Clinical and Immunological Profiles of Patients with Beta-lactam Allergies: An Ambi-directional Study

Principal Investigator (Host): Dr Rosa Muñoz Cano

Host Institute: Department of Allergology, Hospital Clinic, IDIBAPS, Villarroel 170. Barcelona. Spain

Co-investigator (Research fellow): Dr Alpana Mohta, Rajasthan, India

Type of fellowship: Research fellowship

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Abstract

Introduction: Beta-lactam antibiotics, introduced during World War II, are among the most widely used antimicrobials worldwide. Despite their utility, beta-lactam allergies have been overdiagnosed for decades, often based on unverified patient histories. This misdiagnosis leads to unnecessary drug avoidance, alternative antibiotic use, and increased antimicrobial resistance. This study, conducted at the Department of Allergology, Hospital Clínic, Barcelona, with funding from the European Academy of Allergy and Clinical Immunology (EAACI), aimed to evaluate diagnostic protocols for beta-lactam allergies to improve precision and reduce false labeling.

Aims and Objectives

This study sought to classify beta-lactam allergy phenotypes, assess the diagnostic accuracy of in vivo (skin prick, intradermal, and patch tests) and in vitro (IgE, BAT, LTT, and tryptase) tests, evaluate cross-reactivity patterns among beta-lactam subgroups, and explore the impact of retesting and gender differences on diagnostic outcomes.

Methods

An ambi-directional cohort of 152 patients with suspected beta-lactam allergies was analyzed from February 2020 to November 2024. Patients underwent comprehensive testing, including skin tests, drug provocation tests (DPT), and in vitro assays. Diagnostic algorithms were employed to categorize cases as ‘labeled’ or ‘delabeled’.

Results

Of 152 patients, 76.3% were delabeled as non-allergic, while 23.7% were confirmed allergic. DPT, the gold standard, achieved 100% sensitivity and specificity. Skin tests demonstrated moderate sensitivity (55.6%) but excellent specificity (100%). Aminopenicillins were the primary culprits (77.8%), with immediate reactions dominating (77.8%). Retesting within six months improved diagnostic accuracy. Women required more diagnostic tests for both labeling and delabeling. The FASS scale was found to be useful in labeling the severity of reactions.

Conclusion

Beta-lactam allergy overdiagnosis persists due to reliance on patient-reported symptoms. Structured protocols for delabeling drug allergies, including the retesting protocol, can help standardise allergy testing in routine clinical practice. The beta-lactam testing protocol was found to be useful in the accurate diagnosis and delabeling, reducing unnecessary antibiotic restrictions and improving antimicrobial stewardship. We also propose the usage of a modified version of FASS for beta-lactam drug allergy testing.

Background

Beta-lactam antibiotics, such as penicillin, are among the most common causes of drug allergies, affecting approximately 10% of the global population.[1] Notably, a significant proportion of patients labeled as allergic to beta-lactams are found to be tolerant upon further examination.[2] This mislabeling carries substantial risks, leading to the use of alternative antimicrobials that are often less effective and carry a higher risk of adverse effects, including longer hospital stays, increased antibiotic resistance, and greater healthcare costs.

In vitro and in vivo immunological testing is the gold standard for diagnosing suspected cases of drug allergy. However, there is a risk of potential for false-negative results in allergen immunology testing if the immunological tests are not done early after the reaction. Such delays can lead to the unnecessary use of multiple costly tests and have a significant economic impact.

Aims and Objectives

Aim

To evaluate the clinical, diagnostic, and immunological profiles of patients with beta-lactam allergies and assess the efficacy of diagnostic protocols for accurate labeling and delabeling of beta-lactam allergies.

Primary Objectives

1. Clinical Phenotypes:
    - Identify and classify the clinical phenotypes of beta-lactam allergies into immediate, intermediate, and delayed types.
    - Correlate reaction latency, clinical features, and severity (e.g., urticaria, anaphylaxis) with diagnostic outcomes.
2. Prevalence and Sensitization Profiles:
    - Determine the prevalence of beta-lactam allergies among the study cohort.
    - Assess sensitization profiles, including mono-sensitization (single drug or group) and multi-sensitization (multiple drugs or groups).
3. Efficacy of Diagnostic Protocols:
    - Evaluate the diagnostic yield of in vivo tests (skin tests, DPT) and in vitro tests (IgE, BAT, LTT).
    - Compare the sensitivity, specificity, and accuracy of these tests against drug provocation testing (DPT) as the gold standard.
4. Delabeling Spurious Beta-Lactam Allergies:
    - Assess the efficacy of the diagnostic protocol in delabeling patients falsely diagnosed with beta-lactam allergies.
5. Patterns of Cross-Reactivity:
    - Identify patterns of cross-reactivity among beta-lactam subgroups (e.g., aminopenicillin, cephalosporin, carbapenem).

Secondary Objectives

1. Retesting and Time Elapsed:
    - Analyze the effect of the time elapsed between allergic reactions and testing on labeling and delabeling outcomes.
    - Assess the diagnostic yield of retesting and compare outcomes of single-day versus multi-day retests.
2. Tolerance Post-Reaction:

- Document and analyze cases where patients tolerated beta-lactam antibiotics after an initial reaction.
- Investigate patterns of selective versus non-selective reactions.

3. FASS Grading:
    - Correlate the Food Allergy Severity Score (FASS) with diagnostic outcomes.
    - Identify limitations of FASS in capturing clinical features specific to beta-lactam allergies.
4. Intraoperative Reactions:
    - Assess the clinical and diagnostic outcomes of beta-lactam allergies suspected during intraoperative settings.
5. Gender-Based Analysis:
    - Investigate gender differences in the number of tests required for diagnosis and delabeling of beta-lactam allergies.

Methods

Study Design: Ambi-directional (retrospective and prospective) cohort study.

Study Duration: February 1, 2020, to November 14, 2024.

Setting: Department of Allergology, Hospital Clinic Barcelona

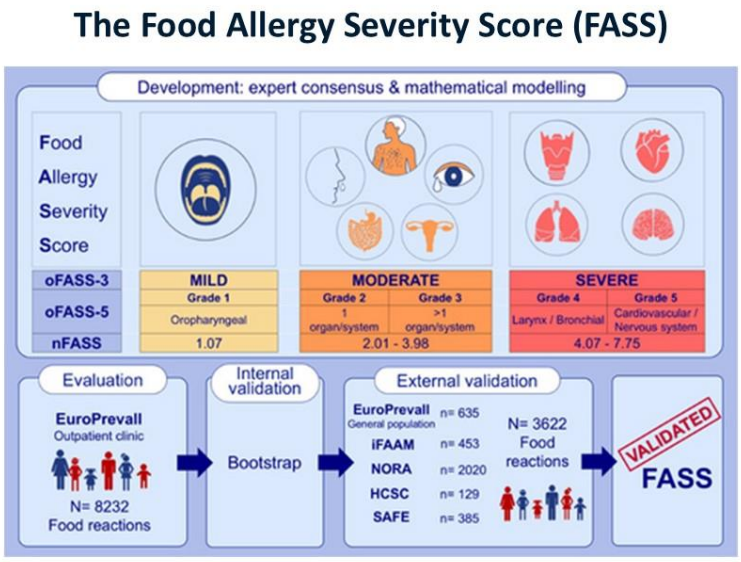
Principal Investigator: Dr Rosa Muñoz Cano

Co-investigator: Dr Alpana Mohta

Participants: 152 patients with suspected beta-lactam allergies. Inclusion criteria included patients aged 18 and above with a documented allergy. Exclusion criteria included pregnancy, and breastfeeding.

Data Collection:

- Demographics, medical history, and details of allergic reactions.
- The Food Allergy Severity Score (FASS) (adapted from Fernández-Rivas et al.) was used to assess the severity of reactions.[3]

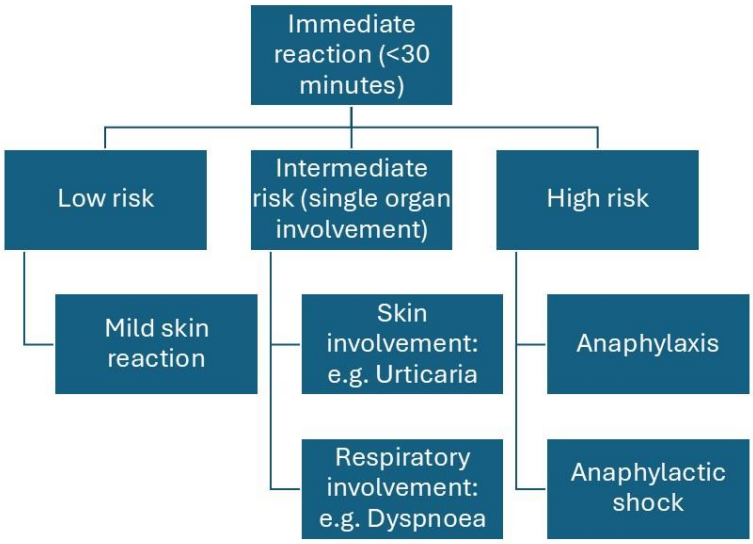


Source: Fernández-Rivas M, Gómez García I, Gonzalo-Fernández A, et al. Development and validation of the food allergy severity score. Allergy. 2022;77(5):1545-1558.

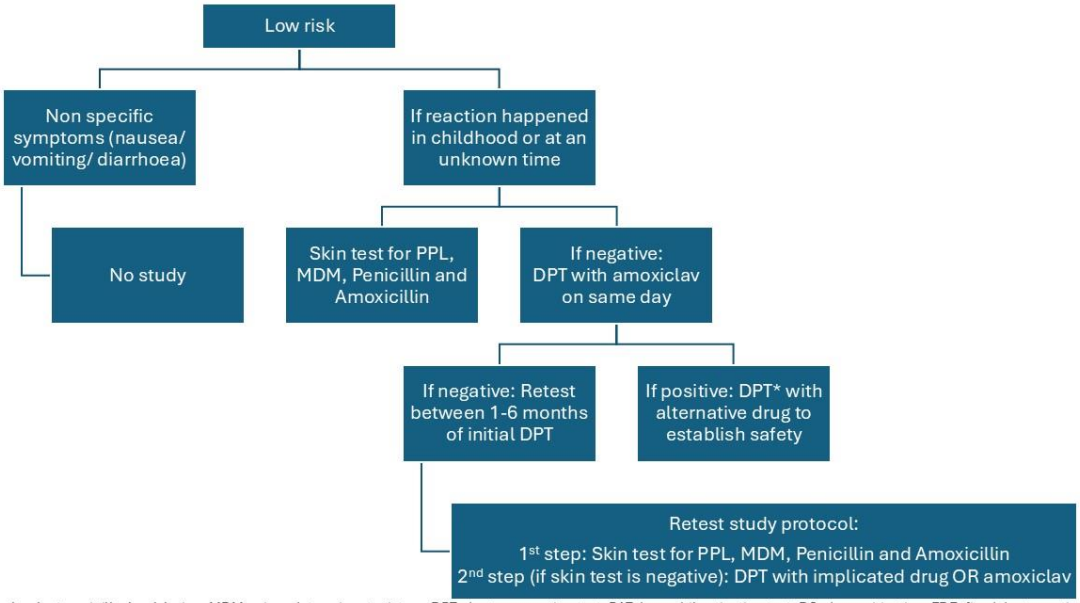
Procedures:

- In-vivo tests: skin prick test, intradermal test, patch test, drug provocation test (DPT).
- In-vitro tests: ImmunoCAP, basophil activation test (BAT), Total and specific IgE levels, lymphocyte transformation test (LTT), tryptase level.
- In patients where more than 1 year had elapsed between the reaction and testing, in-vitro retesting was performed. Ideally, retesting should be conducted within 1 to 6 months, preferably after 1 month.

Diagnostic Algorithm:



PPL: polyvalent penicilloyl-polylysine, MDM: minor determinant mixture, DPT: drug provocation test, BAT: basophil activation test, DS: desensitization, FDE: fixed drug eruption, SCAR: severe cutaneous adverse reaction, FDE: fixed drug eruption, SJS-TEN: Steven Johnson syndrome-toxic epidermal necrolysis, AGEP: acute generalized exanthematous pustulosis, DRESS: drug reaction with eosinophilia and systemic symptoms, LLT: lymphocyte transformation test



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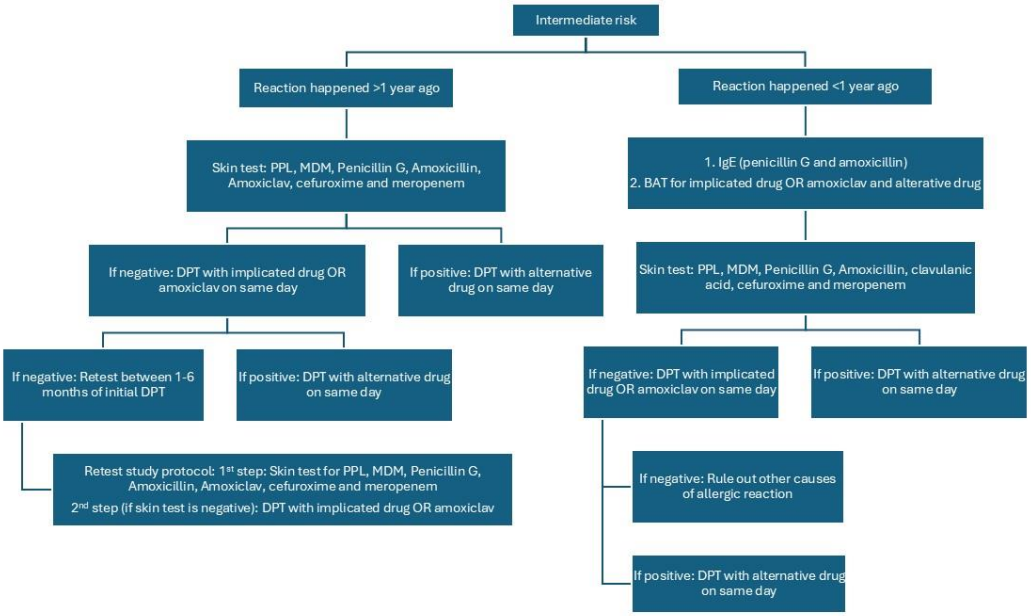

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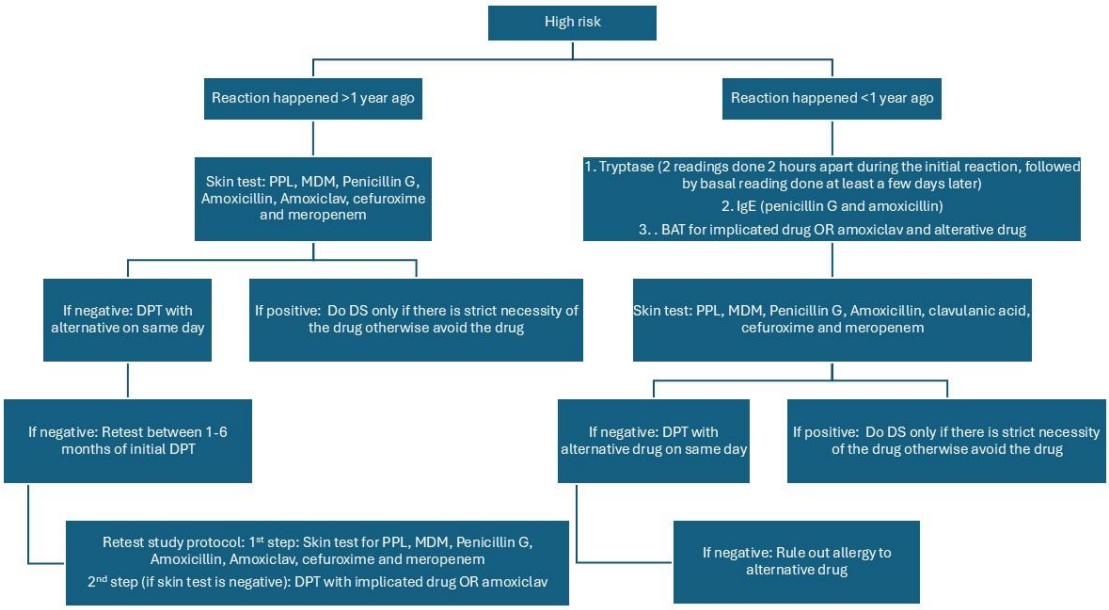

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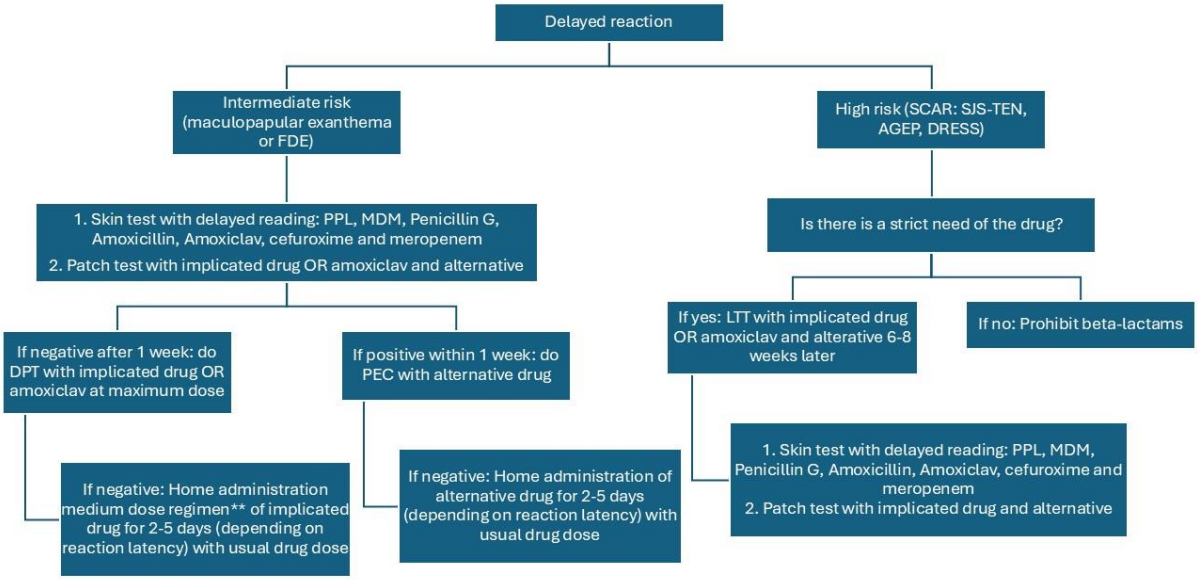

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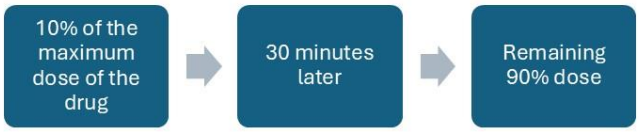
*Beta-lactam antibiotics drug provocation test (DPT) dosage protocol

Protocol 1 (for low to medium risk cases)



Protocol 1 (for selective high risk cases)

****Home Guidelines**

Medium dose regimen for 2-5 days depending on the latency time of the reaction in each patient, and with the usual dosage of the drug

Drug	Maximum total dose	Medium dose (for home regimen)
Penicillin	500 mg	250 mg
Amoxicillin	750 mg	500 mg
Amoxicillin-clavulanic acid	875/125 mg	500/125mg
Cefalosporins	Cefuroxime/cefalexin 5000 mg Ceftriaxone/cefepime 1 gm	Cefuroxime/cefalexin 250 mg
Carbapenemes	Meropenem 1 gm Imipenem 500 mg	
Aztreonam	1 gm	

Key Definitions:

- ***Suspected Case***: A clinical suspicion of hypersensitivity to beta-lactam antibiotics based on patient-reported symptoms (e.g., rash, hives, anaphylaxis) following beta-lactam exposure without confirmatory diagnostic testing.

- ***Labeled Case***: A patient diagnosed with beta-lactam allergy through clinical evaluation and diagnostic testing based on the prescribed diagnostic algorithm (referenced in Annexure 1). These cases are confirmed or presumed allergic and are advised to avoid beta-lactam antibiotics.

- ***Delabeled Case***: A patient initially labelled with a beta-lactam allergy but determined not to have a true allergy following a comprehensive evaluation using the diagnostic algorithm in Annexure 1. These patients are deemed safe to use beta-lactam antibiotics again.

- ***Selective Reaction***: Allergic only to the specific drug originally implicated.

- ***Non-Selective Reaction***: Allergic to multiple related drugs (e.g., aminopenicillins + cefalosporins).

- ***Monosensitization***: Allergic to only one class of beta-lactam drugs.

- ***Multisensitization***: Allergic to multiple drug classes.

Results

Total number of patients included in the study: 152.

Age range: 18-84 years.

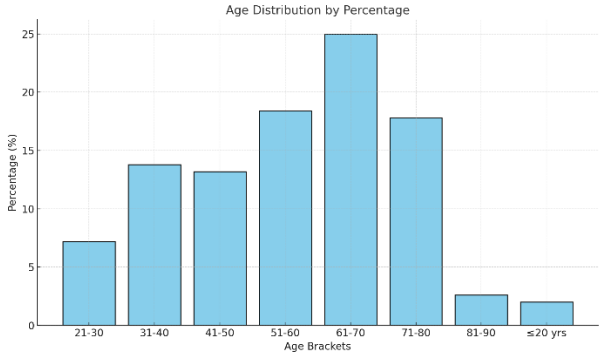
Measures of central tendency: Mean: 55.6±16.6 years.

Median: 59 years

1. **Demographic Data**

Age distribution:

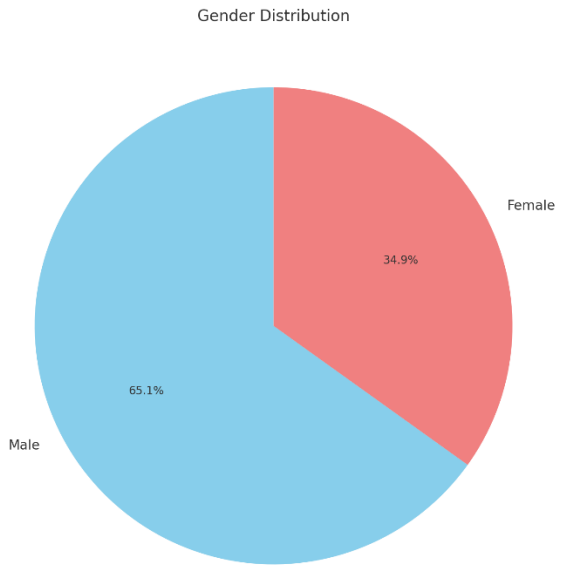
Age brackets	No. (out of 152)	%
≤20 years	3	2.0
21-30 years	11	7.2
31-40 years	21	13.8
41-50 years	20	13.2
51-60 years	28	18.4
61-70 years	38	25.0
71-80 years	27	17.8
81-90 years	4	2.6



Gender distribution:

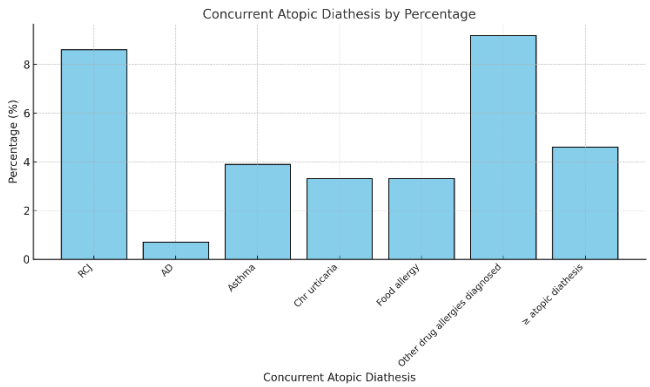
Gender	No. (out of 152)	%

Male	99	65.1
Female	53	34.9



Prevalence of atopic diathesis:

Concurrent atopic diathesis	No. (out of 152)	%
Rhino-conjunctivitis	13	8.6
Atopic dermatitis	1	0.7
Asthma	6	3.9
Chronic spontaneous urticaria	5	3.3
Food allergy	5	3.3
Other drug allergies diagnosed	14	9.2
≥ Atopic diathesis	7	4.6

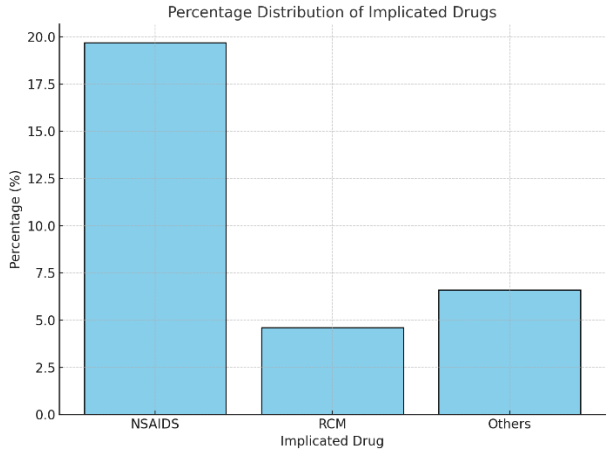


The most common concurrent allergic condition was a previously diagnosed drug allergy to other medications, followed by atopic conditions such as rhinoconjunctivitis, atopic dermatitis, or asthma.

Additionally, at least five patients had a history of chronic spontaneous urticaria, complicating the interpretation of prick and intradermal test results due to variable dermographism observed during testing.

Incidence of ≥1 drugs suspected in drug allergy at presentation

Implicated drug	No. (out of 152)	%
NSAIDS	30	19.7
RCM	7	4.6
Others	10	6.6



Most common 2nd implicated drugs were NSAIDs followed by radiocontrast media.

Other drug allergies: Teicoplanin, levofloxacin, sulfonamide, clindamycin, and spiramycin, and one outlier with suspected drug allergy to multiple drugs (Teicoplanin, midazolam, dexamethasone, propofol, remifentanil, fentanyl, and rocuronium), who was eventually labeled.

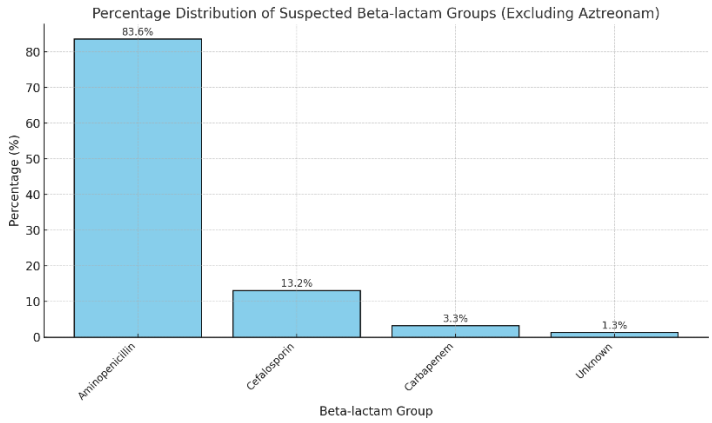
4 out of these 10 patients were eventually labeled as allergic to beta-lactam.

All were allergic to aminopenicillin and aminocephalosporin, 1 was also allergic to cephalosporins, while 1 was allergic to the entire beta-lactam group.

Inference: Concurrent suspected drug allergies could potentially increase the likelihood of being labeled as beta-lactam allergic.

Suspected beta-lactam implicated in primary reaction

Suspected Beta-lactam group implicated in presenting reaction of interest	No. (out of 152)	%
Aminopenicillin	127	83.6
Cefalosporin	20	13.2
Carbapenem	5	3.3
Aztreonam	0	0.0
Unknown	2	1.3

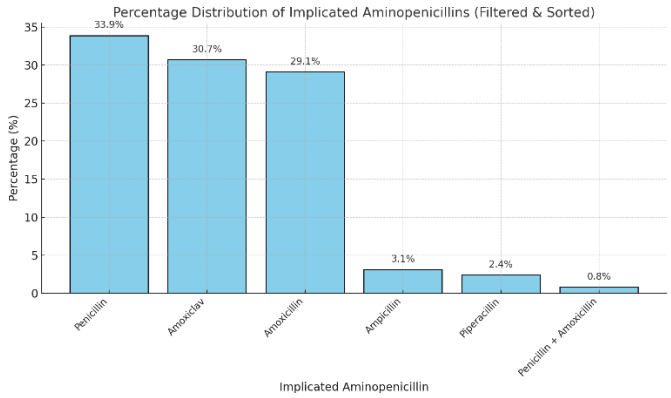


Note: In 4 patients, 2 or more beta lactams were suspected to be culprits.

Subgroup analysis of suspected aminopenicillin drugs

Implicated Aminopenicillin	No. (out of 127)	%
Penicillin	43	33.9
cloxacillin	0	0.0

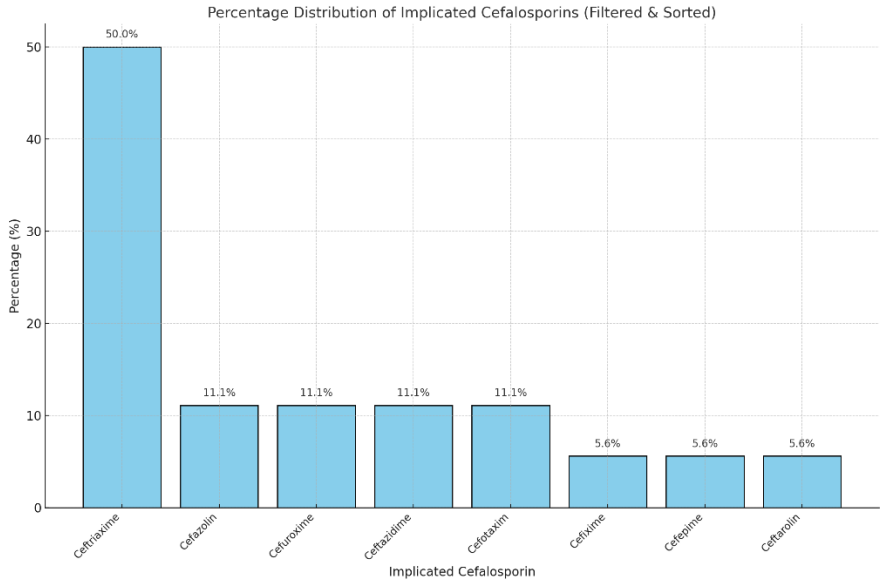
Amoxicillin	37	29.1
Ampicillin	4	3.1
Amoxiclav	39	30.7
Piperacillin	3	2.4
Penicillin + amoxicillin	1	0.8



Subgroup analysis of suspected cefalosporin drugs

Implicated cefalosporin	No. (out of 20)	
Cefadroxil	0	0.0
Cefalexin	0	0.0
Cefazolin	2	11.1
Cefuroxime	2	11.1
Cefprozil	0	0.0
cefaclor	0	0.0
cefixime	1	5.6
ceftriaxime	9	50.0
cefditoren	0	0.0
ceftazidime	2	11.1
cefepime	1	5.6
ceftolozone	0	0.0

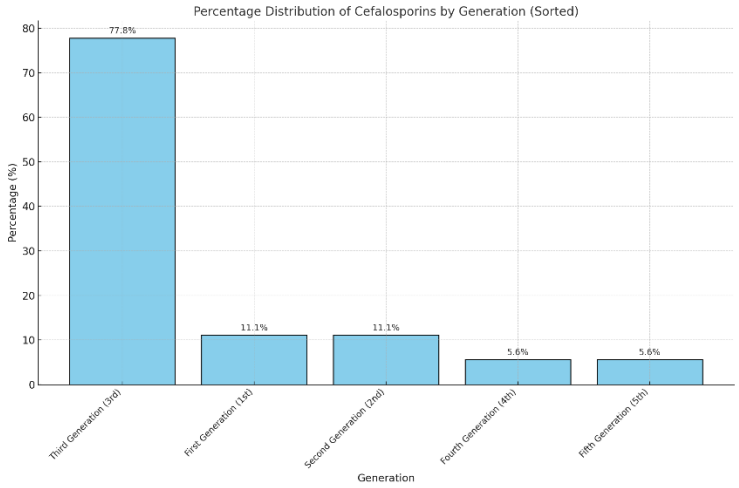
ceftarolin	1	5.6
cefotaxim	2	11.1



Subgroup analysis of suspected cefalosporin drugs based on generation

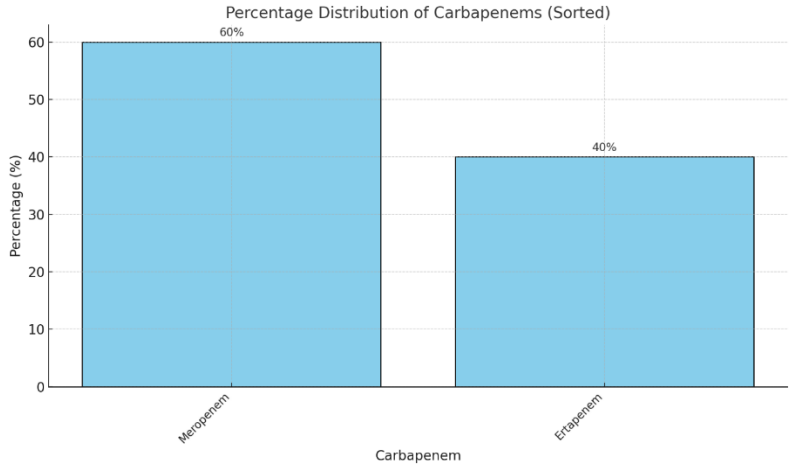
Generation	Drugs	Combined Value	%
First Generation (1st)	Cefadroxil, Cefalexin, Cefazolin	2	11.1
Second Generation (2nd)	Cefuroxime, Cefprozil, Cefaclor	2	11.1
Third Generation (3rd)	Cefixime, Ceftriaxone*, Cefditoren, Ceftazidime, Cefotaxime	14	77.8
Fourth Generation (4th)	Cefepime	1	5.6

Fifth Generation (5th)	Ceftarolin, Ceftolozane	1	5.6



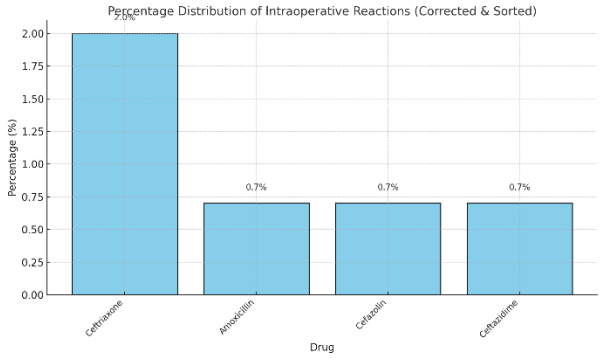
Subgroup analysis of suspected carbapenem drugs

Carbapenem	Number	%
Meropenem	3	60
Ertapenem	2	40
Imipenem	0	0



Intraoperative suspected drugs

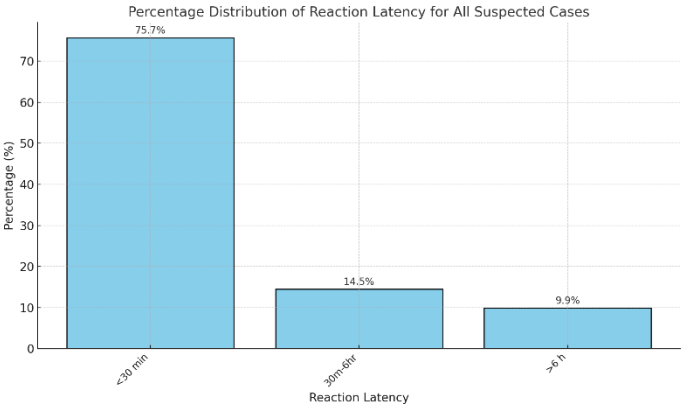
Intraoperative reactions	No. (out of 152)	%
Amoxicillin	1	0.7
Cefazolin	1	0.7
Ceftriaxone	3	2.0
Ceftazidime	1	0.7



Cephalosporins, owing to their wide usage as first-line IV drugs, especially ceftriaxone, were the most common drugs suspected to be culprits in intraoperative reactions.

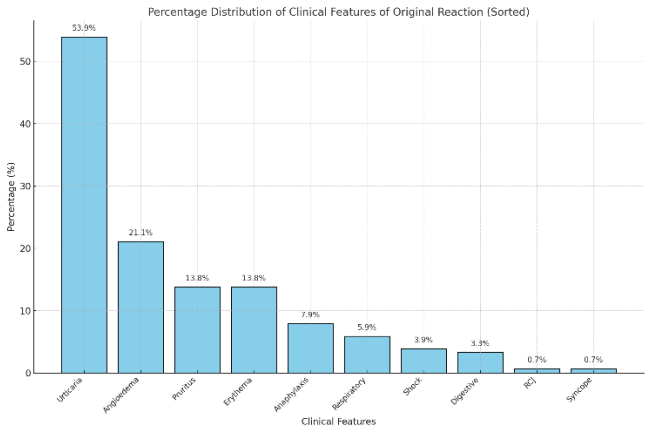
Reaction latency between drug consumption and onset of reaction

Reaction latency for all suspected cases	Number	%
<30 min	115	75.7
30m-6hr	22	14.5
>6 h	15	9.9



Clinical features of original reaction in all suspected cases (only done for immediate reactions)

Clinical features of original reaction in all suspected cases (only done for immediate reactions)	Number=152	%
Urticaria	82	53.9
Angioedema	32	21.1
RCJ	1	0.7
Respiratory	9	5.9
Digestive	5	3.3
Anaphylaxis	12	7.9
Pruritus	21	13.8
Erythema	21	13.8
Shock	6	3.9
Syncope	1	0.7



The Food Allergy Severity Score (FASS) grading of primary reaction in suspected cases (done only in acute and subacute reactions)

FASS of original reaction in suspected cases (done only in acute and subacute reactions)	Number=120	%
G1	3	2.5
G2	77	64.2
G3	4	3.3
G4	7	5.8
G5	10	8.3
Others	19	15.8
Not recorded	17	-

FASS was done only in 120 cases. It could successfully categorize the severity of the initial reaction in 84.2% of cases.
The following symptoms couldn't be recorded by the FASS scale (more than 1 symptom were often present in a single patient)

Isolated angioedema x 9 cases

Erythema x 3 cases

Palatine and lingual ulcers x 1 cases

Pruritus x 2 cases

Itching x 2 cases

Sensation of warmth x 2 cases

Dizziness and generalized malaise x 1 case

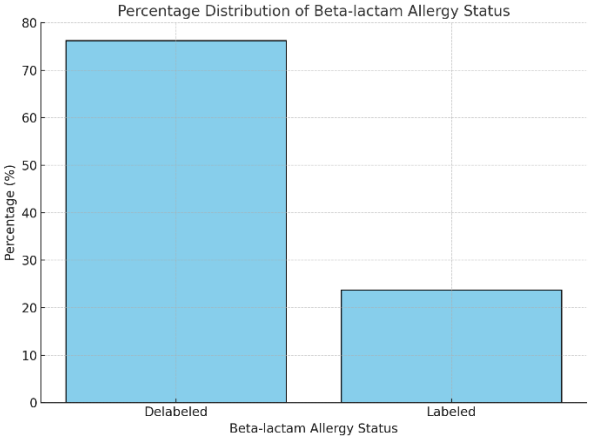
Clinical features of delayed reactions in suspected cases

Clinical features of original reaction (delayed) in suspected cases	Number	%
Urticaria	10	6.5
MP rash	13	8.4
FDE	0	0.0
Scar	0	0.0
Angioedema	4	2.6
Palmoplantar pruritus and scaling	1	0.6

2. Subgroup analysis

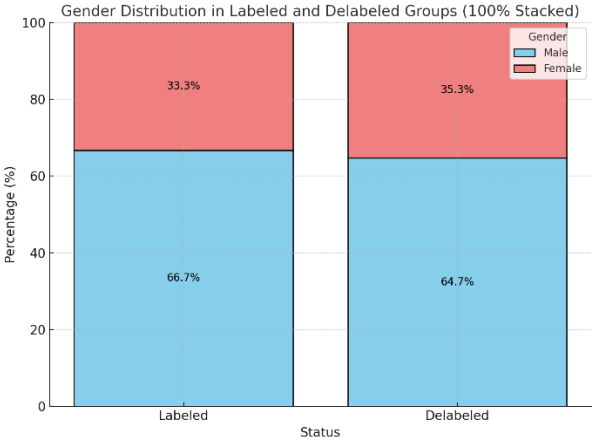
Final Diagnosis

Beta-lactam allergy	No. (out of 152)	%
Delabeled	116	76.3
Labeled	36	23.7



Gender versus diagnosis

Gender	Labeled (Out of 36)	%	Delabeled (Out of 116)	%
Male	24	66.7	75	64.7
Female	12	33.3	41	35.3

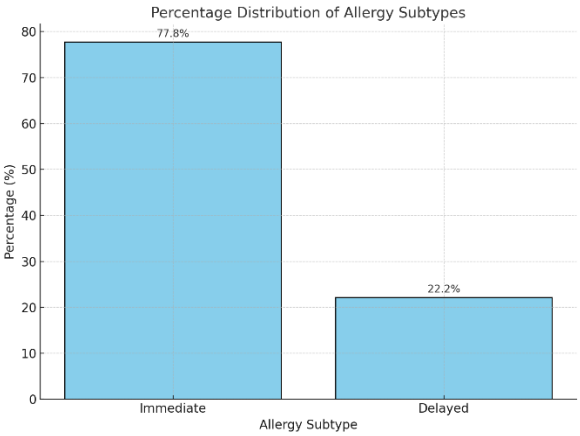


The chi-square statistic is 0.4868. The p-value is .485343. The result is not significant at p < .05.

Inference: Male patients were more likely to present with complaints of drug allergy and also more likely to be labelled as drug allergic.

Allergy subtype

Allergy subtype as per final diagnosis	Number (out of 36)	%
Immediate	28	77.8
Delayed	8	22.2

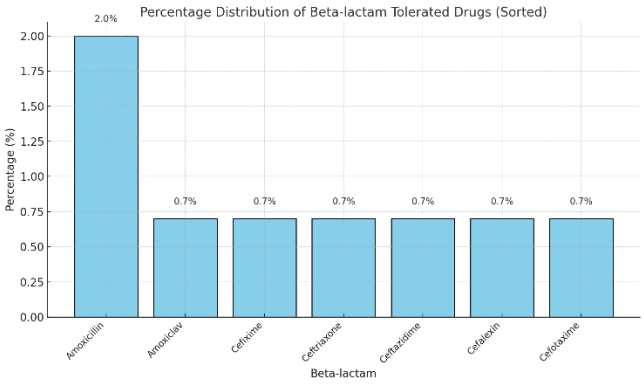


Immediate allergies were much more common than delayed. However, patch tests and LLT were not found to be helpful in making the diagnosis. Nevertheless, the delayed readings of the skin prick test, intradermal test, and DPT could proficiently diagnose delayed reactions.

Beta-lactam tolerated by suspected cases post-reaction

Beta-lactam tolerated by suspected cases post-reaction	No. (out of 152)	%

Amoxicillin	3	2.0
Amoxiclav	1	0.7
cefixime	1	0.7
ceftriaxone	1	0.7
ceftazidime	1	0.7
cefalexin	1	0.7
cefotaxime	1	0.7



While seeking history about the tolerance of similar drugs following the primary drug reaction, 9 patients had tolerated beta lactams on a later date.

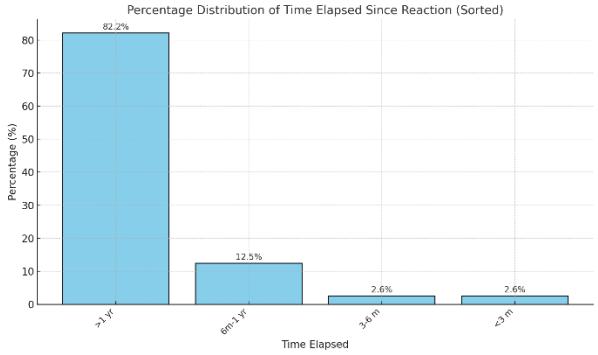
Out of 9 patients who later tolerated beta-lactams, 7 were ultimately labeled as 'non-allergic' by the end of the study. But 2 were labelled as allergic.

- The patient who tolerated amoxiclav was diagnosed as allergic to cephalosporins and was advised to avoid the entire cephalosporin group but could safely use other beta-lactams.
- The patient who tolerated ceftriaxone was found to be allergic to aminopenicillins and aminocephalosporins, but tolerant to penicillin.

This suggests that many beta-lactam allergies may be overdiagnosed. The findings suggest selective allergy patterns (e.g., cephalosporin allergy with tolerance to amoxiclav) and stress the need for individualized testing to avoid unnecessary drug restrictions.

Time elapsed between reaction and testing

Time elapsed	No. (out of 152)	%
>1 yr	125	82.2
6m-1 yr	19	12.5
3-6 m	4	2.6
<3 m	4	2.6



Mean duration

Duration between primary reaction and allergy testing		
Mean	55.04	Range
SD	56.6	12-400 days

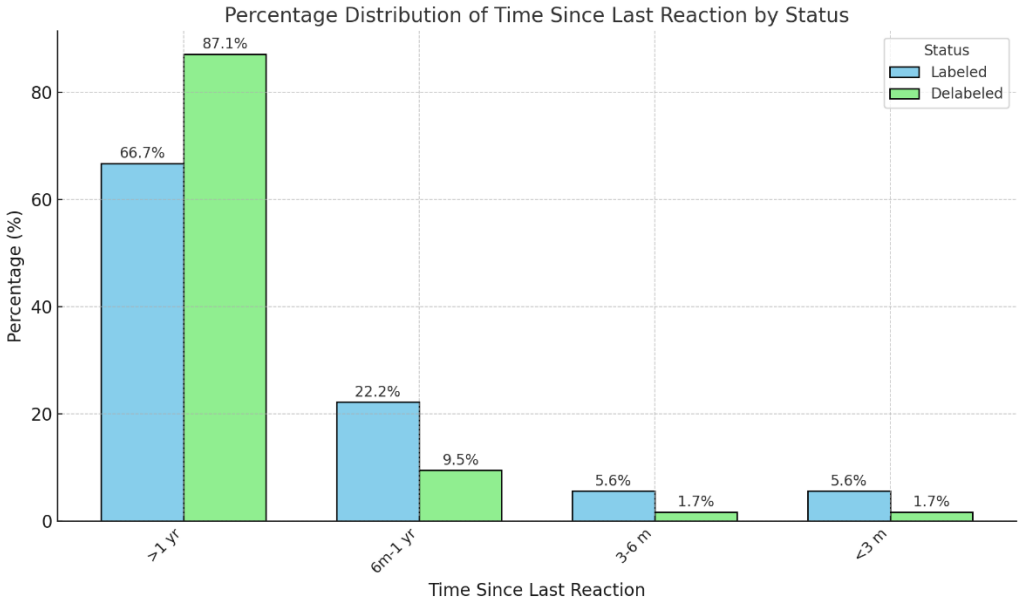
The mean duration between the primary reaction and allergy testing was 55.04 days (SD: 56.6, range: 12–400 days). The high variability was likely due to the COVID-19 pandemic, which disrupted patient mobility, required allergology staff to be posted in COVID-19 wards, and introduced additional demands for testing suspected vaccine allergies.

Mean duration (only for labeled cases)

Duration between tests (only for labeled cases)		
Mean	62.2	Range
SD	47.9	28-162 days

Duration versus diagnosis

Time since last reaction	Labeled	%	Delabeled	%
>1 yr	24	66.7	101	87.1
6m-1 yr	8	22.2	11	9.5
3-6 m	2	5.6	2	1.7
<3 m	2	5.6	2	1.7



The chi-square statistic is 12.0443. The p-value is .007233. The result is significant at $p < .05$.

The chi-square statistic is 12.0443 with a p-value of 0.0072, indicating a significant effect of the time between allergic reaction and testing on labeling versus delabeling ($p < 0.05$). Patients tested within 6 months of the reaction were more likely to be labeled as allergic.

However, this correlation does not imply causation and may be influenced by the small sample size and skewed data.

Incidence of other beta-lactams implicated in reactions in the past

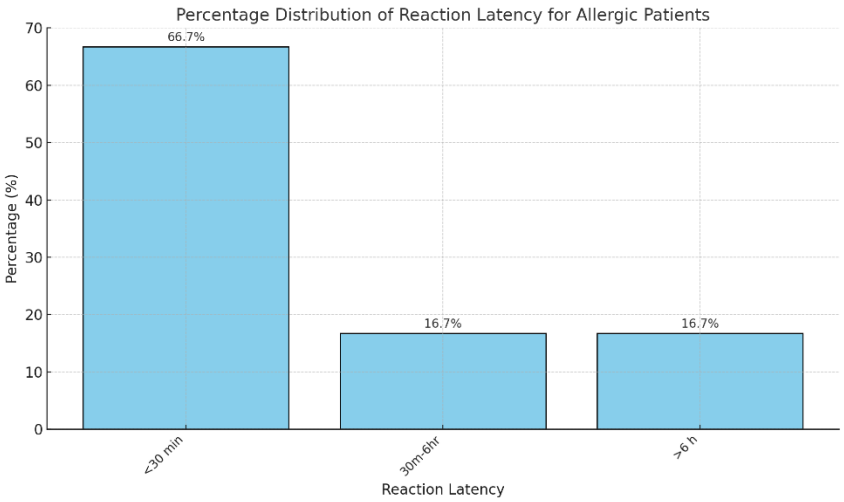
	Number	%

Other beta-lactams implicated in reactions in the past	8	5.3

Among 8 patients (5.3%) with past reactions to other beta-lactams, only 1 was ultimately labeled as allergic after testing. This suggests that patient recall is not a reliable indicator of true beta-lactam allergy. Interestingly, this patient was found allergic to aminopenicillin and aminocephalosporin but tolerant to penicillin—the very drug initially suspected, for which the test result was negative. There is a lot of complexity and unpredictability with clinical histories in allergy diagnosis.

Latency in labeled cases

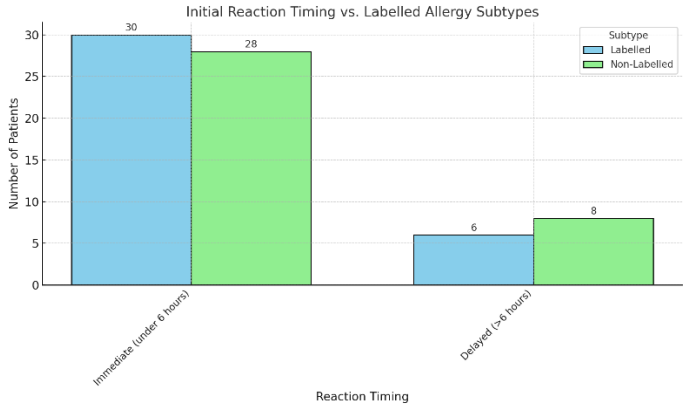
Reaction latency for all allergic patients	Number	%
<30 min	24	66.7
30m-6hr	6	16.7
>6 h	6	16.7



Reaction latency versus diagnosed allergy subtype in labeled cases

	Initial reaction	Labeled allergy subtype
Immediate (under 6 hours)	30	28
Delayed (>6 hours)	6	8

The chi-square statistic is 0.3547. The p-value is .551476. The result is not significant at p < .05.



We observed a really good concordance between the reaction latency of the initial reaction and the diagnosed reaction latency in labeled cases.

FASS in labeled allergic cases

FASS of original reaction in beta-lactam allergy labeled cases (done only in acute and subacute reactions)	Number=30	%
G1	0	0.0
G2	15	50.0
G3	2	6.7
G4	5	16.7
G5	6	20.0
Others	2	6.7
Not recorded	0	0.0

In labeled cases, FASS demonstrated excellent agreement, accurately recording reaction severity in 28 of 30 acute and subacute cases. Notably, G1 in FASS (oral allergy syndrome), typically associated with food allergies, was recorded in 3 beta-lactam allergy cases that were later delabeled. This likely reflects recall bias or observer error, as none of the confirmed drug allergy cases exhibited G1.

FASS shows strong concordance in predicting reaction severity, supporting its application in drug allergy evaluation. However, 2 confirmed allergy cases were uncategorized by FASS—one with maculopapular exanthema and the other with pruritus, both key cutaneous markers of drug allergy that can help distinguish allergies from viral rashes, especially during infections.

A modified FASS incorporating erythema, maculopapular rash, and pruritus could enhance its utility for drug allergies, particularly for antibiotics, which are often administered during infections with overlapping symptoms.

Clinical features of delayed reaction in labeled cases

Clinical features of original reaction (delayed) in labeled cases	Number (N=6)	%
Urticaria	1	16.7
MP rash	4	66.6
Angioedema	1	16.7

Maculopapular rash was the most common cutaneous manifestation in labeled cases with delayed reaction.

3. **Diagnostic prcedures**

In vitro tests done in suspected cases

In vitro tests done in suspected cases	Number	%
ImmunoCAP	29	19.1
BAT	18	11.8
LTT	6	3.9

1. IgE

IgE to beta-lactam tested in 29 cases	Number	%
Positive	9	31.0
Negative	20	69.0

IgE testing inference: All 9 patients were diagnosed as allergic after testing. Only 1 tested positive on BAT (with cefuroxime as the alternative drug).

- 8 had immediate allergies, and 1 had delayed allergy.
- Allergy profiles:
    - 4: Allergic to aminopenicillins and aminocephalosporins, but tolerant to penicillin.
    - 3: Allergic to aminopenicillins, aminocephalosporins, and penicillin.
    - 2: Allergic to aminopenicillins, aminocephalosporins, cephalosporins, and penicillin.
    - 1: Allergic only to clavulanic acid.

Conclusion: IgE testing had the highest diagnostic yield for aminopenicillins and aminocephalosporins.

2. BAT

Basophil activation test (done in 18 cases)		
Positive	4	22.2
Negative	14	77.8

All BAT positive cases were diagnosed with beta lactam allergy eventually.

However, LTT (lymphocyte transformation test) was negative in all

Inference: In-vitro tests have a 100% sensitivity but very low specificity.

3. Serum Tryptase Level

1) Basal Tryptase Levels

- Assessed in 10 cases:
    - Range: 2.98–10.2 ng/ml
    -

Basal Tryptase Level	De-labeled Cases	Labeled Cases
0–8.5 ng/ml*	5	2
>8.5 ng/ml	1	2
Basal tryptase levels >8.5 ng/ml can be suggestive of hereditary alpha tryptasemia (HAT), and such cases tend to have more severe reactions.		

- Chi-square analysis: Chi-square statistic = 1.2698, p-value = 0.2598.
    - Of these two positive cases with basal tryptase >8.5 ng/ml, one Grade 2 FASS reaction (male) and one Grade 5 FASS reaction (female) were noted.
    - The Grade 5 FASS reaction patient experienced anaphylactic shock and was diagnosed as allergic to aminopenicillin and aminocephalosporin, but tolerant to penicillin.

2) Acute Tryptase Levels

- Assessed in 10 cases during acute reactions:
    - Two readings were taken at least 2 hours apart in 8 cases.

Acute Tryptase Reading	De-labeled Cases	Labeled Cases
Indicative of allergic reaction (fall observed between two readings)	1	3
Non-indicative	4	2

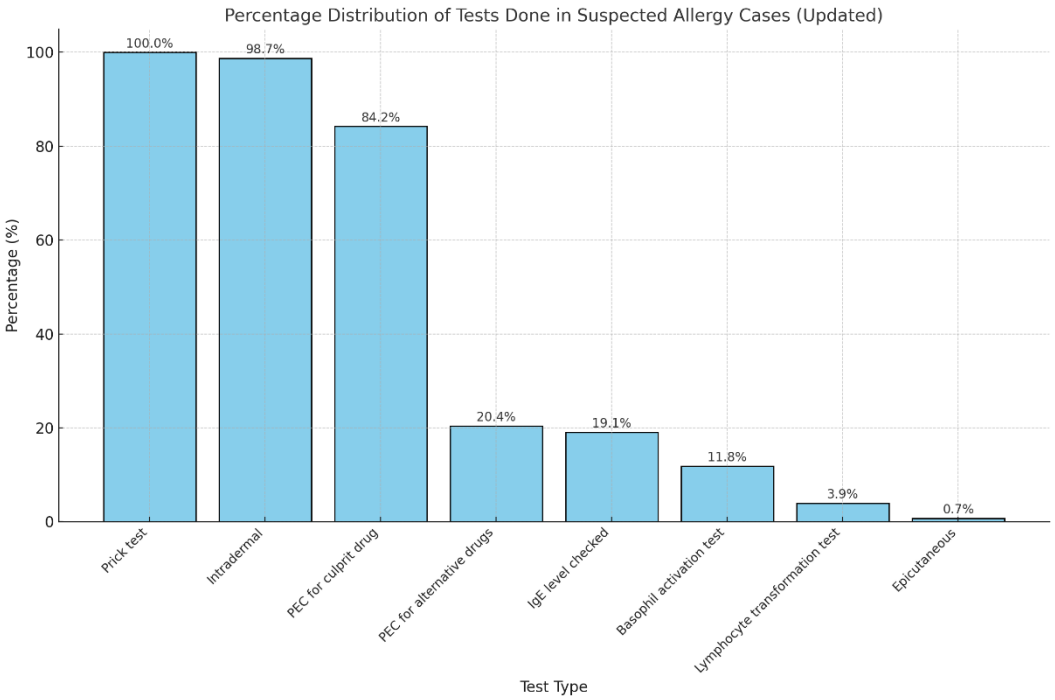
- Chi-square analysis: Chi-square statistic = 1.6667, p-value = 0.1967.

Inference:

1. Basal Tryptase Levels:
    - Elevated basal tryptase levels (>8.5 ng/ml) suggest the possibility of HAT, though the result was not statistically significant in distinguishing between labeled and de-labeled cases.
    - Anaphylaxis and Grade 5 FASS reactions highlight the need for careful evaluation of tryptase in severe cases.
2. Acute Tryptase Levels:
    - A fall in tryptase between two readings is more indicative of an allergic reaction, but the result was not statistically significant in predicting labeled versus de-labeled cases.

Bed side tests done in all patients with suspected allergy

Bed side tests done in all patients with suspected allergy (n=152)	Number	%
Epicutaneous	1	0.7
Prick test	152	100.0
Intradermal	150	98.7
PEC for culprit drug	128	84.2
PEC for alternative drugs	31	20.4



Home challenge for delayed reaction

Home challenge test done only in 2 cases	
Positive	1
Negative	1

A home challenge test, conducted as part of a drug provocation test for suspected delayed drug allergy, was performed over 2–5 days. It yielded a positive result in 1 of 2 cases, with the positive reaction occurring to cefixime in a delayed manner on day 3.

Prick test was done in all cases

Prick test (results with first test)	N=152	%
Positive for culprit	4	2.9
Positive for alternatives	2	1.3
Negative	146	96.1

Intradermal test was done in 150 cases

Intradermal test	N=150	%
Positive for culprit drug	4	2.7
Positive for alternatives	3	2.0
Negative	140	93.3
Delayed positive	3	2.0

DPT was done in a total of 133 cases (129 for suspected and 31 for alternative drug)

DPT for suspected drug	N=129	%
Positive	12	9.3
Negative	116	89.9
Delayed positive	1	0.8

DPT for alternative drug	N=31	%
Positive (for Amoxicillin)	2	6.5
Negative	29	95.5
Delayed positive	0	0

Retested patients

Retested	Number	%
Yes	90	59.2
No	62	40.8

In patients where more than 1 year had elapsed between the reaction and testing, retesting was performed. Out of 152 cases, only 90 (59.2%) underwent retesting. Among those labeled with a drug allergy, 9 were retested, yielding 4 additional positive cases, increasing the diagnostic yield. Ideally, retesting should be conducted within 1 to 6 months, preferably after 1 month.

Retest yield

Type of test	Positives on 1st test	Positives after retest
Skin test (prick and intradermal test)	16	20*
DPT	15	16
*All new positives cases detected with retest were intradermal positive. were 4 (1 patients with penicillin, 2 with amoxicillin and 1 with clavulanic acid): one of those with amoxicillin positivity also had PEC positive (alternative)		

Retesting timeframe

Retest (cutaneous & DPT)	Number (n=90)	%
Same day	79	87.8
Different days	11	12.2

Does retesting in parts affect the outcome?
Of all the labeled cases, 9 underwent retesting. 8 positive cases were retested on the same day, while 1 was retested on different days. This could potentially suggest that retesting on different days may impact the results and tend to give less positives, but further data would be needed for confirmation.

Does the retest yield of skin tests vs. DPT suggest that DPT has a lower threshold for reactions?
Yes, the data seems to support this. The retest yielded 4 new positive cases from skin tests but only 1 new case from PEC (provocation test). This suggests that DPT may require a lower reaction threshold yielding positive results even without the need for a retest compared to skin tests, making DPT a more sensitive test than skin test.

Diagnostic yield of tests

	Final Diagnosis	
	Labeled	Delabeled
Skin test +	20	0
Skin test -	16	116

	Final Diagnosis	
	Labeled	Delabeled

DPT +	16	0
DPT -	0	117

Comparison:

1. Skin Test:

    - Sensitivity: Moderate (55.6%)

    The skin test correctly identifies nearly than half of the individuals with the drug allergy, meaning it has a relatively high false negative rate (44.4% of allergic patients test negative). This limits its utility in detecting all cases of drug allergy.

    - Specificity: Excellent (100%)

The skin test is perfect at ruling out drug allergy in non-allergic individuals, as there are no false positives. This makes it very reliable for confirming that someone does not have a drug allergy if the test is negative.

2. DPT:

    - Sensitivity: Excellent (100%)

    - Specificity: Excellent (100%)

- DPT demonstrates perfect sensitivity and specificity in this dataset, making it the gold standard for confirming allergies. However, DPT requires more resources and may carry a higher risk compared to skin tests.

Inference and limitations of the study:

a) 100% sensitivity and specificity could be a verification bias:

Verification bias happens when the results of a test (in this case, DPT) directly influence or are used to establish the "gold standard" diagnosis. Since the final diagnosis relies on the DPT, it is inevitable that the test will appear to have 100% sensitivity and specificity, as it is both the test and the definitive criterion.

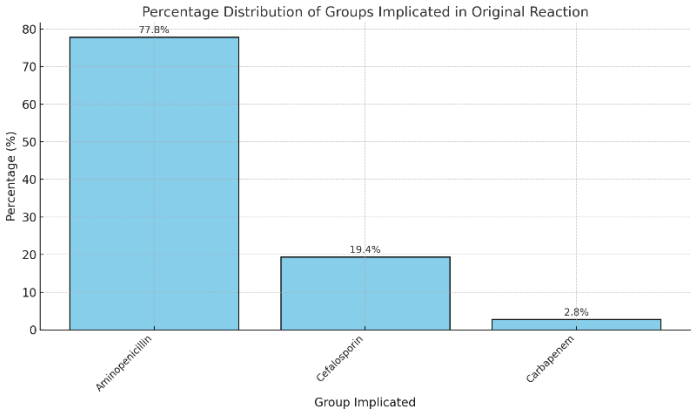
Implication:

1. Inflated Accuracy Metrics: Since no cases would be labeled "false positive" or "false negative" (as the DPT result determines the diagnosis), the test's sensitivity and specificity will always look perfect.
2. Circular Reasoning Issue: Using DPT as both the diagnostic tool and the gold standard creates a circular reasoning problem. This limits the ability to generalize the results to broader, real-world settings where the DPT might face uncertain cases.

Solution: Larger Validation Studies: Conduct studies in a broader population to include more ambiguous cases, which could reveal limitations in sensitivity or specificity.

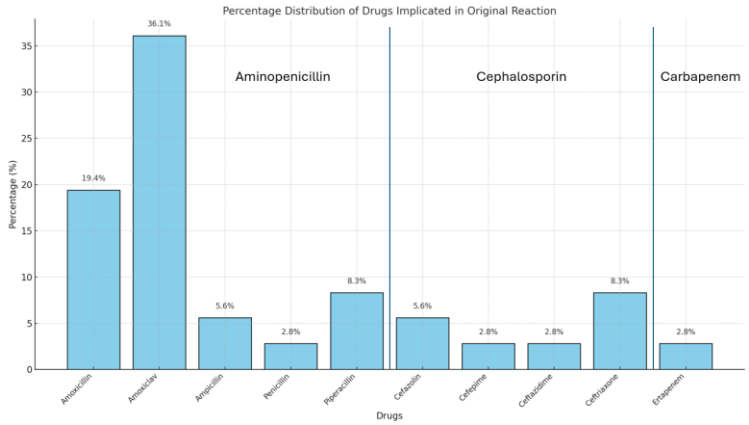
Detailed analysis of allergy in labeled cases

Group implicated in the original reaction	Total	%
Aminopenicillin	28	77.8
Cefalosporin	7	19.4
Carbapenem	1	2.8



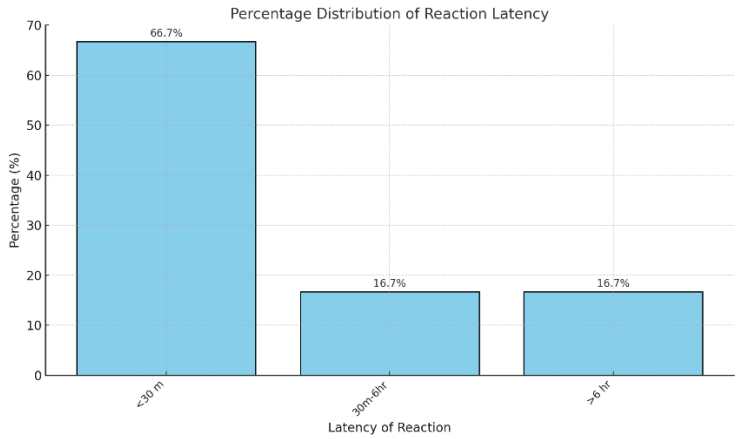
Group implicated in the original reaction	Drug	Number	Total	%
Aminopenicillin	Penicillin	1	28	2.8
	Amoxicillin	7		19.4
	Ampicillin	2		5.6
	Amoxiclav	13		36.1
	Piperacillin	3		8.3
Cefalosporin	Cefazolin	2	7	5.6
	Ceftriaxone	3		8.3
	Ceftazidime	1		2.8

	Cefepime	1		2.8
Carbapenem	Ertapenem	1	1	2.8



Reaction latency

Latency of reaction	Number	%
<30 m	24	66.7
30m-6hr	6	16.7
>6 hr	6	16.7

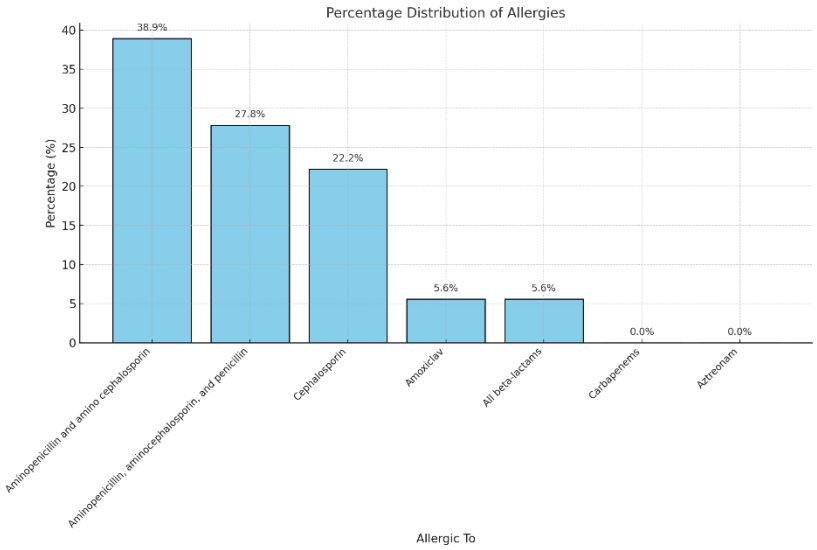


Final Diagnosis

Allergic to:	Immediate	Delayed

Aminopenicillin and amino cephalosporin	13	1
Aminopenicillin, aminocephalosporin, and penicillin	10	0
Cephalosporin	7	1
Carbapenems	0	0
Aztreonam	0	0
Amoxiclav	2	0
All betlactams	2	0

Allergic to:	No. (out of 36)	%
Aminopenicillin and amino cephalosporin	14	38.9
Aminopenicillin, aminocephalosporin, and penicillin	10	27.8
Cephalosporin	8	22.2
Amoxiclav	2	5.6
All beta-lactams	2	5.6
Carbapenems	0	0.0
Aztreonam	0	0.0



Clinical features of the initial reaction	No.out of 36	%
Urticaria	22	61.1
Angioedema	6	16.7
RCJ	5	13.9
Respi	5	13.9
Digestive	1	2.8
Anaphylaxis	6	16.7
Others (1 each: MP rash, malaise, throat blockage, syncope, blurring of vision)	5	13.9
Itching	4	11.1

Analysis of Monosensitization and Multisensitization

We assessed the prevalence of monosensitization (allergy to a single drug or drug class) and multisensitization (allergy to multiple drugs or drug classes) among patients. Our goal was to determine how many patients had selective reactions to the same drug versus non-selective reactions to multiple drugs.

Below is a refined table summarizing the final diagnoses after skin tests, in vitro tests, and provocation tests, alongside the drugs initially suspected to have caused the primary reaction.

		Suspected allergenic drug during primary reaction			
Final Diagnosis	N	Aminopenicillin (Suspected Drug)	Cephalosporin (Suspected Drug)	Carbapenem (Suspected Drug)	Aztreonam (Suspected Drug)
Allergic to aminopenicillin + aminocephalosporin (tolerates penicillin)	15	24	1	0	0
Allergic to aminopenicillin + aminocephalosporin + penicillin	10	6	4	0	0
Allergic to cephalosporin	7	2	5*	0	0
Allergic to beta-lactam (non-selective)	2	2	0	0	0

Allergic to clavulanic acid	2	2	0	0	0
Delayed reaction to aminopenicillin + aminocephalosporin (tolerates penicillin)	2	2	0	0	0
Delayed reaction to cephalosporin	3	1	2	0	0
Delayed reaction to carbapenem	1	0	0	1	0
Delayed reaction to clavulanic acid	1	1	0	0	0

* Note: Out of these 5 patients allergic to cephalosporins, 4 were also allergic to aminopenicillins, aminocephalosporins, and penicillin.

Inference of these tables:

- Aminopenicillins:
    - Most frequent culprit (implicated in 28 cases).
    - High prevalence of delayed and non-selective reactions.
- Cefalosporins:
    - Secondary involvement, often in multisensitized individuals.
    - Selective cefalosporin allergy: N=7, but 4 of these had cross-reactions.
- Carbapenems:
    - Minimal involvement (1 case of delayed reaction).
- Clavulanic Acid:
    - Rare isolated allergy (2 cases).
- Beta-lactams:
    - Two isolated cases, highlighting less frequent broad-spectrum allergy.
- Selective Reactions: Dominated by aminopenicillins, with selective reactions accounting for most cases.
- Non-Selective Reactions: Primarily involve cross-reactivity between aminopenicillins and cefalosporins.
- Monosensitization: Uncommon, with clavulanic acid and beta-lactam-specific reactions making up a small proportion.
- Multisensitization: A significant proportion of cases, especially involving aminopenicillins and cefalosporins.

Clinical Implications

- Cross-reactivity between aminopenicillins and cefalosporins must be carefully evaluated to prevent unnecessary drug avoidance.
- Selective reactions, particularly to aminopenicillins, remain common and should guide clinical decisions in allergic patients.
- Rare cases of monosensitization (e.g., clavulanic acid or carbapenems) suggest the need for individualized allergy management.

Number of tests versus gender

Number of tests done to diagnose and rule out drug allergy			P value
For positives	Total number of tests	Average per person	
Males (n=24)	126	5.1±1.1	0.027
Female (n=12)	64	5.5±1.3	
Total (n=36)	190	5.3±1.3	
For negatives	Total number of tests	Average per person	
Males (n=75)	437	5.6±1.4	0.009
Females (n=41)	243	5.9±1.5	
Total (n=116)	680	5.7±1.3	

Inference: Women required more number of tests to both diagnose and de-label beta-lactam allergy.

Summary and Noteworthy Findings

1. Efficacy of Diagnostic Protocols

- **Delabeling Success Rate**:
    - Out of 152 patients suspected of beta-lactam allergy, **116 (76.3%)** were delabeled after comprehensive testing.
    - Only **36 (23.7%)** were confirmed allergic (labeled).
- **Diagnostic Test Yield**:
    - **Drug Provocation Test (DPT)**: Gold standard with **100% sensitivity and specificity**.
        - Positive for culprit drug: **12 cases (9.3%)**.
        - Delayed positive: **1 case (0.8%)**.
    - **Skin Tests** (Prick and Intradermal): Moderate sensitivity (**55.6%**) but high specificity (**100%**).
        - Positive for culprit drug: **20 cases (13.2%)**.
        - All new positive cases upon retesting were detected by intradermal testing (n=4).

2. Retesting Outcomes

- **Timeframe Impact**:
    - Retesting conducted after **≥1 year** yielded 4 additional positive cases among labeled patients.
    - Retesting yield:
        - Skin test: 4 new positives.
        - DPT: 1 new positive.
    - Diagnostic accuracy significantly decreased with delays in testing.
- **Timing of Retesting**:
    - **87.8%** retested on the same day yielded more positives compared to those tested on different days (**12.2%**).

3. Cross-Reactivity Patterns

- **Cross-Reactivity Between Beta-Lactam Subgroups**:
    - **Aminopenicillins**: Most implicated group (77.8% of labeled cases).
    - **Cefalosporins**: Secondary involvement with high multisensitization (7/36 labeled cases).
    - **Carbapenems**: Minimal involvement (1 case with delayed reaction).
    - **Clavulanic Acid**: Rare isolated allergy (2 cases).
- **Selective vs Non-Selective Reactions**:
    - **Selective Allergy**: Common in aminopenicillins.
    - **Non-Selective Allergy**: High cross-reactivity observed between aminopenicillins and cefalosporins.

4. Clinical Phenotypes

- **Reaction Subtype**:
    - **Immediate Reactions**: 28/36 (77.8%).
    - **Delayed Reactions**: 8/36 (22.2%).
    - Delayed reactions frequently diagnosed using intradermal tests and delayed readings of skin tests.
- **Reaction Latency**:
    - Immediate (<30 min): **66.7%**.
    - Intermediate (30m–6 hr): **16.7%**.
    - Delayed (>6 hr): **16.7%**.
- **Clinical Features**:
    - Most common: **Urticaria (61.1%)**.
    - Severe reactions (e.g., anaphylaxis): **6/36 (16.7%)**.
    - Delayed reactions: Predominantly maculopapular rash (66.6%).

5. Sensitization Profiles

- **Monosensitization**: Uncommon.

    - Rare isolated cases to clavulanic acid (n=2) or carbapenems (n=1).

- **Multisensitization**: Observed in most labeled cases, especially involving aminopenicillins and cefalosporins.

- **Notable Findings**:

    - **14 patients** were allergic to both aminopenicillins and aminocephalosporins but tolerant to penicillin.

    - **10 patients** were allergic to aminopenicillins, aminocephalosporins, and penicillin.

6. In Vitro Testing

- **IgE Testing**:

    - Diagnostic yield: **31.0% positivity rate** (9/29).

    - Best performance for aminopenicillins and aminocephalosporins.

- **Basophil Activation Test (BAT)**:

    - Sensitivity: High, with **22.2% positivity rate** (4/18).

    - Specificity: Low; false negatives observed.

- **Lymphocyte Transformation Test (LTT)**:

    - No positive results observed.

- **Serum Tryptase Levels**:

    - Raised acute tryptase levels can be a good indicative of allergic reactions, but due to variable reporting and infrequent usage in emergency care, their utility often went underutilized by a lot.

7. Delabeling Patterns

- **Beta-Lactam Tolerance Post-Reaction**:

    - 9 patients later tolerated beta-lactams.

    - **7 of these were delabeled as non-allergic**.

    - Specific patterns:

        - Amoxiclav-tolerant patient was found allergic to cefalosporins.

        - Ceftriaxone-tolerant patient was allergic to aminopenicillins and aminocephalosporins.

8. Gender-Based Differences

- Women required significantly more diagnostic tests for both diagnosis and delabeling:
    - Positive cases: **5.5 tests/person** (women) vs **5.1 tests/person** (men), p = 0.027.
    - Negative cases: **5.9 tests/person** (women) vs **5.6 tests/person** (men), p = 0.009.

9. Food Allergy Severity Score (FASS)

- Successfully graded **28/30 labeled cases**.
- Limitations:
    - Failed to categorize 2 confirmed allergy cases (e.g., maculopapular rash, pruritus).
    - Suggested modification: Inclusion of erythema, maculopapular rash, and pruritus for drug allergy evaluation.

10. Cost-Effectiveness

- Delabeling protocols significantly reduced the need for alternative antibiotics, potentially reducing associated healthcare costs and risks (e.g., resistance, side effects).

Conclusion

This study highlights the utility of diagnostic protocols, particularly DPT, in accurately diagnosing beta-lactam allergies and minimizing false-positive cases. Cross-reactivity patterns between beta-lactam subgroups, the utility of FASS, and the importance of timely retesting are critical insights. However, further research with larger cohorts and validation studies is needed to refine these findings and address limitations such as verification bias in DPT.

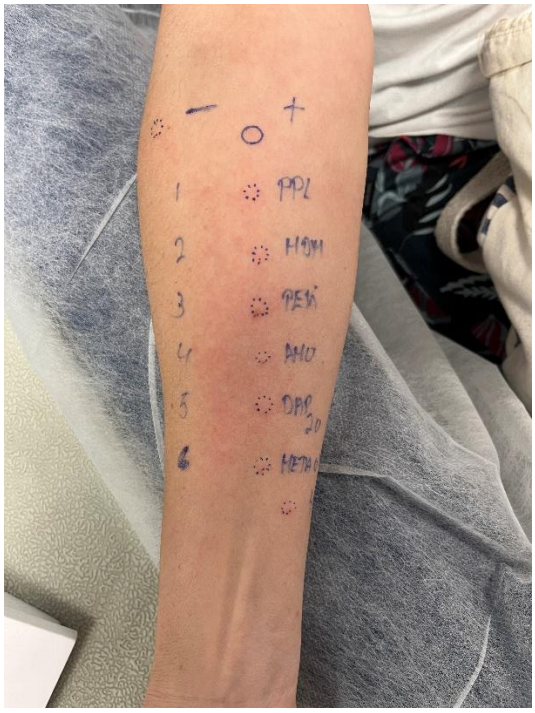


Figure 1: Skin testing over the ventral aspect of the forearm. The right side panel demonstrates a prick test, and the left side shows an intradermal test.

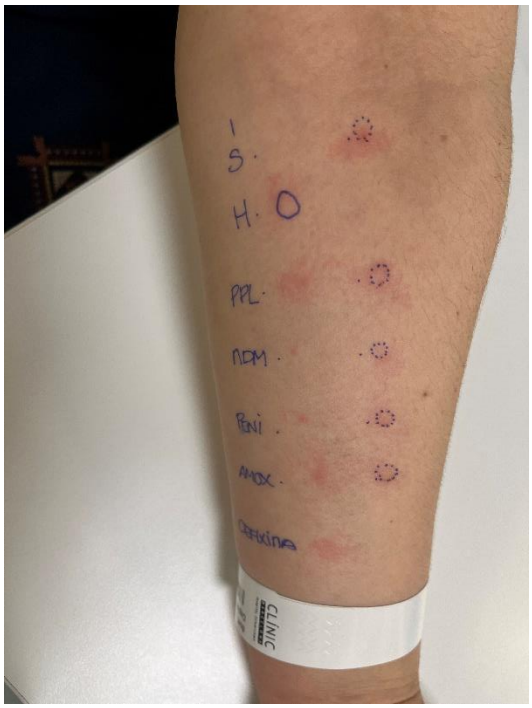


Figure 2: Close-up view of a skin test showcasing both prick and intradermal techniques.

Delayed positive reaction observed to amoxiclav during intradermal testing

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Reflecting on My Fellowship in Allergology at Hospital Clínic de Barcelona

I recently concluded my fellowship in allergology at **Hospital Clínic de Barcelona**, under the mentorship of the exceptional **Dr. Rosa Muñoz Cano**, Head of Research in the Department of Allergology, and with guidance from the Department Head, **Dr. Joan Bartra**.

This fellowship was nothing short of transformative. Over the past two years, I have had the privilege of learning directly from **Dr. Rosa**, not only about allergology but about mentorship, humility, and collaboration—qualities that are often rare in hierarchical medical systems back home.

Clinical and Academic Exposure

My weekly rotations introduced me to a variety of allergic conditions, ranging from drug allergies to food allergies and aeroallergens, including **LTP (lipid transfer protein) allergies**, **NSAID reactions**, and **radiocontrast and chemotherapy hypersensitivities**. I was also immersed in the center's state-of-the-art diagnostic and therapeutic protocols, including:

- **Skin testing** (prick, intradermal, and epicutaneous) and **drug provocation tests (DPT)**.
- Advanced **in vitro testing** in collaboration with the Immunology Department, such as **specific IgE**, **basophil activation tests**, and **lymphocyte transformation tests**.
- Desensitization protocols for **chemotherapy agents**, **antibiotics**, and **food allergens**.
- **Immunotherapy** for aeroallergens and chronic conditions, including biological therapies for **urticaria** and **asthma**.

What stood out was the department's focus on **de-labeling unnecessary drug allergies**. I learned how standardized protocols could demystify and debunk false 'drug allergies', helping patients avoid unnecessary medical and social restrictions.

Case Discussions and Presentations

Weekly meetings focused on complex cases involving drug, food, and aeroallergen allergies, as well as comorbidities like **anaphylaxis** and **asthma**. Weekly seminars covered cutting-edge treatments like biologics and emerging diagnostic tools.

A personal highlight was presenting my review on **the role of cofactors in food allergies in children**, which sparked a vibrant discussion with Dr Rosa, and helped me refine my ability to translate research into clinical practice.

Patient-Centric Workshops

I also attended an **anaphylaxis workshop**, where patients were taught to recognize symptoms of anaphylaxis, manage risks, and use adrenaline injectors correctly.

The Personal Touch

The warmth and inclusivity of my colleagues made my time at HCB unforgettable. Despite my limited grasp of **Castilian Spanish** and **Catalan**, my mentor and teammates—**Dr. Maria Ruano Zaragoza, Dr. David Loli Ausejo, Dr. Patricia Mir Ihara, Dr. Patricia Bigas, Dr. Giovanna Tincopa, Dr. Emilio Narvaez, and Dr. Alberto**—bridged the language gap with patience, humor, and camaraderie.

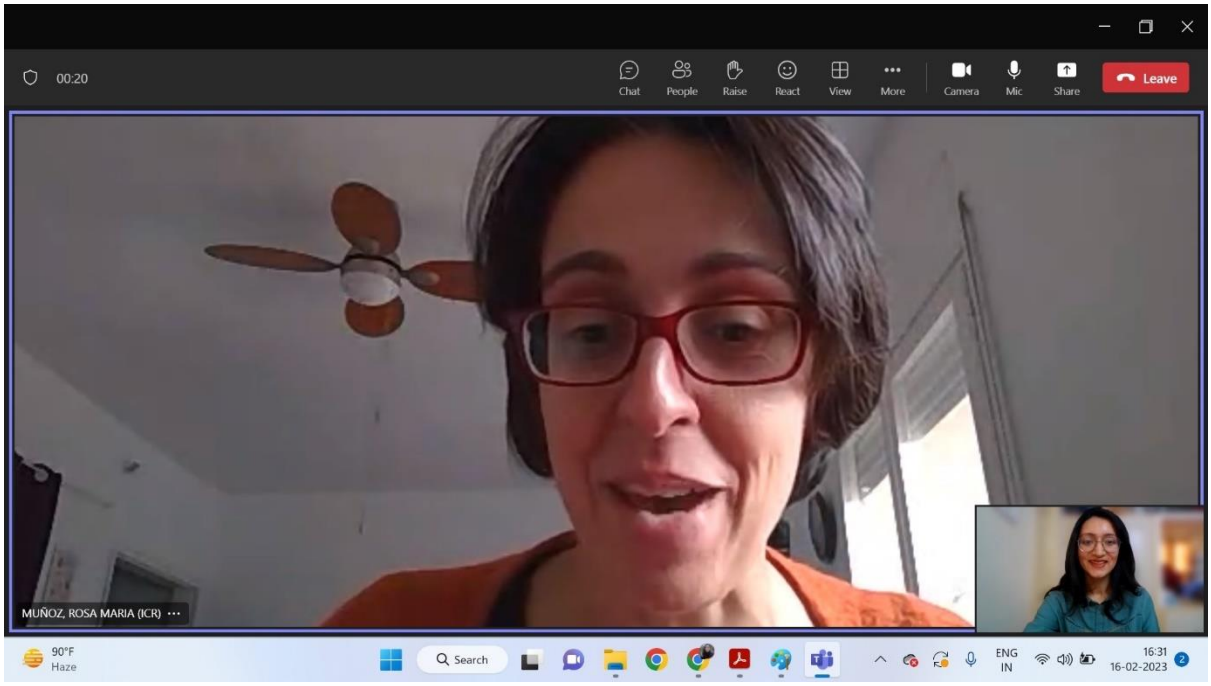
Leaving Barcelona was bittersweet. Handing in my hospital ID and apron felt like closing a chapter, but it’s a chapter that has profoundly shaped my career in allergology.

Looking Forward

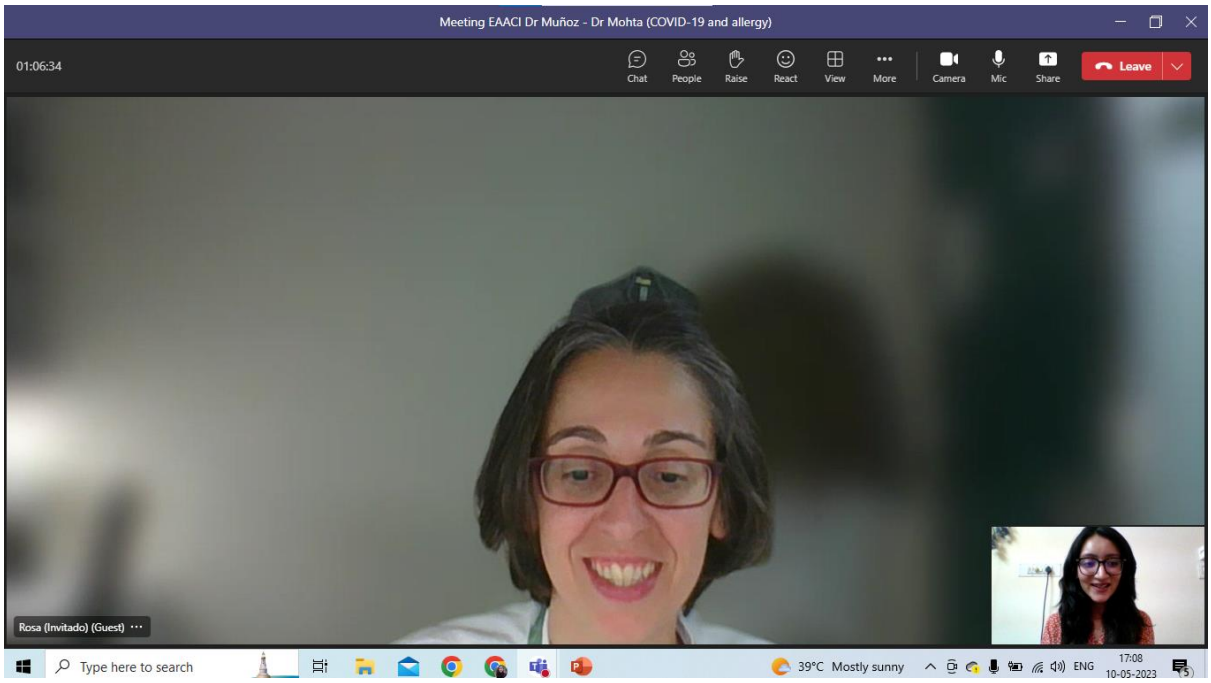
Interestingly, India doesn’t have allergology as a separate specialty yet—it’s bundled with dermatology, internal medicine, and ENT. But with all the intricate testing and growing understanding of immunology, I’m crossing my fingers that it becomes a proper branch someday. Until then, I’ll keep using whatever I’ve learned so far to make a difference wherever I can.

I cannot thank **EAACI**, **Dr. Rosa Muñoz Cano**, **Dr. Joan Bartra**, and the entire allergology team at HCB enough for this once-in-a-lifetime opportunity. It was more than a fellowship—it was an immersive journey into a specialty I’ve grown to deeply value.

With Dr. Rosa Muñoz Cano at the anaphylaxis out-patient clinic



The beginning of a wonderful relationship: Our first meeting in Feb, 2023.



Soon followed by many one-on-one sessions over the course of 2 years

Left to right: Me, Dr Patricia Bigas, Dr David Lolli, Dr Patricia Mir (consultants)

With Dr Maria Ruano

During one of the department parties

An overwhelmed self, captured in one of the hospital corridors on my last working day

To everyone reading this: if you ever get the chance to step out of your comfort zone and learn, do it! You might just find yourself in places (and with people) you'll never forget. :)

Alpana Mohta
MD, DNB, EAACI research fellow
Bikaner, India