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ANDALUSIAN JOURNAL OF DIGESTIVE PATHOLOGY

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*Permission to use photographs forms*

**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](mailto:sulime@sulime.net) or [RAPDonline@sapd.es](mailto:RAPDonline@sapd.es), for the solution of any problem in the submission of manuscripts.

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

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

**A) Specific standard for manuscripts writing**

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

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

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

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1° Structured abstract in Spanish (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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- 5° Declaration on the existence or non-existence of a source of funding for the work, or conflicts of interest.

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- 2° Text: Structured according to the criteria of the author(s), for a better understanding of the topic developed.
- 3° Bibliography: According to the specifications established in the group of common standards (See common standards and other supporting documents).
- 4° Acknowledgements.
- 5° Figure captions
- 6° Tables and Figures in the text.

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

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- 2° Text: Structured according to the criteria of the author(s), for a better understanding of the topic developed.
- 3° Bibliography: According to the specifications established in the group of common standards (See common standards and other supporting documents).
- 4° Acknowledgements
- 5° Figure captions.
- 6° Tables and Figures in the text.

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

The length of the texts in the Clinical Cases section should not exceed 5 pages (2,125 words), excluding bibliographical references and captions to figures and tables, and the number of inserted images should not exceed 5, including tables and figures. However, the RAPD Online editing method allows, in specific cases, the acceptance of longer manuscripts, or the inclusion of a greater number of images, provided that the

characteristics of the material presented so require. Colour illustrations and videos will not represent a financial charge for authors, but the insertion of videos, for technical reasons, will be previously agreed with the editor. No more than 5 authors will be admitted, except in specific and reasoned cases.

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

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- 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.

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

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- 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.

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- 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

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

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

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

- Main body of the manuscript, containing:

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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.

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**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:

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- 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.

Stamatikos M, Sargedi C, Stefanaki C, Safi oleas C, Matthaopoulou I, Safi oleas M. Anthelmintic treatment: An adjuvant therapeutic strategy 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's esophagus. Gastroenterology (2009), doi: 10.1053/j.gastro.2009.02.062.

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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.

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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.

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

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

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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](http://www.house.gov/reform/min/inves_tobacco/index_accord.htm).)

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# FIRST-LINE ERADICATION REGIMENS IN PENICILLIN-ALLERGIC PATIENTS IN ANDALUSIA. RESULTS FROM THE EUROPEAN REGISTRY HP-EUREG IN THE 2013–2025 PERIOD.

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## Abstract

**Introduction and aims:** Eradication treatment of *Helicobacter pylori* (HP) infection remains a challenge in patients allergic to penicillin, particularly in areas with high clarithromycin resistance rates such as Andalusia (close to 20%). Therefore, our objective was to analyze the evolution of first-line regimens in penicillin-allergic naïve patients, assessing effectiveness, safety, and adherence.

**Materials and methods:** A descriptive observational study based on the Hp-EuReg registry was conducted. Penicillin-

allergic patients receiving first-line treatment between 2013 and 2025 in eleven centers in Andalusia were included. Demographic, clinical, and treatment-related variables were analyzed. Effectiveness was assessed using a modified intention-to-treat analysis.

**Results:** Of 5,942 registered patients, 247 (4.2%) were naïve and allergic to penicillin. The most frequently used regimen was single-capsule bismuth quadruple therapy (Pylera®) (61.8%), followed by triple therapies (29.7%). Pylera

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achieved an eradication rate of 93.9%, significantly higher than that of triple therapies ( $p < 0.001$ ). The standard dose of proton pump inhibitors (PPI) was the most commonly prescribed, and the most frequent treatment duration was 10 days; however, neither variable reached statistical significance in terms of effectiveness. Overall adherence was optimal (97.1%), and the incidence of adverse events was low ( $\approx 9\%$ ), predominantly mild.

**Conclusion:** Pylera® has become established as the most effective and safe first-line strategy in penicillin-allergic naïve patients, reflecting appropriate adaptation of clinical practice in Andalusia to the available scientific evidence.

**Abbreviations:** *Helicobacter pylori* (HP), proton pump inhibitor (PPI), mucosa-associated lymphoid tissue lymphoma (MALT), intention-to-treat analysis (ITT), modified intention-to-treat analysis (mITT).

**Keywords:** autoimmune hepatitis, complete biochemical response, refractory disease, second- and third-line therapy, mycophenolate mofetil, complex cases.

## Introduction

*Helicobacter pylori* (HP) infection affects approximately 50% of the world's population and plays a key role in the development of chronic gastritis, peptic ulcer disease, mucosa-associated lymphoid tissue (MALT) lymphoma, and gastric cancer.

To date, five consensus meetings on HP infection have been held in Spain, the most recent in May 2021, focusing on the treatment of this infection<sup>1</sup>. The current consensus establishes a higher therapeutic threshold, requiring that empirical regimens achieve, or preferably exceed, a 90% eradication rate according to the intention-to-treat (ITT) analysis.

Thus, in general, a 14-day concomitant quadruple regimen without bismuth (clarithromycin, amoxicillin, metronidazole, and a proton pump inhibitor [PPI]) is recommended for both first- and second-line treatment, or a quadruple combination with bismuth (PPI, bismuth, tetracycline, and metronidazole) for at least 10 days.

In the specific case of patients allergic to penicillin, this same guideline recommends administering the quadruple regimen with bismuth as first-line therapy. To date, available experience with eradication therapies in patients with penicillin allergy is limited, despite the fact that this situation occurs relatively frequently in clinical practice<sup>2</sup>. However, it should be noted that only a small proportion of patients who

report a history of penicillin allergy actually have a confirmed immune-mediated hypersensitivity; therefore, it is essential to objectively confirm this diagnosis.

Furthermore, factors influencing the efficacy of eradication therapy must be taken into account, such as treatment adherence, prior history of antibiotic use, and, above all, the prevalence of antibiotic resistance. Numerous studies worldwide have demonstrated an increase in HP resistance over the years. The international multicenter study by Schultz *et al.*<sup>3</sup> demonstrates that resistance to clarithromycin and levofloxacin exceeds 15% in more than half of the 31 countries included. Meanwhile, amoxicillin showed rates below 2% in most countries.

Another recent study led by the Hp-EuReg (European Registry on the Management of *Helicobacter Pylori* Infection)<sup>4</sup> found that, in Europe and similarly in Spain, since the 1990s, primary resistance to clarithromycin has fluctuated, remaining consistently above 15%.

On the other hand, resistance to metronidazole has remained high and stable, with prevalence rates exceeding 25%; meanwhile, resistance to levofloxacin has shown a gradual increase, reaching over 19% in recent years.

More specifically in Andalusia, a multicenter study shows that primary HP resistance reaches 18% for clarithromycin and 14% for levofloxacin. Since resistance to clarithromycin exceeds the critical threshold of 15%, guidelines in this region advise against the use of clarithromycin-based triple therapies<sup>5</sup>.

Given, on the one hand, the high rate of resistance to clarithromycin and, on the other, the inability to use amoxicillin in patients allergic to penicillin—a drug considered one of the most effective against *H. pylori* and with low resistance rates—determining the therapeutic approach to *H. pylori* infection in this patient population poses a genuine clinical challenge.

## Objective

The objective of this study was to analyze trends in treatment regimens for *H. pylori* infection in treatment-naïve patients with penicillin allergy, evaluating the effectiveness, safety, and adherence to the various regimens used.

## Materials and methods

A descriptive observational study was conducted using Hp-EuReg, an international prospective registry focused on the management of HP infection, as the data source.

Information was collected using electronic case report forms (e-CRFs) integrated into the AEG-REDCap platform. This is collaborative software developed by the Spanish Association of Gastroenterology and Research Electronic Database Capture, which enables the design, development, and management of electronic data collection forms in research studies, including multicenter studies.

The most frequently used first-line treatments between 2013 and June 2025 were analyzed, including exclusively patients with penicillin allergy. The presence of penicillin allergy was established based on information recorded in the medical records, including both patients with self-reported allergy and those with a previously confirmed diagnosis through evaluation by an Allergy Service. The eleven participating centers were located in the provinces of Malaga, Sevilla, Granada, Almeria, and Cadiz.

Demographic and clinical variables were evaluated, as well as those related to the prescribing, efficacy, and safety of the administered treatments. PPI doses were standardized using omeprazole equivalents and categorized into low-dose (4.5–27 mg omeprazole equivalents/12 h), standard dose (32–40 mg omeprazole equivalents/12 h), and high dose (54–128 mg omeprazole equivalents/12 h). Treatment adherence was defined as taking more than 90% of the prescribed medication. To align the results with routine clinical practice, treatment effectiveness was evaluated using a modified intention-to-treat (mITT) analysis, which includes all patients who completed follow-up and underwent a confirmatory test for eradication success, regardless of treatment adherence.

Descriptive and bivariate statistical analyses were performed, comparing proportions using the chi-square ( $\chi^2$ ) and Fisher's exact tests. Bivariate analysis was used to assess the association between the different treatment regimens and the eradication rate, as well as between treatment effectiveness and the dose of the proton pump inhibitor (PPI) and the duration of treatment. The level of statistical significance was set at  $p < 0.05$ . All statistical analyses were performed using IBM SPSS Statistics software, version 28.0 (IBM Corp., Armonk, NY, USA).

## Results

During the study period, a total of 5,942 patients were included in the Andalusian registry, of whom 247 (4.2%) were treatment-naïve and allergic to penicillin. Between 2014 and 2017, 51.4% of the total sample was recorded, with 2016 and 2017 being the years with the highest number of patients. The mean age was 54 (+/-14.3; range: 18–84) years, and 70% were women. The most common indication for treatment

was dyspepsia (75.3%), followed by peptic ulcer (11.7%), and invasive diagnostic techniques were used in up to 63.2% of patients (Table 1).

Variables	Frequency (n:247)	%	
Year	2013	16	6.5%
	2014	26	10.5%
	2015	28	11.3%
	2016	40	16.2%
	2017	33	13.4%
	2018	18	7.3%
	2019	17	6.9%
	2020	24	9.7%
	2021	19	7.7%
	2022	11	4.5%
	2023	6	2.4%
2024	3	1.2%	
2025	6	2.4%	
Sex	Female	172	69.6%
	Male	75	30.4%
Indication	Dyspepsia with normal endoscopy	110	44.5%
	Uninvestigated dyspepsia	76	30.8%
	Duodenal ulcer	19	7.7%
	Gastric ulcer	10	4%
	Others	32	13%
Diagnosis of infection	Invasive	156	63.2%
	Non-invasive	91	36.8%

**Table 1. Socio-demographic and clinical characteristics of the study population.**

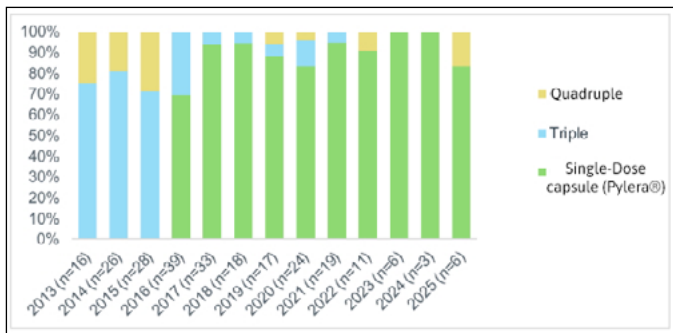
Overall, the most frequently used treatment was Pylera® (61.8%), a quadruple regimen with bismuth in a single capsule that combines metronidazole, tetracycline, and bismuth subcitrate. In second place were triple regimens (29.7%), with the most commonly used regimens being those combining metronidazole with clarithromycin (18.3%) or clarithromycin with levofloxacin (8.9%). Finally, among the quadruple therapies (8.5%), the regimen based on the combination of metronidazole, doxycycline, and bismuth predominated. Regarding PPI potency, approximately half of the patients received the standard regimen, while high doses were the least commonly used. Furthermore, 10-day regimens were the most commonly used (92.7%) (Table 2).

An analysis of treatment patterns over time shows that, at the beginning of the period, triple therapy was the most commonly prescribed regimen. Its use declined significantly

Variables		Frequency (n:247)	%
Treatment regimen	Pylera®	152	61.8
	Triple therapy	73	29.7
	Quadruple therapy	21	8.5
Acid suppression potency of proton pump inhibitors (PPIs)	Low	88	35.6
	Standard	113	45.7
	High	46	18.6
Treatment duration	7 days	1	0.4
	10 days	229	92.7
	14 days	17	6.9

**Table 2. Characteristics of prescribed treatments: treatment regimens used, acid suppression potency of PPIs, and treatment duration.**

starting in 2016, coinciding with the launch of Pylera®, which has since become the predominant option for managing the infection in these patients. Quadruple therapy regimens, on the other hand, have been used to a more limited extent, fluctuating between 28% in 2015 and 17% in 2025 (Figure 1).

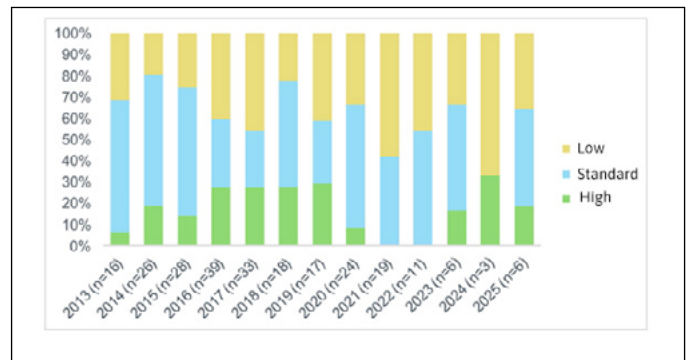


**Figure 1. Treatment regimens used by year**

When assessing the potency of the PPIs used throughout the study period, no clearly defined trend is identified. Despite the observed variability, the standard PPI regimen was the most frequently used, while the use of high doses remained the least common option (Figure 2).

Treatment adherence was optimal, estimated at 97.1%, and the overall effectiveness (mITT) of our sample reached 84% (Table 3).

When evaluating effectiveness based on the most commonly used treatment regimens (Table 4), it was observed that triple therapies with clarithromycin combined with metronidazole or levofloxacin yielded suboptimal results in patients allergic to penicillin, with eradication rates of 65.1% and 76.1%, respectively. The use of Pylera® in this setting substantially improved outcomes, achieving eradication rates of 93.9%, a statistically significant difference compared with the alternatives (p<0.001).



**Figure 2. PPI acid suppression potency patterns by year.**

Variables		Frequency (n:247)	%
Therapeutic adherence	Yes	237	97.1%
	No	7	2.9%
mITT	Success	200	84%
	Failure	38	16%

**Table 3. Overall therapeutic adherence and effectiveness outcomes.**

Variables	Fracaso		Éxito		p
	n	%	n	%	
<b>Treatment regimen</b>					
Triple C+M	15	34.9	28	65.1	<0.001
Triple C+L	5	23.8	16	76.2	
Pylera®	9	6.1	138	93.9	

**Table 4. Effectiveness according to the most frequently used treatment regimens.**

When comparing effectiveness based on PPI dose, eradication rates were similar among the three groups analyzed. In the analysis based on treatment duration, the 10-day regimens showed a higher eradication rate; however, this difference did not reach statistical significance (p = 0.20) (Table 5).

Finally, adverse effects were reported in approximately 9% of patients, with mild gastrointestinal reactions predominating. The most frequent events were nausea, dysgeusia, and dyspepsia. No serious complications requiring treatment discontinuation were observed.

**Discussion**

This study demonstrates that, in our setting, treatment of H. pylori infection in penicillin-allergic patients with Pylera® is the treatment regimen of choice. Previously, the most commonly used option was traditional triple therapy with PPI, clarithromycin, and metronidazole, which in older meta-analyses showed eradication rates exceeding 80% <sup>6</sup>, but

Variables	Failure		Success		p
	n	%	n	%	
<b>PPI acid suppression potency</b>					
Low	13	15.1	73	84.9	0.799
Standard	18	16.4	92	83.6	
High	7	16.7	35	83.3	
<b>Treatment duration</b>					
10 days	32	14.5	188	85.5	0.20
14 days	5	29.4	12	70.6	

**Table 5. Effectiveness according to PPI potency and treatment duration.**

which in more recent Spanish studies has shown a significant decline in effectiveness, with rates below 60%<sup>78</sup>. This finding is related to the increase in HP antibiotic resistance<sup>9-11</sup>. In fact, the significant increase in resistance to clarithromycin has been global, prompting the WHO in 2017 to include clarithromycin-resistant HP on the list of priority pathogens for new antibiotic research. However, although resistance continues to rise in most countries, it was removed from that priority list in 2024, a decision that has been controversial. Similarly, HP resistance to levofloxacin has also increased in several regions, further complicating the selection of other effective eradication regimens<sup>12-21</sup>.

With regard to treatment options, recent studies have evaluated combinations such as PPI, tetracycline, and metronidazole in patients allergic to penicillin. These studies have shown ITT eradication rates of 80–85%<sup>22,23</sup>. The results suggested that this triple combination, or even its quadruple version with the addition of bismuth, could constitute a more effective alternative for first-line treatment in these patients, especially in regions with high resistance to metronidazole or clarithromycin. The efficacy of the quadruple regimen is likely explained by bismuth’s ability to counteract the negative effect of metronidazole resistance<sup>24</sup>, which is also administered for an extended period, at short intervals, and in high doses; and because the regimen’s efficacy is not affected by clarithromycin resistance<sup>25</sup>. Furthermore, HP resistance to tetracycline and bismuth is rare<sup>26</sup>.

In line with this, a prospective multicenter Spanish study compared the efficacy of triple therapy (PPI, clarithromycin, and metronidazole for 7 days) with quadruple therapy (PPI, bismuth, tetracycline, and metronidazole for 10 days) in 267 patients allergic to penicillin<sup>27</sup>. The results showed an ITT eradication rate of 57% with triple therapy, while the quadruple regimen achieved 74%, confirming the superiority of the latter approach in this population.

In line with this, a recent Hp-EuReg study involving more than 1,000 patients allergic to penicillin showed that the effectiveness of triple therapy as a first-line treatment was only 69%, while quadruple therapy with bismuth, whether in its classic form or via the single-capsule Pylera<sup>®</sup>, achieved an eradication rate of 91%<sup>28</sup>.

All of the above supports the findings of our study, which confirms that Pylera<sup>®</sup> is not only the most commonly prescribed therapy but also the only one to demonstrate optimal eradication rates. The advantage of using Pylera<sup>®</sup> as a single-capsule quadruple therapy with bismuth over conventional quadruple therapy with bismuth lies in its more convenient dosing regimen and also overcomes the limited availability of bismuth and tetracycline hydrochloride in many regions. All of this is also in line with the recommendation of the 5th Spanish Consensus on HP Treatment<sup>1</sup>.

In our sample, triple therapies were used secondarily, yielding suboptimal results, findings consistent with previously published evidence. Quadruple therapy regimens have had more limited use, and in some years their use was not recorded, although these absences coincided with periods of a lower number of reported cases. In Spain, the use of quadruple therapy with bismuth has been limited mainly by the lack of availability of tetracycline and because doxycycline, although commercially available, has been associated with lower efficacy rates<sup>29</sup>.

Therefore, we found a clearly significant association between the therapeutic regimen and effectiveness, favoring Pylera<sup>®</sup>. However, when analyzing effectiveness based on PPI dose and treatment duration, our results were inconclusive. This finding could be explained, at least in part, by the fact that these variables were evaluated globally, without differentiating among the multiple treatment regimens described. Although not statistically significant, the 10-day treatment duration yielded better results, perhaps largely because it coincides with that of the commercial formulation of Pylera<sup>®</sup>, the most commonly prescribed treatment.

The main strength of our study is that it is based on a large registry with a long follow-up period, which allows for a detailed analysis of trends in treatment use over time, including a large number of patients and variables. Furthermore, the data is collected from a specific geographic region with common practices in prescribing and managing this clinical scenario. Potential limitations of the study include those arising from the observational nature of the design itself and the existence of periods with fewer recorded data. Furthermore, although

the study includes a large sample from eleven centers in five Andalusian provinces (Malaga, Sevilla, Granada, Almeria, and Cadiz), the absence of data from the provinces of Huelva, Cordoba, and Jaen could slightly limit the external validity of the results for the entire Andalusian region. Nevertheless, we believe that the findings obtained are likely to be quite representative of clinical practice in Andalusia.

## Conclusion

This study demonstrates a significant shift in treatment patterns for penicillin-allergic treatment-naïve patients in Andalusia between 2013 and 2025, marked by the replacement of triple therapy with quadruple therapy using a single-capsule bismuth formulation (Pylera®) as the predominant regimen following its market launch. This evolution has resulted in excellent outcomes, demonstrating eradication rates exceeding 90%, with optimal adherence and a favorable safety profile, featuring a low incidence of adverse events, most of which were mild.

The findings support the use of Pylera® for 10 days as a first-line strategy in this population with limited therapeutic options, and demonstrate a favorable adaptation of Andalusian clinical practice to scientific evidence, with the consequent optimization of clinical outcomes in this patient group.

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# FROM VANCOMYCIN TO FIDAXOMICIN: SHIFTING PARADIGMS IN *CLOSTRIDIoidES DIFFICILE* MANAGEMENT.

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## Abstract

**Introduction:** *Clostridioides difficile* infection (CDI) is one of the leading causes of antibiotic-associated diarrhea and represents a major global public health concern. Its clinical relevance has increased due to rising incidence, greater disease gravity, high recurrence rates, and the emergence of hypervirulent strains, making CDI a persistent challenge in daily clinical practice.

**Objective:** to provide an updated narrative review of the epidemiology, pathogenesis, diagnostic approaches, and current therapeutic strategies for *Clostridioides difficile* infection, with emphasis on key clinical challenges and practical considerations.

**Methods:** a structured literature review was conducted using PubMed/MEDLINE, Scopus, and SciELO databases. DeCS/MeSH terms related to *Clostridioides difficile*, epidemiology, diagnosis, treatment, and prevention were combined using Boolean operators. Articles published in English and Spanish between 2020 and 2025 were included, prioritizing systematic reviews, meta-analyses, original studies, and clinical practice guidelines. The search was last updated in January 2026.

**Results:** CDI pathogenesis is primarily mediated by toxins A and B, which induce epithelial damage and colonic inflammation. Advances in diagnostic tools, particularly nucleic acid amplification tests and multistep diagnostic algorithms, have improved detection rates; however, inappropriate use may lead to overdiagnosis. Oral vancomycin remains a cornerstone

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of therapy, while fidaxomicin, monoclonal antibodies, and fecal microbiota transplantation have shown efficacy in reducing recurrence in selected patients.

**Conclusions:** effective management of CDI requires an integrated approach combining accurate diagnosis, appropriate antimicrobial therapy, and sustained preventive strategies.

**Keywords:** *Clostridioides difficile*, healthcare-associated infection, antimicrobial therapy, diagnostic strategies, infection prevention.

### Introduction

*Clostridioides difficile* infection (CDI) is currently one of the leading causes of healthcare-associated diarrhea and remains a significant clinical challenge in hospitals worldwide. In recent decades, there has been a sustained increase in both its incidence and the severity of its clinical manifestations, particularly in vulnerable populations such as older adults, long-term hospitalized patients, and individuals exposed to broad-spectrum antimicrobials.<sup>1</sup>

*Clostridioides difficile* is a Gram-positive, spore-forming anaerobic bacterium whose transmission occurs predominantly via the fecal–oral route through direct contact with colonized individuals or via contaminated surfaces<sup>2</sup>. Its ability to form highly resistant spores allows it to persist in the hospital environment for prolonged periods and survive adverse conditions, including gastric acidity, facilitating intestinal colonization following antibiotic-induced disruption of the normal microbiota<sup>3</sup>. These mechanisms partly explain its close association with prior antimicrobial use and its behavior as a nosocomial pathogen.

*Clostridioides difficile*; formerly *Clostridium difficile*, the name change proposed in 2016 is based on phylogenetic criteria that distinguish this microorganism from other species of the genus *Clostridium*; however, the abbreviation “*C. difficile*” is still used in routine clinical practice<sup>4</sup>. In addition to the nomenclature aspect, the significance of *C. difficile* lies in its ability to produce a broad clinical spectrum; it is recognized as one of the main causative agents of antibiotic-associated diarrhea, ranging from self-limiting diarrhea to pseudomembranous colitis, fulminant colitis, and toxic megacolon—conditions associated with high morbidity and mortality.

It is estimated that *C. difficile* is responsible for up to 30% of cases of antibiotic-associated diarrhea and affects approximately 1% of hospitalized patients, with recurrence rates close to 20%, which complicates its management and places a significant burden on healthcare systems<sup>5</sup>. The emergence of hypervirulent strains, an aging population, immunosenescence, and the widespread use of antibiotics and gastric acid-suppressing agents have contributed to establishing CDI as a persistent and dynamic problem, still far from being fully controlled.

In this context, recent advances in our understanding of the pathogenesis—particularly the role of toxins A and B—as well as the development of new diagnostic tools and therapeutic strategies, have substantially altered the clinical management of this infection. However, significant controversies, diagnostic limitations, and therapeutic challenges remain, especially regarding recurrence and the effective prevention of new episodes.

### Objective

To critically analyze the available scientific evidence on the pathogenesis, diagnosis, treatment, and prevention strategies for *C. difficile* infection, highlighting recent advances, current controversies, and their clinical implications in the hospital setting.

### Method

A narrative review of the scientific literature from 2020 to 2025 on *C. difficile* infection was conducted. The search was conducted in the PubMed, Scopus, and Google Scholar databases, using terms related to the epidemiology, pathogenesis, diagnosis, treatment, recurrence, and prevention of *C. difficile* infection (CDI). The following health sciences descriptors were used (DeCS/MeSH): *Clostridioides difficile*; Healthcare-associated infection; epidemiology; Antimicrobial therapy; Diagnostic strategies; Infection prevention, combined using Boolean operators. Articles published in English and Spanish were included, covering the period from 2020 to 2025. The search was last updated in January 2026, prioritizing original studies, meta-analyses, systematic reviews, and relevant clinical guidelines.

Original articles, systematic reviews, clinical trials, observational studies, and relevant clinical guidelines published in English and Spanish were included, with no geographic restrictions, prioritizing those with the greatest clinical and methodological impact. Isolated case reports,

duplicate studies, and publications with redundant information or without direct clinical relevance were excluded.

The information obtained was critically analyzed and organized into thematic areas, with an emphasis on consistent findings, areas of controversy, and practical implications for the clinical management and prevention of *C. difficile* infection.

## Results

### Current evidence on pathogenesis and virulence factors

The pathogenesis of *C. difficile* infection is closely linked to the production of its main virulence factors: toxins A (TcdA) and B (TcdB). Both toxins are glycosyltransferases that inactivate Rho-GTPases in the actin cytoskeleton of intestinal epithelial cells, causing disruption of tight junctions, increased epithelial permeability, local inflammation, and cell death<sup>6</sup>.

Although toxin A was historically considered the primary determinant of disease, the most recent experimental and clinical evidence has shown that toxin B plays a central role in the bacterium's virulence<sup>7</sup>. Studies using isogenic mutants have shown that strains producing exclusively toxin B retain the ability to induce significant tissue damage, while those expressing both toxins exhibit greater virulence, suggesting a synergistic effect in disease development<sup>7</sup>.

These findings have had direct implications for the development of new therapeutic strategies, particularly those aimed at neutralizing toxin B, and have helped redefine the classical understanding of the pathogenesis of CDI.

Additionally, the emergence of hypervirulent strains, such as NAP1/BI/027, has been associated with increased toxin production, greater sporulation capacity, and higher rates of recurrence and mortality<sup>8</sup>. However, the distribution and actual impact of these strains in Latin America remain poorly characterized, which limits the direct extrapolation of data from North America and Europe.

### Clinical manifestations and disease severity

*C. difficile* infection presents with a broad clinical spectrum ranging from mild watery diarrhea to severe conditions such as pseudomembranous colitis, fulminant colitis, and toxic megacolon<sup>9</sup>. Diarrhea remains the cardinal symptom; however, the severity of the clinical presentation depends on multiple factors, including bacterial load, toxin production, the host's immune status, and the presence of comorbidities<sup>10</sup>.

In mild to moderate cases, patients present with diarrhea, abdominal pain, and nonspecific systemic symptoms<sup>11</sup>. In contrast, severe forms are characterized by marked leukocytosis, compromised general condition, fluid and electrolyte imbalances, and a high risk of life-threatening complication<sup>11</sup>. In fulminant cases, transmural inflammation of the colon can lead to paralytic ileus and cessation of diarrhea, which delays diagnosis and worsens the prognosis<sup>12</sup>.

Available evidence confirms that advanced age, recent antibiotic exposure, and prolonged hospitalization are consistently associated with greater disease severity and a higher probability of recurrence, establishing CDI as a condition of particular relevance in high-risk hospital populations<sup>12</sup>. The clinical manifestations of CDI can be grouped into distinct clinical phenotypes with different prognostic implications (Table 1).

### Diagnostic advances and limitations of available tests

The diagnosis of CDI is based on the integration of clinical criteria with laboratory tests aimed at detecting toxigenic strains or their toxins in stool samples<sup>13</sup>. Available evidence demonstrates that no single diagnostic test offers optimal performance in all clinical scenarios, which has driven the use of combined diagnostic algorithms<sup>14</sup>.

Molecular tests, such as polymerase chain reaction (PCR) and loop-mediated isothermal amplification (LAMP) techniques, have demonstrated high sensitivity and rapid diagnostic performance; however, their main limitation lies in their inability to distinguish between colonization and active infection, which can lead to overdiagnosis in asymptomatic patients<sup>15</sup>. The main tests used for the diagnosis of CDI have advantages and limitations that determine their clinical utility (Table 2).

On the other hand, toxin detection assays using enzyme-linked immunosorbent assay (ELISA) offer greater clinical specificity, although with limited sensitivity, which increases the risk of false negatives. The cytotoxicity assay continues to be considered a gold standard, but its technical complexity and the time required to obtain results have limited its use in daily clinical practice<sup>16</sup>.

Glutamate dehydrogenase (GDH) is a constitutive enzyme produced by all strains of *C. difficile*, both toxigenic and non-toxigenic; therefore, its detection is used as an initial screening

Clinical presentation	
<b>1. Colitis without pseudomembrane formation</b>	Severe diarrhoea, abdominal pain and abdominal distension. Systemic symptoms may include fever, nausea and dehydration. Stools may contain leukocytes and occult blood, whereas overt gastrointestinal bleeding is uncommon. Colonoscopy typically demonstrates diffuse or patchy mucosal inflammation.
<b>2. Pseudomembranous colitis</b>	Similar to the above presentation, although symptoms are more severe and leukocytosis is common. Colonoscopy reveals the characteristic pseudomembranes*, appearing as raised cream-yellow plaques on the colonic mucosa.
<b>3. Fulminant colitis</b>	In rare cases, CDI may present as fulminant colitis, with marked deterioration in the patient's general condition. Clinical features include severe abdominal pain, abdominal distension and severe systemic manifestations. Transmural intestinal inflammation may result in intestinal paresis and colonic dilatation with paralytic ileus, leading to cessation of diarrhoea.
<b>4. Toxic megacolon</b>	An uncommon but severe complication triggered by progressive inflammation involving the colonic wall, resulting in secondary dilatation of the intestinal lumen. Clinical manifestations vary but generally include severe abdominal pain, abdominal distension, high fever, tachycardia, dehydration and altered mental status. The resulting inflammation and oedema may lead to colonic perforation, sepsis and septic shock.
<b>Notes:</b> CDI exhibits a broad clinical spectrum, ranging from mild colitis to severe and potentially life-threatening disease. The clinical manifestations described above may overlap, and disease severity depends on host-related factors, bacterial burden and the inflammatory response. * The endoscopic findings described, including pseudomembranes, are not pathognomonic of <i>Clostridioides difficile</i> infection and should be interpreted within the patient's overall clinical and microbiological context. Source: Prepared by the authors.	

**Table 1. Clinical phenotypes and associated manifestations of *Clostridioides difficile* infection (CDI).**

test due to its high sensitivity, although with limited clinical specificity<sup>17</sup>.

**Therapeutic evidence and emerging strategies.**

Historically, metronidazole was considered the first-line treatment for mild to moderate cases of CDI. However, accumulating evidence has shown that it is less effective in real-world clinical settings, particularly when compared with oral vancomycin, with lower rates of clinical resolution and a higher risk of recurrence. This finding has been consistent across observational studies and clinical trials, especially in patients with moderate to severe disease<sup>18</sup>.

Additionally, an increase in the minimum inhibitory concentration (MIC) of metronidazole has been documented in some strains, suggesting a progressive decline in bacterial susceptibility, although the mechanisms of resistance are not fully defined. This phenomenon, coupled with its lower clinical efficacy, has contributed to the displacement of metronidazole as the preferred therapeutic option<sup>19</sup>. In this context, the updated guidelines from the Infectious Diseases Society of America and the Society for Healthcare Epidemiology of America (2021) recommend oral vancomycin or fidaxomicin as first-line treatment, relegating metronidazole to specific situations where no other alternatives are available<sup>19</sup>.

The guidelines from the *Infectious Diseases Society of America and the Society for Healthcare Epidemiology of America* (2021) recommend tapering and/or pulsing regimens for vancomycin, which have been shown to reduce the

likelihood of recurrence by enabling more effective eradication of residual spores. These regimens consist of progressively spaced administration of the antibiotic following a standard course, promoting the recovery of the gut microbiota. A common regimen includes 125 mg every 6 hours for 10–14 days, followed by a gradual dose reduction and administration every other day or every 2–3 days for several weeks<sup>20</sup>.

Fidaxomicin has emerged as a relevant therapeutic alternative, especially in patients at high risk of recurrence<sup>21</sup>. Several studies have documented significantly lower recurrence rates compared to vancomycin, which is attributed to its lesser impact on the gut microbiota. In cases of multiple recurrences, fecal microbiota transplantation (FMT) has established itself as one of the most effective therapeutic strategies. Its rationale lies in the restoration of gut microbial diversity, which is altered following antibiotic exposure. From a methodological standpoint, FMT involves rigorous donor selection, clinical and microbiological screening, as well as standardized stool processing; the stool can be administered via colonoscopy, enema, nasogastric tube, or oral capsules<sup>21</sup>.

Accumulated evidence, including clinical trials and real-world studies, has reported resolution rates exceeding 80–90% in recurrent infections, establishing it as a standard-of-care option in this setting. However, challenges remain regarding protocol standardization, long-term safety, and regulatory oversight<sup>22</sup>.

In this context, regulatory-approved microbiota-based therapies have emerged, such as Rebyota (a rectal suspension

Test	Sensitivity	Specificity	Remarks
<b>Glutamate Dehydrogenase (GDH) Enzyme Immunoassays</b>	Very high	Low	Detect the presence of the GDH enzyme, which is produced by all <i>Clostridioides difficile</i> strains. A positive GDH result indicates the presence of the organism but does not confirm toxin production. These assays are useful as an initial screening method owing to their high sensitivity.
<b>Enzyme Immunoassays (EIA)</b>	Moderate	High	Detect toxins A and B produced by <i>Clostridioides difficile</i> in stool samples. They employ toxin-specific antibodies and provide rapid, easily interpretable results. However, their sensitivity is limited, which may result in false-negative findings.
<b>Nucleic Acid Amplification Tests (NAATs)</b>	Very high	Moderate	Detect <i>Clostridioides difficile</i> -specific genetic material in stool samples. These tests are highly sensitive and specific and can provide rapid results. They identify toxigenic strains but do not determine whether toxins are being actively produced at the time of testing (biological activity). They are rapid, sensitive and suitable for use in resource-limited settings.
<b>Notes:</b> Diagnostic tests for CDI vary in sensitivity and specificity; therefore, results should be interpreted in conjunction with clinical findings. In clinical practice, the use of stepwise diagnostic algorithms combining tests with high sensitivity and specificity is recommended in order to reduce overdiagnosis and optimise the identification of clinically relevant cases. <b>Source:</b> Prepared by the authors.			

**Table 2. Main diagnostic tests for *Clostridioides difficile* infection (CDI): advantages and limitations.**

of fecal microbiota) and Vowst (an oral preparation of purified spores), both approved by the Food and Drug Administration for the prevention of CDI recurrence. These therapies represent an evolution toward standardized products with controlled safety profiles and regulated manufacturing processes, overcoming some of the limitations of conventional FMT<sup>23</sup>. Recent data from Europe support the use of these strategies, highlighting a significant reduction in recurrence and adequate tolerability, which reinforces their emerging role within the current therapeutic arsenal<sup>23</sup>.

Other innovative strategies include the use of monoclonal antibodies, such as bezlotoxumab, directed against toxin B, which have been shown to significantly reduce recurrence rates when used as adjuvant therapy. Furthermore, therapies aimed at preserving the gut microbiota during antibiotic use represent a promising line of research in the primary prevention of CDI<sup>24</sup>.

### Colonization, risk factors, and prevention strategies.

Asymptomatic colonization by *C. difficile* is a common phenomenon, particularly in hospital settings and among at-risk populations. It is estimated that 3–8% of healthy adults may be carriers, a figure that can rise to 20–50% among hospitalized patients or residents of long-term care facilities. Although these individuals do not exhibit clinical symptoms, they act as potential reservoirs for the transmission of the microorganism<sup>25</sup>.

The progression from colonization to clinical infection depends on multiple host and environmental factors. Key risk

factors include prior exposure to broad-spectrum antibiotics, advanced age, prolonged hospitalization, the presence of comorbidities, immunosuppression, and the use of proton pump inhibitors. These factors contribute to alterations in the gut microbiota and reduce resistance to colonization<sup>26</sup>.

From a pathophysiological perspective, intestinal dysbiosis resulting from the use of antimicrobials allows *C. difficile* spores to germinate and toxin A- and B-producing vegetative forms to proliferate. These toxins induce epithelial damage, disruption of tight junctions, and a local inflammatory response that leads to the development of clinical symptoms<sup>26</sup>.

Prevention strategies are based on interrupting transmission and preserving the intestinal microbiota. Key measures include the rational use of antimicrobials through optimization programs (PROA in Spanish), hand hygiene with soap and water, isolation of symptomatic patients, and environmental disinfection with sporicidal agents. Additionally, the implementation of appropriate diagnostic protocols helps prevent overdiagnosis and unnecessary treatment.

### Epidemiological implications and the burden on health care systems

Available epidemiological evidence confirms a sustained increase in the incidence and prevalence of CDI globally, particularly in hospital and long-term care settings<sup>27</sup>. This increase is associated not only with higher morbidity and mortality but also with a considerable economic impact, resulting from prolonged hospital stays, frequent readmissions,

and costs associated with managing recurrences and serious complications<sup>27</sup>.

In Europe, *C. difficile* infection continues to represent a significant cause of healthcare-associated infection. In Spain, multicenter studies have documented variable incidence rates across hospitals, attributed to differences in diagnostic algorithms, microbiological surveillance, and antimicrobial use policies<sup>27</sup>. Recent data indicate that the infection predominantly affects elderly, hospitalized patients with prior exposure to antibiotics or proton pump inhibitors. Furthermore, an increase in the identification of community-acquired cases and a significant persistence of recurrences have been reported, which keeps this infection a current clinical and epidemiological problem in Spain<sup>28</sup>.

In the Spanish context, the gradual implementation of antimicrobial optimization programs (PROA) and infection control measures has helped strengthen the preventive approach, although diagnostic challenges and interhospital heterogeneity persist.

Complementarily, the European Society of Clinical Microbiology and Infectious Diseases has published updated recommendations that agree on prioritizing fidaxomicin and vancomycin over metronidazole as initial treatment. However, the ESCMID guidelines take a more conservative approach to the use of fecal microbiota transplantation, reserving it primarily for carefully selected cases of multiple recurrences, while also emphasizing the need for individualized assessment based on clinical severity, therapeutic availability, and the local epidemiological context<sup>29</sup>.

In contrast, the recommendations from the Infectious Diseases Society of America and the Society for Healthcare Epidemiology of America advocate for earlier incorporation of therapies aimed at preventing recurrences, including monoclonal antibodies and microbiota-based products.

These findings underscore the need to implement comprehensive strategies for prevention, prudent use of antimicrobials, and infection control, with the aim of reducing both the clinical burden and the economic impact of CDI on healthcare systems<sup>30</sup>. Various factors have been associated with both the development of the first episode and the recurrence of CDI, with notable differences between the two scenarios (Table 3).

## Discussion

CDI continues to represent a significant clinical and epidemiological challenge, not only due to its high incidence in hospital settings but also because of the complexity inherent in its diagnosis, treatment, and prevention. The evidence analyzed in this review confirms that CDI is no longer a secondary complication of antibiotic use but has established itself as a distinct entity with its own dynamics, influenced by microbiological, clinical, and organizational factors.

One of the main conceptual contributions of recent studies has been the redefinition of the role of toxins in the pathogenesis of the disease. The classical notion of toxin A as the primary determinant of virulence has been superseded by solid experimental evidence that identifies toxin B as an essential factor in tissue damage, and even a dominant one in certain contexts<sup>20</sup>. This evolution in the understanding of pathogenesis is not merely academic but has had direct repercussions on the development of targeted therapies, such as monoclonal antibodies against toxin B, which have been shown to significantly reduce the recurrence of infection.

In the diagnostic realm, the current discussion focuses less on the availability of tests and more on their correct clinical interpretation. Molecular techniques, while having significantly improved diagnostic sensitivity and reduced turnaround times, have introduced the risk of overdiagnosis by failing to adequately distinguish between colonization and active infection. This phenomenon is particularly relevant in hospital settings with a high prevalence of asymptomatic carriers, where the indiscriminate use of highly sensitive tests can lead to unnecessary treatments and increased selective pressure on the gut microbiota. In this context, combined diagnostic algorithms emerge as the most reasonable strategy for balancing sensitivity and specificity, reinforcing the need to integrate laboratory findings with clinical judgment.

From a therapeutic standpoint, the available evidence consistently supports replacing metronidazole as the first-line option with oral vancomycin, particularly in moderate-to-severe cases. This change reflects a shift toward treatment regimens based on more robust clinical outcomes rather than solely on historical or economic considerations. Fidaxomicin, for its part, represents a significant advance in reducing recurrences, although its widespread use remains limited by cost and availability factors, especially in health systems with limited resources.

Managing recurrence remains one of the greatest challenges in CDI. In this context, fecal microbiota transplantation has demonstrated greater efficacy than conventional antibiotic regimens, establishing itself as a key therapeutic intervention in selected cases. However, its large-scale implementation faces logistical, regulatory, and standardization barriers, underscoring the need for more uniform protocols and studies evaluating its long-term safety.

The discussion on CDI prevention transcends the individual patient level and extends to an institutional dimension. Evidence suggests that environmental control strategies, the use of sporicidal disinfectants, and the adoption of contactless disinfection technologies are effective in reducing nosocomial transmission. However, their actual impact depends on adequate adherence to protocols and an organizational culture that prioritizes patient safety. In this sense, the prevention of CDI cannot be understood solely as a technical intervention, but rather as an indicator of the quality of healthcare systems.

Finally, significant gaps in knowledge remain, particularly regarding the regional epidemiology of hypervirulent strains and the impact of new therapeutic strategies in settings other

than high-income countries. The indiscriminate extrapolation of data from North America and Europe may not accurately reflect the epidemiological reality of regions such as Latin America, highlighting the need for local studies to inform prevention and treatment policies tailored to each context.

### Conclusions

CDI constitutes a persistent and complex problem in modern hospital settings, with a significant impact on patient morbidity and mortality and on the economic burden on health systems. The evidence reviewed confirms that effectively addressing this issue requires a comprehensive understanding of the mechanisms of pathogenicity, particularly the central role of toxins A and B, as well as the clinical and epidemiological factors that determine the severity and recurrence of the disease.

Advances in diagnosis have enabled faster and more sensitive detection of the infection; however, these benefits must be balanced with careful clinical interpretation to avoid overdiagnosis and unnecessary treatment. In the therapeutic setting, oral vancomycin has established itself as the first-line treatment, while fidaxomicin, monoclonal antibodies, and

Risk factors for initial episode	Risk factors for recurrent episode(s)
Advanced age (≥65 years)	Advanced age (≥65 years)
Antibacterial therapy	Antibacterial therapy
Cancer chemotherapy	Gastric acid suppressive agents (proton pump inhibitors)
Enteral feeding and gastrointestinal surgery	Exposure to healthcare settings
Gastric acid suppressive agents (proton pump inhibitors)	Impaired immune response
Exposure to healthcare settings	Previous episode(s) of <i>Clostridioides difficile</i> infection (CDI)
Impaired immune response	Underlying chronic comorbidities
Smoking and history of smoking	
Underlying chronic comorbidities	
<p><b>Notes:</b> Risk factors for <i>Clostridioides difficile</i> infection include host-related conditions, exposure to antimicrobial agents and contact with healthcare environments. Disease recurrence is associated with additional factors, such as persistent alterations in the intestinal microbiota and impaired immune response, which increase clinical complexity and the risk of further episodes.</p> <p><b>Source:</b> Prepared by the authors.</p>	

**Table 3.** Risk factors associated with the initial episode and recurrence of *Clostridioides difficile* infection.

fecal microbiota transplantation represent effective strategies for reducing recurrence in selected patients.

Preventing CDI requires interventions that go beyond individual treatment and integrate institutional policies for infection control, rational use of antimicrobials, and strengthening of the patient safety culture. Likewise, there is a clear need to generate regional evidence that allows diagnostic and therapeutic recommendations to be adapted to contexts with limited resources and distinct epidemiological realities.

Overall, the management of *C. difficile* infection requires an interdisciplinary and dynamic approach, grounded in the integration of scientific evidence, clinical judgment, and sustained preventive strategies, as the only way to mitigate the impact of this infection on contemporary healthcare systems.

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# GASTRODUODENAL ARTERY EMBOLIZATION OUTCOMES: COMPLICATIONS AND MANAGEMENT.

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## Abstract

Gastrointestinal bleeding is defined as the acute loss of blood through the gastrointestinal tract. The most common classification is based on the source of the bleeding, dividing it into upper gastrointestinal bleeding (UGIB) and lower gastrointestinal bleeding (LGIB), depending on whether it occurs proximal or distal to the ligament of Treitz, respectively.

Among the most frequent causes of UGIB are peptic ulcers, especially duodenal ulcers, which are particularly important when they are complicated, that is, those associated with massive bleeding, perforation, stenosis, or failure of endoscopic treatment. Bleeding can manifest as hematemesis or melena, and in the most severe cases, it can cause hypotension, tachycardia, or shock.

Initial management focuses on hemodynamic stabilization and the administration of proton pump inhibitors. Endoscopic examination is usually the first step. When bleeding is refractory or not treatable endoscopically, emergency

surgery or selective arterial embolization is performed, the latter being a technique that can lead to complications.

We present the case of a 78-year-old man with a history of upper gastrointestinal bleeding due to a duodenal ulcer and multiple rebleeding episodes, who was admitted for a new episode of melena. Endoscopy revealed a large duodenal ulcer with inflammatory stenosis, not amenable to endoscopic treatment, so gastroduodenal artery embolization was performed. One month later, he was readmitted with sepsis and hemodynamic instability. A CT scan showed a penetrating duodenal ulcer with pancreatic involvement and retroperitoneal fluid collections. Ultimately, conservative management was chosen, with a satisfactory outcome.

**Keywords:** upper gastrointestinal bleeding, arterial embolization, conservative management, post-embolization complications.

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## Introduction

Upper gastrointestinal bleeding (UGIB) is a common reason for emergency department visits in our region, with an estimated incidence of 48 to 160 cases per 100,000 inhabitants. It accounts for approximately 80% of cases of gastrointestinal bleeding and is the form most frequently associated with serious complications and a greater demand for hospital resources. The most significant risk factors include advanced age, the use of gastrointestinal-damaging drugs (notably nonsteroidal anti-inflammatory drugs), and treatment with anticoagulants, among others. Peptic ulcers are one of the leading causes of upper gastrointestinal bleeding, with duodenal ulcers being the most common. Their clinical significance increases in complicated cases, such as those presenting with significant bleeding, perforation, stricture, or when control cannot be achieved through endoscopic treatment. Other notable causes include complications arising from portal hypertension (PH-associated gastropathy, esophagogastric varices), neoplasms, or vascular anomalies<sup>1</sup>.

UGIB is a clinical challenge that often requires urgent intervention. The primary goals of treatment are to stop the acute bleeding episode and prevent rebleeding. Treatment generally requires a multidisciplinary approach with therapeutic options ranging from conservative, endoscopic, or surgical procedures, and sometimes including endovascular techniques<sup>4</sup>.

The procedure to be performed will depend on the patient's hemodynamic status and the location of the bleeding. Hemodynamically unstable patients should receive intensive medical care. Once stabilized, they should undergo endoscopy within the first 12 hours. In hemodynamically stable patients, endoscopy may be performed within the first 72 hours following continuous monitoring of vital signs.

If endoscopic therapy is ineffective due to the patient's condition or massive gastrointestinal bleeding, selective catheterization of the bleeding vessel may be necessary via interventional radiology, a technique not without acute and chronic complications, which, in a high percentage of cases, require medical, endoscopic, or even surgical management.<sup>2</sup>

## Clinical case

We present the case of a 78-year-old man with a history of UGIB due to a duodenal ulcer more than 20 years ago, as well as two subsequent hospitalizations for rebleeding from the same ulcer, manifesting as melena with anemia, in 2024 and 2025.

He was admitted to the Gastroenterology Department for a new episode of upper gastrointestinal bleeding presenting as melena. The patient reported no use of gastrolesive drugs or any new medications. During an upper gastrointestinal endoscopy performed upon admission, a large ulceration was visualized at the duodenal bend with an adherent clot (Forrest IIb), without active bleeding; a nasofibroscope was required to proceed due to marked duodenal stenosis with a significant inflammatory component resulting from the poor healing of the ulcer. Due to the patient's anemia and hemodynamic instability, as well as the impossibility of performing endoscopic treatment, it was decided to perform prophylactic embolization of the gastroduodenal artery.

As no complications were observed following the procedure, he was discharged with close follow-up. One month after discharge, he presented to the emergency department with a febrile syndrome that had been present for approximately 48 hours, as well as hemodynamic instability requiring the initiation of vasoactive medications. He did not present with abdominal pain, jaundice, or any other clinical findings associated with any other condition. Laboratory findings showed elevated acute-phase reactants (CRP, leukocytosis with neutrophilia), anemia with negative urea levels, and an abnormal pancreatic profile. There were no signs of gastrointestinal perforation.

Given the suspicion of an abdominal complication, an abdominal CT scan was performed, revealing inflammatory changes in the duodenum, likely a complicated duodenal ulcer with penetration into the pancreas, as well as a rounded, hypodense lesion within the thickness of the pyloric wall, with parietal thickening of the pylorus, which may correspond to a cystic lesion or abscess. There are no signs of pneumoperitoneum or other collections (Figure 1).

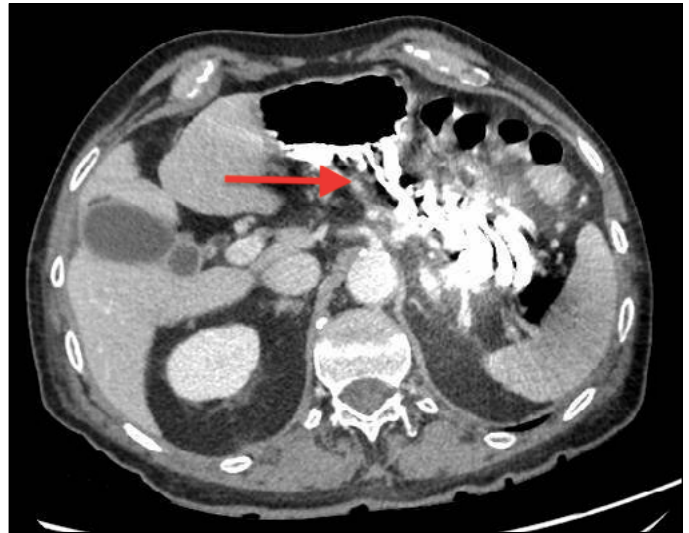
Based on the CT findings, an upper gastrointestinal endoscopy was performed during admission, revealing an inflammatory-appearing stenosis already present prior to embolization, which again prevented the passage of a standard endoscope into the second portion of the duodenum.

Following a review of the case during a medical-surgical conference, surgery was ruled out, and conservative management was therefore initiated, resulting in favorable clinical, laboratory, and radiological outcomes compared to the previous evaluation (Figure 2).

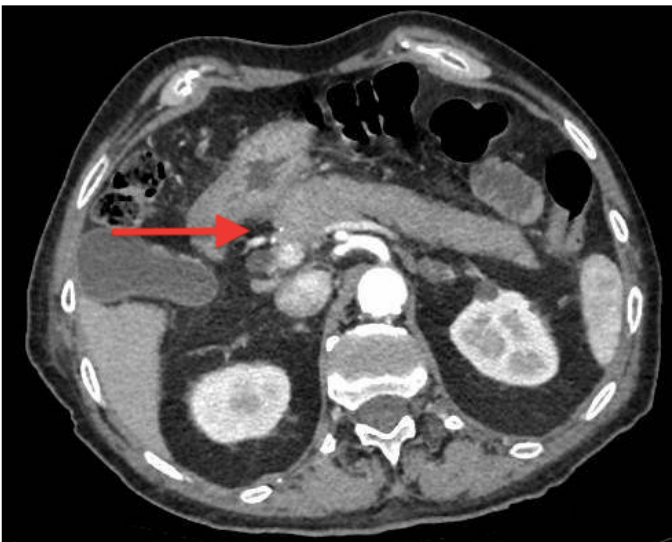
At discharge, a follow-up upper endoscopy was ordered to assess endoscopic dilation of the duodenal stenosis. In this



**Figure 1.** Axial CT scan of the abdomen showing a small ulcer in the duodenum (red arrow), as well as a cystic lesion in the pylorus consistent with a small abscess at that level.



**Figure 3.** Axial CT scan of the abdomen. A perforating duodenal ulcer is observed in the posteroinferior wall of the second portion of the duodenum, along with encapsulated right retroperitoneal collections containing gas and a thread-like passage of oral contrast from the second portion of the duodenum.



**Figure 2.** Axial CT scan of the abdomen. Good radiological improvement compared to the previous study, with resolution of the pyloric abscess observed. Known stenosis in the second portion of the duodenum.

After evaluating all possible treatment options, the patient finally underwent ultrasound-guided percutaneous drainage of the retroperitoneal collection, along with parenteral nutrition and antibiotic therapy.

The patient showed favorable clinical and radiological progress (Figure 4). At discharge, the collections had resolved, there was no evidence of oral contrast leakage on the follow-up CT scan, and the patient tolerated a liquid diet well. The patient was discharged due to overall improvement and was scheduled for close follow-up in the gastroenterology outpatient clinic.



**Figure 4.** Axial CT scan of the abdomen. Good radiological progress compared to the previous study, showing resolution of the previously noted retroperitoneal collections (following percutaneous drainage) and no evidence of leakage of the administered oral contrast.

examination, a deep ulcer was observed on the posteroinferior wall with partially fibrinous surrounding mucosa, likely related to the penetrating ulcer previously described in imaging studies, with no current active bleeding or other apparent complications. An attempt was made to close the defect with a Hemoclip, but this was not possible due to technical difficulty. Given these findings, a decision is made to readmit the patient for updated imaging studies, and a follow-up abdominal CT scan is performed, revealing a penetrating duodenal ulcer in the second portion of the duodenum associated with retroperitoneal collections, gas, and a thread-like passage of oral contrast from the second portion of the duodenum (Figure 3).

## Discussion

UGIB is a medical emergency that carries a risk of complications and places a high demand on hospital resources<sup>1</sup>.

In certain situations, such as recurrent gastrointestinal bleeding, an unclear source of bleeding, or the impossibility of endoscopic therapy, selective catheterization of the bleeding vascular branch via interventional radiology may be necessary. Compared to surgical procedures, interventional radiological strategies for the treatment of upper gastrointestinal bleeding show similar efficacy in terms of technical success and recurrence rates, but with lower mortality<sup>2</sup>.

Arterial embolization in the gastrointestinal tract above the ligament of Treitz is generally considered very safe due to the abundant collateral circulation to the stomach and duodenum. Potential acute post-procedural complications include hematomas at the access site, vascular dissections, contrast-related complications (allergy, nephropathy), or risk of intestinal ischemia<sup>3</sup>. Among chronic complications, duodenal stenosis associated with embolization of the terminal vessels of a bleeding site stands out as a result of severe hypoxia, leading to avascular necrosis<sup>5</sup>. The risk of significant ischemia or stenosis may increase in the presence of additional damage to the collateral circulation due to prior abdominal surgery, radiation therapy, or severe atherosclerosis. In these situations, balloon dilation may be possible, but surgical resection should be considered in refractory cases<sup>3</sup>.

As seen in this case, the patient has a history of UGIB due to a duodenal ulcer and frequent rebleeding and was admitted for melena. Gastroduodenal artery embolization was performed following the failure of endoscopic treatment, due to severe inflammatory stenosis present prior to the embolization. One month later, he developed sepsis due to a penetrating duodenal ulcer with pancreatic involvement, which resolved with conservative management.

Therefore, in the presence of acute or chronic post-embolization complications, it is necessary to discuss possible therapeutic solutions in a medical-surgical conference, as medical treatment is a valid and effective option, as demonstrated in this case.

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# GASTROINTESTINAL AMYLOIDOSIS AS THE INITIAL MANIFESTATION OF SYSTEMIC AMYLOIDOSIS

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## Abstract

Amyloidosis is an extracellular deposition disease, with primary amyloidosis being rare. In addition, gastrointestinal presentation is unusual, rarely the form of onset of the disease.

We describe a case of systemic amyloidosis in which the diagnosis is reached due to the gastrointestinal involvement with digestive clinical debut.

As conclusion, we describe this disease to take it into account as differential diagnosis of certain digestive symptomatology, even if it is non-specific.

**Keywords:** amyloidosis, gastrointestinal, systemic amyloidosis.

## Introduction

Amyloidosis is a disease characterized by the extracellular deposition of fibrillar protein material, which leads to changes in the morphology and function of the tissue where it is deposited. Primary amyloidosis is a rare disease that affects multiple organs and has a poor prognosis<sup>5</sup>.

Gastrointestinal (GI) involvement is rare and usually paucisymptomatic; it is rarely the initial presentation of the disease and is most frequently observed in the context of primary systemic amyloidosis<sup>1,4</sup>. In the GI presentation, endoscopic findings are nonspecific<sup>4</sup>. The diagnosis is based on the demonstration of amyloid deposits in the tissues, and treatment must be individualized based on age, the degree, and type of organ involvement<sup>5</sup>.

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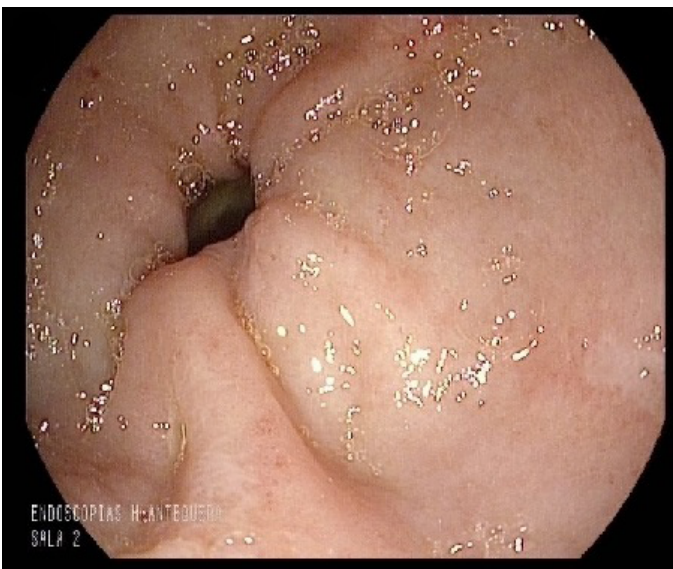
# CLINICAL CASE

## Clinical case

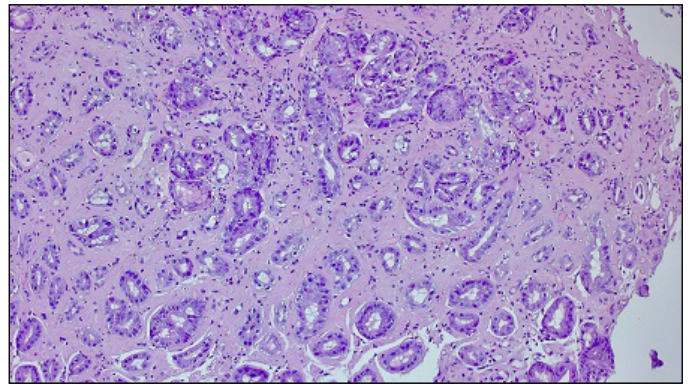
A 74-year-old man was admitted for abdominal pain, vomiting, constipation, and weight loss. During the workup, a gastroscopy was performed, revealing a gastric mucosa with an edematous, nodular appearance and several nonspecific erosions (Figures 1 and 2). With gastritis suspected, biopsies were taken; given the evidence of hyalinization in the lamina propria, the pathology department expanded the investigation. The Congo red histochemical technique was performed, revealing the presence of amorphous and hyaline material exhibiting birefringence, consistent with amyloid material (Figures 3-5). Based on these findings, a diagnosis of gastrointestinal amyloidosis was made.



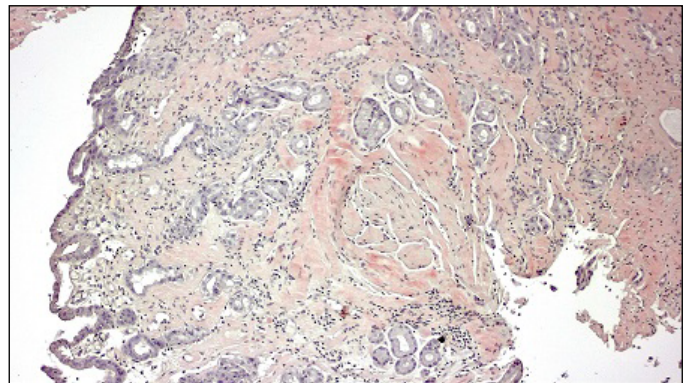
**Figure 1.** Retroverted gastric chamber with a mucosa that appears slightly edematous and erythematous.



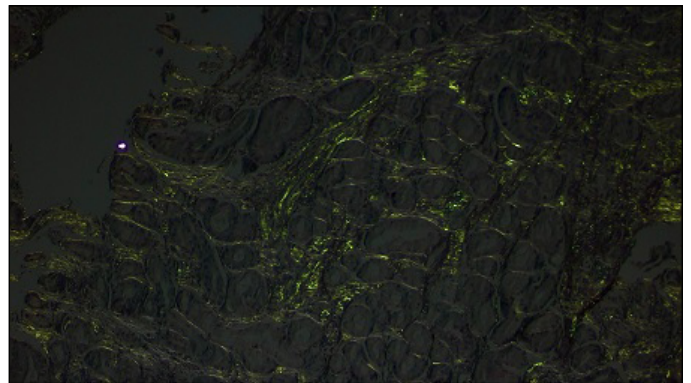
**Figure 2.** Edematous antral mucosa with slightly dyschromic patchy area.



**Figure 3.** Mucosal hyalinization viewed with hematoxylin and eosin staining.



**Figure 4.** Amyloid deposits visualized using the Congo red technique.



**Figure 5.** Visualization of amyloid content with Congo red staining under polarized light.

During follow-up after discharge, the patient reported new symptoms including dyspnea related to decompensated heart failure, neurological problems, and the appearance of a skin lesion that was biopsied and diagnosed as primary systemic kappa-amyloidosis (AL), with follow-up and treatment provided by the Hematology Department.

## Discussion

GI amyloidosis, and specifically gastric involvement, is a rare manifestation of primary systemic amyloidosis, occurring less frequently than renal and cardiac involvement<sup>1,3</sup>.

Gastrointestinal symptoms as the initial presentation are highly uncommon; however, in our case, the onset consisted of gastrointestinal symptoms. It is usually asymptomatic or nonspecific, but may present with symptoms such as: gastrointestinal bleeding, protein-losing gastroenteropathy, malabsorption, and motility disorders, the latter including: nausea, vomiting, gastroesophageal reflux, anorexia, constipation, chronic intestinal pseudo-obstruction, or gastroparesis<sup>1,2</sup>. In our case, symptoms of motility disorders were present.

As was the case in our patient, endoscopic findings are nonspecific, with the main endoscopic findings being erosions, ulcerations, and nodular-appearing mucosa, as well as pseudopolypoid protrusions<sup>4</sup>; diagnosis requires a biopsy to confirm the deposit using Congo red staining<sup>5</sup>.

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# ACUTE EMPHYSEMATOUS CHOLECYSTITIS. AN ENTITY TO BE TAKEN INTO ACCOUNT IN THE DIFFERENTIAL DIAGNOSIS OF ACUTE ABDOMINAL PAIN.

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## Abstract

Acute emphysematous cholecystitis is a rare entity characterised by the presence of gas in the gallbladder wall and/or lumen. Its morbidity and mortality are highly significant due to its rapidly progressive course towards sepsis, shock and even death if an emergency cholecystectomy is not performed. As the initial clinical presentation is not specific and may be similar to that of acute cholecystitis, it is crucial to have a high index of suspicion.

We present the case of a patient who was admitted for acute abdominal pain and required three urgent imaging tests in a brief period of time to achieve a diagnosis of acute emphysematous cholecystitis.

**Keywords:** emphysematous cholecystitis, acute cholecystitis, acute abdominal pain.

## Introduction

Acute emphysematous cholecystitis is a rare form of acute cholecystitis with a potentially fatal course, constituting a surgical emergency. Maintaining a high index of suspicion is essential, as it can pose a diagnostic challenge, particularly in its early stages.

## Clinical case

A 63-year-old man had no known drug allergies, no history of substance abuse, and well-controlled type 2 diabetes mellitus on oral antidiabetic medications as his only relevant medical history. He presented to the Emergency Department complaining of epigastric and right upper quadrant pain, along with nausea and bilious vomiting that had been present for 24 hours. He reports no fever or other symptoms. He denies any dietary indiscretion prior to the onset of symptoms.

## IMAGE IN CLINICAL CASE

On physical examination, the patient appeared in good general condition, although affected by pain. The only notable finding was tenderness on superficial palpation of the epigastrium and right hypochondrium, with no signs of peritonitis.

Blood tests revealed mild hypertransaminasemia (AST 85 IU/L, ALT 90 IU/L) and mild hyperamylasemia (350 U/L). Acute-phase reactants were not elevated.

Given these findings, the Emergency Department decided to admit the patient to the Gastroenterology ward with a suspected diagnosis of acute biliary pancreatitis.

On his first day in the ward, the patient experienced worsening abdominal pain, which remained unresponsive even to second-line analgesia. Urgent laboratory tests were ordered, but no elevation in acute-phase reactants or other new laboratory abnormalities were detected. Based on the clinical presentation, an urgent abdominal CT scan with intravenous



**Figure 1.** Abdominal CT cross-section with intravenous contrast showing no significant pathological findings in the structures depicted, including the gallbladder.

contrast was also ordered, which reported no pathological findings (Figure 1).

Just 12 hours later, and given the persistence of symptoms despite analgesia with strong opioids, an urgent abdominal ultrasound was performed. This revealed subhepatic gas, so a new abdominal CT scan with intravenous contrast was performed, showing tomographic findings consistent with acute emphysematous cholecystitis (Figure 2), with gas in the gallbladder wall and subserosal edema. No gallstones or signs of pancreatic pathology were evident in the radiological examinations performed.



**Figure 2.** Abdominal CT cross-section with intravenous contrast, performed 12 hours later, showing gas in the gallbladder wall (green arrows), with subserosal edema, consistent with acute emphysematous cholecystitis.

In the absence of significant comorbidities, the case was discussed with the Surgery department. Following their evaluation, broad-spectrum empirical antibiotic therapy was initiated, and an urgent laparoscopic cholecystectomy was performed, with a subsequent favorable outcome. Examination of the surgical specimen confirmed the diagnosis of acute emphysematous cholecystitis, with the isolation of pan-sensitive *Clostridium perfringens*.

### Discussion

Emphysematous cholecystitis is a rare form of acute cholecystitis, accounting for 1% of all cases. Its main distinguishing feature is the presence of gas in the gallbladder wall and/or lumen<sup>1</sup>. The microorganisms most commonly involved are *Escherichia coli*, *Klebsiella spp.*, and, as in our case, *Clostridium spp.*<sup>2</sup>. It is more common in men, patients with diabetes, and immunocompromised individuals.

Although abdominal ultrasound is usually the first test performed as an initial approach to evaluating abdominal pain, CT is the most sensitive and specific diagnostic technique and is the method of choice. Initially, the clinical presentation is similar to that of acute cholecystitis, but with an insidious and rapidly progressive course toward sepsis and shock, resulting in high morbidity and mortality rates<sup>3</sup>.

Therefore, it is crucial to always consider this condition in the differential diagnosis of acute abdominal pain, even when initial diagnostic tests are unremarkable.

Cholecystectomy is the definitive treatment of choice and should be performed as soon as possible. In elderly patients or those with significant comorbidities, echoendoscopy-guided

cholecystostomy or percutaneous cholecystostomy may be considered as therapeutic alternatives<sup>4</sup>.

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# THE ANTI-TNF PARADOX: PALMOPLANTAR PUSTULAR PSORIASIS.

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## Abstract

Paradoxical psoriasis induced by anti-TNF therapy is an infrequent reaction in patients with inflammatory bowel disease, characterized by the appearance of cutaneous lesions during biologic treatment, despite these agents also being used to manage psoriasis. It can present in vulgar, pustular, or palmoplantar forms and typically occurs within the first year of therapy. Early recognition is crucial to guide clinical management and consider therapeutic strategies targeting alternative immunological pathways, as illustrated in the case described.

**Keywords:** Crohn's disease, psoriasis, adalimumab.

## Clinical case

A 50-year-old man with no relevant medical history or concomitant medications was diagnosed in 2005 with stenosing ileal Crohn's disease. He began treatment with subcutaneous adalimumab in January 2025, achieving an adequate clinical response in the intestines and improvement in gastrointestinal symptoms.

After approximately eight months of treatment, he developed skin lesions on the palms and soles, characterized by erythema, scaling, and painful pustules. He was evaluated by the Dermatology department, where the lesions were classified as palmoplantar pustular psoriasis, a rare condition

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recognized as a possible paradoxical reaction induced by adalimumab.

Given this suspicion, it was decided to discontinue adalimumab and switch therapy to ustekinumab. Following induction and the first maintenance doses, the patient experienced complete resolution of the skin lesions and maintained adequate control of his inflammatory bowel disease, with no new flare-ups or associated complications.

### Discussion

Anti-TNF-induced paradoxical psoriasis reflects the immunological complexity of these therapies. Sustained TNF blockade may promote the activation of alternative pathways, such as IL-23/IL-17, and the overexpression of type I interferon, which contributes to the development of skin lesions. The therapeutic approach must simultaneously evaluate intestinal activity and dermatological involvement. In moderate to severe cases, switching to a biologic with a different mechanism of action, such as ustekinumab, offers a dual benefit: resolution of skin lesions and stable control of inflammatory bowel disease. This case underscores the importance of identifying these paradoxical reactions early and considering therapeutic strategies based on alternative immune pathways to optimize comprehensive patient care.



**Figure 1.** Erythematous pustular lesions on the soles of both feet, bilaterally and symmetrically distributed, with some confluent lesions and areas of scaling, consistent with paradoxical palmoplantar pustular psoriasis.

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