

XXXI CONGRESO
INTERNACIONAL



XXXI CONGRESO INTERNACIONAL **SCAI 2025** SOCIEDAD CHILENA DE ALERGIA E INMUNOLOGIA

A watercolor-style illustration of a town with a large mountain in the background. The town features several buildings with red-tiled roofs and two prominent churches with domes. The mountain is depicted with soft, blended colors, suggesting snow or a misty atmosphere. The overall scene is peaceful and scenic.

Desetiquetando la alergia a Betalactámicos

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Conflicto de interés

- No presento conflicto de intereses.



Hoja de Ruta

- Generalidades de los Betalactámicos.
- Prevalencia de la alergia a Betalactámicos.
- Repercusiones negativas del etiquetado de alergia a Betalactámicos.
- Desetiquetado de la alergia a Betalactámicos.
- Algoritmo diagnóstico de la alergia a Betalactámicos.
- Desafíos a futuro.



Betalactámicos

2. Betalactámicos:

A. Penicilinas:

- Bencilpenicilinas: bencilpenicilina (penicilina G); fenoximetilpenicilina (penicilina V).
- Isoxazolilpenicilinas: cloxacilina
- Aminopenicilinas: amoxicilina; ampicilina.
- Ureidopenicilinas: piperacilina.

B. Cefalosporinas:

- 1ª generación: cefadroxilo, cefalexina, cefazolina sódica.
- 2ª generación: cefaclor, cefuroxima, cefonicida, cefoxitina, cefminox.
- 3ª generación: cefixima, cefpodoxima proxetilo, cefditoreno pivoxilo, cefotaxima, ceftazidima, ceftriaxona.
- 4ª generación: cefepima.
- 5ª generación: ceftarolina fosami, ceftobiprole medocaril, ceftolozano.

C. Monobactámicos: aztreonam.

D. Carbapenemes: imipenem, meropenem, ertapenem.

E. Inhibidores de las beta-lactamasas (entre paréntesis el betalactámico al que se asocia): (amoxicilina)/ácido clavulánico; (ampicilina)/sulbactam; (piperacilina)/tazobactam; (ceftazidima)/avibactam; (ceftolozano)/tazobactam.



Betalactámicos

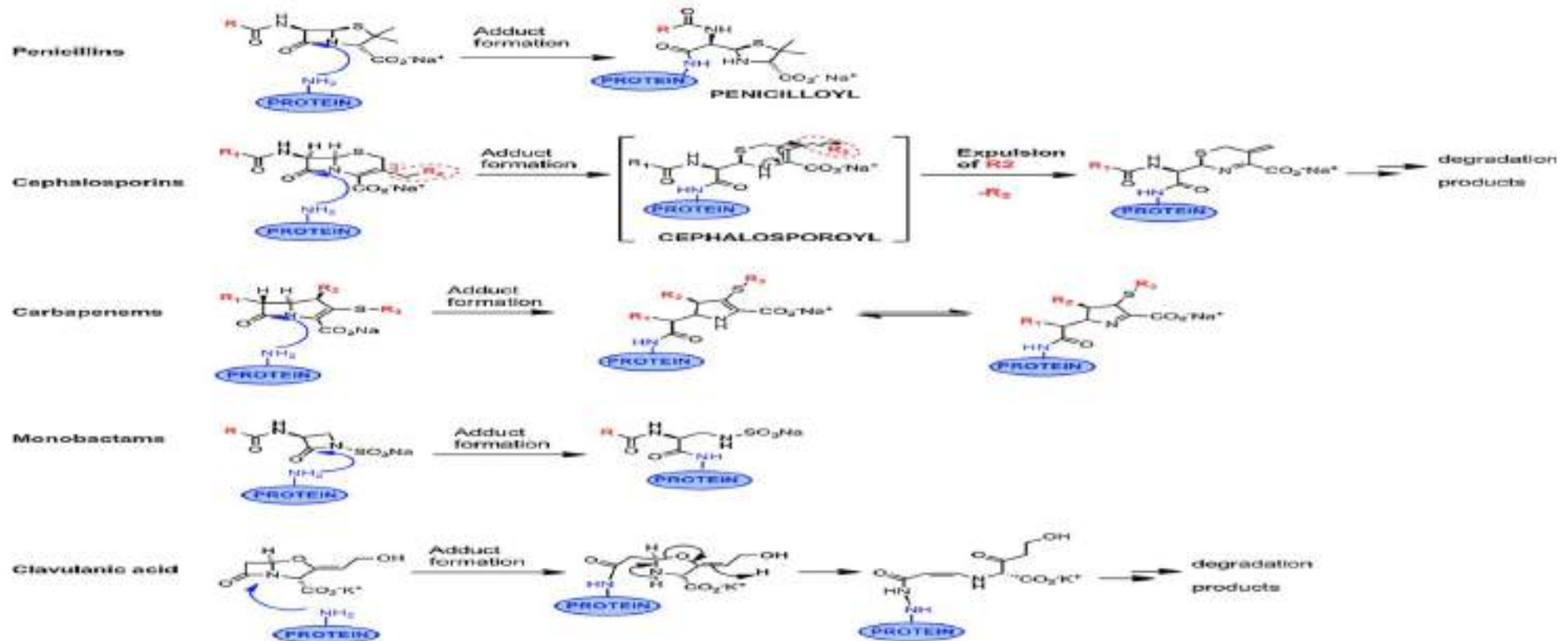


Fig. 2. Conjugation mechanisms for BLs with proteins.

Clasificación de reacciones adversas a fármacos

A		CLASSIFICATION	EXAMPLE	MECHANISM	SYMPTOMS
		OVERDOSE/TOXICITY	Beta-blocker bradycardia	Blockade of the beta-receptors of the adrenergic system.	Bradycardia
• Predictable	• Related drug characteristics	SIDE AND COLLATERAL EFFECTS	C. Difficile associated pseudomembranous colitis	Overgrowth of Clostridioides difficile bacteria because the normal bacterial flora of the intestine has been altered.	Watery diarrhea / Cramps, pain in the abdomen / fever / pus or mucus in stools / nausea / dehydration
		INTERACTIONS	Theophylline-Cimetidine	Non-selective inhibition of Cyt-P450 / reduces renal clearance	Stomach pain / diarrhoea / headache / restlessness / irritability

B		GELL and COOMBS CLASSIFICATION	TYPE OF IMMUNE RESPONSE	MECHANISM	SYMPTOMS
		TYPE I	IgE-specific (allergic)	Mast/Ba cell activation-degranulation	C' / IgG / MRGPR2
• Unpredictable	• Susceptible subjects	TYPE II	Cytotoxic antibodies	IgG / FcReceptor	Blood cell dyscrasia
		TYPE III	Ag-Ab immune-complex deposition	C' / IgG / FcReceptor	Vasculitis
TYPE IV	T cell specific (allergic)	IVa. Th1 (Monocytes) IVb. Th2 (Eosinophils) IVc. Cytotoxic lymphocytes (CD4/CD8) IVd. T cells (Neutrophils)	Eczema DRSS / Exanthema (maculopapular and bullous) SIS/TEN / Eczema / Exanthema (maculopapular, bullous, pustular) Pustular exanthema		

Figure 1. Classification of hypersensitivity reactions to antibiotics.

Prevalencia de la Alergia a Betalactámicos

- Principal familia de medicamentos involucrados en las alergias a fármacos.
 - Inicialmente las Bencilpenicilinas eran los principales fármacos involucrados, actualmente son las Aminopenicilinas y Cefalosporinas.
- Existe una variabilidad geográfica del Betalactámico más involucrado:
 - En **España e Italia** se utiliza ampliamente la combinación Amoxicilina/Acido Clavulánico, esto ha aumentado la reacción a éste fármaco en desmedro de la Amoxicilina.
 - En **USA** las Cefalosporinas son una fuente importante de sensibilización a Betalactámicos.
 - En **América Latina** la prevalencia de la alergia a Betalactámicos es de 13,8%.
 - Amoxicilina es una causa frecuente de anafilaxia inducida por drogas en niños, adultos y tercera edad.



Prevalencia de la Alergia a Betalactámicos



- La prevalencia de la alergia a Betalactámicos reportada es de 5-10% en la población general y de 10-25% en pacientes hospitalizados.
- El 75% de las etiquetas de la alergia a Penicilina se obtiene antes de los 3 años.
- 1-2% de las etiquetas de alergia a Cefalosporinas se desetiquetan. Mas del 90% de los pacientes con antecedente de alergia a betalactámicos son desetiquetados luego de una evaluación alérgica (niños y adultos) las
- 0,37-3,7% de la población refiere ser alérgico a los Carbapenémicos.

Repercusiones negativas de portar etiqueta de alergia a Betalactámicos



Factor	Increased Risk to Patient
<i>Clostridioides difficile</i>	23% inpatient ¹⁷ 26% outpatient ¹⁹
MRSA infection	14% inpatient ¹⁷ 69% outpatient ¹⁹
VRE infection	30% inpatient ¹⁷
Length of stay	0.59 d ¹⁷
Surgical site infection	50% ¹⁸
Increased risk of death	14% ²⁰
Death during hospitalization	1.6 (crude OR 1.56, 95% CI 1.20–2.04)

En suma...

Label Acquisition



- 75% of penicillin allergy labels acquired in childhood by age 3
- Most labels are inaccurate

Labels Persist and Grow in Significance



- 8-25% of adults with penicillin allergy label
- Less than 5% of labeled are actually allergic
- Even true allergy may fade over time
- Label can become a greater liability than the risk of reaction

Consequences of a Label



- Pressure prescribing of 2nd and 3rd line antimicrobials
- Increased inappropriate antibiotic selection
- Increased mortality risk during cancer and infection treatment
- Delay the onset of appropriate antimicrobial therapy
- Increase treatment failures/ surgical infections
- Associated increase in multidrug resistant infections
- Longer lengths of stay
- Higher healthcare costs

Testing/Removal of Unnecessary Labels



- Cost-effective
- Patient reassured on safety
- Reduced expenses
- Avoidance of bad outcomes: treatment failures, surgical infections, multidrug resistant infections

Fundamental para perfeccionar el Programa de optimización del uso de antimicrobianos

Desetiquetando la alergia a Betalactámicos.

- Controversias :

- ¿Deberíamos cambiar la forma en la que evaluamos a los pacientes con alergia a los Betalactámicos?

Estas preguntas han llevado a revisar las directrices y algoritmos de estudio, así como la necesidad de estandarizar los protocolos para el diagnóstico de la hipersensibilidad a los Betalactámicos.

- Para qué se debe realizar un TPO indirecto y cuándo realizarse independientemente del riesgo de alergia verdadera? o ¿Debería solo realizarse un TPO directo en casos de bajo riesgo de alergia verdadera?

¿Deberíamos cambiar la forma en la que evaluamos a los pacientes con historia de alergia a los Betalactámicos?



The Challenge of De-labeling Penicillin Allergy

Cosby A. Stone Jr., MD, MPH¹, Jason Trubiano, MBBS^{2,3,4,5,6}, David T. Coleman, MD¹,
Christine R.F. Rukasin, MD¹, Elizabeth J. Phillips, MD^{1,2,3,4,5,6}

Approaches to minimize (or prevent) penicillin allergy labels in an ambulatory setting

Approach	De-labeling Approach	Strengths	Limitations	Level of Recommendation and Evidence
Select an alternative antibiotic ^{20,17,18,19}	No	<ul style="list-style-type: none"> No risk of provoking penicillin reactions in the individual patient 	<ul style="list-style-type: none"> Alternative antibiotics may be less effective than penicillin Adverse effects from 2nd and 3rd line antibiotics May promote drug resistance over time Does not provide any information on whether the patient can actually take the drug safely Increased cost to patient and healthcare system 	2c, benefits of using alternative agents are unclear, and there are clearly known adverse effects reported across high quality clinical studies. Would suggest use of other approaches
Desensitization at point of care ^{20,21}	No	<ul style="list-style-type: none"> Patient can typically receive the drug that is needed at the point of care safely 	<ul style="list-style-type: none"> Expensive, time and resource intensive, especially for patients with frequent antibiotic utilization (e.g. chronic disease, cancer, transplant suppression) Does not provide any information on whether the patient can actually take the drug safely The majority of patients were not allergic to begin with and there is limited data examining post-desensitization testing to validate need for desensitization 	2c, for select patient populations (see text) but not recommended for general population
De-label using history alone ^{22,23}	Yes	<ul style="list-style-type: none"> Many reactions are easily identified as incompatible with true allergy 	<ul style="list-style-type: none"> The risk of many histories has not yet been validated Possibility for faulty assessment or mistakes Patients may still be fearful to take the drug without objective testing Higher probability of immediate reaction when challenged in the future 	2c, randomized clinical trials of this approach are lacking but observational clinical studies have been performed showing benefit. Currently limited by unclear knowledge of when to use this approach

Approach	De-labeling Approach	Strengths	Limitations	Level of Recommendation and Evidence
De-label using direct ingestion challenge ^{24,25,26,27}	Yes	<ul style="list-style-type: none"> Safe testing approach in patients who are at low risk of immediate hypersensitivity Most patients are low risk of true allergy Provides definitive answer on whether the patient is at risk of immediate reaction Lean resources used to provide an answer 	<ul style="list-style-type: none"> Least conservative approach Some patients may have reactions during testing 	2c, observational studies have been performed particularly in children showing benefit. Currently limited by unclear knowledge of when to use this approach and lack of large studies in adults
De-label using skin testing alone ^{28,29,30,31}	Yes	<ul style="list-style-type: none"> Negative skin testing using appropriate protocols reduces the patient probability that a patient will react when challenged 	<ul style="list-style-type: none"> No skin testing strategy has 100% negative predictive value Epidemiology of penicillin allergy has changed with changing patterns of parental beta lactam use Inadequate to determine true cross-reactivity patterns Future challenge might not be performed in a timely manner 	2c, randomized clinical trials of this approach are lacking but clinical studies have been performed showing benefit.
De-label using skin testing followed by ingestion challenge ^{32,33,34,35}	Yes	<ul style="list-style-type: none"> Most conservative approach Greater reduction in probability of reaction prior to oral challenge Provides definitive answer on whether the patient is at risk of immediate reaction 	<ul style="list-style-type: none"> Greatest testing costs (still cost effective compared to maintaining penicillin allergy label) Time and resource intensive Shortage of resources to perform the volume of penicillin skin testing that is currently needed 	2b, absence of randomized double blind clinical trials of this approach, but a large body of historical evidence including large prospective cohort studies for its use as the current gold standard approach
Risk stratifying approach ^{36,37,38,39,40}	Yes	<ul style="list-style-type: none"> Assesses individual patient's history to determine penicillin allergy testing strategy Low risk patients targeted for direct oral challenge Higher risk patients for proceeding skin testing 	<ul style="list-style-type: none"> Most complex Need for validated risk assessment tools and decision support that have generalizability in different populations 	2c, randomized clinical trials of this combination approach are lacking but clinical and quasi-experimental design studies have been performed showing benefit. Possibility for this approach to become a new gold standard



El proceso diagnóstico de la alergia a Betalactámicos es complejo, largo, no exento de riesgos y costoso, lo que dificulta las estrategias de desetiquetado.



Si, deberíamos cambiar la estrategia de evaluación de los pacientes alérgicos a betalactámicos.

¿Deberían realizarse pruebas cutáneas en todos los casos sospechosos de alergia a Betalactámicos, independientemente del riesgo de alergia verdadera?

O

¿Sólo debería realizarse el test de provocación oral directo en casos de bajo riesgo de alergia verdadera a la Betalactámicos?



- Gran prevalencia de las etiquetas de alergia, pero baja prevalencia de alergia **real** a Los Betalactámicos.
- Las pruebas cutáneas (PC) tienen una sensibilidad y especificidad de 30% y 97% respectivamente, su rendimiento dependerá de la probabilidad pre test de que el paciente sea realmente alérgico.
 - Los falsos positivos son más probables cuando se realizan PC en pacientes con menores probabilidades pre test de una alergia verdadera (grupo de bajo riesgo).



Si, es posible realizar TPO directo, sin pruebas cutáneas, a un grupo seleccionado de pacientes alérgicos a Betalactámicos.

A pesar de las controversias para estratificar a los pacientes de bajo riesgo, la evidencia reciente apoya las estrategias de desetiquetado rápido.

TPO directo ha demostrado ser seguro y eficaz, pudiendo desetiquetar entre el 85 % y el 100 % de los casos de bajo riesgo.

Tasas de reacciones adversas post TPO directo reportadas varían entre el 1% y el 6%, la mayoría leves.

Las estrategias de desetiquetado adecuado a Betalactámicos son fundamentales para los programas de optimización de uso de antimicrobianos.

Estratificación de riesgo:
Variabilidad en definiciones de
paciente bajo riesgo a nivel
internacional.

- **TPO directo ... ¿A quienes?**

- **Historia clínica** completa con detalles de la morfología de la reacción, relación temporal con fármaco índice, otros fármacos involucrados, tolerancia previa o posterior del fármaco índice, presencia de factores de riesgo, tratamiento necesario para tratar la reacción.

- **Estratificación** riesgos.

- **Determinar conducta:** desetiquetado sólo por historia clínica (20% de los casos), TPO directo o mayor estudio.

Desetiquetando la alergia a betalactámicos...

En qué estamos?

Actualmente las herramientas para estratificar el riesgo y los algoritmos de manejo son muy heterogéneos.

Se necesita un enfoque validado y aceptado a nivel universal de algoritmos de manejo de pacientes alérgicos a los Betalactámicos.



as adjunctive tests to support drug causality.

Beta-lactams

CBS 4	We recommend that a proactive effort should be made to delabel patients with reported penicillin allergy, if appropriate.	Strong	Moderate
CBS 5	We recommend against any testing in patients with a history inconsistent with penicillin allergy (such as headache, family history of penicillin allergy, or diarrhea), but a 1-step amoxicillin challenge may be offered to patients who are anxious or request additional reassurance to accept the removal of a penicillin allergy label.	Strong	Low
CBS 6	We suggest penicillin skin testing for patients with a history of anaphylaxis or a recent reaction suspected to be IgE-mediated.	Conditional	Low
CBS 7	We recommend against the routine use of multiple-day challenges in the evaluation of penicillin allergy.	Strong	Low
CBS 8	We recommend against penicillin skin testing prior to direct amoxicillin challenge in pediatric patients with a history of benign cutaneous reaction (such as MDE and urticaria).	Strong	Moderate
CBS 9	We suggest that direct amoxicillin challenge be considered in adults with a history of distant (ie, >5 years ago) and benign cutaneous reactions (such as MDE and urticaria).	Conditional	Low
CBS 10	We suggest that for patients with a history of nonanaphylactic cephalosporin allergy, direct challenges (without prior skin test) to cephalosporins with dissimilar side chains be performed to determine tolerance.	Conditional	Moderate
CBS 11	We suggest that for patients with a history of anaphylaxis to a cephalosporin, a negative cephalosporin skin test should be confirmed prior to administration of a parenteral cephalosporin with a nonidentical R1 side chain.	Conditional	Low
CBS 12	We suggest that for patients with a history of anaphylaxis to a penicillin, a structurally dissimilar R1 side chain cephalosporin can be administered without testing or additional precautions.	Conditional	Moderate
CBS 13	We suggest that for patients with a history of an unverified (not confirmed) nonanaphylactic penicillin allergy, a cephalosporin can be administered without testing or additional precautions.	Conditional	Moderate
CBS 14	We suggest that in patients with a history of an unverified nonanaphylactic cephalosporin allergy, a penicillin can be administered without testing or additional precautions.	Conditional	Low
CBS 15	We suggest that in patients with a history of anaphylaxis to cephalosporins, penicillin skin testing and drug challenge should be performed prior to administration of a penicillin therapy.	Conditional	Low
CBS 16	We suggest against penicillin skin testing in patients with a history of nonanaphylactic cephalosporin allergy prior to administration of a penicillin therapy.	Conditional	Low
CBS 17	We suggest that in patients with a history of penicillin or cephalosporin allergy, a carbapenem may be administered without testing or additional precautions.	Conditional	Moderate
CBS 18	We suggest that in patients with a history of penicillin or cephalosporin allergy, aztreonam may be administered without prior testing unless there is a history of sulfadiazine allergy.	Conditional	Moderate
CBS 19	We recommend that allergist-immunologists collaborate with hospitals and health care systems to implement beta-lactam allergy pathways to improve antibiotic stewardship.	Strong	Moderate

Practice Guideline > J Allergy Clin Immunol. 2022 Dec;150(6):1302-1318.

doi: 10.1016/j.jaci.2022.08.028. Epub 2022 Sep 17.

Drug allergy: A 2022 practice parameter update

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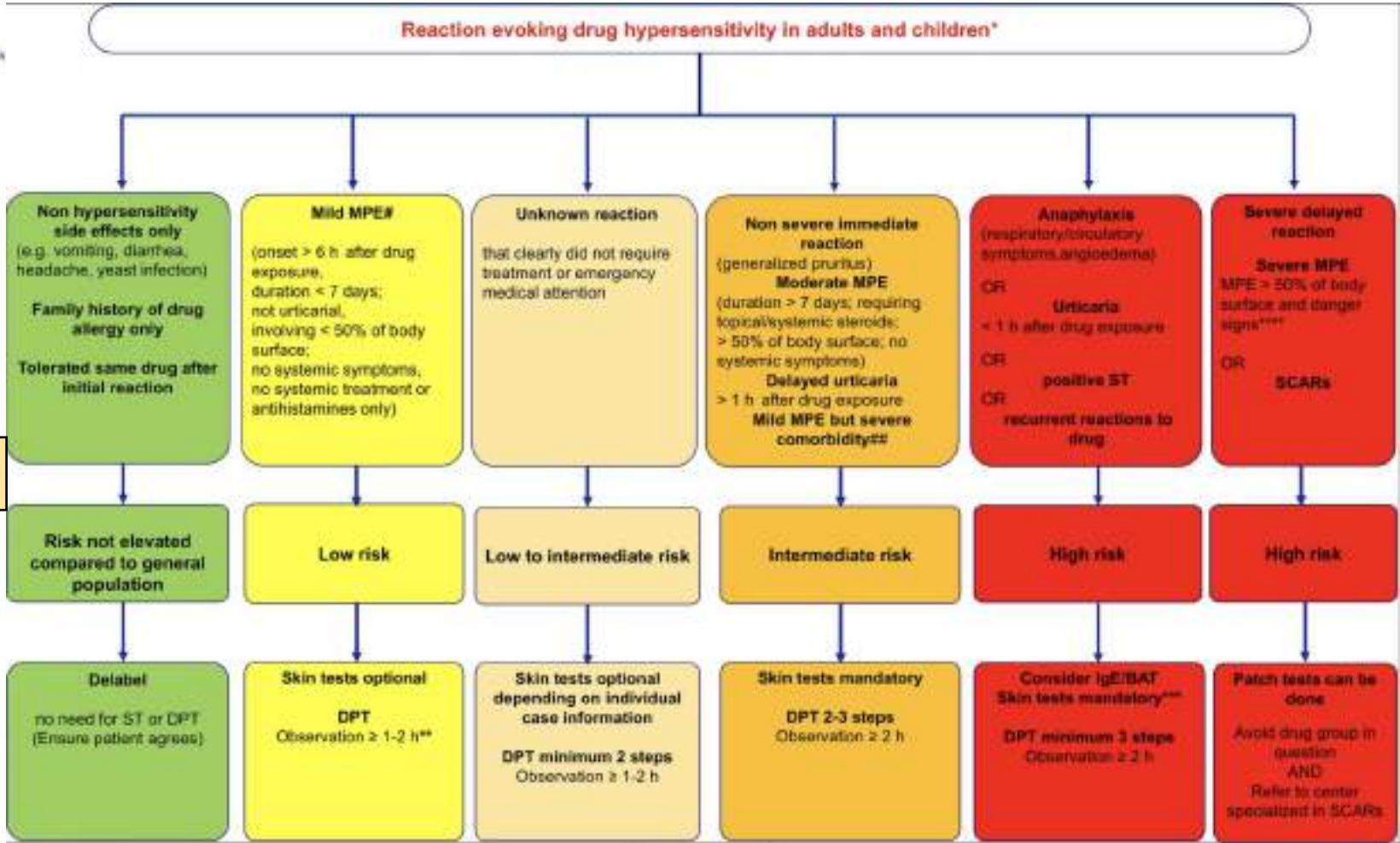


EAACI/ENDA position paper on drug provocation testing

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TABLE 3 Risk stratification and recommendations regarding skin testing and drug provocation tests (DPT) according to risk profile

Definition of patient risk profiles	Recommendations regarding skin testing and DPT
Non-hypersensitivity reactions Well-known non-allergic adverse drug effects: full dose of same drug tolerated after initial reaction; allergy is only suspected in a close relative	Delabeling without skin testing or DPT
Immediate hypersensitivity reactions High-risk patient profile: symptoms: anaphylaxis, hypotension, laryngeal edema, bronchospasm; or time to <math>< 1\text{ h}</math> of drug exposure and/or angioedema, generalized flushing/urticaria Intermediate-risk patient profile: for example, generalized pruritus	Min testing, and if available in vitro testing, must be performed DPT should only be considered if testing is negative Skin testing must be performed before DPT
Non-immediate hypersensitivity reactions Severe cutaneous adverse drug reactions (SCARs): Stevens-Johnson syndrome (SJS), toxic epidermal necrolysis (TEN), DRESS, acute generalized exanthematous pustulosis (AGEP), generalized bullous fixed drug eruption	In SCARs, drug patch tests can be done, and in DRESS, skin tests have to be discussed case by case by highly specialized teams
Non-SCARs : systemic vasculitis, fixed drug eruption, dermatitis, specific drug-induced organ failure (e.g., hepatic, renal, pulmonary) or drug-induced autoimmune diseases	Min testing must be performed before DPT
Intermediate-risk patient profile examples: • moderate DPT (step 1) or requiring topical high-potency corticosteroids, > 50% of body surface, without systemic symptoms and without danger signs (Figures 1) • delayed urticaria with onset > 1 h after drug exposure	Min testing is optional before DPT depending on individual case information
Low-risk patient profile examples: an urticaria that is not urticarial, with onset > 1 h after drug intake, involving less than 50% of the body surface, of <math>< 7\text{ days}</math> duration, without danger signs (see text), lymphadenopathy, systemic involvement, lichen, mucosal involvement or morbilliform, not requiring hospitalization or systemic treatment other than antihistamines	Min testing is optional before DPT depending on individual case information
Unknown reaction Low-intermediate risk	Skin testing is optional before DPT depending on individual case information



How to Define and Manage Low-Risk Drug Allergy Labels

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Drug	Prevalence of Low-Risk Phenotype	Low risk definition	Assessment tools	Approach to low-risk	Required resources	Cross-reactivity concerns
Penicillin	Critical care: 29% ¹⁰ Ambulatory: 15% 4th-75% ¹¹ Nascent: 40% ¹²		Consensus-based algorithm ¹³ PEN-FAST ¹⁴ AAAT ^{15,16} Urinary 1-1-1 criterion ¹⁷	1-step drug challenge	Drug Allergy History - Staff education/training - Standard history form - Clinical decision support - Evaluation protocols (Drug Challenge)	Similar RT chains (aminopenicillins and aminocephalosporins) ¹⁸

- Dependiendo de la definición utilizada, el paciente de bajo riesgo da cuenta del 29 al 70% de los etiquetados de alergia a Penicilina.
- Dependiendo de la herramienta utilizadas S 71-92%, E 61-94% VPN varia entre 80-98%

Penicillin allergy risk assessment tools

Author/country	Primary derivation	User group	Population	Assessment outcomes	Sensitivity (%)	Specificity (%)	NPV (%)	PPV (%)	External validation or meta	Special populations
Sabatini et al 2021 (Europe) ¹⁹	Retrospective-multivariable logistic regression	Allergists	N = 410	1-1-1 criterion CI: tetracortical eruption within the first hour and after the first dose	85	85	80	90	n/a	n/a
Sorenson et al 2020 (AUS) ²⁰	Retrospective-multivariable logistic regression	Allergists	N = 447	Low-risk criteria: non-SCAR rash or rash without angioedema and	80	61	97	n/a	n/a	n/a
Trubiano et al 2020 (AUS/US) ²¹	Prospective data-multivariable logistic regression	Clinicians	N = 622 (primary validation) N = 945 (external validation)	3-point clinical criteria (maximum score 5) Low/moderate/high Low-risk criteria: PEN-FAST score <3	71	70	96	25	USA/Canada/Australia ²² France ²³ (retrospective)	n/a
Morono et al 2020 (Spain) ²⁴	Retrospective (R) logistic regression prospective (P) data	Clinicians	N = 656 (R) N = 615 (P)	Artificial neural network (ANN) ²⁵	90 (R) 81 (P)	86 (R) 96 (P)	92 (R) 95 (P)	82 (R) 91 (P)	n/a	n/a
Siew et al 2019 (UK) ²⁶	Retrospective-multivariable logistic regression	Allergists	N = 1092	Low-risk criteria: no anaphylaxis, reactions >1 year, unknown index drug	n/a	n/a	98	n/a	n/a	n/a
Deschamps et al 2019 (AUS) ²⁷	Expert opinion	Pharmacists/Doctors/Nurses	Adult inpatients/outpatients	Low-risk criteria: childhood rash, MPE >10 years, on/off/on >10	92	94	n/a	n/a	AUS ^{28,29,30}	Paediatric ³¹
Sherry et al 2019 (US) ³²	Expert opinion ³³	Clinicians	Not specified	Low-risk criteria: type A, pruritus without rash, unknown reactions >10 years without IgE fractions, family history	n/a	n/a	n/a	n/a	USA ^{34,35} Canada ³⁶	General practice ³⁷ Long-term care facilities ³⁸
Chiriac et al 2018 (France) ³⁹	Retrospective-multivariable logistic regression	Allergists	N = 1991 (retrospective) N = 200 (prospective)	3-point criteria. No validated low risk	91	75	80	90	n/a	n/a

Low risk was defined as an assessment outcome that led to or recommended a direct oral penicillin challenge.

NPV, maculopapular exanthem; n/a, nonapplicable; NPV, negative predictive value; PPV, positive predictive value; SCAR, Severe Cutaneous Adverse Reaction.

¹⁰ Factors considered were age, time since reaction, culprit antibiotic, route administration, treatment day, latency period, type of reaction, episode duration, and total IgE.

¹¹ Approved and endorsed by the American Academy of Allergy, Asthma & Immunology, Infectious Disease Society of America, and Society for Healthcare Epidemiology of America.

J Allergy. 2020 Jun;75(6):1300–1315. doi: 10.1111/j.1412.

Towards a more precise diagnosis of hypersensitivity to beta-lactams – an EAACI position paper

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eFigure 1. The PEN-FAST clinical decision rule
*Figure extracted for reference*¹⁵.

PEN	Penicillin allergy reported by patient	<input type="checkbox"/> If yes, proceed with assessment
F	Five years or less since reaction ^a	<input type="checkbox"/> 2 points
A	Anaphylaxis or angioedema	<input type="checkbox"/> 2 points
S	Severe cutaneous adverse reaction ^b	
T	Treatment required for reaction ^a	<input type="checkbox"/> 1 point
		<input type="checkbox"/> Total points

Interpretation

Points	Interpretation
0	Very low risk of positive penicillin allergy test <1% (<1 in 100 patients reporting penicillin allergy)
1-2	Low risk of positive penicillin allergy test 5% (1 in 20 patients)
3	Moderate risk of positive penicillin allergy test 20% (1 in 5 patients)
4-5	High risk of positive penicillin allergy test 50% (1 in 2 patients)

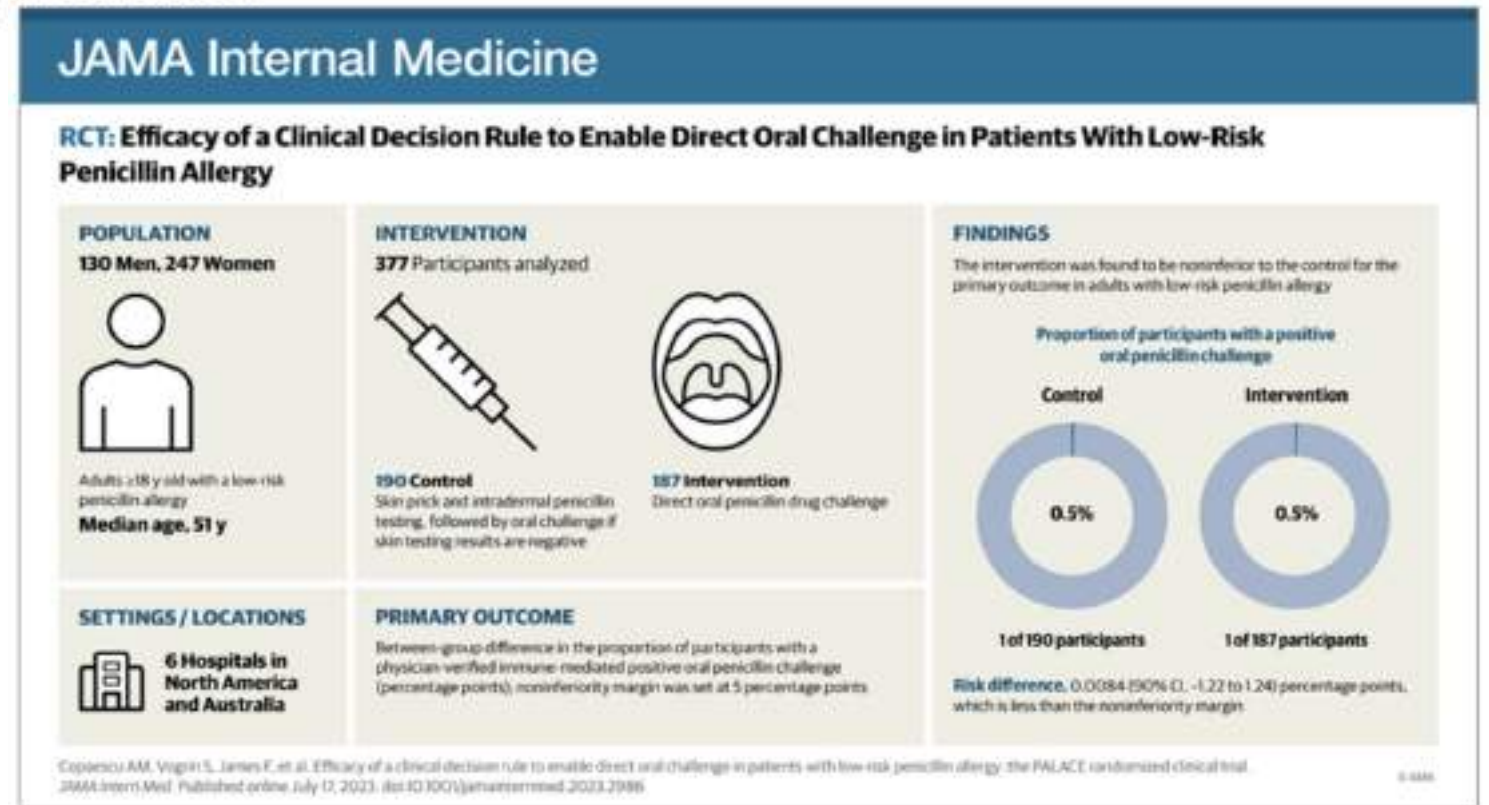
^a Includes unknown

^b Severe cutaneous adverse reactions include potential Stevens-Johnson syndrome, toxic epidermal necrolysis, drug reaction with eosinophilia and systemic symptoms, and acute generalized exanthematous pustulosis. Patients with a severe delayed rash with mucosal involvement should be considered to have a severe cutaneous adverse reaction. Acute interstitial nephritis, drug-induced liver injury, serum sickness and isolated drug fever were excluded phenotypes from the derivation and validation cohorts.

- PEN-FAST es la herramienta que se ha sometido a más esfuerzos de validación.
- PEN-FAST es muy práctica, que utiliza sólo cuatro preguntas para clasificar a los pacientes según su riesgo de alergia a la Penicilina.

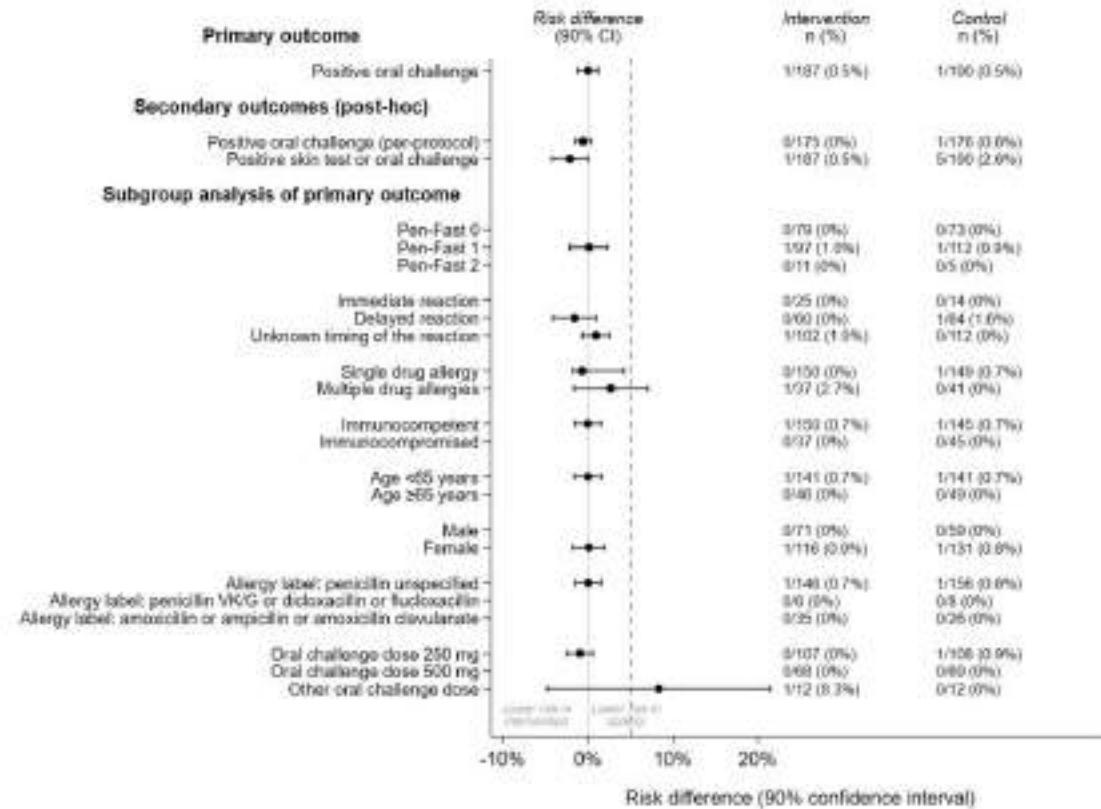
Efficacy of a Clinical Decision Rule to Enable Direct Oral Challenge in Patients With Low-Risk Penicillin Allergy: The PALACE Randomized Clinical Trial

- Estudio Clínico Randomizado.
- 377 pacientes adultos, con antecedente de alergia a penicilina y PEN-FAST menor a 3.
- 2 grupos:
 - Intervención: TPO directo.
 - Control: Pruebas cutáneas y TPO sólo en caso de Pruebas cutáneas negativas.
- Outcome primario: Diferencia en proporción de pacientes con TPO positivo entre ambos grupos.



Efficacy of a Clinical Decision Rule to Enable Direct Oral Challenge in Patients With Low-Risk Penicillin Allergy: The PALACE Randomized Clinical Trial

- Una puntuación PEN-FAST <3 posee un VPN de 96,3% .
- Grupo intervención mostró no inferioridad frente a grupo control.
- Adecuada estratificación de riesgo y seguro.



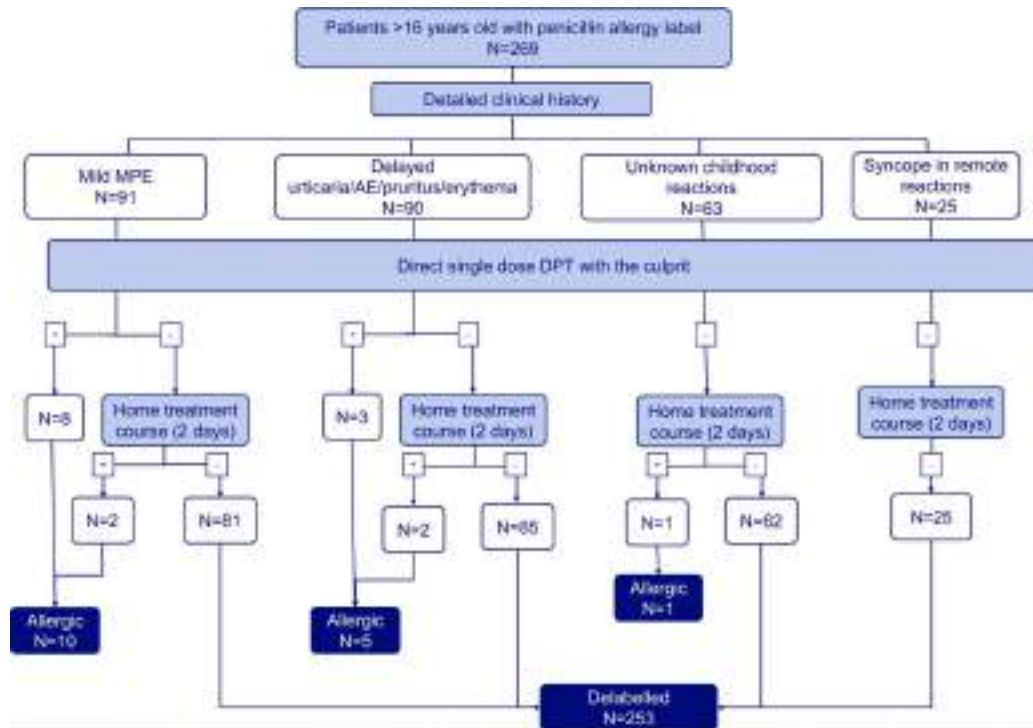
Notes:

(1) The vertical grey lines represent no risk difference, while the dashed line represents the non-inferiority margin of 5%.

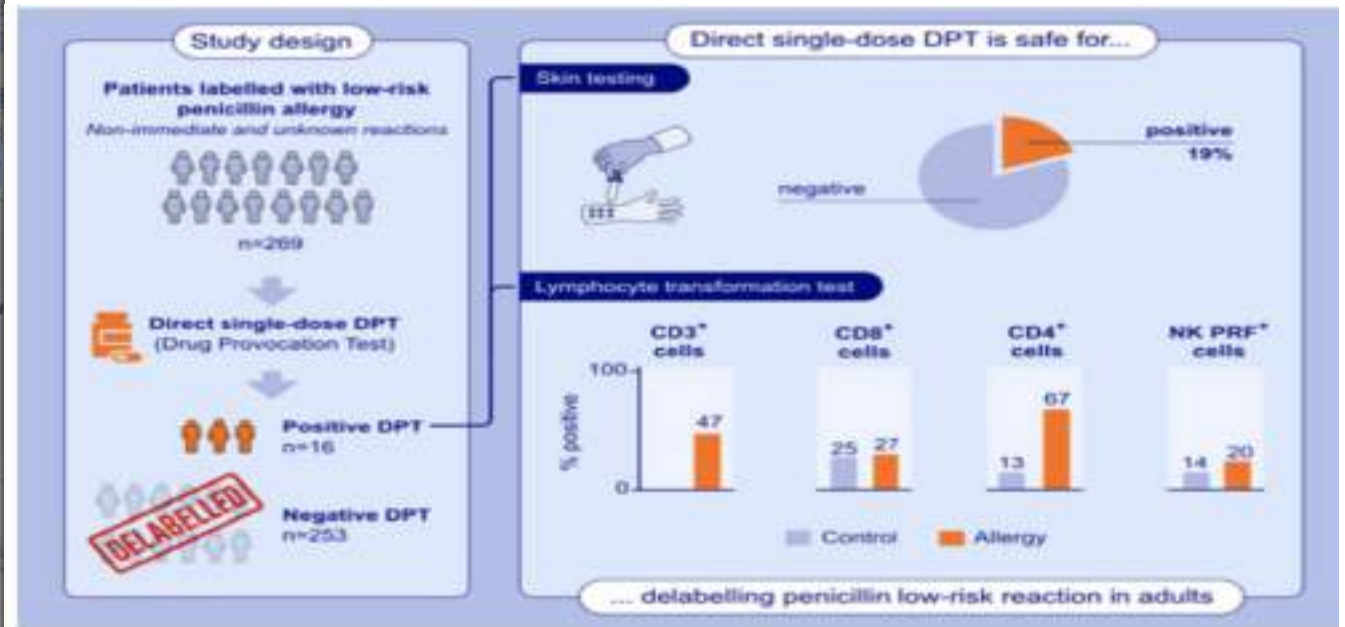
(2) A positive skin test and/or oral challenge occurred in 1/187 (0.5%) patients in the intervention group and 5/190 (2.6%) in the control group with a RD of -2.10 (90% CI, -4.20, 0.01) and a risk ratio of 0.20 (90% CI, 0.03, 1.22).

Direct Single-Dose Drug-Provocation Test Is Safe for Delabelling Penicillin Low-Risk Reactions in Adults

Marina Labeña^{1,2}, Julia Rodríguez de Guzmán^{1,2,3}, Patricia Díez-Echeve¹, María Salas^{1,2}, Rubén Fernández-Santamaría², Cristóbalina Mayorga^{1,2,4}, Inmaculada Doña^{1,2}, María José Torres^{1,2,4,5}



- Se desetiquetó al 94% de los pacientes.
- TPO directo en dosis única es seguro en población bajo riesgo (5,94%).
- La utilidad de las pruebas cutáneas es muy baja en este tipo de pacientes, mayor utilidad el LTT.



Multicenter Study > Clin Infect Dis. 2021 Aug 2;73(3):487-496. doi: 10.1093/cid/ciaa853.

The Penicillin Allergy Delabeling Program: A Multicenter Whole-of-Hospital Health Services Intervention and Comparative Effectiveness Study

- 588 pacientes adultos.
- 62,7% fueron desetiquetados (por historia o TPO directo (200).
- TPO directo fue negativo en el 97% de los pacientes.

Dermatological		Respiratory or Systemic		Unknown	
Skin manifestation	Recommendation & Resultant allergy type	Clinical manifestation	Recommendation & Resultant allergy type	Clinical manifestation	Recommendation & Resultant allergy type
Childhood exanthem (unspecified) Mild rash with no severe features	<input type="checkbox"/> Unlikely to be significant (non-severe)	Laryngeal involvement ("throat tightness" or "hoarse voice")	<input type="checkbox"/> Immediate hypersensitivity (severe)	Unknown reaction < 10 years ago	<input type="checkbox"/> Unknown (non-severe)
Immediate diffuse rash ("itchy immediate rash") < 2 hours post dose	<input type="checkbox"/> Immediate hypersensitivity (non-severe)	Respiratory compromise ("shortness of breath")	<input type="checkbox"/> Immediate hypersensitivity (severe)	Unknown reaction > 10 years ago or family history of penicillin allergy only	<input type="checkbox"/> Unlikely to be significant (non-severe)
Diffuse rash or localized rash/swelling with no other symptoms (non-irradiated or unknown timing)	> 10 years ago or unknown <input type="checkbox"/> Delayed hypersensitivity (non-severe)	Fever ("high temperature") Not explained by infection	<input type="checkbox"/> Delayed hypersensitivity (severe)	Renal	
	≤ 10 years ago <input type="checkbox"/> Delayed hypersensitivity (non-severe)			Severe renal injury, failure or AIN (>50% reduction in eGFR from baseline or absolute serum creatinine increase of ≥26.5µmol/L, or transplantation, or dialysis)	<input type="checkbox"/> Potential immune-mediated (severe)
Angioedema ("lip, facial or tongue swelling")	<input type="checkbox"/> Immediate hypersensitivity (severe)	Anaphylaxis or unexplained collapse	<input type="checkbox"/> Immediate hypersensitivity (severe)	Mild renal impairment (Does not meet criteria in box above)	<input type="checkbox"/> Unlikely immune mediated (non-severe)
Generalized swelling (outside of angioedema)	<input type="checkbox"/> Immediate hypersensitivity (severe)	Haematological		Liver	
Urticaria ("wheals and hives")	<input type="checkbox"/> Immediate hypersensitivity (non-severe)	Low platelets < 150 x 10 ⁹ /L or unknown	<input type="checkbox"/> Potential immune mediated (severe)	Severe liver injury, failure or DILI (≥1x upper limit of normal (ULN) for ALT or AST, or ≥3x ULN for ALT with ≥2x ULN for bilirubin, or ≥2x ULN for ALP, or transplant)	<input type="checkbox"/> Potential immune mediated (severe)
		Low neutrophils < 1x10 ⁹ /L or unknown	<input type="checkbox"/> Potential immune mediated (severe)	Mild hepatic enzyme derangement (Does not meet criteria in box above)	<input type="checkbox"/> Unlikely immune mediated (non-severe)
Mucosal ulceration ("mouth, eye or genital ulcers")	<input type="checkbox"/> Delayed hypersensitivity (severe)	Low haemoglobin < 100 g/L or unknown	<input type="checkbox"/> Potential immune mediated (severe)	Gastrointestinal, Neurological or Infusion-related	
Pustular, blistering or desquamating rash ("skin shedding")	<input type="checkbox"/> Delayed hypersensitivity (severe)	Eosinophilia (>0.7 x 10 ⁹ /L or unknown)	<input type="checkbox"/> Delayed hypersensitivity (severe)	Gastrointestinal symptoms ("nausea, vomiting, diarrhoea")	<input type="checkbox"/> Unlikely immune mediated (non-severe)
Appropriate for supervised direct oral rechallenge (or direct de-labelling)			<input type="checkbox"/> Low risk	Severe neurological manifestation ("seizures or psychosis")	<input type="checkbox"/> Unknown or unclear mechanism
Appropriate for supervised direct oral rechallenge.			<input type="checkbox"/> Low risk		
May be appropriate for referral for specialized skin testing			<input type="checkbox"/> Moderate risk	Anaphylactoid/infusion reaction (e.g. red man syndrome)	<input type="checkbox"/> Unknown or unclear mechanism
May be appropriate for referral for specialized skin testing			<input type="checkbox"/> High risk		



REVIEW

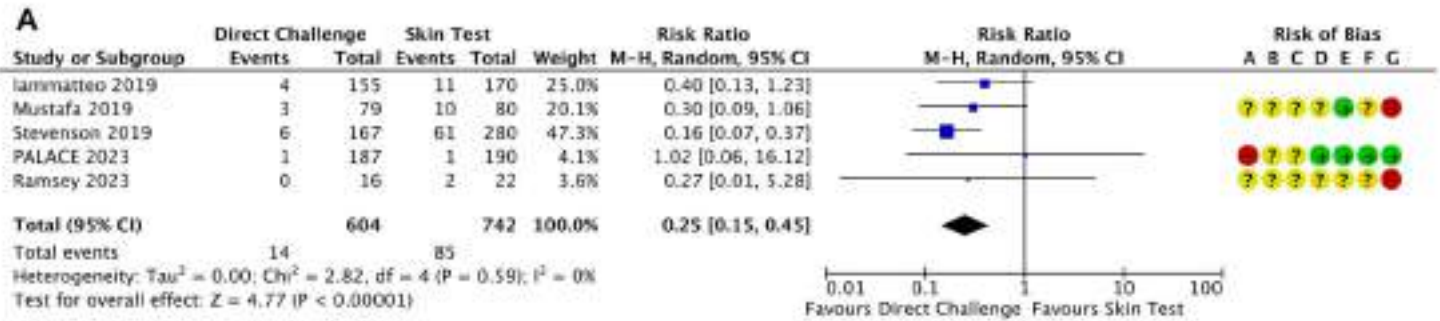
Penicillin Allergy Testing and Delabeling for Patients Who Are Prescribed Penicillin: A Systematic Review for a World Health Organization Guideline

Raf Proenca^{1,2}, Ghazaleh Aali³, Fang Zhu⁴, Brian F. Lewis⁴, Rachel Orvill⁵, Mahmoud Alkhrad^{1,6}, Jonathan L. H. Bray⁷, Ferruccio Pelone¹, Petra Nass⁷, Elisei Marjono⁸, Miryam Cassandra⁷, David S. Celemajer⁹, Farhad Shokosnah⁹

Accepted: 14 March 2024 / Published online: 2 May 2024
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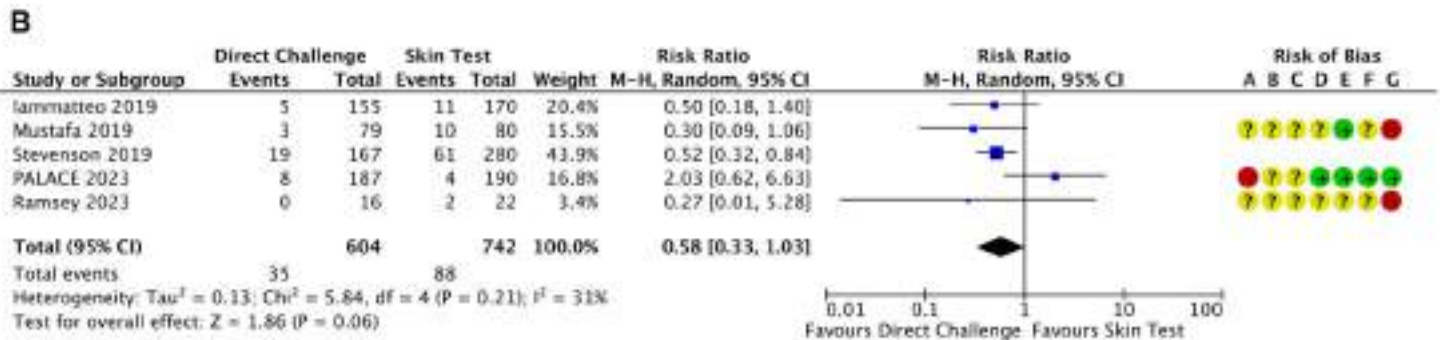
Abstract

- Revisión sistemática de algoritmos de manejo.
- TPO directo es seguro en la población bajo riesgo.



Risk of bias legend

- (A) Random sequence generation (selection bias)
- (B) Allocation concealment (selection bias)
- (C) Blinding of participants and personnel (performance bias)
- (D) Blinding of outcome assessment (detection bias)
- (E) Incomplete outcome data (attrition bias)
- (F) Selective reporting (reporting bias)
- (G) Other bias



Risk of bias legend

- (A) Random sequence generation (selection bias)
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- (F) Selective reporting (reporting bias)
- (G) Other bias

**¿Qué pasa con las
cefalosporinas?...**



Development and validation of a cephalosporin allergy clinical decision rule

F Cox¹, S Vogrin¹, R P Sullivan², C Stone³, D Koo³, E Phillips³, J Li⁴, S L Fernando⁴, M Al Gersim⁵, E Mibi⁶, J De Luca⁶, M Rose⁶, K Y L Chua⁶, N E Holmes⁶, A M Coparescu⁷, J A Trubiano⁸

Table 4

Validation of CEPH-FAST in predicting a positive cephalosporin allergy test result for cross-reactive cephalosporin cohort and implicated cephalosporin cohort in Australia and North America.

	Cross-reactive cephalosporin cohort		Implicated cephalosporin cohort	
	Australian cohort	North American cohort	Australian cohort	North American cohort
No of patients	228	167	191	130
No (%) of positive cephalosporin test	91 (39.9%)	30 (18.0%)	88 (46.1%)	26 (20.0%)
AUROC (95% CI)	0.921 (0.887, 0.955)	0.847 (0.779, 0.914)	0.929 (0.893, 0.965)	0.842 (0.773, 0.911)
Validation of low-risk (CEPH-FAST < 3)				
Sensitivity (95% CI)	93.4% (86.2, 97.5)	70.0% (50.6, 85.3)	93.2% (85.7, 97.5)	73.1% (52.2, 88.4)
Specificity (95% CI)	72.3% (64.0, 79.6)	83.9% (76.7, 89.7)	77.7% (68.4, 85.6)	83.7% (75.1, 90.2)
PPV (95% CI)	69.1% (60.1, 77.1)	48.8% (33.3, 64.5)	78.1% (69.0, 85.6)	52.8% (35.5, 69.6)
NPV (95% CI)	94.3% (88.0, 97.9)	92.7% (86.7, 96.6)	93.0% (85.4, 97.4)	92.6% (85.3, 97.0)

Abbreviations: AUROC: area under receiver-operating characteristic curve; CI: confidence interval; PPV: positive predictive value; NPV: negative predictive value.

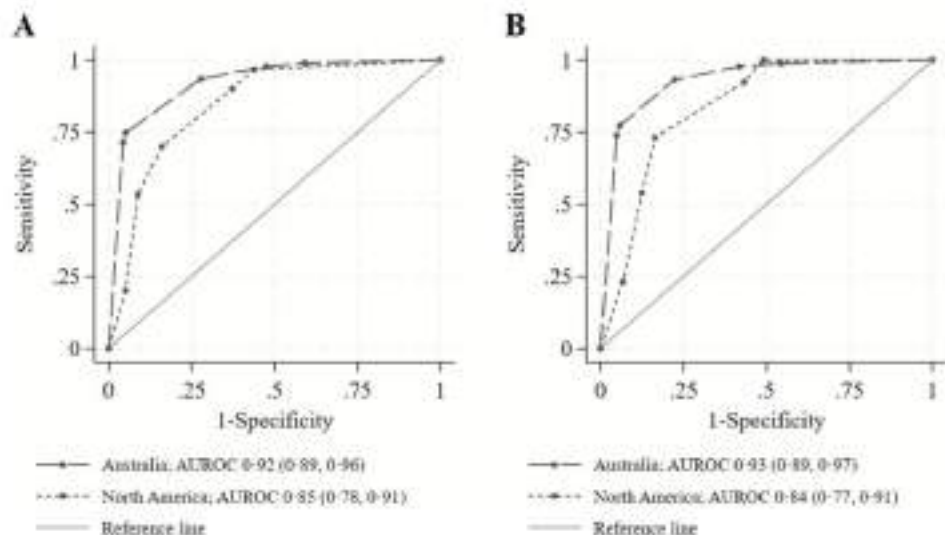


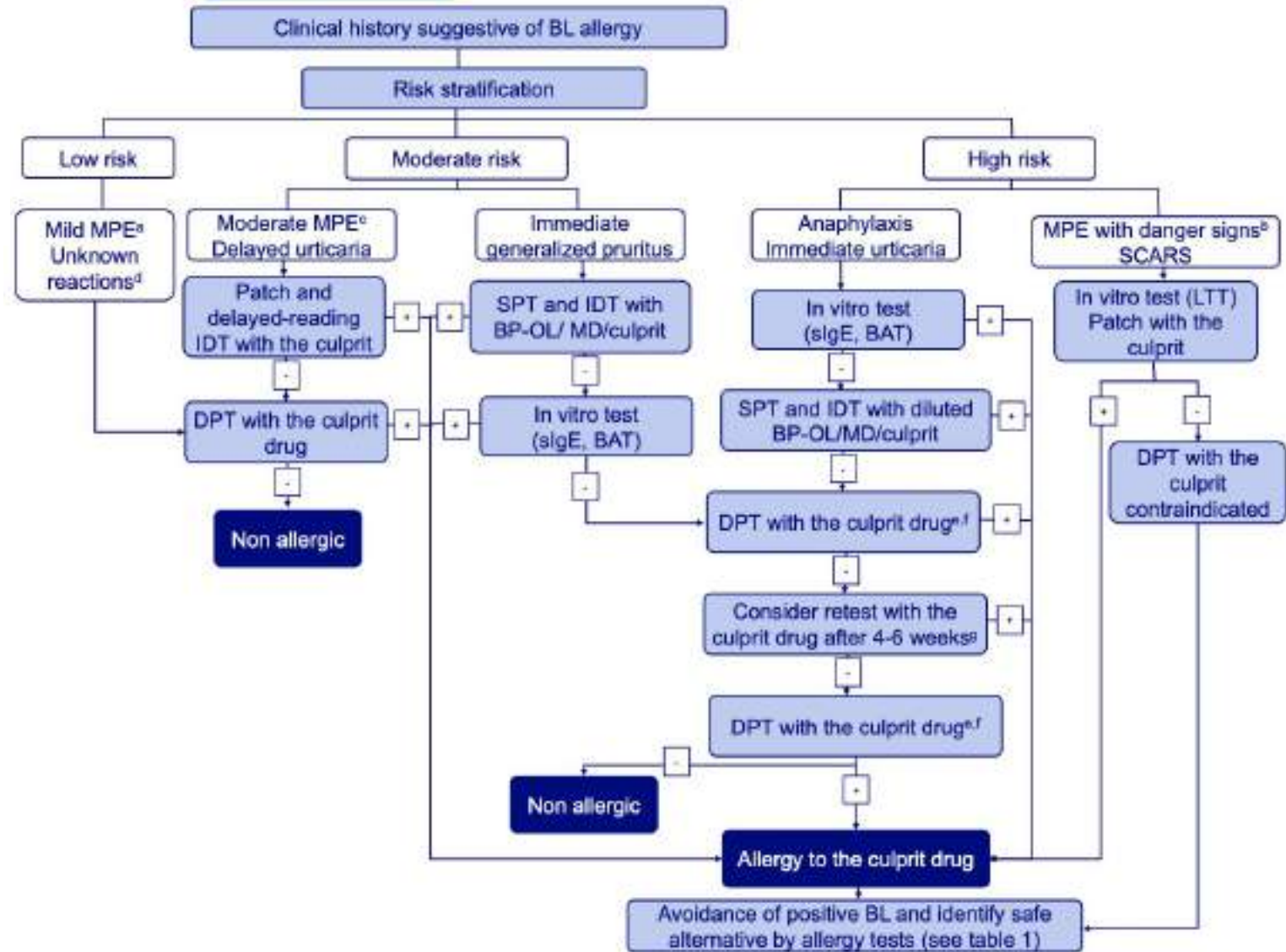
Fig. 2. Receiver-operating characteristic curve for cross-reactive cephalosporin cohort (A) and for implicated cephalosporin cohort (B).

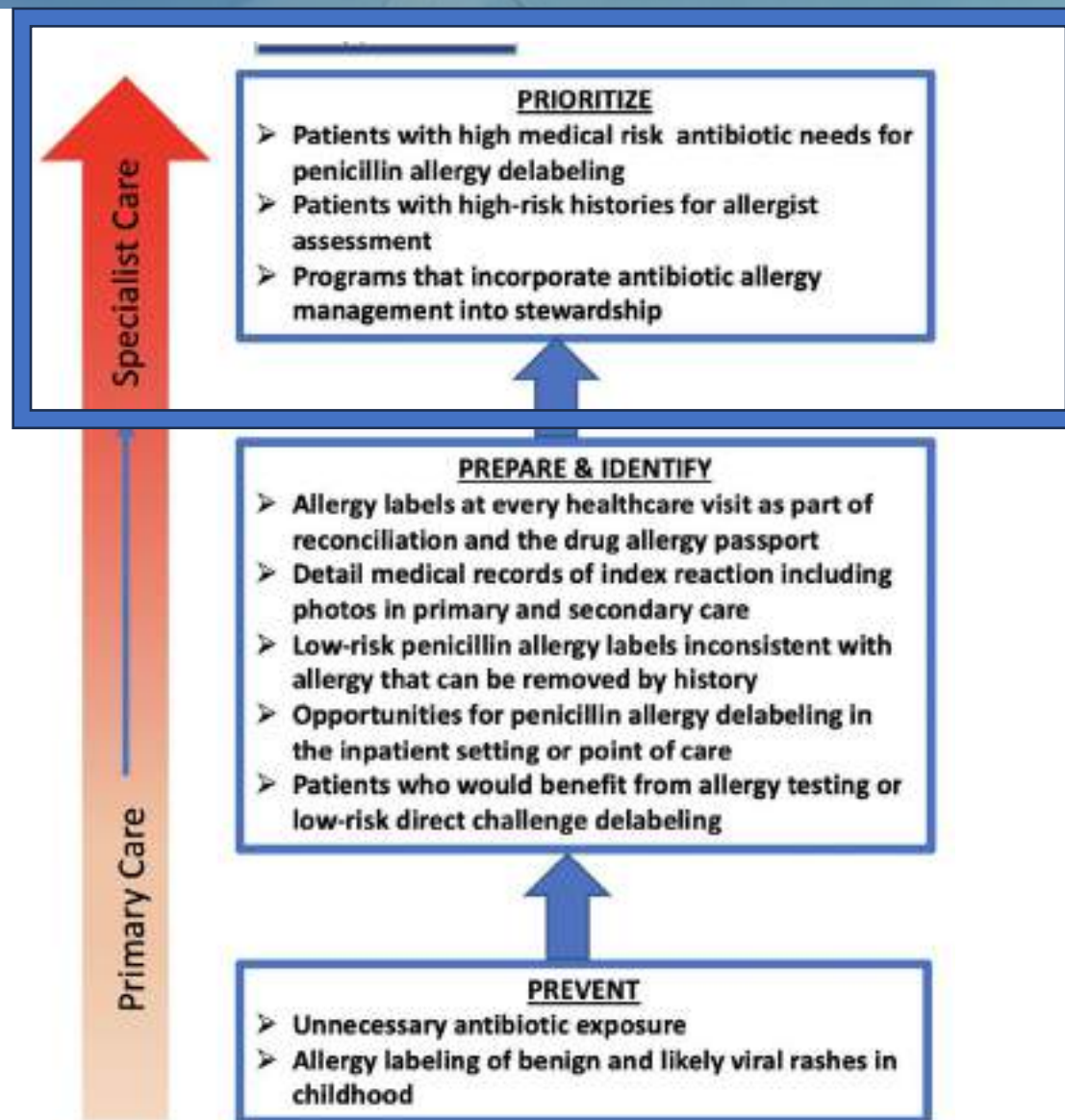
- Estudio retrospectivo
- CEPH-FAST buena discriminación (AUROC 0,92).
- VPN 94%
- Sólo 5,7% presento reacción adverso con TPO directo.
- CEPH-FAST primer algoritmo validado en pacientes bajo riesgo alergia cefalosporinas

Algoritmo diagnóstico de alergia a Betalactámicos



An algorithm for the diagnosis of beta-lactam allergy, 2024 update





Hipersensibilidad a β -lactámicos: Revisión de la literatura y propuesta de manejo en el paciente hospitalizado

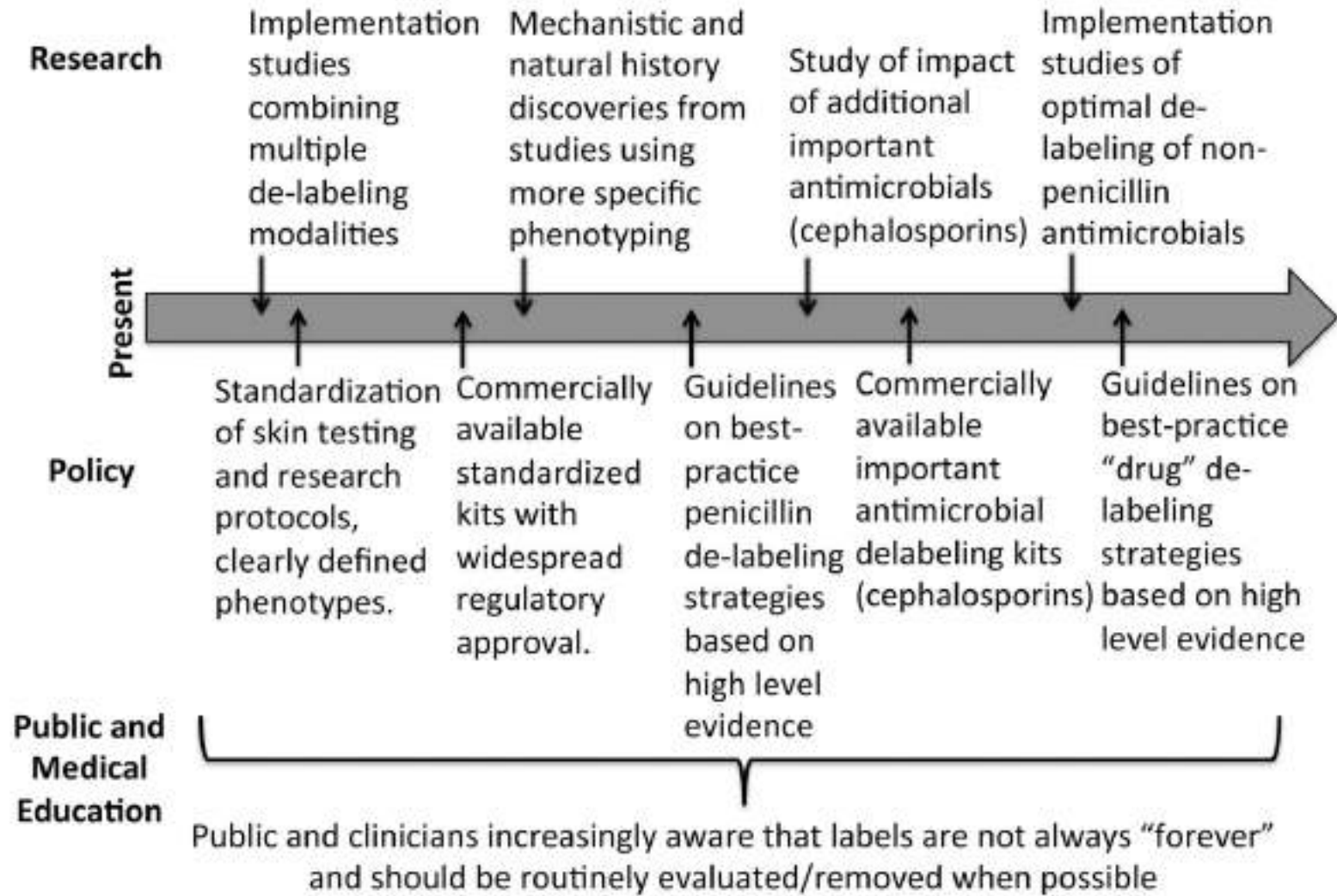
Patricio Rossi¹, Jovanka Reyes-Barros², María Teresa Peraza³, Luis Rojas^{4,5},
Raquel Aguilera-Insuza^{6,7}

- Riesgo bajo: Historia no sugerente, reacciones hace más de 5 años, antecedentes familiares de alergia betalactámicos.
- Riesgo intermedio: Urticaria, angioedema, exantema maculopapular.
- Riesgo alto: anafilaxia, SCARs o compromiso órgano blanco.

Sospecha de hipersensibilidad a β -lactámicos en paciente hospitalizado con indicación de antibióticos						
	Sin alternativas antibióticas no BL igualmente efectivas y seguras			Con alternativas antibióticas no BL igualmente efectiva y segura		
	Riesgo bajo	Riesgo intermedio	Riesgo alto	Riesgo bajo	Riesgo intermedio	Riesgo alto*
Antibiótico a usar (previo a estudio alérgico)	β -lactámicos (prueba de provocación DP)	β -lactámico con baja similitud estructural	Antibiótico no β -lactámico o desensibilización	β -lactámicos (prueba de provocación DP) o No β -lactámico	Antibiótico no β -lactámico	Antibiótico no β -lactámico
Estudio alérgico	Objetivo: Uso del BL de 1ª línea para infección en curso			Objetivo: Desetiquetar para infección futura		
Cuándo estudiar	Durante hospitalización	Durante hospitalización	Durante hospitalización	Posterior al alta	Posterior al alta	Posterior al alta
Cómo estudiar	Prueba de provocación DP	Prueba cutánea. Si (-): Provocación DG	Prueba cutánea. Si (-): Provocación DG	Prueba de provocación DP	Prueba cutánea. Si (-): Provocación DG	Prueba cutánea. Si (-): Provocación DG

Figura 4: Propuesta de manejo del paciente hospitalizado con etiqueta de alergia a penicilina. * Estudio alérgico contraindicado absolutamente en reacciones adversas severas viscerales (DILI, NTI). Estudio alérgico contraindicado de forma relativa en reacciones adversas severas cutáneas. BL: β -lactámico. DP: Dosis plena. DG: Dosis graduada.

Roadmap for Future Directions



Conclusiones

- Las etiquetas de alergia a los Betalactámicos son muy **frecuentes, en gran medida inexactas** y su presencia puede conducir a **tratamientos innecesarios y resultados inferiores**, así como a **consecuencias adversas para la salud pública**.
- Las etiquetas de alergia a los Betalactámicos ya no deberían considerarse entidades pasivas dentro del historial médico.
- Es necesario desarrollar enfoques sistemáticos para gestionar la gran carga mundial de pacientes con sobre-etiquetas.
- Los protocolos actuales de pruebas TPO directo para desetiquetar alergia a Penicilina/Cefalosporinas no están estandarizados a nivel internacional.
- Un modelo exitoso necesitará un enfoque colaborativo y multimodal para poder desetiquetar a pacientes alérgicos a Betalactámicos.



Figure 3. Penicillin allergy delabeling across the care continuum. Colors indicate the frequency with which penicillin allergy delabeling as quality improvement is implemented in these settings in the United States. Settings in dark blue represent opportunities for the expansion of delabeling as quality improvement.



GRACIAS