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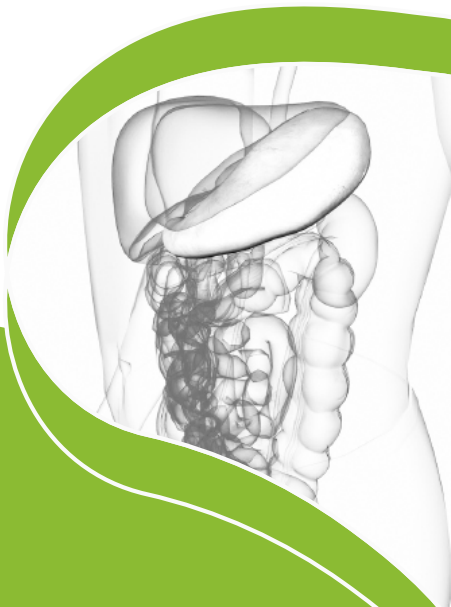
ANDALUSIAN JOURNAL OF DIGESTIVE PATHOLOGY

THEMATIC REVIEWS

CLINICAL CASES

IMAGE IN CLINICAL MEDICINE



Official Body of Sociedad Andaluza de Patología Digestiva

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1. RAPD Objectives and characteristics: The Revista Andaluza de Patología Digestiva is the official publication of the Andalusian Society of Digestive Pathology (SAPD), which since 2007 has been published in electronic format only, under the name RAPD Online. Its purpose is to disseminate all epidemiological, clinical, basic and sociological aspects of digestive diseases, through the contributions sent to the journal from Andalusia and from the entire scientific community. The official language for the publication of this journal is Spanish, but some contributions may be accepted in the author's original language in English, French or Italian. RAPD Online is published bimonthly, with one of the issues being specially dedicated to the Annual Meeting of the SAPD and the Editorial Board deciding to reserve one or more issues per year for the monographic development of a topic related to the speciality.

All submitted contributions must be original and not be simultaneously under review for publication in another journal. The publication of abstracts or posters is not considered duplicate publication. Manuscripts will be evaluated by expert reviewers, appointed by the editorial board, before being accepted for publication, in a process that will take less than 30 days.

2. RAPD Contents: *regular numbers of RAPD Online include defined sections such as:*

- *Original articles on clinical or basic research.*
- *Thematic reviews on specific aspects of Gastroenterology.*
- *Consensus documents.*
- *Clinical cases.*
- *Clinical cases with videos or Videoforum.*
- *Images of the month.*
- *News and updates on gastroenterology and hepatology.*
- *Letters to the Editor.*

Other contributions that are considered of interest by the Editorial Board, relating to different aspects of clinical practice in the recent past, biographical comments, or other contents of a cultural nature, or related to scientific activities in any territorial area, will be inserted in RAPD Online in sections designed specifically for this purpose.

3.Submission of manuscripts: *The preferred way to submit manuscripts is through the SAPD website (https://www.sapd. es), by accessing the RAPD Online page and clicking on the "Submit an original" button located on the same access page to the journal. This will take you to the Manuscript Centre, from where you will be able to send manuscripts and all the required documentation. To use this tool you must be previously registered, access requires a username and password. If you are a member of the SAPD, you can use your usual username. If you are not a member, you can request a username for access to the Manuscript Centre using the form on the website. You can write to sulime@sulime.net or RAPDonline@sapd.es, for the solution of any problem in the submission of manuscripts.*

4. Writing standard for manuscripts: *monographic numbers, thematic reviews, updates and annotated articles will be commissioned by the Editorial Board, but the submission of any of these contributions at the request of an author will be considered by the RAPD Online Management and evaluated with great interest for inclusion in the journal.*

All manuscripts will be subject to specific rules, depending on the type of contribution, and to common ethical and legal standards.

A) Specific standard for manuscripts writing

They refer to the recommended length and structure of each type of manuscript. As a basic unit of length for the text, in any of the contributions, a page of 30-31 lines, spaced 1.5 lines apart, with a font size of 12, with 75-80 characters without spaces per line and a total of 400-450 words per page is considered. Texts should be sent spell-checked and in editable format in all their applications (main text, figures, legends or figure captions, tables, graphs, drawings).

Originals: *originals can be up to 12 pages long (5,100 words), excluding bibliographical references and captions to figures and tables. It is not advisable to insert more than 10 images, including tables and figures. Colour illustrations and videos will not represent an economic charge for the authors, but the insertion of videos, for technical reasons, will be previously agreed with the editor. However, the editing method of RAPD Online allows, in specific cases, the acceptance of longer manuscripts, or the inclusion of a greater number of images, provided that the characteristics of the material presented so require. It is not advisable to have more than 9 authors, except in the case of collaborative works. In these originals, the first nine participants will be listed at the head of the paper and the rest of the participants will be listed at the end of the first page of the manuscript.*

Through the Manuscript Centre, the following information will be required for the submission of an original:

- General data:

1° Full title of the paper in Spanish and English
2° Surnames and first names of all authors.
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4° Full postal address of the responsible author, to whom correspondence should be addressed, including telephone, fax and email address.
5° Declaration on the existence or non-existence of a source of funding for the work, or conflicts of interest.

- Main body of the manuscript, containing:

1° Structured abstract in Spanish (optional also in English) and 3-5 keywords. The abstract will have a maximum length of 250 words and should be structured as follows:

a) Introduction and objectives
b) Material and methods
c) Results
d) Conclusions

2° List of abbreviations used in the text.

3° Text: it will include the following sections:
a) Introduction
b) Material and methods
c) Results

d) Discussion
e) Conclusions; each of them appropriately headed.

4° Bibliography: according to the specifications established in the group of common standards (See common standards and other supporting documents).

5° Acknowledgements.

6° Figure captions.

7° Tables and figures in text.

Thematic Reviews: *texts on Thematic Reviews can be up to 15 pages long (6,375 words), excluding bibliographical references and captions to figures and tables, and chapters corresponding to Update series up to 20 pages (8,500 words). In both cases the number of inserted images should not exceed 15, including tables and figures. However, the RAPD Online editing method allows, in specific cases, for manuscripts of greater length, or the inclusion of a greater number of images, provided that the characteristics of the material presented so require. Illustrations in colour will not be charged to the authors. Exceptionally, the inclusion of videos will be accepted. It is not advisable to include more than 4 authors per chapter.*

Through the Manuscript Centre, and for the submission of Reviews and Issues and Updates, the following information will be required:

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2° Surnames and first names of all authors.
3° Centre(s) of origin(s) (department, institution, city and country).
4° Full postal address of the responsible author, to whom correspondence should be addressed, including telephone, fax and email address.
5° Declaration on the existence or non-existence of a source of funding for the work, or conflicts of interest.

- Main body of the manuscript, containing:

1° Structured abstract in Spanish and English. 3-5 key words. The abstract will have a maximum length of 350 words, emphasising the most important aspects of the manuscript.
2° Text: Structured according to the criteria of the author(s), for a better understanding of the topic developed.
3° Bibliography: According to the specifications established in the group of common standards (See common standards and other supporting documents).
4° Acknowledgements.
5° Figure captions
6° Tables and Figures in the text.

Consensus documents: texts on Consensus documents are not limited in length in terms of text or images and tables. Exceptionally, the inclusion of videos is allowed. It is not advisable to have more than 10 authors per chapter.

Through the Manuscript Centre, and for the submission of Reviews and Updates, the following information will be required:

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2° Surnames and first names of all authors.
3° Centre(s) of origin (department, institution, city and country).
4° Full postal address of the responsible author, to whom correspondence should be addressed, including telephone, fax and email address.
5° Declaration on the existence or non-existence of a source of funding for the work, or conflicts of interest.

- Main body of the manuscript, containing:

1° Structured abstract in Spanish and English. 3-5 key words. The abstract will have a maximum length of 350 words, emphasising the most important aspects of the manuscript.
2° Text: Structured according to the criteria of the author(s), for a better understanding of the topic developed.
3° Bibliography: According to the specifications established in the group of common standards (See common standards and other supporting documents).
4°Acknowledgements
5° Figure captions.
6° Tables and Figures in the text.

Clinical Cases: *the manuscripts included in this section will include 1-5 clinical cases, which due to their infrequent or unusual clinical behaviour, or because they provide some diagnostic or therapeutic novelty, deserve to be reported.*

The length of the texts in the Clinical Cases section should not exceed 5 pages (2,125 words), excluding bibliographical references and captions to figures and tables, and the number of inserted images should not exceed 5, including tables and figures. However, the RAPD Online editing method allows, in specific cases, the acceptance of longer manuscripts, or the inclusion of a greater number of images, provided that the characteristics of the material presented so require. Colour illustrations and videos will not represent a financial charge for authors, but the insertion of videos, for technical reasons, will be previously agreed with the editor. No more than 5 authors will be admitted, except in specific and reasoned cases.

Through the Manuscript Centre, and for the submission of Clinical Cases, the following information will be required:

- General data:

1° Full title of the paper in Spanish (optional also in English).
2° Surnames and first names of all authors.
3° Centre(s) of origin(s) (department, institution, city and country).
4° Full postal address of the responsible author, to whom correspondence should be addressed, including telephone, fax and e-mail address.

- Main body of the manuscript, containing:

1° Structured abstract in Spanish and English. 3-5 key words. The abstract will have a maximum length of 250 words.
2° Introduction. To present the clinical problem reported.
3° Description of the clinical case.
4° Discussion. To highlight the peculiarities of the case and its consequences.
5° Bibliography: According to the specifications established in the group of common standards (See common standards and other supporting documents).
6°Acknowledgements.7° Figure captions.
8° Tables and text figures.

Clinical Cases with Videos or Videoforum: *the manuscripts included in this section will include 1-5 clinical cases, which due to their infrequent or unusual clinical behaviour, or because they provide some diagnostic or therapeutic novelty, deserve to be communicated.*
The length of the texts in the Videoforum section should not exceed 5 pages (2,125 words), excluding bibliographical references and captions to figures and tables, and the number of images inserted should not exceed 5, including tables and figures. However, the RAPD Online editing method allows, in specific cases, the acceptance of longer manuscripts, or the inclusion of a greater number of images, provided that the characteristics of the material presented so require. Colour illustrations and videos will not represent a financial charge for authors, but the insertion of videos, for technical reasons, will be previously agreed with the editor. No more than 5 authors will be admitted, except in specific and reasoned cases.

Videos should be submitted in AVI, MPEG, MP4 OR MOV format, and at a recommended high quality resolution (720p or 1080p). They must not contain personal data of the patients. It is recommended that they be edited to minimise editing time, which should not exceed 10 minutes. If the video includes sound, it must be processed in MP3 format. If the videos to be included are in other formats, please contact the publisher

to verify their validity. They should not exceed 2GB.
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1° Full title of the work in Spanish and English. 2° Surnames and first names of all authors.
3° Centre(s) of origin (department, institution, city and country).
4° Full postal address of the responsible author, to whom correspondence should be addressed, including telephone, fax and email address.

- Main body of the manuscript, containing:

1° Structured abstract in Spanish and English. 3-5 key words. The abstract will have a maximum length of 250 words.
2° Introduction. To present the clinical problem reported. 3° Description of the clinical case.
4° Discussion. To highlight the peculiarities of the case and its consequences.
5° Bibliography: According to the specifications established in the group of common standards (See common standards and other supporting documents).
6°Acknowledgements.7° Figure captions.
8° Tables and figures in text.
9° Videos.

Link tutorial videos: https://www.sapd.es/videoteca/varios/ tutoriales/

Images of the month: *the manuscripts included in this section can take two formats, depending on the authors' preference.*

- Format A. Images with educational value: these shall include images of any kind, clinical, radiological, endoscopic, anatomopathological, macro and microscopic, which contribute to postgraduate training and therefore deserve to be shown because of their peculiarity, or because they represent a characteristic example.
- Format B. Key images for a diagnosis: These will include images of any kind, clinical, radiological, endoscopic, anatomopathological, macro and microscopic, together with a summarised clinical history, which will provide the possible final diagnostic resolution. This will be presented in a separate section in the same issue of the journal.

The length of the texts in the Images of the Month section must not exceed 1 page (425 words) in the clinical approach to the image presented and 2 pages (850 words), excluding bibliographical references and captions to figures and tables, in the commentary on the image (Format A) or in the diagnostic resolution of the case (Format B). However, the RAPD Online editing method allows, in specific cases, the acceptance of longer manuscripts, or the inclusion of a greater number of images, provided that the characteristics of the material presented so require. Colour illustrations and videos will not represent a financial charge for authors, but the insertion of videos, for technical reasons, will be previously agreed with the editor. No more than 3 authors will be accepted, except in specific and reasoned cases.

Through the Manuscript Centre, and for the submission of an Image of the Month, the following information will be required:

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1° Full title of the work in Spanish and English.. 2° Surnames and first names of all authors.
3° Centre(s) of origin (department, institution, city and country).
4° Full postal address of the responsible author, to whom correspondence should be addressed, including telephone, fax and email address.
5° Type of Image of the Month format chosen.

-Main body of the manuscript, containing:

1° Structured abstract in Spanish and English and 3-5 key words. The abstract will have a maximum length of 250 words.
2° Description of the image.
3° Comments on the image.
4° Bibliography: According to the specifications established in the group of common standards (See common standards and other supporting documents).
5° Figure captions.

New developments and updates in gastroenterology and hepatology: this section will be devoted to commenting on the scientific and medical developments that have occurred in recent years in the speciality of Gastroenterology and Hepatology.

This section will systematically and periodically analyse all facets of the speciality.

Texts on " New developments in Gastroenterology" may be up to 5 pages long (2,125 words), excluding bibliographical references and captions to added figures and tables. In both cases the number of inserted images must not exceed 5, including tables and figures. However, the RAPD Online editing method allows,

in specific cases, the acceptance of longer manuscripts, or the inclusion of a greater number of images, provided that the characteristics of the material presented so require. It is not advisable to have more than 3 authors per chapter.

Through the Manuscript Centre, you will be asked to provide the following information:

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1° Name of the bibliographic area reviewed and period analysed 2° Surname and first name of all authors. It is advisable to place a hyphen between the first and second surname.
3° Centre(s) of origin (department, institution, city and country).
4° Full postal address of the responsible author, to whom correspondence should be addressed, including telephone, fax and email address.
5° Declaration on the existence or non-existence of a source of funding for the work, or conflicts of interest.

- Main body of the manuscript, containing:

1° Structured abstract in Spanish and English. 3-5 key words. The abstract will have a maximum length of 250 words.
2° Description of the bibliographic material analysed.
3° Critical comments on the results contained in the selected works.
4° Bibliography: According to the specifications established in the group of common standards (See common standards and other supporting documents). If two or more originals have been chosen for the analysis, it is advisable to divide the section into sections at the authors' discretion.
5° Figure captions.
6° Tables and Figures in text.

Letters to the Editor: *this section will be dedicated to comments on any manuscript published in RAPD Online. This section may also include comments of a more general nature, establishing the authors' own hypotheses and suggestions, within the scientific field of Gastroenterology. The length of the texts in this section of Letters to the Editor should not exceed 2 pages (850 words), including bibliographical references. Two figures or tables may be included and the number of authors should not exceed four.*

Through the Manuscript Centre, and for the submission of a Letter to the Editor, the following information will be required:

- General data:

1° Full title of the work in Spanish and English.
2° Surnames and first names of all authors. It is advisable to place a hyphen between the first and second surname.
3° Centre(s) of origin (department, institution, city and country).
4° Full postal address of the responsible author, to whom correspondence should be addressed, including telephone, fax and e-mail address.
5° Declaration on the existence or non-existence of a source of funding for the work, or conflicts of interest.

- Basic body of the manuscript, containing:

1° Text of the manuscript.
2° Bibliography: According to the specifications set out in the common standards group (See common standards and other supporting documents).

B)Common standards and other supporting documents

This refers to the set of mandatory standards, both for uniformity in the presentation of manuscripts and for compliance with current legal regulations. In general, the style of manuscripts should follow the guidelines set out in the Vancouver Agreement of the International Committee of Medical Journal Editors. (http://www.ICMJE.org).

Units, generic names and abbreviations:

- Units. Biochemical and haematological parameters shall be expressed in International Units (SI), except haemoglobin which shall be expressed in g/dL. Length, height and weight measurements shall be expressed in decimal metric units and temperatures in degrees Celsius. Blood pressure shall be measured in millimetres of mercury.
There is an aid for the conversion of non-international (non-SI) units into international (SI) units. (http://www.techexpo.com/techdata/techcntr.html).

- Generic names. The generic names of medicinal products, clinical instruments and tools and software shall be used. When a brand name is the subject of research, the brand name and the name of the manufacturer, city and country shall be included in parentheses the first time the generic name is mentioned in the Methods section.

- Abbreviations. Abbreviations should be avoided, but if they have to be used, in order not to repeat long technical names, the full word should appear the first time in the text, followed by the abbreviation in brackets, which will already be used in the manuscript.

Bibliographical references: bibliographical references should be presented in the order in which they appear in the manuscript, with a sequential number, which will appear in the appropriate place in the text, in brackets. This numbering will be maintained and will serve to order the list of all references at the end of the manuscript, as normal text and never as a footnote. Personal communications and unpublished data will not be included in the final list of bibliographical references, although they will be mentioned in the appropriate place in the text, in brackets, as appropriate, i.e. personal communication or unpublished data. When the bibliographic citation includes more than 6 authors, the first 6 authors should be cited, followed by the abbreviation et al.

The style of bibliographic references will depend on the type and format of the source cited:

- Medical journal article: journal names should be abbreviated according to the style of the Index. Medicus/Medline (http://www.ncbi.nlm.nih.gov/journals?itool=sidebar).

- Article already published in print and online journals Internet:
The authors (surname and initial of the first name, comma separation between authors), the full name of the manuscript, the abbreviation of the journal, the year of publication and after a semicolon the volume of the journal and after a colon the complete numbers of the first and last page of the paper.

Kandulsky A, Selgras M, Malfertheiner P. Helicobacter pylori infection: A Clinical Overview. Dig Liver Dis 2008; 40:619-626.

Alvarez F, Berg PA, Bianchi FB, Bianchi L, Burroughs AK,Cancado EL, et al. International Autoimmune Hepatitis Group Report: review of criteria for diagnosis of autoimmune hepatitis. J Hepatol 1999; 31:929-938.

- Admitted article, published only on the Internet, but not yet included in a regular number of the journal: the authors, the full name of the manuscript, the abbreviation of the journal, the year and month since the article is available on the Internet and DOI will be noted. The original paper to which reference is made usually details how to cite the manuscript.

Stamatakos M, Sargedi C, Stefanaki C, Safi oleas C, Matthaiopoulou I, Safi oleas M. Anthelminthic treatment: An adjuvant therapeuticstrategy against Echinococcus granulosus. Parasitol Int (2009), doi:10.1016/j.parint.2009.01.002

Inadomi JM, Somsouk M, Madanick RD, Thomas JP, Shaheen NJ. A cost-utility analysis of ablative therapy for Barrett'sesophagus, Gastroenterology (2009), doi: 10.1053/j.gastro.2009.02.062.

- Article from a journal that is published only on the Internet, but arranged in a conventional way: the authors, the full name of the manuscript, the abbreviation of the journal (can be added in brackets online), the year of publication and after a semicolon the volume of the journal and after a colon the complete numbers of the first and last page of the paper. If the original work being referenced provides the DOI and Internet address (URL), these can be added at the end of the reference.

Gurbulak B, Kabul E, Dural C, Citlak G, Yanar H,Gulluoglu M, et al. Heterotopic pancreas as a leading point for small-bowel intussusception in a pregnant woman. JOP (Online) 2007; 8:584-587.

Fishman DS, Tarnasky PR, Patel SN, Raijman I. Managementof pancreaticobiliary disease using a new intra-ductal endoscope: The Texas experience. World J Gastroenterol 2009; 15:1353-1358. Available from: URL: http://www.wjgnet.com/1007-9327/15/1353.asp. DOI: http://dx.doi.org/10.3748/wjg.15.1353

- Article from a journal that is published only on the Internet, but is not conventionally arranged: the authors, the full name of the manuscript, the abbreviation of the journal, the year of publication and the DOI will be listed.

Rossi CP, Hanauer SB, Tomasevic R, Hunter JO, Shafran I, Graffner H. Interferon beta-1a for the maintenance of remission in patients with Crohn's disease: results of a phase II dose-finding study.BMC Gastroenterology 2009, 9:22doi:10.1186/1471-230X-9-22.

-Article published in an abstract or in a supplement of a journal: the authors (surname and first initial, separated by commas between authors), the full name of the manuscript, the word abstract in square brackets, the abbreviation of the journal, the year of publication and after a semicolon the volume of the journal, followed by the abbreviation Suppl, or Supl, in brackets and after a colon the complete numbers of the first and last page of the paper.

Klin M, Kaplowitz N. Differential susceptibility of hepatocytesto TNF-induced apoptosis vs necrosis [Abstract]. Hepatology 1998; 28(Suppl):310A.

- Books: the authors of the book (surname and first initial, comma separated by the authors), the title of the book, the city where it was published, the name of the publisher and the year of publication will be listed.

Takada T. Medical Guideline of Acute Cholangitis and Cholecystitis. Tokyo: Igaku Tosho Shuppan Co; 2005.

- Chapter of a book: the authors of the chapter should be listed (surname and first initial, separated by commas between authors), followed by In: the names of the editors of the book and, after a full stop, the name of the book. The city where it was published, the name of the publisher, the year of publication and after a colon the complete numbers of the first and last page of the work.

Siewert JR. Introduction. In: Giuli R, Siewert JR, Couturier D, Scarpignato C, eds. OESO Barrett's Esophagus. 250 Questions. Paris: Hors Collection, 2003; 1–3.

- Information from a document produced at a meeting: this type of reference should be avoided whenever possible. However, if it has to be cited, the title of the subject, the name of the meeting and the city where it was held should be given. The entity that organised the meeting, and the year. The e-mail address through which the document can be accessed.

U.S. positions on selected issues at the third negotiating session of the Framework Convention on Tobacco Control. Washington, D.C.: Committee on Government Reform, 2002. (Accessed March 4, 2002, at:http://www.house.gov/reform/min/inves_tobacco/index_accord. htm.)

Figures, tables and videos: iconography, whether photographs, radiographs, diagrams or graphs, should be referred to under the generic name of "Figure". References to figures, tables and videos should be highlighted in bold. They should be numbered with Arabic numerals, according to their order of appearance in the text. Panels of two or more photographs grouped together will be considered as a single figure and may be referred to as "Figures 1A, 1B, 1C".

- Photographs: photographs should be sent in digital format TIFF (.TIF), JPEG (.JPG) or BMP, in black and white or colour, well contrasted, with an appropriate resolution (preferably 150-300 dots per inch). In the case of JPEG files, the minimum compression should be used to maintain maximum quality, i.e. in a non-reduced size.

X-ray, ultrasound, CT and MRI images, if not directly available in electronic format, should be scanned in grayscale and saved in JPG format.

Endoscopic images and other techniques generating colour images, if not directly available in electronic format, shall be scanned in colour. Special details shall be indicated by arrows, using for these and any other type of symbols the maximum contrast plot with respect to the figure.

Figure files will be identified according to their order of appearance in the text, with the name of the file, its number and surname of the first signatory (e.g.: fig1_Gómez.jpg) or the title of the article. Each image must have an associated figure caption that serves as a description. Figure captions must be submitted in a separate text document with clear reference to the figures to which they refer. Images may be inserted in Word/PowerPoint files to facilitate their identification or association with the figure captions, but they must always be submitted as separate images in the formats mentioned above.

Photographs of patients must not make them unidentifiable. If it is not possible to obtain them, the publication of the photograph must be accompanied by written permission (Model Photograph Permission Form).

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- Videos: videos must be submitted in AVI or MPEG format, processed with the CINEPAC RADIUS or MPEG codec and at a resolution of 720x576 or 320x288. It is recommended that they are edited to minimise their length, which should not exceed 2 minutes. If the video includes sound, it must be processed in MP3 format. If the videos to be included are in other formats, please contact the publisher to verify their validity. For the inclusion of videos in articles, prior authorisation must be obtained from the editorial board.

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Conflict of interest: *a conflict of interest exists when an author (or the author's institution), reviewer, or editor has, or has had in the last 3 years, financial or personal relationships with other persons, institutions, or organisations, which may unduly influence their activity.*
Authors must declare the existence or non-existence of conflicts of interest to the Manuscript Centre during the article submission process, but are not required to submit a Conflict of Interest Declaration Form when the manuscript is submitted. This will be required later, if necessary, when the manuscript is accepted.

Grants and financial support received by the authors for the research should be specified at the end of the manuscript in the Acknowledgements section.

Statistics: *it is not the aim of RAPD Online to provide an exhaustive description of the statistical methods used in the conduct of a research study, but to specify some requirements that should appear in manuscripts as standards of good practice. Authors can consult a basic document on this subject at: Bailar JC III, Mosteller F. Guidelines for statistical reporting in articles for medical journals: amplifications and explanations. (http://www.sapd.es/ public/guidelines_statistical_ articles_medical_ journals. pdf). Ann Intern Med 1988; 108:266-73.*

- The statistical methods used, as well as the computer programs and the name of the software used should be clearly stated in the Material and Methods Section.
- To express the mean, standard deviation and standard error, the following formats should be used: "mean (SD)" and "mean ± SE". To express the median, the interquartile range (IQR) values should be used.
- P should be used in capital letters, reflecting the exact value and not expressions such as less than 0.05, or less than 0.0001.
- Whenever possible, findings (means, proportions, odds ratios and others) should be quantified and presented with appropriate indicators of error, such as confidence intervals.
- Studies that show levels of statistical significance should include sample size calculations. Authors should report research losses, such as withdrawals from clinical trials.

Other documents and ethical standards:

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REVIEW ARTICLE

THERAPEUTIC OPTIONS IN ACUTE ALCOHOLIC HEPATITIS: SHOULD WE THINK ABOUT LIVER TRANSPLANTATION?

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Abstract

Acute alcoholic hepatitis (AAH) is a common entity that carries a poor prognosis, especially in cases with severe disease. Its treatment is based on five cornerstones: complete alcohol abstinence, prevention of withdrawal syndrome, addressing malnutrition and deficiency states, pharmacological treatment, and liver transplantation (LT). In patients with severe AAH, defined as Maddrey index >32 or MELD>21 points, the first-line treatment is corticosteroids, which have been shown to reduce short-term mortality. However, if the patient does not respond to corticosteroids according to the Lille index calculated on the seventh day after initiation of treatment, this treatment should be discontinued and up to 70% of these patients will die. Traditionally, patients with severe AAH were contraindicated for LT because their withdrawal period was too short and therefore the risk of ethyl alcohol relapse would be very high. In 2020, the Spanish Society of Liver Transplantation (SETH) held a consensus to discuss new possible indications for LT and severe AAH without response to corticosteroids was finally accepted as one of them. The present review addresses the comprehensive treatment of AAH from a practical and multidisciplinary point of view, including those situations in which the reference transplant center should be contacted to consider the option of LT.

Keywords: acute alcoholic hepatitis; liver transplantation; corticosteroids; nutrition; abstinence.

Introduction

Alcohol has been part of human culture for centuries and is currently the most widely consumed psychoactive substance in the world. Despite evidence of a progressive decline in its intake, more than 2.3 billion people (43% of the world's population) currently consume alcohol[1,2]. Paradoxically, the amount of alcohol consumed per capita has risen from 5.5 litres in 2005 to 6.4 litres in 2016, and this trend is expected to continue until at least 2030[3].

Alcoholism causes around 3 million deaths annually, making it the seventh leading cause of death and loss of disability-adjusted life years[4,5]. Deaths secondary to digestive diseases are the most numerous with 21%; hepatic cirrhosis stands out significantly among them[1].

Continued alcohol consumption causes histological changes in the liver including steatosis, inflammation,

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hepatocyte ballooning, fibrosis and eventually cirrhosis. Clinically, the spectrum of alcohol-related liver diseases is very broad, ranging from steatohepatitis to advanced liver cirrhosis.

Acute alcoholic hepatitis (AAH) is a very particular entity within alcoholic liver disease. It usually occurs in patients with chronic alcoholism who present with an increase in alcohol consumption in the 4-6 weeks prior to onset. Patients develop a rapid onset of jaundice, associated with non-specific abdominal discomfort, asthenia and coagulopathy, with or without hepatic decompensation such as ascites or hepatic encephalopathy[6]. On examination, stigmata of alcoholism such as spider veins, bilateral parotid hypertrophy, exophthalmos or Dupuytren's disease, as well as painful hepatomegaly and/or splenomegaly are common. In 2016, the National Institute on Alcohol Abuse and Alcoholism (NIAAA) published a proposal to unify the diagnostic criteria for AAH[7]. This consensus estimated that the minimum amount of alcohol to develop AAH should be at least 40 g/day in women and 60 g/day in men, although these are often much higher. Patients often have a history of alcoholism of more than 5 years and it is common for patients to stop drinking alcohol a few days before admission, coinciding with the onset of symptoms. Alcohol consumption for more than 6 months and abstinence for less than 60 days are fundamental requirements for diagnosis. Analytically, patients should have serum bilirubin levels above 3mg/dl and mild-to-moderate elevation of transaminases, with an AST/ALT ratio >1.5. It is important to remember that AAH is the only acute hepatitis with transaminases below 10 times the upper limit of normal, so both AST and ALT must be below 400 IU/L. Finally, a diagnosis of exclusion must be made in which other pathologies such as viral hepatitis, Wilson's disease, biliary obstruction, Budd-Chiari syndrome or autoimmune hepatitis, among others, must be ruled out by performing the corresponding analytical tests and an abdominal ultrasound. In an epidemiological, clinical, analytical and ultrasound context as described above, the diagnosis of AAH can be established non-invasively. Liver biopsy would be relegated to the most doubtful cases, given the potential complications and restrictions in clinical practice (Figure 1). If required, a transjugular approach is usually necessary due to the presence of coagulopathy and/or ascites in most cases.

Several American and European studies state that the incidence of AAH shows an upward trend in recent years. In a retrospective Danish study, the authors reported an increase in incidence between 1990 and 2008 from 37 to 46 cases per million among men and from 24 to 34 cases per million among women[8,9]. This effect has been exacerbated during the 2019 Coronavirus pandemic (COVID-19)[10]. Mortality varies according to clinical presentation, and can be as high as 70% per month in the most severe forms. Adequate stratification of patients is therefore essential to know the severity and prognosis in order to adopt an appropriate treatment plan.

There are a number of validated indices that are derived from analytical values and allow the identification of severe AAH on admission. The most commonly used are: Maddrey's Discriminant Function (mDF)(>32)[11], the MELD (≥21)[12], the ABIC score (>6.7)[13] and the Glasgow scale for alcoholic hepatitis (GAHS) (>9)[14] (Table 1). The Maddrey score or discriminant function (mDF) was the pioneer and is still used in clinical practice and clinical trials. However, a recent multicentre study of more than 2,500 patients evaluating the accuracy of different indices for predicting short-term mortality in AAH concluded that the MELD score may be more accurate than the mDF for predicting mortality in this clinical scenario[15]. The prognosis of these patients will depend directly on the severity of the episode and especially on the response to medical treatment.

This review aims to address the treatment of AAH from a practical and multidisciplinary point of view, including specific pharmacological treatment, management of malnutrition and deficiency states, prevention of withdrawal syndrome, and liver transplantation. With regard to the latter, the criteria currently in force in Spain for considering LT in patients with severe AAH are specified.

Pharmacological treatment

Complete abstinence is the mainstay for patients with AAH regardless of the severity of the condition. Continued alcohol consumption increases the risk of upper varicose gastrointestinal haemorrhage, ascites, encephalopathy and death[16]. In addition, it is important to carry out a global approach to these patients, paying special attention to nutritional management, vitamin deficiencies, as well as the treatment of possible decompensations (ascites, hepatic encephalopathy...).

Prednisolone at a dose of 40 mg/day for 28 days is the first-line treatment recommended in all clinical practice guidelines for severe AAH. However, its use has been controversial due to inconsistent results in the studies that support it[17,18]. To address this controversy, a multicentre clinical trial involving 1,103 patients was conducted in the UK between 2011 and 2014. This study concluded that corticosteroids improved survival at 28 days compared to pentoxifylline, but the benefit was not maintained at 6 and 12 months follow-up[19].

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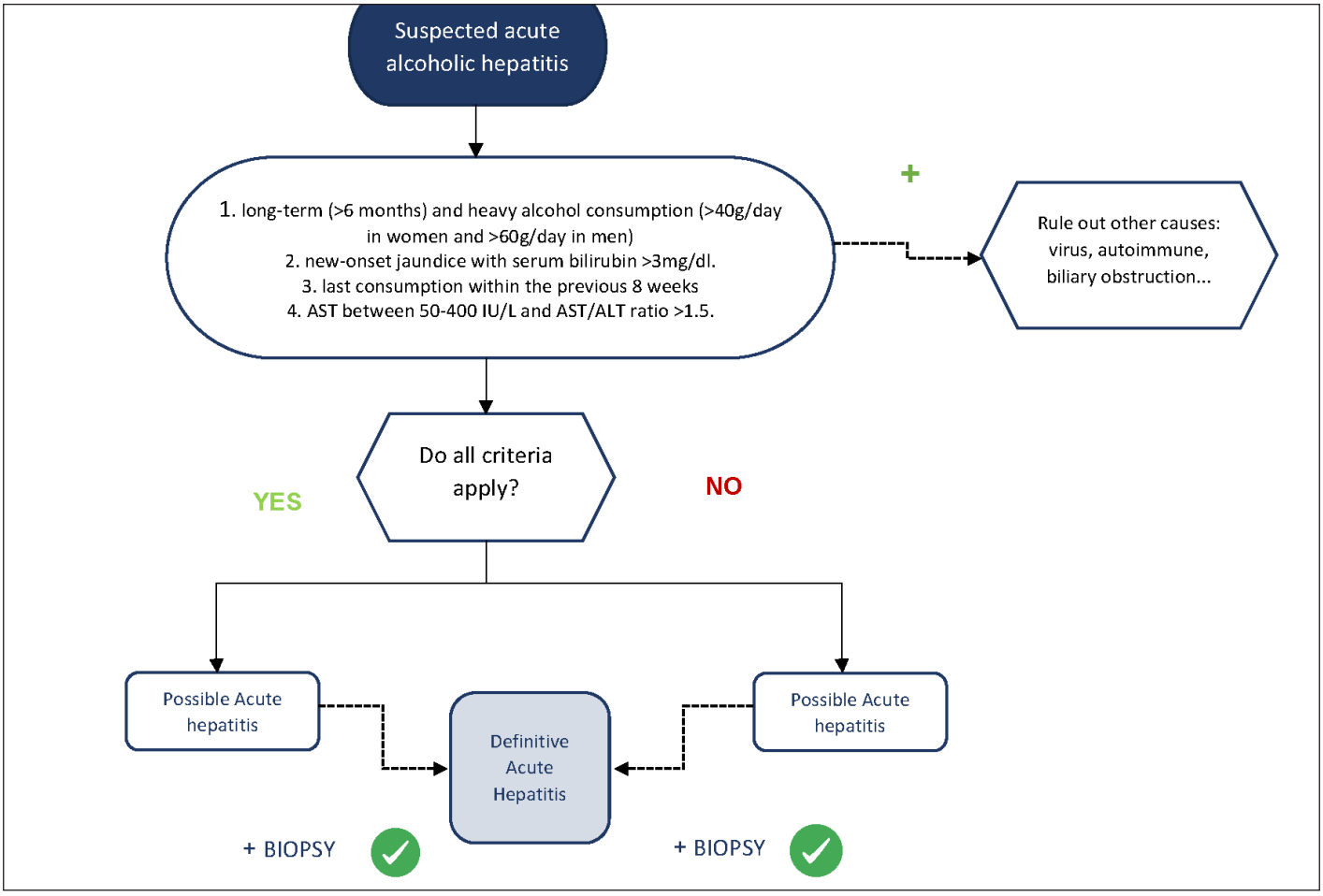

Figure 1. ***Diagnostic algorithm in acute alcoholic hepatitis.***

INDICES	BILIR	TP/INR	Cr/UREA	AGE	LEUK.	ALB	STRATIFICATION	USE
mFD	+	+	-	-	-	-	SEVERE>32	START CS + PROGNOSIS
MELD	+	+	+	-	-	-	SEVERE>32	PROGNOSIS
GAHS	+	+	+	+	+	-	BAD PROGNOSIS >9	START CS IF >9 AND MDF >32
ABIC	+	+	+	+	-	-	HIGH RX >9 MEDIUM 6.71-9 LOW <6.71	PROGNOSIS
LILLE	+	+	+	+	-	+	>0.45 UNRESPONSIVE <0.45 RESPONSIVE	CONTINUE OR STOP CS 7TH DAY

Abbreviations: mDF: Maddrey's Discriminant Function; GAHS: Glasgow Alcoholic Hepatitis Index; ABIC: Age, INR bilirubin and creatine index; CS: corticosteroids.

Table 1. ***Variables of the most commonly used prognostic indices in acute alcoholic hepatitis.***

Given its limited benefit and potential side effects, the cohort of patients receiving this treatment should be appropriately selected. Patients must have severe AAH, defined by an (mFD) of >32[11]and a MELD of ≥21 although the benefit appears to be more pronounced in patients with a MELD between 25 and 39[20]. In addition, there are some relative contraindications that should be evaluated before starting therapy such as sepsis, severe acute renal failure, upper gastrointestinal bleeding.... Once corticosteroids are started, it is important to identify non-responders in order to discontinue them early. The Lille scale is a dynamic scale based on the evolution of bilirubin levels in the first week (day 1 and 7) that predicts the risk of death. The Lille

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score dictates a standard of futility of corticosteroid treatment for those patients with a score above 0.45 on day +7, in whom treatment should therefore be discontinued[21] (Figure 2).

Pentoxifylline (400mg every 8 hours orally) is a phosphodiesterase inhibitor that has historically been used in the treatment of AAH due to the results of the Akrividiadis et al. clinical trial[22], which demonstrated a decrease in in-hospital mortality and the incidence of hepatorenal syndrome. Subsequent studies have failed to support these results. Two French trials failed to demonstrate the survival benefit of pentoxifylline, either in combination with corticosteroid therapy or as an alternative in patients not responding to corticosteroids[23,24]. Similarly, the STOPAH study and several meta-analyses have failed to find any benefit with this drug [19,25,26]. Therefore, there is currently insufficient evidence to recommend the use of pentoxifylline in patients with severe AAH, although its use is still common.

N-acetylcysteine (NAC) has been proposed as a promising therapy given its antioxidant effect. It has been studied in multiple small studies both individually and in combination with other antioxidant agents, without being able to confirm an improvement in survival compared to standard treatment[27,28]. The multicentre study published in 2011 by Nguyen-Khac, E *et al*[29] studied the effects of combined prednisolone and NAC therapy compared with prednisolone and placebo. Mortality at one month of treatment was found to be significantly lower in the corticosteroid arm with NAC, with a reduction in the rate of infections and hepatorenal syndrome. Thus, although the combination of NAC and prednisolone appears to be a promising treatment, its routine use in AAH requires higher quality evidence. It is administered intravenously with the following dosage: on day 1 at doses of 150, 50 and 100 mg/kg bw in 250, 500 and 1000 ml of 5% glucose saline at 30 min, 4 hours and 16 hours periods respectively and on days 2-5 at doses of 100 mg/kg bw in 1000 ml of 5% glucose saline per day.

In recent years, the number of clinical trials investigating new lines of treatment based on the pathophysiology of AAH has increased markedly[30-33]. Most therapies are aimed at promoting effective liver regeneration, controlling liver

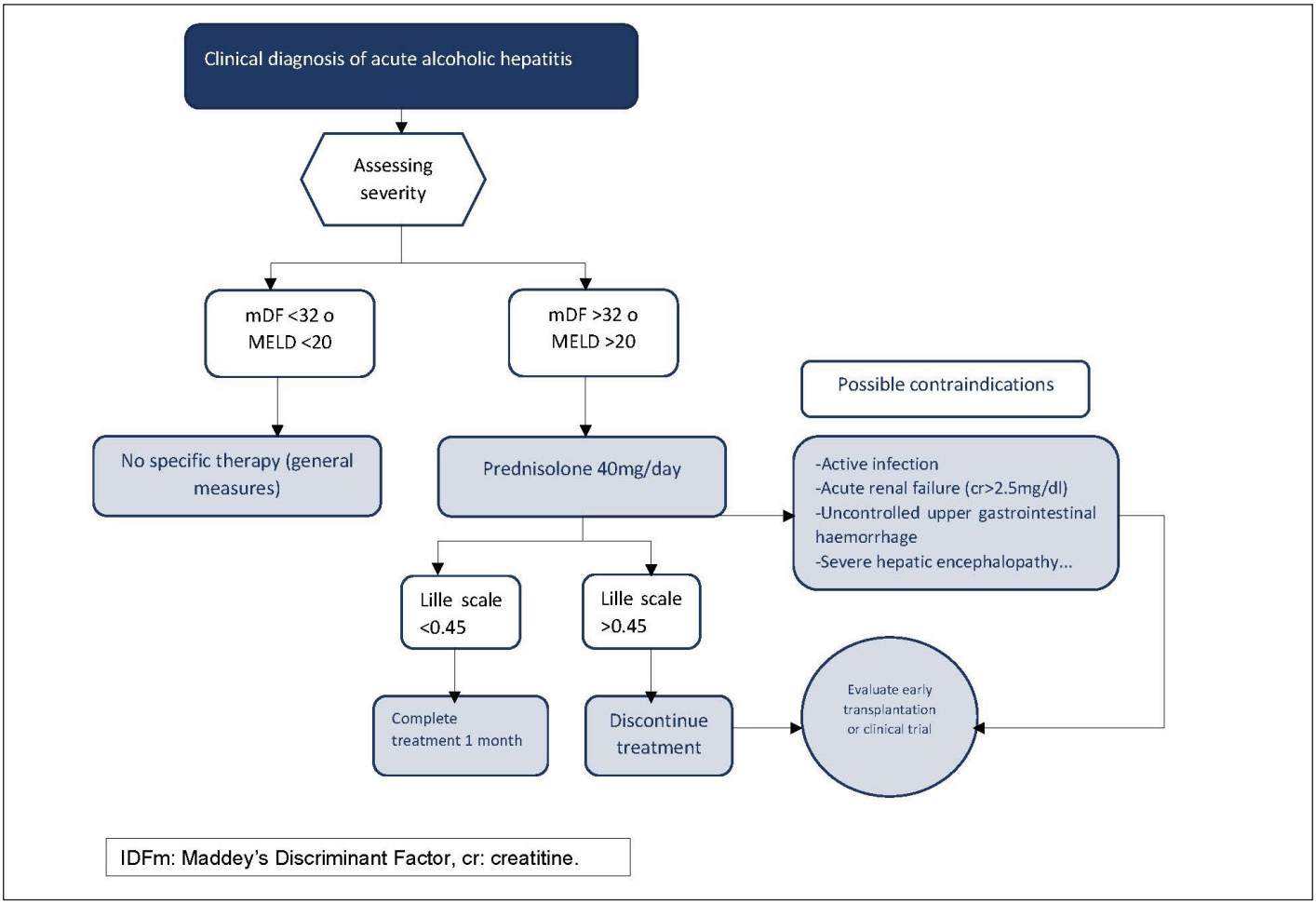

Figure 2. ***Treatment algorithm in acute alcoholic hepatitis.***

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inflammation, reducing oxidative stress, or renewing intestinal dysbiosis.

Granulocyte colony-stimulating factor (G-CSF) (5 µg/kg s.c. every 12h for 5 days) acts by mobilising haematopoietic stem cells and inducing liver regeneration. A prospective, randomised, double-blind study comparing standard therapy with and without G-CSF reported improved survival at 3 and 6 months, as well as a reduction in the rate of infections[34]. However, a recent European study failed to demonstrate this benefit[35]. Similarly, interleukin-22 (IL-22) in a current pilot study has shown a high rate of clinical improvement in patients with moderate-severe AAH with decreased markers of inflammation and increased markers of liver regeneration[36].

Although tumour necrosis factor (TNF) is an important mediator of inflammation, pilot trials with anti-TNF agents (infliximab and etanercept) were stopped prematurely due to increased sepsis mortality in the treatment arm[37]. Similarly, other anti-inflammatory molecules such as anakinra (anti-IL-1) have not shown greater benefit than corticosteroids in patients with severe AAH[38]. However, new clinical trials with other anti-inflammatory therapies, such as canakinumab[39] and DUR-928[40], are currently underway with promising results.

Metadoxine stands out among the antioxidant drugs under study. It has been shown to improve survival rates at 3 and 6 months in patients treated with prednisolone and metadoxine vs. those treated with the corticosteroid alone[41].

Alcohol-induced dysbiosis is associated with increased intestinal permeability and bacterial translocation, both critical factors for the development and progression of AAH. Therefore, therapies targeting the microbiota present another attractive line of research including faecal transplantation, the use of probiotics and non-absorbable oral antibiotics.

Nutritional management

Malnutrition consistently affects patients with advanced liver disease, with the highest prevalence rates and most severe forms identified in alcohol liver disease[42]. Such nutritional deficit is generated by liver dysfunction and the presence of a hypermetabolic state associated with decreased oral intake and intestinal absorption of nutrients. Specifically, in AAH the prevalence of malnutrition reaches almost 100% even in the earliest stages[43,44]. These data are worrying as malnutrition is an independent risk factor for mortality and local/systemic infections[45-47].

Assessment of the nutritional status of the patient with AAH in the first days of admission is a fundamental aspect in order to provide individualised nutritional support. The European Society for Clinical Nutrition and Metabolism (ESPEN) recommends the use of subjective global assessment (SGA) and anthropometric assessment to identify patients at risk, and bioimpedance to quantify the degree of malnutrition[48]. SGA is a simple tool that allows us to obtain information about the nutritional status of the patient through anamnesis (usual dietary intake, gastrointestinal symptoms...) and physical examination (presence of edema, ascites...)[49]. Due to the pathophysiology of liver disease, classical methods such as Body Mass Index (BMI), measurement of the tricipital fold or calculation of classical biochemical values (albumin, prealbumin...) are not suitable methods for assessing the nutritional status of these patients. Force measurement with a hand-held dynamometer, which is quick and simple, has been proposed as the optimal method. Moreover, it has been correlated with other markers of malnutrition in liver disease and is an indicator of functional status. Finally, bioimpedance is commonly used for the study of body composition and is recommended in patients with liver disease despite its possible limitations in hydropic decompensation.

Current clinical practice guidelines recommend an average protein intake of 1.2-1.5 g/kg per day and a caloric intake of 30-40 kcal/kg per day in patients with AAH[50,51]. Surprisingly, an intensive enteral nutrition regimen via a nasogastric tube has been shown to be of no benefit compared to oral nutrition and may have serious side effects especially in patients with hepatic encephalopathy[52].

Apart from protein-calorie malnutrition, micronutrient (vitamin and mineral) deficiencies exist, although there is little evidence about the possible benefit of supplementation. Zinc deficiency is common in patients with ALD. Some studies[53,54]have highlighted its role in maintaining the intestinal barrier and intracellular mechanisms that protect hepatocytes from alcohol-mediated injury. These potential benefits coupled with minimal side effects mean that supplementation is generally recommended in the treatment of AAH. Deficiencies of vitamin A, E, B12, D and magnesium are common, although there is insufficient evidence to support their supplementation in AAH[55].

Prevention of withdrawal syndrome

Approximately 50% of patients with heavy alcohol consumption develop some degree of alcohol withdrawal syndrome (AWS) after an abrupt cessation or reduction of

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alcohol intake[56]. The presentation of AWS varies from mild symptoms such as irritability, tachycardia, high blood pressure, hyperreflexia, anxiety, headache, nausea and tremors to severe forms with seizures, alcoholic hallucinosis, delirium tremens (characterised by mental status changes and intense autonomic hyperactivity), coma and cardiorespiratory arrest [57].

According to a recent systematic review, among patients hospitalised for any medical condition with a history of alcohol use disorder, 2-7% will develop severe AWS[58]. However, the incidence and clinical impact of AWS in patients with liver disease is unknown [59]. In the case of AAH, high alcohol intake and prolonged alcohol consumption, together with the need for hospitalisation, place the patient at high risk of developing AWS. A recent multicentre study evaluating the prevalence and clinical impact of AWS in patients with AAH concluded that AWS occurs in up to one third of patients admitted for AAH. In addition, patients who develop AWS were shown to be at increased risk of hepatic encephalopathy, infection and need for mechanical ventilation. Furthermore, in that study, AWS independently increased short- and long-term mortality in AAH and the use of high-dose intravenous sedatives to control AWS was also associated with worse outcomes [60].

Although clinical practice guidelines for the management of AAH include some comments on the management of AWS, there is little evidence to support that the routine use of prophylactic drug therapy is safe or effective. Thus, there is great variability in management[61]. Most European centres choose AWS prophylaxis in high-risk patients, including patients with AAH, whereas this practice is very uncommon in the United States[62].

Early identification of AWS is crucial for its correct management. Severity scales for AWS can be useful, although they are not validated in patients with AAH. An example is the Clinical Institute Withdrawal Assessment of Alcohol Scale (CIWA-Ar) where a score > 8 indicates moderate AWS and a score ≥ 15 indicates severe AWS (Table 2)[63]. Symptom-based pharmacological treatment is recommended for moderate and severe AAS rather than fixed doses, with the aim of preventing drug accumulation [64].

Benzodiazepines are considered the gold standard in the treatment of AWS because of their efficacy in reducing withdrawal symptoms, the risk of seizures and delirium tremens[65]. Long-acting benzodiazepines (e.g. diazepam) provide greater protection against seizures and delirium, but short- and intermediate-acting benzodiazepines (e.g. lorazepam, oxazepam) are safer in elderly patients and in hepatic failure[66]. In Europe, the use of clomethiazole, a thiamine derivative with hypnotic and sedative capabilities, is widespread. Both benzodiazepines and clomethiazole have a potential risk of abuse, which is higher in patients with alcohol use disorder. Therefore, the use of these drugs should be avoided beyond 10-14 days and benzodiazepines with an intermediate half-life such as lorazepam should be chosen whenever possible. Other medications such as baclofen and sodium oxybate have been approved for the treatment of AWS, with the additional value that they are also indicated for the prevention of alcohol relapse [67]. The safety of current therapies has not been validated in patients with acute or severe hepatic failure, such as in AAH[68].

Liver transplantation

Classically, a minimum of 6 months of complete alcohol abstinence has been imposed before LT can be considered as an option. This fact, together with the lack of knowledge about prognosis, management problems on the waiting list and the negative social impact they sometimes represent, has excluded patients with severe AAH from being potential transplant candidates until a few years ago. However, the "6-month abstinence" rule has not been shown to predict the risk of alcohol relapse after liver transplantation[69]. In 2011, the Franco-Belgian group published the observational case-control study including an early liver transplantation protocol for patients with a first episode of severe AAH unresponsive to corticosteroid treatment[70]. Patients were considered as candidates for transplantation if they met the following criteria: strong family support, absence of psychiatric comorbidity and commitment of the patient and family members to indefinite complete alcohol abstinence. Under these assumptions, the percentage of transplants for severe AAH compared to the total number of transplants performed in the same period was 2.9%. A highly significant benefit in terms of 6-month survival was observed in the LT group compared to controls (77% vs 23%; $p<0.001$). There were 3 cases (11.5%) of alcohol relapse in the longer term but no patients developed graft failure and the authors concluded that the impact of alcohol relapse is limited. After this initial experience, several retrospective observational studies have followed which have reproduced the initial results of the Franco-Belgian group[71-74]. The post-transplant alcohol relapse rate in these studies ranges from 15% to 20%, which is also associated with an increased risk of cancer and graft loss. In the largest study to date, a North American multicentre study including 147 patients with AAH who underwent early liver transplantation, the rate of alcohol relapse was 17% and one patient died of acute alcohol intoxication[73]. Therefore, although LT offers a very pronounced survival benefit for patients with

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NAUSEA AND VOMITING	TACTILE DISTURBANCES
0: No nausea and vomiting 1: Mild nausea without vomiting 2 3 4: Intermittent nausea with dry exertion 5 6 7: Constant nausea and vomiting	0: None 1: Very slight sensation (stinging, burning) 2: Ditto mild 3: Ditto moderate 4: Moderate hallucinations 5: Severe hallucinations 6: Extreme hallucinations 7: Continuous hallucinations
TREMOR	**HEARING DISTURBANCES**
0: No tremor 1: Not visible, can be felt in the fingers 2 3 4: Moderate with arms outstretched 5 6 7: Severe, even with arms not outstretched	0: None 1: Very faint dry or frightening sounds 2: Ditto mild 3: Ditto moderate 4: Moderate hallucinations 5: Severe hallucinations 6: Extreme hallucinations 7: Continuous hallucinations
SWEAT	**VISUAL DISTURBANCES**
0: Not visible 1: Damp palms 2 3 4: Sweat on the forehead 5 6 7: Soaked	0: None 1: Very mild 2: Ditto mild 3: Ditto moderate 4: Moderate hallucinations 5: Severe hallucinations 6: Extreme hallucinations 7: Continuous hallucinations
ANXIETY	**HEADACHE**
0: Not anxious 1: Slightly 2 3 4: Moderate 5 6 7: Acute panic attack	0: Not present 1: Very mild 2: Mild 3: Moderate 4: Moderately severe 5: Severe 6: Very severe 7: Extremely severe
AGITATION	**ORIENTATION AND HIGHER FUNCTIONS**
0: Normal activity 1: Somewhat hyperactive 2 3 4: Moderately restless 5 6 7: Continuous change of posture	0: Oriented and can calculate 1: Cannot calculate, undecided on date 2: Temporarily disoriented (< 2 calendar days) 3: Further temporal disorientation (> 2 days) 4: Spatial and/or personal disorientation 5 6 7

Table 2. ***CIWA-Ar scale. Assessment of alcohol withdrawal syndrome.***

AAH who do not respond to corticosteroids, even greater than in other accepted transplant indications, alcohol relapse is a prevalent and clinically relevant problem that requires the application of very strict candidate selection measures, while adapting the post-transplant follow-up strategy.

In this context, the Spanish Society of Liver Transplantation (SETH) proposed to expand the criteria for liver transplantation in 2020, after years of progressive shortening of transplant waiting lists due to the generalisation of hepatitis C treatments and the increase in the donor pool in relation to asystole donation. Among the possible areas of expansion of transplant criteria, it was decided to incorporate AAH as a formal indication for liver transplantation[75]. Table 3 summarises the requirements for LT to be considered in a patient with AAH. For a patient with severe AAH to be considered as a potential transplant candidate, it must be a first episode of AAH in which the patient was unaware of previous cirrhosis. If the patient was aware of a previous diagnosis of cirrhosis or if the patient has had an AAH episode in the past and has nevertheless not been able to maintain stable alcohol abstinence, the patient should not be considered as a suitable transplant candidate due to the high risk of alcohol relapse. The second requirement is that it is a severe AAH, defined as mFD score > 32 or MELD ≥ 21, and unresponsive to corticosteroids (Lille model score ≥ 0.45 on day +7). In addition, a transplant evaluation should be performed in which no contraindications for transplantation are demonstrated.

In this scenario, multidisciplinary assessment is particularly important, in which a psychosocial assessment is essential to predict the risk of alcohol relapse, which is the main limitation for the inclusion of these patients in transplant programmes. Likewise, in the pre-transplant evaluation of these patients, special attention should be paid to the

FIRST EPISODE OF ACUTE ALCOHOLIC HEPATITIS
EPISODE OF SEVERE ACUTE ALCOHOLIC HEPATITIS DEFINED AS MADDREY INDEX>32 OR MELD>20
NON-RESPONSE TO CORTICOSTEROIDS (LILLE INDEX AT DAY +7 >0.45)
FAVOURABLE PSYCHO-SOCIAL ASSESSMENT
FAVOURABLE ADDICTION SPECIALIST ASSESSMENT USING VALIDATED TOOLS
ABSENCE OF CLASSICAL TRANSPLANT CONTRAINDICATIONS: INFECTIONS, CANCER...
ADDICTIONS SPECIALIST INTEGRATED IN TRANSPLANT UNIT
POST-TRANSPLANT FOLLOW-UP BY ADDICTIONS SPECIALIST

Table 3. ***Requirements necessary to consider the option of liver transplant in patients with acute alcoholic hepatitis in Spain. The recommendations presented have been adapted from the consensus document on criteria for extending the indications for transplantation by the Spanish Society of Liver Transplantation (SETH).***

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exclusion of latent infections and malignancy. A rapid discontinuation of corticosteroids would be prudent in case of non-responders according to the Lille index who are potential candidates for liver transplantation, since in the ACCELERATE-AH study, corticosteroids prior to liver transplantation were associated with increased mortality in the immediate post-transplant period, mainly due to infectious causes[73].

A key issue in these patients is to ensure lasting abstinence after transplantation, which is influenced by factors such as awareness of illness, existence of psychiatric comorbidities or other addictions, number of drinks per day, existence of repeated quit attempts and socio-familial support[76]. An association has been identified in different cohorts of younger age as a possible predictor of post-transplant alcohol use. A thorough and comprehensive assessment of all these factors by a multidisciplinary team including addiction specialists and psychiatrists is important[77]. The applicability of transplantation should be established on the basis of the degree of alcohol dependence, as well as the existence of factors favourable for lasting abstinence[78].

There are different standardised prognostic instruments that combine some of these parameters into a risk scale, but they are not designed for patients with AAH undergoing early LT and none of them has a solid external validation[79-81]. The SALT ("Sustained Alcohol use post-LT") score is so far the only one designed for patients with AAH and a pre-LT alcohol abstinence period of less than 6 months[82]. It assesses 4 parameters with a specific score for each of them and a final score ranging from 0 to 11 points (Table 4). It is a simple system with an acceptable ability to predict severe alcohol relapse post LT (AUROC 0.76). A SALT score <5 had a negative predictive value of 95% while a SALT score≥5 had a positive predictive value of 25%, which would be an unacceptable rate in the context of LT. In other words, following this system, the population prevalence of severe post-LT ethylism in the population would be 5%. Internal validation in the study indicated a good consistency of the model but it still lacks external validation[79-82].

After liver transplantation, a multidisciplinary approach with the participation of different specialists such as hepatologists, addiction specialists or social workers is essential to adequately address the problem of alcohol relapse. This approach makes it possible to prevent relapse, to better interpret the different relapse behaviours and their appropriate treatment[83].

RISKS FACTORS	SCORE
>10 DRINKS/DAY CURRENTLY	+4 POINTS
≥ 2 PREVIOUS UNSUCCESSFUL REHABILITATION ATTEMPTS	+4 POINTS
HISTORY OF ALCOHOL-RELATED LEGAL PROBLEMS	+1 POINTS
HISTORY OF ABUSE OF ILLEGAL SUBSTANCES OTHER THAN CANNABIS	+1 POINTS

Table 4. ***SALT scale. Prognostic instruments for predicting alcohol relapse after liver transplantation.***

On the other hand, the patient transplanted for ALD has a higher cardiovascular risk than other aetiologies and is especially prone to develop head and neck and lung cancer. Therefore, especially modifiable risk factors such as tobacco use, obesity and sedentary lifestyle should be avoided[83].

Conclusions

Alcohol-related liver disease is a public health problem that is most severe in AAH. The incidence of AAH has increased in recent years, especially during the SARS-CoV-2 pandemic. In patients with severe AAH, prednisolone is recommended unless there is an active infection or active gastrointestinal bleeding. There is no evidence that other treatments such as pentoxifylline or N-acetyl cysteine increase survival in these patients. Prevention of withdrawal syndrome and individualised nutritional management are fundamental pillars in the treatment of AAH. In very selected cases with a first episode of AAH that does not respond to corticosteroid treatment, early liver transplantation offers a clear survival benefit, but the risk of ethyl alcohol relapse is significant, so a multidisciplinary approach is required, including joint assessment and follow-up with the addiction specialist.

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REVIEW ARTICLE

INTESTINAL OVERGROWTH. ARE WE ON THE RIGHT TRACK?

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Abstract

In recent years, bacterial overgrowth has become one of the trendy diseases in social media, where "influencers" advise its investigation and treatment in the event of symptoms such as bloating, distension, diarrhea or constipation. For many years it has been known as a cause of malabsorption and even malnutrition, usually associated with anatomic alterations in the small intestine and we must always keep in mind the conditions and clinical scenarios that increase its risk. Another question would be if it can be responsible for other digestive symptoms (bloating, diarrhea) without causing this malabsorption. It seems that it could be more frequent in patients with irritable bowel syndrome and distension / functional abdominal bloating, although the great heterogeneity and in occasions the low quality of the available studies make a low level of evidence to recommend its systematic investigation in these patients.The generalization and massive use of breath test as a manner of diagnosis has contributed to the great boom of this entity, while these tests have low sensitivity and specificity, especially if lactulose is used as a substrate. Antibiotics are going to be the base of the treatment, with rifaximin being the one with the highest level of evidence. Like in other aspects of the microbiota, a better approach to this way of dysbiosis will be defining what a normal microbiota is, or better, what a normal bacterial function is.

Keywords: small intestinal bacterial overgrowth, intestinal methanogen overgrowth, irritable bowel disease.

Introduction

In recent times we have witnessed an extraordinary spread of intestinal bacterial overgrowth (IBO) on social media, with numerous videos appearing in which "influencers" and users explain how their symptoms (usually bloating, abdominal distension, diarrhoea...) are due to this pathology, easily diagnosed by a breath test and how they are resolved after antibiotic treatment. This leads to many patients coming to the clinic asking directly about this disease as if it were a new and emerging pathology. On the other hand, especially since the second half of the last decade, there has been a notable increase in scientific publications on the subject, due, on the one hand, to greater interest in the microbiota and its role in some diseases and, above all, to the popularisation of breath tests as a form of diagnosis. But in reality we are dealing with an entity that has been known for many decades. As early as 1890 White and later Barker in 1939 described a series of patients with megaloblastic anaemia associated with alterations of the small intestine, such as stenosis. Card in 1959

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perfectly described the classic clinical picture, in which various conditions in the small intestine such as massive diverticulosis or stenosis, caused a similar clinical picture, with malnutrition, anaemia and steatorrhoea. In 1960 Baldenoch described the clinical spectrum of IBO, indicating the existence of a medical and surgical group[1-3]. This is therefore a disease that has been known and described for some time.

Definition

Although there is no unanimous definition, the most accepted definition defines IBO as a clinical condition whose symptoms or signs are caused by the presence of an excessive and/or abnormal type of bacteria in the small intestine, most commonly found in the colon. Initially, the number of 100,000 colony forming units (CFU) per millilitre (ml) was set as the minimum number to establish the diagnosis, when the diagnosis was made by jejunal aspirate. This was based on classical IBO studies in patients with anatomical abnormalities. More recent studies indicate that in healthy volunteers it is rare to find more than 100-1000 CFU/ml in duodenal-jejunal aspirate, so this is the value currently accepted by most authors[4].

Risk factors

As previously mentioned, the duodenum has a low number of bacteria, usually less than 1000 CFU/ml, mainly lactobacilli and streptococci. As we move to more distal sections, we will find a greater bacterial population: 10,000 CFU/ml in jejunum and 100,000 in distal ileum. The colon is densely populated by anaerobes, usually more than 1000000000000 CFU/ml.The small intestine, therefore, despite its length, is an area in which we will find a relatively low number of bacteria, especially in the more proximal sections. There are several factors that favour this fact. One of the most important is intestinal motor activity, especially the interdigestive migrating motor complex phase III, a powerful tonic contraction that is generated in the distal stomach and proximal duodenum during fasting phases and which plays an important role in the clearance of intestinal contents and bacteria. On the other hand, gastric and bilio-pancreatic secretions also exert an antiseptic role. The integrity of the intestinal mucosa and an adequate commensal flora also contribute. Finally, the competence of the ileocaecal valve hinders the access of bacteria and colonic material to the small intestine[5].

Taking these protective factors into account, it is easy to understand which conditions will facilitate bacterial overgrowth (Table 1)[5]:

- Alterations in intestinal motility. This will be one of the most determining factors. These alterations can be found in: diabetic neuropathy, systemic sclerosis, chronic use of opioids, use of anticholinergic drugs, hypothyroidism.

- Anatomical alterations, especially those that cause stasis of intestinal contents: diverticulosis of the small intestine, surgical modifications (Billroth II, end-to-side anastomosis), stenosis (Crohn's disease, radiation surgery), blind loops, jejuno-colic fistulas and, as mentioned above, when the function of the ileo-caecal valve is lost (incompetence or resection).

- Decreased gastric secretion, especially post-surgery. As for chronic use of proton pump inhibitors, although some studies show an increased risk of IBO when taken on a long-term basis, it appears to be a concomitant rather than an exclusive factor in the development of this disease.

- Immunodeficiencies involving a loss of mucosal defence capacity: congenital immunodeficiencies, Ig A deficiency or acquired immunodeficiencies (AIDS or malnutrition).

- Multifactorial mechanism: chronic pancreatitis (decreased pancreatic secretion, altered motility due to the inflammatory process, use of opioid analgesics that decrease motility), celiac disease (altered motility, decreased mucosal defence capacity, association with pancreatic failure), Crohn's disease (presence of stenosis, fistulas, loss of mucosal defence capacity), liver disease, end-stage renal failure and other less frequent entities reflected in table 1.

An important point is that just as we should not overdiagnose IBO in some cases, we should also take into account this entity in circumstances that meet some of the predisposing factors previously listed, as it may be important in the clinical management of these patients, such as: advanced age, with a relative risk (RR) 2-3 times higher, especially in cases of diarrhoea and malnutrition, diabetes mellitus (RR 4. 18), scleroderma (RR 12.21), celiac disease (RR 5.1), Crohn's disease (RR 10.9) or liver cirrhosis (RR 6.8)[6].

Pathophysiology

Most of the knowledge regarding the pathophysiology of IBO comes from classic case studies of maldigestion/malabsorption in patients with predisposing anatomical factors (stenosis, surgery, etc.) in which this entity is capable of causing a picture of malabsorption and malnutrition. The pathways by which this clinical condition can occur are: mucosal injury, competition for host nutrients and the effect of bacterial metabolism (Figure 1)[5].

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INTESTINAL MOTILITY DISTURBANCES	ANATOMICAL ABNORMALITIES	IMMUNODEFICIENCIES	MULTIFACTORIAL
-Diabetic autonomic neuropathy -Systemic sclerosis / scleroderma -Amyloidosis -Hypothyroidism Idiopathic intestinal pseudo-obstruction -Achromegaly -Gatroparesis -Myotonic muscular dystrophy -Chronic use of opioids -Chronic use of drugs that decrease motility	-Small bowel diverticulosis -Surgical anatomical modifications (Billroth II, gastrectomy, end-to-side anastomosis) -Stenosis (Crohn's, radiation, surgery) -Blind loops -Gastrocolic or jejuno-colic fistulas -Hypochlorhydria (post-surgical, pharmacological acid suppression)	-Congenital -Acquired (AIDS, severe malnutrition)	-Chronic pancreatitis -Celiac disease -Tropical sprue -Crohn's disease -Cystic fibrosis -Intestinal failure -Radiation enteropathy -Liver disease -End-stage renal failure

Table 1. ***Conditions associated with bacterial overgrowth.***

Mucosal injury

An excessive colonisation by colon bacteria in the small intestine can cause a loss of the brush border of the enterocyte, with the corresponding malabsorption of carbohydrates, which will be fermented by these micro-organisms, with the consequent production of excess gases such as hydrogen, methane or hydrogen sulphide. On the other hand, due to the effect of bacteria or their enterotoxins, such as lipopolysaccharide from Echerichia coli, damage to intercellular junction complexes occurs, resulting in increased intestinal permeability. Finally, mucosal damage leads to activation of proinflammatory cytokines, which increases tissue injury and may result in decreased nutrient absorption.

Competition for host nutrients

IBO is typically associated with vitamin B12 deficiency, both through bacterial consumption and decreased absorption. There is also a reduction in thiamine and nicotinamide levels. Interestingly, there is an increase in folate, which is synthesised by the bacteria.

Effect of bacterial metabolism

One of the most clinically relevant consequences is that abnormal colonisation of bacteria in the small intestine leads to deconjugation of bile salts, resulting in an excess of unabsorbed primary acids in the ileum, which are metabolised to secondary and tertiary acids, which in the colon increase intestinal motility and act as secretagogues, this being one of the most important factors in generating diarrhoea in IBO. In addition, this can lead to a depletion of bile acids, with a consequent decrease in fat-soluble vitamins. Finally, other consequences of bacterial metabolism are hyperammonaemia and increased lactic acid and alcohol production.

Thus, we have an entity that is a recognised cause of malabsorption, steatorrhoea and malnutrition and that can be reversed with antibiotic treatment. The question that arises is whether IBO, without actually causing malabsorption, could be responsible for symptoms such as bloating, distension, abdominal pain and diarrhoea, which are common in irritable bowel syndrome. As we have seen, this condition is potentially capable of producing deconjugation of bile salts, increased hydrogen and methane, a state of chronic mucosal inflammation and increased intestinal permeability, all of which are recognised pathophysiological concepts in the aetiopathogenesis of irritable bowel syndrome (IBS). Therefore, could IBO as a form of dysbiosis be behind the symptoms of a proportion of patients diagnosed with IBS? Before we try to answer this question, we will first explain the diagnostic methods currently available to us, as this will be one of the most limiting factors that we will encounter.

Diagnostic methods

The methods available for the diagnosis of IBO are:

- Duodenal-jejunal aspirate culture, traditionally considered the "gold standard".

- Exhaled hydrogen-methane breath test, using two substrates: glucose and lactulose.

- New techniques: intestinal gas capsule, ribosomal RNA sequencing 16s....

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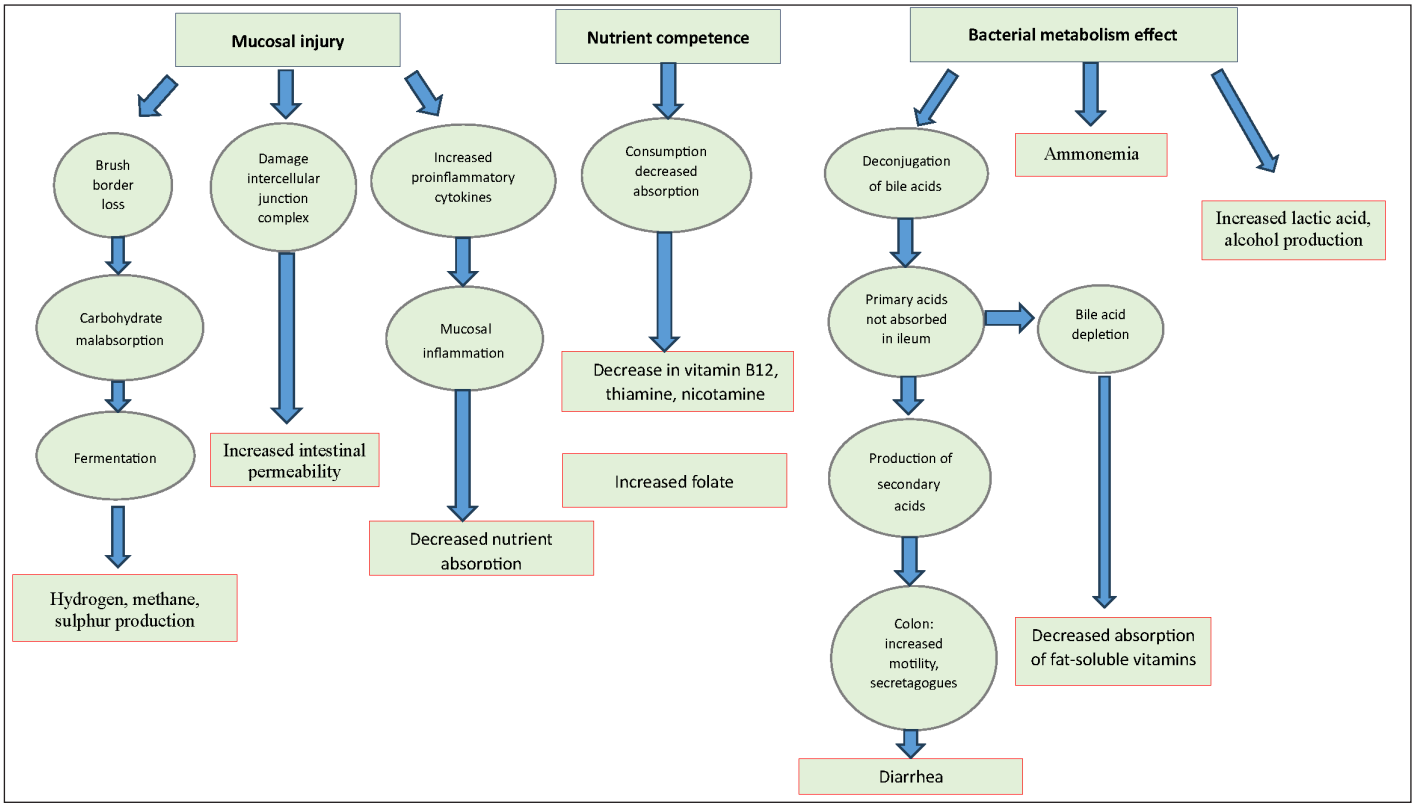

Figure 1. ***Pathophysiology of maladigestion/malabsorption in intestinal bacterial overgrowth.***

Duodenal-jejunal aspirate culture

Considered the "gold standard" or at least the best diagnostic method. Generally, an aspirate of intestinal contents is performed at the level of the 3rd-4th duodenal portion, taking 3-5 ml with a catheter with multiple lateral holes. Some authors use a dual lumen catheter to minimise oropharyngeal contamination. Subsequently, an aerobic-anaerobic culture is performed on MacConkey agar or blood agar. As mentioned above, the limit to be considered positive is currently set at more than 1000 CFU/ml. The main problem is that it is a time-consuming, costly technique with the inherent risks of endoscopy and sedation, and therefore will not be performed in routine clinical practice. In addition, it has the problem of oropharyngeal contamination, which may be present in 20 % of cases. On the other hand, only 20-30 % of bacteria will be cultured and, since the aspirate is duodenal, it does not detect distal IBO[7].

Exhaled hydrogen-methane breath test

Based on the fact that mammals are not capable of producing certain gases such as hydrogen, methane and hydrogen sulphide and, therefore, their appearance in breath after administration of a sugar indicates bacterial fermentation at the intestinal level. Two substrates will be used: glucose and lactulose, which are conceptually different.

Glucose is a monosaccharide that once administered will be rapidly absorbed in the proximal intestine. In the case of IBO, microorganisms compete with the host, so that part of it will not be absorbed and will be fermented, with the consequent production of hydrogen, methane and sulphur that diffuse rapidly into the blood, reach the alveoli and are eliminated early via the respiratory tract. Lactulose is a synthetic disaccharide that the body is unable to digest or absorb in the intestine, reaching the large intestine unchanged, where it is fermented. In the case of IBO, part of the lactulose is fermented in the small intestine, causing an early peak of hydrogen, sulphur and sometimes methane[8].

One of the main limitations that we will find when using breath tests are false positives when there is a rapid intestinal transit, which can cause an early gas peak when the substrate has already reached the colon. This problem will be greater when using lactulose, with some authors advising a concomitant measurement of intestinal transit time by scintigraphy, which will be unfeasible in most cases. False positives may also occur in situations leading to increased proximal glucose exposure, such as in partial gastrectomy, although in clinical practice this will be less relevant. False negatives may also occur, especially in situations leading to slowed bolus transit (achalasia, gastric outlet obstruction or proximal enterocutaneous fistula). Another cause of false negatives may be glucose absorption proximal to the area of overgrowth, especially if the overgrowth is distal[9].

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The diagnostic criteria to be used in most cases are those published in the American consensus. It recommends the use of 75 grams of glucose or 10 grams of lactulose, with subsequent measurement of hydrogen, methane and C02 over the next three hours every 30 minutes. An elevation of hydrogen levels above basal level greater than 20 parts per million (ppm) in the first 90 minutes or more than 10 ppm methane at any time during the study is considered positive[10]. However, the most recently published European consensus, while advising 50 grams of glucose, with a study duration of 120 minutes, concludes that no uniformly accepted diagnostic criteria can be established, due to limited interpretation of the results because of the presence of several confounding factors, especially variability in orocaecal transit[11]. Some studies comparing bowel aspirate culture with the breath test show surprisingly low concordance, with a kappa index of -0.02[12].

Diagnostic performance will be established by comparison with intestinal aspirate culture, which as mentioned above is not the best possible "gold standard". Using it as a reference, the sensitivity of the glucose test is 54 %, while the lactulose test is 42 %. In terms of specificity, the glucose test has a specificity of 83 %, while the lactulose test has a specificity of 71 %. One of the most important parameters to take into account is the positive likelihood ratio (PLR) (the ratio of the probability that a positive test has the disease to the probability that a negative test has the disease) and the negative likelihood ratio (NLR) (the ratio of the probability that a negative test has the disease to the probability that a negative test does not have the disease). In the case of the first parameter, a test is considered excellent if the value is equal to or greater than 10, good between 5-10 and acceptable between 2-5. In the case of the second, excellent if it is equal to or less than 0.1, good between 0.1 and 0.2 and acceptable between 0.2 and 0.5. The glucose test shows a PLR of 2.45, with an NLR of 0.60. The lactulose test shows a PLR of 1.30 and an NLR of 0.79, i.e. very discrete values, especially when lactulose is used. The area under the curve (ratio between sensitivity and specificity, ideal value 1) is 0.7418 for the glucose test and 0.5582 for the lactulose test[13].

New techniques

-Intestinal gas capsule. This is a device that, once ingested, allows the levels of hydrogen and methane to be measured and transmitted wirelessly and in real time after ingestion of a sugar in the different intestinal segments. In this way it does not interfere with the orocecal transit time. It is a quasi-experimental technique used in very few centres and its clinical impact is therefore very limited[14].

-Sequencing of 16s ribosomal RNA in intestinal contents aspirate. The 16s ribosomal RNA is a small RNA fragment of the minor subunit of the ribosome of prokaryotic cells. Its sequence has remained unchanged, without mutation, over thousands of years and is specific for each bacterium. Its sequencing using new high-throughput techniques makes it possible to determine the bacteria in a sample and to carry out a taxonomic classification of the sample, studying its diversity. Studies using this technique together with aspirate culture show that patients with IBO show a decrease in alpha diversity, more marked the greater the bacterial overgrowth, and a predominance of certain bacteria such as Echerichia coli, Shigella and Klebsiella[15]. It also shows that patients with bloating or functional abdominal distension also show a decrease in bacterial diversity, with an increase in proteobacteria and a decrease in actinobacteria, and this decrease in bacterial diversity is also more pronounced when associated with IBO[16].

Relationship between intestinal bacterial overgrowth and irritable bowel syndrome

As mentioned above, the question that arises is whether IBO, without actually causing a picture of malabsorption, with diarrhoea, malnutrition and nutrient deficiencies, may play a certain role in the aetiopathogenesis of some patients with irritable bowel syndrome (IBS). The main limitation when interpreting the different studies on this association is that they are very heterogeneous and it is difficult to draw global conclusions, as they use different diagnostic techniques (aspirate, breath test), with different substrates, diagnostic cut-off points and clinical selection criteria. Moreover, as mentioned above, most of them base the diagnosis on exhaled breath tests which, as explained above, have low sensitivity, specificity and are influenced by several confounding factors.

One of the first studies linking the two entities was published by Mark Pimentel (one of the authors with the most studies on microbiota, BIO and the relationship with IBS), published in 2000. In this study with 202 patients with IBS according to Rome I criteria, 78% of them tested positive for lactulose breath test and, in addition, those who had a negative breath test after antibiotic treatment had a significant symptomatic improvement compared to those who did not test negative after treatment[17]. However, studies with contradictory results subsequently emerged, which did not find a higher prevalence of IBO in patients with IBS[18]. In 2009, one of the first meta-analyses was published, which included 12 studies, all of which included more than 90 cases, both series and case-controls. It found that, compared to controls, patients with IBS have an RR between 3.45-4.7, depending on the diagnostic

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cut-off point used. In this study, the large difference in the prevalence of IBO according to the diagnostic method used is striking (54 % when using lactulose test, 31 % with glucose and 4 with jejunal aspirate >100000 CFU/ml)[19]. Another major meta-analysis published in 2018 found an RR of IBO in IBS of 4.7 (3.5 after adjusting for publication bias). The overall prevalence was 38%, but also varied according to the diagnostic method used (19% in jejunal aspirate, 31% with glucose test and 47% with lactulose). Furthermore, it was higher in patients with diarrhoea subtype IBS (42 %), compared to other IBS subtypes (25 % constipation, 31 % mixed or 17 % indeterminate[20]. One of the latest and most important meta-analyses was published in 2020, including 3192 patients with IBS versus 3320 controls. The RR of IBO in patients with IBS was 3.7 (4.9 in studies with healthy controls), being more frequent in the diarrhoea subtype, with an RR of 1.86 compared to the constipation subtype. In this study it is striking that, compared to the glucose test, the lactulose breath test had a 3.5-fold higher positive rate in patients with IBS and 7.8-fold higher in controls[21]. Finally, one of the latest published meta-analyses involving more than 5300 patients shows a 36% positivity with either test, with a relative risk of 4.2 when using glucose and 3.2 when using jejunal aspirate culture. In this meta-analysis the relative risk with lactulose was only 1.6, with no statistically significant difference, attributed by the authors to the high false positive rate due to increased orocaecal transit. It was also more frequent in the diarrhoea subtype (RR of 1.4 versus other subtypes)[22]. Although the symptoms most frequently associated with overgrowth are bloating, distension and abdominal pain, only diarrhoea, both before and during the glucose breath test, showed significant (but modest) values as a predictor of the presence of IBO[13].

Methanogenic intestinal overgrowth

Methane infusion into the intestine of animal models induces a decrease in intestinal transit, increasing contractility and reducing the speed of the peristaltic wave. The main methane producers in the organism are archaea, which constitute a third domain, together with prokaryotic and eukaryotic cells. Specifically, Methanobrevibacter Smithii is the main methane-producing archaeon, which is found not only in the small intestine, but also in the colon. For all these reasons, in order to unite all these concepts, some authors advise using the term methanogenic intestinal overgrowth[4]. A meta-analysis of 1654 patients with IBS versus 713 controls showed a methane breath test positivity of 29 % with lactulose and 11.5 % using glucose, with a RR of 1.2 in patients with IBS. The prevalence was significantly higher in patients with constipation subtype (37.7 % vs. 12.4 % in diarrhoea subtype, with a RR of 3.1). The same study showed that patients with inflammatory bowel disease had a lower methane test positive rate compared to healthy controls[23].

In summary, different studies and meta-analyses show a higher positivity of the tests used for the diagnosis of IBO (mainly breath test and to a lesser extent intestinal aspirate culture) in patients with IBS, although the great heterogeneity of the studies in terms of patient selection, method used, diagnostic criteria and low sensitivity and specificity of the tests used make it necessary to take these data with caution.

Treatment

As in other aspects of this entity, treatment recommendations are based on studies with great heterogeneity and, in some cases, small series of patients. The treatment options are: diet, probiotics, faecal microbiota transplantation and antibiotics.

In terms of diet, the aim would be to reduce potentially fermentable products. Some studies show that the FODMAP diet reduces bacterial fermentation products, as measured by the breath test. However, there is insufficient evidence to recommend the FODMAP diet in these patients[4].

Some studies show that probiotic administration reduces hydrogen production measured in exhaled air, although the level of evidence is still low to recommend its use. Transplantation of faecal microbiota is anecdotal in this entity and as a curiosity, one study showed that patients with Clostridium Difficile colitis who received the transplant from donors with a pathological bacterial overgrowth test (by breath test) had more symptoms such as abdominal distension compared to donors without a positive breath test[4].

Antibiotics are going to be the main therapeutic arm when considering treatment in IBO. The aim of using antibiotics is not to eradicate the intestinal microbiota, but to modulate it in order to bring about symptomatic improvement. It must be considered that this is an empirical treatment, as in the vast majority of cases culture and antibiogram are not available. It should cover aerobic and anaerobic bacteria. Generally, a single treatment of 7-10 days will be sufficient. It should be kept in mind that relapses are frequent (up to 44% in 9 months). It will not be necessary to repeat the diagnostic test in case of symptomatic improvement[24]. The antibiotics used, dosage

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and efficacy are listed in table 2[4]. These data, especially the efficacy data, should be treated with caution as in many cases they are based on results from studies with few patients.

Rifaximin is the one with which we will have the most extensive and highest quality studies, extrapolated from studies on diarrhoea subtype IBS. It is a synthetic derivative of rifampicin and is a broad-spectrum antibiotic with activity against aerobes and anaerobes. Intestinal absorption is minimal, less than 4%. It has several mechanisms of action: it inhibits bacterial RNA synthesis, has a bactericidal-bacteriostatic effect, reduces the inflammatory response, reduces cytokine expression and has a eubiotic effect[25]. It is supported by phase III studies that demonstrated its efficacy in patients with irritable bowel syndrome subtype diarrhoea and led the FDA to authorise its use in these patients, and its use was also recommended in the latest clinical guidelines published by the European Society of Neurogastroenterology and Motility[25]. This study showed that patients receiving 550 mg three times daily for 14 days of rifaximin showed greater improvement in both global symptom scores and abdominal bloating than those receiving placebo[26]. In addition, another phase III follow-up study showed that re-treatment of patients who had initially responded but relapsed over time was effective versus placebo in overall response and improvement in abdominal pain, but not in response to diarrhoea[27]. One of the few meta-analyses analysing the use of rifaximin in IBO shows an overall eradication rate of 70.8 %, being similar in patients with IBS (71.6 %). In logistic regression analysis, only a dose of 1200 mg daily or higher was significant. In the 10 studies assessing symptomatic response, 67.7 % of patients who eradicated IBO improved symptomatically[28]. Another more recent meta-analysis shows a 59 % eradication rate by intention-to-treat and 63 % by protocol, being dose-dependent, finding the maximum eradication rate at 1600 mg daily and finding no differences with different treatment durations[29]. As for side effects, most studies show that they are low, similar to placebo and with virtually no cases of C. difficile infection[26,28]. A recent study showed that patients with IBS subtype diarrhoea who had a positive lactulose test for IBO had a greater symptomatic improvement after treatment with rifaximin than those with a negative breath test, and that this was greater in those who had a negative initial positive test30.

ANTIBIOTIC	RECOMMENDED DOSE	EFFICACY
Rifaximin	400-550 mg every 8 hours	61-78 %
Amoxicillin-clavulanic acid	875 mg every 12 hours	50 %
Ciprofloxacin	500 mg every 12 hours	43-87 %
Doxycycline	100 mg every 6-12 hours	Not available
Metronidazol	250 mg every 8 hours	43-87 %
Neomycin	500 mg every 12 hours	33-55 %
Norfloxacin	400 mg 24 hours	30-100 %
Trimethoprim-Sulfa-methox.	160/800 mg every 12 hours	95 %

Table 2. ***Antibiotics and doses used in intestinal overgrowth***

There is less scientific evidence for the other antibiotics, with studies involving fewer patients. A European study showed that the rotation of an azole-type antibiotic with quinolone was superior to a single treatment with either of them[31]. Similarly, it appears that the combination of rifaximin and neomycin is superior to single treatment for treating methanogenic intestinal overgrowth[32].

Conclusions. Future directions.

IBO is a recognised cause of malabsorption in patients with anatomical alterations that generate intestinal stasis. It is also important to consider it in elderly and diabetic patients, especially in the presence of diarrhoea and evidence of malabsorption. It can be very frequent in patients with scleroderma, due to the severe alterations in intestinal motility caused by this disease. It should also be considered in patients with coeliac disease and Crohn's disease who have an inadequate therapeutic response. Studies show that IBO is more frequent in patients with IBS and may play a role in the aetiopathogenesis of some of them. The problem is that the diagnostic tests we use to reach these cases have a limited diagnostic yield, with low sensitivity and specificity, overdiagnosing many cases, which means prescribing antibiotic treatment unnecessarily. There is no consistent scientific evidence to recommend its systematic investigation in these patients, although it could be considered in those with diarrhoea subtype IBS, ruling out other possibilities and with poor therapeutic response, as well as in cases of constipation subtype IBS to investigate the presence of methanogenic intestinal overgrowth.

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Possibly to assess the true impact that dysbiosis and BIO may have, it would be important to define what the microbiome of "healthy" patients would be, which is not easy, as this "normal" microbiome may vary in different individuals. There seem to be more similarities in metatranscriptomics (genetic expression of a bacterial community) and metabolomics (set of small molecules and metabolites produced by the bacterial community), which will condition a "normal" microbial function, with certain functions and capacity of resistance to external stimuli. The aim of treatment would therefore be to restore an adequate microbiome-host symbiotic interaction[5].

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REVIEW ARTICLE

ALCOHOL USE DISORDER. THE OTHER DISEASE.

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Abstract

Alcohol consumption throughout history has been conditioned by cultural and social elements, and its widespread use has led to a sometimes dangerous normalization in certain countries. Globally, it is known that alcohol-related disease causes around three million deaths per year[1].

Our aim as health promoters should be to intervene early in order to detect mild and moderate cases of Alcohol Use Disorder (AUD) in order to prevent them from being treated in specialized hepatology units.

Addiction treatment centers are the first specialized step in the approach to this pathology, so knowledge of specific pharmacotherapy for moderate and severe AUD is required, as well as the necessary psychotherapeutic tools for this purpose.

Coordination between the different hospital services involved in the treatment of organic pathology and addiction treatment centers should be considered as a necessary strategy in the approach to patients with severe alcohol use disorder, as well as a relapse prevention tool in transplant patients.

Keywords: alcoholism, pharmacotherapy, dual pathology, liver disease.

Definition and diagnosis

"*Alcohol use disorder*", as it is now called according to DSM-5, was listed as "alcohol addiction" in DSM-1 in 1952, although it was not recognised by the WHO as a nosological entity per se until the 1960s[2].

Alcohol use disorder is defined according to DSM-5 (Diagnostic and Statistical Manual of Mental Disorders, 5th edition) as[3]:

1. A problematic pattern of alcohol consumption that results in clinically significant impairment or distress and is manifested by at least two of the following events within 12 months

- Alcohol is often consumed in greater quantities or for a longer period than intended.

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- Persistent craving or unsuccessful efforts to reduce or control alcohol consumption.

- A lot of time is spent on the activities necessary to obtain alcohol, consume alcohol or recover from the effects of alcohol.

- Craving or strong desire or urge to consume alcohol.

- Recurrent alcohol use resulting in a failure to perform essential duties at work, school or home.

- Continued use of alcohol despite persistent or recurrent social or interpersonal problems caused or exacerbated by the effects of alcohol.

- Significant withdrawal from social, occupational or recreational activities due to alcohol use.

- Recurrent alcohol use in situations where it causes physical risk.

- Continued use of alcohol despite knowledge of a persistent or recurrent physical or psychological problem that is likely to be caused or exacerbated by alcohol.

- Tolerance, defined by any of the following:

* A need to consume increasing amounts of alcohol to achieve the desired intoxication or effect.

* A markedly diminished effect with continued use of the same amount of alcohol.

- Abstinence, as manifested by any of the following:

* Presence of the withdrawal syndrome that is characteristic of alcohol.

* Alcohol (or a very similar substance, such as a benzodiazepine) is used to relieve or avoid withdrawal symptoms.

2. Symptoms cause clinically significant distress or impairment in social, occupational or other important areas of functioning.

3. The symptoms are not better explained by an unrelated mental or medical disorder, and are not due to another medical condition.

4. If criteria for more than one severity level are met, the alcohol use disorder should be diagnosed with the highest severity that is fulfilled.

The previous classification, DSM-IV[4], established the terms "abuse" and "addiction", however, the current classification determines the categories of mild, moderate and severe depending on the number of symptoms met, with 2-3 for mild, 4-5 for moderate and 6 or more for severe.

Historical framework of the treatment centers

The Outpatient Addiction Treatment Centres (CTA for its Spanish abbreviation) arose at the end of the 1980s in response to the need to cover the demand caused by the appearance of the first heroin addicts in Spain, which would later become the great epidemic of the time.

With the passing of the years and the stabilization of patients dependent on opiates thanks to the introduction of substitution programmes and other programmes of dishabituation, these centers have been modifying their population and expanding their therapeutic offer, and are now able to attend to all types of addictions and associated pathologies.

The treatment of alcoholism, dependence on cannabis, cocaine and other stimulants, as well as attention to pathological gambling and non-substance addictions, has given way in recent years to the appearance of a new patient profile.

These centers are the first step in the treatment of AUD, and there are also inpatient centers known as Therapeutic Communities scattered throughout Andalusia; these are accessed from the CTA where the assessment by the three professional figures, psychologists, doctors and social workers, is essential for referral to these resources. The approach is therefore multidisciplinary, both on an outpatient and inpatient basis, due to the biopsychosocial component of the addictive disease.

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On the other hand, the Hospital Detoxification Units (UDH) are another alternative for those patients who find it difficult to undergo outpatient treatment, and there are currently three hospitals in Andalusia where they are carried out: Hospital Universitario Punta Europa in Algeciras, San Cecilio in Granada and Cruz Roja in Seville.

Approach and outpatient treatment

What we could call the "therapeutic itinerary" begins with the first "Welcome" appointment, where the motivational interview plays an important role, since our objective is to achieve adherence and "therapeutic alliance" with the patient. Empathy and reflexive listening, avoiding direct confrontation, are fundamental pillars in this first interview, encouraging the patient's self-efficacy and decision-making, thus avoiding an authoritarian or imposing attitude on the part of the interviewer[5].

Many patients come after a period of abstinence, which implies motivation to change and therefore does not require an outpatient detoxification programme, but if it is carried out, the collaboration of the family is important, if possible, both to control the drugs and to assess the patient's condition. In this sense, benzodiazepines have historically been the treatment of first choice, with those with a long half-life, such as diazepam, being the most recommended, and in cases of advanced liver disease, lorazepam, as it is not metabolized in the liver. Clomethiazole has also been widely used for years; more widely used in Europe than in the USA, this drug can be considered a good ally in the treatment of "delirium tremens", but its high addictive power, as well as cross-tolerance with alcohol and a greater number of adverse effects, means that its use should be restricted, especially in the home and outpatient setting[6]. Despite having been the first-line treatment for Alcohol Withdrawal Syndrome (AAS) for decades, its capacity to generate addiction, as well as its adverse effects, have led to the search for safer alternatives.

The emergence of new generation anticonvulsants has brought a new paradigm in detoxification treatments for both alcohol and other substances. In clinical practice, oxcarbazepine, gabapentin or pregabalin are frequently used in the treatment of AUD, both in the detoxification process and in the control of anxious symptoms related to the disease. These drugs decrease the likelihood of seizures in AAS, reduce craving and are useful in patients with mood disorders. According to the evidence, almost all of them will help in the detoxification process, favoring a slight or moderate improvement with respect to benzodiazepines, although gabapentin has the best safety profile and can be used up to 1600 mg daily[7].

In the search for drugs that can contribute to clinical improvement during the dishabituation process, research has focused on those that could have an "anticraving" and "antipriming" effect. Craving, in the context of addiction, is the desire or need to consume impulsively or to carry out the addictive behaviour; priming is a sign that could be said to be almost pathognomonic of AUD, manifesting itself as the inability to stop consumption once the subject has been exposed to a minimum amount of alcohol.

In the literature there is a large sample of studies on the main drugs developed to combat craving, with naltrexone, acamprosate and nalmefene providing the most evidence (Table 1). In 2022, an interesting review was published on the subject, with a large sample obtained from 156 publications[8].

DRUG	LEVEL OF EVIDENCE	NUMBER OF PUBLICATIONS
Naltrexone	High	54
Acamprosate	High	35
Nalmefene	High	9
Topiramate	Medium/Low	12
Gabapentin	Low	6
Baclofen	?	14
Disulfiram	High	13
Others	-	13

Table 1. ***Level of evidence for drugs used in withdrawal.***

In addition to the drugs that have already been proven to be effective, others such as topiramate, baclofen or even atypical antipsychotics and antidepressants were included; although disulfiram was also included, it is a deterrent or interdictor drug, as we will see later on and which will be dealt with in a separate section.

Naltrexone and nalmefene are two opioid receptor antagonists, the difference being that naltrexone is also a partial agonist, so that blocking these receptors in the central nervous system reduces the reward sensation associated with alcohol consumption. On the other hand, nalmefene has shown some ability to control priming, but there is currently no drug specifically designed for this purpose. Although both have

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demonstrated their efficacy, there are many publications on the use of naltrexone, but not on nalmefene, which has a higher dropout rate in the publications reviewed, mainly due to the appearance of adverse effects. On the other hand, the studies carried out compare nalmefene with placebo, which in practice is of little value to clinicians, as it would have supported more evidence if it had been done with naltrexone[8].

Acamprosate acts by restoring normal GABAergic activity, diminished by chronic alcohol consumption, while reducing the state of hyperfunction of glutamatergic excitatory neurotransmission, thus alleviating the state of residual hyperexcitability of the central nervous system that would persist after cessation of alcohol consumption in people who have developed alcohol dependence[9].

The dosage of naltrexone and nalmefene, 50 mg and 18 mg a day respectively, facilitates therapeutic compliance, but this is not the case with acamprosate, which requires two 333 mg tablets every 8 hours, which in clinical practice leads to a high dropout rate in patients with certain difficulties in complying with treatment.

It is worth mentioning another drug that has sometimes shown favourable results, baclofen, but which has nevertheless been found to have mixed results attributable to methodological differences, so that more studies are needed to give it more importance in the treatment of alcohol dishabituation[8].

Austria and Italy have pioneered the use of **Gamma hydroxybutyrate (GHB)** in the treatment of alcohol dishabituation, but since it is a recreational drug known as "liquid ecstasy", it is used in very restricted contexts and for hospital use, and is the only country in Europe where it is approved[10].

The conclusion, therefore, with regard to drugs that favour the reduction of craving, is that the evidence supports the use of naltrexone, acamprosate and nalmefene as highly effective drugs in the treatment of alcohol withdrawal, although in clinical practice we may encounter difficulties in compliance due to both adverse effects and difficulties in dosage.

Disulfiram is a so-called 'deterrent' or 'interdictor' drug, whose mechanism of action is based on blocking the action of the enzyme aldehyde dehydrogenase, thereby causing the accumulation of acetic acid and generating the full range of symptoms when alcohol is consumed.

It is striking that disulfiram has attracted little interest in research over the decades despite being a widely used drug with a high degree of evidence. In 2014, Sebastián Girón[11] published an interesting review including all the studies existing up to that time, establishing three groups of authors among all the publications, whether in observational studies, trials or meta-analyses (Table 2).

The authors conclude that it is a drug with a high degree of evidence as long as it is taken under supervision. In this regard, there are several publications on the subject, with studies showing that abstinence rates after six months of treatment were 78% in patients who took the drug under supervision, compared to 58% who took it unsupervised[12]. On the other hand, other studies conclude that the results are even better if the patients have good family and social support, a non-alcoholic partner and the treatment providers are trained to improve the quality of supervision[13].

De Sousa et al. published several studies comparing the days of abstinence in patients treated with disulfiram versus others treated with naltrexone and acamprosate, with the days of abstinence being significantly longer in those treated with disulfiram[14].

	TYPES OF STUDIES			TOTAL
Opinion groups of authors	Clinical trials	Naturalistic, observational and series of cases	Reviews and meta-analyses	
Support efficacy	5	12	10	27
Determine moderate efficacy	4	1	6	11
Do not support efficacy or consider it a second-choice treatment	2	0	7	9
Total	11	13	23	47

Table 2. ***Opinion groups regarding the efficacy of disulfiram.***

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And although in view of these results it might seem that the approach to addictive pathology is fundamentally based on pharmacotherapy, we must not forget that there are certain contraindications or adverse effects of the drugs we have just analysed that prevent their use. This is why psychotherapy plays an essential role, as well as the treatment of the underlying psychiatric pathology.

Alcohol use disorder often coexists with other pathologies, especially depressive or anxiety disorders, which are frequently aggravated or induced by alcohol consumption itself and which tend to improve with abstinence; however, sometimes they are independent entities, and it is this comorbidity that we call dual pathology, with the evolution of the process being favoured by the joint approach of both, which would merit a separate space for detailed analysis.

Alcohol use disorder, liver disease and transplant patients

Alcoholic liver disease (ALD) encompasses various liver conditions caused by alcohol consumption, ranging from hepatic steatosis to steatohepatitis and ultimately cirrhosis. It is the leading cause of advanced liver disease and liver cirrhosis in Europe, including Spain. Together with non-alcoholic steatohepatitis, they are the most frequent causes of chronic liver disease. In contrast, viral hepatitis B and C, thanks to advances in prevention and treatment, are experiencing a decrease in their prevalence as causes of liver disease, especially in our region, so that ALD has now become the most frequent indication for liver transplantation. When advanced liver diseases do not improve with alcohol abstinence, liver transplantation is the only curative option. The assessment of these patients is complicated and involves consideration of the risk of relapse[15].

Relapse in general terms in addiction is the use of the "problem" substance after a period of abstinence, and if AUD is characterized by anything, it is the inability to control the substance; however, there is no evidence that mild relapse, defined as occasional "slips", can have a significant impact on engraftment or patient survival[16].

Post-transplant alcohol relapse rates vary between 15% and 50%, and several studies have investigated the demographic and clinical factors associated with alcohol relapse. In this regard, the importance of psychiatric evaluation and treatment of AUD and comorbid pathology is critical to reduce these figures[17].

For the selection of patients with advanced alcoholic liver disease suitable for liver transplantation, most programmes worldwide require a six-month abstinence period. However, the usefulness of this six-month rule as a predictor of long-term sobriety is controversial18. What has been shown is that early liver transplantation improves survival in patients with a first severe episode of Alcoholic Hepatitis (AH) unresponsive to medical treatment[15].

AUD is a chronic and relapsing disease and therefore the focus should be on an intensive therapeutic approach, including psychotherapy and pharmacotherapy primarily in high-risk patients before and after transplantation. Cognitive behavioural therapy, motivational enhancement therapy together with self-help groups and pharmacotherapy[19], play a crucial role in the treatment of SAD in patients with cirrhotic alcoholic liver disease and patients in need of transplantation. Naltrexone and acamprosate could be an effective and safe alternative (Table 3), although the former should be avoided in severe hepatic dysfunction, and acamprosate in chronic renal failure[17].

DRUG	FDA/ EMA	APA RECOMMENDATIONS	ADVANCED LIVER DISEASE	INTERACTION WITH IMMUNOSUPPRESSANTS	HEPATOTOXICITY	RENAL INSUFFICIENCY
Naltrexone	Approved	First line	Avoid in Child-Pugh C	None	Possible	Allowed
Acamprosate	Approved	First line	Allowed	None	None	Reduce dose if Cr Cl 30–50 ml/min/1.73 m2, avoid if Cr Cl <30 ml/min/1.73 m2

FDA, Food and Drug Administration; EMA, European Medicines Agency; APA, American Psychiatric Association

Table 3. ***Pharmacotherapy in AUD in cirrhotic and/or transplanted patients.***

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Conclusiones

AUD is a chronic and relapsing disease that is managed in the CTAs. Knowing the existing resources, as well as the correct referral to them, facilitates the access of patients to the treatment circuit.

The professionals involved in this long process must know the pharmacological and psychotherapeutic tools; naltrexone, acamprosate and disulfiram are first-line drugs with proven evidence, provided they are prescribed within a psychotherapeutic framework. A correct assessment and diagnosis of dual pathology favours adherence and improves the prognosis of patients with alcoholic liver disease, as well as a lower relapse rate in transplant patients.

Coordination between Hepatology Departments and CTAs should therefore be considered a necessity in the management of these patients, especially in those who have undergone liver transplantation, in whom post-transplant follow-up could reduce the relapse rate by allowing the assessment and treatment of possible comorbid psychiatric pathology.

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BOUVERET'S SYNDROME AND DIGESTIVE ENDOSCOPY AS DIAGNOSTIC SUPPORT

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Abstract

We present the case of an 80-year-old woman with a history of cholelithiasis who was admitted for epigastralgia and vomiting. A study was performed with complementary tests confirming Bouveret's syndrome by oral endoscopy and an attempt was made to resolve it endoscopically with all available instruments without success, so surgical treatment was performed.

Keywords: Bouveret's syndrome, biliary colic, intestinal obstruction, endoscopy.

Introduction

Bouveret's syndrome is a rare form of biliary ileus that involves the passage of a large lithiasis (usually larger than 2 cm) from the gallbladder into the intestinal lumen through a cholecystoduodenal fistula, causing obstruction to the gastric outflow or the proximal intestine. It was first described in 1896 by Léon Bouveret (Lyon, France)[1-3].

Clinical Case

This is an 80-year-old woman with a history of cholelithiasis who was admitted to hospital for epigastralgia, postprandial fullness feeling and vomiting. Once hospitalised, a further study was performed with cholangioresonance imaging and abdominal tomography (Figure 1), which identified an oval lesion occupying the duodenal bulb, as well as aerobilia and air in the gallbladder together with the known lithiasis. In view of these findings, an oral endoscopy was requested, confirming a fistula and an oval lithiasis of approximately 30 mm in the duodenal bulb (Figure 2), which prevented passage to the second portion of the duodenum. Endoscopic fragmentation was attempted with all available instruments (loop, biopsy forceps, tripod, etc.) and even direct extraction without success. Subsequently, the patient was evaluated with an advanced endoscopy unit of reference (given that we do not have endoscopic retrograde cholangiopancreatography in our centre) to assess electrohydraulic lithotripsy, but this was rejected due to unsatisfactory results in other patients with similar characteristics as well as the current evidence in this regard. Therefore, she was assessed by the surgical team and scheduled surgical extraction of the stone was performed with an acceptable subsequent evolution.

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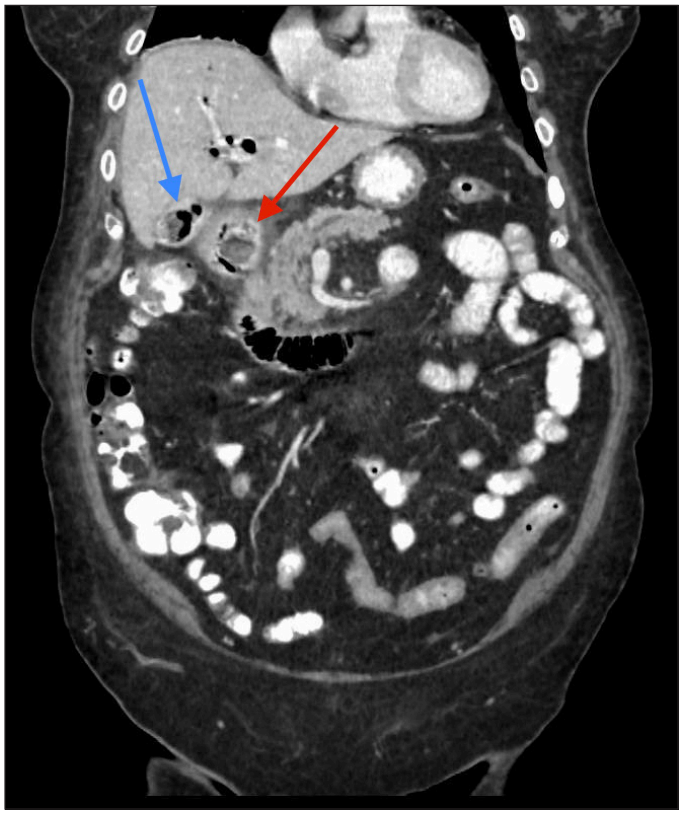

Figure 1. ***Abdominal CT scan showing an oval image in the red arrow corresponding to a large lithiasis in the duodenal bulb. Blue shows the gallbladder with other lithiasis and air.***

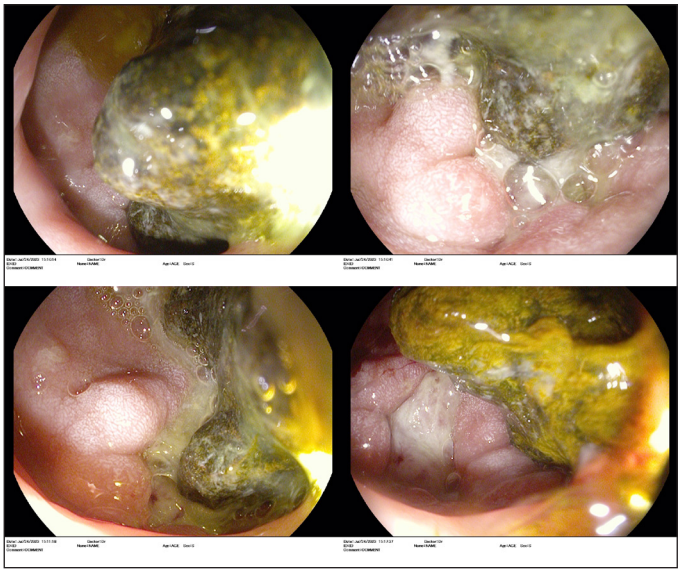

Figure 2. ***Endoscopic view of the duodenal bulb showing a large lithiasis that prevents passage to the second portion of the duodenum, as well as a fistula on the anteroinferior side that appears to communicate with the gallbladder.***

Discussion

This syndrome usually occurs in women over 70-75 years of age with comorbidity and its clinical presentation consists of a high intestinal obstruction (gastric distension that improves with vomiting, frequent and abundant vomiting, as well as epigastric or right hypochondrium pain)[3,4].Pathophysiologically, the formation of the fistula between the gallbladder and the lumen of the digestive tract is due to a chronic inflammatory reaction, which stops the free perforation and allows the passage of the lithiasis. However, only 6% of lithiasis that pass into the digestive tract result in intestinal obstruction due to size, occurring mainly in the terminal ileum (50-90%), proximal ileum and jejunum (20-40%) as well as the duodenum (less than 5% of cases)[5].

Clinical suspicion is essential for diagnosis, although a summary is made on the basis of clinical, radiological and endoscopic factors. Plain abdominal X-ray may show Rigler's triad (small bowel obstruction, pneumobilia and ectopic lithiasis) but is present in only one third of cases[2,3,5]. Ultrasound of the abdomen is useful to exclude acute cholecystitis. CT scan is diagnostic in 60% of cases, which can be complemented by magnetic resonance cholangiopancreatography, since 15-25% of cholelithiasis are isodense. Finally, endoscopy supports the diagnosis as it allows direct visualisation of the lithiasis (up to 70% of the time), the orifice of the duodenal fistula and to rule out other differential diagnoses (such as neoplasms)[3-5].

Regarding treatment, both endoscopic and percutaneous treatment options have been described, including retrieval basket or polypectomy loop and fragmentation methods with mechanical lithotripsy, laser, extracorporeal shock wave and intracorporeal hydraulics[3,4,6]. Given the advanced age and comorbidity that patients with Bouveret's syndrome often present, endoscopic removal should be attempted in the first instance[4]. However, the overall success rate with endoscopic procedures is only 37-43% and in many cases all endoscopic alternatives fail, especially in cases of large (> 2-3 cm) impacted lithiasis[4,7]. Cappel et al. have reported a therapeutic success rate with YAG-laser lithotripsy of 60% and only 25% and 20% for mechanical lithotripsy and extracorporeal shock wave lithotripsy, respectively[8]. On the other hand, cases have been described of Bouveret's syndrome complicated by distal small bowel obstruction due to impaction of part of the original previously fragmented lithiasis, whose removal required a new endoscopic procedure or, more frequently, surgical treatment[4]. Therefore, up to 91% of cases will require surgery due to failure of these therapies, consisting of lithiasis removal as well as fistula repair, with a success rate of more than 80%[3,4]. Cholecystectomy is usually optional but mandatory in case of

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intravesicular lithiasis[3,4,9].Due to the age and comorbidity of the patients, Bouveret's syndrome has a morbidity of 60% and a mortality of 12-30%[3].

In conclusion, this is a pathology that requires close collaboration between endoscopists and surgeons. Although there are no standardised protocols for the management of these patients, endoscopy is diagnostically useful and potentially therapeutic. In case of large impacted lithiasis, endoscopists should be prepared to use multiple endoscopic instruments including lithotripsy to maximise success rates. In case of failure of endoscopic treatment, lack of experience or unavailability, a surgical option would be justified[6].

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URINARY ASCITES AFTER TRANSURETHRAL RESECTION IN A CIRRHOTIC PATIENT

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Abstract

Urinary ascites is a rare entity, usually secondary to iatrogenic or traumatic bladder perforation. Given the infrequency of the entity, it is a diagnosis for which high clinical suspicion is required, and when a patient presents with ascites, it is common to attribute it to other causes. Especially in cirrhotic patients, where ascites is most often secondary to portal hypertension, although this is not always the cause. It is therefore important to always make an appropriate differential diagnosis, assessing the patient's history, the characteristics of the ascitic fluid and the response to treatment. We present the case of a patient with cirrhosis, with a history of transurethral resection (TUR) of a bladder tumour, which was initially classified as oedema-ascites decompensation and after completing the diagnostic process was attributed to urinary ascites.

Keywords: uroperitoneum, ascites, cirrhosis.

Introduction

Ascites is a clinical situation of special frequency and relevance in digestive pathology, being usually related, in our area, to cirrhosis or digestive tumours. However, any patient who begins with ascites must undergo an appropriate diagnostic process, evaluating and ruling out the different causes of ascites. Among the causes of ascites, an extremely infrequent one that can be observed in patients who have undergone bladder or laparoscopic surgery is ascites of urinary origin due to perforation of the bladder dome, which constitutes the peritoneal portion of the urinary bladder. Diagnosis is based on ascitic fluid analysis, surgical history and computerised tomography (CT). Treatment is based on bladder catheterisation and management of the perforation, which is usually carried out conservatively.

Clinical case

We report a 92-year-old patient, with a history of Child A5 cirrhosis, who underwent transurethral resection of the bladder as treatment for bladder neoplasia. The patient reported progressive abdominal distension, without associated peripheral edema, with evidence of grade 2 ascites and oliguria. An abdominal ultrasound scan showed a heterogeneous liver ultrastructure with blunt and irregular borders compatible with chronic liver disease and moderate ascites. Laboratory tests showed creatinine of 6 mg/dl, CRP of 136, normal liver markers and normal coagulation parameters. A diagnostic paracentesis was performed with leukocytes 2450 with 65% PMN, creatinine

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in ascitic fluid of 2.4 mg/dL, urea 89 mg/dL and albumin 1.6 g/dL. With a serum-ascitic albumin gradient of 1.5. A diagnosis of first edema-ascitic decompensation and spontaneous bacterial peritonitis (SBP) was made. For which, treatment was started with albumin at a dose of 1.5 g/kg on the first day and 1g/kg on the third day, together with antibiotic coverage with 3rd generation cephalosporins. Given the acute renal failure, diuretics were not initiated.

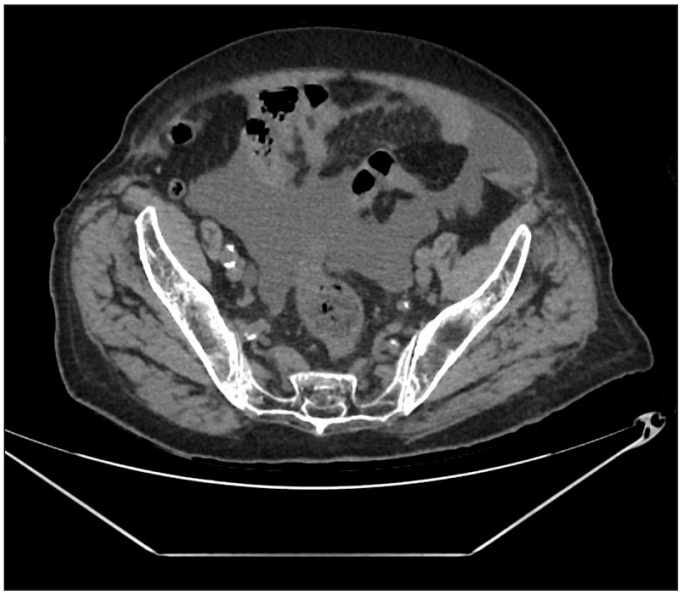

Figure 1. ***This image shows an axial CT scan of the abdomen, without contrast, showing free fluid corresponding to ascites.***

However, after indicating bladder catheterisation for diuresis quantification, there was an evident decrease in ascites and a rapid improvement in renal function to normal figures. After this, and given the history of TUR, urology was contacted and a Uro-CT scan was requested. This test revealed a perforation in the bladder dome and intraperitoneal contrast material, and the case was classified as urinary ascites secondary to this perforation. Given that the patient was stable and a progressive resolution of the ascites was observed with bladder catheterisation, conservative treatment of the perforation was decided upon. After maintaining bladder catheterisation and antibiotic coverage for 3 weeks, and in view of the patient's clear improvement, a new control Uro-CT scan was performed, which confirmed closure of the perforation, after which the patient was discharged.

Discussion

Ascites consists of the presence of serous fluid in the peritoneal cavity, the causes of this condition are varied, one of

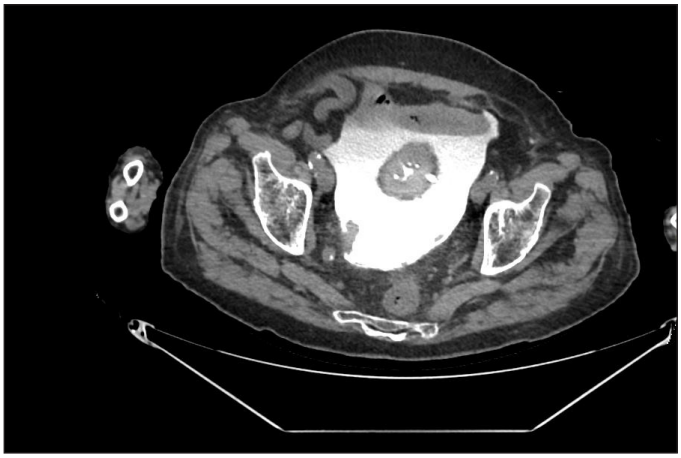

Figure 2. ***CT abdomen and pelvis, with contrast in the excretory phase, showing contrast leakage secondary to bladder perforation.***

the most frequent being portal hypertension, usually linked to hepatic cirrhosis (up to 75% of the causes of ascites). There are also other common causes such as those related to a decrease in plasma oncotic pressure, such as heart failure or nephrotic syndrome[1].There are other causes such as tuberculosis, secondary to peritoneal carcinomatosis or pancreatic carcinomatosis. There may also be a large group of rare causes including urinary ascites.

Urinary ascites is a rare diagnosis characterised by the presence of ascites attributable to bladder perforation, usually following a therapeutic procedure on the urinary bladder[2]. Elevated urea and creatinine levels are usually found in ascitic fluid analysis. In addition, an even higher elevation of creatinine is often found in the blood, and diuresis is reduced due to the passage of urine into the peritoneal space. The higher elevation of plasma creatinine is explained by the fact that the peritoneum allows creatinine to pass from the abdominal cavity into the plasma[3]. A very characteristic feature is the decrease in plasma creatinine levels and resolution of ascites after bladder catheterisation. A key factor in its diagnostic evaluation is the history of an invasive procedure on the urinary bladder and late-phase contrast-enhanced CT scan, which allows the existence of bladder perforation to be detected. Treatment consists of reducing the passage of urine into the peritoneal cavity by bladder catheterisation and closure of the defect which, depending on its characteristics and the patient's clinical condition, can be managed conservatively or by surgical intervention.

In our case, despite the initial diagnosis of oedema-ascitic decompensation, the non-advanced stage of cirrhosis, the absence of hyponatraemia or plateletopenia, the

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characteristics of the fluid and the decrease in ascites after catheterisation led us to suspect an alternative diagnosis, which was confirmed after performing the Uro-CT scan. The particularity of this case probably lies in the fact that it is a patient with hepatic cirrhosis, which, being the most frequent cause of ascites, does not, from the outset, lead us to orient the differential diagnosis towards a history of recent bladder surgery.

In summary, ascites requires a comprehensive diagnostic approach in order to find the etiological cause. We must not forget that even in cirrhotic patients presenting with ascites, we must always be attentive to the patient's characteristics and history, as well as the analysis of ascitic fluid and imaging tests, in order to make an appropriate differential diagnosis.

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GASTROSTOMY TUBE DISLODGEMENT INTO THE PERITONEAL CAVITY AFTER ITS MANUAL INSERTION

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Abstract

Percutaneous endoscopic gastrostomy is a usual technique in our daily clinical practice. Although it is a very safe procedure, it is important to know its complications for their prevention and early detection. We present a patient with abdominal pain after manual insertion after accidental removal.

Keywords: tube dislodgement, percutaneous endoscopic gastrostomy, enteral nutrition.

Introduction

Percutaneous endoscopic gastrostomy is a technique that involves the placement of a tube through the abdominal wall using different techniques for the administration of fluids, enteral nutrition and/or medication or for gastric decompression. The most frequent related complications are peristomal leakage and infection, tube obstruction or tube dislodgement, among others[1,2]. Accidental removal of the gastrostomy tube is one of the most frequent reasons for consultation of these patients in the emergency department, and is resolved in most cases after manual insertion of a new tube.

Clinical case

An 84-year-old woman with no known previous personal history was diagnosed with oropharyngeal neoplasia. Due to dysphagia and inability to meet her nutritional requirements, a percutaneous gastrostomy was performed endoscopically for enteral nutrition by means of a direct introduction technique through gastric pexias. The procedure passed without complications and enteral nutrition could be started without incident.

Five weeks later, she came to the emergency department due to accidental removal of the feeding tube at home, and a new one was inserted blindly by hand through the previous stoma, with no immediate complications.

Twenty-four hours later, she was seen again for severe abdominal pain after administration of enteral nutrition through the tube, with no fever or other associated symptoms. An urgent computed tomography (CT) scan was performed, which revealed a dislodgement of the tube, identifying the distal end in the peritoneal cavity, outside the gastric cavity (Figure 1). The tube was removed and empirical antibiotic therapy with metronidazole was started, and a new percutaneous endoscopic gastrostomy was performed. The patient progressed favourably until the condition was resolved.

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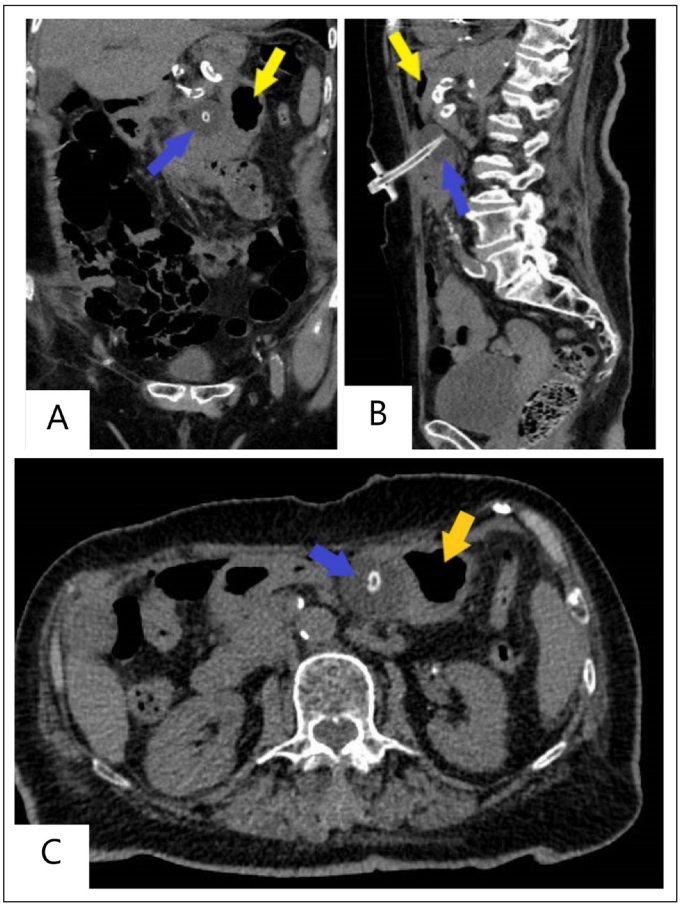

Figure 1. ***Non-contrast abdominal CT scan showing the dislodgement of the gastrostomy tube into the peritoneal cavity. Its distal end with the sterile saline-filled balloon (blue arrow) can be seen outside the gastric cavity (yellow arrow). A) Coronal plane, B) sagittal plane and C) axial plane.***

Discussion

Dislodgement of the gastrostomy tube is a complication that can occur after tube removal (accidental or due to tube defect) in patients with an immature gastrocutaneous fistula (less than 4 weeks old) in which the stomach serosa has not properly adhered to the parietal peritoneum, and manual blind reinsertion in these patients should be avoided[1,3].

Although manual insertion is considered safe after 4 weeks, as in this case, it is important to detect this complication early, and in case of doubt, a water-soluble contrast study should be performed to confirm the correct placement of the tube before feeding is started[3].

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