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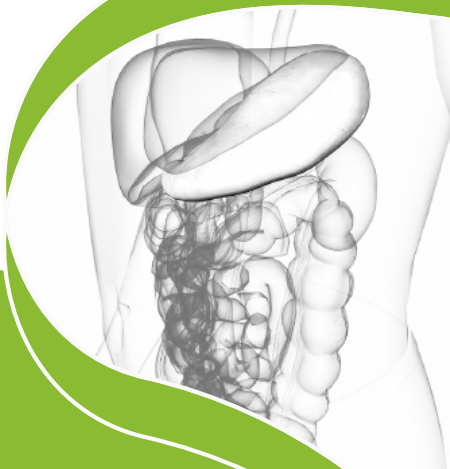

Official Body of Sociedad Andaluza de Patología Digestiva

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

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

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

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

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

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

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

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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.

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4° Full postal address of the responsible author, to whom correspondence should be addressed, including telephone, fax and email address.
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1° Structured abstract in Spanish and English. 3-5 key words. The abstract will have a maximum length of 350 words, emphasising the most important aspects of the manuscript.
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3° Centre(s) of origin (department, institution, city and country).
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5° Declaration on the existence or non-existence of a source of funding for the work, or conflicts of interest.

- Main body of the manuscript, containing:

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

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

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

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

- Main body of the manuscript, containing:

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

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

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

to verify their validity. They should not exceed 2GB.
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3° Centre(s) of origin (department, institution, city and country).
4° Full postal address of the responsible author, to whom correspondence should be addressed, including telephone, fax and email address.

- Main body of the manuscript, containing:

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

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

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

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

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

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

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

-Main body of the manuscript, containing:

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

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

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

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

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

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- General data:

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

- Main body of the manuscript, containing:

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

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

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

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

- Basic body of the manuscript, containing:

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

B)Common standards and other supporting documents

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

Units, generic names and abbreviations:

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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REVIEW ARTICLE

INTERCELLULAR SPACE DILATATIONS AS HISTOLOGICAL MARKERS IN GASTROESOPHAGEAL REFLUX DISEASE: A REVIEW.

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Abstract

Despite its high prevalence in the general population, the diagnosis of Gastroesophageal Reflux Disease (GERD) remains a current challenge. The Montreal and Lyon consensus guidelines provide significant assistance in schematizing this problem; however, their recommendations and protocols cannot be applied in centers where the sophisticated methodology proposed does not exist, such as in Community Hospitals. For nearly six decades, the histological method has been used, with various approaches and success, as a useful procedure in the diagnosis of GERD. Nevertheless, although its description and methodology also date back to that time, the analysis and evaluation of Dilated Intercellular Spaces (DIS) as a histological marker of microscopic esophagitis has been scarcely considered. DIS appear wherever there is damage to the esophageal mucosa, generally caused by refluxed acid and/or alkali, regardless of whether endoscopic lesions are present or not. In this regard, they have been found in very high percentages in erosive GERD but also, with lower frequency, in non-erosive GERD, whether refractory to PPIs or not. The finding of DIS in Hypersensitive Esophagus (physiological pH-metry) is very surprising, and with much lower frequency, similar to that of controls, in Functional Heartburn. This could be explained by the high sensitivity of DIS, which appear even under conditions of minimal or physiological reflux. This review proposes the determination of DIS for the diagnosis of microscopic esophagitis.

Keywords: Gastroesophageal reflux disease, dilated intercellular spaces, microscopic esophagitis..

1. Definition and diagnostic procedures for Gastroesophageal Reflux Disease.

Gastroesophageal reflux disease (GERD) is a very common disease with prevalence rates that vary depending on the latitude considered. In the general population of Western countries, the prevalence is 10-20% and, to a lesser extent, although growing, in Asia[1]. GERD occurs when stomach

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contents (acid, alkali, or gas) reflux into the esophagus, causing symptoms (heartburn and/or regurgitation) and/or complications (esophagitis, stricture, Barrett's esophagus, and adenocarcinoma). Symptoms are only considered when they affect the subject's well-being; mild, infrequent, and insignificant symptoms can occur in up to 40% of the general population and should not be considered GERD. For this reason, questionnaires are often used that only consider GERD if the presence of symptoms is of sufficient intensity/frequency[2,3].

Clinical definition. Montreal, Lyon, and Los Angeles Consensus Statement.

The Montreal Consensus Statement[3] proposes that GERD consists of esophageal syndromes (symptomatic syndrome and syndrome with endoscopic lesions) and extraesophageal syndromes, with established or proposed associations (Figure 1).

Thanks to the Montreal and Lyon I and II[3-5], Consensus Statements, the definition of GERD has been established as precisely as possible. This seemingly trivial fact is of great importance in narrowing down as much as possible the clinical spectrum of GERD, which, until now, had shown variability that prevented the correct design and comparison of research studies. With regard to upper gastrointestinal (GI) endoscopy, this consensus had already been achieved following the acceptance of the Los Angeles criteria for esophageal lesions induced by gastroesophageal reflux (GER)[6]. Upper GI endoscopy has high specificity (≈100%) for the diagnosis of GERD, but low sensitivity, as approximately two-thirds of patients with GERD symptoms do not have endoscopic lesions[7-9]. To date, the clinical and endoscopic diagnosis of GERD has been achieved with sufficient reliability, as it allows us to divide these patients into: 1) those with GERD with endoscopic lesions (Los Angeles grades A-D) or erosive GERD (EE), and 2) those with no or minimal endoscopic lesions (Los Angeles grades N and M) or non-erosive GERD (NERD).

Study of the quality and quantity of refluxed material

After performing an upper GI endoscopy, methodological problems arise when studying the different phenotypes of NERD. Following the protocol, the diagnostic test to be performed at this point would be, whenever possible, a combined test, 24-hour pH monitoring ± multichannel intraluminal impedance monitoring (pH-MII), which allows both acid and alkaline GER to be analyzed. This test subdivides NERD into: "true" NERD (tNERD), if pH-MII is pathological, and "functional" NERD (fNERD), if pH-MII is normal. It has been reported that between 37-60% of all NERD cases have normal pH monitoring, which should correspond to the percentage of patients with fNERD[7]. Today, according to the Rome IV criteria[7], fNERD is not part of GERD, as it is considered a functional process of the esophagus

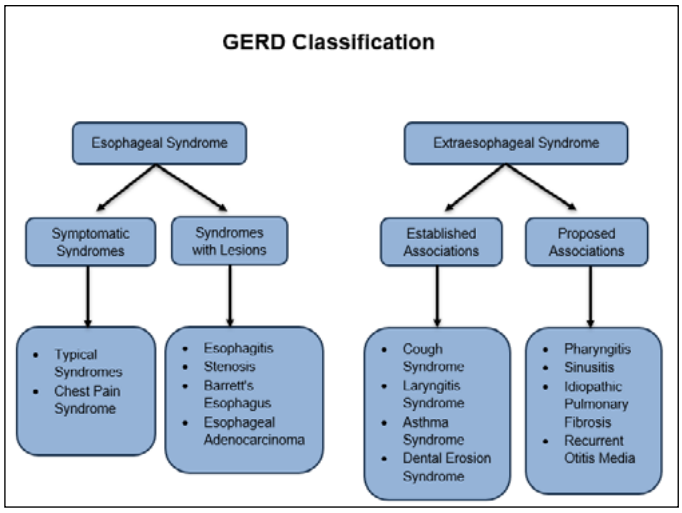

Figure 1. ***Classification and syndromes of GERD according to the Montreal Consensus[3].***

and, therefore, part of the spectrum of Disorders of Gut-Brain Interaction (DGBI). fNERD consists of two entities: Esophageal Reflux Hypersensitivity (RH) when SAP/SI (Symptom Association Probability and Symptom Index, tests that relate episodes of GERD to the onset of GERD symptoms) are positive, and Functional Heartburn (FH) when SAP/SI are negative (Figure 2). pH-MII can differentiate tNERD from fNERD and, therefore, in the absence of better (especially more sensitive) procedures, it is considered the gold standard among GERD diagnostic tests. However, pH monitoring without associated impedance monitoring has some problems:

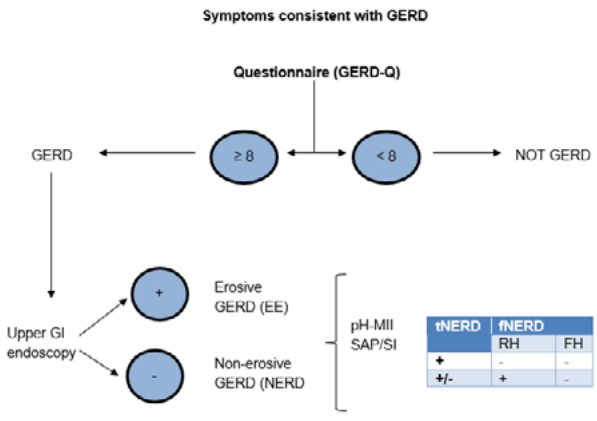

Figure 2. ***Current diagnosis of GERD (tNERD = "true" NERD; fNERD = "functional" NERD; RH = Reflux Hypersensitivity; FH = functional heartburn; pHMII = 24-hour pH monitoring ± impedance monitoring; SAP/SI = Probability of symptom-reflux association/Symptomatic index.***

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-Lack of sensitivity, with up to 23-34% false negatives[8,10,11] in EE, although with good specificity (85-100%)[7,12]. Recently, it has been shown that certain forms of pepsin can be active at higher pH levels, explaining some normal pH measurements in patients with EE. This finding could be important in NERD with slightly acidic GER or in patients studied under PPI treatment.[13,14].

-Intra-individual variability, which explains why a patient or control may have pathological pH measurements on one day and normal pH measurements on another day close to it, or vice versa. This is logical, as GERD is a dynamic, unpredictable, and intermittent process that depends on multiple factors (diet, posture, transient relaxation of the LES, stress, exercise, motility, esophageal clearance, etc.)[15].

-The Lyon II Consensus[5] establishes pathological GER values as pH < 4 for > 6% of the recording time (24 hours). Until then, pathological values had been considered to be percentages of > 4%, > 5.5% (with a borderline between 3.5-5.5%)[10,16] or a DeMeester score ≤ 14.72[17]. Therefore, studies have considered what constitutes pathological or normal GER in very different ways. Thus, the frequencies of tNERD and fNERD have varied widely depending on the method, timing, reference, and researcher considered.

-It is an invasive test, uncomfortable for the patient, time-consuming, expensive, and, most importantly, not available in many hospitals, such as regional hospitals.

One last step: evaluating the condition of the esophageal mucosa.

The final diagnostic test to consider in GERD is the histological study of esophageal biopsies, a procedure that has been minimized in recent decades but whose usefulness has been revived in recent years. The esophageal mucosa, composed of a partially keratinized stratified squamous epithelium (similar to that of the skin), has three layers: 1) The most superficial, luminal, or functional layer is the stratum corneum. 2) The middle layer, or prickle layer, contains cells that, joined by desmosomes, differentiate and migrate toward the functional bed.[18]. 3) The deepest layer, the basal or germinative layer, is where the dividing cells are found, which will subsequently renew the epithelium. Although the study of the esophageal mucosa under an optical microscope (OM) is long-standing, it was not until the early 1970s that several elementary alterations related to GER-induced damage were reported. After extensive and prolonged debate, recent studies have concluded that there are no lesions or sets of lesions exclusively induced by GER[19] as they lacked specificity (basal layer hyperplasia, papillary elongation, and intraepithelial lymphoid inflammatory infiltrate) and/or sensitivity (erosions/necrosis, intraepithelial neutrophil and eosinophil infiltrates) necessary for a correct diagnosis of microscopic GERD or microscopic esophagitis (ME)[12,16,20-23]. However, it should be noted that many of the differences between the various studies are methodological in nature[24]: small number of patients, different criteria for defining GERD, sporadic performance of upper GI endoscopy and/or pH-MII, poor selection of the control group (which would include a correct definition of GERD, practice of upper GI endoscopy, pH-MII, and even manometry), "patchy" distribution of lesions (requiring multiple biopsies), reproducibility of observation (inter-observer variations), and absence of a PPI "washout" period (≈ 4 weeks), definition of the number and location of biopsies (recommended to take them at the squamocolumnar junction or "Z" line or, better still, in the 2 cm most proximal to it, at 3 o'clock and preferably in reddened areas)[25-29], correct orientation of biopsies (essential for evaluating basal layer hyperplasia and papillary elongation). Some parameters accepted as an expression of GER damage are not sufficiently agreed upon (pathological limits of ≥ 15% basal layer hyperplasia and ≥ 2/3 of total thickness in papilla elongation have been considered excessive[19,20,30-35]). Finally, quantitative methods, such as those proposed by Zentilin *et al*[16]. and the EsoHisto Project, are time-consuming.[20,22].

All these are reasons why, although they continue to be used in daily practice, the parameters on which the histological diagnosis of GERD is based are being questioned.

The discovery of intercellular space dilations (ISDs)

In the late 1970s, having previously observed them in experimental studies[36], Poppe in 1978 [37] y Hopwood en 1979[38] described, for the first time in humans, alterations under the electron microscope (EM) that they considered to be the result of the damaging effect of GERD on the esophageal mucosa. These were intercellular space dilations (ISDs), more apparent in the basal layer and, to a lesser extent, in the squamous and spinous layers. These findings were subsequently confirmed in 1996 by Tobey et al.[39], using transmission EM and a laborious measurement method (Figure 3). They found that ISD had a mean maximum diameter ≥ 2.4 µm in 73% of the 11 patients with heartburn (vs. 0% in 13 controls, 0.46 µm), with no significant differences between those with EE (55% of patients, 0.80 µm) or NERD (45% of patients, 1.0 µm); perhaps due to the small number of cases evaluated and the fact that in those with EE, the biopsy was taken from non-lesioned areas (always in the most distal 5 cm). The sensitivity of the procedure for differentiating GERD from controls, based on a value of ≥ 2.4 µm, was 73%, and the specificity was 100%. Subsequently, it was

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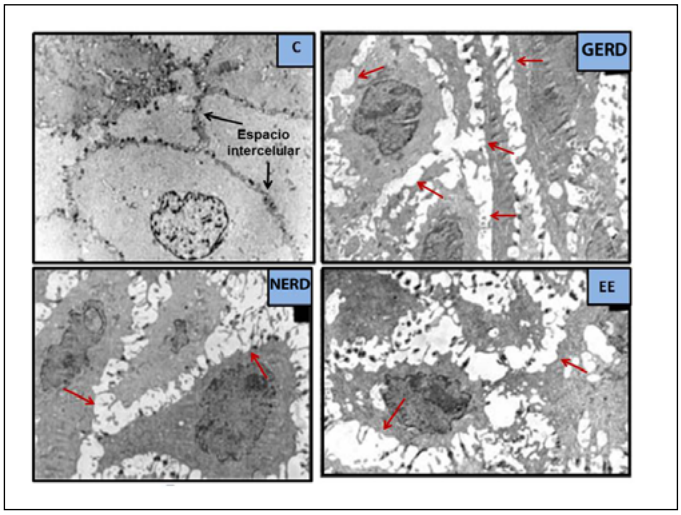

Figure 3. ***Dilatations of Intercellular Spaces on EM (modificado de Calabrese et al.[76], 2003. ISD = eaded formations, white on EM, indicated with red arrows. They are absent in the asymptomatic control subject [C] and present in patients with severe heartburn [GERD], non-erosive GERD [NERD], or erosive GERD [EE]).***

confirmed that, in healthy asymptomatic men, the intercellular space analyzed in the surface layer or stratum corneum is narrower and more variable, between 0.45-0.56 µm, than in the other two deeper layers[40,41] (Table 1). The group led by Tobey *et al.*[39] postulated that these ISDs would be the result of greater paracellular permeability to acid, a consequence of the damage induced by acid in the membranes of epithelial cells, worsening sodium transport and causing water to accumulate in the intercellular space[36] (Figure 4). If the mechanisms that cause the lesion are balanced with those of repair, there will be no lesion (NERD); on the contrary, if the former exceeds the latter, EE[41]will appear. It has been found that ISDs are more frequent in Barrett's esophagus vs. EE[42] and in EE vs. NERD, so they could be considered early signs of esophagitis or the

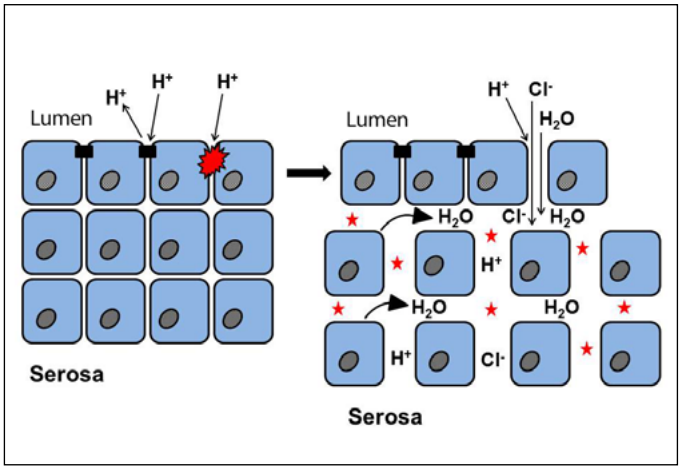

Figure 4. ***Rupture of intercellular protein junctions (tight junctions, adherens junctions, and desmosomes) by concentrated intraluminal acid (H+), decrease in mucosal resistance (impedance), and increase in paracellular permeability. The parallel entry of high concentrations of Cl- into the intercellular spaces induces an osmotic gradient, which draws water into them, causing them to dilate; these are the ISDs (asterisks). Figure created by the author.***

intensity of mucosal damage. In this regard, measuring ISDs could be useful in recognizing which NERD could progress to EE, as it is known that approximately 15-89% of patients with NERD can progress to EE within 4-10 years, although regressions have also been detected over time[43-47].

2. Experimental studies of GERD: pathophysiological findings of reflux-induced mucosal damage.

Experimental studies have shown that exposure of the esophageal mucosa to acid causes an increase in the potential difference of the mucosa, which then gradually decreases until it reaches zero. At the onset of GER-induced aggression, and as long as it is not very intense and repetitive, ISDs appear, and subsequently, if the aggression persists, endoscopic lesions appear[36,38]. In this sense, ISDs would be a very early histological manifestation of microscopic esophagitis (ME). The cells of the esophageal mucosa are bound together by a triple protein complex: 1) claudins and occludins in tight junctions, 2) e-cadherin in adherens junctions (AJs), and 3) desmoglein and desmocollin in desmosomes[18,48,49]. When these junctions fail due to the effect of acid, ISDs appear as the intercellular membranes separate. At this point, the resistance of the mucosa decreases and permeability to luminal contents increases via the paracellular route, rather than the transcellular route. Two conditions are necessary for ISD to occur: 1) high concentrations of H+ that break the epithelial barrier and increase paracellular permeability, and 2) high concentrations of Cl- that diffuse through these breaks into the intercellular spaces and give rise to an osmotic gradient that draws water into them, dilating them[50] (Figure 4). ISDs do not appear with sulfuric acid, as SO4- ions are too large to penetrate intercellular spaces and create an osmotic gradient. One study[41] showed that ISDs are not uniformly distributed, preferentially localizing in the upper part of the squamous epithelium.

In addition, alterations in desmosomes were related to the intensity of GER-induced damage, although the expression of claudins 1 and 2 was similar in patients with EE, NERD, and controls. They suggest that desmosome damage is related to the appearance and size of ISDs. In contrast, another study, also investigating the distribution of various intercellular junction proteins such as occludin, claudin-1, claudin-2, zonula occludens-1, and zonula occludens-2 in patients with EE and NERD, observed only overexpression of the two claudins in EE, although without correlation with the presence and size of ISDs. ISDs, especially those seen in the lower half of the mucosa, have also been linked to eosinophil and/or neutrophil infiltration, as well as to the loss/alteration of the glycoconjugates that seal the intercellular spaces. Following immunohistochemical analysis using CD-15 monoclonal

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Study	Type of observation	Intercellular space dilation (ISD)					
		Ø Mean or maximum ISD (µm)			% of patients with ISD		
		NERD	EE	Control	NERD	EE	Control
Tobey'96[39]	EM (Bx ≤ 5 cm). Cut-off Ø maximum 2.4 µm (SS-SP: 73-100%) (13C,6EE,5NERD)	1.0 ± 0.2	0.8 ± 0.1	0.5 ± 0.1*	80	67	0
Calabrese´03[76]	EM (Bx 5 cm; PPIsW 2 weeks) Cut-off Ø average 0.74 µm (12C,11EE,17NERD)	2.2 ± 0.5	2.4 ± 0.4	0.6 ± 0.1*	100	100	0
Caviglia´05[78]	EM (Bx 5 cm; PPIsW 3 weeks) Cut-off Ø average 0.47 µm (7C,9NERDpH+,11FH)	pH+: 1.49 pH-: 1.45	-	0.45*	pH (±) 100	-	14
Vela'11[85]	EM-morphometry (Bx 5 cm. PPI refractories) Cut-off Ø average 0.68 µm (11C,15EE+NERD+RH, 11FH)	0.87		0.32* (PF: 0.42)	Cut-off > 0.68 µm: 60% ERGE vs. 9% PF		
Solcia'00[52]	EM+OM (Bx 2-3 cm) Qualitative changes (12C,22EE,44NERDpH+)	DEI: SS: 72%: ESP: 92%			68	90	8
Villanacci´01[84]	OM-semi-quantitative (0-3) and morphometric (ISD area). (Bx 3 cm) (14EE,7NERD)	272 µm2	278 µm2	-	71	100	-
Armstrong´03[93]	OM (Bx GEJ y 2 cm) Cut-off Ø maximum 2.4 µm	-	-	-	UGE 77 2cm 41	UGE 96 2cm 66	-
Vieth´04[28]	OM 44-Pirosis + red spots on endoscopy	-	-	-	Red spots: 91	56	
Bove´05[71]	OM (10C,7EE,10NERD): before vs. after 30 minutes of acid perfusion	-	-	-	80 vs 70	86 vs 86	22 vs 44*
Zentilin´05[16]	OM (Bx 2-4 cm. PPIsW 2-4 weeks). Semi-quantitative (20C,48EE,59NERDpH+, 12FH)	ISD: SS: 86%: SP: 70'%			83 (pH+) 67 (pH-) 80 (pH ±)	94	30
Takubo'05[35]	OM (38C,69EE,49EsC, 16Autopsy)	-	-	-	EsC 33 Autopsy 0	48	21
Cui'11[79]	OM-morphometry + EM (Bx 2-3 cm) OM and EM correlation (r=0.60) Cut-off Ø average 0.85 µm (SS-SP: 93-100%) (42C,61NERD,58EE)	1.07 ± 0.3	1.29 ± 0.2	0.58 ± 0.16*	-	-	-
Savarino'13[83]	OM (Bx 2 cm. PPIsW 2-4 weeks) (20C,22tNERD,20RH, 20EE,15FH)	-	-	-	tNERD 95 RH 70 FH 33	95	25

Table 1. ***Main studies that have evaluated intercellular space dilation (ISD) (* significant vs. control; Ø = mean or maximum diameter, in µm; EM = electron microscope; MO = optical microscope; NERD = non-erosive GERD; tNERD = "true" non-erosive GERD or with positive pH measurement; EE = erosive GERD; C = control; RH = reflux hypersensitivity; FH = functional heartburn; Bx = biopsy; PPIsW = PPIs washout; SS-SP = sensitivity-specificity; GEJ = gastroesophageal junction; EsC = esophageal carcinoma.***

antibodies against these glycoconjugates, an alteration in these glycoproteins was observed, with loss of their normal laminar and compact pattern. These changes are most evident in the upper half of the mucosa and possibly represent an early alteration in mucosal barrier function, prior to mucosal injury, in response to external aggression. They may be focal or subtle, and therefore undetectable in a routine histological study[52]. EIn more severe cases, along with mucosal injury, these

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findings are also seen in the deeper spinous layer and even in the basal layer. Solcia *et al.*[52] assert that the irregular and peculiar shape of ISDs makes them easily identifiable by OM, so a simple qualitative assessment would be a good alternative to more complex morphometric studies by EM/OM[39] (Figure 5). The acid is initially neutralized by the bicarbonate present in the medium, but there comes a point when this is insufficient to neutralize the aggression, resulting in two events: 1) The receptors of chemosensitive nociceptive neurons (sensitive to acid and/or alkali) are activated, sending signals via the spinal cord to the brain, which are perceived centrally as symptoms (heartburn)[53].

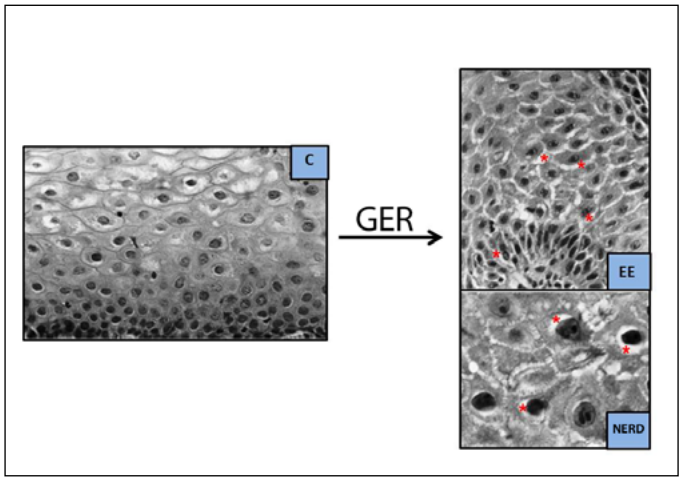

Figure 5. ***Dilatation of intercellular spaces on OM (modified from Solcia et al.[52], 2000. H&E staining, magnifications x350 [C and EE] and x900 [NERD]. ISDs marked with asterisks).***

The receptors of nociceptive neurons, such as the transient receptor potential vanilloid subtype 1 (TRPV-1) receptor and acid-sensitive ion channels (ASIC), are located in the sensory nerve endings of the esophageal mucosa and respond to changes in pH, even if there is no injury[39,54-58]; that is, as is characteristic of GERD, there may be symptoms without injury. 2) Acidification of the intercellular space exposes the basolateral membrane to acid, leading to cytosolic acidification, changes in cellular osmoregulation, edema, and cell death[59,60]. In another experimental study, Tobey *et al.*[61] found that ISDs allowed the passage of molecules the size of 20 kD dextran, favoring the entry of salivary EGF (6 kD) into the basal layer, promoting its regeneration and repair. The consequence of this entire process would be the appearance of a microscopic marker of damage/repair, such as basal layer hyperplasia. The presence of ISDs has also been confirmed in adult patients with microscopic lymphocytic or eosinophilic esophagitis[63,64], in children with eosinophilic esophagitis[64], food allergies, and even stress, as well as in experimental studies involving exposure of the esophageal mucosa to acid, bile, alcohol, ASA, or *C. albicans* infection[65-67]. In the case of stress, mechanisms similar to those observed in the skin or lower digestive tract are involved, with an increase in mast cells in the submucosa[67-70].

The appearance of ISD in healthy humans following the harmful infusion of an acidic solution with a pH of 1[71] has also been confirmed, and the harmful role of bile in the development of EE and Barrett's esophagus has been demonstrated[72]. The classic experimental study in rabbits by Farré *et al.*[66] demonstrated the early tissue damage caused by bile, by verifying the appearance of various functional alterations in the mucosa: a decrease in transepithelial electrical resistance (TER), increased permeability, and, finally, the appearance of ISD after contact of the esophageal mucosa with bile together with a weak acid (pH = 4-7, similar to that found in patients treated with PPIs) and, to a greater extent, than when only acid was used. Furthermore, in human volunteers, the appearance of ISDs after infusion of solutions of different acidity/alkalinity into the esophagus was very rapid, at 50 min (30 min of perfusion + 20 min of waiting, before taking biopsies), affecting both the infused area and the proximal areas. However, this harmful infusion was not accompanied by symptoms, so in "some NERD," these could be caused by factors other than ISD (could they be fNERD?), perhaps through substances such as TRPV-1, ASIC, and purinergic P2X P2X[56,57,73]receptors.

3. Clinical research on ISDs in humans (Table 1).

First studies of ISDs under the electron microscope (EM)

A few years after the study by Tobey *et al.*[39], in 2000, Enrico Solcia's group[52] reported the existence of ISDs under the EM in 90% of patients with EE, 68% of patients with NERD, and 8% of asymptomatic controls. Although ISDs are more common in the distal esophagus and deeper layers, they can also be seen in the proximal esophagus, with stable alterations over time[74,75]. ISDs have the great advantage of not requiring correct sample orientation, presenting greater sensitivity than inflammatory infiltrates. In 2003, Calabrese *et al.*[76], confirmed Tobey *et al.*'s[39] findings in a study of EM, finding no differences between patients with acid GERD vs. biliary GERD (measured by Bilitec®), or those with NERD vs. EE. Patients were evaluated symptomatically and by performing upper GI endoscopy, pH monitoring (in the classic study by Tobey *et al.*[39], pH monitoring was not performed), and histology.

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The importance of performing pH monitoring on the control group was justified by the exclusion of two asymptomatic subjects, initially part of the control group, who showed pathological pH monitoring and ISD. They claim that the best parameter for evaluating ISDs was their mean diameter (Ø), rather than their maximum diameter, with a cut-off value of Ø between controls and patients of 0.74 µm (vs. 2.4 µm maximum diameter, according to Tobey *et al.*[39]). All controls had a significantly lower Ø than patients with GERD (< 1.69 µm vs. 9.36 µm). In the same year, Vieth *et al.*[77] demonstrated the importance of taking biopsies from the right location. They found ISD at OM in NERD and EE in 77% and 96% of samples taken at the gastroesophageal junction and 41% and 66% in samples taken 2 cm from it, respectively. They recommend that if red spots, precursors of erosions, are found in the esophageal mucosa, biopsies should be taken from these spots, as ISD was detected there in 90.5% vs. 56.1% in macroscopically normal areas. They conclude that ISD assessment should be incorporated into the routine histological study of the esophageal mucosa in relation to GER-induced damage. Subsequently, in 2005 *et al.*[78] observed that the Ø of ISDs in NERD, both with pathological and normal pH monitoring, was three times greater than in controls: 1.49 µm if pH monitoring was pathological and 1.45 µm if pH monitoring was normal vs. 0.45 µm in controls (p<0.001), similar to what was observed with the mean maximum diameters (3.78 µm vs. 1.6 µm; p<0.001), and with no differences between NERD with pathological and normal pH monitoring. They consider ISD to be a characteristic alteration of NERD, a marker of GERD symptoms and an expression of a decrease in mucosal resistance, regardless of the pH monitoring result.

Study of ISDs under an optical microscope (OM). Diagnosis of microscopic esophagitis (ME).

Following the first report by Solcia[52] in 2000, the group led by Zentilin *et al.*[16] once again highlighted the importance of the OM, emphasizing the diagnostic value of classic elementary lesions induced by GER, to which they added the evaluation of ISDs. They developed a global scoring system for biopsies taken in a "Z" line, 2 and 4 cm more proximal, in 135 patients with atypical and atypical GERD symptoms. The six elementary lesions analyzed were: basal layer hyperplasia, papillary elongation, ISD, intraepithelial infiltration of eosinophils and neutrophils, and the presence of necrosis/erosion, which they evaluated in 20 controls, 48 EE, 59 NERD, and 12 fNERD (RH+FH). They conclude that histological studies at the OM are a good procedure for detecting the existence of GERD, since microscopic esophagitis (ME) was observed in 84% of GERD vs. 15% of controls (p<0.00001), with a significant correlation between the overall histological score and the percentage of time with pH<4 (r = 0.43, p<0.001), indicating that ME was mainly due to GER. The sensitivity for the diagnosis of GERD was 84%, comparable to the classic studies by Ismail-Beigi et al.[19] and Behar *et al.*[30], with a specificity of 85% (in other studies, the specificity of the diagnosis of GERD with data obtained by OM ranged from 27-78%)[31,32].

They reported that, in total NERD, ISDs had a diagnostic value similar to that of basal layer hyperplasia (found in 83% and 92%, respectively). Sensitivity in the set of histological lesions evaluated was 96% in EE, 80% in tNERD, 58% in fNERD (76% in total NERD) vs. 30% in controls. It can be assumed that, in the few cases of FH (normal upper GI endoscopy and normal pH monitoring) with histological lesions, the symptoms could be caused by weakly acidic, non-acidic, or alkaline reflux. This group also states that the use of histology is more cost-effective than pH monitoring, which is burdened by an unacceptable number of false negatives in EE[8,10-12].

In 2009, the same group obtained similar results and conclusions in another study at OM[24], confirming that the existence of ISD had a sensitivity-specificity of 80%-70%. The frequency of these lesions was 94% in EE, 83% in NERD, 67% in fNERD, and 30% in controls[16]. This group recommends that biopsy samples be taken along the "Z" line or within 2 cm proximal to it, as the frequency of all elementary lesions evaluated decreases proximally. However, an explanation must be given for the high percentage (30%!) of ISD in controls. The selection of a control group requires that subjects be strictly asymptomatic at the time of the study and prior to it, that they have not taken PPIs in the previous 4-6 weeks, that their upper GI endoscopy be normal (Los Angeles: N or A), that their pH monitoring be normal, and that their EM be negative. These criteria are almost never met in almost any study, making it difficult to compare results. What does it mean that 30% of the control group has ISD? It has been proven that there is physiological GER, which could cause mild histological alterations, especially in the "Z" line or a few cm more proximally; that is, it could be accepted that a control had mild histological lesions (Los Angeles M or A?) and only in the most distal part of the esophagus (≤ 2 cm?). The criteria that a control subject must meet for studies related to GERD may be more or less strict, but today, this is still a matter of debate, although not without interest. In a recent and excellent study using OM-morphometry and EM, the Chinese group of Cui *et al.*[79] verified the diagnostic validity of ISD in GERD, with good Kappa consistency (k = 0.691) and correlation (r = 0.605) between the measurements obtained by OM and EM, with significantly higher OM Ø values in 58 patients with EE and 61 with NERD vs. 42 controls. The cut-off for ISD Ø values, which differentiated NERD from controls, was 0.85 µm (sensitivity 93%, specificity 100%) (Tabla 1). Despite the obvious

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advantages of OM studies over EM studies, the former have a limitation in resolution, as only ISDs ≥ 0.2 µm are visible, which would therefore be the minimum size of ISD quantifiable with OM. Few studies have been reported on the presence of ISDs in children with symptoms suggestive of GERD or eosinophilic esophagitis[64].

The first study was that of Ravelli *et al*[80]. in 2006, conducted with OM in 48 children with EE. Their results were similar to those obtained later, in 2012, by the group of Mancini *et al*.[81], who evaluated the presence of ISD using EM in 20 children with EE and 24 with NERD vs. 10 asymptomatic controls. They found that the size of the ISDs was significantly greater in cases of EE and NERD vs. controls (values of Ø ± SD: 1 ± 0.2 mµ and 0.9 ± 0.2 mµ vs. 0.5 ± 0.2 mµ), although there was no relationship between the diameter of the ISDs and the various parameters evaluated in pH monitoring, nor with their consideration as pathological or normal. They conclude that, in children, ISDs are also an early and sensitive marker of mucosal damage induced by GER, without being able to differentiate between the two GERD phenotypes or correlate with pH monitoring results. In 2014, the same group led by Borreli *et al*.[82] studied children with chronic cough (15 patients vs. 12 controls), suggestive of being caused by GER, using pH monitoring and an evaluation of ISDs with EM. They point out the importance of quantifying ISD in these cases as an expression of acid-induced mucosal injury, although their presence and diameter were not related to any of the pH monitoring parameters, whether pathological or normal.

4. Methodology for quantifying the presence of ISD.

Approximately ≥ 2/3 of patients with NERD have histological alterations compatible with ME, one of which is ISD[83]. Various studies, either using OM or EM, have evaluated the quantification of ISD in order to better discriminate between the values of different GERD phenotypes and asymptomatic controls. Solcia *et al*.[52] attempted to quantify (presence/absence) ISD using ultrathin sections (0.5-1 µm), but their results were inconclusive (ISD: 72% of patients vs. 8% of controls. Sensitivity 72%, specificity 92%), making it impossible for them to distinguish cases with mild esophagitis from controls. Other studies have also attempted to quantify ISDs using quantitative, semi-quantitative, and even morphometric and automated procedures, both in proximal and distal biopsies (2, 5, and 10 cm more proximal from the "Z" line). In reality, EM studies are satisfied with the arduous task of taking multiple measurements (10 measurements x photo, in 10 photos = 100 measurements per patient) and using the mean diameter (Ø) parameter as a comparison value.The complexity of this procedure explains the small number of patients included in studies of ISDs at EM. However, it is studies at OM that have provided a more practical, albeit complex, approach to quantifying ISDs[12,16,67,76,84]. One example is the sophisticated method recently developed in the EcoHisto Proyect[20,22], study, which proposes a detailed process for quantifying ISDs, defined as rounded and irregular dilations or diffuse widening of the intercellular space (at 40x magnification). Initially, they were quantified as 0 = absent, 1 = small, and 2 = large or very large, and later redefined in a more detailed but also more complex way (Table 2). Clinical practice requires the use of the first attempt. Almost all studies conclude that EM studies are superior in the assessment of ISDs, a procedure they consider to be the "gold standard," as there is no overlap between the data from patients and those from the control group. In any case, the results obtained with quantitative tests (86% sensitivity) are preferable to semi-quantitative tests (with lower specificity). However, they also recognize that EM studies are very exclusive, expensive, and time-consuming, which makes them of little or no use in clinical practice.

Score	Simple formula	Complex formula
0	Absent	≤ 5 small*
1	Small	≥ 6 small + ≤ 5 big**
2	Large or very large	≥ 6 large
ISDs can be recognized under the microscope (x40) as rounded, irregular dilations or as a diffuse widening of the intercellular space (Figures 5-8). * Small ISD = Ø < lymphocyte size ** Large ISD = Ø ≥ lymphocyte size		

Table 2. ***Recognition and evaluation of Intercellular Space Dilatations (ISD) using OM[20].***

5. Usefulness of ISD in the diagnosis of Functional Heartburn.

The distinction between EE and NERD is straightforward after performing an upper GI endoscopy, but not so between tNERD and fNERD (RH and FH, functional disorders of the esophagus, according to Rome IV criteria[7]), since their diagnosis requires pH monitoring and assessment of GER symptoms/episodes using SAP/SI. This is where the diagnostic procedure for GERD is "blocked." What to do after performing an upper GI endoscopy: 1) pH monitoring with the aforementioned drawbacks, or 2) a more accessible and less expensive histological study, even with the lack of specificity of the elementary lesions mentioned or the difficulty in studying some of them (correct orientation). It is necessary to separate tNERD, whose treatment is basically antisecretory, from

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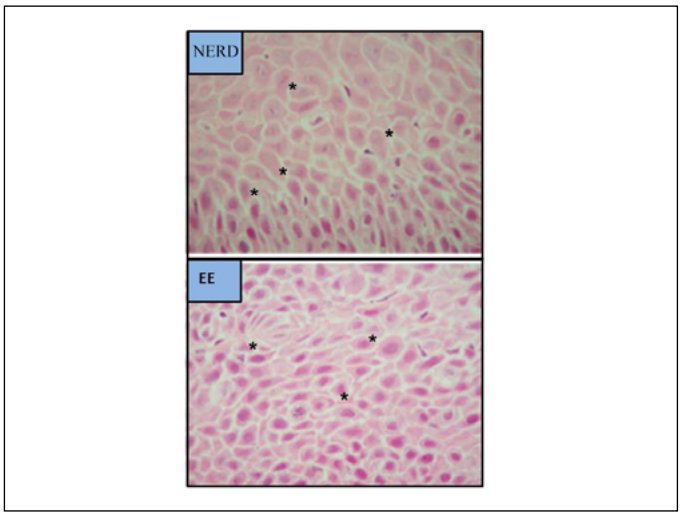

Figure 6. ***Dilatations of Intercellular Spaces on OM (modified from Kandulski et al.[21], 2013. H&E staining, magnification x400. ISDs marked with asterisks).***

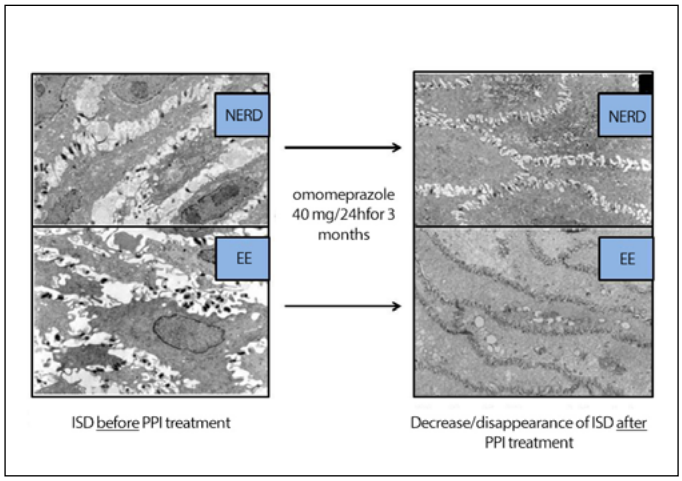

Figure 7. ***Improvement/disappearance of ISDs on OM in patients with GERD and EE after treatment with omeprazole (40mg/24h/3 months) (modified from Calabrese et al.[86], 2005) .***

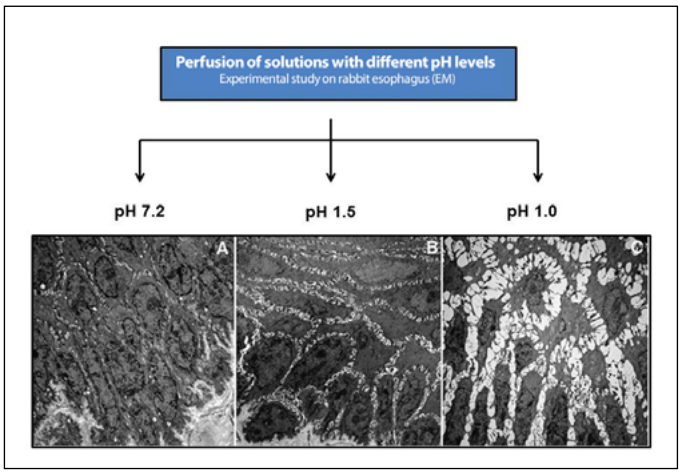

Figure 8. ***Appearance of ISDs after damage induced in the esophageal mucosa by perfusion of acidic solutions of different pH (modified from Farré et al.[98], 2011. Experimental study in rabbits).***

fNERD, where neuromodulatory or neuroleptic drugs may be necessary, associated or not with PPIs (especially in RH).Vela *et al.*[85] studied EM in patients refractory to PPIs, the difference in ISD size in EE + NERD (tNERD + RH, n=15), FH (n=11), and 11 controls, noting significant differences between their respective values (0.87 µm vs. 0.42 µm vs. 0.32 µm) ; showing ISD in 60% of EE + NERD vs. 9% of controls (p<0.01). The upper limit of the normal ISD value in controls (95% percentile) was 0.68 µm (cut-off); with similar values in controls and FH (p=ns). In other studies, the mean Ø value of ISD in controls ranged from 0.47 µm to 0.85 µm[76,78,79] and the mean maximum diameter value was ≤ 2.4 µm[39] (Table 1).

Therefore, they state that these ISD values could be used to differentiate patients with PPI-refractory GERD from those with FH (PPI-refractory patients are those who obtain partial symptomatic relief and <50% after 6 weeks of treatment with double-dose PPIs)[85,87]. Up to 40% of patients with GERD symptoms treated with PPIs have a negative response, which may be due to insufficient inhibition, the presence of RH (symptoms, even with high pH after PPI inhibition) or FH. In this regard, Kandulski*et al.*[21] attempted to analyze the histological differences between patients with NERD (10 tNERD + 10 RH), EE (n=23), and FH (n=19), all of whom were refractory to PPIs, using a semi-quantitative assessment of three lesions (ISD, papillary elongation, and basal layer hyperplasia) and comparing their data with 25 controls (Figure 6). No differences were observed between groups in terms of the symptoms evaluated according to the RDQ questionnaire, but there were differences between the overall histological score and the ISD values of patients with NERD (whether considered globally as tNERD + RH or individually) vs. FH and controls (p<0.0001). The ISD value in FH was 0.75 µm vs. 1.75 µm in NERD (controls 0.72 µm). The respective values of the overall histological score were 3.8, 6.3, and 3.3 (p<0.0001). In addition, they found a weak correlation between the presence of ISD and acid exposure time (% of time with pH<4) or number of episodes of acid or gas reflux, concluding that histological examination can differentiate from FH in patients refractory to PPIs. The ROC curve study showed a cut-off ≥ 5 for the overall histological score that differentiates NERD from FH (sensitivity-specificity of 83%-64%). A similar study also demonstrated the validity of histological examination in differentiating between NERD and FH[83], both in the individualized score for each of the elementary lesions evaluated and in the overall score. They considered that an overall histological score ≥ 0.35 was diagnostic of ME, finding it in 95% of EE, 77% of NERD, 65% of RH vs. 13% of FH and 15% of controls (p<0.0001). Given the low frequency of ME in patients with FH (similar to controls), it could be stated with a high degree of probability that this would be the diagnosis for patients with GERD symptoms, normal pH monitoring, and no Me. The presence of ISD in these groups

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was 95%, 95%, 70%, 33%, and 25%, respectively (p<0.0001). They conclude that the good sensitivity of the histological study in the diagnosis of GERD (81%) and NERD (74%), together with its high specificity in FH (87%) and controls (85%), demonstrate its validity as a diagnostic method in GERD.

6. Relationship between GERD symptoms and ISD.

Some studies have found a correlation between the presence of ISD and GERD symptoms such as heartburn[74,78,88], regardless of the pH monitoring results[78]; improvement in ISD and symptoms has been observed after treatment with PPIs[76,88]. However, some patients with ISD continue to experience GER symptoms after acid inhibition with PPIs, which could be related to weakly acidic or alkaline GER (RH?), which is more or less persistent. The study by Tadiparthi *et al.*[90] showed that EE and NERD were not different in terms of symptom assessment (using GER-Q and RDQ questionnaires) or the presence of histological lesions. However, although there was a significant relationship between symptom scores and histological scores (specifically, the presence of ISD and lymphocytic infiltrate), this was only seen in the EE group. Therefore, we must admit that the symptoms of some NERD may be caused by factors other than ISD, perhaps, as already mentioned, by the action of substances such as TRPV-1, ASIC, and P2X purinergic receptors.[56,57,67,73].

7. Regression of ISD after antisecretory treatment.

Studies have shown that treatment with PPIs can restore ISD to normal values in >70% of patients[77,86,91,92] equivalent to antireflux surgery[33]. At OM, three elementary lesions evaluated (basal layer hyperplasia, papillary elongation, and ISD) were found to improve/normalize after antisecretory treatment, especially ISD. Thus, the study by Armstrong *et al.*[93], using esomeprazole (40mg/d/4wks) or ranitidine (300mg/d/4wks), showed an improvement/normalization of ISDs, from 76% to 53% and from 80% to 69% of patients, respectively. The group of Calabrese *et al*[86], treated 22 NERD and 16 EE with omeprazole (40 mg/day/3 months) in a study on EM, observing a disappearance of ISD and symptoms in 92% of the 38 cases. After another 3 months of treatment, in the 3 patients who did not respond, they managed to normalize symptoms and ISD in 2 of them (97.4% regression after 6 months of treatment), confirming the parallelism between symptoms and ISD (Figure 7). After 3 months of treatment, the Ø of the ISDs went from 2.04 µm to 0.54 µm in NERD and from 1.95 µm to 0.65 µm in EE, both in patients with acid and alkaline GER, all of them with pH-MII (+). The pathological ISD cut-off was ≥ 0.74 µm. Other studies did not achieve such high frequencies of lesion/symptom reversibility with PPIs, reaching only < 30%; this could be due to the short treatment time (4 weeks vs. 3 months)[86,94-96].

In fact, a recent study confirms that patients with GERD refractory to PPIs maintain ISD[89], which would suggest that the cause of ISD and/or symptoms is not acid but other refluxed substances (bile and pancreatic juice components)[66,67]. Logically, in these cases, dual pH-MII monitoring would be mandatory. On the other hand, it should be mentioned that in some studies it was not possible to perform MII as it was approved by the FDA in 2002, and instead the alkaline detector called Bilitec® was used. In the study by Ravelli et al., the presence of ISD at EM and OM was evaluated in 22 children with PPI-refractory eosinophilic esophagitis (4-6 weeks) clinically and histologically vs. 30 controls, as well as its improvement after treatment with corticosteroids and/or exclusion diets. The Ø values of ISD in patients were 2.26 ± 0.21 mµ (OM and morphometry) and 2.24 ± 0.28 mµ (EM) vs. 0.62 ± 0.08 mµ and 0.33 ± 0.24 mµ in controls.After treatment, ISD values decreased to 1.23 ± 0.20 mµ (OM and morphometry) and 0.98 ± 0.19 mµ (EM), confirming that the efficacy of the treatment is related to the reduction in mucosal damage and ISD. At this point, as a complement to the improvement/resolution of ISD after treatment with PPIs, it is interesting to note the results of an experimental study by Farré et al.97 who verified the "preventive/protective" role of antioxidant substances (NAC and Vitamin C) with respect to the appearance of ISD[12,74,78,88]. lthough, as mentioned above, a relationship between the presence of ISD and the symptom of heartburn has been suggested, this has not been clearly demonstrated, with possible pathophysiological mechanisms being suggested to explain it. If this relationship is demonstrated, ISD could be considered a marker of NERD. This is based on the following reasons: 1) they have been found in patients with NERD (normal upper GI endoscopy and pathological pH monitoring), 2) they normalize after treatment with PPIs, while symptoms such as heartburn disappear, and 3) they can be induced in healthy asymptomatic controls after esophageal acid infusion.

8. Impedance measurement, a method for evaluating esophageal mucosal function. The importance of ISD.

The evaluation of the electrical conductivity of the esophageal mucosa is a parameter closely related to its proper functioning. The group led by Farré *et al.*[66] demonstrated in experimental and human studies that the drop in basal impedance of the esophageal mucosa is related to that of the TER and damage to the esophageal mucosa induced by acidic, weakly acidic, or alkaline GER, both in erosive and NERD[98,99]. The infusion of pH 1.0 and 1.5 solutions induced decreases in basal mucosal impedance parallel to those in TER and the appearance of ISDs,[100], concluding that, in patients with GERD,

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the use of these methods may be useful in the study of GER-induced mucosal damage (Figure 8). The Chinese group of Zhou *et al.*[101] evaluated the sensitivity and specificity of five common tests in the diagnosis of GERD in 352 patients: GERD-Q questionnaire (58% and 49%), impedance measurement (66% and 43%), pH-MII (94% and 43%), ISD > 0.9 mμ (61% and 56%), and PPI response test (71% and 44%). However, none of these tests was sufficient for an individualized diagnosis. Another study of 20 patients NERD and 30 with FH found that patients with NERD had lower baseline impedance vs. FH, slower recovery of impedance after acid infusion (pH 1, for 10 min.), possibly due to repeated episodes of GER in NERD vs. FH, and greater sensitivity to acid (RH?), perhaps because the mucosa becomes more vulnerable to symptom perception during the prolonged period of recovery from baseline values[102-104]. Acidification of the esophagus can induce mast cell degranulation, activation of capsaicin-sensitive afferent neurons, and release of neurokinins. It has been suggested that these mediators could be responsible, after episodes of acidification, for the onset of ISD and the hypersensitivity demonstrated in NERD (RH?)[105].

Another Chinese group, led by Zhong[106] studied the basal impedance of the esophageal mucosa as a measure of damage induced after acid infusion in 229 patients with GERD and 34 controls. They performed pH-MII, upper GI endoscopy, GERD-Q questionnaire, measurement of ISD (OM and EM), and expression of tight junction proteins (claudin 1 and 3 and occludin). They found that baseline impedance in EE(1752 ± 1018 Ω) and NERD (2640 ± 1143 Ω) was significantly lower than in the control group (3360 ± 1258 Ω); with the cut-off point differentiating GERD patients from controls being 2167 Ω (sensitivity 94%, specificity 51%).They also observed a significantly greater decrease in mucosal impedance in NERD patients vs. controls (3360 ± 1258 Ω) after being infused with acidic solutions (2510 ± 1239 Ω), weakly acidic solutions (2801 ± 1156 Ω), and acidic/weakly acidic mixtures (2393 ± 1009 Ω). Weakly basic solutions have little effect on impedance, as already verified by Farré *et al.*[66]. There were also significant differences in the basal impedance recorded between the degrees of EE (esophagitis C and D: 970 ± 505 Ω and esophagitis A and B: 1921 ± 1024 Ω). Baseline impedance was significantly lower in GERD-Q positive questionnaires (≥ 8 points) than in negative ones (< 8 points) (2200 ± 1153 Ω vs. 2709 ± 1244 Ω). In this regard, it has also been reported that the GERD-Q questionnaire score was positively related to acid episodes measured by pH-MII[107,108].

There was a negative correlation between baseline impedance and acid exposure time (r = -0.41, p<0.001), claudin-1 levels (r = -0.65, p<0.001), but not with claudin-3 or occludin levels, and ISD size (r = -0.64, p>0.001); larger ISD were found in EE vs. NERD and controls: 1.29 mμ vs. 1.10 mμ and 1.01 mμ, respectively. The three proteins analyzed participate in the formation of paracellular ion channels and ion selection, thereby modulating paracellular conductance and relating to changes in TER and ISD[109]. TIn both humans and experimental animals, the relationship between ISD and TER (negative correlation), impedance and TER (positive correlation)[98109], and impedance and acid exposure time (negative correlation)[110] had already been proven, but in humans, this study is the first to demonstrate the inverse relationship between ISD and basal impedance[106]. Therefore, impedance measurement and ISD measurement could be very useful in the clinical diagnosis of GERD without lesions or with few symptoms, a field in which upper GI endoscopy and pH-MII are of little use. In another study on esophageal mucosal impedance, Kandulski *et al.*[111] evaluated impedance and the presence of ISD in 19 EE, 16 NERD, and 17 FH. They concluded that impedance measurement is a marker of mucosal dysfunction and integrity, as it differentiates patients with GERD (EE and NERD), with a greater drop in impedance, from those with FH. In addition, impedance values were inversely related to acid exposure time (r = -0.45, p<0.008), with a cut-off of 2100 Ω differentiating GERD from FH (sensitivity of 78%, specificity of 71%), and with the size of the ISDs (r = -0.28, p<0.06). Basal impedance is a marker of mucosal integrity, and its determination may be useful in the evaluation of patients with GERD, especially those refractory to PPIs (most FH with normal basal impedance). With current devices, esophageal mucosal impedance can be measured during the endoscopic procedure itself[112]. If the measurement is taken 2 cm from the Z-line, an impedance value > 2970 Ω excludes GERD (sensitivity 96%, specificity 88%). In a recent attempt to further refine the histological diagnosis of ME, Kataria *et al.*[113]conducted a review and meta-analysis of 2,871 studies, from which they selected 10 (8 with a control group) that met their inclusion criteria, in order to determine the most sensitive elementary lesions for the diagnosis of ME in patients with NERD (histology, ISD, normal pH measurement, and no PPI use; therefore, it includes patients with RH). The lesions evaluated were basal layer hyperplasia, papillary elongation, ISD, and eosinophil count, with biopsy samples taken at two levels: < 3 cm and ≥ 3 cm from the squamo-columnar junction. In the more distal samples (< 3 cm), the best sensitivities were for eosinophil count (91%), ISD (88%), and basal layer hyperplasia (85%). In biopsies taken at ≥ 3 cm, the highest sensitivity was for papillary elongation (84%) and eosinophil count (77%). In biopsies taken at ≥ 3 cm, the highest sensitivity was for papillary elongation (84%) and eosinophil count (77%). This study demonstrates that the combined analysis of ISD and eosinophil count in esophageal biopsies is highly sensitive for the diagnosis of ME.

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9. New procedures for detecting ISDs.

New endoscopic techniques such as high-resolution endoscopy[96,114-116], cromoendoscopia virtual ± lugol (i-Scan y FICE, Fuji Intelligent Color Enhancement), virtual chromoendoscopy ± lugol (i-Scan and FICE, Fuji Intelligent Color Enhancement), confocal laser endomicroscopy[95,117-122] or Narrow Band Imaging (NBI) with magnification[116,123] have made it possible to visualize alterations in the tissue and vessels of the esophageal mucosa more accurately than conventional endoscopy, helping to improve the Los Angeles classification system and better distinguish erosive from NERD. One study found the use of i-Scan + chromoendoscopy with Lugol's iodine useful in detecting minimal GERD lesions (mucosal micro-tears and red spots)[118-121], and in another study, FICE differentiated between grades N (normal) and M (minimal lesions: erythema without clear demarcation, whitish turbidity, and secondary invisibility of vessels) in patients with NERD[119-122]. The use of confocal laser endomicroscopy has also been useful,[120,121], revealing a greater number of interpapillary capillary loops in patients with NERD vs. controls (8.3 vs. 5.6, p<0.01. Cut-off > 6 per image, with sensitivity-specificity 68%-72%), larger diameter (19.5 vs. 15.9 µm, p<0.04. Cut-off > 17.2 µm, with sensitivity-specificity 81%-76%) and larger Ø in the ISD (3.4 vs. 1.9, p<0.04. Cut-off > 2.4 µm, with sensitivity-specificity 86%-91%), correlating with the ISD values found at EM (r = 0.75, p< 0.01). When the first and third findings were combined, specificity was 100%[121].

A new pathophysiological mechanism has recently been proposed for the formation of intercellular space dilations[126]. The adipose tissue of the GEJ in obese patients, with or without GERD, secretes substances that induce the production of free radicals, which activate HIF-2α, which, directly or indirectly, after entering the nucleus of esophageal squamous tissue cells and regulating genes associated with the innate immune response, increases caspase-1 inflammasome and, consequently, IL-1β production. This pro-inflammatory interleukin increases MLCK enzymatic activity, transforming MLC into MLCp. This MLCp causes the cytoskeleton to contract through actin-myosin activity, which, at the level of the surface cells of the squamous epithelium, decreases the function of the mucosal barrier, with an increase in permeability and the entry of solutes, ions, and water into the intercellular space. Conversely, the contraction of the cytoskeleton at the level of the basal layer of the squamous epithelium, where there are no tight junctions but rather adherens junctions, leads to the dilation of intercellular spaces (Figure 9).

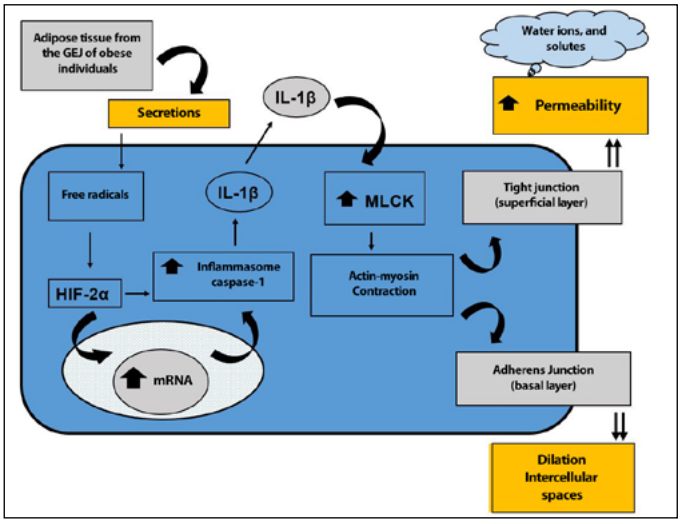

Figure 9. ***New pathophysiological mechanism proposed for the formation of intercellular space dilations. (GEJ = gastroesophageal junction; HIF-2α = hypoxia-inducible factor 2α; MLCK = myosin light chain kinase; MLC = myosin light chain; MLCp = phosphorylated myosin light chain). (Modified from: Paris S et al [126]).***

Conclusions

- ISDs are real alterations and biological markers of GERD: They do not result from biopsy manipulation and constitute the most recent biological marker of the disease while other markers are being validated.

- Relationship with mucosal damage: ISD are directly related to damage to the esophageal mucosa and appear together with a drop in impedance, an decrease in TER, and greater mucosal permeability. They are observed with both acid reflux and alkaline biliary or pancreatic reflux and do not correlate with the results of pH monitoring.

- Frequency, distribution, and early onset: ISDs are common and nonspecific in non-erosive esophagitis and are distributed preferentially in the distal five centimeters of the esophagus. They appear very soon after chemical aggression, and quantifying them beyond presence or absence is complex and time-consuming, especially in electron microscopy. Their main advantage is that they do not require precise biopsy orientation.

- Diagnostic value and comparison with other tests: In humans, ISD determination shows sensitivity and specificity comparable to pH-MII and is technically simpler. In strict reviews, ISDs appear much more frequently in patients with non-erosive esophagitis than in controls. They also frequently appear in asymptomatic controls, which may be due to non-strict control selection.

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- Measurements and observation limits: The average diameters of ISDs under electron microscopy and their prevalence under optical microscopy vary between controls and disease phenotypes. The observation limit under optical microscopy is below 0.2 microns.

- Clinical utility for differential diagnosis: Evaluation of ISDs helps differentiate EE, tNERD, and RH from FH (which behaves like controls) and allows differentiation of non-erosive esophagitis refractory to PPIs.

- Relationship with symptoms and response to treatment. The relationship between ISD and GERD symptoms is unclear. ISDs decrease or disappear after treatment with PPIs.

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REVIEW ARTICLE

MANAGEMENT OF KIDNEY FAILURE IN PATIENTS WITH ADVANCED CHRONIC LIVER DISEASE

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Abstract

The management of renal failure in patients with advanced chronic liver disease (ACLD) is crucial due to its high prevalence and associated morbidity and mortality. Renal dysfunction is classified as acute kidney injury (AKI), acute kidney disease (AKD), or chronic kidney disease (CKD), depending on duration and severity, primarily determined by serum creatinine levels, which are essential for AKI subclassification.

The main causes of AKI in ACLD fall into three categories: prerenal, intrinsic, and postrenal. Prerenal causes are the most common, with hepatorenal syndrome (HRS) as the predominant entity.

Portal hypertension is the central mechanism in the pathophysiology of renal impairment in cirrhotic patients. It induces systemic circulatory dysfunction characterized by splanchnic vasodilation, reduced effective arterial blood volume, compensatory renal vasoconstriction, cardiac dysfunction, and a proinflammatory state. These alterations can be exacerbated by precipitating factors such as volume depletion, circulatory failure, nephrotoxic exposure, and inflammatory triggers.

Early diagnostic assessment should include evaluation of intravascular volume status, renal function, and identification of precipitating factors, together with AKI phenotyping. Prompt recognition enables implementation of targeted therapeutic strategies, particularly in hepatorenal syndrome–acute kidney injury (HRS-AKI), where vasoconstrictor therapy has demonstrated significant prognostic benefit.

Keywords: advanced chronic liver disease, kidney failure.

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Introduction

Acute kidney injury (AKI) is one of the most common complications in patients with advanced chronic liver disease (ACLD), with a variable prevalence of between 27% and 53% of hospitalized patients with decompensated ACLD[1]. In general, AKI is associated with a high morbidity and mortality rate and a higher incidence of chronic kidney disease after liver transplantation. Progression to advanced stages of AKI portends a worse prognosis in cirrhotic patients[2,3]. In 2012, the Acute Disease Quality Initiative (ADQI) and the International Club of Ascites (ICA) promulgated new diagnostic criteria for AKI[4]; which were recently revised in 2023-24 given the significant advances made in this field over the last decade[5].

Definitions and classification

Currently, we define AKI as an increase in serum creatinine (sCr) ≥ 0.3 mg/dL in less than 48 hours or a percentage increase in sCr ≥ 50% from baseline in the last 7 days[6,7]. As a new criterion in the latest ADQI and ICA consensus, it is proposed to include urine output (UO) ≤ 0.5 ml/kg for ≥ 6 hours as a criterion for AKI, taking into account the difficulty of closely monitoring it and that it may be low in the initial hours of follow-up of these patients with ACLD. Even so, we emphasize the introduction of this new criterion, not so much as a diagnostic criterion, but as a criterion to be taken into account in order to detect patients with AKI earlier and thus act promptly[5,8]. In turn, AKI is staged in different degrees according to the percentage increase in sCr from baseline, which we break down in Table 1 below.

The ADQI-ICA5 consensus recommends using the lowest stable sCr value obtained in the last 3 months as the baseline value, or, if this is not possible, the lowest stable value up to 12 months prior. Monitoring the baseline sCr value will allow us to distinguish between AKI, acute kidney disease (AKD), and chronic kidney disease (CKD) (Table 1, Figure 1)[5-7,9]:

- Acute kidney disease (AKD): glomerular filtration rate (GFR) < 60 ml/min/1.73m^2 or percentage increase in sCr ≥ 50% (1.5-2 times) from baseline in ≤ 3 months. Following the definition, we can understand that AKI is a subset of acute kidney disease (Figure 1).

- Chronic kidney disease (CKD): glomerular filtration rate (GFR) < 60 ml/min/1.73m^2 persisting for > 3 months. Within this, episodes of acute renal dysfunction may occur, which we must act on.

Etiology and pathophysiology of kidney disease

Main etiologies:

We can define three main groups as causes of AKI in cirrhotic patients, which may coexist in the same patient[3,10,11]:

- Prerenal: caused by renal hypoperfusion, it is the most common cause of this dysfunction in cirrhotic patients. Noteworthy etiologies in this group include hypovolemia (27-50% of cases) and hepatorenal syndrome (15-20%.

- Intrinsic: resulting from direct damage to the renal parenchyma. The main etiological factor in this group is acute tubular necrosis (ATN) (14-30%), which can occur in cases of hypovolemic or septic shock or also due to the direct action of nephrotoxic drugs or iodinated contrast media. Other processes to consider are those that lead to acute interstitial nephritis (AIN), such as: biliary acid nephropathy, glomerulonephritis (IgA-mediated in alcoholic patients or membranous/membranoproliferative in cirrhotic patients with HBV/HCV).

- Postrenal: this includes processes that cause obstruction of the urinary tract (lithiasis, tumors, etc.). It usually occurs in less than 1% of cases.

Hepatorenal syndrome:

Hepatorenal syndrome (HRS) is a phenotype of prerenal AKI that occurs in patients with ACLD and ascites, characterized by impaired renal function secondary to reduced renal perfusion due to hemodynamic alterations in arterial circulation and hyperactivity of endogenous vasoactive systems. Systemic inflammation contributes to the neurohumoral and vasodilator disorders that give rise to this type of renal dysfunction, which is persistent with volume expansion therapies and may be reversible with vasoconstrictor therapy[12-14]. It is therefore essential that in all patients with ACLD and ascites who present with AKI, we carry out an adequate and rapid evaluation and differential etiological diagnosis in order to ensure timely etiological recognition and management, always taking into account the possibility of coexisting causes of AKI[3,5,12]. Currently, following the latest consensus reached, we can discard the old concepts of type 1 and type 2 HRS, which have been replaced by the terms HRS-AKI, HRS-AKD, and HRS-CKD, whose diagnostic criteria are outlined in the following table (Table 2)[5]:

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Concept	Definition
Baseline sCr	Lowest stable sCr value obtained in the three months prior to the event if this is not possible, the lowest stable value in the previous twelve months.
AKI	Increase in sCr ≥ 0.3mg/dl in less than 48 hours or percentage increase in sCr ≥ 50% from baseline in the last 7 days and/or urine output ≤ 0.5ml/kg for ≥ 6 hours
AKI 1	Increase in sCr ≥ 0.3mg/dl and/or increase 1.5-2 times above baseline AKI 1A: sCr < 1.5 mg/dl at diagnosis AKI 1B: sCr ≥ 1.5 mg/dl at diagnosis
AKI 2	Increase in sCr > 2-3 times above baseline
AKI 3	Aumento de sCr > 3 veces respecto al valor basal o Increase in sCr > 3 times baseline or Scr ≥ 4mg/dl together with acute increase ≥ 0.3mg/dl and/or initiation of renal replacement therapy
AKD	GFR < 60 ml/min/1.73 m^2 or percentage increase in SCR ≥ 50% (1.5-2 times) from baseline in ≤ 3 months
CKD	GFR < 0 ml/min/1.73 m^2 or percentage increase in SCR ≥ 50% (1.5-2 times) from baseline over > 3 months

Table 1. ***Definitions and criteria for kidney disease according to the ADQI-ICA consensus.***

The following aspects of these new diagnostic criteria should be highlighted in comparison with those previously established[5,15-17]:

- Assessing response to volume expansion with albumin over 48 hours: this criterion is excluded because in euvolemic patients or those with intravascular fluid overload, 48 hours of albumin infusion can be harmful, promoting fluid accumulation and delaying diagnosis and initiation of vasoconstrictor therapy.

- No improvement in renal function despite adequate volume expansion for 24 hours: it is recommended to assess the patient's volemia status for 24 hours with adequate intravenous fluid infusion, either balanced crystalloids (Ringer's Lactate or PlasmaLyte) or 20% albumin solution at a rate of 1 g/kg of weight (maximum 100 g per day), depending on the patient's clinical condition. If there is no improvement in sCr within 24 hours, a diagnosis of HRS-AKI should be considered.

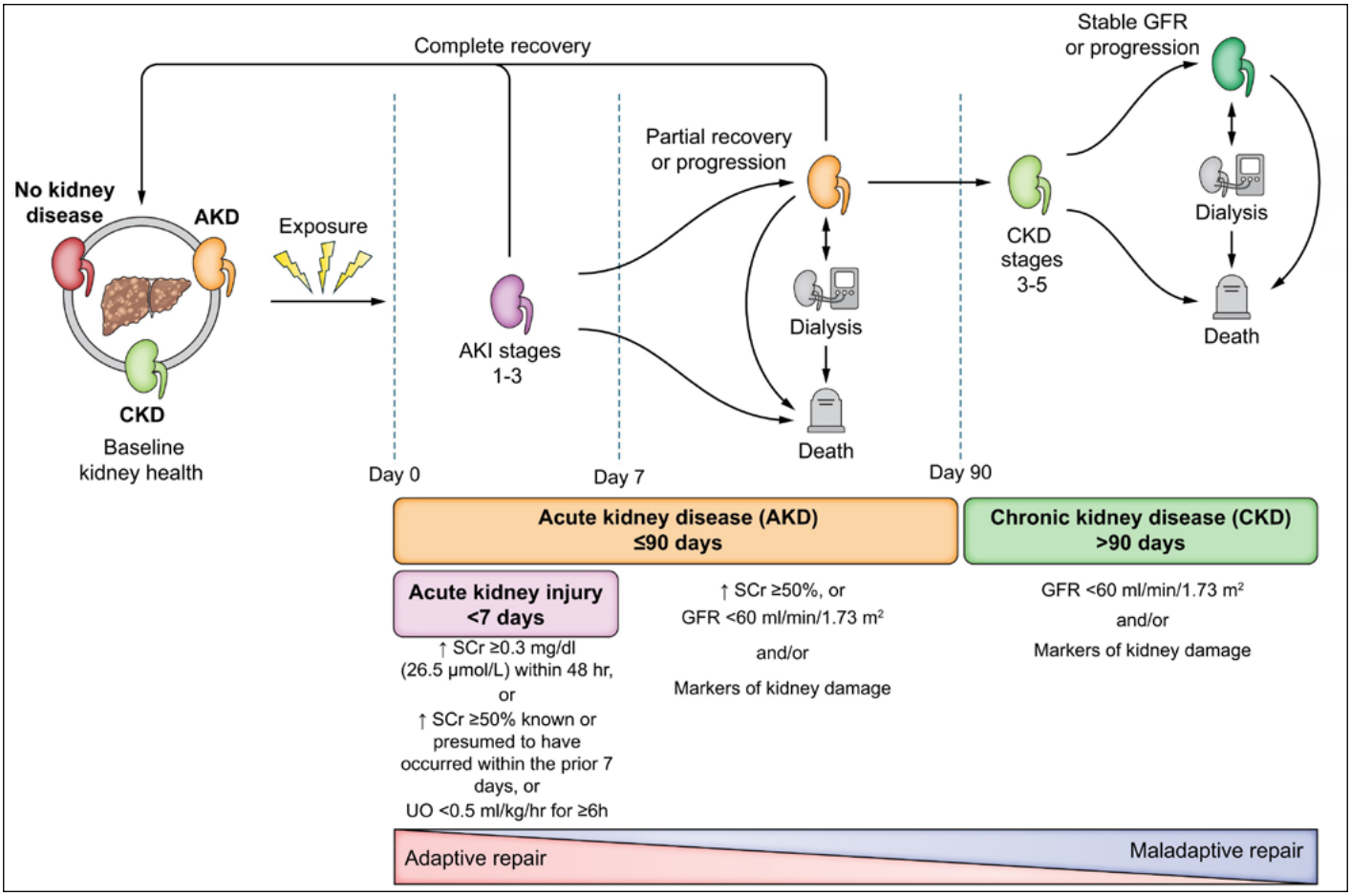

Figure 1. ***Progression of kidney dysfunction in patients with advanced chronic liver disease. Extracted from: Nadim MK, Kellum JA, Fomi L, et al. Acute kidney injury in patients with cirrhosis: Acute Disease Quality Initiative (ADQI) and International Club of Ascites (ICA) joint multidisciplinary consensus meeting. J Hepatol. 2024; 81: 163-83.***

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- Coexistence of other etiologies: the presence of underlying kidney disease does not currently exclude a superimposed diagnosis of HRS, which is why HRS can coexist with other causes of AKI, which we must always take into account in the diagnosis. Therefore, in all patients with AKI or suspected HRS, we must look for an alternative explanation such as septic shock requiring vasopressors, acute tubular necrosis, renal obstruction, etc.

We will therefore distinguish between AKI, AKD, and CKD types of HRS depending on the timing and duration of renal dysfunction. HRS lasting less than 90 days would be classified as AKI-HRS, while HRS lasting more than 90 days would be classified as CKD-HRS[5].

Example 1: A patient with baseline HRS-AKD who develops acute renal dysfunction or AKI should be classified at this new stage as HRS-AKI.

Example 2: A patient with pre-existing ACLD and CKD due to diabetic nephropathy who develops acute renal dysfunction with HRS criteria will be classified as HRS-AKI in CKD.

Diagnostic criteria for HRS according to the ADQUI-ICA 2024 consensus
Decompensated cirrhosis with ascites
Diagnosis of AKI, AKD, or CKD based on ADQUI-ICA criteria
No improvement in serum creatinine and/or urine output within 24 hours after adequate volume resuscitation
No solid evidence for an alternative explanation as the primary cause of renal failure

Table 2. ***Diagnostic criteria for HRS according to the ADQUI-ICA 2024 consensus.***

Pathophysiology

Patients with ACLD, and particularly those with ascites, are more susceptible to AKI due to hemodynamic alterations resulting from portal hypertension. The degree of hepatic, renal, and circulatory dysfunction, together with precipitating events, can give rise to a variety of clinical phenotypes of AKI[3,5,18,19].

The pathophysiology of this dysfunction is based on four axes (Figura 2), with portal hypertension being the basis of everything:

Systemic circulatory dysfunction:

The initial mechanism in the pathogenesis of portal hypertension is increased intrahepatic resistance secondary to distortion of the hepatic architecture and/or increased vascular tone of the splanchnic axis. This increase in resistance, together with the systemic proinflammatory state resulting from liver disease and reduced hepatic elimination of endogenous substances, promotes increased production of endogenous vasodilator factors such as nitric oxide, carbon monoxide, and endocannabinoids in the splanchnic circulation. These vasodilator mediators promote splanchnic arterial vasodilation, causing a redistribution of systemic blood flow to this splanchnic vascular territory, thus decreasing arterial perfusion of other vascular territories (effective arterial hypovolemia). As a result of all this, mean arterial pressure (MAP) decreases, promoting the activation of compensatory mechanisms, mainly the renin-angiotensin-aldosterone system (RAAS), the sympathetic nervous system (SNS), and arginine vasopressin. These systems are progressively activated in order to maintain blood pressure, effective arterial blood volume, and renal perfusion, leading to a state of hyperdynamic circulation.

As liver disease progresses, portal hypertension and splanchnic vasodilation increase, leading to hyperactivation of compensatory systems to such an extent that there is an increase in water and solute-free sodium retention, causing effective arterial hypovolemia that results in the development of ascites, edema, or hypervolemic hyponatremia, among other conditions[3,20,21].

Renal vasoconstriction

At the renal level, as a result of this state of hypovolemia and progressive activation of the RAAS and SNS, vasoconstriction of the renal arteries and a reduction in the glomerular filtration rate occur.

Under physiological conditions, renal blood flow remains constant despite variations in blood pressure, a phenomenon known as autoregulation of renal circulation. In advanced stages of liver disease, this balance is lost, leading to a disproportionate increase in renal vascular resistance, thus causing a decrease in renal perfusion and glomerular filtration rate[22-24].

Cardiac dysfunction

In the early stages of ACLD with associated portal hypertension, a hyperdynamic circulatory state is favored in order to maintain MAP within the normal range and maintain tissue perfusion. This hyperdynamic state is

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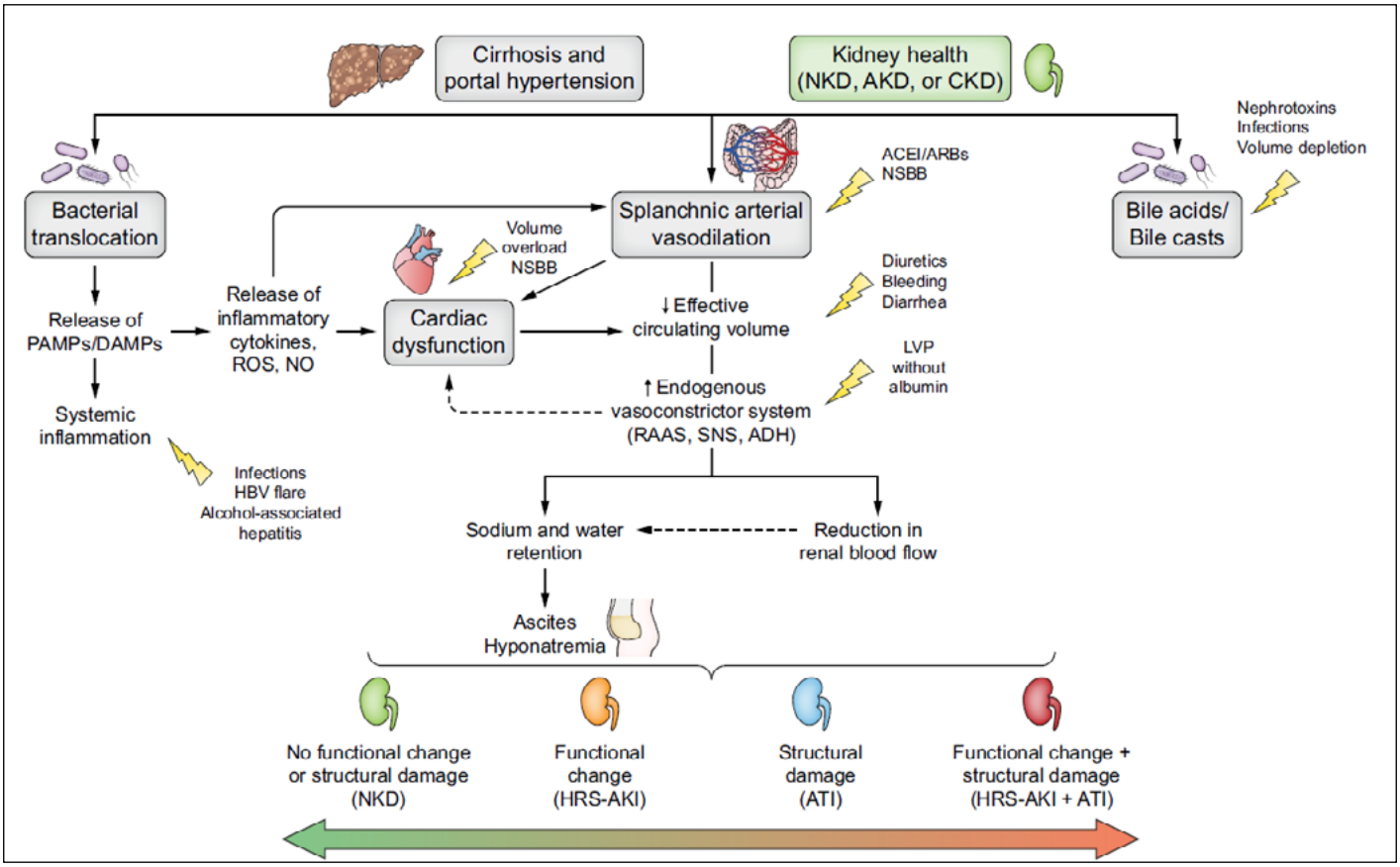

Figure 2. ***Pathophysiology of renal dysfunction in patients with advanced chronic liver disease and triggering factors. Extracted from: Nadim MK, Kellum JA, Fomi L, et al. Acute kidney injury in patients with cirrhosis: Acute Disease Quality Initiative (ADQI) and International Club of Ascites (ICA) joint multidisciplinary consensus meeting. J Hepatol. 2024; 81: 163-83.***

characterized by increased cardiac output, heart rate, and plasma volume. However, in the advanced stages of the disease, after a long period of maintaining this hyperdynamic state, both systolic and diastolic cardiac dysfunction (called "cirrhotic cardiomyopathy") occurs, contributing to renal hypoperfusion[25,26].

Proinflammatory state

Systemic inflammation is a common condition in patients with decompensated ACLD, presenting elevated levels of proinflammatory cytokines such as interleukin 6, tumor necrosis factor α, and C-reactive protein, among others. This proinflammatory state in cirrhotic patients is associated with increased intestinal permeability, thus promoting bacterial translocation from the intestine to the portal circulation. The passage of bacteria into the bloodstream activates antigen-presenting cells (macrophages, monocytes, and dendritic cells) through pathogen-associated molecular patterns (PAMPs), endotoxins, and bacterial DNA. In addition to these factors associated with bacterial translocation, cirrhotic patients present a proinflammatory state secondary to liver cell damage induced by the various noxious agents that cause the disease, which trigger the release of damage-associated molecules (DAMPs) such as uric acid, S100 proteins, etc., which also promote the activation of the innate immune system. Therefore, the activation of innate immune cells promotes the release of proinflammatory and vasodilatory cytokines, leading to increased systemic vasodilation and worsening of the hyperdynamic circulatory state in these patients[27-32].

Precipitating factors

This renal failure can occur spontaneously secondary to disease progression and exhaustion of the compensatory system, or it can be associated with a series of precipitating factors[3,5]:

- Potentiation of the proinflammatory state: infectious processes, mainly spontaneous bacterial peritonitis (the most frequent trigger of AKI); persistence of active hepatic noxious agents (alcohol, HBV, HCV, etc.).
- Systemic volume depletion: gastrointestinal bleeding, large-volume paracentesis, excessive diuresis (excessive use of diuretics), diarrhea/ dehydration, etc.

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- Circulatory dysfunction: refractory ascites, drug-induced vasodilation (ACE inhibitors, ARBs, beta-blockers, etc.), impaired renal circulation autoregulation (NSAIDs) Renal damage: nephrotoxic substances (NSAIDs, aminoglycosides, iodinated contrast media, etc.).

Diagnosis and evaluation of renal function

The diagnostic evaluation of patients with ACLD and AKI should be based on determining intravascular volume status, evaluating renal function, and thoroughly screening for possible triggering factors and phenotyping AKI[5].

Intravascular volume assessment

Today, this remains a complex clinical challenge, as most of the tools available for hemodynamic monitoring have not been validated in patients with ACLD.

Point-of-care ultrasound (POCUS) is proposed as a basic tool for assessing the patient's intravascular volume status at the bedside, but it has certain limitations, such as interobserver variability and difficulty in use in patients with significant ascites. Other options have been proposed, such as urinary sediment analysis or even renal biopsy, but all of these have significant limitations, which means that intravascular volume assessment remains a challenge to be resolved in the coming years[3,5,15,33,34].

Assessment of renal function

Scr is the established marker for determining the diagnostic criteria and stages of renal failure in cirrhotic patients. However, it is a marker with certain limitations, such as being influenced by muscle mass, changes in distribution volume, or even possible interference with bilirubin. These limitations are common in cirrhotic patients and can delay the diagnosis of renal failure[34,35].

The latest ADQI-ICA consensus proposes the use of the CKD-EPI equation without the racial variable and using cystatin C (CysC) instead of sCr to assess the estimated glomerular filtration rate in cirrhotic patients, as this allows for a better estimation of renal function with less associated bias in these patients[5,36,37].

Trigger factors and phenotyping of AKI

In addition to studying renal function, recent consensus statements on renal failure in cirrhotic patients recommend early detection of possible triggers of renal failure[38].

For this investigation, we must rely on a correct patient history and use various biochemical markers, including those related to kidney damage, in order to facilitate the detection of AKI, identify its origin, and thus be able to direct the therapeutic strategy more accurately[5].

The study of albumin and proteins in urine, together with urinary neutrophil gelatinase lipocalin (uNGAL), are proposed as markers of structural kidney damage. NGAL is a widely studied and promising biomarker, which is not easily found in our hospitals, mainly due to its high cost. It will facilitate the differential diagnosis between acute tubular necrosis and the prerenal origin of renal dysfunction. NGAL values ≥ 220 pg/d of creatinine point to a structural origin of AKI[39-41].

Prevention

The development of renal dysfunction in cirrhotic patients is a common and serious complication, so it is essential that all patients with advanced chronic liver disease undergo a complete assessment of their renal and hepatic health (Figure 3) based on a comprehensive medical history that evaluates the patient's susceptibility to developing AKI based on their history; knowledge of drugs and events that trigger such dysfunction, and awareness of the patient's renal and hepatic function[5,4243].

Based on all of the above, and mainly on the various main triggering events, the ADQI-ICA proposes the following strategies to prevent the development of AKI in cirrhotic patients (Table)[5]:

General therapeutic strategy for acute renal failure

In general, in all patients with hepatic ACLD and development of AKI, a therapeutic strategy should be implemented based on knowledge of the patient's hepatic and renal health and the AKI phenotype encountered[5,15].

Initially, we will carry out an assessment of the patient's overall health, focusing mainly on the liver and kidneys, and proceed to investigate any triggering events and their subsequent correction and/or suspension if necessary (Figure 4)[5,15,44].

Once this step has been completed and the probable phenotyping of the causal origin of the dysfunction has been carried out, we will direct therapy based on the suspected AKI phenotype, maintaining optimal hemodynamic and volumetric status in the patient at all times[3,5,15]:

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Intrinsic: any causative nephrotoxic agent should be discontinued, and if the patient does not show proper clinical progress, a renal biopsy should be considered.

In specific cases of specific glomerular pathology, the use of specific treatment necessary for the condition should be considered, in consultation with the appropriate specialists.

En los casos concretos de patología glomerular específica, se debe valorar el empleo de tratamiento específico necesario para la misma, en consonancia con los especialistas oportunos.

Postrenal: the therapy to be followed will be assessed in consultation with the urology department of our centers, based primarily on the obstructive cause and renal function.

Prerenal: an initial overall assessment of the patient's volume status is recommended in order to carry out a correct and safe restoration of systemic volume, thus avoiding iatrogenic volume overload (Figura 5).

The latest ADQI-ICA consensus recommends the use of balanced crystalloid solutions[45,46] as first-line therapy for volume replacement in patients with renal dysfunction who require volume resuscitation, unless there is a specific indication for the use of other fluids. Even so, we recommend that the choice of fluids should be individualized, depending on the specific condition of the patient[3.5,15,47]:

- Intravascular volume depletion: replacement with balanced crystalloid solutions, combined with replacement with blood products in cases of gastrointestinal bleeding.
- Euvolemic state (e.g., bacterial peritonitis): replacement with 20% albumin solution at a dose of 1 g/kg of weight (maximum of 100 g per day).

Twenty-four hours after starting effective volume replacement, sCr monitoring is recommended:

- If renal function improves: continue with volume replacement adjusted to the patient's needs and monitor renal function until values close to baseline are achieved.
- No improvement or worsening of renal function: ensure effective volume replacement, and if so, assess HRS-AKI criteria and consider initiating early measures for this AKI phenotype.

Therapeutic strategy for HRS-AKI

Once a diagnosis of suspected HRS-AKI has been established, vasoconstrictor therapy (terlipressin as the first-line agent) (Table 4) should be initiated as soon as possible in combination with 20% albumin (20-40 g per day)[5,12,49].

Once this therapy has been initiated, close monitoring of the patient and control of systemic volume are recommended to avoid adverse reactions[49-52]:

- Ischemic events: (cardiac, peripheral, and/or mesenteric), mainly associated with vasoconstrictor therapy and usually controlled by the use of infusion versus boluses of these drugs, or in certain cases requiring a reduction or even suspension of these.
- Volume overload: the combination of vasoconstrictor drugs with intravenous albumin infusion promotes an increase in systemic volume. For this reason, close monitoring is recommended, and in the event of signs and/or symptoms suggestive of fluid overload, temporary suspension of albumin, reduction of vasoconstrictor drug doses, and consideration of co-administration of diuretic drugs is advised.

Twenty-four hours after starting this therapy, monitoring of sCr is recommended.

Decrease in sCr ≥ 25% from the previous level: continue with the treatment initiated and monitor the patient and renal function until values close to baseline are achieved.

NO decrease in sCr ≥ 25% from the previous level: a gradual increase in the dose of vasoconstrictor drugs and continuous monitoring of the patient and renal function are recommended until the target is achieved.

In this situation, it is also advisable to monitor mean arterial pressure (MAP), as various studies have shown an improvement in renal function when associated with an increase in MAP ≥ 15 mmHg in patients treated with vasoconstrictor therapy. Therefore, if this increase in MAP occurs without an improvement in sCr, alternative causes of AKI should be reevaluated[53,54].

Discontinuation of vasoconstrictor therapy should be considered if renal function does not improve after a maximum of 14 days of treatment or after 48 hours at maximum tolerated doses, if serious adverse events develop, or if another alternative therapy is indicated[5,12].

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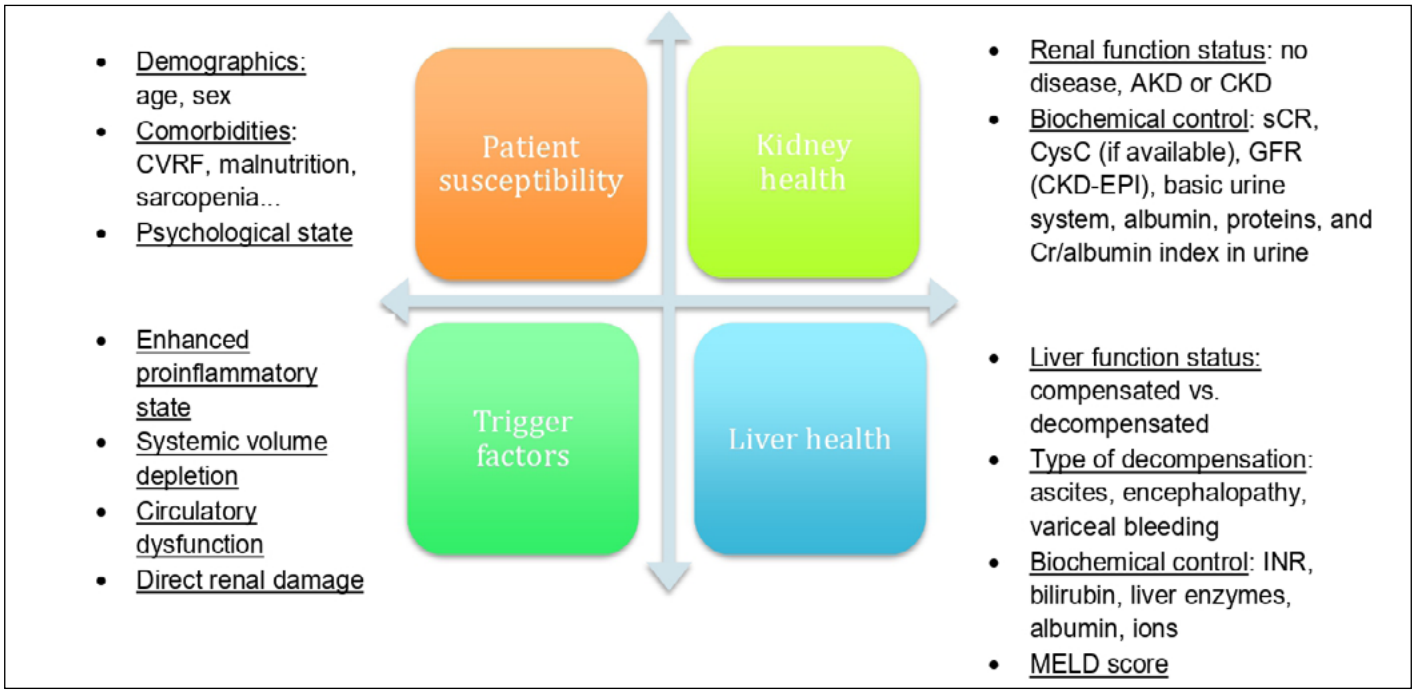

Figure 3. ***Comprehensive assessment of renal and hepatic health in cirrhotic patients. Adapted from: Nadim MK, Kellum JA, Fomi L, et al. Acute kidney injury in patients with cirrhosis: Acute Disease Quality Initiative (ADQI) and International Club of Ascites (ICA) joint multidisciplinary consensus meeting. J Hepatol. 2024; 81: 163-83.***

Noxa	Preventive strategy
Iodinated contrast media	-Low incidence of AKI induced by iodinated contrast media. -Monitor at-risk population: female sex, refractory ascites, advanced liver disease, active infection, and severe kidney disease. -Optimize the patient's internal volume status. -Discontinue diuretics in patients with signs of hypovolemia. -NO benefit from the use of N-acetylcysteine or intravenous bicarbonate.
Volume depletion (diarrhea, excessive diuresis, etc.)	-Volume expansion with balanced crystalloid solutions (Ringer's Lactate or PlasmaLyte). -Suspension of diuretics, laxatives, etc.
Large-volume paracentesis (≥5 L)	-Replace with 20-25% albumin solution at a dose of 8 g per liter extracted, starting at 5 liters
Variceal bleeding	-Volume expansion with balanced solutions and red blood cell concentrates if necessary (restrictive transfusion) -Intravenous antibiotic therapy for 5-7 days. E.g.: third-generation cephalosporin (ceftriaxone 1g) -Suspend diuretics and beta-blockers -Consider TIPS implantation in selected candidates depending on the clinical context
Bacterial peritonitis	-Systematic administration of antibiotics and 20% albumin -The dose and duration of albumin treatment should be adjusted daily, taking into account the patient's systemic volume, hemodynamic status, and clinical and laboratory progress -In case of septic shock, target mean arterial pressure > 60-65 mmHg
Bacterial infection (not SPB)	-Volume expansion with balanced crystalloid solutions (Ringer's Lactate or PlasmaLyte) -Avoid expansion with albumin, given the associated risk of volume overload -Fluid doses should be administered according to the patient's systemic volume and hemodynamic status to avoid excessive or insufficient resuscitation -In case of septic shock, target mean arterial pressure > 60-65 mmHg
Nephrotoxic drugs	-Ensure optimal management of drugs, taking into account their nephrotoxic load and avoiding overdose: consider discontinuation, dose adjustment, or alternative therapies
Major abdominal surgery	-Monitor for postoperative ascites -Optimize intravascular fluid status and avoid excessive administration of sodium and NSAIDs
Alfapump	-Optimize intravascular fluid status and avoid excessive administration of sodium and NSAIDs

Table 3. ***Preventive strategies to prevent AKI in patients with cirrhosis according to possible triggering factors. *Alfapump®, abdominal cavity-to-bladder pump for the treatment of ascites. Adapted from: Nadim MK, Kellum JA, Fomi L, et al. Acute kidney injury in patients with cirrhosis: Acute Disease Quality Initiative (ADQI) and International Club of Ascites (ICA) joint multidisciplinary consensus meeting. J Hepatol. 2024; 81: 163-83.***

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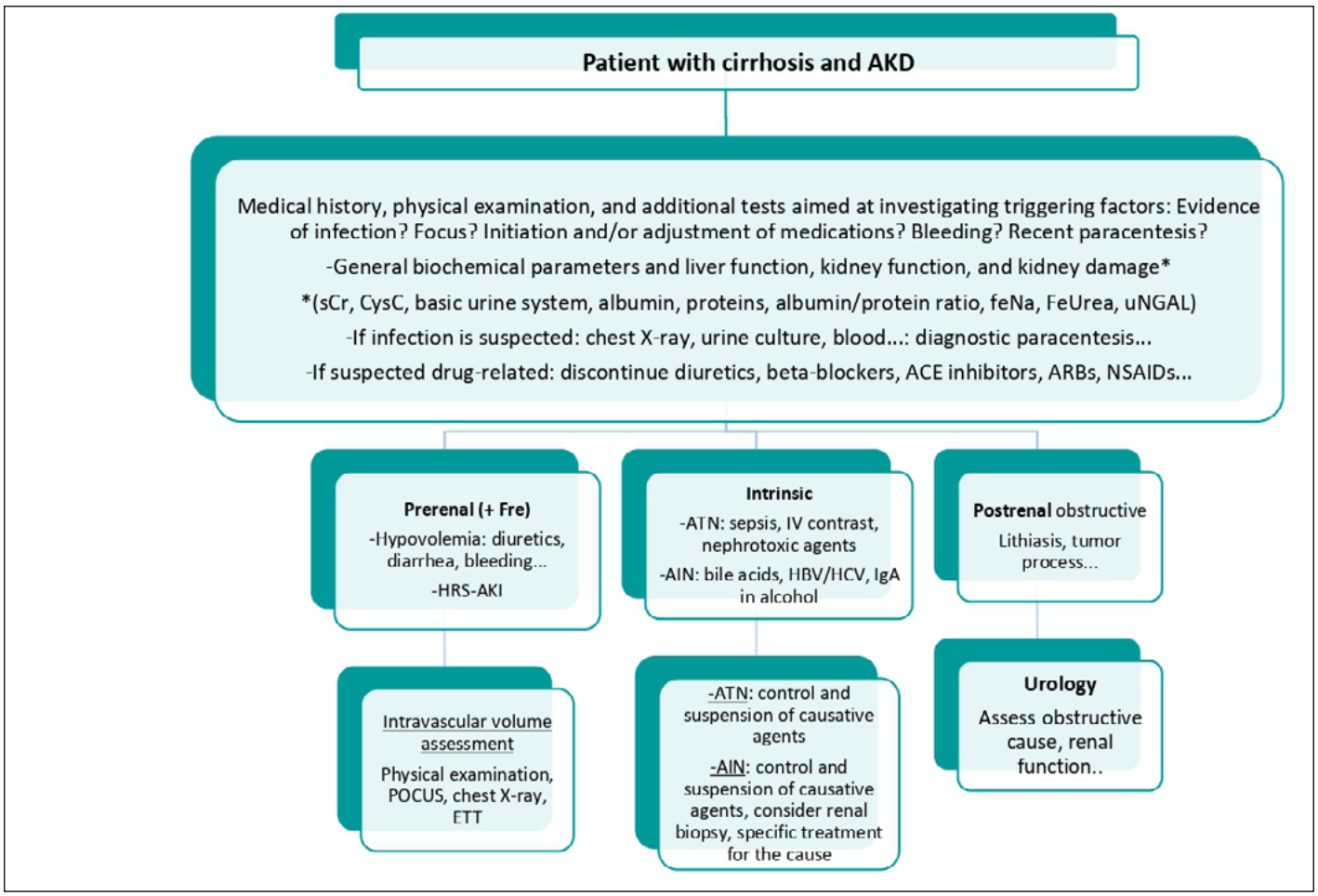

Figure 4. ***Initial management of patients withadvanced chronic liver disease and acute renal dysfunction.***

Other therapeutic options

Renal replacement therapy (RRT)

Early initiation of RRT should be considered in cirrhotic patients who develop AKI and experience adverse events that are refractory to targeted medical treatment, such as hyperkalemia, acidosis, or intravascular volume overload that does not respond to diuretic treatment or cannot be corrected with diuretics without causing serious adverse events, such as electrolyte disturbances or hepatic encephalopathy[55-57].

It is also considered as a bridge therapy option to transplantation in patients with HRS-AKI who do not respond to vasoconstrictor therapy or who experience severe adverse events to it, requiring its discontinuation. If the patient is not a candidate for liver transplantation, RRT is considered futile therapy, and its use should be assessed on an individual basis[12].

Liver transplantation (LT)

Episodes of AKI are associated with a high risk of short-term mortality in cirrhotic patients, especially those with a high baseline MELD score. For this reason, accelerated evaluation for LT is recommended in patients with decompensated ACLD after overcoming an episode of AKI.

In patients who develop HRS-AKI, liver transplantation is the treatment of choice and should be considered regardless of the response to vasoconstrictor therapy. Simultaneous kidney and liver transplantation is a potential therapeutic option in cases of patients who are candidates for liver transplantation and have prolonged renal dysfunction, as recovery of renal function is less likely in these patients than in those with a shorter duration of renal dysfunction. In 2017, the Organ Procurement and Transplantation Network established the following criteria for simultaneous liver and kidney transplantation: prolonged duration of acute renal dysfunction (≥ 6 weeks), need for renal replacement therapy, and presence of CKD[58-60].

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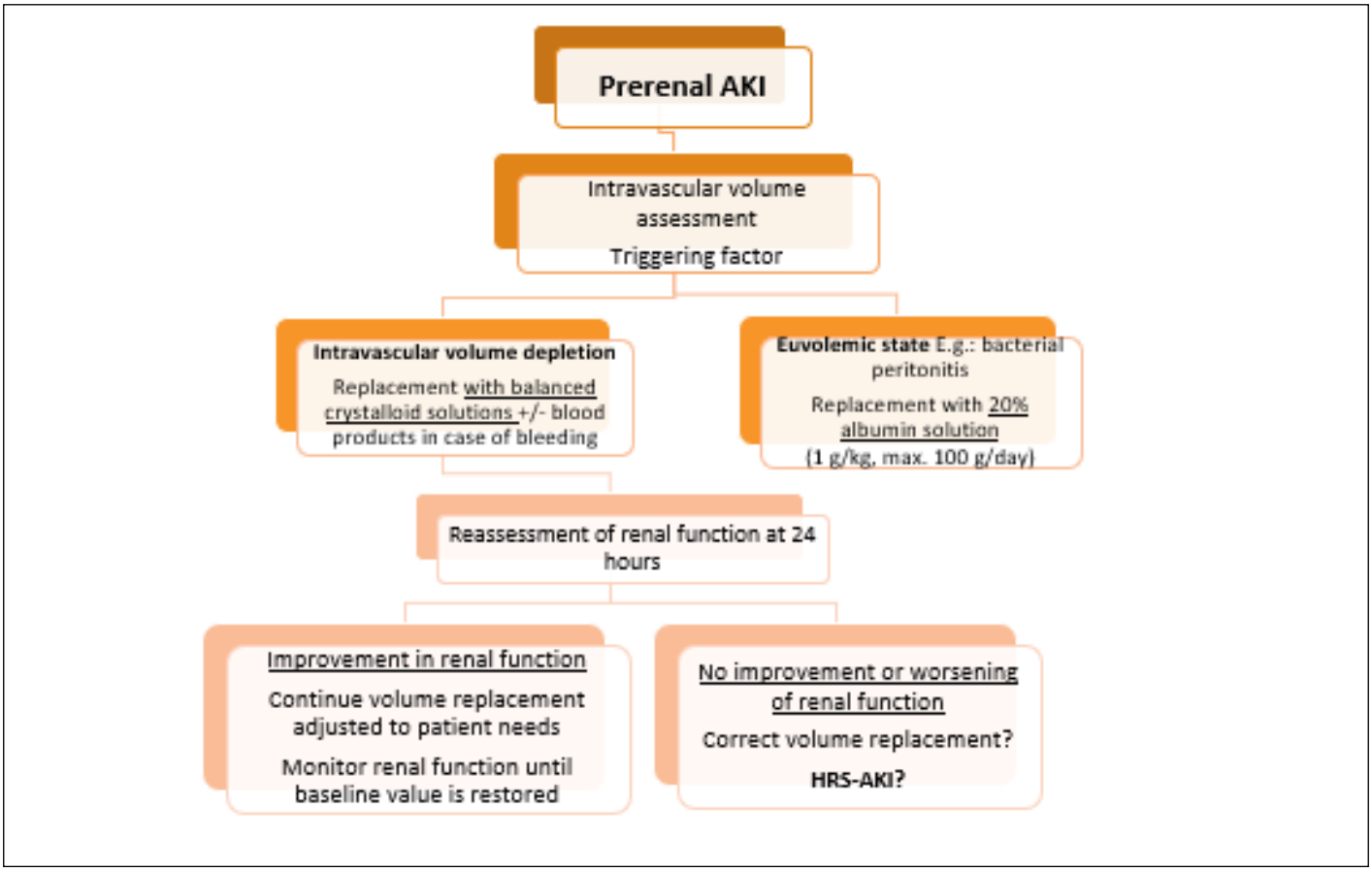

Figure 5. ***Treatment regimen for patients with prerenal AKI.***

Drug	Via/Dose	Comments
Terlipressin	Continuous infusion 2-12mg/day > intravenous boluses 1-2mg/6h	-Close monitoring of the patient and systemic volume to avoid adverse events: ischemic (cardiac, peripheral, and/or mesenteric) and volume overload. -Titration: if infusion, increase by 1-2 mg every 6 hours every 24 hours
Noradrenaline	Continuous infusion 0.5-3 mg/h	-Second-line therapy if terlipressin is contraindicated -Requires admission to intensive care unit and administration via central line -Monitoring of the patient to avoid adverse events: ischemic, arrhythmias -Titration: increase of 0.5mg/h every 4h, up to a maximum dose of 3mg/h
Midodrine + octreotide	Oral: 7.5-15 mg/8 h Subcutaneous: 100-200 mg/8 h	-Third-line therapy, if previous therapies are not available -Risk of bradyarrhythmias associated with midodrine
Criteria for discontinuing vasoconstrictor therapy		
-Development of serious adverse events -No improvement in renal function after a maximum of 14 days of treatment or after 48 hours at maximum tolerated doses -Indication for alternative therapy: renal replacement therapy, liver and/or kidney transplant, etc.		

Table 4. ***Vasoconstrictor therapies available for the treatment of HRS-AKI: routes of administration, doses, recommendations for use, and criteria for discontinuation.***

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Transjugular intrahepatic portosystemic shunt (TIPS)

There is currently insufficient evidence to support the use of TIPS for the treatment of AKI[3,5,12]. Several clinical trials are underway to provide evidence of the benefits of this therapy in renal dysfunction in cirrhotic patients[61-64]. Of particular note is the result of a meta-analysis suggesting that TIPS implantation leads to a significant improvement in renal function in cirrhotic patients with HRS-AKI, as it improves renal function by redistributing systemic blood volume and thus reducing portal pressure[65].

Outpatient follow-up

The period following hospital discharge after acute renal failure in cirrhotic patients is a critical time when dynamic changes in liver and kidney function can determine the patient's prognosis. In fact, after this episode of hospitalization, these patients have a higher associated risk of recurrent episodes of AKI, progression to CKD, dependence on renal replacement therapy, and morbidity and mortality[66-70].

It is recommended that, at least one month after hospital discharge, the renal and hepatic health of cirrhotic patients be reassessed to confirm the degree of recovery or progression of renal disease. In this assessment, it is advisable to evaluate the patient's liver function using standard prognostic scores and kidney function, including determination of sCr, serum CysC levels (which provide more reliable values of kidney function status) if available, and detection of albumin and proteins in urine. Several studies have shown that these latter values help us identify patients who are at greater risk of progression to CKD.

This assessment should also be based on continuing preventive measures to care for the patient's renal and hepatic function, based on the key elements mentioned above (Figure 3); a fundamental pillar of these assessments being therapeutic reconciliation with the patient, especially with diuretic and beta-blocker drugs, in order to establish a balance between renal and hepatic function[71-74].

In cases of persistent renal dysfunction at 90 days, these patients should be formally evaluated for possible

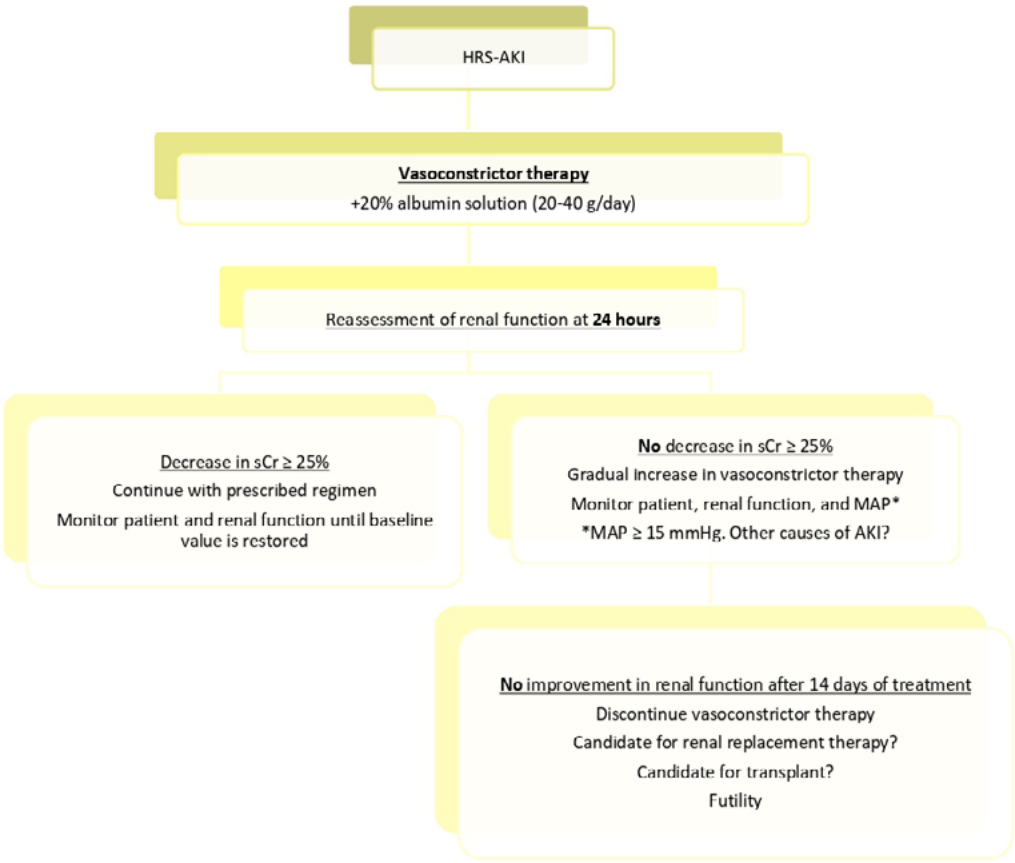

Figure 6. ***Therapeutic regimen for patients with HRS-AKI.***

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development or progression to CKD; These patients are eligible for a multidisciplinary approach focused on their life prognosis and hepatorenal health status, to determine whether they are candidates for transplantation or, on the contrary, require comprehensive management in which palliative care plays a fundamental role in the follow-up and planning of patient care[5,75,76].

Conclusions

- Acute kidney injury (AKI) is a common complication in patients with advanced chronic liver disease (ACLD), with a variable prevalence of up to 53% in patients with decompensated ACLD, and a marker of high morbidity and mortality and progression to chronic kidney disease after transplantation.

- The diagnostic criteria for AKI have evolved, incorporating decreased urine output as a complementary criterion, reflecting an effort to advance the detection and management of AKI in the cirrhotic population.

- The etiology of AKI in cirrhotic patients is multifactorial, with causes including prerenal, intrinsic, and postrenal factors, with renal hypoperfusion and hepatorenal syndrome (HRS) being particularly prevalent.

- HRS has been redefined and more appropriately classified into HRS-AKI, HRS-AKD, and HRS-CKD, based on a detailed assessment that includes the absence of response to adequate volume expansion over 24 hours, preferably with balanced crystalloid solutions, and the absence of strong evidence for an alternative explanation as the primary cause of renal failure.

- The pathophysiology of AKI in the context of ACLD is complex and involves systemic circulatory dysfunction, renal vasoconstriction, cardiac dysfunction, and proinflammatory states, all of which are influenced by portal hypertension and its hemodynamic consequences.

- The prevention of AKI should be based on a comprehensive assessment of renal and hepatic health, as well as on knowledge and management of the factors that trigger renal dysfunction.

- The therapeutic strategy for managing AKI in cirrhotic patients should be personalized and targeted according to the suspected etiology, with the correction and/or suspension of the triggering noxa, the assessment and replacement of volume, and the early evaluation of alternative therapies: vasoconstrictor therapy if HRS-AKI develops, renal replacement therapy, and/or simultaneous liver and/or kidney transplantation.

- Outpatient follow-up is crucial for reassessing renal and hepatic health after an episode of AKI, with particular emphasis on preventing progression to chronic kidney disease, adjusting diuretic and beta-blocker therapy, and planning care in the event of persistent renal dysfunction.

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CLINICAL CASE

DYSPHAGIA LUSORIA: WHEN DIAGNOSIS HIDES IN THE ANATOMY.

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Abstract

Dysphagia lusoria is a condition in which difficulty swallowing is related to a congenital anomaly of the subclavian artery, most commonly the right one, resulting in compression of the esophagus. Although rare, it is the most frequent cause of vascular-origin dysphagia. The severity of symptoms ranges from mild to severe, depending on the degree of compression. Diagnosis requires imaging tests such as CT angiography, MRI, or barium esophagogram to identify the aberrant artery and its relationship with the esophagus. Treatment varies according to severity, from dietary modifications to surgery to ligate or reposition the aberrant subclavian artery in order to relieve the compression.

Keywords: dysphagia lusoria, congenital anomaly, esophageal compression.

Introduction

We present the case of a 53-year-old woman diagnosed with a congenital anomaly that plays an important role in the differential diagnosis of dysphagia, especially in young patients with no preexisting conditions or obvious risk factors for other esophageal pathologies.

Clinical case

A 53-year-old woman with no relevant medical history was referred from primary care for long-standing dysphagia, initially affecting solids but now also progressing to liquids and accompanied by occasional vomiting and a feeling of a lump in her throat. Given the normal laboratory results and the lack of response to treatment with proton pump inhibitors (PPIs), an upper gastrointestinal endoscopy was requested,

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revealing a posterior indentation at the level of T3 suggestive of a retroesophageal aberrant right subclavian artery. Following these results, a series of esophagogastroduodenal images was requested, showing the impression caused by extrinsic compression on the posterior wall of the esophagus (Figure 1) and a CT angiogram (Figures 2 and 3), which confirmed the presence of this congenital aberrant artery, originating in the aortic arch, distal to the left subclavian artery and with a retroesophageal course, responsible for the dysphagia she presented. With all this information, the patient was referred to vascular surgery and scheduled for arterial bypass, pending assessment of the technique, with or without endovascular occlusion.

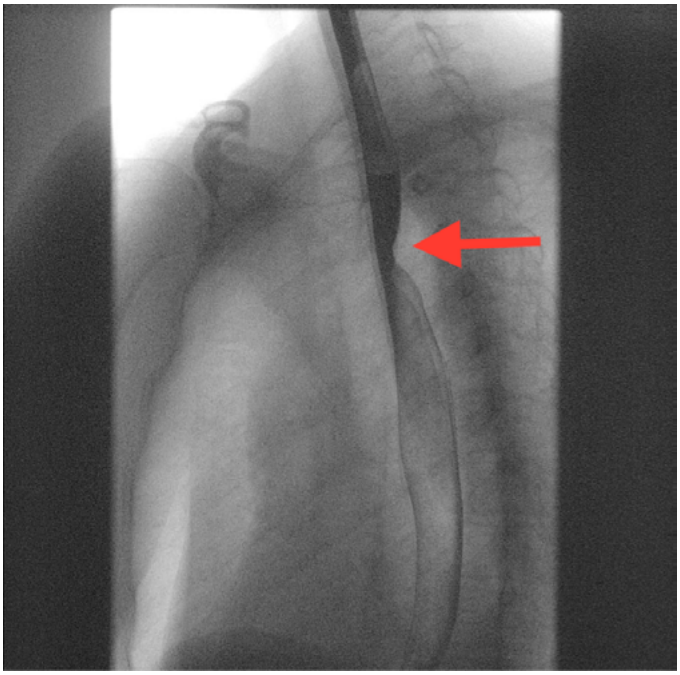

Figure 1. ***Esophagogastroduodenal series showing extrinsic compression on the posterior wall of the esophagus (red arrow).***

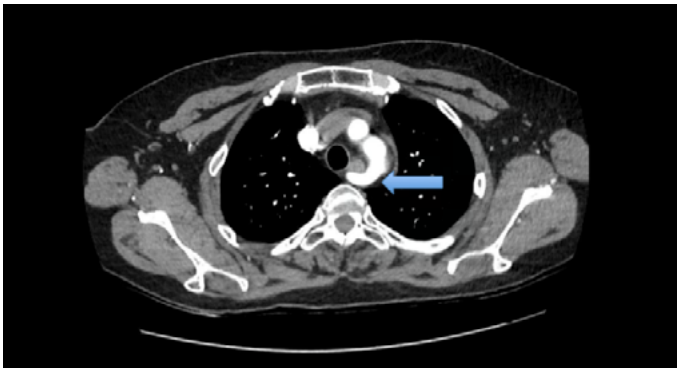

Figure 2. ***Axial CT scan of the chest showing the aberrant right subclavian artery emerging from the left aortic arch (blue arrow).***

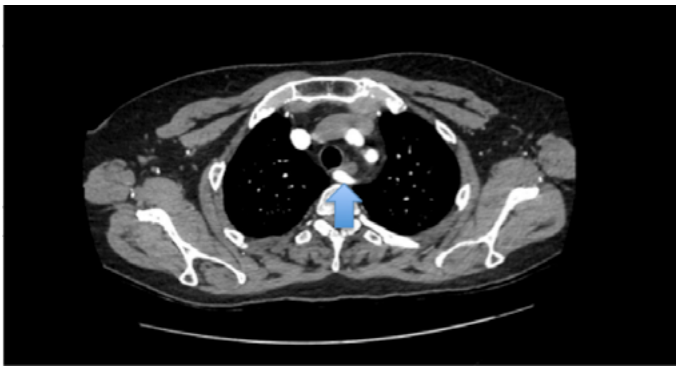

Figure 3. ***Axial CT scan of the chest showing esophageal compression by the aberrant right subclavian artery (blue arrow).***

Discussion

Esophageal dysphagia can be caused by a variety of factors, including motility disorders, inflammatory diseases, and mechanical diseases. Among the most common causes are gastroesophageal reflux, eosinophilic esophagitis, ingestion of caustic substances, the presence of foreign bodies, achalasia, and extrinsic compressions, including those of vascular origin. It is important to consider vascular causes in the differential diagnosis of dysphagia, especially in young patients without preexisting diseases or obvious risk factors for other esophageal pathologies.

The prevalence of subclavian artery anomaly causing luscious dysphagia varies between 0.5 and 1.8% and is more common on the right side. This condition arises due to the persistence of the seventh right intersegmental artery and abnormal involution of the fourth aortic arch during embryonic development. In 80% of cases, the vessel is retroesophageal, in 15% it is located between the trachea and the esophagus, and in 5% it is pretracheal.

The aberrant subclavian artery is often discovered incidentally during imaging tests performed for other reasons, and is usually asymptomatic. However, it can have a significant impact if it causes symptoms by compressing vital structures related to the abnormal path of the vessel (dysphagia if it compresses the esophagus, respiratory distress if it compresses the trachea or pulmonary artery, and even Horner's syndrome if it affects the cervical sympathetic plexus). The average age at which these symptoms begin to manifest is after 50 years of age, which may be related to the loss of flexibility of the esophagus due to aging, increased esophageal compression caused by progressive aneurysmal dilation of the aberrant artery, or stiffness caused by arteriosclerosis in the vessel wall.

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Effective management of this condition requires accurate evaluation, including relevant imaging tests such as CT and MRI, which are considered the gold standard. Other tests, such as barium esophagography and endoscopy, remain essential for guiding the initial diagnosis. In addition, a multidisciplinary and personalized therapeutic approach is needed, involving gastroenterologists, radiologists, and vascular surgeons, which will vary depending on the severity, from dietary changes to surgery to ligate or reposition the aberrant subclavian artery and thus relieve the compression.

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CLINICAL CASE

METABOLIC DYSFUNCTION ASSOCIATED WITH PATCHY HEPATIC STEATOSIS

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Abstract

MASLD (Metabolic Dysfunction Associated Steatotic Liver Disease) is a recently clarified clinical entity, which we consider very useful for the management of this kind of patients in primary care. We describe a case diagnosed as a result of the setup and development of an urban ultrasound point of care. The patient was a 27-year-old woman who drank beer on weekends (500 cc/24 h) and showed slight elevations of transaminases and gamma-glutamyl transpeptidase in two metabolic controls (AST 63, ALT 144, and GGT 227). The patient is leading a completely normal life with control of her cardiovascular risk factors.

Keywords: primary care, fatty liver, diagnostic imaging, general practitioners.

Introduction

Patchy hepatic steatosis is a form of fat accumulation in the liver. Instead of the uniform distribution seen in generalized hepatic steatosis, patchy hepatic steatosis is characterized by the presence of specific areas of fat accumulation in the liver, leaving other areas of the liver relatively free of fat. This irregular distribution can be detected by imaging tests[1,2].

Hepatic steatosis may be associated with various conditions, such as obesity, insulin resistance, type 2 diabetes, excessive alcohol consumption, viral hepatitis, among others. It is important to monitor this condition because, in some cases, it can progress to more serious liver diseases, such as metabolic dysfunction-associated steatohepatitis (MASH)[3,4] or liver cirrhosis. Management generally involves lifestyle

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changes, such as diet[5] and exercise, and in some cases, specific medications and regular medical follow-up.

Clinical case

The patient was a 27-year-old woman who drank beer on weekends (500 cc/24 h) and presented with a very slight elevation of transaminases and gamma-glutamyltranspeptidase in two metabolic tests (AST 63, ALT 144, and GGT 227). She had gained about 15 kilograms in the last three years. The patient underwent a clinical ultrasound in primary care (Figures 1-3) , which revealed patchy hepatic steatosis. She was referred to the local gastroenterologist with these ultrasound images. She continues to be monitored by a specialist with a diagnosis of hypertransaminasemia, probably related to MASLD (Metabolic Dysfunction Associated Steatotic Liver Disease). She has been advised to follow a low-fat diet and abstain completely from alcohol.

Discussion

Ultrasound supports various specialties[6-8], in their diagnostic and therapeutic work. Family physicians have the opportunity to receive specific training in ultrasound for solving clinical problems in their workplace[9].

MASLD (Metabolic Dysfunction Associated Steatotic Liver Disease) is a recently clarified clinical entity[10], that is very useful for managing these patients in primary care[11,12]. MASLD encompasses a wide spectrum of hepatic manifestations ranging from hepatic steatosis, steatohepatitis, or advanced forms of liver disease such as cirrhosis and its various forms of decompensation. The common feature is ectopic intrahepatic fat deposition. In this case, the diagnosis arose from patchy hepatic steatosis identified by clinical ultrasound. The patient in question is leading a completely normal life with control of cardiovascular risk factors.

Just over thirty years ago, a similar case with a clear alcoholic etiology mobilized several departments[13] at a tertiary care hospital[14]. In addition to developing clinical reasoning mechanisms[15], this study defends the efficiency of clinical ultrasound in healthcare centers ("point-of-care ultrasound")[16].

MASLD is an increasingly prevalent health problem that increases costs, especially when associated with type 2 diabetes mellitu[17]. Farnesoid X factor agonists appear to have a positive effect on fibrosis and steatosis[18] in these patients.

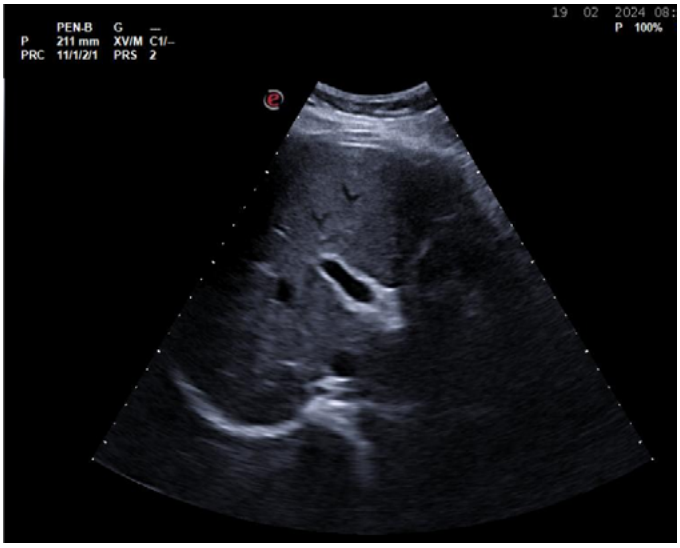

Figure 1. ***Heterogeneous echogenicity of the liver with hyperechogenicity of segments III, IV, V, VI, and VII.***

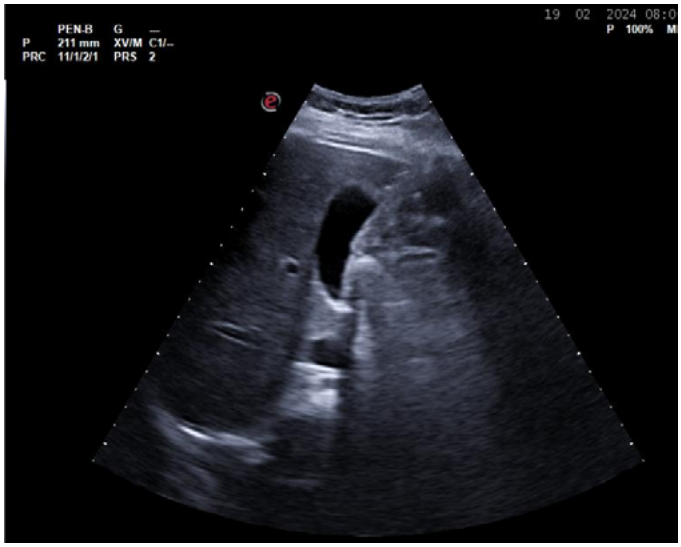

Figure 2. ***Hyperechogenicity of segments V and VI, adjacent to the gallbladder, which shows no abnormalities.***

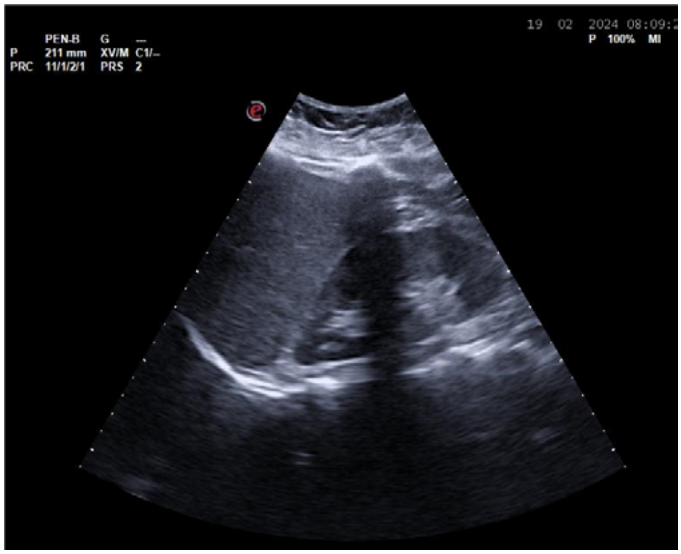

Figure 3. ***Hyperechogenicity of segments V, VI, and VII with respect to the renal cortex, which appears hypoechoic with respect to the liver (they should be seen with similar echogenicity).***

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BEYOND THE INTESTINE: ACUTE PANCREATITIS SECONDARY TO EOSINOPHILIC GASTROENTERITIS.

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Abstract

Eosinophilic gastroenteritis (EGE) is a rare disease characterized by eosinophilic infiltration of the gastrointestinal tract in the absence of secondary causes such as parasites, medications, or neoplasms. It can involve different layers of the intestinal wall, including the mucosa, muscularis, and serosa, leading to a wide variety of clinical manifestations. In exceptional cases, eosinophilic inflammation may extend beyond the digestive tract and affect adjacent structures such as the pancreas, resulting in acute pancreatitis, as illustrated in the case described.

: eosinophilic gastroenteritis, acute pancreatitis.

Clinical case

A 33-year-old male with no relevant personal history presented to the emergency department with severe abdominal pain in the mesogastrium and diarrhea without pathological findings. Laboratory tests revealed leukocytosis with marked eosinophilia, and computed tomography (CT) showed thickening of the duodenum and jejunal loops with mesenteric engorgement and reactive lymph nodes consistent with duodenoyejunitis (Figure 1). The study was completed with gastroscopy and colonoscopy, revealing cobblestone mucosa and multiple fibrinous ulcerations in the duodenum, which were biopsied. Pathological examination showed an increase in eosinophils forming microabscesses, leading to a diagnosis of eosinophilic gastroenteritis (Figure 2). Twenty-four hours after admission, the patient showed clinical worsening and hyperamylasemia, requiring an urgent CT scan to rule out perforation of a hollow viscus, but findings of acute pancreatitis were observed (Figure 3). He was discharged and later returned to the emergency room complaining of pain. A CT scan was performed, revealing radiological findings consistent with acute pancreatitis. After ruling out other conditions (Table), this was related to the eosinophilic inflammatory intestinal process. Given the suspected diagnosis, treatment with intravenous corticosteroids was initiated, resulting in progressive clinical improvement and resolution of the symptoms.

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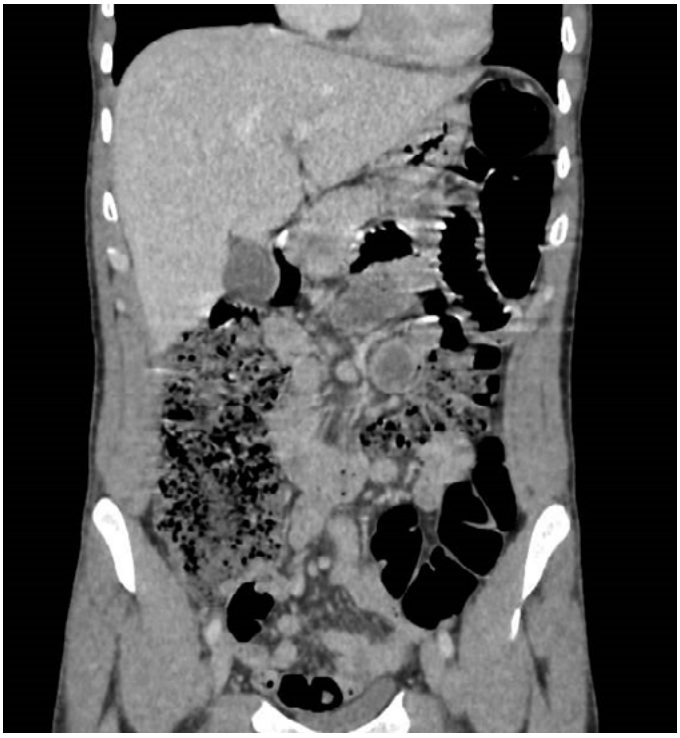

Figure 1. ***CT image showing distension of jejunal loops approximately 3 cm in caliber, located in the left hypogastrium and umbilical region with intramural fluid content and slight wall thickening. Adjacent reactive-appearing lymph nodes in the mesentery. Minimal amount of free fluid in the pelvis.***

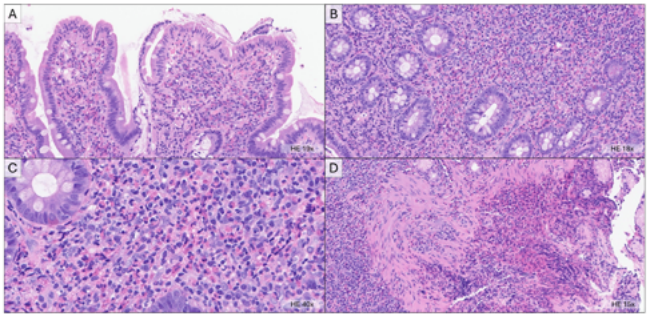

Figure 2. ***A-C: Duodenal mucosa with reparative-regenerative characteristics, with preserved architecture and villous height. The lamina propria shows a diffuse mixed inflammatory infiltrate composed predominantly of eosinophils, as well as lymphocytes, plasma cells, and neutrophils in smaller proportions. Groups of eosinophils forming microabscesses (accumulations of 4 or more eosinophils) are observed. D: Inflammatory infiltrate in the lamina propria, lymphoplasmacytic and mainly eosinophilic, reaching the muscularis mucosae and converging to form an extensive eosinophil microabscess. Duodenal mucosa in the vicinity preserved with reparative-regenerative changes.***

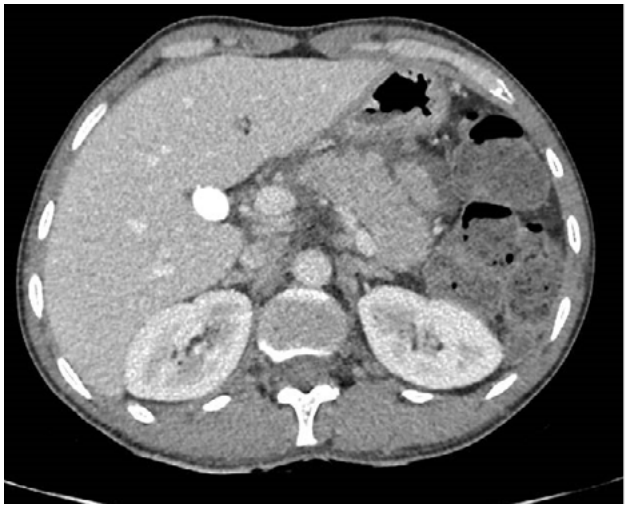

Figure 3. ***CT image showing diffusely thickened pancreas with rarefaction of peripancreatic fat, changes suggestive of acute edematous-interstitial pancreatitis.***

Parameter	Result	Reference values
Complete blood count		
Leukocyte count	14.180 /µL	4.000 – 10.000 /µL
Neutrophils (%)	27,8 %	40 – 70 %
Absolute neutrophils	4.130 /µL	1.500 – 7.500 /µL
Eosinophils (%)	45,8 %	< 5 %
Absolute eosinophils	9.360 /µL	< 500 /µL
Biochemistry		
Total bilirubin	0,58 mg/dL	0,2 – 1,2 mg/dL
AST	15 U/L	< 40 U/L
ALT	45 U/L	< 41 U/L
GGT	68 U/L	10 – 50 U/L
Amylase	1.081 U/L	25 – 125 U/L
Lipase	800 U/L	10 – 140 U/L
Triglycerides	140 mg/dL	< 150 mg/dL
Immunology		
IgG	601 mg/dL	700 – 1.600 mg/dL
IgG4	1,7 mg/dL	4 – 86 mg/dL
Total IgE	700 UI/mL	< 100–150 UI/mL
ANA	Negative	Negative

Table 1. ***Summary of the patient's laboratory abnormalities described in the text.***

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Discussion

Eosinophilic gastroenteritis (EGE) is a rare condition characterized by eosinophilic infiltration of the gastrointestinal tract in the absence of secondary causes such as parasites, drugs, or neoplasms. Its manifestations depend on the layers of the intestinal wall involved and may affect the pancreas to a limited extent secondary to obstruction of the biliary system. Imaging tests often reveal thickening of the duodenal wall, which is also observed by endoscopy, with the diagnosis being confirmed histologically by the presence of eosinophilic infiltrate in the gastric and/or intestinal tissue. This case emphasizes the importance of considering EGE as a cause of acute pancreatitis in patients with eosinophilia and digestive symptoms, especially when other common causes have been ruled out[1-3].

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BUDD-CHIARI SYNDROME: AN UNCOMMON COMPLICATION IN POST-LIVER TRANSPLANTATION

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Abstract

Budd-Chiari syndrome is a rare condition characterized by partial or complete obstruction of hepatic venous flow, which can present in either an acute or chronic form. Its etiology is classified as primary, associated with hematological disorders and hypercoagulability conditions, or secondary, caused by extrinsic venous compression or invasion. In this context, we present a case of acute Budd-Chiari syndrome as a vascular complication following a liver transplant.

Keywords: Budd-Chiari syndrome, hepatic veins, liver transplant, TIPS.

Introduction

Budd-Chiari syndrome is a rare condition characterized by partial or complete obstruction of hepatic venous flow, which can occur acutely or chronically. Its etiology is classified as primary, associated with hematological disorders and hypercoagulable conditions, or secondary, caused by extrinsic venous compression or invasion. In this context, we present a case of acute Budd-Chiari syndrome as a vascular complication following liver transplantation.

Clinical Case

A 23-year-old patient with chronic liver disease secondary to Wilson's disease, recently transplanted with preservation of the vena cava or piggyback technique, without immediate postoperative complications. She came to the emergency room with abdominal distension that had been developing for 24 hours, without other associated symptoms. Laboratory tests revealed acute renal failure and impaired liver function with elevated cholestasis enzymes and coagulopathy. An urgent computed tomography (CT) scan was performed, revealing acute Budd-Chiari syndrome with thrombosis at the confluence of the vena cava and the suprahepatic veins (Figure 1), as well as a moderate amount of ascites. The case was presented to a multidisciplinary committee, which decided to initiate

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anticoagulation therapy and scheduled the placement of an endovascular prosthesis, which was ultimately not feasible due to technical difficulties. One week later, in the absence of improvement, a therapeutic approach was decided upon using a transjugular intrahepatic portosystemic shunt (TIPS), achieving TIPS patency and partial improvement of the thrombus. Finally, the patient was discharged in good clinical condition.

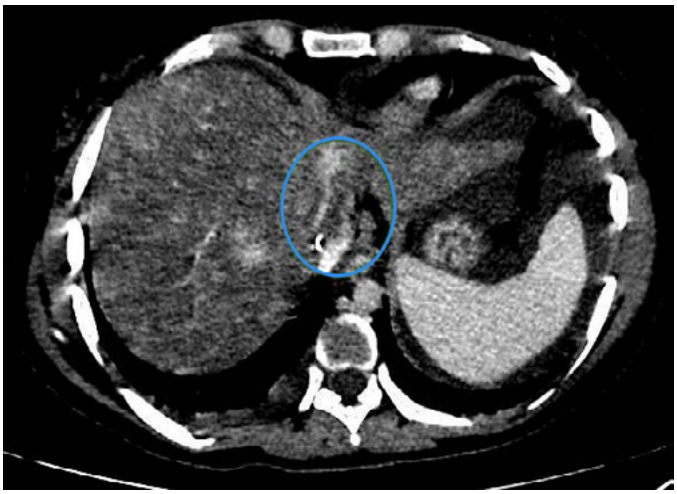

Figure 1. ***Enlarged liver graft with heterogeneous enhancement after contrast administration (congestive hepatopathy), showing a filling defect at the confluence of the vena cava and the suprahepatic veins.***

Discussion

Budd-Chiari syndrome is a rare condition, in most cases associated with hematological disorders, and its presentation as a vascular complication of liver transplantation is exceptional. In this context, a possible relationship with the piggyback surgical technique has been proposed, so it should be included in the diagnostic algorithm for the immediate post-transplant period, especially in patients with decompensated ascites associated with impaired liver function.

The form of presentation is variable and depends on the extent of venous flow obstruction and the speed of onset. Secondary symptoms of liver failure are common. Diagnosis is based on Doppler ultrasound, with CT or MRI being necessary in some cases. With regard to treatment, it is essential to initiate anticoagulation immediately. In the absence of response to anticoagulation, a multidisciplinary approach is recommended to evaluate therapeutic options for restoring hepatic venous drainage, including transhepatic venous angioplasty, TIPS, or, in critical situations, liver retransplantation[1-4].

In conclusion, it is essential not to overlook this condition, although rare, but potentially fatal in the context of post-liver transplantation, in order to ensure appropriate clinical management. Thus, paradoxically, liver transplantation can be both the cause and the treatment of Budd-Chiari syndrome.

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