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National expert consensus on the management of antibiotic prophylaxis in surgical patients with a penicillin allergy label based on the Delphi method

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Background: Patients with a penicillin allergy label have an increased risk of surgical site infection. Although a decision tree was published in 2019 to define which patients could benefit from direct cephalosporin use in the perioperative setting, this strategy remains unvalidated. This consensus statement aimed to adapt it based on an expert consensus to cover persisting caveats and to adapt it to an environment with poor allergist resources.

Methods: Perioperative antibiotic prophylaxis and allergy experts were invited to participate. The Delphi method was implemented using an online-secured network. The panellists were given 3 weeks to answer each round. A consensus was reached if more than 75% of the experts rated the item ≥ 7 and if less than 25% rated the item ≤ 3 .

Results: Sixteen experts participated. A high level of agreement was obtained after four rounds, defining four categories of the index reaction: unknown, not compatible, or compatible with an immediate or delayed hypersensitivity

reaction. Twelve items were defined to stratify the risk of true penicillin allergy according to the index reaction history. The experts agreed that patients with high-risk reactions could benefit from either an allergy work-up or beta-lactam alternatives use. Those at low risk could benefit from direct cephalosporin administration.

Conclusions: This resulted in an adapted decision tree to promote cephalosporin prescription in patients with penicillin allergy labels. It will be used in a stepped-wedge prospective multicentric randomized study to assess its applicability and acceptability to promote first- and second-generation cephalosporin administration in the perioperative period.

Introduction

Surgical site infection (SSI) occurs within 90 days after surgery and up to 1 year after surgery in patients receiving implants,¹ with a 2% incidence.^{2,3} SSIs are responsible for an increased length of stay and mortality with important related health costs.^{4,5} Within other factors, prevention of SSI may rely, when indicated, on timely administration of selected antibiotic prophylaxis,¹ depending on the surgical type and the microbiological species targeted. β -Beta-lactam antibiotics are the primary class family recommended during elective surgeries.⁶ They target the main organisms causing SSIs: skin flora, including *Staphylococcus aureus* (*S. aureus*) and coagulase-negative staphylococci, in association with Gram-negative rods and *enterococci* in clean-contaminated procedures. First- and second-generation cephalosporins are mostly recommended as they represent a good compromise between antimicrobial spectrum, cost, absence of adverse effects, selection of resistant species and proof of efficacy. Therapeutic alternatives (mostly vancomycin or clindamycin) are recommended for patients with reported penicillin allergies. However, no strategies are available to decide whether or not to switch to a beta-lactam alternative based on the patient's allergy history. Indeed, the 2013 clinical guidelines on antimicrobial prophylaxis in surgery only recommended to avoid cephalosporins in patient with IgE-mediated reaction and severe cutaneous delayed reactions, without more details for minor reactions, non-severe delayed reactions or unknown clinical symptoms.⁷

Epidemiologic studies have reported a 10% rate of patients reporting a penicillin allergy.^{8–10} However, most of these patients never benefited from an allergy work-up, and could be labelled as allergic because of a childhood non-specific reaction or from an unrelated reaction.¹¹ Penicillin allergy occurs in 7%–23% of patients who have a history of penicillin allergy, depending on age, delay after drug intake, severity of the reaction or recruitment mode.^{12,13} Most epidemiological studies have reported a 20%–25% cephalosporin prescription rate in the operating room for patients with a penicillin allergy label,^{14–16} which varies from less than 10%¹⁷ to 40%.^{18,19} Patients with a penicillin allergy label have been reported to have a 50% increased risk of SSI,²⁰ and an increased risk of infections related to methicillin-resistant *S. aureus* and *Clostridioides difficile*.^{20–23}

Early cephalosporin formulations were likely to be contaminated with penicillin, leading to estimates of β -lactam cross-reactivity higher than 2%. Currently, β -lactam true cross-reactivity is mostly predicted by shared R1 side chains,²⁴ although it could be more rarely based on the core β -lactam ring or the R2 side chain.

R1 side chains are displayed by all beta-lactams, whereas only cephalosporins display the R2 chain at carbon C3 (Figure 1). Identical R1 side chains pose the greatest risk in patients with IgE-mediated or T-cell-dependent hypersensitivity. Third- and fourth-generation cephalosporins and some first- and second-generation cephalosporins (including cefazolin) do not share a common R1 chain with penicillins.²⁵ As such, the rate of allergy cross-reactivity between penicillins and cephalosporins is likely to be less than 1%,^{24,26–30} with a 0.7% estimate according to a recent meta-analysis.³¹

In 2019, an international group of experts published a flow chart to promote cephalosporin prescription in these patients while reducing the need for specialist allergist review.²³ We aimed to evaluate this decision tree in France. Unfortunately, it did not seem applicable by non-experts in perioperative allergies as it stands because of remaining caveat, such as the management of low-risk reactions,²⁵ and of the scarcity of allergists. The expert consensus presented herein is the adaptation of the decision tree using Delphi method. Its objective is not to remove the penicillin allergy label but to support the use of cephalosporin depending on the probability of a real penicillin allergy. The validated algorithm will be used in a stepped-wedge prospective multicentre randomized study that aims to evaluate the feasibility and acceptability of a decision tree to promote the prescription of first- and second-generation cephalosporins in the perioperative setting among patients with a penicillin allergy label (NCT06067919).

Materials and methods

Methods

Ethics approval for the PROPHYLAL study (Delphi method and patient inclusion) was obtained from the Comité de Protection des Personnes Ouest V on 16 May 2023 (reference: 2023-A00664-41).

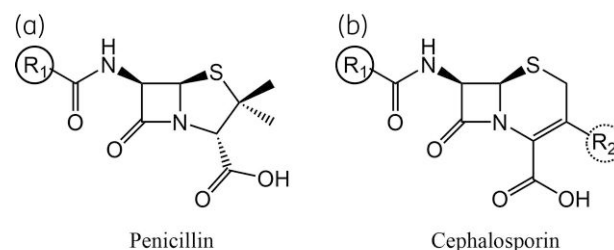


Figure 1. Chemical structures of (a) penicillin and (b) cephalosporin. The R1 side chain is indicated in plain circle, and R2 in dotted circle.

The Delphi method is a well-known process for obtaining group consensus in health care, as it encourages decision-making and new ideas to be formed by whole group feedback.³² The method involves several rounds of anonymous questionnaires. After each round, propositions can be improved based on aggregated responses from the previous round. It is widely accepted for achieving the convergence of opinions concerning knowledge solicited from experts, and it has been adopted for priority setting in medicine.³³

Panellist recruitment

To ensure the broad input of professionals from different geographical settings, a national panel of multidisciplinary experts was recruited, including allergists, anaesthesiologists and intensive care physicians, infection control physicians and infectious disease specialists. All of them had an expertise in antibiotic allergies and/or in healthcare-related infectious diseases. In France, surgeons are not involved in antimicrobial stewardship and were thus not invited to participate. We created an e-mail invitation template outlining the project and explaining the requirements of prospective panellists, which allowed them to participate voluntarily. The number of rounds was not defined *a priori*, as it was stated that it would depend on the answers provided to each round. Anonymous demographic data, including age, gender, type of centre, years of professional experience and area, were gathered to determine the location of practice and experience. Based on previous publications, 15–20 panellists were targeted.

Delphi statements

The Delphi method was applied between January 2023 and June 2023. Panellists were given 2 weeks for each round to answer each round. Reminder e-mails were sent on Days 7 and 10 to the experts who had not yet replied. The results were provided anonymously, with only the medical speciality of the responder available. A 3-week interval between rounds was used to summarize the data, design the updated decision tree based on scores and comments provided by the panellists and then program the next round.

Survey design and data collection

The questionnaires for the Delphi statement were distributed using a web application developed by the clinical research department of Bichat Hospital. All the documents were provided in French. For each intersection in the decision tree, the experts were asked if they agreed with the proposition and if the wording was sufficiently precise. The experts were also asked if, in their opinion, the number of options after an intersection covered all the situations. The participants were asked to rate their agreement with each question on a Likert scale ranging from 1 (strongly disagree) to 9 (strongly agree).³⁴ For each value equal to or less than 3, the experts had to provide a comment to explain their opposition to the proposal. Regardless of the score, an open text box for suggestions or opinions was also available at the end of each question to gather suggestions or opinions.

After full validation, an additional survey was provided to evaluate the experts' workload imposed by the Delphi method, their satisfaction with their comments handling and their willingness to participate again. Finally, they were asked if they believed that the decision tree improved after the Delphi process and could be applied in the operating room by anaesthesiologists.

Data analysis

The experts' responses were collected anonymously. Overall consensus for each statement was gathered according to the score number obtained. A consensus was reached if more than 75% of the experts rated the item within the highest region of the scale (≥ 7 on the 9-point Likert

scale) and if less than 25% of the experts rated the item within the lowest region of the scale (≤ 3 on the 9-point Likert scale).

The median and interquartile range are presented, or the proportion is presented when applicable. Statistical analyses were performed with R software version 4.1.0 (R Foundation, Vienna, Austria).

Results

Among the 19 experts invited to participate, two declined because of scheduled conflicts, and one never answered either the first or subsequent e-mails. The final panellist team comprised five anaesthesiologists and intensivists, four allergists, four infection control physicians and three infectious disease specialists (Table 1). All 16 experts participated in rounds 1–4 and in the additional survey. Four rounds were necessary to reach a global consensus over a 5-month period. All experts' answers were weighted equally.

The first version of the tree distinguished four categories of the index reaction: no symptoms, unknown, not compatible with an allergic reaction and compatible with an allergic reaction. The experts disagreed with that classification and required a more detailed classification. The decision tree was amended to consider four situations based on the patient's interrogation, and an agreement was reached during the second round (Table 2). The final categories were not compatible with a hypersensitivity reaction (rate 9 [9–10]), unknown symptoms (rate 9 [8.75–10]), compatible with an acute hypersensitivity reaction (rate 9 [8.75–10]) and compatible with a delayed hypersensitivity reaction (rate 8.5 [8–10]). The second round also focused on strategies for patients with unknown reactions and patients whose symptoms were noncompatible with a hypersensitivity reaction. The third and fourth rounds focused on dedicated strategies for patients with symptoms compatible with an acute or a delayed hypersensitivity reaction. For patients with severe acute reactions, the experts recommended referring the patient to an allergist and/or using

Table 1. Expert characteristics

Experts (<i>n</i> = 16)	Number
Gender female, <i>n</i> (%)	7 (43%)
Age, years	53 [43; 58]
University hospital, <i>n</i> (%)	15 (94%)
Years of experience, years	22 [14; 28]
Region, <i>n</i> (%)	
Paris	6 (38%)
South–West	5 (31%)
West	3 (19%)
South–East	1 (6%)
Centre	1 (6%)
Specialty, <i>n</i> (%)	
Anaesthesia and intensive care	5 (31%)
Allergy	4 (25%)
Infection control	4 (25%)
Infectious diseases	3 (19%)

The results are presented as medians [interquartile ranges] or percentages (absolute values).

Table 2. Experts' level of consensus on each item of the decision tree

Item	Consensus
Index reaction	
Not compatible with a hypersensitivity reaction	9 [9–10]
Unknown symptoms	9 [8.75–10]
Compatible with an acute hypersensitivity reaction	9 [8.75–10]
Compatible with a delayed hypersensitivity reaction	8.5 [8–10]
Index reaction not compatible with a hypersensitivity reaction	
The experts recommend the administration of first- or second-generation cephalosporin for surgical antimicrobial prophylaxis.	10 [9–10]
Unknown symptoms	
The experts recommend looking for any consultation requirements following the index reaction.	9 [8.75–10]
If there was a consultation, the experts recommend referring the patient to an allergist and/or using non-beta-lactam alternatives to cephalosporin for surgical antimicrobial prophylaxis.	9 [8–10]
If there was no consultation or if this is unknown, the experts recommend the administration of first- or second-generation cephalosporin for surgical antimicrobial prophylaxis.	9 [9–10]
Index reaction compatible with an acute hypersensitivity reaction	
The experts recommend evaluating the severity of the reaction.	9 [9–10]
For patients with no severe acute reaction, the experts recommend the administration of first- or second-generation cephalosporin for surgical antimicrobial prophylaxis.	9 [8.5–9.0]
For patients with severe acute reactions, the experts recommend referring the patient to an allergist and/or using non-beta-lactam alternatives to cephalosporin for surgical antimicrobial prophylaxis.	9 [9–10]
Index reaction compatible with a delayed hypersensitivity reaction	
For patients with severe delayed reactions, the experts recommend referring the patient to an allergist and/or using non-beta-lactam alternatives to cephalosporin for surgical antimicrobial prophylaxis.	9 [9–10]
For patients with no severe delayed reaction, the experts recommend to refer the patient to an allergist and/or to use non-beta-lactams alternatives to cephalosporin for surgical antimicrobial prophylaxis. Direct cephalosporin administration can be performed under specific conditions.	8 [6–8]

The results are presented as the median [interquartile range].

non-beta-lactam alternatives to cephalosporin (rate 9 [9–10]). Otherwise, for acute hypersensitivity reactions with low-risk symptoms, the experts recommended the administration of cephalosporin (rate 9 [8.5–9.0]). For most patients with severe delayed reactions, the experts recommended referring the patient to an allergist and/or using non-beta-lactam alternatives to cephalosporin.

Only the first four categories distinction were initially the subject of poor agreement, as was the handling of the low-risk

reactions (non-cutaneous symptoms and isolated cutaneous symptoms). Experts provided comments and guidance to suggest how the algorithm should be improved. These were used to amend the algorithm, allowing a high agreement over the next round.

Overall, the experts were satisfied with their participation, all of whom considered a global improvement of the decision tree over the rounds (ranking 9 [8–10]) (Figure 2).

Discussion

After four rounds and based on the initial algorithm published by experts in perioperative allergies,²³ strong agreement among multidisciplinary experts was obtained for all items of the adapted decision tree, which aims to promote cephalosporin prescription based on the probability of a true penicillin allergy according to the patient's allergy history and given the low cross-reactivity between penicillin and cephalosporin.³¹ The experts were confident that the final version of the decision tree would be applicable by all anaesthesiologists in the operating room (ranking 9 [8–9.25]).

In the perioperative setting, cephalosporins are often recommended because they offer the best compromise in terms of spectrum, site diffusion and cost. Sustaining their prescription is crucial for decreasing SSI incidence. Since 2010, several strategies have been developed to promote cephalosporins in the perioperative context in patients with a penicillin allergy label.^{22,35–37} The first was skin testing in surgical wards prior to cardiac,^{38,39} orthopaedic⁴⁰ and general surgery.¹⁰ The second relied on an allergy work-up before surgery,⁴¹ which is unfortunately minimally feasible because of the scarcity of allergists in most healthcare systems. Current CDC guidelines may also allow for an oral challenge in some cases, and skin testing in others (Cdc.gov/antibiotic-use/media/pdfs/penicillin-factsheet-508.pdf). While skin testing is not performed by non-allergist physicians in France, direct oral challenges using some tools such as the PEN-FAST could be used, although the 10% false negative rate might preclude some clinicians from using it routinely. The third strategy was based on preoperative questionnaires and decision trees that helped physicians with antibiotic prescriptions.^{42,43} In inpatient units, such a strategy led to an increase in the use of cephalosporins,^{8,37,44,45} without any major side events reported.^{23,46,47} In the perioperative context, cephalosporin prescriptions increased drastically with this strategy (all with different algorithms used) from 40% to 80% in Canada,¹⁸ from 18% to 42% in Australia⁴⁸ and from 15% to 91% in the USA.⁴⁵

The application of the decision tree published in the BJA²³ was challenging to apply in France based on the extremely limited resources available for drug allergy testing. Some situations were not fully addressed, such as minor symptoms in accordance with potential IgE-mediated reactions, or unknown symptoms. The 2013 multi-society guidelines presented the same caveats with poor details on how to classify patients with self-reported allergies.⁴⁹

Patients with unknown symptoms are common in clinical practice. The experts considered that the key question was the necessity of a consultation related to this reaction, which would suggest severe symptoms. According to the review published by Shenoy *et al.*,³⁷ patients are considered at low risk of developing

an allergic reaction to penicillin if they report an unknown reaction without features suggestive of an IgE-mediated reaction. As such, if no severe reaction occurred (i.e. no consultation required), experts considered the risk for a real penicillin allergy to be low and, thus, the direct cephalosporin administration to be safe (while still referring the patient for penicillin skin testing).

The classification of urticaria reactions is largely controversial, as it has been classified as a high,²⁵ moderate³⁷ or low⁵⁰ risk of true penicillin allergy. Shenoy *et al.*³⁷ suggested that even if most skin reactions are considered low risk, patients should be considered moderate risk because the retrospective distinction between urticaria and a benign rash might be challenging. Here, experts have included urticaria with the severe clinical signs group, excluding these patients from direct cephalosporin administration. For immediate hypersensitivity reactions, all experts confirmed that patients with cutaneous reactions without generalized urticaria and no systemic symptoms were at low risk, as were patients with minor symptoms (conjunctivitis, digestive disorders or rhinitis), and could benefit from cephalosporin administration.

The last category included patients with possible severe delayed reactions, precluding, in most cases, the use of cephalosporins without prior allergy evaluation. A mild maculopapular exanthema is defined as any rash 'that is not urticarial, involving less than 50% of the body surface, without systemic involvement, occurring more than 6 h after the drug intake, of less than 7-day duration, and not requiring hospitalization or systemic treatment other than antihistamines'.⁵¹ Romano *et al.*²⁵ stratified these patients as low-risk, sustaining a direct cephalosporin administration, in accordance with the EAACI.⁵¹ This last classification might be the most difficult to apply for anaesthesiologists because of the major uncertainty during patients' allergy interrogation that they are not trained to perform.

Our study has several limitations. Participants from four different specialist areas were invited to participate. Increasing the diversity and number of panellists could have been beneficial for increasing the validity and avoiding persisting caveats in the decision tree. However, we believe that the 16 experts invited could cover almost all perspectives on this translational topic. Experts were invited based on their research interests, but not randomly selected, which could represent a potential bias. In France, perioperative antibiotic prophylaxis is only managed by anaesthetists: surgeons and pharmacists are not involved in the prescription and selection process. Prescriptions are based on national experts' recommendations, which are updated every 10 years, based on the up-to-date literature. The final decision tree could be applied in countries with high penicillin allergy rates. For countries with lower rates, such as those in the Asia-Pacific region,⁵² a less conservative approach might be possible. As a general perspective, the final decision tree strength relies on a conservative approach, with almost all clinical situations covered. This strength relates to a limitation: the complexity of the decision tree. Anaesthesiology evaluation often relies on patients' interrogation, but without as many details as during an allergy consultation. One might be afraid that the decision tree will not be applicable as it stands. However, the experts were confident it would be. The algorithm was not tested prior to commencing the PROPHYLAL study, as this would represent a methodology caveat and was already planned in the study protocol. We are

confident that the ongoing prospective study PROPHYLAL will answer all those questions.

Conclusion

This Delphi method resulted in an adapted decision tree to promote cephalosporin prescription for perioperative prophylaxis in patients with a penicillin allergy label without a prior allergy work-up. It offers additional patient classification compared to the previous decision tree. Antibiotic prophylaxis in allergic patients is difficult to address, as this question covers several aspects of medicine. The Delphi method applied here allowed expertise from panellists with different perspectives, supporting its validation by several medical disciplines. According to the initial clinical presentation, four major categories were defined based on 12 items: not suggestive of an allergic reaction, unknown, and compatible with an immediate or delayed allergic reaction. The evaluation of this decision tree in the ongoing randomized PROPHYLAL study will help to evaluate the applicability and feasibility of such a strategy to increase cephalosporin prescription in patients with a penicillin allergy label.

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Transparency declarations

J.-R.Z. is a lecturer and consultant for MSD and Pfizer and a lecturer for Advanz-Pharma and Gilead. M.L. is a consultant for AOP Pharma and Viatrix and a lecturer for Shionogi. M.B. is a consultant and lecturer for Becton Dickinson and a consultant for Edwards Lifes Sciences. C.R. is a consultant for bioMerieux and Viatrix and a lecturer for MSD, Pfizer, Shionogi, AOP Orphan and Advanz Pharma. M.G. is a lecturer for LFB and Shionogi. These conflicts of interests were unrelated to the present work. A.G.-C., A.D., E.M., C.N., A.B., S.K., G.B., S.R.-B., P.L., S.D., R.G., C.D.-F., P.D., A.C., A.D., P.M. and E.M. have no conflicts of interest to declare.

Author contributions

All authors fulfil the ICJME criteria for authorship.

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