APJAI
Asian Pacific Journal of
Allergy and Immunology

ORIGINAL ARTICLE

Evaluation of diagnostic approach and clinical outcomes in children with suspected beta-lactam allergy

Wang Chin Eileen Ng,[1] Marcus Wing Choy Loe,[1] John Zhong Heng Low,[1] Si Hui Goh,[2] Kok Wee Chong[2]

Abstract

Background: Beta-lactams (BLs) are commonly implicated in hypersensitivity reactions among children. However, majority of self-reported BL allergies may be viral exanthems and antibiotics side effects. International guidelines have recommended de-labelling BL allergies in children with delayed mild hypersensitivity reactions via direct drug provocation tests (DPTs) without prior skin testing. However, studies on the safety of direct DPTs in Asia remain limited.

Objective: Our study aims to describe the diagnostic approach and clinical outcomes in children with suspected BL allergies and evaluate the safety of direct DPTs for children with immediate and delayed mild BL hypersensitivity reactions.

Methods: This is a retrospective cohort study involving 395 children who underwent 425 BL DPTs for suspected BL hypersensitivity reactions, with or without skin testing.

Results: Median age of children at the time of DPT was 8.0 years, with 47.3% being males. The onset of hypersensitivity symptoms was immediate (within one hour from last BL dose) in 21.3% of children, delayed in 30.1% while the remaining had unknown onset. Of the diagnostic direct oral DPTs to index BLs, 89.3% passed and were successfully de-labelled. Majority (88.9%) of challenge reactions in diagnostic direct oral DPTs were mild cutaneous symptoms, except for three cases (8.3%) of cytokine release syndrome and one case of anaphylaxis (2.8%). A younger age at index reaction was the only statistically significant factor associated with passing diagnostic direct oral DPTs.

Conclusion: Direct oral DPT is a safe method for de-labelling BL allergies in children for both immediate and delayed mild hypersensitivity reactions.

Key words: Beta-lactams, anti-bacterial agents, drug hypersensitivity, child, retrospective studies

Citation:
Ng, W. C. E., Loe, M. W. C., Low, J. Z. H., Goh, S. H., Chong, K. W. (0000). Evaluation of diagnostic approach and clinical outcomes in children with suspected beta-lactam allergy. *Asian Pac J Allergy Immunol*, 00(0), 000-000. https://doi.org/10.12932/ap-250226-2241

Affiliations:
[1] Ministry of Health Holdings, Singapore 139691
[2] Allergy Service, Department of Paediatrics, KK Women's and Children's Hospital, Singapore 229899

Corresponding author:
Chong Kok Wee
KK Women's and Children's Hospital, 100 Bukit Timah Road, Singapore 229899
E-mail: chong.kok.wee@singhealth.com.sg

Introduction

Beta-lactam (BL) antibiotics, including penicillins and cephalosporins, are among the most frequently prescribed antimicrobial agents in the paediatric population due to their efficacy, safety, and broad spectrum of activity. BLs are, however, also amongst the most commonly implicated drugs in drug hypersensitivity reactions among children both internationally[1,2] and in Singapore.[3] Studies have estimated that the prevalence of self-reported BL allergies in various paediatric populations ranges between 1% and 10%.[1] In Singapore, BLs account for 45% to 57% of parent-reported drug allergies in children.[3,4]

The majority of BL allergies among children are self-reported and may not be true hypersensitivity reactions. Symptoms such as viral exanthems, and common antibiotics side effects such as diarrhoea, are often misinterpreted and reported as drug allergies.[5,6] Previous studies have consistently shown that upon formal evaluation including skin prick tests (SPT), intradermal tests (IDT), and drug provocation tests (DPT), over 90% of children with suspected drug hypersensitivities are tolerant.[7,8] Inaccurate labelling of BL allergies can lead to unnecessary use of second-line antibiotics, which are often more expensive, less effective, and associated with higher risks of antimicrobial resistance, longer hospital stays, and increased healthcare costs.[9,10]

In recent years, there has been a paradigm shift in the evaluation of children with suspected BL hypersensitivities. Several studies have demonstrated that performing direct DPT, which is DPT without prior skin testing, is safe and effective in low-risk children who present with mild, non-immediate index reactions such as urticaria or maculopapular exanthems.[11] This has also been reflected in international guidelines by the European Academy of Allergy and Clinical Immunology (EAACI),[1] British Society for Allergy and Clinical Immunology (BSACI),[12] as well as the Joint Task Force on Practice Parameters selected by the American Academy of Allergy, Asthma, and Immunology (AAAAI) and the American College of Allergy, Asthma, and Immunology (ACAAI),[13] which recommend risk-stratified approaches to de-labelling BL allergies via direct DPTs in selected paediatric populations. However, evidence from Asian populations, where genetic, environmental, and healthcare delivery factors differ, remains limited. In addition, there remains little consensus on the safety of direct DPTs for immediate index hypersensitivity reactions. Immediate drug hypersensitivity reactions may be mediated by IgE or non-IgE mechanisms including IgG-antigen interactions, MRGPRX2 transmembrane proteins or cytokine release.[14] On the other hand, delayed reactions occur due to T cells-mediated responses. The EAACI 2016 guidelines suggested for all children with immediate BL hypersensitivity reactions to undergo skin testing before DPT due to higher risk of immediate hypersensitivity reactions.[1] However, some centres have recently begun performing direct DPTs even for immediate reactions, due to the low sensitivity and time-consuming nature of skin testing. In a large meta-analysis[15] of 8334 direct DPTs in children, including 17.9% of patients from Asia, direct DPT was a safe and effective de-labelling tool. Among the 28 studies in the meta-analysis, 15 included patients with both immediate and delayed reactions.

Various studies have also explored the factors associated with true BL allergies in children. These include female gender, concomitant drug allergies or atopy history, history of anaphylaxis and short time interval between index reaction and drug evaluation.[16,17] In studies involving Asian populations, history of food allergies and concomitant angiotensin-converting enzyme inhibitor use were some of the additional factors cited.[18,19] Understanding these factors can help identify children who are more likely to benefit from a direct DPT without prior skin testing. However, research into these risk factors is limited in our local context.

The primary aim of our study is to evaluate the clinical characteristics, diagnostic approach, and outcomes of BL allergy assessment in a large cohort of children referred to the allergy service in a paediatric tertiary hospital in Singapore. This includes the evaluation of the safety of direct DPTs for both immediate and delayed hypersensitivity reactions. Our secondary aims are to analyse factors associated with passing direct oral DPTs to index BLs, and to explore the cross-reactivity patterns within BLs by studying the results of DPTs to alternative BLs.

Methods

This retrospective cohort study included all children who were referred for evaluation and deemed suitable to undergo DPTs for suspected BL hypersensitivity reaction in KK Women's and Children's Hospital (KKH) in Singapore over a five-year period from 1st July 2019 to 31st July 2024. There were no exclusion criteria.

Diagnostic approach

Based on clinical history, reactions that began within one hour of BL administration were considered immediate, while those occurring after one hour were considered delayed. Reactions were classified as mild if they involved only the muco-cutaneous system. Reactions were severe if they were multi-systemic with involvement of airway, respiratory or cardiovascular systems, or encompass fever, mucosal erosions, blistering rash, internal organs involvement indicative of anaphylaxis or Severe Cutaneous Adverse Reactions (SCAR).[20,21]

DPTs were considered direct if performed without prior skin tests. DPTs were considered diagnostic if performed with the same index drug that caused the initial hypersensitivity reaction. Alternative DPTs were performed using another BL that was not the index drug. Drug allergy workups were carried out at least four weeks after the onset of initial hypersensitivity reactions.[22]

In our center, patients with mild reactions, whether of immediate or delayed onset, were offered a diagnostic direct DPT. Patients with severe reactions would undergo skin testing prior to DPT to determine which BL should be used during the DPT. Additionally, in all patients with suspected reactions (regardless of severity) to BLs only available as intravenous formulations, skin testing was performed prior to diagnostic DPT. Our center retained skin testing for mild reactions to intravenous drugs given the invasiveness and increased risk of diagnostic parenteral challenge. If skin tests were positive to index drug, DPT to an alternative BL was performed.

Skin Prick Test (SPT) and Intradermal Test (IDT)

SPTs were performed using parental preparation of index drugs, histamine positive control, diluent negative control and, when applicable, a standard BL panel consisting of (1) benzylpenicilloyl octa-L-lysine, (PPL, Diater Laboratorios, Madrid, Spain) (2) sodium benzylpenilloate, (MD, Diater Laboratorios) (3) benzylpenicillin, (4) ampicillin, (5) cefazolin, and (6) ceftriaxone. Reagent concentrations were standardised as per the recommendations of the European Network of Drug Allergy (ENDA)/ EAACI for benzylpenicillin (10,000 U/mL), ampicillin (20 mg/mL), cefazolin (2 mg/mL), and ceftriaxone (2 mg/mL).[23] Positive SPT results were defined as a mean wheal size of at least 3 mm relative to the negative control.

IDTs were performed with the maximum non-irritating concentration of drugs as per ENDA/EAACI.[23] Positive IDT results were defined as a mean wheal size of at least 3 mm relative to the initial bleb or persistence of wheals after 20 minutes with flare and itching.

Drug Provocation Test (DPT)

All children were evaluated by a consultant allergist prior to their DPT. Oral DPTs were performed with a single therapeutic dose of BL administered via oral route under a physician's supervision in an outpatient setting. If there was no initial reaction in clinic, patients continued therapeutic dose of the antibiotics at home for the next two days. Oral DPT was carried out over three days to increase diagnostic yield, while balancing against the risk of antibiotic resistance with longer exposure and increased costs of testing.[24,25] Intravenous (IV) DPTs were performed as a one-day protocol, in graded steps (two steps – 10%, 90% or four steps – 1%, 10%, 50%, 100%; depending on the severity of index reaction) in the same outpatient allergy unit.

Patients who underwent multi-day oral DPTs were monitored in the clinic after the first dose and subsequently at home for symptoms of hypersensitivity reaction. Symptoms that occurred at home (if any) were reported via an online form, including photo-documentation, to the allergy unit and the cases were then reviewed by a consultant paediatric allergist to assess if the reactions were considered hypersensitivity reactions. Parents of patients undergoing multi-day oral DPTs who did not report any home symptoms via the online form were contacted at the end of the three-day challenge via telephone to ascertain that no reactions had occurred. DPTs were considered passed if there was no reaction after the IV challenge or after completing the three-day course of the prescribed oral BL.

Ethics approval

This study was approved with waiver of consent by the SingHealth Institutional Review Board (reference number #2022/2309).

Statistical analysis

Data regarding the children's personal and family atopy history, index reaction as well as their SPT, IDT and DPT results were extracted from electronic case notes onto standardised data collection forms. Statistical analysis was carried out using IBM SPSS Statistics ver. 27.0 (IBM Co., Armonk, NY, USA). Patients' characteristics and their index reactions were described using percentages, with continuous data described using median and range. When comparing those who failed and passed their diagnostic direct oral DPTs, differences were determined using the chi-squared analysis. Logistic regression was performed to ascertain adjusted odd ratios for factors associated with passing direct oral DPTs to index drug. Variables for inclusion in the multivariable logistic regression model were selected based on clinical relevance established from prior international studies[16-19] demonstrating associations with true BL allergies (including child's atopy history and characteristics of index reaction), and statistical significance with a univariable p-value threshold of < 0.05. For both the chi-square analysis and logistic regression, p-value < 0.05 was considered statistically significant.

Results

Study demographics

Over the five-year study period, 395 children with suspected BL reactions were identified, with 425 DPTs performed. Of these children, 372 underwent one DPT, 18 had two DPTs, three had three DPTs and two children had four DPTs during the study period (**Table 1**). The median age at the time of DPT was 8.0 years (range 0–19 years), with 47.3% (187/395) being males. Thirteen children (3.3%) had documented allergies to two or more BLs. Of the 131 children with known date of index reaction, the median duration between index reaction and DPT was 183 days (range 34–3824) days.

Description of index reactions

The commonly implicated drugs were amoxicillin-clavulanate (174/395; 44.1%), amoxicillin (125/395; 31.6%) and cefalexin (37/395; 9.4%) (**Table 1**). The most frequently reported reactions were urticaria (144/395; 36.5%), maculopapular rash (137/395; 34.7%) and angioedema (113/395; 28.6%). There were nine cases (2.3%) of anaphylaxis. The onset of symptoms was immediate (within one hour from last BL dose) in 21.3% of children (84/395) while 30.1% (119/395) had delayed hypersensitivity reactions and 48.6% (192/395) with unknown onset.

SPTs and IDTs

Of the 395 children, 34 (8.6%) underwent skin testing prior to DPT - nine had index anaphylactic reactions, 20 had index reactions to IV drugs, and five for other reasons. All SPTs were negative. Five of the IDTs were positive (four to IV cefazolin, one to IV cefotaxime) (**Table 2**).

Table 1. Characteristics of children included in the study and their initial hypersensitivity reactions.

	Total no. of patients (n = 395)
Age at DPT in years, median (min - max)	8 (0 – 19)
Males, n. (%)	187 (47.3)
Race	
Chinese, n. (%)	301 (76.2)
Malay, n. (%)	47 (11.9)
Indian, n. (%)	22 (5.6)
Other races, n. (%)	18 (4.6)
Family history of beta-lactam allergy, n. (%)	37 (9.4)
Personal history of atopy	
Allergic rhinitis, n. (%)	165 (41.8)
Asthma, n. (%)	28 (7.1)
Eczema, n. (%)	104 (26.3)
Food allergy, n. (%)	30 (7.6)
Recurrent urticaria, n. (%)	20 (5.1)
Chronic spontaneous urticaria, n. (%)	4 (1.0)
Personal history of drug allergy	
Allergies to two or more beta-lactams, n. (%)	13 (3.3)
Non-beta lactam drug allergy, n. (%)	6 (1.5)
Beta-lactam causing index reaction	
Penicillins	
Amoxicillin, n. (%)	125 (31.6)
Amoxicillin-Clavulanate, n. (%)	174 (44.1)
Ampicillin, n. (%)	5 (1.3)
Cloxacillin, n. (%)	2 (0.5)
Penicillin V or G, n. (%)	8 (2.0)
Piperacillin, n. (%)	1 (0.3)
Cephalosporins	
Cefalexin, n. (%)	37 (9.4)
Cefazolin, n. (%)	11 (2.8)
Cefaclor, n. (%)	3 (0.8)
Cefuroxime, n. (%)	3 (0.8)
Ceftriaxone, n. (%)	21 (5.3)
Cefixime, n. (%)	1 (0.3)
Cefpodoxime, n. (%)	1 (0.3)
Unknown, n. (%)	3 (0.8)

	Total no. of patients (n = 395)
Description of index reaction[a]	
Anaphylaxis[b], n. (%)	9 (2.3) n = 3 had respiratory involvement n = 4 had cardiovascular involvement n = 2 had both respiratory and cardiovascular involvement
Angioedema, n. (%)	113 (28.6)
Urticaria, n. (%)	144 (36.5)
Maculopapular rash, n. (%)	137 (34.7)
Pustular rash, n. (%)	2 (0.5)
Non-specific rash, n. (%)	87 (22.0)
Severe Cutaneous Adverse Reactions (SCAR), n. (%)	0 (0.0)
Gastrointestinal manifestations[c], n. (%)	13 (3.3)
Serum sickness-like reaction, n. (%)	0 (0.0)
Number of beta-lactam doses to index reaction	
First dose, n. (%)	112 (28.4)
First day of treatment, but not first dose, n. (%)	48 (12.2)
Second day of treatment, n. (%)	36 (9.1)
After second day of treatment, n. (%)	73 (18.5)
After end of treatment, n. (%)	11 (2.8)
Others/Unknown, n. (%)	115 (29.1)
Onset of index reaction from last beta-lactam dose	
< 15 minutes, n. (%)	30 (7.6)
15-60 minutes, n. (%)	54 (13.7)
1-6 hours, n. (%)	79 (20.0)
6-24 hours, n. (%)	26 (6.6)
> 24 hours, n. (%)	14 (3.5)
Unknown, n. (%)	192 (48.6)
Duration between index reaction and DPT in days, median (min - max)	183 (34 – 3824)

[a]Each child may report > 1 symptoms in their initial hypersensitivity reaction.
[b]Anaphylaxis: Four patients had perioperative anaphylaxis.
[c]Gastrointestinal symptoms did not occur in isolation.

Table 2. Details of positive SPTs and IDTs.

Sex	Age at SPT/IDT	Personal atopy history	Index reaction	SPT/IDT results	DPT results
F	12	Nil	Urticaria within 15 minutes of first dose of IV ceftriaxone	**IDT cefotaxime - positive** IDT ceftazidime - negative SPT beta lactam panel, cefotaxime, ceftazidime -negative	Diagnostic DPT to IV ceftriaxone failed – angioedema within 15-60 minutes of ceftriaxone Alternative DPT to IV ceftazidime passed
M	12	Allergic rhinitis, eczema, food allergy	Angioedema and urticaria within 15 minutes of first dose of IV cefazolin	**IDT cefazolin - positive** IDT ceftriaxone - negative SPT beta lactam panel, cefazolin, ceftriaxone - negative	Alternative DPT to oral cefalexin passed
F	16	Nil	Anaphylaxis within 15 minutes of first dose of IV cefazolin	**IDT cefazolin - positive** IDT ceftriaxone - negative SPT beta lactam panel - negative	Alternative DPT to oral cefalexin passed
F	14	Nil	Angioedema, urticaria within 15-60 minutes after first dose of IV cefazolin	**IDT cefazolin - positive** **SPT cefazolin - borderline positive**	Alternative DPT to oral cefalexin passed
M	16	Allergic rhinitis	Urticaria within 15-60 minutes of last dose after second day of treatment with IV cefazolin	**IDT cefazolin - positive** SPT cefazolin - negative	Alternative DPT to oral cefuroxime passed

Description of all DPTs

There was a total of 425 DPTs performed – 93.2% (396/425) via oral and 6.8% (29/425) via IV route of administration (**Table 3**). 78.6% (334/425) of challenges involved the penicillin group, with amoxicillin-clavulanate (176/425; 41.4%) and amoxicillin (146/425; 34.4%) comprising the majority of BLs tested. 21.4% (92/425) of challenges involved cephalosporins, with cefalexin (53/425; 12.5%) and ceftriaxone (19/425; 4.5%) being most common. Majority (363/425; 85.4%) of DPTs were diagnostic, i.e. performed to the index drug that was implicated in the initial hypersensitivity reaction, with 14.6% (62/425) of DPTs being performed to alternative drugs. DPT pass rate was 87.3% (371/425) of all DPTs (**Table 3**).

Among the failed DPTs, common reactions were urticaria (33/54; 61.1%) and maculopapular rash (18/54; 33.3%). Other observed reactions following DPTs include anaphylaxis (1/54; 1.9% described in **Table 4**), cytokine release syndrome (3/54; 5.6% described in **Table 4**), angioedema (8/54; 14.8%), gastro-intestinal manifestations such as vomiting (5/54; 9.3%; all gastro-intestinal symptoms occurred concurrently with cutaneous or systemic manifestations). There were no cases of SCAR observed. Cytokine release syndrome was diagnosed if these children developed symptoms of acute systemic inflammation with each BL exposure, which included fever, generalised flushing as well as raised inflammatory markers.[26] These symptoms did not meet the criteria for IgE-mediated anaphylaxis as they were delayed in onset and did not resolve adequately with intramuscular adrenaline. Septic workup in these children was also negative, supporting the diagnosis of cytokine release syndrome as the inflammatory response was likely triggered by the BL instead.

Table 3. Details of DPTs performed.

	Number of DPTs (% of total DPTs)	Number of failed DPTs (% DPT failure in each category)
Total number of all DPTs, n. (%)	425 (100)	54 (12.7)
Types of DPTs		
Diagnostic DPTs to index drug	363 (85.4)	46 (12.7)
DPTs to alternative drug[a]	**62 (14.6)**	8 (12.9)
Route of drug administration		
Oral, n. (%)	396 (93.2)	42 (10.6)
Intravenous, n. (%)	29 (6.8)	12 (41.4)

Table 3. (Continued)

	Number of DPTs (% of total DPTs)	Number of failed DPTs (% DPT failure in each category)
Type of beta-lactam administered during DPT		
Penicillins		
Amoxicillin, n. (%)	146 (34.4)	14 (9.6)
Amoxicillin-clavulanate, n. (%)	176 (41.4)	23 (13.1)
Ampicillin, n. (%)	2 (0.5)	-
Cloxacillin, n. (%)	2 (0.5)	-
Penicillin V or G, n. (%)	8 (1.9)	-
Cephalosporins		
Cefalexin, n. (%)	53 (12.5)	5 (9.4)
Cefazolin, n. (%)	4 (0.9)	1 (25.0)
Cefaclor, n. (%)	3 (0.7)	-
Cefuroxime, n. (%)	7 (1.6)	-
Ceftriaxone, n. (%)	19 (4.5)	10 (52.6)
Cefpodoxime, n. (%)	1 (0.2)	-
Cefotaxime, n. (%)	1 (0.2)	-
Ceftazidime, n. (%)	3 (0.7)	1 (33.3)
Cefepime, n. (%)	1 (0.2)	-

[a]Indication for alternative drug challenge include failed DPTs to index drug, positive SPT/IDT to index drug, anaphylaxis at index reaction, parental preference especially when index drug was intravenous and preference for oral alternative.

Table 4. Characteristics of children with severe challenge reactions (anaphylaxis, cytokine release syndrome/CRS).

Sex	Race	Personal history of atopy	Age at index reaction	Index drug	Index reaction	Age at DPT	DPT drug	DPT reaction
M	Malay	Allergic rhinitis, asthma	15	Augmentin	Generalised flushing, chest tightness, dyspnea within 45 minutes from second dose of BL. The child was admitted for monitoring. Acute tryptase not elevated and septic workup negative. Fever resolved within 24 hours of discontinuation of BL.	16	Oral augmentin	CRS: rigors, generalised flushing, chest tightness, drowsiness and vomiting within two and half hours from BL administration. The child was admitted and given intramuscular (IM) adrenaline and antihistamine. Fever resolved within 48 hours.
F	Chinese	Allergic rhinitis	15	Augmentin	Generalised flushing, swelling of extremities, dyspnea, abdominal pain within five hours after first dose of BL. The child was admitted for monitoring. Acute tryptase not elevated and septic workup negative. Fever resolved within 24 hours of discontinuation of BL.	16	Oral augmentin	CRS: fever with rigors, generalised flushing, swelling of face and extremities, dyspnea, abdominal pain and vomiting within four hours after BL. The child was admitted and given IM adrenaline and antihistamine. Fever resolved within 48 hours.

Table 4. (Continued)

Sex	Race	Personal history of atopy	Age at index reaction	Index drug	Index reaction	Age at DPT	DPT drug	DPT reaction
F	Chinese	Allergic rhinitis	14	Amoxicillin	Urticaria within 30 minutes from first BL dose, before subsequently developing fever and flushing. Unknown duration to resolution	15	Amoxicillin	CRS: Generalised flushing, fever, giddiness and fatigue three to four hours from BL administration. The child was not admitted.
F	Chinese	Eczema	5	Cefalexin	Generalised urticaria and flushing within 30 minutes from first BL dose which resolved within one day after discontinuation of BL	6	Cefalexin	Anaphylaxis: Urticaria, hypotension, drowsiness and vomiting within 30 minutes from BL administration. The child responded to 2 doses of IM adrenaline, antihistamine, IV fluids and was admitted for observation.

DPT reaction was immediate (within one hour of BL administration) in 37.0% (20/54) of patients. Remaining patients experienced delayed reactions on day 1 (17/54; 31.5%), day 2 (8/54; 14.8%), day 3 (3/54; 6.2%) and day 4 (6/54; 11.1%).

Diagnostic direct oral DPTs (index drug challenge without skin tests)

Of the 425 DPTs, 335 were diagnostic direct oral DPTs to index drug. Diagnostic direct oral DPTs had a pass rate of 89.3% (299/335) and this includes 14.7% with an immediate index reaction. Allergic reactions occurred in 10.7% (36/335) of direct oral DPTs to index drug, with 88.9% of symptoms being mild cutaneous urticaria or maculopapular rash. There were three cases (8.3% of reactions) of cytokine release syndrome[26] and one case (2.8%) of anaphylaxis that responded to two doses of intramuscular (IM) adrenaline.

When comparing patient characteristics and clinical history between children who passed and failed diagnostic direct oral DPTs (**Table 5**), age at index reaction was the only statistically significant factor (p = 0.011). Children who passed the DPT were significantly younger than those with failed DPTs. Age at index reaction remained significant (adjusted odds ratio 0.914, 95% confidence interval 0.839–0.996, p = 0.041) after logistic regression adjustment controlling for personal atopy history, time to onset of index reaction, speed of resolution of index reaction as well as time between index reaction and DPT.

Table 5. Comparison of characteristics of children with passed and failed diagnostic direct oral DPTs to index beta-lactam.

	Failed DPT (n = 36)	Passed DPT (n = 299)	Crude *p*-value	Adjusted odds ratio[a] [95% Confidence Interval]	Adjusted *p*-value
Characteristics of children					
Male, n. (%)	15 (41.7)	144 (48.2)	0.461	-	-
Chinese, n. (%)	27 (75.0)	227 (76.0)	0.329	-	-
Malays, n. (%)	6 (30.0)	35 (11.7)			
Indians, n. (%)	3 (8.3)	17 (5.7)			
Others, n. (%)	0 (0.0)	20 (6.7)			
Family history of beta lactam allergy, n. (%)	3 (8.3)	25 (8.4)	1.000	-	-
Age at index reaction, median (min - max)	**6 (1-15)**	**3 (1-16)**	**0.011**	**0.914 [0.839, 0.996]**	**0.041**
Age at DPT, median (min - max)	10 (2-18)	8 (1-18)	0.319	-	-
Number of years between index reaction and DPT, median (min - max)	1 (0-13)	2 (0-16)	0.087	1.09 [0.968, 1.22]	0.158

Table 5. (Continued)

	Failed DPT (n = 36)	Passed DPT (n = 299)	Crude *p*-value	Adjusted odds ratio[a] [95% Confidence Interval]	Adjusted *p*-value
Personal history of atopy, n. (%)	24 (66.7)	185 (61.9)	0.575	0.917 [0.424, 1.98]	0.825
Allergic rhinitis, n. (%)	18 (50.0)	118 (39.5)	0.224	-	-
Asthma, n. (%)	2 (5.6)	21 (7.0)	0.742	-	-
Eczema, n. (%)	11 (30.6)	82 (27.4)	0.692	-	-
Food allergy, n. (%)	2 (5.6)	21 (7.0)	0.742	-	-
Non-beta lactam drug allergy, n. (%)	4 (11.1)	26 (8.7)	0.632	-	-
Chronic spontaneous urticaria, n. (%)	0 (0.0)	3 (1.0)	1.000	-	-
Recurrent urticaria, n. (%)	4 (11.1)	16 (5.4)	0.168	-	-
Type of beta-lactam					
Penicillin, n. (%)	31 (86.1)	261 (87.3)	0.842	-	-
Cephalosporin, n. (%)	5 (13.9)	38 (12.7)	0.842	-	-
Index reaction characteristics					
Intravenous administration for index reaction, n. (%)	1 (2.8)	8 (2.7)	0.971	-	-
Index reaction within first day of exposure	13 (36.1)	114 (38.1)	0.814	-	-
Index reaction within one hour from last dose	9 (25.0)	44 (14.7)	0.110	0.456 [0.162, 1.28]	0.137
Severe index reaction – Anaphylaxis OR require admission, n. (%)	0 (0.0)	0 (.0)	1.000	-	-
Urticaria, maculopapular or non-specific rash	35 (97.2)	277 (92.6)	0.305	-	-
Gastrointestinal or respiratory symptoms	3 (8.3)	7 (2.3)	0.081	-	-
Duration of symptoms after discontinuation of beta-lactam					
< 24 hours, n. (%)	8 (22.2)	53 (17.7)	0.509	-	-
1-3 days, n. (%)	11 (30.6)	95 (31.8)	0.882	-	-
> 3 days, n. (%)	3 (8.3)	54 (18.1)	0.142	2.70 [0.728-10.02]	0.137
Unknown, n. (%)	14 (38.9)	97 (32.4)	0.438	-	-

[a]Logistic regression was performed to assess odds of a passed diagnostic direct oral DPT, controlling for factors of age at index reaction, number of years between index reaction and DPT, personal history of atopy, index reaction within one hour from last dose, and symptoms resolution within three days of discontinuation of beta-lactam.

Discussion

Safety of direct DPTs

Our study adds to the growing body of evidence[8,15] supporting the safety and efficacy of direct DPTs in the evaluation of suspected BL allergies in children with mild initial hypersensitivity reactions, whether immediate or delayed reactions. Our findings align with recent large-scale studies demonstrating that true allergic reactions to BLs are uncommon, with 89.3% passing the diagnostic direct oral DPTs, and minor adverse reactions observed in the majority (88.9%) who reacted in our study.

Our unit had reported a pass rate of 93% and good safety profile of diagnostic direct DPTs in children with mild, delayed hypersensitivity reactions.[27] Since then, we had expanded indications and performed diagnostic direct oral DPTs in children with mild index reactions, whether immediate or delayed in nature. Outcomes are comparable to international meta-analyses. Blumenthal's meta-analysis in 2024 included both immediate and delayed hypersensitivity reactions and showed a 6.6% prevalence of reactions to direct penicillin DPTs in 5005 children, including three cases of immediate anaphylaxis and one case of delayed fever with maculopapular rashes and raised lymphocytes during the DPTs.[28] Similarly, an earlier study by Kuniyoshi found that only 7% of children with mild, non-immediate initial reactions reacted in the direct DPTs.[8] The high rate of false BL allergies in children is likely contributed by the difficulty in clinically differentiating infection-induced exanthems from allergic reactions.[29] Other commonly cited hypotheses included the misdiagnosis of BL side effects as allergic reactions, and the natural resolution of sensitisation, particularly for immediate reactions.[30]

Multiple studies have demonstrated the safety of direct DPTs for non-immediate BL hypersensitivity reactions[31,32] while there is relatively less consensus regarding those with immediate reactions. In the updated EAACI/ENDA position paper in 2023,[22] the risk stratification algorithm recommended skin testing in patients with non-severe, immediate reactions prior to DPT. Our finding that time to onset of initial hypersensitivity reaction was not significantly associated with DPT results supports growing evidence[15] that it is safe to extend direct DPTs to all cases of mild initial hypersensitivity reactions, including those of immediate onset. This is particularly relevant in the paediatric population, given the commonality of childhood infectious exanthems, the difficulty in history-taking (in our study, 48.6% of parents could not recall timing of reaction onset) and the technicalities of performing skin testing in an uncooperative patient. Diagnostic direct DPTs challenge the traditional paradigm requiring prior skin testing for all immediate reactions, potentially paving the way for more cost-effective de-labelling of BL allergies. However, given that anaphylaxis occurred in our cohort, direct DPTs must be performed under trained medical supervision with immediate access to resuscitation equipment and emergency treatments to ensure patient safety in line with guidelines.[33]

In children with severe initial reactions such as anaphylaxis, our findings support maintaining the current practice of skin testing prior to DPTs.[9] This aligns with the updated EAACI position paper's risk stratification approach. In our study, the nine patients with index anaphylaxis underwent skin testing to guide evaluation, and these patients proceeded to pass diagnostic (n = 4) and alternative (n = 5) BL challenges.

Factors associated with passing diagnostic direct oral DPTs

With the increased use of direct BL DPTs, understanding potential predictive factors for passing direct DPTs is vital to improve patient selection. Our study revealed that younger age at index reaction was the only significant predictor of passing diagnostic direct oral DPTs. This is a novel finding which warrants further investigation. The association may be explained by the higher incidence of viral infections in young children leading to exanthems that are misdiagnosed as drug allergies. Unlike previous studies that identified female gender, history of other drug allergies or atopy as risk factors,[16,17] these were not significant predictors in our population. This highlights the importance of population-specific research in developing risk stratification approaches.

Cross-reactivity between BLs

In order to increase antibiotic options for children with BL allergies and reduce the negative consequences of second-line antibiotics use, it is also essential to understand the pattern of cross-reactivity between BLs. Cross-reactivity refers to the risk of reaction to a BL that is chemically related to the one causing the initial hypersensitivity reaction.[34] Cross-reactivity between BLs demonstrated in past studies were greatly varied, ranging from less than 1% to over 30% between penicillins and cephalosporins depending on the generation of cephalosporins and type of penicillin.[35] For instance, an individual with amoxicillin allergy is likely able to tolerate third-generation ceftriaxone and fourth-generation cefepime.[36] Given the variable cross-reactivity of BLs, the EAACI has advocated that for patients with penicillin allergies, skin testing with cephalosporins with a different side chains can be considered. If the child passes skin testing to the alternative BL, they can then proceed with graded DPT. In the event of urgent need for alternative BL before skin testing can be done, giving a full dose of the alternative, non-structurally related BL can also be an option under close supervision. However, the safety of SPT/IDT or DPTs to alternative BLs have yet to be demonstrated in our local and Asian populations.

Of the 62 DPTs performed to alternative BL (**Table 3**), 87.1% passed alternative BL DPTs, allowing the children viable BL options for future infections. Past studies have shown that cross-reactivity among BL is more likely due to structural similarities in their side-chains rather than the BL ring.[37] It is rare for individuals to have allergies to all BLs due to either immediate or non-immediate hypersensitivity responses to the common BL ring. This supports the use of skin testing and DPTs to identify alternative BLs in cases of true allergies.

Strengths and limitations of study

Our study involves one of the largest cohorts of children with BL DPTs in Asia and has demonstrated that it is safe for direct DPTs for both immediate and delayed mild hypersensitivity reactions. This is also the first study in Singapore to evaluate for possible prognostic factors for passing diagnostic direct oral DPTs, which can guide clinical selection of children for direct DPTs.

However, there are a few limitations of our study. This is a single centre study and future involvement of other allergy testing centres in Singapore and beyond will be useful to ensure the generalisability of our findings. There was real-life heterogeneity in our population and drug allergy evaluation. While the majority of patients underwent direct diagnostic oral DPT, we also reflected the spectrum of patients being evaluated at our allergy unit. We included the subset of patients who, based on shared decision making, underwent skin testing and alternative challenges in order to reflect the safety of drug allergy evaluation as a whole. As a retrospective study, there were also intrinsic limitations such as information bias from missing data, including nearly half of children with unknown onset of index reactions, as well as recall bias from parental report of initial hypersensitivity reactions. Future studies could also consider including a longer-term follow-up after drug provocation testing to evaluate the accuracy of the de-labelling of BL allergies.

Conclusion

Our findings support recent international guidelines advocating for direct DPTs in evaluating mild BL hypersensitivity reactions and extend the safety profile to include mild immediate reactions. The identification of younger age as a positive predictor for successful diagnostic direct oral DPTs provides a novel consideration for risk stratification. The high success rate of alternative BL challenges reinforces the selective nature of most BL allergies and supports a pragmatic approach to providing alternative options. These results can facilitate more cost-efficient de-labelling of BL allergies while maintaining appropriate safety measures for high-risk cases.

Acknowledgments

We would like to thank everyone in the Allergy Service in KK Women's and Children's Hospital for their care of children with drug allergies including the administration of drug provocation tests which made this study possible.

Conflict of Interest

The authors declare no conflict of interest.

Funding

There is no funding involved in this study.

References

1. Gomes ER, Brockow K, Kuyucu S, et al. Drug hypersensitivity in children: Report from the pediatric task force of the EAACI Drug Allergy Interest Group. Allergy. 2016;71(2):149-161. doi:10.1111/all.12774
2. Norton AE, Konvinse K, Phillips EJ, et al. Antibiotic allergy in pediatrics. Pediatrics. 2018;141(5): e20172497. doi:10.1542/peds.2017-2497
3. Tan V, Gerez I, Van Bever H. Prevalence of drug allergy in Singaporean children. Singapore Med J. 2009;50(12):1158-1161.
4. Kidon MI, See Y. Adverse drug reactions in Singaporean children. Singapore Med J. 2004;45(12):574-577.
5. Atanaskovic-Markovic M, Gaeta F, Medjo B, et al. Non-immediate hypersensitivity reactions to beta-lactam antibiotics in children - Our 10-year experience in allergy work-up. Pediatr Allergy Immunol. 2016;27(5):533-538. doi:10.1111/pai.12565
6. Rebelo Gomes E, Fonseca J, Araujo L, et al. Drug allergy claims in children: From self-reporting to confirmed diagnosis. Clin Exp Allergy. 2008;38(1):191-198. doi:10.1111/j.1365-2222.2007.02870.x
7. Tonson la Tour A, Michelet M, Eigenmann PA, et al. Natural history of benign nonimmediate allergy to beta-lactams in children: A prospective study in retreated patients after a positive and a negative provocation test. J Allergy Clin Immunol Pract. 2018;6(4):1321-1326. doi:10.1016/j.jaip.2017.10.008
8. Kuniyoshi Y, Tsujimoto Y, Banno M, et al. Beta-lactam allergy and drug challenge test in children: A systematic review and meta-analysis. Pediatr Res. 2023;93(1):22-30. doi:10.1038/s41390-022-02076-x
9. Arıkoğlu T, Kuyucu S, Caubet JC. New diagnostıc perspectives in the management of pediatrıc beta-lactam allergy. Pediatr Allergy Immunol. 2022;33(3):e13745. doi:10.1111/pai.13745
10. Macy E, Contreras R. Health care use and serious infection prevalence associated with penicillin "allergy" in hospitalized patients: A cohort study. J Allergy Clin Immunol. 2014;133(3):790-796. doi:10.1016/j.jaci.2013.09.021
11. Vezir E, Dibek Misirlioglu E, Civelek E, et al. Direct oral provocation tests in non-immediate mild cutaneous reactions related to beta-lactam antibiotics. Pediatr Allergy Immunol. 2016;27(1):50-54. doi: 10.1111/pai.12493
12. Mirakian R, Leech SC, Krishna MT, et al. Management of allergy to penicillins and other beta-lactams. Clin Exp Allergy. 2015;45(2):300-327. doi:10.1111/cea.12468
13. Khan DA, Banerji A, Blumenthal KG, et al. Drug allergy: A 2022 practice parameter update. J Allergy Clin Immunol. 2022;150(6):1333-1393. doi:10.1016/j.jaci.2022.08.028
14. Jakubovic BD, Vecillas LL, Jimenez-Rodriguez TW, et al. Drug hypersensitivity in the fast lane: What clinicians should know about phenotypes, endotypes, and biomarkers. Ann Allergy Asthma Immunol. 2020;124(6):566-572. doi:10.1016/j.anai.2020.04.005
15. Srisuwatchari W, Phinyo P, Chiriac AM, et al. The safety of the direct drug provocation test in beta-lactam hypersensitivity in children: A systematic review and meta-analysis. J Allergy Clin Immunol Pract. 2023;11(2):506-518. doi: 10.1016/j.jaip.2022.11.035
16. Sipahi Cimen S, Hizli Demirkale Z, Yucel E, et al. Risk factors of challenge-proven beta-lactam allergy in children with immediate and non-immediate mild cutaneous reactions. Int Arch Allergy Immunol. 2023;184(6):539-549. doi:10.1159/000529084
17. Salden OAE, Rockmann H, Verheij TJM, et al. Diagnosis of allergy against beta-lactams in primary care: Prevalence and diagnostic criteria. Fam Pract. 2015;32(3):257-262. doi:10.1093/fampra/cmv018
18. Li PH, Siew LQC, Thomas I, et al. Beta-lactam allergy in Chinese patients and factors predicting genuine allergy. World Allergy Organ J. 2019;12(8):100048. doi:10.1016/j.waojou.2019.100048
19. Park CS, Yang M-S, Kang D-Y, et al. Risk factors of beta-lactam anaphylaxis in Korea: A 6-year multicenter retrospective adult case-control study. World Allergy Organ J. 2021;14(9):100580. doi: 10.1016/j.waojou.2021.100580
20. Stone CA, Jr., Trubiano J, Coleman DT, et al. The challenge of de-labeling penicillin allergy. Allergy. 2020;75(2):273-288. doi:10.1111/all.13848
21. Castells M, Khan DA, Phillips EJ. Penicillin allergy. N Engl J Med. 2019;381(24):2338-2351. doi:10.1056/NEJMra1807761
22. Barbaud A, Garvey LH, Torres M, et al. EAACI/ENDA position paper on drug provocation testing. Allergy. 2024;79(3):565-579. doi:10.1111/all.15996
23. Brockow K, Garvey LH, Aberer W, et al. Skin test concentrations for systemically administered drugs — an ENDA/EAACI Drug Allergy Interest Group position paper. Allergy. 2013;68:702-712. doi: 10.1111/all.12142
24. Kulalert P, Phinyo P, Chiriac AM, et al. Is a prolonged drug provocation test better than a single-day drug provocation test? A systematic review and meta-analysis. J Allergy Clin Immunol Pract. 2024;12(2):431-448. doi:10.1016/j.jaip.2023.11.028
25. Ben-Shoshan M. Extended- or single-day drug challenge, That is the question. J Allergy Clin Immunol Pract. 2024;12(2):449-450. doi:10.1016/j.jaip.2023.11.046
26. Tan LL, Lee MP, Goh SH, et al. Cytokine release syndrome - a unique entity of augmentin hypersensitivity reaction. Asia Pac Allergy. 2022;12(1):e9. doi:10.5415/apallergy.2022.12.e9
27. Goh SH, Chong KW, Chiang WC, et al. Outcome of drug provocation testing in children with suspected beta-lactam hypersensitivity. Asia Pac Allergy. 2021;11(1):e3. doi: 10.5415/apallergy.2021.11.e3
28. Blumenthal KG, Smith LR, Mann JTS, et al. Reaction risk to direct penicillin challenges: A systematic review and meta-analysis. JAMA Intern Med. 2024;184(11):1374-1383. doi:10.1001/jamainternmed.2024.4606
29. Brockow K, Wurpts G, Trautmann A. Patients with questionable penicilllin (beta-lactam) allergy: Causes and solutions. Allergol Select. 2022;6:33-41. doi: 10.5414/ALX02310E
30. Romano A, Gaeta F, Valluzzi RL, et al. Natural evolution of skin-test sensitivity in patients with IgE-mediated hypersensitivity to cephalosporins. Allergy. 2014;69(6):806-809. doi:10.1111/all.12390
31. Liccioli G, Giovannini M, Caubet JC, et al. Simplifying the drug provocation test in non-immediate hypersensitivity reactions to amoxicillin in children: The experience of a tertiary care allergy unit. Pediatr Allergy Immunol. 2022;33(6):e13809. doi: 10.1111/pai.13809.
32. Prieto A, Muñoz C, Bogas G, et al. Single-dose prolonged drug provocation test, without previous skin testing, is safe for diagnosing children with mild non-immediate reactions to beta-lactams. Allergy. 2021;76(8):2544-2554. doi: 10.1111/all.14800.

33. Aberer W, Bircher A, Romano A, et al. Drug provocation testing in the diagnosis of drug hypersensitivity reactions: General considerations. Allergy. 2003;58(9):854-863. doi:10.1034/j.1398-9995.2003.00279.x
34. Montañez MI, Ariza A, Mayorga C, et al. Cross-reactivity in beta-lactam allergy: Alternative treatments. Curr Treat Options Allergy. 2015;2(2):141-154. doi:10.1007/s40521-015-0050-4
35. Romano A, Atanaskovic-Markovic M, Barbaud A, et al. Towards a more precise diagnosis of hypersensitivity to beta-lactams - an EAACI position paper. Allergy. 2020;75(6):1300-1315. doi:10.1111/all.14122
36. DePestel DD, Benninger MS, Danziger L, et al. Cephalosporin use in treatment of patients with penicillin allergies. J Am Pharm Assoc. 2008;48(4):530-540. doi: 10.1331/JAPhA.2008.07006.
37. Caruso C, Valluzzi RL, Colantuono S, et al. β-lactam allergy and cross-reactivity: A clinician's guide to selecting an alternative antibiotic. J Asthma Allergy 2021:31-46. doi: 10.2147/JAA.S242061.