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PII: S2213-2198(21)00041-6

DOI: <https://doi.org/10.1016/j.jaip.2020.12.051>

Reference: JAIP 3361

To appear in: *The Journal of Allergy and Clinical Immunology: In Practice*

Received Date: 8 September 2020

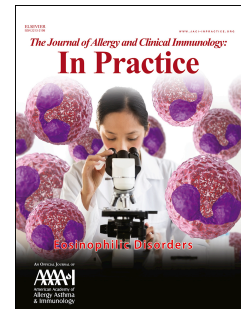
Revised Date: 3 December 2020

Accepted Date: 16 December 2020

Please cite this article as: Casimir-Brown RS, Kayode OS, Siew LQC, Makris M, Tsilochristou O, Chytiroglou E, Nakonechna A, Kennard L, Rutkowski K, Mirakian R, Wagner A, PIPERACILLIN-TAZOBACTAM HYPERSENSITIVITY: A LARGE, MULTICENTRE ANALYSIS *The Journal of Allergy and Clinical Immunology: In Practice* (2021), doi: <https://doi.org/10.1016/j.jaip.2020.12.051>.

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PIPERACILLIN-TAZOBACTAM HYPERSENSITIVITY: A LARGE, MULTICENTRE ANALYSIS

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This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors. Conflicts of interest: The authors declare that they have no relevant conflicts of interest.

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ABSTRACT

Background

Piperacillin/tazobactam is a broad-spectrum penicillin. Hypersensitivity reactions are less commonly reported than with other penicillins except in patients with cystic fibrosis.

Objective

Detailed clinical characterization of a patient cohort referred with suspected piperacillin-tazobactam hypersensitivity.

Methods

Retrospective analysis of the demographic characteristics, clinical presentation, investigation and management of 87 patients presenting to 5 European allergy centers. Patients underwent skin prick and intradermal testing with piperacillin/tazobactam, major (penicilloyl-polylysine) and minor (sodium penilloate) determinants, amoxicillin, benzylpenicillin, flucloxacillin, co-amoxiclav, clavulanic acid and meropenem with immediate and where appropriate, delayed reading of tests. Skin test negative patients underwent drug provocation to piperacillin/tazobactam and/or other penicillins. A multistep protocol was used, depending on risk assessment.

Results

Forty-eight of 87 (55%) patients were diagnosed with hypersensitivity to piperacillin/tazobactam with either positive skin or drug provocation tests, of whom 10 (21%) had a diagnosis of cystic fibrosis. Twenty-six (54%) patients presented with immediate and 22 (45%) with non-immediate hypersensitivity. Patients with cystic fibrosis predominantly presented with non-immediate hypersensitivity (70%). Reactions were severe in 52% of immediate reactors (Brown's anaphylaxis grade 3) and moderately severe (systemic involvement) in 75% of non-immediate reactors. The number of patients with negative skin tests tolerating re-introduction was comparable in immediate (80%) and non-immediate (88%) hypersensitivity. One third of patients were cross-sensitized to other penicillins. Cross-sensitization pattern raised the possibility of tazobactam allergy in 3 patients. In 21 patients

selectively sensitized to piperacillin/tazobactam (12 immediate, 9 non immediate), tolerance to other beta lactams was demonstrated by drug provocation testing.

Conclusion

Piperacillin-tazobactam caused immediate and non-immediate hypersensitivity with similar frequency. The majority of patients were selectively sensitized and tolerated other penicillins. Some patients may be allergic to the beta-lactamase inhibitor only.

HIGHLIGHTS BOX

What is already known about this topic?

Piperacillin-tazobactam causes both immediate and non-immediate hypersensitivity reactions. To date, only small case series or individual cases have been reported.

What does this article add to our knowledge?

Frequency of immediate and non-immediate hypersensitivity is similar. Re-introduction in a small group of skin test negative patients was tolerated by the majority. Selectively sensitized patients tolerate other penicillins. Cross-sensitization patterns suggest allergy to tazobactam in a minority of patients.

How does this study impact current management guidelines?

Patients with selective piperacillin-tazobactam hypersensitivity tolerate other penicillins, which must be included in skin testing panels. Drug provocation testing is safe in skin test negative patients. Tazobactam may be the allergen in some patients.

KEY WORDS

Immediate hypersensitivity; non-immediate hypersensitivity; anaphylaxis; piperacillin; tazobactam; beta-lactam; drug allergy; skin prick test; drug provocation test; penicillins

62 ABBREVIATIONS

- 63 AGEP (acute generalized exanthematous pustulosis)
64 CF (cystic fibrosis)
65 DHR (drug hypersensitivity reaction)
66 DPT (drug provocation test)
67 DRESS (drug reaction with eosinophilia and systemic symptoms)
68 HLA (human leukocyte antigen)
69 IDT (intradermal test)
70 IH (immediate hypersensitivity)
71 IHR (immediate hypersensitivity reaction)
72 IV (intravenous)
73 MD (minor determinant, sodium penilloate)
74 MPE (maculopapular exanthem)
75 NIH (non-immediate hypersensitivity)
76 NIHR (non-immediate hypersensitivity reaction)
77 PPL (benzyl penicilloyl-poly lysine)
78 PPZ (piperacillin)
79 PPZ-TZB (piperacillin-tazobactam)
80 sIgE (specific immunoglobulin E)
81 SJS (Stevens-Johnson syndrome)
82 SPT (skin prick test)
83 ST (skin test)
84 TEN (toxic epidermal necrolysis)
85 TZB (tazobactam)

INTRODUCTION

Piperacillin-tazobactam (PPZ-TZB) is a broad-spectrum beta-lactam antibiotic consisting of two components: the semi-synthetic ureidopenicillin, piperacillin (PPZ) and the beta-lactamase inhibitor, tazobactam (TZB). TZB is a penicillanic acid sulfone derivative which contains a beta lactam ring and irreversibly binds many bacterial beta-lactamases, thus reducing the degradation of PPZ. PPZ-TZB is administered intravenously (IV) and indications include septicemia, severe respiratory (including *Pseudomonas aeruginosa*), soft tissue, abdominal, pelvic and bone infections^{[1][2]}.

PPZ-TZB was first approved for use in 1981. Immediate, IgE-mediated hypersensitivity reactions (IHR) to PPZ-TZB have been reported since 1984^{[3][4]}, including cases of IHR due to occupational sensitization^{[4][5]}. Similarly, small cohorts of patients with non-immediate hypersensitivity reactions (NIHR) have been described since 1993, including: Fixed Drug Eruption^[6]; Generalized Fixed Drug Eruption^[7]; Drug Rash with Eosinophilia and Systemic Symptoms (DRESS)^{[8][9]}; Acute Generalized Exanthematous Pustulosis (AGEP)^{[10][11][12]}; DRESS/AGEP overlap^[13] and Stevens-Johnson Syndrome (SJS)/ Toxic Epidermal Necrolysis (TEN)^{[14][15][16]}. In patients with cystic fibrosis (CF), PPZ-TZB has been cited as the most frequent cause of drug hypersensitivity reactions (DHR), with NIHR more frequent than IHR^{[17][18][19]}.

Two decades of multicenter studies on IHR and NIHR to beta lactam antibiotics have resulted in guidelines for investigation and management of patients with penicillin allergy^{[20][21]}. In a significant proportion of patients with confirmed beta lactam allergy, it is now known that the immune response is directed against the unique side chain of individual beta lactams^{[3][22][23][24]}. For these patients, there is evidence that it is unnecessary to avoid all beta lactams^{[21][25]}. However, in some patients cross-reactivity is demonstrated and specific 'phenotypes' of cross-reactivity have been described by Gallardo et al^[26]. Thus, current efforts are focused on improving the precision of diagnosing allergy to specific penicillins, in

recognition of the detrimental effects on healthcare costs and patient outcomes of a 'false' label of beta lactam allergy^{[22] [27] [28]}.

We undertook a retrospective analysis of patients referred to five European allergy centers for investigation of suspected PPZ-TZB allergy, between 2012 and 2019, to gain insight into cross-sensitization and/or tolerance to other beta lactams, as well as the clinical value of skin tests, and the safety of IV drug provocation testing (DPT).

METHODS

Four UK (Guy's and St Thomas', London; Addenbrooke's, Cambridge; Royal Hallamshire Hospital, Sheffield; Royal Liverpool University Hospital, Liverpool) and one Greek (Attikon University Hospital, Athens) allergy centers collected data from patients referred to their services between 2012 and 2019 with a history of suspected PPZ-TZB allergy.

All data collected were obtained for solely clinical reasons and no identifiable information was available to clinicians who were not part of the clinical team. Ethical approval for this observational, non-interventional review was not required. All patients received standard care. Patients gave written consent for DPT. The patients' age, gender, time from presentation to diagnosis, index reaction, medical history, skin prick test (SPT), intradermal test (IDT), DPT results, baseline and acute tryptase measurements and specific IgE (sIgE) to penicillins [Penicilloyl V, Penicilloyl G, Amoxicilloyl, Ampicilloyl (Thermofisher Scientific UK)] were retrieved from the medical records.

The provisional diagnosis of IHR and NIHR to PPZ-TZB was based on the timing of the index reaction according to the ENDA (European Network for Drug Allergy) classification of DHR^[29] and updated by the Drug Allergy Interest Group (DAIG)^{[21][22]}. The severity of IHR was graded according to Brown's classification of systemic reactions^[30]. A diagnosis of DRESS was made using the RegiSCAR criteria^[31].

Concentrations for skin testing were consistent with those suggested by ENDA, with some local variation where indicated. These are summarized in **Table I**. A 4-step IV DPT protocol for PPZ-TZB was used (45, 450, 1000 and 3000mg). DPT to other beta lactams were carried out with either a single-dose, 2-step or 3-step graded oral challenge with intervals of 30 minutes between doses depending on risk assessment, followed by a three day course in patients with a history of delayed hypersensitivity to PPZ-TZB.

A positive SPT was defined as a wheal ≥ 3 mm when read at 15 to 20 minutes in the context of a positive histamine (positive control) and negative normal saline SPT result. A positive IDT result was defined as a wheal increase of 3 mm or more from baseline at 20 to 30 minutes after 0.03 to 0.05 mL of the drug was injected intradermally, in the context of a negative saline control. Delayed IDT reactions were recorded by the patient with repeated photographs or with visual inspection by a clinician over a 72-hour period.

Patients with a clinical history compatible with immediate PPZ-TZB allergy and either a positive SPT or IDT result or immediate reaction to IV DPT to PPZ-TZB were classified as having IH to PPZ-TZB (allergic). Patients with a clinical history compatible with a non-immediate reaction to PPZ-TZB and either a positive delayed IDT result or delayed positive DPT result (delayed hypersensitivity reaction, e.g. rash +/- systemic symptoms more than 6 hours after administration of PPZ-TZB) were classified as having NIH to PPZ-TZB (allergic). Patients were classified as non-allergic to PPZ-TZB if they had negative SPT and IDT and passed IV DPT. In patients who did not undergo DPT, clinicians gave advice based on clinical history and skin test (ST) results.

RESULTS

Eighty-seven patients were referred with suspected PPZ-TZB hypersensitivity, of which 23 (26%) had comorbid CF. Forty-one (47%) presented with a history of IHR, of whom 8 (20%) had a diagnosis of CF. Forty-six (53%) presented with NIHR, of whom 15 (33%) had CF.

A diagnosis of allergy was made on the basis of clinical history in combination with positive ST or DPT in 48 patients (55%), with immediate hypersensitivity (IH) confirmed in 26 (54%) and non-immediate hypersensitivity (NIH) in 22 (46%). Ten (21%) had CF, more of whom had NIH (7 patients/ 70%) than IH (3 patients/ 30%).

Immediate Hypersensitivity

Patient demographics are presented in **Table II**.

Twice as many females (n=28) than males (n=13) were referred with IHR. Male patients had a lower median age (28 years) than female patients (49.5 years). Females were more likely to have a positive ST than males (p=0.045). CF was comorbid in 8 of 41 patients (20%).

Results of testing are shown in **Figures 1a and b**.

Patients with positive ST to PPZ-TZB

ST were positive in 25 of 41 patients (61%) with a history of IHR: SPT in 11 (44%) and IDT in 14 (56%). One patient with positive SPT to PPZ-TZB, Benzylpenicillin and amoxicillin suffered a systemic reaction during ST (urticaria and wheeze; treated with IV chlorphenamine, hydrocortisone, salbutamol nebulizer and IM adrenaline).

While the majority of patients were seen within a year of the index reaction, 9% of patients with a positive SPT and 14% of those with positive IDT were tested more than 1 year after the index reaction. The longest interval was 2.3 years.

Four patients were nurses and reacted with only occupational exposure to PPZ-TZB (all female). All suffered anaphylaxis (two Brown's Grade 2, two Brown's Grade 3) when

preparing PPZ-TZB for administration. All had positive skin tests. Three of 8 patients with CF were ST positive.

Brown's anaphylaxis grades of the 25 patients with positive immediate skin tests were: Grade 3 in 13 (52%), Grade 2 in 8 (32%) and Grade 1 in 4 (16%) patients. There was a statistically significant difference ($p=0.003$, t -test) in the severity of presentation, compared to those with negative ST (see below), with the majority of ST positive patients presenting with a Grade 3 reaction.

In 12 of 25 patients (48%) diagnosed with immediate hypersensitivity on skin testing, serum tryptase measurements were available. All 12 showed a significant rise in serum tryptase during the acute reaction (median 34.7, range 8.9 - 58.7) compared to baseline (median 5.5, range 3.1 - 10.2). The mean rise in serum tryptase was 5.85-fold ($P<0.0001$). 6 of these 12 patients (50%) had positive SPT and 6 (50%) positive immediate IDT.

Tolerance to other penicillins

Twenty-four of 25 ST positive patients underwent skin tests to other penicillins: MD, PPL, benzylpenicillin, amoxicillin, co-amoxiclav, ampicillin (2 of 5 centers), and flucloxacillin (4 of 5 centers). One patient was not tested to any other penicillins and 6 patients were not tested to flucloxacillin.

Sixteen of 24 patients (66.6%) were sensitized to PPZ-TZB only (selectively sensitized). Twelve of 16 patients (75%) were further investigated, 11 patients underwent DPT to: amoxicillin (6); co-amoxiclav (2); flucloxacillin (2); penicillin V (1) and 1 additional patient underwent therapeutic re-administration with flucloxacillin. All 12 tolerated the respective penicillins.

Cross-sensitization to other penicillins

Cross-sensitization to other penicillins was seen in 8 of 24 patients (33.3%) either on SPT, immediate IDT, or specific IgE testing (see **Table III** and **Figure 1b**). Cross-sensitization

occurred to amoxicillin, co-amoxiclav, benzylpenicillin, MD, PPL and ampicillin but none to flucloxacillin. One patient was tested with clavulanic acid and found to be positive to this component and to co-amoxiclav; she tolerated DPT with oral amoxicillin. Sixteen of 24 patients (66.6%) also underwent serum specific IgE testing to other penicillins (amoxicilloyl, ampicilloyl, PenV and PenG) and 3 were positive; 2 of these 3 patients showed skin test cross-reactivity to the corresponding drugs.

Patients with negative ST to PPZ-TZB

Negative ST to PPZ-TZB and other penicillins were recorded in 16 of 41 (39%) patients (8 female, 8 male). Their index reactions were: Grade 3 in 1 (6%); Grade 2 in 9 (56%) and Grade 1 in 6 (38%) patients.

Subsequent IV DPT to PPZ-TZB was conducted in 4 of 16 IHR patients with negative ST and 1 patient underwent therapeutic re-administration. Four patients (index reactions Grades 1 and 2) were tolerant, while one patient during IV DPT (Grade 1 index reaction) developed urticaria after the second dose (495mg cumulative dose). Re-introduction was therefore tolerated in 4 of 5 patients.

The majority (8 of 11) of ST negative patients who did not undergo formal DPT or therapeutic re-administration were advised by their clinician that they were unlikely to be allergic to PPZ-TZB and thus cautious reintroduction in a hospital environment was recommended if and when clinically indicated. Further information about whether this was done was not available for these patients. Only the 2 patients, each with a significant rise in serum tryptase during the index reaction, were advised to avoid PPZ-TZB. One patient's clinical management decision was not documented.

Non-Immediate Hypersensitivity

Patient demographics are presented in **Table IV**.

There were roughly equal numbers of females (n=22) and males (n=24) referred. Male patients had a lower median age (27 years), than female patients (40 years).

CF was comorbid in 15 of 46 patients (33%) referred with NIHR. These patients were aged 17 – 40 years and comprised 67% (14 of 21) NIHR patients under 34 years of age.

Results of testing are shown in **Figures 2a and b**.

One patient who was referred due to Symmetrical Drug Related Intertriginous and Flexural Exanthema (SDRIFE) did not undergo ST but reacted similarly upon DPT with 0.5g IV PPZ-TZB (11% of a standard 4.5g dose), 10 hours after administration. The delayed IDT result of 1 patient who was referred with AGEP was not available.

Patients with positive ST to PPZ-TZB

Delayed IDT results were positive in 20 of 44 patients tested (45%). Only one of 13 patients who presented for ST more than 1 year after the index reaction had positive ST, with an interval of 1.5 years. Seven of 15 patients (47%) with CF were ST positive.

The majority (75%) of patients with positive delayed IDT had a history of DRESS (2 definite, 6 probable, 7 possible) and 25% maculopapular exanthem (MPE). No patients had a systemic reaction upon ST.

Tolerance to other beta-lactams

Patients underwent skin tests to other beta lactams: amoxicillin, co-amoxiclav, ampicillin, benzylpenicillin, MD, PPL, flucloxacillin and meropenem.

Fourteen of 20 patients (70%) were selectively sensitized to PPZ-TZB. Nine of 14 patients (64%) were further investigated using DPT to other beta lactams (2 patients; 1 with a history of probable DRESS, 1 MPE) or subsequent therapeutic re-administration (7 patients; 4 with a history of possible DRESS, 3 MPE). These were: co-amoxiclav (2 DPT, 4 therapeutic administration); co-amoxiclav and amoxicillin (1); flucloxacillin (1); meropenem (1). All 9 tolerated the respective beta lactams.

Cross-sensitization to other beta-lactams

Cross-sensitization to other beta lactams was observed in 6 of 20 patients (30%) (see **Table V** and **Figure 2b**). A positive delayed IDT result was seen to co-amoxiclav and amoxicillin in 2 patients (33%), to co-amoxiclav alone in 2 patients (33%), and to meropenem in 2 patients (33%). The patients sensitized to meropenem had this administered either alongside PPZ-TZB or shortly after the onset of the index reaction.

Patients with negative ST to PPZ-TZB

Negative skin tests to PPZ-TZB and all other penicillins were recorded in 24 of 44 patients (55%) with a history of NIHR (10 female; 14 male). In ST negative patients, only 2 of 24 (8%) presented with possible DRESS while 17 patients (71%) reported MPE. Other reactions were: Fixed drug reactions (2), MPE with fever (1), delayed urticaria/angioedema on day 3 (1), mixed MPE/ delayed urticaria on day 4 (1).

Subsequent IV DPT to PPZ-TZB was conducted in 7 of 24 patients with negative ST and 1 patient underwent therapeutic re-administration. Only one patient, presenting with MPE years before testing, was positive on IV DPT and showed a similar reaction within 24 hours of a single dose of 4.5g. Re-introduction was therefore tolerated in 7 of 8 patients.

The majority (11 of 16) of the ST negative patients who did not undergo formal DPT or therapeutic re-administration were advised by their clinician that they were unlikely to be allergic to PPZ-TZB and thus cautious reintroduction in a hospital environment was recommended if and when clinically indicated. Further information about whether this was done was not available for these patients. Five patients (31%) were advised to avoid PPZ-TZB (with index reactions of possible DRESS in 1 and MPE in 4), despite negative ST.

DISCUSSION

To our knowledge, this is the largest clinical review to date of patients with suspected PPZ-TZB hypersensitivity. We confirm that PPZ-TZB can cause both IH and NIH. NIH comprised a large proportion (44%) of PPZ-TZB allergy compared to that observed with other beta lactams; for example, for flucloxacillin, IH is significantly more common (82.5%, Kennard et al 2019)^[25].

In patients with comorbid CF in particular, NIH was more common (70%) confirming previous observations^[32]. In this group, PPZ-TZB is frequently given and is the most frequent cause of adverse reactions^[19]. With CF patients representing 26% of the cohort, this has also contributed to the large number of younger patients.

IH to PPZ-TZB was four times as common in females, a pattern seen in other beta-lactams^{[25] [33]}. In contrast, NIH was only marginally more common in females (1.2 : 1). Males were twice as frequently affected by NIH than IH.

There were 4 nurses in the cohort, presenting with IHR due to occupational exposure only. Previous case reports of PPZ-TZB hypersensitivity occurring upon both occupational skin contact and inhalation^{[4] [5]} prompt suggestions that PPZ-TZB may have a significant potential to elicit hypersensitivity in this way.

Although skin testing in DRESS has historically been avoided, we found it was safe in the vast majority of patients, for both IHR and NIHR; none of the patients with NIH and only 1 patient with IH (with a history of occupational exposure) had a systemic reaction with ST. This confirms findings for antibiotic testing in general^{[34] [35]}. Our results emphasize, once more, both the critical clinical value and the safety of ST and further strengthen the recommendation for skin testing before considering drug provocation^{[21] [22]}. This should be confirmed in further, larger studies for PPZ-TZB.

We found that ST were likely to be positive in patients presenting with severe reactions, for both IHR and NIHR. In NIH, 75% patients with a positive delayed IDT presented with reactions suggestive of DRESS rather than MPE. This confirms previous findings by

Cabañas and Calderón: in a cohort of 8 patients affected by DRESS, PPZ-TZB was shown to be the most frequent causative agent^{[8] [36]}, prompting the authors to suggest inclusion of PPZ-TZB in the list of drugs that cause DRESS. Recent data implies a role of human leukocyte antigen (HLA) alleles in susceptibility to PPZ-TZB hypersensitivity^[37], particularly in patients with DRESS^[38].

It has been previously found that ST are more likely to be positive in patients where testing is performed early^[39]. The majority of our patients were tested within a year of the index reaction. For IHR, there was no difference seen between ST positive and negative groups. However, only 1 of 13 patients with NIHR seen more than 1 year from index reaction had a positive ST. Thus, in our cohort, early ST in NIHR confirmed allergy in a larger number of patients than late testing.

IV DPT is not routinely performed in most allergy centers due to concerns about patient safety. Selecting patients with negative skin tests and a history of mild reaction for IV DPT appears to be safe. The starting dose for challenges was 1/100 of a full dose and none of the patients reacted to this dose. Only a minority (15%) of patients failed IV DPT (2 of 13: 1 immediate at 1/10 of dose, 1 non-immediate at full dose) and none of the patients needed adrenaline or inpatient treatment. These results are encouraging, and larger studies are needed to confirm this. Clinicians' advice for ST negative patients who had not undergone DPT varied. Seven patients (2 immediate, 5 delayed) were told to avoid PPZ-TZB despite negative skin tests. This may not be in the best interest of patients^{[27] [40]}. We provide evidence for safe practice of IV DPT following a negative ST in those whose index reaction was not severe.

The majority of patients demonstrated selective hypersensitivity to PPZ-TZB, which confirms reports by others^{[3] [23] [26] [41] [42] [43]}. In this review, ST to other beta lactams were negative in 67% IH and in 70% NIH patients. Our data validates this selective sensitization in 21 patients for a number of beta lactams, either through subsequent formal DPT or therapeutic re-administration by attending clinical teams. This finding supports 'de-labelling' of allergy to

other beta lactams in patients who show selective hypersensitivity to PPZ-TZB on ST^[44].

This furthers principles of antibiotic stewardship, which advise against limiting the choice of antibiotics unnecessarily^{[20] [27] [45]}.

Our results demonstrate cross-sensitization on ST (and/or sIgE in IH) to other beta lactams in one-third of patients (IH, 36%; NIH, 30%). sIgE is known to have low sensitivity and should not be used alone to establish cross-reactivity^[22]. Different cross-sensitization phenotypes have been described in patients with IH to PPZ-TZB by Gallardo et al^[26]. They define two phenotypes, one showing cross-sensitization to amoxicillin only and one showing cross-sensitization to benzylpenicillin/PPL/MD/amoxicillin. Our results confirm this, with one patient reacting to amoxicillin/ampicillin only, and 6 others showing sensitization to benzylpenicillin/PPL/MD +/- amoxicillin. In the NIH cohort, we did not find evidence of sensitization to the beta lactam ring. However, cross-sensitization to amoxicillin (and co-amoxiclav) was seen in 2 patients.

Furthermore, we report a phenotype not previously described: in 1 IH and 2 NIH patients, the pattern of cross-sensitization with co-amoxiclav only suggests reactivity to TZB, the beta lactamase inhibitor. Cross-sensitization between beta-lactamase inhibitors has been suggested^[46], and indeed, one of our patients tested positive on SPT to clavulanic acid, another beta lactamase inhibitor. Rank & Park^[47] surmise that TZB hypersensitivity could be responsible for positive IV challenges to PPZ-TZB in the context of negative ST, as TZB may be represented in insufficient quantity when skin testing with PPZ-TZB. Unfortunately, it is not currently possible to test for TZB as an individual component.

Cross-sensitization to meropenem was demonstrated in two patients with NIH, both of whom had been given the drug during the hypersensitivity reaction to PPZ-TZB. Cross-sensitization to meropenem is rare^[48], hence, we suggest sensitization may have occurred as a bystander effect during an already ongoing immune reaction, rather than through genuine primary cross-reactivity, as described by Pichler et al^[49].

Albeit the largest cohort to date, we acknowledge that this was a retrospective observation, and some data are inevitably missing. The absolute number of patients referred with suspected PPZ-TZB hypersensitivity was small and referral bias cannot be excluded. A further limitation is in the small number of patients who underwent DPT.

In summary, our key findings were: (1) PPZ-TZB causes both IH and NIH. The proportion of NIH reactions is greater than seen in other penicillins. (2) Patients with CF are over-represented, particularly in the group of patients with NIH. (3) PPZ-TZB is a cause of occupational hypersensitivity. (4) Skin testing was safe and we found DPT to be safe in patients with a history of mild to moderate reaction and negative ST (5) Most patients (both with IH and NIH) display selective PPZ-TZB hypersensitivity and may tolerate other beta lactams. (6) Cross-sensitization, as seen in one-third of patients showed variable patterns. (7) A minority of patients may be allergic to the TZB (beta lactamase inhibitor) component only.

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FIGURE LEGENDS

(1a) Results of all tests in patients with a history of immediate reaction.

(1b) Overview of all patients referred with suspected immediate hypersensitivity to piperacillin-tazobactam.

(2a) Results of all tests in patients with a history of non-immediate reaction.

(2b) Overview of all patients referred with suspected non-immediate hypersensitivity to piperacillin-tazobactam.

TABLE LEGENDS

(I) Concentrations and manufacturer details of drugs used for skin prick testing (SPT) and intradermal testing (IDT)

(II) Demographic details of patients presenting with immediate hypersensitivity reactions (IHR), by positive and skin negative tests to PPZ-TZB

(III) Results of all testing to beta lactam antibiotics in patients with positive immediate skin tests to piperacillin-tazobactam. Cross-sensitization was seen in 8 patients; each had a unique pattern of cross-reactivity. sIgE = specific IgE, BenPen = benzylpenicillin, MD = major determinant, sodium penilloate, PPL= Penicilloyl-polylysine; PenV = penicilloyl V; Pen G = penicilloyl G.

(IV) Demographic details of patients presenting with non-immediate hypersensitivity reactions (NIHR), by PPZ-TZB test results

(V) Results of all testing to beta lactam antibiotics in patients with positive delayed skin tests to piperacillin-tazobactam. Cross-sensitization was seen in 6 patients using delayed IDT. There were 3 phenotypic patterns of cross-reactivity: co-amoxiclav and amoxicillin (2); co-amoxiclav only (2); meropenem only (2)

BenPen = benzylpenicillin, MD = major determinant, sodium penilloate, PPL= Penicilloyl-polylysine.

Table I

Drug	Concentration used for SPT (mg/mL)	Concentration used for IDT (mg/mL)
Piperacillin-Tazobactam (Tazocin) <i>Bowmed Ibisqus, Wrexham, UK; Pfizer Hellas, Greece</i>	200	20
Sodium benzylpenilloate (MD) <i>Diater, Leganés, Madrid, Spain</i>	0.5	0.5
Penicilloyl-polylysine (PPL) <i>Diater, Leganés, Madrid, Spain</i>	0.04	0.04
Benzylpenicillin <i>Genus Pharmaceuticals, Huddersfield, UK; Cooper Pharmaceuticals, Athens, Greece</i>	6 (10,000 U) <i>Cambridge: 150</i>	6 (10,000 U) <i>Cambridge: 15</i>
Amoxicillin <i>GlaxoSmithKline, Middlesex, UK; Ibigen S.r.l, Aprilia, Italy</i>	20 <i>Cambridge: 200</i>	20
Co-amoxiclav (Augmentin) <i>Bowmed Ibisqus, Wrexham, UK; GlaxoSmithKline, UK</i>	20/4 <i>Cambridge: 200/40</i>	20/4
Meropenem <i>Bowmed Ibisqus, Wrexham, UK; Hospira, UK</i>	2 <i>Cambridge: 50</i>	2 <i>Cambridge: 5</i>
Flucloxacillin* <i>Hospira, Maidenhead, UK; Wockhardt UK Limited, Wrexham, UK</i>	50	5
Ampicillin <i>Bowmed Ibisqus, Wrexham, UK; Cooper Pharmaceuticals, Athens, Greece</i>	20	20
Clavulanic acid⁺ <i>DAP, Diater, Leganés, Madrid, Spain</i>	20	20

* Flucloxacillin was not tested in the Greek center

⁺ Not routinely tested

Table II

IHR (n = 41)	ST positive (n=25)	ST negative (n=16)
<i>Gender distribution</i>		
Female	20	8
Male	5	8
F:M	4	1
<i>Age, years (median, range)</i>		
Total	48 [10,68]	32.5 [20,76]
Female	49 [10,63]	52 [27,76]
Male	28 [22,68]	28 [20,74]
<i>Time from index reaction to ST[^]</i>		
Mean years [range]	0.69 [0.1, 2.3]	0.57 [0.1, 2.0]
<1 year	17	14
>1 year	3	2
<i>Severity of Index reaction</i>		
Grade 1	4	6
Grade 2	8	9
Grade 3	13	1
Statistically significant difference (p= 0.003) in the severity of presentation between skin test positive and negative patients.		
<i>Comorbidities</i>		
CF	3	5
Chronic lung disease	4*	2**
Autoimmune conditions	3 [†]	1 ^{††}
Occupational exposure	4	0

[^] data was not available for 5 patients

*asthma

**bronchiectasis

[†] rheumatoid arthritis (RA), systemic lupus erythematosus (SLE), Hashimoto's thyroiditis

^{††} hypothyroidism

Table III

Cross-Reactors	Amoxicillin	Ampicillin	BenPen	MD	PPL	Pen V	Pen G	Co-amoxiclav	Clavulanic acid
<i>Patient 1</i>	SPT *		SPT *						
<i>Patient 2</i>	IDT	IDT	IDT	IDT					
<i>Patient 3</i>			IDT						
<i>Patient 4</i>				IDT	IDT				
<i>Patient 5</i>	IDT + slgE	IDT							
<i>Patient 6</i>						slgE	slgE	IDT	IDT
<i>Patient 7</i>	IDT + slgE			IDT	IDT	slgE	slgE		
<i>Patient 8</i>	slgE *					slgE *			

SPT/ IDT/ slgE: test type of the positive result to other beta lactam antibiotic

*SPT positive to piperacillin-tazobactam

All others tested positive to piperacillin-tazobactam on immediate IDT

Table IV

NIHR (n = 46)	ST positive (n=20)	ST negative (n=24)	Other ⁺ (n=2)
<i>Gender distribution</i>			
Female	11	10	1
Male	9	14	1
F:M	1.22	0.7	1
<i>Age, years (median, range)</i>			
Total	27.5 [6, 68]	38 [17, 81]	
Female	39 [6, 68]	47 [21, 81]	53
Male	24 [12, 62]	34 [17, 62]	61
<i>Time from index reaction to ST (mean years)[^]</i>			
Mean years	0.53	1.9	
<1 year	16	11	
>1 year	1	12	
Range	[0.1, 1.5]	[0.1, 21]	
<i>Severity of Index reaction</i>			
MP	5	17	
Possible DRESS	7	2	
Probable DRESS	6	0	
Definite DRESS	2	0	
Other	0	5 ⁺⁺	2
<i>Comorbidities</i>			
CF	7	8	
Chronic lung disease	3 [*]	4 ^{**}	
Autoimmune conditions	3 [†]	6 ^{††}	
Occupational exposure	0	0	

⁺ 2 patients did not undergo full skin testing: 1 patient with AGEP and 1 patient with SDRIFE who was confirmed PPZ-TZB hypersensitive using DPT.

[^] data was not available for 6 patients

⁺⁺ Other reactions were: Fixed drug reactions (2), MP with fever (1), delayed urticaria/angioedema on day 3 (1), mixed MP/ delayed urticaria on day 4 (1)

^{*} alpha-1-antitrypsin COPD, bronchiectasis (2)

^{**} bronchiectasis (2), COPD, recurrent atypical mycobacterial infection

[†] ulcerative colitis (UC) on azathioprine, TPO positive hypothyroidism, non-specified immunodeficiency

^{††}psoriasis, rheumatoid arthritis (RA) on methotrexate and prednisolone, RA on hydroxychloroquine and prednisolone, granulomatosis with polyangiitis (GPA), Type 1 diabetes mellitus (T1DM), systemic lupus erythematosus (SLE)/ coeliac disease/ CVID/ transverse myelitis/ antiphospholipid syndrome

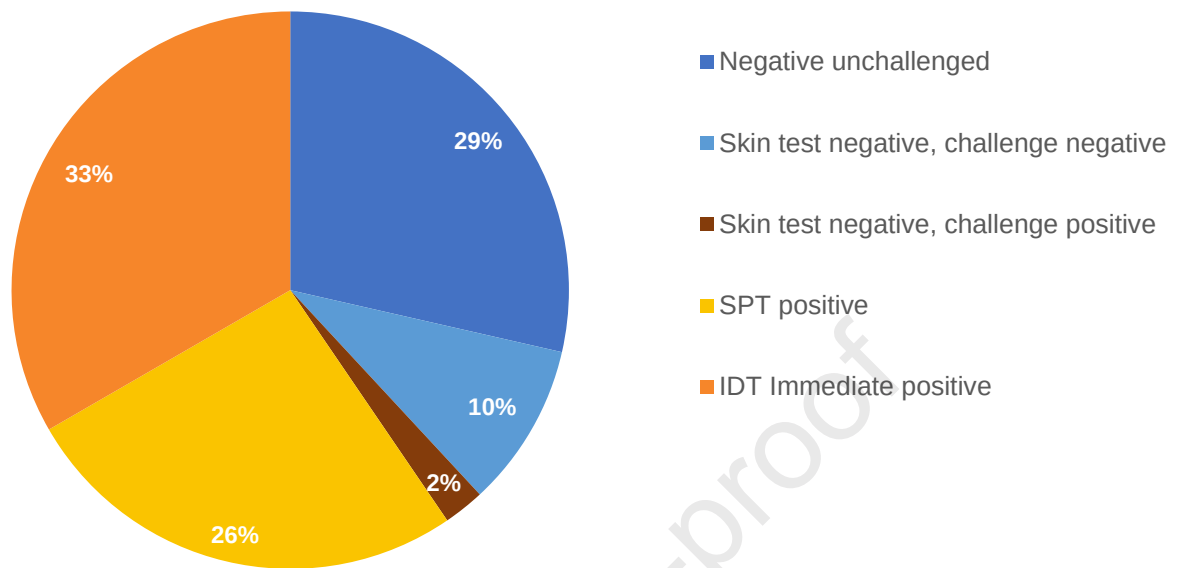
ST (skin test); MP (maculopapular); DRESS (drug reaction with eosinophilia and systemic symptoms); CF (cystic fibrosis); COPD (chronic obstructive pulmonary disease); TPO (thyroid peroxidase)

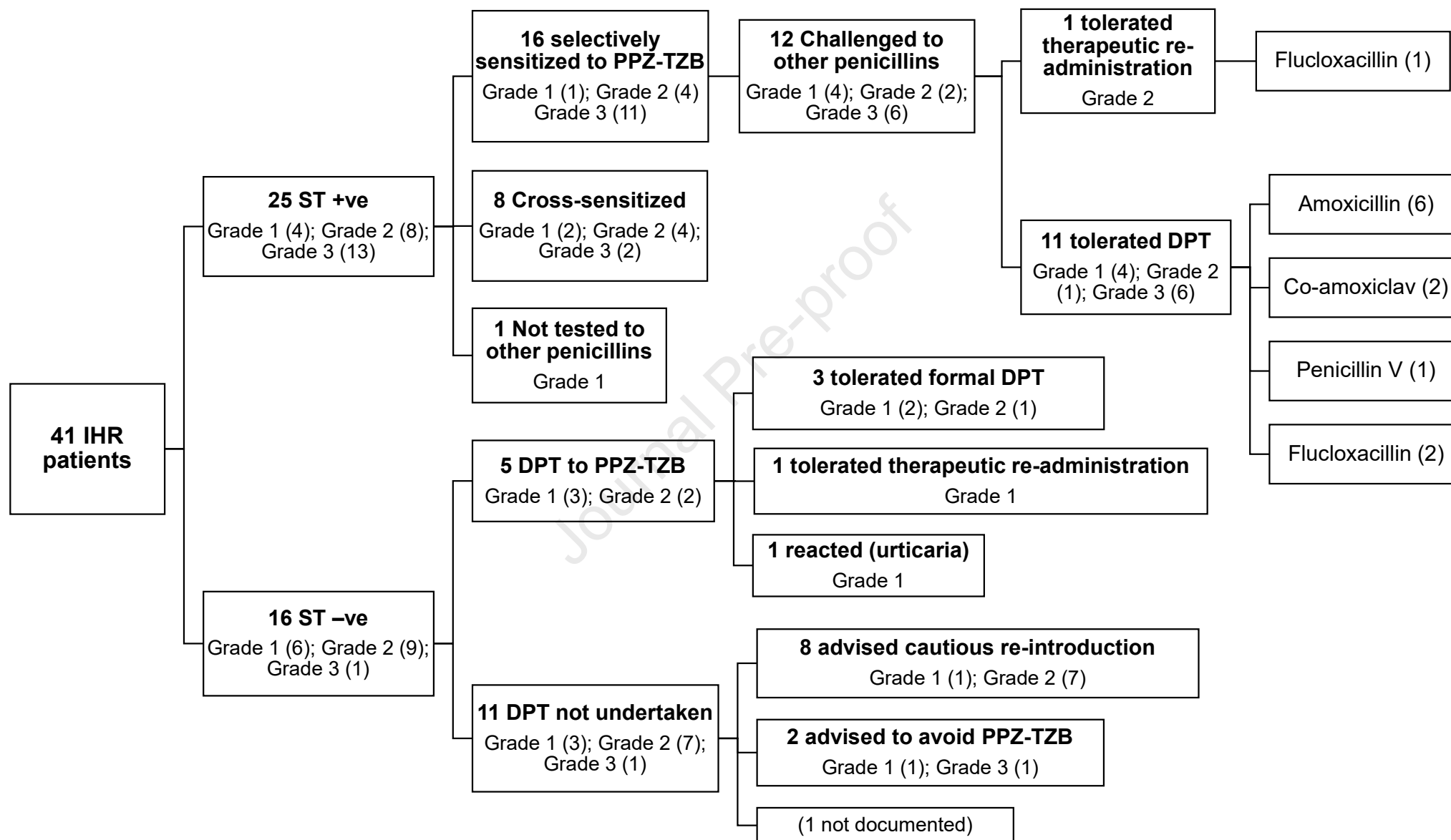
Table V

Cross-Reactors	Amoxicillin	Ampicillin	BenPen	MD	PPL	Co-amoxiclav	Meropenem
Patient 1	IDT					IDT	
Patient 2	IDT					IDT	
Patient 3						IDT	
Patient 4						IDT	
Patient 5							IDT
Patient 6							IDT

All patients were positive on delayed IDT to PPZ-TZB and the beta lactam antibiotics indicated

Immediate Hypersensitivity: Results of Testing





Non-immediate hypersensitivity: Results of Testing