RESEARCH LETTER

De-labelling antibiotic allergy through five key questions

To the Editor,

The selection of an antibiotic for treatment of bacterial infection should ideally be based on clinical findings, guideline recommendations and microbiological test results. Meanwhile, up to 10% of the European and North American population report to be allergic to penicillin.[1] Once a suspicion of allergy is made, treating physicians find themselves forced to administer an alternative antibiotic, even if a β-lactam would be the antibiotic of choice. As a result, suspected allergy to standard antibiotics commonly triggers the inappropriate use of broad-spectrum or reserve antibiotics and may thus catalyse the problem of microbial resistance.

In order to meet this important topic, allergists around the world need to ensure that documents attesting antibiotic allergy are only issued after thorough history and appropriate testing. If immediate allergy testing in case of an acute infection is not an option due to the lack of time or equipment, the risk of antibiotic allergy should be categorized as being high or low to determine whether the use of alternative antibiotics is really necessary. Several algorithms aiming to question pre-existing labels of antibiotic allergy have been published in recent years.[2-4] While the proposed algorithms accurately consider different reaction patterns by covering the frequent to the extremely rare, they tend to be complex, time-consuming and hardly suitable for everyday practice.

Patients attending our clinic between January 2017 and May 2019 underwent standardized questioning whenever a history of antibiotic allergy was given. If antibiotic therapy was necessary, the medication of first choice was administered even if an allergy to this antibiotic or corresponding class of antibiotics was reported—provided that allergy was considered unlikely according to our algorithm (Figure 1). The antibiotic was administered in all cases under close medical supervision, either as part of inpatient treatment of an infection or in context of a controlled provocation after negative skin testing. During provocation testing in the outpatient clinic, patients were monitored until 4 hours after the last dose; they were advised to present for objective examination if any symptoms developed within the next days.

The evaluated algorithm is based on the assumption that antibiotic allergy most commonly triggers either an acute anaphylactic reaction within a few minutes of intake or infusion or an exanthematous skin rash beginning several hours to days later.[5,6] *Question one*

(Figure 1) aims to identify patients with a history of pharmacological side-effects or any complaints unrelated to antibiotic treatment. This includes a history of urticaria or exanthem if the onset was more than two days or more than one week, respectively, after discontinuation of antibiotic treatment. The question is to be answered with "no" in cases who are unable to reliably discriminate urticaria from exanthem. An urticarial or exanthematous rash in childhood and adolescence is mostly caused by bacterial or viral infections,[7] while genuine allergy is rare (*question two*).

Question three was developed to discern IgE-mediated anaphylaxis from spontaneous or infection-triggered urticaria. An IgE-mediated anaphylactic reaction develops within a few minutes after exposure to the eliciting agent and mostly include not only cutaneous signs, but varying combinations of other organ symptoms. Anaphylaxis to antibiotics is in Europe nowadays most commonly caused by certain cephalosporins including cefazolin, ceftriaxone and cefuroxim. If an episode of urticaria without systemic signs of anaphylaxis relapses for several ongoing days despite stopping antibiotic treatment, allergy can be reasonably ruled out. Any short-term episode of urticaria occurring in close temporal relationship to the administration of an antibiotic would result in a referral to *question five*. In the absence of extracutaneous signs of anaphylaxis, IgE-mediated allergy is rather unlikely, and the suspected antibiotic may be re-administered at an acceptable residual risk.
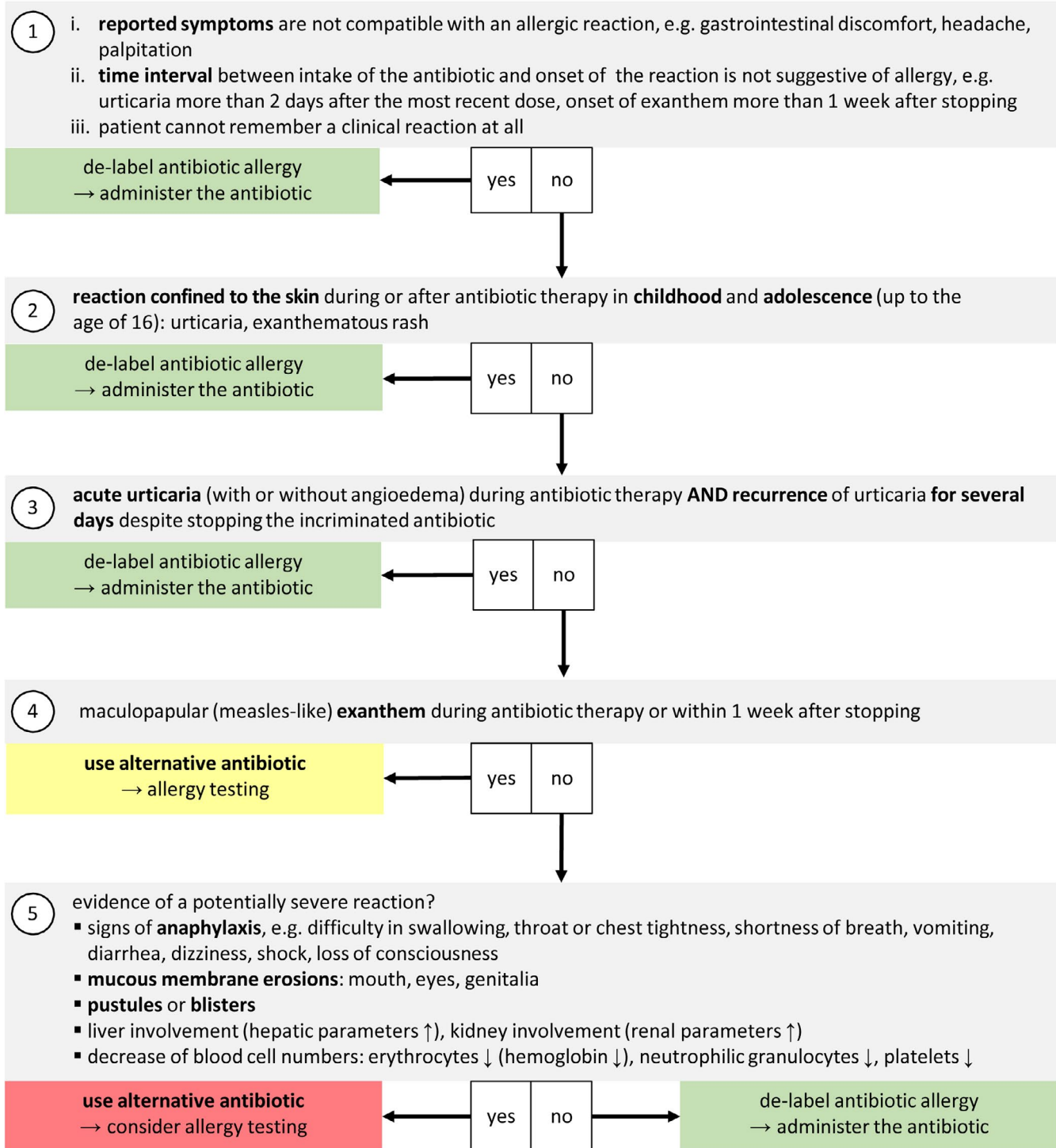
Delayed-type allergic hypersensitivity to antibiotics covers a wide spectrum of clinical reaction patterns, the "uncomplicated" exanthem, a maculopapular (measles-like) rash without relevant systemic symptoms being by far the most common. Patients with pre-existing sensitization develop the exanthem mostly within a few hours to 2 days upon re-exposure to the eliciting antibiotic. Adult patients with a history of exanthem in appropriate timely relation to antibiotic therapy should undergo allergy testing (question 4). Compared to other antibiotics, the aminopenicillins (amoxicillin, ampicillin) are by far the most common elicitors of an exanthematous rash.

Question five aims to retrospectively identify high-risk reactions. This includes both IgE-mediated anaphylaxis and less frequent manifestations of delayed-type reactions such as pustular exanthem, fixed drug eruption and the even rarer systemic hypersensitivity reaction with accompanying hepatitis, or a severe bullous skin

1.
   i. **reported symptoms** are not compatible with an allergic reaction, e.g. gastrointestinal discomfort, headache, palpitation
   ii. **time interval** between intake of the antibiotic and onset of the reaction is not suggestive of allergy, e.g. urticaria more than 2 days after the most recent dose, onset of exanthem more than 1 week after stopping
   iii. patient cannot remember a clinical reaction at all

   de-label antibiotic allergy → administer the antibiotic ← yes | no ↓

2. **reaction confined to the skin** during or after antibiotic therapy in **childhood** and **adolescence** (up to the age of 16): urticaria, exanthematous rash

   de-label antibiotic allergy → administer the antibiotic ← yes | no ↓

3. **acute urticaria** (with or without angioedema) during antibiotic therapy **AND recurrence** of urticaria **for several days** despite stopping the incriminated antibiotic

   de-label antibiotic allergy → administer the antibiotic ← yes | no ↓

4. maculopapular (measles-like) **exanthem** during antibiotic therapy or within 1 week after stopping

   use alternative antibiotic → allergy testing ← yes | no ↓

5. evidence of a potentially severe reaction?
   - signs of **anaphylaxis**, e.g. difficulty in swallowing, throat or chest tightness, shortness of breath, vomiting, diarrhea, dizziness, shock, loss of consciousness
   - **mucous membrane erosions**: mouth, eyes, genitalia
   - **pustules** or **blisters**
   - liver involvement (hepatic parameters ↑), kidney involvement (renal parameters ↑)
   - decrease of blood cell numbers: erythrocytes ↓ (hemoglobin ↓), neutrophilic granulocytes ↓, platelets ↓

   use alternative antibiotic → consider allergy testing ← yes | no → de-label antibiotic allergy → administer the antibiotic

FIGURE 1 Algorithm for managing patients with a medical history of antibiotic allergy. If the path ends in a green field, the antibiotic in question may be administered. Yellow and red fields indicate that allergy testing is necessary and an alternative antibiotic should be given when treatment is immediately needed

reaction, suspicion of which clearly justifies the use of an alternative antibiotic.

The algorithm was applied in 200 patients; the results are summarized in Figure 2 and Table S1 (online only). β-lactams were the most commonly incriminated class of antibiotics. Standardized questioning corroborated the suspicion of antibiotic allergy in 70 patients (58x yes in question four and 12x yes in question five); therefore, potentially severe clinical reactions were suspected in only 6.0% of the series. In 48 cases, question one was answered with yes, because neither type nor temporal course of the described complaints was compatible with an
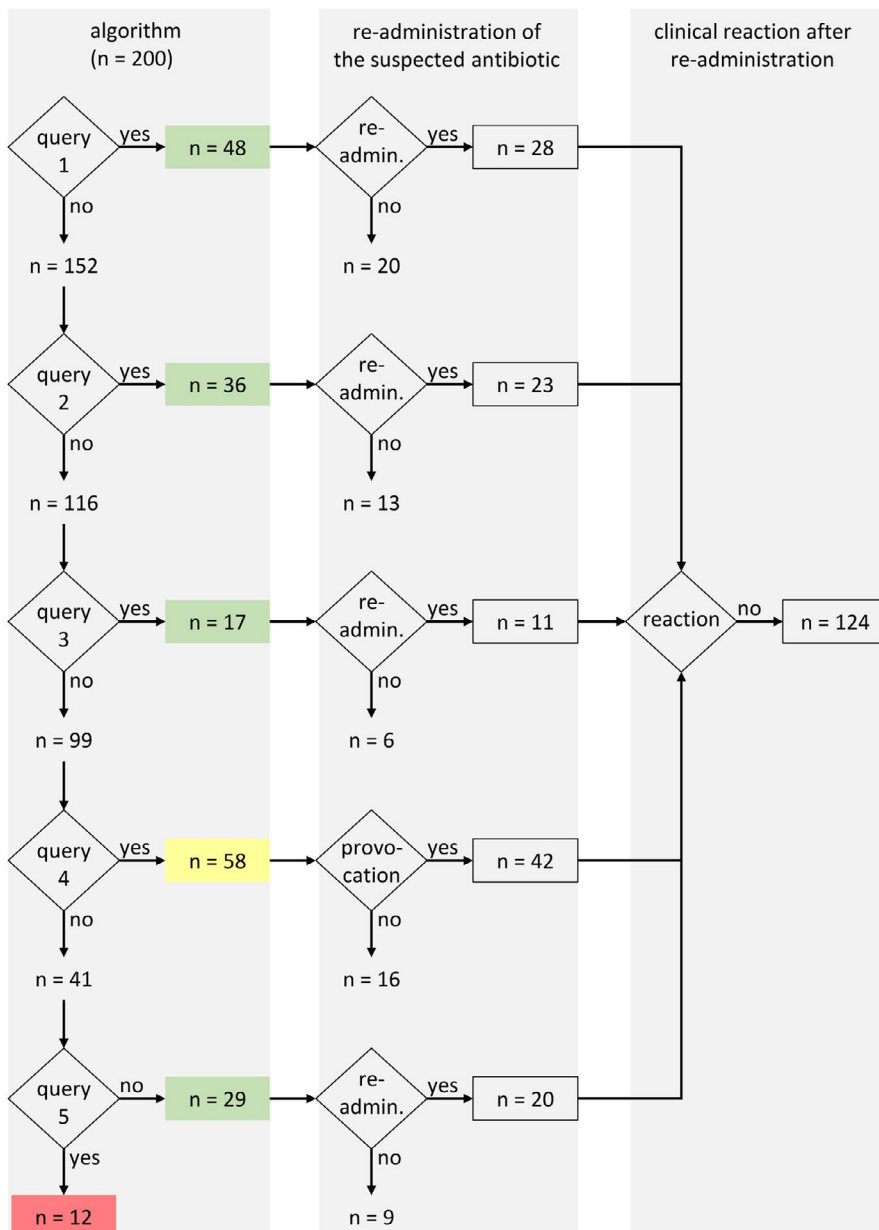
FIGURE 2 The algorithm was applied in 200 cases. A total of 124 patients tolerated the incriminated antibiotic without any reaction: 82 cases in form of a therapeutic administration because antibiotic treatment was urgently needed, 42 in a controlled provocation after negative skin testing

allergic reaction. In some cases, antibiotic allergy was considered very unlikely despite documentation in records because patients cannot remember any reaction. In 48 out of the total cohort of 200 cases, there was no urgent need for treatment with the incriminated antibiotic, and 16 patients (out of the 58 answering yes in question four) refused allergy testing (Figure 2). All 124 patients who received the suspected antibiotic again tolerated the re-administration: 82 were treated with the antibiotic as indicated (mostly because of soft tissue infection), and 42 received the antibiotic in a controlled provocation following negative skin testing (Figure 2). A total of 104 patients received exactly the same antibiotic that caused the initial reaction, whereas in 20 patients a different substance out of the β-lactam group was administered: 11x aminopenicillin instead of the incriminated phenoxymethylpenicillin, 4x cephalosporin instead of phenoxymethylpenicillin, 4x cephalosporin instead of aminopenicillin and 1x aminopenicillin instead of cephalosporin.

Our data show that, in the majority of cases, the antibiotic of choice can be safely administered despite allergy claims. The presented algorithm takes into account both the frequency of certain clinical reactions and—based on individual patient's history—the risk of a severe allergic reaction categorized as being low or high. The method's validity is limited by the potential inaccuracy of retrospective data with regard to time intervals and clinical symptoms. As a consequence, both the clinician and the patient are obliged to accept a residual risk.

Claims of allergy commonly hamper guideline-directed antibiotic therapy and trigger the use of alternative antibiotics, which may be less effective, have more side-effects and/or promote the development of microbial resistance.[8] Correction of unjustified allergy claims constitutes a pivotal element in the fight against increasing antibiotic resistance.[9] Targeted questioning according to the presented algorithm permits to remove the label of antibiotic

allergy in the majority of cases. Though questionnaire-based de-labelling does not fully exclude a reaction upon re-exposure of the antibiotic in question, the risk of a severe reaction is considered to be low.

However, further validation studies are needed to evaluate the proposed algorithm, in populations including a substantial proportion of patients with confirmed antibiotic allergy, in order to determine its sensitivity and specificity.

CONCLUSION

Guideline-directed anti-infectious therapy is commonly hampered by reports of antibiotic allergy. Standardized questioning permits the administration of first-line antibiotic treatment in a substantial proportion of cases by sorting out unjustified suspicions while reliably identifying potential high-risk patients.

Although the development of an algorithm to reduce unnecessary prescription of alternative antibiotics is likely to be feasible and safe, formal validation using a methodologically rigorous approach is required before such an algorithm may be implemented for routine application.

CONFLICT OF INTEREST
The authors declare no conflict of interest.

AUTHOR CONTRIBUTIONS
AT initiated data evaluation. AR, KR, AT and JS analysed and interpreted the data. AR and AT wrote the first draft of the article. AR, KR, JS and AT revised and edited the manuscript and approved the final version.

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SUPPORTING INFORMATION
Additional supporting information may be found online in the Supporting Information section.