

SYPHILIS: from Alpha to Omega

Martí Vall-Mayans

Department of Infectious Diseases

Badalona, Catalonia (Spain)

Salut/



Germans Trias i Pujol
Hospital



anys Hospital
Germans Trias



Resistance and penicillin allergy: problems to be solved

α MR: good news (for now)

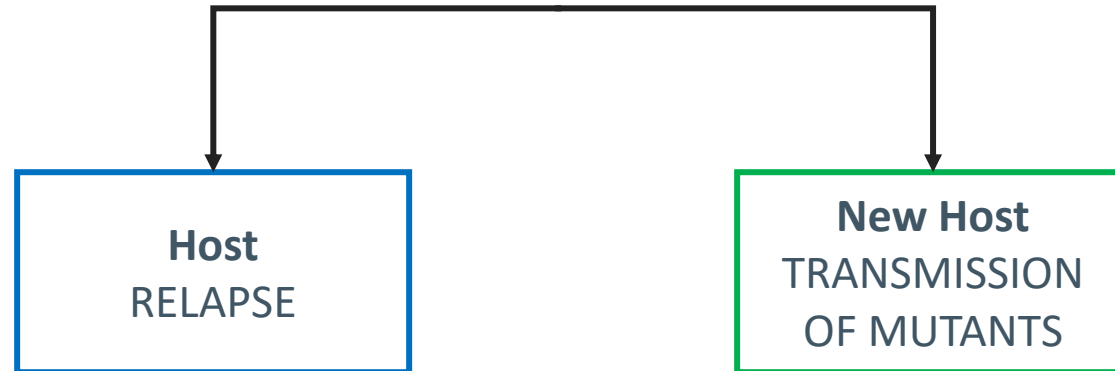
β LA: no good news (so far)

Antibiotic resistance for treatment of syphilis

Antimicrobial agent or class	Described mechanisms of resistance
Penicillins	No penicillin resistance documented in <i>T pallidum</i>
Tetracyclines	No tetracycline resistance documented in <i>T pallidum</i>
Macrolides	Chromosomal point mutations in the 23sRNA genes (A2058G and A2059G)
Cephalosporins	No cephalosporin resistance documented in <i>T pallidum</i>

Hypothesis regarding how the TP develops penicillin resistance-related mutants

- 25% TP neuroinvasion
 - BPG does not achieve therapeutic levels in CSF
 - Penicillin subtherapeutic levels in CNS
 - Selection pressure for mutants with low-level penicillin resistance



Penicillin resistance-related gene mutations of TP

- Penicillin binding proteins (PBP): *pbp1*, *pbp2*, *mrcA*
- B-lactamase: *Tp47*

> [Sex Transm Dis.](#) 2023 Aug 1;50(8):490-493. doi: 10.1097/OLQ.0000000000001810.
Epub 2023 Mar 23.

Doxycycline Postexposure Prophylaxis Could Induce Cross-Resistance to Other Classes of Antimicrobials in *Neisseria gonorrhoeae* : An In Silico Analysis

[Thibaut Vanbaelen](#)¹, [Sheeba Santhini Manoharan-Basil](#)¹, [Chris Kenyon](#)

Affiliations + expand

PMID: 36952471 DOI: [10.1097/OLQ.0000000000001810](#)

Abstract

We found that tetracycline resistance-associated mutations and genes in *Neisseria gonorrhoeae* are linked to mutations causing resistance to other antimicrobials. Therefore, the use of doxycycline postexposure prophylaxis may select for resistance to other antimicrobials.

Prevalence of reported allergy to penicillin?

1) 3%

2) 5%

3) 7%

4) 8%

5) 10%

PENICILLIN MAY BE AN OPTION FOR MORE PATIENTS THAN YOU THINK

Some patients incorrectly self-report penicillin allergy¹



Report being allergic



Are truly allergic

Many patients outgrow their penicillin allergy

80%

Lose their sensitivity after 10 years¹



Retesting for penicillin allergy may offer surprising results



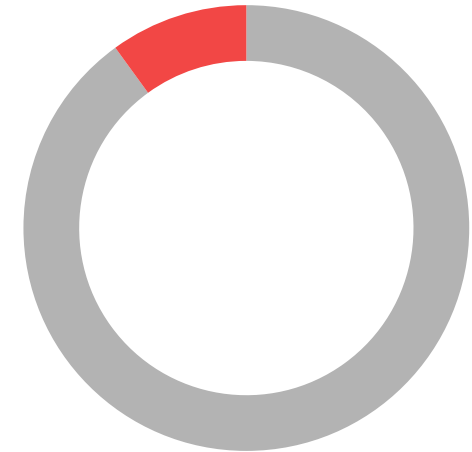
96% of tests are negative²



98% negative predictive value³

Penicillin allergy differential diagnosis

- Drug intolerance
- Idiosyncratic reaction
- Coincidental viral exanthem
- Drug-infection interaction (EBV)
- Side-effects



Untoward medical occurrences in patients who have received penicillin

- Adverse drug reaction (ADR): pharmacologically predictable
- Hypersensitivity reaction (HSR): ADR immunologically mediated
 - Immediate (IgE mediated)
 - Delayed (T-cell mediated)

Penicillin anaphylaxis

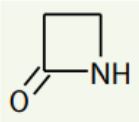
- 0.001% for parenteral exposures
- 0.0005% for oral exposures
- 1/52,000 -cephalosporins

In UK (1972-2007): **1** fatal case of amoxicillin anaphylaxis

β -Lactam structure and cross-reactivity

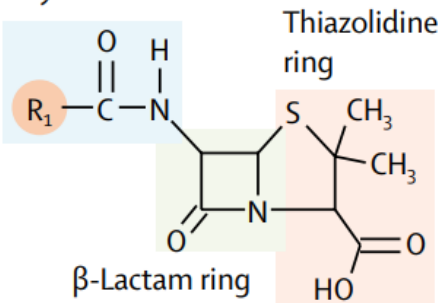
Basic structures

β -Lactam ring



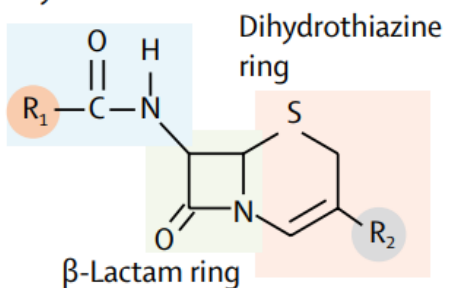
Penicillin structure

Acyl side chain

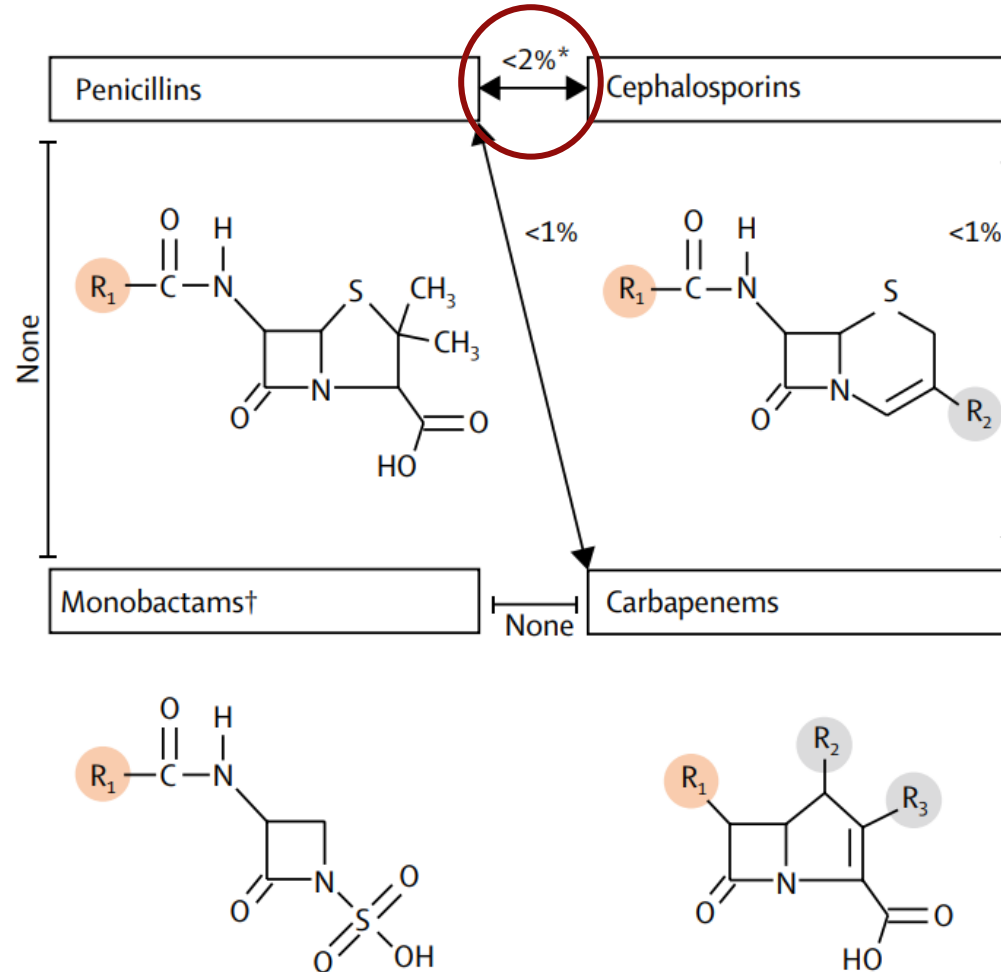


Cephalosporin structure

Acyl side chain



β -Lactam structures and rates of cross-reactivity



Clinically relevant cross-reactivity

Similar side-chains penicillins (R1):

- Penicillin VK and penicillin G

Shared side-chains, penicillins, and cephalosporins (R1):

- Amoxicillin[†] and cefadroxil, cefprozil, cefatrizine
- Ampicillin[†] and cefaclor, cephalexin, cephadrine, cephaloglycin

Shared side-chains cephalosporins (R1):

- Cefadroxil, cefprozil, cefatrizine
- Cefaclor, cephalexin, cephadrine, cephaloglycin
- Cefepime, ceftriaxone, cefotaxime, cefpodoxime, ceftizoxime
- Ceftazidime and aztreonam

No shared side-chains, penicillins, and cephalosporins (R1):

- Cefazolin

Management of persons who report a history of penicillin allergy

- 1) Medical history

- 2) Skin testing

- 3) Oral challenge

Questions to ask in a penicillin allergy assessment

SEVERITY—severe or nonsevere

1. Do you remember the details of the reaction?
2. How was the reaction managed? Did it require treatment or hospitalisation?

TIMING—**immediate** (onset within hours of first or second dose) or **delayed** (onset after days); **recent** or **distant past**

3. How long after taking the antibiotic did the reaction occur?
4. How many years ago did the reaction occur?

ANTIBIOTICS TOLERATED SINCE REACTION

5. Since the reaction, have you taken any other antibiotics without problems? Having tolerated an antibiotic before an allergic reaction does not mean you will tolerate it after the reaction.

STI: severity, timing, itinerary (course)

Medical history-based risk stratification for suspected diagnosis of β -lactam allergy

1. No evidence of an unexpected β -lactam hypersensitivity reaction

- Gastrointestinal reaction only (e.g., nausea, vomiting, diarrhea)
- Only nonspecific reaction (e.g., headache, rhinoconjunctivitis, palpitations), often associated with fear of drug hypersensitivity
- Urticaria with onset > 1 day after discontinuation of β -lactam or persisting for days after drug discontinuation
- Exanthem with onset > 1 week after discontinuation of β -lactam
- Only family history positive for drug hypersensitivity

2. Indications of questionable reactions with low risk

- Urticaria occurring only after a delay (> 6 hours after ingestion)
- Non-remembered reaction > 10 years ago without therapy
- Mild rash in childhood, especially associated with infection

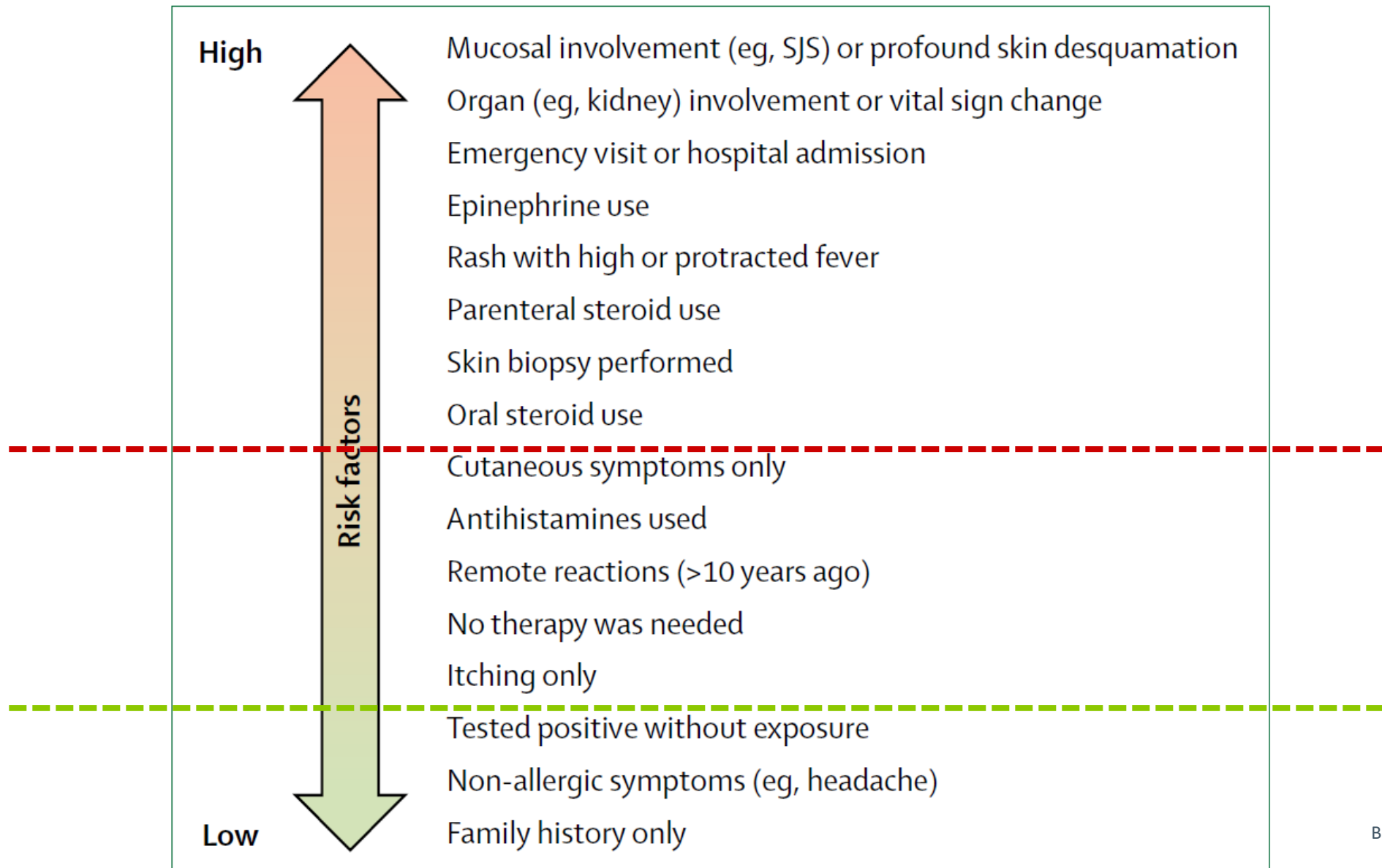
3. Evidence of non-severe delayed-onset drug exanthema

- Maculopapular (uncomplicated) drug-induced exanthema with therapy < 10 years ago

Medical history-based risk stratification for suspected diagnosis of β -lactam allergy

4. Indications of moderately severe immediate reactions
– Urticaria
– Angioedema
– Tachycardia
5. Evidence of severe drug reactions with high risk
– Vomiting, diarrhea along with other anaphylaxis symptoms
– Wheezing / dyspnea
– Blood pressure drop
– Unconsciousness
– Anaphylaxis
– Cardiovascular and/or respiratory arrest
6. Indications of possible severe β-lactam hypersensitivity reactions that cannot be treated with sufficient safety in case of recurrence and therefore usually leads to an elimination of β-lactams and administration of alternative antibiotics
– Drug reaction with eosinophilia and systemic symptoms (DRESS, drug hypersensitivity syndrome)
– Hemolytic anemia or cytopenia
– Acute nephritis or hepatitis
– Serum sickness
– Severe exanthema with blistering of the skin and/or mucosa (Stevens-Johnson syndrome, toxic epidermal necrolysis)

Patient-reported history for risk stratification



PEN-FAST: point-of-care risk assessment for adults reporting penicillin allergies

Figure. PEN-FAST Penicillin Allergy Clinical Decision Rule

PEN	Penicillin allergy reported by patient	<input type="checkbox"/> <i>If yes, proceed with assessment</i>
F	Five years or less since reaction ^a	<input type="checkbox"/> 2 points
A	Anaphylaxis or angioedema	<input type="checkbox"/> 2 points
S	OR Severe cutaneous adverse reaction ^b	
T	Treatment required for reaction ^a	<input type="checkbox"/> 1 point
<hr/>		
<input type="checkbox"/> Total points		
Interpretation		
Points		
<input type="checkbox"/> 0	Very low risk of positive penicillin allergy test <1% (<1 in 100 patients reporting penicillin allergy)	
<input type="checkbox"/> 1-2	Low risk of positive penicillin allergy test 5% (1 in 20 patients)	
<input type="checkbox"/> 3	Moderate risk of positive penicillin allergy test 20% (1 in 5 patients)	
<input type="checkbox"/> 4-5	High risk of positive penicillin allergy test 50% (1 in 2 patients)	

PRE-PEN®

(benzylpenicilloyl polylysine injection USP)
Skin Test Antigen

[FOR US HEALTHCARE PROFESSIONALS](#)

[Important Safety Information](#)

[Prescribing Information](#)

[Contact Us](#)

[BENEFITS OF PENICILLIN
ALLERGY TESTING](#)

[IMPLEMENTING PENICILLIN
ALLERGY SKIN TESTING](#)

[DOWNLOADABLE
RESOURCES](#)

[FAQs](#)

Perform penicillin allergy skin testing with PRE-PEN® by following these 3 steps.

[Expand All](#)

STEP 1: Prick/Puncture testing



IF PRICK/PUNCTURE TEST IS NEGATIVE...

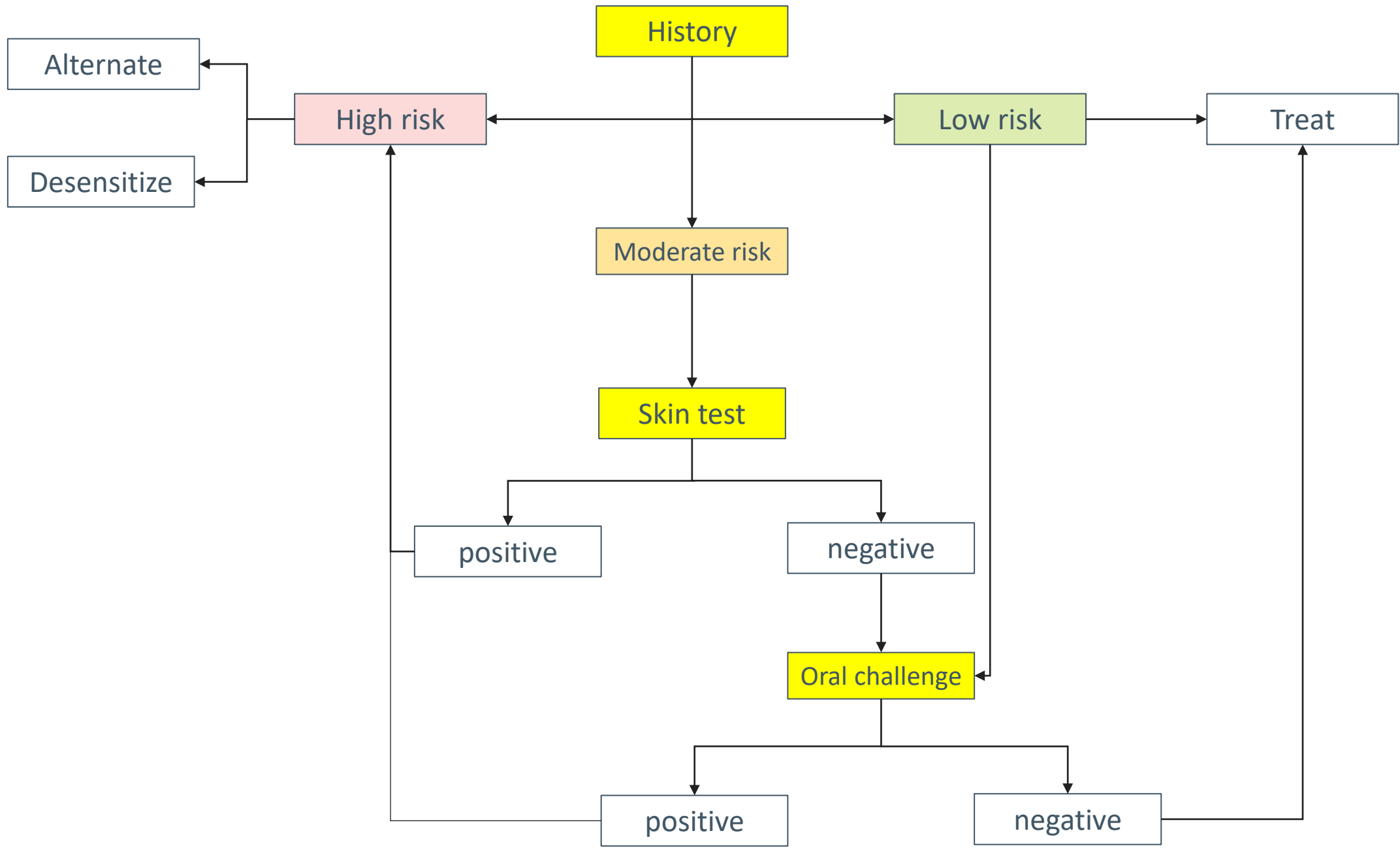
STEP 2: Intradermal testing



IF INTRADERMAL TESTING IN STEP 2 IS NEGATIVE...

STEP 3: Optional oral challenge





Should allergy testing be incorporated in STI clinics?

- Penicillin and other β -lactam antibiotics have a crucial role in treating STI
- Contribution to Antimicrobial Stewardship Programmes

O8.5 - Validation of an Easy to Administer Algorithm to Define Penicillin Allergy Status in STI Clinic Outpatients

Low-Risk History

N=206

Randomized to:

- Skin Test + Oral Challenge
- Oral Challenge

Higher-Risk History

N=75

Excluded

O8.5 - Validation of an Easy to Administer Algorithm to Define Penicillin Allergy Status in STI Clinic Outpatients

Stratification of Allergy Risk - Questionnaire

• Low-Risk History

- Isolated GI upset
- Chills
- Headache
- Fatigue
- Itching, self-limited
- Rash (including maculopapular rash)
- Hives (greater than 5 years ago)
- Flushing / redness
- Family history
- Patient denies allergy history but is in medical record

Higher-Risk History

- Angioedema (swelling of lip, tongue, or around eyes)
- Wheezing / chest tightness moderate or severe shortness of breath
- Throat tightness which affected ability to breathe
- Hypotension without rapid recovery
- Arrhythmia / irregular heartbeat or palpitation
- Syncope / light-headedness
- Anaphylaxis or sudden drop in blood pressure
- Hives (5 years or less)

Late effects

(higher-risk events which occurred >24 hours after drug administration)

- Stevens-Johnson syndrome or Erythema multiforme
- Organ injury (liver, kidney)
- Low Platelets
- DRESS
- Acute generalized exanthem (rash with pustules)
- Dystonia or muscles became very stiff or very weak
- Serum sickness
- Anemia
- Documented drug fever

O8.5 - Validation of an Easy to Administer Algorithm to Define Penicillin Allergy Status in STI Clinic Outpatients

Testing
Results: Per
Protocol
Population

	N	% (% CI)
Any Penicillin Skin Test		
Allergic	0	0 (0, 3.55)
Not Allergic	101	99.02 (94.66, 99.98)
Uninterpretable	1	0.98 (0.02, 5.34)
Skin Testing + Oral Challenge		
Allergic	3	3.03 (0.63, 8.6)
Not Allergic	96	96.97 (91.4, 99.37)
Graded Oral Challenge		
Allergic	8	7.69 (3.38, 14.6)
Not Allergic	95	91.35 (84.21, 95.97)
Discontinued Early	1	0.96 (0.02, 5.24)
Overall Allergy Status		
Allergic	11	5.34 (2.7, 9.35)
Not Allergic	191	92.72 (88.27, 95.87)
Uninterpretable	1	0.49 (0.01, 2.67)
Discontinued Early	3	1.46 (0.3, 4.2)

Improve your patients' antibiotic options through penicillin allergy skin testing.



More than 9 out of 10 patients who report a penicillin allergy are likely not allergic.^{1,2}

Most patients lose their penicillin allergy over time.¹



Increasing antibiotic resistance is an urgent health care concern.³

Patients without a true penicillin allergy may be unnecessarily treated with broad-spectrum antibiotics, contributing to the spread of multidrug-resistant bacteria.²

Why should you skin test for penicillin allergy with PRE-PEN®?



The American Academy of Allergy, Asthma, and Immunology recommends routine penicillin allergy skin testing.³

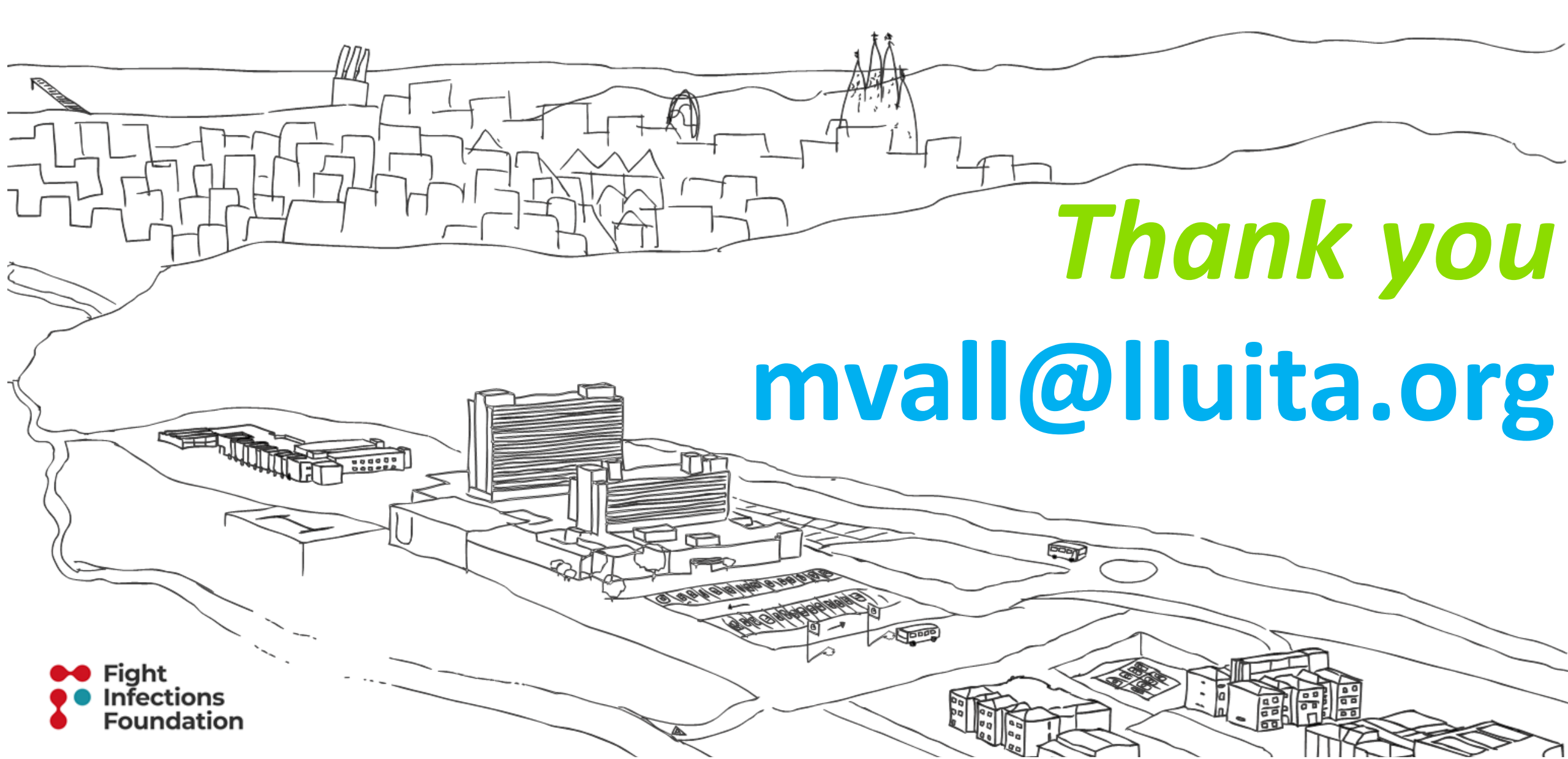
Penicillin allergy skin testing can be a novel tool for antimicrobial stewardship in patients with self-reported penicillin allergy.



A penicillin allergy skin test can be completed in about an hour.⁴

Penicillin allergy skin testing is a 2-step process:

- Perform a puncture test; if negative, follow with intradermal testing⁴
- After a negative skin test, an optional ingestion challenge can be administered⁵



Thank you
mval@luita.org



Salut/



Germans Trias i Pujol
Hospital



anys Hospital
Germans Trias