

Clinical Communications

Allergy to third- and second-generation cephalosporins in confirmed penicillin-allergic patients

Andrada Chiron, MD^{a,b}, Hafida Gaouar, MD^{a,b},
Jean-Eric Autegarden, MD^{a,b}, Emmanuelle Amsler, MD^{a,b},
Annick Barbaud, MD, PhD^{a,b}, and
Angèle Soria, MD, PhD^{a,b,c}

Clinical Implications

- Clinically relevant cross-reactivity between penicillins and third- and second-generation cephalosporins could be between 1% and 2%. In 234 confirmed penicillin-allergic subjects (180 immediate-type and 54 delayed-type hypersensitivity reactions), we found a cross-reactivity risk below 1%.

Beta-lactams (BLs) are a major cause of hypersensitivity reactions (HSRs) to drugs, both immediate hypersensitivity reactions (IHRs) and delayed hypersensitivity reactions (DHRs).¹ Historic risk of cross-reactivity to cephalosporins in penicillin-allergic patients (10%-30%) was probably overestimated.^{2,3} Cross-reactivity between penicillins and cephalosporins seems to be related mainly to side-chain similarities,¹ as administration of potential identical side-chain first-generation cephalosporins and second-generation cephalosporins (2GCs) is associated with an HSR risk exceeding 30%,^{1,2} whereas risk with dissimilar side-chain third-generation cephalosporins (3GCs) can be as low as 1%.² However, skin test (ST) followed by a drug provocation test (DPT) of negatively tested compounds remains the gold standard.^{1,2}

Our objective was to assess allergy to 3GCs and 2GCs in penicillin-proven allergic patients.

We conducted a retrospective study including 234 adults with proven HSRs to penicillin, based on history according to European Academy of Allergy and Clinical Immunology criteria⁴ and positive ST result (immediate or delayed readings) to at least 1 penicillin, explored for 3GC and 2GC allergy (see [Methods](#) and [Tables E1](#) and [E2](#) in this article's Online Repository at www.jaci-inpractice.org).

The study group has a mean age of 52 years (range 17-93 years) and female/male sex ratio of 1.7/1, with 180 patients (77%) and 54 patients (23%) with proven IHRs and DHRs to penicillin, respectively ([Table 1](#)). Six subjects among 240 evaluated were excluded because of lacking DPT at the time of the workup ([Figure 1](#)).

The 234 patients reported 270 HSRs (196 IHRs and 74 DHRs): only 1 reaction for 203 (87%) and more than 1 for 31 (13%). Anaphylaxis,⁵ acute or delayed urticaria, and/or angioedema and cutaneous adverse drug reaction (CADR) were reported in 118, 52, and 49 cases, respectively ([Table 1](#)). Although most DHRs were benign maculopapular drug eruptions (56%), we report 5 severe CADRs: 2 drug reactions with eosinophilia and systemic symptoms, 2 acute generalized exanthematous pustulosis, and 1 bullous drug reaction ([Table 1](#)).

All 234 patients had positive ST results with amoxicillin and/or amoxicillin-clavulanic acid, as follows: 84 (47%) on skin prick test and 96 (53%) on intradermal ST (IDT) among IHRs and 8 (15%) positive on patch test and 51 (95%) on delayed-reading IDT among DHRs, respectively (5 positive for both) ([Figure 1](#)).

In 180 IHR penicillin-allergic patients, there were 409 negative ST results with 2GC cefuroxime (n = 79) and 3GC (n = 330), that is, ceftriaxone (n = 154), cefpodoxime (n = 172), and cefixime (n = 4) ([Figure 1](#)). Only 1 patient among 80 (1.3%) with IHR tested with cefuroxime (2GC) had positive immediate ST result with cefuroxime and negative ST and DPT results with cefpodoxime and ceftriaxone (3GCs) ([Figure 1](#); see [Table E3](#) in this article's Online Repository at www.jaci-inpractice.org). Among 54 patients with DHRs to penicillin, there were 126 negative ST results with 2GCs (n = 26) and 3GCs (n = 100), that is, ceftriaxone (n = 48), cefpodoxime (n = 50), and cefixime (n = 2) ([Figure 1](#)).

DPTs were performed in all 234 patients: 18 had DPT only with 2GC cefuroxime, 15 with one 3GC, 140 with two 3GCs, 53 with one 2GC and one 3GC, and 8 with two 3GCs and one 2GC (see [Table E4](#) in this article's Online Repository at www.jaci-inpractice.org). A total of 442 negative challenges were performed with 3GCs, that is, ceftriaxone (n = 159), cefpodoxime (n = 198), and cefixime (n = 6), and with 2GC cefuroxime (n = 79). Only 1 of 160 (0.6%) penicillin-allergic patient with IHR challenged with ceftriaxone had positive immediate DPT result (with acute urticaria), tolerating the subsequent DPT with cefpodoxime, another 3GC, whereas both ceftriaxone ST and post-DPT skin retest results were negative ([Figure 1](#) and [Table E3](#)). Negative predictive value for ceftriaxone ST was 99% for IHR and 100% for DHR.

Concerning IHRs, we found a very low percentage of positive ST result to 2GC (1 of 106 tested, 0.9%), no positive ST result with 3GC (0 of 232 STs with at least 1 3GC), and only 1 positive DPT result to ceftriaxone (1 of 160 challenges), confirming data on a negligible risk of cross-reactivity with 3GCs and some 2GCs.⁶ In line with this, the largest, prospective cohort of penicillin-allergic patients with IHRs of Romano et al reports positive ST results with cefuroxime (2GC), or ceftriaxone (3GC) in 7 of 252 (2.8%) patients, with positive responses in immediate-reading ST to at least 1 penicillin (mostly aminopenicillin) and negative DPT results with aforementioned molecules in all 244 patients in a study group with a similar percentage of anaphylaxis (70%) as ours (66%).³ Moreover, results for ST to cephalosporins we tested (2 of 4: cefuroxime and ceftriaxone) and 7 other cephalosporins from group A (ceftazidime, cefotaxime, cefepime), group C (cefamandole), and group B aminoccephalosporins (cephalexin, cefaclor, and cefadroxil) show that the highest risk of cross-reactivity (38%) is related to similar side-chain aminoccephalosporins.³

As already published, none of the 54 patients with DHRs to penicillins cross-reacted with 2GCs and 3GCs. All the 97 patients with positive responses in late-reading STs to at least 1 penicillin evaluated by Buonomo et al⁷ had negative DPT result with cefixime and ceftriaxone, confirming a low cross-reactivity

TABLE I. Clinical characteristics and results of penicillin-allergic population studied

Variable	All (n = 234)	Immediate HSRs (N = 180)		Delayed HSRs (N = 54)	
		All (n = 180)	Negative ST results and challenge with 2GCs and 3GCs* (cefepodoxime and/or ceftriaxone and/or cefixime) (n = 178)	Positive ST results (n = 1) and challenge (n = 1) with 2GCs and 3GCs* (cefepodoxime and/or ceftriaxone and/or cefixime)	
			All (n = 54)		
Clinical characteristics					
Age (y), median (range)	51 (17-93)	50 (17-88)	50 (17-88)	56 (55-57)	59 (20-93)
Women, n (%)	147 (63)	109 (61)	108 (61)	1 (50)	38 (70)
Atopic background, n (%)	69 (29)	52 (29)	52 (29)	1 (50) (+CU)	14 (26)
Positive ST results to other allergens, n (%)	13 (6)	6 (3) [†]	6 (3)	0	7 (13) [‡]
Time interval (mo) between HSR and skin testing, median (range)	5 (1-532)	5 (1-532)	5 (1-532)	48	11 (2-429)
Clinical manifestations, n (%)					
Anaphylaxis	118 (50)	118 (66) [§]	118 (66)	0	0
Urticaria and/or angioedema	52 (22)	47 (26)	45 (25)	2 (100)	5 (9)
Rash	11 (5)	11 (6)	11 (6)	0	—
Unknown immediate HSR	4 (2)	4 (2)	4 (2)	0	—
Cutaneous adverse drug reaction	49 (21)	—	—	—	49 (91)
AGEP	2 (1)	—	—	—	2 (4)
DRESS	2 (1)	—	—	—	2 (4) [¶]
MPE	30 (13)	—	—	—	30 (56)
FDE	2 (1)	—	—	—	2 (4)
Bullous drug reaction	1 (0.4)	—	—	—	1 (2) [#]
SDRIFE	1 (0.4)	—	—	—	1 (2)
Eczematous drug reaction	1 (0.4)	—	—	—	1 (2)
Unknown delayed HSR	10 (4)	—	—	—	10 (19)
Penicilline positive ST results, n (%)**					
AX	173 (74)	135 (75)	134 (75)	1 (50)	38 (70)
AX-Clav	24 (10)	21 (11)	20 (11)	1 (50)	3 (6)
AX and AX-Clav	37 (16)	24 (13)	24 (13)	0	13 (24)

AGEP, Acute generalized exanthematous pustulosis; AX, amoxicillin, AX-Clav, amoxicillin-clavulanic acid; DRESS, drug reaction with eosinophilia and systemic symptoms; FDE, fixed drug eruption; MPE, maculopapular drug eruption; SDRIFE, symmetrical drug-related intertriginous and flexural exanthema.

*See detail in Table E3.

[†]One positive for fluoroquinolones, 3 for macrolides (+1 white beans), 1 for cotrimoxazole, and 1 for latex.

[‡]Four positive for macrolides, 2 for cotrimoxazole, 1 for fluoroquinolones; for extra information on ST procedures, see the Online Repository and Table E2.

[§]Thirty-three patients with anaphylactic shock.

^{||}With positive penicillin patch test result for one and negative penicillin patch test result with positive delayed-reading IDT for the other.

[¶]With positive penicillin patch test results for both.

[#]With negative penicillin patch test and positive delayed-reading IDT results.

**Patients were tested either with AX or with AX-Clav, depending on the culprit penicillin; 16% tested for both AX and AX-Clav were positive.

with penicillins, whereas the rate of cross-reactivity on ST and DPT with similar side-chain aminoccephalosporins (cephalexin and cefaclor) was higher (11%).

All 4 cephalosporins we tested share the common methoxyimino group on the R1 side-chain, belonging to group A cephalosporins based on chemical structure (see Figure E1 in this article's Online Repository at www.jaci-inpractice.org) and present no structural similarities with amoxicillin (no amino group).¹ Therefore, positive ST results with dissimilar side-chain cephalosporins from group A could be related to coexisting sensitivities,¹ or, less likely, to cross-reactions due to sensitization to nuclear structures.³

First limitations of our study are the retrospective character and the limited type of cephalosporins tested, belonging exclusively to group A cephalosporins, possibly underestimating allergic risk for other cephalosporins, especially identical side-chain aminoccephalosporins. Second, lacking intravenous formulas for 2 of 4 cephalosporins (ie, cefepodoxime and cefixime) imposed testing by skin prick test only, possibly reducing sensitivity. Third, not all cephalosporins investigated are available in other countries, and, last, exclusion of sensitization to clavulanic acid by skin testing with amoxicillin was not systematic in amoxicillin-clavulanic acid ST-positive patients.

In conclusion, this series of 234 truly penicillin-allergic patients (aminopenicillins) confirms that cross-reactivity between

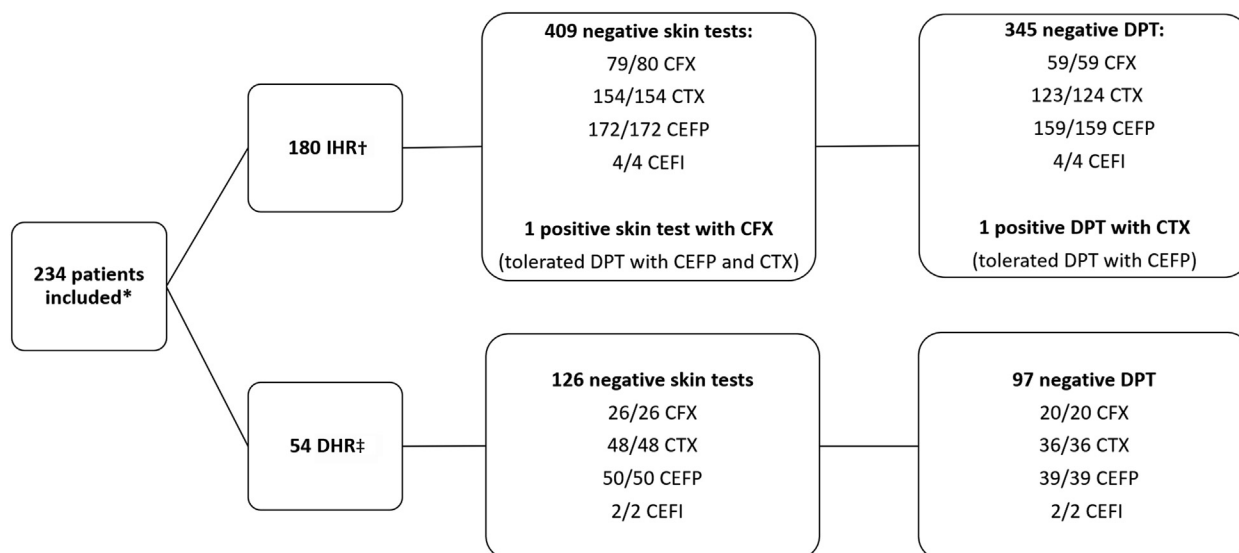


FIGURE 1. Results of 2GC and 3GC STs and DPTs in 234 penicillin-allergic patients. *CEFI*, Cefixime; *CEFP*, cefpodoxime; *CFX*, cefuroxime; *CTX*, ceftriaxone. *Six patients excluded (lack of DPT). †ST results for penicillin allergy were positive on prick test for 84 (47%) and on IDT for 96 (53%). ‡Two ST results for penicillin allergy were positive on patch test for 8 (15%) and on delayed-reading IDT for 51 (94%). Five patients were positive for both.

penicillin and dissimilar side-chain cephalosporins, such as group A cefuroxime, ceftriaxone, and cefpodoxime, is very low (between 1% and 2%). Should urgent administration of different chemical structure cephalosporins be required, in both IHR- or DHR-confirmed penicillin-allergic patients, it could be undertaken in hospitalized patients under close surveillance, after negative ST result.

Acknowledgments

We thank Dr Claude Ponvert (MD, PhD, Department of Paediatrics, Pulmonol-Allergol Unit, Hôpital des Enfants Malades, Paris, France) for his help in proofreading this manuscript.

^aService de Dermatologie et d'Allergologie, Hôpital Tenon, Paris HUEP, APHP, Paris, France

^bSorbonne Universités, Paris, France

^cCentre d'Immunologie et des Maladies Infectieuses — Paris (Cimi-Paris), INSERM U1135, Paris, France

Conflicts of interest: The authors declare that they have no relevant conflicts of interest.

Received for publication October 19, 2019; revised February 21, 2020; accepted for publication March 10, 2020.

Available online ■ ■

Corresponding author: Andrada Chiron, MD, Département d'immunologie biologique, Hôpital Bicêtre, APHP, 78 Rue du Général Leclerc, 94270 Le Kremlin-Bicêtre, France. E-mail: andrada.chiron@aphp.fr.

2213-2198

© 2020 American Academy of Allergy, Asthma & Immunology

<https://doi.org/10.1016/j.jaip.2020.03.021>

REFERENCES

- Romano A, Gaeta F, Arribas Poves MF, Valluzzi RL. Cross-reactivity among beta-lactams. *Curr Allergy Asthma Rep* 2016;16:24.
- Liu X-D, Gao N, Qiao H-L. Cephalosporin and penicillin cross-reactivity in patients allergic to penicillins. *Int J Clin Pharmacol Ther* 2011;49:206-16.
- Romano A, Valluzzi RL, Caruso C, Maggioletti M, Quarantino D, Gaeta F. Cross-reactivity and tolerability of cephalosporins in patients with IgE-mediated hypersensitivity to penicillins. *J Allergy Clin Immunol Pract* 2018;6:1662-72.
- Demoly P, Kropf R, Bircher A, Pichler WJ. Drug hypersensitivity: questionnaire. EAACI Interest Group on Drug Hypersensitivity. *Allergy* 1999;54:999-1003.
- Sampson HA, Muñoz-Furlong A, Campbell RL, Adkinson NF, Bock SA, Branum A, et al. Second symposium on the definition and management of anaphylaxis: summary report—Second National Institute of Allergy and Infectious Disease/Food Allergy and Anaphylaxis Network Symposium. *J Allergy Clin Immunol* 2006;117:391-7.
- Campagna JD, Bond MC, Schabelman E, Hayes BD. The use of cephalosporins in penicillin-allergic patients: a literature review. *J Emerg Med* 2012;42:612-20.
- Buonomo A, Nucera E, Pecora V, Rizzi A, Aruanno A, Pascolini L, et al. Cross-reactivity and tolerability of cephalosporins in patients with cell-mediated allergy to penicillins. *J Invest Allergol Clin Immunol* 2014;24:331-7.

ONLINE REPOSITORY

METHODS

Patient selection

We conducted a retrospective study including adult patients with allergological workup in the Allergology Unit of the Dermatology and Allergology Department of the Tenon Hospital in Paris between 2013 and 2017 for a history of HSRs to penicillins. Inclusion criteria was a positive ST result to at least 1 penicillin, either on immediate-reading skin testing (prick test or IDT) or on delayed-reading skin testing (patch test and/or IDT). Exclusion criteria were pregnancy, severe cardiovascular, renal, or respiratory diseases, or the lack of DPT. Therefore, 6 of the 240 patients evaluated were excluded because DPT has not been performed at the time of the workup. All subjects received information about risks of allergologic tests and an eventual challenge with BLs.

Skin tests

Patch tests were performed with the commercial Chemotechnique Diagnostics Cutaneous Adverse Drug Reaction Series (CAD-1000, Chemotechnique, Vellinge, Sweden), by applying to uninvolved skin of the back's interscapular region or of the upper arm, IQ chambers (Chemotechnique) containing amoxicillin (amoxicillin-trihydrate), cefotaxime (cefotaxime-sodium salt), cefuroxime (cefuroxime-sodium), cefixime (cefixime-trihydrate), and cefpodoxime (Cefpodoxime-proxetil), or by using the BL molecule prepared by the hospital pharmacy diluted 30% in petrolatum for amoxicillin-clavulanic acid. Patch test reading was performed between day (D) 2 and D5, according to Barbaud.^{E1} A positive patch test result implied DHRs to the tested molecule. In case of a negative patch test result, late-reading IDTs (between D1 and D5) were performed using BL commercial solutions provided by the hospital pharmacy: for injectable compounds,

we used the intravenous form, freshly prepared under sterile conditions, and for noninjectable BLs we used the crushed tablets for prick test. No IDT was performed with noninjectable forms. All BLs were serially diluted in sterile saline. The concentrations used are indicated in [Table E1](#).

Procedures for STs with other drugs (ie, fluoroquinolones, macrolides, cotrimoxazole) were similar. Prick tests and IDTs were realized with drug concentrations depicted in [Table E2](#).

A 3-mm increase in diameter of the wheal above baseline accompanied by erythema, 20 minutes after performing, was considered as a positive ST response for IHR, and late reactions to IDT were considered positive in case of an infiltrated erythema.^{E1}

Drug provocation tests

In patients with negative responses in STs to the various BLs tested, we performed hospitalized single-blind challenges (ie, the patient was unaware of the order in which the cephalosporin and the placebo were administered), on different days, with therapeutic doses of the drug intravenously or orally according to the molecule: ceftriaxone (up to 1 g), amoxicillin (up to 1 g), amoxicillin-clavulanic acid (up to 1 g/125 mg), cefuroxime-axetil (up to 250 mg), cefpodoxime (up to 100 mg), and cefixime (up to 200 mg). Patients were carefully monitored during all allergy testing and for 4 hours after challenges and were advised to call in case of any positive response after DPT. Delayed-onset tolerance was confirmed by the lack of skin manifestation over the next 7 days. DPT result was considered positive if saturation decreased to less than 90% and/or blood pressure decreased by more than 30% and/or a skin eruption and/or other clinical anaphylactic manifestations occurring up to 2 hours after the DPT for IHRs and cutaneous eruption occurring up to 7 days after the challenge, with similar clinical characteristics as those with the initial reaction for DHR.

TABLE E1. BLs and concentrations (mg/mL) used for STs

BLs	Prick tests	IDTs
Amoxicillin	200	2-20*
Amoxicillin/clavulanic acid	200/40	2/0.4-20/4
Cefuroxime	250	2.5-25
Ceftriaxone	100	1-10
Cefixime	†	ND
Cefpodoxime	†	ND

ND, Not done (because of lack of IV formula).

*Lower concentrations (down to 10^{-3} dilution) were used for prick tests and IDTs in case of history of anaphylaxis to penicillins.

†Crushed tablets of 200 mg (cefixime) and 100 mg (cefpodoxime), respectively.

TABLE E2. Other drugs and concentrations used for STs

Other drugs	Prick tests*	IDTs*
Ofloxacin	5	0.005-0.05
Moxifloxacin	1.6	0.0016-0.016
Cotrimoxazole (trimethoprim/sulfamethoxazole)	80/16	0.008/0.0016-0.8/0.16
Spiramycin	375,000†	37.5†

*Concentrations in mg/mL.

†Concentration for spiramycin in U/mL.

TABLE E3. Clinical characteristics and allergologic data in patients with positive responses to cephalosporins in STs (n = 1) or DPTs (n = 1)

Patient, n	Sex	Age (y)	Atopic background	Culprit penicillin with positive ST results	Type of reaction	Cephalosporin STs			Cephalosporin challenges	
						CTX	CEFP	CFX	CTX	CEFP
44	F	55	No	AX	UA	NEG	NEG	POS	NEG	NEG
59	M	57	ARC	AX	UA	NEG	NEG	NEG	POS (U)	NEG

ARC, Allergic rhinoconjunctivitis; AX, Amoxicillin; CEFP, cefpodoxime; CFX, cefuroxime; CTX, ceftriaxone; F, female; M, male; NEG, negative; POS, positive; U, acute urticaria; UA, acute urticaria and angioedema.

TABLE E4. Negative DPT result with 2GCs and 3GCs in 234 penicillin-allergic patients

2GCs and 3GCs	CFX	CTX	CEFP	CEFI
CEFP			9 of 9*	—
CFX	18 of 18*	6 of 6	47 of 47	—
CTX	6 of 6	6 of 6*	134 of 135	5 of 5
CTX + CFX			7 of 7	1 of 1

CEFI, Cefixime; CEFP, cefpodoxime; CFX, cefuroxime; CTX, ceftriaxone.

*DPTs with only one cephalosporin.

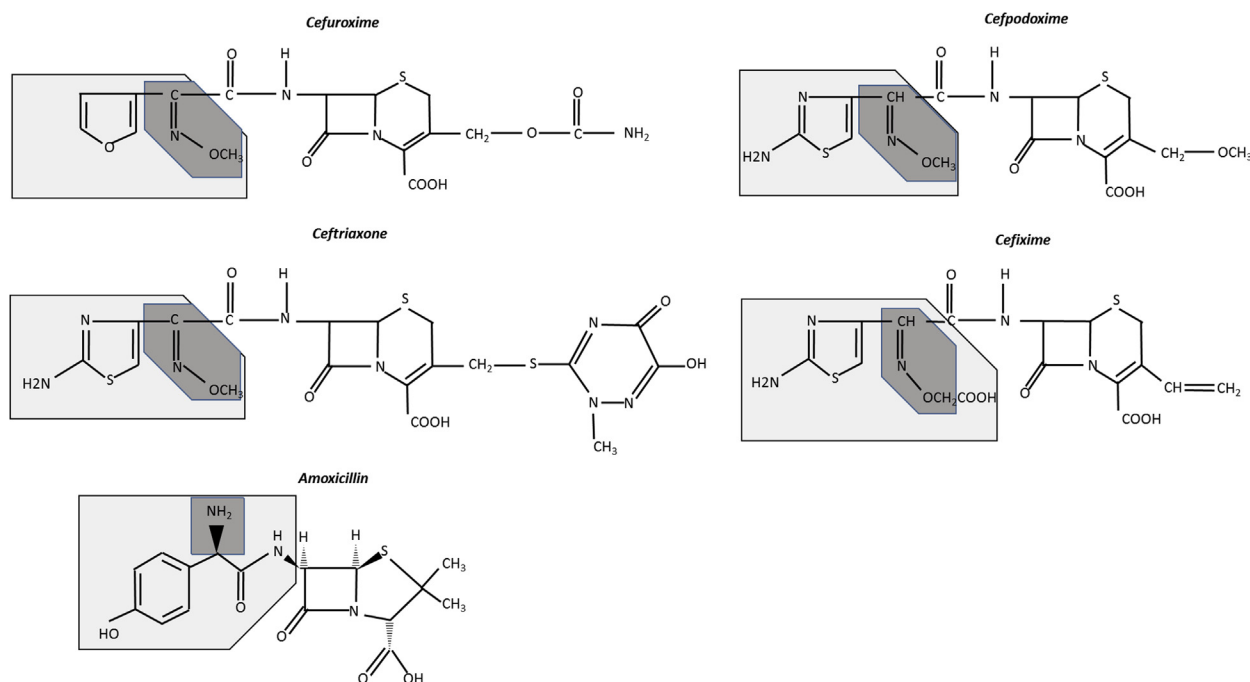


FIGURE E1. Chemical structure of cephalosporins tested and structural comparison with amoxicillin. The methoxyimino group of cephalosporins of group A according to Romano et al^{E2} and the amino group of amoxicillin are highlighted in dark gray. Light gray highlights the R1 side-chain (ie, C7 position).

REFERENCES

- E1. Barbaud A. Skin testing and patch testing in non-IgE-mediated drug allergy. *Curr Allergy Asthma Rep* 2014;14:442.
- E2. Romano A, Gaeta F, Arribas Poves MF, Valluzzi RL. Cross-reactivity among beta-lactams. *Curr Allergy Asthma Rep* 2016;16:24.