

Alleged Allergy to Penicillin and Isolation Issues: Toward New Practices for French Navy?

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ABSTRACT

Introduction:

According to the literature, 8% of the population claim to have an allergy to penicillin. Allergy tests show that 90% of these patients tolerate this molecule. Physicians working in the French Navy are faced with situations of real isolation and only have a limited number of antibiotics on board, the majority of which are penicillins. They must anticipate the risks linked to the prescription of antibiotics before the mission. However, there is no French recommendation, either military or civilian, intended for general practitioners clarifying the management and allergy assessments of patients alleging a history of allergy to penicillin. This study is the first to evaluate the professional practices of French military practitioners taking care of these patients. The main objective was to evaluate the proportion of sailors who reported an allergy to penicillin and who have never been referred for a consultation with an allergist, by studying the medical files of all the submariners working on the submersible ballistic nuclear submarines squadron in Brest. The secondary objective was to compare these data with the practices of Navy doctors by means of questionnaires.

Material and methods:

Our work is composed of two parts: monocentric study of the digital and paper medical files of Brest submariners ($n = 814$) looking for allergist consultation reports in cases alleging an allergy to penicillin, then comparison with a multicentric collection of all Navy doctors' practices collected by an anonymized questionnaire ($n = 37$ out of 53 practicing at the time of the study).

Results:

Forty-seven subjects out of 814 alleged an allergy to penicillin (5.8%). Among them, only 12 (25.5%) had undergone allergy tests, of which 3 (6.4%) were confirmed to be allergic, with no cross-reaction between β -lactam antibiotics. Yet, according to the questionnaire, 25 doctors (67%) report referring their patients to an allergist and 16 (43%) report having had difficulties at sea in connection with the prescription of antibiotics for these patients.

Conclusions:

A study of medical records shows that the allergic risk is not anticipated for 74.5% of patients labeled allergic, despite the difficulties encountered at sea. Standardization of practices within the French Navy is necessary to avoid the prescription of second-line antibiotics, less effective and sometimes unavailable on board, and to improve patient safety in isolation situations. In agreement with French military allergists, we propose, in this article, guidelines for a systematic exploration of allegations of allergy to penicillin in the French Navy.

INTRODUCTION

The French military health support doctrine is to provide a doctor in each combat ship (role 1). The medicalization of military ships dates back to the 18th century and was initially provided by barbers, progressively trained in surgery at the Naval Medical School of Rochefort, established in 1720. These barber surgeons were embarked on the French royal frigates to provide trepanations, amputations, and then medical care on all the oceans. Since then, this medicalization has met the front care standards: from role 1 on frigates or

submarines to role 2 on larger ships such as aircraft carriers or amphibious helicopter carriers. These ships have hospital beds, operating theatres, and CT scan and resuscitation facilities.

The doctor assigned to a ship ensures the medical follow-up of its crew, both at sea and on land. The preparation of the mission is based on regular medical check-ups of the sailors to reassess their fitness for embarkation and to detect any pathologies likely to occur at sea.

Doctors and nurses on submarines or surface ships carry out their missions in situations of real isolation. The use of telemedicine assistance is sometimes possible, but the conditions for medical evacuation are often difficult and the delays can be very long. The management of serious cases is therefore a major challenge. Certain operations of the French Navy are of strategic interest, and the evacuation of a wounded person is likely to jeopardize the mission such as that of the nuclear-powered ballistic missile submarines (SSBN). Avoidable causes of evacuation must therefore be anticipated as far

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in advance of the mission as possible. The risk of allergic hypersensitivity is assessed in this context.

General Information on Penicillin Allergy and the Issues for the French Navy

Epidemiology and risk assessment

In the current context of antibiotic misuse and bacterial resistance, hypersensitivity to penicillin represents a public health issue. Approximately 8% of the general population in Europe and the USA report a history of hypersensitivity to penicillin and 1% to cephalosporins.¹ The majority of reactions occur before the age of 20 years.² Among these subjects, only 0.1% have undergone allergy tests to explore their reaction.³ However, the tests show that 90% of these patients can tolerate the molecule and that the reaction would therefore not be allergic.⁴ Hypersensitivity to penicillin is relatively rare, anaphylaxis occurs in 0.02% of prescriptions.⁵ Albin shows that 37% of subjects reporting a reaction to penicillin said they had experienced exanthema, 11.8% said that they had experienced angioedema, and 6.8% said that they had experienced anaphylactic shock.⁶ The risk of cross-reaction between penicillins and cephalosporins must also be taken into account as it is evaluated around 3%, mainly with 1st Generation (C1G) and 2nd Generation (C2G) cephalosporins, and 1% with carbapenems.²

Recommendations for treatment by general practitioners

Penicillin allergy is a public health problem, but patient care remains unclear for general medicine. In 2014, the French Agency for the Safety of Health Products recommends that an allergy test be carried out, regardless of the severity of the reaction to penicillin. Penicillin and cephalosporins should be avoided in the event of a severe reaction, while waiting for the allergy test. The prescription of a cephalosporin is possible in case of a late and not serious reaction.⁷ The French Society of Anaesthesia and Resuscitation currently recommends avoiding amoxicillin and C1G in the event of an immediate reaction that is not serious; the use of C2G (except cefamandole) and C3G (cephalosporin third generation) is possible. In the event of a reaction occurring during anesthesia, an investigation is imperative to identify the allergen responsible.⁸

As far as general practitioners (GPs) are concerned, therefore, there is no recommendation from the HAS (French National Health Authority) or a scholarly society, recommending that an allergy test be carried out systematically, or giving a course of action to be followed in the event of an alleged allergy to penicillins.

Allergy test: which diagnostic tests are to be carried out?

The first-line test is the skin prick test, if it is negative and the product is available in injectable form, it may be supplemented by an intradermal reaction (IDR) test. If there is no reaction, an oral provocation test (OPT) can then be carried out in hospital. This is the only test that can confirm

the absence of hypersensitivity to the molecule.⁹ If the prick tests or the IDR are positive, the OPT is contraindicated as a precaution and the allergy diagnosis is made.

Pharmacopoeia in the French Navy: is penicillin allergy a problem?

SSBN doctors and nurses isolated on nuclear attack submarines have a fixed supply of antibiotics for their mission. It is updated annually. Conversely, the doctors in charge of the infirmary on each surface ship choose their own supply of medicines. They select the molecules they consider indispensable, as well as their quantities, from a "surface ships" catalog of the French Armed Forces Health Products Supply Division according to the duration and area of deployment. β -lactam antibiotics are the family of antibiotics comprising the most molecules (penicillins, cephalosporins, carbapenems, and monobactams), with penicillins in first position (43%).

Risks of penicillin allergy in isolation situations

Risk of cross-allergy The management of penicillin hypersensitivity in isolation can be particularly complex and sometimes life-threatening. The removal of the uncertainty regarding the suspicion of allergy is necessary, in the first instance, because of the potential seriousness of the clinical situation. In the case of a confirmed allergy to penicillin, it is then essential to look for a cross-reaction with another β -lactam antibiotic, to ensure that second-line antibiotics are safe to use and do not cause a new reaction. In other words, the management of a "poly-allergic" patient at sea is not conceivable.

The "alleged" allergy to penicillin case Amoxicillin is responsible for 50% of anaphylactic reactions to antibiotics, followed by cephalosporins, quinolones, and pristinamycin.¹⁰ Penicillin secondary anaphylaxis occurs in 0.015%-0.004% of cases and is fatal in 0.0015%-0.002% of cases.¹¹

Alleged "allergy" to penicillins before boarding a French Navy ship: the objectives of our study

Penicillin allergy leads today to the eviction of the suspected molecule and often to that of cephalosporins for fear of a cross-reaction. At sea, the physician then deprives the patient of a prescription for 43% of the available pharmacopoeia that is necessary in more than 90% of the indications. The "alleged" allergy to penicillin is far from being systematically explored, even though a majority of these patients are not allergic. An allergy to penicillin is not a contraindication to joining military forces, but it can restrict certain military aptitudes.^{12,13}

To date, no study has been carried out on the prevalence and evaluation of treatment by the GP of patients labeled as allergic in the French military forces. Without a formal recommendation, the allergological management of these declared allergies is therefore dependent on the Navy doctor. It then

seemed necessary to evaluate the practices of frigate, submarine, or support unit doctors taking care of these sailors.

The main objective was to assess the proportion of sailors who had reported an allergy to penicillin and had never been referred to an allergist. The secondary objective was to describe the level of assessment for these patients by Navy doctors. In particular, they were asked about the degree of investigation carried out into the alleged allergy, from simple questioning to the most complete allergy test.

MATERIAL AND METHOD

This is an observational and retrospective study of occupational practices concerning the management of the alleged allergy to penicillins by GPs serving in the French Navy. The study was carried out in two stages. The first was the collection of information on the allergy history from the computerized medical files of the unique medical-military software “LUMM” and the former “paper” files of all the submariners assigned to the SSBN squadron in Brest (single-center and exhaustive). The second was sending a questionnaire to all French Navy doctors currently working in all the French Navy operational units.

Step 1: Study of the SSBN Squadron’s Medical Records

Subject characteristics

SSBN crews are seen in a strict fitness medical examination exclusively by Brest’s submarine doctors before each departure. The criteria for inclusion were to be a submariner assigned on SSBN, during the period from May to November 2019, and to have an LUMM doubled by a former paper file. The criterion for exclusion was the absence of one of either the LUMM or the paper file, which did not allow the full recovery of the data. All data processing was carried out anonymously.

Data collection

The LUMM software has an “allergy” section. This section was studied for 864 computer files that were opened one by one. The notion of allergy to penicillin was first researched in the medical summary of the file. If the patient was noted without allergy to penicillin or if the heading was not filled in, the file was closed and the subject was considered “non-allergic”. If the allergy to penicillin was known, a more complete exploration of the file was carried out with the search for an allergological report or a letter addressed to an allergist and a history of treatment with penicillin despite the notion of allergy. The collection was then completed by the study of the paper file with the search for the allergy declared during the initial medical examination. A subject noted as allergic in only one of the two files, and above all in both, is considered as alleging a history of allergy. An allergy report was sought throughout the entire paper file when the subject was noted to be allergic.

The flow chart of this data collection is presented below in [Figure 1](#). Fifty of the 864 subjects were lost in follow-up of the paper files because of a change in crew assignments in the summer of 2019. These 50 computer files, including two noted as allergic and not explored on “LUMM”, could not be completed by the study of the paper files. They were therefore excluded from the study.

Step 2: Questionnaire to Navy Doctors

A 5-item questionnaire, in [Table I](#), was made available online or sent to all the 53 Navy medical officers stationed in operational units in November 2019. These doctors are in charge of aptitude examinations within the submarine forces and the surface fleet in Brest, Toulon, and overseas (exhaustive multi-centered). The objective was to evaluate their care for sailors alleging an allergy to penicillin. The questions have been designed to spread out the types of care offered, from the simple recording of the allergy declared by the patient in the medical record, to an allergist expertise. The last part of the questionnaire was used to find out whether practitioners had ever been put in difficulty, in an operational situation, by a patient’s supposed allergy when administering an antibiotic.

Ethics

The design of the study—a retrospective study of data from medical records and a questionnaire sent to practitioners and anonymized—complies with the principles of the Declaration of Helsinki and the ethical and patient safety imperatives imposed by the amended French Jardé law of March 5, 2012. It has been validated by the ethics committees of the Faculty of Medicine and the Military Hospital of Brest. The study has also been authorized by the medical authorities of the operational staff of the submarine forces and the surface fleet.

RESULTS

Results of the LUMM and Paper Files Study ([Fig. 1](#))

Our data collection covered 814 records, and 5.8% of the subjects ($n = 47$) reported an allergy to at least one β -lactam antibiotic, the majority of which concerns penicillins. Only one case of cross-reaction was found between amoxicillin and a C1G (2.1% of all allergy allegations). The semiology of the alleged reactions is presented in [Table II](#).

Among the subjects explored, only three cases had an allergy test during childhood, found by the Navy doctor in the health record. One case was confirmed to be allergic to cefaclor (C1G). Another case alleging an allergy to oracillin had negative prick tests according to his civilian health record but was still considered “allergic” in LUMM. Finally, one case reported an angioedema when taking a cephalosporin, while his civilian health record indicates that the allergy was disproved. The questioning was therefore not sufficient to confirm the allergy for this case. Two other cases reported an angioedema but were not explored, either in childhood or in the Navy.

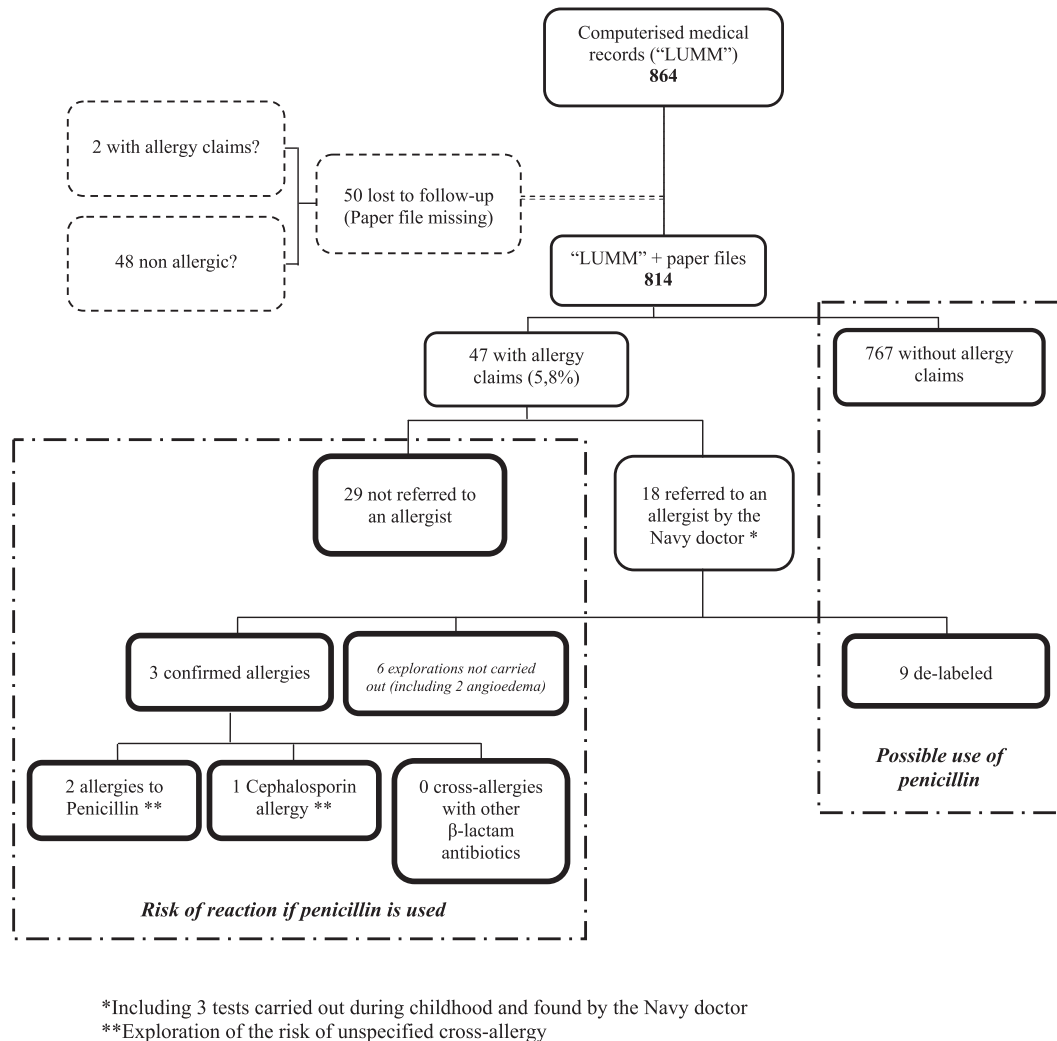


FIGURE 1. Population diagram of SSBN submariners.

Certain subjects, although labeled allergic in their files, received treatment with β -lactam antibiotics: a case noted as “allergic” to penicillin received treatment with penicillin, a case allergic to cephalosporins, without precision of the generation with eviction of the molecule recommended by an allergist, received a combination of amoxicillin—clavulanic acid. Another case, allergic to this association, received cefpodoxime (C3G) and no complications following this reintroduction were reported in the file.

Eighteen patients (38.3%) have been referred to an allergist by Navy physicians. Of these, 12 have indeed been explored, and 6 remain unresolved. Among those explored, only three allergies were confirmed (25%). Twenty-nine patients (61.7%) claiming to be allergic to penicillin, including the only case of alleged cross-allergy (penicillin—cephalosporin), were not referred to an allergist. Possible crosses with cephalosporins and in particular cefazolin, useful in surgery, have therefore not been tested.

In our cohort as in the literature, C1Gs are the most implicated cephalosporins.^{2,14} Five cases report a reaction to C1G, compared to none with C3G. Among 12 alleged allergies explored, 2 allergies to penicillins and 1 allergy to cephalosporins, without specifying the generation, were authenticated. No allergy to cefazolin has been reported. Although the literature shows that there is an immediate 3% cross-allergy between cephalosporin and penicillin, our study did not find any among the subjects explored.²

Allergy tests ruled out the suspicion of allergy in 75% of cases. These results are slightly lower than those in the literature, which reveal 80% to 90% tolerance to the antibiotic.¹⁵

In total, out of 47 sailors declaring themselves to be allergic, 38 (80.8%) still have a contraindication to penicillin (35 unexplored + 3 confirmed allergic), and theoretically, to all β -lactam antibiotics, (Fig. 1). This represents 4.7% (38/814) of submarine sailors on board SSBNs.

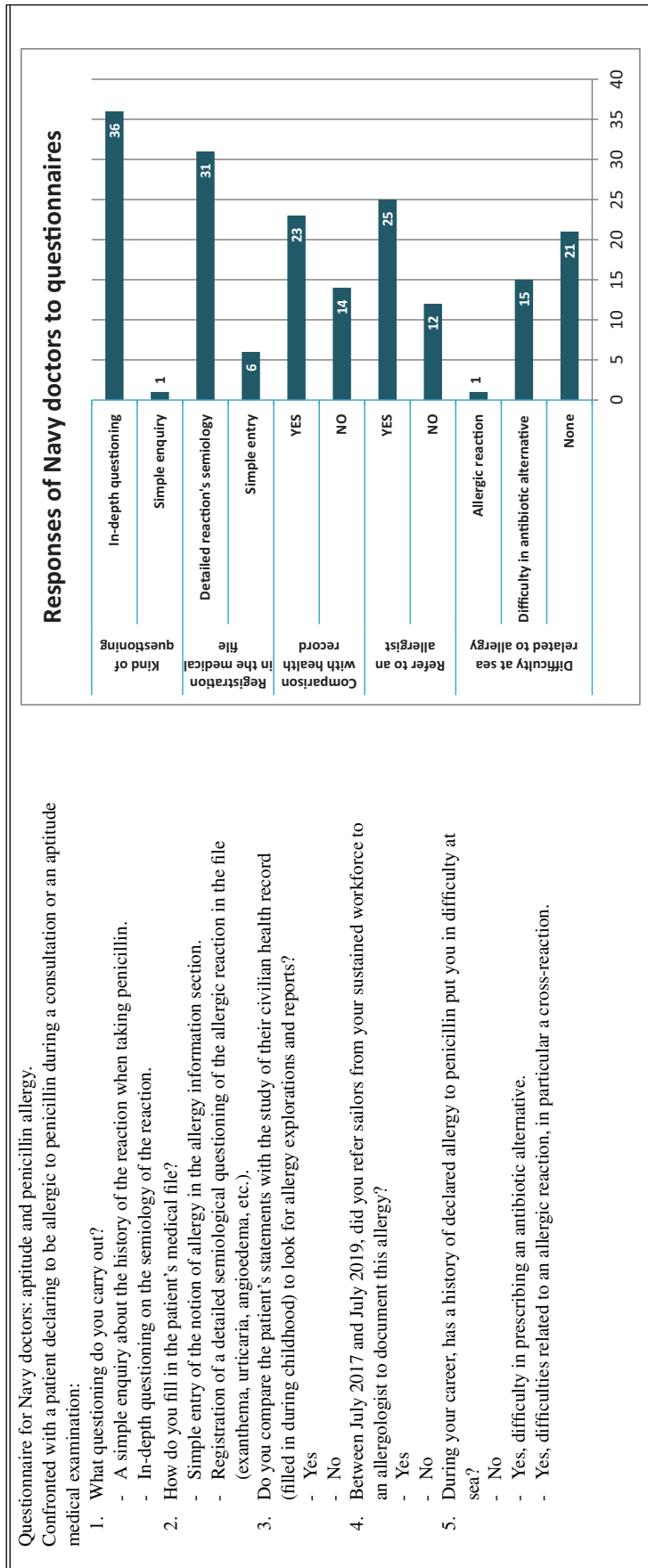
TABLE I. Responses to Questionnaires Addressed to Navy Doctors, Assigned on a Ship in 2019 ($n = 37\%$ -70% Response Rate)

TABLE II. Semiologies of Alleged Secondary Reactions to Penicillin Described by the Subjects from SSBN Squadron in Brest

Semiology	Number of cases
Not described	28
Exanthema	5
Urticaria	6
Eczema	3
Grainy rash	1
Unspecified edema	1
Angioedema	3
Total	47

Results of the Questionnaire for Navy Doctors

The questionnaire was sent to the 53 doctors assigned to operational units of the French Navy, 37 responded (70% response rate). The answers are shown in [Table I](#).

Thirty-six (97%) unit doctors thoroughly research the medical history of the supposed allergic reaction (semiology, time of onset, and duration of the reaction). As the civilian health record is not often available, only 23 (62%) are able to compare their questioning with data from childhood. Twenty-five doctors (67%) say they ask for an allergist's expertise. Sixteen doctors (43%) stated that they had already encountered difficulties on mission related to the alleged allergy, including one doctor who reported a case of cross-reaction.

DISCUSSION

Our study is original. Its objective was to evaluate the professional practices of Navy doctors with regard to the problem of the alleged allergy to penicillin in sailors. In France, practices on this subject suffer from conflicting recommendations for civilian and military GPs. They deserved to be studied.

Study of Medical Records

Thanks to its almost exhaustive collection with a high number of subjects ($n = 814$), our study is consistent with the literature. Our collection found 5.8% allegations of allergy, compared to 8% in the general population.¹⁶ As expected, the rate of allegations without exploration is high (74,5%). The study of the files was monocentric but almost exhaustive, covering all the computer and paper files of the Brest submarine sailors and representing 10% of all sailors embedded in the French Navy (which has ~9,000 sailors on board a vessel, and 37,784 sailors in total in 2019).

However, the exploration of the files did neither take into account the sailors of the naval base nor of the surface ships, which do not have the same references of fitness for employment as the population of submarine sailors studied.

The quality of our study depended on record keeping and the safeguarding of information during the transition from paper files to computer files "LUMM" in 2014. The study of the incorporation file in paper format filled in by the patients themselves was aimed at reducing this bias. Our population is not very representative of the general population because

it has its own epidemiological characteristics: almost all the subjects included are men (only three women, with no allegation of allergy), young and in good health. Another selection bias is because of the exclusion of people with severe allergies who are not suitable for military service.

According to our results, the majority of the LUMM and paper files are incomplete on the semiological description of the reaction, from the time of enlistment in the army. When the clinical situation is reported, 11 out of 47 correspond to an exanthema, eczema, or urticaria, and 3 describe an angioedema. This observation is consistent with the literature, where the majority of penicillin allergy claims are maculopapular rash.¹⁷

Questioning and clinical description alone are not sufficient to assess whether the reported reaction is a genuine allergy. Indeed, one patient explored for angioedema out of the three of our cohort was ultimately found to be non-allergic. Hives or angioedema should be explored, most of which are non-allergic.¹⁰ Moreover, when the clinical situation described is strongly suggestive of a real allergy, the search for cross-reactions is essential.¹⁵

A minority of allergy allegations were formally explored: only 18 out of 47 cases were referred to an allergist, i.e., 38.3%. A lack of patient compliance in going to the specialist may explain the low number of allergy reports found in the files. The literature shows that only 0.1% of cases declaring an allergy to penicillin in the USA undergo allergy tests, despite the American recommendations.^{3,18}

The subjects explored in our cohort show no cross-allergy to C3G, including those for whom allergy to C1G is confirmed. Allergy tests confirm the complete safety of use of C3G what is crucial for our sailors.

The most interesting result is the rate of submariners for whom the use of β -lactam antibiotics would be contraindicated because of their supposed or confirmed "allergy", amounting on average to 4.7% of a crew, which is considerable.

About the Navy Doctor Questionnaire

This part of our study is interesting because it looks at all the Navy doctors currently practicing in operational units in the field (mostly in surface ship). The response rate of 70% ensures the representativeness of our results. It might seem difficult to compare them with the data from the file review, which is based only on submarine sailors' files. However, all sailors, before becoming submariners, are seen during an initial aptitude test by at least one Navy doctor. The file study therefore reflects the overall practice of "Navy doctors".

Before starting the study, we assumed that Navy practitioners rarely made referrals to allergists for patients alleging an allergy to penicillin. The questionnaire reveals that they prescribe an allergy test in almost two-thirds of cases. This result differs from that of the file review, which found a prescription for an allergy test for just 38% of "allergic" patients.

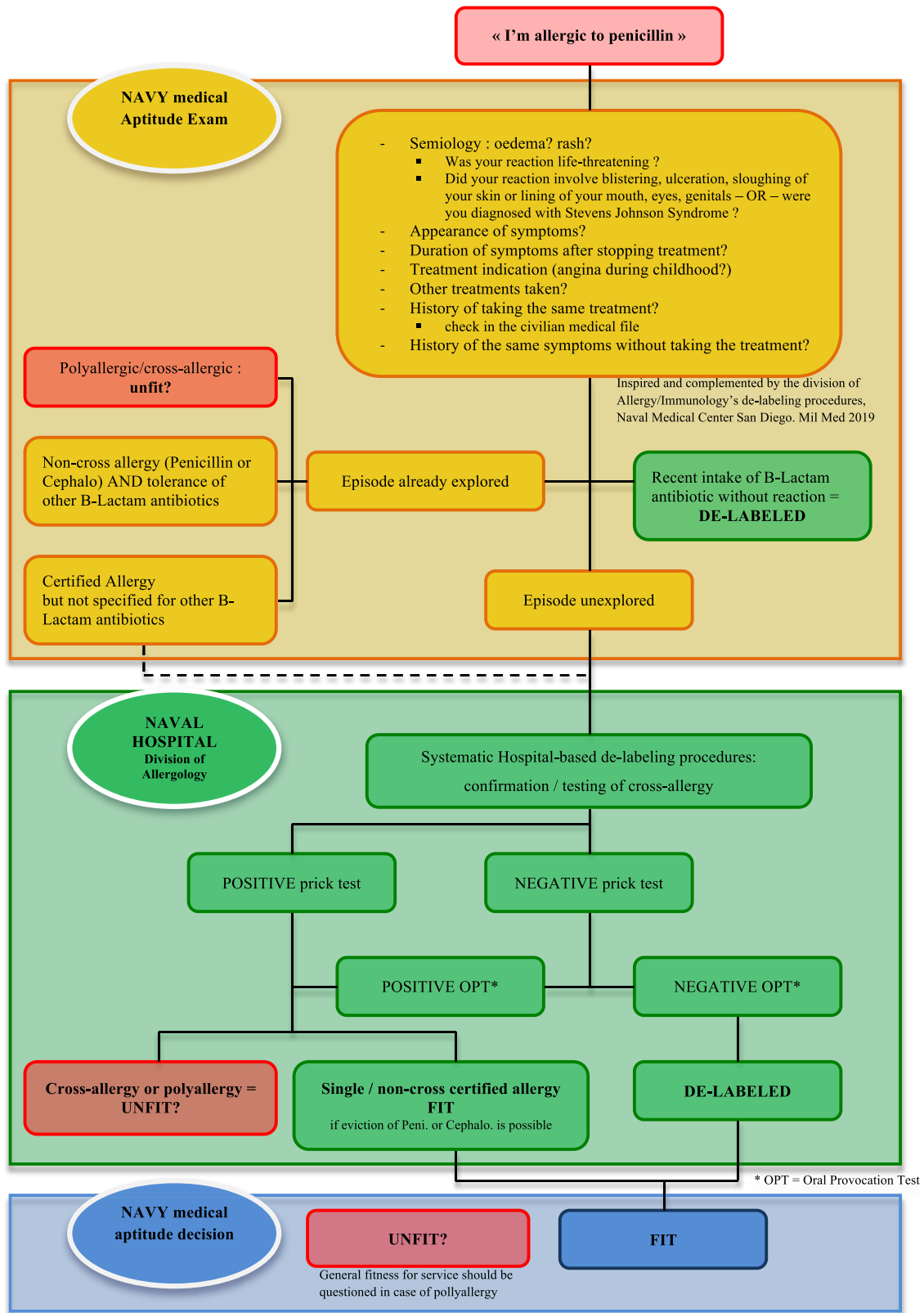


FIGURE 2. Decisional procedure for penicillin allergy in the French Navy.

This difference can be explained by the declarative nature of the questionnaire. These answers, which do not reflect the field observations noted in the study of the files, do, however, show that Navy GPs are aware of the problem that penicillin allergy can pose at sea. Sixteen out of 37 (43%) report having had a difficulty at sea related to the choice of a second-line molecule, including a cross-reaction. These data show that the issue of allergy to penicillin is a very real problem on operations. A risk is assessed by confronting an occurrence with seriousness: here, more than 40% of the doctors had difficulty at sea with alleged allergy, and the consequences could have been serious.

As the majority of the alleged allergies are unfounded, it is therefore justified to explore them in order to avoid the unnecessary and less effective use of a second-line antibiotic.

Is It Possible to Do Better? Update on the Recommendations and Relevance of Allergy Tests

The European Network of Drug Allergy proposes a questionnaire to specify the medical history of the reaction in order to determine the causality of the drug and the mechanism of hypersensitivity. This questionnaire, difficult to carry out in general medicine, has a significant memory bias, and its PPV (positive predictive value) is poor (17% to 46%).¹⁹ Autegarden evaluates another algorithm for GPs, based on a medical questioning to assess the authenticity of the penicillin allergy. The author finally recommends not using this protocol in non-hospital practice, where the risk of a serious reaction remains possible.²⁰ French military allergists Valois and Paleiron do not recommend exploring each soldier alleging an allergy to penicillin. They propose an operational approach by discussing the suitability of the soldier on a case-by-case basis according to the results of the allergy tests and the specifics of his position, whereas American military allergists recommend this for essentially readiness, economic, and bacterial ecology reasons.^{13,21}

Faced with the large number of negative tests, the reliability of prick tests at a distance from the reaction has been questioned. Numerous studies have shown that the sensitivity of prick tests decreases from the first year after the reaction, until it becomes negative after 6 years.^{22,23} The optimal period for performing prick tests is between 1 month and 1 year.¹⁰ Exploring the reactions that took place during childhood is therefore difficult to interpret.

Moreover, the risk that prick tests would re-sensitize the patient and then OPT would cause the clinical reaction is discussed. Solensky showed that the repetition of prick tests does not cause their conversion, and Blanca showed that re-sensitization can occur when antibiotics are administered, even at sub-therapeutic doses, in subjects with negative allergy tests.^{24,25} Other teams do not guarantee total desensitization to the allergen over time and recommend continuing to avoid it despite negative prick tests although skin tests alone are not conclusive.^{23,26}

For those reasons, OPT is recommended in the case of negative skin tests to affirm the absence of allergy. Aberer proposes to carry it out on the same day as the prick tests if they are negative and Garcia recommends repeating remote OPT to eliminate asymptomatic re-sensitization in the first battery of tests.^{9,27} Finally, Demoly concludes that the OPT reaches a negative predictive value of 94% and even if OPT protocols are not standardized and practices vary, it is unlikely that an OPT will be negative by induction of tolerance during the test.^{28–30}

CONCLUSION

Our study reveals that the allergic risk is not anticipated for 74.5% of sailors labeled allergic before going to sea, whereas 43% of Navy practitioners state that they have already been put in difficulty by this allergy allegation. As expected, the problem of treating penicillin allergy is therefore very real in the French Navy, and a standardization of practices is necessary.

Studies show that 90% of these patients tolerate the molecule and that the questioning by a physician would not be sufficient to formally exclude an allergy nor to affirm it.¹⁵ Allergy tests with skin tests and, if negative, an oral challenge would therefore be indicated. The use of a second-line antibiotic, and the potential risk of a cross-allergy on a necessary prescription of C3G, could be easily avoided by sending the patient to an allergist.

Anaphylaxis because of cross-allergy or therapeutic deadlock because of lack of alternative antibiotics are rare on French Navy vessels. However, in a situation of isolation, the risk is not a question of occurrence but of managing a serious clinical situation in a degraded environment. In agreement with the military allergists, we therefore formulate recommendations for a de-labeling procedure in the French Navy (protocol in Fig. 2). The objectives are to confirm or rule out a suspected allergy and to look for cross-allergies or polyallergies that could call into question the sailor's aptitude to sail safely.

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CONFLICT OF INTEREST STATEMENT

None declared.

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