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A UK national survey of investigations for beta lactam hypersensitivity - heterogeneity in practice and a need for national guidelines - *On behalf of British Society for Allergy and Clinical Immunology (BSACI)*

Condensed title: A UK survey of investigations for beta lactam hypersensitivity

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Introduction

Beta lactams are the most widely prescribed antibiotics in the UK and the commonest cause of immediate and non-immediate drug induced hypersensitivity reactions (1). Allergy has been reported to all drugs containing a beta lactam ring but in many cases the antigenic determinant is a side chain such as with amoxicillin or the cephalosporin drugs.

Approximately 10% of hospitalised patients report an allergy to penicillin (2-5). True

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prevalence and incidence rates of beta lactam hypersensitivity in the general population are not accurately known because epidemiological studies are confounded by over-reporting and under-investigation. Investigation of allergic reactions is often suboptimal and patients are rarely referred for specialist evaluation (6). When investigations are undertaken an IgE-mediated reaction can be confirmed in only 7-21% (7). Diagnosis of an immediate hypersensitivity reaction requires a combination of accurate clinical history and demonstration of either specific IgE or a positive drug provocation test (DPT).

European guidelines specifically on beta-lactam hypersensitivity were originally devised in 2003 by the European Network for Drug Allergy (ENDA) on behalf of the European Academy of Allergy and Clinical Immunology (EAACI)(8). The British Society for Allergy and Clinical Immunology (BSACI) has published guidelines on the principles underpinning the investigation and management of all drug allergy, which are broadly supportive of ENDA guidelines (9). However, details of methodology and implementation of beta lactam testing are not covered. In the UK, National Health Service (NHS) allergy services are provided by a range of different specialists with heterogeneous allergy training requirements. There is also a recognised 'unmet need' with deficiencies in the number of allergy centres and geographic distribution across the UK (10). Differences in both the prevalence of beta lactam allergy and the delivery of allergy services across Europe, highlights the need for UK data and guidelines. This survey was designed to investigate how closely UK practice adheres to the UK guidelines on drug allergy and most specifically to the ENDA guidelines given the known variation in allergy service provision in the UK.

Methods

All consultant members of the BSACI and 'Travellers' (the UK Immunology consultant group), were invited, *via* email, to complete an online survey with a reminder. Individuals in both BSACI and Travellers groups received a further email. This strategy was aimed at reaching all consultants who might practice drug allergy in the UK. These groups encompass

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both adult physicians and paediatricians (n=165) who offer an allergy service including consultants who do not consider allergy their primary specialty.

The survey was constructed and data collated, using surveymonkey.com software (California, USA). The questionnaire was based on the ENDA guidelines - considered the 'standard' for this survey (Appendix-1 for detailed questions). Questions were asked to determine the proportion of allergy specialists who undertook beta lactam testing and how many paediatric and adult patients were seen annually. Participants were asked whether they routinely undertook skin and drug provocation tests (DPT) and/or measured serum specific IgE (SsIgE). Criteria for skin and drug provocation testing were explored as well as the methods, reagents and dosages employed. Questions also explored safety issues and methods of evaluation for delayed hypersensitivity reactions.

Questions were not obligatory, multiple answers and free text comments were permitted to capture the likely diversity of beta-lactam testing in the UK. This meant that there were different total (absolute) numbers in some sections and therefore to ensure clarity results have been presented both as nearest whole percentage (%) and number (n) of respondents. Results are presented as a group and also separately according to age cohort (adult, paediatric, adult and paediatric) and number of patients reviewed per year.

RESULTS

Description of responders

The response rate was 48% (n=81 of 165 individuals emailed). Beta lactam allergy testing was practiced by 77% (n=60/78) of all respondents (three individuals failed to give sufficient data on testing). The primary specialty of responders and non-responders is described in table 1. The reasons given for why beta lactam testing was not undertaken include:

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- The centre does not have time or facilities, 37% (n=7/19)
- Numerous other antibiotics are available, 23% (n=3)
- An accurate history is sufficient to make a diagnosis, 11% (n=2)
- Centralised service and so refer elsewhere, 11% (n=2)
- No demand, 11% (n=2)
- Insufficient training, 11% (n=2)
- Skin testing is inaccurate and not a useful tool, 5% (n=1)

Age cohort data, available from 59/60 respondents that undertook beta lactam testing, revealed that 50% (n=29/59) of respondents saw adults only, 35% (n=21) children only and 15% (n=9) saw a mixed cohort. A summary of beta lactam testing according to age cohort of patient treated is described in table 2.

Serum Specific IgE testing

All responders requested SsIgE, although four responders stated it was rarely requested. Indications for SsIgE testing varied with 49% (n=27/55) of responders undertaking SsIgE in all patients being investigated for beta lactam hypersensitivity, 44% (n=24) only if there was a supportive history, 5% (n=3) when there was an inconclusive history and 2% (n=1) only if skin testing was negative. Penicillin V and G SsIgE were both requested routinely by 94% (n=58) of respondents when beta-lactam testing was considered necessary and in addition Amoxicillin by 84% (n=52) and Ampicillin by 48% (n=30) in different combinations (figure 1). Eight respondents tested for Cefaclor if indicated.

Skin testing

Skin testing was undertaken by 87% (n=52/59) of respondents who perform beta lactam testing. Of the seven respondents that did not offer skin testing, five practised paediatric allergy. Five out of these seven offered DPT as a definitive test and two responders diagnosed beta lactam allergy based on SsIgE testing alone. Of the 52 respondents who undertook skin testing 17% (n=9) undertook SPT only, 77% (n=40) performed skin prick. This article is protected by copyright. All rights reserved.

testing (SPT) followed by intra-dermal testing (IDT) if the former were negative or indeterminate, 6% (n=3) performed SPT and IDT in all cases. Patch testing in addition to SPT and DPT was undertaken by 4% (n=2) of respondents.

Skin prick testing: The Diater penicillin determinant kit was used by 67% (n=35/52) of respondents that undertook SPT and of these n=27/35 additionally used whole drugs at known non-irritant concentrations. Whole drugs were used alone by (31%, n=16) and one responder used an 'in house' kit (2%).

Intra-dermal testing: was undertaken by 83% (n=43/52) respondents who undertake beta lactam skin testing. PPL (used by 58%, n=25/43) and MDM reagents (63%, n=27) were administered at between 1/1000th and therapeutic concentration. Amoxicillin (77% (n=33) of respondents) was used at concentrations between 0.25-250mg/ml and benzyl penicillin (58% (n=25) of respondents) at 0.006-60mg/ml. Cephalosporins were tested at 0.002 – 25mg/ml by the 3 respondents that stated a concentration specifically, one respondent undertook Flucloxacillin IDT at 5mg/ml and the Co-amoxiclav concentration varied from 20-75mg/ml of Amoxicillin. The starting dilutions used by respondents varied between undiluted to 1:1000 dilutions but some started at a known non-irritant concentration (table 3).

Only 39 of the 43 respondents who undertake IDT gave details on their protocols: 56% (n=22/39) of responders increased the concentration of reagents once a lower dilution was shown to be negative, 23% (n=9) performed IDT at one dilution only but for 3 of these they would repeat the IDT at a lower concentration if the initial test was positive. For 21% (n=8) of responders the IDT protocol was individually adapted to the patient.

Side chain reactivity: Thirty seven % (n=18/49) of respondents who undertake beta lactam testing continue with investigation for specific side chain hypersensitivity (to check tolerance to a different penicillin) in patients with positive responses on skin testing.

Skin testing safety: Systemic reactions associated with skin testing were reported by 23% (n=10/44) of responders who undertook skin testing and responded to this question (n=44/53). Two responders reported reactions to SPT alone, six to IDT and two to both SPT and DPT. One respondent reported between 6-10 reactions in the last 5 years, the remainder between 1-5 reactions. The reactions reported, following skin testing, ranged from local redness, swelling and itching to difficulty breathing because of swelling and/or wheezing, feeling faint or actual collapse / loss of consciousness graded. Using the Mueller grading system (11) the frequency of severity stated was: grade 1 (n=4), grade 2 (n=3), grade 3 (n=2) and grade 4 (n=1). There were no deaths and no cases of systemic reactions in respondents who reviewed paediatric patients only.

Drug provocation testing

Drug provocation testing was undertaken by 85% (n=45/52) of respondents who answered this question and undertook testing for beta lactam allergy. Testing was undertaken in all patients with no demonstrable specific IgE by 33% (n=16/45) of responders and the remainder (67%, n=29) offered DPT on an individual basis according to the: underlying health of the patient, the importance of the drug for treatment, route of administration and severity of underlying reaction. Of the seven responders that did not perform DPT, six stated they did not have the facilities or resources to carry out testing and one was happy to reassure on the basis of no demonstrable specific IgE.

The dose range for the starting concentrations varied by a factor of 10^3 mg/ml, from less than 1000^{th} of a whole dose to whole dose for Penicillin V, Amoxicillin, Benzylpenicillin and 'culprit drug' (table 4a). The large majority of final dosages were the full therapeutic dose of a drug (table 4b).

The commonest time interval between DPT doses was 16-30 minutes [67% (n=25)] but this ranged from 0-15 minutes [13% (n=5)] to 46-60 minutes [8% (n=3)] (table 4c). The number

of DPT dose steps undertaken varied from a single step [13% (n=5/39)] to over 5 steps [33% (n=13)] (table 4d). The five responders that performed a single step DPT gave the full dose in all cases. Forty four percent (n=17) of responders, who undertook DPT, did not follow a prescriptive regimen. Eighty five percent (n=34/40) of responders had specific criteria for defining a positive DPT.

The positive DPT rate varied from 0-5% [64% (n=28/52)] to greater than 20% in one centre (table 4e). This is likely to reflect heterogeneity in testing and also the referral pattern and patient selection for beta lactam testing either to confirm or disprove allergy.

Delayed reactions

Non immediate reactions were monitored for by 85% (n=39/46) of responders. Routine review in clinic at 48/72 hours was only undertaken by 2 responders and the remainder relied on patient-directed monitoring. Patch testing was not undertaken by any responder for delayed reactions implying that the two responders that undertook patch testing were doing this to assess immediate reactions. An emergency treatment pack was provided to the patient after testing by 38% (n=19/50) of responders.

Advice following testing

The majority of respondents 79% (n=37/47) advised avoidance of all penicillins after a positive test. The remaining respondents recommended additional avoidance of 1st and 2nd generation cephalosporins in 13% (n=6), all cephalosporins in 4% (n=2), monobactams in 2% (n=1) and carbapenems in 2% (n=1). No responder checked for resensitisation; 48% (n=21/44) of responders felt this was unnecessary and 53% (n=23) reported a lack of resources for re-evaluation. In the free text two responders said that they had experience of re-sensitisation.

Practice according to number of patients seen annually

The number of patients tested for beta lactam allergy annually varied between 0-5 individuals and greater than 40. The data were analysed according to whether specialists saw > 20 or ≤ 20 patients per year. This cut-off was considered because twenty was the midpoint on the frequency distribution. The centres that saw >20 patients per year for beta lactam testing were all located within large teaching hospitals in cities, (data not shown) and predominantly saw adults. For all parameters, the high throughput centres equally or more commonly complied with ENDA guidelines than lower throughput centres (table 5). This may be partially explained by the cohort of patients seen as paediatric patient performed less skin testing. There were no large differences between adult specialists who undertook beta lactam testing (table 1a).

All (n=19) specialists that saw greater than 20 patients a year complied with skin testing guidelines, in contrast with 59% (n=16/39) of specialists who saw less than 20 patients a year. Similarly 84% of specialists who saw more than 20 patients a year followed guidelines to use the PPL and MDM determinants in contrast to 59 % who saw less than 20 patients. Drug provocation testing was not performed by 15% (n=6) of respondents who saw ≤ 20 patients per year and 6% (n=1) of those that see more than 20 per year. All respondents that saw greater than 20 patients per year monitored for delayed reactions in some way, however 21% (n=7) of specialists who saw ≤ 20 patients did not.

Discussion

Beta lactam hypersensitivity testing is practised in the UK by both adult and paediatric specialists in allergy, immunology and organ based allergists. This survey demonstrates significant heterogeneity in practice and deviation from ENDA/EAACI recommendations. The need for complex protocols arises because there is no perfect test to diagnose or exclude beta lactam hypersensitivity and a combination of tests are required. The lack of

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standardisation highlights an urgent need for high quality allergy training and UK based guidelines.

The full ENDA protocol spans 2-5 days for beta lactam testing. A number of respondents stated that limitations of time and resources played a major role in their ability to fully investigate patients and this echoes The Royal College of Physicians report on the 'unmet need' of Allergy services (10). Much of the data that contributes to the ENDA guidelines comes from non-UK based practice and some protocols may be difficult to implement in the UK because of limited resources within the specialty. Most responders undertake significantly shorter protocols and the low adverse event rate suggests that a more limited testing regimen is likely to be safe. A health economic argument can be made for using accelerated testing regimens but these should be standardised to develop an appropriate evidence base. Until clinical utility and safety of protocols are established, testing should be undertaken in high throughput centres that have knowledge and expertise in this field as well as relevant training and clinic infrastructure required to manage anaphylaxis so that patient safety is not compromised. Determining the optimum 'cut off' for patient throughput relating to quality assurance is not within the remit of this survey. However, it is interesting to note that centres investigating fewer than twenty patients per year complied less with standard recommendations than those that saw greater numbers and demonstrated evidence of unsafe practice. This can be partially explained by the high number of paediatricians that have a small throughput for beta lactam testing. Paediatric practice differs in that less skin testing and more drug provocation testing is undertaken. Separate guidelines for adult and paediatric specialists and then re-audit may improve practice in low throughput centres. An option is to restrict testing to high throughput centralised services, although, this approach would further limit patient access to allergy services. The paucity and distribution of allergy clinics in the NHS already results in long waiting times and may involve significant travel and inconvenience for patients(10). These are important considerations when multiple appointments are required for beta lactam testing under current ENDA recommendations. This article is protected by copyright. All rights reserved.

The lack of studies from the UK means that guidelines will be based on international studies, consensus option between experts and influenced by practical limitations and health economic considerations. A number of important considerations have been highlighted by this survey. Firstly, should serum specific IgE testing be restricted. The very limited sensitivity of this test means that a high level of knowledge of beta lactam hypersensitivity is required for correct interpretation. There are a number of specialists that are using this testing in isolation and this practice is anecdotally common in general practice where skin testing is not available. Given serious concerns over its poor sensitivity, the authors propose that availability of SsIgE testing should be restricted to specialist centres.

Secondly, skin testing protocols should be standardised with regards the testing methods, number of steps and dilutions performed and the reagents used, all of which varied widely in this survey. Such standardisation is required to ensure patient safety and should also generate the evidence base for high quality studies. Our survey found that many paediatricians do not routinely use intra-dermal testing. The clinical importance of this is uncertain and there needs to be a balance between unnecessary skin testing and exposing children to excessive drug provocation testing. The Royal College of Paediatrics and Child Health (RCPCH) acknowledges that the evidence base for drug allergy testing in paediatric practice is small (12) and it is likely that separate guidelines for paediatrics will be devised. Reassuringly no responders that saw paediatric cohorts experienced a systemic reaction to skin testing.

Thirdly, future guidelines should recommend that centres undertaking beta-lactam testing have the resources to undertake DPT. Drug provocation remains the 'gold standard' for diagnosis in beta-lactam hypersensitivity due to limited sensitivity of both skin tests and SsIgE even if optimal protocols are followed. The combined sensitivity of skin tests (SPT and IDT) with PPL, MDM, Benzylpenicillin, Amoxicillin and Ampicillin and SsIgE (Penicillin V, Penicillin G, Amoxicillin, Ampicillin) is only 70% (13) and this sensitivity may wane further

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with time. The relevance of using Ampicillin is also questionable in the UK as prescription rates are low. A large European case series reported that amoxicillin sIgE was rarely demonstrable five years after the index reaction, although it was unclear if this cohort of patients remained clinically allergic(14). This survey has highlighted significant shortcomings as well as heterogeneity in UK practice for beta lactam allergy testing putting patients at risk of allergic reactions upon re-exposure. Drug provocation should be undertaken in specialist centres because of the risk of anaphylaxis. Evaluation of a patient for DPT should consider the benefit of the result, the severity of previous reaction, skin testing results, comorbidities and ability to tolerate anaphylaxis. The responders that reported a DPT reaction rate of over 10% from the questionnaire were all moderate to high throughput centres with similar compliance with ENDA recommendations to centres with lower rates (data not shown). It is plausible that patient selection criteria are a significant variable in the DPT rate, although this was not directly explored by the questionnaire.

Lastly, monitoring for delayed reactions should be standardised. In this survey, 15% of respondents offered no routine monitoring for delayed reactions and practice varied widely for those that did undertake monitoring. Delayed intra-dermal testing is useful in the assessment of patients with non-immediate reactions to beta lactams with a good negative predictive value, although the positive predictive value is not known (15, 16). Standardising and recording delayed reactions after testing would also contribute to the literature. A third of respondents supplied their patients with an emergency treatment pack to take home in case of an allergic reaction. There is no evidence base for the frequency and severity of late reactions and the necessity for treatment is unknown. Although non-immediate reactions are unlikely to cause acute cardiorespiratory compromise, late cutaneous reactions may still need treatment and this practice should be considered in future guideline updates. Testing for re-sensitisation following skin testing is recommended by ENDA but UK allergy specialists believe this is mostly unnecessary and not cost effective. There is only limited evidence for the frequency of re-sensitisation and little consensus for the optimum interval or

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frequency of retesting, if at all (17-20). Two responders stated they had experienced a case each of re-sensitisation. A possible explanation could be a false negative DPT as it is impossible to replicate the inflammatory conditions experienced during the infection for which an antibiotic is given and plausible that these could alter the allergenicity of the drug.

Future UK guidelines will need to provide advice following positive beta lactam testing and by doing so will greatly facilitate prescription of antibiotics. This survey revealed heterogeneous advice which will be subsequently confusing to hospital physicians and general practitioners alike. The advice should be based on the current evidence for cross reactivity with other drugs. Avoidance of all penicillins is appropriate general advice, although in a very small number of patients it may be important to determine side chain reactivity in order to allow prescription of a specific penicillin (for example in neuro-syphilis). Approximately a third of centres undertake further investigation for side chain reactivity and given the limited resources in UK allergy clinics, it could be argued that this is not indicated routinely and this testing should be restricted to specialist centres and for selected patients. Avoidance of 1st and 2nd generation cephalosporins is sensible as there is a small but significant risk of cross-reactivity. The risk of cross reactivity with 3rd-5th generation cephalosporins, monobactams and carbapenems appears negligible from recent studies (21-23) so it would be inappropriate to advise against these drugs. There are currently no guidelines for investigation of cross-reactivity and skin testing protocols are not well established.

A limitation to this study was the low response rate, which is a recognised shortcoming in a questionnaire based study. Allergy is practised by a large spectrum of physicians in the NHS and in order to reach all individuals that might practise allergy testing, the questionnaire was distributed through the two largest bodies of clinicians practising allergy in the UK. Many immunologists, paediatricians and organ based specialists that belong to these groups, would not consider drug allergy testing as part of their clinical remit and it would not have

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been part of their specialist training, which may also explain the low response rate. The advantage of casting the net wide was that the survey captured the practice of the majority of specialists that undertake beta-lactam testing. It is also likely that beta lactam allergy is being practiced by specialists and general practitioners who are not members of either groups surveyed and it is therefore difficult to assess the quality of this testing.

Beta-lactam hypersensitivity is a common clinical problem in the UK that has been shown to be over-reported and associated with significant unnecessary health care costs. Data from this UK national survey has highlighted significant heterogeneity in practice and demonstrated an urgent need for guidelines. Some centres reported procedures for testing that were inadequate and could potentially result in life-threatening reactions on re-exposure if allergy was falsely excluded. Testing for beta lactam allergy should be undertaken by centres with adequate facilities, training, experience, and high patient throughput. Evidence based UK national guidelines for both children and adults would facilitate standardised and safe delivery of beta lactam testing.

Conflict of interest:

MTK is a member of Standards of Care Committee and national audit lead for BSACI. He is also co-opted member for NICE clinical guideline development group for 'drug allergy'.

MTK's department has received sponsorship from 'Allergy Therapeutics' for 'PracticAllergy' course and he has been invited as 'keynote speaker' for this company organised symposium on penicillin allergy testing. All other authors have no conflict of interest to declare.

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Table 1: Main specialty of responders and cohort of patients seen

MAIN SPECIALTY	RESPONDERS		NON RESPONDERS 51% of all contacted (N=84/165)*
	Undertake BL testing 74% of responders (N= 59/78)	Don't undertake BL testing 36% of responders (N=19/78)	
Allergy	100% of specialty (n= 6/6)	0 % of specialty (n= 0/6)	2% of all non-responders (n= 2/84)
Immunology	92% (n=24/26)	8% (n=2/26)	52% (n=44/84)
Paediatrics	70% (n=23/33)	30% (n=10/33)	32% (n=27/84)
Adult respiratory	63% (n=5/8)	37% (n=3/8)	7% (n=6/84)
ENT	0% (n=0/1)	100% (n=1/1)	0% (n=0/84)
Dermatology	0% (n=0/2)	100% (n=2/2)	4% (n=3/84)
Unknown	N=1	N=1	N=2

*Eighty one individuals responded but there was only sufficient data on beta lactam testing to describe 59 responders that undertake beta lactam (BL) testing and 19 that didn't (total 78) out of a total of 165 specialists contacted.

1a) Proportion of specialty that follow specific ENDA recommendations

ENDA Recommendation	Number and percentage that follow ENDA recommendation			
	Main Specialty of Respondent			
	Allergy	Immunology	Paediatrics	Other specialties
Undertakes skin testing	100% (n=6/6)	96% (n=23/24)	74% (n=17/23)	100% (n=6/6)
IDT if SPT -ve	100% (n=6/6)	91% (n=21/23)	53% (n=9/17)	67% (n=4/6)
SSIgE if skin testing -ve	17% (n=1/6)	0% (n=0/23)	0% (n=0/17)	0% (n=0/6)
DPT with culprit drug	100% (n=6/6)	86% (n=18/21)	95% (n=18/19)	50% (n=3/6)
5(+) step DPT	17% (n=1/6)	71% (n=12/17)	38% (n=6/16)	33% (n=2/6)
Monitor for delayed reactions	100% (n=6/6)	94% (n=15/16)	88% (n=14/16)	67% (n=4/6)

Check for resensitisation	0% (n=0/6)	0% (n=1/16)	0% (n=0/6)	0% (n=0/6)
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Table 2: Beta lactam testing according to age cohort of patients treated

	Adult (n=29)	Children (n=21)	Mixed (n=9)
SslgE only (no SPT/IDT)	0% (n=0/29)	21% (n=5/21)	11% (n=1/9)
SPT alone	3% (n=1/29)	36% (n=8/21)	11% (n=1/9)
SPT & IDT	97% (n=28/29)	36% (n=8/21)	78% (n=7/9)
DPT	81% (n=21/26)	89% (n=17/19)	63% (n=5/8)

Number of patients seen per year	0-5	3% (n=1/29)	42% (n=9/21)	0% (n=0/9)
	6-10	17% (n=5)	19% (n=4)	20% (n=2)
	11-20	38% (n=11)	29% (n=6)	30% (n=3)
	21-40	28% (n=8)	5% (n=1)	30% (n=3)
	>40	14% (n=4)	5% (n=1)	10% (n=1)

SslgE: Serum specific IgE, SPT: skin prick test, IDT: intra-dermal test, DPT: drug provocation test. Data from 59 respondents that undertook beta lactam testing and the number of patients they test annually.

Table 3: Starting dilution for intradermal testing

Dilution N= (%)	Neat drug	1:10	1:100	1:1000	Known NIC*	Response Count
Drug (starting concentration)						
Penicillin PPL (major) determinant (0.04mg/ml)	7 (35%)	3 (15%)	4 (20%)	1 (5%)	5 (25%)	20
Penicillin MDM (minor) determinant (0.5 mg/mL)	7 (35%)	4 (20%)	3 (15%)	1 (5%)	5 (25%)	20

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Amoxicillin (250mg/ml)	3 (10%)	10 (34%)	3 (10%)	4 (14%)	9 (23%)	29
Benzypenicillin (100,000 Mu/ml)	4 (19%)	7 (33%)	2 (10%)	1 (5%)	7 (33%)	21

*NIC – non-irritant concentration. Dilutions based on stated standard concentrations.

Table 4: Dose range (starting and final) for drug provocation testing

a) Starting dose for drug provocation testing

Concentration % (n= / total)	2X dose	Full dose	1:2	1:5	1:10	1:50	1:100	1:1000	<1:1000
Penicillin V (500mg), n=26	0	7% (2)	0	7% (2)	23% (6)	15% (4)	27% (7)	12% (3)	7% (2)
Amoxicillin (250mg), n=34	6% (2)	12% (4)	3% (1)	3% (1)	18% (6)	21% (7)	24% (8)	9% (3)	6% (2)
BP (600mg), n=6	0	17% (1)	0	0	0	17% (1)	17%(1)	17% (1)	67% (2)
Other culprit drug, n=20	0	15% (3)	0	15% (3)	10% (2)	15% (3)	25% (5)	10% (2)	10% (2)

b) Final dose for drug provocation testing

Concentration % (n=)	2x full dose	Full dose	1:2
Penicillin V (500mg, oral) n=26	7.5% (n=2)	85% (n=22)	7.5% (n=2)
Amoxicillin (250mg, oral) n=34	15% (n=5)	85% (n=29)	0
BP (600mg, parenteral) n=9	0	89% (n=8)	11% (n=1)
Other culprit drug n=23	4% (n=1)	91% (n=21)	4% (n=1)

c) Interval between steps

Interval between steps (Minutes)	0-15	16-30	31-45	46-60
100% (n=40)	20% (n=8)	60% (n=24)	12.5% (n=5)	7.5% (n=3)

d) Number of steps routinely undertaken

DPT steps	1	2	3	4	5	>5
100% (n=39)	13% (n=5)	5% (n=2)	15% (n=6)	13% (n=5)	21% (n=8)	33% (n=13)

e) DPT positive reaction rate

Positive DPT rate	0-5%	6-10%	11-15%	16-20%	>20%
100% (n=41)	63% (n=26)	24% (n=10)	7% (n=3)	2% (n=1)	2% (n=1)

Table 5: Compliance with ENDA recommendations according to number of patients seen per year

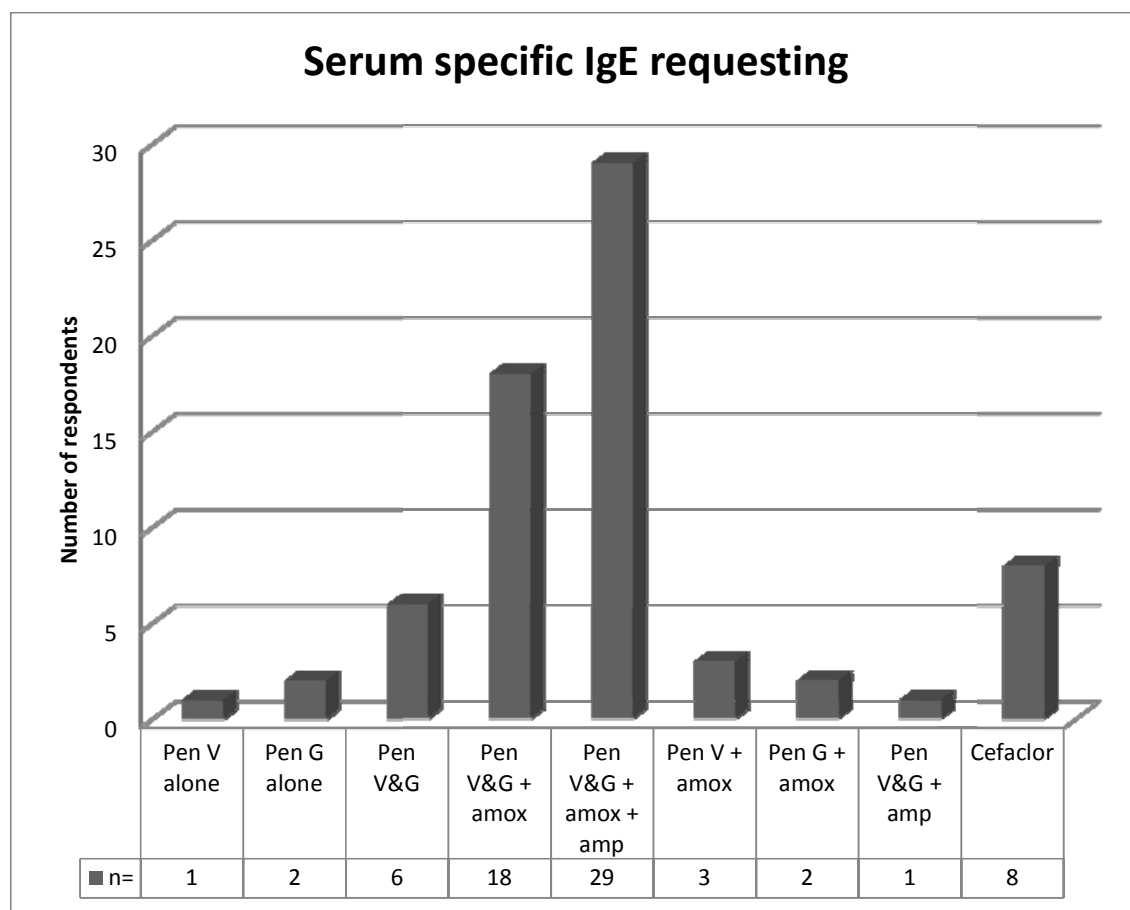
	Data according to number of patient seen per year	
	Less than 20	Greater than 20
Number of responders	N=41	N=18
Age cohort of patients:		
Paediatrics	46% (19/41)	11% (n=2/18)
Mixed	8% (n=3/41)	22% (n=4/18)
Adult	46 % (n=19/41)	67% (n=12/18)

ENDA Recommendation	Number and percentage that follow ENDA recommendation	
Undertakes skin testing	83% (n=34/41)	100% (n=18/18)
IDT if SPT -ve	54% (n=22/41)	100% (n=18/18)
SSlgE if skin testing -ve	0% (n=0)	6% (n=1/18)
DPT with culprit drug	84% (n=31/37)	93% (n=14/15)
5(+) step DPT	54% (n=14/26)	54% (n=7/13)
Monitor for delayed reactions	84% (n=26/31)	100% (n=13/13)
Check for resensitisation	3% (n=1/33)	0% (n=0/15)

SslgE: Serum specific IgE, SPT: skin prick test, IDT: intra-dermal test, DPT: drug provocation test, -ve negative. The number of responses varied for some questions so the percentage is clarified by the total number of answers in brackets. Percentages don't always add to 100% as numbers rounded to nearest whole percent.

Figure 1: Serum specific IgE requesting

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Pen V= penicillin V, Pen G=penicillin G, amox=amoxicillin, amp=ampicillin