

To challenge or not to challenge: Literature data on the positive predictive value of skin tests to beta-lactams



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Clinical Implications

- This review corroborates the underlying evidence supporting the current practice of not challenging patients with positive skin test results to beta-lactams. The positive predictive value of these tests in well-characterized patients is high and reaches 100% in patients with histories of anaphylaxis.

TO THE EDITOR:

Skin tests (STs) to β -lactams (BLs) have evolved widely over the past 50 years, with variations in testing techniques, reagents, and interpretation.^{1,2} However, the expert panel of the International Consensus of Drug Allergy³ acknowledged their crucial role and value in virtually all patients who carry an “allergic-to-BL” label. If positive in immediate or delayed reading, STs to nonirritating concentrations⁴ of BL antibiotics are interpreted as a strong presumptive risk of an allergic reaction to such agents.

However, little is known about the positive predictive value (PPV) of these tests, because confirmatory challenges have rarely been performed because of understandable ethical concerns about patients’ safety. Most available data suggest that between 40% and 100% of penicillin ST-positive patients will develop immediate allergic reactions on being challenged with the BL.^{2,5}

The aim of the present study was to investigate data related to PPV of STs to BLs. We performed a literature review in the PubMed database, by cross-referencing the terms “skin test,” “beta-lactam,” and “drug hypersensitivity,” to retrieve available literature data on the PPV of STs to BLs. We included articles in English and French published between 1966 and 2017. References of selected articles were reviewed for additional sources. Reports concerning patients with positive ST results were retrieved and analyzed. These reports included the following 4 clinical situations that we considered would prove the “allergy-revealing” (rather than just “sensitization-revealing”) value of a positive ST result to BL, assuming that concentrations used are the nonirritant published ones^{1,2}: (1) re-administration (either accidental or by drug provocation test [DPT]) of the culprit, ST-positive BL; (2) systemic drug hypersensitivity reaction (DHR) occurring during positive BL ST result; (3) administration (either accidental or by DPT) of a supposedly side-chain cross-reactive BL based on known side-chain similarities; and (4) DHR occurring during a desensitization protocol performed in ST-positive patients. The following reports were excluded: (1) overlapping patient populations (ie, by investigators at the same institution); (2) patients with positive ST result but no clinical history for BL antibiotics (eg, controls); (3) patients with positive ST result to amino-penicillins and good tolerance to

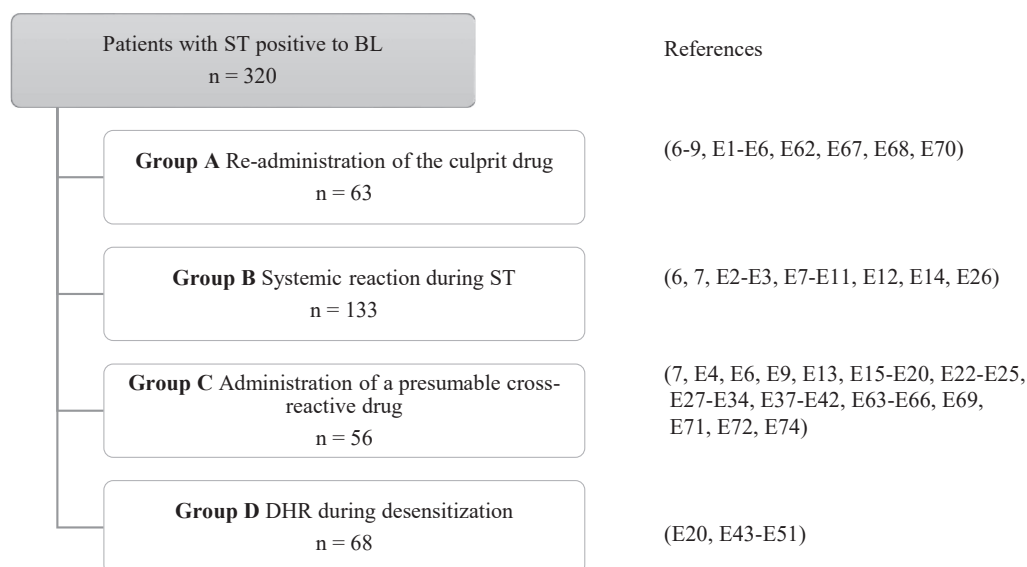


FIGURE 1. Distribution of BL ST-positive cases according to the 4 analyzed groups. E-references are available in this article’s Online Repository at www.jaci-inpractice.org.

TABLE I. Description of ST-positive patients who underwent DPT to the culprit ST-positive BL (group A patients)*

Reference	No. of patients	Patient no.	Time of onset	Clinical history	Suspected drug	Positive ST result	Negative ST result	Tested drug	Reaction	Comments (or delay)
Demoly et al ⁸	1	1	IR	Shock	Ceftriaxone	Ceftriaxone Cefazoline	PPL, MDM, PG, AX, AP	Ceftriaxone	Anaphylaxis	Patient had DPTs to all positive- and negative-ST drugs
Sastre et al ^{E2}	2	1	IR	GP, urticaria, AO	AX	AX	PPL, MDM, PG	AX	GP, erythema	
Vega et al ^{E6}	5	2	IR	Urticaria, AO	AX	AX	PPL, MDM, PG	AX	PG, AO exanthema	
		1	IR	Anaphylaxis	AP	AX	BPO, MDM, PG	AX	Anaphylaxis	
		2	IR	Anaphylaxis	AX	AX, AP	BPO, MDM, PG	AX	Shock	
		3	IR	Urticaria, AO	AX	AX, AP	BP, MDM, PG	AX	Urticaria	
		4	IR	Anaphylaxis	AX	AX	BPO	AX	Anaphylaxis	
Padial et al ^{E5}	2	5	IR	Anaphylaxis	AP	AX	PPL, MDM, PG, AP	AX	Anaphylaxis	
		1	NIR	Desquamative MPE	AX	AX, AP	PPL, MDM, BPO			Patch
		2	NIR	Desquamative MPE	Cloxacilline	Cloxacilline	PPL, MDM, BPO, AX, AP	Cloxacilline	Exanthema in 24 h	
Romano et al ^{E3}	18	1	NIR	MPE	AX, AP, PV	AX, AP	PG	AX, AP	MPE, AO >6 h later	
		2	NIR	MPE	AX, AP, PV	AX, AP	PG	AX, AP	MPE, AO >6 h later	
		3	NIR	MPE	AX, AP, PV	AX, AP	PG	AX, AP	MPE, AO >6 h later	
		4	NIR	MPE	AX, AP, PV	AX, AP	PG	AX, AP	MPE, AO >6 h later	
		5	NIR	MPE	AX, AP, PV	AX, AP	PG	AX, AP	MPE, AO >6 h later	
		6	NIR	MPE	AX, AP, PV	AX, AP	PG	AX, AP	MPE, AO >6 h later	
		7	NIR	MPE	AX, AP, PV	AX, AP	PG	AX, AP	MPE, AO >6 h later	
		8	NIR	MPE	AX, AP, PV	AX, AP	PG	AX, AP	MPE, AO >6 h later	
		9	NIR	MPE	AX, AP, PV	AX, AP	PG	AX, AP	MPE, AO >6 h later	
		10	NIR	MPE	AX, AP, PV	AX, AP	PG	AX, AP	MPE, AO >6 h later	
		11	NIR	MPE	AX, AP, PV	AX, AP	PG	AX, AP	MPE, AO >6 h later	
		12	NIR	MPE	AX, AP, PV	AX, AP	PG	AX, AP	MPE, AO >6 h later	
		13	NIR	MPE	AX, AP, PV	AX, AP	PG	AX, AP	MPE, AO >6 h later	
		14	NIR	MPE	AX, AP, PV	AX, AP	PG	AX, AP	MPE, AO >6 h later	
		15	NIR	MPE	AX, AP, PV	AX, AP	PG	AX, AP	MPE, AO >6 h later	
		16	NIR	MPE	AX, AP, PV	AX, AP	PG	AX, AP	MPE, AO >6 h later	
		17	NIR	MPE	AX, AP, PV	AX, AP	PG	AX, AP	MPE, AO >6 h later	
		18	NIR	MPE	AX, AP, PV	AX, AP, PG	None	AX, AP, PV	MPE	6 h
Richter et al ⁹	1	1	NIR?	UNK	BL	PPL, MDM, AX	—	AX	MPE	Delayed
Romano et al ^{E4}	5	1	NIR	MPE	Aminopenicillin	Aminopenicillin	Patch negative	Aminopenicillin	MPE	Delayed
		2	NIR	Erythema	AX	AX	Patch negative	AX	Erythema	5 h
		3	NIR	MPE	Aminopenicillin	Aminopenicillin	Patch negative	Aminopenicillin	Tolerance	
		4	NIR	Urticaria	AX	AX	Patch negative	AX	Tolerance	

(continued)

TABLE I. (Continued)

Reference	No. of patients	Patient no.	Time of onset	Clinical history	Suspected drug	Positive ST result	Negative ST result	Tested drug	Reaction	Comments (or delay)
Blanca et al ⁷	4	5	NIR	Erythema	AP	AP	Patch negative	AP	Tolerance	
		1	IR	Shock	AX	AX	BPO, MDM, AP	AX	Generalized erythema	
		2	IR	Shock	AX	AX, AP	BPO, MDM, AP	AX	Generalized erythema	
		3	NIR	Generalized erythema	UNK	AX?	BPO, MDM, AP?	AX	Urticaria	Delayed
		4	NIR	Generalized urticaria	AX	AX?	BPO, MDM, AP?	AX	Generalized erythema	Delayed
Romano et al ^{E1}	1	1	NIR	AO, MPE	Cefalexine	AX, AP, cefalexine	— ?? (plenty)	Cefalexine	MPE	Delayed
Audicana et al ⁶	1	1	IR?	Urticaria	AP	AX, AP, cephalixin	PPL, MDM, ceftazidime	Cephalexin	Generalized urticaria	UNK
Christiansen et al ^{E62}	7	1	IR	Shock	Cefuroxime	Cefuroxime	—	Cefuroxime	UNK	
		2	IR	Shock	Cefuroxime	Cefuroxime	—	Cefuroxime	UNK	
		3	IR	Shock	Cefuroxime	Cefuroxime	—	Cefuroxime	UNK	
		4	IR	Shock	Cefuroxime	Cefuroxime	—	Cefuroxime	UNK	
		5	IR	Shock	Cefuroxime	Cefuroxime	—	Cefuroxime	UNK	
		6	IR	Shock	Cefuroxime	Cefuroxime	—	Cefuroxime	UNK	
		7	IR	Anaphylaxis	Cefuroxime	Cefuroxime	—	Cefuroxime	UNK	
Weisser and Ben-Shoshan ^{E68}	1	1	NIR	Rash	AX	Pre-Pen	—	AX	Hives	15 min
Cabanas et al ^{E70}	1	1	NIR	DRESS	Pip/Taz	Pip/Taz	—	Pip/Taz	Maculopapular rash and increase in liver enzymes	Patch 5 h after a single dose
Barni et al ^{E67}	3	1	NIR	Mild reaction	AX	AX	—	AX	Urticaria	Day 1
		2	NIR	Mild reaction	AX	AX	—	AX	Urticaria	Day 1
		3	NIR	Mild reaction	AX	AX	—	AX	Tolerance	
Tannert et al ^{E56}	11	1	IR	Urticaria	PV	PV/PG	AX, AP, DX, MC	PV	Positive	
		2	IR	Anaphylaxis	AX/Clav	AX	PV/PG, AP, DX, MC	AX/Clav	Positive	
		3	NIR	Urticaria	PV	PV/PG, AX, AP	DX, MC	PV	Positive	
		4	IR	AO	PV	PV/PG	AX, AP, DX, MC	PV	Positive	
		5	NIR	Urticaria	PV	PV/PG	AX, AP, DX, MC	PV	Tolerance	
		6	NIR	Urticaria	PV	PV/PG	AX, AP, DX, MC	PV	Tolerance	
		7	IR	Urticaria	PV	PV/PG	AX, AP, DX, MC	PV	Tolerance	
		8	IR	Urticaria	PV	PV/PG	AX, AP, DX, MC	PV	Tolerance	
		9	IR	UNK	PV	PV/PG	AX, AP, DX, MC	PV	Tolerance	
		10	IR	AO	PV	PV/PG	AX, AP, DX, MC	PV	Tolerance	
		11	IR	AO	AX/Clav	AX, AP	PV/PG, DX, MC	AX/Clav	Tolerance	

AO, Angioedema; AP, ampicillin; AX, amoxicillin; AX/Clav, amoxicillin/clavulanic acid; BPO, major determinant benzylpenicillol; DRESS, drug reaction with eosinophilia and systemic symptoms; DX, dicloxacillin; GP, generalized pruritus; IR, immediate reaction; MC, mecillinam; MDM, minor determinant mix; MPE, maculopapular exanthema; NIR, nonimmediate reaction; PG, penicillin G; Pip/Taz, piperacillin/tazobactam; PPL, penicilloyl poly-L-lysine; PV, penicillin V; UNK, unknown.

E-references are available in this article's Online Repository at www.jaci-inpractice.org.

*In Tannert et al,^{E56} it is not clear whether 8 patients with a clinical history to PV had positive ST result to PV or PG. If the latter is correct, then these patients would be excluded from group A. PPV would increase for IRs group to 95% (1 tolerant patient out of 20 exposed) and to 88.5% (4 tolerant patients out of 35 exposed) for NIRs. The details are presented in Table I.

benzyl-penicillin; and (4) patients with positive ST result challenged with subtherapeutic doses, if exposure to these doses turned out to be negative (eg, challenge with penicillin-contaminated food and administration of prophylactic intracameral cefuroxime in ophthalmic surgery).

Of 1432 articles, 73 met the inclusion criteria. Taken together, 320 reported cases were analyzed, 119 of them corresponding to the administration (either accidental or by challenge test) of the culprit drug ($n = 63$) or a presumable cross-reactive drug ($n = 56$), 133 to systemic reactions during ST, and 68 to DHR during desensitization protocols to BL (Figure 1).

In group A (Table 1), of 26 patients with an immediate index reaction (9 with anaphylactic shock, 6 with anaphylaxis without shock, 10 with urticaria/angioedema, 1 with unspecified manifestations) and positive immediate-reading ST, 21 reacted on reexposure (PPV = 80.7%). For patients with anaphylaxis (with or without shock), the PPV was 100%. Among the 37 patients with nonimmediate index reactions, 6 tolerated the DPT with the ST-positive drug (PPV = 83.7%). If mentioned, the main reason for DPT was “to verify ST positivity.”

Group B comprised systemic iatrogenic DHR occurring during ST to BL (see Table E1 in this article's Online Repository at www.jaci-inpractice.org), confirming that the positive ST result stands for allergy and not just sensitization. We identified 133 reports of such reactions. Most of them (92 cases, 69.2%) occurred in patients with a clinical history of immediate reactions, whereas only 6 cases (4.5%) occurred in nonimmediate reactors and 35 cases (26.3%) in patients with clinical DHR history with nonspecified chronology. Of note, systemic DHRs were also elicited while testing controls (not included in the analysis) or in patients with negative ST result at the injection site.⁷ Among all BLs, penicillins were the most frequent elicitors (83%). All ST techniques were involved (even the open test, ie, no breaking of skin^{E41}), but the intradermal test (IDT) was the culprit technique in 86% of the cases. Overall, in about half the cases, the reaction elicited during ST was less severe than the index reaction. Two cases of fatal anaphylaxis during STs to BLs were identified in this series of cases.^{E17,E42} Three more cases were retrieved, but they were not included in this analysis (1 patient had supposedly no previous reaction to BLs^{E35} and the other 2 cases were mentioned by the authors as unpublished and occurring between 1953 and 1968).

Data from groups C (PPV = 16%; see Table E2 in this article's Online Repository at www.jaci-inpractice.org) and D (PPV = 61.7%) are presented in this article's Online Repository at www.jaci-inpractice.org. Other studies have reported re-administration of BLs in BL ST-positive patients, but no details concerning the provoked patients (with regard to the culprit BL and the ST-positive BL) were available. We therefore did not mingle these reports to patients in group A, who are well phenotyped, but rather decided to present them separately (see Table E3 in this article's Online Repository at www.jaci-inpractice.org).

Learned societies recommend, on the basis of a few regularly cited articles,^{E5,E19,E20,E50,E52-E55} that ST-positive patients should avoid BLs and if need be, undergo desensitization.³ This review brings additional data to support this attitude by taking into account and studying in detail a multitude of articles published over several decades in different countries and continents. They show that for well-phenotyped patients (ie, patients with a

clinical history of DHR for a BL, positive ST result for this BL, and DPT for the same BL), PPV is high enough (>80%) in both immediate and nonimmediate DHRs. Along with the proof of the iatrogenicity of ST to BL (systemic and even fatal reactions could be induced by ST, as shown in group B), we believe that sufficient data exist to date to discourage DPTs in patients with positive ST result to BL. The potential iatrogenicity of STs to BLs emphasizes the need to perform them in a stepwise manner, with appropriate concentrations of extracts for prick tests before IDT.³

We did not take into account cases that did not meet the inclusion criteria from studies tackling PPV in the following manner: (1) while performing DPT to positive ST BL, which are different from the culprit BL^{E53,E73}; (2) while performing DPT to the positive ST BL, in case of clear mismatch between the chronology of the index reaction and that of ST positivity^{E72}; and (3) while performing DPT to patients with previously positive ST result to BL, but negative ST result at the time of DPT.^{E57} We believe that the inclusion of such studies as proof of PPV of ST to BL actually renders the PPV result inaccurate, by diluting the denominator. Similarly, after analyzing patients in groups C and D, we consider that these groups bring little to the knowledge on PPV.

This retrospective analysis has the limitation of having considered studies with heterogeneous methodology, mainly regarding criteria used for positive ST results.

Certain studies^{E5,E19,E20,E50,E52-E55} postulate that up to 60% of patients with a positive ST result were challenged negative to the culprit penicillin; however, these studies, cited frequently when addressing PPV, often have an imprecise methodology, which prompted us to exclude some of the cases they mention. Nevertheless, some ST-positive patients may indeed be challenge-negative. A recent study^{E57} questioned whether histamine is a key mediator in a positive penicillin-induced intradermal test based on lack of histamine release in most of the patients with penicillin allergy during penicillin intradermal test. However, in this study, the PPV of a positive ST result in group A was of 100% (2 patients reacted out of 2 patients with positive ST result at the time of DPT). Regardless of the mechanism involved, clinical practice in this review proves that the PPV with ST in BL is high. Data regarding the natural history of BL allergy are limited, with proof of declined rates of sensitivity to BL over time^{E58,E59} for IgE-mediated reactions and also of natural antibiotic tolerance acquisition reported in children,^{E60} suggesting that some forms of DHRs to BLs may not be a permanent condition, contrary to evidence coming from studies addressing severe nonimmediate DHRs.^{E61} The expert panel of the International Consensus of Drug Allergy recommends lifelong avoidance of the drug and cross-reactive drugs when drug-induced anaphylaxis has occurred (expert recommendation, Grade D).³ In this review, PPV of ST to BL for an index reaction of anaphylaxis was 100%. Whether it is ethical and worthwhile to challenge patients with previous positive ST result and current negative ST result with the culprit drug is highly questionable. As clinicians working in the drug allergy field, we believe that this issue is primarily a scientific one and lacks proven therapeutic interest considering the existing alternatives (desensitization, administration of an alternative BL).

References to the PPV of ST to BL are biased by the trend to cite selective studies, erroneously prompting peers to conclude

that it would be low. This thorough review of literature shows that data on the PPV do exist and that PPV in well-characterized patients is not low, quite the contrary (>80% in both immediate and nonimmediate reactors). The experience of numerous groups working in BL drug allergy over decades cannot be changed or standardized to current knowledge or techniques. However, nor should it be misinterpreted.

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Group C (Table E2) comprised patients with a supposedly selective allergy (ie, no BL ring involvement), as demonstrated by the ST profile. Patients with positive ST result only for aminopenicillins (amoxicillin, ampicillin, or both) were tested for suspected side-chain cross-reactive amino-cephalosporins (eg, cephalexin, cefadroxil, and cefaclor) or vice versa. DPT elicited a reaction in 9 of 56 patients (PPV = 16%). Of note, in some studies some patients had been tested and had negative ST result for the BL administered during DPT. Therefore, the aforementioned value is not truly standing for PPV but rather to

cross-reactivity assessment. Based on data from *in vitro* cross-reactivity studies with antibenzylpenicilloil specific IgE antibody from patients and cefamandole protein conjugates, 11 patients with positive ST result for either BPO and/or benzylpenicillin (or both) were challenged to cefamandole (without previous ST to cefamandole), resulting in 2 positive reactions (18.2%).

Desensitizations to BL resulting in allergic reactions can be regarded as a positive challenge in ST-positive patients (group D, detailed data not shown). Of 68 reports (including 67 immediate reactors and 1 nonimmediate reactor), 42 cases (61.7%) presented a DHR during the desensitization protocol.

TABLE E1. Systemic DHR during ST to BL (group B patients)

Reference	No. of patients	Patient ID	Time of onset	Clinical history	Suspected drug	Positive ST result	Negative ST result	Type of positive test	Reaction	Comments (or delay)
Valyasevi and Van Dellen ^{E27}	2	1	UNK	MPE	Penicillin	PG, Pre-Pen, penicilloate	—	IDT	Anaphylaxis	
		2	UNK	MPE	Penicillin	Pre-Pen	—	IDT	Generalized urticaria	
Gadde et al ^{E18}	9	1	UNK	Urticaria	Penicillin	MDM	PPL	IDT	Anaphylaxis	Immediate
		2	UNK	Urticaria	UNK	PPL	MDM	Scratch, IDT	Urticaria	5-25 min
		3	IR	Anaphylaxis	UNK	PPL, MDM	—	IDT	Pruritus	5-25 min
		4	IR	Anaphylaxis	UNK	PPL	MDM	IDT	Pruritus	5-25 min
		5	UNK	Urticaria	UNK	PPL, MDM	—	Scratch, IDT	Pruritus	5-25 min
		6	UNK	Urticaria	UNK	PPL, MDM	—	Scratch, IDT	Pruritus	5-25 min
		7	UNK	Urticaria	UNK	PPL, MDM	—	IDT	Pruritus	5-25 min
		8	IR	Anaphylaxis	UNK	PPL, MDM	—	IDT	Pruritus	5-25 min
		9	UNK	Exanthema	UNK	PPL	MDM	Scratch, IDT	Pruritus	5-25 min
del Real et al ^{E16}	1	1	UNK	UNK	UNK	UNK	PG	IDT	Urticaria	Immediate
Co Minh et al ^{E15}	13	1	IR	Shock	UNK	PPL, CFTR	MDM, PG, AX, AP	SPT	Anaphylaxis	
		2	IR	Anaphylaxis	UNK	PPL, MDM, AP, PG	AX	IDT	Shock	
		3	IR	Shock	UNK	AX, AP	PPL, MDM, PG	SPT	Anaphylaxis	
		4	IR	Anaphylaxis	UNK	PPL, MDM, PG, AX, AP, CFTR, CFRD, CFUR, CFALO	UNK	SPT	Shock	
		5	IR	Shock	UNK	PG, AX, AP, AG	PPL, MDM	IDT	Shock	
		6	UNK	Urticaria	UNK	AX, AP	PPL, MDM, PG	IDT	Generalized urticaria	
		7	UNK	Urticaria	UNK	PPL	MDM, PG, AX, AP	IDT	Generalized urticaria	
		8	IR	Anaphylaxis	UNK	AX	PPL, MDM, PG, AP	IDT	Anaphylaxis	
		9	IR	Shock	UNK	MDM, PG, AX	PPL, AP	SPT	Anaphylaxis	
		10	IR	Anaphylaxis	UNK	PPL, MDM, AX	PG, AP	IDT	Shock	
		11	IR	Anaphylaxis	UNK	PG, AX, AP, CETR	UNK	IDT	Anaphylaxis	
		12	IR	Anaphylaxis	UNK	AX	PPL, MDM, PG, AP	IDT	Anaphylaxis	
		13	UNK	MPE	UNK	PPL, PG, AX, P	MDM	SPT	Generalized urticaria	
Torres et al ^{E25}	33	1	IR	Urticaria/AO	UNK	AX	BPO, MDM, AP	IDT	Generalized pruritus	
		2	IR	Urticaria/AO	UNK	MDM	BPO, AX, AP	IDT	Erythema, conjunctivitis	
		3	IR	Urticaria/AO	UNK	MDM	BPO, AX, AP	IDT	Anaphylactic shock	
		4	IR	Urticaria/AO	UNK	BPO	MDM, AX, AP	IDT	Urticaria	
		5	IR	Urticaria/AO	UNK	AX	BPO, MDM, AP	IDT	Urticaria/AO	
		6	IR	Urticaria/AO	UNK	MDM	BPO, AX, AP	SPT	Erythema, conjunctivitis	
		7	IR	Urticaria/AO	UNK	AX	BPO, MDM, AP	IDT	Anaphylaxis	
		8	IR	Urticaria/AO	UNK	AX	BPO, MDM, AP	IDT	Urticaria/AO	
		9	IR	Urticaria/AO	UNK	BPO	MDM, AX, AP	IDT	Anaphylactic shock	

			10	IR	Urticaria/AO	UNK	MDM	BPO, AX, AP	IDT	Anaphylactic shock
			11	IR	Urticaria/AO	UNK	AX	BPO, MDM, AP	IDT	Erythema, conjunctivitis
			12	IR	Urticaria/AO	UNK	AX	BPO, MDM, AP	IDT	Anaphylaxis
			13	IR	Urticaria/AO	UNK	BPO	MDM, AX, AP	IDT	Urticaria
			14	IR	Urticaria/AO	UNK	AX	BPO, MDM, AP	IDT	Anaphylaxis
			15	IR	Urticaria/AO	UNK	MDM	BPO, AX, AP	IDT	Urticaria, nausea
			16	IR	Urticaria/AO	UNK	BPO	MDM, AX, AP	IDT	Anaphylaxis
			17	IR	Urticaria/AO	UNK	AX	BPO, MDM, AP	IDT	Urticaria, conjunctivitis
			18	IR	Urticaria/AO	UNK	AX	BPO, MDM, AP	IDT	Generalized pruritus
			19	IR	Urticaria/AO	UNK	BPO	MDM, AX, AP	IDT	Anaphylaxis
			20	IR	Urticaria/AO	UNK	AX	BPO, MDM, AP	IDT	Urticaria, abdominal cramps
			21	IR	Urticaria/AO	UNK	BPO	MDM, AX, AP	IDT	Erythema, conjunctivitis, nausea
			22	IR	Urticaria/AO	UNK	AX	BPO, MDM, AP	IDT	Anaphylaxis
			23	IR	Urticaria/AO	UNK	AX	BPO, MDM, AP	IDT	Anaphylaxis
			24	IR	Urticaria/AO	UNK	AX	BPO, MDM, AP	SPT	Anaphylaxis
			25	IR	Urticaria/AO	UNK	AP	BPO, MDM, AX	IDT	Anaphylaxis
			26	IR	Urticaria/AO	UNK	BPO	MDM, AX, AP	IDT	Anaphylaxis
			27	IR	Urticaria/AO	UNK	AX	BPO, MDM, AP	IDT	Anaphylaxis
			28	IR	Urticaria/AO	UNK	BPO	MDM, AX, AP	IDT	Urticaria
			29	IR	Urticaria/AO	UNK	BPO	MDM, AX, AP	IDT	Anaphylaxis
			30	IR	Urticaria/AO	UNK	AP	BPO, MDM, AX	IDT	Erythema, conjunctivitis, nausea
			31	IR	Urticaria/AO	UNK	AX	BPO, MDM, AP	IDT	Urticaria, abdominal cramps
			32	IR	Urticaria/AO	UNK	AX	BPO, MDM, AP	IDT	Urticaria, nausea
			33	NIR	Desquamative exanthema	AX	AX, AP	PPL, MDM	IDT	Mild localized exanthema
Schnyder et al ^{E22}	1	1		NIR	Exanthema	PG	PG, AX	—	IDT	Generalized exanthema
Brown et al ^{E13}	4	1		UNK	UNK	UNK	PPL	—	IDT	Anaphylaxis
		2		UNK	UNK	UNK	PPL	—	IDT	Urticaria or pruritus
		3		UNK	UNK	UNK	PPL	—	IDT	Urticaria or pruritus
		4		UNK	UNK	UNK	PPL	—	IDT	Urticaria or pruritus
Goldberg and Confino-Cohen ^{E19}	1	1		UNK	UNK	UNK	UNK	UNK	IDT	Urticaria
Dogliotti ^{E17}	1	1		IR	Acute reaction	Peni	PG	—	Scratch	Shock, death

(continued)

TABLE E1. (Continued)

Reference	No. of patients	Patient ID	Time of onset	Clinical history	Suspected drug	Positive ST result	Negative ST result	Type of positive test	Reaction	Comments (or delay)
Miranda et al ^{E9}	2	1	IR	Urticaria, AO	AX	AX, AP	BPO, MDM	IDT	Systemic symptoms	
		2	IR	Anaphylaxis	AX-CLV	AX	BPO, MDM, AP	IDT	Systemic symptoms	
Green et al ^{E20}	3	1	IR	Urticaria	UNK	PG	PPL	IDT	Urticaria	Immediate
		2	IR	Urticaria	UNK	PG	PPL	IDT	Anaphylaxis	Immediate
		3	NIR	Serum sickness	UNK	PPL	PG	IDT	Urticaria, AO	6 h
Sullivan et al ^{E23}	4	1	UNK	UNK	UNK	PPL	PG, PA	IDT	GP, urticaria	Immediate
		2	UNK	UNK	UNK	PPL, PG	PA	IDT	GP, urticaria	Immediate
		3	UNK	UNK	UNK	PPL, PA	PG	IDT	GP, urticaria	Immediate
		4	UNK	UNK	UNK	PA	PPL, PG	SPT	GP, urticaria, dizziness	Immediate
Macy and Burchette ^{E21}	4	1	UNK	UNK	UNK	UNK	UNK	SPT	Pruritus, urticaria	Immediate
		2	UNK	UNK	UNK	UNK	UNK	SPT	Pruritus, urticaria	Immediate
		3	UNK	UNK	UNK	UNK	UNK	SPT	Pruritus, urticaria	Immediate
		4	UNK	UNK	UNK	UNK	UNK	IDT	Cough	Immediate
Weber-Mani and Pichler ^{E28}	1	1	IR	Anaphylaxis	AX-CLV	UNK	UNK	IDT	Shock	Immediate
Vega et al ^{E6}	9	1	IR	Anaphylaxis	AX	AX, AP	BPO, MDM, PG	IDT	Anaphylaxis	Immediate
		2	IR	Urticaria/AO	AX	AX, AP	BPO, MDM, PG	IDT	Anaphylaxis	Immediate
		3	IR	Anaphylaxis	AP	AX, AP	BPO, MDM, PG	IDT	Shock	Immediate
		4	IR	Anaphylaxis	AX-CLV	AX	BPO, MDM, PG, AP	IDT	Generalized urticaria	Immediate
		5	IR	Anaphylaxis	AX	AX, AP	BPO, MDM, PG	IDT	Facial erythema and lip angioedema	Immediate
		6	IR	Anaphylaxis	AX	AX	BPO	IDT	Anaphylaxis	Immediate
		7	IR	Anaphylaxis	AX	AX	BPO, MDM	IDT	Generalized urticaria	Immediate
		8	IR	Anaphylaxis	AX	AX	BPO, MDM, PG, AP	IDT	Shock	Immediate
		9	IR	Urticaria/AO	AX	AX	BPO, MDM	IDT	Urticaria	Immediate
Nolan et al ^{E29}	1	1	IR	Bronchospasm	AX-CLV	PPL, MDM, AX, BP	—	IDT	Anaphylaxis	20 min
Chiba et al ^{E33}	1	1	IR	Anaphylaxis	Cefotiam	Cefotiam	—	Patch	Anaphylaxis	15 min
Romano et al ^{E4}	1	1	NIR	MPE	AX, AP	AX, AP	—	IDT	MPE	Delayed
Macy ^{E36}	1	1	IR	Urticaria	UNK	UNK	UNK	SPT or IDT	Pruritus	Immediate
Blanca et al ^{E74}	1	1	IR	Shock	AX	AX	BPO, MDM	SPT or IDT	Erythema and generalized pruritus	Immediate
Blanca et al ⁷	5	1	IR	Shock	AX	AX, AP	BPO, MDM	IDT	UNK	Immediate
		2	IR	Generalized erythema	AX-CLV	AX	BPO, MDM, AP	IDT	UNK	Immediate
		3	IR	Shock	AX	AX	BPO, MDM, AP	IDT	UNK	Immediate
		4	IR	Urticaria	AX	None	BPO, MDM, AP, AX	IDT	Hypotension	Immediate
		5	IR	Shock	AX	None	BPO, MDM, AP, AX	IDT	Systemic pruritus	Immediate
Andre et al ^{E30}	1	1	NIR	SDRIFE	PG	PG, AX, AP	PPL, MDM	IDT, Patch	SDRIFE	8 h
Atanaskovic-Markovic ^{E31}	1	1	IR	Anaphylaxis	PG	PG	PPL, MDM, AX, AP	IDT	Urticaria	5 min

Barbaud et al ^{E32}	1	1	NIR	Generalized eczema	AX	AX	UNK	IDT	Generalized eczema	UNK
Novalbos et al ^{E37}	1	1	UNK	MPE	AX	AX	PPL, MDM, PG	IDT	UNK	Immediate
Riezzo et al ^{E42}	1	1	UNK	UNK	Ceftriaxone	Ceftriaxone	ND	IDT	Fatal anaphylaxis	5 min
Raison-Peyron et al ^{E41}	1	1	IR	Shock	AX	PPL, MDM, AX, AP, PG, ceftriaxone, cefapirine	None	SPT	Shock	Immediate
		Same patient came back	IR	Shock	AX	AX	None	Open test, no breaking of skin	Urticaria, conjunctivitis	15 min
Hausermann and Bircher ^{E34}	1	1	IR	Itchy periocular dermatitis	Ceftriaxone	Ceftriaxone	None	IDT	Anaphylaxis	Immediate
Nugent et al ^{E38}	1	1	UNK	UNK	PG	UNK	UNK	IDT	Anaphylaxis	UNK
Ponvert et al ^{E40}	6	1	UNK	UNK	UNK	UNK	UNK	IDT	Anaphylaxis	Immediate
		2	UNK	UNK	UNK	UNK	UNK	IDT	Urticaria	NIR
		3	UNK	UNK	UNK	UNK	UNK	IDT	Urticaria	NIR
		4	UNK	UNK	UNK	UNK	UNK	IDT	Urticaria	NIR
		5	UNK	UNK	UNK	UNK	UNK	IDT	Urticaria	NIR
		6	UNK	UNK	UNK	UNK	UNK	IDT	Urticaria	NIR
Pichichero and Pichichero ^{E39}	3	1	IR?	UNK	UNK	UNK	UNK	UNK	Pruritus	Immediate
		2	IR?	UNK	UNK	UNK	UNK	UNK	Pruritus	Immediate
		3	IR?	UNK	UNK	UNK	UNK	UNK	Urticaria	Immediate
Torres et al ^{E24}	1	1	IR	Anaphylaxis	AX	AX	None	IDT	Mild systemic symptoms	Immediate
Celik et al ^{E63}	4	1	IR	UNK	Peni G & V	PPL	—	UNK	Cough with sore throat	Quickly responded to treatment
		2	IR	UNK	Peni G & V	PPL	—	UNK	Cough with sore throat	Quickly responded to treatment
		3	IR	UNK	Peni G & V	PPL	—	UNK	Cough with sore throat	Quickly responded to treatment
		4	IR	UNK	Penic G & V	PPL	—	UNK	Cough with sore throat	Quickly responded to treatment
Gonzalez-de-Olano et al ^{E64}	1	1	IR	Anaphylaxis	AX	AX	PPL, MDM, PG	IDT	Kounis Syndrome	Immediate
Antico et al ^{E65}	5	1	IR	Anaphylaxis	AX	AX	—	SPT	Urticaria-AO	
		2	IR	Anaphylaxis	Not mentioned	MDM	—	IDT	Pruritus and shock	
		3	IR	Urticaria-AO	AX	AX	—	IDT	Urticaria-AO	
		4	IR	Anaphylaxis	AX	AX	—	SPT	Pruritus and rash	
		5	IR	Urticaria-AO	AX	AX	—	IDT	Urticaria-AO	

(continued)

TABLE E1. (Continued)

Reference	No. of patients	Patient ID	Time of onset	Clinical history	Suspected drug	Positive ST result	Negative ST result	Type of positive test	Reaction	Comments (or delay)
Confino-Cohen et al ^{E66}	1	1	IR	UNK	UNK	AX	—	SPT	Pruritus, urticaria	Immediate
Blanca-Lopez et al ^{E69}	2	1	IR	Anaphylaxis	AX-CLV	AX	—	IDT	Generalized pruritus with erythema + nausea-vomiting	
		2	IR	Anaphylaxis	AX-CLV	AX	—	IDT	Mild systemic pruritus and facial erythema	
Rimawi et al ^{E71}	1	1	UNK	UNK	UNK	Pre-Pen	—	IDT	Hives, edema, itching	6 min
Tannert et al ^{E56}	3	1	IR?	UNK	UNK	UNK	UNK	IDT	UNK	UNK
		2	IR?	UNK	UNK	UNK	UNK	IDT	UNK	UNK
		3	IR?	UNK	UNK	UNK	UNK	UNK	UNK	UNK

AO, Angioedema; AP, ampicillin; AX, amoxicillin; AX-CLV, amoxicillin + clavulanic acid; BPO, major determinant benzylpenicilloly; CETR, cefatrizine; CFALO, cefalotine; CFRD, cefradine; CFTR, ceftriaxone; CFUR, cefuroxime; GP, generalized pruritus; IDT, intradermal test; IR, immediate reaction; MDM, minor determinant mix; MPE, maculopapular exanthema; ND, not done; NIR, nonimmediate reaction; PA, penicillin A; Peni, penicillin, unspecified; PG, penicillin G; PPL, penicilloyl poly-L-lysine; PV, penicillin V; SDRIFE, symmetrical drug-related intertriginous and flexural exanthema; SPT, skin prick test; UNK, unknown.

TABLE E2. Group C patients (cross-reactive for similar side-chains)

Reference	No. of patients	Patient ID	Time of onset	Clinical history	Suspected drug	Positive ST result	Negative ST result	Tested drug	Reaction	Comments (or delay)
Miranda et al, ^{E9} Spain	15	1	IR	Anaphylaxis		AX,	BPO, MDM, AP	Cefadroxil	GP	
		2	IR	Anaphylaxis		AX, AP	BPO, MDM	Cefadroxil	GP	
		3	IR	Anaphylaxis		AX, AP	BPO, MDM	Cefadroxil	Erythema, palmo-plantar pruritus	
		4	IR	Urticaria, AO		AX	BPO, MDM, AP	Cefadroxil	Shock	
		5	IR	Urticaria, AO		AX, AP	BPO, MDM	Cefadroxil	Tolerance	
		6	IR	Anaphylaxis		AX, AP	BPO, MDM	Cefadroxil	Tolerance	
		7	IR	Anaphylaxis		AX	BPO, MDM, AP	Cefadroxil	Tolerance	
		8	IR	Anaphylaxis		AX, AP	BPO, MDM	Cefadroxil	Tolerance	
		9	IR	AO		AX, AP	BPO, MDM	Cefadroxil	Tolerance	
		10	IR	Anaphylaxis		AX	BPO, MDM, AP	Cefadroxil	Tolerance	
		11	IR	Anaphylaxis		AX	BPO, MDM, AP	Cefadroxil	Tolerance	
		12	IR	Anaphylaxis		AX, AP	BPO, MDM	Cefadroxil	Tolerance	
		13	IR	Anaphylaxis		AX	BPO, MDM, AP	Cefadroxil	Tolerance	
		14	IR	Anaphylaxis		AX, AP	BPO, MDM	Cefadroxil	Tolerance	
		15	IR	Anaphylaxis		AX, AP	BPO, MDM	Cefadroxil	Tolerance	
Herve et al, ^{E8} France	1	1	UNK	UNK	UNK	UNK	UNK		GP	Accidental challenge
Sastre et al ^{E2}	11	1	UNK	Urticaria, AO		AX	PPL, MDM, PG	Cefadroxil	Yes, UNK	
		2	UNK	Urticaria, AO		AX	PPL, MDM, PG	Cefadroxil	Tolerance	
		3	UNK	Urticaria, AO		AX	PPL, MDM, PG	Cefadroxil	Tolerance	
		4	UNK	UNK		AX	PPL, MDM, PG	Cefadroxil	Tolerance	
		5	UNK	Anaphylaxis		AX	PPL, MDM, PG	Cefadroxil	Tolerance	
		6	UNK	MPE		AX	PPL, MDM, PG	Cefadroxil	Tolerance	
		7	UNK	Urticaria, AO		AX	PPL, MDM, PG	Cefadroxil	Tolerance	
		8	UNK	MPE		AX	PPL, MDM, PG	Cefadroxil	Tolerance	
		9	UNK	UNK		AX	PPL, MDM, PG	Cefadroxil	Tolerance	
		10	UNK	Anaphylaxis		AX	PPL, MDM, PG	Cefadroxil	Tolerance	
		11	UNK	UNK		AX	PPL, MDM, PG	Cefadroxil	Tolerance	
Blanca et al ⁷	11	1	IR	AO	Peni	PG	BPO, AX, AP	Cephmandole	Shock	
		2	IR	Shock	Peni	PG	BPO, AX, AP	Cephmandole	Shock	
		3	IR	Shock	Peni	PG	BPO, AX, AP	Cephmandole, cephaloridine	Tolerance	
		4	IR	Shock	Peni	BPO, PG	AX, AP	Cephmandole, cephaloridine	Tolerance	
		5	IR	Generalized MPE	Peni	BPO, PG	AX, AP	Cephmandole, cephaloridine	Tolerance	

(continued)

TABLE E2. (Continued)

Reference	No. of patients	Patient ID	Time of onset	Clinical history	Suspected drug	Positive ST result	Negative ST result	Tested drug	Reaction	Comments (or delay)
		6	IR	Shock	Peni	BPO, PG	AX, AP	Cephmandole, cephaloridine	Tolerance	
		7	IR	Erythema	Peni	BPO, PG	AX, AP	Cephmandole, cephaloridine	Tolerance	
		8	IR	Generalized MPE	Peni	BPO	PG, AX, AP	Cephmandole, cephaloridine	Tolerance	
		9	IR	Anaphylaxis	Peni	BPO	PG, AX, AP	Cephmandole, cephaloridine	Tolerance	
		10	IR	Erythema	Peni	BPO, PG	AX, AP	Cephmandole, cephaloridine	Tolerance	
		11	IR	Shock	Peni	PG	BPO, AX, AP	Cephmandole, cephaloridine	Tolerance	
Romano et al ^{E3}	1	1	NIR	MPE	AX, AP, PV	AX, AP, PG	—	AX, AP, PV	MPE, 6 h later	
Audicana et al ⁶	8	1	IR	Anaphylaxis		AP	PPL, MDM, AX, cephalixin, ceftazidime	Cephalexin, ceftazidime	Tolerance	
		2	IR	MPE		AP, AX	PPL, MDM, cephalixin, ceftazidime	Cephalexin, ceftazidime	Tolerance	
		3	IR	Anaphylaxis		AX	PPL, MDM, AP, cephalixin, ceftazidime	Cephalexin, ceftazidime	Tolerance	
		4	IR	MPE, AE		AX	PPL, MDM, AP, cephalixin, ceftazidime	Cephalexin, ceftazidime	Tolerance	
		5	IR	Shock		AP, AX	PPL, MDM, cephalixin, ceftazidime	Cephalexin, ceftazidime	Tolerance	
		6	IR	MPR		AP, AX	PPL, MDM, cephalixin, ceftazidime	Cephalexin, ceftazidime	Tolerance	
		7	IR	MPE		AP	PPL, MDM, AX, cephalixin, ceftazidime	Cephalexin, ceftazidime	Tolerance	
		8	IR	Shock		AP, AX	PPL, MDM, cephalixin, ceftazidime	Cephalexin, ceftazidime	Tolerance	
Novembre et al ^{E10}	7	1	IR	Anaphylaxis	Cefaclor	Cefaclor	PPL, MDM	AX	Tolerance	
		2	IR	Shock	Cefaclor	Cefaclor	PPL, MDM	AX	Tolerance	
		3	IR	Shock	Cefaclor	Cefaclor	PPL, MDM	AX	Tolerance	
		4	IR	Shock	Cefaclor	Cefaclor	PPL, MDM	AX	Tolerance	
		5	IR	Anaphylaxis	Cefaclor	Cefaclor	PPL, MDM	AX	Tolerance	
		6	IR	Shock	Cefaclor	Cefaclor	PPL, MDM	AX	Tolerance	
		7	IR	Shock	Cefaclor	Cefaclor	PPL, MDM	AX	Tolerance	
Ahmed et al ^{E12}	2	1	UNK	—	AX	AX	PPL, MDM	Cefalexin	Tolerance	
		2	UNK	—	AX	AX	PPL, MDM	Cefalexin	Tolerance	

AO, Angioedema; AP, ampicillin; AX, amoxicillin; AX + Cla, amoxicillin + clavulanic acid; Az, aztreonam; B, bacampicillin; BPO, major determinant benzylpenicilloly; Cef, cefixime; Cfc, cefaclor; Cfl, cephalixin; Cft, ceftibuten; Cfu, cefuroxime; Cl, cloxacillin; Ctx, ceftriaxone; GP, generalized pruritus; IDT, intradermal test; Im, imipenem; IR, immediate reaction; M, mezlocillin; MDM, minor determinant mix; MPE, maculopapular exanthema; ND, not done; NIR, nonimmediate reaction; PA, penicillin A; Peni, penicillin (unspecified); PG, penicillin G; Pi, piperacillin; PPL, penicilloyl poly-L-lysine; PV, penicillin V; Sul, sulbactam; Ti, ticarcillin; UNK, unknown.

TABLE E3. Miscellaneous data retrieved from articles tackling PPV of STs to BLs

Author, Year	ST-positive patients undergoing DPT	No. of positive challenges (and reported PPV, as calculated from raw data)	Comments
Warrington et al, ^{E75} 1978	6	0 (0%)	"Six patients with weakly positive skin reactions (wheal 3 mm in diameter) were treated with penicillin or its derivatives and no adverse reaction occurred."
Chandra et al, ^{E76} 1980	5	5 (100%)	"The inadvertent administration of penicillin in 5 patients with positive tests resulted in rapid generalized urticaria in each."
Solley et al, ^{E77} 1982	8	4 (50%)	"Of the 108 patients with at least one positive skin test, eight were treated subsequently with penicillin. Four of these eight patients (50%) developed an allergic response during the penicillin therapy. None of the reactions was immediate in onset."
Macy and Burchette, ^{E21} 2002 (multiyear follow-up study)	9	3 (33.3%)	"There were only three (33%) adverse drug reactions reported in the nine penicillin skin test-positive individuals who, at least initially, were inadvertently exposed to a total of 14 courses of oral penicillin. All had rashes starting more than 24 h after the first post penicillin skin test penicillin exposure. None received any treatment beyond discontinuing the penicillin and taking an oral antihistamine."
Goldberg and Confino-Cohen, ^{E19} 2008 (follow-up study)	67 on first evaluation 70 on second evaluation	7 (10.4%) 2 (2.8%)	"The study excluded patients with an index reaction of life-threatening anaphylaxis. Irrespective of the response to skin testing, an oral challenge was performed with either penicillin V or amoxicillin, and cross-over challenge was performed 2 to 5 months after the first evaluation."
Macy et al, ^{E78} 2011 (multiyear follow-up study)	1	0 (0%)	"There was 1 penicillin skin test-positive female, age 74 years when she was intradermal skin test-positive to penicilloate only in 2000. She received oral amoxicillin in 2005 and intravenous ampicillin in 2007, with no desensitization prior to either episode and no reactions noted."

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