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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 tests 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.

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To the Editor,

Skin tests to β-lactams (BL) have evolved widely over the past fifty years, with variations in testing techniques, reagents and interpretation (1,2). However, the expert panel of the International Consensus (ICON) of Drug Allergy (3) acknowledged their crucial role and value in virtually all patients that carry an "allergic to BL" label. If positive in immediate or delayed-reading, skin tests (ST) to non-irritating concentrations (4) 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, as confirmatory challenges have rarely been performed due to understandable ethical concerns about patients' safety. Most available data suggest that between 40 to 100% of penicillin ST-positive patients will develop immediate allergic reactions upon being challenged with the BL (2,5).

The aim of the present study was to investigate data related to PPV of ST to BL. We performed a literature review in the PubMed database, by cross-referencing the terms "skin test", "beta-lactam" and "drug hypersensitivity", in order to retrieve available literature data on the PPV of ST to BL. 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 were retrieved and analyzed. These reports included the following four clinical situations that we considered would prove the "allergy-revealing" (rather than just "sensitization-revealing") value of a positive ST to BL, assuming that concentrations used are the non-irritant published ones (1,2): (i) re-administration (either accidental or by drug provocation test, DPT) of the culprit, ST-positive BL, (ii) systemic Drug hypersensitivity reaction (DHR) occurring during positive BL ST, (iii), administration (either accidental or by DPT) of a supposedly side-chain cross-reactive BL based on known side-chain similarities, (iv) DHR occurring during a desensitization protocol performed in ST-

positive patients. The following reports were excluded: (i) overlapping patient populations (i.e., by investigators at the same institution), (ii) patients with positive ST but no clinical history for BL antibiotics (e.g., controls), (iii) patients with positive ST to amino-penicillins and good tolerance to benzyl-penicillin, (iv) patients with positive ST challenged with sub-therapeutic doses, if exposure to these doses turned out to be negative (e.g., challenge with penicillin-contaminated food, 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 w/o shock, 10 with urticaria/angioedema, 1 with unspecified manifestations) and positive immediate-reading ST, 21 reacted upon re-exposure (PPV= 80.7%[1]). For patients with anaphylaxis (with or w/o shock), the PPV was 100%. Amongst the 37 patients with non-immediate 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 (Table E1), confirming that the positive ST 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 non-immediate reactors and 35 cases (26.3%) in patients with clinical DHR history with non-specified chronology. Of note, systemic DHR were also elicited while testing controls (not included in

[1] In reference E56, it is not clear whether 8 patients with a clinical history to penicillin V had positive ST to penicillin V or penicillin G. If the latter is correct, then these patients would be excluded from group A. PPV would increase for immediate reactions group to 95% (1 tolerant patient out of 20 exposed) and to 88.5% (4 tolerant patients out of 35 exposed) for non-immediate reactions. The details are presented in Table 1.

99 the analysis) or in patients with negative ST at the injection site (7). Amongst all BL,
100 penicillins were the most frequent elicitors (83%). All ST techniques were involved (even the
101 open test, i.e., no breaking of skin (E41)), but the intradermal test (IDT) was the culprit
102 technique in 86% of the cases. Overall, in about half of the cases, the reaction elicited during
103 ST was less severe than the index reaction. Two cases of fatal anaphylaxis during ST to BL
104 were identified in this series of cases (E17, E42). Three more cases were retrieved, but they
105 were not included in this analysis (one patient had supposedly no previous reaction to BL
106 (E35) and the other two cases were mentioned by the authors as unpublished and occurring
107 between 1953-1968).
108 Data from Groups C (PPV=16%, Table E2) and D (PPV=61.7%) are presented in the
109 Supplementary Material 1. Other studies have reported re-administration of BL in BL ST
110 positive patients, but no details concerning the provoked patients (with regards to the culprit
111 BL and the ST positive BL) were available. We therefore did not mingle these reports to
112 patients in Group A, who are well phenotyped, but rather decided to present them separately
113 (Table E3).
114 Learned societies recommend, based on a few regularly cited papers (E5, E19, E20, E50,
115 E52-55), that ST-positive patients should avoid BL and if need be, undergo desensitization
116 (3). This review brings additional data to support this attitude by taking into account and
117 studying in detail a multitude of articles published over several decades in different countries
118 and continents. They show that for well-phenotyped patients (i.e., patients with a clinical
119 history of DHR for a BL, positive ST for this BL and DPT for the same BL), PPV is high
120 enough (>80%) in both immediate and non-immediate DHR. Along with the proof of the
121 iatrogenicity of ST to BL (systemic and even fatal reactions could be induced by ST, as
122 shown in Group B) we believe that sufficient data exists to date to discourage DPTs in
123 patients with positive ST to BL. The potential iatrogenicity of ST to BL emphasizes the need

124 to perform them in a stepwise manner, with appropriate concentrations of extracts for prick
125 tests prior to IDT (3).
126 We did not take into account cases that did not meet the inclusion criteria from studies
127 tackling PPV in the following manner: (i) while performing DPT to positive ST BL, that are
128 different from the culprit BL (E53, E73); (ii) while performing DPT to the positive ST BL, in
129 case of clear miss-match between the chronology of the index reaction and that of ST
130 positivity (E72); (iii) while performing DPT to patients with previously positive ST to BL, but
131 negative ST at the time of DPT (E57). We believe that the inclusion of such studies as proof
132 of PPV of ST to BL actually renders the PPV result inaccurate, by diluting the denominator.
133 Similarly, after analyzing patients in Group C and D, we consider that these groups bring little
134 to the knowledge on PPV.
135 This retrospective analysis has the limitation of having considered studies with heterogeneous
136 methodology, mainly regarding criteria used for positive ST.
137 Certain studies (E5, E19, E20, E50, E52-55) postulate that up to 60% of patients with a
138 positive ST were challenged negative to the culprit penicillin; however those studies, cited
139 frequently when addressing PPV, often have an imprecise methodology, that prompted us to
140 exclude some of the cases they mention. Nevertheless, some ST-positive patients may indeed
141 be challenge negative. A recent study (E57) questioned whether histamine is a key mediator
142 in a positive penicillin- induced intradermal test based on lack of histamine release in most of
143 the penicillin-allergic patients during penicillin intradermal test. However, in this study, the
144 PPV of a positive ST in the Group A was of 100% (2 patients reacted out of 2 patients with
145 positive ST at the time of DPT). Regardless of the mechanism involved, clinical practice in
146 this review proves that the PPV with ST in BL is high. Data regarding the natural history of
147 BL allergy are limited, with proof of declined rates of sensitivity to BL over time (E58,E59)
148 for IgE-mediated reactions and also of natural antibiotic tolerance acquisition reported in

children (E60), suggesting that some forms of DHR to BL may not be a permanent condition, contrary to evidence coming from studies addressing severe non-immediate DHR (E61). The expert panel of the ICON 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 and current negative ST 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 does exist and that PPV in well-characterized patients is not low, quite the contrary (>80% in both immediate and non-immediate 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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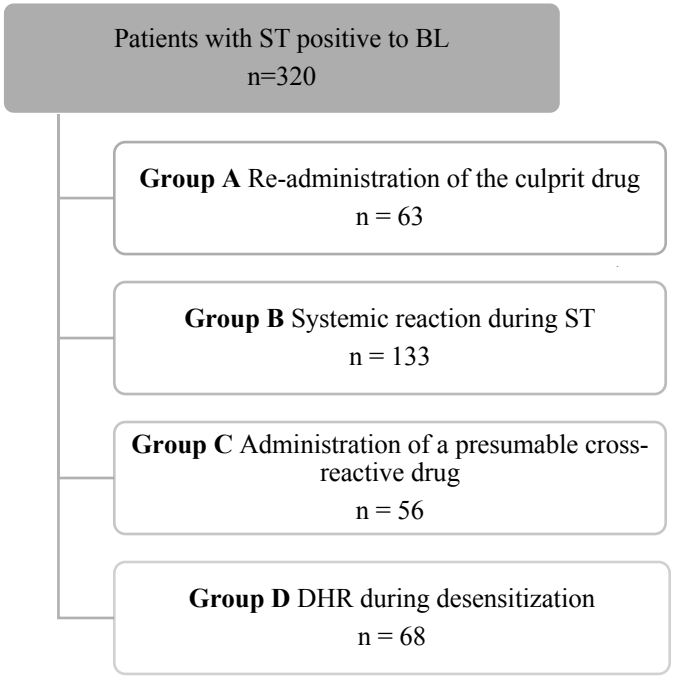
Figure 1: Distribution of BL ST-positive cases according to the four analyzed groups.
BL, beta-lactam; ST, skin test



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(6-9, E1-6, E62, E67, E68, E70)

(6, 7, E2-3, E8-10, E12)

(7, E4, E6, E9, E13, E15- 20, E22-25, E27-34, E37-42, E63-66, E69, E71, E72, E74)

(E20, E43-51)

Table 1. Description of ST-positive patients who underwent DPT to the culprit ST-positive BL (Group A patients).

Ref	Number of patients	Patient number	Time of onset	Clinical history	Suspectd drug	Positive ST	Negative ST	Tested drug	Reaction	Comments (Or delay)
(8) Demoly et al	1	1	IR	Shock	Ceftriaxone	Ceftriaxone Cefazoline	PPL, MDM, PG, AX, AP	Ceftriaxone	Anaphylaxis	Patient had DPTs to all positive and negative-ST drugs
(E2) Sastre et al	2	1	IR	GP, urticaria, AO	AX	AX	PPL, MDM, PG	AX	GP, erythema	
		2	IR	urticaria, AO	AX	AX	PPL, MDM, PG	AX	PG, AO exanthema	
(E6) Vega et al	5	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	
		5	IR	Anaphylaxis	AP	AX	PPL, MDM, PG, AP	AX	Anaphylaxis	
(E5) Padial et al	2	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 24h	
(E3) Romano et al	18	1	NIR	MPE	AX, AP, PV	AX, AP	PG	AX, AP	MPE, AO >6h later	
		2	NIR	MPE	AX, AP, PV	AX, AP	PG	AX, AP	MPE, AO >6h later	
		3	NIR	MPE	AX, AP, PV	AX, AP	PG	AX, AP	MPE, AO >6h later	
		4	NIR	MPE	AX, AP, PV	AX, AP	PG	AX, AP	MPE, AO >6h later	
		5	NIR	MPE	AX, AP, PV	AX, AP	PG	AX, AP	MPE, AO >6h later	
		6	NIR	MPE	AX, AP, PV	AX, AP	PG	AX, AP	MPE, AO >6h later	
		7	NIR	MPE	AX, AP, PV	AX, AP	PG	AX, AP	MPE, AO >6h later	
		8	NIR	MPE	AX, AP, PV	AX, AP	PG	AX, AP	MPE, AO >6h later	
		9	NIR	MPE	AX, AP, PV	AX, AP	PG	AX, AP	MPE, AO >6h later	
		10	NIR	MPE	AX, AP, PV	AX, AP	PG	AX, AP	MPE, AO >6h later	
		11	NIR	MPE	AX, AP, PV	AX, AP	PG	AX, AP	MPE, AO >6h later	
		12	NIR	MPE	AX, AP, PV	AX, AP	PG	AX, AP	MPE, AO >6h later	
		13	NIR	MPE	AX, AP, PV	AX, AP	PG	AX, AP	MPE, AO >6h later	
		14	NIR	MPE	AX, AP, PV	AX, AP	PG	AX, AP	MPE, AO >6h later	
		15	NIR	MPE	AX, AP, PV	AX, AP	PG	AX, AP	MPE, AO >6h later	

		16	NIR	MPE	AX, AP, PV	AX, AP	PG	AX, AP	MPE, AO >6h later	
		17	NIR	MPE	AX, AP, PV	AX, AP	PG	AX, AP	MPE, AO >6h later	
		18	NIR	MPE	AX, AP, PV	AX, AP, PG	None	AX, AP, PV	MPE	6h
(9) Richter et al	1	1	NIR?	UNK	BL	PPL, MDM, AX	-	AX	MPE	Delayed
(E4) Romano et al	5	1	NIR	MPE	Aminopenicillin	Aminopenicillin	Patch negative	Aminopenicillin	MPE	Delayed
		2	NIR	Erythema	AX	AX	Patch negative	AX	Erythema	5h
		3	NIR	MPE	Aminopenicillin	Aminopenicillin	Patch negative	Aminopenicillin	Tolerance	
		4	NIR	Urticaria	AX	AX	Patch negative	AX	Tolerance	
		5	NIR	Erythema	AP	AP	Patch negative	AP	Tolerance	
(7) Blanca et al	4	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
(E1) Romano et al	1	1	NIR	AO, MPE	Cefalexine	AX, AP, Cefalexine	- ?? (plenty)	Cefalexine	EMP	delayed
(6) Audicana et al	1	1	IR?	Urticaria	AP	AX, AP, Cephalexin	PPL, MDM, Ceftazidine	Cephalexin	Generalized urticaria	UNK
(E62) Christiansen et al	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	
(E68) Weisser et al	1	1	NIR	Rash	AX	Pre-pen®	-	AX	Hives	15 minutes
(E70) Cabanas et al	1	1	NIR	DRESS	Pip/Taz	Pip/Taz	-	Pip/Taz	Maculopapular rash and increased in liver enzymes	patch 5hours after a single dose

(E67) Barni et al	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	
(E56) Tannert et al	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 ; BL, Beta-lactam; EM; BPO, Major determinant benzylpenicilloly; DX, dicloxacillin; GP, Generalized pruritus; IR, Immediate reaction; MC, mecillinam; MDM, Minor determinant mix; MPE, Maculopapular exanthema; NIR, Non-immediate reaction; PG, Penicillin G;* Pip/Taz*, Piperacillin/Tazobactam; PV, Penicillin V; PPL, Penicilloyl poly-L-lysine; UNK, Unknown*