

Helicobacter pylori treatment results in Slovenia in the period 2013–2015 as a part of European Registry on Helicobacter pylori Management

Bojan Tepes¹, Marko Kastelic¹, Miroslav Vujasinovic², Polona Lampic³, Maja Seruga⁴, Natasa Brglez Jurecic⁵, Olga P. Nyssen⁶, Maria G. Donday⁶, Colm O'Morain⁷, Francis Megraud⁸, Adrian G McNicholl⁶, Javier P. Gisbert⁶

¹ Abakus Medico, Diagnostic Center Rogaška, Rogaška Slatina, Slovenia

² General Hospital Slovenj Gradec, Slovenj Gradec, Slovenia

³ Diagnostic Center Bled, Bled, Slovenia

⁴ General Hospital Murska Sobota, Murska Sobota, Slovenia

⁵ General Hospital Trbovlje, Trbovlje, Slovenia

⁶ Gastroenterology Unit, Hospital Universitario de La Princesa, Instituto de Investigación Sanitaria Princesa (IIS-IP) and Centro de Investigación Biomédica en Red de Enfermedades Hepáticas y Digestivas (CIBEREHD), Madrid, Spain

⁷ Beacon Consultants Clinic, Dublin, Ireland

⁸ Laboratoire de Bactériologie-Enfants Hôpital Pellegrin 33076 Bordeaux cedex, France

Radiol Oncol 2018; 52(1): 1-6.

Received 11 September 2017

Accepted 5 November 2017

Correspondence to: Prof. Bojan Tepeš M.D., Ph.D., FEBGH, AM DC Rogaška, Prvomajska 29 A, 3250 Rogaška Slatina, Slovenia.
E mail: bojan.tepes@siol.net

Disclosure: No potential conflicts of interest were disclosed.

Background. *Helicobacter pylori* (*H. pylori*) is the most common chronic bacterial infection in the world affecting over 50% of the world's population. *H. pylori* is a grade I carcinogen, responsible for the development of 89 % of non-cardia gastric cancers. In the present study we analyzed the data for *H. pylori* eradication treatments in Slovenia.

Patients and methods. Slovenia is a part of the European Registry on Helicobacter pylori Management from the beginning. In seven medical institutions data for *H. pylori* eradication treatments was collected for 1774 patients from April 16th 2013 to May 15th 2016. For further modified intention to treat (mITT) analysis 1519 patients were eligible and for per protocol (PP) analysis 1346 patients.

Results. Patients' dropout was 11.4%. Eradication rate for 7 day triple therapy with proton pump inhibitor (PPI) + Clarithromycin (C) + Amoxicillin (A) was 88.7% PP and 72.0% mITT; for PPI + C + Metronidazole (M) 85.2% PP and 84.4% mITT. Second line 14 day therapy PPI + A + Levofloxacin had 92.3% eradication rate PP and 87.1% mITT. Ten to fourteen day Bismuth quadruple therapy was the therapy in difficult to treat patients. At the end all patients that adhered to prescribed regimens were cured of their *H. pylori* infection.

Conclusions. High dropout rate deserves further analysis. Slovenia is still a country with < 15% *H. pylori* resistance to clarithromycin, triple therapy with PPI plus two antibiotics reaches PP eradication rate > 85%, but mITT eradication rates are suboptimal.

Key words: *Helicobacter pylori*; eradication treatment; European Registry on *Helicobacter pylori* management; Slovenian results

Introduction

Helicobacter pylori (*H. pylori*) is the cause of the most common chronic bacterial infection in the world, affecting over 50% of the world's popula-

tion.¹ Approximately 20% of infected patients will develop peptic ulcer disease, mucosa associated lymphoid tissue lymphoma or gastric cancer at some point in their lives.² The WHO's International Agency for Research on Cancer classified *H. pylori*

as a definite (group 1) carcinogen.^{3,4} *H. pylori* is the leading infectious cause of cancer worldwide and it was estimated that some 660 000 new cancer cases globally were directly attributable to *H. pylori* infection in 2008, which accounts for 33% of all infection-associated cancers, including 46% in developed regions and 29% in the developing regions.⁵

Several national guidelines have recommended eradication in all *H. pylori*-infected individuals to prevent the spread of infection and reduce the future burden of *H. pylori*-induced diseases, particularly gastric cancer.^{6,7} In the Kyoto consensus on *H. pylori* gastritis the recommendation is to treat all *H. pylori* infected patients independent of whether clinical manifestations are present.⁸

The basis of modern *H. pylori* therapy is a proton pump inhibitor (PPI) plus two / three antibiotics for 7–14 days.² The desired eradication rate is > 90%, the acceptable eradication rate for first line therapy is > 80%.⁹

The treatment success depends on *H. pylori*'s susceptibility to antibiotics and patient's compliance. *H. pylori* resistance rate to antibiotics as well as treatment results should be carefully recorded and those results should guide the therapy in a certain country or region.² The European Registry on *H. pylori* management (Hp-EuReg) has been introduced in 2013 with the idea to collect treatment results, side effects, patients' compliance and antimicrobial susceptibility in different European countries. Thirty one countries and 280 recruiting investigators are included in the Hp-EuReg. So far, more than 15.000 patients have been included, and 12.270 patients have finished follow-up.¹⁰

We would like to present the Slovenian data collected in Hp-EuReg from April 16th 2013 to May 15th 2016.

Patients and methods

European Registry on *H. pylori* Management

The present manuscript is an interim analysis using the Slovenian data of the "European Registry on *H. pylori* Management" (Hp-EuReg), an international multicenter prospective non-interventionist registry that will last over ten years, promoted by the *European Helicobacter and Microbiota Study Group* (www.helicobacter.org). The Scientific Committee of the project is comprised by Javier P. Gisbert (Principal Investigator), Francis Megraud, Colm O'Morain and Adrian G. McNicholl (Scientific Coordinator).

Ethics

Hp-EuReg protocol was approved by the Ethics Committee of the La Princesa Hospital (Madrid, Spain) that acted as reference IRB, and was prospectively registered at ClinicalTrials.gov under code NCT02328131.

National coordinators

A list of 30 European Countries has been selected. In each country a National Coordinator was elected based on its clinical and research activity. Slovenian National Coordinator is Bojan Tepes. The National Coordinators constitutes the monitoring and drafting committee of the registry in a certain country.

Recruiter investigators

The Recruiting Investigators are gastroenterologists attending an adult population with a gastroenterology outpatient clinic that assists *H. pylori* infected patients. Eradication confirmation tests have to be performed routinely. Patients are managed and registered following routine clinical practice. Slovenian recruiting investigators are authors BT, MK, MV, PL, MS and NBJ.

Electronic Case Report Form (e-CRF)

Study data were collected and managed using REDCap electronic data capture tools hosted at Asociación Española de Gastroenterología (AEG; www.aegastro.es).¹¹ AEG is a non-profit Scientific and Medical Society focused on Gastroenterology, and it provided this service free of charge, with the sole aim of promoting independent investigator driven research. REDCap (Research Electronic Data Capture) is a secure, web-based application designed to support data capture for research studies, providing (1) an intuitive interface for validated data entry; (2) audit trails for tracking data manipulation and export procedures; (3) automated export procedures for seamless data downloads to common statistical packages; and (4) procedures for importing data from external sources.

Variables and outcomes

The e-CRF includes 290 variables including demographics, history and comorbidity, data on infection and diagnosis, previous eradication attempts, current treatment, compliance, adverse events and

efficacy. All patient data was anonymized. Main outcome is confirmed eradication at least 4 weeks after treatment.

Per protocol (PP) analysis include all patients who finished follow-up and took at least 90% of the treatment drugs, as defined in the approved protocol. As the registry is ongoing, a pure Intention to treat (ITT) analysis cannot be provided. A modified ITT (mITT) was designed trying to reach the closest result to those obtained in clinical practice. This mITT includes for analyses all patients whose outcome has been registered by their doctors (eradication success, failure or lost to follow up), plus those that although their result has not been registered were treated more than a year prior to analysis. Patients classified as failure, lost or without registered outcome will be considered treatment failure in the mITT analysis.

Statistical analyses

Continuous variables are presented as the arithmetic mean and SDs. Qualitative variables are presented as proportions and 95% confidence intervals (CIs). The statistical analyses of the results were carried out using the χ^2 -test. The 95% CIs were calculated by normal approximation. One- and two-sided tests were used for the analyses and the P-value cut off for significance was set to less than 0.05. The analyses were carried out using IBM SPSS Statistics 22.0.0.

Results

Data was collected in seven medical institutions in Slovenia from April 16th 2013 to May 15th 2016 for 1774 patients (Table 1).

Two hundred and fifty-five (14.4%) patients were excluded from the analysis because they either had incomplete/invalid data (e.g.: missing age, gender, compliance data etc.) or because they were treated within the last year of this analysis and the outcome of their treatment was not yet registered.

All the remaining 1519 patients were eligible for further analysis in the modified intention to treat (mITT) group; 918 (60.4%) were female patients and 601 (39.6%) were male patients (Table 2; $p = 0.00$).

Out of those, 1346 patients had their outcome registered and were eligible for analysis in the per protocol (PP) group.

There were 173 patients (11.4%) who did not have their outcome recorded and were treated more than a year prior to this analysis. We consider

TABLE 1. Medical institutions participating in the Slovenian part of EU-HpReg

Institution	Number	Excluded from analysis (% of hosp. data) ¹		Dropout (%) ²	
AM DC Rogaska	805 (45.4%)	146	(18.1%)	16	(2.4%)
SB Slovenj Gradec	464 (26.2%)	8	(1.7%)	81	(17.8%)
DC Bled	287 (16.2%)	0	(0%)	60	(20.9%)
SB Murska Sobota	73 (4.1%)	10	(13.7%)	0	(0%)
SB Trbovlje	68 (3.8%)	34	(50%)	1	(2.9%)
UKC Ljubljana	66 (3.7%)	50	(75.8%)	14	(87.5%)
MC Heliks	11 (0.6%)	7	(63.6%)	1	(25%)
Total	1774 (100.0%)	255	(14.4%)	173	(11.4%)

¹ Excluded from analysis because of incomplete/invalid data or because the visit was within last year and there is no follow up data yet; ² Patients whose visit was more than a year ago and who had no follow up (dropout = modified intention to treat [mITT] – per protocol [PP])

TABLE 2. Demographic data for modified intention to treat (mITT) patient group

Gender	N (percent)	Minimum Age	Maximum Age	Mean Age	Std. Deviation
Female	918 (60.4%)	18	91	52.3	15.14
Male	601 (39.6%)	18	88	53.3	14.76
Total	1519	18	91	52.7	15.0

that group a drop out patients group. We do not know if these patients took their therapy or whether they had the UBT done in the primary medical care and because of that did not return to their gastroenterologist, which can be a realistic option.

Only in 56 patients who took part in a RCT, primary *H. pylori* resistance to antibiotics was recorded (Table 3). The highest resistance rate was for metronidazole (M; 28.6%), resistance rate to clarithromycin (C) was 14.3% and to amoxicillin (A) was 3.6%. All the other antimicrobial susceptibility tests have been performed in treatment failure patients. The percentage of resistance to different antibiotics rose with the number of treatment attempts.

Ten different 7–14 days triple combinations were used in 1305 patients as a first line treatment. The majority of patients (1.154) were treated accordingly to our therapeutic guidelines (Table 4) with 7 day triple therapies: PPI clarithromycin / amoxicillin / metronidazole. The eradication rate for PPI + Clarithromycin + Amoxicillin was 72.0% for the mITT group *vs.* 88.1% for the PP group. The eradication rate in 7 day PPI + Clarithromycin + Metronidazole was 84.4% for the mITT group *vs.* 85.2% for the PP group. No significant differences were found regarding the type of PPI used.

Six different triple 7-14 days treatments were used in 176 patients whose *H. pylori* was not eradicated with the first line treatment (Table 5). The

TABLE 3. *Helicobacter pylori* antibiotic resistance

Antibiotic	First treatment (95% C.I.)		Second treatment (95% C.I.)		Third treatment (95% C.I.)		Fourth treatment	Fifth treatment
No resistance	62.5%	(50.0%–75.4%)	6.1%	(0%–15.6%)	14.3%	(0%–36.4%)	0%	0
Nitroimidazole	28.6%	(16.7%–40.8%)	45.5%	(28.1%–63.0%)	57.1%	(30.0%–83.3%)	100%	100%
Clarithromycin	14.3%	(5.7%–24.2%)	87.9%	(75.7%–97.3%)	85.7%	(63.6%–100%)	100%	100%
Amoxicillin	3.6%	(0%–9.3%)	0%		0%		0%	0
Quinolone	0%		6.1%	(0%–15.6%)	7.1%	(0%–23.5%)	50%	0
Tetracycline	0%		3%	(0%–100%)	7.1%	(0%–23.5%)	0%	0
Total	N = 56		N = 33		N = 14		N = 2	N = 1

C. I. = confidence interval

majority of them used 14 days PPI 40 mg bid, Amoxicillin (A) 1000 mg bid, and Levofloxacin (L) 500 mg o.d. with 92.3% eradication rate PP and 87.1% eradication rate mITT. This treatment is according to our guidelines the recommended one for second line. Dropout rate for the second treatment attempt was 6.3%.

Bismuth is not available in Slovenia and those that need third or fourth line treatment regimen should buy it in Germany or in any other country in Europe where it is available. At the moment this treatment is not reimbursed (Tables 6,7). Dropout rate after third line therapy was 18.2%. Seven patients were treated with fourth line treatment regimen (Table 7), one was treated with fifth, and one with sixth line treatment. No drop out has been recorded in the group with four or more treatment attempts.

At the end all patients that start their treatment and comply with the treatment regimens were cured of their *H. pylori* infection.

Discussion

High dropout rate - 11.4% - in the Slovenian Hp-EuReg data is the first important message. This per-

centage is lower than in the EU Hp-EuReg (13%).¹⁰ Some logistic reasons can influence this high dropout rate. All 66 patients (3.73% of all patients) from University Medical Centre did not come back to their gastroenterologist. They were most probably controlled by their general practitioner, but we are not aware of their UBT results. And many more dropout patients from other medical centers could be treated in the same way. Real patients' compliance was never an issue, also in our previous reports / studies.^{12,13}

H. pylori resistance to clarithromycin is still low in Slovenia. It was 10.5% in a recently published study and 25.9% for metronidazole.¹² In our Hp-EuReg data primary resistance to clarithromycin was recorded in a small subgroup of patients and was 14.3% and 28.6% for metronidazole. That can explain the still relatively good eradication results for 7 day triple therapy (TT). The PP eradication rate for PPI A C was 88.7% (72.0% mITT) and 85.2% PP for PPI C M (84.4% mITT). This is an acceptable eradication rate in PP analysis, but still not satisfactory, because it did not reach > 90% eradication rate. In some other parts of the world due to the increasing incidence of *H. pylori* resistance to clarithromycin, the cure rates of 7 day triple therapy (TT) have decreased to less than 80%, which is

TABLE 4. First line treatment results for treatment regimens with more than 15 patients

Treatment	mITT			PP		
	N	Success % (95% C.I.)		N	Success % (95% C.I.)	
Clarithromycin, amoxicillin, PPI, 7 days	664	72.0%	(68.6%–75.4%)	538	88.7%	(85.9%–91.3%)
Clarithromycin, metronidazole, PPI, 7 days	486	84.4%	(81.2%–87.5%)	481	85.2%	(82.0%–88.4%)
Clarithromycin, amoxicillin, PPI, 10 days	38	55.3%	(39.1%–71.1%)	27	77.8%	(60.7%–92.9%)
Clarithro., amoxicillin., metro., PPI, 7 days	17	88.2%	(70.6%–100%)	15	93.3%	(77.8%–100%)

metro. = metronidazole; mITT = modified intention to treat; PP = per protocol; PPI = proton pump inhibitor

TABLE 5. Second line treatment results for treatment regimens with more than 15 patients

	mITT			PP		
Treatment	N	Success % (95% C.I.)		N	Success % (95% C.I.)	
Amoxicillin, Levofloxacin, PPI, 14 days	70	87.1%	(78.8%–94.6%)	65	92.3%	(85.3%–98.3%)
Amoxicillin, Levofloxacin, PPI, 10 days	24	91.7%	(78.6%–100%)	23	95.7%	(85.7%–100%)
Amoxicillin, Metronidazole, PPI, 7 days	18	44.4%	(21.1%–68.4%)	17	47.1%	(23.1%–72.2%)
Amoxicillin, Metronidazole, PPI, 10 days	16	87.5%	(68.4%–100%)	15	93.3%	(77.8%–100%)

C. I. = confidence interval; mITT = modified intention to treat; PP = per protocol; PPI = proton pump inhibitor

considered to be unacceptably low (14). Maastricht IV suggest not to use 7 day triple therapy in countries with *H. pylori* resistance to clarithromycin over 15%. Our *H. pylori* resistance rate to clarithromycin is still under this value, but we must continue to audit eradication rates with triple therapies in Slovenia as well as continuously measure primary *H. pylori* resistance rate to clarithromycin and other antibiotics.

Ten different 7-14 days triple combinations were used as a first line therapy. In our last *H. pylori* treatment guidelines⁷ only two TT (PPI A C and PPI C M) were recommended. This shows us that real clinical practice in Slovenia is not ideal, which was also recognized in some other countries shown in Hp-EuReg data.¹⁰

We did not show any benefits of esomeprazole over other PPIs in the eradication rates as was shown in some other studies.^{10,15} Because Caucasians have higher prevalence of high metabolizers (56%-81%) compared to Asians, higher doses of esomeprazole or rabeprazole are recommended, as they can control gastric pH adequately and allow better antibiotic efficacy.^{16,17}

When *H. pylori* infection is found, it is very important to control the eradication rate and prescribe second or even further treatments to cure the infection.² In our data, dropout rate for second line therapy is still too high (6.3%). Results in Hp-EuReg are even worse with only 27% of first line eradication failures being retreated.¹⁰ In Maastricht IV quadruple bismuth therapy is recommended as the second line treatment in low clarithromycin resistant regions.² The fact is that this therapy is not available in Slovenia at this moment. That is why the majority of second line treatments were 14 days PPI A L. In the National recommendation⁷ only 14 day therapy should be used as a second line treatment. But in real practice, gastroenterologists use therapies from 7-14 days. This variations need to be corrected, because longer duration of second line

therapies mean also better cure rates.^{2,18} Our eradication rate for PPI A L is 92.3% in PP group and 87.1% in mITT group, which is a satisfactory result. We know that this is due to low *H. pylori* resistance to quinolones in Slovenia (3.1–4.4%).^{19,20}

Other possible second line treatment could also be sequential or non-bismuth concomitant therapy with PPI and all three antibiotics (C, M, E). This therapy has been proven to be very effective (> 90% by ITT) in Slovenia¹⁰ but is not used at the moment in clinical practice. These therapies can be effective also in the regions with *H. pylori* resistance to clarithromycin > 15%.²¹⁻²³ Only if dual resistance to clarithromycin and metronidazole is > 15%, the eradication rate of non-bismuth quadruple therapies will be impaired and bismuth quadruple therapies should be used.²⁴

In the third and fourth line treatment PPI A L was used in some patients not treated with this regimen before, as well as bismuth quadruple therapies. Some patients were treated with 14 day therapies, but not all, which should also be corrected.

In Maastricht recommendations culture and antibiotic susceptibility should be done after two unsuccessful therapeutic attempts², but we seldom use this approach. The reason for this is non-reimbursement for culture by our National health fund.

One patient has been treated for the fifth time and one for the sixth time, both successfully. So finally all patients who were compliant with the prescribed therapeutic regimens were eradicated of *H. pylori* infection in the end, which is similar to our and international previously published data.^{13,25}

Conclusions

Hp-EuReg is a very important clinical registry which helps us audit real clinical practice in the field of *H. pylori* eradication as well as collect eradication rates for different first, second line

and beyond treatments. From the analysis of our Slovenian data we can figure out some clinically important conclusions:

Seven days PPI A/M /C results has unacceptable low mITT eradication rates. Treatment duration should be prolonged to 14 days.

Dropout rate is too high. We must provide all general practitioners with the possibility to use urea breath test or monoclonal stool antibody test in all patients with *H. pylori* eradication therapies. No patients should be without confirmation of eradication success.

Treatment failures of the first line regimen should be retreated according to National guidelines, that is with 14 day PPI A L regimen

Primary *H. pylori* resistance to antibiotics and treatment results should be continuously monitored

Acknowledgements

We want to thank the data monitors of the study, Mercedes Ramas, Lorena Lee and Irene Barbado for their large efforts to ensure the validity of the data and quality of their work. We want to thank Pau Alarcón who performed advanced data managing and programming for this project. We want to thank the Spanish Association of Gastroenterology (AEG) and the Scientific Director of AEG-REDCap (Adrian G. McNicholl) for providing the e-CRF service free of charge.

References

- Hunt RH, Xiao SD, Megraud F, Leon-Barua R, Bazzoli F, van der Merwe S, et al. World Gastroenterology Organization. Helicobacter pylori in developing countries. World Gastroenterology Organisation Global Guideline. *J Gastrointest Liver Dis* 2011; **20**: 299-304. doi: 10.1097/MCG.0b013e31820fb8f6
- Malfertheiner P, Megraud F, O'Morain CA, Atherton J, Axon ATR, Bazzoli F, et al. Management of Helicobacter pylori infection – the Maastricht IV/Florence Consensus Report. *Gut* 2012; **61**: 646-64. doi: 10.1136/gutjnl-2012-302084
- International Agency for Research on Cancer. Infection with Helicobacter pylori. *IARC Monogr Eval Carcinog Risks Hum* 1994; **61**: 177-240.
- IARC Helicobacter pylori Working Group (2014). Helicobacter pylori Eradication as a Strategy for Preventing Gastric Cancer. Lyon, France: International Agency for Research on Cancer IARC Working Group Reports 2014; **8**: 1-181.
- de Martel C, Ferlay J, Franceschi S, Vignat J, Bray F, Forman D, Plummer M. Global burden of cancers attributable to infections in 2008: a review and synthetic analysis. *Lancet Oncol* 2012; **13**: 607-15. doi: 10.1016/S1470-2045(12)70137-7
- Asaka M, Kato M, Takahashi S, Fukuda Y, Sugiyama T, Ota H, et al. Japanese Society for Helicobacter Research. Guidelines for the management of Helicobacter pylori infection in Japan: 2009 revised edition. *Helicobacter* 2010; **15**: 1-20. doi: 10.1111/j.1523-5378.2009.00738.x
- Tepeš B, Štabuc B. [Slovenian Society for Gastroenterology and Hepatology Guidelines on the management of Helicobacter pylori infection]. Guidelines on the management of Helicobacter pylori infection. [Slovenian]. *Zdrav Vestn* 2011; **80**: 647-56.
- Sugano K, Tack J, Kuipers EJ, Graham DY, El-Omar EM, Miura S, et al. Kyoto global consensus report on Helicobacter pylori gastritis. *Gut* 2015; **64**: 1353-67. doi: 10.1136/gutjnl-2015-309252
- Graham DY, Dorea MP. Helicobacter pylori therapy: a paradigm shift. *Expert Rev Anti-infe* 2016; **14**: 577-85. doi: 10.1080/14787210.2016.1178065
- McNicholl AG, Gasbarrini A, Tepeš B, Bordin DS, Lerang F, Leja M, et al. Pan-European registry on *H. pylori* management (HP-EUREG). *Gastroenterology* 2016; **150**: S875-76. doi: 10.1016/S0016-5085(16)32952-3
- Harris PA, Taylor R, Thielke R, Payne J, Gonzalez N, Conde JG. Research electronic data capture (REDCap) - A metadata-driven methodology and workflow process for providing translational research informatics support. *J Biomed Inform* 2009; **42**: 377-81. doi: 10.1016/j.jbi.2008.08.010
- Tepeš B, Vujanović M, Šeruga M, Stefanović M, Forte A, Jeverica S. Randomized clinical trial comparing 10-day sequential, 7-day concomitant and 7-day standard triple therapies for Helicobacter pylori eradication. *Eur J Gastroenterol Hepatol* 2016; **28**: 676-83. doi: 10.1097/MEG.0000000000000590
- Tepeš B, Zvezdana O. [Cumulative Helicobacter pylori eradication rates in Slovenia in the year 2008]. [Slovenian]. *Zdrav Vestn* 2010; **79**: 19-24.
- Graham DY, Fischbach L. Helicobacter pylori treatment in the era of increasing antibiotic resistance. *Gut* 2010; **59**: 1143-53. doi: 10.1136/gut.2009.192757
- McNicholl AG, Linares PM, Nyssen OP, Calvet X, Gisbert JP. Meta-analysis: esomeprazole or rabeprazole vs. first-generation pump inhibitors in the treatment of Helicobacter pylori infection. *Aliment Pharmacol Ther* 2012; **36**: 414-25. doi: 10.1111/j.1365-2036.2012.05211.x
- Serrano D, Torrado S, Torrado-Santiago S, Gisbert J P. The influence of CYP2C19 genetic polymorphism on the pharmacokinetics/- pharmacodynamics of proton pump inhibitor-containing Helicobacter pylori treatments. *Curr Drug Metab* 2012; **13**: 1303-12. doi: 10.2174/138920012803341393
- Tang HL, Li Y, Hu YF, Xie HG, Zhai SD. Effects of CYP2C19 loss-of-function variants on the eradication of *H. pylori* infection in patients treated with proton pump inhibitor-based triple therapy regimens: a meta-analysis of randomized clinical trials. *PLoS One* 2013; **8**: e62162. doi: 10.1371/journal.pone.0066730
- Tai WC, Lee CH, Chiou SS, Kuo CM, Kuo CH, et al. The clinical and bacteriological factors for optimal levofloxacin-containing triple therapy in second-line Helicobacter pylori eradication. *PLoS One* 2014; **9**: e105822. doi: 10.1371/journal.pone.0105822
- Jeverica S, Tepeš B, Ihan A, Skvarč M. [Primary resistance of Helicobacter pylori]. [Slovenian]. *Zdrav Vestn* 2010; **79**: 25-30.
- Megraud F, Coenen S, Versporten A, Kist M, Lopez-Brea M, Hirschl AM, et al. Helicobacter pylori resistance to antibiotics in Europe and its relationship to antibiotic consumption. *Gut* 2013; **62**: 34-42. doi: 10.1136/gutjnl-2012-302254
- Molina-Infante J, Lucendo AJ, Angueira T, Rodríguez-Tellez M, Perez-Aisa A, et al. Optimised empiric triple and concomitant therapy for Helicobacter pylori eradication in clinical practice: the OPTRICON study. *Aliment Pharmacol Ther* 2015; **41**: 581-9. doi: 10.1111/apt.13069
- McNicholl AG, Marin AC, Molina-Infante J, Castro M, Barrio J, Ducons, et al. Randomised clinical trial comparing sequential and concomitant therapies for Helicobacter pylori eradication in routine clinical practice. *Gut* 2014; **63**: 244-9. doi: 10.1136/gutjnl-2013-304820
- Molina-Infante J, Gisbert JP. Optimizing clarithromycin-containing therapy for Helicobacter pylori in the era of antibiotic resistance. *World J Gastroenterol* 2014; **20**: 10338-47. doi: 10.3748/wjg.v20.i30.10338
- Graham DY, Lee YC, Wu MS. Rational Helicobacter pylori therapy: evidence-based medicine rather than medicine-based evidence. *Clin Gastroenterol Hepatol* 2014; **12**: 177-86. doi: 10.1016/j.cgh.2013.05.028
- Rokkas T, Sechopoulos P, Robotis I, MargantisG, Pistiolas D. Cumulative *H. pylori* eradication rates in clinical practice by adopting first and second line regimens proposed by Maastricht III consensus and a third line empirical regimen. *Am J Gastroenterol* 2009; **104**: 21-5. doi: 10.1038/ajg.2008.87