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Indications of *Helicobacter pylori* Eradication Treatment and Its Influence on Prescriptions and Effectiveness (Hp-EuReg)

Samuel J. Martínez-Domínguez[1,2,3] | Olga P. Nyssen[4] | Ángel Lanas[1,2,3] | Enrique Alfaro[1,2,3] | Laimas Jonaitis[5] | Umud Mahmudov[6] | Irina Voynovan[7] | Babayeva Gülüstan[8] | Luis Rodrigo[9] | Giulia Fiorini[10] | Ángeles Perez-Aisa[11] | Javier Tejedor-Tejada[12] | Bojan Tepes[13] | Ludmila Vologzanina[14] | Emin Mammadov[8] | Frode Lerang[15] | Quliyev Fərid Vidadi Oğlu[16] | Natalia V. Bakulina[17] | Rustam Abdulkhakov[18] | Ilchishina Tatiana[19] | Thomas J. Butler[20] | Aiman Silkanovna Sarsenbaeva[21] | Renate Bumane[22] | Alfredo J. Lucendo[23] | Marco Romano[24] | Luis Bujanda[3,25,26] | Sayar R. Abdulkhakov[17] | Oleg Zaytsev[27] | Manuel Pabón-Carrasco[28] | Alma Keco-Huerga[28] | Maja Denkovski[29] | Jose M. Huguet[30] | Monica Perona[31] | Óscar Núñez[32] | Matteo Pavoni[10] | Galyna Fadieienko[33] | Sergey Alekseenko[34] | Sinead M. Smith[35] | Luis Hernández[36] | Juozas Kupcinskas[37] | Dmitry S. Bordin[38,39,40] | Mārcis Leja[41] | Antonio Gasbarrini[42] | Oleksiy Gridnyev[33] | Anna Cano-Català[43] | Pablo Parra[4] | Leticia Moreira[44] | Francis Mégraud[45] | Colm O'Morain[46] | Javier P. Gisbert[4] | on behalf of the Hp-EuReg Investigators

[1]Department of Gastroenterology, Hospital Clínico Universitario Lozano Blesa, Zaragoza, Spain | [2]Instituto de Investigación Sanitaria de Aragón (IIS Aragón), Facultad de Medicina, Universidad de Zaragoza, Zaragoza, Spain | [3]Centro de Investigación Biomédica en Red en Enfermedades Digestivas y Hepáticas (CIBERehd), Madrid, Spain | [4]Instituto de Investigación Sanitaria Princesa (IIS-Princesa), Centro de Investigación Biomédica en Red de Enfermedades Hepáticas y Digestivas (CIBERehd), Hospital Universitario de La Princesa, Universidad Autónoma de Madrid (UAM), Madrid, Spain | [5]Department of Gastroenterology, Lithuanian University of Health Sciences, Kaunas, Lithuania | [6]Modern Hospital, Baku, Azerbaijan | [7]Department of Gastroenterology, A.S. Loginov Moscow Clinical Scientific Center, Moscow, Russia | [8]Azerbaijan State Advanced Training Institute for Doctors Named by A.Aliyev, Baku, Azerbaijan | [9]Department of Gastroenterology, University of Oviedo, Oviedo, Spain | [10]IRCCS Azienda Ospedaliero-Universitaria di Bologna, Bologna, Italy | [11]Department of Gastroenterology, Redes de Investigación Cooperativa Orientada a Resultados en Salud (RICORS), Hospital Universitario Costa del Sol, Marbella, Spain | [12]Department of Gastroenterology, Hospital Universitario de Cabueñes, Gijón, Asturias, Spain | [13]Department of Gastroenterology, DC Rogaska, Rogaska Slatina, Slovenia | [14]Gastrocenter, Perm, Russia | [15]Østfold Hospital Trust, Grålum, Norway | [16]National Oncology Centre, Baku, Azerbaijan | [17]I.I. Mechnikov North-Western State Medical University of the Ministry of Health of the Russian Federation, Saint Petersburg, Russia | [18]Department of Hospital Medicine, Kazan State Medical University, Kazan, Russia | [19]Department of Gastroenterology, SM-Clinic, Saint-Petersburg, Russia | [20]Department of Gastroenterology, Clinical Medicine, Trinity College Dublin, Tallaght University Hospital, Dublin, Ireland | [21]Department of Gastroenterology, Chelyabinsk Regional Clinical Hospital, Chelyabinsk, Russia | [22]Digestive Diseases Centre GASTRO, Riga, Latvia | [23]Department of Gastroenterology, Instituto de Investigación Sanitaria Princesa (IIS-Princesa), Centro de Investigación Biomédica en Red de Enfermedades Hepáticas y Digestivas (CIBERehd), Hospital General de Tomelloso, Tomelloso, Spain | [24]Gastroenterology and Endoscopy Unit, Dipartimento di Medicina di Precisione, Università Vanvitelli, Naples, Italy | [25]Department of Gastroenterology, Biodonostia Health Research Institute, San Sebastián, Spain | [26]Department of Medicine, Universidad del País Vasco (UPV/EHU), San Sebastián, Spain | [27]First Clinical Medical Centre, Kovrov, Russia | [28]Department of Gastroenterology, Hospital Universitario de Valme, Sevilla, Spain | [29]Interni Oddelek, Diagnostic Centre, Bled, Slovenia | [30]Department of Gastroenterology, Hospital General Universitario de Valencia, Valencia, Spain | [31]Department of Gastroenterology, Hospital Quirón Marbella, Marbella, Spain | [32]Department of Gastroenterology, Hospital Universitario Sanitas La Moraleja, Madrid, Spain | [33]Department the Division for the Study of the Digestive Diseases and its Comorbidity with Noncommunicable Diseases, Government Institution L.T. Malaya Therapy National Institute of NAMS of Ukraine, Kharkiv, Ukraine | [34]Far Eastern State Medical University, Khabarovsk, Russia | [35]School of Medicine, Trinity College Dublin, Dublin, Ireland | [36]Gastroenterology Unit, Hospital Santos Reyes, Aranda de Duero, Spain | [37]Department of Gastroenterology, Institute for Digestive Research, Lithuanian University of Health Sciences, Kaunas, Lithuania | [38]Department of Pancreatic, Biliary and Upper Digestive Tract

Abbreviations: A, amoxicillin; AEs, adverse events; B, bismuth salts; C, clarithromycin; CI, confidence interval; Conc, concomitant; GERD, gastroesophageal reflux disease; *Helicobacter pylori*, *H. pylori*; Hp-EuReg, European Registry on *Helicobacter pylori* management; ITT, intention-to-treat; M, metronidazole; mITT, modified intention-to-treat; *N*, number of cases; NA, not applicable; NSAIDs, non-steroidealnon-steroidal anti-inflammatory drugs.; OR, odds ratio; PP, per protocol; PPI, proton pump inhibitor; Quad, quadruple; Seq, sequential; T, tinidazole; Tc, tetracycline; Y, years.

Samuel J. Martínez-Domínguez and Olga P. Nyssen contributed equally to this work.

Corporate authorship named "on behalf of the Hp-EuReg Investigators" is detailed in File S1.

Disorders, A. S. Loginov Moscow Clinical Scientific Center, Moscow, Russia | [39]Department of Outpatient Therapy and Family Medicine, Tver State Medical University, Tver, Russia | [40]Department of Propaedeutic of Internal Diseases and Gastroenterology, Russian University of Medicine, Moscow, Russia | [41]Department of Gastroenterology, Digestive Diseases Centre, Institute of Clinical and Preventive Medicine, University of Latvia, Riga, Latvia | [42]Medicina Interna e Gastroenterologia, Fondazione Policlinico Universitario Agostino Gemelli IRCCS, Rome, Italy | [43]Gastrointestinal Oncology, Endoscopy and Surgery (GOES) Research Group, Institut de Recerca i Innovació en Ciències de la Vida i de la Salut de la Catalunya Central (IRIS-CC), Althaia Xarxa Assistencial Universitària de Manresa, Manresa, Spain | [44]Department of Gastroenterology, Centro de Investigación Biomédica en red en Enfermedades Hepáticas y Digestivas (CIBERehd), Institut d'Investigacions Biomèdiques August pi i Sunyer (IDIBAPS), Hospital Clínic de Barcelona, University of Barcelona, Barcelona, Spain | [45]INSERM U1312 Bric, Université de Bordeaux, Bordeaux, France | [46]Faculty of Health Sciences, Trinity College Dublin, Dublin, Ireland

Correspondence: Samuel J. Martínez-Domínguez (sjmartinezdo@salud.aragon.es)

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Keywords: compliance | effectiveness | *Helicobacter pylori* | indications | safety

ABSTRACT

Background: The influence of indications for *Helicobacter pylori* investigation on prescriptions and effectiveness is unknown. The aim of the study was to assess the impact of indications for *H. pylori* investigation on prescriptions, effectiveness, compliance, and tolerance.

Methods: International, prospective, non-interventional registry of the management of *H. pylori* infection by European gastroenterologists (Hp-EuReg). Treatment-näive patients registered from 2013 to 2023 at e-CRF AEG-REDCap were analyzed. The effectiveness was assessed by modified intention-to-treat analysis.

Results: Overall, 53,636 treatment-naïve cases from 34 countries were included. Most frequent indications were: dyspepsia with normal endoscopy (49%), non-investigated dyspepsia (20%), duodenal ulcer (11%), gastric ulcer (7.7%), and gastroesophageal reflux disease (GERD) (2.6%). Therapy effectiveness varied by indication: duodenal ulcer (91%), gastric ulcer (90%), preneoplastic lesions (90%), dyspepsia with normal endoscopy (89%), GERD (88%), and non-investigated dyspepsia (87%). Bismuth-metronidazole-tetracycline and clarithromycin-amoxicillin-bismuth quadruple therapies achieved 90% effectiveness in all indications except GERD. Concomitant clarithromycin-amoxicillin-tinidazole/metronidazole reached 90% cure rates except in patients with non-investigated dyspepsia; whereas sequential clarithromycin-amoxicillin-tinidazole/metronidazole proved optimal (≥90%) in patients with gastric ulcer only. Adverse events were higher in patients treated for dyspepsia with normal endoscopy and duodenal ulcer compared with the remaining indications (23% and 28%, $p < 0.001$). Therapeutic compliance was higher in patients with duodenal ulcer and preneoplastic lesions (98% and 99%, $p < 0.001$).

Conclusion: In Europe, patients with gastric or duodenal ulcers and preneoplastic lesions showed higher *H. pylori* treatment effectiveness. Bismuth and non-bismuth quadruple therapies achieved optimal results in almost all indications.

Trial Registration: ClinicalTrials.gov identifier: NCT02328131.

1 | Introduction

Helicobacter pylori infects approximately half of the world's population, with marked heterogeneity between geographical areas [1]. *H. pylori* is involved in the development of peptic ulcer disease, dyspepsia, mucosa-associated lymphoid tissue (MALT) lymphoma, gastric adenocarcinoma, and other extra-gastric conditions such as unexplained iron-deficiency anemia, vitamin B12 deficiency and some cases of idiopathic thrombocytopenic purpura [2, 3].

National and international scientific guidelines such as Maastricht VI/Florence consensus 2023 have established formal indications for the investigation and eventual treatment of *H. pylori* when this strategy provides a clinical benefit [4, 5]. However, the adherence to these recommendations in real clinical practice has been suboptimal in both gastroenterology (1.7%–7.2% of inadequate indications) and primary care levels (up to 35.9% of inadequate *H. pylori* investigations) [6–9].

Factors such as the number of antibiotics, treatment duration, treatment line, proton pump inhibitor (PPI) dosages, and antibiotic resistances were associated with treatment effectiveness [10, 11]. Nevertheless, there is limited evidence on how the indications for *H. pylori* investigation impact treatment effectiveness, compliance, or tolerance.

Longer treatment durations have been associated with a higher incidence of adverse events (AEs) [12]. The indication for *H. pylori* diagnosis could potentially affect the occurrence of AEs or therapeutic adherence, as symptoms can vary widely from oligosymptomatic dyspepsia to peptic ulcer disease or malignancy [1].

The aim of the current study was to assess the effectiveness, therapeutic compliance, and safety of empirical first-line treatment for *H. pylori* infection in Europe based on the indications that prompted the diagnosis of the infection. The secondary objective was to assess the evolution of their corresponding treatment effectiveness in the study time span (from 2013 to 2023).

2 | Materials and Methods

The European Registry on *H. pylori* management (Hp-EuReg) is an international (34 countries), prospective, multicentre (300 investigators), non-interventional registry that started in 2013 promoted by the European Helicobacter and Microbiota Study Group (www.helicobacter.org) [13].

The Hp-EuReg protocol was approved by the Ethics Committee of La Princesa University Hospital (Madrid, Spain), which acted as a reference Institutional Review Board (20 December 2012), and was conducted according to the guidelines of the Declaration of Helsinki, was classified by the Spanish Drug and Health Product Agency. In addition, this study followed STROBE guidelines. Detailed information is summarized in File S2.

2.1 | Participants

Data were collected into the registry's database (REDCap) by gastroenterologists who routinely managed patients with *H. pylori* treatment indication, using an Electronic Case Report Form (e-CRF) [14]. The REDCap database is managed and hosted by the "Asociación Española de Gastroenterología" (AEG, Madrid, Spain, www.aegastro.es), a non-profit Scientific and Medical Society that focuses on Gastroenterology research. Data were anonymized. Written informed consent was obtained from all patients included in the study.

For the purpose of the current study, all records registered until July 2023 and treated with a first-line empirical treatment were included in the analysis.

2.2 | Statistical Analysis

2.2.1 | Variables Categorization and Definition

To ease the synthesis of information, six countries with the highest number of records were selected a priori for further analyses: Spain, Russia, Italy, Slovenia, Azerbaijan, and Lithuania; altogether reaching 81% of the total of the first-line treatments included. Then, data for each country was reported.

The six first-line therapeutic schemes with the highest number of records were selected for further analyses: triple-CA (clarithromycin, amoxicillin, and PPI), triple-CM (clarithromycin, metronidazole, PPI), sequential-CAT-CAM (clarithromycin, amoxicillin, tinidazole/metronidazole, PPI), concomitant-CAT-CAM (clarithromycin, amoxicillin, tinidazole/metronidazole, PPI), quadruple-BMTc (prescribed as a single capsule containing bismuth salts, metronidazole and tetracycline concomitantly with a PPI; or in the classical form with all drugs given separately) and quadruple-CAB (clarithromycin, amoxicillin, bismuth salts, PPI).

The different dosages prescribed with the different PPIs (omeprazole, lansoprazole, pantoprazole, rabeprazole, and esomeprazole), were collected in the Hp-EuReg dataset. Thereafter, it was decided to calculate the different PPI dosages by standardizing the PPI potency—in terms of the duration of intragastric pH >4/24 h (pH 4-time)—to rank PPIs, where relative potency varied from 4.5 mg omeprazole equivalents (20 mg pantoprazole) to 72 mg omeprazole equivalents (40 mg rabeprazole), as described by Graham, Lu, and Dore [15] and Kirchheiner et al. [16]. These authors reported such standardization would allow the interchangeable use of PPIs based on relative potency, and so, following this method, the different PPI schedules and types were grouped into three categories: low dose, if the potency of PPI was between 4.5 and 27 mg omeprazole equivalents when given twice daily; standard dose, between 32 and 40 omeprazole equivalents when given twice daily; and high dose, between 54 and 128 mg omeprazole equivalents when given twice daily.

The duration of treatment was assessed using three categories corresponding to the most frequently prescribed lengths: 7, 10, and 14 days.

Adequate compliance with treatment was defined as having taken at least 90% of the prescribed drugs.

The indications were registered by the investigators as one of the following categories: non-investigated dyspepsia, dyspepsia with normal endoscopy (meaning "normal" as resulting in no ulcerative or cancerous finding), duodenal ulcer, gastric ulcer, preneoplastic lesions (atrophic gastritis or intestinal metaplasia), non-steroidal anti-inflammatory drugs (NSAIDs) or aspirin treatment, long-term treatment with PPI, surgical or endoscopic resection of gastric cancer, MALT lymphoma, first-degree relatives of patients with gastric cancer, unexplained iron deficiency anemia, vitamin B12 deficiency or idiopathic thrombocytopenic purpura. The investigators were instructed to record an indication for each patient focusing on the one that primarily motivated the eradication of the infection. In case the indication did not fit into any of the previous groups, the investigators recorded them as free text and were recorded in another category labeled "other". All "free-text" recorded cases were reviewed and reclassified into the previous or new groups, whenever possible.

2.2.2 | Data Analysis

Qualitative variables were presented using absolute and relative frequencies with percentages (%) and corresponding 95% confidence intervals (CI). Continuous variables were summarized

using the mean and standard deviation (SD) or median and interquartile range (IQR), as appropriate.

Differences between groups were analyzed with the Chi-square test or Fisher's test, as appropriate. Multiple comparisons between proportions were calculated according to the Bonferroni method. Statistical significance was considered in case of $p < 0.05$ (two-tailed).

The effectiveness was assessed using the modified intention-to-treat (mITT) analysis that included all cases registered up to July 2023 who had completed the follow-up (a confirmatory test—success or failure—was available after the eradication treatment), regardless of compliance. This approach was designed to achieve the results closest to real-world clinical practice.

To assess the different factors that may influence the mITT effectiveness of first-line treatment schemes, a multivariate analysis was performed using a logistic regression model where mITT eradication (treatment success) was set as the dependent variable. The independent variables included were: age, gender (female [reference category] vs. male), therapeutic scheme (triple-CA, triple-CM [reference category], sequential-CAT-CAM, concomitant-CAT-CAM, quadruple-BMTc, quadruple-CAB, and other), duration of treatment (7 [reference category], 10, or 14 days), PPI dose (low [reference category], standard, or high), therapeutic compliance (no [<90% drug intake: reference category] vs. yes: ≥90% drug intake) and treatment indication (non-investigated dyspepsia [reference category], dyspepsia with normal endoscopy, duodenal ulcer, gastric ulcer, preneoplastic lesions, GERD, and the category "others"). Results were presented as an odds ratio (OR) together with the 95% CI.

Finally, we analyzed the mITT effectiveness according to the indication as a function of time. For this purpose, we used the Microsoft Power BI tool (https://www.microsoft.com/es-es/power-platform/products/power-bi/#tabs-pill-bar-ocb9d418_tab0), combining advanced statistical analysis and artificial intelligence functionalities.

3 | Results

From May 2013 to July 2023, 34 European countries participating in the Hp-EuReg collected data with the collaboration of 300 recruiters. Overall, 65,239 records were included; of these, 53,636 cases were first-line eradication treatments. Further demographic information is presented in File S3 and Table S1.

3.1 | Baseline Characteristics

The six most frequent indications for *H. pylori* investigation covered 92% in first-line treatment: dyspepsia with normal endoscopy with 26,431 (49%) cases, non-investigated dyspepsia with 10,590 (20%), duodenal ulcer with 5612 (11%), gastric ulcer with 4143 (7.7%), GERD with 1379 (2.6%) and preneoplastic lesions with 1364 (2.5%). All indications and their distribution in the six highest participating countries are detailed in Tables S1–S3. Dyspepsia with normal endoscopy and duodenal ulcer decreased over the years: from 47% in 2013 to 35% in 2023 and 15% in 2013 to 6% in 2023, respectively. Non-investigated dyspepsia increased from 17% in 2013 to 24% in 2023. The evolution of the remaining indications for *H. pylori* investigation is detailed in Figure 1.

3.2 | Evolution of Regimen Selection for *H. pylori* Based on Indications

Triple-CA use decreased during the decade (from >40% in 2013 to approximately 20% in 2023) for non-investigated dyspepsia, dyspepsia with normal endoscopy, and duodenal ulcer. In case of preneoplastic lesions, a greater decrease in triple-CA prescription was observed from 61% in 2013 to 11% in 2023. However, the prescription of triple-CA experienced an increase during the study time spam for those cases with GERD (from 46% in 2013 to 54% in 2023). Triple-CM was, overall, infrequently used (0%–8%) and tended to decrease through the years in almost all indications even disappearing by the end of 2023, especially in those with preneoplastic lesions. However, higher prescription rates were observed in GERD patients and a significant increase in the prescription was reported in those cases with gastric ulcer (from 3% in 2013 to 8% in 2023) and GERD (>40% in 2015 and 2016).

The use of quadruple-BMTc (including the single capsule) increased from 1%–2% in 2013 to 20%–25% by 2023 for patients with non-investigated dyspepsia, dyspepsia with normal endoscopy, and duodenal ulcer. A lower increase in the prescription of quadruple-BMTc was observed for preneoplastic lesions (given those patients received a higher proportion of quadruple-CAB prescriptions) going from 0% in 2013 to 16% in 2023, in those cases with GERD (from 4% in 2013 to 12% in 2023), and those with gastric ulcer (given those patients received most frequently triple-CA) reporting 3% of prescriptions in 2013 to 8% in 2023.

In general, the use of concomitant-CAT-CAM decreased across the years in almost all indications (non-investigated dyspepsia: from 34% in 2013 to 22% in 2023; dyspepsia with normal endoscopy, duodenal ulcer and preneoplastic lesions: from 16%–17% in 2013 to approximately 11% at the end of the decade) except in patients with GERD, who experienced an increment in the aforementioned prescription, and cases with gastric ulcer who experienced a greater decrease in prescription. This decrease in concomitant-CAT-CAM favored quadruple-BMTc, mainly due to the high increase in the single capsule prescription from 2016. Prescription of the sequential-CAT-CAM scheme almost disappeared in all indications in 2023.

The prescription of quadruple-CAB increased in all indications (non-investigated dyspepsia: from 0% in 2013 to 4% in 2023; dyspepsia with normal endoscopy and GERD: from <5% in 2013 to 12%–15% in 2023; duodenal ulcer, gastric ulcer, and preneoplastic lesions: from <5% in 2013 to 25%–45% in 2023).

The evolution of the most frequent first-line treatment prescriptions in each indication is detailed in Figure 2 and Table S4.

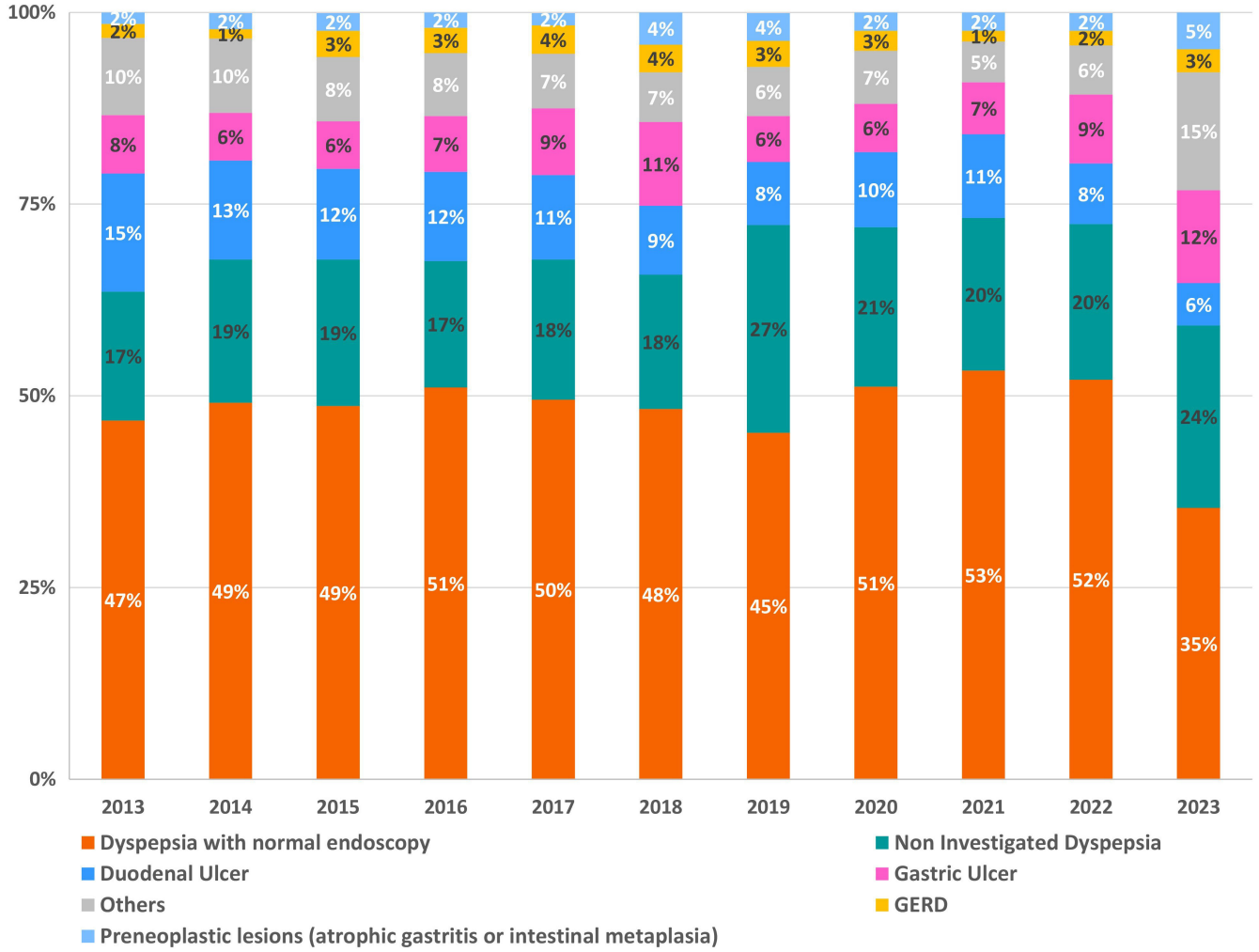

FIGURE 1 | Evolution of the six most frequent indications for *Helicobacter pylori* investigation. GERD, gastroesophageal reflux disease.

3.3 | Effectiveness by Indication

Both the triple-CA and triple-CM treatment schemes had an overall effectiveness below 90% in all indications, being lowest in those with non-investigated dyspepsia (triple-CA: 82%; triple-CM: 67%, $p < 0.001$). The detailed analysis by country confirmed lower eradication rates for non-investigated dyspepsia in Spain (triple-CA: 75%, $p < 0.001$; triple-CM: 56%, $p = 0.829$) and Italy (triple-CA: 69%, $p = 0.015$). Lithuania was the only country with optimal effectiveness when triple-CA was prescribed in patients with non-investigated dyspepsia (99%, $p = 0.009$) (Table 1). The triple-CM scheme represented a small number of records in most countries except in Slovenia and Azerbaijan, with a 22% and 19% proportion of use with respect to the remaining first-line prescriptions, respectively.

The sequential-CAT-CAM therapy had an overall effectiveness lower than 90% for all indications except for gastric ulcer (91%). A lower effectiveness was found in patients with non-investigated dyspepsia and GERD (81% and 77%, respectively). In Italy, the effectiveness of non-investigated dyspepsia decreased to 78% ($p = 0.004$).

The quadruple concomitant-CAT-CAM therapy showed an overall effectiveness above 90% for all indications except for non-investigated dyspepsia (88%, $p < 0.001$). In patients with duodenal ulcer, the effectiveness increased to 94% ($p < 0.001$) compared with the remaining indications. Most of concomitant-CAT-CAM therapies (36%) were prescribed in Spain, where the effectiveness was under 90% in the case of non-investigated dyspepsia (87%), dyspepsia with normal endoscopy (89.8%) and GERD (89%) ($p < 0.001$). The regimen was only prescribed in 10% of cases in Italy and <1% of cases in Russia, Azerbaijan, Slovenia, and Lithuania.

The quadruple-BMTc (including the single capsule) had an overall effectiveness above 90% for all indications except for GERD. Likewise, in the overall analysis, the effectiveness with quadruple-BMTc was lower in patients with non-investigated dyspepsia as compared to those with dyspepsia with normal endoscopy, although in all cases the effectiveness was still optimal (91.8% vs. 93.9%, $p = 0.047$). In Spain, these latter results were also confirmed in the same indications (92% vs. 94%, $p = <0.05$). A similar scenario was observed for this therapy in patients with dyspepsia from Russia and Italy, however, differences between groups did not reach statistical significance.

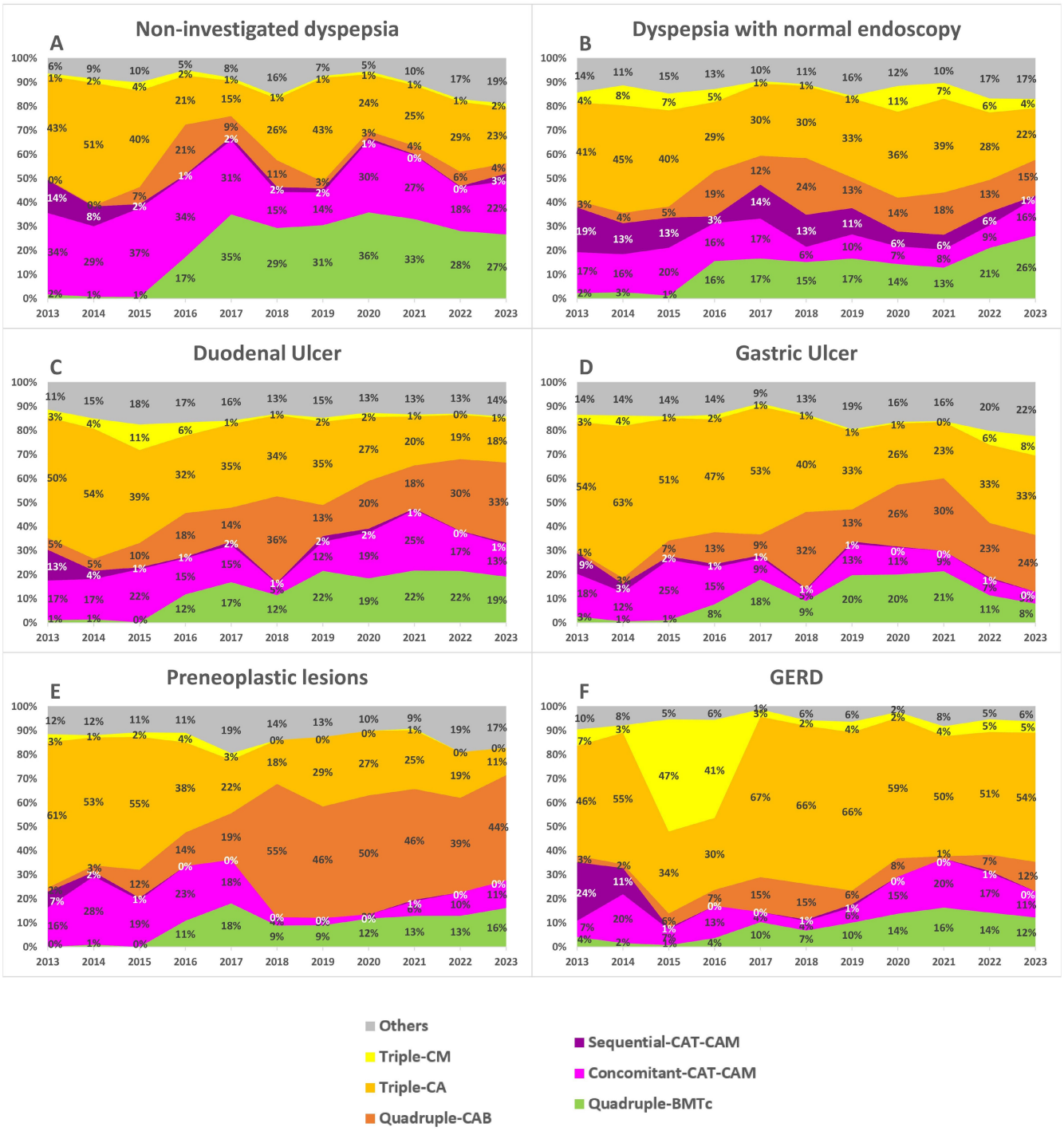

FIGURE 2 | Evolution of treatment prescription by indication for *Helicobacter pylori* investigation, (A) non-investigated dyspepsia, (B) dyspepsia with normal endoscopy, (C) duodenal ulcer, (D) gastric ulcer, (E) preneoplastic lesions, and (F) GERD. GERD, gastroesophageal reflux disease. Therapeutic schemes: A (amoxicillin), B (bismuth salts), C (clarithromycin), M (metronidazole), PPI (proton pump inhibitor), Tc (tetracycline). Others: Unexplained iron deficiency, first-degree relatives of patients with gastric cancer, MALT lymphoma, gastritis without atrophy or intestinal metaplasia features, etc.

The quadruple-CAB achieved an optimal (>90%) effectiveness for all indications except for GERD, and similar effectiveness rates for non-investigated dyspepsia and dyspepsia with normal endoscopy were observed (93%) also confirmed in Spain, Russia and Azerbaijan. In Spain, a higher effectiveness was observed for duodenal and gastric ulcer compared with dyspepsia (96% and 98% vs. 92%, respectively, $p = 0.195$). The summary of the first-line treatment effectiveness by indication is depicted in Figure 3.

When all first-line treatment schemes were analyzed together, the mITT eradication success was: 87% for non-investigated

TABLE 1 | Overall effectiveness (by modified intention-to-treat) of first-line treatment schemes by country and indication for *Helicobacter pylori* investigation.

Indications, *n* (%)	Spain	Russia	Azerbaijan	Italy	Slovenia	Lithuania	Others	Total
Triple-CA								
Non-investigated dyspepsia	577 (75.3)[b]	348 (84.9)	37 (92.5)	31 (68.9)[b]	378 (89.6)	68 (98.6)[a]	920 (82.1)[b]	2359 (82.1)[b]
Dyspepsia with normal endoscopy	1208 (86.2)[a]	847 (82.8)	1532 (90.9)	76 (87.4)	900 (90.7)	799 (85.4)	1027 (86.4)	6389 (87.4)[a]
Peptic ulcer	558 (89.0)[a]	570 (81.9)	366 (92.0)	33 (91.7)	327 (91.6)	103 (81.7)	462 (89.5)[a]	2419 (87.8)[a]
Preneoplastic lesions	94 (83.9)	52 (92.9)	2 (100.0)	0 (0.0)	18 (94.7)	1 (50.0)	125 (88.0)	292 (87.4)
GERD	35 (89.7)	69 (75.8)	27 (96.4)	5 (83.3)	282 (92.5)	7 (87.5)	44 (83.0)	469 (88.5)
Total	2472 (83.9)	1886 (82.9)	1964 (91.2)	145 (82.9)	1905 (90.9)	978 (85.7)	2578 (85.4)	11,928 (86.4)
p	**<0.001**	0.068	0.769(b)	**0.008(b)**	0.666	**0.011(a)**	**0.001**	**<0.001**
(a) Excluding the following categories: Preneoplastic lesions; (b) Excluding the following categories: Preneoplastic lesions and GERD								
Triple-CM								
Non-investigated dyspepsia	15 (55.6)	0 (0.0)	1 (100.0)	1 (100.0)	26 (81.3)	3 (100.0)	41 (62.1)	87 (66.9)[b]
Dyspepsia with normal endoscopy	35 (61.4)	11 (61.1)	532 (93.3)	2 (100.0)	371 (84.1)	18 (90.0)	67 (77.9)	1036 (86.8)[a]
Peptic ulcer	15 (68.2)	6 (60.0)	58 (92.1)	1 (100.0)	98 (90.7)	3 (100.0)	22 (73.3)	203 (85.7)
Preneoplastic lesions	1 (33.3)	2 (100.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	3 (60.0)	6 (54.5)[b]
GERD	1 (100.0)	0 (0.0)	9 (100.0)	0 (0.0)	119 (83.2)	0 (0.0)	4 (100.0)	133 (84.7)
Total	67 (60.9)	19 (63.3)	600 (93.3)	4 (80.0)	614 (84.8)	24 (92.3)	137 (71.7)	1465 (84.7)
p	0.665(b)	1.000(c)(1)	0.605(c)(1)	—	0.295(a)	—	0.099(b)	**<0.001**
(a) Excluding the following categories: Preneoplastic lesions; (b) Excluding the following categories: Preneoplastic lesions and GERD; (c) Excluding the following categories: Non-investigated dyspepsia, preneoplastic lesions and GERD								
Sequential-CAT-CAM								
Non-investigated dyspepsia	64 (84.2)	0 (0.0)	0 (0.0)	40 (78.4)[b]	4 (100.0)	0 (0.0)	60 (77.9)	168 (80.8)[b]
Dyspepsia with normal endoscopy	77 (77.8)	13 (86.7)	0 (0.0)	1671 (91.6)[a]	14 (93.3)	1 (100.0)	179 (81.7)	1955 (89.9)[a]
Peptic ulcer	35 (83.3)	6 (85.7)	0 (0.0)	24 (88.9)	6 (100.0)	0 (0.0)	80 (88.9)	151 (87.8)
Preneoplastic lesions	0 (0.0)	0 (0.0)	0 (0.0)	1 (100.0)	0 (0.0)	0 (0.0)	6 (85.7)	7 (87.5)
GERD	0 (0.0)	0 (0.0)	0 (0.0)	1 (100.0)	0 (0.0)	0 (0.0)	16 (76.2)	17 (77.3)
Total	176 (81.1)	19 (86.4)	0 (0.0)	1737 (91.2)	24 (96.0)	1 (100.0)	341 (82.4)	2298 (88.9)
p	0.514(b)	1.000(c)(1)	—	**0.004(d)(1)**	—	—	0.232(a)	**<0.001(a)**

(Continues)

TABLE 1 | (Continued)

Indications, *n* (%)	Spain	Russia	Azerbaijan	Italy	Slovenia	Lithuania	Others	Total
(a) Excluding the following categories: Preneoplastic lesions; (b) Excluding the following categories: Preneoplastic lesions and GERD; (c) Excluding the following categories: Non-investigated dyspepsia, preneoplastic lesions, and GERD; (d) Excluding the following categories: Peptic ulcer, Preneoplastic lesions, and GERD								
Concomitant-CAT-CAM								
Non-investigated dyspepsia	1974 (86.8)[b]	1 (100.0)	0 (0.0)	57 (95.0)	3 (75.0)	0 (0.0)	220 (92.1)	2255 (87.5)[b]
Dyspepsia with normal endoscopy	2097 (89.8)	30 (88.2)	0 (0.0)	219 (95.2)	9 (90.0)	0 (0.0)	456 (94.8)	2811 (90.9)
Peptic ulcer	1098 (93.4)[a]	29 (87.9)	0 (0.0)	20 (87.0)	2 (100.0)	1 (100.0)	104 (90.4)	1254 (93.0)[a]
Preneoplastic lesions	123 (94.6)	0 (0.0)	0 (0.0)	4 (80.0)	0 (0.0)	0 (0.0)	6 (100.0)	133 (94.3)
GERD	73 (89.0)	1 (100.0)	0 (0.0)	34 (97.1)	0 (0.0)	0 (0.0)	20 (95.2)	128 (92.1)
Total	5365 (89.5)	61 (88.4)	0 (0.0)	334 (94.6)	14 (87.5)	1 (100.0)	806 (93.5)	6581 (90.2)
p	**<0.001**	1.000(c)(1)	—	1.000(b)(1)	—	—	0.259(a)	**<0.001**
(a) Excluding the following categories: Preneoplastic lesions; (b) Excluding the following categories: Peptic ulcer, preneoplastic lesions, and GERD; (c) Excluding the following categories: Non-investigated dyspepsia, preneoplastic lesions, and GERD								
Quadruple-BMTc								
Non-investigated dyspepsia	1762 (91.5)[b]	38 (92.7)	0 (0.0)	153 (93.9)	0 (0.0)	0 (0.0)	149 (92.0)	2102 (91.8)[b]
Dyspepsia with normal endoscopy	2144 (94.1)[a]	125 (94.0)	0 (0.0)	403 (95.7)	2 (100.0)	0 (0.0)	350 (90.7)	3024 (93.9)[a]
Peptic ulcer	827 (94.1)	37 (94.9)	0 (0.0)	53 (91.4)	0 (0.0)	0 (0.0)	100 (85.5)	1017 (93.0)
Preneoplastic lesions	83 (92.2)	2 (66.7)	0 (0.0)	23 (100.0)	0 (0.0)	0 (0.0)	10 (100.0)	118 (93.7)
GERD	70 (90.9)	0 (0.0)	0 (0.0)	19 (90.5)	0 (0.0)	0 (0.0)	8 (80.0)	97 (89.8)
Total	4886 (93.1)	202 (93.5)	0 (0.0)	651 (94.9)	2 (100.0)	0 (0.0)	617 (90.1)	6358 (93.0)
p	**0.013**	0.722(c)(1)	—	0.299(b)	—	—	0.200(a)	**0.026**
(a) Excluding the following categories: Preneoplastic lesions; (b) Excluding the following categories: Preneoplastic lesions and GERD; (c) Excluding the following categories: Peptic ulcer, preneoplastic lesions, and GERD								
Quadruple-CAB								
Non-investigated dyspepsia	274 (91.6)	219 (94.4)	2 (100.0)	0 (0.0)	0 (0.0)	4 (100.0)	25 (100.0)	524 (93.2)
Dyspepsia with normal endoscopy	455 (91.5)	2069 (93.3)	157 (98.7)	0 (0.0)	0 (0.0)	31 (83.8)	92 (81.4)	2804 (92.7)
Peptic ulcer	144 (96.6)	737 (92.7)	470 (97.7)	0 (0.0)	1 (100.0)	6 (100.0)	41 (77.4)	1399 (94.2)
Preneoplastic lesions	26 (86.7)	132 (91.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (100.0)	49 (96.1)[a]	208 (91.6)
GERD	13 (86.7)	58 (89.2)	0 (0.0)	0 (0.0)	1 (100.0)	0 (0.0)	0 (0.0)	72 (88.9)

(Continues)

TABLE 1 | (Continued)

Indications, *n* (%)	Spain	Russia	Azerbaijan	Italy	Slovenia	Lithuania	Others	Total
Total	912 (92.1)	3215 (93.1)	629 (98.0)	0 (0.0)	2 (100.0)	42 (87.5)	207 (85.5)	5007 (93.1)
p	0.122(a)	0.499	0.535(c)(1)	—	—	—	**0.020(b)**	0.164
(a) Excluding the following categories: GERD; (b) Excluding the following categories: Non-investigated dyspepsia and GERD; (c) Excluding the following categories: Non-investigated dyspepsia, preneoplastic lesions, and GERD								
Other								
Non-investigated dyspepsia	122 (72.6)	190 (92.7)	0 (0.0)	26 (76.5)	5 (100.0)	3 (100.0)	440 (88.0)	786 (85.8)
Dyspepsia with normal endoscopy	188 (82.8)	820 (86.0)	190 (85.6)[b]	173 (80.5)	46 (95.8)	53 (88.3)	975 (84.9)[b]	2445 (85.1)[b]
Peptic ulcer	71 (80.7)	428 (86.8)	170 (92.9)[a]	5 (100.0)	18 (100.0)	4 (80.0)	464 (91.2)[a]	1160 (89.2)[a]
Preneoplastic lesions	10 (90.9)	104 (90.4)	0 (0.0)	1 (100.0)	0 (0.0)	0 (0.0)	38 (95.0)	153 (91.6)[a]
GERD	2 (100.0)	20 (87.0)	5 (100.0)	2 (100.0)	8 (80.0)	0 (0.0)	17 (85.0)	54 (87.1)
Total	393 (79.2)	1562 (87.3)	365 (88.8)	207 (80.5)	77 (95.1)	60 (88.2)	1934 (87.2)	4598 (86.4)
p	0.065(a)	0.097	**0.030(b)**	0.645(c)(1)	0.134(d)(1)	—	**0.005**	**0.002**
(a) Excluding the following categories: GERD; (b) Excluding the following categories: Non-investigated dyspepsia, preneoplastic lesions, and GERD; (c) Excluding the following categories: Peptic ulcer, preneoplastic lesions, and GERD; (d) Excluding the following categories: Non-investigated dyspepsia, peptic ulcer, and preneoplastic lesions								

Note: Therapeutic schemes: A (amoxicillin), B (bismuth salts), C (clarithromycin), M (metronidazole), and Tc (tetracycline). The table shows "success" rates of eradication schemes. Other countries: Norway, Ireland, Ukraine, Latvia, Greece, Croatia, Portugal, Serbia, Czech Republic, Poland, Turkey, Hungary, United Kingdom, Switzerland, Germany, Bulgaria, Israel, France, Romania, North Macedonia, Belgium, The Netherlands, Austria, Denmark, Malta, Albania, Finland and Slovakia. Data are presented as number (%). Chi-square test was used, performing multiple comparisons between proportions according to the Bonferroni method. If the Chi-square test could not be applied, Firsher's test was used (1). *p*-values in bold format indicate statistical significance ($p < 0.05$). —, The test could not be performed.

Abbreviation: GERD, gastroesophageal reflux disease.

[a]The group "Success" was statistically significantly associated with the indication.

[b]The group "Failure" was statistically significantly associated with the indication.

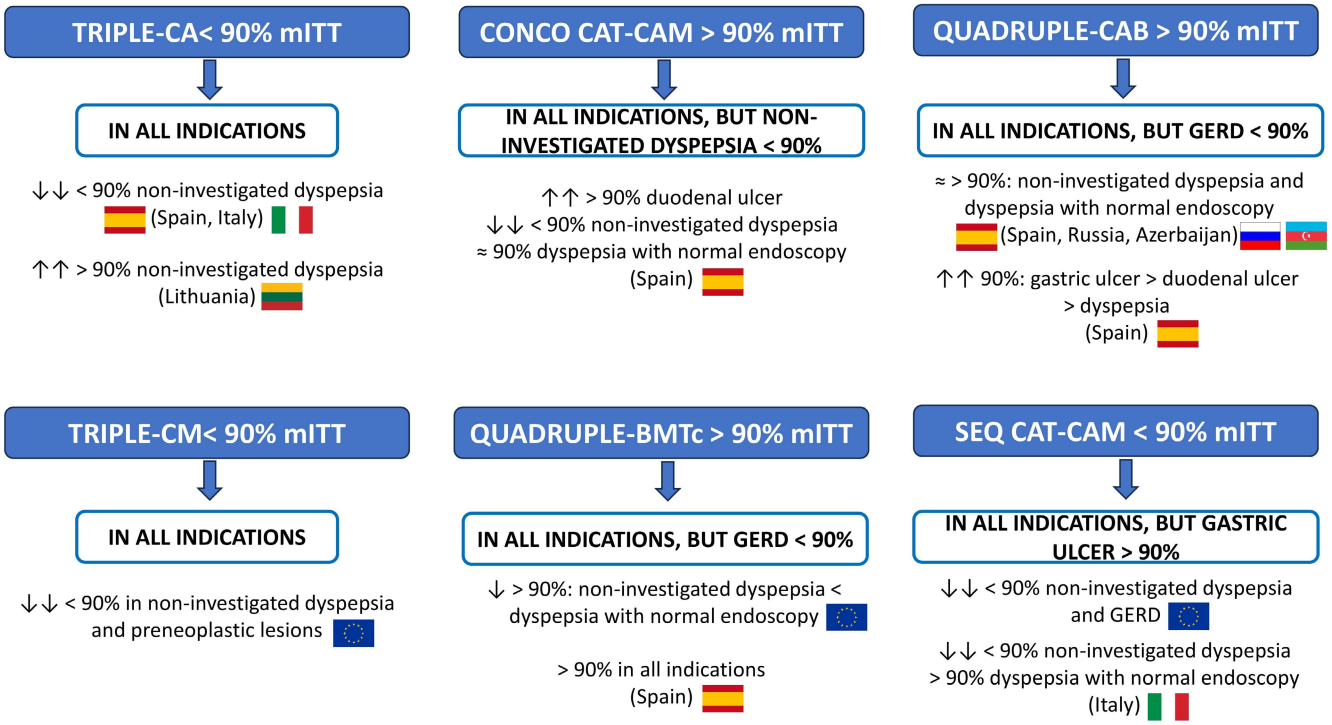

FIGURE 3 | First-line treatment effectiveness (by modified intention-to-treat) by indication for *Helicobacter pylori* investigation. Conco, concomitant; GERD, gastroesophageal reflux disease; mITT, modified intention-to-treat; Seq, sequential. Therapeutic schemes: A (amoxicillin), B (bismuth salts), C (clarithromycin), M (metronidazole), Tc (tetracycline). ↑↑: Marked increase. ↓: Decrease. ↓↓: Marked decrease. The flags indicate that these data only apply to the either the corresponding geographic area or the whole Europe.

dyspepsia, 89% for dyspepsia with normal endoscopy, 91% for duodenal ulcer, 90% for gastric ulcer, 90% for preneoplastic ulcer and 88% for GERD (Table S5). Other variables associated with treatment success were being a male (89.9% vs. 88%, $p < 0.001$), longer treatment durations (7 days 82% vs. 10 days 89% vs. 14 days 91%, $p < 0.001$), higher acid inhibition in adjuvant therapy (low 86% vs. standard 91% vs. high 92%, $p < 0.001$), being adherent to treatment (non-compliant 45% vs. compliant 89.8%, $p < 0.001$) and prescribing either concomitant or bismuth quadruple therapy(triple-CA 86%, triple-CM 85%, sequential-CAT-CAM 89%, concomitant-CAT-CAM 90%, quadruple-BMTc 93%, quadruple-CAB 93%, $p < 0.001$).

3.4 | Multivariate Analysis

The indications for *H. pylori* investigation were significantly associated with mITT eradication success. Compared with patients treated for non-investigated dyspepsia, patients treated for the following indications showed higher probability of success: dyspepsia with normal endoscopy (OR 1.455, 95% CI [1.345–1.574], $p < 0.001$), duodenal ulcer (OR 1.559, 95% CI [1.382–1.760], $p < 0.001$), gastric ulcer (OR 1.691, 95% CI [1.476–1.939], $p < 0.001$) and preneoplastic lesions (OR 1.546, 95% CI [1.230–1.943], $p < 0.001$).

3.5 | Effectiveness by Gender

Information on the effectiveness analyzed by gender is shown in File S4 and Tables S6 and S7.

3.6 | Evolution of Effectiveness

Although the overall analysis of effectiveness reported rates below 90% in all indications in 2013, a slight increase was observed over the years, with cure rates exceeding 90% from 2022 onwards in all of them (Figure 4).

Effectiveness for non-investigated dyspepsia reached 90% uniquely in 2022 and 2023, whereas effectiveness for dyspepsia with normal endoscopy was above 90% consistently since 2018.

In those cases with gastric ulcer and duodenal ulcer, cure rates evolved in a similar way to those patients with dyspepsia with normal endoscopy being optimal from 2018 onwards; however, the effectiveness in patients with GERD and preneoplastic lesions was reported constant around the threshold from 2018 onwards.

The evolution of the first-line therapy effectiveness (by mITT) in each indication is detailed in Figures S1–S5.

Evolution of the effectiveness of first-line schemes by year and indication is shown in Table 2. Triple-CA had overall a suboptimal (<90%) effectiveness in most years of the study time span in all indications evaluated; however, therapy reached the 90% threshold by 2023 in all cases. The effectiveness of concomitant-CAT-CAM, quadruple-BMTc, and quadruple-CAB ranged around 90%, being >90% in most indications. In patients treated for dyspepsia with normal endoscopy and patients with gastric ulcers, the effectiveness of quadruple-BMTc was consistently

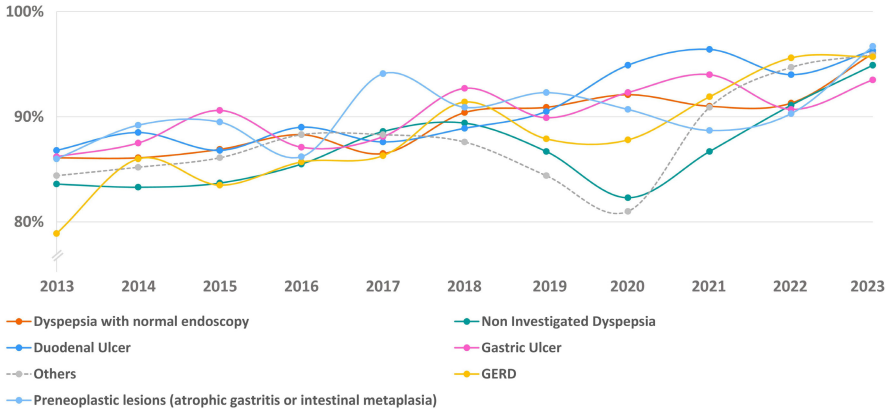

FIGURE 4 | Evolution of first-line treatment effectiveness by modified-intention-to-treat between 2013 and 2023, according to the indications for *Helicobacter pylori* investigation. GERD, gastroesophageal reflux disease.

above 90% from 2014 to 2023. Triple-CM and sequential-CAT-CAM had an effectiveness <90% through the years in all indications.

3.7 | Safety and Therapeutic Compliance

When all first-line treatments were analyzed together, the incidence of at least one AE was: 18% for non-investigated dyspepsia, 23% for dyspepsia with normal endoscopy, 28% for duodenal ulcer, 21% for gastric ulcer, 18% for preneoplastic lesions and 19% for GERD (Table S5). AEs were significantly higher in patients with dyspepsia with normal endoscopy and duodenal ulcer as compared to the remaining groups ($p < 0.001$).

Regarding treatment tolerance, a high variability was observed between countries (Table S8). For instance, patients with preneoplastic lesions showed the highest incidence of AEs when triple-CA and triple-CM were prescribed (23% and 36%, respectively), and patients with duodenal ulcer had the highest incidence of AEs when treated with concomitant-CAT-CAM therapy (43%, $p < 0.001$) and the quadruple-BMTc therapy (40%, $p < 0.001$), compared with the remaining indications of each therapeutic scheme. This finding was also confirmed in Spain (concomitant-CAT-CAM 43%, $p < 0.001$; quadruple-BMTc 42%, $p < 0.001$) and Russia (concomitant-CAT-CAM 95%, $p = 0.231$; quadruple-BMTc 39%, $p < 0.05$). In addition, duodenal ulcer was the indication that most frequently presented AEs lasting more than 7 days for both therapeutic schemes (concomitant-CAT-CAM 64%, $p < 0.001$; quadruple-BMTc 61%, $p = 0.035$) (Table S9). The quadruple-CAB reported a higher incidence of AEs in patients with non-investigated dyspepsia (33%), dyspepsia with normal endoscopy (34%), and GERD (32%).

The incidence of serious AEs was between 0% and 4% in all treatment schemes with no significant differences between indications (Table S10).

When all first-line eradications were analyzed together, the proportion of adequate therapeutic adherence (>90% of drug intake) was: 97% in those with non-investigated dyspepsia, 97% in dyspepsia with normal endoscopy, 98% in duodenal ulcer, 96% in gastric ulcer, 99% in both preneoplastic lesions and GERD; and compliance was significantly higher in the three latter indications as compared to the remaining indications ($p < 0.001$) (Table S5).

The rate of compliance was observed highest in patients with preneoplastic lesions prescribed with triple-CA (99.5%, $p < 0.001$) and quadruple-CAB (99.6%, $p = 0.001$), compared with the remaining indications of each therapeutic scheme. In addition, the highest rate of compliance was observed for patients with duodenal ulcers when prescribed with either triple-CA (98.7%, $p = 0.001$) or quadruple-CAB (99.6%, $p < 0.05$) in Azerbaijan, and with concomitant-CAT-CAM in Europe or Spain (99%, $p < 0.05$). No differences in therapeutic compliance were observed when triple-CM, sequential-CAT-CAM, and quadruple-BMTc (including single capsule) were prescribed, regardless of the treatment indication (Table S11).

4 | Discussion

This study showed that indications for *H. pylori* eradication treatment influenced the management of the infection by European gastroenterologists. Additionally, the effectiveness of the different prescriptions, therapeutic tolerance, and compliance varied between indications, and it was consistent across several countries. Therefore, our findings support that the indication for *H. pylori* eradication is an important factor to consider in the clinical management of the infection.

Responsible use of antibiotics is the cornerstone to address the exponential increase in antibiotic resistance, a major concern worldwide [17, 18]. Consequently, *H. pylori* infection should only be investigated in the presence of underlying pathologies or symptoms potentially related to the bacterium, according to international consensus [5, 19].

In recent years, the therapeutic schemes recommended for *H. pylori* treatment have notably changed due to several factors, but mainly given the increasing prevalence of resistance to clarithromycin, metronidazole, and levofloxacin, showing rates above 15% in most countries encompassing the regions of World Health Organization (WHO) [20, 21]. In this sense, only bismuth quadruple therapies lasting at least 10 days

TABLE 2 | Overall effectiveness (by modified intention-to-treat) of first-line schemes by year and indication for investigation of *Helicobacter pylori*.

	2013–2018	2019–2023	Total
Non-investigated dyspepsia			
Triple-CA	1103 (79.7)	1256 (84.4)	2359 (82.1)
Triple-CM	57 (68.7)	30 (63.8)	87 (66.9)
Sequential-CAT-CAM	149 (80.5)	19 (82.6)	168 (80.8)
Concomitant-CAT CAM	1273 (88.9)	982 (85.8)	2255 (87.5)
Quadruple-BMTc	614 (93.0)	1488 (91.2)	2102 (91.8)
Quadruple-CAB	339 (92.4)	185 (94.9)	524 (93.2)
Other	346 (82.4)	440 (88.7)	786 (85.8)
Total	3881	4400	8281
Dyspepsia with normal endoscopy			
Triple-CA	3306 (84.8)	3083 (90.3)	6389 (87.4)
Triple-CM	445 (80.9)	591 (91.8)	1036 (86.8)
Sequential-CAT-CAM	1317 (89.0)	638 (91.9)	1955 (89.9)
Concomitant-CAT CAM	1809 (90.4)	1002 (91.9)	2811 (90.9)
Quadruple-BMTc	1120 (94.9)	1904 (93.3)	3024 (93.9)
Quadruple-CAB	1166 (89.4)	1638 (95.2)	2804 (92.7)
Other	1226 (83.4)	1219 (86.9)	2445 (85.1)
Total	10,389	10,075	20,464
Peptic ulcer			
Triple-CA	1601 (86.1)	818 (91.2)	2419 (87.8)
Triple-CM	133 (84.2)	70 (88.6)	203 (85.7)
Sequential-CAT-CAM	132 (86.8)	19 (95.0)	151 (87.8)
Concomitant-CAT CAM	703 (91.8)	551 (94.5)	1254 (93.0)
Quadruple-BMTc	329 (92.7)	688 (93.2)	1017 (93.0)
Quadruple-CAB	534 (91.0)	865 (96.3)	1399 (94.2)
Other	590 (86.6)	570 (91.9)	1160 (89.2)
Total	4022	3581	7603
Preneoplastic lesions			
Triple-CA	190 (88.4)	102 (85.7)	292 (87.4)
Triple-CM	6 (60.0)	0 (0.0)	6 (54.5)
Sequential-CAT-CAM	6 (85.7)	1 (100.0)	7 (87.5)
Concomitant-CAT CAM	97 (94.2)	36 (94.7)	133 (94.3)
Quadruple-BMTc	39 (95.1)	79 (92.9)	118 (93.7)
Quadruple-CAB	81 (88.0)	127 (94.1)	208 (91.6)
Other	71 (88.8)	82 (94.3)	153 (91.6)
Total	490	427	917
GERD			

(Continues)

TABLE 2 | (Continued)

	2013–2018	2019–2023	Total
Triple-CA	228 (85.1)	241 (92.0)	469 (88.5)
Triple-CM	115 (85.2)	18 (81.8)	133 (84.7)
Sequential-CAT-CAM	16 (76.2)	1 (100.0)	17 (77.3)
Concomitant-CAT CAM	58 (93.5)	70 (90.9)	128 (92.1)
Quadruple-BMTc	32 (94.1)	65 (87.8)	97 (89.8)
Quadruple-CAB	43 (84.3)	29 (96.7)	72 (88.9)
Other	30 (83.3)	24 (92.3)	54 (87.1)
Total	522	448	970
Others			
Triple-CA	633 (82.2)	227 (85.7)	860 (83.1)
Triple-CM	25 (75.8)	24 (82.8)	49 (79.0)
Sequential-CAT-CAM	54 (85.7)	8 (80.0)	62 (84.9)
Concomitant-CAT CAM	405 (90.8)	324 (87.6)	729 (89.3)
Quadruple-BMTc	279 (94.9)	480 (94.1)	759 (94.4)
Quadruple-CAB	219 (88.7)	90 (91.8)	309 (89.6)
Other	183 (81.7)	153 (89.5)	336 (85.1)
Total	1798	1306	3104

Note: Therapeutic Schemes: A (amoxicillin), B (bismuth salts), C (clarithromycin), M (metronidazole), Tc (tetracycline). The table shows the "success" rates of eradication schemes. Other countries: Norway, Ireland, Ukraine, Latvia, Greece, Croatia, Portugal, Serbia, Czech Republic, Poland, Turkey, Hungary, United Kingdom, Switzerland, Germany, Bulgaria, Israel, France, Romania, North Macedonia, Belgium, The Netherlands, Austria, Denmark, Malta, Albania, Finland and Slovakia. Data are presented as number (%).
Abbreviation: GERD, gastroesophageal reflux disease.

(especially when the three-in-one single capsule was administered) and 14-day concomitant treatments demonstrated over 90% eradication rates in daily clinical practice [6, 22]. This study, as previously published [6], confirmed an overall decrease in the prescription of triple therapies over the time parallel to the increase of prescription of quadruple-CAB and quadruple-BMTc, although in our study such treatment evolution remained variable among the different indications evaluated. For instance, patients with preneoplastic lesions experienced a greater decrease in triple regimens in favor of quadruple therapy (mainly quadruple-CAB), whereas gastric ulcer and GERD (the latter, an indication for treatment which is currently not accepted in consensus conferences) showed a higher proportion of triple-CA prescriptions in 2023, as opposite to the remaining indications.

Despite the differences in the infection management for each indication, there was an overall increase in first-line treatment effectiveness in all indications between 2013 and 2023 (Figure 4). While effectiveness was reported lower than 90% in all indications in 2013, an increase was observed during the years reaching above 90% in 2023. This finding might probably be justified by the changes in the prescription of therapeutic treatment schemes during these last 10 years.

The influence of multiple factors on eradication success has been previously studied, such as the number and type of antibiotics, the treatment duration or the PPI dose concomitantly prescribed with therapy [23–25]. Nevertheless, current evidence on the potential influence of the treatment indication at baseline is limited.

As a novelty, our study found overall lower eradication rates in patients with non-investigated dyspepsia as compared to those cases treated for dyspepsia with normal endoscopy. This finding was consistent in different triple and quadruple regimens with the exception of quadruple-CAB, which showed success rates of 93% in both non-investigated dyspepsia and dyspepsia with normal endoscopy across the six countries with the highest number of records.

Quadruple-CAB and quadruple-BMTc reached 90% effectiveness for both non-investigated dyspepsia and dyspepsia with normal endoscopy, whereas concomitant-CAT-CAM only achieved 90% for dyspepsia with normal endoscopy. The differences between non-investigated dyspepsia and dyspepsia with normal endoscopy could be explained because non-investigated dyspepsia is a tentative clinical diagnosis often exhibiting heterogeneous symptoms; however, dyspepsia with normal endoscopy involves prior exclusion of other secondary causes that could also potentially cause dyspepsia.

Gastroesophageal reflux disease has no proven causal association with *H. pylori* infection and treatment for *H. pylori* infection in patients with erosive esophagitis does not improve symptom response or healing rates [26–28]. In the current

study, quadruple-BMTc was the only scheme to achieve 90% effectiveness in Spain, and both triple regimens and the remaining quadruple therapies—usually successful across indications and countries, such as the concomitant-CAT-CAM or quadruple-CAB—provided suboptimal results in GERD cases. Effectiveness rates under 90% in patients with GERD have been already published in previous studies [28, 29].

The analysis by country should be interpreted with caution because some therapeutic schemes were most frequently used in some of the countries, while in others, their use was residual due to current national recommendations, drug accessibilities, or routine clinical practice in those geographic areas. In this respect, although Spain was the country with the highest number of patients treated with concomitant-CAT-CAM therapy, its effectiveness was under 90% in both non-investigated dyspepsia and dyspepsia with normal endoscopy cases, whereas in Europe, rates for the aforementioned therapy were above 90% in the latter indication.

The analysis by gender found higher effectiveness rates for triple-CA, triple-CM, sequential-CAT-CAM, and concomitant-CAT-CAM in dyspeptic males, consistent with the findings reported by Chang et al. in patients with chronic gastritis [30, 31]. However, quadruple-BMTc showed higher effectiveness rates in females with dyspepsia and normal endoscopy, and in females with non-investigated dyspepsia.

Safety and therapeutic compliance did not apparently explain the differences in terms of effectiveness observed between indications. Indeed, previous studies reported that only 1%–5% of patients stopped medication due to AEs, leading to a decrease in effectiveness [12, 32, 33]. In general terms, no increased incidence of AEs was observed in patients with non-investigated dyspepsia as compared with patients suffering from functional dyspepsia (18% vs. 23%, respectively). Considering patients with dyspepsia, a higher incidence of AEs was identified in patients with dyspepsia and normal endoscopy treated with triple-CA, quadruple-BMTc, and quadruple-CAB, while patients with non-investigated dyspepsia showed a higher incidence of AEs if treated with triple-CM and sequential-CAT-CAM.

Patients treated for dyspepsia with normal endoscopy and patients treated for non-investigated dyspepsia showed similar therapeutic compliance (97%). Paradoxically, patients with duodenal ulcers showed higher rates of AEs and, at the same time, higher therapeutic compliance. It is possible that inflammatory phenomena in the digestive tract could amplify the appearance of AEs. Also, the presence of an organic pathology could favor therapeutic compliance because both clinician and patients are more involved in treatment adherence. In fact, low disease activity and mild symptomatology have been previously associated with non-adherence to treatment in other pathologies [34, 35].

4.1 | Limitations and Strengths

The main limitation of the current study is that not all European regions are equally represented, inherent to observational non-interventional registries. Variability in the number of records included in each country could be explained by the participation of recruiters and the number of patients with *H. pylori* infection treated by gastroenterologists. To ensure adequate comparability, first-line data were analyzed for each therapeutic regimen, given effectiveness or tolerability vary greatly between them. Interpretations should be made cautiously in those treatment schemes with a small sample size, especially in countries with lower participation. Another limitation could be the high number of indications, which mostly represent a small sample size and can sometimes coexist, which led us to choose the six most frequent for the analysis of effectiveness, safety, and therapeutic compliance.

Despite the above-mentioned drawbacks, it should be noted that multicentre collaborations through international registries such as the Hp-EuReg represent an excellent tool to report the management of *H. pylori* infection in daily clinical practice with enough statistical power and meaningful conclusions. To the best of our knowledge, this study constitutes the first large study cohort focused on evaluating the influence of the indications for *H. pylori* investigation.

5 | Conclusion

The present study showed that patients with gastric or duodenal ulcers and preneoplastic lesions had higher effectiveness, as well as bismuth and non-bismuth quadruple therapies achieved optimal results in almost all indications.

Author Contributions

Samuel J. Martínez-Domínguez, Enrique Alfaro, and Ángel Lanas coordinated the current study; analyzed, synthetized, and interpreted the data; wrote the first draft and approved the submitted manuscript. Laimas Jonaitis, Ángeles Pérez-Aísa, Giulia Fiorini, Bojan Tepes, Umud Mahmudov, Irina Voynovan, Dmitry S. Bordin, Gülüstan Babayeva, Luis Bujanda, Manuel Pabón-Carrasco, Alma Keco-Huerga, Alfredo J. Lucendo, Maja Denkovski, Ludmila Vologzanina, Emin Mammadov, Luis Rodrigo, Frode Lerang, Quliyev Fərid Vidadi Oğlu, Natalia V. Bakulina, Ilchishina Tatiana, Thomas J. Butler, Rustam Abdulkhakov, Renate Bumane, Marco Romano, Sayar R. Abdulkhakov, Oleg Zaytsev, Galyna Fadieienko, Jose M. Huguet, Monica Perona, Óscar Nuñez, Matteo Pavoni, Sergey Alekseenko, Sinead M. Smith, Luis Hernández, Kuozas Kupcinskas, Marcis Leja, Antonio Gasbarrini, Oleksiy Gridnyev, Aiman Silkanovna Sarsenbaeva, Javier Tejedor-Tejada: collected data, critically reviewed the manuscript's drafts, and approved the final submitted manuscript. Anna Cano-Català (Technical Project Manager) and Pablo Parra (Data Project Manager), performed the monitoring and quality check of the data and approved the final manuscript. Olga P. Nyssen, Hp-EuReg Scientific Director, planned and coordinated the current study, performed the data extraction, supervised the monitoring and the quality check, assisted with analysis, interpretation, and synthesis of data, critically reviewed the manuscript's drafts and approved the final submitted manuscript. Anna Cano-Català, Pablo Parra, Leticia Moreira, Olga P. Nyssen, Francis Mégraud, Colm O'Morain, and Javier P. Gisbert, are all members of the Hp-EuReg Scientific Committee; critically reviewed the manuscript's drafts, and approved the final submitted manuscript. Javier P. Gisbert, Principal investigator of the registry, directed the project, obtained funding, designed the protocol, planned and coordinated the current study, recruited patients, critically reviewed the manuscript drafts, and approved the final submitted manuscript. All authors approved the final version of the article, including the authorship list.

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Ethics Statement

The Hp-EuReg protocol was approved by the Ethics Committee of La Princesa University Hospital (Madrid, Spain), which acted as a reference Institutional Review Board (20 December 2012), and was conducted according to the guidelines of the Declaration of Helsinki, was classified by the Spanish Drug and Health Product Agency.

Consent

Informed consent was obtained from all subjects involved in the study.

Conflicts of Interest

Dr. Samuel J. Martínez-Domínguez has served as a speaker for Juvisé. Dr. Ángel Lanas has served as a speaker for Juvisé. Dr. Javier P. Gisbert has served as a speaker, a consultant, and advisory member for or has received research funding from Mayoly, Allergan, Diasorin, Biocodex, Juvisé, and Richen. Dr. Olga P. Nyssen has received research funding from Mayoly, Allergan, Diasorin, Biocodex, Juvisé, and Richen. Dmitry S. Bordin has served as a speaker for Abbott, AstraZeneca, Biocodex, and PRO.MED.CS Praha a.s, KRKA, Dr. Reddy's Laboratories. The remaining authors declare no conflicts of interest.

Data Availability Statement

Data available on reasonable request from the corresponding authors.

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Supporting Information

Additional supporting information can be found online in the Supporting Information section.