

Flucloxacillin Hypersensitivity: Patient Outcomes in a Multicenter Retrospective Study



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What is already known about this topic? To date, no large cohorts of either immediate or nonimmediate flucloxacillin hypersensitivity have been reported.

What does this article add to our knowledge? Nearly two-third of patients with immediate flucloxacillin hypersensitivity were selective reactors on skin testing. This highlights the importance of drug provocation test with an alternative penicillin in these patients. In contrast, most patients with nonimmediate hypersensitivity were cross-reactors on skin testing.

How does this study impact current management guidelines? Broad penicillin avoidance may not be necessary in all patients with immediate flucloxacillin hypersensitivity. Standardized approaches to testing and challenge are needed.

BACKGROUND: Flucloxacillin is a narrow-spectrum, beta-lactamase-resistant penicillin. Type I (IgE-mediated) and type IV (T-cell-mediated) reactions are less frequently reported than with other penicillins.

OBJECTIVE: To undertake a detailed clinical characterization of a cohort of patients referred with suspected flucloxacillin hypersensitivity.

METHODS: We retrospectively analyzed demographic characteristics, presentation, investigation, and management of 108 patients presenting to 4 UK centers. Patients underwent skin prick and intradermal testing with flucloxacillin, major (benzylpenicilloyl poly-L-lysine) and minor determinants, amoxicillin, and benzylpenicillin with immediate and, where appropriate, delayed reading of the test. In the immediate group, a further 14 patients were tested to ampicillin and 16 to Augmentin (co-amoxiclav—combination of clavulanic acid and amoxicillin). Skin test-negative patients underwent oral drug provocation. A multistep protocol was used, depending on risk assessment.

RESULTS: Forty of 108 (37%) patients were diagnosed with hypersensitivity to flucloxacillin, of whom 33 (82.5%) showed immediate and 7 (17.5%) nonimmediate hypersensitivity, respectively. In the immediate group, most reactions were severe: 19 of 33 (58%). Intradermal testing had a higher negative predictive value (86%) in the immediate group than in the nonimmediate group (67%). Only a minority of patients (6 of 17 [35%]) with IgE-mediated allergy were cross-sensitized on intradermal testing with other penicillins, compared with 3 of 4 (75%) in the delayed group.

CONCLUSIONS: Immediate hypersensitivity reactions to flucloxacillin are more common than delayed. Cross-sensitization to other penicillins appears higher in delayed reactions than in immediate. The negative predictive value of intradermal testing is higher in the immediate group than in the nonimmediate group. Drug provocation testing remains the diagnostic criterion standard. © 2019 American Academy of Allergy, Asthma & Immunology (J Allergy Clin Immunol Pract 2019;7:2212-7)

Key words: Isoxazoloyl; Flucloxacillin; Penicillin; Anaphylaxis; Drug; Allergy; Skin prick test; Intradermal test; Challenge

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INTRODUCTION

Penicillins, clinically the most important beta-lactams, are the most commonly reported cause of immunologically mediated drug hypersensitivity, and are a rare cause of fatal anaphylaxis. Flucloxacillin is a semisynthetic penicillin. It belongs to the group of isoxazoloyl penicillins that includes oxacillin, cloxacillin, and dicloxacillin. In the United States, flucloxacillin is not available, but the related isoxazoloyl penicillins are used. Antigenic cross-reactivity within this group has been described.¹ Flucloxacillin is a narrow-spectrum antibiotic that, because of its beta-lactamase resistance, is widely used in the United Kingdom for the treatment of cellulitis and for perioperative

Abbreviations used

DPT- Drug provocation test

IDT- Intradermal test

NPV- Negative predictive value

SPT- Skin prick test

prophylaxis during surgery. Flucloxacillin differs in the specific side-chain structure from amino, ureido, and carboxypenicillins. Type I and type IV immune-mediated hypersensitivity reactions to this class of antibiotics can be directed both to the shared beta-lactam ring and to the specific side chains.²⁻⁵

Evidence exists that clinical cross-reactivity between penicillins may be not as high as originally thought. This is mainly due to predominant recognition of side chains rather than the shared beta-lactam ring.¹ The extent of cross-reactivity with penicillins with different side chains in patients with flucloxacillin allergy has not been systematically investigated in large cohorts, but case reports suggest that it might be low in IgE-mediated allergy.¹ These diagnoses were not oral challenge confirmed.

The criterion standard test to confirm the presence or absence of clinically significant immunologically mediated hypersensitivity to penicillin remains the oral challenge with a therapeutic dose.⁶ However, the current consensus is that skin test—positive patients with a history of a significant systemic reaction should not be challenged.

Current testing includes skin prick test (SPT) and intradermal test (IDT) with commercially available penicillin determinants (benzylpenicilloyl poly-L-lysine and minor determinants), the index drug, amoxicillin, and benzylpenicillin followed by oral drug provocation test (DPT) if skin test results are negative. Some centers will also test to ampicillin and Augmentin (co-amoxiclav). There is no flucloxacillin-specific IgE testing available and in penicillin allergy, IgE testing is generally of limited clinical utility due to its low sensitivity.⁷

We have retrospectively studied a large cohort of patients with suspected flucloxacillin allergy from 4 different UK allergy centers. This study ultimately aims to establish the basis for harmonization of the diagnostic process among allergy centers and a shared management plan for these patients.

METHODS

Four UK centers (Guy's London, Cambridge, Liverpool, and Sheffield) submitted clinical data from 108 adult patients (older than 18 years) referred to their allergy clinics with a history of suspected flucloxacillin allergy between 2010 and 2018. The clinical history of immediate and nonimmediate flucloxacillin allergy was based on the timing of the index reaction, according to the ENDA classification of drug hypersensitivity, validated by international consensus.⁸⁻¹¹

The patient's age, sex, time from presentation to diagnosis, index reaction, medical history, SPT, IDT, and DPT results, and baseline and acute tryptase and specific IgE levels to penicillins were retrieved from the medical notes.

Only patients with negative skin test results and/or negative specific IgE to penicillins underwent oral drug provocation.

Patients with a clinical history compatible with immediate flucloxacillin allergy and either a positive SPT or IDT result or immediate reaction to oral challenge to flucloxacillin were classified as

having immediate hypersensitivity to flucloxacillin (flucloxacillin allergic).

Patients with a clinical history compatible with a delayed cutaneous/T-cell—mediated reaction to flucloxacillin and either a positive delayed IDT result or delayed DPT result (1-3 days of flucloxacillin) were classified as having delayed hypersensitivity to flucloxacillin. All patients with negative SPT, IDT, and oral challenge results were classified as negative for hypersensitivity to flucloxacillin.

Patients gave written consent for oral drug provocation. Ethical clearance for this retrospective anonymized study was not required in the United Kingdom. All data collected were obtained purely for clinical reasons, and no patient-identifiable information was available to clinicians who were not part of the clinical care team.

Concentrations for skin testing were consistent with those suggested by ENDA, with some local variation as follows.¹²

Skin testing

All centers performed SPT and IDT with benzylpenicilloyl poly-L-lysine (0.04 mg/mL) and minor determinants (0.5 mg/mL) (DAP, Diater, Leganés, Madrid, Spain) following Diater protocol.

Benzylpenicillin 6 mg/mL (10,000 U) (Genus Pharmaceuticals, Huddersfield, UK) was used for both SPT and IDT in all centers, except for Cambridge where SPT was carried out at 150 mg/mL and IDT at 15 mg/mL.

Flucloxacillin (Hospira, Maidenhead, UK, and Wockhardt UK Limited, Wrexham, UK) testing was performed with a concentration of 20 to 50 mg/mL for SPT and 2 to 5 mg/mL for IDT.

Amoxicillin (GlaxoSmithKline, Middlesex, UK, and Ibigen S.r.l, Aprilia, Italy) was used at 20 to 25 mg/mL for SPT and IDT in all centers except for Cambridge where SPT was carried out at 200 mg/mL.

Co-amoxiclav (Augmentin) (Bowmed Ibisqus, Wrexham, UK) was used at a dose of either 20/4 mg/mL or 25/5 mg/mL for amoxicillin and clavulanic acid, respectively, for SPT and IDT in all centers except for Cambridge where SPT was performed at 200/40 mg/mL. (It should be noted that co-amoxiclav testing was routine in 2 centers and was carried out ad hoc by other centers.)

Ampicillin (Bowmed Ibisqus, Wrexham, UK) was used at 20 mg/mL for SPT and IDT. (It should be noted that ampicillin testing was not routine, except in 2 centers.)

A positive SPT result was defined as a wheal increase of 3 mm or more from baseline when read at 15 to 20 minutes in the context of a positive histamine (positive control) and saline (negative control) 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 is injected intradermally with an associated negative saline control. For the nonimmediate patients, the skin reactions were recorded by photographs every 24 hours or visual inspection by a clinician for 72 hours to look for a positive result.

DPT protocols varied by site and were guided by the clinicians' clinical judgment.

Cambridge and Guy's: Immediate oral challenges (DPT in patients with a history of immediate hypersensitivity) were carried out with either a single-dose challenge or a 2-step challenge or 3-step graded challenge with intervals of 30 minutes between doses depending on risk assessment.

Liverpool: Either single-dose challenge or 3-step or 5-step graded challenge with intervals of 30 minutes between doses was used.

Sheffield: Either a single-dose challenge or a graded 7-step challenge with intervals of 30 minutes between doses was used.

The cumulative dose of flucloxacillin used during the oral challenge was between 500 and 800 mg. The observation window after the top dose varied in different centers between 1 and 2 hours. Delayed DPTs were carried out with 250-mg single dose followed by 250-mg oral flucloxacillin 4 times a day to be taken at home for up to 3 days.

Index reaction severity was graded using published methodology as follows.¹³ Grade 1: mild affecting skin and subcutaneous tissues only; grade 2: moderate with features suggesting respiratory, cardiovascular, or gastrointestinal involvement, including dyspnea, stridor, wheeze, nausea, vomiting, dizziness (presyncope), diaphoresis, chest or throat tightness, or abdominal pain; grade 3: severe resulting in hypoxia (cyanosis or $\text{SpO}_2 \leq 92\%$), hypotension (systolic blood pressure < 90 mm Hg), or neurological compromise (including confusion, collapse, loss of consciousness, or incontinence). Statistical analyses were performed using Prism (Graphpad Software Inc, La Jolla, Calif) and were documented next to each figure.

RESULTS

A total of 108 patients were referred with suspected flucloxacillin hypersensitivity (89 with a history of an immediate reaction, 13 a nonimmediate reaction, and 6 with the time of onset being unknown). After completing the diagnostic workup, patients with unknown history were allocated to the nonallergic group.

The age range of the cohort referred was 20 to 83 years (median and mean, 53 years). Female patients were more frequently referred: 72 of 108 (67%). In 40 of 108 patients (37%), flucloxacillin hypersensitivity was confirmed: immediate in 33 patients (82.5%) and nonimmediate in 7 (17.5%). In the remaining 68 patients (63%), flucloxacillin hypersensitivity was excluded (Figure 1).

The indications for flucloxacillin in the immediate group were known in 13 of 33 patients; these included abscess in 1, mastitis in 1, surgical prophylaxis in 5, and cellulitis in 6.

The indication for flucloxacillin in the nonimmediate group was known in 5 of 7 patients and included cellulitis in 1, post-surgical wound infection in 2, and surgical prophylaxis in 2.

Immediate hypersensitivity reactions to flucloxacillin

In 33 of 108 (31%) patients referred, a diagnosis of immediate flucloxacillin hypersensitivity was confirmed. The age range was 23 to 82 years, with a median age of 52 years and a mean age of 50 years. The female to male ratio was 2:1 (22 females: 11 males).

The severity of the index reaction was documented in 32 of 33 patients: grade 3 (severe) in 19 (56%) cases, grade 2 (intermediate) in 4 (12%) cases, and grade 1 (mild) in 9 (27%) cases (Figure 2).

The time lag between the index reaction and skin testing was less than 1 year in 55% (18 of 33), 1 to 2 years in 9% (3 of 33), and more than 2 years in 36% (12 of 33) of patients. The longest interval known was 54 years.

Only 7 of 33 (21%) patients were diagnosed with a positive immediate SPT result with flucloxacillin. Most patients (17 of 33 [52%]) were diagnosed with a positive immediate IDT result, and the remainder after a positive DPT result in oral flucloxacillin challenge: 9 of 33 (27%) with immediate objective signs including urticaria, angioedema, and wheeze (Figure 2).

Eight of 17 (47%) patients with positive IDT result had their index reactions more than 2 years before skin testing.

All centers were required to have more than 3-mm increase from baseline and from negative control. The center with the highest concentration used for intradermal testing had 6 of 17 patients with immediate intradermal positive result. The mean increase in wheal size was 9 mm, median 8 mm, and range 6 to 18 mm, respectively.

Of the 7 patients who had a positive SPT result to flucloxacillin, all had severe (6 of 7) or intermediate (1 of 7) index reactions. None of the patients who had mild reactions had positive SPT result.

In patients referred with a history of immediate hypersensitivity reactions to flucloxacillin after negative SPT result, the negative predictive value (NPV) of IDT was 86%. There were 56 patients referred with a history of immediate reaction to flucloxacillin who were confirmed nonallergic after SPT, IDT, and DPT counted for the NPV calculation as true negatives.

Eleven of 33 (33%) patients allergic to flucloxacillin had mast cell tryptase level measured at the time of the index reaction. Tryptase level rose acutely in all these patients ($P = 0.001$) (acute range, 13.8–400 ng/mL; median, 67 from a baseline range of 3.1–12 ng/mL; median, 6). Of these patients, 9 of 33 had a grade 3 reaction (severe), 1 of 11 grade 2 (intermediate), and 1 of 11 grade 1 (mild). In the patients with elevated tryptase level, their flucloxacillin allergy diagnosis was supported by positive IDT result in 7 of 11 (64%), by SPT in 2 of 11 (18%), and by oral challenge in 2 of 11 (18%).

Eighteen of 33 patients allergic to flucloxacillin had specific IgE testing to other penicillins. Only 3 of 18 (17%) were positive.

Nine patients underwent DPT; of these, 7 of 9 had documented emergency treatment: 7 of 9 required oral antihistamines, 6 of 9 prednisolone, 2 of 9 salbutamol (1 nebulized, 1 inhaler), and 2 of 9 epinephrine. One patient required antihistamines and prednisolone for a systemic reaction after positive SPT results.

Cross-sensitization with other penicillins (amoxicillin, benzylpenicillin, benzylpenicilloyl poly-L-lysine, minor determinants) was low. Overall 9 of 33 (27%) patients showed cross-sensitization to other penicillins on SPT, IDT, or specific IgE testing. This was seen in 1 of 7 (14%) SPT-positive patients and 6 of 17 (35%) IDT-positive patients. Only 18 patients underwent serum specific IgE testing to other penicillins and 3 of 18 (11%) were positive. Of these 3 patients, only 1 had skin test cross-reactivity with the other penicillins (see Tables E1 and E2 in this article's Online Repository at www.jaci-inpractice.org).

Patients with negative SPT and IDT results to other penicillins were not routinely challenged to alternate penicillins; however, 4 patients did tolerate oral DPT with amoxicillin. Of these patients, 2 of 4 were positive to flucloxacillin on oral challenge and 2 of 4 positive to flucloxacillin on IDT and therefore declared allergic to flucloxacillin.

The management advice given to patients at the time of diagnosis varied. All patients allergic to flucloxacillin (33 of 33) were advised to avoid flucloxacillin; 26 of 33 (79%) patients were advised to avoid all penicillins; 4 of 33 (12%) patients were advised that they could have amoxicillin only as an alternative antibiotic (having had negative SPT results and passed an amoxicillin challenge). The remaining 3 of 33 (9%) were advised to avoid only flucloxacillin and could have other penicillins if no suitable alternative was available.

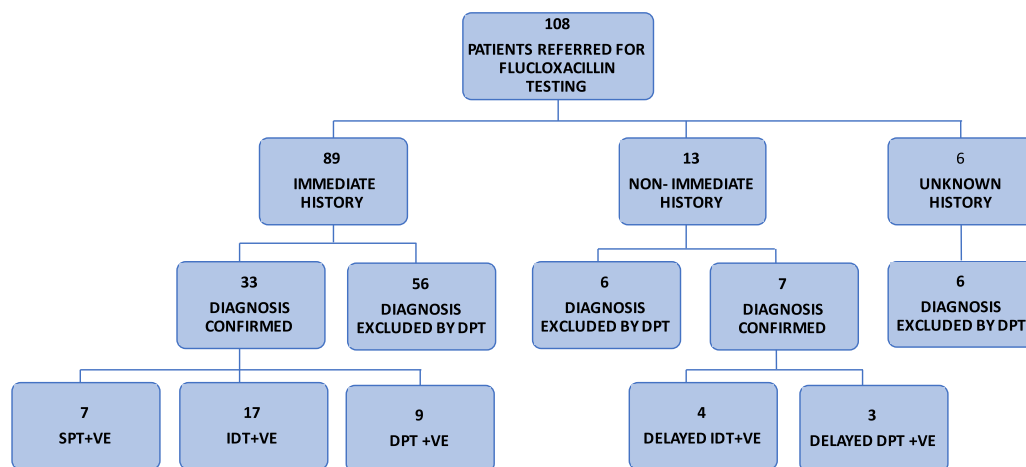


FIGURE 1. Overview of all patients referred with suspected flucloxacillin reactions.

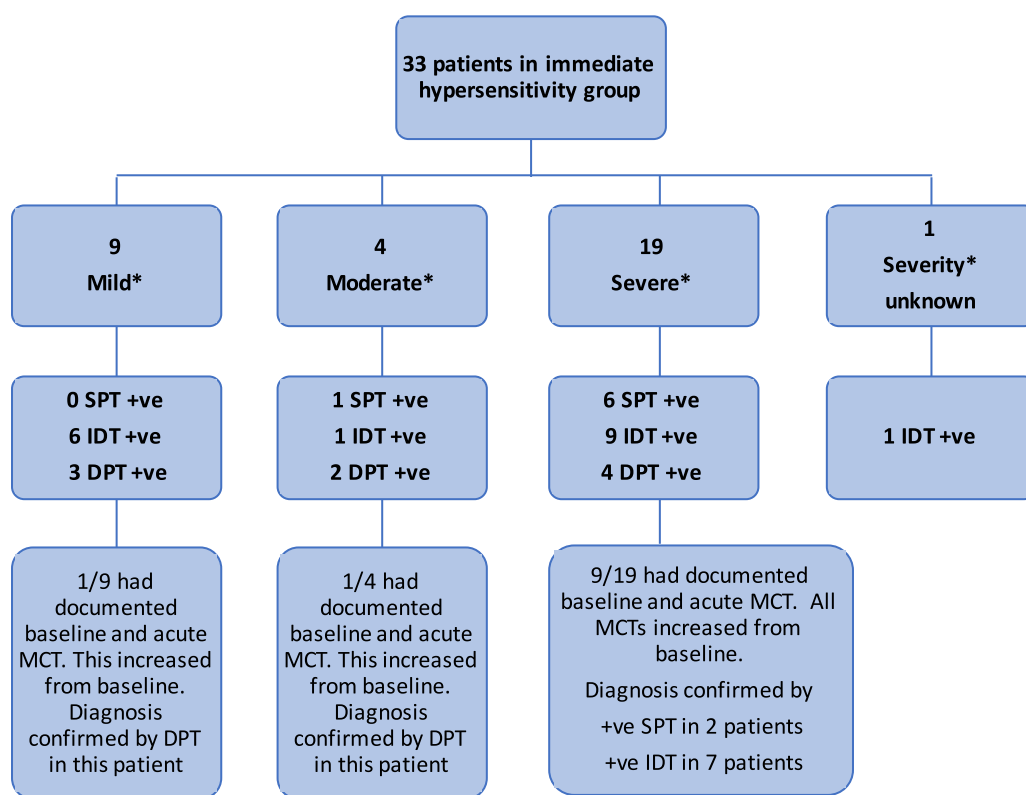


FIGURE 2. Index reaction severity and methodology used to confirm diagnosis. *MCT*, Mast cell tryptase. *Severity—Brown's anaphylaxis grading.

Nonimmediate hypersensitivity reactions to flucloxacillin

Seven of 108 (6%) patients experienced nonimmediate reactions (1 drug reaction with eosinophilia and systemic symptoms and 6 delayed cutaneous reactions). The age range of the cohort with nonimmediate hypersensitivity was 41 to 83 years (median, 57 years; mean, 54.81 years). The male to female ratio was 3:4. In terms of delay from index reaction to skin testing,

75% (3 of 4) with a positive delayed IDT had waited 1 year or less and 25% (1 of 4) more than 2 years.

As expected, SPT result to flucloxacillin was negative in all patients. Most patients (4 of 7 [57%]) were diagnosed with a positive delayed IDT result (including the patient with drug reaction with eosinophilia and systemic symptoms); the remainder were diagnosed by oral flucloxacillin challenge (3 of 7 [43%]) and the patients were all positive to oral

challenge within 24 hours with delayed cutaneous reactions (Figure 1).

In patients referred with a history of nonimmediate hypersensitivity reactions to flucloxacillin, the NPV of the delayed IDT in the context of a negative SPT result was 67% in our study. There were 6 patients referred with a history of nonimmediate reaction to flucloxacillin who were confirmed nonallergic and had a diagnosis of delayed hypersensitivity to flucloxacillin excluded after SPT, IDT, and DPT counted for the NPV calculation as true negatives.

In patients with positive flucloxacillin skin test result, cross-sensitization to other penicillins was high and was seen in 75% (3 of 4) (see Tables E3 and E4 in this article's Online Repository at www.jaci-inpractice.org). One patient negative on IDT to the other penicillins tolerated a benzylpenicillin DPT. None of these patients had mast cell tryptase or specific IgE testing to penicillins.

Skin testing in patients with a history of nonimmediate hypersensitivity reactions was generally safe because none of these patients required emergency treatment. During delayed DPT with flucloxacillin, 2 of 3 (66.6%) patients were given oral prednisolone in the community.

At the time of diagnosis, all patients (7 of 7) with a diagnosis of nonimmediate hypersensitivity were advised to avoid flucloxacillin; 1 of 7 (14%) patients was advised to avoid flucloxacillin only, and 1 of 7 (14%) was advised to avoid all penicillins except benzylpenicillin having tolerated oral provocation test. The remainder were advised to avoid all penicillins.

DISCUSSION

To our knowledge this is the largest multicenter study investigating patients referred with suspected flucloxacillin allergy. The retrospective nature of the study and the large cohort of patients studied inevitably include differences in the diagnostic process. We believe this limitation does not critically affect the overall relevance of the results. We acknowledge that these results represent patients who mostly suffered from moderate/severe immediate hypersensitivity reactions often with anaphylaxis as their index reaction. Furthermore, these immediate reactions were marked by a significant rise in mast cell tryptase level during the acute episode, where recorded. Therefore, our cohort differs from a cohort of patients seen in the community with predominantly benign maculopapular rashes following flucloxacillin treatment.

Controversies still exist in how best to diagnose penicillin allergy and to avoid giving patients a false label. In particular, it is thought that specific IgE testing for penicillins may have little clinical utility.⁷

DPT with a therapeutic dose of the index penicillin remains the diagnostic criterion standard. We acknowledge that the positive predictive value of skin tests has not been precisely established¹⁴ and that there is a risk of labeling patients "allergic" when only using penicillin skin testing. However, by only considering skin test results of more than 5-mm increase in wheal from the baseline wheal size as positive, this risk is reduced.¹⁵ Reassuringly, where results were documented in detail, all positive IDT results showed larger than 6-mm increase from baseline wheal size with associated flare in our cohort.

On these grounds, in our group of mostly high-risk patients, skin test (either SPT or IDT) results when positive were considered diagnostic in both groups of patients. Under these circumstances,

DPT in this cohort of patients with positive skin test results would be considered unethical, being outside a research setting.

In our cohort, immediate hypersensitivity to flucloxacillin is more common than nonimmediate hypersensitivity. Immediate hypersensitivity affects twice as many women as men, and this is in agreement with previous findings in beta-lactam allergy.^{16,17} A smaller increased female preponderance was also seen in the nonimmediate group.

The NPV of the IDT to flucloxacillin was high (86%) in the immediate hypersensitivity cohort. This is despite a delay of more than 2 years before assessment in a third of patients and 47% (8 of 17) in the group with positive IDT result. This suggests that immunologic memory can persist for years. In the nonimmediate cohort, the NPV of delayed IDTs was less (67%) and of the 4 patients with positive IDT results, only 25% (1 of 4) had a delay over 2 years.

In our cohort, 27% (9 of 33) of the immediate and 43% (3 of 7) of the nonimmediate group required oral challenge to confirm the diagnosis. Our protocol has been found to be safe and can replace the more traditional, longer protocols because it allows for a more efficient use of clinical capacity.^{18,19}

All patients with delayed hypersensitivity reacted within 24 hours of their oral challenge and were managed in the community.

Our results indicate that most patients with immediate hypersensitivity to flucloxacillin are selectively sensitized. This confirms the antigenic role of the side chain of the flucloxacillin molecule, in line with similar findings for amoxicillin sensitization.² Thus, the results in our large cohort of patients confirm the results obtained in a small cohort by Baldo et al¹ over 20 years ago.

Four patients with immediate hypersensitivity, who had negative IDT results to the other penicillins, subsequently passed amoxicillin DPT, validating the results of the skin tests.

Our findings have significant clinical implications for most patients with immediate hypersensitivity who are monosensitized.

Conversely, a higher level of cross-sensitization in intradermal testing was observed in the patient group with nonimmediate, cutaneous reactions (75%), than in the immediate hypersensitivity group (35%). Only 1 patient with delayed hypersensitivity underwent and passed a benzylpenicillin oral provocation test.

These differences between immediate and nonimmediate hypersensitivity to flucloxacillin may be explained by differences in antigen presentation, processing, and recognition.

In summary, IgE-mediated flucloxacillin allergy showed mainly a selective immune recognition for this antibiotic, with low levels of cross-reactivity with other penicillins. In our cohort of patients, intradermal tests have a high NPV (86%) for flucloxacillin allergy in the context of a negative SPT result and history of immediate reaction. This suggests that after careful risk-benefit analysis, amoxicillin DPT should be considered and these patients would be expected to pass the oral challenge.

Conversely, in patients with nonimmediate reactions, delayed IDT showed a modest NPV (67%). Furthermore, there were high levels of cross-reactivity to other penicillins on IDT, and we would not routinely advocate challenge with alternate penicillins in this group.

There is a significant danger of depriving individuals with immediate hypersensitivity reactions to flucloxacillin of alternative penicillins that they may tolerate if skin test result is negative. Further research with systematic DPT with alternative penicillins is needed in patients allergic to flucloxacillin who are

not sensitized to other penicillins on skin testing. Careful and clear documentation to alert clinicians of the outcome of the patient's status to other penicillins must be undertaken to avoid mistakes. Standardized testing and challenge procedures are needed to ensure harmonized outcomes for patients.

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ONLINE REPOSITORY

TABLE E1. Pattern of CR seen with other penicillins in patients with immediate hypersensitivity reactions to flucloxacillin

Patient	SPT	IDT	IgE (kU/L)
1	PPL, MD, amoxicillin, benzylpenicillin	ND	Negative to phenoxymethylpenicillin, benzylpenicillin, and amoxicilloyl
2	No CR	PPL, MD, Augmentin	Negative to phenoxymethylpenicillin, benzylpenicillin, and amoxicilloyl
3	No CR	PPL, MD, benzylpenicillin	Negative to phenoxymethylpenicillin, benzylpenicillin, and amoxicilloyl
4	No CR	Ampicillin	Negative to phenoxymethylpenicillin, benzylpenicillin, and amoxicilloyl
5	No CR	Ampicillin, amoxicillin	Positive phenoxymethylpenicillin 11.2, benzylpenicillin, amoxicilloyl 5.1
6	No CR	Ampicillin	Negative to phenoxymethylpenicillin, benzylpenicillin, and amoxicilloyl
7	No CR	PPL, MD	ND
8	No CR	ND	Positive phenoxymethylpenicillin 0.57
9	No CR	No CR (flucloxacillin SPT positive, IDT performed to other penicillins)	Positive amoxicilloyl 8.2, phenoxymethylpenicillin 1.34

CR, Cross-reactivity; MD, minor determinants; ND, not done; PPL, benzylpenicilloyl poly-L-lysine.

It should be noted that ampicillin testing was not carried out at all centers. Bold indicates a positive test result.

TABLE E2. Cross-reactivity frequency to alternate penicillins seen in patients with immediate flucloxacillin allergy

Patient	Drug	No. of patients allergic to flucloxacillin who had a positive result on IDT to alternate penicillin (%)
1	Benzylpenicilloyl poly-L-lysine	3 of 26 (12)
2	Minor determinants	3 of 26 (12)
3	Benzyl penicillin	1 of 26 (4)
4	Amoxicillin	1 of 26 (4)
5	Augmentin	1 of 14 (7)
6	Ampicillin	3 of 12 (25)

TABLE E4. Frequency of cross-reactivity to other penicillins seen on IDT in patients with nonimmediate hypersensitivity reactions to flucloxacillin

Penicillin	Cross-reactivity to other penicillins, n (%)
Benzylpenicilloyl poly-L-lysine	0 of 7 (0)
Minor determinants	0 of 7 (0)
Benzyl penicillin	3 of 7 (43)
Amoxicillin	2 of 7 (29)

TABLE E3. Pattern of CR seen with other penicillins in patients with nonimmediate hypersensitivity reactions to flucloxacillin

Patient	SPT	IDT	IgE (kU/L)
1	No CR	Benzylpenicillin	ND
2	No CR	Amoxicillin, benzylpenicillin	ND
3	No CR	Amoxicillin, benzylpenicillin	ND

CR, Cross-reactivity; ND, not done.

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