).
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4 94 According to the European Network for Drug Allergy (ENDA) de diagnosis of
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6 95 immediate IgE-mediated reactions to beta-lactams should be based on clinical
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8 96 history, skin tests (ST) (skin prick test [SPT] and intradermal tests [IDT]), in vitro
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10 97 laboratory tests as serum specific IgE determination and drug provocation tests
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12 98 (DPT) (11).

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15 99 For the diagnosis of non-immediate reactions there are not standardized tests
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17 100 available. Although the pathogenic mechanism is unknown, it is believed to be T-
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19 101 cell mediated (12). Late reading IDT or patch tests show very low sensitivity (4-
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21 102 6,8) therefore in mild skin reactions, which are the majority, performing DPT
22
23 103 without previous skin test work up has been proposed (13). Even though
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25 104 considered the gold standard test for the diagnosis of drug allergy, DPT also lacks
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27 105 standardization and there are concerns whether the number of days of drug
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29 106 administration may influence its outcome and the diagnosis of delayed
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31 107 hypersensitivity reactions.

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33 108 We have retrospectively reviewed 213 pediatric patients evaluated for beta-
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35 109 lactam allergy in the Complejo Hospitalario Universitario A Coruña (CHUAC)
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37 110 between the years 2011 to 2013. Our aim is to assess the performance of DPT,
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39 111 with no previous skin test evaluation, in cases of mild and moderate delayed skin
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41 112 reactions regarding safety and diagnosis effectiveness as well as to propose a
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43 113 new DPT.

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52 115 METHODS

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54 116 Charts from 213 children under 15 years of age referred to the Pediatric Allergy
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56 117 Unit of CHUAC for suspected BL allergy from 2011 to 2013, were reviewed.
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4 118 Patients with severe nonimmediate reactions (drug reaction with eosinophilia and
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6 119 systemic symptoms, toxic epidermal necrolysis, generalized exanthematic
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9 120 pustulosis and Steven-Johnson syndrome) were excluded from the study.

10
11 121 The study was approved by the Hospital's Ethics Committee.
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15 123 Clinical data

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17 124 Reactions were classified as immediate if they occurred within 1 hour after
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19 125 antibiotic intake and non-immediate if they occurred more than 1 hour after
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21 126 antibiotic intake.
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24 127 Both types of reactions were graded as mild (no treatment required), moderate
25
26 128 (patients responded readily to appropriate treatment and no hospitalization was
27
28 129 needed) or severe (reaction required treatment in hospital, was life threatening o
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30 130 resulted in death).
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33 131 Patients were asked to sign a written informed consent before their children were
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35 132 tested.
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40 134 Patient involvement

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42 135 Patients were not directly involved in the design of this study.
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48 137 Skin tests

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50 138 For immediate reactions SPT were performed with the major determinant
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52 139 penicilloyl-polylysine (PPL) (Diater, Madrid), minor determinant mixture (MDM)
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54 140 (Diater, Madrid), AMX (20mg/ml), cefuroxime (2,5mg/dl), penicillin G
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4 141 (10.000UI/ml) and AMX-clavulamate (20mg/ml). Children older than 12 years
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6 142 also underwent ID testing at the same concentrations.

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9 143 Readings were made 15 minutes after. ST were considered positive if wheal
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11 144 diameter was ≥ 3 mm larger than the negative control (normal saline solution),
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13 145 with a flare. As positive control we used histamine hydrochloride (ALK, Madrid).
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15 146 Children reporting delayed reactions underwent IDT and patch tests at the
16
17 147 concentrations above mentioned. Readings were made at 48, 72 and 96 hours.
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23 149 Serum specific IgE

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25 150 For immediate reactions within the previous year to clinical evaluation, serum
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27 151 specific IgE to the suspected drug, if available, was determined by ImmunoCAP
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29 152 (Uppsala, Sweden). Specific IgE levels over 0,35 kU/L was considered as
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31 153 positive.
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36 155 Drug provocation tests

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39 156 Children with mild and moderate immediate reactions whose skin tests were
40
41 157 negative, underwent open DPT with a full dose of the drug, calculated by weight,
42
43 158 with one hour of observation at the Hospital setting.

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45 159 In cases of severe immediate reactions, doses were fractionated: 1/10, 1/2 and
46
47 160 total dose, administered every 30 minutes, with one hour of observation.

48
49 161 DPT was not performed with the suspected antibiotic in case of positive ST.

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54 163 Patients reporting non-immediate reactions received a full dose of the antibiotic
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56 164 calculated by weight and they were observed during one hour. Then daily
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4 165 therapeutic doses of the antibiotic were prescribed at home. If the reported
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6 166 reaction took place within the first 3 days of treatment, DPT was carried on for 3
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8 167 days. If the reaction took place from day 4 on of treatment, patient was asked to
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11 168 take the antibiotic for 5 days.

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13 169 In case of a home reaction, parents were instructed to stop antibiotic and to
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15 170 contact us by phone as well as to visit their primary care physician.
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20 172 If the patient or the family could not remember the interval between antibiotic
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22 173 intake and reaction, ST were performed as described above and DPT was carried
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24 174 on during 5 days, in case of negative ST.

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27 175 DPT was considered positive if objective skin, respiratory and/or cardiovascular
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29 176 symptoms were observed.

30
31 177 In case of positive DPT with AMX, DPT with cefuroxime was performed in order
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33 178 to provide antimicrobial therapeutic alternatives given the high rate of tolerance
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35 179 to cephalosporins among patients with delayed hypersensitivity to AMX (14, 15).
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41 181 Statistical analysis

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43 182 A descriptive analysis was performed of all the variables under study, expressing
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45 183 quantitative variables as mean \pm standard deviation, median and range, and
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47 184 qualitative variables as absolute frequencies and percentages.

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50 185 The association between qualitative variables was analyzed with the Chi-square
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52 186 test or Fisher's exact test. Means were compared with the Mann-Whitney test or
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54 187 Kruskal-Wallis test based on the number of groups being compared after verifying
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56 188 the normality assumption by means of the Kolmogorov-Smirnov test. The
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4 189 statistical analysis was performed with the SPSS 19.0 software. We defined
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6 190 statistical significance as a p-value of less than 0.05.
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10 11 192 RESULTS

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13 193 From January 2011 to December 2013, charts from 213 children referred with
14
15 194 suspected hypersensitivity reactions to beta-lactam antibiotics were reviewed.

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17
18 195 There were 108 girls (50.7%) and 105 boys (49.3%). Mean age at the time of the
19
20 196 reaction was 3.66 ± 3.06 years. Mean age at the time of the allergic workup was
21
22 197 6.26 ± 3.9 years. Demographic characteristics are summarized in Table I.

23
24 198 Most children (195 patients, 91.5%) reacted to one BL. Seventeen children (8%)
25
26 199 reacted to two different BL antibiotics and one child reacted to three different BL
27
28 200 antibiotics. A total of 232 suspected hypersensitivity reactions to BL antibiotics
29
30 201 were reported. One hundred and fifty-four reactions (67.2%) were non-
31
32 202 immediate, 24 (10.5%) were reported as immediate and 51 patients (22%) could
33
34 203 not remember the interval between antibiotic intake and reaction. AMX-
35
36 204 clavulanate was the most frequently implicated antibiotic (63.4%), followed by
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38 205 AMX alone (19.4%), cefuroxime (6.9%) and cefaclor (4.7%). Mild to moderate
39
40 206 skin manifestations were most frequently reported: maculopapular exanthema in
41
42 207 52.2% of cases, urticaria (UA) in 33.6%, angioedema in 13.4% and 6.5% of
43
44 208 patients developed serum sickness-like reaction. No patient reported history of
45
46 209 anaphylaxis. Delayed reactions took place after a mean of 3.5 ± 3.2 days of
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48 210 antibiotic intake.

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50 211 These and other clinical characteristics are summarized in Table II.

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4 213 Regarding ST, 32 children older than 12 years with non-immediate skin reactions
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6 214 underwent IDT. All IDT were negative. Two of the 194 children who underwent
7
8 215 patch testing, yielded positive results. The involved antibiotic was amoxicillin in
9
10 216 both cases. These two patients were diagnosed as allergic to amoxicillin and they
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12 217 tolerated cefuroxime on DPT. One patient reporting an immediate reactions,
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14 218 presented positive SPT with penicillin G and was diagnosed of beta-lactam
15
16 219 allergy.

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20 220 Serum specific IgE to the suspected drug was negative in patients referring
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22 221 immediate reactions.

23
24 222 DPT confirmed the diagnosis of drug hypersensitivity in 17 (7.3%) cases. All
25
26 223 patients had delayed skin reactions. While DPT at home, 16 patients developed
27
28 224 mild skin rashes that could be treated with antihistamines and one child
29
30 225 developed generalized urticaria and edema of knees, wrists and ankles
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32 226 suggestive of serum sickness, and needed treatment with oral steroids as well.

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38 228 All patients reporting immediate reactions with negative ST tolerated the
39
40 229 suspected antibiotic on DPT. ST and DPT results are summarized in Table III.

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42 230 Two patients (11,8%) with confirmed BL allergy, reported family history of drug
43
44 231 allergy. There were non significant differences regarding family history of drug
45
46 232 allergy between BL allergic and non allergic children (p 0.356).

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48 233 Eight patients (42,1%) of BL allergic patients presented personal history of
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50 234 atopy. There were non significant differences regarding personal history of
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52 235 atopy between BL allergic and non allergic children in our population (p 0.189).

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4 237 For nonimmediate hypersensitivity reactions, skin tests show very low sensitivity
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6 238 and are time consuming. Since 2014, we do not perform skin tests for the work
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9 239 up of delayed adverse reactions in our daily practice: after a carefully clinical
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11 240 history, patients with mild and moderate nonimmediate reactions to antibiotics
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13 241 undergo DPT as described previously.
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17 18 243 DISCUSSION

19
20 244 Delayed skin maculopapular or urticarial rashes are frequently reported in
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22 245 children receiving beta-lactam antibiotics. From that moment on, the majority of
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24 246 those children are labeled as “allergic to beta-lactams” and they are prescribed
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26 247 alternative antibiotics that may be less effective and/or more expensive (10).
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29 248 Establishing an accurate diagnosis is associated not only with a more rationale
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31 249 use of antibiotics but also with lower rates of health care utilization (16).

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34 250 Until recently, the diagnosis of non-immediate BL allergy was assessed by ST as
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36 251 IDT and patch tests, followed by DPT in those patients with negative ST results.
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38 252 This diagnostic work up has been reconsidered since ST are not efficient for the
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40 253 diagnosis of mild and moderate non-immediate reactions to beta-lactams in
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42 254 children, they are time-consuming and IDT are painful and difficult to perform in
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44 255 small children.

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47 256 DPT confirmed BL hypersensitivity in 7,3% of included children our population.
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49 257 These 17 patients, who presented delayed hypersensitivity reactions, showed
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51 258 negative ST. We assumed the diagnosis of BL allergy in those patients with
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53 259 positive ST. Recently, Caubet and cols (17) reported that 7 out of 11 patients with
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55 260 positive ID tests tolerated the suspected drug on DPT, yielding a positive
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4 261 predictive value for ST of 36% in that population. Vyles and cols (18) also
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6 262 reported that 3 children with positive ST to beta-lactams, tolerated the antibiotic
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8 263 on DPT. Given these observations we wonder if the 3 patients with positive ST in
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10 264 our study (2 with delayed reactions and 1 reporting immediate reaction) would
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12 265 had tolerated the suspected antibiotic on DPT.

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15 266 Based on our findings, since 2014 we do not performed ST in children referred to
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17 267 us with nonimmediate mild to moderate skin reactions related to antibiotics.
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19 268 Diagnostic procedure has become simpler, less time consuming and it is safe.
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21 269 Up to date we have not had severe reactions during DPT at home. Considering
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23 270 our results and based in our experience, we conclude that non-severe antibiotic
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25 271 hypersensitivity may be initially studied by DPT-based protocols, as previously
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27 272 suggested (13,15,17,19, 20).

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30 273 Even though DPT is considered the gold standard for the diagnosis of non-
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32 274 severe, non-immediate skin reactions, it is not standardized in children.

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34 275 The duration of the DPT and the dose administered vary from one study to
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36 276 another. Although according to the members of the Task Force panel (12), a full
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38 277 single therapeutic dose should be enough to diagnose delayed hypersensitivity
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40 278 reactions, there are concerns whether the number of days of drug administration
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42 279 may influence the outcome of DTP and therefore the diagnosis. There is the
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44 280 possibility that short DPT protocols would not identify all allergic children with
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46 281 delayed skin reaction. Mill et al (15) studied 818 children with suspected AMX
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48 282 allergy. They performed a graded DPT with an only dose of antibiotic and found
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50 283 that 6% of patients reacted to it: 2% reacted within the hour after the last dose
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52 284 administered and 4% developed late reactions. Among those patients tolerating
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4 285 AMX on DPT, 10.9% requiring subsequent full treatment with AMX developed
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6 286 delayed skin reactions identical to the initial reactions.
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9 287 Tonson la Tour et al (21) reported high negative predictive value (96.7%) of a 2-
10
11 288 day DPT but still, 4% of children with negative DPT reacted when retreated at
12
13 289 home with the suspected antibiotic.
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15 290 Mori et al (6) evaluated 200 children with suspected drug allergy. After ST, a 5-
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17 291 day DPT was performed. First dose was administered gradually, and if there were
18
19 292 no adverse reactions, patients received daily therapeutic doses at home for 5
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21 293 days. From the 17 patients (9.6%) who reacted on DPT, 14 did it on day 5. As
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23 294 they point out, shorter DPT would not identify 7.3% of late reactors leading to
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25 295 miss diagnosis.
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27 296 To minimize adverse reactions as diarrhea or vomiting as well as the impact on
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29 297 bacterial microbiota and with the aim to diagnose the majority of true
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31 298 hypersensitivity reactions, we propose a different DPT protocol based on the
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33 299 timing of the initial reaction: for children reacting during the first 3 days of
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35 300 treatment, DPT lasts 3 days. In cases of later reactors (from day 3 on), DPT lasts
36
37 301 5 days. Based on this protocol, we found a similar prevalence of BL allergy to
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39 302 what has been previously reported by other authors (3-5).
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41 303 Regarding risk factors for beta-lactam allergy in children Faitelson et al (22)
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43 304 recently found significant association between family history of drug allergy and
44
45 305 Mill et al (16) reported the same observation. Among patients diagnosed of BL
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47 306 allergy by DPT included in the present study, 11,8% (2 patients) referred family
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49 307 history of drug allergy. We could not confirm the suggested association between
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51 308 family history of drug allergy and BL allergy in children.
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4 309 On the other hand, although personal history of asthma and food allergy have
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6 310 been reported as significant risk factors for the development of AMX allergy (22)
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8 311 we found non-significant differences regarding personal history of atopy between
9
10 312 BL allergic and non-allergic patients in our population.
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15 314 In summary, skin tests are not useful for the diagnosis of nonimmediate
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17 315 hypersensitivity reactions to beta-lactams in children. In cases of mild and
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19 316 moderate skin manifestations, DPT without previous ST is safe, effective and less
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21 317 time consuming. There would be interesting to unify the different DPT protocols
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23 318 with the aim to achieve an accurate diagnosis minimizing the potential adverse
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25 319 drug reactions.
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30 321 ACKNOWLEDGEMENTS

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35 323 We thank our nurses, Ofelia Alba Lago, Maria Jesús Fernández Hermida and
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37 324 Isabel Cabana Blanco for their dedication and excellence performing skin tests
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39 325 and drug provocation tests.
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4 328 1. What is already known on this topic:

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6 329 - For diagnosis of non-immediate reactions there aren't standardized tests
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9 330 available. - Skin tests show low sensitivity. It has been proposed to perform only
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11 331 DPT for the diagnosis of non-severe hypersensitivity reactions.

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13 332 - There are concerns whether the number of days of drug administration during
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15 333 DPT may influence its outcome.

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20 335 2. What does this study add?

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22 336 - We conclude that performing DPT without previous skin tests in pediatric
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24 337 patients with non-severe delayed drug reactions is safe and effective.

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26 338 - We propose a new 3-5 day drug provocation test protocol, based on the timing
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28 339 of the initial reaction.

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30 340 - It supports the recommendation of drug provocation test without previous skin
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32 341 tests for the diagnosis of non-severe beta-lactam allergy in children.

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vii. TABLES

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471

 Number of
reactions
N=232

Age at reactionMean \pm SD (years-old)6.66 \pm 3.06

Median (range)

3 (1-14)

Type of reaction

Immediate

24 (10.5%)

Delayed

154 (67.2%)

Not determined

51 (22%)

**Number of
patients**
N = 213

Age
Mean \pm SD (years old)

Median (range)

6.26 \pm 3.87

5 (1-15)

Sex

Male, n (%)

105 (49.3%)

Female, n (%)

108 (50.7%)

Personal history of atopy

Rhinitis, n (%)

63 (29.7%)

Asthma, n (%)

33 (15.5%)

Atopic dermatitis, n (%)

35 (16.4%)

Food allergy, n (%)

18 (8.5%)

2 (0.9%)

Family history of drug allergy

Parents

13 (6.1%)

Grandparents

6 (2.8%)

Brothers

6 (2.8%)

1 (0.5%)

Table I. Demographic

characteristics of children

with suspected

hypersensitivity reactions

to beta-lactam antibiotics

Symptoms			
472	Urticaria (UA)	78 (33.6%)	Table II. Clinical characteristics of children with suspected hypersensitivity reactions to beta-lactam antibiotics
473	Angioedema (AE)	31 (13.4%)	
	Exanthema	121 (52.2%)	
	Serum sickness like	15 (6.5%)	
Antibiotics			
475	Penicilin V	3 (1.3%)	
	Amoxicilin	45 (19.4%)	
476	Amoxicilin/clavulanate	147 (63.4%)	
	Cefuroxime	16 (6.9%)	
	Cefaclor	11 (4.7%)	
477	Cefixime	6 (2.6%)	
	Cefotaxime	1 (0.4%)	

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491 Table III. Outcome of skin tests and drug provocation tests for the diagnosis of
492 beta-lactam hypersensitivity

Test	Positive N (%)	Negative N (%)	Type of reported reaction
SPT (n=)	1 (0.4%)	225 (97%)	Immediate
IDT (n=)	0 (0%)	32 (13.8%)	Delayed
Patch test (n=)	2 (0.9%)	192 (82.8%)	Delayed
DPT (n=)	17 (7.3%)	93 (83.2%)	Delayed

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494 SPT, skin prick test; IDT, intradermal tests; sIgE, serum specific IgE; DPT, drug provocation
495 tests.
496

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BMJ Paediatrics Open

Mild to moderate hypersensitivity reactions to beta-lactams in children, a single centre retrospective review

Journal:	<i>BMJ Paediatrics Open</i>
Manuscript ID	bmjpo-2019-000435.R1
Article Type:	Original article
Date Submitted by the Author:	28-Jan-2019
Complete List of Authors:	Vila, Leticia; Complejo Hospitalario Universitario A Coruña, Pediatrics Garcia, Vanesa; CHUAC, Allergy Martinez Azcona, Oihana; Complejo Hospitalario Universitario A Coruna, Pediatrics Pineiro, Loreley; Complejo Hospitalario Universitario A Coruna, Pediatrics Meijide, Angela; Complejo Hospitalario Universitario A Coruna, Allergy Balboa, Vanesa; Complejo Hospitalario Universitario A Coruna, Epidemiology and Biostatistics
Keywords:	Allergy, Paediatric Practice

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Manuscripts

TITLE PAGE

Title: Mild to moderate hypersensitivity reactions to beta-lactams in children, a single center retrospective review

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Word count for the text: 2463

Word count for the abstract: 239

Number of Tables: 3

Number of Figures:1

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9 34 The authors declare that they have no conflicts of interest related to the
10
11 35 manuscript contents.
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15 37 All authors declare that there were no sources of funding for the research
16
17 38 reported in the manuscript.
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22 40 ABSTRACT

23
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25 41 Objective

26
27 42 Beta-lactam (BL) antibiotics are the most reported drugs in hypersensitivity
28
29 43 reactions in children. More than 90% of these children tolerate the suspected
30
31 44 drug after diagnostic work up.
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34 45 Skin tests (ST) show low sensitivity. Our aim was to assess the performance of
35
36 46 drug provocation tests (DPT) without previous ST in mild and moderate delayed
37
38 47 reactions and to propose a new DPT protocol.
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40
41 48 Design of the study

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43 49 Charts from 213 children under 15 years of age referred for suspected BL-
44
45 50 allergy from 2011 to 2013, were reviewed.
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47
48 51 Prick, intradermal and patch tests were performed with major determinant
49
50 52 penicilloyl-polylysine, minor determinant mixture, AMX, cefuroxime, penicillin G
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52 53 and AMX-clavulamate.
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55 54 Children with negative skin tests underwent DPT. After an initial full dose of
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57 55 antibiotic, DPT was carried on for 3 days at home in patients reacting within the
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4 56 first 3 days of treatment. If the reaction took place from day 4 on of treatment,
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6 57 patients took the antibiotic for 5 days.
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9 58 Results

10
11 59 We included 108 girls and 105 boys. Mean age at the time of reaction was 3.66
12
13 60 \pm 3.06 years. 195 patients (91,5%) reacted to one BL. 154 reactions (67.2%)
14
15 61 were non-immediate. Mild to moderate skin manifestations were most frequently
16
17 62 reported. AMX-clavulanate was the most frequently involved (63.4,4%). DPT
18
19 63 confirmed the diagnosis of drug hypersensitivity in 17 (7.3%) cases. These 17
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21 64 patients had negative ST.
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25 65 Conclusion

26
27 66 In mild and moderate cases of BL hypersensitivity, diagnosis can be performed
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29 67 by DPT without previous ST
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32 68
33
34 69 Key words: beta-lactam allergy, delayed hypersensitivity, amoxicillin, drug
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36 70 provocation test.
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4 71 MAIN TEXT
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9 73 TITLE: Mild to moderate hypersensitivity reactions to beta-lactams in children, a
10 74 single centre retrospective review.
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13 75

14 76 INTRODUCTION
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18
19 78 Although around 10% of parents report drug hypersensitivity in their children (1,
20
21 79 2), after a careful evaluation, more than 90% of these children are able to tolerate
22
23 80 the suspected drug (1, 3-5).
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25
26 81 In the pediatric population, antibiotics, mainly beta-lactam (BL) and specially
27
28 82 amoxicillin (AMX) (6, 7) are the most commonly involved drugs, followed by
29
30 83 nonsteroidal anti-inflammatory drugs (1, 3). Unlike adults, children usually
31
32 84 experience mild nonimmediate skin reactions, as maculopapular exanthema and
33
34 85 nonimmediate urticarial rash (8). Most of these benign skin reactions are not truly
35
36 86 allergic but related to the underlying infectious disease or due to the interaction
37
38 87 between the antibiotic and the infectious agent (5, 9).
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41 88 An accurate diagnosis of antibiotic hypersensitivity not based only on clinical
42
43 89 history is mandatory since antibiotic allergy labels imply the use alternative
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45 90 antibiotics which may be more expensive, less effective and may contribute to an
46
47 91 increase in antibiotic-resistant bacteria (10).
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51 92 According to the European Network for Drug Allergy (ENDA) de diagnosis of
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53 93 immediate IgE-mediated reactions to beta-lactams should be based on clinical
54
55 94 history, skin tests (ST) (skin prick test [SPT] and intradermal tests [IDT]), in vitro
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4 95 laboratory tests as serum specific IgE determination and drug provocation tests
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6 96 (DPT) (11).

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9 97 For the diagnosis of non-immediate reactions there are not standardized tests
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11 98 available. Although the pathogenic mechanism is unknown, it is believed to be T-
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13 99 cell mediated (12). Late reading IDT or patch tests show very low sensitivity (4-
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15 100 6,8) therefore in mild skin reactions, which are the majority, performing DPT
16
17 101 without previous skin test work up has been proposed (13). Even though
18
19 102 considered the gold standard test for the diagnosis of drug allergy, DPT also lacks
20
21 103 standardization and there are concerns whether the number of days of drug
22
23 104 administration may influence its outcome and the diagnosis of delayed
24
25 105 hypersensitivity reactions.

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29 106 We have retrospectively reviewed 213 pediatric patients evaluated for beta-
30
31 107 lactam allergy in the Complejo Hospitalario Universitario A Coruña (CHUAC)
32
33 108 between the years 2011 to 2013. Our aim is to assess the performance of DPT,
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35 109 with no previous skin test evaluation, in cases of mild and moderate delayed skin
36
37 110 reactions regarding safety and diagnosis effectiveness as well as to propose a
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39 111 new DPT.

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44 45 113 METHODS

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48 114 Charts from 213 children under 15 years of age referred to the Pediatric Allergy
49
50 115 Unit of CHUAC for suspected BL allergy from 2011 to 2013, were reviewed.
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52 116 Patients with severe nonimmediate reactions (drug reaction with eosinophilia and
53
54 117 systemic symptoms, toxic epidermal necrolysis, generalized exanthematic
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56 118 pustulosis and Steven-Johnson syndrome) were excluded from the study.

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4 119 The study was approved by the Hospital's Ethics Committee.
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9 121 Clinical data

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11 122 Reactions were classified as immediate if they occurred within 1 hour after
12
13 123 antibiotic intake and non-immediate if they occurred more than 1 hour after
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15 124 antibiotic intake.

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18 125 Both types of reactions were graded as mild (no treatment required), moderate
19
20 126 (patients responded readily to appropriate treatment and no hospitalization was
21
22 127 needed) or severe (reaction required treatment in hospital, was life threatening o
23
24 128 resulted in death).

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27 129 Patients were asked to sign a written informed consent before their children were
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29 130 tested.

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33 132 Patient involvement

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35 133 Patients were not directly involved in the design of this study.

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41 135 Skin tests

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43 136 For immediate reactions SPT were performed with the major determinant
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45 137 penicilloyl-polylysine (PPL) (Diater, Madrid), minor determinant mixture (MDM)
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47 138 (Diater, Madrid) and the suspected drug at the following concentrations: AMX
48
49 139 (20mg/ml), cefuroxime (2,5mg/dl), penicillin G (10.000UI/ml) and AMX-
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51 140 clavulamate (20mg/ml). Children older than 12 years also underwent ID testing
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54 141 in case of negative SPT.
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4 142 Readings were made 15 minutes after. ST were considered positive if wheal
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6 143 diameter was ≥ 3 mm larger than the negative control (normal saline solution),
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9 144 with a flare. As positive control we used histamine hydrochloride (ALK, Madrid).
10
11 145 Children reporting delayed reactions underwent SPT and if negative, IDT (if older
12
13 146 than 12 years of age) and patch tests were performed at the concentrations
14
15
16 147 above mentioned. Readings were made at 48, 72 and 96 hours.
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20 149 Serum specific IgE

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22 150 For immediate reactions within the previous year to clinical evaluation, serum
23
24 151 specific IgE to the suspected drug, if available, was determined by ImmunoCAP
25
26 152 (Uppsala, Sweden). Specific IgE levels over 0,35 kU/L was considered as
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29 153 positive.
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34 155 Drug provocation tests

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36 156 Children with mild and moderate immediate reactions whose skin tests were
37
38 157 negative, underwent open DPT with a full dose of the drug, calculated by weight,
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41 158 with one hour of observation at the Hospital setting.
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43 159 In cases of severe immediate reactions, doses were fractionated: 1/10, 1/2 and
44
45 160 total dose, administered every 30 minutes, with one hour of observation.
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50 162 Patients reporting non-immediate reactions received a full dose of the antibiotic
51
52 163 calculated by weight and they were observed during one hour. Then daily
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54 164 therapeutic doses of the antibiotic were prescribed at home. If the reported
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57 165 reaction took place within the first 3 days of treatment, DPT was carried on for 3
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4 166 days. If the reaction took place from day 4 on of treatment, patient was asked to
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6 167 take the antibiotic for 5 days.

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9 168 In case of a home reaction, parents were instructed to stop antibiotic and to
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11 169 contact us by phone as well as to visit their primary care physician.

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15 171 If the patient or the family could not remember the interval between antibiotic
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17 172 intake and reaction, ST were performed as described above and if negative, DPT
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19 173 was carried on during 5 days, in case of negative ST.

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22 174 DPT was considered positive if objective skin, respiratory and/or cardiovascular
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24 175 symptoms were observed.

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27 176 In case of positive DPT with AMX, DPT with cefuroxime was performed in order
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29 177 to provide antimicrobial therapeutic alternatives given the high rate of tolerance
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31 178 to cephalosporins among patients with delayed hypersensitivity to AMX (14, 15).

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36 180 Statistical analysis

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39 181 A descriptive analysis was performed of all the variables under study, expressing
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41 182 quantitative variables as mean \pm standard deviation, median and range, and
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43 183 qualitative variables as absolute frequencies and percentages.

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45 184 The association between qualitative variables was analyzed with the Chi-square
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47 185 test or Fisher's exact test. Means were compared with the Mann-Whitney test or
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49 186 Kruskal-Wallis test based on the number of groups being compared after verifying
50
51 187 the normality assumption by means of the Kolmogorov-Smirnov test. The
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53 188 statistical analysis was performed with the SPSS 19.0 software. We defined
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55 189 statistical significance as a p-value of less than 0.05.
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191 RESULTS

192 *Clinical results*

193 From January 2011 to December 2013, charts from 213 children referred with
194 suspected hypersensitivity reactions to beta-lactam antibiotics were reviewed.

195 There were 108 girls (50.7%) and 105 boys (49.3%). Mean age at the time of the
196 reaction was 3.66 ± 3.06 years. Mean age at the time of the allergic workup was
197 6.26 ± 3.9 years. Demographic characteristics are summarized in Table I.

198 Most children (195 patients, 91.5%) reacted to one BL. Seventeen children (8%)
199 reacted to two different BL antibiotics and one child reacted to three different BL
200 antibiotics. A total of 229 suspected hypersensitivity reactions to BL antibiotics
201 were reported. One hundred and fifty-four reactions (67.2%) were non-
202 immediate, 24 (10.5%) were reported as immediate and 51 patients (22%) could
203 not remember the interval between antibiotic intake and reaction. AMX-
204 clavulanate was the most frequently implicated antibiotic (63.4%), followed by
205 AMX alone (19.4%), cefuroxime (6.9%) and cefaclor (4.7%). Mild to moderate
206 skin manifestations were most frequently reported: maculopapular exanthema in
207 52.2% of cases, urticaria (UA) in 33.6%, angioedema in 13.4% and 6.5% of
208 patients developed serum sickness-like reaction. No patient reported history of
209 anaphylaxis. Delayed reactions took place after a mean of 3.5 ± 3.2 days of
210 antibiotic intake.

211 These and other clinical characteristics are summarized in Table II.

212

213 *Testing results*

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4 214 Regarding ST, 32 children older than 12 years with non-immediate skin reactions
5
6 215 underwent IDT. All IDT were negative. Only 2 of 205 children who underwent
7
8 216 patch testing, yielded positive results. The involved antibiotic was amoxicillin in
9
10 217 both cases and they reported a non immediate reaction. These two patients were
11
12 218 diagnosed as allergic to amoxicillin and they tolerated cefuroxime on DPT. One
13
14 219 patient reporting an immediate reaction, presented positive SPT with penicillin G
15
16 220 and was diagnosed of beta-lactam allergy. Serum specific IgE to the suspected
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18 221 drug was negative in patients referring immediate reactions. Diagnosis algorithm
19
20 222 and results are showed with a flow chart in Figure 1.
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25 223 DPT confirmed the diagnosis of drug hypersensitivity in 17 (7.5%) cases. All
26
27 224 patients had delayed skin reactions. While DPT at home, 16 patients developed
28
29 225 mild skin rashes that could be treated with antihistamines and one child
30
31 226 developed generalized urticaria and edema of knees, wrists and ankles
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33 227 suggestive of serum sickness, and needed treatment with oral steroids as well.
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39 229 All patients reporting immediate reactions with negative ST tolerated the
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41 230 suspected antibiotic on DPT. ST and DPT results are summarized in Table III.
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43 231 Two patients (11,8%) with confirmed BL allergy, reported family history of drug
44
45 232 allergy. There were non significant differences regarding family history of drug
46
47 233 allergy between BL allergic and non allergic children (p 0.356).
48

49 234 Eight patients (42,1%) of BL allergic patients presented personal history of
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51 235 atopy. There were non significant differences regarding personal history of
52
53 236 atopy between BL allergic and non allergic children in our population (p 0.189).
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4 238 For nonimmediate hypersensitivity reactions, skin tests show very low sensitivity
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6 239 and are time consuming. Since 2014, we do not perform skin tests for the work
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9 240 up of delayed adverse reactions in our daily practice: after a carefully clinical
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11 241 history, patients with mild and moderate nonimmediate reactions to antibiotics
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13 242 undergo DPT as described previously.
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17 18 244 DISCUSSION

19
20 245 Delayed skin maculopapular or urticarial rashes are frequently reported in
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22 246 children receiving beta-lactam antibiotics. From that moment on, the majority of
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24 247 those children are labeled as “allergic to beta-lactams” and they are prescribed
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26 248 alternative antibiotics that may be less effective and/or more expensive (10).
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28 249 Establishing an accurate diagnosis is associated not only with a more rationale
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30 250 use of antibiotics but also with lower rates of health care utilization (16).
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35 251 Until recently, the diagnosis of non-immediate BL allergy was assessed by ST
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37 252 as IDT and patch tests, followed by DPT in those patients with negative ST
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39 253 results. This diagnostic work up has been reconsidered since ST are not
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41 254 efficient for the diagnosis of mild and moderate non-immediate reactions to
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43 255 beta-lactams in children, they are time-consuming and IDT are painful and
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45 256 difficult to perform in small children. The reasons for the low sensitivity of ST are
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47 257 not well understood. It could be due to the use of a drug structure or conjugate
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49 258 that is not well recognized by the immune system since BLs are haptens that
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51 259 need to bind to proteins covalently to elicit an immune response (17).
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4 260 DPT confirmed BL hypersensitivity in 7,5% of cases in our population. These 17
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6 261 patients, who presented delayed hypersensitivity reactions, showed negative ST.
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8 262 We assumed the diagnosis of BL allergy in those patients with positive ST.
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10 263 Recently, Caubet and cols (18) reported that 7 out of 11 patients with positive ID
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12 264 tests tolerated the suspected drug on DPT, yielding a positive predictive value for
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14 265 ST of 36% in that population. Vyles and cols (19) also reported that 3 children
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16 266 with positive ST to beta-lactams, tolerated the antibiotic on DPT. Given these
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18 267 observations we wonder if the 3 patients with positive ST in our study (2 with
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20 268 delayed reactions and 1 reporting immediate reaction) would had tolerated the
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22 269 suspected antibiotic on DPT.
23
24 270 Based on our findings, since 2014 we do not performed ST in children referred to
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26 271 us with nonimmediate mild to moderate skin reactions related to antibiotics.
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28 272 Diagnostic procedure has become simpler, less time consuming and it is safe.
29
30 273 Up to date we have not had severe reactions during DPT at home. Considering
31
32 274 our results and based in our experience, we conclude that non-severe antibiotic
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34 275 hypersensitivity may be initially studied by DPT-based protocols, as previously
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36 276 suggested (13,15,18,20,21).
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38 277 Even though DPT is considered the gold standard for the diagnosis of non-
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40 278 severe, non-immediate skin reactions, it is not standardized in children.
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42 279 The duration of the DPT and the dose administered vary from one study to
43
44 280 another. Although according to the members of the Task Force panel (12), a full
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46 281 single therapeutic dose should be enough to diagnose delayed hypersensitivity
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48 282 reactions, there are concerns whether the number of days of drug administration
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50 283 may influence the outcome of DTP and therefore the diagnosis. There is the
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4 284 possibility that short DPT protocols would not identify all allergic children with
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6 285 delayed skin reaction. Mill et al (15) studied 818 children with suspected AMX
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9 286 allergy. They performed a graded DPT with an only dose of antibiotic and found
10
11 287 that 6% of patients reacted to it: 2% reacted within the hour after the last dose
12
13 288 administered and 4% developed late reactions. Among those patients tolerating
14
15 289 AMX on DPT, 10.9% requiring subsequent full treatment with AMX developed
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17 290 delayed skin reactions identical to the initial reactions.

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19
20 291 Tonson la Tour et al (22) reported high negative predictive value (96.7%) of a 2-
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22 292 day DPT but still, 4% of children with negative DPT reacted when retreated at
23
24 293 home with the suspected antibiotic.

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26
27 294 Mori et al (6) evaluated 200 children with suspected drug allergy. After ST, a 5-
28
29 295 day DPT was performed. First dose was administered gradually, and if there were
30
31 296 no adverse reactions, patients received daily therapeutic doses at home for 5
32
33 297 days. From the 17 patients (9.6%) who reacted on DPT, 14 did it on day 5. As
34
35 298 they point out, shorter DPT would not identify 7.3% of late reactors leading to
36
37 299 miss diagnosis.

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40 300 To minimize adverse reactions as diarrhea or vomiting as well as the impact on
41
42 301 bacterial microbiota and with the aim to diagnose the majority of true
43
44 302 hypersensitivity reactions, we propose a different DPT protocol based on the
45
46 303 timing of the initial reaction: for children reacting during the first 3 days of
47
48 304 treatment, DPT lasts 3 days. In cases of later reactors (from day 3 on), DPT lasts
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50 305 5 days. Based on this protocol, we found a similar prevalence of BL allergy to
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52 306 what has been previously reported by other authors (3-5).
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4 307 Regarding risk factors for beta-lactam allergy in children Faitelson et al (23)
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6 308 recently found significant association between family history of drug allergy and
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8 309 Mill et al (16) reported the same observation. Among patients diagnosed of BL
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10 310 allergy by DPT included in the present study, 11,8% (2 patients) referred family
11
12 311 history of drug allergy. We could not confirm the suggested association between
13
14 312 family history of drug allergy and BL allergy in children.
15
16 313 On the other hand, although personal history of asthma and food allergy have
17
18 314 been reported as significant risk factors for the development of AMX allergy (23)
19
20 315 we found non-significant differences regarding personal history of atopy between
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22 316 BL allergic and non-allergic patients in our population.
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29 317
30 318 In summary, skin tests are not useful for the diagnosis of nonimmediate
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32 319 hypersensitivity reactions to beta-lactams in children. In cases of mild and
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34 320 moderate skin manifestations, DPT without previous ST is safe, effective and less
35
36 321 time consuming. There would be interesting to unify the different DPT protocols
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38 322 with the aim to achieve an accurate diagnosis minimizing the potential adverse
39
40 323 drug reactions.
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46 325 ACKNOWLEDGEMENTS

47 326 We thank our nurses, Ofelia Alba Lago, Maria Jesús Fernández Hermida and
48
49 327 Isabel Cabana Blanco for their dedication and excellence performing skin tests
50
51 328 and drug provocation tests.
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4 329 1. What is already known on this topic:

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6 330 - For diagnosis of non-immediate reactions there aren't standardized tests
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8 331 available. - Skin tests show low sensitivity. It has been proposed to perform only
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11 332 DPT for the diagnosis of non-severe hypersensitivity reactions.

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13 333 - There are concerns whether the number of days of drug administration during
14
15 334 DPT may influence its outcome.

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20 336 2. What does this study add?

21
22 337 - We conclude that performing DPT without previous skin tests in pediatric
23
24 338 patients with non-severe delayed drug reactions is safe and effective.

25
26 339 - We propose a new 3-5 day drug provocation test protocol, based on the timing
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28 340 of the initial reaction.

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30 341 - It supports the recommendation of drug provocation test without previous skin
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32 342 tests for the diagnosis of non-severe beta-lactam allergy in children.

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446 TABLES

447 **Table I.** Demographic characteristics of children with suspected hypersensitivity reactions to
 448 beta-lactam antibiotics
 449

	Number of patients N = 213
Age	
452 Mean \pm SD (years-old)	6.26 \pm 3.87
Median (range)	5 (1-15)
Sex	
454 Female, n (%)	108 (50.7%)
Male, n (%)	105 (49.3%)
Personal history of atopy	
455 Rhinitis, n (%)	63 (29.7%)
456 Asthma, n (%)	35 (16.4%)
Atopic dermatitis, n (%)	18 (8.5%)
457 Food allergy, n (%)	2 (0.9%)
Family history of drug allergy	
458 Parents	13 (6.1%)
Grandparents	6 (2.8%)
459 Brothers	6 (2.8%)
	1 (0.5%)

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463 **Table II.** Clinical characteristics of children with suspected hypersensitivity reactions to beta-
464 lactam antibiotics
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	Number of reactions N=232
Age at reaction	
Mean \pm SD (years-old)	6.66 \pm 3.06
Median (range)	3 (1-14)
Type of reaction	
Delayed	154 (67.2%)
Not determined	51 (22%)
Immediate	24 (10.5%)
Symptoms	
Exanthema	121 (52.2%)
Urticaria (UA)	78 (33.6%)
Angioedema (AE)	31 (13.4%)
Serum sickness like	15 (6.5%)
Antibiotics	
Amoxicilin/clavulanate	147 (63.4%)
Amoxicilin	45 (19.4%)
Cefuroxime	16 (6.9%)
Cefaclor	11 (4.7%)
Cefixime	6 (2.6%)
Penicilin V	3 (1.3%)
Cefotaxime	1 (0.4%)

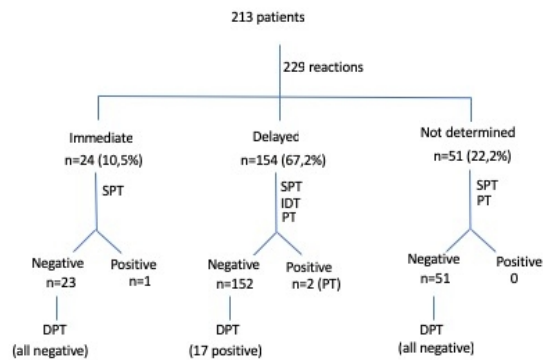
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476 **Table III.** Outcome of skin tests and drug provocation tests performed for the diagnosis of beta-
477 lactam hypersensitivity.
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Test	Positive n (%)	Negative n
SPT (n=229)	1 (0,4%)	228
IDT (n=32)	0	32
Patch test (n=205)	2 (0,9%)	203
DPT (n=226)	17(7,5%)	226

479 SPT, skin prick test; IDT, intradermal tests; DPT, drug provocation tests.
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Figure 1. Diagnostic work up for suspected BL hypersensitivity



SPT: Skin prick test; IDT: intradermal test; PT: patch test; DPT: drug provocation test

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BMJ Paediatrics Open

Mild to moderate hypersensitivity reactions to beta-lactams in children, a single centre retrospective review

Journal:	<i>BMJ Paediatrics Open</i>
Manuscript ID	bmjpo-2019-000435.R2
Article Type:	Original article
Date Submitted by the Author:	08-Mar-2019
Complete List of Authors:	Vila, Leticia; Complexo Hospitalario Universitario A Coruna Garcia, Vanesa; Complexo Hospitalario Universitario A Coruna Martinez Azcona, Oihana; Complexo Hospitalario Universitario A Coruna, Pediatrics Pineiro, Loreley; Complexo Hospitalario Universitario A Coruna, Pediatrics Mejjide, Angela; Complexo Hospitalario Universitario A Coruna, Allergy Balboa, Vanesa; Complexo Hospitalario Universitario A Coruna, Epidemiology and Biostatistics
Keywords:	Allergy, Paediatric Practice

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Manuscripts

TITLE PAGE

Title: Mild to moderate hypersensitivity reactions to beta-lactams in children, a single center retrospective review

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Word count for the text: 2463

Word count for the abstract: 239

Number of Tables: 3

Number of Figures:2

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9 34 The authors declare that they have no conflicts of interest related to the
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11 35 manuscript contents.
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16 37 All authors declare that there were no sources of funding for the research
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18 38 reported in the manuscript.
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22 40 ABSTRACT

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24 41 Objective

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27 42 Beta-lactam (BL) antibiotics are the most reported drugs in hypersensitivity
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29 43 reactions in children. More than 90% of these children tolerate the suspected
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31 44 drug after diagnostic work up.
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34 45 Skin tests (ST) show low sensitivity. Our aim was to assess the performance of
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36 46 drug provocation tests (DPT) without previous ST in mild and moderate delayed
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38 47 reactions and to propose a new DPT protocol.
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41 48 Design of the study

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43 49 Charts from 213 children under 15 years of age referred for suspected BL-
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45 50 allergy from 2011 to 2013, were reviewed.
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48 51 Prick, intradermal and patch tests were performed with major determinant
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50 52 penicilloyl-polylysine, minor determinant mixture, AMX, cefuroxime, penicillin G
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52 53 and AMX-clavulamate.
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55 54 Children with negative skin tests underwent DPT. After an initial full dose of
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57 55 antibiotic, DPT was carried on for 3 days at home in patients reacting within the
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4 56 first 3 days of treatment. If the reaction took place from day 4 on of treatment,
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6 57 patients took the antibiotic for 5 days.
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9 58 Results

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11 59 We included 108 girls and 105 boys. Mean age at the time of reaction was 3.66
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13 60 \pm 3.06 years. 195 patients (91,5%) reacted to one BL. 154 reactions (67.2%)
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15 61 were non-immediate. Mild to moderate skin manifestations were most frequently
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17 62 reported. AMX-clavulanate was the most frequently involved (63.4,4%). DPT
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19 63 confirmed the diagnosis of drug hypersensitivity in 17 (7.3%) cases. These 17
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21 64 patients had negative ST.
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25 65 Conclusion

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27 66 In mild and moderate cases of BL hypersensitivity, diagnosis can be performed
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29 67 by DPT without previous ST
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34 69 Key words: beta-lactam allergy, delayed hypersensitivity, amoxicillin, drug
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36 70 provocation test.
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71 MAIN TEXT

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73 TITLE: Mild to moderate hypersensitivity reactions to beta-lactams in children, a
74 single centre retrospective review.

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76 INTRODUCTION

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78 Although around 10% of parents report drug hypersensitivity in their children (1,
79 2), after a careful evaluation, more than 90% of these children are able to tolerate
80 the suspected drug (1, 3-5).

81 In the pediatric population, antibiotics, mainly beta-lactam (BL) and specially
82 amoxicillin (AMX) (6, 7) are the most commonly involved drugs, followed by
83 nonsteroidal anti-inflammatory drugs (1, 3). Unlike adults, children usually
84 experience mild nonimmediate skin reactions, as maculopapular exanthema and
85 nonimmediate urticarial rash (8). Most of these benign skin reactions are not truly
86 allergic but related to the underlying infectious disease or due to the interaction
87 between the antibiotic and the infectious agent (5, 9).

88 An accurate diagnosis of antibiotic hypersensitivity not based only on clinical
89 history is mandatory since antibiotic allergy labels imply the use alternative
90 antibiotics which may be more expensive, less effective and may contribute to an
91 increase in antibiotic-resistant bacteria (10).

92 According to the European Network for Drug Allergy (ENDA) the diagnosis of
93 immediate IgE-mediated reactions to beta-lactams should be based on clinical
94 history, skin tests (ST) (skin prick test [SPT] and intradermal tests [IDT]), in vitro

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4 95 laboratory tests as serum specific IgE determination and drug provocation tests
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6 96 (DPT) (11).
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9 97 For the diagnosis of non-immediate reactions there are not standardized tests
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11 98 available. Although the pathogenic mechanism is unknown, it is believed to be T-
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13 99 cell mediated (12). Late reading IDT or patch tests show very low sensitivity (4-
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15 100 6,8) therefore in mild skin reactions, which are the majority, performing DPT
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17 101 without previous skin test work up has been proposed (13). Even though
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19 102 considered the gold standard test for the diagnosis of drug allergy, DPT also lacks
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21 103 standardization and there are concerns whether the number of days of drug
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23 104 administration may influence its outcome and the diagnosis of delayed
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25 105 hypersensitivity reactions.
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29 106 We have retrospectively reviewed 213 pediatric patients evaluated for beta-
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31 107 lactam allergy in the Complejo Hospitalario Universitario A Coruña (CHUAC)
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33 108 between the years 2011 to 2013. Our aim is to assess the performance of DPT,
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35 109 with no previous skin test evaluation, in cases of mild and moderate delayed skin
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37 110 reactions regarding safety and diagnosis effectiveness as well as to propose a
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39 111 new DPT.
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44 113 METHODS

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47 114 Charts from 213 children under 15 years of age referred to the Pediatric Allergy
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49 115 Unit of CHUAC for suspected BL allergy from 2011 to 2013, were reviewed.
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51 116 Patients with severe nonimmediate reactions (drug reaction with eosinophilia and
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53 117 systemic symptoms, toxic epidermal necrolysis, generalized exanthematic
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55 118 pustulosis and Steven-Johnson syndrome) were excluded from the study.
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4 119 The study was approved by the Hospital's Ethics Committee.
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9 121 Clinical data

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11 122 Reactions were classified as immediate if they occurred within 1 hour after
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13 123 antibiotic intake and non-immediate if they occurred more than 1 hour after
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15 124 antibiotic intake.

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18 125 Both types of reactions were graded as mild (no treatment required), moderate
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20 126 (patients responded readily to appropriate treatment and no hospitalization was
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22 127 needed) or severe (reaction required treatment in hospital, was life threatening o
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24 128 resulted in death).

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27 129 Patients were asked to sign a written informed consent before their children were
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29 130 tested.

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33 132 Patient involvement

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35 133 Patients were not directly involved in the design of this study.
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41 135 Skin tests

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43 136 For immediate reactions SPT were performed with the major determinant
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45 137 penicilloyl-polylysine (PPL) (Diater, Madrid), minor determinant mixture (MDM)
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47 138 (Diater, Madrid) and the suspected drug at the following concentrations: AMX
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49 139 (20mg/ml), cefuroxime (2,5mg/dl), penicillin G (10.000UI/ml) and AMX-
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51 140 clavulamate (20mg/ml). Children older than 12 years also underwent ID testing
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54 141 in case of negative SPT.
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4 142 Readings were made 15 minutes after. ST were considered positive if wheal
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6 143 diameter was ≥ 3 mm larger than the negative control (normal saline solution),
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9 144 with a flare. As positive control we used histamine hydrochloride (ALK, Madrid).
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11 145 Children reporting delayed reactions underwent SPT and if negative, IDT (if older
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13 146 than 12 years of age) and patch tests were performed at the concentrations
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16 147 above mentioned. Readings were made at 48, 72 and 96 hours.
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20 149 Serum specific IgE

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22 150 For immediate reactions within the previous year to clinical evaluation, serum
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24 151 specific IgE to the suspected drug, if available, was determined by ImmunoCAP
25
26 152 (Uppsala, Sweden). Specific IgE levels over 0,35 kU/L was considered as
27
28 153 positive.
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34 155 Drug provocation tests

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36 156 Children with mild and moderate immediate reactions whose skin tests were
37
38 157 negative, underwent open DPT with a full dose of the drug, calculated by weight,
39
40 158 as follows: amoxicillin 50mg/kg/dose; amoxicillin-clavulanate: 50mg/kg/dose;
41
42 159 cefuroxime: 15mg/kg/dose; cefaclor 8mg/kg/dose. They stayed for one hour of
43
44 160 observation at the Hospital setting,
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48 161 In cases of severe immediate reactions, doses were fractionated: 1/10, 1/2 and
49
50 162 total dose, administered every 30 minutes, with one hour of observation.
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55 164 Patients reporting non-immediate reactions received a full dose of the antibiotic
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57 165 calculated by weight and they were observed during one hour. Then daily
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4 166 therapeutic doses of the antibiotic were prescribed at home. If the reported
5
6 167 reaction took place within the first 3 days of treatment, DPT was carried on for 3
7
8 168 days. If the reaction took place from day 4 on of treatment, patient was asked to
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10
11 169 take the antibiotic for 5 days.

12
13 170 In case of a home reaction, parents were instructed to stop antibiotic and to
14
15 171 contact us by phone as well as to visit their primary care physician.

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19
20 173 If the patient or the family could not remember the interval between antibiotic
21
22 174 intake and reaction, ST were performed as described above and if negative, DPT
23
24 175 was carried on during 5 days, in case of negative ST.

25
26 176 DPT was considered positive if objective skin, respiratory and/or cardiovascular
27
28 177 symptoms were observed.

29
30 178 In case of positive DPT with AMX, DPT with cefuroxime was performed in order
31
32 179 to provide antimicrobial therapeutic alternatives given the high rate of tolerance
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34 180 to cephalosporins among patients with delayed hypersensitivity to AMX (14, 15).

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39 182 Diagnosis algorithm is shown in Figure 1.

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44 184 Statistical analysis

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46 185 A descriptive analysis was performed of all the variables under study, expressing
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48 186 quantitative variables as mean \pm standard deviation, median and range, and
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50 187 qualitative variables as absolute frequencies and percentages.

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52 188 The association between qualitative variables was analyzed with the Chi-square
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54 189 test or Fisher's exact test. Means were compared with the Mann-Whitney test or

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4 190 Kruskal-Wallis test based on the number of groups being compared after verifying
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6 191 the normality assumption by means of the Kolmogorov-Smirnov test. The
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9 192 statistical analysis was performed with the SPSS 19.0 software. We defined
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11 193 statistical significance as a p-value of less than 0.05.
12

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15 195 RESULTS

16 196 *Clinical results*

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20 197 From January 2011 to December 2013, charts from 213 children referred with
21
22 198 suspected hypersensitivity reactions to beta-lactam antibiotics were reviewed.

23
24
25 199 There were 108 girls (50.7%) and 105 boys (49.3%). Mean age at the time of the
26
27 200 reaction was 3.66 ± 3.06 years. Mean age at the time of the allergic workup was
28
29 201 6.26 ± 3.9 years. Demographic characteristics are summarized in Table I.

30
31 202 Most children (195 patients, 91.5%) reacted to one BL. Seventeen children (8%)
32
33 203 reacted to two different BL antibiotics and one child reacted to three different BL
34
35 204 antibiotics. A total of 229 suspected hypersensitivity reactions to BL antibiotics
36
37 205 were reported. One hundred and fifty-four reactions (67.2%) were non-
38
39 206 immediate, 24 (10.5%) were reported as immediate and 51 patients (22%) could
40
41 207 not remember the interval between antibiotic intake and reaction. AMX-
42
43 208 clavulanate was the most frequently implicated antibiotic (63.4%), followed by
44
45 209 AMX alone (19.4%), cefuroxime (6.9%) and cefaclor (4.7%). Mild to moderate
46
47 210 skin manifestations were most frequently reported: maculopapular exanthema in
48
49 211 52.2% of cases, urticaria (UA) in 33.6%, angioedema in 13.4% and 6.5% of
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51 212 patients developed serum sickness-like reaction. No patient reported history of
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4 213 anaphylaxis. Delayed reactions took place after a mean of 3.5 ± 3.2 days of
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6 214 antibiotic intake.

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9 215 These and other clinical characteristics are summarized in Table II.

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11 216

12
13 217 *Testing results*

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15 218 Regarding ST, 32 children older than 12 years with non-immediate skin reactions
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17 219 underwent IDT. All IDT were negative. Only 2 of 205 children who underwent
18
19 220 patch testing, yielded positive results. The involved antibiotic was amoxicillin in
20
21 221 both cases and they reported a non immediate reaction. These two patients were
22
23 222 diagnosed as allergic to amoxicillin and they tolerated cefuroxime on DPT. One
24
25 223 patient reporting an immediate reaction, presented positive SPT with penicillin G
26
27 224 and was diagnosed of beta-lactam allergy. Serum specific IgE to the suspected
28
29 225 drug was negative in patients referring immediate reactions. Results are showed
30
31 226 with a flow chart in Figure 2.

32
33 227 DPT confirmed the diagnosis of drug hypersensitivity in 17 (7.5%) cases. All
34
35 228 patients had delayed skin reactions. While DPT at home, 16 patients developed
36
37 229 mild skin rashes that could be treated with antihistamines and one child
38
39 230 developed generalized urticaria and edema of knees, wrists and ankles
40
41 231 suggestive of serum sickness, and needed treatment with oral steroids as well.

42
43 232

44
45 233 All patients reporting immediate reactions with negative ST tolerated the
46
47 234 suspected antibiotic on DPT. ST and DPT results are summarized in Table III.

235 Two patients (11,8%) with confirmed BL allergy, reported family history of drug
236 allergy. There were non significant differences regarding family history of drug
237 allergy between BL allergic and non allergic children (p 0.356).

238 Eight patients (42,1%) of BL allergic patients presented personal history of
239 atopy. There were non significant differences regarding personal history of
240 atopy between BL allergic and non allergic children in our population (p 0.189).

241

242 For nonimmediate hypersensitivity reactions, skin tests show very low sensitivity
243 and are time consuming. Since 2014, we do not perform skin tests for the work
244 up of delayed adverse reactions in our daily practice: after a carefully clinical
245 history, patients with mild and moderate nonimmediate reactions to antibiotics
246 undergo DPT as described previously.

247

248 DISCUSSION

249 Delayed skin maculopapular or urticarial rashes are frequently reported in
250 children receiving beta-lactam antibiotics. From that moment on, the majority of
251 those children are labeled as “allergic to beta-lactams” and they are prescribed
252 alternative antibiotics that may be less effective and/or more expensive (10).

253 Establishing an accurate diagnosis is associated not only with a more rationale
254 use of antibiotics but also with lower rates of health care utilization (16).

255 Until recently, the diagnosis of non-immediate BL allergy was assessed by ST
256 as IDT and patch tests, followed by DPT in those patients with negative ST
257 results. This diagnostic work up has been reconsidered since ST are not
258 efficient for the diagnosis of mild and moderate non-immediate reactions to

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4 259 beta-lactams in children, they are time-consuming and IDT are painful and
5
6 260 difficult to perform in small children. The reasons for the low sensitivity of ST are
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8
9 261 not well understood. It could be due to the use of a drug structure or conjugate
10
11 262 that is not well recognized by the immune system since BLs are haptens that
12
13 263 need to bind to proteins covalently to elicit an immune response (17).

14
15
16
17 264 DPT confirmed BL hypersensitivity in 7,5% of cases in our population. These 17
18
19 265 patients, who presented delayed hypersensitivity reactions, showed negative ST.
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21 266 We assumed the diagnosis of BL allergy in those patients with positive ST.
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23 267 Recently, Caubet et al. (18) reported that 7 out of 11 patients with positive ID
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25 268 tests tolerated the suspected drug on DPT, yielding a positive predictive value for
26
27 269 ST of 36% in that population. Vyles et al. (19) also reported that 3 children with
28
29 270 positive ST to beta-lactams, tolerated the antibiotic on DPT. Given these
30
31 271 observations we wonder if the 3 patients with positive ST in our study (2 with
32
33 272 delayed reactions and 1 reporting immediate reaction) would had tolerated the
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35 273 suspected antibiotic on DPT.

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39 274 Based on our findings, since 2014 we do not performed ST in children referred to
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41 275 us with nonimmediate mild to moderate skin reactions related to antibiotics.
42
43 276 Diagnostic procedure has become simpler, less time consuming and it is safe.
44
45 277 Up to date we have not had severe reactions during DPT at home. Considering
46
47 278 our results and based in our experience, we support previous reports proposing
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49 279 DPT-based protocols for the study of non-severe antibiotic hypersensitivity in
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51 280 children (11, 20, 21).
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54
55 281 Even though DPT is considered the gold standard for the diagnosis of non-
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57 282 severe, non-immediate skin reactions, it is not standardized in children.
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4 283 The duration of the DPT and the dose administered vary from one study to
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6 284 another. Although according to the members of the Task Force panel (12), a full
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9 285 single therapeutic dose should be enough to diagnose delayed hypersensitivity
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11 286 reactions, there are concerns whether the number of days of drug administration
12
13 287 may influence the outcome of DTP and therefore the diagnosis. There is the
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15 288 possibility that short DPT protocols would not identify all allergic children with
16
17 289 delayed skin reaction. Mill et al. (15) studied 818 children with suspected AMX
18
19 290 allergy. They performed a graded DPT with an only dose of antibiotic and found
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21 291 that 6% of patients reacted to it: 2% reacted within the hour after the last dose
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23 292 administered and 4% developed late reactions. Among those patients tolerating
24
25 293 AMX on DPT, 10.9% requiring subsequent full treatment with AMX developed
26
27 294 delayed skin reactions identical to the initial reactions.

28
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31 295 Tonson la Tour et al. (22) reported high negative predictive value (96.7%) of a 2-
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33 296 day DPT but still, 4% of children with negative DPT reacted when retreated at
34
35 297 home with the suspected antibiotic.

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37
38 298 Mori et al. (6) evaluated 200 children with suspected drug allergy. After ST, a 5-
39
40 299 day DPT was performed. First dose was administered gradually, and if there were
41
42 300 no adverse reactions, patients received daily therapeutic doses at home for 5
43
44 301 days. From the 17 patients (9.6%) who reacted on DPT, 14 did it on day 5. As
45
46 302 they point out, shorter DPT would not identify 7.3% of late reactors leading to
47
48 303 miss diagnosis.

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51 304 To minimize adverse reactions as diarrhea or vomiting as well as the impact on
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53 305 bacterial microbiota and with the aim to diagnose the majority of true
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55 306 hypersensitivity reactions, we propose a different DPT protocol based on the
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4 307 timing of the initial reaction: for children reacting during the first 3 days of
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6 308 treatment, DPT lasts 3 days. In cases of later reactors (from day 3 on), DPT lasts
7
8
9 309 5 days. Based on this protocol, we found a similar prevalence of BL allergy to
10
11 310 what has been previously reported by other authors (3-5).

12
13 311 Regarding risk factors for beta-lactam allergy in children Faitelson et al. (23)
14
15 312 recently found significant association between family history of drug allergy and
16
17 313 Mill et al. (16) reported the same observation. Among patients diagnosed of BL
18
19 314 allergy by DPT included in the present study, 11,8% (2 patients) referred family
20
21 315 history of drug allergy. We could not confirm the suggested association between
22
23 316 family history of drug allergy and BL allergy in children.

24
25
26
27 317 On the other hand, although personal history of asthma and food allergy have
28
29 318 been reported as significant risk factors for the development of AMX allergy (23)
30
31 319 we found non-significant differences regarding personal history of atopy between
32
33 320 BL allergic and non-allergic patients in our population.

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36 321 The main limitation of this study to be considered, is its retrospective design that
37
38 322 as previously reported, may over-estimate the incidence of true allergy (4).

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41 323 In summary, skin tests are not useful for the diagnosis of nonimmediate
42
43 324 hypersensitivity reactions to beta-lactams in children. In cases of mild and
44
45 325 moderate skin manifestations, DPT without previous ST is safe, effective and less
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47 326 time consuming. There would be interesting to unify the different DPT protocols
48
49 327 with the aim to achieve an accurate diagnosis minimizing the potential adverse
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51 328 drug reactions.

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57 330 **ACKNOWLEDGEMENTS**
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331 We thank our nurses, Ofelia Alba Lago, Maria Jesús Fernández Hermida and
332 Isabel Cabana Blanco for their dedication and excellence performing skin tests
333 and drug provocation tests.

Confidential: For Review Only

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4 334 1. What is already known on this topic:

5
6 335 - For diagnosis of non-immediate reactions there aren't standardized tests
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9 336 available. - Skin tests show low sensitivity. It has been proposed to perform only
10
11 337 DPT for the diagnosis of non-severe hypersensitivity reactions.

12
13 338 - There are concerns whether the number of days of drug administration during
14
15 339 DPT may influence its outcome.

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19
20 341 2. What does this study add?

21
22 342 - We conclude that performing DPT without previous skin tests in pediatric
23
24 343 patients with non-severe delayed drug reactions is safe and effective.

25
26 344 - We propose a new 3-5 day drug provocation test protocol, based on the timing
27
28 345 of the initial reaction.

29
30 346 - It supports the recommendation of drug provocation test without previous skin
31
32 347 tests for the diagnosis of non-severe beta-lactam allergy in children.

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453 TABLES

454 **Table I.** Demographic characteristics of children with suspected hypersensitivity reactions to
 455 beta-lactam antibiotics
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	Number of patients N = 213
Age	
459 Mean \pm SD (years-old)	6.26 \pm 3.87
Median (range)	5 (1-15)
Sex	
19 Female, n (%)	108 (50.7%)
20 Male, n (%)	105 (49.3%)
Personal history of atopy	
22 Rhinitis, n (%)	63 (29.7%)
23 Asthma, n (%)	33 (15.5%)
24 Atopic dermatitis, n (%)	35 (16.4%)
25 Food allergy, n (%)	18 (8.5%)
26	2 (0.9%)
Family history of drug allergy	
28 Parents	13 (6.1%)
29 Grandparents	6 (2.8%)
30 Brothers	6 (2.8%)
31	1 (0.5%)

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469
470 **Table II.** Clinical characteristics of children with suspected hypersensitivity reactions to beta-
471 lactam antibiotics
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	Number of reactions N=232
Age at reaction	
Mean \pm SD (years-old)	6.66 \pm 3.06
Median (range)	3 (1-14)
Type of reaction	
Delayed	154 (67.2%)
Not determined	51 (22%)
Immediate	24 (10.5%)
Symptoms	
Exanthema	121 (52.2%)
Urticaria (UA)	78 (33.6%)
Angioedema (AE)	31 (13.4%)
Serum sickness like	15 (6.5%)
Antibiotics	
Amoxicilin/clavulanate	147 (63.4%)
Amoxicilin	45 (19.4%)
Cefuroxime	16 (6.9%)
Cefaclor	11 (4.7%)
Cefixime	6 (2.6%)
Penicilin V	3 (1.3%)
Cefotaxime	1 (0.4%)

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483 **Table III.** Outcome of skin tests and drug provocation tests performed for the diagnosis of beta-
484 lactam hypersensitivity.
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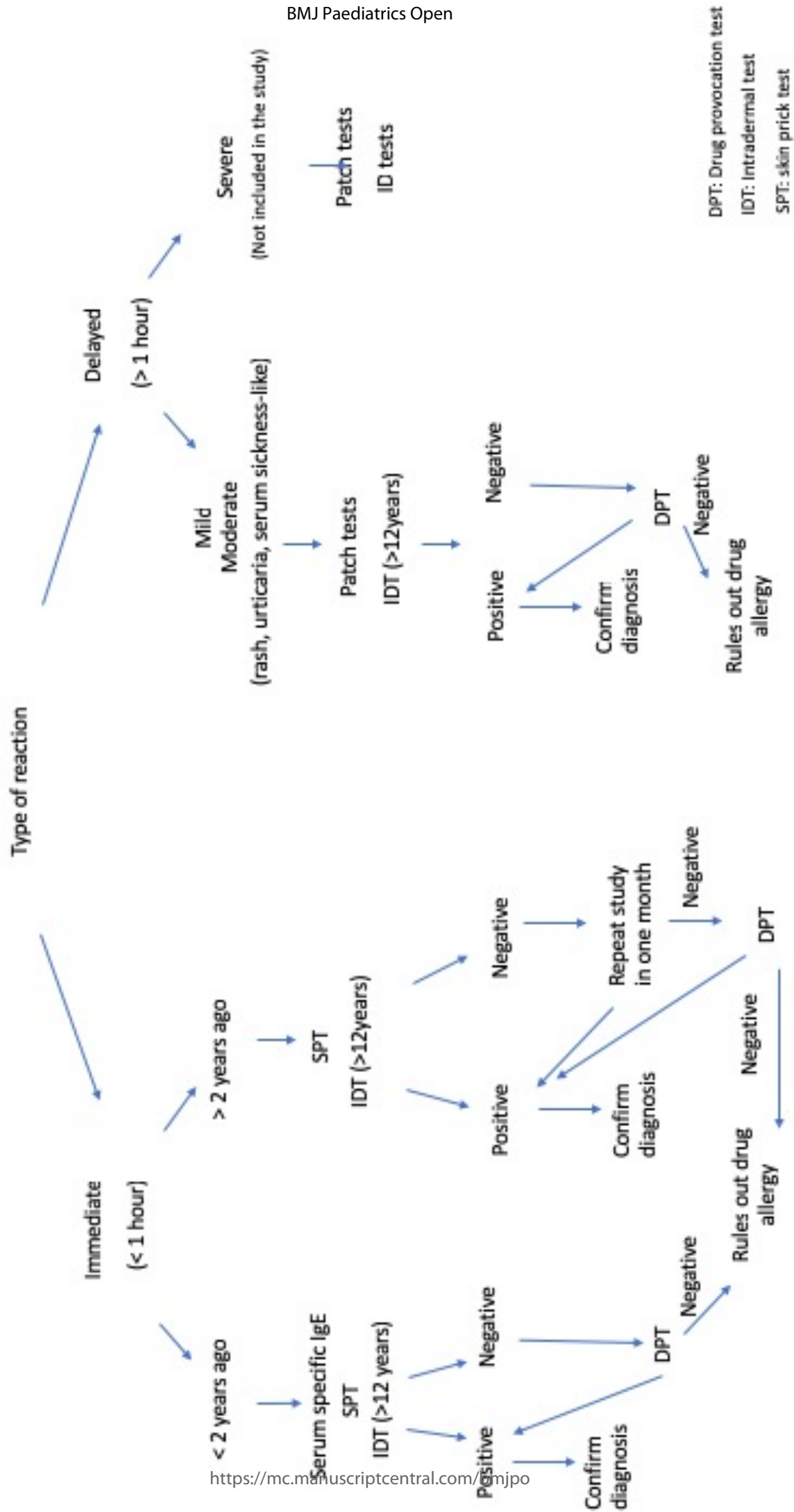
Test	Positive n (%)	Negative n
SPT (n=229)	1 (0,4%)	228
IDT (n=32)	0	32
Patch test (n=205)	2 (0,9%)	203
DPT (n=226)	17(7,5%)	226

486
487 SPT, skin prick test; IDT, intradermal tests; DPT, drug provocation tests.
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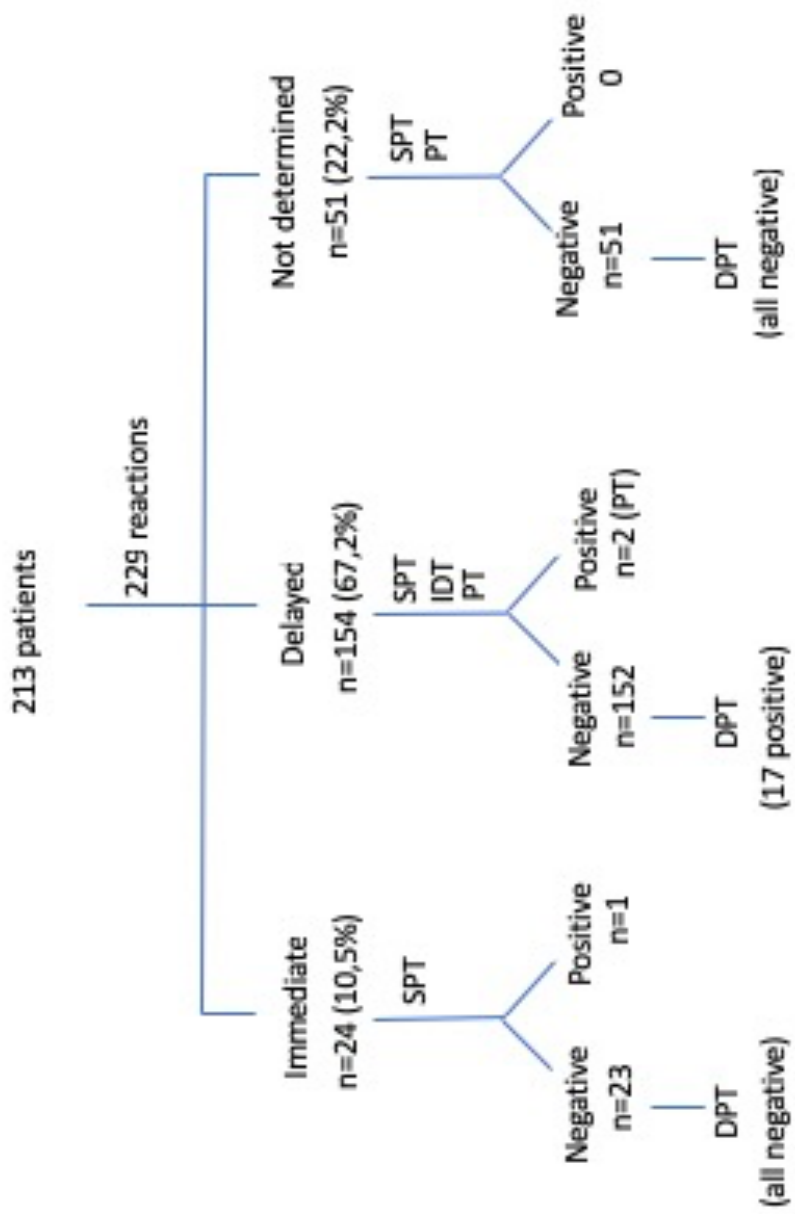
Figure 1. Diagnosis algorithm for hypersensitivity reactions to beta-lactams in children



DPT: Drug provocation test
IDT: Intradermal test
SPT: skin prick test

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Figure 2. Results based on diagnosis algorithm



SPT: Skin prick test; IDT: intradermal test; PT: patch test; DPT: drug provocation test