

Epidemiology

Diagnosis of allergy against beta-lactams in primary care: prevalence and diagnostic criteria

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Abstract

Background. Secondary care studies showed that a recorded allergy to beta-lactams could not be confirmed by valid allergy testing in >85% of cases. In daily practice, recorded beta-lactam allergies probably cause prescription of secondary choice antibiotics. This overrating of beta-lactam allergy hampers appropriate use of narrow spectrum antibiotic and generates unnecessary cost and bacterial resistance.

Objective. To assess registration and over diagnosis of allergies against beta-lactams in Dutch primary care.

Methods. A retrospective cohort study in 8288 primary care subjects was performed. Patients with recorded allergy were identified through International Classification for Primary Care coding. Signs and symptoms of the recorded allergic reaction and patient's characteristics were extracted from patient's files and patients were sent a questionnaire. The probability of allergy was based on a composite reference standard that was scored by two authors independently.

Results. One hundred sixty-three subjects had a recorded allergy (2.0%). In 51.5% of cases, no characteristics of the recorded allergic reaction were reported in patients' medical files. Based on our composite reference standard, allergy was excluded in 19 subjects (11.7%). Risk factors for allergy registration were female gender, age <4 years, and the comorbidities—asthma, allergies and skin disorders.

Conclusions. The prevalence of recorded allergy against beta-lactam antibiotics in a large Dutch primary care centre was 2%. Due to lack of registration of accompanying signs and symptoms of the recorded allergy, this diagnosis is uncertain in most patients. Better documentation and classification by a screening algorithm of future possible allergic reactions to beta-lactams are needed in primary care.

Keywords: Beta-lactams, hypersensitivity, prevalence, primary health care, probability, risk factors, The Netherlands.

Introduction

Beta-lactam antibiotics are among the most frequently prescribed drugs in general practice worldwide. They provide good bacterial coverage and have low toxicity. Unfortunately, they also account for many antibiotic allergy labels noted in the medical records of patients (1,2).

Patients with recorded beta-lactam allergies are likely to be treated with secondary choice, more toxic, broad-spectrum and more expensive antibiotics (3–6). Therefore, diagnosis and registration of allergy against beta-lactams should be as accurate as possible. However, secondary care studies have shown that reported allergy to beta-lactam antibiotics as reported by patients and as reported in

medical records is not reliable and could not be confirmed by a valid allergy test in over 85% of cases (1–6). Possible explanations for this overestimation of beta-lactam allergy include incorrect attribution to allergy while the suggestive symptoms (commonly rashes) were caused by the underlying infectious disease or interactions between the microbial agent and the antibiotic (7).

In patients with indication of antibiotic treatment, this overrating of beta-lactam allergy hampers appropriate use of narrow spectrum antibiotic and generates increased unnecessary use of alternative antibiotics that should be preserved for the management of severe infections. This leads to subsequent increased cost, worse patient outcomes and bacterial resistance against antibiotics as shown in some earlier studies (8,9). However, these few studies were done in secondary care. Since the majority of beta-lactams are prescribed in primary care, it is also pivotal to assess the magnitude and nature of this problem in primary care.

This study aimed to assess the prevalence of recorded allergy against beta-lactam antibiotics in a primary care population and aimed to investigate to what extent beta-lactam allergies in primary care setting can be made more or less plausible based on available data. In addition, we aimed to explore patient characteristics and signs and symptoms related to reported allergy.

Research questions

(i) What is the prevalence of recorded beta-lactam allergies in a primary care setting? (ii) How does this recorded allergy correspond with a composite reference standard for allergy? (iii) Which patients are at risk for obtaining a label of allergy against beta-lactams? (iv) Which relevant information concerning recorded beta-lactam allergies is lacking in primary care?

Methods

Study design

This is a single-centre, retrospective cohort study performed among all 8288 patients at the academic health care centre Terwijde at Leidsche Rijn Utrecht (10).

Study population

The study population consisted of all patients with a label of allergy against beta-lactam antibiotics in their electronic health record system. These labels were identified through the International Classification for Primary Care 2 (ICPC-2) codes: A92 (allergy/allergic reaction not otherwise specified), A85 (adverse effect medical agent) or standardized mark 'hypersensitivity' in the electronic medical file. We consequently left out other ICPC codes, for example, A84 (poisoning of medical agent) and A87 (complication of medical treatment), because in our experience these labels are not allocated to patients who experience reactions after beta-lactam use.

In addition, we gathered all beta-lactam and cephalosporin allergy labels registered by the pharmacy in our health centre. The majority of patients at our academic health care centre are registered with this pharmacy.

Measurements

For all patients identified with a recorded allergy, the following information was extracted from their medical file: gender, age at diagnosis, comorbidities and signs and symptoms during the episode of allergy. Relevant comorbidities were defined as asthma, allergies, immunologic (immunodeficiency, dermatomyositis, inflammatory bowel disease, HIV, etc.) and skin disorders (eczema, psoriasis) as these increase the risk for rashes in general.

A questionnaire based on literature (8,11) was sent to all patients with a recorded allergy label investigating the signs and symptoms related to the recorded allergy (see questionnaire in [Supplementary material 1](#)). Patients who did not respond within 2 weeks were contacted by phone.

Reference standard

Because of the lack of a commonly applied gold standard to determine the presence or absence of a true allergy against beta-lactam antibiotics in primary care settings, a 'composite reference standard' was applied. This is a predefined fixed rule based on multiple test results. The main advantage of such a reference test is reproducibility of results, which is made possible by a transparent and consistent approach for obtaining a final clinical diagnosis across study subjects (the composite reference standard is shown in [Supplementary material 2](#)) (12).

The composite reference standard was based on literature (8,11,13,14) and accepted knowledge of drug allergic reactions ([Table 1](#)). Two authors independently scored the composite reference standard based on results from the retrospective review of patients' medical records and, if data were missing, the patients' questionnaires. Initial discrepancies between independent reviewers were resolved by discussion and reported results are based on full consensus.

Clinical diagnosis of beta-lactam allergy was classified according to the two relevant types of drug hypersensitivity reactions defined by Gell and Coombs: (i) Type I (immediate type, immunoglobulin E mediated) and (ii) Type IV (delayed type, T cell mediated) ([Table 1](#)) (11). The probability of the subtypes of allergy was scored as probable, possible or unlikely.

Statistical analysis

Statistical analysis was based primarily on results of patient's medical records. If data in this respect were missing, results obtained through patient reported questionnaires were used.

Table 1. Relevant types of beta-lactam hypersensitivity reactions according to Gell and Coombs and their characteristics

Reaction type	Immune mechanism	Symptoms	Common diagnostic tests in secondary care
I (immediate)	IgE—basophils and/or mast cells	Hives/angio-oedema/anaphylaxis within 1 hour after exposure	Skin and intradermic test, RAST, basophil histamine release
IV (late)	T cells	Exanthema 2–10 days after exposure, potentially lasting for weeks	Epidermal (patch) and intradermic test

IgE, immunoglobulin E.

Data were expressed as mean $\pm$ SD for continuous variables and as frequencies (%) for categorical data. Comparison between the study group characteristics and the general population at Terwijde Health Centre for categorical variables was performed using Fisher's exact tests. Independent samples *t*-tests were used to compare means of continuous variables.

Analyses were conducted using SPSS, version 20 (SPSS, Inc., Chicago, IL) and GraphPad Prism version 5.0 (GraphPad Software Inc., La Jolla, CA).

Results

Study characteristics

The age distribution of the study population showed that 33.3% of patients was younger than 19 years old, while in the general Dutch population, 23.1% is younger than 12 years old (15). The comparison is shown in [Supplementary material 3](#). Out of a total number of 8288 patients enlisted at the academic health care centre Terwijde, 163 individual patients (2.0%) had a recorded allergy to beta-lactam antibiotics and were included in the study. Data collection through the 163 medical records concerning patient's characteristics and signs and symptoms of the recorded allergy resulted in 79 cases (48.5%) in which data were complete and in 84 cases (51.5%) in which data were incomplete. Of the 163 sent questionnaires, 80 (49%) were returned by the patients. In 64 of the remaining patients (39%), questionnaires were completed by contacting patients by phone. In 19 patients (12%), questionnaires were not completed due to different reasons ([Fig. 1](#)).

[Table 2](#) shows the characteristics of the study population with recorded allergy. The mean age of the group was 21.7 years, with a range of 4.3–39.1 years. Sex ratio (f/m) was 2:1, with 66.9% of the group with recorded allergy being female.

What is the prevalence of recorded beta-lactam allergies in a primary care setting?

The prevalence of recorded beta-lactam allergy in our primary care centre was 2.0%.

How does this recorded allergy correspond with a composite reference standard for allergy?

Based on a composite reference standard, we found that in 25 of 163 patients (15.3%), data were insufficient to score probability of allergy to beta-lactam antibiotics. From the 163 patients, 8 (4.9%) were scored as having a probable allergy and 111 (68.1%) were scored as having a possible allergy for beta-lactams. In 19 patients out of 163 (11.7%), allergy to beta-lactams was scored to be unlikely ([Table 3](#)).

In 60 out of 163 patients (36.8%), the possible allergic reaction could not be further specified into Type I or Type IV reaction because of insufficient information; therefore, the severity of the reaction could not be estimated. Consequently, these patients were classified into the subgroup 'possible Type I or IV reaction'.

Which patients are at risk for obtaining the label 'allergic to beta-lactams'

Compared to the general population at the health care centre Terwijde, patients with recorded allergy were more often very young

Table 2. Patient characteristics of subjects with a recorded allergy in Dutch primary care in 2014

Characteristics	Allergy group (N = 163)
Age at diagnosis, mean (SD)	21.7 $\pm$ 17.5
Age, N (%) ^a	
0–4	34 (24.1)
5–14	26 (18.4)
15–24	23 (16.3)
25–54	52 (36.9)
>55	6 (4.3)
Female, N (%)	109 (66.9)
Relevant comorbidities, N (%) ^b (asthma, allergies, immunologic and skin disorders)	104 (67.1)

^aData concerning age at diagnosis are missing in 22 cases.

^bData concerning comorbidities are missing in eight cases.

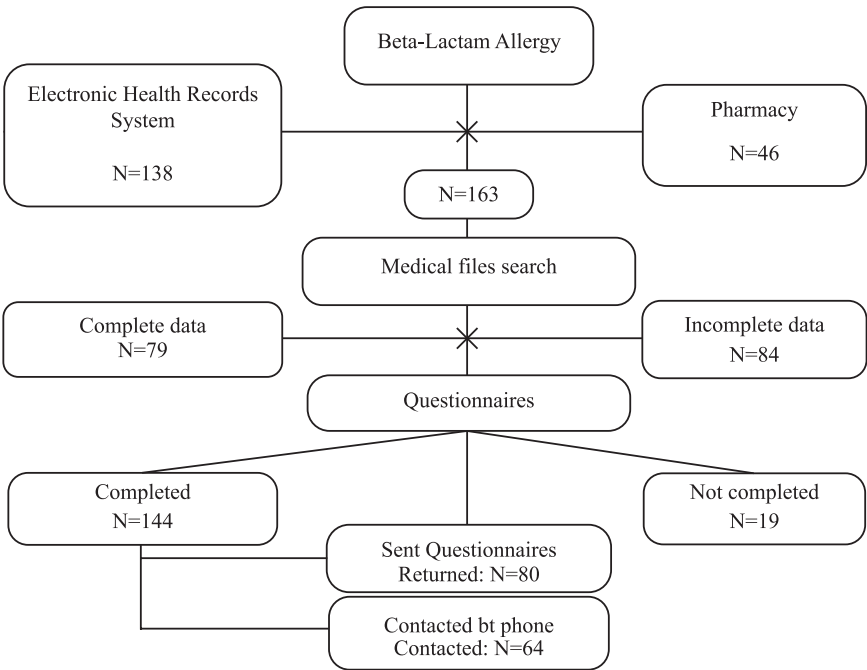


Figure 1. Flowchart of data collection in 163 subjects with a recorded allergy.

Table 3. Frequency of subjects per assigned risk class of allergy as defined by a composite reference standard

	Type I	Type IV	Type I or IV	Unlikely	Missing
Probably, N (%)	1 (0.6)	7 (4.3)	–	–	–
Possibly, N (%)	10 (6.1)	41 (25.2)	60 (36.8)	–	–
Total, N (%)	11 (6.7)	48 (29.4)	60 (36.8)	19 (11.7)	25 (15.3)

(0–4 years), less often aged >54 years and more frequently female. In addition, more patients with recorded allergy had the following comorbidities: asthma, allergies and skin disorders (primarily eczema) (Table 4).

Which relevant information concerning recorded beta-lactam allergies is lacking?

In the 103 patients in whom information on symptoms was available, 84 patients (81.6%) had skin symptoms, of whom 8 patients (7.8%) reported urticaria and in 21 patients (20.4%), skin symptoms were not further specified. Two patients (1.9%) suffered from hypotension or collapse, five suffered from dyspnoea (3.8%) and in eight patients (7.8%), the only symptoms mentioned were nausea, diarrhoea or vomiting.

In 51.5% of cases, no characteristics of the recorded allergic reaction were reported in patients' medical files. After the questionnaires in 35 cases (21.5%), data concerning time interval between beta-lactam exposure and symptom onset were missing, and in 60 out of 163 study subjects (36.8%), data concerning skin symptoms were missing.

Discussion

Summary

In this study, we found a prevalence of a recorded allergy in primary care setting of 2.0%. Based on our composite reference standard, allergy in this group was scored unlikely in 11.7% ($n = 19$) of subjects. In the majority of patients, allergy was possible, but insufficient information was available to make a more definitive diagnosis. Risk factors for allergy registration were female gender, age <4 years and comorbidities—asthma, allergies and skin disorders.

Strengths and limitations

To our knowledge, this is the first study on the prevalence and risk factors of recorded allergies against beta-lactam antibiotics in primary care setting. However, when interpreting the results, some considerations should be made.

This study was performed in a single health care centre with a relatively young population, which affects generalizability and may have caused a slight overestimation of the prevalence of recorded allergy. Due to the lack of a commonly applied gold standard for beta-lactam allergy in primary care, we used a self-constructed composite reference standard to estimate the probability of allergy to beta-lactams across study subjects. The optimal reference standard would be to have all subjects undergo skin prick testing and oral challenge in whom allergy could not be excluded based on history taking (8,11). However, this was not feasible in our study, where the aim was to assign more certainty on the allergy status based on readily available data. Reference standards generally are considered to be superior to an 'expert panel diagnosis' (12) because of reproducibility and transparency. The composite reference test was based on current accepted knowledge of accompanying symptoms

of drug hypersensitivity reactions (13,14). However, our composite reference standard was not validated. Another possible limitation of our study is that we had to base our data analysis partly on results from patients reported questionnaires, which response was restricted and completed by telephone interviews. These patient-reported data, however, may be less reliable due to information and recall bias and may thus affect validity. On the other hand, our results reflect daily practice as assumptions about drug allergies are often based on patient reporting. Finally, questionnaires were filled in by patients or were completed by telephone. The questionnaire may show different diagnostic characteristics when recorded by patients on paper than when completed by telephone, and using a standardized method may have resulted in better precision.

Comparison with existing literature

As mentioned, studies concerning the prevalence of allergies against beta-lactams in primary care setting are scarce and based on patient reporting. Branellec *et al.* (16) assessed self-reported penicillin allergy in a cross-sectional study among GPs in France. 9.4% of 1057 patients in this study declared to be allergic to penicillin. In a cross-sectional survey of a general adult population from Portugal, Gomes *et al.* (17) reported on the self-reported drug allergy and found a 4.4% prevalence of self-reported allergy to penicillin's and other beta-lactams. The lower prevalence of beta-lactam allergies in our study compared to previous studies could be explained by a more restrictive antibiotic prescribing behaviour of the Dutch physicians compared to physicians in other European countries (18). Also our results were primarily based on physician and pharmacy recorded allergy, which is probably lower than patient self-reported allergies.

Concerning risk factors for beta-lactam allergy registration, female gender and young age were previously mentioned as predictors of a recorded allergy to beta-lactams (2,3,5,6), which was confirmed by our data. It is interesting to note, however, that female gender and young age are not believed to be independent aetiological risk factors for true allergy (1,2).

What do these results mean?

In the majority of cases (51.5%), no characteristics of the recorded beta-lactam reaction were reported in the patients' medical files. Especially important information about time interval between beta-lactam exposure and symptom onset and on skin symptoms was missing. Therefore, the possibility of allergy diagnosis remained unclear in many cases. This poor documentation could be explained by the absence of practical guidelines or reported consensus for management of suspected allergy in primary care. In addition, we think that time constraints may also have caused poor reporting of data concerning alleged allergy. Furthermore, many misconceptions exist regarding allergies to beta-lactams and many patients will not meet the criteria for a possible allergy when questioned about signs and symptoms of their presumed allergy. Often patients report allergies when they have in fact experienced side effects during antibiotics use (19).

Table 4. Comparison between patients in allergy group to general population in the health care centre

	Allergy group (N = 163)	GP's population (N = 8288)	P-value
Age at diagnosis, mean (SD)	21.7 (17.5)	30.5 (20.0)	<0.001
Age at diagnosis, N (%) ^a			
0–4	34 (24.1)	924 (11.1)	<0.001
>54	6 (4.3)	882 (10.6)	0.012
Gender, N (%)			
Female	109 (66.9)	4187 (50.5)	<0.001
Comorbidities, N (%) ^a			
Airways	22 (14.2)	640 (7.7)	0.006
Allergies	43 (27.7)	1537 (18.5)	0.007
Immunologic	6 (3.9)	386 (4.6)	0.847
Skin	33 (21.3)	1168 (14.1)	0.015

^aData concerning age at diagnosis are missing in 22 cases.

^bData concerning comorbidities are missing in eight cases.

In all patients with a recorded allergy to beta-lactams, the most important characteristics of the reaction should be investigated and documented immediately (Supplementary material 2) in order to separate patients with a possible reaction from patients in whom allergy is unlikely. This could easily be explored in all patients with newly suspected beta-lactam allergy in primary care. With a better documentation of suspected reactions, differentiation between possible Type I and possible Type IV reactions will also be feasible and enable a restricted and efficient selection of patients in whom more extensive allergy testing including skin prick testing and oral challenge should be considered (11). In patients in whom allergy is uncertain, one could also decide to use an alternative antibiotic when indicated like macrolides. However, although we think a more detailed and structured registration of signs and symptoms could in itself improve the assessment of beta-lactam antibiotic allergy identifying real probable allergy without missing real allergy, more evidence-based information about the true prevalence (based on valid allergy testing) and clinical predictors of beta-lactam allergy in primary care is needed.

Conclusions

In the present study, the physician diagnosed allergy in primary care was 2%; however, in many cases, registration of accompanying signs and symptoms was insufficient to determine the probability of allergy. Better registration of characteristics of suspected allergy is needed to reduce unnecessary diagnosis of allergy to beta-lactam antibiotics.

Supplementary material

Supplementary material is available at *Family Practice* online.

Declaration

Funding: none declared.

Ethical approval: All data were anonymized in the Health Center. We submitted our study proposal to the Medical Research Ethics Committees (MREC/METC) of the University Medical Center Utrecht (UMCU), The Netherlands. They issued our project as non-WMO (Medical Research Involving Human Subjects Act) research meaning that no further approval for the retrospective review of patient data and the questionnaires was needed.

Conflict of interest: none.

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Supplementary material 1: Questionnaire “suspected antibiotic allergy”

In your medical record, an antibiotic allergy is registered

To which antibiotic did you have a reaction in the past: (circle all that apply)

Penicillin / Amoxicillin / Augmentin (amoxicillin clavulanic acid) / Cefalosporin / Broxil
(feneticillin) / Floxapen (flucloxacillin) / Ampicillin / Clamoxyl

(In case of multiple reactions to the above antibiotics, please fill in the questioner based on the – in your opinion- most severe reaction)

What was the indication for the antibiotic treatment? (Free text)

What was the date of the reaction? (Approximately) dd-mm-yyyy

What was at that time, your approximate age?

1. Where there any of the following symptoms?

Itch only (without skin symptoms)	Yes / No / Unknown
Skin symptoms (itch, redness, swelling)	Yes / No / Unknown
Oedema (lips, eyes, hands, feet)	Yes / No / Unknown
Dyspnoea, hoarseness	Yes / No / Unknown
Drop in blood pressure	Yes / No / Unknown
Collapse / loss of consciousness	Yes / No / Unknown

Other symptoms: (Free text)

2. What was the time to onset of symptoms after first exposure to the antibiotic?

0 directly after the intake of the first dosage, namely after minutes
0 A couple of hours after the start of treatment namely after hours
0 A couple of days after the start of treatment namely after days
0 Unknown

3. Did you seek medical assistance during this reaction? Yes / No / Unknown

(General practitioner, ER, hospitalization) (circle all that apply)

4. Was there any medication prescribed to treat the reaction to the antibiotic?

- ☐ Yes, namely: anti-histamine / corticosteroids / epinephrine / unknown
- ☐ No
- ☐ Unknown

5. Was the treatment with the antibiotic to which you reacted interrupted?

- ☐ Yes → After how much time did symptoms disappear?
- ☐ No → Did the symptoms subside?
Yes / No / Unknown

6. Did you use the same antibiotic again after you had the above mentioned reaction?

- ☐ Yes → Where there symptoms? Yes / No / Unknown
- ☐ No
- ☐ Unknown

7. Have you ever had a similar reaction to other antibiotics? If yes, which antibiotics? (Free text)

....

8. Was a dermatologist consulted for this possible allergic reaction to an antibiotic?

- ☐ Yes: Was the allergy confirmed by the dermatologist?
Yes / No / Unknown
- ☐ No

Space for comments:

Supplementary material 2: Composite reference standard

Variable	Type 1 probable	Type 1 possible	Type 4 probable	Type 4 possible	Possible type I/IV	Allergy improbable
Time to symptoms	< 2 hours	< 2 hours or unclear	> 2 hours	> 2 hours or unclear	>2 hours or unclear	> 14 days OR any time
	AND	AND				AND
Symptoms						
Urticaria	YES and/or	YES and/or	No	No	YES and/or	No
Angio-edema	YES and/or	YES and/or	No	No	No	No
Rash/ exanthema	YES and/or	YES and/or	YES	YES	YES and/or	No
	AND two of 1-5	AND one of 1-3 or 5				
¹ Dyspnoea	¹	¹	No	No	No	No
² Collapse	²	²	No	No	No	No
³ Nausea, vomiting, diarrhoea	³	³				
			AND one of 4-5			AND/ OR
⁴ Repeated reaction when re-exposition to beta-lactams	⁴	No	⁴	No	No	No reaction to re-exposition with the same antibiotic to which recorded allergy
⁵ Confirmed by dermatologist	⁵	⁵	⁵	No	No	No

**Supplementary material 3 : Age distribution of
population of the Terwijde health care center
compared to the Dutch general population**

Age (years)	Study population (%)	General population (%)
0-19	33,3	23,1
20-39	31,2	24,6
40-64	29,2	35,5
65-79	5,1	12,6
>80	1,2	4,2