European Registry on *Helicobacter pylori* Management (Hp-EuReg): First-line Therapy in Israel

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ABSTRACT **Background:** The antibiotic resistance profile of *Helicobacter pylori (H. pylori)* is constantly changing. Up-to-date and reliable data for the effectiveness of first-line *H. pylori* treatment protocols are necessary to provide evidence-based best-practice guidelines.

Objectives: To determine the effectiveness, compliance and safety of first-line treatment for *H. pylori* in Israel.

Methods: An observational, prospective, multicenter study was conducted in tertiary referral centers in Israel, as part of the European registry on *H. pylori* management (Hp-EuReg). *H. pylori*-infected patients were included from 2013 to March 2020. Data collected included demographics, clinical data, diagnostic tests, previous eradication attempts, current treatment, compliance, adverse events, and treatment outcome result.

Results: In total, 242 patients were registered, including 121 (50%) who received first-line therapy, 41% of these individuals received clarithromycin based triple therapy and 58.9% received a four-drug regimen. The overall effectiveness of first-line therapy was 85% and 86% by modified intention-to-treat and per protocol analyses, respectively. The effectiveness of both sequential and concomitant therapies was 100% while clarithromycin-based triple therapy achieved an eradication rate of 79%. Treatment eradication was higher among patients who received high dose proton pump inhibitor (PPI) compared to those treated with low dose PPI (100% vs. 81.5% respectively, $P < 0.01$). No difference in treatment effectiveness was found between 7-, 10-, and 14-day treatment.

Conclusions: The effectiveness of clarithromycin-based triple therapy is suboptimal. First-line treatment of *H. pylori* infection should consist of four drugs, including high dose PPI, according to international guidelines.

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Despite almost 40 years of experience in treating *Helicobacter pylori* (*H. pylori*) infection, the optimal regimen for first-line treatment is still unclear. Increasing rates of antibiotic resistance, in particular to clarithromycin, have rendered a one-size-fits-all approach to treatment ineffective. Instead, treatment for *H. pylori* infection must be carefully adapted according to location-specific antibiotic resistance data or given on the basis of the established effectiveness of an antibiotic protocol in a particular population [1]. Alternatively, treatment may be reliably tailored to a patient following susceptibility testing with culture or molecular methods, however this approach is usually invasive, costly and not feasible for the vast majority of treatment-naïve patients [2].The need to tailor treatment to local data is reflected in both international and national consensus guidelines [3-7]. Due to changes in *H. pylori* antibiotic resistance, there is a need to continually publish data on the effectiveness of *H. pylori* treatment protocols so that evidence-based recommendations can be made for the large number of patients who seek treatment. In the past we have provided retrospective data for the effectiveness of first-line therapy as well as laboratory data for antibiotic resistance in our region [8,9]. Prospectively collected, real world data for the effectiveness of first-line therapy for *H. pylori* therapy are lacking. The recent *H. pylori* management guidelines published on behalf of the Israeli Gastroenterology Association recommends that a 4-drug regimen be used for first-line treatment [7].These include sequential (amoxicillin followed by clarithromycin and a nitroimidazole, together with a proton pump inhibitor [PPI]), concomitant (amoxicillin, clarithromycin, a nitroimidazole, and a PPI given together) and bismuth-based protocols (bismuth, tetracycline, a nitroimidazole, and a PPI). In the present study we determined the effectiveness, compliance, and safety of first-line treatment for *H. pylori* in Israel.

PATIENTS AND METHODS

EUROPEAN REGISTRY ON H. PYLORI MANAGEMENT

This is a sub-analysis of the dataset of the European Registry on H. pylori Management (Hp-EuReg), an international multicenter prospective non-interventional registry that began in 2013. The registry is promoted by the European Helicobacter and Microbiota Study Group (EHMSG) (www.helicobacter.org). The Protocol of the European Registry on the management of H. pylori infection (Hp-EuReg) has been recently published [10] and the study was approved by the Ethics Committee of La Princesa University Hospital, Madrid, Spain and registered at ClinicalTrials.gov under the code NCT02328131. The Hp-EuReg research team consists of an international Scientific Committee currently comprised of 5 members: Javier P. Gisbert (Principal Investigator), Francis Mégraud, Colm A. O'Morain, Ignasi Puig, and Olga P. Nyssen (the last two also Scientific Directors). A list of 27 participating countries was selected, with a National Coordinator designated as the top investigator of each country and responsible of the recruiting investigators, who had to be adult gastroenterologists. Recruiting investigators were required to manage H. pylori-infected patients over 18 years old. Data were recorded in an Electronic Case Report Form (e-CRF) and collected and managed using REDCap hosted at Asociación Española de Gastroenterología (AEG [www.aegastro.es]), a non-profit scientific and medical society focused on gastroenterology research.

VARIABLES AND OUTCOMES

The e-CRF registers 290 variables including demographics, history and co-morbidity, data on infection and diagnosis, previous eradication attempts, current treatment, compliance, adverse events, and effectiveness. All personal data were anonymized. The main outcome was eradication of *H. pylori* confirmed at least 4 weeks after treatment. Compliance was defined as having taken at least 90% of the prescribed drugs. Adverse events and compliance were evaluated with both open-ended questions and a predefined questionnaire as well as a follow-up telephone interview. Data extraction was performed in March 2020.

The intention-to-treat (ITT) analysis included all patients who had been registered until September 2019 to allow at least a 6-month follow-up. Cases lost to follow-up were considered treatment failure. Modified ITT (mITT) included all cases that had completed follow-up, regardless of treatment result or whether they had a confirmatory test after the eradication treatment. Per-protocol (PP) analysis included all cases that finished follow-up and had taken at least 90% of the treatment drugs, as defined in the approved protocol. In the current study, mITT and PP effectiveness results are provided.

STATISTICAL ANALYSES

Continuous variables were presented as mean and standard deviation. Qualitative variables were presented as percentages and 95% confidence intervals (95%CI). Chi-square test (for more than two values) or Fisher's exact test (for two categorical values) were used to compare the value of categorical variables between study groups. Significance was considered at $P < 0.05$. PPI dosage was standardized in three categories [11]. Low dose PPI (4.5–27 mg omeprazole equivalents, twice daily), standard dose PPI (32–40 mg omeprazole equivalents, twice daily), and high dose PPI (54–128 mg omeprazole equivalents, twice daily).The variable treatment length was assessed using three categories, corresponding with the most frequent treatment durations: 7, 10, and 14 days.

ETHICS

The study was conducted in accordance with the principles of the Declaration of Helsinki and Good Clinical Practice. The European registry on *H. pylori* management (Hp-EuReg) protocol was approved by the internal review board at Rabin Medical Center, which acted as a reference for participation of other tertiary referral centers in Israel. A waiver to obtain written informed consent was granted.

RESULTS

OVERVIEW

A total of 242 patients were prospectively entered into the registry, including 121 (50.0%) who received first-line, 38 (15.7%) second-line, 57 (23.6%) third-line, and 26 (10.7%) fourth-line therapy. Of the 121 patients who received first-line therapy, data were available for 112 patients who formed the ITT group. Forty-six (41.1%) patients received clarithromycin-based triple therapy, 26 (23.2%) received concomitant therapy (consisting of PPI, amoxicillin, clarithromycin and a nitroimidazole), 33 (29.5%) received sequential therapy, and 7 (6.3%) received bismuth quadruple therapy (consisting of PPI, bismuth, doxycycline, and a nitroimidazole).

Treatment prescriptions

We found that patients who were treated with clarithromycin-based triple therapy were more often treated with low-dose PPI (91.3%) compared to those receiving sequential or concomitant therapy (91.3% vs. 25.0% and 19.2%, respectively, $P < 0.0001$ for variance) [Table 1].

The duration of treatment was 14 days in the majority of patients who received concomitant therapy, compared to 10 days in the majority of patients who received clarithromycin-based triple or sequential therapy ($P < 0.0001$ for variance) [Table 1].

OVERALL EFFECTIVENESS

The overall effectiveness of first-line therapy was 57.1%, 85.3%, and 85.9% in the ITT, mITT and PP analyses, respectively. The effectiveness (mITT) of first-line therapy according

Table 1. Potency of acid inhibition and treatment duration in first-line treatment

	PPI dose***, % (n)				Treatment duration, % (n)			
	Low	Standard	High	Total	7 days	10 days	14 days	Total
PPI+A+C	91 (42)	4 (2)	4.3 (2)	100 (46)	40 (18)	51 (23)	9 (4)	100 (45)
Sequential*	25 (6)	0 (0)	75.0 (18)	100 (24)	0 (0)	95 (18)	5(1)	100 (19)
PPI+M+D+B	57 (4)	0 (0)	42.9 (3)	100 (7)	0 (0)	14 (1)	86 (6)	100 (7)
PPI+A+C+M	19 (5)	4 (1)	76.9 (20)	100 (26)	0 (0)	41 (9)	59 (13)	100.0 (22)
Other**	33 (2)	17 (1)	50.0 (3)	100 (6)	33 (2)	0 (0)	67 (4)	100 (6)
Total	54 (59)	4 (4)	42.2 (46)	100 (109)	20 (20)	52 (51)	28 (28)	100 (99)

*Sequential: PPI + A followed by PPI + C + M
**Other: PPI + C + M; PPI + A + L; PPI + C + L; PPI + B + L +Tc
***Standard dose PPI: 32–40 mg omeprazole equivalents, twice daily (i.e., 40 mg omeprazole equivalents, twice daily), high dose PPI = 54–128 mg omeprazole equivalents, twice daily (i.e., 60 mg omeprazole equivalents, twice daily). Chi square showed statistically significant differences of treatment length and PPI dose by treatment use with a *P* value < 0.001
A = amoxicillin, B = bismuth salt, C = clarithromycin, D = doxycycline, L = levofloxacin, M = metronidazole or tinidazole, mITT = modified intention-to-treat, PPI = proton pump inhibitor, Tc = tetracycline

to treatment protocol is shown in Table 2. The effectiveness of both sequential and concomitant therapy was 100% while clarithromycin-based triple therapy was successful in 79% (mITT). The differences in effectiveness of the treatment protocols were not statistically significant ($P = 0.41$).

Table 2. Effectiveness by modified-intention-to-treat in first-line treatment

First-line treatments	mITT, % (n/N)	(95% confidence interval)
PPI + A + C	79 (34/43)	(66–92)
Sequential*	100 (13/13)	(75–100)
PPI + M + D + B	75 (3/4)	(19–99)
PPI + A + C + M	100 (10/10)	(69–100)
Other**	80 (4/5)	(28–99)
Total	85 (64/75)	(77–94)

*Sequential: PPI + A followed by PPI + C + M.
**Other: PPI + C + M; PPI + A + L; PPI + C + L; PPI + B + L + Tc
A = amoxicillin, B = bismuth salt, C = clarithromycin, D = doxycycline, L = levofloxacin, M = metronidazole or tinidazole, mITT = modified intention-to-treat, PPI = proton pump inhibitor, Tc = tetracycline

Effectiveness by treatment schemes

Treatment was more likely to be successful among patients who received high dose PPI compared to low dose PPI (100% vs. 81.5%, respectively, $P = 0.009$) [Table 3].

Treatment was more likely to be successful among patients who received treatment for 14 days however this did not reach statistical significance (92.9% vs. 81.0% respectively, $P = 0.606$) [Table 3].

Compliance and safety

Compliance was high with 97.5% (79/81) receiving at least 90% of the prescribed medication. Treatment was well tolerated with only 4 (3.6%) patients reporting adverse effects. These were generally mild and did not lead to treatment discontinuation. No severe adverse events were reported [Table 4].

DISCUSSION

The availability of reliable, up-to-date, location-specific data for the effectiveness of the different antibiotic protocols for the treatment of H. pylori infection is crucial in order to provide evidence-based recommendations for the thousands of patients who seek treatment each month in Israel. We found that the prescribing practices of Israeli gastroenterologists with regard to first-line treatment for H. pylori were highly variable. For patients, 57% (mITT) received clarithromycin-based triple therapy, and the remainder received other treatments usually consisting of four drugs. This variability is probably due to the fact that during the study period local consensus guidelines were lacking, and international guidelines linked their recommendations to local resistance data, which were scarce [4,12-17].

This analysis of prospectively collected data provides support for the recent management guidelines published on behalf of the Israeli Gastroenterology Association and endorsed by the Institute for Quality in Medicine under the auspices of the Israeli Medical Association, which state that the effectiveness of clarithromycin based triple therapy is unacceptable and should be abandoned [7]. *H. pylori* treatments can be classified as excellent (> 95% PP success), good (> 90 success), borderline acceptable (85–89% success), or unacceptable (< 85% success) [18]. It can therefore be said that the overall success of first-line therapy in Israel during the study period was borderline acceptable (85.9% PP), and that

Table 4. Overall safety of first-line treatment

	N (%)
Any	4 (3.9)
Dysgeusia	1 (0.9)
Diarrhea	1 (0.9)
Nausea	1 (0.9)
Other	1 (0.9)
Severe	0 (0.0)
Leading to treatment cessation	0 (0.0)

the effectiveness of sequential and concomitant therapy was excellent 100% PP).Furthermore, it can be presumed that the effectiveness of clarithromycin-based triple therapy would be even lower today than the borderline acceptable results we reported for the period 2013–2019 due to the ever-increasing resistance of *H. pylori* to clarithromycin. It should also be noted that during the study period more local resistance data became available, which lent support for the recommendation to favor a 4-drug regimen for first-line treatment in Israel.

Previous prospective studies conducted in Israel found that the effectiveness of clarithromycin-based triple therapy was 79.9% in 2005 and 82.5% in 2007, which is similar to 79.1% (mITT) found in the present study [19,20]. A retrospective analysis of a large Israeli cohort (N=7842) between 2010 and 2015 found that the effectiveness of clarithromycin-based triple therapy was 79.4%, and the effectiveness of sequential and concomitant therapies were 82.7% and 81.3%, respectively [8]. Similarly, in the pan-European Hp-EuReg cohort, triple therapy with amoxicillin and clarithromycin achieved an overall 77.9% eradication rate. Also, concomitant therapy achieved 89% eradication in a previous study [21]. Due to the suboptimal effectiveness of clarithromycin based triple therapy in regions with a high rate (> 15%) of clarithromycin resistance, triple therapy is slowly being abandoned by primary care physicians. In an electronic questionnaire, the proportion of primary care physicians in Israel who recommended a four-drug treatment protocol increased from 3.8% in 2015 to 37.1% in 2018 [22]. Pan-European data from the Hp-EuReg cohort showed that triple therapies decreased from over 50% of prescriptions in 2013/14 to less than 25% in 2017/18 [23].

An important finding in this study is that treatment was more likely to be successful among patients who received high dose PPI. PPIs are crucial for the success of *H. pylori* treatment. *H. pylori* replicates at an optimal pH of 6.0-8.0, whereas intragastric pH between meals is 1.4. *H. pylori* achieves a periplasmic pH is above 6.0 by secreting urease, which catalyses the hydrolysis of urea to carbon dioxide and ammonia. Antibiotics (particularly amoxicillin) exert their effect during bacterial replication, and therefore require the synergism of PPIs

Table 3. Effectiveness of first-line treatment according to the proton-pomp inhibitor dose and treatment length

	Treatment success % (N)		
	ITT (N)	mITT (N)	PP (N)
PPI dose*			
Low dose	75 (59)	81.5 (54)	81 (52)
Standard	0 (4)	0 (1)	0 (0)
High	39 (46)	100 (18)	100 (18)
Total	57 (109)	85 (73)	86 (70)
P value	< 0.001	0.001	0.05
Treatment duration			
7 days	77 (22)	81 (21)	81 (21)
10 days	61.5 (52)	86.5 (37)	85 (34)
14 days	46 (28)	93 (14)	93 (14)
Total	61 (102)	86 (72)	85.5 (69)
P value	0.01	NS	NS

*Standard dose PPI: 32–40 mg omeprazole equivalents, twice daily (i.e., 40 mg omeprazole equivalents, twice daily), high dose PPI: 54–128 mg omeprazole equivalents, twice daily (i.e., 60 mg omeprazole equivalents, twice daily). Chi square test showed statistically significant differences of treatment length and PPI dose in the overall effectiveness by ITT, mITT, and PP analyses
A = amoxicillin, B = bismuth salt, C = clarithromycin, D = doxycycline, L = levofloxacin, M = metronidazole or tinidazole, mITT = modified intention-to-treat, PPI = proton pump inhibitor, Tc = tetracycline

for their action. Since different PPIs were favored by different recruiting physicians, we standardized PPI dose by using omeprazole-equivalents [11]. In this manner, esomeprazole 40 mg twice daily is equivalent to a daily omeprazole dose of 128 mg. This lends support to the recommendation to favor new-generation PPIs such rabeprazole (currently unavailable in Israel) and esomeprazole (available) for *H. pylori* treatment, since a higher dose can be achieved with fewer pills [3-7]. Several studies, including meta-analyses have demonstrated the superiority of new-generation PPIs in the context of triple therapy and quadruple therapy for the treatment of *H. pylori* [24,25]. The benefit of new-generation PPIs is greatest in extensive PPI metabolizers. We found an over-representation of patients receiving a low PPI dose among those treated with clarithromycin-based triple therapy. This could indicate that physicians who favored this regimen were unfamiliar with *H. pylori* management guidelines, both regarding drug choice and dosing.

LIMITATIONS

The main limitation of our analysis is the relatively small sample size, which precluded subgroup analyses or analysis of changes in

prescribing practice over time, or an assessment of an association between compliance and treatment success. For example, it is unclear whether the low success rate of clarithromycin-based triple therapy is due to clarithromycin resistance or due to a lower PPI dose in this subgroup. Similarly, it is plausible that our finding that a lower PPI dose was associated with lower treatment success was due to an over-representation of patients who received clarithromycin-based triple therapy in this group. Multivariate analysis may have resolved this issue, but was not feasible due to the small size of subgroups. The fact that we did not find a significant difference in treatment effectiveness among 7-, 10-, and 14-day protocols is also likely to be a reflection of the small size of subgroups and this finding should be interpreted with caution. *H. pylori* management guidelines recommend continuing treatment for 10 to 14 days, and specifically advise against shorter treatment periods [3-7]. Another limitation is that this is not a randomized, controlled trial, so effectiveness data should be interpreted cautiously. Furthermore, only gastroenterologists recruited patients for inclusion, and these data may not be reflective of primary care. The strength of this study is the prospective, real life design, which provides ample data to support practice guidelines.

CONCLUSIONS

The effectiveness of clarithromycin-based triple therapy is suboptimal and should be abandoned if antimicrobial susceptibility testing cannot be performed. First-line treatment of *H. pylori* infection should consist of four drugs, including high dose PPI, in accordance with the Israeli Gastroenterology Association Guideline for the Management of *H. pylori* infection.

CONFLICT OF INTEREST

J.P. Gisbert has served as a speaker, consultant, and advisory member or has received research funding from Casen Recordati, Mayoly, Allergan, Advia, Diasorin

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