VOLUME 48 · N°3 · MAY- JUNE 2025

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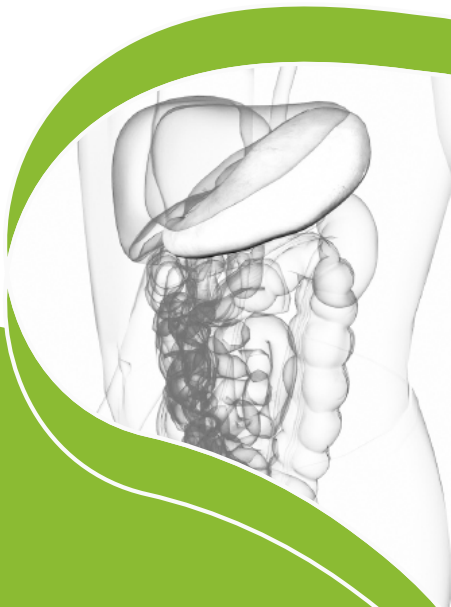

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ANDALUSIAN JOURNAL OF DIGESTIVE PATHOLOGY

OFFICIAL BODY OF THE ANDALUSIAN SOCIETY OF DIGESTIVE PATHOLOGY

Edition
Sulime Diseño de Soluciones, S.L.U.
Edificio Centris. Glorieta Fernando Quiñones s/n
Planta BSS- Módulo 7A - 41940 Tomares (Sevilla)
Tlf. 954 15 75 56
Email: bbriones@sulime.net - *Web:* www.sulime.net

Legal Deposit: M-26347-1978
Valid support com: 07/2
ISSN: 1988-317X

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.*

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

A) Specific standard for manuscripts writing

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

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

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

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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.

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

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4° Full postal address of the responsible author, to whom correspondence should be addressed, including telephone, fax and email address.
5° Declaration on the existence or non-existence of a source of funding for the work, or conflicts of interest.

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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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5° Declaration on the existence or non-existence of a source of funding for the work, or conflicts of interest.

- Main body of the manuscript, containing:

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

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

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

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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.

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

- 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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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.
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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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- 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

RISK FACTORS OF HEPATIC ENCEPHALOPATHY AFTER AN EPISODE OF UPPER GASTROINTESTINAL BLEEDING IN PATIENTS WITH LIVER CIRRHOSIS

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Abstract

Introduction: Hepatic encephalopathy (HE) is defined as a set of potentially reversible neuropsychiatric alterations secondary to hepatocellular failure and/or portosystemic shunting, being a frequent complication in the evolution of liver cirrhosis. One of the triggers of HE is upper gastrointestinal bleeding (UGB); however, there are few studies that analyse the predisposing factors for the development of HD in this clinical context, as well as its impact on patient prognosis.

Objective: To compare the clinical and blood test characteristics of the group of patients with UGB who develop HE with those who do not, identifying predisposing factors; and to analyse the prognosis of the patients with respect to the group to which they belong.

Methods: Retrospective analysis of a prospective registry including all patients with UGB treated at the Hospital Universitario Virgen de las Nieves between 2013 and 2021, who underwent urgent gastroscopy and presented clinical and/or radiological data of liver cirrhosis. Clinical, biochemical and evolution data (during admission and deferred) were obtained.

Results: Of the 258 patients with liver cirrhosis admitted for UGB, 66 developed HE. Of the variables analysed, only ascites, albumin and urea on admission were found to be independent factors in the development of HE. Furthermore, it was found that the development of HE only significantly increased in-hospital mortality.

Conclusions: The development of HE during an admission for UGB is associated with an increased risk of in-hospital

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Lancho Muñoz A, Ortega Suazo EJ, López Tobaruela JM, Tendero Peinado C, López Vico M, Fernández García R et al. Risk factors of hepatic encephalopathy after an episode of upper gastrointestinal bleeding in patients with liver cirrhosis. RAPD 2025;48(3):93-98. DOI: 10.37352/2025483.1

mortality, with liver function variables and urea on admission being the only parameters independently related to the development of HE, with no significant patient-intrinsic data or variables regarding the type of bleeding.

Keywords: liver cirrhosis, hepatic encephalopathy, upper gastrointestinal bleeding.

Introduction

Hepatic encephalopathy (HE) is a group of potentially reversible neuropsychiatric alterations secondary to hepatocellular insufficiency and/or portosystemic shunting, being a frequent complication in the evolution of liver cirrhosis. Given the wide variety of symptoms with which HE expresses itself, the clinical practice guideline made by the American Association for the Study of Liver Diseases (AASLD) and the European Association for the Study of the Liver (EASL) defines it as ``A cerebral dysfunction caused by hepatic insufficiency and/or portosystemic shunt; manifesting as a wide spectrum of neurological or psychiatric abnormalities ranging from subclinical alterations to coma''[1]. The abrupt or progressive loss of hepatocyte functions, as well as, collateral portosystemic hepatic circulation produces an imbalance between hepatic elimination of toxic substances from the intestine, which pass directly into the general circulation, causing neuronal dysfunction, cerebral edema, intracranial hypertension and finally hepatic encephalopathy[2]. The mechanisms underlying HE are multifactorial. Initially, the appearance of encephalopathy in cirrhotic patients was considered to be a direct effect of the increase in serum ammonium levels, generated by the intestinal flora from dietary proteins that through the portal circulation passes to the liver where it is metabolized by the urea cycle. The decrease in hepatic clearance of ammonium induces hyperammonemia, being directly toxic to the central nervous system, acting especially indirectly on glutamatergic and GABAergic neurotransmission[3]. However, ammonia is currently considered a necessary but not sufficient risk factor for the development of HD in the progression of liver cirrhosis. Recent studies have identified other factors such as inflammatory cytokines, manganese, benzodiazepine-like compounds, mercaptans, aromatic amino acids and the microbiota as being involved in the pathophysiology of encephalopathy[4,5].

Specifically in liver cirrhosis, the development of HE results in a decompensated stage of the disease that occurs in response to one or more triggers. The most common triggers are infections including spontaneous bacterial peritonitis, urinary tract infections, respiratory infections, skin infections, among others. Other factors that also favor the development of HE are electrolyte disorders, diuretic overdose, constipation and digestive bleeding[1,2]. However, not only triggering factors are necessary but also the existence of predisposing factors such as the existence of minimal hepatic encephalopathy, a history of an episode of hepatic encephalopathy, sarcopenia, hyponatremia, renal failure, high bilirubin levels, hypoalbuminemia, use of PPIs, or treatment with beta-blockers[2,5].

There are few studies that analyze the incidence and predisposing factors for the development of HD after an episode of gastrointestinal bleeding in cirrhotic patients. Studies such as that of Sharma P *et al.*[6] and Wen J *et al.*[7]; analyze this aspect in a secondary manner when attempting to demonstrate the efficacy of lactulose as primary prophylaxis of hepatic encephalopathy after bleeding from esophageal varices. A more recent study identifies Child Pugh stage C, hypokalemia less than 3.5 mmole/L, leukocytosis greater than 10000 U/mm3 and hemoglobin less than 8 gm/dL as predisposing factors for the development of HD after upper gastrointestinal bleeding due to esophageal varices (HDAV)[8].

The aim of our study is to analyze the development of HE in patients with liver cirrhosis admitted to our hospital for melenas and/or hematemesis, with the objective of identifying predisposing factors to favor early diagnosis, as well as to study the repercussion of HE in the evolution of these patients.

Material and methods

Study design and population

This is a prospective registry in which we consecutively included all those patients seen in the Emergency Department of the University Hospital Virgen de las Nieves with a diagnosis of upper gastrointestinal bleeding (UGB) between 2013 and 2021. From this registry, we performed a subanalysis of patients with liver cirrhosis admitted for this reason and compared those who developed HE during admission and those who did not.

The inclusion criteria were:[1] age over 18 years;[2], UGB defined as the presence of hematemesis and/or melena; and[3] presenting diagnostic, clinical and radiological criteria for liver cirrhosis at the time of admission. Exclusion criteria were[1] Refusal to sign the informed consent for the study or refusal to undergo endoscopy on admission; and[2] Clinical instability or inadequate baseline situation contraindicating urgent endoscopy.

Patients were followed up during hospitalization and 6 months after hospital discharge. All patients included in the study underwent urgent gastroscopy, defined as gastroscopy

 DOI: 10.37352/2025483.1

performed within 12 hours of admission to the emergency department.

The criteria for defining the development of hepatic encephalopathy during admission were those included in the 2022 EASL guidelines, classifying severity according to the West Haven criteria[1].

Variables studied

Demographic variables, comorbidities, pharmacological treatments prior to admission or the episode of UGB, including the use of proton pump inhibitors (PPIs), hemodynamic status and laboratory tests at the time of arrival at the emergency department were collected. The occurrence of hepatic complications including the development of ascites, hepatic encephalopathy and spontaneous bacterial peritonitis were documented. Data were collected on the etiology of UGB, endoscopic treatment performed, as well as the need for additional treatments.

In relation to the prognostic variables studied, in-hospital mortality was defined as that occurring during hospitalization; and deferred mortality as that occurring in the first 6 months after the episode of UGB and hospital stay.

Statistical analysis

Statistical analysis was performed using Python v3.10.1 and R v4.3.2. Categorical variables were compared using the Chi-square test or Fisher's exact test, depending on the minimum expected cell size (>5). Continuous variables were evaluated using the Shapiro-Wilk test for normality, the Levene test for homogeneity of variances and, subsequently, the t-test for independent samples was applied, with or without Welch's correction, or the Mann-Whitney test. Finally, multivariate analysis was performed to identify independent risk factors for variables with statistically significant differences, calculating Odds Ratios (OR) and their 95% confidence intervals (95%CI).

Results

Of the total of 258 cirrhotic patients admitted with UGH, 152 (59%) had variceal upper gastrointestinal bleeding and 106 (41%) had non-variceal upper gastrointestinal bleeding. A total of 66 (19%) patients developed hepatic encephalopathy.

Patients who developed hepatic encephalopathy had a higher frequency of active enolism (57.69% vs. 38.72% p=0.02) and a higher score on the MELD scale (18 vs. 13 p= 0.0002). Regarding analytical alterations at admission, HE patients differed in creatinine (1.37 vs1.6 p=0.003), bilirubin (4, 78 vs 2.18 p=0, 000015), albumin (2.63 vs 3.04 p= 0.000056), INR (1.77 vs 1.65 p= 0.005), ascites (48% vs 29.1% p= 0.015) and urea (95.72 vs 70.53 p=0.00017). Table 1 shows the remaining patient characteristics.

Regarding prognostic variables, HE patients presented a higher mortality rate during admission, without finding statistically significant differences for the rest of the variables studied.

There were 31 deaths in HE patients, 21 of which occurred during admission.

After multivariate analysis by logistic regression, albumin (OR 0.41 CI95% 0.23-0.7), the presence of ascites (OR 1.65 CI95% 1.01-2.71) and urea on admission (OR 1.01 CI95% 1-1.02) were identified as independent risk factors for HE, as shown in table 2. The inclusion of both urea and creatinine in the logistic regression allowed the multivariate model to be corrected for the latter, ruling out the existence of a confounding effect. Additionally, a partial correlation between HE and urea was performed, using creatinine as a control variable. It was observed that the positive correlation between the two variables was maintained (Rho = 0.141 p= <0.01). All this evidences that urea acts as a predictor of hepatic encephalopathy independent of renal function, as determined by creatinine.

Discussion

There are few studies that analyze the factors that favor the development of HE in the context of gastrointestinal bleeding. As indicated in the introduction, most of them analyze this aspect in a secondary manner.

The most widespread conception in the literature is that HE is a decompensated stage of liver cirrhosis, so that those patients with worse liver function as assessed by the Child Pugh Score or the MELD score are at greater risk of developing it. Our study shows that patients who develop an episode of HE have worse liver function, as measured by a higher MELD score. In addition, analytical parameters associated with liver dysfunction such as hyperbilirubinemia, hypoalbuminemia, coagulation disorders or the presence of ascites correlate significantly with respect to the development of HE in the univariate analysis; only albumin on admission and the presence of ascites were significant factors related to liver function in the multivariate analysis. These data are similar to those reported in the literature, where it is described that advanced liver cirrhosis defined as Child Pugh C would be the

DOI: 10.37352/2025483.1

most relevant clinical parameter in the development of hepatic encephalopathy after variceal bleeding[7,8].

Certainly, in the literature, not only has the role of liver failure been analyzed, but also analytical parameters such as alterations in the blood series or the existence of ionic alterations have been proposed as predisposing factors for HE. In our study, no significant differences were observed in hemoglobin levels at admission in both groups. This differs from the pre-existing literature in which we found two studies where hemoglobin lower than 8 mg/dl is identified as a significant predictor in the development of hepatic encephalopathy[7,8]. Another analytical alteration proposed as a triggering factor for HE is hypokalemia[8]. However, in our analysis, no significant differences were observed in both groups with respect to potassium levels.

Our study does find urea on admission to be a predictor of the development of HE after an episode of UGB. It could be suggested that the elevation of urea on admission could be altered secondary to a worsening of renal function due to a situation of low output in relation to digestive losses or due to a situation of decompensation of liver cirrhosis[9]. However, as indicated in the results section, the existence of a confounding effect of creatinine was ruled out, and the relationship between urea and HE persisted.

Regarding variables related to patient comorbidities, as in the literature, no significant differences were found. We even analyzed possible confounding factors such as the presence of a history of HE episodes and the presence of TIPs. These variables had little impact on our "results" given that only one patient had required TIPS placement for refractory variceal UGB and only 13 (19.6%) of the patients had had previous

Hepatic encephalopathy	Present (N=66)	Absent (N=192)	P-value
Age	59 ± 13	62 ±12	0.46
Male sex	60%	16 %	0.37
MELD	18.08 ±7	13 ±7,67	0.00002
Alcohol	57.69%	38.72%	0.02
Tabacco	37.25%	33.66%	0.75
PPIs	50%	48%	0.84
Hemoglobin	8.2 ±2.23	8.9 ± 2.44	0.31
Bilirubin	4.78 ±7.7	2.18 ± 3.24	0.000015
Albumin	2.63 ± 0.57	3.04 ±1.28	0.000056
INR	1.77 ± 0.62	1.65 ±0.82	0.0056
Creatinine	1.37 ± 0.7	1.6 ± 6.41	0.0036
Platelets	125945 ±72209	140502 ±94082	0.66
Ascites	48.07%	29.12%	0.015
Urea	95.72 ±57.69	70.53 ±42.63	0.00017
Active endoscopic bleeding	38,46%	32,04%	0,47
Rebleeding	19,23%	15,6%	0,67
Need for intervention (endoscopy, transfusion, surgery or radiology)	59,61%	65,04%	0,79
Days of admission	11,75 ± 12	10,43 ±12,22	0,32
Mortality admission	33%	16%	0,00016
Mortality delayed	16%	12%	0,19

Table 1. ***Baseline characteristics of patients developing hepatic encephalopathy.***

DOI: 10.37352/2025483.1

Variables	OR (95% CI)	P-value
Bilirubin	1,07 (1 - 1,16)	0,064
Albumin	0,41 (0,23 - 0,7)	0,0017
INR	1,10 (0,73 - 1,56)	0,58
Creatinine	0,77 (0,5 - 1,12)	0,18
Ascites	1,65 (1,01-2,71)	0,04
Urea on admission	1,01 (1 – 1,02)	0,0005

***Table 2.* Multivariate logistic regression results. Independent factors of hepatic encephalopathy, with ascites, hypoalbuminemia and elevated urea on admission being the most relevant predictors in the model.**

episodes of hepatic encephalopathy, requiring secondary prophylaxis with rifaximin and maintenance lactulose.

In our cohort, the development of hepatic encephalopathy during admission for UGB did not lengthen hospital stay; however, it did significantly increase mortality during admission. With respect to deferred mortality, relevant differences were observed in the descriptive analysis, with a higher percentage of deaths in the group that developed HE, although this difference was not statistically significant.

The results obtained in our study suggest the possible predictive role in the development of HE of analytical and clinical characteristics present on admission after UGB. Among the alterations analyzed, urea is postulated as one of the most relevant variables with respect to HE, acquiring a new prism as a predictor of hepatic complications, beyond its diagnostic role in gastrointestinal bleeding. Nevertheless, parameters related to liver function continue to be a fundamental pillar in the early diagnosis of the development of HE.

The main limitation of our investigation is the inclusion of patients from a single center, which may imply a lower applicability of the results. However, since it is a reference center, patients of different complexities have been included, which may mitigate this limitation. On the other hand, this study, unlike others previously performed, includes episodes of gastrointestinal bleeding, both variceal and of other origin, which provides more information on the pathophysiology of HE in this clinical context, beyond variceal UGB. On the other hand, we must consider the sample size as a limitation, given that we have only been able to analyze 66 patients who have developed HE, which is a small cohort of patients. However, an advantage of the study is that it is a prospective registry of patients, with data collection carried out systematically by the research team.

For the time being, more studies with larger sample sizes are needed to clarify how these variables influence the development of HE, and predictive scores can be developed in the future to help us make an early diagnosis.

Conclusions

After the results obtained, we can say that HE developed during admission for UGB in cirrhotic patients implies a higher risk of mortality during admission, and it may be useful to assess albumin, the presence of ascites and urea on admission, since they correlate with a higher risk of HE and may be factors that allow us to make an early diagnosis in the future.

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 DOI: 10.37352/2025483.1

REVIEW ARTICLE

FERTILITY AND PREGNANCY IN INFLAMMATORY BOWEL DISEASE

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Abstract

Inflammatory bowel disease (IBD) is a chronic condition that includes Crohn's disease (CD) and ulcerative colitis (UC). Both conditions can impact patients' quality of life, particularly during their reproductive years. The influence of IBD on fertility and pregnancy has been widely studied, emphasizing the importance of proper management to minimize maternal-fetal risks and optimize reproductive outcomes.

The aim of this review is to understand the impact of IBD on fertility, pregnancy, and perinatal outcomes, as well as to explore recommended management strategies to ensure adequate clinical follow-up in accordance with clinical guidelines and the most up-to-date literature on these topics.

Fertility in women with IBD is comparable to that of the general population, although it may be reduced in cases of active disease, a history of abdominal surgery, or psychological factors. IBD activity during pregnancy is associated with increased obstetric complications, making preconception planning and continuous medical monitoring essential.

Most IBD treatments are considered safe during pregnancy and breastfeeding, except for certain medications such as methotrexate, JAK inhibitors, and sphingosine-1-phosphate inhibitors. Regarding delivery, cesarean section is recommended only in specific cases, such as active perianal disease or the presence of an ileoanal reservoir. Lastly, breastfeeding is encouraged whenever possible, and vaccination schedules for neonates exposed to immunosuppressants should be adjusted accordingly.

Keywords: fertility, pregnancy, Inflammatory Bowel Disease, breastfeeding.

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Lázaro Sáez M, Fernández Carrasco M, Sánchez Moreno S. Fertility and pregnancy in Inflammatory Bowel Disease. RAPD 2025;48(3):99-104. DOI: 10.37352/2025483.2

Introduction

IBD is a chronic pathology of autoimmune nature that affects the gastrointestinal tract, whose incidence is increasing like the rest of the immune-mediated diseases, and can occur in different periods of life of the patients. There is a peak at childbearing age, at 29 years of age in CD and at 39 years of age in UC. Since IBD affects patients in their reproductive stage, its impact on fertility, pregnancy and quality of life is a fundamental aspect to consider, and it is essential that patients are adequately informed about the disease and its treatments in order to optimize family planning, minimizing the risks for both mother and fetus[1].

Fertility in women with IBD is comparable to that of the general population; however, a lower birth rate is observed in this population. Fertility remains stable when the disease is inactive and in patients with no history of previous surgery, but disease activity can reduce fertility due to inflammation of the fallopian tubes, metabolic alterations and oxidative stress that negatively impacts hormone levels, which can decrease ovarian reserve due to a decrease in anti-Müllerian hormone and cause dyspareunia, making conception difficult. Active disease is associated with an increased risk of adverse effects during pregnancy, especially in the first trimester, underscoring the importance of close preconception and gestational surveillance. Other factors that may also play a role are toxic habits, the use of certain drugs, e.g. sulfasalazine which can cause reversible oligospermia and asthenozoospermia in males. Treatments with teratogenic risk should be suspended prior to conception in women, although they do not affect fertility in men, although it is recommended to evaluate fertility in men who plan to conceive and are on prolonged treatment[1,2].

Pregnancy in patients with IBD is associated with an increased risk of complications, such as gestational diabetes, fetal death, premature delivery, premature rupture of membranes, and low birth weight. Patients should be informed about the inherited risk, which is up to 8 times higher in CD and 4 times higher in UC, with a possible predisposition associated with female sex in the case of CD[3]. Patients with IBD have high rates of sexual dysfunction due to corticosteroid side effects, perianal disease and intimacy problems, affecting up to 40% of sexual intercourse.

Pelvic surgeries related to IBD may decrease fertility and conception rate in women, although the laparoscopic approach seems to reduce this risk. Rectal preservation in patients undergoing surgery has been described to be recommended to reduce the risk of sexual and ejaculatory dysfunction[4]. Because these surgeries may reduce the success rate in assisted reproductive treatments, sperm preservation is recommended in some cases before certain interventions[1].

Other factors that may reduce fertility include depression and nutritional deficiencies. In addition to voluntary factors such as the decision not to have children due to misinformation about the disease, treatments and the possibility of genetic inheritance, being more frequent in patients with Crohn's disease than with ulcerative colitis, with rates reported between 17% and 38%. Proper planning and close medical follow-up are essential to ensure the best possible reproductive health in these patients[2].

Pregestational phase

Pregnancy follow-up in patients with IBD begins with a preconception evaluation to ensure that the disease is in stable remission for at least 3 to 6 months before conception, thus reducing the risk of complications. Family planning and preconception counseling are essential, as they address questions about fertility, treatments, and possible complications. Factors such as misinformation, fear of intimacy, depression and surgical sequelae such as colectomy can affect reproductive capacity and quality of life, so it is crucial to provide adequate medical guidance to improve decision making and reduce anxiety.

Before pregnancy, it is recommended to evaluate disease activity by means of biomarkers such as CRP, hemoglobin and fecal calprotectin, the latter being the most specific during gestation, since the rest may vary due to the biological process of gestation itself. As for pre-pregnancy diagnostic tests, the same as in the general population can be used. The ideal scenario for management would be referral of all patients to tertiary centers with multidisciplinary teams including gynecologists, gastroenterologists, and IBD surgeons[1,4].

To optimize maternal health before conception, it is recommended to evaluate the nutritional status and correct vitamin deficiencies, to update the vaccination avoiding alive virus if there is immunosuppression and to encourage the abandonment of toxic habits such as tobacco, alcohol and recreational drugs. As for treatment, it will be evaluated below, but teratogenic drugs such as methotrexate, JAK inhibitors (JAKi) and ozanimod should be discontinued, the continuity of biologic therapy should be evaluated, and folic acid should be administered in patients with sulfasalazine. Reproductive counseling should also address possible disease transmission, contraceptive use and plan joint follow-up with gastroenterology and obstetrics. To achieve an uncomplicated pregnancy, it is essential to tailor treatment according to

DOI: 10.37352/2025483.2

Pregestational phase	Recommendations
Preconception evaluation	Determine disease **activity** and look for clinical remission. Screen for **anemia, vitamin deficiencies and nutritional** status. Update vaccination, avoiding live virus vaccines if immunosuppression is present. Encourage cessation of tobacco, alcohol and recreational drugs.
Optimization of treatment	Suspend **teratogenic** drugs (methotrexate, JAK inhibitors, ozanimod). Evaluate the need to **continue biologic therapy**. Administer **folic acid** (2 mg/day in case of sulfasalazine use).
Reproductive counseling	Inform about possible disease **transmission**. Address fertility **concerns** and contraceptive use. Plan **multidisciplinary** follow-up with gastroenterology and obstetrics.

Table 1. ***Recommendations to be followed in the pregestational phase.***

need, optimize nutritional status, and ensure stable clinical remission[3].

Gestational stage

The main goal is to keep IBD in remission to minimize maternal and fetal risks. This requires close follow-up with gastroenterology and obstetrics, with periodic controls based on biomarkers such as fecal calprotectin, which has been shown to be an indicator of disease activity in pregnant women. In addition, evaluation with intestinal ultrasound is recommended to avoid invasive techniques. Monitoring should also include control of nutritional status and maternal weight to ensure adequate fetal development[1,3].

For the assessment of disease activity, fetal-safe imaging tools are recommended. Ultrasonography is the technique of choice, especially useful in the 20th week of gestation. MRI is a viable alternative as long as gadolinium is not used, due to the lack of conclusive studies on its fetal safety. Endoscopy is safe, but should be reserved for strictly necessary cases, given the risk of bronchoaspiration and impairment of maternal-fetal oxygenation; in these cases, it is recommended that sedation be administered by an obstetrical anesthesiologist. On the contrary, computed tomography, radiographs and any test with radiation are contraindicated, as well as capsule endoscopy, since there is insufficient data to support their safety during gestation[1].

Gestational stage	Recommendations
Evaluate withdrawal/ maintenance of treatment	Assess the need to **continue, adjust or discontinue** medications according to disease status and fetal safety.
Establish a delivery plan and route of delivery	Define whether delivery will be **vaginal or cesarean** based on disease activity and patient's clinical history.
Monitor adequate weight gain	Ensure adequate **weight** gain and monitor maternal **nutrition** to avoid fetal complications.
Monitor possible adverse effects on the fetus	Identify possible **adverse effects on fetal development** and adjust treatment if necessary.
Assess maintenance of treatment during breastfeeding	Review the compatibility of medications with **breastfeeding** and decide on continuation of **treatment**.
Safety of vaccines in the infant	Ensure that **vaccines** are safe for the **newborn** and avoid live virus vaccines in neonates exposed to immunosuppressants.
Management plan with the family physician and obstetrician	Maintain a **comprehensive follow-up** plan with specialist physicians to optimize disease management during pregnancy..

Table 2. ***Recommendations to follow in the gestational phase.***

Pharmacological treatment

The pharmacological management of IBD during pregnancy requires careful evaluation of the risks and benefits of each treatment. Most drugs used for IBD are safe during pregnancy, but some require special precautions. Maintaining disease remission has been shown to reduce maternal and fetal risks, so continued appropriate treatment is recommended. Among the most commonly used drugs are aminosalicylates, corticosteroids, tumor necrosis factor alpha inhibitors (anti-TNF) and immunomodulators such as thiopurines. Methotrexate, JAKi, ozanimod are recommended to be avoided due to their teratogenic effects and lack of data in humans[3].

Aminosalicylates

Aminosalicylic acid derivatives reach very low levels in the fetal circulation due to their limited transplacental transfer and rapid renal elimination, making them safe drugs during pregnancy. Sulfasalazine, although it crosses the placenta and interferes with folic acid absorption, has not been associated with teratogenic or embryogenic effects. To minimize risks, its use accompanied by folic acid supplementation at high doses (2 g/day) is recommended during conception and gestation, in order to prevent neural tube defects[3,5].

DOI: 10.37352/2025483.2

Corticosteroids

Corticosteroids are widely used drugs in the treatment of IBD, although they cross the placenta and may affect the fetus. Prednisolone, however, has a lower placental transfer capacity, so it is considered the first-line option if the use of corticosteroids is necessary during pregnancy. Despite their usefulness, they have limitations, as their administration in the first trimester has been associated with an increased risk of orofacial malformations, while their use in late pregnancy could lead to suppression of the neonatal adrenal axis, associated with an increased risk of hypertension, gestational diabetes and preeclampsia. Nevertheless, they are still considered relatively safe and their use is approved when the clinical situation requires it, always using the lowest possible dose and for the shortest time necessary to minimize risks[5].

Immunosuppressants

Regarding the use of immunosuppressants in pregnancy, thiopurines (azathioprine, 6-MP) have shown congenital anomalies in animal studies, but they have not been shown to increase the risk of malformations in humans, so they are considered safe throughout pregnancy, although their initiation in pregnancy is not recommended due to their late effect[1]. However, it is important to consider that, in patients with IBD who are not pregnant, discontinuation of thiopurine in combination therapy does not carry a significant risk of relapse in the following two years[6].

Cyclosporine has been used in cases of severe relapse, with no evidence of genetic malformations, although there is an increased risk of preterm delivery and low birth weight, which could be due to disease activity or to the drug itself. On the other hand, methotrexate is completely contraindicated in pregnancy due to its teratogenic effect, so it should not be administered to women who are planning to conceive or who are not using a safe contraceptive method. It is recommended to suspend it 3 to 6 months before conception and to administer folic acid in high doses to minimize risks. In case of accidental pregnancy under its use, it should be discontinued immediately and the patient should be referred to an obstetrician to evaluate the risk of teratogenicity[6,7].

Anti-TNF

Anti-TNF drugs, such as infliximab and adalimumab, cross the placenta in the third trimester, although, according to different series analyzed, exposure to these drugs is not associated with an increase in congenital malformations, spontaneous abortions, premature birth, low birth weight or infant infections, The results currently evaluated show that exposure to biologics, or a combination of thiopurines and biologics, does not increase the rate of perinatal complications or infections in the first year of life. Certolizumab is a Fab fragment of the monoclonal anti-TNF and not the complete IgG, its passage through the placenta being more limited, which could be an advantage over the use of infliximab and adalimumab; however, it has no indication in the technical file for IBD.

Its interruption may increase the risk of maternal relapse, and it has now been demonstrated that disease activity is a more relevant risk factor than exposure to these drugs for spontaneous abortion and premature delivery, also increasing the risk of postpartum disease activity. So, with the available evidence, anti-TNF therapy can be maintained throughout pregnancy in women with IBD to control the disease and reduce associated complications.[1,8].

JAK inhibitors

JAKi are small molecules that can cross the placenta and generate early exposure in pregnancy. Preclinical animal studies have revealed serious concerns about their teratogenicity. Tofacitinib has been shown to be feticidal and teratogenic in rabbits at doses six times the maximum dose in humans. Filgotinib, at doses equivalent to those used in humans, has been associated with fetal death and severe malformations in rats and rabbits. Upadacitinib has been shown to cause musculoskeletal and cardiovascular malformations at doses similar to those used in humans.

The limited exposure to these drugs in humans precludes drawing firm conclusions, so it is recommended that tofacitinib and upadacitinib be discontinued at least four weeks before planned conception, and filgotinib at least one week before. In specific and selected cases, where the clinical situation requires continuation of treatment, the patient should be fully informed of the risks in order to make a consensual decision.

Antisphingosine

S1P receptor modulators (anti-SP1), such as ozanimod and etrasimod commonly used for the treatment of multiple sclerosis, have been approved for the treatment of ulcerative colitis. These drugs have demonstrated teratogenic effects in animal studies, including fetal death and severe malformations at human-equivalent doses. Currently, there are no controlled clinical studies that determine the risk of fetal development in pregnant women exposed to these drugs. Prescribing information recommends the use of effective contraception to

DOI: 10.37352/2025483.2

prevent unplanned pregnancies while taking these drugs and for up to three months after discontinuation[10,11].

Anti-interleukin and anti-integrins

Interleukin inhibitor drugs such as ustekinumab, which inhibits IL-12 and IL-23, and vedolizumab, anti-integrin alpha4-beta7, have a favorable safety profile during pregnancy, with no available studies reporting increased adverse effects in pregnant women. This has led to their consideration as safe options for use in this context. Although there are limited data on risankizumab and mirikizumab (IL-23 inhibitors), their mechanism of action and safety profile suggest that they may follow similar dynamics during gestation.[12,13].

Drug	Recommendation
Aminosalicylates	Safe during pregnancy, with minimal transplacental transfer. **Folic acid** supplementation is recommended when using **sulfasalazine**.
Corticosteroids	**First trimester: risk of orofacial malformations.** Second and third trimester: risk of **hypertension, gestational diabetes and preeclampsia.**
Thiopurines and immunosuppressants	**Thiopurines are considered** safe, but their initiation in pregnancy is not recommended**.** **Cyclosporine:** risk of premature delivery and low birth weight. **Methotrexate** contraindicated.
Anti-TNF	**Infliximab and adalimumab** cross the placenta in the third trimester, so it is suggested to evaluate their suspension. The passage of **certolizumab** through the placenta is more limited, which could be an advantage over other anti-TNFs.
JAK inhibitors	Suspend during pregnancy. **Tofacitinib and upadacitinib**: discontinue four weeks before conception and **filgotinib** at least one week before.
Antisphingosine	**Ozanimod and etrasimod:** teratogenic.
Anti-interleukin and anti-integrin	**Ustekinumab and vedolizumab** have a good safety profile during pregnancy. It is recommended to maintain them in patients with active IBD in the periconceptional period or in those with particularly refractory disease. **Risankizumab, Mirikizumab:** there are few data to date.

Table 3. ***Use of drugs in pregnancy.***

Childbirth

A higher probability of cesarean delivery has been reported in patients with UC compared to patients with CD, the main factors influencing the decision for cesarean delivery in UC being smoking, pancolitis and the presence of an ileoanal reservoir, while in Crohn's disease, a history of previous surgery and active perianal disease are determinants. A higher incidence of preterm delivery has also been documented in women with uncontrolled IBD, underscoring the need for optimal disease management during pregnancy.

The route of delivery in women should be individualized according to each patient's condition. Cesarean section is recommended in cases of active perianal disease or in patients with ileoanal reservoir, as these conditions increase the risk of pelvic floor dysfunction and postpartum complications[13].

It has also been documented that preterm delivery is more frequent in women with uncontrolled IBD, highlighting the importance of proper disease management during pregnancy[1,3].

Breastfeeding

Breastfeeding is recommended in women with IBD, as a protective effect on the health of newborns has been demonstrated. Biologic drugs such as infliximab, adalimumab and certolizumab pegol show minimal transfer into breast milk, with concentrations of less than 1% of the maternal serum level, and are therefore safe during lactation. However, if corticosteroids are administered in high doses, it is recommended to wait at least 4 hours before breastfeeding to reduce infant exposure[3].

Most treatments, including aminosalicylates and biologic therapies, can be maintained during lactation. However, the use of small molecules and antisphingosine is not recommended due to lack of data on their safety. In these cases, the risk-benefit ratio should be carefully evaluated and safe alternatives should be considered[14].

Vaccination

It is advisable to follow the usual vaccination schedule in infants exposed to immunosuppressive drugs during gestation, with the exception of live attenuated virus and BCG vaccines. These vaccines should be postponed until 12 months of age to avoid the risk of reactivation of latent infections, especially in infants exposed to anti-TNF, where cases of severe disseminated infection have been documented. Rotavirus vaccination before 6 months of age is safe.

Recent studies have shown that the response to vaccines such as hepatitis B, Haemophilus influenzae type B, and pneumococcus is similar between children exposed and not exposed to biologic drugs, although some reports suggest a

DOI: 10.37352/2025483.2

	Recommendation
Delivery	**Vaginal** delivery is the recommended option, unless there are obstetric contraindications. **Cesarean section** in UC with ileoanal anastomosis or CD with active perianal disease or ileoanal reservoir.
Breastfeeding	Breastfeeding is **safe and recommended**. Increase caloric and Omega-3 intake. Treatment with anti-TNF or other biologics should not be discontinued, except for small molecules and anti-SP1 which should be avoided.
Vaccination	Follow usual schedule except in children exposed to immunosuppressants, in this case postpone **live vaccines** for 12 months.

Table 4. ***Recommendations during labor, pregnancy and lactation.***

lower initial response, which normalizes after the booster dose at 12 months[3,15].

Conclusion

Pregnancy planning in patients with IBD should be performed with a multidisciplinary approach to ensure disease control and reduce maternal-fetal risks. Most treatments can be maintained during gestation and lactation, always prioritizing disease remission to avoid complications.

Adequate information to patients of childbearing age is key for informed decision making and optimization of perinatal outcomes. It is essential to coordinate with the obstetric team the delivery plan and breastfeeding, ensuring adequate follow-up for both mother and newborn.

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DOI: 10.37352/2025483.2

REVIEW ARTICLE

HIGH-RISK GASTROINTESTINAL CANCER CLINIC

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Abstract

High-Risk Colorectal Cancer Clinics were established within Gastroenterology to prevent colorectal cancer in the high-risk population. Over time, these clinics have expanded their scope and evolved into High-Risk Gastrointestinal Cancer Clinics, which now address individuals at high risk for various digestive neoplasms beyond just colorectal cancer. Gastroenterologists with expertise in genetics coordinate the programs; however, a multidisciplinary team is essential to ensure comprehensive care for high-risk patients. It is important to note that these clinics differ from standard Digestive System consultations. The focus is on the family instead of the individual, and the primary objective is prevention at the family level, rather than treatment for individual patients.

Keywords: genetics, gastrointestinal cancer, prevention, multigen panel.

Introduction

Approximately 5-10% of cancers are hereditary, i.e., they are due to germline mutations in certain genes[1]. Patients carrying these mutations are at high risk of developing cancer. There are also familial forms of cancer in which we observe an aggregation of cases in the family, but no genetic alteration responsible is identified.

Colorectal cancer is one of the cancers with the highest frequency of hereditary and familial forms, so it is essential to identify individuals at increased risk to establish appropriate preventive programs[2]. In this sense, the High-Risk Colorectal Cancer Clinics emerged in the Gastroenterology Units to offer specific and specialized care to the population at high risk of colorectal cancer[3]. In recent decades, the spectrum of these clinics has been expanding to cover other digestive neoplasms, so that we can now call them High-Risk Gastrointestinal Cancer Clinics or Gastrointestinal Cancer Prevention Clinics. Two main

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RAPD 2025;48(3):105-111. DOI: 10.37352/2025483.3

factors have determined this evolution: 1) The implementation of multigene panels for genetic analysis, which allows us to diagnose a greater diversity of hereditary cancer syndromes[4-8]; and 2) The growing evidence of the effectiveness of screening in individuals at high risk of digestive neoplasms other than colorectal cancer such as, for example, pancreatic cancer[9-12].

High-Risk Gastrointestinal Cancer Clinics *vs.* Genetic Counseling Units

In parallel to the development of High-Risk Gastrointestinal Cancer Clinics, many centers have established Genetic Counseling Units. Although both models are aimed at the care of the population at high risk of cancer, they present important differences in their structure. High-Risk Gastrointestinal Cancer Clinics are coordinated by gastroenterologists with training in Genetics, focus on the prevention of digestive neoplasms, and offer coverage to both familial and hereditary forms of these neoplasms. In contrast, Genetic Counseling Units are coordinated by geneticists or, more frequently, oncologists and cover all types of hereditary neoplasms. Furthermore, while the objective of the HHigh-Risk Gastrointestinal Cancer Clinic is the comprehensive care of such individuals, including diagnosis, follow-up, and treatment if necessary, many Genetic Counseling Units focus their activity mainly on diagnosis and refer individuals to the relevant specialists after diagnosis. Therefore, these are two different models that can coexist without problem in tertiary centers to ensure comprehensive care for all types of hereditary cancer syndromes.

Fundamental characteristics of High-Risk Gastrointestinal Cancer Clinics

As previously mentioned, High-Risk Gastrointestinal Cancer Clinics are led by gastroenterologists who must be trained in Genetics. However, to meet the objective of providing comprehensive care to individuals at high risk of digestive neoplasms, the participation of a multidisciplinary team is essential for the different stages of diagnosis, follow-up, and treatment (Figure 1). In this regard, the role of specialties such as Pathology (including molecular pathology studies), Genetics (with the capacity to perform new generation sequencing), Radiology (including advanced imaging techniques), Digestive Endoscopy (including advanced endoscopic techniques, both diagnostic and therapeutic), Digestive Surgery, Oncology, Gynecology, Clinical Psychology, and many others that may vary depending on the type of syndrome identified (for example Urology, Dermatology, etc.) should be highlighted.

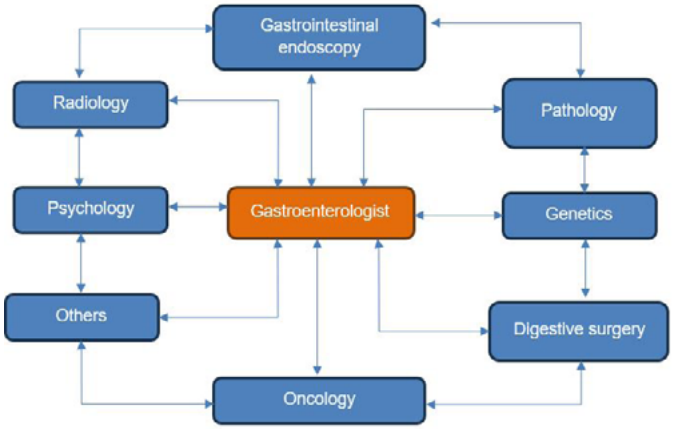

Figure 1. ***Multidisciplinary team of the High-Risk Gastrointestinal Cancer Clinics. The High-Risk Gastrointestinal Cancer Clinic is coordinated by a gastroenterologist with expertise in Genetics but requires the participation of a multidisciplinary team to ensure comprehensive care for high-risk patients.***

High-Risk Gastrointestinal Cancer Clinics have distinct characteristics that set them apart from other Digestive System Consultations. In these specialized clinics, while we do care for patients, we often focus on healthy individuals as well. Additionally, the emphasis in these clinics is on the family unit rather than the individual patient, which is typical in other healthcare settings. The main objective of the High-Risk Gastrointestinal Cancer Clinic is prevention and early diagnosis, whereas other consultations generally focus the treatment of existing digestive disorders.

Criteria for referral to the High-Risk Gastrointestinal Cancer Clinic

All patients with suspected hereditary or familial digestive cancer should be referred for evaluation in a High-Risk Gastrointestinal Cancer Clinics. In general, this suspicion is established by the occurrence of multiple tumors in a patient or a family, by the diagnosis of neoplasms at early ages or by rare tumors.

As a guideline, we could suggest more specific referral criteria as outlined in Figure 2. It should be noted that in those centers with a Genetic Counseling Unit, some of these patients may be initially seen. However, we believe that in those cases where a syndrome is suspected, in which the most frequent manifestation is the development of a digestive tumor (for example, Lynch syndrome), referral to a High-Risk Gastrointestinal Cancer Clinic would be more appropriate to ensure comprehensive care.

DOI: 10.37352/2025483.3

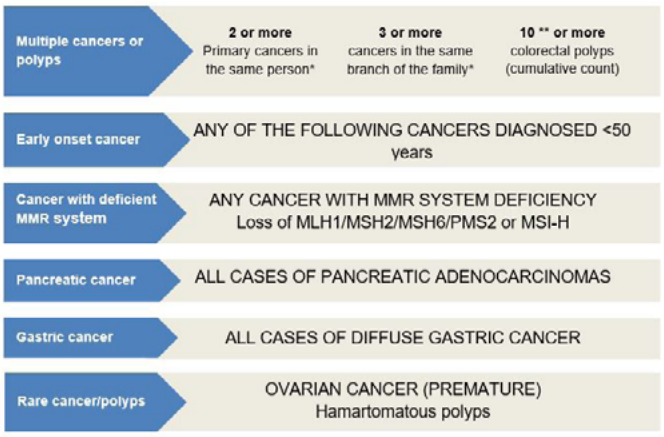

Figure 2. ***Criteria for referral to the High-Risk Gastrointestinal Cancer Clinic * Mainly digestive tumors or Lynch-spectrum neoplasms (stomach, endometrium, ovary, urothelial tumors, biliary tract and brain) ** In the case of adenomatous polyps. For serrated polyps the criteria for referral would be: Criteria 1) ≥ 5 serrated polyps proximal to rectum, all size ≥ 5 mm, with 2 being ≥ 10 mm ; or Criteria 2) > 20 serrated polyps of any size along the large bowel, ≥ 5 proximal to the rectum. MMR system = DNA mismatch repair system.***

Schedule of visits in the High-Risk Gastrointestinal Cancer Clinic

Patient management in the High-Risk Gastrointestinal Cancer Clinic is organized according to the following schedule of visits:

- First visit: Cancer genetic risk assessment. Genetic counseling 1 (pre-test).
- Second visit: Genetic counseling 2 (post-test). Establishment of a personalized preventive program.
- Third and subsequent visits. Follow-up visits.

First visit

The main objective of this visit is to assess the genetic risk of cancer in the family. For this purpose, our main tool is the family history or pedigree. In this first visit, we will draw a detailed family tree that encompassess at least three generations, including all cases of both benign and malignant neoplasms (type, location, and age at diagnosis), as well as the age and cause of all deaths. To draw a family tree with high-quality information, it is important that the patients are notified before the visit, so that they can review the necessary information and, if possible, provide reports of the cases of neoplasia. Likewise, on our part, it is essential to verify as far as possible all the information provided by checking the electronic medical records available to us. It should be emphasized that, although building a family tree is laborious and time-consuming, it should not be replaced by a written collection of family history in the medical record. In this sense, the pedigree is much more useful since it provides a visual snapshot of the family, in which we identify cancer cases but also the family structure, detect if the family is not very informative (small size, numerous cases of death at early ages due to causes other than cancer, little information available on any family branch, etc.), visualize possible inheritance patterns and identify all the individuals at risk that we would have to evaluate in the case of establishing the diagnosis of a hereditary syndrome.

In addition to the family tree, there are other tools that help us to establish the genetic risk of cancer. In this sense, the pathology reports of the tumors diagnosed in the family are of great help. Sometimes, we also have tumor molecular studies that allow us to assess the status of the DNA mismatch repair system (MMR system), such as immunohistochemistry of MMR system proteins and microsatellite instability. These molecular tests are performed as screening for Lynch syndrome, as this syndrome is caused by a mutation in a gen of the MMR system and is characterized by a malfunction in this system, resulting in the appearance of microsatellite instability and/or loss of expression of the protein corresponding to the mutated gene[13]. According to current guidelines, all patients diagnosed with colorectal cancer should undergo molecular screening for Lynch syndrome[14-16].

Gastrointestinal endoscopy reports can also be useful, especially colonoscopy reports in cases of polyposis (characteristics, location, and number of polyps).

Predictive models have been developed that, based on personal and family history, allow us to establish the probability of an individual carrying a mutation in the genes of the MMR system (for example, the PREMM5 model)[17] or in a broader panel of genes (PREMMplus model)[18].

Finally, the tool that will allow us to confirm the diagnosis of a suspected hereditary syndrome is germline genetic testing (performed in blood or saliva). Classically, a single gene or a small number of genes were studied using Sanger sequencing. In recent decades, thanks to the development of next-generation sequencing (NGS) technologies, it has become increasingly common to perform multigene panels (including in the panel genes associated with colorectal cancer, digestive neoplasms, or cancer in general) or even to sequence the entire exome (coding part of the DNA).

During this initial visit, if we identify any suspicion of a hereditary syndrome within the family and a germline genetic study is recommended, we will conduct pre-test genetic counseling before proceeding with the request (refer to the section on Genetic Counseling).

DOI: 10.37352/2025483.3

Second visit

In this visit, we have already received the requested results of the genetic study, and we will carry out a post-test genetic counseling to inform the patient (see section on Genetic Counseling). We will plan a personalized preventive program based on their genetic testing results, which may include endoscopic and/or radiological surveillance, preventive surgeries, and, in some cases, chemopreventive strategies. Likewise, if a pathogenic variant is identified in any of the evaluated genes, we will initiate cascade genetic screening in first-degree relatives. Finally, the identification of a germline mutation can be useful if the patient requires oncological treatment since it allows us to choose genotype-based treatment.

Third and subsequent visits

Since the objective of the High-Risk Gastrointestinal Cancer Clinic is providing comprehensive care of high-risk individuals, patients will not be discharged after a diagnosis of a hereditary syndrome, instead, we will follow them with a periodicity determined by the preventive program that we establish and surveillance findings.

Indications for multigene panel testing

At present, both the indications for multigene panel testing and the genes that should be included in such studies are subject to debate. Different societies have published recommendations in this regard with the aim of unifying criteria and trying to make the studies cost-effective. However, given that the main limiting factor is economic, it is foreseeable that as prices continue to decrease, the indications for multigene panel testing will expand. Some guidelines that can serve as a reference for clinical practice in the consultation of High-Risk Gastrointestinal Cancer Clinics are those published by the following societies:

- Collaborative Group of the Americas on Hereditary Gastrointestinal Cancer[19] (recommendations only for colorectal and/or polyposis cancer)
- American Society of Clinical Oncology (ASCO)[20]
- National Comprehensive Cancer Network (NCCN):

https://www.nccn.org/guidelines/guidelines-detail?category=2&id=1544 (colorectal, endometrial, and stomach cancer).

https://www.nccn.org/guidelines/guidelines-detail?category=2&id=1545 (pancreas, breast, ovarian and prostate).

- Joint position document of the Spanish Association of Gastroenterology (AEG), Spanish Society of Medical Oncology (SEOM), Spanish Association of Human Genetics (AEGH) and IMPaCT-GENÓMICA consortium[21].

Interpreting genetic test results

When a genetic study identifies genetic variants in any of the evaluated genes, these should be classified according to the recommendations of the American College of Medical Genetics (ACMG) in one of the following categories[22]:

- Benign variant
- Likely benign variant
- Variant of uncertain significance
- Likely pathogenic variant
- Pathogenic variant

In practice, both benign and likely benign variants are considered as a single category. These variants do not affect the function of the corresponding protein and therefore, from a clinical point of view, do not require any action. Likewise, pathogenic and likely pathogenic variants are considered as a single category. These variants allow us to diagnose a hereditary syndrome and their identification has clinical implications. In those cases in which we have performed multigene panel testing or whole exome sequencing, we may encounter different clinical scenarios. The ideal scenario would be to identify a pathogenic variant in a high penetrance gene that fits well with the phenotype of the family, since in these cases the diagnosis is solid and we will have well-established clinical guidelines for the follow-up of carrier individuals. A second scenario would be to identify a pathogenic variant in a gene with high penetrance but that does not match well with the family phenotype (e.g., amutation in the *BRCA2* gene in a family that meets the Amsterdam criteria). In these cases, we cannot establish that the family phenotype is secondary to the identified variant and in addition to the preventive measures recommended in the clinical guidelines for the diagnosed syndrome, we should consider additional preventive measures based on the family phenotype (in our example, consider colorectal cancer screening in carriers). Finally, we may find a pathogenic variant in a gene of moderate penetrance. In

DOI: 10.37352/2025483.3

these cases, we will not have well-established clinical practice guidelines to guide us since the available evidence is usually quite limited and recommendations change frequently as new studies are published.

Finally, in cases where variants of uncertain significance are identified, we will not have sufficient evidence to propose a preventive program focused on the risks associated with the corresponding gene alteration. In this situation, we should periodically review the variant in the available databases as it may end up being reclassified as benign or pathogenic, which will allow us to modify our recommendations accordingly in individuals who are carriers[23,24].

Genetic counseling

Genetic counseling was legally regulated in Spain in 2007 by the Biomedical Research Law (Law 14/2007 of July 3). This law defines genetic counseling as the "procedure aimed at informing a person about the possible consequences for him or her or his or her offspring of the results of a genetic analysis or screening and its advantages and risks and, where appropriate, to advise him or her about the possible alternatives derived from the analysis. It takes place both before and after a genetic test or screening and even in the absence of the same".

In addition, some Autonomous Communities also have laws that regulate genetic counseling, such as the Order of March 3, 2005, of the Regional Ministry of Health, which regulates the organizational devices that carry out genetic counseling in cancer in the Valencian Community, or Law 11/2007, of November 26, 2007, regulating genetic counseling, the protection of the rights of persons who undergo genetic analysis and human DNA banks in Andalusia.

Genetic counseling must be carried out in two phases, one before requesting the test (pretest genetic counseling) and the other after receiving the test results (posttest genetic counseling).

Pre-test genetic counseling

Pre-test genetic counseling is essential for the patient to understand the implications of undergoing a genetic study and to be able to make informed decisions about accepting or declining genetic testing. It is key for the patient to understand the overall benefits, risks, and limitations of the study, as adequate information at this stage can facilitate adaptation to the results later on. Some key points to address during this phase of genetic counseling are as follows:

- Provide general information about the test and its purpose.
- Description of the disorder(s) included in the test.
- Advantages, risks, and limitations of the test. Confidentiality of the information obtained in the test and the need for authorization prior to its performance (informed consent).
- Explanation of the possible results: positive, negative, variants of uncertain significance, and secondary or unexpected results.
- How these results would be interpreted according to the patient's family and medical history.
- Possible medical, reproductive, and psychosocial implications of genetic test results, including implications for family members.
- Management options without genetic test results compared with recommendations associated with possible test results.
- Patient education and support.

Regarding the benefits of genetic testing, it is important to convey to the patient that if the diagnosis of a hereditary syndrome is established, it will be possible to design an individualized surveillance strategy according to his or her specific cancer risk. Furthermore, depending on the syndrome, surgical options can be considered to reduce the risk of cancer development. On the other hand, if the patient develops cancer, we will be able to adapt the treatment recommendations according to the results of the genetic tests. Finally, we will be able to study family members at risk and offer specific preventive measures to those who are carriers.

On the other hand, it is important to emphasize that the test does not always allow us to reach a diagnosis and that we may obtain results that are difficult to interpret (for example, variants of uncertain significance) or unexpected (incidental findings, i.e., that are not related to the reason for which the test was requested and that may or may not have implications for health and clinical significance)[25].

Post-test genetic counseling

This second phase of genetic counseling focused on clearly explaining the results obtained from the test and their implications. When diagnosing a hereditary syndrome,

DOI: 10.37352/2025483.3

we will estimate the associated cancer risks and establish an appropriate prevention plan. We will also ask the patient to share genetic testing results with first degree relatives to set up a cascade genetic screening.

We should also bear in mind that the results of the genetic study may have implications for the choice of oncological treatments if the carrier is a patient with cancer or develops cancer during follow-up.

Conclusions

The High-Risk Gastrointestinal Cancer Clinic provides comprehensive care (identification, follow-up, and treatment if necessary) and specialized care for individuals at high risk of developing colorectal cancer and/or different digestive neoplasms. This model of care is currently very useful because the increasing implementation of next-generation sequencing in clinical practice (multigene panel testing and even whole exome sequencing) has resulted in the identification not only of a greater proportion of hereditary colorectal cancer syndromes,but also of a broader variety of hereditary syndromes, some of which confer a high risk of certain digestive neoplasms that can benefit from appropriate preventive programs. To set up a High-Risk Gastrointestinal Cancer Clinic, it is necessary to have gastroenterologists with training in Genetics and a multidisciplinary team that includes, among others, specialties such as Genetics, Pathology, Radiology, Digestive Endoscopy, Digestive Surgery, Oncology and Clinical Psychology. This approach emphasizes the family rather than just the individual patient, aiming primarily to prevent the development of digestive neoplasms in those recognized as being at high risk, as well as in all family members who share this increased risk.

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DOI: 10.37352/2025483.3

CLINICAL CASE

HEPATIC ANGIOSARCOMA WITH ELEVATED ALPHA-FETOPROTEIN: A DIAGNOSTIC CHALLENGE.

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Abstract

The elevation of alpha-fetoprotein is typically associated with hepatocellular carcinoma, hepatoblastoma, and germ cell tumors, but we can also find high levels of alpha-fetoprotein in vascular mesenchymal tumors such as hepatic angiosarcoma.

We present the case of a 74-year-old patient who initially presented with Budd-Chiari syndrome and a significant elevation of alpha-fetoprotein, with a high level of suspicion of hepatocellular carcinoma. However, hepatocellular carcinoma was reasonably ruled out after complementary tests were performed. The patient's clinical and analytical progression pointed towards the presence of a hepatic angiosarcoma, which can be associated with elevated alpha-fetoprotein levels and may represent a diagnostic challenge if there is not a high level of suspicion.

Keywords: alpha-fetoprotein, hepatocellular carcinoma, mesenchymal tumor.

Introduction

Elevated alpha-fetoprotein (AFP) is mainly associated with hepatocellular carcinoma (HCC), hepatoblastoma and germ cell tumors, but there may be other tumors that produce it, such as hepatic angiosarcoma, for whose diagnosis it is important to have a high index of suspicion.

Clinical Case

A 74-year-old patient with a history of metabolic syndrome and pneumoconiosis (due to occupational exposure to vinyl chloride) debuts with Budd-Chiari syndrome (BCS) with elevated alpha-fetoprotein (AFP: 6500 ng/ml). He presented a constitutional picture with dissociated cholestasis and radiological signs suggestive of chronic liver disease with thrombosis of the intrahepatic vena cava with extension to the suprahepatic vein.

Despite the high diagnostic suspicion of HCC, the dynamic liver study did not reveal compatible lesions and the

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RAPD 2025;48(3):112-113. DOI: 10.37352/2025483.4

liver biopsy was negative for malignancy. In addition, other tumors that can elevate AFP (teratoblastoma, germ cell tumor, Hodgkin's disease and gastric tumor) are ruled out. After initiation of anticoagulant treatment, the control angio-CT scan reveals a rapid radiological progression with extension of the described occupation to the right atrium in less than a month, with progressively increasing AFP levels (10,800 ng/ml). PET-CT (Figure 1) confirms moderate metabolic hyperuptake in the walls of the inferior vena cava from the right renal vein to the entrance into the right atrium, suggesting angiosarcoma as a first possibility. Combined surgical treatment (vascular and cardiac surgery) was proposed, but it was not possible because the patient died before the intervention.

Despite not having a histological diagnosis (we do not have the necropsy consent), we believe it is a case of scientific interest due to its infrequency, unfavorable prognosis and the importance of establishing early suspicion.

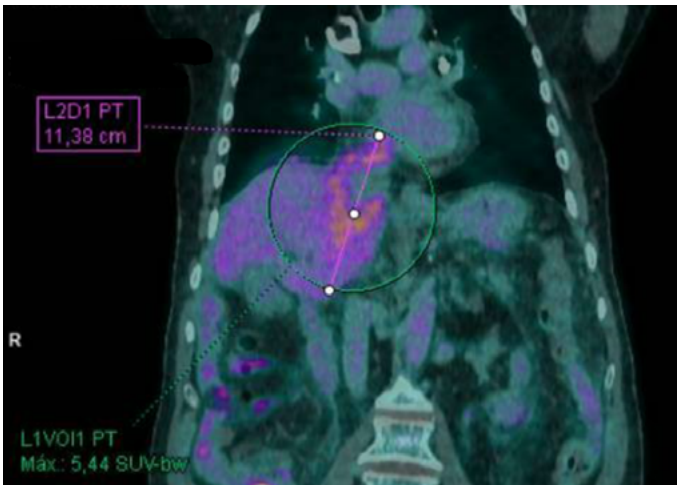

Figure 1. ***PET-CT. Moderate intensity metabolic hyperenhancement extending from the inferior vena cava and right renal vein to the right suprahepatic veins, reaching the entrance of the right atrium.***

Discussion

Vascular mesenchymal tumors are infrequent and have an insidious presentation with non-specific symptoms due to the formation of collateral circulation, and the diagnosis is made late in most cases[1]. Based on the evidence presented and the clinical course of the patient, we believe that the primary tumor may have been a hepatic angiosarcoma with massive secondary SBC, whose diagnosis was delayed given the initial suspicion of multicentric HCC based primarily on AFP levels. This represents the most common sarcoma in the liver and has been associated with exposure to carcinogens such as vinyl chloride and arsenic[2]. The other option proposed was leiomyosarcoma of the inferior vena cava of which there are some published cases[3]. However, the elevation of AFP is more indicative of the former, since its elevation is associated with HCC, hepatoblastoma and germ cell tumors, but it can be found characteristically elevated in other tumors such as hepatic angiosarcoma[4].

This case highlights the importance of excluding other rare vascular neoplasms in the presence of elevated AFP without clear evidence of HCC.

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DOI: 10.37352/2025483.4

CLINICAL CASE

CHRONIC DIARRHEA IN AN HIV PATIENT: GASTROINTESTINAL INVOLVEMENT BY HISTOPLASMA CAPSULATUM.

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Abstract

Histoplasmosis is a systemic granulomatous mycosis caused by *Histoplasma capsulatum*, primarily affecting immunocompromised patients. Its gastrointestinal presentation is rare and can mimic other infectious or inflammatory colitides, making diagnosis challenging and delaying early treatment.

We present the case of a 26-year-old male with a history of HIV infection who sought medical attention due to chronic diarrhea lasting several months. He was ultimately diagnosed with intestinal histoplasmosis, as biopsies revealed granulomatous duodenitis and ileocolitis with the presence of *Histoplasma capsulatum*.

Keywords: chronic diarrhea, histoplasmosis, HIV infection.

Introduction

Histoplasmosis is a systemic granulomatous mycosis caused by infection with the fungus Histoplasma capsulatum. It is an endemic infection in tropical regions, with special incidence in immunocompromised patients, particularly those with advanced stages of human immunodeficiency virus (HIV) infection[1].

Exclusive gastrointestinal involvement is infrequent and, in the absence of treatment, leads to high mortality. Its presentation is usually subacute, with non-specific symptoms, especially chronic diarrhea and constitutional syndrome[2]. The most common location is the ileocecal area, where it can manifest in three endoscopic patterns: stenotic, ulcerative and edematous.

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Given the rarity of this entity in our environment, and with the aim of emphasizing the importance of differential diagnosis in immunocompromised patients with chronic diarrhea, we present the case of a male with previously undiagnosed HIV infection, who presented with duodenitis and granulomatous ileocolitis due to Histoplasma capsulatum.

Clinical Case

A 26-year-old man from Colombia, with no known allergic history, recently diagnosed with HIV infection stage C3, in antiretroviral treatment. He consulted for diffuse abdominal pain, predominantly in the right flank, of 4 months of evolution, associated with semi-liquid diarrhea (4-5 stools per day), asthenia, unquantified fever, hyporexia and weight loss of 20 kg.

His personal history included syphilis of undetermined duration and occult hepatitis B. He was not immunized against hepatitis B. he had no immunization against hepatitis A, hepatitis C, SARS-CoV-2, pneumococcus or human papillomavirus.

Physical examination revealed cachexia (BMI: 14.5 kg/m^2), with no relevant findings on cardiorespiratory auscultation. The abdomen was painful on palpation in the right flank, with no signs of peritoneal irritation, masses or visceromegaly.

Complementary tests showed bicytopenia (Hb 8.8 g/dL; leukocytes 4,800/mm^3), CD4+ lymphopenia of 50/mm^3, viral load of 26,000 copies/mL and C-reactive protein 7.8 mg/L. Colonoscopy showed deep ulcers in the cecum, ascending colon and ileocecal valve (Figure 1), findings confirmed by contrast-enhanced abdominopelvic CT, which revealed thickening of the right colon and terminal ileum, as well as locoregional and periduodenal adenopathies. The PET-CT scan showed hypermetabolism in the duodenum, cecum and right colon (Figure 2).

Suspecting duodenal involvement, gastroscopy was performed, showing erythematous and inflamed mucosa in the second duodenal portion, with fibrin-covered ulcers (Figura 3). Biopsies confirmed the presence of Histoplasma capsulatum by positive Grocott staining.

Induction antifungal treatment was started with intravenous liposomal amphotericin B (4 mg/kg/day) for 14 days, followed by oral itraconazole (200 mg/8 h for 3 days and then 200 mg/12 h for at least 12 months). However, one month after starting treatment, the patient presented postprandial abdominal pain with vomiting and no new diarrhea. Gastrointestinal transit showed interruption of passage at the duodenal knee level, compatible with obstruction due to postinflammatory fibrosis (Figure 4), so gastrojejunal bypass with resection of the duodenum and ileum and entero-enteric anastomosis was performed.

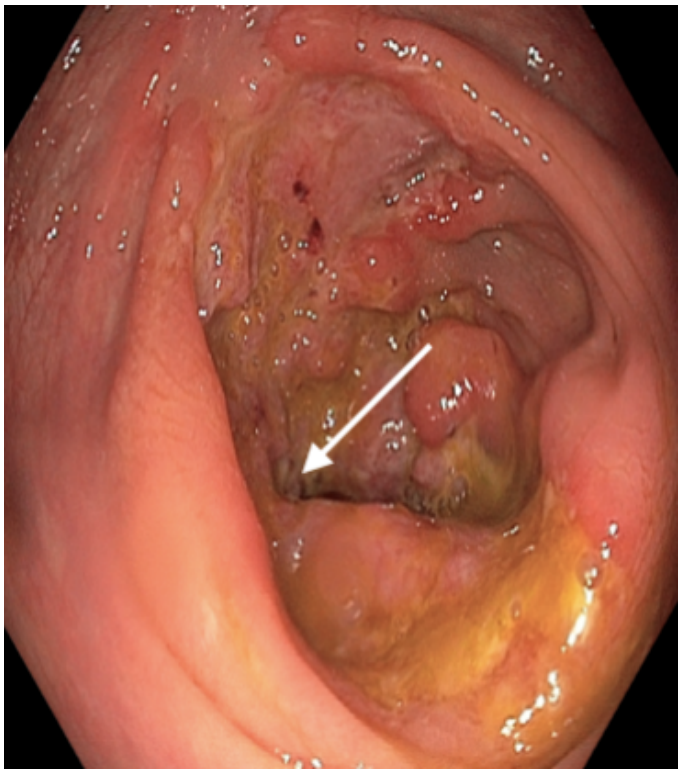

Figure 1. ***Multiple cecal ulcers and deformed ileocecal valve (arrow) evidenced at colonoscopy.***

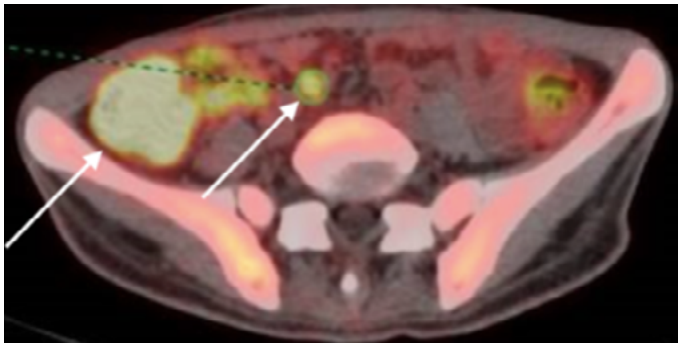

Figure 2. ***Hyperenhancement at the level of the duodenum (medial) and right colon (lateral) in PET-CT study.***

Postoperative evolution was favorable, with no immediate or delayed complications. Currently, the patient remains asymptomatic and under ambulatory follow-up, with no evidence of recurrence.

Discussion

Gastrointestinal involvement by Histoplasma capsulatum is an atypical form of presentation of this endemic mycosis, especially in immunocompromised patients from endemic areas such as Central and South America, Southeast Asia and

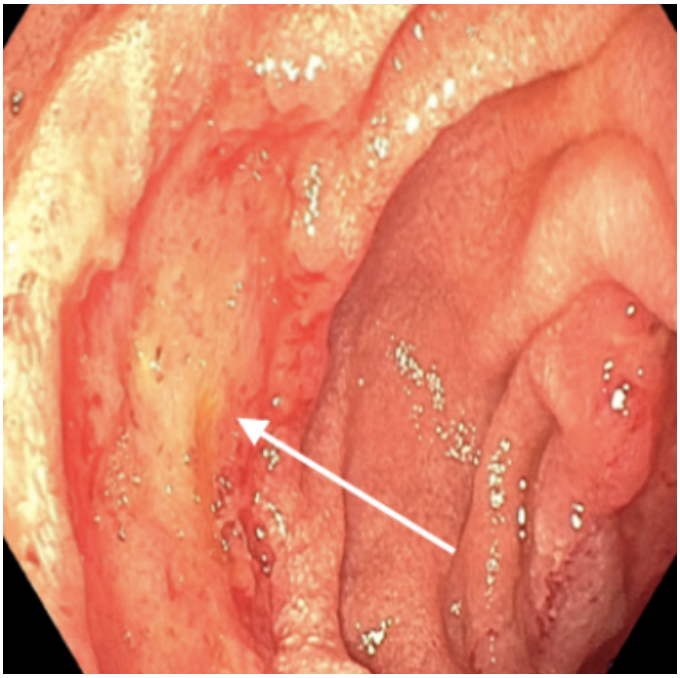

Figure 3. ***Fibrillated ulcer in the second duodenal portion observed at gastroscopy.***

certain areas of Africa[1]. The nonspecific clinical features, together with endoscopic findings that may mimic other infectious or inflammatory colitis, make its initial diagnosis difficult.

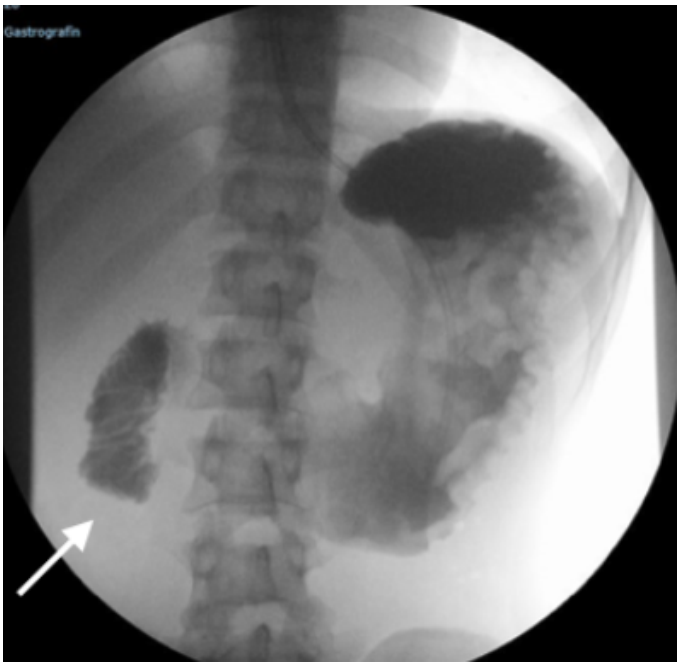

Figure 4. ***Duodenal obstruction visualized in the gastrointestinal transit.***

The differential diagnosis should include intestinal tuberculosis, due to its high prevalence in this population, as well as inflammatory bowel disease[2]. Diagnostic confirmation requires identification of the fungus in tissue samples by histological techniques and culture[3].

Although it is an uncommon entity in Europe, its inclusion in the diagnostic algorithm is essential in immunosuppressed patients with chronic diarrhea and compatible epidemiological history. The prognosis, without treatment, is severe, but with appropriate antifungal therapy, the outcome is usually favorable[4].

This case highlights the need for a multidisciplinary approach - gastroenterology, microbiology, surgery - given the potential variability of the clinical picture and the resulting complications, such as postinflammatory intestinal stenosis. Individualization of treatment is key, adapting it to the extent of the disease and the patient's comorbidities.

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DOI: 10.37352/2025483.5

GIANT EPIDERMOID SPLENIC CYST AS A RARE INCIDENTAL FINDING

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Abstract

Primary epidermoid splenic cysts are rare, congenital in nature, and benign lesions. Due to their low incidence, they may require a broad differential diagnosis, including differentiation from malignant lesions.

We present a case of an epidermoid splenic cyst diagnosed incidentally in the context of a biliary colic episode.

Keywords: splenic cyst, congenital, laparoscopic cystectomy.

Clinical case

A 28-year-old female patient, with no relevant history, was admitted for complicated biliary colic. Laboratory tests showed elevated cholestasis enzymes (total bilirubin 3.7 mg/dL) and mild hypertransaminasemia (AST 70 U/L, ALT 91 U/L), without inflammatory markers. Abdominal ultrasound and magnetic resonance imaging (MRI) were performed with findings of multiple cholelithiasis without signs of cholecystitis and mild dilatation of the biliary tract without obstruction, incidentally revealing a 9 cm unilocular splenic cyst homogeneously hyperintense in T2 and hypointense in T1, without signs of complication.

Due to its large size, given the risk of complication, laparoscopic cystectomy was performed after preventive vaccination. The anatomopathological study confirmed a fibrous wall cyst lined by benign squamous epithelium, without malignancy.

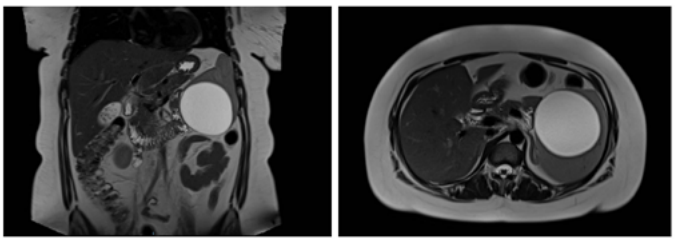

Figure 1. ***Magnetic resonance image with visualization of large splenic cyst with homogeneous content.***

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Fernández Carrasco M, Rodríguez Mateu A, Villegas Pelegrina P. Giant epidermoid splenic cyst as a rare incidental finding. RAPD 2025;48(3):117-118. DOI: 10.37352/2025483.6

Discussion

Primary splenic cysts are rare lesions, classified as primary (true) or secondary (pseudocysts). The primary ones include the epidermoid ones and are very rare, derived from embryologic anomalies. Secondary ones are usually post-traumatic, hemorrhagic, infectious or post-splenic infarction[1].

They are usually asymptomatic, being an incidental finding, but may present complications such as infection, hemorrhage or rupture. Their diagnosis is based on imaging studies. In ultrasound, epidermoid cysts appear as well-defined, thin-walled lesions with scattered internal echoes, and may present septa and trabeculations. On computed tomography (CT), these cysts appear as round, well-defined structures, without enhancement and with a water-like attenuation. On the other hand, false cysts, which lack a cellular lining, present more variable appearances on ultrasound, such as peripheral "eggshell" shaped calcifications and thick fibrous walls. On magnetic resonance imaging they appear hyperintense on T2 and hypointense on T1. Definitive confirmation requires histological analysis, showing the epithelial lining of the cyst[2].

Treatment of a splenic cyst may include total splenectomy, either open or laparoscopic. Options such as percutaneous drainage, sclerosis or partial splenectomy minimize recurrence and favor recovery[3]. Laparoscopic cystectomy is preferable in order to preserve splenic function and avoid the risk of receiving, which was the management performed in this patient[1,2].

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