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SECOND-LINE TREATMENT FOR HELICOBACTER PYLORI: SYSTEMATIC REVIEW STUDY

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Abstract:

Background: *Multiple Helicobacter pylori second-line schedules have been described as potentially useful. It remains unclear, however, which are the best combinations, and which features of second-line treatments are related to better cure rates. The aim of this study was to determine that second-line treatments achieved excellent (>90%) cure rates by performing a systematic review*

Methods: *A systematic review for studies evaluating second-line Helicobacter pylori treatment was carried out in multiple databases.*

Results*: The systematic review identified 115 eligible studies, including 203 evaluable treatment arms. The results were extremely heterogeneous, with 61 treatment arms (30%) achieving optimal (>90%) cure rates.*

Conclusion: *Second-line Helicobacter pylori treatments achieving>90% cure rates are extremely heterogeneous. Quadruple therapy and 14-day treatments seem better than triple therapies and 7-day ones. No single characteristic of the treatments was related to excellent cure rates.*

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INTRODUCTION:

Helicobacter pylori infection is one of the most common chronic bacterial infections in the world and has been defined as a major cause of gastritis, peptic ulcer disease, and gastric cancer [1,2]. Clarithromycin resistance is increasing, reaching 20% in many countries such as France [3,4]. Clarithromycin resistance is the main risk factor for treatment failure; resistance was reported to reduce the efficacy of the first-line therapy by up to 70% [5]. Fluoroquinolones, such as levofloxacin, are often used for rescue therapy in second or third-line treatment. However, levofloxacin resistance has also increased in recent years and has also been shown to be correlated with treatment failure [3,6]. The mutations leading to resistance are now well known for clarithromycin and levofloxacin, although they are still unclear for metronidazole and extremely rare for amoxicillin [7]. In routine practice, the detection of clarithromycin and levofloxacin resistance can be based on phenotypic methods performed after culture, but these methods are time-consuming, fastidious and can take up to two weeks to be completed [8]. however, bacterial antibiotic resistance is still challenging the outcome of H. pylori eradication treatment. The "key" antibiotics in the treatment of H. pylori infection are clarithromycin and levofloxacin, and the prevalence of H. pylori strains resistant to these antibiotics has been increasing over the last decades [9]. Several international guidelines have been published over the last two years pointing out new recommendations for the treatment of H. pylori infection, with particular attention to the issue of antimicrobial resistance.

In western population, the most widely used schedules were triple therapy including a PPI, amoxicillin, and levofloxacin [10,11] and a quadruple therapy combining a PPI with bismuth salts, metronidazole, and tetracycline.[9,12] many other antibiotics and schedules have been described as potentially useful, but the results of the studies have varied widely. It remains unclear, therefore, which are the best combinations or which features of second-line treatments are related to better cure rates this review provides recent evidence from systematic reviews and clinical trials on the treatment of H. pylori infection. This review should help physicians to choose the most adequate treatment for their patients with H. pylori infection.

METHOD:

Search strategy: A systematic computerized literature search limited to full-text published articles was conducted in PubMed and the ISI Web of Knowledge from 1996 to June 2019. References in the retrieved articles, significant reviews, and the personal databases of the authors were also checked for eligible publications. The search strategies were ((second line OR rescue OR failure) AND pylori)) in PubMed, and Title =(pylori) and Title =(second line or rescue) in the ISI Web of Knowledge.

Inclusion criteria: We included published full-text articles that met the following criteria: reports of randomized clinical trials (RCTs) or quasi-RCTs or observational studies, which evaluated rescue therapy after a first Hp treatment failure. Only articles published in Spanish, Italian, French, and English were included.

Exclusion criteria: Exclusion criteria were as follows: articles in Asian languages, duplicate publications, letters to the editor, expert opinion, and reviews.

Statistical analysis: The systematic review was conducted in accordance with the MOOSE recommendations for conducting systematic reviews and meta-analyses of observational data.19 Continuous variables were expressed as median ± standard deviation. Categorical variables were expressed as proportions with their 95% confidence intervals (95% CI). Categorical variables were compared with the chi-squared test; for continuous variables, t test and nonparametric tests were used when appropriate. A value of $P < .05$ was considered to be statistically significant.

RESULTS:

The original searches retrieved more than 2000 articles. After review of the abstracts, 172 full-text articles were assessed for eligibility. Studies reporting duplicate data were excluded. After careful evaluation, 115 studies (with 203 treatment arms, including 16 304 patients) reporting second-line treatment were included in the systematic review. (fig 1)

Of these, 61 arms (30%) showed PP cure rates >90%.Two studies (two arms) evaluated a dual therapy (rabeprazole and amoxicillin), 34 arms evaluated a triple therapy (Table 1), The length of treatment ranged from 5 to 14 days, the most frequent being 7 days (40%), followed by 14 days (30.8%) and 10 days (26.2%). A large proportion of studies achieving excellent cure rates were performed in Asian populations (70.8%), the majority of them (47%) from Japan. The most frequent successful arm schedules were triple therapy including a PPI, metronidazole, and amoxicillin (31.1%); quadruple therapy, PPI, bismuth, metronidazole, and

tetracycline (22.9%); and triple therapy with a PPI, amoxicillin, and levofloxacin (14.7%)

FIGURE 1 Flow of information through the different phases of the selection of the studies

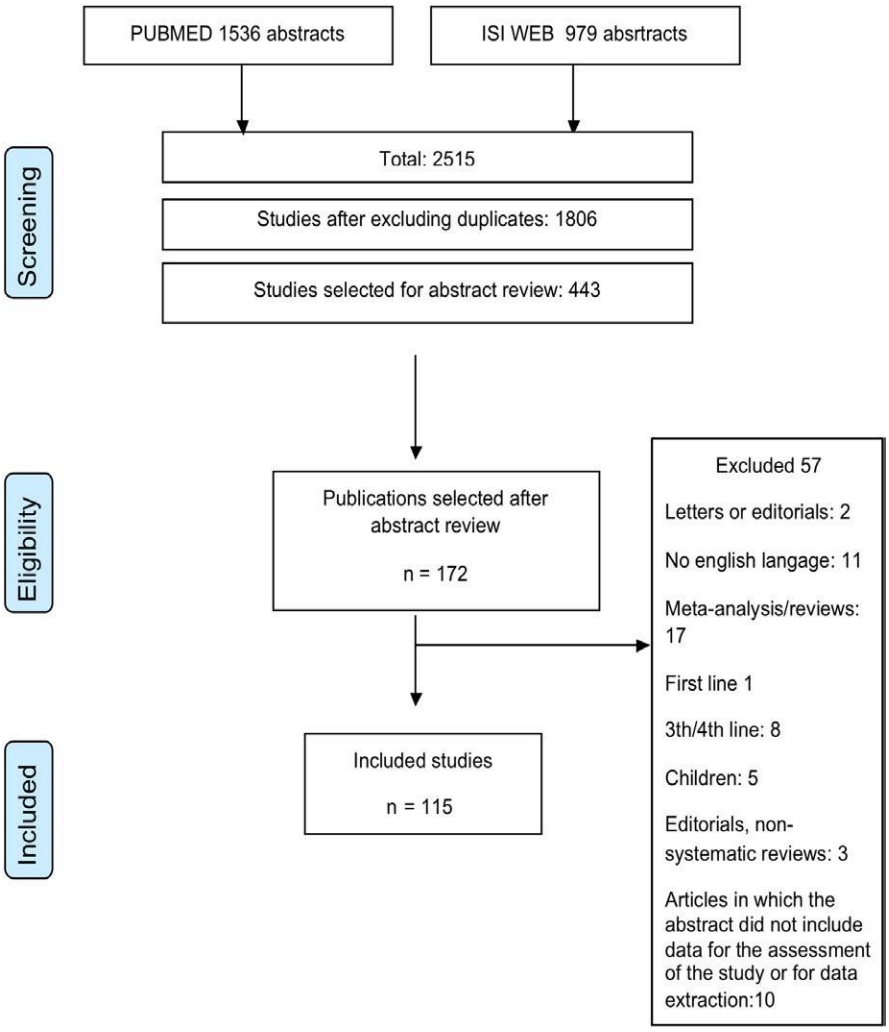

TABLE 1 Schedules achieving >90% cure rates: dual and triple therapy

Author	Journal	Year	Country	n	Second- line treatment	Duration	PP (95% CI)	ITT (95% CI)
Dual therapy								
Furuta, T	Hepatogastroenterology	2003	Japan	17	RAB 10 + AMO 500/6 h	14	100 (0,7-0,9)	100 (0.7-0.9)
Shirai, N	Eur J Clin Pharmacol	2007	Japan	66	RAB 10 + AMO 500/6 h	14	93.7 (0.7-0.9)	90.9 (0.7-0.9)
Triple therapy								
Amoxicillin and Metronidazole								

Fukuda S	Jpn J Infect Dis	2006	Japan	41	LAN 30, AMO 750, MET 250/12 h	5	95.1 (0.8-0.9)	95.1 (0.8-0.9)
Fukuda S	Jpn J Infect Dis	2006	Japan	42	LAN 30, AMO 750, MET 250/12 h	7	95.2 (0.8-0.9)	95.2 (0.8-0.9)
Hori, K	Helicobacter	2011	Japan	82	RAB 10, AMO 750, MET 250/12 h	14	100 (0.9- 1)	96 (0.8-0.9)
Matsuhisa	Helicobacter	2006	Japan	121	O 20, AMO 750, MET 250/12 h	7	90.6 (0.8-0.9)	87.60 (0.7- 0.9)
Matsumoto	Dig Liver Dis	2005	Japan	30	LAN 20, AMO 1000, MET 500/12 h	7	100 (0.8- 1)	96.7 (0.8-1)
Murakami	Aliment PharmTher	2003	Japan	92	RAB 20, AMO 750, MET 250/12 h	7	91 (0.8-0.9)	88.04 (0.8- 0.9)
Murakami	J Clin Gastroenterol	2008	Japan	58	RAB 10, AMO 750, MET 250/12 h	7	91.3 (0.8-0.9)	91.3 (0.8-0.9)
Murakami	J Clin Gastroenterol	2008	Japan	56	LAN 30, AMO 750, MET 250/12 h	7	92.7 (0.8-0.9)	91 (0.8-0.9)
Murakami	J Clin Gastroenterol	2008	Japan	55	O 20, AMO 750, MET 250/12 h	7	94.3 (0.8-0.9)	90.9 (0.8-0.9)
Murakami	Helicobacter	2006	Japan	31	FAM 40, AMO 750, MET 250/12 h	7	94 (0.7- 1)	94 (0.7- 1)
Nagahara	J Gastroenterol Hepatol	2001	Japan	80	O 20/12 h, AMO 500/6 h, MET 250/12 h	10	91.5 (0.8-0.9)	81.2 (0.7-0.9)
Nagahara	J. Gastroenterol	2004	Japan	11	O 20/12 h, AMO 500/8 h, MET 250/12 h	10	90.9 (0.5-0.9)	87.5 (0.5-1)
Nagahara	J. Gastroenterol	2004	Japan	20	LAN 30, AMO 750, MET 250/12 h	10	100 (0.8- 1)	95 (0.7- 1)
Nagahara	J. Gastroenterol	2004	Japan	61	O 20/12 h, AMO 500/8 h, MET 250/12 h	10	93 (0.8-0.9)	82 (0.7-0.9)

Nagahara	J. Gastroenterol	2004	Japan	59	LAN 30, AMO 750, MET/12 h	10	95 (0.8-0.9)	93 (0.8-0.9)
Author	**Journal**	**Year**	**Country**	**n**	**Second- line treatment**	**Duration**	**PP (95% CI)**	**ITT (95% CI)**
Dual therapy								
Furuta, T	Hepatogastroenterology	2003	Japan	17	RAB 10 + AMO 500/6 h	14	100 (0,7-0,9)	100 (0.7-0.9)
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Triple therapy								
Amoxicillin and Metronidazole								
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Nagahara	J. Gastroenterol	2004	Japan	20	LAN 30, AMO 750, MET 250/12 h	10	100 (0.8- 1)	95 (0.7- 1)
Nagahara	J. Gastroenterol	2004	Japan	61	O 20/12 h, AMO 500/8 h, MET 250/12 h	10	93 (0.8-0.9)	82 (0.7-0.9)
Nagahara	J. Gastroenterol	2004	Japan	59	LAN 30, AMO 750, MET/12 h	10	95 (0.8-0.9)	93 (0.8-0.9)

DISCUSSION:

The present study highlights the fact that the evidence regarding second-line therapy is extremely heterogeneous. Although an acceptable proportion (30%) of the second-line therapies evaluated achieved cure rates over 90%, the results are inconsistent and the current evidence does not allow us to identify a schedule that consistently achieves excellent cure rates. Another important aspect may be antibiotic and PPI blood levels, which were not measured in any of the studies. A large proportion of successful studies (and practically all those using triple therapy) was performed in individuals of eastern Asian ethnicity, who have a lower mean body mass index and a much higher proportion of slow metabolizers than Caucasians, thus allowing the drugs to achieve higher plasma levels. Indeed, few treatments have obtained cure rates over 90% in western populations and the only article reporting a rate above 90% since 2010 used a levofloxacin and bismuth containing quadruple therapy for 14 days. However, even these quadruple therapies show irregular performance, a second similar study has recently been published in Chinese patients, with cure rates below 80%.

The results of our analysis show that the approach to secondline therapy has been not systematic and that many, very diverse treatments have been attempted without a clear rationale for de - signing the therapies, often with the hope that the organisms in the study would be susceptible to some of the antibiotics chosen and that the doses and durations of therapy were correct. Empiric second-line therapy should be based on many rules of thumb. First is that as secondary resistances are very high, some antibiotics as clarithromycin and levofloxacin should never be repeated. Second, as far as possible, the treatments should be based on strong data about populations susceptibility testing. Third, we should select the doses and durations and antibiotics that will achieve high cure rates. This currently means fourteen-day four drug therapies and high-dose PP.

CONCLUSION:

In conclusion, the systematic review shows that 30% of the therapies evaluated obtained cure rates above 90%. Triple therapy including a PPI, metronidazole, and amoxicillin (31.1%) and quadruple therapy with a PPI, bismuth, metronidazole, and tetracycline (22.9%) were successful approaches. Interestingly, since 2010 only one article has reported cure rates above 90% in a western population. The results of our analysis show that, until now, the research on H. pylori second-line therapy has been not systematic. It is suggested that any new treatment should be designed considering antibiotic resistance data and H. pylori treatment basic principles.

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