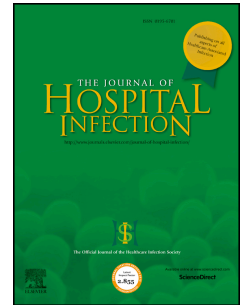


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Antimicrobial stewardship intervention: optimizing antibiotic treatment in hospitalized patients with reported antibiotic allergy

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Running title: Optimal therapy in antibiotic allergy

Keywords: antibiotic allergy, antimicrobial stewardship, drug challenge

Abstract

Background: Reported antibiotic allergy in hospitalized patients seems to be related to more adverse events, the use of reserve antibiotics and longer hospitalizations. Most patients reporting an antibiotic allergy can be de-labelled and therefore an antimicrobial stewardship intervention was set up.

Aim: To determine the impact of reported antibiotic allergy on the antibiotic treatment of hospitalized patients and prevent unnecessary deviation from the preferred antibiotic treatment by a proactive antimicrobial stewardship intervention.

Methods: An intervention study in a teaching hospital in the Netherlands. Hospitalized patients reporting an antibiotic allergy were included in a three-month period between March and May 2019. Physicians received a training and were provided with a recommendation in the electronic medical record (EMR) in case the preferred antibiotic treatment was unnecessarily avoided due to the allergy label and the patient was eligible for a drug challenge.

Findings: A total of 492 patients were identified accounting for 558 hospital admissions. In 93 cases the antibiotic allergy label interfered with the preferred antibiotic treatment of which 68 were eligible for a drug challenge. A total of 42 patients were challenged. In 40 (95%) patients no allergic reaction was observed, and the preferred antibiotic treatment was given. Two (5%) patients developed a non-severe skin reaction after drug challenge and continued an alternative antibiotic regimen.

Conclusion: This antimicrobial stewardship intervention can be used to provide patients with reported antibiotic allergy labels with the preferred antibiotic treatment and to de-label them after uneventful re-exposure to the antibiotic agent.

Introduction

Antibiotic allergy is the most common drug allergy reported by patients and is reported in up to 25% of hospitalized patients [1,2]. A documented antibiotic allergy can cause the avoidance of the preferred antibiotic treatment and is associated with more adverse events, more use of reserve antibiotics, longer hospitalizations and higher costs [3–6]. In case of a penicillin allergy, cephalosporins are also prescribed less frequently, for reasons of cross-reactivity [4]. The long-lasting dogma that cephalosporin allergy occurs in approximately 10% of penicillin-allergic patients has been shown to be incorrect. The actual rate of cross-reactivity is probably less than 1% [7].

Upto 95% of hospitalized patients with a documented penicillin allergy can be de-labelled by performing an oral drug challenge with or without prior skin testing [8]. Patients with non-severe reactions to antibiotics can be challenged without preceding skin testing, whereas the risk of a recurrent allergy reaction is low and symptoms appear to be mild in case an allergic reaction does occur [9–11]. In addition, antibiotic allergy wanes after years due to lost sensitivity [12,13].

In the Netherlands, most hospitals have established Antimicrobial Stewardship teams (A-teams) to monitor the quality of antibiotic use. Generally, an A-team consists of an infectious diseases physician, a clinical microbiologist and a hospital pharmacist [14]. Since reported antibiotic allergy seems to be related to negative outcomes and most patients reporting an antibiotic allergy can be de-labelled as such, we set up an intervention study. The aim of this study was to determine the impact of reported antibiotic allergy on the antibiotic treatment of hospitalized patients and to prevent unnecessary deviation from the preferred antibiotic treatment by a proactive antimicrobial stewardship intervention.

Methods

Study cohort

The study was carried out at the Meander Medical Centre (MMC) in Amersfoort, the Netherlands. The MMC is a teaching hospital and has 422 beds and approximately 26 200 hospital admissions annually. We conducted a prospective cohort study wherein patients aged 18 years and older reporting an antibiotic allergy upon hospital admission were included.

Enrolment of patients with antibiotic allergy labels took place from 5th March 2019 until 31st May 2019. The antibiotic allergy could be reported by patients to the treating physician or to a pharmacist assistant during medication verification. The medication verification took place before hospital admission in case of a planned admission or within 24 hours of admission at patient bedside in case of unplanned admission. During this medication verification, the national exchange point was accessed to obtain health information from the general practitioner and the community pharmacy of the patient when consent was given. In addition, the allergy could already be known from previous hospital admissions in the electronic medical record (EMR) Easycare (Easycare Healthcare, Deventer, The Netherlands) or the hospital pharmacy information system Zamicom (HI-systems, Oosterhout, The Netherlands). Patients admitted for day treatment and admissions of less than two days were excluded.

The intervention is part of the routine quality improvement and therefore no formal approval of the ethics committee was needed. Patients data were registered anonymously in Castor Electronic Data Capture (Ciwit BV, Amsterdam, The Netherlands).

Intervention

The hospital has a local digital antibiotic formulary based on the national formulary of the Dutch Working Party on Antibiotic Policy (SWAB). This formulary is constantly revised and updated. Advice regarding optimal antibiotic treatment was based on the local antibiotic formulary and a local protocol on antibiotic treatment and drug challenge in patients reporting antibiotic allergy. In addition, none of the cephalosporins used in our hospital share similar side chains with penicillins and can therefore be used in penicillin-allergic patients [15].

The severity of allergy symptoms was determined based on Table I, which is adapted from Cox et al. [16]. After a risk assessment of the severity and last exposure to the antibiotic of allergy, it could be decided to perform a drug challenge (Figure 1). A drug challenge was performed in case the

antibiotic of allergy was the preferred treatment and the symptoms of allergy were mild and delayed and the last exposure to the antibiotic of allergy occurred longer than 12 months ago. A drug challenge was also performed in patients with an immediate type reaction with one or two symptoms where the last exposure to the antibiotic of allergy occurred more than 10 years ago [13]. In all other cases, the patient was not eligible for a drug challenge and was referred to an allergologist for further testing and advise.

In case of reported penicillin allergy, patients were orally challenged with 500mg amoxicillin or 500mg/125mg amoxicillin-clavulanic acid depending on the preferred treatment followed by 60 minutes observation. If no immediate reaction was observed, the full dose of the preferred penicillin was given orally or intravenously. For other antibiotic allergies, the patient was orally challenged with the full dose of the preferred antibiotic during the IV-to-oral switch. The drug challenge was performed under medical supervision with the presence of an emergency kit and an already existing intravenous line to deal with potential anaphylactic reactions. Patient consent was asked and documented in the EMR before doing a drug challenge.

The antimicrobial stewardship intervention was a combination of the following components: educating physicians, handing out pocket-sized cards and providing recommendations in the EMR. Before the start of this intervention study, the relevant background information on antibiotic allergies and possibilities of performing a drug challenge was presented during a training for the physicians. Pocket-sized cards about the criteria to perform a drug challenge were distributed amongst the physicians. Lastly, the treating physician of a patient was also provided with a recommendation in the EMR in case of unnecessary deviation from the preferred treatment and a drug challenge was indicated.

Outcomes

The number of admitted patients with an antibiotic allergy was determined. Subsequently it was determined which patients received antibiotics, in how many cases the antibiotic allergy interfered with the preferred antibiotic regime and how many patients could be challenged. Patients who underwent a drug challenge were monitored by the treating physician for immediate reactions as well as delayed reactions during the entire hospitalization.

Statistical analysis

Descriptive statistics were reported using frequencies for categorical data and means or medians for continuous parameters. Statistical analyses were performed using SPSS Statistics 25 (IBM Corp, Armonk, NY, USA)

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Results

Characteristics of the study population

The characteristics of patients with reported antibiotic allergy are summarized in Table II. Throughout the study period, 492 patients were identified accounting for 558 hospital admissions. The mean age of the patients was 66.7 ($\pm$ 17.4) years and 72.4% was female. Allergy to one specific antibiotic or antibiotic group was documented for 340 (69.1%) patients. Allergy to two antibiotic groups was documented for 82 (16.7%) patients and 70 (14.2%) patients had documented allergies for three or more antibiotic groups. Of the patients reporting an allergy to three or more antibiotic groups, 43 patients had documented allergy to penicillins, cephalosporins and carbapenems.

The most common reported antibiotic allergy was to penicillins, which was reported by 320 (65.0%) patients. Of approximately 60% of these patients, it was known that the specific penicillin of allergy was amoxicillin or amoxicillin-clavulanic acid. The most reported symptoms were rash and pruritus, which were reported by 192 (39.0%) and 95 (19.3%) patients, respectively.

The described symptoms of allergy in 68 (13.8%) patients were categorized as adverse events or coincidental symptoms unrelated to the use of antibiotics. The severity of symptoms was often mild, but there were cases wherein the reported symptoms were severe, such as drug induced liver injury, achilles tendon rupture and nerve impairment. In these cases, the specific antibiotic was contraindicated and a challenge was not performed. Of the remaining 424 patients, 188 were graded as mild, 53 were graded as moderate and 40 were graded as severe reaction. The allergy severity of 143 patients could not be determined due to no documentation or no recollection of symptoms by the patient.

Antibiotic treatment during hospitalization

In 323 (57.9%) admissions an antibiotic was prescribed. Antibiotic prophylaxis was given in 149 (46.1%) admissions, antibiotic therapy was given in 155 (48.0%) admissions and in 19 (5.9%) admissions both antibiotic prophylaxis and therapy was given.

In 131 (40.6%) admissions the antibiotic allergy did not interfere with the preferred antibiotic treatment (Figure 2). In 99 (30.7%) admissions cephalosporins were the preferred treatment and were chosen correctly in penicillin-allergic patients. In 93 (28.8%) admissions, the antibiotic allergy

label interfered with the preferred antibiotic treatment. Based on the severity of symptoms, 68 of these patients were eligible for a drug challenge. The remaining 25 cases were not eligible for a drug challenge. This was due to the severity of symptoms, recent exposure to the antibiotic of allergy or atypical symptoms where a severe reaction could not be ruled out.

Drug challenge and consequences

There were 11 patients who did not undergo a drug challenge. In three cases the indication for the antibiotic was surgical prophylactic use and the recommendation in the EMR came too late. In eight cases the recommendation for a drug challenge was given, but the physician chose to continue the alternative treatment. Fifteen patients had a documented allergy to all beta-lactams, while patients themselves could only confirm the allergy to penicillins. Therefore, they could receive a cephalosporin or carbapenem as empirical treatment during hospital admission. No patients developed an allergic reaction in this group to cephalosporins or carbapenems. Of the remaining 42, 40 patients had a history of a mild delayed reaction and two patients had a history of a possible immediate reaction which occurred longer than 10 years ago. 40 (95%) patients had an uneventful challenge and could be treated with the preferred antibiotic treatment. The other two (5%) patients developed a non-severe skin reaction after drug challenge and continued an alternative antibiotic treatment.

Use of reserve antibiotics and rationality of alternative treatments

A total of 25 patients were not eligible for a drug challenge and 11 patients were eligible but did not undergo a drug challenge. Of these 36 patients, 11 (31%) patients received reserve antibiotics such as meropenem, moxifloxacin, vancomycin, ceftriaxone and ciprofloxacin. All these deviations in treatment were according to the local antibiotic formulary or were rational in case the formulary did not provide an alternative for the antibiotic of allergy, except for one case. This specific case was the only one where a cephalosporin was avoided in a penicillin-allergic patient.

Discussion

In this study, we investigated the impact of reported antibiotic allergy on the antibiotic treatment of hospitalized patients and implemented a proactive antimicrobial stewardship intervention to prevent unnecessary deviation from the preferred antibiotic treatment and to promote drug challenge in order to de-label patients. In almost a third of the admissions, antibiotic allergy labels interfered with the preferred antibiotic treatment. Based on a risk assessment, a drug challenge was indicated in most of these cases and the preferred antibiotic treatment could be given after an uneventful drug challenge. Only 5% of patients with mild delayed or possible immediate allergies had a non-severe skin reaction after drug challenge.

This is an important finding since antibiotic allergies are reported frequently and will likely influence the antibiotic treatment choice during hospitalization. Macy and Vyles showed that approximately 5% of patients with a history of low risk penicillin allergy of both the immediate and delayed reaction type undergoing drug challenge developed an allergic reaction. Subjective reactions were more common than objective reactions, meaning that the actual rate may be even lower [17]. In most studies drug challenges were executed in the outpatient setting by an allergologist [10,11,18–21]. The drug challenge in our study was conducted in the clinical setting as part of an antimicrobial stewardship intervention and performing a drug challenge in selected cases in the clinical setting appeared to be safe, whereas the results correlated well with those of studies conducted by allergologists.

This study also showed that in our hospital, especially in surgical antibiotic prophylaxis, cephalosporins were not avoided in case of a penicillin allergy, except for one case. Other studies showed that early generation cephalosporins were prescribed less often in penicillin-allergic patients [4,22,23]. Although it appears that cephalosporins are not avoided in penicillin-allergic patients in our hospital, the misperception that all beta-lactams should be avoided in these patients still seems to be present in the primary care setting. Allergy to carbapenems was reported for almost 10% of patients in this study, while a recent meta-analysis showed that the risk of carbapenem cross-reactivity in penicillin-allergic patients is less than 1% [24]. None of the patients with reported allergy to all beta-lactams in our study developed an allergic reaction to cephalosporins or carbapenems. Altogether this seems to indicate that these patients had a reported penicillin allergy and were falsely labelled with a beta-lactam allergy.

Antibiotic allergy labels are also related to the use of reserve antibiotics, such as carbapenems [25,26]. Powell et al. reported that the use of meropenem was approximately six times higher in hospitalized patients reporting a penicillin allergy compared to patients with no penicillin allergy [26]. We did not compare the use of reserve antibiotics in patients with and without antibiotic allergy. However, when the first-line antibiotic was avoided due to a reported antibiotic allergy, almost a third of the patients in our study received a reserve antibiotic.

Approximately 70% of the patients included in this study were female. This female predominance is in accordance with previously conducted studies on antibiotic allergies [4,23,26]. Loikas et al. showed that women were prescribed antibiotics more often compared to men, which may partially explain why this sex distribution has been seen across different studies on antibiotic allergy [27].

Strengths and limitations of this study

Studies conducted on antibiotic allergy often focused on the relation between an allergy label and study outcomes. This study prospectively followed patients with antibiotic allergy labels and determined in which cases the allergy label genuinely interfered with antibiotic treatment, which is a strength.

Patients who were challenged and had an uneventful re-exposure continued their treatment. In the hospital these patients were closely monitored on a recurring allergic reaction. Some of these patients continued the antibiotic treatment at home after discharge. It is not known whether these patients developed a delayed reaction at home, which is a limitation.

In addition, symptoms of allergy were reported by patients themselves, which is dependent on their perception and recollection. Therefore, it was often difficult to determine whether allergies were immediate or delayed, which is another limitation. Although details of an allergic reaction are not always known, this study showed that it was still possible to select patients to undergo a drug challenge based on a risk assessment.

Lastly, the number of patients challenged in our study was relatively small, which is a limitation. Our study shows that an antimicrobial stewardship intervention to identify patients who would be eligible for a drug challenge is effective and safe. However, larger studies on performing a direct drug challenge in the clinical settings are needed to confirm our findings.

Clinical implications and future research

Since patients often suffered a mild reaction and the risk of a recurrent reaction is low in these patients, it should be stressed to obtain a more detailed history of the reported antibiotic allergy before deviating to an alternative antibiotic. At least an estimation of the year of the allergic reaction and description of symptoms and severity should be noted in the patient's file. The majority described mild skin reactions, gastrointestinal symptoms or no recollection of symptoms or allergy. One could assume that no recollection often indicates a mild reaction as it did not impact the patient as much to still remember the event. In a recent review of Banks et al. an unknown history of allergy is also considered to be of low risk [28].

In addition, performing a drug challenge under medical supervision without prior skin testing in selected cases should be considered as an alternative strategy to de-label patients with an antibiotic allergy. Studies have shown that skin tests have a low positive predictive value, whereas direct oral challenge in a secure setting is a safe and effective way to de-label patients [10,28,29]. Especially since not all hospitals offer skin testing on site and in facilities that do offer skin testing waiting lists do apply.

Future research should focus on removing antibiotic allergy labels from the EMR when drug challenge is successful and on preventing reintroduction of the allergy label during future hospitalizations [30]. Since most antibiotic allergy labels originate in the primary care setting, efforts should also be focused on optimizing antibiotic allergy labelling and de-labelling strategies in the primary care setting.

In conclusion, in almost a third of hospital admissions of patients with a reported antibiotic allergy, the reported antibiotic allergy interfered with the preferred antibiotic treatment. An antimicrobial stewardship intervention, consisting of a training, pocket cards, and providing written recommendations in the EMR on antibiotic treatment and when to consider a drug challenge, can be used in selected cases to provide these patients with the preferred antibiotic treatment, limit the use of reserve antibiotics and to de-label patients from their antibiotic allergy label after an uneventful re-exposure.

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Conflict of interest statement

None declared.

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Table I The classification of the severity of allergy symptoms. (Adapted from Cox et al. J Allergy Clin Immunol. 2010)

Mild

Rash, rhinitis, gastrointestinal symptoms

Moderate

Urticaria, oedema, mild dyspnoea, fever, indication for hospitalization and absence of the criteria mentioned under severe

Severe

Angioedema, stridor, severe dyspnoea, hemodynamic instability, (nor)epinephrine use, severe skin reactions (Stevens Johnson Syndrome, toxic epidermal necrolysis), admission to monitoring ward

Table II Baseline characteristics of hospitalized patients reporting an antibiotic allergy

Characteristics	Patients reporting antibiotic allergy
Total patients	492
Mean (SD) age, years	66.7 (17.4)
Female sex	356 (72.4)
Length of stay in days, median (IQR)	4 (2-7)
Antibiotic allergy reported	
Penicillins	320 (65.0)
Tetracyclines	60 (12.2)
Cephalosporins	59 (12.1)
Sulfonamides	56 (11.4)
Quinolones	55 (11.2)
Nitrofurantoin	53 (10.8)
Carbapenems	46 (9.3)
Macrolides	38 (7.7)
Lincosamides	24 (4.9)
Other antibiotics	40 (8.1)
Reported symptoms	
Rash	192 (39.0)
Urticaria and other skin reaction	34 (6.9)
Pruritus	95 (19.3)
Angioedema*	39 (7.9)
Anaphylactic shock	3 (0.6)
Gastrointestinal symptoms	38 (7.7)
Severity of allergy symptoms	
Mild	188 (38.2)
Moderate	53 (10.8)
Severe	41 (8.3)
Adverse event	68 (13.8)
Unknown	142 (28.8)
- no recollection	57 (11.6)
- not documented	85 (17.3)
Total hospital admissions	558
Specialism of admission	
Surgery	109 (19.5)
Internal medicine	91 (16.3)
Orthopedics	59 (10.6)
Respiratory	55 (9.9)
Gynaecology & obstetrics	46 (8.2)
Cardiovascular	43 (7.7)
Neurology	40 (7.2)
Gastroenterology	35 (6.3)
Urology	29 (5.2)
Other	51 (9.1)

SD, standard deviation; IQR, interquartile range. Values are numbers (percentages) unless stated otherwise.

*includes swelling of the face.

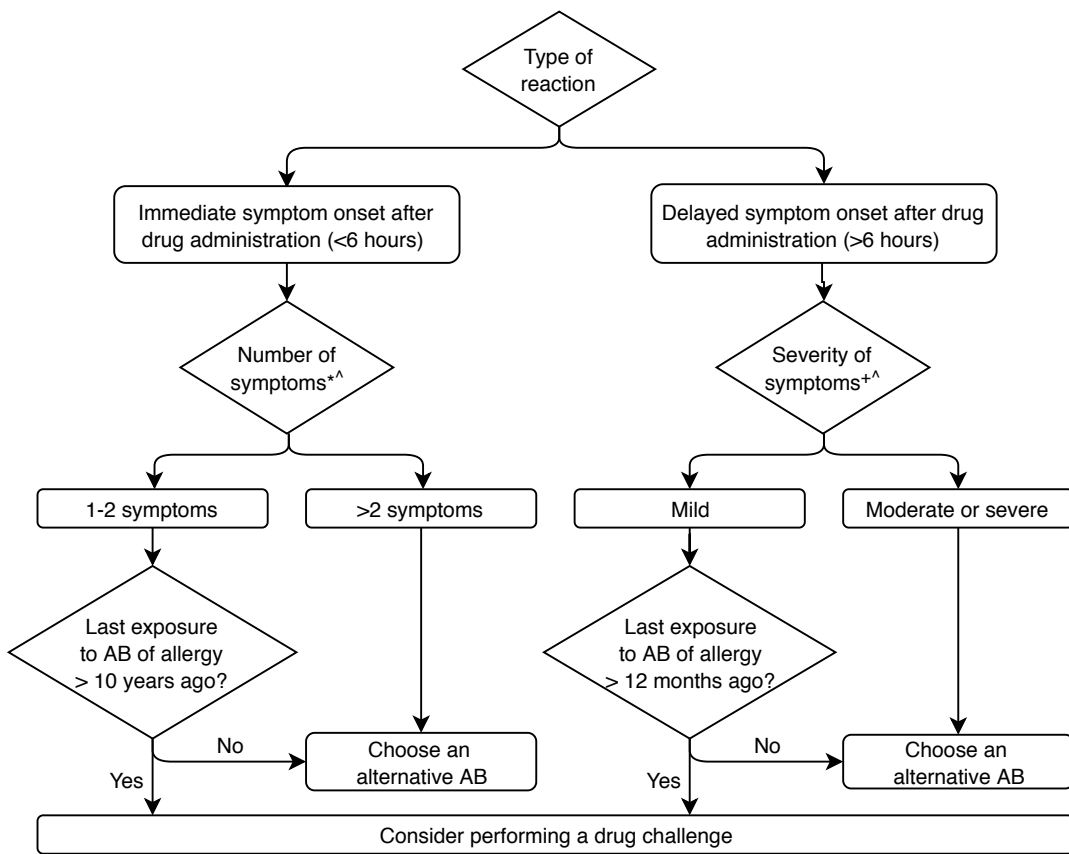


Figure 1 The antibiotic allergy policy on when to consider performing a drug challenge based on the symptom onset, number or severity of symptoms and time of last exposure to the antibiotic of allergy. AB, antibiotic. *regardless of symptom severity. + based on the symptom with the highest severity. ^ according to Table I.

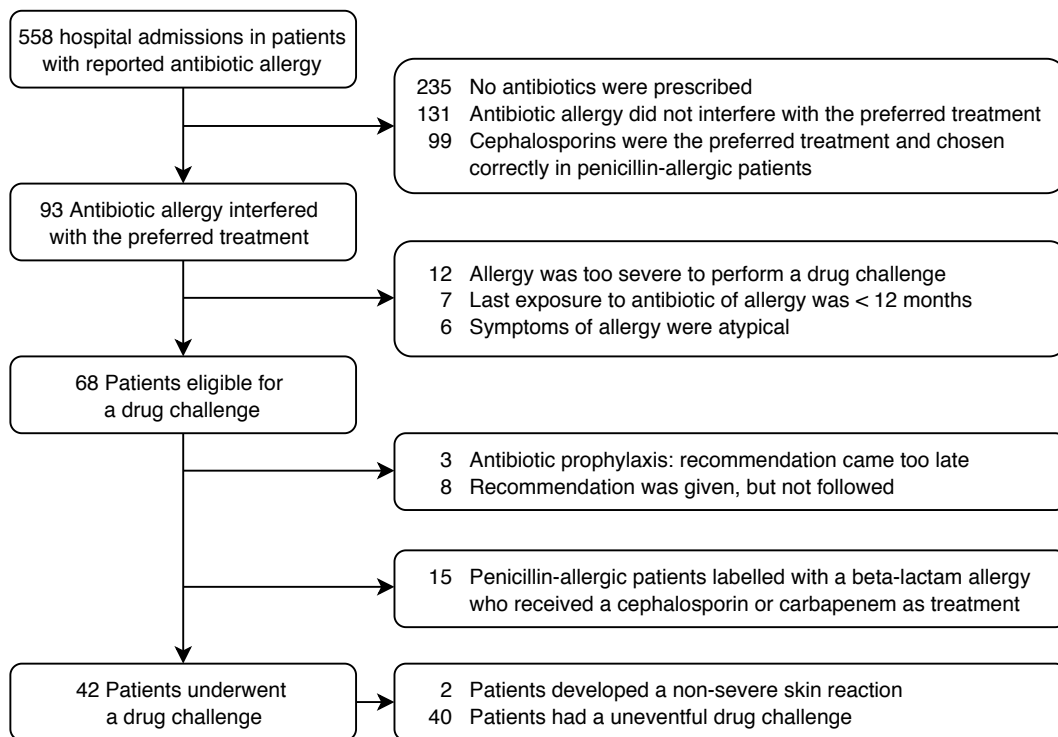


Figure 2 The impact of reported antibiotic allergy on the antibiotic treatment, the number of patients undergoing drug challenge and the consequences of it.