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Title: Lack of uniformity in the investigation and management of suspected β -Lactam Allergy in children

Authors: Foong, Ru-Xin Melanie¹; Logan, Kirsty¹; Perkin, Michael Richard², du Toit George^{1,3}

¹Department of Paediatric Allergy, Guys and St. Thomas' Hospitals NHS Foundation Trust, London, UK

² Population Health Research Institute, St. George's, University of London

³ Division of Asthma, Allergy and Lung Biology, Department of Allergy, King's College London at St. Thomas' Hospital, Westminster Bridge Road, London SE1 7EH, UK

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Author correspondence: Dr. George du Toit, Division of Asthma, Allergy and Lung Biology, Department of Allergy, King's College London at St. Thomas' Hospital, Westminster Bridge Road, London SE1 7EH, UK; george.dutoit@kcl.ac.uk

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Abstract Page

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Authors: Foong RX, Logan K, Perkin MR, du Toit G

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Abstract:

Background: Beta-lactam allergy is commonly suspected in childhood with health implications for the individual and wider public. Diagnostic modalities include skin prick tests (SPT), specific-immunoglobulin E (sp-IgE) tests, intradermal tests (IDT) and drug provocation challenges (DPC). The aim of this research was to establish whether variation exists around the world in the investigation and management of beta-lactam allergy.

Methods: Anonymized electronic questionnaire surveys were distributed over 3 months through International Allergy Societies for completion by clinicians who investigate drug allergy in children.

Results: 81 clinicians, practicing in 16 countries completed the questionnaire. There is variability in the selection of diagnostic tests used by clinicians around the world and poor agreement on positive cut off values (sp-IgE, SPT and IDT) and practical techniques used to measure SPT or IDT wheal diameters. DPC were considered the gold standard investigation with 94% of respondents undertaking DPC over the last 12 months; 64% of respondents considered DPC extremely useful for both exclusion and confirmation of beta-lactam allergy. However, there is a lack of consensus on when and how DPC should be performed. Overall, DPC are safe- only 3% of our respondents had patients who required intramuscular adrenaline and none had patients requiring admission to intensive care.

Conclusions:

There is lack of consistency amongst clinicians in different countries in the diagnosis and management of suspected beta-lactam allergy. The development of a standardized approach is a priority.

Key words: beta-lactam allergy, drug provocation test, paediatric, diagnostic procedures

Author correspondence: Dr. George du Toit, Division of Asthma, Allergy and Lung Biology, Department of Allergy, King's College London at St. Thomas' Hospital, Westminster Bridge Road, London SE1 7EH, UK; george.dutoit@kcl.ac.uk

Introduction:

Beta-lactam allergy is the commonest drug allergy referred to specialist services for investigation, especially in children (1). Allergic drug reactions take two forms: immediate reactions occur within the first hour of drug administration or ingestion and clinical symptoms include urticaria, bronchospasm, angioedema and anaphylactic shock; non-immediate reactions occur more than one hour after drug administration and symptoms are usually maculopapular cutaneous reactions or delayed urticaria or angioedema (2).

It is likely that the prevalence of beta-lactam allergy has been over-estimated (3, 4) as clinical suspicion typically arises in children who present with a history of an infective illness who then receive a beta-lactam and develop a delayed maculopapular or urticarial rash after treatment (5). Many children may then be labeled as 'penicillin allergic' due to the fear of a severe allergic reaction and lack of access to specialist allergy services (5-7). National Institute of Clinical Excellence recommendations are for specialist referral of such children if complicating clinical factors are present i.e. treatment is needed for a disease or condition that can only be treated with a beta-lactam antibiotic or there is need for frequent beta-lactam administration for immunodeficiency or recurrent bacterial infections (8). However, it has been proposed that children with 'uncomplicated' suspected beta-lactam allergy should proceed to drug provocation challenge (DPC) bypassing in-vitro and other in-vivo tests to minimize the unnecessary use of alternative antibiotics which may compromise clinical care, increase health costs and contribute to antibiotic resistance (9).

Studies based on both skin prick tests SPT and DPC have shown that 10-15% of children diagnosed with suspected beta-lactam hypersensitivity have a confirmed allergy (10). Diagnosis has traditionally consisted of SPT, specific immunoglobulin-E (sp-IgE) tests, intradermal tests (IDT) and, if all are negative, a DPC which is considered the gold standard for immediate and non-immediate drug reactions (5, 9, 11, 12). Studies have shown SPT to have limited accuracy and reactions on subsequent DPC have also occurred in patients who have had negative IDT (6). DPC without previous SPT are well tolerated in children (5, 10) and studies have shown high negative predictive values (94-98%) from challenges (2, 7, 13, 14). However, DPC are not without risk as they potentially expose a child to a risk of anaphylaxis and are logistically demanding although the incidence of severe reactions is low (1/100,000) (5, 15).

At present, there is no universal standardized diagnostic protocol for drug allergy testing in children. The aim of this research was to establish whether variation exists amongst clinicians who investigate children with suspected beta-lactam allergy.

Methods:

An anonymous web-based questionnaire was created using SNAP Survey Software (Version 10 London 2009) and distributed by email link. Organisations invited to help with the distribution of the survey via email included International Allergy Societies: World Allergy Organisation, the European Academy of Allergy and Clinical Immunology (EAACI) Drug Interest Group, Allergy Society of South Africa, Australasian Society of Clinical Immunology and Allergy, Allergy New Zealand and members of the Paediatric Allergy Group. Recipients of the email were asked whether they investigated children for suspected drug allergy. If so, they were asked to complete the full questionnaire which included 54 questions and a common clinical scenario in order to compare approaches to investigation and management. Respondents included Paediatric Allergy Consultants, Paediatric Allergy Nurse Specialists and General Paediatricians and General Practitioners with a special interest in allergy.

Results:

A total of 99 completed questionnaires were returned; 18 respondents indicated that they did not investigate children for the diagnosis of drug allergy and did not go on to complete the questionnaire. We therefore present data from 81 questionnaires from clinicians who practice in 16 different countries around the world.

Of the respondents, 77% (62/81) were Specialty Allergists (registered/board certified/working in a tertiary center), 16% (13/81) were General Paediatricians with a special interest in allergy, 6% (5/81) were Allergy Nurse Specialists and 1% (1/81) were General Practitioners with a special interest in allergy. Their country of origin is shown in Figure 1, with 89% (72/81) practicing in the UK and Europe including Israel. The majority, 51% (41/81), had over 20 years experience in the clinical practice of allergy, 30% (24/81) had 5-10 years of experience and 20% (16/81) had less than 5 years experience. Fifty-four respondents (67%) reported that their service had a designated doctor responsible for investigating drug allergies. Over 50% of respondents had investigated fewer than 15 patients for beta-lactam allergy over the preceding 12-month period (Figure 2).

Decision making

Use was made of the following clinical scenario; *“An otherwise healthy 6-year-old presents for the assessment of amoxicillin allergy. The referring doctor has noted a maculopapular rash that developed on day six of the illness and after two days (4 doses) of amoxicillin administration; the antibiotic was prescribed for the treatment of tonsillitis. The antibiotic was stopped and the rash faded over 12 hours.”*

57% (46/81) of respondents would perform allergy tests (e.g. SPT, sp-IgE, DPC) (Table 1). Thirty-one (38%) would not perform any allergy tests and would not advise beta-lactam avoidance restrictions as they felt this was unlikely to represent an allergic reaction but rather an infective rash. Four (5%)

respondents would not perform any allergy tests but would advise life-long avoidance of all beta-lactams as allergy is possible and there is cross reactivity between amoxicillin and beta-lactam antibiotics.

Of the 46 respondents who would perform tests there was a large degree of variability as to the cut off range that they would consider as a positive result; 47% used a threshold of 0.35kUA/L and 15% used 0.10kUA/L. 48% (21/44) of respondents would not proceed with an oral drug challenge if the patient had a positive sp-IgE result to amoxicillin, 57% (25/44) would not proceed if they had a positive SPT result to amoxicillin, 55% would not proceed if they had a positive IDT to amoxicillin and 32% (14/44) would proceed regardless of any of the aforementioned tests being positive. A comparison of the types of test that would be performed for the questionnaire's Clinical Scenario was made between UK respondents and respondents from the rest of the world (Table 2). The percentage of respondents from the UK and from the rest of the world who would use ODPC was high, 95% and 96% respectively. The largest difference was seen in the use of sp-IgE testing with only 25% of respondents from the UK who would use them compared to 76% in the rest of the world group ($p=0.001$).

Views on Testing Methodology

Oral drug provocation challenges (ODPC)

94% (76/81) of respondents had performed ODPC in the last year with 51% (41/81) performing over 100 ODPC. The numbers of positive ODPC are described in Table 3. A multidisciplinary team was involved in performing challenges including the respondents, paediatric general nurses, allergy nurse specialists and other paediatricians. Location of ODPC varied: 54% (41/76) performed them in hospital on a day care unit, 29% (22/76) in hospital (outpatient setting), 13% (10/76) in hospital ward based settings and 4% (3/76) in community based practices. There were no respondents who advised for trials to be performed at home. Of those who witnessed beta-lactam challenges ending in a reaction, 3% (2/76) had fewer than 5 patients who required intramuscular adrenaline to be given and nobody had a child requiring admission to high dependency or intensive care.

Symptom presentation instigating the need for ODPC

The majority of respondents (74% (60/81)) would never perform a challenge if the clinical history suggested that a beta-lactam had induced mucosal membrane or conjunctiva involvement (e.g. erythema or blistering) compared to 23% who would perform a challenge only if an appropriate alternative drug was not available for treatment and clinical circumstances indicated a need for it. However, if patients' reported previous antibiotic-induced anaphylaxis, only 27% (22/81) of respondents chose not to perform a diagnostic ODPC whereas the majority (58/81) would conduct a challenge only if SPT, sp-IgE and IDT were all negative and clinical need dictated.

Methodology of performing ODPC

ODPC methodology also varied: on Day 1 of a 5-day challenge, 12% (9/76) administer a single dose versus 88% who use at least 2 incremental doses. If a child had a reaction during an ODPC, 62% (47/76) reported that it occurred on the same day, 32% (24/76) observed it on Day 2-5 and 5% (4/76) witnessed it after completion of the antibiotic course (Day 5). Interestingly, 41% of respondents had patients who had a negative ODPC to a beta-lactam antibiotic, but then reacted to the same antibiotic on a separate occasion.

For children with a positive ODPC to amoxicillin, 15% (11/76) always challenged them to a cephalosporin to establish cross-reactivity status regardless of any other test results already conducted to the cephalosporin in question, 47% (35/76) only performed the challenge if other test results were negative, 33% (25/76) would not perform tests as cross-reactivity was thought to be very low and increased caution would be unnecessary and 4% (3/76) would not perform them as they considered them to be dangerous. ODPC are also conducted to test for reactions to antibiotic additives or excipients. 26% (21/81) of respondents conducted them although few had positive ODPC; only 8 challenges were positive for tablet-based excipients and 25 were positive for syrup-based excipients in the last 12 months (Appendix 1).

Symptoms that would lead to a challenge being stopped are listed in Table 4. Over 80% of respondents would stop a challenge if there was evidence of circulatory or respiratory compromise, perioral or periorbital angioedema, vomiting on multiple occasions or general oedema.

Other types of allergy tests

42% of respondents would conduct intravenous drug provocation challenges (IV-DPC) if the index reaction occurred after IV beta-lactam administration. Reasons for not performing IV-DPC included safety (62% (29/47)), lack of experienced staff (34% (16/47)), or ODPC was felt to be adequate enough even if it was performed to a slightly different beta lactam (49% (23/47)).

Regarding SPT, most respondents used the traditional broad shouldered metal lancet (75% (61/81)). 48% recorded the widest wheal diameter, 41% (33/81) the average of the widest wheal diameter and its perpendicular and 11% (9/81) the average of the two widest wheal diameters irrespective of the angle between them.

For IDT, 42% (34/81) recorded the widest bleb diameter, 46% (37/81) recorded the average of the widest bleb diameter and the perpendicular and 12% (10/81) the average of the two widest bleb diameters irrespective of the angle between them. 72% (58/81) considered an increase in bleb diameter of 3mm or more to be positive compared to 28% (23/81) who required the diameter to

exceed 3mm to be positive. Regarding the shape of the bleb, 54.3% (44/81) accepted an asymmetrical bleb shape compared to 45.7% (37/81) who only accepted a symmetrical bleb shape. Only 21% (17/81) of our respondents felt that IDT in children were well tolerated.

Respondents considered ODPC as the most useful test for both exclusion and confirmation of beta-lactam allergy with 64% assigning a rating of 'extremely useful' (scale 1 (not useful) to 5 (extremely useful)). IDT were viewed to be more useful in confirming beta-lactam allergy compared to both SPT and sp-IgE tests which were considered the least useful in diagnosing beta-lactam allergy.

Beta-lactam desensitization

In the last 12 months, beta-lactam desensitization had been performed by 37% (30/81) of respondents, with 97% of them performing this on less than 10 patients. The majority of respondents undertaking desensitization reported that in 76-100% of children both the initial desensitization was successfully achieved and that when a further course of the drug was required, this had also been tolerated. Regarding subsequent oral administration of the index drug following desensitization, 14% (4/28) of respondents made no modification to their typical dosing regime, 14% (4/28) recommended 3 incremental doses and 71% (20/28) would repeat the desensitization protocol.

Discussion:

We compared the diagnosis, investigation and management of beta-lactam allergy in childhood amongst respondents from the international community. The questionnaire was written by an expert in paediatric drug allergy (GduT) and revised by other paediatric allergy experts to reduce ambiguity and ensure applicability to professionals in other countries.

Through the use of a typical clinical scenario, there was variability in the decision of respondents to initiate allergy testing. Of those who would perform allergy tests for the scenario, the UK respondents were less likely to perform sp-IgE compared to respondents from the rest of the world. However, internationally, the preferred test of choice was the ODPC, with a high percentage of respondents in both groups who would perform them.

ODPC were considered to be the gold standard test and used on a regular basis. A third of respondents said that they would proceed to ODPC regardless of any positive SPT, sp-IgE or IDT results performed beforehand. They were described as the most useful test for excluding and confirming beta-lactam allergy, and were considered very safe procedures as no participants had to

admit any children to high dependency or intensive care as a result of a challenge and very few had to administer intramuscular adrenaline during a challenge. This concurs with Demoly et al's study (2), which showed a high negative predictive value (94.1%) for DPT and none of the false negative patients experienced a life-threatening reaction emphasizing the test's safety. Interestingly, 41% of our respondents had patients who had a negative ODPC to a beta-lactam but subsequently reacted to the same antibiotic on a separate occasion. Unfortunately we did not ask any follow on questions, but understanding the false positive rates of ODPC for beta-lactams would be an important area for future research.

There was also agreement on the type of symptoms that would indicate the need to stop a challenge. Despite agreeing that this was the best test for investigating and diagnosing beta-lactam allergy, there was still some variability in practice seen. The methodology of how to conduct challenges, for example, the antibiotic dosing during a challenge, was not consistent.

There were respondents who accepted a positive SPT, Sp- IgE and IDT result as a definitive diagnosis and did not perform ODPC for confirmation of beta-lactam allergy. Even within the interpretation of other tests, differences existed amongst practitioners, specifically with regards to accepted positive cut off values for sp-IgE tests and the measurement of wheal diameters in the interpretation of positive SPT and IDT.

Study limitations include an inability to assess true response rate as the questionnaire was sent by email through external organizations. The number of responses was low, considering the number of allergy organizations approached; however this may reflect a low number of clinicians who investigate and manage antibiotic allergy. The majority of respondents worked in the UK and Europe despite the questionnaire being disseminated through multiple international allergy organizations. Hence beyond the UK, our responses cannot be seen as indicative of the overall practice in any individual country or region. Whilst approximately half of the respondents had over 20 years of experience, the absolute number of children that they were investigating each year varied significantly with half seeing approximately one child per month or less.

The questions in our survey were primarily about any drug allergic reactions in children and did not specifically ask questions about immediate and non-immediate drug reactions. This would be interesting to consider in future work but overall this study gave insight into current practices of the respondents. Of note, this questionnaire was also undertaken prior to publications recommending ODPC for children with uncomplicated beta-lactam presentations (9).

There have been attempts to standardize drug allergy management in children (1, 2); however these are largely based on research in adults and further work is needed to establish what are the safest and most accurate diagnostic methods for the investigation of children's beta-lactam allergy.

Conclusion:

There is poor consensus among clinicians around the world in the diagnosis and management of beta-lactam allergy in childhood. There is variability in the indications used for practical methods and interpretation of allergy testing (SPT, IDT and ODP) practice. These findings highlight the need to establish a stronger evidence base for the investigations that should be performed to achieve an international consensus for the diagnosis and management of drug allergy in children.

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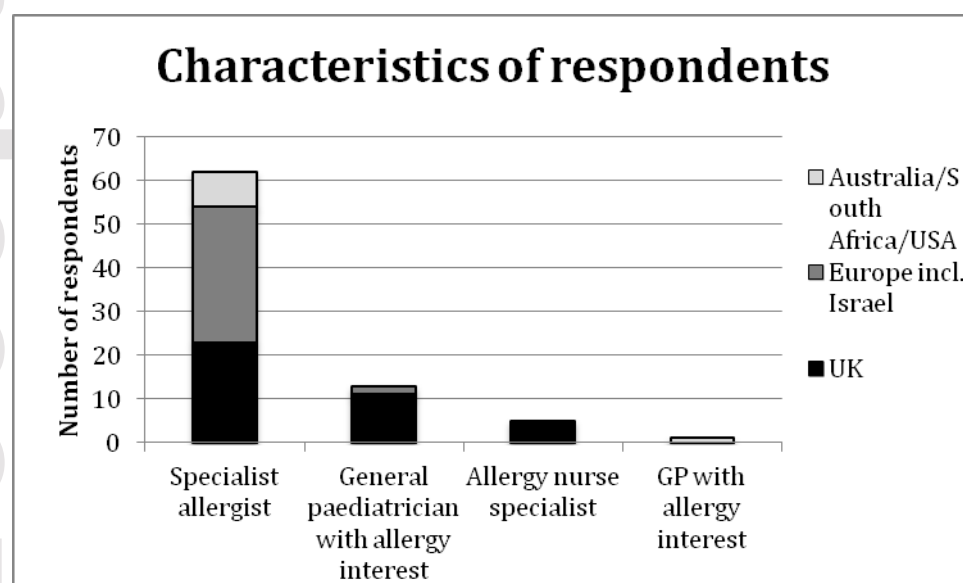


Figure 1: Type of Specialist and Country of Origin of our respondents

Percentage of patients seen over 12 months

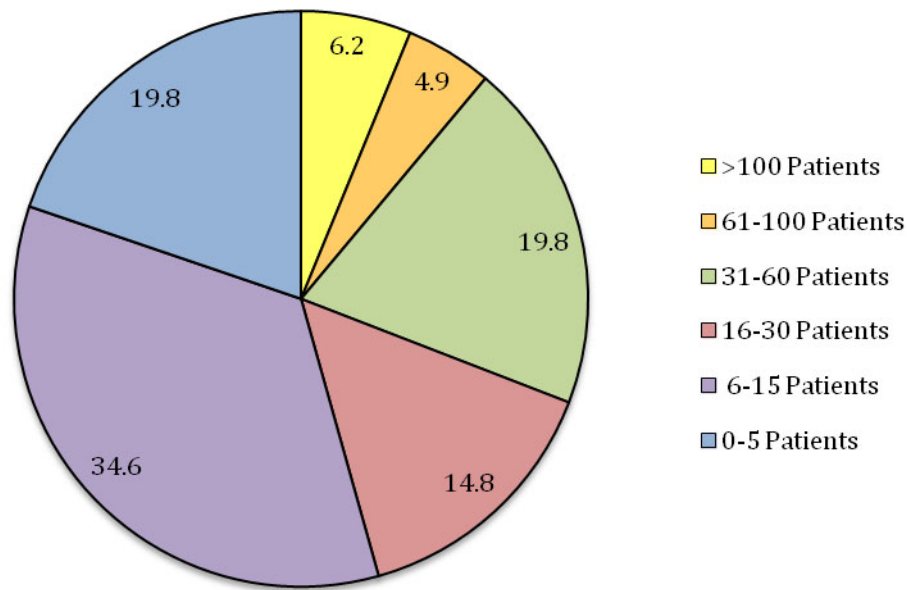


Figure 2: How many patients seen by participants over 12 months

Table 1: Specific allergy tests that respondents would perform for the Clinical Scenario

Test	Amoxicillin n (%)	Minor Determine ntMixture (MDM) n (%)	Penicilloyl polylysine (PPL) n (%)	Penicillin G n (%)	Cefaclor n (%)	Index drug* n (%)
SPT	27 (59)	18 (39)	18 (39)	17 (37)	5 (11)	4 (9)
Intradermal	24 (53)	19 (41)	19 (41)	14 (30)	6 (13)	3 (7)
sp-IgE test	21 (46)	3 (7)	5 (11)	15 (33)	6 (13)	1 (2)
Patch test	6 (13)	0	0	0	0	0
Basophil activation testing (BAT)	1 (2)	0	0	0	0	0
Oral drug challenge	44 (96)	0	0	0	0	0

* Not indicated previously

Table 2: Comparison of the type of allergic tests chosen between UK and the Rest of World Respondents who would use allergy tests for the *Clinical Scenario*

	UK % (n=20)	Rest of World % (n=26)	P-value*
SPT	55 (11)	62 (16)	0.65
sp-IgE	25 (5)	73 (19)	0.0001
IDT	35 (7)	56 (14)	0.20
Patch test	0 (0)	24 (6)	0.03
Basophil activation test	0 (0)	4 (1)	1.00
ODPC	95 (19)	96 (25)	1.00

*Chi square or Fisher's exact test as appropriate

Table 3: Percentage of ODPC that were positive in the last 12 months

ODPC (%)	Number of respondents (%)
0	20 (26)
1-5	32 (42)
6-10	13 (17)
11-25	6 (8)
26-50	4 (5)
51-75	1 (1)
76-100	0 (0)

Table 4: Symptoms that would result in stopping a drug challenge if occurring within 2 hours of administration.

Symptom	Number of participants who would stop (n (%))
≤2 hives concurrent non-contact urticaria persisting for at least 5 minutes	16 (20)
≥3 hives concurrent non-contact urticaria persisting	63 (78)
Perioral or periorbital angioedema	77 (95)
≤2 hives concurrent non-contact urticaria persisting for at least 5 minutes AND angioedema	61 (75)
General oedema	68 (84)
Onset of maculopapular rash	60 (74)
Onset of morbilliform rash	59 (73)
Vomiting – single occasion (excluding gag reflux)	24 (30)
Vomiting – multiple occasions (excluding gag reflex)	71 (88)
Evidence of circulatory compromise	80 (99)
Evidence of respiratory compromise	79 (98)
Acute aversion or dislike	13 (16)
Diarrhoea	28 (35)

APPENDIX

Appendix 1: Oral drug challenge results to excipients

Excipients	Positive oral drug challenge
TABLETS	
Dilutants (e.g. lactose, microcrystalline cellulose)	1

Disintegrants (e.g. sodium starch glycolate, croscarmellose sodium)	1
Binders (e.g. PVP, HPMC)	2
Colouring agents	3
Lubricants (e.g. magnesium stearate)	1
SYRUPS	
Solvents/co-solvents (e.g. aqueous vehicle, propylene glycol, glycerol)	0
Buffering agents (e.g. citrate, gluconates, lactates)	0
Preservatives (e.g. sodium benzoate, parabens (Me, Pr, Bu), BKC)	8
Antioxidants (e.g. BHT, BHA, ascorbic acid)	2
Welting or anti-foaming agents (e.g. polysorbates, sorbitan esters)	1
Thickening agents (e.g. methycellulose, hydroxyethylcellulose)	3
Sweetening agents (e.g. sorbitol, saccharin, aspartame, acesulfame)	1
Flavouring agents (peppermint, lemon oils, butterscotch)	2
Colouring agents	3
Humectants (propylene glycol, glycerol, sorbitol)	5

1 Appendix 1: Oral drug challenge results to excipients

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Colouring agents	3
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SYRUPS	
Solvents/co-solvents (e.g. aqueous vehicle, propylene glycol, glycerol)	0
Buffering agents (e.g. citrate, gluconates, lactates)	0
Preservatives (e.g. sodium benzoate, parabens (Me, Pr, Bu), BKC	8
Antioxidants (e.g. BHT, BHA, ascorbic acid)	2
Welting or antifoaming agents (e.g. polysorbates, sorbitan esters)	1
Thickening agents (e.g. methylcellulose, hydroxyethylcellulose)	3
Sweetening agents (e.g. sorbitol, saccharin, aspartame, acesulfame)	1
Flavouring agents (peppermint, lemon oils, butterscotch)	2
Colouring agents	3
Humectants (propylene glycol, glycerol, sorbitol)	5

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