ΠΡΟΣΚΕΚΛΗΜΕΝΕΣ ΞΕΝΟΓΛΩΣΣΕΣ ΑΝΑΚΟΙΝΩΣΕΙΣ ΕΛΛΗΝΩΝ ΕΡΕΥΝΗΤΩΝ

14 Days sequential or hybrid regimen for *Helicobacter pylori* eradication in clinical practice in Southern Greece. A prospective pilot study

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INTRODUCTION: First line empirical treatment, non bismuth quadruples either 10-day sequential therapy with omeprazole and amoxicillin 5 days followed by omeprazole clarithromycin, metronidazole for another 5 days or concomitant the same drugs for 10 days, in previous studies, in our area (southern Greece) achieve PP eradication 86% and 92% respectively (1,2)

AIMS & METHODS: Investigation in a prospective, randomized, pilot study whether prolonging the treatment duration of sequential therapy and/or continuing the amoxicillin throughout the 14 days (sequential-concomitant hybrid) could raise the PP eradication rate to >95%. METHODS: 3 years single centre study.130 naïve *H. pylori* infected patients were randomly assigned to receive either: Sequential (omeprazole 20 mg and amoxicillin1gr for 7 days followed by omeprazole 20 mg, clarithromycin 500 mg, and metronidazole 500 mg for 7 days; n = 65) or Sequential-Concomitant hybrid: (Sq-Con hybrid) (omeprazole 20 mg and amoxicillin 1 gr for 7 days followed by omeprazole 20mg, amoxicillin1 gr, clarithromycin 500 mg, and metronidazole 500 mg for 7 days; n = 65). All of them given twice daily. UBT or endoscopy was performed 4-8 weeks post treatment to assess the outcome.

RESULTS: 65% male, mean age 46.25 +/- 14.7 years, 55% endoscopic lesions (ulcer, erosions), 35% smokers. Eradication rate by intention to treat analysis was 84%; (95% CI, 76.7% - 90.9%) for 14 days sequential, 91% (95% CI, 86.5% - 97.3%) for sq-con hybrid therapy. Per-protocol analysis yielded 88% (95% CI, 82, 4% - 93.9%) for 14 days sequential and 93% (95% CI, 90.4% - 97.9%) for sq-con hybrid therapy. Both regimens exhibited similar adverse events (42% vs. 46%) and treatment compliance (95 % vs. 97%).

CONCLUSION: Our pilot study, apart from the number of tablets needed per day, is unable to support that extending the duration of sequential therapy to 14-days, neither adopting the hybrid regimen, as first line empirical treatment, will achieve better results than the obtained by either sequential 10 or concomitant in *H. pylori* eradication in our area.

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2nd line levofloxacin-based triple therapies provide similar *Helicobacter pylori* eradication rates to bismuth-based quadruple therapies

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INTRODUCTION: The eradication rate of 1st line treatment with standard triple therapy in Greece remains persistently under 80% since 2007 and parallels Clarithromycin resistance of > 20%. Quadruple bismuth containing regimens were the standard of care as 2nd line treatments until 2010 when bismuth was withdrawn from the market.
AIMS & METHODS: The aim of our study was to evaluate the efficacy of 2nd line treatments over the periods before and after bismuth withdrawal.
Patients – Methods: Data from patients, who received 2nd line treatment for Helicobacter pylori, were collected retrospectively. Two periods were compared in terms of eradication success: period A (≤2010) and period B (≥2011). During period A patients received: {proton pump inhibitor bid + metronidazole 500mg tid + amoxicillin 1gr bid+ bismuth subcitrate 120mg qid} for 14 days while during period B: {proton pump inhibitor bid + levofloxacin 500mg bid + amoxicillin 1gr bid} for 10 days. Patients tested with urea breath test (UBT) 4-6 weeks after completion of treatment were analyzed. Susceptibility to levofloxacin was evaluated by E-test.
RESULTS: 159 patients (61 men), age (mean±SD = 51.7±12.3 years). Period A: 88 (34 men), and B: 71 (27 men). The 2 groups did not differ neither for age, gender, smoking and other demographic parameters nor for endoscopic lesions. Eradication rates according to UBT results for the 2 periods are shown in table 1. Eradication rates according to UBT results for period B ≥2011 are shown in table 2. For the years 2011-2013 the primary levofloxacin resistance rate as evaluated continuously in samples of our population remained stable (8-9%).

Table1

Table2

CONCLUSION: 1) 2nd line treatment with 10 days of levofloxacin-based treatment is equally effective to 14 days of quadruple bismuth-based treatment, with a levofloxacin resistance of <10% for the studied period. 2) During 4 years of levofloxacin use, the success rate did not change in this group and parallels the stability of levofloxacin resistance rates. However, increase of resistance is probable in the future and it may affect the efficacy of levofloxacin-based treatments.

A randomized study comparing 10 days concomitant and sequential treatments for the eradication of *Helicobacter pylori*, in a high clarithromycin resistance area

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Aims: Our study compares quadrupie non-bismuth "concomitant" and "sequential" regimens for *H. pylori* eradication in a high clarithromycin resistance area.
Patients and methods: Multicenter prospective randomised clinical trial from Greece. We included *H. pylori* positive, treatment naïve, patients. All had positive CLO-test and/or histology and culture. They received either sequential (esomeprazole 40mg, amoxicillin 1gr bid for 5 days, followed by 5 days of esomeprazole 40mg, clarithromycin 500mg and metronidazole 500mg bid), or concomitant treatment (all drugs taken concomitantly bid for 10 days). Eradication confirmed by 13C-urea breath test or histology 4-6 weeks after treatment. Adverse events and adherence were evaluated.
Results: One hundred ten patients (47F/63M, aged 19-83, mean 54 years, 38% smokers, 24% ulcer disease) allocated to concomitant and 109 (51F/58M, aged 21-94, mean 51.7 years, 33% smokers, 20% ulcer disease) to sequential treatment. Positive cultures 181/210 (86%), resistances: 35% metronidazole, 23% clarithromycin, 7.7% dual. Eradication rates were respectively, 89,1% (98/110) versus 80.7% (88/109) by intention to treat (p=0.1) and 93.4% (98/105) versus 83.8% (88/105) per protocol (p=0.04, 95%CI:0.91-18.4). Overall adherence was 98% (95%CI 95.9-99.6). Eradication rates according to resistances were: dual sensitive strains 44/44 (100%), 53/46 (94%) (p=0.4), metronidazole single resistant 21/21 (100%), 21/28 (75%) (p=0.04), clarithromycin single resistant 11/14 (79%), 11/14 (79%) (p=1), and dual resistant 7/9 (78%), 215 (40%) (p=0.2) for concomitant and sequential regimens, respectively. Side effects were reported by 40% of patients, comparable among regiments, and without treatment discontinuation.
Conclusions: Concomitant treatment eradication rate overcomes 90% per protocol and has a significant advantage over sequential therapy. This is probably due to its better efficacy on metronidazole resistant strains. Both regiments were well tolerated and safe.

Protective role of *Helicobacter pylori* infection against severe reflux esophagitis

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Introduction: Possible interaction between *H. pylori* infection and gastroesophageal reflux disease (GERD) is derived from data showing that as the prevalence of HP infection decreased in the West, the prevalence of GERD and esophagitis increased.
Methods: The aim was to investigate the prevalence of HP infection among patients with reflux esophagitis. A retrospective analysis was conducted on all patients with reflux esophagitis (n=361), during a 3-year-period (2011-2013). Seventy asymptomatic patients that were submitted to esophagogastroduodenoscopy because of iron deficiency anemia, without clinical or endoscopic evidence of esophagitis, were used as controls HP status was confirmed through histology or breath test.
Results: Esohagitis was graded into four groups, according to L.A. classification: grade A (168 patients), B (94 patients), c (68 patients) and D (31 patients). The prevalence of HP infection was lower (but not significantly(in patients with esophagitis compared to controls (51.24% vs 55.7%, NS). After separating patients into two groups, according to esophagitis severity (mild esophagitis: grade A+B, severe esophagitis: grade C+D), HP prevalence was the following: 57.25% of patients with mild esophagitis (NS compared to controls), and 35.35% of patients with severe esophagitis ($p<0.05$ compared to controls).
Conclusion: A remarkably lower prevalence of HP infection was noted in patients with severe esophagitis (grade C+D), but not in patients with mild esophagitis (grade A+B). This supports a possible protective role of the HP infection against the development of severe esophagitis.

Sequential versus concomitant treatment against *H. pylori* study in a greek population

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Introduction: Maastricht consensus IV clearly suggests that countries with high claraithromycin and metronidazole resistance rates should use as first-line regiments against *H. pylori* either sequential or concomitant treatment.
Aim: Comparison of Sequential (ST) and Concomitant (CT) as first-line treatments againsts H.pylori in a prospective study of a Greek population.
Method: 212 patients (average age: 51.6 years), HP (+), answered a preformed interview (history, habits, symptoms) and randomly received a 10-day eradication treatment either with:1) ST:PPIs X 2 plus: i) Amoxicillin 1g x 2, for the first 5 days; ii) Clarithromycin 500 mg x 2 and Tinidazole 500 mg x 2 for the next 5 days [104 patients (M:51, F53)]. 2) CT:PPIs x 2, Clarithromycin 500mg x 2, Amoxicillin 1 g x 2 and Tinidazole 500 mg x 2 [108 patients (M:39, F:69)].
6-8 weeks after completing treatment all patients were controlled for eradication with UBT. Results were analyzed per-protocol (PP analysis) as well as with univariate logistic regression analysis (z test).
There is no statistical significance among the eradication percentages of ST and CT (p=0.587). Of all parameters studied, none showed any statistically significant difference (sex and ex-smokers being at the cut-off).
Conclusion: The two regiments appear of equivalent value for Greek *H. pylori* positive patients.

Concomitant treatment against *H.* pylori infection in a Greek population – a multivariate analysis

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Introduction: High clarithromycin and metronidazole resistance rates in our country has set the quest for effective first-line treatments that align with the updated European guidelines.
Aim: Presentation of preliminary results of a perspective study of the concomitant treatment (CT) used for first-line *H. pylori* eradication, with an attempt to allocate possible factors that may relate with a successful eradication.
Method: 108 ouptatients (Average Age: 52.9 years, M: 39, F: 69), diagnosed as HP-positive, were interviewed using a preformed questionnaire, recording: sex, age, smoking, alcohol consumption, NSAID and long-term PPI intake, symptoms, anemia, personal history from upper GI and family history (FH) of gastric Ca. All received 10-day CT: PPIs x 2, Amoxicillin 1 g x 2, Clarithromycin 500 mg x 2 plus Tinidazole 500 mg x 2. 6-8 weeks after ending of treatment, all patients received UBT and compliance control. Results were analyzed per-protocol (PP analysis) and by univariate logistic regression analysis (z test).
Results:

Eradicate	M/F	Age 45≥/45<	Smoking -/+/	Alcohol -/+	NSAID -/+	Dyspepsia -/+	GOR -/+
+	36/62	71/27	93/31/28	85/13	85/13	34/64	46/52
-	3/7	8/2	3/1/6	8/2	8/2	3/7	5/5
Eradicate	Anemia -/+	Gastric ulcer -/+	Duodenal ulcer -/+	PPIs -/+	FH Ca -/+		
+	64/34	94/4	83/15	84/14	87/11		
-	7/3	8/2	10/0	7/3	9/1		

PP:90.74% (90.74% eradicated *H. pylori*)

None of the parameters studied showed any statistically significant difference between pateitns that achieved eradication and those that did not.
Conclusion: So far, the concomitant treatment, used as first-line eradication regiment against H. pylori, appears effective enough for Greek H.P. positive patients and in alignment with the European guidelines. None of the factors under study was related with the eradication result.

High rate of Clarithromycin resistance in *Helicobacter* pylori clinical isolates obtained from children in Greece: a retrospective study, 2000-2013

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Helicobacter pylori (Hp) resistance to antibiotics is increasing worldwide, compromising the success of empirical anti-Hp standard regimens. Our aim was to evaluate the primary Hp resistance from children to conventional antibiotics during a 14-year period in Greece. Furthermore, we detected the gene mutations associated with clarithromycin and levofloxacin resistance. The study enrolled 222 Hp clinical isolates from children (age 10.70±3.16 years). For comparison purposes, the 2000-2013 timeframe was divided in three periods; period 2000-2005 (77 Hp isolates) period 2006-2009 (88 Hp isolates) and period 2010-2013 (65 Hp isolates). Hp antibiotic susceptibility was assessed by E-test, adopting the EUCAST MIC breakpoints. The presence of genetic mutations was determined by Real-Time PCR in clarithromycin-resistant and by sequencing analysis of the Hp gyrase A gene in Levofloxacin-resistant strains.

No resistance to tetracycline was detected. Resistance to amoxicillin was observed only in period 2000-2005 (3.9% [3/77]). An increase in clarithromycin-resistance and levofloxacin-resistance was observed in our study population, with prevalence rates, ranging from 26% to 47.7% and 2.5% to 6.2%, respectively. In contrast, metronidazole-resistance showed a decrease through the study period (from 35% to 21,5%). The predominant mutations correlated with clarithromycin-resistance were A2143G and A2142G in the 23S rRNA gene, and the Asn87Lys mutation in the gyrA gene for levofloxacin-resistant strains. The high prevalence of Hp clarithromycin-resistance and the emergence of levofloxacin-resistance in children patients highlight the need for adopting an appropriate first line therapy on the basis of antimicrobial susceptibility testing, in order to avoid treatment failure and the development of secondary resistance.

Two-year multicenter surveillance of *Helicobacter* pylori antibiotic resistance from adult patients in Greece

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The increasing worldwide prevalence of *Helicobacter pylori* (Hp) antibiotic resistance is a major cause of treatment failure, with variations observed within and between countries. Our aim was to evaluate the primary resistance of Hp isolates from adult patients, from different regions of Greece, to conventional antibiotics and to detect the gene mutations associated with clarithromycin (CLA) and levofloxacin (LEV) resistance.

A total of 196 Hp isolates from adult patients (age 52.4±14.93) were collected throughout the country over a 2-year period (2012-2014). Hp antibiotic susceptibility was assessed by E-test adopting the EUCAST MIC breakpoints. The presence of point mutations was analyzed by Real-Time PCR in CLA-resistant and by sequencing analysis of the Hp gyrase A gene in LEV-resistant strains.

No resistance to amoxicillin or terracycline was detected. Overall, primary resistance levels to metronidazole (MET), CLA and LEV were determined at 34.7% (68/196), 25.5% (50/196) and 9.2% (18/196), respectively. Multi-drug resistance was observed for MET-CLA (17/196, 8.7%), for MET-LEV (5/196, 2.6%) and for MET-CLA-LEV (3/196, 1.5%). No statistically significant differences in antibiotic resistance were found between Hp isolates from different regions of the country ($P>0.05$). The predominant mutations correlated with CLA-resistance were A2143G in 23S rRNA gene, and the Asn87Lys mutation in gyrA gene for LEV-resistant strains.

The high rates of primary antibiotic resistance, particularly to CLA, have been associated with the high antibiotic consumption observed in our country. This consideration highlights the importance of antibiotic susceptibility testing prior to the implementation of treatment strategies using CLA in our country.