



ORDINE PROVINCIALE
DEI MEDICI CHIRURGHI E
DEGLI ODONTOIATRI
DI VENEZIA



CORSO DI FARMACOALLERGOLOGIA: SPUNTI DI DISCUSSIONE SULLE ALLERGIE AI FARMACI

LE REAZIONI ALLERGICHE AGLI ANTIBIOTICI BETA-LATTAMICI

Patrizia Bonadonna
USD Allergologia Verona
European Network Drug Allergy

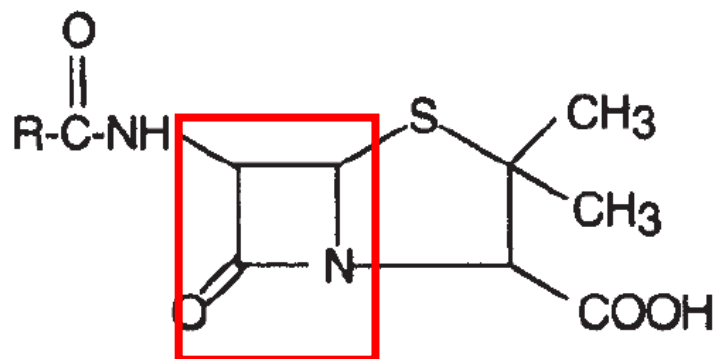


- **Gli antibiotici rappresentano la più frequente causa di reazioni allergiche a farmaci .**
- **Tra le diverse classi di antibiotici i beta-lattamici sono quelli più spesso coinvolti.**
- **47% delle reazioni allergiche a farmaci in soggetti non ospedalizzati sono da imputare ad antibiotici, e di questi il **73%** sono causate da **amoxicillina****

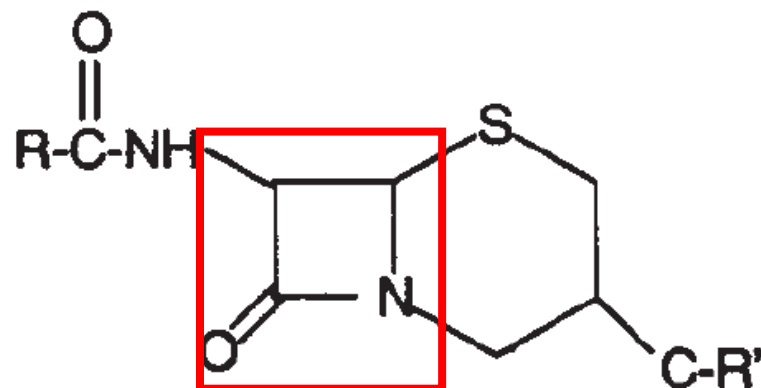
Thong BY, British journal of clinical pharmacology 2011; 71(5): 684-700

Blanca M. Allergy 2009; 64(2): 183-93.

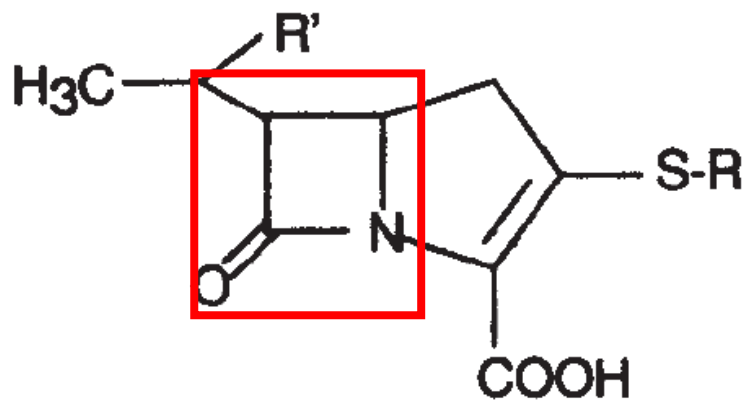
Beta-lactamine



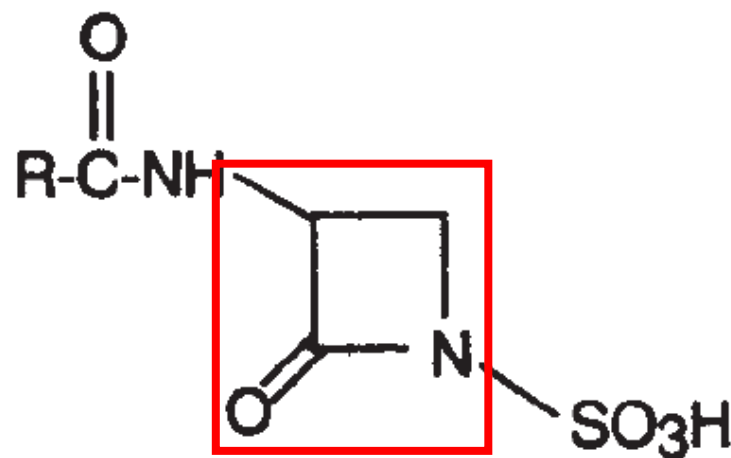
Penicillins



Cephalosporins



Carbapenems



Monobactams

R1 CHAIN

R1 CHAIN+ β lactam ring

β lactam ring + Thiazol ring

Thiazol Ring

β lactam ring + Dihydrothiaz ring + R2 CHAIN

Dihydrothiaz ring + R2 CHAIN

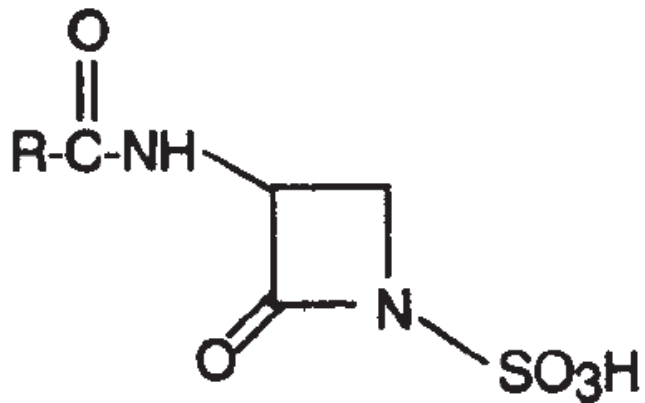
R2 CHAIN

Betalactam WHOLE MOLECULE

Rate of Adverse reactions to Cephalosporins in Penicillin-Allergic Patients according to Previous Assessment with Cephalosporins Skin Tests

Study	N°di pts	Skin Test Reactions %	Comments
Girard (1968)	23	NS 2 (8,7)	cephaloridine*
➤ I test cutanei negativi per le cefalosporine in soggetti allergici alle penicilline sono utili indicatori di tollerabilità del farmaco ➤ Nei soggetti allergici alle penicilline prima di escludere a priori la possibilità di assumere le cefalosporine bisogna eseguire i test.			
TOT.	321	9 (4,1)	

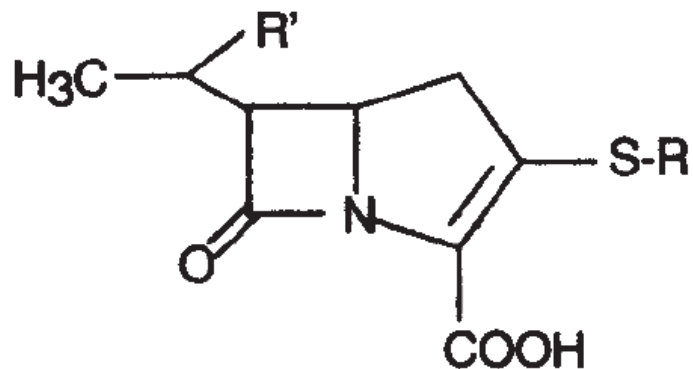
*These cephalosporins have the same side chain of benzilpenicillin



Monobactams



AZTREONAM



Carbapenems



MEROPENEM

® *Merrem*



IMIPENEM ® *Tienam*

Cross-reactivity between Penicillins and Carbapenems

- 9 (**47.4%**) out of 19 patients with positive penicillin skin tests were also positive to imipenem/cilastatin and/or imipenem metabolites

A Saxon et al, J Allergy Clin Immunol 1988

In the past administration of carbapenems is considered potentially harmful

Quindi la pratica di evitare i Carbapenemi nei soggetti con allergia alle penicilline dovrebbe essere riconsiderata. Ma è raccomandato eseguire prima dei test cutanei (ID and PATCH TEST) e graded challenges

MEROPENEM in adults : A Romano et al, Ann Intern Med 2007

MEROPENEM in childrens: M. Atanaskovic Allergy 2008

IMIPENEM in delayed cell-mediated : Schiavino Allergy 2009

Tolerance to aztreonam in patients allergic to betalactam antibiotics

- **Aztreonam seems to have a very weak cross-reactivity with other classes of beta-lactams**
- **Aztreonam seems to be well tolerated by patients with IgE-mediated hypersensitivity to penicillins**

Adkinson 1990

JM Vega et al, Allergy 1991

- **Aztreonam is generally well-tolerated also in patients with CF who have had previous reactions to β -lactam**

Moss 1984

- **NO cross-reactivity between Aztreonam and β -lactam**
- **YES Cross-reactivity with CEFTAZIDIME**

Identical Side Chains R-1 :

- Cefotaxime ® *Zariviz* and Ceftriaxone ® *Rocefin*
- Cephalexin ® *Ceporex* and Ampicillin
- Cefaclor ® *Panacef* and Ampicillin
- Cefadroxil and Amoxicillin
- Ceftazidime (® *Glazidim*) and Aztreonam
- Cefaclor ® *Panacef* and Cephalexin

Similar Side Chains Catene R-1

- Cefotaxime ® *Zariviz* e Cefuroxime® *Curoxim*
- Cephalotin e Benzilpenicillina
- Cefaloridina e Benzilpenicillina
- Imipenem e Benzilpenicillina
- Ceftazidime e Cefuroxime
- Cefaclor and Cefadroxil
- Cefuroxime and Ceftriaxone

Possibilità diagnostiche

"...PRIMUM: NO
NOCERE

Approccio Superato !!!!!



Memorandum SIAIC 1998

“Anche per farmaci per i quali le cutireazioni sono attendibili, l’indicazione al loro impiego deve essere data solo nei casi in cui:

- 1. anamnesi positiva per quel farmaco, senza la possibilità di farmaci alternativi;*
- 2. anamnesi negativa, ma con dati a rischio di allergia per il gruppo di appartenenza del farmaco da usare*

In linea massima le cutireazioni vanno eseguite tanto nel momento in cui sia prevista la somministrazione del farmaco”

Approccio Superato !!!!!

ESISTE UN FARMACO ALTERNATIVO CHE SIA ALTRETTANTO EFFICACE?

SI e/o NO

NO

Test di tolleranza
con farmaco alternativo

Negativo

SI utilizzare il farmaco

Esistono test diagnostici affidabili?

SI

Eseguire i test

Positivo

Desensibilizzazione

NO

Test di tolleranza

Negativo

**Continuare
il trattamento**

“ Il pomfo agli antibiotici ovvero la costanza delle cattive abitudini”

Giornal It Allergol Immunol Clin 1998

Senna GE. Crivellaro MA.

Bonadonna P. Dama AR.



Test diagnostici per le reazioni di ipersensibilità IMMEDIATA ai farmaci

Tipo Di reazione	Tipo di test	Fase Acuta	Remissione
Immediata	<i>In vitro</i>	Triptasi sierica Istamina sierica Metilistamina sierica	IgE specifiche BAT LTT
	<i>In vivo</i>		Test cutanei Test di provocazione



Prick test



AZIENDA OSPEDALIERA - ISTITUTI OSPITALIERI DI VERONA
Servizio di Immunopatologia e Trasfusione
Unità Operativa di Allergologia

Nome e Cognome: Bozzi Erika Data di nascita: 20/05/1980

Test cutanei e di tolleranza con Farmaci antiemorroidici

Test cutanei e di tolleranza con Farmaci antiemorroidici	Prick test	Intradermo 1:100	Intradermo 1:100	Intradermo 1:10	Sottocutanea 1:100
Eparina sodica (5000 U/0.2 ml)					
Eparina Calcio (5000 U/0.2 ml)					
Androparina Calcio (5000 U/0.2 ml)					
Polioeparina sodica (5000 U/0.2 ml)					
Polioeparina sodica (5000 U/0.2 ml)					
Pentasa polioeparina (100 mg/ml)					
Fondaparina (2.5 mg/0.5 ml)					

Conclusioni:
Clorfeniramina
Clorfeniramina

VERONA

1990

del 01/10/00

10/10.

Sottocute
Dose
apentica



SERVIZI
OSPEDALIERI
GRUPPO MANUTENCIO





Test Intradermico





TEST CUTANEI

- **Antibiotici BETA-LATTAMICI:**
 - Penicilline
 - Cefalosporine
 - **ANESTETICI GENERALI:**
 - Curarici
 - Narcotici
 - Oppiacei
 - **ANESTETICI LOCALI**
-
- **MEZZI DI CONTRASTO IODATI**
 - **INIBITORI DI POMPA**
 - **STEROIDI SISTEMICI**

POSITION PAPER

Skin test concentrations for systemically administered drugs – an ENDA/EAACI Drug Allergy Interest Group position paper

K. Brockow¹, L. H. Garvey², W. Aberer³, M. Atanaskovic-Markovic⁴, A. Barbaud⁵, M. B. Bilo⁶, A. Bircher⁷, M. Blanca⁸, B. Bonadonna⁹, P. Campi¹⁰, E. Castro¹¹, J. R. Cernadas¹¹, A. M. Chiriac¹², P. Demoly¹², M. Grosber¹, J. Gooi¹³, C. Lombardo⁹, P. M. Mertes¹⁴, H. Mosbech², S. Nasser¹⁵, M. Pagani¹⁶, J. Ring¹, A. Romano¹⁷, K. Scherer⁷, B. Schnyder¹⁸, S. Testi¹⁰, M. Torres⁸, A. Trautmann¹⁹, I. Terreehorst²⁰ on behalf of the ENDA/EAACI Drug Allergy Interest Group

Skin tests are of paramount importance for the evaluation of drug hypersensitivity reactions. Drug skin tests are often not carried out because of lack of concise information on specific test concentrations. The diagnosis of drug allergy is often based on history alone, which is an unreliable indicator of true hypersensitivity. To promote and standardize reproducible skin testing with safe and nonirritant drug concentrations in the clinical practice, the European Network and European Academy of Allergy and Clinical Immunology (EAACI) Interest Group on Drug Allergy has performed a literature search on skin test drug concentration in MEDLINE and EMBASE, reviewed and evaluated the literature in five languages using the GRADE system for quality of evidence and strength of recommendation. Where the literature is poor, we have taken into consideration the collective experience of the group. We recommend drug concentration for skin testing aiming to achieve a specificity of at least 95%. It has been possible to recommend specific drug concentration for betalactam antibiotics, perioperative drugs, heparins, platinum salts and radiocontrast media. For many other drugs, there is insufficient evidence to recommend appropriate drug concentration. There

**Allergy
2013**

“ Natural evaluation of skin test sensitivity in patients allergic to lactam antibiotics ”

(Blanca M et al JACI 1999)

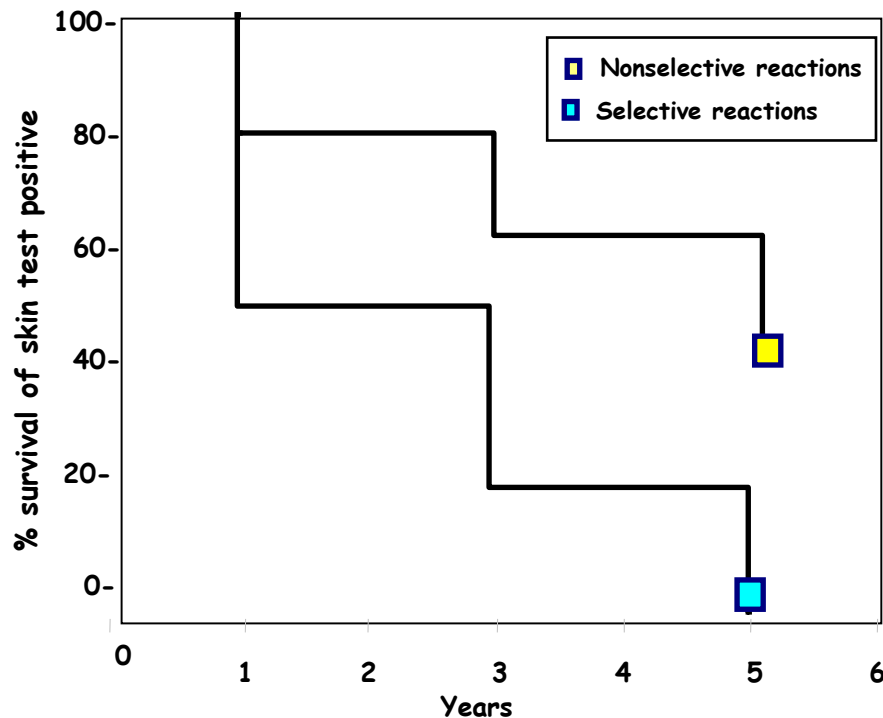
DOPO 5 anni dalla reazione

- **40% delle pos. per PPL-MDM si negativizza**
- **100% delle pos. per Amoxicillina si negativizza**

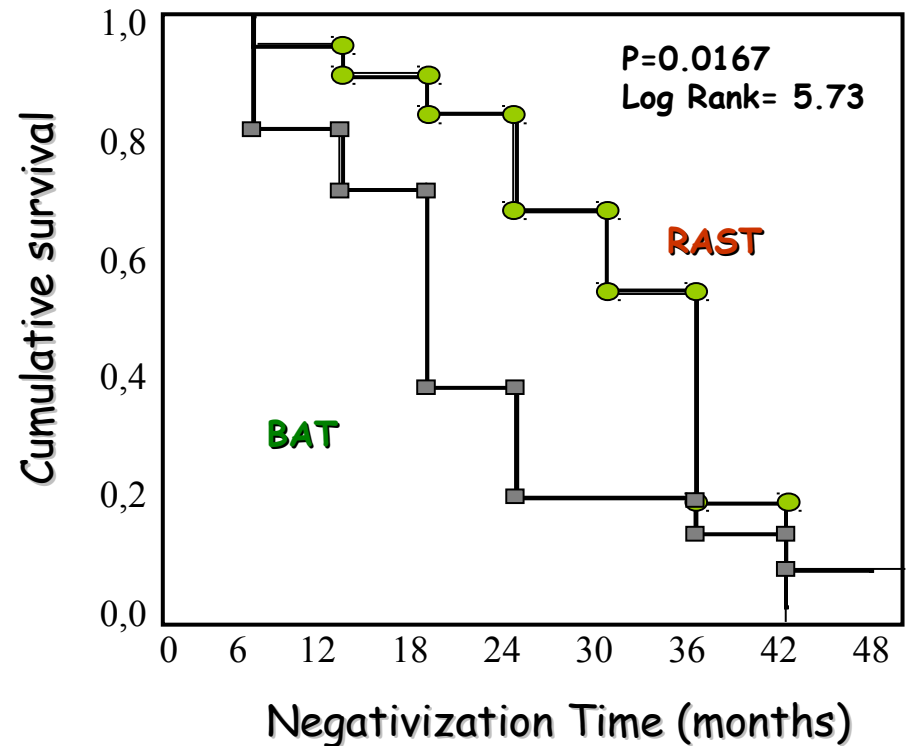
I test vanno eseguiti prima possibile !!!

(Rispettando però il Periodo Refrattario: 15 gg circa)

SKIN TEST, IgEs and BAT SENSITIVITY OVER TIME



Blanca M, et al, JACI 1999



Fernández TD, et al. Clin Exp Allergy 2008

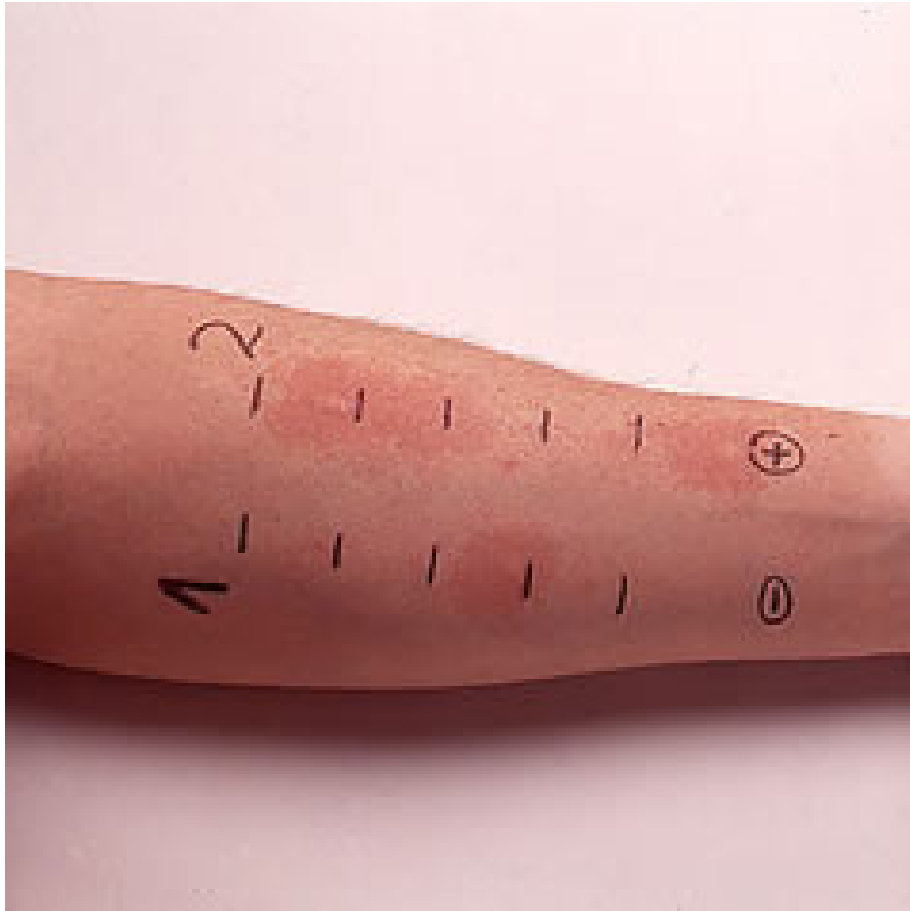
with permission of MJ Torres

REAZIONI RITARDATE

Test in VIVO



TEST CUTANEI per Reazioni Ritardate



Lettura Ritardata dei test Intradermici

**Dopo 48/ 72 h dall'esecuzione
del test cutaneo**



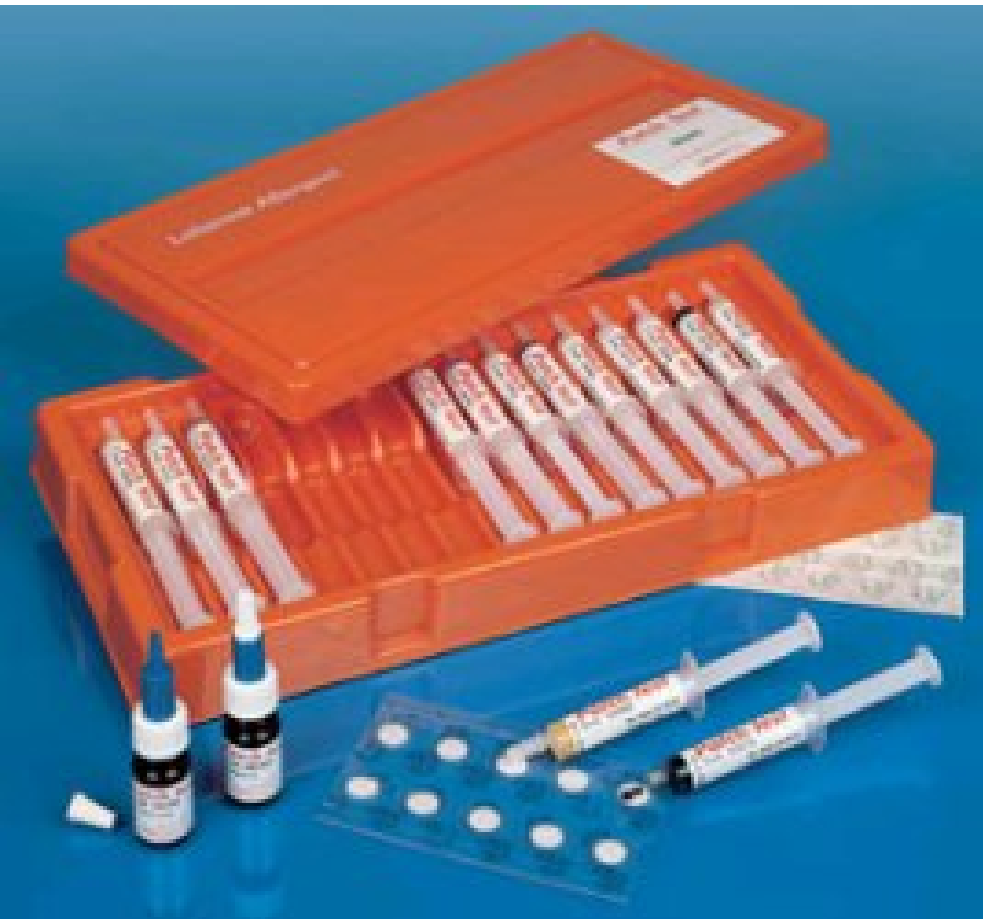


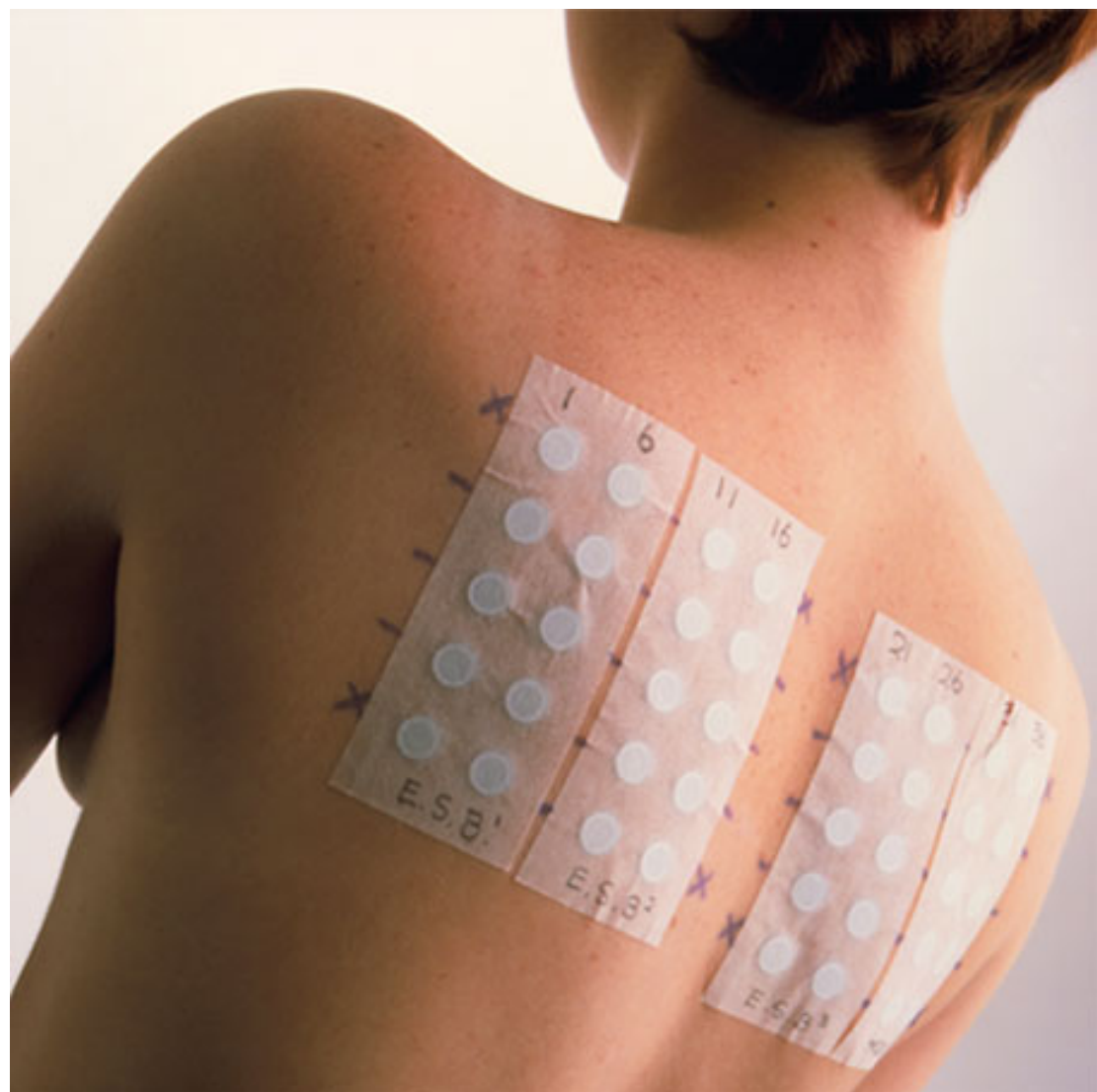
11A
PEN
110

11B
PEN
110

11C
PEN
110

Patch test

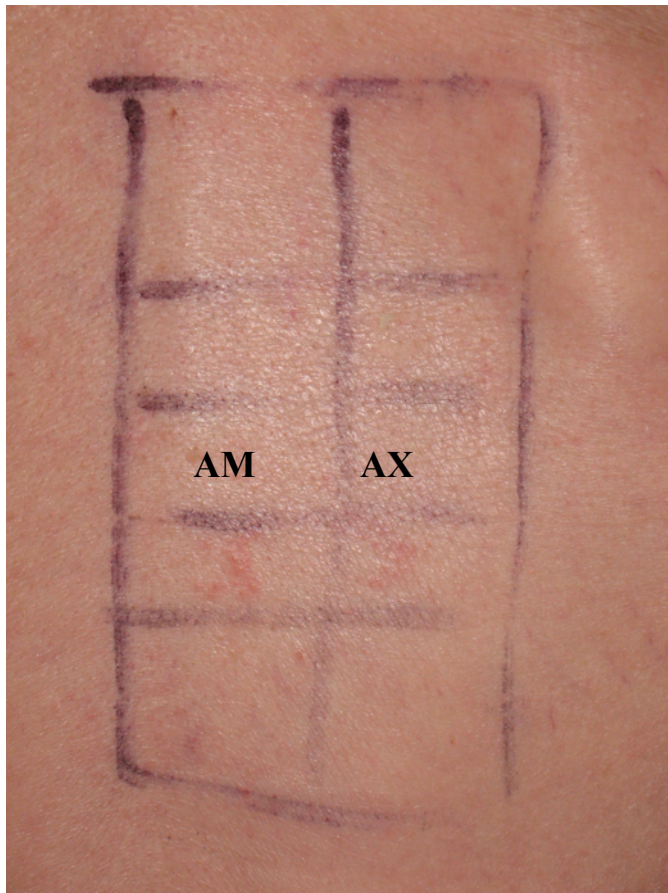




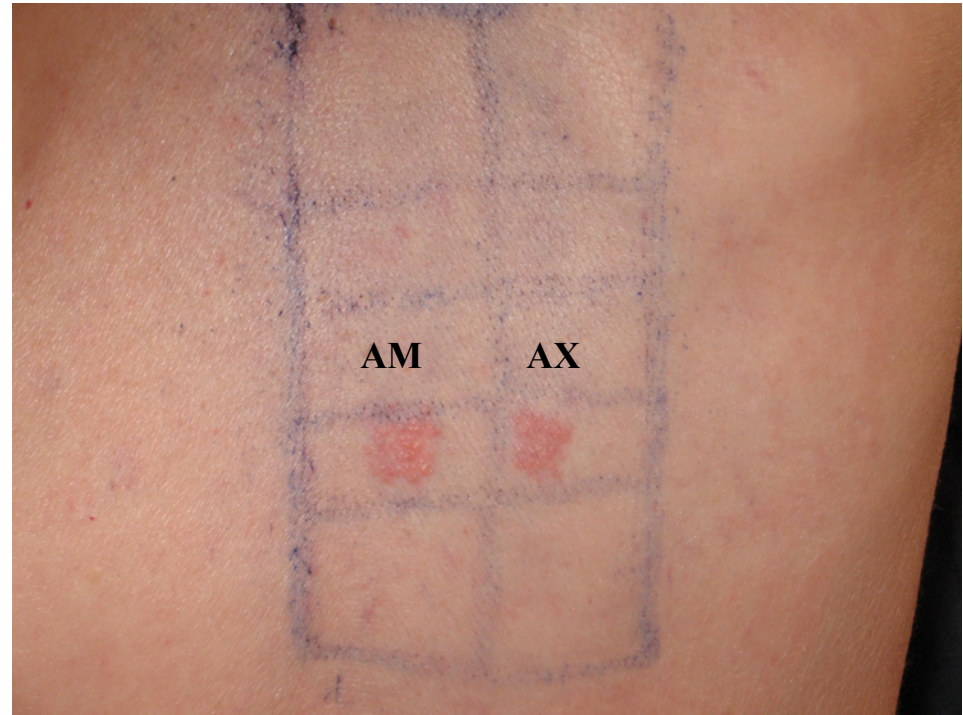


Patch test Results

Reading at 72 hours (D3)



Reading after 2 days (D5) of removal



Apteni disponibili

➤ patch test :

Antibiotici

Corticosteroidi

AMPICILLINA

AMOXICILLINA

PENICILLINA G

KANAMICINA

CEFALOTINA

CEFUROXIME

CEFAZOLINA

ERITROMICINA

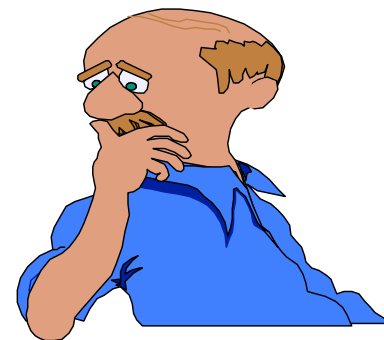
NEOMICINA

Anestetici Locali

➤ ID a lettura ritardata dei farmaci testati



TEST IN VITRO



Reazione

Test

Fase acuta

Fase di remissione

Immediata

In vitro

Triptasi sierica
Istamina sierica
Metilistamina urinaria

IgE specifiche
Sieriche
BAT
LTT

Test in VITRO



Determinazione IgE specifiche

Farmaci come apteni

Penicilline:

- penicillolyl G
- penicilloyl V
- Amoxicillina
- Ampicillina

Cefalosporine:

- Cefaclor

Farmaci come Ag completi

- Gelatina
- Succinilcolina
- ACTH
- Protamina
- Tetano tossoide
- Chimopapaina
- Insulina (bovina, porcina, umana)
- **Morfina**
- **Clorexidina**

Test di provocazione con farmaci = Graded Challenge

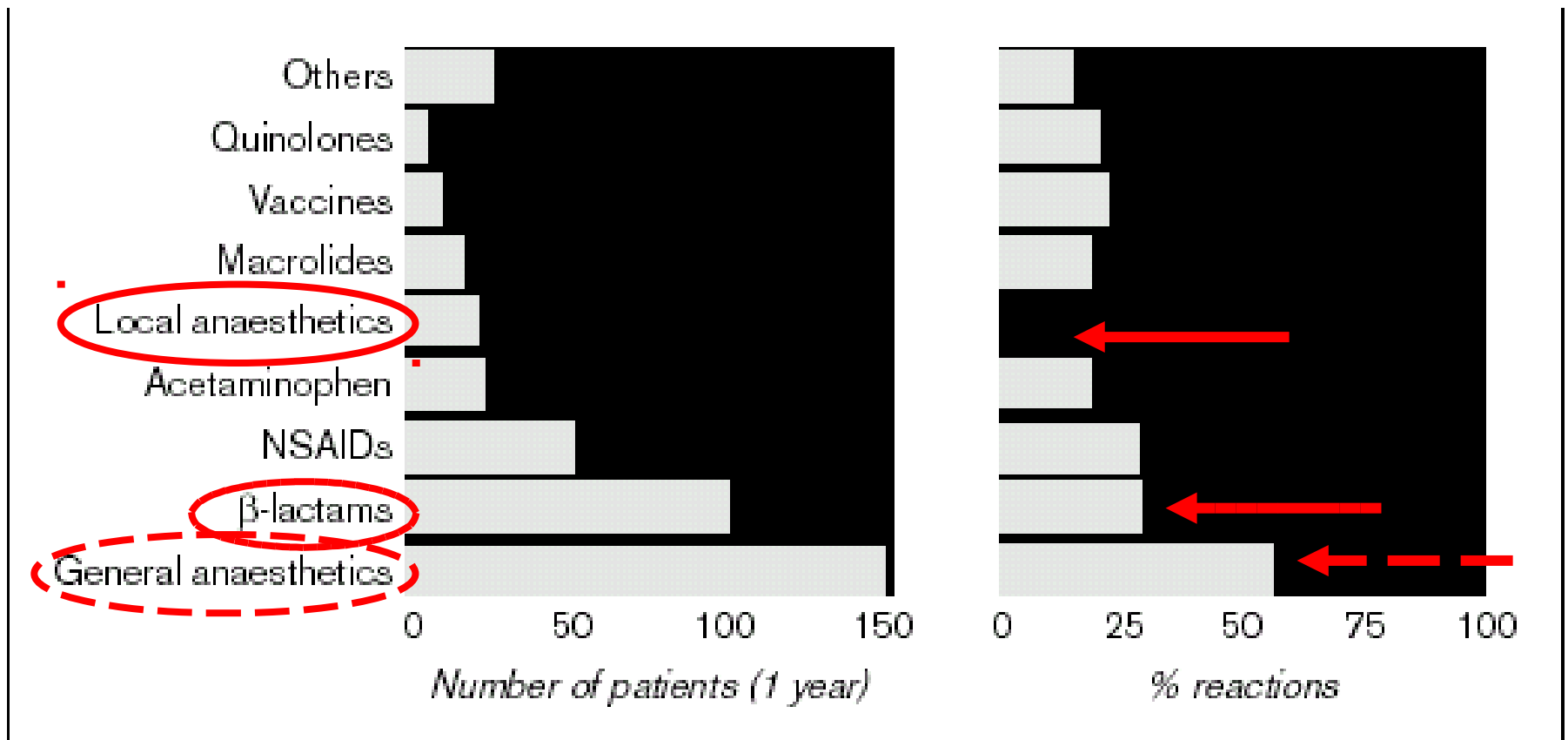


- Un test di provocazione con farmaci è la somministrazione controllata del farmaco ad un paziente con una storia suggestiva di allergia a farmaci

Test di provocazione con farmaci

Può essere fatto a scopo :

- 1) **Diagnostico** : per verificare la responsabilità di quel farmaco (si somministra il farmaco responsabile)
- 2) **Terapeutico** : per trovare un farmaco alternativo (si somministra un farmaco diverso da quello che ha scatenato la reazione)



442 subjects with history of ADR

↳ **Underwent skin test and provocation tests**

40% YES DHR

60% NO DHR

"Nocebo Effect"

"Occurrence of troublesome symptoms after the administration of inert substances: Placebo"



→ Affects up to **30% of patients**

→ Prevalence significantly higher in **women** than in men

→ **Subjective** symptoms but also objective!

Evaluation of the nocebo effect during oral challenge in patients with adverse drug reactions

Gennaro Liccardi^a, Gianenrico Senna^b, Maria Russo^a,
Patrizia Bonadonna^b, Mariangiola Crivellaro, Annarita Dama^b,
Maria D'Amato^a, Gennaro D'Amato^a, Giorgio Walter Canonica^c,
Giovanni Passalacqua^c



J Invest Allergol Clin Immunol 2003; Vol. 14(4)



Demographic and Clinical Data

VR	NA	GE	total	
Patients	200	200	200	600
Age range	9/69 yrs	7/76 yrs	15/72 yrs	7/76 yrs
Male/	75/125	46/151	58/142	182/418
Female				
Pt reacting to placebo	54(27%)	60(30%)	48(24%)	162 (27%)
M/F	22/32	9/51	7/41	38/124
of pt reacting to placebo				19%/30%

				VR	NA	GE	tot
Itching				14	23	18	55
Nausea/vomiting abdominal pain				13	11 8		32
Headache				5	0	4	9
Dyspnea/cough				6	5 3		14
Hypotension/ tachycardia				1	1	4	6
Erytema,rash Urticaria				11	12	7	30
Other				4	8 4	16	
Total				54	6048	162	

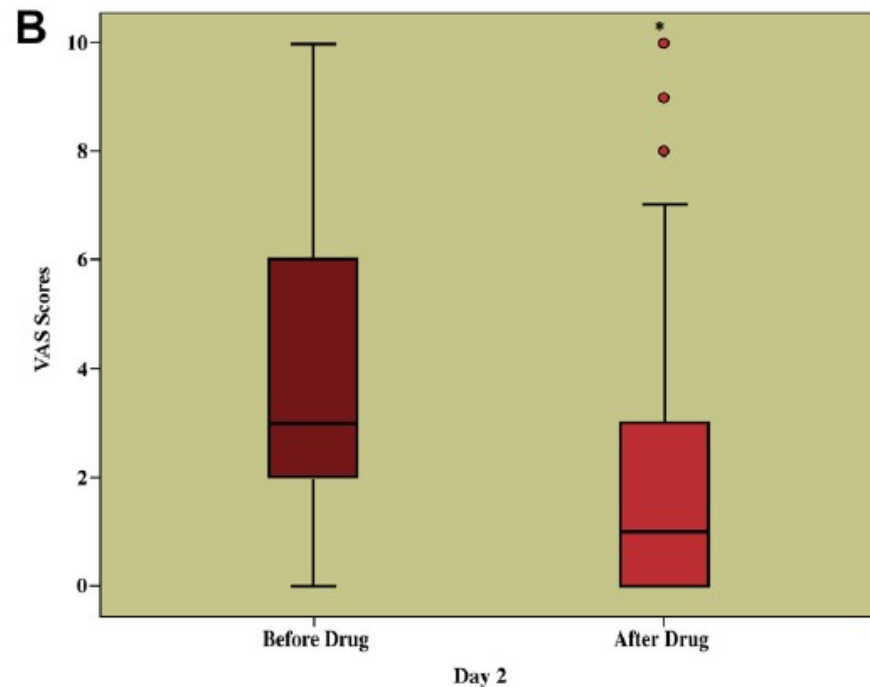
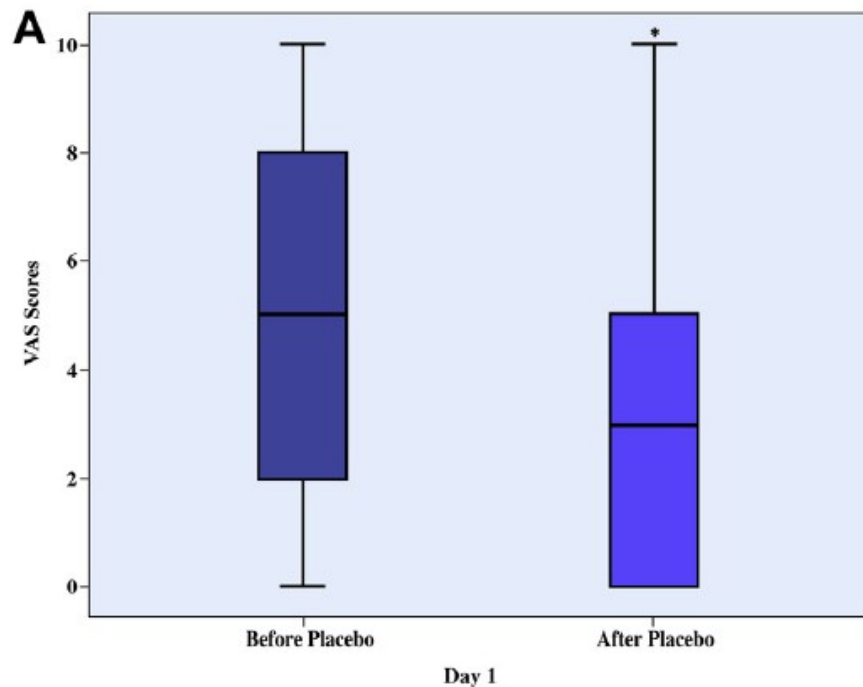
Evaluation of drug provocation test–related anxiety in patients with drug hypersensitivity

Şadan Soyyiğit, MD*; Ömür Aydın, MD*; İnsu Yılmaz, MD*; Seçil Kepil Özdemir, MD*;
Vesile Şentürk Cankorur, MD†; Cem Atbaşoğlu, MD†; Gülfem Elif Çelik, MD*

Ann Allergy Asthma Immunol 117 (2016) 280-284



- **Patients who were allergic to drugs had more psychiatric disorders symptoms, such as hysteria, depression, anxiety, and somatization, than patients with allergic rhinitis and asthma**
- **Most drug allergic patients had high anxiety levels before DPTs. Fear of the recurrence of previous reactions was the main cause of this anxiety**



- Anxiety scores significantly decreased each day after a negative test result
- The anxiety related to the active drug test day was lower than on the placebo day.
- Patients feel more confident about the tests after a negative test result and feel less anxiety

In all patients a "Single Blind PLACEBO-controlled Provocation Test" should be done before an "active" DPT

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