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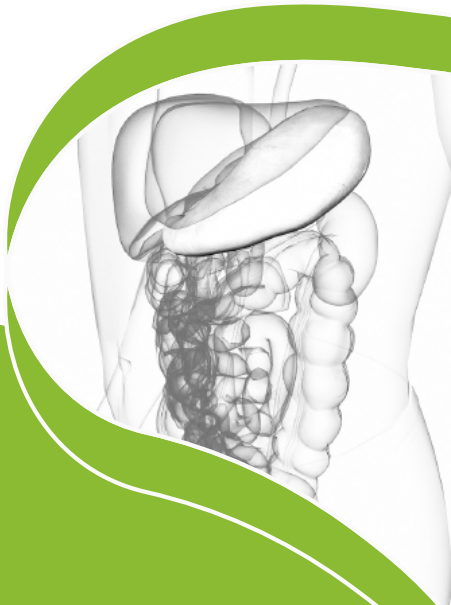

Official Body of Sociedad Andaluza de Patología Digestiva

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AUTHOR STANDARDS **2025**

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.*

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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:

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4° Full postal address of the responsible author, to whom correspondence should be addressed, including telephone, fax and email address.
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- 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.

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4° Full postal address of the responsible author, to whom correspondence should be addressed, including telephone, fax and email address.
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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.
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3° Centre(s) of origin (department, institution, city and country).
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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
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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.

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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.

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- General data:

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:

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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".

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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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Images and data relating to the health of individuals have been obtained and used in accordance with clause 5 of this agreement.

Other documents and ethical standards:
Human research: publications on human research should show in a prominent place in the original paper that: a) written informed consent has been obtained from each patient, b) The study protocol conforms to the ethical standards of the Helsinki Declaration of 1975 and has been approved by the ethical committee of the institution where the study was conducted.
Animal research: experimental animal studies must show in a prominent place in the original paper that they receive care according to the criteria outlined in the "Guide for the Care and Use of Laboratory Animals" written by the National Academy of Sciences and published by the National Institutes of Health (http://www.nap.edu/readingroom/books/labrats).
Controlled clinical trials: the development of controlled clinical trials should follow the CONSORT standard, available at: http://www.consort-statement.org and be registered before patient inclusion begins.
Data obtained by microarray: data must be sent to a repository such as Gene Expression Omnibus or ArrayExpress before submission of the manuscript.

Data protection
The personal data requested from the authors will be used by the Andalusian Society of Digestive Pathology (SAPD), exclusively for the purpose of managing the publication of the article submitted by the authors and accepted in the RAPD online. Unless otherwise indicated, by submitting the article the authors expressly authorise that their data relating to name, surname, institutional postal address and e-mail address be published in the RAPD online, possibly in the annual abstracts published by the SAPD on CD support, as well as on the SAPD website and in Medline, or other bibliographic search agencies, to which the RAPD online may have access.

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RAPD Online does not require an exhaustive description of the statistical methods used in carrying out a research study, but it does specify certain requirements that must appear in the manuscripts as standards of good practice. A basic document on this subject can be found 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 software and the name of the software used must be clearly stated in the Material and Methods Section.
-To express mean, standard deviation and standard error, the following formats must be used: "mean (SD)" and "mean ± SE". To express the median, the values of the interquartile range (IQR) must be used.
- The P must be used in capital letters, reflecting the exact value and expressions such as less than 0.05, or less than 0.0001 should be avoided.
- Whenever possible, findings (means, percentages, odds ratios and others) should be quantified and presented with appropriate error indicators, such as confidence intervals.
- Studies showing levels of statistical significance should include the calculation of sample size. Authors should state research losses, such as dropouts from clinical trials.

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ORIGINAL

DEVELOPMENT AND TRAINING OF A CONVOLUTIONAL NEURAL NETWORK FOR THE DETECTION OF ESOPHAGITIS IN ENDOSCOPIC IMAGES

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Abstract

Introduction and objectives: digestive endoscopy provides a direct evaluation of the gastrointestinal tract, although inter-operator variability can limit its precision. This study aimed to develop a convolutional neural network (CNN) based on InceptionResNetV2, tailored for the automated detection of esophagitis in endoscopic images, with the objective of improving diagnostic accuracy and optimizing clinical workflow.

Materials and methods: the model was implemented using Python, Keras, and TensorFlow on Google Colab Pro with an Nvidia A100 GPU. Starting from the InceptionResNetV2 architecture pretrained on ImageNet, dense layers were added to perform binary classification (normal Z-line vs. esophagitis). Training was conducted using 2000 images from the KVASIR dataset (80% for training and 20% for validation). Evaluation was extended to 1164 images from the HyperKVASIR dataset, excluding mild cases, and to 203 images from the Hospital Regional Universitario de Málaga.

Results: the model demonstrated high accuracy, as evidenced by confusion matrices and ROC curves, with an AUC of 0.884 for the KVASIR dataset and 0.970 for HyperKVASIR. Greater precision was observed in the detection of advanced esophagitis, correlating the severity of the lesion with increased diagnostic accuracy.

Conclusions: the study highlights the potential of CNNs in AI-assisted diagnosis in endoscopy. Although the model shows high sensitivity in advanced lesions, additional research is required to improve detection in early stages and to validate its application in heterogeneous clinical contexts.

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Diego Martínez R, Cano de la Cruz JD, Sánchez Sánchez MI, Vázquez Pedreño LA, Jiménez Pérez M. Development and training of a convolutional neural network for the detection of esophagitis in endoscopic images. RAPD 2025;48(2):46-50. DOI: 10.37352/2025482.1

Keywords: digestive endoscopy, convolutional neural networks, esophagitis, deep learning, artificial intelligence.

Introduction

Digestive endoscopy can provide a direct and minimally invasive assessment of the gastrointestinal tract; however, the assessment remains subject to some inter-operator variability, resulting in significant differences in the efficiency of the technique depending on who performs it.

In this context, artificial intelligence (AI) and, in particular, convolutional neural networks (CNNs), have emerged as promising tools to improve the accuracy and reproducibility of endoscopic diagnosis. These deep learning architectures, inspired by the way neurons in the human brain interconnect, are composed of multiple layers of artificial neurons that are trained to recognize patterns from data. During training, each layer extracts features or characteristics of increasing level of complexity, constantly adjusting the weights of their connections in order to improve their classification or detection ability. In current clinical practice, AI has begun to be used in the detection of colorectal polyps, characterization of gastric lesions and other applications that seek to support endoscopic diagnosis.[1,2].

The present work focuses on the development of a convolutional neural network specifically trained for the detection of esophagitis in endoscopic images. Through the use of image processing and deep learning techniques, we seek to improve the automated diagnostic capability. This approach not only has the potential to improve clinical decision making, but also to streamline workflow in medical settings, facilitating faster and more accurate diagnosis for patients.

In this article, the process of developing and training the AI model, as well as its validation using an endoscopic imaging dataset, will be described. In addition, the challenges and future perspectives in the integration of these systems into clinical practice will be discussed, with the aim of improving the quality of endoscopic diagnosis and care for patients with esophageal diseases.

Subject matter and methods

In this project, the Python programming language together with the Keras and TensorFlow[3] software libraries were used to implement and train a deep neural network architecture. The working environment selected was Google Colab Pro, which provides access to powerful graphics processing units (GPU), in this case an Nvidia A100. This is essential to significantly reduce training times and to be able to handle large volumes of image data.

The base architecture chosen was InceptionResNetV2[4], originally developed by Google researchers and trained on the massive, public ImageNet[5] dataset. IInceptionResNetV2 combines the advantages of the convolutions of the Inception family with the stability and efficiency of residual-type connections, resulting in a model that maintains an appropriate balance between accuracy and training speed.

The original InceptionResNetV2 model, after being trained on the classification of thousands of ImageNet categories, was adapted for our specific use case. For this purpose, the output layers were replaced by custom layers designed to perform binary classification. In particular, three dense (fully connected) layers were added, culminating in an output layer with the ideal activation (to distinguish between two classes: esophagitis versus a normal Z-line (Figure 1).

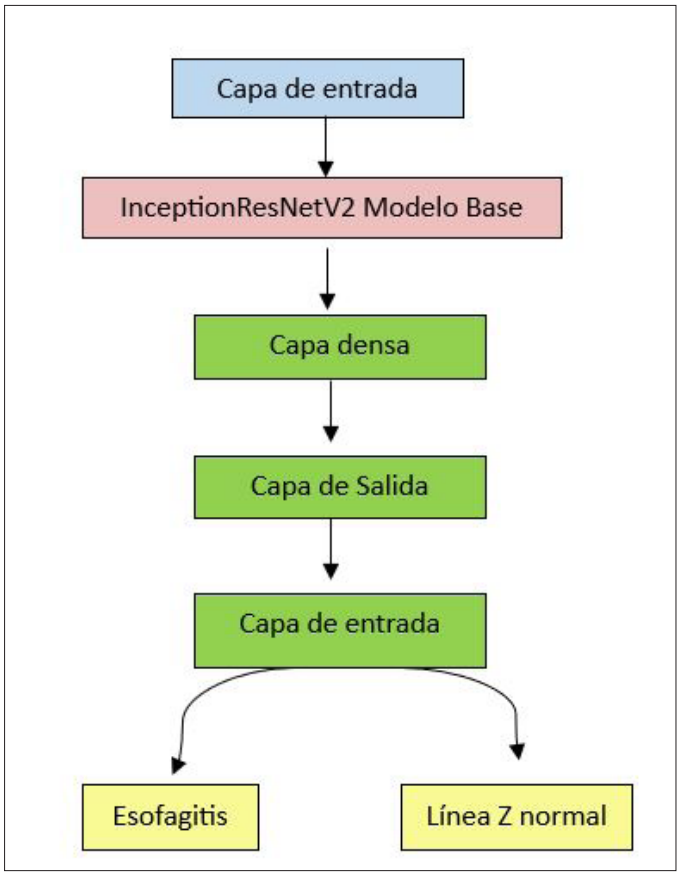

Figure 1. ***Scheme of the model created, in green the layers added to the InceptionResNetV2 base model shown in red.***

The fine-tuning process was carried out by keeping the initial layers of the model - those responsible for extracting features - fixed and retraining specific final layers. In this way, we took advantage of the richness of the weights obtained from

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ImageNet and oriented the network towards the discrimination of our two clinical categories of interest. This allows a much more efficient use of data and training time by avoiding training the model from scratch.

We trained the model with the KVASIR endoscopic image set[6], a repository covering digestive endoscopy images. In particular, we used 2000 images corresponding to both normal Z-line and different degrees of esophagitis, dividing the data into 80% for training and 20% for validation. This balance in data partitioning allowed robust training of the model and a reliable preliminary assessment of its performance.

To perform a more thorough validation, we employed the HyperKVASIR image set[7], totaling 1164; 932 normal Z-line and 232 esophagitis. At this stage, milder cases were excluded, focusing only on grades B, C and D of the Los Angeles classification, in order to assess the ability of the model to identify more advanced lesions. Additionally, a third set of images from the Regional University Hospital of Malaga was incorporated. This set consisted of 203 esophagitis images (all of them pathological) that included different degrees of severity (76 images of Los Angeles grade A, 42 of grade B, 28 of grade C, 22 of grade D and 18 in the category of others intended for when the endoscopist did not specify the degree of esophagitis) thus reinforcing the diversity and clinical representativeness of the data used in the study (Table 1).

Results

A detailed example of the individual predictive ability of our model is presented below, showing the confidence percentages assigned to each diagnostic category. To illustrate this aspect, we have randomly selected five images (Figure 2).

When evaluating the detection in the image sets, the following was observed. In the KVASIR set-corresponding to the 20% of images reserved for evaluation and not used during training-of the 200 images that corresponded to normal Z-line, the model correctly identified 164, while 36 were misclassified as esophagitis. Similarly, of the 200 images that actually corresponded to esophagitis, 153 were correctly classified, and 47 were mistaken for normal Z-line (Table 2).

On the other hand, in the HyperKVASIR image set, the confusion matrix revealed that, of 932 normal Z-line images, the model correctly classified 833 and failed in 99 cases. On the other hand, of the 232 images corresponding to esophagitis, 216 were correctly identified, while 16 were misclassified as normal Z-line (Table 3).

To compare both evaluations we will use the ROC curve metric, which is essential to determine the overall performance of our classification system. A relevant aspect was the exclusion of grade A esophagitis only in the HyperKVASIR database, in order to evidence that by having a higher contrast between the control image and the pathological image, the model can discriminate more effectively, which favored the efficiency in pathology detection, achieving area under the curve (AUC) values of 0.884 for the KVASIR dataset and 0.970 for the HyperKVASIR dataset. These results point to a high level of diagnostic accuracy (Figure 3).

Likewise, the graph below illustrates the percentage of hits obtained by the model when evaluated with the cohort from the Regional Hospital of Malaga. This independent analysis is essential to corroborate the applicability of the model in diverse clinical settings and to validate the robustness of the methodology in real circumstances (Figure 4).

Finally, when classifying performance according to esophagitis severity, a positive correlation was observed between the increase in severity and the percentage of hits. This finding suggests that the algorithm is particularly efficient in detecting more advanced lesions (Figure 5).

Discussion

The findings of this study highlight the potential of the InceptionResNetV2 architecture for the detection and classification of esophagitis based on endoscopic images. The use of pre-trained layers with the extensive ImageNet dataset, along with fine tuning focused on the esophagitis vs. normal Z-line problem.

AUC (area under the ROC curve) value obtained on the two main validation sets - KVASIR and HyperKVASIR - provided evidence of both the consistency and generalizability of the model. The exclusion of milder grades of esophagitis (grade A) in HyperKVASIR showed how greater contrast between normal and pathological images facilitates sharper discrimination, reinforcing the hypothesis that the model performs particularly robustly in more severe lesions. This aspect becomes clinically relevant, given that, in practice, advanced lesions often require more timely diagnosis and treatment.

Independent analysis on the image set of the Regional University Hospital of Malaga provides further evidence of the applicability of the approach in a variety of settings. The results confirm the usefulness of the methodology not only in public databases, but also in a real clinical setting, with variations

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Image set	Number of images	Description	Use
KVASIR[6]	2000	Images of normal Z-line and different degrees of esophagitis.	Training and validation of the model.
HyperKVASIR[7]	1164	Images of normal Z-line (932) and esophagitis (232)	Evaluation of model performance in advanced lesions.
Regional University Hospital of Malaga	203	Images of esophagitis with different degrees of severity.	External validation in a real clinical setting.

Table 1. ***Table summarizing the data sets used in the project.***

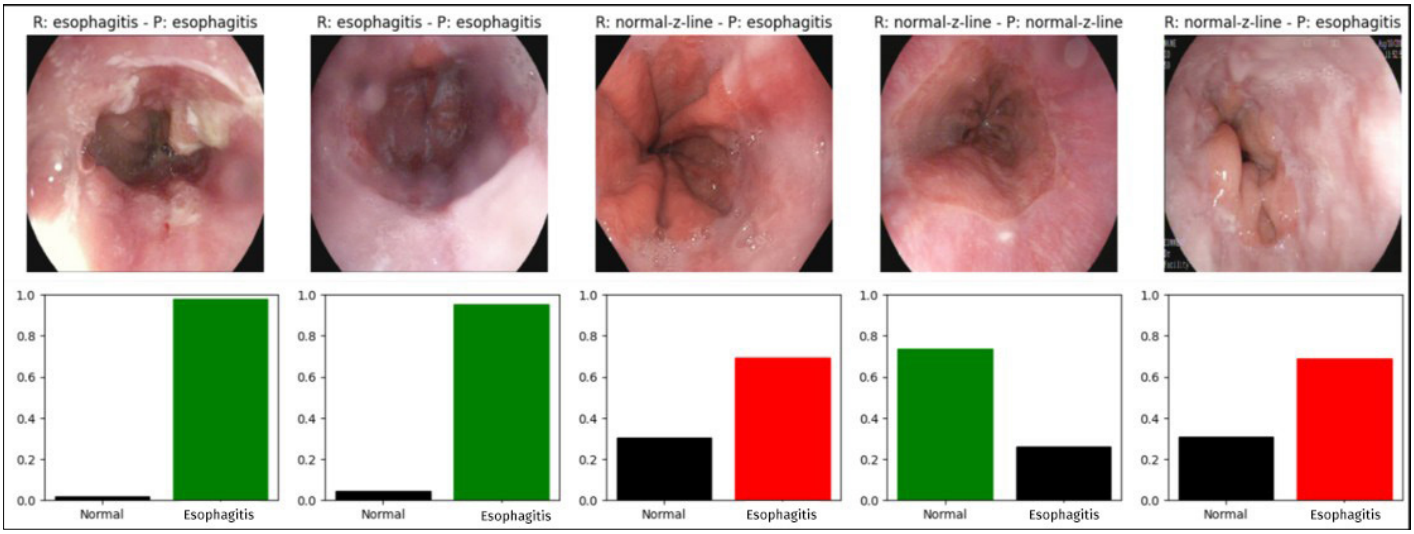

Figure 2. ***Representation of the individual predictions made by our model. Above each image is shown the actual label (R:) and the predicted label (P:) and below a bar chart with the confidence percentage assigned to each class in the prediction which is colored green if it is correct and red if it fails.***

KVASIR	Z line Normal (Predicted)	Esophagitis (Predicted)
Z line Normal (Real)	164	36
Esophagitis (Real)	47	153

Table 2. ***Confusion matrix of the prediction of the 400 images of the KVASIR image set corresponding to the 20% of images we have reserved for evaluation.***

HyperKVASIR	Z line Normal (Predicted)	Esophagitis (Predicted)
Z line Normal (Real)	833	99
Esophagitis (Real)	16	216

Table 3. ***Confusion matrix of the prediction of the 400 images of the HyperKVASIR image set.***

in imaging conditions, types of endoscopic equipment and population characteristics.

The fact that the performance of the model increases in relation to the degree of severity of esophagitis suggests that the neural network is able to detect more accurately the most evident structural alterations. However, further classification of incipient lesions is necessary, as early identification is essential in medical practice to prevent future complications and improve the prognosis of the condition.

Despite the promising results, this study has some limitations. On the one hand, the total number of images, although significant, could be expanded to cover a greater representativeness of the different forms of esophagitis presentation, especially those of grade A. On the other hand, factors such as variability in image quality and the presence of artifacts during endoscopy may influence the accuracy of the model.

Conclusions

Although the usefulness of this model is not yet applicable to clinical practice, this study highlights the potential of deep neural networks in endoscopy and underlines the importance of collaboration between hospitals to create multicenter databases. Increasing both the number and diversity of images is crucial to train models that, in the future, can be implemented in more relevant clinical contexts. The results obtained here highlight that, although the model shows high

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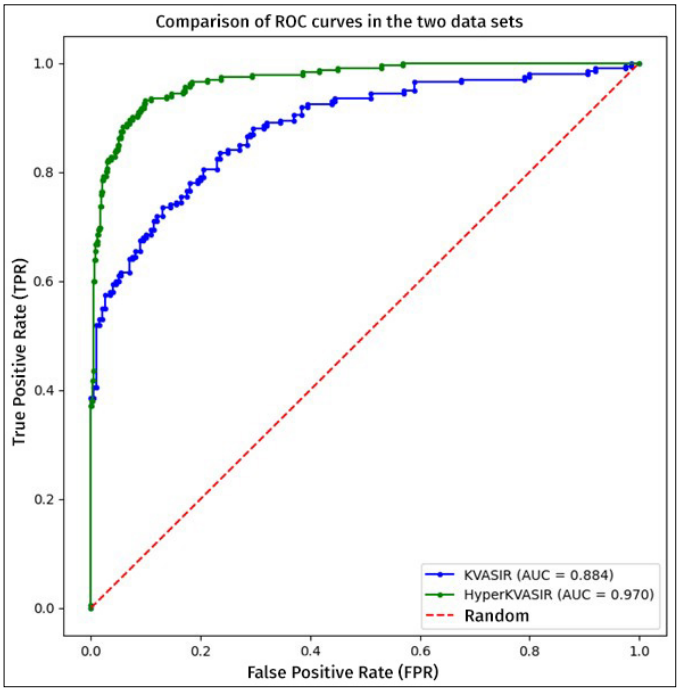

Figure 3. ***Representation of the ROC curves in the validation with KVASIR (which includes esophagitis of all degrees of severity) and HyperKVASIR (which only includes grades B, C and D, discarding the mildest cases) in which a better curve is observed in the latter set.***

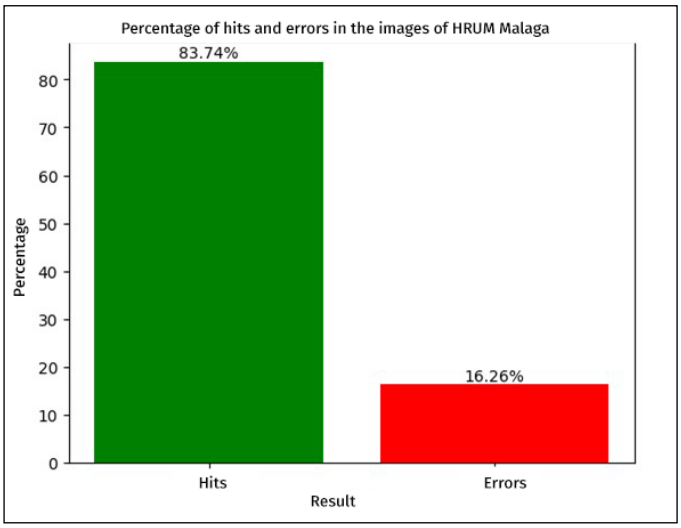

Figure 4. ***Percentage of hits in the images of the set created with cases from the Regional University Hospital of Malaga.***

sensitivity in advanced lesions, challenges are still faced in the identification of incipient stages and in the adaptation to different imaging conditions. Practically speaking, multicenter validity, the use of data augmentation techniques and the integration of these systems into clinical workflows could, in the long term, favor more agile and accurate diagnoses for a variety of gastrointestinal pathologies.

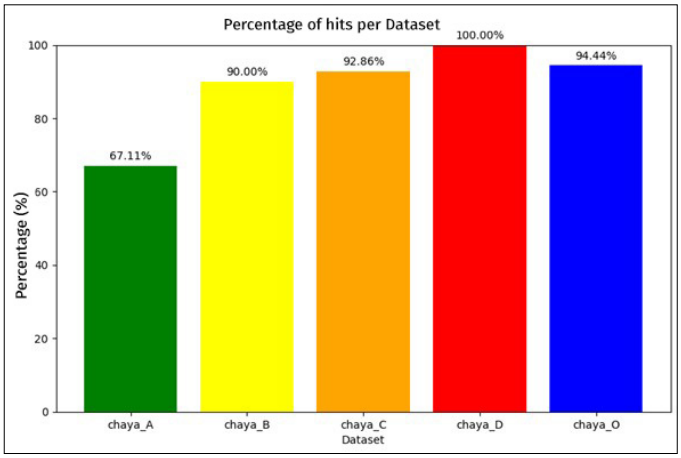

Figure 5. ***Percentage of hits stratified by the degree of severity of Los Angeles classification (grade A, B, C and D) the category chaya_O (Other) includes all images in which the endoscopist did not specify the grade.***

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REVIEW ARTICLE

MICROSCOPIC COLITIS

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Abstract

Microscopic colitis is a chronic inflammatory condition of the colon, primarily presenting with persistent diarrhea. This term refers to two specific subtypes: lymphocytic colitis and collagenous colitis. Both have seen a rise in incidence and prevalence in recent years. Although the exact cause is still unknown, research has identified several risk factors that can help guide the diagnosis. The condition is typically diagnosed through colonoscopy and confirmed by specific histological findings from colon biopsies, as other diagnostic tests mainly serve to exclude alternative causes. Budesonide is the treatment of choice for inducing remission, and in many cases, long-term maintenance therapy is also required.

This discussion will emphasize the latest updates in microscopic colitis, focusing on practical applications. We will particularly highlight recent clinical guidelines and the importance of close collaboration between Gastroenterology and Pathology in managing this condition

Keywords: microscopic colitis, lymphocytic colitis, collagenous colitis, chronic diarrhea, colonoscopy, colon biopsies.

Introduction

Microscopic colitis (MC) is an inflammatory disease affecting the large intestine that includes collagenous colitis (CC), lymphocytic colitis (LC) and recently incomplete forms of the same: incomplete MC[1]. Its diagnosis is based mainly on histological findings obtained by studying colonic biopsies in patients with persistent watery diarrhea. It is a pathology whose incidence has increased in recent years, equating in

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some regions to inflammatory bowel disease. The involvement and collaboration of the gastroenterologist and the pathologist are important for an adequate diagnosis of the patient.

Definition

MC, according to the recommendations of the Spanish MC group, is a generic term that includes LC and CC. It refers to an inflammatory bowel disease characterized by the existence of chronic or intermittent diarrhea, without blood in the stool, with macroscopic findings on colonoscopy that are normal or near normal and that present defined histological features[2]. When these histological features are not completely fulfilled in patients with compatible symptoms, the term incomplete MC has been coined[3].

Epidemiology

CC was first described more than four decades ago in 1976 by Lindstrom. The term MC was introduced by Read et al. in 1980 and finally Lanzeby introduced the term LC[4]. Today, the term MC includes CC, LC and incomplete MC[1].

The incidence of MC globally is estimated at 11.4 cases per 100,000 inhab/year[3]. There are differences between countries ranging from 6.8 to 24.7 per 100,000 inhabitants/year.[1]. With respect to CC, in Northern Europe and North America it varies between 5.2 and 10.8 cases per 100,000 inhabitants/year, being lower in Spain at less than 2.9 cases per 100,000 inhabitants/year. LC is more frequent, with an incidence in Northern Europe and North America of 4 to 19 cases per 100,000 inhabitants/year and in Spain of 2.3 to 16 cases per 100,000 inhabitants/year[2]. Its incidence has been increasing in recent decades, although it seems to have reached stable levels since the 2010s[1]. This increase has caused its incidence to match that of inflammatory bowel disease and in some countries to exceed the incidence of Crohn's disease[5,6]. The increased incidence is attributed to increased access to colonoscopy, increased suspicion and awareness on the part of gastroenterologists and pathologists, and increased exposure to risk factors, but none of these aspects have been confirmed by studies designed for this purpose.[1,6].

The incidence is 2 to 8 times higher in women than in men. This difference is greater the older the age at diagnosis and is higher in CC than in lymphocytic[1-3].

The risk of developing MC increases with age, with a peak incidence occurring in the seventh decade of life with a mean age at diagnosis of CC of 64.9 years and 62.2 years in LC, between 61.1 +/- 6.5 years in MC overall[2,7]. However, up to 25% of cases occur in children under 45 years of age and cases have also been reported in children[2].

The estimated prevalence of MC is 119 cases/100,000 population, being 50.1 per 100,000 population for CC and 61.7 per 100,000 population for LC[3].

Pathogenesis

The pathogenesis of MC is unknown. The most accepted hypothesis is the existence of an inadequate immune response, in response to stimuli of the colonic mucosa, in genetically susceptible individuals. This response provokes an inflammation of the mucosa that gives rise to the fundamental symptom of the disease, which is diarrhea[1,6] (Figure 1).

Regarding the immune response, the infiltrate observed in the lamina propria in MC is formed by cytotoxic CD8 lymphocytes and CD4 helper lymphocytes. Their presence causes an increase in cytokines, interleukins, tumor necrosis factor and interferon gamma that act as proinflammatory factors. Collagen formation is associated with an imbalance in its production and destruction process, associated with increased expression of tumor growth factor beta(TGF-β). (1,6) This inflammatory response causes an increase in intestinal permeability, mediated by IFN-gamma and TGF-β and associated with a decrease in claudins, proteins responsible for the intercellular junctions of the colonic epithelium[1].

The triggers of this inappropriate immune response are unknown. They primarily involve exposure to bacterial products, drugs or other chemicals. In relation to bacteria, a recent Danish study associates the incidence of MC with enteric infections by *Campylobacter jejuni* and *Campylobacter concisus*, without association with infection by *Salmonella spp*. The microbiota is also implicated in the pathogenesis of the disease based on its improvement when fecal flow is diverted by ileostomy, or the appearance or improvement of the picture when a fecal transplant is performed. Some noteworthy findings in the microbiota of patients with MC are the existence of a dysbiosis with a reduction in species diversity. Among them, a reduction in the family *Ruminococcaceae, Collinsela, Coriobacteriaceae, Clostridiales, Akkermansia and Alistipes* is observed. However, further studies are needed to corroborate these findings[1]. Drugs that are associated with an increased risk of MC are proton pump inhibitors (PPIs), non-steroidal anti-inflammatory drugs (NSAIDs) and selective serotonin reuptake inhibitors (SSRIs)(Tabla 1). However, this association does not imply their causal relationship. Chronic use of PPIs significantly increases the risk of CM with an OR of 2.95 (95% CI: 1.82-4.8). This risk is higher for CC. The proposed mechanism

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for this increased risk appears to be related to modification of intestinal permeability and intestinal microbiota. NSAIDs also increase the risk of MC with an OR of 2.4 (95% CI: 1.99-2.89). Concomitant use of PPIs and NSAIDs could further increase the risk. Finally, SSRIs also increase the risk with an OR of 2.98 (95% CI, 2.35-3.78). The mechanisms by which NSAIDs and SSRIs favor the development of MC are not known. Other drugs that may increase the risk are hormone replacement therapy in women, with a higher risk associated with a longer treatment time. Oncological immunotherapy also produces enterocolitis, which in some cases meets the histological criteria for MC. In these cases there is a response to budesonide and they have a better prognosis than other forms of enterocolitis caused

Figure 1. ***Risk factors and pathogenesis of CM.***

by these drugs. Less evidence of their implication in the development of CM has ticlopidine, beta-blockers, angiotensin converting enzyme inhibitors (ACE inhibitors), angiotensin 2 receptor antagonists (ARA-2), oral antidiabetics and statins[1,3].

Smoking is another factor that increases the risk of developing MC. A history of smoking increases the risk with an OR of 1.6 (95% CI, 1.4-1.9), whereas active smoking increases the risk with an OR of 2.99 (95% CI, 2.15-4.15), being higher for CC (OR: 5.5, 95% CI: 3.4-8.9). The mechanism implicated is alteration of the intestinal barrier, alteration of humoral and cellular immunity, alteration of the intestinal microbiota and stimulation of fibrogenesis by TGF-β stimulation[1,3].

A lower body mass index could increase the risk of MC. There are no conclusive data regarding the consumption of alcoholic beverages[1].

Drugs with the most evidence	OR
PPIs	2,95 (CI 95%: 1,82-4,8)
NSAIDs	2,4 (CI 95%: 1,99-2,89)
SSRIs	2,98 (CI 95%, 2,35-3,78)
Other associated drugs	
Hormone replacement therapy	
Ticlopidine	
Oncological immunotherapy (checkpoint inhibitors)	
Beta-blockers	
ARA-2	
Oral antidiabetics	
Statins	

Table 1. ***Drugs associated with an increased risk of MC. PPIs: Proton pump inhibitors. NSAIDs: non-steroidal anti-inflammatory drugs. SSRIs: selective serotonin reuptake inhibitors. ARA-2: Angiotensin II receptor antagonists.***

Finally, from the genetic point of view, haplotypes of the HLA complex have been detected that increase the risk of developing MC. Specifically, the ancestral haplotype HLA 8.1 is associated with CC, although not with LC. CC has also been associated with more frequent alleles in Crohn's disease and ulcerative colitis. It has also been associated with alterations in chromosome 6 (HLA DQ2) associated with celiac disease[1,6].

Clinical features

The main symptom of MC is watery, chronic or intermittent, non-bloody diarrhea. The intensity of diarrhea can be variable, although the average is usually 6-7 dep/day. The onset of diarrhea may be acute in one third of cases, but it is usually insidious and before diagnosis may persist for about 6 months. Nocturnal diarrhea may be present in 25-50% of cases[2,3].

To determine the severity of diarrhea it is recommended to use the Hjortswang criteria which state that there is clinical remission of colitis when there is an average over a week of less than 3 stools per day and less than 1 watery stool per day. There is also a CM activity index (MCDAI) that includes as severity criteria the number of unformed stools per day, nocturnal episodes, abdominal pain, weight loss, defecatory urgency and fecal incontinence. The Hjortswang criteria have been used in more studies including clinical trials, proving their usefulness in real life, so they are the ones recommended by the European guidelines[3].

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Figura 2. ***Imagen tipo de deglución y reflujo. An Pediatr Contin. 2013;11(2):110-6.***

The mechanism by which diarrhea occurs in MC is not completely known, but it seems to be of multifactorial origin. Firstly, there is an osmotic component since fasting improves symptoms. There is also an associated inflammatory and secretory mechanism. The role of bile acid malabsorption in the clinic of diarrhea and the pathogenesis of MC is not clearly established. Up to 44% of patients with MC have associated bile acid malabsorption demonstrated by SeHCAT. In addition, a decrease of the farnesoid X receptor at the colonic level is observed in patients with MC, and in animal studies, the use of farnesoid X receptor agonists reduces the degree of colonic inflammation. However, these are studies with limited samples[1,2].

In addition to diarrhea, other frequent symptoms are abdominal pain (50-70 %), abdominal distention, defecatory urgency (70%) overlapping symptoms therefore with functional diarrhea or irritable bowel syndrome with predominance of diarrhea. Fecal incontinence (40%) and discrete weight loss may also occur in up to 50% of cases[2].

The presence of autoimmune diseases is more frequent in patients with MC, being present in 30-50% of cases. The most frequent of all is celiac disease, being present in 2-20% of patients with CM, recommending its serological screening in patients with CM and especially if there is no response to treatment[2,3]. Other associated autoimmune diseases include type 1 diabetes, autoimmune thyroiditis, rheumatoid arthritis, Sjögren's syndrome and psoriasis.[2].

Natural history

CM can present as a single episode of diarrhea lasting a few months, as chronic persistent diarrhea or with intermittent episodes of diarrhea. Spontaneous remission rates are unknown, but are around 51%. In the remainder, corticosteroid dependence is observed in 22% of cases and recurrence after a first episode in 28% of cases[2,3].

It remains unclear whether CC and CL are two histological subtypes of the same disease or are different diseases.[2]. The natural history of incomplete MC is also unknown, although data suggest that it has a greater tendency to spontaneous remission[3].

MC is not associated with increased mortality, increased risk of inflammatory bowel disease, or increased risk of colorectal cancer, so specific screening strategies for colorectal cancer are not recommended[1,3]. Rare complications include colonic perforation spontaneously or after colonoscopy[2].

Although no increased mortality is observed, MC is associated with a lower quality of life that correlates with increased disease activity and severity of the disease and its comorbidities. Quality of life improves with budesonide treatment. However, even in the absence of activity, quality of life questionnaires provide lower scores than the healthy population, with higher prevalence of anxiety, depression and somatization[1].

Diagnosis

The diagnosis of MC, as mentioned at the beginning, is based on the finding of defined histological features in colonic biopsies obtained by colonoscopy. Therefore, the performance of colonoscopy, the taking of biopsies and their subsequent anatomopathological analysis are crucial for the diagnosis. This is due to the fact that neither from the clinical nor analytical point of view, nor from the macroscopic findings of colonoscopy, are there criteria to establish a diagnosis.

The differential diagnosis of chronic watery diarrhea includes organic processes such as infections, celiac disease, inflammatory bowel disease, bacterial overgrowth and colon cancer. However, functional pathology such as diarrhea-predominant irritable bowel syndrome and chronic functional diarrhea are also included[8]. In a meta-analysis it was observed that 33.4% of cases with CM would meet the diagnostic criteria for IBS-D. In another study, between 6-9% of cases with CM met the diagnostic criteria for IBS-D. In another study, 6-9% of patients with IBS-D and chronic functional diarrhea actually had MC when colonoscopy with biopsies was performed[1,3]. In an attempt to reduce the number of colonoscopies and biopsies and increase the diagnosis of MC, a scoring system was established. This system scores age greater than or equal to 55 years, diarrhea course of less than or equal to 6 months, 5 or more bowel movements per day, body mass index less than 30 kg/m^2, active smoking, and treatment with NSAIDs or SSRIs. A score greater than or equal to 10 had a sensitivity of 91-93 % with a specificity of 49 % for the diagnosis of MC (Table 2)[9]. However, the recommendations of the European and Spanish MC guidelines state that colonoscopy with biopsies should be performed in patients with a clinical diagnosis of IBS-D or functional diarrhea, when there is no response to treatment or when there are risk factors for MC. The recommendations of the AGA regarding the performance of colonoscopy with biopsy in the context of IBS-D and functional diarrhea are more ambiguous, considering them as not necessary in the absence of alarm symptoms or in children under 50 years of age in cases of IBS-D, although it refers that it is the only method to rule it out in cases of FD[8].

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Laboratory tests are useful in the differential diagnosis with other organic disorders, such as, for example, stool stool cultures or parasites to rule out infectious processes or serology for celiac disease. Celiac disease is frequently associated with CM and should be ruled out[3]. Regarding fecal biomarkers, there are no studies to support their use for the diagnosis or follow-up of CM. Although fecal calprotectin in some studies shows discretely elevated levels in MC versus functional disorders, its predictive value is very low and the European guideline discourages its use[3].

Colonoscopy with ileoscopy is indicated in the study of chronic diarrhea[2,3]. Macroscopic findings of the colonic mucosa in MC are generally normal when colonoscopy is performed. However, nonspecific findings such as edema, erythema, nodularity, altered vascular patterns, linear erosions and pseudomembranes may be found in up to 40% of cases. No differences in these findings have been demonstrated between LC and CC[3].

In the context of chronic watery diarrhea with normal macroscopic findings, colonic biopsies are considered essential, because MC is the most frequent cause of chronic diarrhea with normal endoscopic findings[2]. In addition, it can also diagnose some cases of Crohn's colitis or infectious colitis. Biopsy collection is cost effective in the context of chronic watery diarrhea and its ratio is superior to duodenal biopsy collection in the study of diarrhea, anemia or first-degree history of celiac disease[2]. Biopsy collection should be performed perpendicular to the colon wall, to facilitate the measurement of the collagenous band in the case of CC diagnosis. There is consensus that biopsies should be taken in separate canisters from the right and left colon. Although the clinical usefulness of separating these canisters is controversial, it can help the diagnosis given the difference in cellularity in the lamina propria of the right and left colon. According to the Spanish clinical guidelines, at least 2 biopsies should be taken from the ascending, transverse, descending and sigmoid colon[2]. The European guidelines recommend taking biopsies from the right and left colon, without specifying the specific location or number of biopsies[3].

In all cases of MC it is recommended to rule out the coexistence of celiac disease. However, the study of bile acid malabsorption is not recommended[3].

Histological diagnosis

From the definition of MC derives the importance of a careful histological study of the submitted specimens, always taking into account the histological characteristics of the colon in each of its locations. The specification of the location is essential to avoid misinterpretation.

Predictors of CM in chronic diarrhea[9]	
Factor	Points assigned
Age ≥ 55 years	6
Duration of diarrhea ≤ 6 months.	5
BMI less than 30 kg/m2	3
Number of bowel movements ≥ 5 /d (mean since symptom onset)	3
Active smoking	3
Current treatment with SSRIs or SNRIs	2
Current treatment with NSAIDs	2
Score ≥ 10 points: sensitivity 91-93 %, specificity 49 % for the diagnosis of CM.	

Table 2. ***Predictors of CM in chronic diarrhea. BMI: Body mass index. SSRIs: Selective serotonin reuptake inhibitors. SNRI: Serotonin-norepinephrine reuptake inhibitors. NSAIDs: Non-steroidal anti-inflammatory drugs.***

The histological criteria for microscopic colitis have been established with a certain rigidity, a fact that leads to the suspicion that it is not easy to differentiate two pictures with similar findings, while at the same time it is deduced that these criteria could change depending on the establishment of a consensus that is more rigid or flexible and to which it is necessary to adapt.

The criteria are the following:

Lymphocytic colitis

· Intraepithelial lymphocytosis (20 intraepithelial lymphocytes / 100 epithelial cells) without associated architectural distortion of the crypts. This counting can, if necessary, be supported by the use of immunohistochemical techniques that reveal the presence of T lymphocytes in the sample. The CD3 marker is generally used for this purpose, and it should be noted that the samples evaluated with this stain end up obtaining slightly higher T lymphocyte counts than those obtained with routine stains (hematoxylin and eosin, HE).

· Perinuclear lymphocytic halo (not always present).

· Degenerative or regenerative changes of the superficial epithelium, variable (flattening, vacuolization, mucin depletion...).

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· Only discrete thickening of the subepithelial collagenous band (less than 10 µm).

· Increased cellularity in the lamina propria, with frequent presence of eosinophils.

· Neutrophilic cryptitis and cryptic abscesses may be present but neutrophilic activity may only be focal[10,11].

Collagenous colitis

· Thickening of the subepithelial collagen band at the superficial level (greater than 10 µm).

· The thickening is easier to identify between the crypts.

· Within the band we can find capillaries, red blood cells and inflammatory cells.

· Increased epithelial damage and, therefore, more frequent detachment of the surface epithelium.

· An increase in the number of intraepithelial lymphocytes can be identified, which is minor and not necessary for diagnosis.

· Histochemical techniques can be used to demonstrate the collagen band (Masson, tenascin...).

· Similar criteria at the lamina propria level as LC[10,11].

Incomplete MC

· The clinical features are consistent with the entity, but the characteristic histology is incomplete (the minimum number of intraepithelial lymphocytes or the minimum thickness of the stratum collagen is not reached).

· Increased number of intraepithelial lymphocytes but less than 20/100.

· Increased subepithelial collagenous layer thickness but less than 10 µm[12].

Treatment

Treatment with oral budesonide is the treatment of choice to achieve remission in MC (Figure 3). It is a treatment approved by the European Medicines Agency, and although neither this nor any other is approved by the FDA, it is recommended by the American, Spanish and European MC guidelines[1,3]. With moderate evidence in CC and low evidence in LC, treatment with budesonide achieves a histological clinical response and an improvement in quality of life[3].

Induction treatment is at a dose of 9 mg/day orally for 6-8 weeks, with a remission rate of 81% in CC and 95% in LC. Neither progressive dose reduction nor concomitant use of calcium and vitamin D is necessary[3,13,14]. Nor is it necessary to confirm histologic response by repeat colonoscopy with biopsies[3].

Despite achieving high induction rates, recurrence is frequent. Therefore, when a second relapse occurs after induction treatment, maintenance treatment with budesonide is recommended, with greater evidence in CHD. The doses used in the research studies were 6 mg/day, or alternating 3 and 6 mg each day, with the recommendations of the European guidelines being to try to use the lowest effective dose[2,3]. Long-term use of budesonide is safe. Although there could be a decrease in bone mineral density with maintenance treatment, no increase in the risk of fractures has been demonstrated, so although some authors recommend adding vitamin D and calcium, especially if other risk factors for osteoporosis coexist, the European guidelines do not[3,13].

In cases in which there is no response to induction treatment with budesonide, it is recommended to rule out other causes of chronic diarrhea, such as bile acid malabsorption, irritable bowel syndrome or celiac disease. In addition, discontinuation of smoking and of drugs related to MC is recommended, although the evidence for these measures is scarce and is usually considered at the time of diagnosis of the disease. Once these premises have been met, if symptoms persist, the first recommended measure is to add cholestyramine and/or loperamide to the treatment. Both drugs can also be used in mild cases of the disease (less than 3 dep/day, and less than 1 watery stool per day)[3,13].

Cholestyramine (3-4 gr/ 2 or 3 times a day) has shown efficacy in remission, especially when there is an association of MC with bile acid malabsorption. In this sense, the European guidelines recommend its use, with low evidence, only in cases in which both diseases coexist, while the Spanish guidelines do not make such differentiation[2,3].

Loperamide (2-16 mg/day) has no controlled studies that support its efficacy in MC. Based on case series, it is recommended to reduce the number of bowel movements, improve fecal incontinence and therefore quality of life. No effect on the pathogenesis of the disease is attributed to it and it is considered a symptomatic treatment[2,3].

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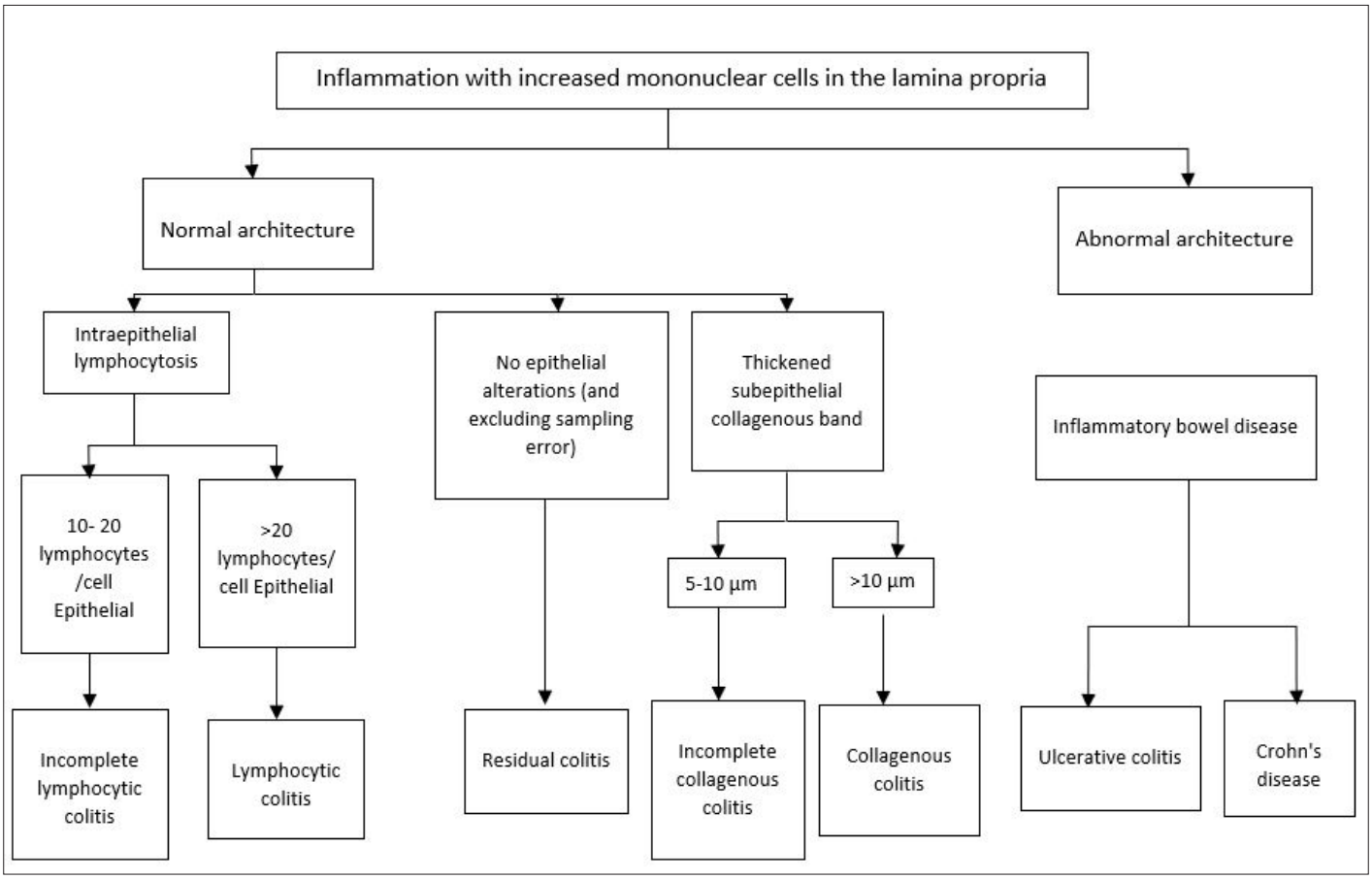

Figure 2. ***Histological differential diagnosis of colitis.***

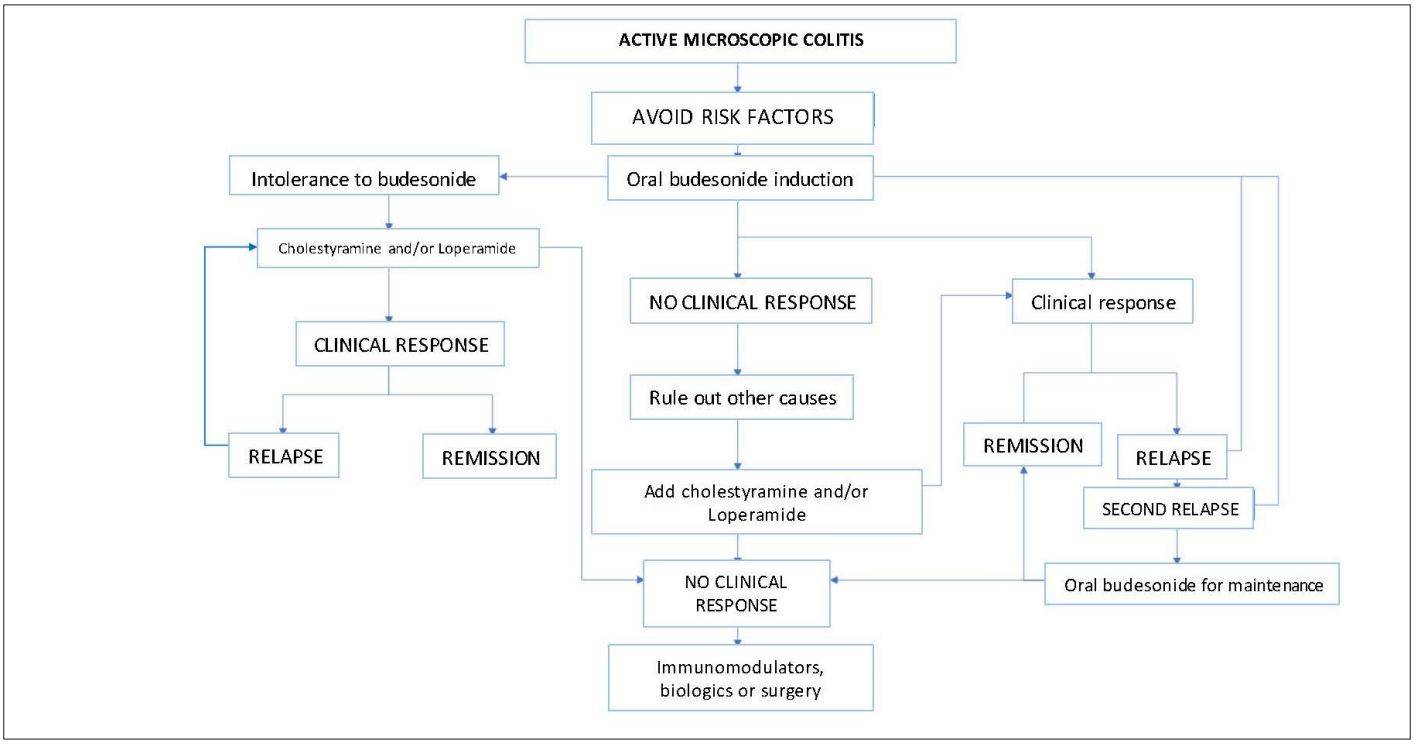

Figure 3. ***Treatment scheme for active MC. Induction budesonide: 9 mg/24h/voral for 6-8 weeks. Maintenance: 3-6 mg/24h/voral. Cholestyramine: 3-4 gr/8-12h/voral. Loperamide: 2-16 mg/24h/voral.***

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The use of antibiotics, probiotics, mesalazine, bismuth subsalicylate or other corticosteroids in the treatment of the disease is not recommended[1-3].

When there is no response to induction treatment with budesonide or budesonide plus cholestyramine/loperamide, or to maintenance treatment with budesonide, CM is considered refractory. In these cases, the recommendations are the use of immunomodulators such as azathioprine or 6-mercaptopurine, and among biologics, anti-tumor necrosis factor drugs and vedolizumab. The use of methotrexate is not recommended. However, experience is scarce and cases should be selected[3].

Finally, surgery (ileostomy, sigmoidostomy, or proctocolectomy with ileoanal pouch) could be a rescue treatment in very selected cases[3].

Conclusion

MC is a disease of increasing incidence and prevalence. Although it is not associated with increased mortality, it has a negative impact on the quality of life of patients. Its pathogenesis is unknown and progress must be made in this regard to improve the understanding of the disease and finally establish the relationship between lymphocytic and collagenous colitis and its natural history. Diagnosis still depends on colonoscopy with colonic biopsies. One line of research would be to search for biomarkers of the disease or to develop new clinical scoring studies to predict the risk of MC. This would avoid performing colonoscopies and taking biopsies in patients with functional pathology. Taking biopsies in separate left and right colon bins is recommended; although this circumstance, along with the number of biopsies required, should be clarified in the future. In addition, the natural history and clinical relevance of incomplete MC should be determined. Budesonide is the treatment of choice with frequent need for maintenance treatment with this drug, which has a good safety profile. New drug studies would be necessary in case of refractoriness to budesonide.

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REVIEW ARTICLE

EOSINOPHILIC ESOPHAGITIS. BEYOND THE DIET.

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Abstract

Eosinophilic esophagitis is a chronic, progressive, immune-mediated (Th2 antigen) disease that exclusively affects the esophagus. It is characterized histologically by intraepithelial infiltration of eosinophils (> 15 eosinophils per high-power field), leading to esophageal dysfunction, primarily manifested as dysphagia and food impaction. Initially, it is an inflammatory disease that can progress to a fibrostenotic pattern and is considered the most common cause of chronic dysphagia and esophagitis, second only to gastroesophageal reflux disease. As such, it currently represents the second most common cause of chronic esophagitis and the leading cause of dysphagia and food impaction in children and young adults, accounting for 7% of endoscopic diagnoses of esophageal symptoms.

EoE is considered an emerging disease with increasing incidence, likely due to the widespread use of upper gastrointestinal endoscopy in the evaluation of gastrointestinal pathology, alongside greater awareness and recognition of this condition by endoscopists and clinicians.

As a chronic disease that can progress to a fibrotic pattern, early detection and appropriate treatment are crucial.

In this review, we examine the current management of eosinophilic esophagitis, reviewing the latest evidence on the various treatment options. We analyze the therapeutic approach to follow based on the disease pattern, potential clinical and endoscopic follow-up for maintenance treatment, as well as the possibility of treatment discontinuation in selected cases.

Keywords: eosinophilic esophagitis, PPI, topical steroids, dupilumab, empiric diet.

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Introduction

Eosinophilic esophagitis (EoE) is a chronic inflammatory disease of the esophagus characterized by eosinophilic infiltration of the esophageal mucosa. Since its initial description, EoE has been the subject of increasing clinical and scientific interest, given its increasing prevalence and the complexity of its management. Understanding the evolution of the disease is fundamental to establish an adequate therapeutic approach, since it can evolve to more severe forms (fibrostenotic pattern) if it is not diagnosed early and adequate treatment is not established..

The management of EoE has evolved significantly in recent years, reflecting a better understanding of the pathogenesis of the disease and its impact on patients' quality of life. Current lines of treatment focus on addressing both esophageal inflammation and associated symptoms, and may include dietary strategies, pharmacological and, in some cases, endoscopic interventions. In addition, new therapeutic options, including biologic treatments, are being explored that promise to improve outcomes in patients with more severe forms of the disease. The decision to initiate one line of treatment or another, always using it in monotherapy, will depend on the pattern of the disease and on the decision agreed with the patient after informing him/her of the different treatment options available, the main objective of the treatment being to induce and maintain clinical and histological remission of the disease..

Therapeutic approach

Currently, several therapeutic alternatives are available for the management of EoE, aimed at controlling inflammation (by means of pharmacological or dietary treatments) and managing fibrosis and stenosis (by means of endoscopic intervention). It is possible to combine endoscopic dilatation with anti-inflammatory treatment; however, the latter will always be administered in monotherapy.

The therapeutic strategy is defined according to the two main patterns of the disease: inflammatory and fibrostenotic.

Inflammatory pattern

This pattern is characterized by inflammatory signs with or without the presence of incipient esophageal rings. In these cases, four therapeutic options are available as first-line treatments: proton pump inhibitors (PPIs), topical corticosteroids, food elimination diets and biological treatment with dupilumab (indicated as first-line only in cases of concomitance with other poorly controlled Th2-mediated disease).

The choice of treatment will depend on the availability and specific characteristics of the patient, and should be agreed with the patient. If the initial treatment is not effective (both clinically and histologically), it should be discontinued and another option should be tried until a favorable response is obtained. For patients refractory to PPIs, elimination diets and topical corticosteroids, the only alternative currently available is dupilumab.

Fibrostenotic pattern

In this pattern, initial treatment will focus on controlling inflammation with topical corticosteroids. Subsequently, endoscopic management will be carried out by progressive dilatations. In cases of refractoriness, the use of dupilumab will be indicated, accompanied by endoscopic treatment as needed.

Proton pump inhibitors (PPIs)

Over the last decade, the use of PPIs in EoE has evolved significantly from being a diagnostic tool to differentiate EoE from gastroesophageal reflux disease to being considered a therapeutic option in this pathology. This transition was the result of the International Consensus Conference for Diagnostic Criteria for EoE: Appraisal of Guidelines for Research and Evaluation II (AGREE), which supports PPI therapy for EoE in children and adults[1].

Several studies have demonstrated the efficacy of PPIs in reducing eosinophilic inflammation in patients with EoE. In a meta-analysis by Molina-Infante and Lucendo (2017), it was evidenced that more than 50 % of patients treated with PPIs presented a significant decrease in the eosinophil count in the esophageal mucosa. Additionally, improvement of symptoms, such as dysphagia, has been reported in multiple randomized clinical trials[2].

Another significant study evaluating its efficacy is the European EoE CONNECT registry[3]. This registry collects clinical, environmental and genetic data from patients with EoE, facilitating multicenter research on this disease. A recent analysis evaluated the efficacy of PPIs in a cohort of 630 patients with EoE. The results indicated that 48% of patients treated with PPIs achieved histologic remission (< 15 eos/CGA) and 71% found improvement in their symptoms. They also found

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no significant difference in efficacy between the different types of PPIs when administered at equivalent doses.

These findings support the use of PPIs as an effective therapeutic option in approximately half of the patients with EoE. In the future, the identification of factors predictive of response to PPI could optimize the selection of patients for this treatment, improving clinical and histologic outcomes.

Mechanism of action

The mechanisms by which PPIs work to reduce eosinophilia in EoE have been the subject of considerable debate and research effort[1,4]. Proposed mechanisms include PPI-induced gastric acid suppression leading to a restoration of esophageal barrier function and, on the other hand, a direct anti-inflammatory effect, inhibiting the production of proinflammatory cytokines such as interleukin 4 (IL-4), interleukin 5 (IL-5), and most prominently IL-13[5].

IL-13 plays a crucial role in the pathogenesis of EoE, since it promotes the expression of eotaxin-3, a chemokine responsible for the recruitment of eosinophils to the esophageal mucosa. This anti-inflammatory action is achieved by acting at 4 levels[6]: blocking the expression of cell surface adhesion molecules, inhibiting the migration of inflammatory cells to the esophageal epithelium; blocking STAT6-mediated eotaxin-3 (transcription factor) expression, reducing eosinophil recruitment to the esophageal epithelium; stimulation of the aryl hydrocarbon receptor, normalizing the expression of genes involved in barrier function, including filaggrin, loricrin and involucrin, through inhibition of the IL-4/IL-13-STAT6 pathway; and inhibition of ATP12A, non-gastric H-type P2, K-ATPase activity. IL-4-mediated induction of eotaxin-3 secretion is sensitive to ATP12A inhibition.

What dose of PPIs do we use to induce remission?

According to clinical guidelines, standard PPI therapy for EoE would be the standard twice-daily dose of either PPI[7]; however, there are limited data directly comparing PPI dose combinations for the treatment of EoE.

In a recent study involving a total of 305 patients with EoE, various doses of PPIs were evaluated for at least 8 weeks[8]. They found that the twice-daily prescribed PPI dose induced higher histologic response rates compared with the once-daily PPI dose, even when the total daily dose was equivalent. Histological response rates were higher with the twice-daily dosing regimen (moderate 52.8 % / high 54.3 %) compared to once-daily (standard 11.8 % / moderate 10 %) ($P < 0.0001$). In addition, double-dose treatment (40 mg omeprazole twice daily) did not appear to provide additional benefit over the moderate twice-daily dose (20 mg twice daily).

Therefore, based on the results of this study, the standard twice-daily PPI dose (20 mg omeprazole twice daily or equivalent) may be the optimal PPI regimen for inducing remission in EoE.

How long should one treat with PPIs to induce remission?

According to the recommendation of clinical practice guidelines, PPI treatment should be maintained for a minimum of 8 weeks before endoscopic evaluation[7]. However, a more recent study compiling data on the efficacy of PPIs from the multicenter EoE CONNECT database examines whether the duration of PPI treatment influences the effectiveness in achieving clinical-histologic remission of EoE[3]. The results they obtained show that PPI treatment duration of 8 to 10 weeks (56-70 days) provides a remission rate of 50.4 %; by prolonging treatment between 71 and 90 days (10 to 12 weeks), the remission rate increases to 65.2 %; however, treatment beyond the third month (>90 days) decreases effectiveness to 44.1 %, possibly due to lower patient adherence. Therefore, according to the results obtained in this study, we could consider that treatment duration of up to 12 weeks correlates with a higher probability of inducing EoE remission compared to treatments shorter than 10 weeks.

Food elimination diet

History and evolution of dietary treatment of EoE

The first study employing dietary treatment in patients with EoE was published in 1995 by Kelly [10]. In this study, 10 children were treated with an elemental diet, achieving complete histologic remission in 8 of them and clinico-histologic improvement in the remaining 2. These findings demonstrated that EoE is caused by a food allergy.

Eleven years later, in 2006, the first study on the empirical six-food elimination diet was published, showing somewhat lower response rates than the elemental diet, but reaching 74%[11]. Since then, numerous studies have confirmed the effectiveness of this dietary strategy in the treatment of EoE.

The six-food elimination diet is the most studied and has demonstrated the highest response rates[12]. However, it is a highly restrictive diet that requires a prolonged diagnostic period (at least 42 weeks) and the performance of up to seven

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Diet	Eliminated food	Response rate (%)	Pros	Cons
Elimination 6 foods	Animal milk Wheat Egg Soybeans* (legumes) Nuts Fish/Seafood	40-73	- Best studied diet - Best remission rate of the elimination diets.	- Most restrictive elimination diet. - Higher number of endoscopies. - Higher cost. - Lower adherence.
Elimination 4 foods	Animal milk Wheat Egg Soy* (legumes)	41-60	- Less restrictive. - More varied diet. - Shortened diagnostic process	- Possible lower rate of remission. - Higher cost. - Lower adherence.
Elimination 2 food	Animal milk Wheat	43	- Even less restrictive. - Avoids unnecessary restrictions. - Diagnostic process shortened. - Less impact on quality of life.	-Possible lower rate of remission.
Elimination 1 food	Animal milk	34-65	- Least restrictive diet. - Avoids unnecessary restrictions. - Shortened diagnostic process. - Fewer endoscopies. - Less impact on quality of life.	Possible lower remission rate.

Table 1. ***Empirical elimination diets. Adapted from Chang JW, Kliewer K, Haller E, Lynett A, Doerfler B, Katzka DA, et al. Development of a practical guide to implement and monitor diet therapy for eosinophilic esophagitis. Clin Gastroenterol Hepatol. 2023 Jul;21(7):1690–8.***

gastroscopies. Therefore, less restrictive alternatives have been developed, such as four-food, two-food, and single-food elimination diets (Table 1).

In 2018, Molina-Infante proposed the Step-Up strategy for diagnosis and treatment by empiric diet in patients with EoE. This strategy starts with a two-food elimination diet and, in case of no response, is progressively increased to four and six foods[13].

Protocol for the dietary management of EoE [12]

Once treatment is initiated with the elimination diet agreed with the patient, a gastroscopy with biopsies will be performed at 6-8 weeks. In case of lack of response (no histological remission), a more restrictive diet or a change to pharmacological treatment will be considered. Otherwise, food will be reintroduced, starting from the least allergenic (fish and seafood) to the most allergenic (milk of animal origin). After the reintroduction of the first food, a new gastroscopy will be performed after 4-6 weeks. If histological remission persists, the next food will be added, with endoscopic control at 4-6 weeks. In case of recurrence of the eosinophilic infiltrate after the introduction of a food, it will be identified as a trigger and definitively withdrawn. After a washout period of 4-6 weeks, another food will be introduced. This cycle will be repeated until all foods initially eliminated have been evaluated. Definitive treatment will consist of permanent exclusion of the food(s) identified as triggering the disease.

Food elimination diets based on allergy tests

Food elimination diets based on allergy tests (such as skin prick test, patch test or serum Ig test) have shown lower efficacy compared to empirical diets, as evidenced by three meta-analyses[14-16]. Currently, these tests are not recommended, as mentioned in the latest published guideline on EoE[17]. This is because these tests detect IgE-mediated allergies, whereas EoE is a lymphocyte-mediated type 2 immunity disorder characterized by delayed hypersensitivity, in which IgE does not play a relevant role. In those patients with suspected IgE-mediated food allergy, as well as before the reintroduction of food after a long period of dietary restriction, an evaluation by Allergology will be necessary, especially in children, because cases of severe immediate reactions, such as anaphylaxis, have been documented.

Topical corticosteroids

Effectiveness of topical corticosteroids in EoE

Topical corticosteroids, such as budesonide and fluticasone, have been shown to be highly effective in the

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treatment of EoE through numerous prospective, retrospective studies and up to 13 randomized, double-blind, placebo-controlled clinical trials in adults and children[18-23]. Its mechanism of action is based on the reduction of esophageal inflammation mediated by eosinophils and other inflammatory mediators through inhibition of proinflammatory cytokines, reduction of the production of key interleukins in Th2 inflammation (IL-4, IL-5 and IL-13), which promote eosinophil activation and survival; modulation of transcription factors that inhibit nuclear factor kappa B (NF-κB) and activator protein-1 (AP-1), responsible for the transcription of proinflammatory genes; reduction of eosinophilic chemotaxis (they decrease the expression of eotaxin-3, a chemokine essential for the recruitment of eosinophils to esophageal tissue); induction of eosinophil apoptosis; inhibition of Th2 differentiation; and enhancement of the epithelial barrier, promoting tissue repair, which contributes to reducing chronic damage and progression to fibrostenosis. These molecular and histological actions are essential to control chronic inflammation and prevent complications arising from fibrosis in disease progression[24].

Different formulations have been used for the treatment of EoE with topical corticosteroids (Table 2), initially with devices designed for the treatment of other organs such as inhalation devices or nasal drops. Subsequently, budesonide or viscous fluticasone preparations have been used, and are still used today, either magistral formulas prepared by pharmacists or home-made solutions. Recently, budesonide orodispersible tablets have been developed, which have shown clinical, endoscopic and histologic response rates above 95%[18]. Similar formulations of fluticasone are in phase 3 development. A recent study showed that switching to orodispersible tablets improves quality of life, treatment satisfaction, and histologic outcomes (<15 eosinophils/CGA and even <6 eosinophils/CGA), as well as endoscopic response [25].

In addition, topical corticosteroids have been shown to be more effective than PPIs and diets in both first- and second-line treatments[26]. They also achieve high long-term histologic response maintenance rates of greater than 60%, with excellent treatment adherence and low rate of adverse effects[27].

According to data from the European EoE CONNECT registry[26], fluticasone is used more frequently than budesonide (6:4 ratio). Nasal drops are the most common presentation of fluticasone, whereas for budesonide master formulations predominate, followed by orodispersible tablets. The analysis also showed that budesonide is more effective than fluticasone, budesonide orodispersible tablets are more effective than other formulations, high doses (2 mg budesonide, 0.8 mg fluticasone) are more effective than low doses, and that the severity of symptoms is inversely proportional to the response to topical corticosteroid treatment.

Adverse effects[5]

Topical corticosteroids are safe in the long term, as evidenced by a study of nearly 1,000 patients, where adverse effects were mainly mild to moderate[28]. The most common was oral and esophageal candidiasis, frequently asymptomatic and rarely requiring discontinuation of treatment. Its management includes topical (clotrimazole) or systemic (fluconazole) antifungal agents, dose reduction or temporary suspension in severe cases. Adrenal insufficiency is a rare complication. Although adrenal function monitoring is not required in short treatments, it could be considered in prolonged therapies.

Biologic treatment. Dupilumab.

Dupilumab is the first biologic drug approved for EoE. Its indications would be: adult and adolescent patients aged 12 years and older, weighing at least 40 kg, who are inadequately controlled, intolerant or not candidates for conventional drug therapy. The recommended dose is 300 mg every week, administered by subcutaneous injection[29-30].

It is a recombinant human IgG4 monoclonal antibody that inhibits interleukin-4 (IL-4) and interleukin-13 (IL-13) signaling through the type I receptor (IL-4Rα/γc) and type II receptor (IL-4Rα/IL-13Rα). IL-4 and IL-13 are the main drivers in type 2 inflammation present in diseases such as atopic dermatitis, asthma or EoE. Blockade of the IL-4/IL-13 pathway by dupilumab interrupts a critical pathway in the inflammatory response observed in the esophageal epithelium in patients with EoE.

Efficacy

The evaluation of the efficacy of dupilumab in EoE is based on a randomized, double-blind, multicenter, placebo-controlled, phase 3 clinical trial[31]. The study consisted of 3 parts: A, B, and C. Parts A and B each consisted of a 24-week double-blind treatment period. After this treatment period, patients in parts A and B had the option to enter part C, which consisted of a 28-week treatment extension period, the objective of which was to evaluate safety and efficacy up to 52 weeks of treatment with dupilumab. The results they obtained were that the proportion of patients achieving histological deep remission < 6 eos/CGA was significantly higher in patients treated with dupilumab, regardless of receiving dupilumab weekly or every 2 weeks versus the placebo group.

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	Formulation	Doses	Remission rates
Fluticasone 59%	nasal drops 74%	0,8 mg/day 68,7%	66,2%
		0,4 mg/day 12%	29,6%
Budesonide 41%	compounded formula 57,4%	2 mg/day 68,7%	80,2%
		1 mg/day 6,5%	63,6%
	orodispersible tablet 26%	2 mg/day 55,7%	100%
		1 mg/day 44,3%	86,2%
	home-made 9,1%	2 mg/day 44,1%	80%
		1 mg/day 41,2%	100%
	inhaler 7,5%	2 mg/day 67,9%	93,3%
		1 mg/day 17,9%	-

Table 2. ***Use of topical corticosteroids in daily clinical practice. Data from Laserna-Mendieta EJ, Navarro P, Casabona-Francés S, Savarino EV, Amorena E, Pérez-Martínez I, et al. Swallowed topical corticosteroids for eosinophilic esophagitis: utilization and real-world efficacy from the EoE CONNECT registry. United European Gastroenterol J. 2024 Jun;12(5):585–595.***

In contrast, when analyzing clinical improvement in dysphagia, they found that patients receiving weekly dupilumab achieved greater symptom control after 4 weeks of treatment when compared with the placebo group. However, such clinical improvement was not obtained in the group of patients who were administered every 2 weeks.

Therefore, taking into account these results, and the fact that the histological remission rates are similar when prescribed weekly or every 2 weeks, the use of dupilumab could be evaluated in one way or another depending on the patient's symptoms.

Safety

Clinical trials and post-marketing studies have shown that dupilumab has a favorable safety profile in patients with EoE, similar to that observed in other indications (such as atopic dermatitis or asthma). Most of the adverse effects reported are mild to moderate, mainly injection site reactions (erythema, pain, inflammation). Among patients with EoE, the frequency of conjunctivitis was low and similar between the dupilumab or placebo group and there were no cases of keratitis[31,32].

Other emerging biologic therapies

Currently an area of intense research activity, there are a large number of biologic drugs that could be used for the treatment of EoE and other gastrointestinal eosinophilic diseases. The drawback is that we do not know the medium- and long-term efficacy and safety of the new molecules. Nor have they demonstrated the ability to modify the natural history of EoE.

These therapies target different cytokines involved in the inflammatory response in EoE. Ongoing studies of agents targeting IL-5, such as mepolizumab, reslizumab, and benralizumab should provide more information on whether targeting this pathway is feasible. It is expected that ongoing studies evaluating agents targeting other novel pathways, such as Siglec-8 (lirentelimab), IL-13 (cendakimab), sphingosine 1-phosphate receptor (etrasimod), and TSLP blocker (tezepelumab) will provide additional options for chronic management of EoE[33,34].

Endoscopic treatment: Can endoscopic dilatation be performed?

Experts recommend that adult patients with dysphagia due to stenosis associated with EoE should undergo endoscopic dilatation rather than no dilatation[35]. It should be taken into account that this is a chronic and fibrostenotic disease, which over time produces esophageal remodeling that can lead to the formation of permanent rings and changes in caliber (narrow esophagus) that will require endoscopic dilatations to resolve them. Esophageal dilatation is a mechanical procedure with no anti-inflammatory effect, aimed at widening the lumen of an esophagus of reduced caliber and leads to rapid symptomatic improvement in 95% of patients[36].

Dilatation is therefore indicated in patients with fibrous strictures or narrow-caliber esophagi that condition dysphagia

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or frequent episodes of food impaction despite effective pharmacological or dietary treatment. The American guidelines state that the ideal goal would be to reach 15-18 mm[37]. In any case, dilatation should not exceed 3 mm per session due to the risk of complications, and the ideal interval between sessions remains to be determined[38]. Balloons or rigid dilators can be used, and care should always be taken to look closely at the mucosa after removing the dilator and before increasing the caliber to detect tears. Risk factors for complications are young age, previous dilatations, upper esophageal stenosis and inability to pass with the endoscope[39]; however, complications of dilatation in EoE are rare, and although there is a risk of perforation of less than 0.4%, no mortality has been reported.

It should be kept in mind that endoscopic dilatation does not modify the underlying eosinophilic inflammation; therefore, it should not be used as the only therapeutic option for EoE, but should always be combined with effective anti-inflammatory treatment (PPI, diet, glucocorticoids or biologic therapy)[39].

Issues to be resolved in the management of the patient with EoE.

We know, therefore, that EoE is a chronic immune-mediated disease that, in the absence of treatment, presents a high probability of recurrence and can progress to structural complications, such as fibrostenosis, with the primary goal of treatment being to achieve clinical, histologic, and endoscopic remission of the disease[40].

One of the major outstanding issues in EoE is the lack of robust evidence on the efficacy and safety of long-term maintenance therapy. Currently, there are few studies designed to evaluate how to maintain clinical and histologic remission without exposing the patient to prolonged side effects or compromising treatment adherence. Furthermore, there is no consensus on the optimal time to perform revision endoscopies, either in the context of therapeutic de-escalation or during the maintenance phase[41]. Finally, doubts persist as to whether it is possible to discontinue treatment in certain patients who achieve sustained remission, and what would be the criteria for making this decision safely. These unknowns underscore the need for long-term prospective studies and more personalized approaches to disease management.

1. What is the optimal clinical and endoscopic follow-up?

The scientific evidence on the follow-up of patients with EoE is limited. However, there is a consensus document developed by North American and European experts that provides recommendations on how to perform this follow-up[42].

Monitoring in EoE seeks to determine whether the patient is improving, but this poses challenges due to the chronic nature of the disease, its recurrence upon discontinuation of treatment, and the potential loss of therapeutic efficacy over time. Long-term follow-up is required, evaluating symptoms, endoscopic and histologic findings to get a complete picture of disease activity. Symptoms, although fundamental, have limited correlation with the biological parameters of the disease. They may improve while active inflammation persists, due to avoidance behaviors or esophageal dilations, or they may persist even after controlling inflammation due to factors such as undetected strictures, esophageal hypervigilance, or feeding dysfunction. It is essential to inquire in detail about dysphagia, feeding behaviors and feeding dysfunction. The EREFS system is recommended to assess endoscopic response. Complete normalization corresponds to a score of 0, although a score ≤2 is a reasonable goal. Comparing pre- and post-treatment findings helps to assess evolution. Histologically, the goal is to achieve <15 eos/hpf (<60 eos/mm^2), so biopsies should be taken at each follow-up endoscopy.

The ideal concept of "deep resolution" combines symptom resolution and endoscopic and histologic normalization. However, it is achievable in few patients; for example, only 9.4% of patients in a Swiss study achieved this remission, and the median relapse was 22 weeks after stopping treatment. This highlights the need for continued follow-up even in patients in remission.

The follow-up interval varies according to treatment and individual characteristics. We will perform endoscopy after 8-12 weeks of starting PPIs, topical corticosteroids or elimination diet. Dupilumab requires 12-24 weeks to evaluate response. If there are no complications (impaction, perforations, malnutrition), clinical follow-up can be regular. However, a gap in care longer than 2 years increases the risk of fibrostenosis.

Although up to now biopsies are still essential, less invasive methods are being explored such as transnasal endoscopy that reduces costs and exposure to anesthesia, especially in children, cytosponge which is a capsule with a cytological brush that collects tissue when extracted; it has good tolerance and acceptable sensitivity, esophageal String Test that manages to detect inflammatory markers by absorbing them during their stay in the esophagus and other techniques such as mucosal impedance and EndoFLIP, which evaluate biomechanical and structural characteristics during endoscopies.

2. Is it possible to interrupt treatment in EoE?

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EoE is a chronic immune-mediated disease that requires continuous management to prevent persistent inflammation and structural complications, such as fibrosis and stenosis. For this reason, treatment discontinuation is a topic of debate in the scientific and clinical community, especially in patients who achieve sustained clinical and histologic remission.

Current management guidelines, such as those of the American Gastroenterological Association (AGA)[43] and the European Society for Pediatric Gastroenterology, Hepatology and Nutrition (ESPGHAN)[44], recommend a continuous treatment approach for most patients, given the risk of disease recurrence and progression. Several studies have evaluated the impact of withholding specific treatments, such as diet and medical treatment.

The results show that most patients experience clinical and histological relapse after discontinuation, even in those with sustained remission.

However, we believe that in certain selected cases a "suspension test" could be considered, especially in patients with mild EoE (no fibrostenotic pattern) and those who have maintained clinical and histologic remission for a prolonged period (>12 months). In these scenarios, discontinuation should be performed with close follow-up with periodic clinical and endoscopic evaluation to detect early relapses. This decision to discontinue treatment should be based on an individualized assessment that considers disease activity, risk of complications, and patient preferences. Future studies will help to better define patient subgroups that could benefit from therapeutic de-escalation strategies.

Conclusions and areas for improvement

EoE is a chronic and progressive disease[40]. These inherent characteristics of the disease have several practical consequences. First, once diagnosed, EoE requires a long-term management strategy. Second, maintenance treatment should be continued after achieving clinico-histologic remission. Third, patients with ongoing treatment need to have regularly scheduled clinical follow-up to assess for disease-related adverse events and side effects of medications or diets. Fourth, because the absence of symptoms is not a guarantee of endoscopic or histologic remission, periodic assessment of inflammatory activity by endoscopy and biopsy should be considered. There is little data to guide the frequency of clinical and endoscopic evaluations, although expert opinion dictates that at least once a year a complete evaluation should be done.

Regarding the possibility of discontinuing treatment, this remains a challenge, as most patients require long-term maintenance treatment to avoid relapses and complications, such as esophageal stricture. Although some patients with mild disease who manage to maintain a sustained histologic remission may be candidates for stopping treatment, most of them should be closely monitored to prevent disease recurrence.

Considering the natural history of the disease, there are several areas that could be improved to optimize the management of EoE. First, the identification of specific biomarkers that can predict relapses and allow more precise treatment personalization. Second, further studies on treatment discontinuation are essential to more clearly define clinical criteria and strategies for safe medication tapering. In addition, research on the long-term impact of current therapies on remission and relapse is essential to improve disease management.

In summary, treatment of EoE requires an individualized approach, rigorous monitoring and continuous assessment of therapeutic response. In the future, further studies will be needed to expand knowledge on the efficacy and long-term effects of therapies, which would allow the management of this chronic disease to be optimized.

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REVIEW ARTICLE

UPDATE ON THE MANAGEMENT OF ACUTE-ON-CHRONIC LIVER FAILURE

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Abstract

Acute-on-chronic liver failure (ACLF) is an acute decompensation of liver disease that is associated with high short-term mortality. Early diagnosis and identification of potential precipitating factors are essential for its correct management. ACLF is a dynamic entity, so assessment of the prognosis during its course is essential to assess the need, or conversely, the futility of different support measures and liver transplantation. Although many aspects of its pathophysiology are unknown, the exacerbated systemic inflammatory response and dysregulation of the immune system are the basis of it.

Keywords: acute-on-chronic liver failure, chronic liver disease, acute descompensation, liver trasplant.

Introduction

Chronic liver disease presents a complex natural history in which two fundamental phases can be distinguished: the compensated and the decompensated phase. Hepatic decompensation, which confers decreased survival at 3-5 years, is defined as the development of ascites, hepatic encephalopathy, gastrointestinal bleeding, bacterial infection or combination of these, and its occurrence is conditioned by the presence of clinically significant portal hypertension, defined as a hepatic venous pressure gradient ≥ 10 mmHg[1]. In recent years, three patterns of hepatic decompensation have been recognized that differ in clinical course, degree of systemic inflammation, and survival: stable, unstable, or pre-ACLF decompensation[2].

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Acute-on-chronic liver failure (ACLF), a term proposed by Jalan and Williams in 2002, is an acute decompensation characterized by organ failure and high short-term mortality[3].

In recent years different scientific groups have made efforts to define the concept of ACLF; however, these definitions present important differences probably due to the different prevalence of the triggering factors and the etiology of the underlying liver disease in each geographic area.

Despite this heterogeneity, they agree that ACLF is an acute decompensation with a pathophysiology and course of the disease different from the rest of the usual decompensations of cirrhosis.

There are currently three definitions according to the European Association for the Study of the Liver-Chronic Liver Failure (EASL-CLIF) Consortium, the Asian Pacific Association for the Study of Liver (APASL) and the North American Consortium for Study of End-stage Liver Disease (NACSELD), whose most relevant differences are shown in Table 1[4].

The most widespread definition in our setting is that of the EASL-CLIF Consortium, which arose from the CANONIC project, a multicenter, prospective study that included more than 1300 patients from 29 European hospitals admitted for acute hepatic decompensation, and whose main objective was to define the concept of ACLF. It was concluded that ACLF is an acute hepatic decompensation associated with organ failure and high mortality (more than 30% at 28 days), and organ failure was assessed using a modified scale of the well-known Sequential Organ Failure Assessment score (SOFA) called CLIF-C Organ Failure score (CLIF-C OF). This scale included 6 organ systems (liver, kidney, brain, circulation, respiratory, coagulation), and according to the number and type of organ failure different grades of ACLF were differentiated[5,6]. The prevalence of ACLF was 30% (20% on admission and 10% during hospitalization), similar to studies conducted in other geographical areas[4].

Different studies have shown that the ACLF criteria according to APASL and NACSELD in comparison with those of the EASL-CLIF Consortium underestimate the 28- and 90-day mortality of patients with acute hepatic decompensation, since a non-negligible percentage of them would be erroneously diagnosed and stratified as ACLF, which would have direct clinical implications, especially in the field of liver transplantation[7,8].

Phatophysiology

The pathophysiology of ACLF is extremely complex and many aspects of the mechanisms responsible are still unknown. However, it is well known that systemic inflammation and dysregulation of the immune system play an essential role.

This hypothesis, which is currently the most widely accepted, stems precisely from the CANONIC study in which it was found that elevated levels of C-reactive protein (CRP) and leukocytes, which are proinflammatory markers, were associated with a worse prognosis[5]. The mechanisms responsible for this variegated systemic inflammation are reflected in Figure 1.

Inducers of systemic inflammation

Inducers of the systemic inflammatory response can be divided into:

A) **Exogenous inducers.** These are the well-known pathogen-associated molecular patterns (PAMPs), molecules originating from bacterial agents. These PAMPs are not only produced in the context of bacterial infection, such as the classic lipopolysaccharide present in the wall of Gram-negative bacteria, but also originate from bacterial translocation derived from intestinal bacterial overgrowth, increased permeability of the intestinal barrier and dysfunction of the intestinal immune system in this context.

B) **Endogenous inducers**. These are the damage-associated molecular patterns (DAMPs), cellular degradation products originating from host cell damage. Several mechanisms of cell damage are known, such as alcohol-induced apoptosis in acute alcoholic hepatitis, necrosis caused by hepatitis B virus hepatitis, or hepatic ischemia-reperfusion in cases of sepsis or severe gastrointestinal bleeding.

These PAMPs and DAMPs are recognized by pattern recognition receptors (PRRs) that are expressed on cells of the innate immune system, such as toll-like receptors (TLRs). Their binding induces an intracellular signaling cascade whose end result is the transcription and synthesis of multiple inflammatory mediators known as the "*cytokine storm*"[4].

Mechanisms of organ failure

The exacerbated immune response in ACLF has three main implications leading to organ failure:

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	APASL Asian Pacific Association for the Study of Liver	EASL-CLIF European Association for the Study of Liver-Chronic Failure	NACSELD North American Consortium for Study of End-stage Liver Disease
Origin	Expert consensus and observational studies	Prospective, observational study	Prospective study in patients with cirrhosis and infections
Population included	Compensated chronic liver disease	Compensated and decompensated chronic liver disease	Decompensated chronic liver disease
Exclusion criteria	First hepatic decompensation, infections	Hepatocarcinoma outside Milan, HIV	HIV Previous organ transplantation
Diagnosis of ACLF	Liver failure (ascites/ encephalopathy)	Hepatic and extrahepatic liver failure	Extrahepatic failure
Most common precipitants	HBV reactivation HEV superinfection	Alcoholic hepatitis Infections Unknown	Infections

Table 1. ***Comparison of the most widespread ACLF definitions.***

1. Systemic vasoconstriction and hypoperfusion. PAMPs stimulate nitric oxide (NO) production which causes intense systemic vasodilation and with it a decrease in effective arterial volume. This activates the systemic neurohormonal systems (renin-angiotensin-aldosterone system and sympathetic system) and as a consequence causes systemic vasoconstriction and renal hypoperfusion.

2. Mitochondrial dysfunction. Decreased β-oxidation of mitochondrial fatty acid in peripheral organs, leading to decreased oxidative phosphorylation and ATP production and thus energy depletion.

3. Immune-mediated tissue damage. The inflammatory response leads to direct tissue damage with the consequent release of cellular products that behave as DAMPs, which sustains and exacerbates this immune response[9].

Immunosuppressed state

Alterations leading to an ineffective compensatory immune response have been observed in patients with ACLF, such as the presence of immune cell groups with defective antimicrobial functions or decreased production of inflammatory cytokines by monocytes, which would explain, among other aspects, the susceptibility of these patients to the development of bacterial infections[4].

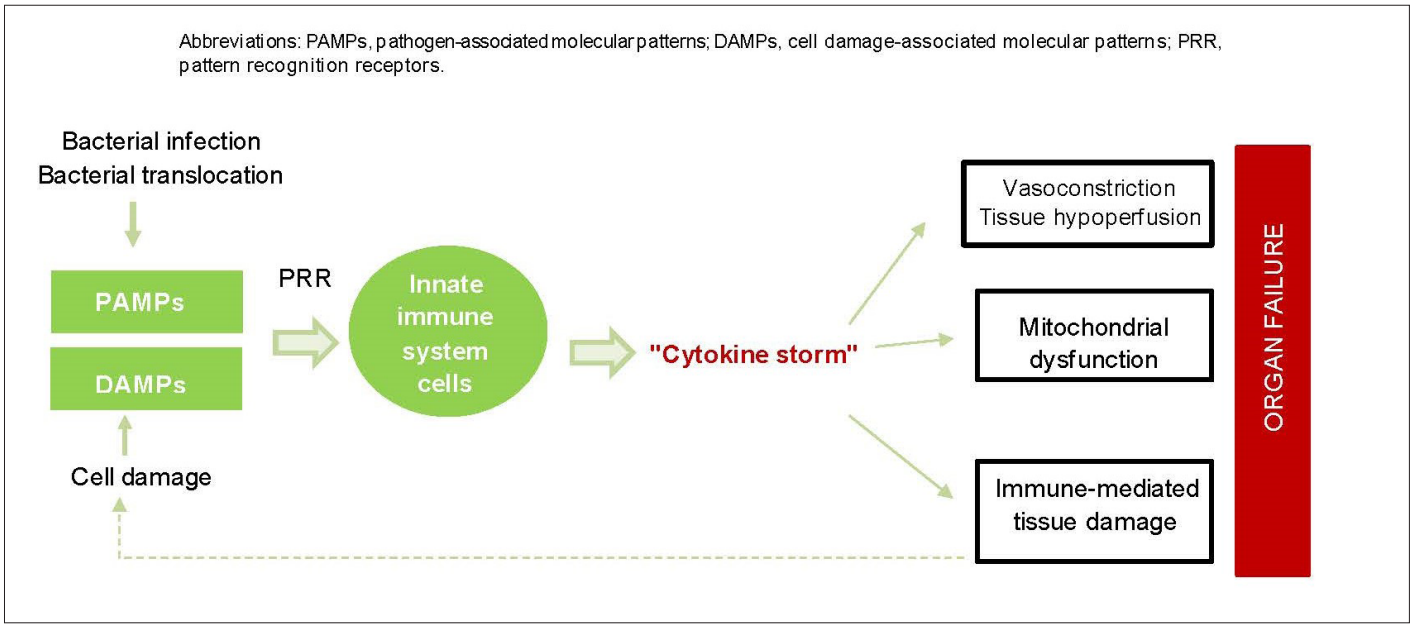

Figure 1. ***Systemic inflammatory response inducers and mechanisms involved in organ failure.***

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Diagnosis of acute on chronic liver failure

Organ failure

As mentioned above, to assess the presence and severity of organ failure the modified CLIF-C OF scale is used (Table 2). The CANONIC study demonstrated that failure of any of these six organ systems defined by this index and the number of organs involved is associated with a worsening prognosis at 28 days[5].

Severity of ACLF

According to the failure and the number of affected organs (liver, kidney, brain, circulation, respiratory, coagulation), ACLF is classified into different grades as reflected in Table 3. As a novelty, ACLF grade 3 has been subdivided into two: grade 3a (three organ failures) and grade 3b (more than three organ failures)[6].

Precipitating factors for acute on chronic liver failure

The PREDICT study[2] is the only prospective study published to date aimed at identifying precipitating factors of ACLF, establishing a series of main triggers: bacterial infections, severe acute alcoholic hepatitis, gastrointestinal bleeding with instability, acute hepatitis E virus (HEV) infection and acute hepatic encephalopathy. In Europe and the United States, the main triggers are bacterial infections and excessive alcohol consumption while in Asia the most important factor is hepatitis B virus (HBV)-related pathology. However, in up to 30-40% of cases it is not possible to identify any precipitating factor despite exhaustive study.

On the other hand, the number of precipitating factors that are identified simultaneously is considered a prognostic factor and are determinant in the short-term evolution of patients with ACLF. Consequently, patients with two or more recognized precipitants have a higher 90-day mortality than those with one or none identified.

The most frequently found combination is constituted by bacterial infections and acute alcoholic hepatitis. However, in the study by Fernandez *et al.*[10], the presence of bacterial infection both at diagnosis and follow-up of patients with ACLF-1 and ACLF-2 was described as an independent mortality factor.

Therefore, when faced with a patient with ACLF, it is essential to actively search for the most frequent known precipitating factors:

a. **Intrahepatic factors**

- Acute alcoholic hepatitis:
  - Diagnosed on the basis of both clinical and histological criteria.
- Primoinfection or reactivation of viral hepatitis:
  - HBV, mostly in Asia.
  - HEV, especially in cases where it triggers significant liver damage defined as AST and ALT >400 IU/ml and total bilirubin > 3mg/dl[6].

Organ system	Variable	Score = 1	Score = 2	Score = 3
Liver	Bilirubin (mg/dL)	< 6	6 to ≤ 12	> 12
Kidney	Creatinine (mg/dL)	< 2	2 to < 3.5	≥ 3.5 or RRT
Cerebral	Encephalopathy (West-Haven classification)	0	1-2	3-4
Coagulation	INR	< 2	2 to < 2.5	≥ 2.5
Circulation	MAP (mmHg)	≥ 70	< 70	Use of vasopressives
Respiratory	PaO2/FiO2 SatO2/FiO2	> 300 / > 357	≤ 300 a > 200 ≤ 357 a > 214	≤ 200/≤ 214

Abbreviations: RRT, renal replacement therapy; MAP, mean arterial blood pressure; PaO2, partial pressure of arterial oxygen; SatO2, oxygen saturation measured with pulse oximetry..

***Table 2.* CLIF-C Organ Failure Index for the diagnosis of organ failure.**

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ACLF Grades	Diagnostic criteria	
Does not meet ACLF criteria	No organ failure	
	Any organ failure (except renal) + creatinine < 1.5 mg/dL or no hepatic encephalopathy	
ACLF grade 1	Grade 1a	Single renal failure (creatinine > 2 mg/dL)
	Grade 1b	Any organ failure (except renal) + Creatinine > 1.5 mg/dL or hepatic encephalopathy
ACLF grade 2	Two-organ failure	
ACLF grade 3	Grade 3a	Three-organ failure
	Grade 3b	More than three organ failure

Table 3. ***Grades of acute over chronic liver failure.***

b. **Extrahepatic factors**

- Bacterial infections:
  - Bacterial translocation plays a key role in facilitating the systemic circulation of PAMPs (pathogen-associated molecular patterns).
  - Examples: spontaneous bacterial peritonitis, spontaneous bacterial empyema, spontaneous or secondary bacteremia after invasive procedure, urinary tract infection, pneumonia, bronchitis, skin infections, cholangitis, secondary bacterial peritonitis or Clostridium difficile infection.
- Unstable gastrointestinal bleeding:
  - Gastroesophageal variceal bleeding is the most relevant entity in this section, although any other GI bleeding involving hemodynamic instability or significant hemacytometric alteration (loss of 2 or more hemoglobin points) may be a precipitant of ACLF.
- Drug-triggered encephalopathy:
  - Mainly sedative medication, especially benzodiazepines or opioids.
  - inhibitors, antibiotics (penicillin/tazobactam, meropenem, ciprofloxacin, norfloxacin, metronidazole) or antifungals (fluconazole).
- Drug-induced renal damage:
  - Mainly non-steroidal anti-inflammatory drugs, renin-angiotensin-aldosterone axis antagonists, alpha-1 adrenergic antagonists, intravenous iodinated contrast or antibiotics (vancomycin, aminoglycosides), among others.

In case none of the previously described entities have been identified after an exhaustive examination of the patient, rarer causes should be ruled out, always under clinical suspicion depending on the patient's situation:

a. **Intrahepatic factors:**

- Viral infections: hepatitis delta virus superinfection in patients with HBV hepatitis, hepatitis A virus infection or hepatitis C virus infection.
- Drug-induced liver damage (DILI).
- Wilson's disease.
- Autoimmune hepatitis outbreak
- Ischemic hepatitis.

b. **Extrahepatic factors:**

- Viral infections: Epstein Barr virus, Cytomegalovirus, Human Immunodeficiency virus, Herpes Simplex

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virus, Varicella-Zoster virus, Parvovirus B19, SARS-CoV-2, influenza A and B virus, respiratory syncytial virus.

- Parasitic infections such as visceral Leishmaniasis.
- Invasive surgical or radiological interventions in the previous 7 days.

Therapeutic options in acute-on-chronic liver failure

The treatment of ACLF should be comprehensive and multidisciplinary, addressing both the specific management of precipitating factors and the support of the affected organs, offering individualized treatment according to clinical severity.

Intensive Care Unit organ support treatment

Patients with ACLF, especially the more severe grades, often require admission to Intensive Care Units (ICU) to ensure close monitoring or to receive supportive treatment (respiratory, circulatory, etc). Access to these units is sometimes not easy, as classically there has been a preconceived idea that these patients have a poor prognosis despite receiving these supportive measures and are therefore considered futile. However, recent work has refuted this concept by demonstrating that supportive treatment improves the prognosis of patients with advanced liver disease and they are comparable with the rest of the population[11]. Therefore, patients with ACLF should be evaluated like the rest of the general population regardless of their underlying liver disease, and comorbidities should be assessed on a case-by-case basis.

The main indications for admission to ICU are:

- Close monitoring that cannot be ensured on the hospital ward.
- Need for organ support measures: vasoactive drugs, mechanical ventilation, renal replacement therapy.
- Airway isolation due to massive gastrointestinal bleeding or West-Eaven grade III/IV hepatic encephalopathy.
- Septic shock.

On the other hand, limitation of life support should be considered in the following scenarios:

- Comorbidities associated with an unfavorable prognosis.
- Limited previous baseline status.
- Advanced neoplasia with life expectancy < 6 months.
- Frailty secondary to severe sarcopenia or a Karnofsky index ≤ 40.
- Failure of 4 or more organs or a CLIF-C ACLF index > 70 points after 3-7 days of ICU stay in a patient with no options for liver transplantation.

Treatment of precipitating factors

The following are the therapeutic strategies for the main precipitating factors.

1. **Bacterial infections**

As previously mentioned, bacterial infections are frequent in patients with ACLF, with a high prevalence at diagnosis (37%) and an incidence of 46% in the first 4 weeks[10]. They are usually more severe and require a longer stay in the ICU, and are also more frequently associated with multidrug-resistant microorganisms. For all these reasons, it is important to always maintain a high level of suspicion in order to initiate treatment early:

- Early empirical antibiotherapy when there is suspicion of infection or unexplained clinical deterioration. The use of broad-spectrum antibiotics adapted to local resistance and individual risk factors is recommended.
- Adjustment of antibiotic therapy: early de-escalation (24-72 hours) of treatment is recommended, if possible guided by culture and sensitivity.
- Empirical antifungal treatment: the incidence of fungal infection in patients with ACLF is 2-16%[12], so empirical treatment could be considered in case of nosocomial septic shock. The most prevalent etiologies are invasive candidiasis (70-90%) and aspergillosis (10-20%).
- Adjustment of antimicrobial dose according to patient characteristics, if necessary, and monitoring of clinical and microbiological response.

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2. **Hepatitis B**

In HBV reactivation with ACLF, 3-month mortality reaches 50-55%[13] in non-transplanted cases. Core(s)tide analogues have been shown to improve survival, with no significant difference between tenofovir and entecarvir. For the above reasons:

- Initiate antiviral treatment early without waiting for viral DNA results.
- Consider liver transplantation especially in severe cases (MELD >30, ACLF 2-3) with absence of early virological response (less than 2 log reduction in the first 2 weeks) and/or absence of clinical improvement.

3. **Acute alcoholic hepatitis**

The management of patients with severe acute alcoholic hepatitis and ACLF should be multifactorial, including alcohol abstinence, prevention of withdrawal syndrome, nutritional support, corticosteroids and, in selected cases, liver transplantation may be considered.

- Limited use of corticosteroids: As the severity of ACLF increases, efficacy decreases (52.2% ACLF-1 vs. 8.3 ACLF-3)[14] and the risk of bacterial infection increases. Therefore, their use is not recommended in patients with ACLF-3 or in case of uncontrolled active infection.
- Infection screening: It is recommended before and during corticosteroid therapy.
- Lack of response: Lack of response to corticosteroids in patients with ACLF is associated with an increased risk of infections (83.3% vs. 57.7%) [14].

4. **Autoimmune hepatitis**

In patients with ACLF due to autoimmune hepatitis (AIH), liver biopsy may be necessary to confirm the diagnosis (especially in cases of seronegative AIH) and/or to differentiate it from acute liver failure. The use of corticosteroids is controversial and should be individualized.

- There is currently little evidence in these cases.
  * It seems to increase survival at 3 months in patients without sepsis on admission (p = 0.02), reduces the length of stay in the ICU (p < 0.0001) with a similar incidence of sepsis during evolution (p = 0.32) [15].
- It is contraindicated in case of uncontrolled active infection.
  * A prevalence of bacterial infection of 76% at admission has been described [16], which limits the number of patients who could benefit from treatment.
- Close monitoring of efficacy and infection screening should be performed during treatment.
  * According to expert opinion[17], if there is no improvement in bilirubin or MELD-Na in the first 7 days, treatment should be suspended and the need for liver transplantation should be considered.

5. **Hemorrhage due to esophageal variceal rupture**

The treatment of this situation in ACLF should follow the general recommendations.

- TIPS: the risk of rebleeding in these patients is almost doubled, so the possibility of TIPS, both preventive and rescue, should be considered. Acute hepatic encephalopathy should not be considered a contraindication.
  * In the study by Trebicka *et al.*[18], a 75% mortality reduction is described, although it only includes patients with ACLF-1 and 2.
  * Another study[19] concludes that the higher the MELD score, the greater the impact on survival after preemptive TIPS.
- Non-selective beta-blockers (NSBB):
  * During the event, the decision to maintain them, discontinue them or reduce the dose should be individualized.
  * After the episode of ACLF, it is recommended to initiate or restart NSBB with progressive doses to ensure a MAP > 65mmHg. Although there are no specific studies, their use is recommended due to their beneficial effect on systemic inflammation.

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Prognosis

The development of ACLF, as previously mentioned, is accompanied by high mortality (approximately 30-50% at 28 days), with different risk factors such as ascites, arterial hypotension, anemia or obesity having been described over the last few years, two of which were observed in the CANONIC study[5]:

1. First hepatic decompensation. It was found that patients who had not had previous hepatic decompensation (20%) had a more severe disease course and therefore a shorter short-term survival. These patients were excluded according to the APASL definition.

2. CRP and leukocyte levels. Patients with ACLF had higher levels of leukocytes and CRP than those who did not meet ACLF criteria, and this was proportionally related to a worse prognosis.

Despite this high mortality, ACLF is a dynamic and potentially reversible entity. The clinical evolution 3 and 7 days after hospitalization is the best predictor of prognosis and not the initial severity of the condition[20], and therefore, a thorough assessment of prognosis is especially important for correct risk stratification and thus facilitate decision-making, which can range from the assessment of liver transplantation to the limitation of life support.

For this purpose, the CLIF-C ACLF index, which combines the CLIF-C OF index with age and leukocyte count, was designed based on data from the CANONIC study and is more accurate than the MELD, MELD-Na and Child-Pugh index in predicting 28- and 90-day mortality[5,21].

Prognostic evaluation of patients without ACLF

Although the short-term mortality of patients admitted for acute hepatic decompensation without ACLF criteria is lower, it is important to identify high-risk patients in order to monitor them closely and prevent progression to ACLF[6].

Similar to the CLIF-C ACLF index, the CLIF-C AD index was developed for patients without ACLF criteria, consisting of age, serum sodium, leukocyte count, creatinine, and INR. This index, validated internally and externally, provides a score from 0 to 100 and classifies patients into three risk groups[5]. This index also better predicts 90-, 180- and 365-day mortality than the MELD, MELD-Na and Child-Pugh index[22].

Both indexes can be calculated on the web at https://efclif.com/research-infrastructure/score-calculators/clif-c-of-aclf-ad/. Figure 2 reflects the algorithm proposed to assess the prognosis of patients admitted for acute hepatic decompensation.

Liver transplantation

Liver transplantation (LT) is the only definitive treatment that has been shown to improve survival in patients with ACLF. Its benefit is particularly important in patients with ACLF-3, who have traditionally been considered futile candidates.

General considerations for transplantation in ACLF.

- Positive impact:
  - LT should be considered in cases of severe ACLF (grades 2-3) as it can reverse secondary multiorgan failure and are associated with a clear improvement in survival over those not transplanted (80.9% vs 10%, at 6 months[20]).
  - In addition, survival rates comparable to those of other transplant groups have been described (86% in ACLF-2 vs 90% without ACLF, at 1 year [23]).
- Therapeutic window:
  - Early identification of candidates is essential due to the risk of infection and rapid progression of ACLF that may condition irreversible organ failure, both possible reasons for contraindication of LT.
  - Patients with ACLF grades 2 and, especially 3, should be prioritized on waiting lists since delay in LT is associated with increased mortality both on the waiting list (almost 50% per year in ACLF-3[24]) and post-transplant.
- Obstacles:
  - Despite favorable results in terms of survival, a higher rate of complications (especially vascular and biliary) and longer hospital and ICU length of stay have also been described, especially in ACLF-3.

Considerations in ACLF-3

- Promising results:

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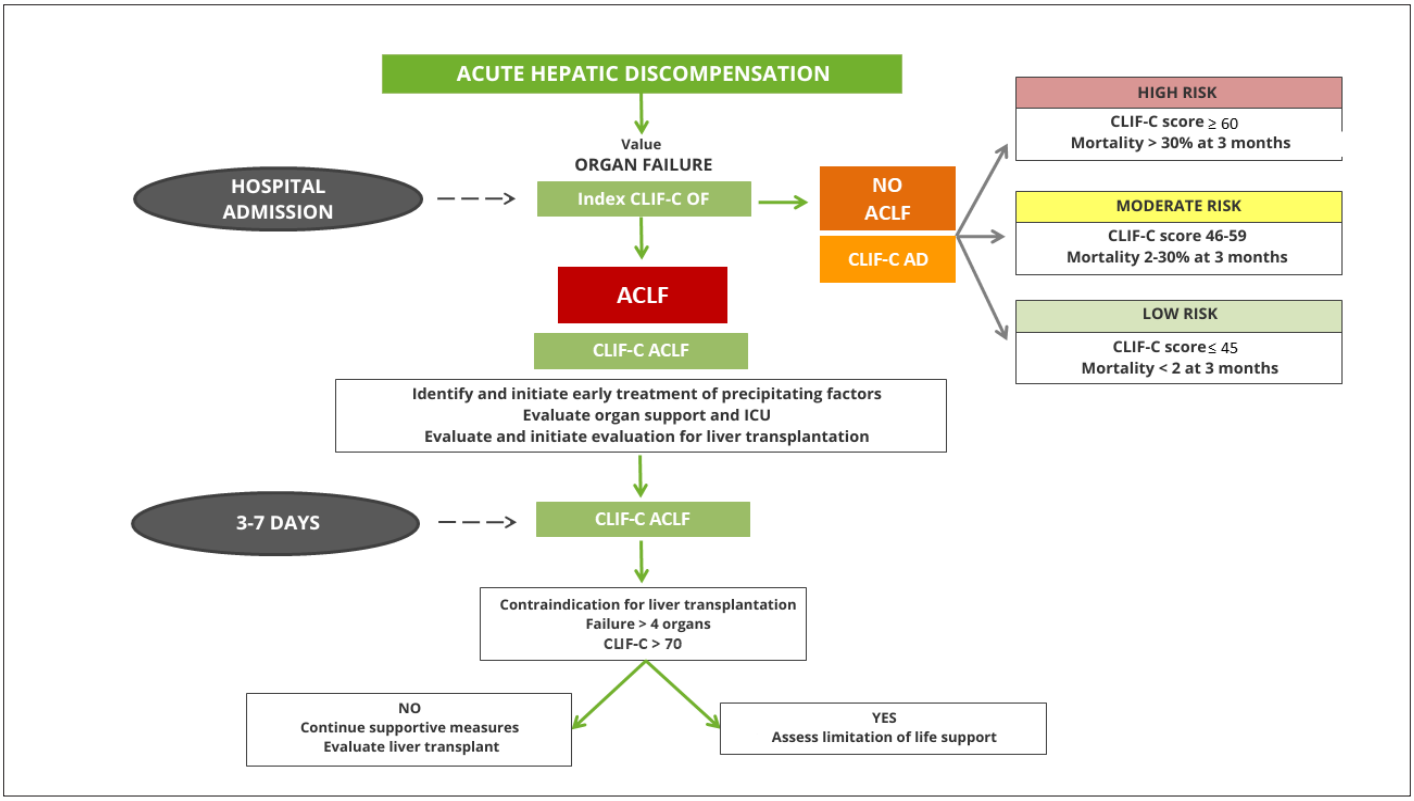

Figure 2. ***Proposed algorithm for the evaluation of prognosis in patients admitted for acute hepatic decompensation.***

* Historically, patients with ACLF-3 have been considered futile for LT due to their high mortality without intervention.

* Recent evidence refutes this perception by demonstrating survival rates at 1 year of 84% and 60-70% at 5 years[23], similar to other transplant patient groups.

* However, given the delicate clinical balance of these patients and the higher percentage of complications derived from LT, studies are needed to establish firm futility criteria in this group.

Multidisciplinary approach

- Selection criteria:

  * Candidate selection should be accurate, taking into account factors such as comorbidities, active infections, and irreversible dysfunction.

  * Multidisciplinary teams should include hepatologists, intensivists and transplant surgeons to evaluate and prioritize appropriately.

- Bridging therapies and stabilization:

  * The primary goal in patients on the LT waiting list should be to maintain clinical stability.

  * Technologies such as MARS® and plasmapheresis can stabilize patients and improve their condition prior to LT.

  * In some cases, living donors or expanded criteria donors offer viable alternatives for critically ill patients, especially ACLF-3.

Future perspectives and areas of research

- Waiting list organization protocols:

  * Prioritization protocols that take into account rapid progression of ACLF need to be implemented given that the current one based on MELD (Na) underestimate the mortality of these patients.

- Biomarkers:

  * Recent studies seek to identify biomarkers that allow accurate risk stratification and prioritization based on objective prognoses[25,26].

- Strategies in LT:

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* Use of living donors, organ preservation technologies or immunological optimization, among others.

In conclusion, LT is an essential therapeutic option for patients with ACLF, even in its most advanced forms. The perception of futility should be replaced by an evidence-based approach that supports the potential of transplantation to transform the prognosis and quality of life of these patients.

Conclusions

Acute-on-chronic liver failure is a severe entity different from the usual decompensations of cirrhosis, a consequence of exacerbated systemic inflammatory response and host immune system dysfunction. Early diagnosis, treatment of precipitating factors and organ support in the Intensive Care Unit when necessary are essential, without the underlying liver disease being a limitation for access to these specialized units. The clinical evolution 3 and 7 days after admission is the best predictor of prognosis, so its systematic evaluation during follow-up is essential using indexes such as the CLIF-C ACLF. Liver transplantation is an essential therapeutic option in severe forms of ACLF, and it is necessary to implement prioritization protocols to reduce waiting list mortality.

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CLINICAL CASE

TRANSANAL EXTRACTION OF A GIANT CALCIFIED FECALOMA

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Abstract

Fecalomas are a common complication of chronic constipation, but cases of calcified fecal material due to long-standing impaction are rarely reported. Here, we present a case of a giant calcified fecaloma where conventional extraction methods were unsuccessful. However, we were able to avoid the need for laparotomy and bowel resection by performing a successful transanal extraction.

Keywords: giant fecaloma, constipation, transanal extraction.

Introduction

Chronic constipation can sometimes cause the formation of hard stools in the rectum or colon, which cannot be expelled spontaneously and are known as fecalomas. There are few published cases of calcified giant fecalomas and the method of removal used has not been previously described in the literature.

Clinical case

We present the case of a 75-year-old woman who came to the surgery consultation because of pain in the hypogastrium of more than one year of evolution. In addition, she presented liquid diarrhea without pathological products accompanied by rectal tenesmus and sensation of incomplete evacuation. No rectal or abdominal masses were palpable.

She had been previously referred to Gynecology by her primary care physician due to the finding of a calcification in the pelvic area observed in an abdominal X-ray, ruling out pathology in this area (Figure 1A).

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Díaz Brito JA, Herrera Gutiérrez L, Grilo Bensusan I. Transanal extraction of a giant calcified fecaloma. RAPD 2025;48(2):80-81. DOI: 10.37352/2025482.5

An abdominopelvic CT scan with contrast was indicated, showing the existence of a rectal occupation by a densely calcified material measuring 7 x 9 cm, with digitiform extensions suggestive of calcified fecaloma (Figure 1B).

A colonoscopy confirmed the existence of a stony fecaloma at the rectal level that could not be passed, nor could it be approached for fragmentation due to its size, consistency and shape.

Given the impossibility of endoscopic treatment, nor response to treatment with enemas, it was decided to extract the fecaloma transanal with surgical instruments. For this purpose, under general anesthesia and in lithotomy position, the fecaloma was fragmented and several fragments were extracted using Rochester forceps with teeth, Foester forceps and hemostasis forceps. Intraoperative colonoscopy was performed and other fragments were extracted by means of a polypectomy loop, leaving the entire rectum and rectosigma free (Figures 1C and 1D). Postoperative evolution was satisfactory, tolerating oral diet at 24 hours, presenting normal stools at 48 hours and being discharged at 72 hours.

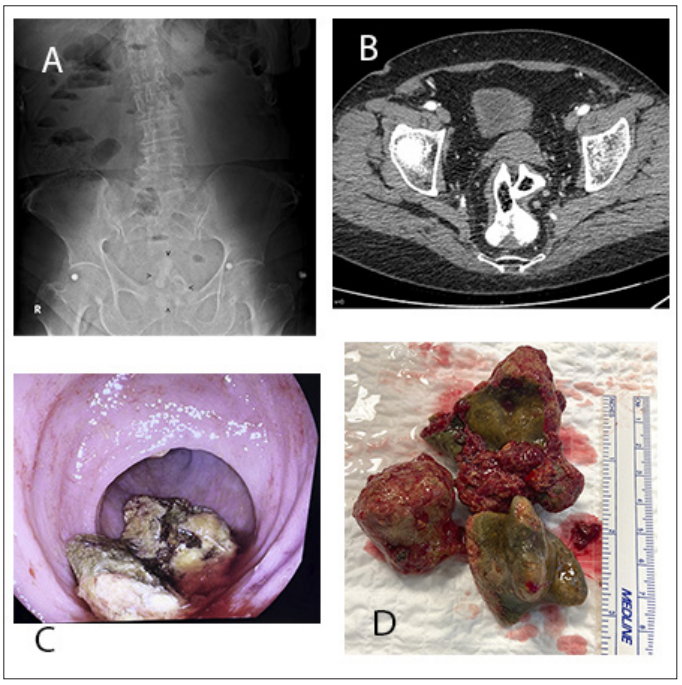

Figure 1. ***A: Abdominal X-ray showing a calcified lesion in the rectum (arrowheads). B: Abdominal CT scan of the pelvis showing the calcified fecaloma in the rectum. C: Colonoscopy image with calcified fragments of the fecaloma after the rupture procedures. D: Stone fragments of the extracted fecaloma.***

Discussion

The usual treatment of fecalomas is conservative with the use of enemas and digital extraction.[1]. E Endoscopic treatment by injection with sclerosis needles of different substances and their fragmentation and extraction with a polypectomy loop or biopsy forceps represents a new therapeutic step.[2]. If the previous measures fail, surgical removal by laparotomy can be considered, sometimes associating partial colectomies. [3]. This case is interesting because of the exceptional nature of calcified fecalomas and the success of a technique, whose previous description we have not found in the medical literature and which could be an option to avoid laparotomy[4,5].

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CLINICAL CASE

TYPE 1 AUTOIMMUNE PANCREATITIS: A DIAGNOSTIC CHALLENGE WITH AN ATYPICAL PRESENTATION.

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Abstract

Autoimmune pancreatitis (AIP) is a rare chronic inflammatory disease of the pancreas with benign behavior, typical histologic findings and a positive response to corticosteroid treatment. Although there are well standardized criteria to establish its diagnosis, sometimes its presentation may raise doubts with other diseases affecting the pancreas, such as adenocarcinoma and pancreatic cystic neoplasms. We present the case of a 51-year-old male debuting with constitutional symptoms and radiological findings which suppose a challenge in differential diagnosis of pancreatic pathology.

Keywords: Autoimmune pancreatitis, pancreatic collection, differential diagnosis.

Introduction

We present the case of a 51-year-old man diagnosed with autoimmune pancreatitis type 1 based on clinical and serological criteria with unusual radiological findings that pose an added difficulty to the differential diagnosis of pancreatic inflammatory pathology.

Clinical case

A 51-year-old male patient with a history of type 2 diabetes mellitus and dyslipidemia came to the emergency department for 48 hours of pain in the right hypochondrium radiating to the back and oral intolerance, with associated weight loss, without jaundice or fever. Blood tests on arrival showed creatinine 1.5 mg/dL, albumin 3g/dL, hemoglobin 11 g/dL, CRP 12 mg/dL and

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leukocytosis with neutrophilia; amylase, total bilirubin and the rest of the liver profile were normal.

An abdominal CT scan with contrast was performed with findings suggestive of an inflammatory process at the pancreaticoduodenal junction, without being able to rule out underlying tumor etiology, with several associated pancreatic collections, the largest of about 5 cm, which produced obliteration of the first duodenal portion and ectasia of the extrahepatic biliary tract, with associated locoregional lymphadenopathy (Figure 1).

The tumor marker CA 19.9 was normal, and an echoendoscopy was performed (unable to progress to the second duodenal portion due to extrinsic compression) suggesting the cystic origin of the previously described pancreatic lesions with a homogeneous enlargement of the pancreas without other focal lesions, which points to the inflammatory origin of the picture.

Serologic analysis detected an elevated immunoglobulin G (2090 mg/dL; VN 700-1600 mg/dL) with IgG4 of 1110 mg/d (>2 times the VLSN). Subsequently the study was completed with an MRI that showed a diffuse enlargement of the pancreas with peripheral hypointense halo and collections of liquid content, suggesting an autoimmune pancreatitis given the clinical and analytical context of the patient (Figures 2 and 3).

Treatment with corticosteroids was started and the patient showed clinical improvement with progressive oral tolerance and favorable radiological findings after two weeks, with a decrease in the size of the pancreatic collections as well as the locoregional lymphadenopathies.

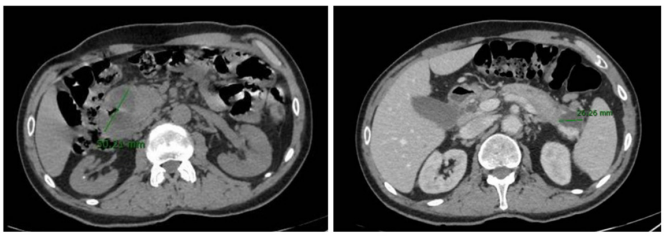

Figure 1. ***Abdominal CT. Pancreatic collections on admission (in pancreatic head and tail).***

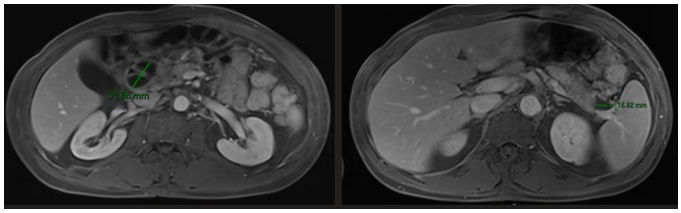

Figure 2. ***Abdominal MRI. Decrease in size of pancreatic collections after initiation of steroid treatment.***

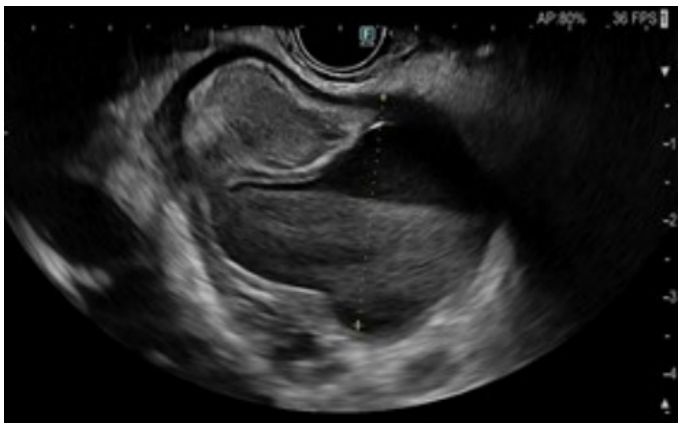

Figure 3. ***Echoendoscopy. Periduodenal collection.***

Discussion

Autoimmune pancreatitis (AIP) refers to a chronic inflammatory and fibrosing disease of the pancreas, of benign behavior and autoimmune origin, with response to treatment with corticosteroids.

Type 1 IAP can be considered as a pancreatic manifestation within the spectrum of IgG4 diseases and the involvement of other extra-pancreatic organs is frequent, while in type 2 IAP there is usually no serum elevation of IgG4 and it can be related to inflammatory bowel disease[1].

Currently, the criteria most commonly used to make the diagnosis of autoimmune pancreatitis are those of the International Consensus (2011), based on histology, radiological findings, serum IgG4 levels[2], involvement of other extra-pancreatic organs and response to corticosteroid treatment. Depending on their combination, the probable or definitive diagnosis of IAP can be established[3].

While type 1 IAP can be diagnosed with high accuracy without pancreatic biopsy, a diagnosis of type 2 IAP almost always requires histologic confirmation. In our case, the presence of compatible radiological findings together with significant elevation of IgG4 levels and a favorable response to corticosteroids allowed us to make the diagnosis of type 1 IAP with high accuracy.

The main differential diagnosis of IAP should be established with pancreatic adenocarcinoma since the clinical features of the disease (constitutional syndrome, obstructive jaundice, vomiting and oral intolerance) and the radiological findings (diffuse or focal pancreatic enlargement) often raise the suspicion of a pancreatic neoplasm. In fact, a not inconsiderable percentage of patients undergoing duodenopancreatectomy

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for suspected cancer are eventually diagnosed with PAI[1]. It is also important to include in the differential diagnosis of IAP other neoplasms that can affect the pancreas, such as neuroendocrine tumor and pancreatic lymphoma.

On the other hand, the presence of acute collections and pseudocysts in IAP has classically been described in the literature as an infrequent finding that can contribute confusion to the diagnosis; nevertheless, in recent years some series have been published indicating that the incidence of these lesions in patients with IAP can be between 9.7% and 22.4%[4,5]. The appearance of pancreatic cystic lesions in the setting of autoimmune pancreatitis seems to be related to local inflammation of the pancreatic segments affected by the disease together with stenosis of the intra-pancreatic bile ducts that can lead to secondary retention of pancreatic secretion. Generally these lesions affect the pancreatic body and tail[5], can be single or multiple and, on very rare occasions, of hemorrhagic or necrotic content, sometimes simulating a pancreatic cystic neoplasm[6]. In our case, the elevated levels of immunoglobulin G were decisive in guiding the diagnosis.

The appearance of pancreatic cystic lesions in a synchronous manner is one of the particularities of our case, as well as the duodenal compression secondary to the largest lesion (> 3cm) with manifest clinical repercussions in our patient, with impossibility of oral intake and significant improvement after the initiation of corticosteroids.

With our case we want to highlight the importance of considering IAP in the differential diagnosis of pseudocyst and acute pancreatic collections[7], and we provide evidence in favor of early management of these lesions in IAP with corticosteroid treatment given the high rate of regression after its onset, being more exceptional the surgical approach in these cases.

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