GUIDELINES

Management of Patients with Suspected or Confirmed Antibiotic Allergy: Executive Summary of Guidelines from the Spanish Society of Infectious Diseases and Clinical Microbiology (SEIMC), the Spanish Society of Allergy and Clinical Immunology (SEAIC), the Spanish Society of Hospital Pharmacy (SEFH) and the Spanish Society of Intensive Medicine and Coronary Care Units (SEMICYUC)

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Abstract

Suspected or confirmed antibiotic allergy is a frequent clinical circumstance that influences antimicrobial prescription and often leads to the avoidable use of less efficacious and/or more toxic or costly drugs than first-line antimicrobials. Optimizing antimicrobial therapy in patients with antibiotic allergy labels has become one of the priorities of antimicrobial stewardship programs in several countries. These guidelines aim to make recommendations for the systematic approach to patients with suspected or confirmed antibiotic allergy based on current evidence. An expert panel (11 members of various scientific societies) formulated questions about the management of

patients with suspected or confirmed antibiotic allergy. A systematic literature review was performed by a medical librarian. The questions were distributed among panel members who selected the most relevant references, summarized the evidence, and formulated graded recommendations when possible. The answers to all the questions were finally reviewed by all panel members. A systematic approach to patients with suspected or confirmed antibiotic allergy was recommended to improve antibiotic selection and, consequently, clinical outcomes. A clinically oriented, 3-category risk-stratification strategy was recommended for patients with suspected antibiotic allergy. Complementary assessments should consider both clinical risk category and preferred antibiotic agent. Empirical therapy recommendations for the most relevant clinical syndromes in patients with suspected or confirmed ß-lactam allergy were formulated, as were recommendations on the implementation and monitoring of the impact of the guidelines. Antimicrobial stewardship programs and allergists should design and implement activities that facilitate the most appropriate use of antibiotics in these patients.

Key words: Antibiotic allergy. Drug hypersensitivity reaction. Skin tests. Drug provocation test. Allergy label. Antimicrobial stewardship.

Resumen

En la práctica clínica, un antecedente de alergia a los antibióticos, confirmada o sospechada, es frecuente y condiciona la selección de antibióticos, requiriendo con frecuencia el uso de fármacos menos eficaces, más tóxicos o más caros que los antibióticos de primera línea. La optimización del uso de antibióticos en pacientes con este antecedente es una de las prioridades de los programas de optimización de uso de antibióticos (PROA) en varios países. Estas guías pretenden formular recomendaciones para evaluar de una manera sistemática a estos pacientes mediante una aproximación basada en la evidencia. Un panel multidisciplinar constituido por alergólogos, infectólogos, farmacéuticos hospitalarios e intensivistas formularon una serie de preguntas sobre el manejo de estos pacientes; una documentalista realizó la revisión bibliográfica. Las preguntas se distribuyeron entre los miembros del grupo de trabajo, quienes seleccionaron las referencias más relevantes y formularon las correspondientes recomendaciones, que fueron revisadas y aprobadas por todos los miembros del grupo. Es necesaria una aproximación sistemática a los pacientes con antecedentes de alergia a antibióticos para optimizar la selección del tratamiento antibiótico y mejorar los resultados clínicos de estos pacientes cuando precisan antibioterapia. El presente documento recomienda una estrategia de estratificación clínica del riesgo en 3 categorías. La recomendación de realizar evaluaciones complementarias se basa en el riesgo clínico y el antibiótico de primera línea necesario. Además, se formulan recomendaciones de tratamiento antibiótico empírico para los principales síndromes infecciosos en pacientes con alergia confirmada o sospechada. Finalmente, se formulan recomendaciones sobre la implementación y monitorización del impacto de las recomendaciones de la guía. Los programas PROA y los alergólogos deben trabajar conjuntamente en el diseño y ejecución de actividades dirigidas a facilitar el correcto uso de antibióticos en estos pacientes; y también deben trabajar conjuntamente en el diseño y ejecución de actividades dirigidas a facilitar el correcto uso de antibióticos en estos pacientes.

Palabras clave: Alergia a antibióticos. Reacción de hipersensibilidad a medicamentos. Test cutáneos. Pruebas de exposición controlada a medicamentos. Etiqueta de alergia. Administración antimicrobiana.

1. Introduction: Aims and Scope of the Guidelines

Antibiotic allergy, whether suspected or confirmed, is a frequent present or past diagnosis (antibiotic allergy label) that significantly influences antimicrobial therapy, mainly because it often leads to the selection of second-line agents that are less efficacious, more toxic, or more costly than first-line antibiotics. Furthermore, second-line agents often have increased potential for induction and/or selection of antimicrobial-resistant microorganisms or *Clostridium difficile*.

Many antibiotic allergy labels do not truly represent hypersensitivity or immune-mediated drug reactions, thus necessitating a clinical approach and, eventually, the use of additional tests in order to better define the presence of antibiotic allergy and the drugs involved. In recent years, antimicrobial stewardship programs (ASPs) have prioritized patients diagnosed with antibiotic allergy, and multiple interventions targeting this population have been designed and conducted in coordination with allergists. Outcomes have been highly successful.

The Spanish Society of Infectious Diseases and Clinical Microbiology (SEIMC) and the Spanish Society of Allergy and Clinical Immunology (SEAIC) found significant room for improvement in the selection of antibiotic therapy among patients with antibiotic allergy labels in Spain, mainly because of the heterogenous approach to these patients throughout the country. As scientific production in this field has been quite fertile, SEIMC and SEAIC considered that clinical practice guidelines could help to improve antibiotic selection and infection management in suspected or known allergic patients. It was deemed necessary to include other health care providers involved in the management of these patients, such as pharmacists, through the Spanish Society of Hospital Pharmacy (SEFH), and intensive care specialists, through the Spanish Society of Intensive Medicine and Coronary Units (SEMICYUC).

The main aim of these guidelines is to formulate evidence-based recommendations that improve the management of patients with suspected or confirmed antibiotic allergies. More specifically, it aims to standardize the approach of clinicians prescribing antimicrobials to patients with an antibiotic allergy label and of allergists confirming or excluding the antibiotic allergy label. In addition, it can help to define the extent of the disease and the drugs that might and might not be safely prescribed. These guidelines are not restricted to patients of a

specific sex or age group but takes a comprehensive approach, covering allergy to all antibiotic groups. Nevertheless, the available evidence is disproportionately skewed towards ß-lactams in general and penicillins in particular. Similarly, although we did not restrict the scope of the guidelines to a specific level of care within the health care system, most of the references retrieved were in the hospital care setting.

In addition, the guidelines also aim to facilitate patient prioritization, structuring, and monitoring of local or regional activities and interventions that help to put the recommendations contained in these guidelines into practice.

Finally, an extensive and detailed version of this consensus, with all the items and tables developed and the corresponding bibliographic support, is available in the online repository (See also Supplementary Material). All tables referred to can be found in the Supplementary Material.

2. Methods

SEIMC and SEAIC chose 1 coordinator each (JRPP and CCS, respectively). The coordinators proposed 2 experts in infectious diseases (JdPL and PRG) and 3 experts in allergy (JLCS, EMR, and MJTJ), as accepted by the SEIMC and SEAIC executive committees, respectively. SEFH and SEMICYUC were invited to participate through their executive committees and proposed 2 hospital pharmacists (SCS and LPP) and 2 critical care specialists (PVC and ARO).

The coordinators followed the SEIMC recommendations to elaborate clinical practice guidelines and the Agree II Collaboration guidance to draft an outline, which was shared, discussed, and adapted in conjunction with the other panel members. It was decided to structure the document based on clinically relevant questions addressing the assessment of the antibiotic allergy label and its implications, as well as on recommended empiric antimicrobial therapy for the most frequent infectious syndromes. The questions were distributed among the panel members according to their area of expertise.

A specific systematic literature search was performed for each question by an expert in medical information retrieval from the Aragon Healthcare Sciences Institute (IACS). The original search was performed in July 2018. The references retrieved were distributed to the corresponding experts, who selected the most relevant, summarized the evidence, and formulated recommendations. Recommendations were graded in 2 domains according to the Infectious Diseases Society of America (IDSA) grading system, namely, the strength of the recommendation (A, good evidence to support a recommendation for or against use; B, moderate evidence; C, poor evidence) and the quality of the evidence (I, evidence from >1 properly randomized clinical trial; II, evidence from >1 well-designed clinical trial, without randomization, or from cohort or case-controlled analytic studies from multiple time series or dramatic results from uncontrolled experiments; III, evidence from opinions of respected authorities, based on clinical experience, descriptive studies, or reports of expert committees) (see Supplementary Material).

The systematic literature search did not retrieve the information needed to provide recommendations on empirical antimicrobial empirical therapy in patients with antibiotic allergy labels (Question 4.2). Thus, the main infectious syndromes were selected once the panel members agreed upon the clinical risk–stratification categories. Then, the main etiologies and the epidemiology of antimicrobial resistance were considered, and recommendations for empirical therapy for each clinical syndrome were formulated and shared for discussion among panel members.

Lastly, we analyzed potential barriers that might negatively affect the implementation of the guidelines and provided input on how they could be overcome. Indicators to monitor the impact of the guidelines were also suggested. Before its publication, the guidelines were distributed among the SEIMC membership for review and comments.

We are planning to perform a new literature search in 2023. Analysis of the references retrieved will determine whether an update is necessary. In that case, health care professionals with other specialties, mainly primary care and pediatrics, will be invited to join the panel.

3. Summary

3.1. Epidemiology

3.1.1. How frequently are antibiotic allergies reported?

- Antibiotics are the most common cause of drug allergy and drug hypersensitivity reactions (See also Table 1 in the Supplementary Material).
- The prevalence of reported antibiotic allergy is probably the best measure of the burden of this public health problem. Penicillins account for most antibiotic allergy labels, and while significant variations are observed between institutions and countries and in specific populations, overall, 10%-12% of the population reports allergy to penicillin [1] (See also Table 2 in the Supplementary Material).
- The risk of reported antibiotic allergy (likelihood of reported antibiotic allergy in patients exposed to a given antibiotic) has been found to be highest for sulfonamides (2%-4%), followed by penicillins (1%).
- The incidence of reported antibiotic allergy is higher in females for all antibiotic classes.
- Severe antibiotic hypersensitivity reactions account for a minority of all reported antibiotic allergies (4%-7%). Sulfonamides may be associated with the highest risk of severe antibiotic allergic reaction followed by clindamycin, fluoroquinolones, and penicillins.
- Nevertheless, these figures overestimate the frequency of true antibiotic allergies, given that many reactions labeled as antibiotic allergy are not hypersensitivity reactions but non–immune-mediated reactions and even non–adverse drug reactions [2].

3.1.2. What are the consequences of receiving second-line antimicrobial therapy because of a ß-lactam allergy label?

- An antimicrobial allergy label has been found to be associated with prolonged hospitalization, increased rates of readmission, increased hospital costs, and/or mortality in several large cohort studies with hospitalized

patients. These findings have also been observed in more specific populations, such as patients with hematologic-oncological disease.
- Second-line antimicrobial agents used for prophylaxis in penicillin allergic patients are associated with increased risk of infection and increased toxicity.
- Patients labeled as penicillin-allergic have an increased risk of *C difficile* infection and of infections caused by antimicrobial-resistant microorganisms. There is evidence of an association between a penicillin allergy label and infections caused by multidrug-resistant microorganisms, mainly methicillin-resistant *Staphylococcus aureus* [3].

3.1.3. How frequently does an antibiotic allergy label not represent an antibiotic hypersensitivity reaction?

- Antibiotic allergy labels, more specifically those associated with penicillin or ß-lactam antibiotics, overestimate true antibiotic hypersensitivity reactions.
- Between 70% and >95% of patients with penicillin allergy labels have not had penicillin hypersensitivity reactions and may tolerate penicillins or other ß-lactams.
- The frequency of true drug hypersensitivity reactions (DHRs) among patients with penicillin allergy labels is lowest among children and outpatients.
- Poorly detailed drug allergy histories contribute to overestimation of antibiotic allergy through misinterpretation of non–immune-mediated adverse reactions as true DHRs and failure to identify subsequent tolerance to the culprit antibiotic [4].
- Even with a comprehensive drug history, many patients labeled as penicillin-allergic would benefit from a specific allergy work-up with in vivo and/or in vitro tests (A-II).

3.2. Risk Assessment for Patients With Antibiotic Allergy Labels

3.2.1. Can the risk of allergic reactions in patients with antibiotic allergy labels be stratified using clinical assessment?

- Although the gold standard for delabeling penicillin allergy is to perform a complete allergology study, the approach to patients with an antibiotic allergy label should be individualized (A-II).
- A standardized clinical assessment of patients with antibiotic allergy labels should start by identifying those with a history of non–immune-mediated symptoms as the isolated manifestation of a drug reaction (See also Table 3 in the Supplementary Material) (A-II).
- Anaphylaxis, bronchospasm, angioedema, laryngeal edema, or hypotension should be considered high-risk type I immediate DHRs (A-II).
- Other high-risk conditions include suspected nonimmediate severe type II-IV DHRs, such as Stevens-Johnsons syndrome, toxic epidermal necrolysis, acute interstitial nephritis, drug rash eosinophilia with systemic symptoms (DRESS), and hemolytic anemia (A-II).
- Having received epinephrine and having had a reaction that required hospital care indirectly suggest severe DHR (A-II).
- Although a history of drug allergy has significant limitations, mainly owing to the time elapsed since the episode of alleged allergy and the nonspecific clinical presentation of DHRs, a risk assessment–based, systematic approach (See also Table 3 and Table 4 in the Supplementary Material) can help to stratify the clinical risk of reported drug reactions and to guide further allergy tests, especially when deciding which patients can undergo direct antibiotic challenge and which patients can safely receive alternative ß-lactams if necessary [5] (A-II).

3.2.2. Can antibiotic allergy be ruled out in patients with self-reported antibiotic allergy by means of clinical assessment? In which patients?

- Clinical assessment based on a detailed drug allergy history and risk stratification is of limited value for ruling out antibiotic allergy.
- Patients in whom the detailed drug allergy history is conclusive of non–immune-mediated drug adverse effects, such as nausea, vomiting, diarrhea, headache, or paresthesia, can be delabeled, and further specialized evaluation or testing is not necessary [6] (A-III).
- Patients in whom subsequent tolerance to the culprit antibiotic has been documented can be delabeled, and further specialized evaluation or testing is not necessary (A-III).
- Further research is needed on the efficacy and safety of mathematical diagnostic models based on data obtained from clinical assessment to delabel reported antibiotic allergies.

3.3. Assessment of Patients With Antibiotic Allergy Through Additional Tests

3.3.1. What is the role of skin tests in patients with clinically suspected antibiotic allergy?

- Skin tests are the most widely validated method for confirming or excluding ß-lactam allergy, although skin test reactivity declines over time. Some cases become positive again after a new contact with a ß-lactam [7].
- Skin tests are not recommended in patients with nonsuggestive allergic adverse events (A-III).
- It is hard to estimate the sensitivity and specificity of skin tests accurately, since the diagnostic gold standard (eg, drug provocation test) is not performed universally for ethical reasons. Assuming this limitation, the sensitivity of skin tests is estimated to be as high as 70% if major and minor determinants of penicillin, amoxicillin, and the suspected ß-lactam are used.
- Based on the limited number of drug provocation tests performed in patients with positive skin test results for ethical reasons, the positive predictive value has been estimated to be between 40% and 100%.
- Skin tests are generally safe, although systemic reactions may occur, especially in patients with a previous history of anaphylaxis.
- In severe reactions or in patients who have experienced mild symptoms but are at special risk, intradermal tests,

and even the prick test, should begin with a dilution of 1/1000 or 1/100, which is increased gradually until the appearance of a positive skin response or until a nonirritant concentration is reached [8] (A-II).
- When the culprit antibiotic is an aminopenicillin or a cephalosporin, the reactivity is frequently due to the side chain.
- Benzylpenicilloyl, sodium benzylpenilloate, benzylpenicillin, amoxicillin, and the suspected penicillin or cephalosporin should be tested, as should ß-lactams that share the same side chain (A-II).
- Before skin testing, any medications that could interfere with the results of skin tests (eg, antihistamines) should be temporarily discontinued. ß-Blockers should be discontinued for at least 24 hours, since they could interfere with the use of adrenalin if a systemic reaction occurs (A-II).
- For immediate drug hypersensitivity reactions to ß-lactams, prick tests are recommended for initial screening (A-II). An intradermal test should be performed if no reaction is observed, as these tests are more sensitive for IgE-mediated reactions [8] (A-II).
- In immediate hypersensitivity reactions to ß-lactams, readings should be taken after 15-20 minutes (A-II).
- In skin prick tests, a wheal larger than 3 mm accompanied by erythema with a negative response to the saline control is considered positive (A-II).
- We recommend intradermal skin tests and patch tests with delayed readings to diagnose nonimmediate drug reactions to ß-lactams (A-II).
- In intradermal tests, the wheal area is marked initially and 20 minutes after testing, and an increase in diameter greater than 3 mm with erythema is considered positive (A-II).
- A late reading should be taken in those cases with an unknown timeline or suspicion of nonimmediate reactions (A-II).

3.3.2. What is the role of drug provocation tests in the assessment of patients with suspected antibiotic allergy?

- The drug provocation test is considered the gold standard for establishing a diagnosis of drug hypersensitivity. Up to one-third of penicillin-allergic patients have a negative result in skin tests [9].
- Drug provocation tests should be performed only after performing skin tests (A-III). Nevertheless, in patients with severe infections and unconfirmed penicillin or cephalosporin allergy, and if skin testing is not feasible, a controlled drug challenge with an alternative ß-lactam with low cross-reactivity with the culprit drug might have a favorable risk/benefit balance and could therefore be considered appropriate (See question 4.1).
- Drug provocation tests can be used to assess cross-reactivity between ß-lactam antibiotics.

3.3.3. What is the role of desensitization in patients with antibiotic allergy?

- Drug desensitization is indicated when the antibiotic is irreplaceable or when the drug if more effective than the alternatives [10] (A-III).
- Drug desensitization should generally not be performed in patients at increased risk of severe complications owing to significant comorbidity and is absolutely contraindicated in patients who have experienced severe, life-threatening immunocytotoxic reactions, vasculitis, or bullous skin diseases and other severe cutaneous adverse drug reactions (B-III).
- Drug desensitization is characterized by an extremely high level of risk and complexity and must be conducted by an allergist and nursing staff with specific training in a hospital location where patients who develop a severe reaction can be treated (A-III).

3.4. Selection of Antibiotics in Patients With Reported Penicillin or Cephalosporin Allergy

3.4.1. Can ß-lactams be used in patients labeled penicillin-allergic? Which ß-lactams? In which patients?

- In patients with a history consistent with non–immune-mediated adverse events to penicillins or cephalosporins, ß-lactams can be administered unrestrictedly (See also Table 3 in the Supplementary Material) [11] (A-II).
- To decide which ß-lactam to choose in ß-lactam allergy–labeled patients, it is essential to consider the chemical structure of the ß-lactam responsible for the reaction and that of the alternative, as well as the type of reaction, as tolerance may differ between immediate and nonimmediate reactions (A-II).
- Of all the ß-lactams, aztreonam (0%) and carbapenems (0.87%) cross-react least with penicillin and can be safely administered to most patients labeled penicillin-allergic (A-II).
- There are significant differences in the frequency of cross-reactivity between cephalosporins and penicillins (See also Table 5 in the Supplementary Material). These differences are due to variations in the chemical structure, mainly the R1 and sometimes the R2 side chains, of the penicillin and cephalosporin involved. Patients allergic to ceftazidime might experience cross-reactivity with aztreonam owing to structural similarities.
- There is a high degree of cross-reactivity between semisynthetic penicillins, especially aminopenicillins (ie, amoxicillin, ampicillin, bacampicillin, and pivampicillin), which share an amino group in their side chain. Nevertheless, some patients with amoxicillin allergy tolerate benzylpenicillin, and patients allergic to clavulanic acid may tolerate amoxicillin.
- The gold standard procedure for administering a ß-lactam in patients with suspected immune-mediated reactions is to perform skin and drug provocation tests before administration and delabeling (A-II).
- Nevertheless, in the absence of skin tests, in some hospitalized patients with moderate and severe infections and a penicillin or cephalosporin allergy label, controlled drug challenge with an alternative ß-lactam with low probability of cross-reactivity, has a favorable risk/benefit ratio (See also Table 5 and Table 6 in the Supplementary Material) [12] (A-II).
- Patients with suspected immune-mediated hypersensitivity reactions exposed to alternative ß-lactams in the absence

of a standardized allergy work-up should be referred to an allergist before delabeling (A-III).
- In patients with a history of severe type 2-4 drug hypersensitivity reactions, ß-lactams should be avoided if possible (A-III).

3.4.2. What is the recommended antimicrobial therapy for the main infectious syndromes in patients with a nonconfirmed label of penicillin and/ or ß-lactam allergy?

See Table 7 in the supplementary material.

3.4.3. How should antibiotic allergy be reported in the medical records?

- All patients should receive a medical report from the allergology department; this must meet the established minimum recommended quality standards (A-III).
- Antibiotic allergy should be clearly visible in the medical record [13] (A-III).
- If a patient had a prior allergy but has been delabeled, the status of the antibiotic allergy should be updated in the medical record, specifying the date of delabeling (A-III).
- Electronic health records have been shown to improve the safety and quality of patient care, especially when clinical decision support is implemented (A-II).

3.5. Which Interventions to Improve the Administration and Appropriateness of Antimicrobials Have Proven Useful in Patients With Self-Reported ß-Lactam Allergy?

- Formal assessment of self-reported ß-lactam allergy (SRBA) in hospitalized patients receiving antibiotics increases the likelihood of ß-lactam use and decreases the chance of receiving more expensive, more toxic, and less efficacious, second-line antibiotics [14] (A-II).
- Formal assessment of SRBA in hospitalized patients is associated with cost savings that persist beyond the intervention (A-II).
- The clinical impact of SRBA is still uncertain (A-II).
- When implemented in the setting of an ASP, clinical assessment tools such as guidelines and algorithms have can help identify patients unlikely to be allergic and patients at low risk of severe immune-mediated reactions after a new ß-lactam exposure. These patients can safely receive ß-lactams other than aztreonam and carbapenems, such as cephalosporins and, in the former case, even penicillins (A-II).
- The integration of clinical assessment tools with penicillin skin testing and oral ß-lactam challenge when appropriate, if performed by trained personnel, increases the yield of formal assessment of SRBA (A-II).
- Formal assessment of SRBA is most cost-effective among patients with severe infections, especially if prolonged therapy is needed. The same is true of patients with endocarditis and osteoarticular infections and patients receiving highly valued antibiotics to treat SRBA [15] (A-II).
- One of the circumstances that may diminish the potential impact of interventions designed to assess SRBA formally is inefficient delabeling of the allergies ruled out (A-II).

3.6. Implementation of the Guidelines

3.6.1. Which barriers might interfere with the implementation of the recommendations contained in these guidelines? Are there any facilitators?

- The main barriers to the implementation of the recommendations contained in these guidelines are as follows: (*a*) the large size and widespread distribution of the population affected; (*b*) insufficient and inequitable access to allergists; (*c*) resistance of doctors and patients to using ß-lactams in patients labeled as penicillin-allergic; (*d*) lack of training and support for using alternate ß-lactams in patients with low-risk and non–immune-mediated reactions in the acute care setting; and (*e*) insufficient human resources capabilities within ASPs.

3.6.2. How should the recommendations contained in these guidelines be put into practice?

- Patients labeled with antibiotic allergy should be prioritized as follows: (*a*) patients with sepsis or septic shock; (*b*) patients with infections leading to hospitalization; (*c*) immunocompromised individuals; (*d*) patients who are undergoing high-risk surgeries from an infectious perspective (ie, oncological procedures); and (*e*) patients with recurrent infections (ie, urinary tract or biliary infections).
- ASPs are probably the best vehicle for implementing the recommendations contained in these guidelines, both in the hospital and in primary care.
- Activities to improve the management of patients with suspected or confirmed antibiotic allergy should count on the active participation of specialists in allergy.
- Endorsement of these guidelines by the Spanish National Action Plan Against Antimicrobial Resistance (PRAN) might increase its impact, especially through the involvement of Autonomous Communities and regional health care systems.

3.6.3. What resources are needed for the implementation of the recommendations included in these guidelines?

- Specific, protected time should be allocated to ASP team members, as well as allergists and skilled nurses, according to the estimated needs associated with the interventions.
- Ready-to-use or easily adaptable educational materials (in printed or e-format) of several kinds might help decrease the workload for ASP members associated with implementing the recommendations contained in these guidelines.

3.6.4. How is the implementation of these guidelines going to be monitored?

- Table 8 in the Supplementary Material summarizes several indicators for monitoring the implementation of these guidelines.

- A nationwide survey run at 2 time points might help with the implementation of these guidelines.

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Conflicts of Interest

The authors declare that they have no conflicts of interest.

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