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ORIGINAL CONTRIBUTIONS

Cumulative Helicobacter Pylori Eradication Rates by Adopting First- and Second- Line Regimens Proposed by the Maastricht IV Consensus in Obese Patients Undergoing Gastric Bypass Surgery

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Abstract
Aims and Methods Our aim was to assess, in obese patients undergoing Roux-en-Y gastric bypass (RYGB) surgery, the cumulative Helicobacter pylori (HP) eradication rates by adopting Maastricht IV guidelines in areas of high clarithromycin resistance rates (CLT)—14 days concomitant first-line therapy with proton-pump inhibitor (PPI) bid, CLT 500 mg bid, metronidazole (MTZ) 500 bid, and amoxicillin (AMX) 1000 mg bid and 14 days second-line therapy with PPI bid, AMX 1000 mg bid and levofloxacin (LVF) 500 mg od. Single-center prospective study was over 4 years. Endoscopy and HP assessment (by histology or C13 urea breath test) were performed at baseline and post-treatment HP status was assessed by C13 urea breath test 4–6 weeks after the end of therapy.
Results Seven hundred seventy-seven consecutive HP-positive patients completed concomitant first-line treatment: 636 (81.9%) female, age 41.1 (± 10.2) years. HP was eradicated in 556 patients—71.56% (95% CI: 68.28–74.62%). In the remaining 221 patients, second-line LVF-based regimens eradicated HP in 121 patients—54.75% (95% CI: 48.16–61.18%). These results give 87.13% (95% CI: 84.58–89.31%) ITT and 89.43% (95% CI: 87.03–91.44%) PP cumulative eradication rates. Eradication rates were not significantly different by gender, age, endoscopy findings, and smoking habits.
Conclusions By adopting Maastricht IV consensus quadruple concomitant first-line treatment and second-line LVF-based therapy, high cumulative HP eradication rates are achieved but still leaves around 10.6% of obese patients undergoing RYGB in need of the culture and susceptibility testing prior to third-line treatment.

Keywords Bariatric surgery · Obesity · Helicobacter pylori infection, therapy

Introduction

The European Guidelines on surgery of severe obesity [1] and the American Society of Gastrointestinal Endoscopy on endoscopy of the bariatric patient [2] recommends Helicobacter pylori (HP) eradication in obese population undergoing Roux-en-Y gastric bypass surgery (RYGB).

The high prevalence of HP infection in Portuguese obese population undergoing RYGB (around 70%) with its associated risks (further described in reference [3, 4]) led us to adopt a policy of systematic HP screening and eradication in this group of patients, in line with the European and American guidelines [1, 2].

In 2013, the updated guidelines of the American Association/The Obesity Society/American Society for Metabolic and Bariatric Surgery further reinforced our policy trough recommendation of HP screening in patients belonging to high prevalence areas [5].

There are plausible reasons to follow these guidelines:

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- First, eradication should decrease the risk of gastroduodenal peptic lesions in the gastrojejunostomy site after RYGB with positive impact in early and later ulcer- related postoperative symptoms and complications [6].
- Second, HP is a class I carcinogen in the development of gastric cancer with an odds ratio of 2.0–5.9 [7].
- A recent systematic review [8] showed that five out of six gastric cancers after RYGB were in the excluded stomach further emphasizing the need to eliminate mucosal carcinogen risk factors of the bypassed stomach.

In Southern Europe, eradication rates with Maastricht III consensus [9] clarithromycin (CLT)-based first-line therapy are falling alarmingly due mainly to antibiotic resistance, which underlines the need for continuous eradication monitoring [10] in order to identify differences in time trends.

As previously reported [11], from 2006–2008 to 2009–2010, the first-line CLT-based triple therapy decreased from 79.1 to 58.6% and from 83.7 to 62.9% by intention-to-treat (ITT) and per-protocol (PP) analysis, respectively, not reaching anymore the 80% eradication rate cut-off recommended by the Maastricht III and IV guidelines [9, 12].

The Maastricht IV consensus [12] no longer recommends CLT triple therapy for first-line HP eradication in areas with high CLT resistance as it is the case of Portugal [6]. However, in Portugal, the unavailability of bismuth only leaves place for first-line quadruple non-bismuth therapy as recommended by the Maastricht IV consensus [12].

The prevalence of antibiotic resistance is regionally variable and appears to be markedly increasing with time in many countries, which are in most cases associated with the overuse of antibiotics [13]. Therefore, the development of population-tailored new regimen to improve eradication rate remains the principal challenge.

Since 2011, we have implemented local guidelines for HP eradication with 14 days quadruple concomitant (also called four drugs, three antibiotics, non-bismuth-containing therapy) first-line therapy and second-line empirical levofloxacin (LVF) therapy.

The aim of this study was to assess the cumulative HP eradication rate with quadruple concomitant first-line therapy and second-line empirical LVF-based treatment in obese patients undergoing RYGB.

Patients and Methods

This is a single-center prospective observational study over a 4-year period.

Over a 4-year period, 2011–2015, 1216 adult patients with body mass index ≥ 40 or ≥ 35 kg/m^2 with at least two obesity-associated morbidities were assessed for RYGB surgery. All patients had upper endoscopy with histological examination of corpus and antrum gastric mucosa. The ones whose biopsy did not show HP colonization were reassessed for HP infection by C13 urea breath test (Helico-test, Isomed, Madrid, Spain or Heliprobe, Kibion, Sweden.

The study cohort consisted of 777 (63.9%) adult HP-positive patients (18.1% male/81.9% female, mean (±SD) age 41.1 (± 10.2) years, median age of 41 years, age range: 17–64 years) consecutively assessed for RYGB surgery between 2011 and 2015.

HP first-line treatment was in line with the Maastricht IV recommendations for geographical areas with high CLT resistance rates: 14 days quadruple concomitant therapy [12]—proton-pump inhibitor (PPI) bid, CLT 500 mg bid, metronidazole (MTZ) 500 mg bid, and amoxicillin (AMX) 1000 mg bid. In case of treatment failure, a second-line empiric triple regimen consisting of PPI bid, AMX 1000 mg bid, and LVF 500 mg od was prescribed for 14 days (Fig. 1).

Four to 6 weeks after the end of therapy, post-treatment HP status was assessed by C13 urea breath test (Helico-test, Isomed, Madrid, Spain or Heliprobe, Kibion, Sweden) using citric acid as test meal.

As this study was observational, these treatments were not prescribed as part of a clinical trial. Therefore, there was no need for study approval of the Hospital's Ethics Committee. All patients signed formal consent.

Data from a prospectively maintained database recording demographic data (age, gender, smoking) and HP therapy (drugs and duration) were analyzed.

Age data were described as mean value and respective standard deviation. Counts and proportions were reported for categorical variables.

Success rates were assessed by ITT (inclusion of all eligible patients enrolled in the study regardless of compliance with the study protocol; patients with no evaluable data were assumed to have been unsuccessfully treated) and PP (exclusion of patients with poor adherence therapy and patients with no evaluable therapy) and 95% confidence intervals (CI) were calculated for those percentages, using the modified Wald interval.

Univariable associations with eradication were tested using the chi-square test.

Results

Patients' socio-demographic and clinical characterization is presented in Table 1.

The results are summarized in Fig. 1. For the 2011–2015 time range, out of 777 consecutive HP-positive patients who received first-line treatment, all completed the treatment and none withdrew. HP was eradicated in 556 patients with 71.56% (95% CI: 68.28–74.62%) by ITT and by PP analysis. In the remaining 221 HP-positive patients, 201 patients

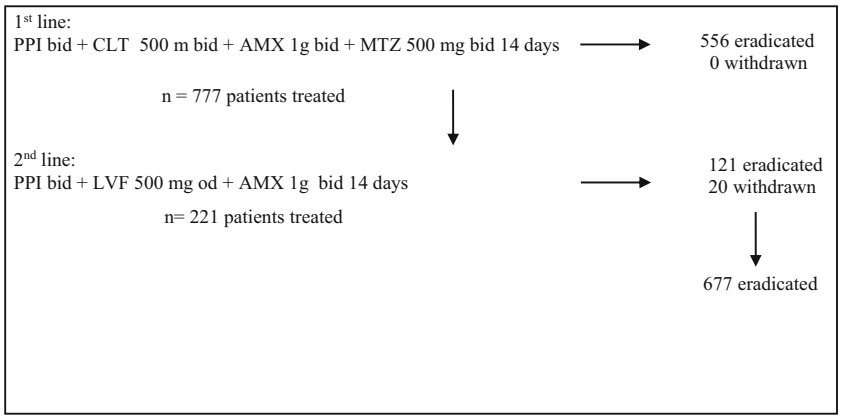

Fig. 1 Flow chart summarizing eradication rate results over 4 years (2011–2015), for first- and second-line HP eradication therapy, in obese patients undergoing RYGB. PPI proton-pump inhibitor, CLT clarithromycin, AMX amoxicillin, MTZ metronidazole, LVF levofloxacin

completed the second-line treatment and 20 patients withdrew (lost to follow-up). HP was eradicated in 121 patients (ITT = 54.75%; 95% CI: 48.16–61.18%; PP = 60.20%, 95% CI: 53.30–66.72%; Fig. 1). Thus, out of 777 patients initially included in this period of the study, HP was eradicated in 677 patients, 20 patients withdrew, and 80 patients remained positive. These results confer 87.13% (95% CI: 84.58–89.31%) ITT and 89.43% (95% CI: 87.03–91.44%) PP cumulative HP eradication rates.

Eradication rates were found to be independent of gender, diagnosis, and patient's smoking habits (Table 2).

Discussion

As previously mentioned, there is scientific data (6–8) supporting HP eradication in obese patients, particularly in those undergoing GBYR in whom a large part of the stomach will be inaccessible to upper endoscopy after surgery.

The projections by the WHO [14] predicting that gastric cancer will become one of the ten leading causes of death worldwide by 2030 emphasizes the critical role of risk factor elimination in groups with gastric cancer risk, as are patients submitted to gastric surgeries.

However, current HP treatment remains empiric despite over time alarmingly fallen eradication levels to ranges between 60 and 70% in some geographical areas [15, 16], rates that do not achieve the 80% cut-off eradication rate recommended by the Maastricht guidelines [9, 12].

In our previous study [11], by adopting CLT first-line therapy proposed by the Maastricht III consensus [7] and an empirical second-line LVF-based therapy, we reached a 92.9% PP cumulative eradication rate in 2006–2008 that decreased to 82.6% in 2009–2010. As LVF second-line eradication rate remained stable, the fallen cumulative eradication levels were caused by decreased CLT first-line eradication rate, by ITT and PP, from 79.1% (PP) and 83.7% (ITT) in the time span of 2006–2008 to 71% (PP) and 56.4% (ITT) in the time span of 2009–2010.

The antibiotic resistance to CLT has been identified as one of the major factors affecting the ability to cure HP infection, and the rate of resistance to this antibiotic seems to be increasing in many geographical areas [17]. Therefore, the high CLT

Table 1 Socio-demographic and clinical characterization of patients at baseline (n = 777)

		Statistics
Age (years)	Mean (±SD)	41.1 (± 10.2)
	Min–max	17–64
Gender	Male	141 (18.1%)
	Female	636 (81.9%)
Smoking habits (n = 688)	Non-smoker	604 (87.8%)
	< 10 cig/day	36 (5.2%)
	10–20 cig/day	31 (4.5%)
	> 20 cig/day	17 (2.5%)
Endoscopy findings	Normal	542 (69.8%)
	Esophagitis	46 (5.9%)
	Gastro-duodenal erosions and peptic ulcers	56 (7.2%)
	Gastritis	96 (12.4%)
	Others	37 (4.8%)

Data are presented as n (%), unless otherwise indicated

Table 2 Univariable associations with eradication

		1st-line eradication		*p*	2nd-line eradication		*p*	Cumulative eradication		*p*
		No	Yes		No	Yes		No	Yes	
Gender	Male	44 (19.9%)	97 (17.4%)	0.422	17 (21.3%)	22 (18.2%)	0.590	22 (22%)	119 (17.6%)	0.284
	Female	177 (80.1%)	459 (82.6%)		63 (78.8%)	99 (81.8%)		78 (78%)	558 (82.4%)	
Age	< 50 years	163 (73.8%)	425 (76.4%)	0.432	57 (71.3%)	94 (77.7%)	0.302	69 (69%)	519 (76.7%)	0.096
	≥ 50 years	58 (26.2%)	131 (23.6%)		23 (28.8%)	27 (22.3%)		31 (31%)	158 (23.3%)	
Smoking habits	No	165 (86.4%)	439 (88.3%)	0.486	61 (89.7%)	89 (85.6%)	0.428	76 (87.4%)	528 (87.9%)	0.895
	Yes	26 (13.6%)	58 (11.7%)		7 (10.3%)	15 (14.4%)		11 (12.6%)	73 (12.1%)	
Endoscopy findings	Normal	143 (64.7%)	399 (71.8%)	0.350	49 (61.3%)	82 (67.8%)	0.810	61 (61%)	481 (71%)	0.363
	Esophagitis	15 (6.8%)	31 (5.6%)		6 (7.5%)	8 (6.6%)		7 (7%)	39 (5.8%)	
	Gastric and duodenal erosions/peptic ulcers	21 (9.5%)	35 (6.3%)		7(8.8%)	11 (9.1%)		10 (10%)	46 (6.8%)	
	Gastritis	30 (13.6%)	66 (11.9%)		14 (17.5%)	14 (11.6%)		16 (16%)	80 (11.8%)	
	Others	12 (5.4%)	25 (4.5%)		4 (5%)	6 (5%)		6 (6%)	31 (4.6%)	

resistance (22%) found in Portuguese population [17] could explain the decreasing over time HP eradication rates in our patients and the need to implement new first-line therapy.

Non-bismuth eradications schemes are recommended as first-line therapy in areas with high CLT resistance (> 15–20%) when bismuth-containing quadruple therapy is not locally available [12]. A priori, the high rate of MTZ resistance (34.1%) in Portugal [17], categorizing our population as a dual resistance one could pose an additional difficulty in HP eradication. However, in this respect, Wu et al. [18] reported that dual resistance did not influence the level of eradication of the concomitant therapy and Molina Infante et al. [19] concluded that concomitant therapy may have acceptable eradication rates even in dual (CLT and MTZ) resistant HP strains.

Therefore, in line with the conclusion that the first-line CLT-based Maastricht III consensus eradication was no longer effective in bariatric patients, indicating the need to test new regimens, since 2011, we adopted concomitant therapy as first-line HP eradication, a decision that was later validated by the Maastricht IV guidelines for high CLT resistance areas [12].

In this study, between 2011 and 2015, in obese patients undergoing RYGB, we assessed cumulative HP eradication rates in 777 patients by adopting the concomitant first-line regimen, in the meantime recommended by the Maastricht IV consensus [12], and a second-line LVF-based empirical therapy, also recommended by the last two Maastricht guidelines [9, 12]. The concomitant first-line HP eradication rate was 71.56%, which is still under the lower limit of 80% recommended by the Maastricht guidelines [12]. These unsatisfactory data were already discussed in our former publication [4].

These results give further emphasis to the need of eradication monitoring in Portugal, a country where bismuth is not available, which limits first-line and second-line Maastricht therapeutic recommendations [12].

First-line eradication failure leaves LVF-based therapy as the only choice for second-line one. Comparing bismuth-based quadruple therapy with LVF-based therapy, two recent meta-analyses [20, 21] have suggested that LVF-based "rescue" regimen is more effective and safer than bismuth based quadruple therapy.

The present results suggest that it is not possible anymore to overcome CLT resistance probably because of growing genotypic resistance, even with new therapeutic regimens.

Concerning the second-line LVF-based therapy, the former 2006–2010 eradication rates, around 50%, is 10% less than the present study rate (60%). The finding of an increased LVF-based second-line eradication rate suggests that, in opposition to CLT resistance, LVF resistance did not increase over time.

Two Southern European studies, performed in Spain [22] and in Greece [23], reported higher eradication rates with LVF. Gisbert et al. reported a modified ITT rate of 74% with LVF-based second-line therapy and Rokkas T et al. reported an ITT rate of 70% with LVF-based third-line therapy.

These results reflect the finding that, despite increased second-line HP eradication rates that are surrogate markers to stable or decreased LVF resistance levels, Portugal keeps, among European countries, a unique pattern of high LVF resistance rate: 20.9% [17].

After two eradication failures, Maastricht IV guidelines [12] recommend culture to select a third-line treatment based on microbial sensitivity to antibiotics. HP culture is a time-consuming and expensive procedure only performed in research centers. Until 2008, less than 10% of our obese patients would have to be submitted to another endoscopy and biopsy for HP cultures; the need of these techniques doubled in 2009–2010.

With a therapeutic gain of 10% with the second-line LVF therapy, the present cumulative eradication levels approached the former levels of 2006–2008 [11]. This therapeutic gain is clinically significant due to positive impact in the decreased

need for the expensive, time-consuming, and difficult access HP culture technique.

According to our protocol that follows Maastricht recommendations, our patients with two eradication failures were submitted to another endoscopy with gastric biopsy samples to test HP antimicrobial sensitivity and a third treatment was prescribed based on these test results before RYGB surgery.

The challenging problem of HP eradication in a country with high resistance rates to most common antibiotics used for HP eradication and no bismuth availability continues to push us to new solutions, particularly at first-line eradication therapy, not easy in an era of growing antibiotic resistance and lack of new antibiotics in the horizon.

As it is not possible to work more efficiently with first-line therapeutic regimens that include CLT, it is crucial to determine the current rates of local antibiotic resistance and implement new regimens taking into account this data.

In near future, if easier and wider available HP antibiotic resistance tests are developed, such research may also serve as potential basis for a transition to individualized analysis prior to HP treatment.

All these efforts culminating in a shift in therapy from global recommendations with regional variations to patient-tailored therapy could lead to acceptable eradication levels as suggested by Graham et al. [10].

To the best of our knowledge, this is the first study to assess cumulative HP eradication rates by adopting first-line quadruple concomitant and second-line LVF-based therapy in obese patients undergoing RYGB.

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Conflict of Interest The authors declare that they have no conflict of interest.

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