Multidisciplinary consensus on the approach to hospital malnutrition in Spain

A. García de Lorenzo1, J. Álvarez Hernández2, M. Planas3, R. Burgos4 and K. Araujo5; the multidisciplinary consensus work-team on the approach to hospital malnutrition in Spain


Abstract

Rationale: Disease-related malnutrition constitutes a highly prevalent healthcare problem with high costs associated. In Spain, the prevalence of malnutrition in hospitalized patients has been reported from 30% to 50%.

Objectives: Main purposes of this consensus document were to establish recommendations that facilitate decision-making and action to prevent and early-diagnose disease-related hospital malnutrition, on the management of nutritional support methods and actions to evaluate nutritional treatment compliance and efficacy.

Methods: A systematic bibliographical search of authors was performed, complemented by updated bibliography by author references up to 2010. From this review, some recommendations were defined, modified and critically evaluated by the representatives of scientific societies in a consensus conference (Dec 2010) following a structured brainstorming technique: the Metaplan® technique. A double validation process was undertaken until final recommendations were obtained.

Results: 30 consensus recommendations for the prevention and management of hospital malnutrition are presented in this document. Recommendations cover all clinical care settings as well as prevention, screening, diagnosis, treatment and follow-up of disease-related malnutrition.

Conclusions: Nutritional screening is strongly recommended at all clinical settings when nutritional risk factors are identified or there is clinical suspicion of malnutrition. Nutritional assessment should be designed and performed according to centers’ resources, but clearly identified protocols should be available.

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Key words: Disease-related malnutrition. Hospital malnutrition. Consensus conference. Malnutrition prevalence.

Resumen

La desnutrición relacionada con la enfermedad constituye un problema sanitario de elevada prevalencia y altos costes. En España, la prevalencia de desnutrición de los pacientes hospitalizados se ha estimado entre el 30% y el 50%.

Objetivos: El objetivo principal de este consenso fue establecer recomendaciones para facilitar la toma de decisiones para la prevención y el diagnóstico precoz de la desnutrición hospitalaria, el manejo del soporte nutricional, y las acciones para evaluar el cumplimiento de la intervención nutricional y su eficacia.

Métodos: Se realizó una búsqueda sistemática de autor complementada por bibliografía actualizada por referencias de autor hasta el año 2010. A partir de esta revisión, se definieron algunas recomendaciones que fueron criticadas y modificadas por los representantes de las Sociedades Científicas participantes en una conferencia de consenso (Diciembre 2010) siguiendo una técnica de brainstorming estructurada: la técnica Metaplan®. Se realizaron dos vueltas de validación de las recomendaciones hasta obtener las recomendaciones finales.

Resultados: Este documento presenta 30 recomendaciones para la prevención y el manejo de la desnutrición hospitalaria. Las mismas cubren todas las áreas de actuación clínica así como la prevención, cribado, diagnóstico, tratamiento y seguimiento de la desnutrición hospitalaria relacionada con la enfermedad.

Conclusiones: Se recomienda enérgicamente el cribado nutricional en todas las áreas de actuación clínica cuando se identifiquen factores de riesgo nutricional o sospecha clínica de desnutrición. La valoración del estado nutricional debe diseñarse y realizarse de acuerdo a los recursos disponibles en cada centro, disponiendo de claros protocolos de actuación.
Abreviattions

ENHA: European Nutrition Health Alliance.
ESPEN: European Society for Clinical Nutrition and Metabolism.
EU: European Union.
MNA: Mini-Nutritional Assessment.
MNA-SF: Mini-Nutritional Assessment Short Form.
MUST: Malnutrition Universal Screening Tool.
NICE: National Institute for health and Clinical Excellence.
PREDYCES: Prevalence of Hospital Malnutrition and Additional Costs in Spain.
SENPE: Spanish Society of Parenteral and Enteral Nutrition.
SIGN: Scottish Intercollegiate Guidelines Network.

Rationale

Disease-related malnutrition constitutes a highly prevalent healthcare problem with high costs associated. It affects some 30 million people in Europe and entails an associated annual cost of around 170 billion euros.1

Under the Czech presidency of the European Union (EU), representatives from the EU member states’ Ministries of Health, medical experts, representatives of healthcare administrations and healthcare insurance groups, ESPEN (European Society for Clinical Nutrition and Metabolism) and ENHA (European Nutrition Health Alliance), signed the Prague Declaration on June 11th, 2009, and came to the unanimous conclusion that disease-related malnutrition is an urgent public health and healthcare problem in Europe. This declaration emphasizes the importance of adopting appropriate actions to prevent malnutrition, a cause of unnecessary morbidity and mortality. Thus, progress should be made to help the efficacy of European healthcare systems2 and maintain ongoing commitment to improve patient quality of life.

The actions to fight against disease-related malnutrition should be integrated to the EU healthcare strategy (“Together for health: a Strategic Approach for the EU 2008-2013”)4 continuing along the recommendation lines proposed in the resolution on Food and Nutritional Care in hospitals, promulgated by the Council of Europe Committee of Ministers in 2003.5 This resolution highlighted the importance of malnutrition in hospitals, as well as measures aimed at its prevention and treatment.

Hospital Malnutrition

Malnutrition in the hospitalized patient is the result of a complex relationship between disease, food and nutrition. When the nutritional status is deficient there is a delay in recovery, hospital stay is prolonged, the rate of premature re-admission increases, there is greater susceptibility to infection and the individual’s independence and quality of life is considerably altered, contributing to an increase in morbidity and mortality as well as an increase in healthcare costs.6-10

Malnutrition is a clinical situation caused by nutritional deficiency, either due to inadequate intake; increase in losses or because of an increase in nutritional requirements. Malnutrition increases during hospital stays because of several factors. First, the patient’s disease may involve an inadequate intake of nutrients due to anorexia, difficulties in food intake, chewing problems, dysphagia, mucositis or lack of autonomy for eating, but also other factors involved may be, difficulty in digestion or absorption of foods, or even an increase in nutritional requirements either due to metabolic stress or varying levels of loss of nutrients. Furthermore, certain diagnostic or therapeutic procedures may contribute to the development of malnutrition if fasting is indicated to conduct specific examinations, if the patient is in the postoperative period, or if digestive rest is required as part of the treatment for certain pathophysiological situations.

There may also be questionable dietary indications or not taking into account possible negative effects of certain therapeutic actions on nutritional status. Furthermore, it is a reality that hospital food services may be incurring in deficiencies for not offering attractive menus, not always using best quality ingredients and, occasionally, using deficient dietary protocols that are poorly suited to specific patients. Finally, the lack of awareness of healthcare professionals cannot be overlooked, given the limited training received regarding nutrition, the ignorance of the significance of malnutrition in patient evolution, and the dilution of responsibilities regarding patient nutrition and nutritional support protocol availability. This means that methods for detecting and monitoring patients with nutritional problems are not applied and existing resources for nutritional support are poorly used.11-15

It is worth pointing out that there is not a universally-accepted definition for disease-related malnutrition. Some authors use elements related to clinical and biochemical expression,22 functionality,23 or the aetiological concept of it, as was most recently brought-up in a consensus written by an International ad-hoc Committee (ASPEN – ESPEN).24, 25

The prevalence of disease-related malnutrition is reported to be from 20-50%.26-28 The use of screening tools is the first step in the prevention and treatment of patients at risk of malnutrition and undernourishment. The information obtained from the EuroOOPS Study, which used Nutritional Risk Screening 2002 (NRS 2002) tool to evaluate 5061 patients admitted to European hospitals, shows a risk of malnutrition of 32.6%.29

Hospital Malnutrition in Spain

In Spain, the prevalence of malnutrition in hospitalized patients has been reported from 30% to 50%, and...
as in other countries, it increases with the duration of in-hospital stay. However, these data were extracted from partial studies with that did not allow us to know the real extent of the healthcare (prevalence) or financial (costs) problem.31–34

The recent PREDYCES® study (Prevalence of Hospital Malnutrition and Additional Costs in Spain) conducted by the Spanish Society of Parenteral and Enteral Nutrition (SENPE) provides very important data.35 It was conducted on 1597 patients in 31 hospitals, representative of the healthcare map throughout the national territory and under regular clinical practice conditions. The results include:

- 23% of patients admitted to a Spanish hospital are at risk of malnutrition (according to NRS 2002®). Patients over the age of 70 have a significantly greater risk than the rest of patients (37% vs. 12.3%; p<0.001). Both at admission and discharge, the greatest prevalence of malnutrition was found in the group over the age of 85 years, with 47% malnutrition at admission and 50% at discharge.
- Conditions significantly associated to a greater prevalence of malnutrition were dysphagia, neurological diseases, cancer, diabetes and cardiovascular disease. Furthermore, poly-medicated patients presented double the prevalence of malnutrition with respect to non poly-medicated patients.
- 9.6% of patients not malnourished at admission developed malnutrition during hospitalization and 28.2% of patients who were admitted at nutritional risk did not present malnutrition upon discharge.
- Patients with malnutrition (at admission or discharge) had a significantly higher mean in-hospital stay (11.5 days vs. 8.5 days; p<0.001 and 12.5 days vs. 8.3 days; p<0.001). In financial terms, hospital costs were higher in patients who were admitted with nutritional risk compared to those who did not present risk on admission (€8 207 vs. €6 798; p<0.05), with a mean difference of €1 409 per patient. After analyzing costs related to nutritional status, the most marked difference was found between those who underwent malnutrition during hospitalization (malnourished at discharge but not at nutritional risk upon admission) compared to those who did not present malnutrition at any time (€12 237 vs. €6 408; p<0.01).

Objectives

1. To establish recommendations that facilitates decision-making in different clinical care settings to prevent disease-related hospital malnutrition.
2. To establish recommendations that facilitate action in different clinical care settings to early-detect disease-related hospital malnutrition.
3. To establish recommendations to facilitate action in different clinical care settings in order to manage age and set-up nutritional support methods for patients with disease-related hospital malnutrition.
4. To establish recommendations to facilitate action in different clinical care settings to evaluate nutritional treatment compliance and efficacy.

Consensus methodology

The methodological process for drafting this document started from a previous study consisting in several phases. At first stage, a systematic bibliographical search of authors was performed, in which the reference document that most corresponded with the requirements of the references formulated, by their practical and healthcare characteristics, was the NICE review “Nutrition Support for Adults Oral Nutrition Support, Enteral Tube Feeding and Parenteral Nutrition”,36 complemented by updated bibliography by author references up to 2010. From this review, some recommendations were defined, modified and critically evaluated by the representatives of scientific societies in a consensus conference following a structured brainstorming technique: the Metaplan® technique.

This conference was held in December 2010. In order to study in detail the recommendations for prevention and management of malnutrition, participants were divided into 3 working groups. All of them represented different scientific societies and were joined by a member of SENPE (coordinators). Each group focused on a period of time when condition can be prevented, detected or treated: prior to admission and hospital discharge, at hospital admission and during hospital in-stay. In order to facilitate team-debate, the groups independently studied the previously proposed recommendations.

The main objective of Metaplan® methodology was that said technique allows free and structured knowledge to be obtained—based, when available, on clinical guidelines and evidence—from those consulted, with the aim of achieving an organized debate, the structuring of knowledge and, as a result of contributions from all the participants, the identification of consensuses and disagreements, individual reflection and a free and structured participation.

After the working group stage, in-office work was carried out in which the contributions of each group were collected and synthesized. New recommendations were drawn up from said information, and first validated by the consensus coordinators.

The final recommendations were classified according to the modified Scottish Intercollegiate Guidelines Network (SIGN) system (Table 1), which is characterized by allowing the quality of scientific evidence to be classified and grading the strength of the recommendations with simplicity and transparency and is based on the Centre for Evidence-Based Medicine in Oxford.
(CEBM) system for screening and diagnostic methods questions (Table 2) and SIGN for the rest of the questions.37 Given the difference in the experimental designs according to objective types, this modification allows us to avoid underestimation in the critical assessment of the evidence studies collected. Subsequently, said recommendations were sent twice via e-mail to all the participating scientific societies to obtain their final validation.

**Consensus recommendations for the prevention and management of hospital malnutrition**

**Recommendations prior to hospital admission**

Screening in the primary care setting

1. The use of a nutritional status screening method should be implemented in primary care centers for any patient who presents clinically suspicious criteria for malnutrition.36,38-40 **Grade of recommendation:** D

Clinical suspicion includes, for example, involuntary weight loss, substantial muscle and subcutaneous fat loss, persistent lack of appetite, problems regarding food-intake, swallowing, digestion or absorption of nutrients, as well as an increase in nutrients lost (prolonged vomiting and diarrhea) and the presence of prolonged intercurrent disease, among others.36

2. It is advisable to use The “Malnutrition Universal Screening Tool” (MUST)42 for adults in primary care. **Grade of recommendation:** D

3. The Mini-Nutritional Assessment Short Form (MNA SF)43-44 is the most suitable for use in the elderly in primary care. **Grade of recommendation:** D

4. Screening should be performed by trained and experienced healthcare professionals, involved directly in the patient’s care.42 **Grade of recommendation:** D

**Table I**

<table>
<thead>
<tr>
<th>Levels of Scientific Evidence</th>
<th>Grades of Recommendation</th>
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<tr>
<td>I++</td>
<td>High quality meta-analyses, systematic reviews of Randomized Clinical Trials (RCTs) or RCTs with a very low risk of bias.</td>
</tr>
<tr>
<td>I+</td>
<td>Well conducted meta-analyses, systematic reviews, or RCTs with a low risk of bias.</td>
</tr>
<tr>
<td>I-</td>
<td>Meta-analyses, systematic reviews, or RCTs with a high risk of bias.</td>
</tr>
<tr>
<td>2++</td>
<td>High quality systematic reviews of case control or cohort studies.</td>
</tr>
<tr>
<td>2+</td>
<td>High quality case control or cohort studies with a very low risk of bias and a high probability that the relationship is causal.</td>
</tr>
<tr>
<td>2-</td>
<td>Well conducted case control or cohort studies with a low risk of confounding or bias and a moderate probability that the relationship is causal.</td>
</tr>
<tr>
<td>3</td>
<td>Case control or cohort studies with a high risk of confounding or bias and a significant risk that the relationship is not causal.</td>
</tr>
<tr>
<td>4</td>
<td>Non-analytical studies, e.g. case reports, case series.</td>
</tr>
<tr>
<td>4</td>
<td>Expert opinion.</td>
</tr>
<tr>
<td>4</td>
<td>Good Clinical Practice</td>
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</tbody>
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- **Recommended practice,** based on clinical experience and the consensus of the drafting team.

Occasionally, the drafting group realises that there is some important practical aspect they wish to emphasise but for which there is probably no scientific evidence to support it. In general, these cases are related to some aspect of treatment considered to be good clinical practice and normally no one would question it. These aspects are assessed as points of good clinical practice. These messages are not an alternative to the scientific evidence-based recommendations, but rather should be considered only when there is no other way to highlight said aspect.37

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4. Screening should be performed by trained and experienced healthcare professionals, involved directly in the patient’s care.42 **Grade of recommendation:** D
5. In general medicine offices, after recording the screening test result at the opening of a patient’s medical record, screening should be repeated at 6 months or in the event of any additional medical condition. Grade of recommendation: D.

6. Institutionalized patients should be screened (Grade of recommendation: D, for the options described):
   a) Upon admission to the centre.
   b) If they present clinical suspicion criteria for malnutrition* (*See recommendation 1).
   c) If they present risk of malnutrition, understood as: having eaten little or nothing for more than 5 days and/or having a tendency to eat little or nothing in at least the next 5 days or more, or increase in nutritional needs due to acute disease or worsening of digestive function.

7. Screening should be performed by trained and experienced healthcare professionals, involved directly in the patient’s care. Grade of recommendation: D.

8. In institutionalized patients, after recording the screening test result at the opening of a patient’s medical record, screening should be repeated at 6 months as a minimum, or beforehand if there are clinical changes or clinical suspicion of malnutrition. Grade of recommendation: D.

9. Diagnosis in primary care and residential settings

   9. A nutritional status assessment should be performed in those patients with positive screening results. It should be performed by trained and experienced staff, according to the available resources. The methodology to be used will depend on the patient and the available scientific evidence. Grade of recommendation: D.

8. In the first 24-48 hours of hospital admission, screening should be performed for early detection of malnutrition. Grade of recommendation: A.

   Level of evidence Ib/1++: results of trials have shown that the prevalence of malnutrition can be reduced with suitable nutritional care and nutritional therapy in malnourished patients after early detection. They have shown a significant reduction in length of hospital stay and costs associated to treatment.
Several publications have studied the benefits and cost-effective relationship of an early therapeutic approach, showing that associated morbidity and mortality are reduced significantly, as is length of hospital stay.\textsuperscript{48-54}

11. Each centre should use the screening method most feasible to apply. The following are to be considered as minimal screening variables: BMI (<18.5 kg/m\textsuperscript{2}), involuntary weight changes (weight loss >5\% in 3 months or >10\% in 6 months) and modifications in regular food-intake in the previous month.\textsuperscript{36} \textit{Grade of recommendation: D.}

12. Screening should be performed by trained and experienced healthcare professionals, involved directly in the patient’s care.\textsuperscript{36} \textit{Grade of recommendation: D.}

13. A methodology should be established (according to the action algorithm and the screening tool chosen) so that patients with positive screening results can be identified for necessary subsequent actions.\textsuperscript{36} \textit{Grade of recommendation: D.}

\textbf{Diagnosis}

14. A nutritional status assessment should be performed in those patients screened positive at hospital admission. It should be performed by trained and experienced staff, according to the available resources. Methodology to be used will depend on the patients’ characteristics as well as available scientific evidence.\textsuperscript{36} \textit{Grade of recommendation: D.}

\textbf{Recommendations during hospitalization}

\textbf{Screening}

15. Patients screened negative for nutritional risk at admission should be reassessed; frequency will depend on the patient’s condition and nutritional risk factors present. It is recommended to re-screen at least every week.\textsuperscript{36} \textit{Grade of recommendation: D.}

\textbf{Diagnosis}

16. Each hospital should clearly establish malnutrition criteria. Those established by the SENPE-SEDOM consensus document, published in bulletin no. 29 of the Technical Office of the ICD-9 of the Spanish Ministry of Health, Social Policy and Equality in June 2008 are recommended. Each hospital should define the malnutrition diagnosis protocols and circuits.\textsuperscript{35} \textit{Grade of recommendation: V.}

\textbf{Follow-up}

17. For those patients with malnutrition at hospital discharge, it should be prescribed nutritional council and/or support to be followed at home. Patient and caregivers should be adequately informed regarding prescribed treatment, both verbally and written, and should be included in the discharge report.\textsuperscript{36} \textit{Grade of recommendation: D.}

18. Disease-related malnutrition as well as the dietary intervention (including both enteral and parenteral nutrition), should be noted in the discharge report so it can be encoded.\textsuperscript{36} \textit{Grade of recommendation: D.}

Recommendations for nutritional intervention in patients with positive nutritional assessment or screening

19. Food intake assessment should be performed in patients screened positive.\textsuperscript{36} \textit{Grade of recommendation: D.}

20. Once diagnosis of malnutrition has been established (documented in the patient’s medical record), the patient’s nutritional requirements should be determined, based on their clinical situation and baseline condition. Requirements should be re-evaluated over time according to evolution. This should be performed by trained and experienced healthcare professionals involved in direct patient care.\textsuperscript{36} \textit{Grade of recommendation: D.}

21. When food intake is insufficient, properly qualified personnel from the centre should assess the causes and record them systematically. In these cases, intake should be individualized, adapted and enriched, if necessary, to cover patient’s requirements.\textsuperscript{36} \textit{Grade of recommendation: D.}

22. When food intake is insufficient, menus should be individualized and enriched, adapting them, if necessary, to cover requirements. \textit{Grade of recommendation: A.}

Level of evidence 1++: multiple studies results and added meta-analysis have shown scientific evidence of the effectiveness of oral nutritional supplements. An exhaustive systematic literature review that included all types of combinations and specialties (complete supplements containing a balanced mixture of proteins, energy, vitamins and minerals, other homemade supplements, incomplete supplements, etc.) have shown their capacity to decrease the prevalence of malnutrition and with adequate nutritional care in malnourished patients contribute to a significant reduction in mean in-hospital stay as well as costs associated with treatment.\textsuperscript{31,42,55-88}

23. Prescribe nutritional supplementation if diet modifications do not cover the nutritional needs of the patient (energy, proteins, minerals, vitamins, etc.). If the prescription of oral nutritional supplements is considered, selection of supplement should attend:

- Patient’s requirements according to their needs
- Physiological and pathological conditions of the patient
– Suitability of the presentation given the patient’s situation and preferences

Grade of recommendation: A. Based on the references of scientific evidence from the previous recommendation.

24. If the patient presents inadequate oral intake despite diet modifications and the use of oral nutritional supplements, administration of enteral nutrition should be considered as long as, based on clinical judgment, the gastrointestinal tract is functional both in terms of absorption capacity and motility. Grade of recommendation: A.

Level of evidence 1+: despite evidence showing improvement of nutritional status in these cases (p value <0.001 to 0.012) results are not convincing with respect to in-hospital stay improvement or associated morbidity and mortality, perhaps due to the wide variability in patients requiring this type of therapy and also sometimes because of the short recording period, not allowing the relationship between intervention and healthcare endpoints to be confirmed. Grade of recommendation: D.

25. In those patients requiring enteral nutrition because of their clinical situation or baseline disease, the most suitable digestive access shall be chosen based on:

– The patient’s disease
– The current clinical condition of the patient
– Safety and tolerance of access
– Foreseen length of enteral nutrition
– Availability of resources

If gastric access is not believed to be safe, post-pyloric access should be assessed. Grade of recommendation: √

26. The selection and administration of enteral nutrition will, at all times, depend on the patient’s requirements according to their needs as well as their physiological and pathological conditions. All decisions will be reported to and agreed upon with the patient. Grade of recommendation: D.

27. Parenteral nutrition shall be reserved for those cases in which enteral nutrition is contraindicated, cannot be carried out in which is unable to meet the patient’s nutritional requirements. Grade of recommendation: D.

28. Interventions shall include a nutritional support plan for those patients needing it, after nutritional assessment. The professional or team responsible for treatment should be identified and nutritional intervention protocols should be established at each healthcare level. This will involve the medical team, nursing and auxiliary staff at centers that do not have a nutritional support unit to manage at-risk and/or malnourished patients. The team responsible will be clearly identified. Grade of recommendation: D.

29. Compliance, efficacy, tolerance and safety of any nutritional action should be monitored and recorded. For this, a specific form should be designed. Grade of recommendation: D.

30. Nutritional action procedures should be distributed to the personnel involved to facilitate compliance via the contribution of necessary measures. Compliance with procedures should be evaluated periodically with the aim of improving them and adjusting them to the needs of each healthcare level (primary care, specialized care). Grade of recommendation: D.

Conflict of interest statement

Economic and technical support for this study came from an unrestricted grant from Nestlé Healthcare Nutrition, S. A. Iberia. All authors, except for K Araujo, declare independence from the sponsoring body in the analysis of evidence and the formulation of recommendations, and deny any conflicts of interest with the organization mentioned above.

Statement of authorship

All authors, except for K Araujo, are members of the Consensus Coordination Committee and participated in all stages of this work. A García de Lorenzo, M Planas and J Álvarez participated in the consensus concept development and take-off. K Araujo searched available scientific literature, reviewed the evidence and gave methodological support to the consensus. J Álvarez, M Planas and R Burgos, proposed first recommendations based on the evidence, reviewed every round of recommendations validation process, as well as the manuscript writing and reviewing process. All authors reviewed and approved the manuscript final version.

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Table III
Multidisciplinary consensus work-team on the approach to hospital malnutrition in Spain and scientific societies represented

<table>
<thead>
<tr>
<th>Participating Societies (societies presented in alphabetic order)</th>
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<tr>
<td>Arantza Ruiz de las Heras, MD.</td>
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<td>Eduardo Cabré, MD.</td>
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<td>Jesús M. Culebras, MD.</td>
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<td>Gregorio Varela, MD.</td>
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<td>Joan Gabriele</td>
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<td>Ana Isabel de Cos Blanco, MD.</td>
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<td>Francisco Martí, MD.</td>
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<td>Irene Bértot, MD.</td>
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<td>Ana Pastor, MD.</td>
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<td>Alberto López, MD.</td>
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<td>Begoña Omedilla, MD.</td>
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<td>Inmaculada Alfageme, MD.</td>
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<td>Mª Luisa López Díaz-Ufano, MD.</td>
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<td>Ana Mañas, MD.</td>
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Gómez MD, Angel Moreno MD (Spanish Society of Internal Medicine-SEMI), Ángel Moreno MD (Spanish Society of Medical Documentation-SEDOM), Juan Antonio Virizuela MD (Spanish Society of Medical Oncology-SEOM), Guillermina Barril MD, Rosa Sánchez MD (Spanish Society of Nephrology-SENI), Begoña Omedilla MD, Inmaculada Alfageme MD, Spanish Society of Pneumology and Chest Surgery-SEPAR, Mª Luisa López Díaz-Ufano MD, Ana Mañas MD, Spanish Society of Primary Care Doctors-SEMERGEN, Ana Mañas MD, Spanish Society of Radiotherapeutic Oncology-SEOR (table III).

References