

# Immediate allergic reactions to cephalosporins and penicillins and their cross-reactivity in children

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Penicillins and cephalosporins are the most important betalactams inducing IgE-mediated reactions. The safety of administering cephalosporins to penicillin-allergic children is a particular problem, because cephalosporin allergenic determinants have not been properly identified. A study was undertaken to evaluate the frequency of anaphylactic reactions to cephalosporins and penicillins and their cross-reactivity in a pediatric population. A prospective survey was conducted in a group of 1170 children with suspected immediate allergic reactions to cephalosporins and/or penicillins, which were examined during a period of 8 yr. *In vivo* (skin tests and challenges) and *in vitro* tests (for specific IgE) were performed with standard concentration of penicillins and cephalosporins. When 1170 children with a clinical history of allergy to penicillins and/or cephalosporins were tested *in vivo* for immediate hypersensitivity to betalactams, 58.3% cases overall were found to be skin or challenge test positive. Among them, 94.4% patients were positive to penicillins and 35.3% to cephalosporins. The frequency of positive reactions in the *in vivo* testing was in the range from 36.4% to 88.1% for penicillins and from 0.3% to 29.2% for cephalosporins. However, 31.5% of the penicillin allergic children cross-reacted to some cephalosporin. If a child was allergic to a cephalosporin, the frequency of positive reactions to penicillin was 84.2%. The cross-reactivity between cephalosporins and penicillins varied between 0.3% and 23.9%. The cross-reactivity among different generations of cephalosporins varied between 0% and 68.8%, being the highest for first and second-generation cephalosporins and 0% for third generation cephalosporins. The frequency of immediate allergic reactions to cephalosporins is considerably lower compared to penicillins, and the degree of cross-reactivity between cephalosporins and penicillins depends on the generation of cephalosporins, being higher with earlier generation cephalosporins. The cross-reactivity among cephalosporins is lower compared to cross-reactivity between penicillins and cephalosporins.

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Penicillins and cephalosporins are the most commonly prescribed betalactam antibiotics able to induce severe and sometimes even life-threatening IgE-mediated reactions (1). According to the time interval between drug administration and the onset of symptoms, these reactions have generally been classified as immediate or delayed

(2, 3). Immediate reactions to betalactams are characterized by well-defined clinical entities such as anaphylaxis and urticaria with or without angioedema (2, 3), and usually appear within a maximum interval of 1 h after the drug intake (4). Penicillin allergy has been the best-studied drug allergy so far, and is considered to be the

model of drug allergy (5). Unlike well-established structural heterogeneity of penicillin allergenic determinants, cephalosporin allergenic determinants have not been properly identified. Allergic reactions to cephalosporins may occur because of sensitization to determinants shared with penicillins or to unique cephalosporin haptens. Moreover, not all aspects of the cross-reactivity pattern between penicillins and cephalosporins have been clarified. When evaluating immediate reactions to cephalosporins, it is crucial to test the suspect drug in addition to penicillin determinants (6). So far, different degrees of cross-reactivity have been reported, and it has been widely accepted that the betalactam ring plays a major role in clinically observed cross-reactivity reactions. Regarding the importance of structural heterogeneity of the acyl side-chain in betalactam allergy, different views exist, ranging from the dominant role in betalactam allergy (5–13) to the higher importance ascribed to the entire molecule (14).

Betalactam antibiotics are widely used to treat common infections and they are often the first-line prophylaxis before many types of surgery. Numerous studies have been performed to evaluate drug reactions and their cross-reactivity in adults or in populations of adults and children. However, the patterns of reactivity to these commonly prescribed antibiotics, the frequency of anaphylactic reactions to them, and possible specificities of cross-reactivity patterns in children, have never been studied in a large pediatric population.

This was the purpose of our study that covered an 8-yr period (from 1993 to 2001) of monitoring drug reactions at the University Children's Hospital in Belgrade and included 1170 children with suspected immediate reactions to penicillins and/or cephalosporins.

## Methods

### Patients

A group of 1170 children with suspected immediate allergic reactions to penicillins and/or cephalosporins (60 min within the drug intake) were referred to our clinic in order to confirm or rule out the diagnosis of allergy to betalactams. The diagnosis of drug allergy was split into two parts, which differ between the acute stage and the later stage. During the acute stage, a general practitioner or a doctor from emergency units of our clinic treat children and fill in all the necessary information (e.g., responsible drug, manifestation of drug reaction...) in a questionnaire. At the later stage, the allergologist might

be asked to find out which of the different drugs taken may have caused the reaction. During the 8-yr period, the average number of patients per year was similar and varied from 117 to 173. Various clinical reactions were described as being induced by drugs (the number of patients affected is shown in parentheses): urticaria or angioedema or both (595), anaphylaxis (87), bronchoconstriction (25), urticaria and erythema (30), rash (410), information could not be obtained (23). The time period that had elapsed from the occurrence of the reaction to the performance of skin testing varied from 6 months to 10 yr (mean time 21.36 months). Out of the total of 1170 tested children, 611 (52.2%) were boys and 559 (47.8%) were girls. The ages ranged from 6.5 months to 14 yr (mean age  $7.62 \pm 3.93$ ). The Ethical Committee of the University Children's Hospital in Belgrade approved the study.

### Skin testing

Prick and intradermal skin tests were performed on the volar side of the forearm with a standard concentration of penicilloyl-polylysine (PPL), minor determinant mixture (MDM), benzylpenicillin (BP), phenoxymethylpenicillin (PhMP), amoxicillin (AX), ampicillin (AM), cefalexin (CE), cefaclor (CF), ceftriaxone (CEF), and cefotaxime (CFT) diluted in 0.9% sodium chloride and administered at increasing concentrations every 15–20 min, as previously described (5, 15), which was in accordance with general ENDA/EAACI guidelines for evaluating and diagnosing subjects with a suspicion of immediate allergic reactions to betalactams (16). The highest concentrations used in the test were:  $5 \times 10^{-5}$  mmol/l for PPL,  $2 \times 10^{-2}$  mmol/l for MDM, 20–25 mg/ml for semisynthetic penicillins and 1–2 mg/ml for cephalosporins. These concentrations were shown to be specific and non-irritant by testing a negative control group of 100 subjects (which had previously tolerated these drugs). Skin tests were interpreted as positive if a wheal larger than 3 mm in diameter accompanied by erythema was present 20 min later. For intradermal tests the wheal area was marked initially and 20 min after testing, and an increase in diameter greater than 3 mm was considered positive (4, 16). Histamine hydrochloride was used as the positive control and 0.9% sodium chloride as the negative one.

### *In vitro* test

Commercially available assays for specific IgE (UniCAP System; Pharmacia, Uppsala, Sweden)

were performed for penicilloyl G (BPO), penicilloyl V (PMPO), amoxicilloyl (AXO) and ampicilloyl (AMO). Levels of specific IgE greater than 0.35 kU/l were considered positive.

If the skin tests were positive to the apparent culprit drug, the child was considered to be allergic to that drug; but if skin tests were negative, a drug provocation test with the culprit drug was performed in accordance with the position paper (4).

#### Challenge tests

In children where *in vivo* tests were negative, independently of the results of *in vitro* tests, single blind, placebo-controlled challenges with progressively increasing amounts (0.01, 0.1, and 1.0) of the respective therapeutic doses of drugs were performed at 1-h intervals (each on a different day), as previously described (5, 8).

#### Results

When 1170 children with a clinical history of allergy to penicillins and/or cephalosporins were tested *in vivo* for immediate hypersensitivity to betalactams, overall 682 (58.3%) cases were found to be skin or challenge test positive. Among them, 644 (94.4%) patients were positive to penicillins and 241 (35.3%) to cephalosporins.

The frequency of positive reactions in the *in vivo* tests (both skin prick and challenge tests) was in the range from 36.4% (PhmP) to 88.1% (PPL, MDM, and BP, all marked as BP positive) for penicillins and from 0.3% (CFT) to 29.2% (CF) for cephalosporins. In the group of 682 children that were shown to be allergic to some of the tested drugs, 601 (88.4%) were demonstrated to be allergic to BP determinants. The frequency of positive reactions in the population of 682 children shown to be allergic by both skin prick and challenge tests, is given in Table 1. The percentage of positive reactions obtained by challenge tests, if the skin test was negative, was quite low when compared to the number of patients determined to be allergic by skin testing.

The percentages of selective sensitizations (positive reaction demonstrated only to a single drug with a good tolerance to all other drugs investigated in the study) were calculated from the total number of the patients positive to that particular drug. The obtained results were as follows: 0% for CFT and CEF, 6.3% for CE, 11% for CF, 4.8% for AMP, 5.2% for AX, 2.4% for PhmP, and 26.3% obtained for BP determinants.

Table 1. The frequency (%) of positive skin prick tests and challenge tests to penicillins and cephalosporins in a population of 682 children shown to be allergic

| Tested drug | Positive in skin prick test (%) | Positive in challenge test (%) | Overall percentage of positivity (%) |
|-------------|---------------------------------|--------------------------------|--------------------------------------|
| BP          | 86.7                            | 1.5                            | 88.1                                 |
| PhmP        | 35.6                            | 0.7                            | 36.4                                 |
| AX          | 40.9                            | 1.6                            | 42.5                                 |
| AM          | 42.7                            | 1.8                            | 44.4                                 |
| CE          | 24.9                            | 0.9                            | 25.8                                 |
| CF          | 27.9                            | 1.3                            | 29.2                                 |
| CEF         | 0.9                             | 0.1                            | 1.0                                  |
| CFT         | 0.3                             | 0                              | 0.3                                  |

Although the time range from the occurrence of the reaction to the investigation of drug sensitivity was quite wide (6 months to 10 yr), the majority of patients (87.9%) visited the clinic to investigate the drug sensitivity within the range of 5 yr. The mean range for the elapsed time was 21.36 months. We also compared the positive responses obtained for a group of patients tested after 6 months from the occurrence of the reaction to the group of patients that came in 10 yr (Table 2). According to the results, quite similar percentages were obtained for both groups and for all investigated drugs.

Allergy to penicillins was examined by an *in vitro* test for specific IgE. According to the results of these tests, which included only penicillins (penicillin G, penicillin V, amoxicillin, and ampicillin), the frequency of positive values is much lower than that obtained by *in vivo* testing. All the children that were demonstrated to be positive to the penicillin drug by *in vitro* testing

Table 2. The values of *in vivo* tests to betalactams in children according to time interval between allergic reactions and diagnostic testing

| Drugs | <i>In vivo</i> tests | Number of children according to time interval (%) |              |            |              |
|-------|----------------------|---------------------------------------------------|--------------|------------|--------------|
|       |                      | 0.5 yr                                            | Total number | 10 yr      | Total number |
| BP    | Positive             | 124 (56.62)                                       | 219          | 15 (55.55) | 27           |
|       | Negative             | 95 (43.37)                                        |              | 12 (44.45) |              |
| PhmP  | Positive             | 49 (22.37)                                        | 170 (77.63)  | 6 (22.22)  | 21 (77.78)   |
|       | Negative             | 170 (77.63)                                       |              | 21 (77.78) |              |
| AX    | Positive             | 65 (29.68)                                        | 154 (70.32)  | 8 (29.62)  | 19 (70.38)   |
|       | Negative             | 154 (70.32)                                       |              | 19 (70.38) |              |
| AMP   | Positive             | 64 (29.22)                                        | 155 (70.78)  | 8 (29.62)  | 19 (70.38)   |
|       | Negative             | 155 (70.78)                                       |              | 19 (70.38) |              |
| CE    | Positive             | 41 (18.72)                                        | 178 (81.28)  | 5 (18.52)  | 22 (81.48)   |
|       | Negative             | 178 (81.28)                                       |              | 22 (81.48) |              |
| CF    | Positive             | 35 (15.98)                                        | 184 (84.02)  | 5 (18.52)  | 22 (81.48)   |
|       | Negative             | 184 (84.02)                                       |              | 22 (81.48) |              |
| CEF   | Positive             | 0 (0)                                             | 219 (100)    | 0 (0)      | 27 (100)     |
|       | Negative             | 219 (100)                                         |              | 27 (100)   |              |
| CFT   | Positive             | 1 (0.45)                                          | 218 (99.55)  | 0 (0)      | 27 (100)     |
|       | Negative             | 218 (99.55)                                       |              | 27 (100)   |              |

Table 3. The cross-reactivity between BP and semisynthetic penicillins and cephalosporins

| Drug tested                                                                         | AX         | AM         | PhmP       | CE         | CF         | CEF      | CFT     |
|-------------------------------------------------------------------------------------|------------|------------|------------|------------|------------|----------|---------|
| Number of (+) patients                                                              | 290        | 293        | 248        | 176        | 199        | 7        | 2       |
| Number of BP (+) patients, (%)                                                      | 269 (92.8) | 271 (92.5) | 240 (96.8) | 150 (85.2) | 170 (85.4) | 4 (57.1) | 2 (100) |
| Overall number of patients (+) to BP, or the drug tested, or both                   | 622        | 623        | 609        | 627        | 630        | 604      | 601     |
| Percentage of patients that are cross-reactive among the overall number of patients | 43.2       | 43.5       | 39.4       | 23.9       | 23.8       | 0.7      | 0.3     |

also showed a positive reaction to *in vivo* testing. No child had positive *in vitro* tests to the culprit drug, but negative skin and/or challenge tests. Two hundred and fifty two children (41.9% of the children shown to be allergic in the *in vivo* tests) had positive sera to BPO, whereas 123 (49.59%) were positive to PMPO. Only 111 children (38.27%) had positive sera to AXO, while 107 children (36.51%) reacted to AMO. Some of the sera tested were positive to two drugs in the *in vitro* testing. Eighty-two children (34.16%) were positive both to BPO and PMPO, 89 (33.08%) to BPO and AXO, 88 (32.47%) to BPO and AMO, 67 (28.89%) to PMPO and AXO, 67 (29.13%) to PMPO and AMO, and 84 (32.55%) to AXO and AMO. Some of the sera were positive to four drugs in the *in vitro* testing. Sixty-seven children (25.1%) were positive to BPO, PMPO, AXO, and AMO.

From the group of 644 children allergic to any of the penicillins tested (as demonstrated by *in vivo* tests, both SPT and challenge test), 203 children showed a positive reaction to a cepha-

losporin, so 31.5% of penicillin allergic patients were cross-reactive to some of the cephalosporins. However, if a child was allergic to a cephalosporin, the frequency of positive reactions to penicillin was 84.2% (203 cases out of 244).

Regarding individual drugs, cross reactivity to benzylpenicillin and other penicillins was virtually complete. Amino penicillin allergic patients in 92.8% of cases reacted to BP; 92.5% of amoxicillin allergic patients reacted in to BP, while 92.8% of ampicillin allergic patients and 96.8% of PhmP allergic patients reacted to BP as well. The cross-reactivity between benzylpenicillin and cephalosporins was also quite high, but still lower than among the penicillins (Table 3).

Among the group of amino penicillin positive patients, the incidence of cross-reactions to cephalosporins was lower compared to the benzylpenicillins. Moreover, the lowest percentage of cross-reactivity reactions was obtained for third generation cephalosporins (CEF) (Table 4), the same drug that was the least cross-reactive to

Table 4. The cross-reactivity between aminopenicillins and cephalosporins

|                                                                                     | CE (+) (%) | CF (+) (%) | CEF (+) (%) | CFT (+) (%) |
|-------------------------------------------------------------------------------------|------------|------------|-------------|-------------|
| Number of (+) patients                                                              | 176        | 199        | 7           | 2           |
| Number of AX (+) patients, (%)                                                      | 114 (64.8) | 135 (67.8) | 2 (28.6)    | 1 (50)      |
| Overall number of patients (+) to AX or the drug tested or both                     | 352        | 354        | 295         | 291         |
| Percentage of patients that are cross-reactive among the overall number of patients | 32.4       | 38.1       | 0.7         | 0.3         |
| Number of AM (+) patients, (%)                                                      | 116 (65.9) | 141 (70.9) | 1 (14.3)    | 1 (50)      |
| Overall number of patients (+) to AM or the drug tested or both                     | 353        | 351        | 299         | 294         |
| Percentage of patients that are cross-reactive among the overall number of patients | 32.4       | 38.5       | 0.7         | 0.3         |

Table 5. The cross-reactivity among cephalosporins

|                                                                                     | CEF (+)  | CFT (+) | CF (+)     |
|-------------------------------------------------------------------------------------|----------|---------|------------|
| Number of patients (+) to the drug                                                  | 7        | 2       | 199        |
| Number of CE (+), (%)                                                               | 2 (28.6) | 0 (0)   | 137 (68.8) |
| Number of the patients (+) to CE and the drug tested                                | 181      | 178     | 238        |
| Percentage of patients that are cross-reactive among the overall number of patients | 1.1      | 0       | 57.6       |
| Number of CF (+), (%)                                                               | 4 (57.1) | 1 (50)  | —          |
| Number of the patients (+) to CF and the drug tested                                | 202      | 200     | —          |
| Percentage of patients that are cross-reactive among the overall number of patients | 2.0      | 0.5     | —          |
| Number of CFT (+), (%)                                                              | 0 (0)    | —       | —          |
| Number of the patients (+) to CFT and the drug tested                               | 9        | —       | —          |
| Percentage of patients that are cross-reactive among the overall number of patients | 0        | —       | —          |

BP (Table 3). Thirty-two children (9.9%) had positive skin tests with AX, but negative results with AM, whereas 258 children (79.4%) had positive *in vivo* tests both to AX and AM.

In 932 children (79.6%), skin tests to both CE and CF were negative. Sixty-two children (31.2%) had positive skin tests with CF but tolerated CE. The values for cross-reactivity between cephalosporins are shown in Table 5.

Out of a total of 240 children allergic to CE, CF, and/or CFE, only one child (0.4%) reacted positively to all of them. No children out of the 241 allergic to any of the cephalosporins tested (CE, CF, CFE, and CFT) reacted positively to all of them.

No children had systemic symptoms induced by skin testing or challenge testing with any of the tested drugs.

## Discussion

Allergic hypersensitivity reactions to betalactams (17) are the most frequent type of adverse drug reactions mediated by an immunological mechanism (18). Selective sensitizations to cephalosporins or semi synthetic penicillins with good tolerance of other betalactams have been described in some reports (7–11, 18–24). Most studies emphasize the concept that cross-reactivity is virtually complete among semi synthetic penicillins, while there is highly variable and incomplete cross-reactivity between penicillins and cephalosporins (25). Baldo observed that there appears to be less cross-reactivity among cephalosporins than among penicillins and also less cross-reactivity between cephalosporins and penicillins (26). The results of our study are in line with these reports. Despite the generally high rates of antibiotic prescription to children in most countries (27), few prospective studies on betalactam allergy in pediatric populations have been performed (13, 24, 28–32).

In our study AX was positive in 42.5% of the children. Other author's observed similar percentages of positive allergic reactions to AX in children (30, 31) and adults (5, 33), whereas the occurrence displayed in the Blanca study (12.55%) was lower than the others (34). These differences can be related to the pattern of consumption of AX.

In a group of 228 cases evaluated for allergy to penicillins, 15% of all reactors were positive only to AMP (35). In our group of allergic children, 44.4% were positive to AMP, whereas Torres et al. detected 33% positive to AMP in a large series of 290 cases (34). The same authors reported that 22% were positive to BP (34), while we found

that 88.1% were positive to BP. Our results are four times higher than previously reported (34), and could be ascribed to the pattern of consumption, or prescription habits specific for a particular region or country.

Blanca reported that CF was an effective and well-tolerated drug and in only 2.3% of cases did any type reaction occur (18). Our results are higher. Namely 29.2% of children were positive to CF. The striking difference between his and our study is that he examined an adult population while we studied a pediatric population of allergic patients. Moreover, CF used to be a frequently prescribed drug for children in our country.

Audicana et al. found that 29 out of 34 patients diagnosed as allergic to penicillins and with negative skin tests to CE tolerated this drug (5). We found that 451 out of 601 children (75%) were positive to BP but negative to CE, which could be a good alternative drug for BP allergic patients.

Torres et al. reported that in some cases antibodies found in patients who develop anaphylactic reactions to cephalosporins can be cross-reactive to other betalactams but in some instances specific antibodies that recognize only certain cephalosporins may exist (36).

All patients with a hypersensitivity reaction to penicillin are usually warned about a potential cross-reaction to cephalosporins. However, some authors have suggested that the incidence is quite low, approximately 5% (37, 38). Volz and Nelson reported that allergic reactions to cephalosporins may occur more often in penicillin-allergic patients and it was 16% in these patients (39). A recent study by Romano et al. showed that only 18% of subjects who had an immediate response to a cephalosporin were cross-reactive with penicillin determinants, the others being positive to one or more cephalosporins (7). According to our results, the cross-reactivity between cephalosporins and penicillins depends on the generation of cephalosporins and varies between 0.3% and 23.9% (Tables 4 and 5). However, the incidence of positive reactions to BP determinants among cephalosporin allergic patients is variable and can be quite high (57–100%) (Table 3). Novalbos et al. found that the risk of suffering from an allergic reaction on administering cephalosporins to penicillin-allergic patients seems to be very low, provided that cephalosporins with a different side chain to the penicillin responsible for the allergic reaction are used (40). However, patients with a history of penicillin allergy, but negative skin tests, may not be at an increased risk for cephalosporin allergy (41).

We found that all the children with negative *in vivo* tests (41.7%) had generalized urticaria and/or angioedema in their history, which could have been a coincidental reaction of an underlying disease rather than an allergic reaction to the administered drug. Others have reported similar results (28, 42, 43). However the time elapsed between the reactions and testing must always be considered if negative results emerge, because IgE-mediated sensitivity declines in the absence of antigen exposure (29).

Overall we have found 58.3% cases to be skin or challenge test positive. Taking into consideration the natural evolution of skin test sensitivity in patients allergic to betalactam antibiotics (44), it is likely that for a group of patients, we got the false negative results. With a shorter period of time, it is also very likely that the overall percentage of patients found positive would be higher. However, when analyzing the patients divided in two groups according to time interval between allergic reaction and diagnostic testing (short, 6 months vs. long, 10 yr), we showed no striking differences, meaning that for our group of patients tested 10 yr ago from the occurrence of the reaction we were able to demonstrate quite high positivity to a culprit drug by *in vivo* test. Our results cannot be compared with literature data from several reasons: we did not follow the patients through several successive years, we had only a very small percentage of patients selectively sensitive to a single drug (i.e., amoxicillin) while the majority of patients showed strong cross-sensitivities to another drug or even several drugs, and finally, our study population was completely pediatric.

In our study we showed that the cross-reactivity among different generations of cephalosporins varied between 0% and 68.8%, being the highest among the first and second-generation cephalosporins (CE and CF) (Table 5). The results of our study also point to the specificity of the allergic response in a population of children, when compared to the results obtained by author's who studied the responses only in adult or adult and child populations.

In conclusion, immediate allergic reactions to penicillins and cephalosporins remain a relevant problem due to the wide variety of these drugs available nowadays. This is the first large study to date on immediate allergic reactions to penicillins and cephalosporins in a pediatric population and although the findings need to be compared with those from other countries, it might contribute to the determination of safe alternative drugs for future use.

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