Appendix (draft) - The Dutch Working Party on Antibiotic Policy (SWAB) guideline for the approach to suspected Antibiotic Allergy

Appendix

Literature search

Q1

For Q1 we searched for epidemiological studies of true antibiotic allergy. We emphasized the search on the diagnostic tests for allergy, i.e. proven antibiotic allergy. The focus was led upon meta-analyses and systematic reviews. Key search terms were “skin tests”, “intradermal tests”, “drug provocation tests”, “antibiotic allergy”, “antibiotic hypersensitivity”, “beta lactam allergy or hypersensitivity”, “penicillin allergy”, “cephalosporin allergy”, “drug eruption” or “anaphylaxis”. The literature search resulted in 1059 references (Pubmed 957, Embase 289 (61 unique), Cochrane 73 (41 unique)). For the additional literature review we excluded articles that were already included in the systematic reviews and studies that were published > 15 years ago and/or included < 500 patients. We included studies that used skin tests and preferably drug provocation tests to confirm antibiotic allergy. We performed a general search on all antibiotics. However, since the search yielded mostly studies based on penicillin allergy or other beta-lactam antibiotics, the conclusions and recommendations were formulated based on these studies.

Q2

For Q2 we used the literature of the British (BSACI) guideline by Mirakian et al. (2015) regarding management of penicillin allergy and other beta-lactam antibiotics. In addition we used articles that were identified with the search performed for key question 1, in particular a position paper by Romano et al (2019). In these studies however, risk factors of true antibiotic allergy were not the primary endpoint. A separate search was performed using the terms “ risk factors” or “probability” in addition to the different search terms for “antibiotic allergy”. This search strategy resulted in 267 references (Pubmed 129, Embase 109 (12 unique), Cochrane 132 (126 unique)), but did not provide additional relevant literature to the abovementioned strategy.

Q3

The literature search for Q3 was emphasized on different search terms for “allergy labeling”, “self-reported” or “patient reported allergy” and different terms of antibiotic allergy. After literature

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review we decided to include studies that used a risk stratification, algorithm or questionnaire for allergy assessment. The reason for this approach was that these studies include the minimum of information needed to assess if a reaction is likely the result of true allergy or not. We searched for similarities in the elements used in these risk stratifications or algorithms, since it was believed that these elements were relevant to classify the index reaction as suspected of true antibiotic allergy (type B reactions) or side effects (type A reactions) and to determine the severity of the index reaction. The search strategy resulted in 462 references (Pubmed 240, Embase 332 (130 Unique) and Cochrane 102 (92 unique)). Since this question was initially addressed as one of the last topics of the guideline, a few additional studies, retrieved from previous literature searches (mainly the search performed for Q5), were included.

Q4

For this chapter we emphasized the search strategy upon “antibiotic allergy” and search terms for “direct delabeling” or “removal of label”. The search resulted in 105 references of which 91 from Pubmed, 75 from Embase (6 unique) and 11 from the Cochrane library (8 unique). Most of these studies were already discussed in key question 3. The literature search, however, yielded many delabeling studies that evaluated the safety of performing a “direct challenge test” in “low risk” patients. Since this was not the aim of this key question, we included only the studies that evaluated which index reactions could be assigned as probably “non-allergic” based on detailed allergy history alone (without a skin or challenge test).

Q5

For this key question, other search terms that were used for re-exposure were “repeat administration”, “ repeat therapy”, “repeat treatment” or “re-challenge”. The search resulted in 596 references (Pubmed 442, Embase 431 (125 unique), Cochrane 61 (29 unique)). After in-depth review of the available literature that resulted from the search, studies that included “low-risk” patients for a direct challenge with the culprit antibiotic were selected. Since most of these challenges were tolerated in the “low-risk” patients, the guideline committee concluded that these patients had a very low risk of occurrence of (severe) allergic reaction upon re-exposure to the culprit drug. However, the studies that were selected did show heterogenicity in the definition of low risk patients. We decided to focus on the similarities in the various definitions of “low risk” patients.

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Q6

For this chapter we only included systematic reviews or meta-analyses since additional literature review showed studies with similar results already discussed in the systematic reviews. The literature search resulted in 342 references, of which 293 from Pubmed, 256 Embase (49 unique) and 6 from the Cochrane library (0 unique).

Q7

This key question was added to the chapter during the formation of the guideline, a few articles were already found with other literature searches. A separate literature search was conducted based on the PICO, which yielded only a few additional observational studies. The combination of the search terms “Penicillin allergy” and “cross reactivity” was used for “a different penicillin”. This search strategy resulted in 444 references (Pubmed 287, Embase 126 (94 unique), Cochrane 67 (8 unique)). The selected studies mostly included patients allergic to amoxicillin that investigated the potential cross reactivity with benzylpenicillin and flucloxacillin. Conclusions and recommendations are therefore based on these limited studies. During review of this chapter, information regarding piperacillin cross reactivity was missing. Therefore an additional search was performed which resulted in 2 relevant studies for piperacillin.

Q8a and b

For key question 8, the literature search resulted in 253 studies (Pubmed 112, Embase 211 (112 unique), Cochrane 41 (29 unique)). For this key question we focussed on studies that included patients with a proven allergy to penicillin by means of skin tests and/or drug provocation tests. Preferable the cross reactivity was established using skin tests and drug provocation tests with cephalosporins. Studies that included patients with a reported allergy for penicillin that received a treatment with cephalosporin were included as well, but these studies were counted less heavily in the final conclusions and recommendations.

Q9

The literature search performed for Q9 resulted in 71 references (Pubmed 50, Embase 71 (19 unique), Cochrane 6 (2 unique)). For this key question the search was focussed on studies that included patients with a *proven* allergy to penicillin by means of skin tests and / or drug provocation

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tests. In addition the studies that performed drug provocation tests or direct challenges with the carbapenem or monobactam were prioritized.

Q10

For this key question, different search terms for “cross reactivity”, “cephalosporin allergy” and “penicillin allergy” were used. The literature search yielded 47 references (Pubmed 24, Embase 40 (21 unique), Cochrane 4 (2 unique)). Studies that included patients with a proven cephalosporin allergy by skin test and/ or drug provocation tests were selected. Preferably, skin tests and / or drug provocation tests with penicillin (determinants) were performed in these studies to be able to assess cross reactivity.

Q11

For this question, studies were selected when they included patients with a proven cephalosporin allergy proven by skin tests or drug provocation tests that received skin tests or drug provocation tests with ≥ 1 different cephalosporin. However since the available studies were scarce, studies that included patients with reported cephalosporin allergy not proven by a formal allergy work up were also included. The first search strategy that was performed resulted in 952 references (Pubmed 526, Embase 302 (187 Unique) and Cochrane 352 (239 Unique)). In this search Mesh terms for cephalosporins were used and cephalosporin allergy in general. The second search included the search term “cross reactivity” or “cross allergy” or “cross hypersensitivity” and resulted in 114 references that were also found in the aforementioned search strategy.

Q12

The focus of the search was set on patients with cephalosporin allergy preferably confirmed by formal allergy work up. Since the literature search yielded very little results, we also included studies that investigated specific groups, for example patients with cystic fibrosis. The broader search strategy with terms for “cephalosporin allergy” or “cephalosporin hypersensitivity” and terms used for “monobactams” or “carbapenems”, resulted in 193 references (Pubmed 120, Embase 152 (54 unique)). When applying the search term “cross reactivity”, “cross allergy” or “cross hypersensitivity” only 60 references were found and relevant studies were missing. The more broad search strategy, mentioned above, was used.

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Q13

For this chapter the literature search yielded 233 references, but no relevant studies for the mentioned PICO, probably since carbapenem and monobactam allergy are both very rare. When adjusting the search strategy and focus on carbapenem or monobactam allergy, the results were similar. Vice versa, as is reported in key question Q9, there is literature available regarding cross reactivity with carbapenems and monobactam in penicillin allergic patients. However, the question remains whether you can extrapolate the literature upon cross reactivity or allergy with carbapenems and monobactams in penicillin allergic patients in this other direction.

Q14

The search strategy that was applied included different terms for “cephalosporins”, “drug hypersensitivity”, “carbapenems” and “monobactams”. The term cross reactivity or cross allergy was not used, since the results were very limited already with the broader search. The search yielded 170 references, but no relevant literature regarding carbapenem allergy and cross reactivity with a cephalosporin. We used the literature retrieved from Q12 to formulate recommendations for this key question. For monobactam allergy, studies were searched that reported on cross reactivity with ceftazidime.

Q15 & Q 16

A more broad search strategy was performed that included both question 13 and question 14. In the first search we applied terms for “re-exposure” or “cross reactivity”, but since that did not produce many relevant articles we decided to apply a different search strategy. When we used the search term “non-beta-lactam antibiotics”, the literature was polluted with studies regarding beta lactam antibiotics. Therefore we searched for the 5 most frequently used antibiotics in the hospitals in the Netherlands according to the Nethmap. A special search technique was used, i.e. proximity operators. With proximity operators we set position requirements of words to each other: word 1 [macrolide] and word 2 [allergy] are at a certain distance from each other, next to each other or with a certain maximum number of arbitrary other words in between. This search strategy can only be applied in Medline, Cochrane and Embase. This search yielded 702 references (Pubmed 587, Embase 562 (94 unique) and Cochrane 30 (21 unique). For the descriptive summary we used articles found with the previous search and included a new search specific for vancomycin and cotrimoxazole.

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