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REVIEW

Prevalence of *Helicobacter pylori* resistance after failure of first-line therapy. A systematic review☆

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KEYWORDS
Helicobacter pylori;
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Abstract There are no systematic data on the rates of antibiotic resistance after the failure of a first eradication treatment. The objective of this study was to determine the prevalence of secondary resistance to antibiotics by conducting a systematic review of studies evaluating the secondary resistance of *Helicobacter pylori*. We identified 31 studies (2787 patients). Resistance was determined in 1764 patients. A percentage of 99.1 of patients received clarithromycin as first-line treatment and 58.7% developed resistance. A percentage of 24.3 received metronidazole and 89.7% developed resistance. Secondary resistance to amoxicillin was extremely rare. Secondary resistance after first-line treatment was very common. These findings support the recommendation not to repeat clarithromycin or metronidazole after the failure of a first eradication treatment.

PALABRAS CLAVE
Helicobacter pylori;
Segunda línea;
Resistencias

Prevalencia de las resistencias de *Helicobacter pylori* tras el fracaso de una primera línea de tratamiento. Revisión sistemática

Resumen No hay datos sistemáticos sobre cuáles son las tasas de resistencia a antibióticos tras el fracaso de un primer tratamiento erradicador. El objetivo del estudio es determinar la prevalencia de las resistencias secundarias a los antibióticos mediante una revisión sistemática de estudios que evaluaban las resistencias secundarias de *Helicobacter pylori*. Se identificaron

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31 estudios (2.787 pacientes). Se determinaron resistencias en 1.764 pacientes. El 99,1% de los pacientes recibieron claritromicina como tratamiento de primera línea, y un 58,7% desarrollaron resistencias. El 24,3% de los pacientes recibieron metronidazol, desarrollando resistencias el 89,7%. La resistencia secundaria a amoxicilina fue excepcional. Las resistencias secundarias tras un primer tratamiento son muy elevadas. Estos hallazgos dan soporte a la recomendación de no repetir claritromicina o metronidazol tras el fracaso de un primer tratamiento erradicador.

Introduction

Helicobacter pylori is one of the most common infections in humans. It is estimated that approximately 50% of the world's population is chronically infected by *H. pylori*. The infection is associated with a significant number of gastrointestinal diseases, such as peptic ulcer, chronic gastritis, functional dyspepsia, lymphoma of the lymphoid tissue associated with the gastric mucosa and gastric cancer.[1,2] Since the discovery of *H. pylori* infection in 1982,[3] multiple treatment options have been described. Until relatively recently, the standard treatment was triple therapy, which included two antibiotics (clarithromycin and amoxicillin or metronidazole) and a proton-pump inhibitor.[4] However, the efficacy of this treatment has decreased, primarily because of resistance to clarithromycin and metronidazole; the rate of resistance to clarithromycin has increased to over 20% in many countries.[5] In response to the poor results with triple therapy, the current guidelines have changed their recommendations to longer and more complex quadruple therapies.[6–9] Although the new treatments achieve better cure rates than the triple therapy, the first-line treatment for *H. pylori* continues to fail in approximately 10–20% of patients.[4]

The majority of the consensus documents state that *H. pylori* resistance to antibiotics is very high after the failure of a first eradication therapy.[4,9] However, that conclusion is based on a very small number of studies which analyse primary and secondary resistance together.[8,10–12] To our knowledge, there are no systematic reviews which have analysed the secondary resistance rate after the failure of a first-line eradication therapy (proton-pump inhibitor, amoxicillin and clarithromycin). Having accurate figures for these resistance rates could be extremely useful for designing second- and third-line treatments.

In a recent systematic review, our group assessed the effectiveness of the second-line therapies for the eradication of *H. pylori*.[13] The study showed that few treatments achieve cure rates of over 90%. It also showed that no individual treatment consistently obtained excellent results. A number of the studies included in our systematic review reported the resistance to antibiotics after failure of the initial treatment and made it possible to estimate secondary resistance rates for the most commonly used antibiotics.

The objective of this study is therefore to carry out a systematic evaluation to determine the prevalence of resistance to antibiotics after failure of the first-line treatment for *H. pylori* infection.

Material and methods

The study was conducted in accordance with the PRISMA[14] and MOOSE[15] guidelines for systematic reviews and meta-analyses. The MOOSE checklist is shown in Appendix 1 and the PRISMA flow chart in Fig. 1.

Search strategy

We carried out a systematic search of the literature limited to full-text articles published in PubMed and the Web of Science (formerly ISI Web of Knowledge) from 1996 to June 2015. The references in the selected articles, the systematic reviews and the personal databases of the authors were also reviewed. 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 Web of Science.

Inclusion criteria

We included published full-text articles which met the following criteria: (a) randomised or quasi-randomised clinical trials or observational studies; (b) which evaluated the rescue treatment after failure of a first treatment for *H. pylori*; and (c) studies that determined resistance levels. Only articles published in Spanish, Italian, French and English were included.

Exclusion criteria

The exclusion criteria were articles in Asian languages, duplicate publications, letters to the editor, expert opinions and reviews.

Data extraction process

The data were extracted independently by two of the authors (NM and XC). The decision to include or exclude studies was made by the two authors separately.

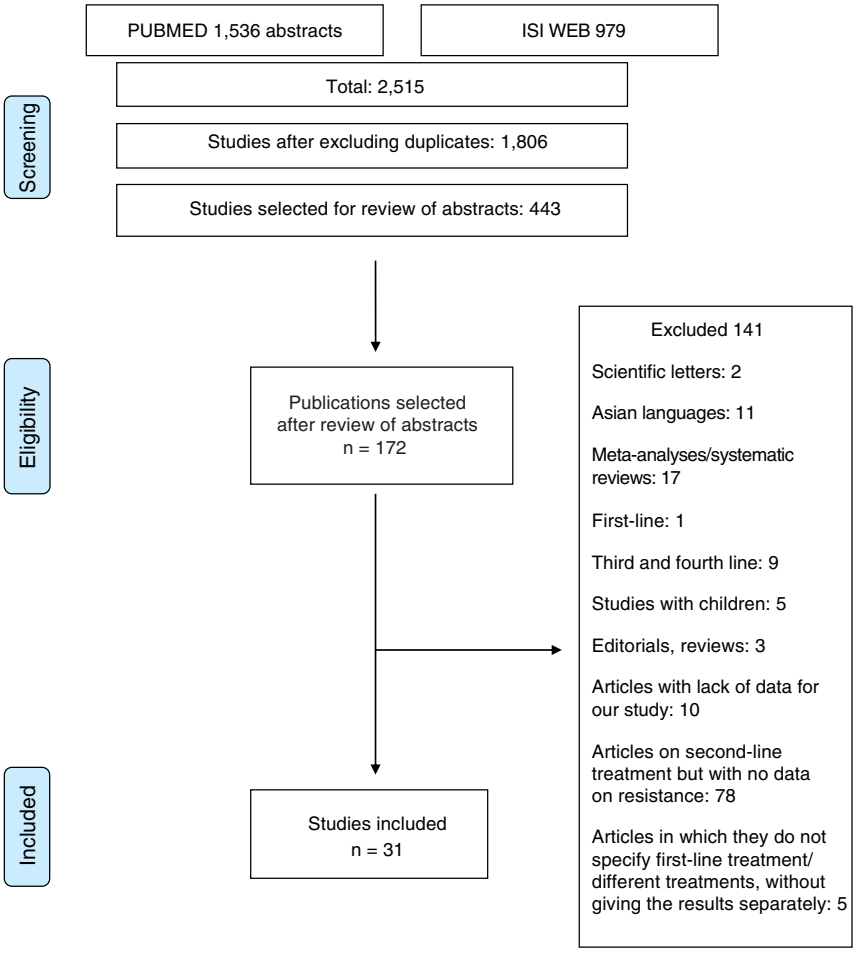

Figure 1 Flow of information through the different study selection phases.

Disagreements were resolved by consensus. The level of agreement between the two authors who selected the relevant articles was above 90%. Data extraction was standardised using a data extraction table and was performed separately for each study by the two authors. In the event of disagreement, the data were reviewed and, if necessary, a consensus was arrived at. The variables compiled for this study were: year of publication; country where the study was conducted; number of patients; number of cultures and method for determining resistance and resistance rates according to the previous treatment administered; and antibiotic resistance after first-line failure.

Risk of bias

Two reviewers (NM and JSD) independently assessed the risk of bias according to the current recommendations of the Cochrane Collaboration for randomised clinical trials and the suggestions in the Methods Guide for Effectiveness and Comparative Effectiveness Reviews for observational studies.[16] Any discrepancies in the interpretation were resolved with a third reviewer (XC).

Results

Over 2000 articles were obtained with the original search. After reviewing the abstracts, 172 full-text articles were assessed to determine their eligibility. Duplicated studies were excluded. After careful assessment, 31 articles[17–47] (2787 patients) were selected which made sensitivity determinations and analysed resistance rates.

Studies excluded

One hundred and forty-one studies were finally excluded, for the following reasons: (1) studies that included paediatric patients; (2) articles that only reported results for patients in first-, third- or fourth-line treatment; (3) articles in Asian languages; (4) letters to the editor or editorials or reviews of *H. pylori* treatment; (5) articles in which the data provided did not allow the evaluation of study eligibility or data extraction; and (6) articles on second-line treatments without data on resistance or without data on first-line treatment (Appendix 2).

Figure 2 Risk of bias table. NC: non-controlled studies; RCT: randomised controlled clinical trials.

Studies included

Thirty-one articles describing the rate of resistance after the failure of a first eradication therapy (2787 patients) were included in the systematic review.

Study quality

Fig. 2 shows the risk of bias assessment. Of the 31 articles, 18 were randomised clinical trials, 12 were observational and one was retrospective.

Table 1 Review articles. Methods for determining resistance.

Year	Author	Method	MIC AMO	MIC CLAR	MIC MET	MIC LEV	MIC TET	MIC RIFAB
2006	Borody et al.[17]	E-test	>4	≥1	>8		≥1	≥0.002
2003	Chi et al.[20]	E-test	>2	>1	>8		>2	
2012	Chuah et al.[23]	E-test	>4			>1	>8	
2012	Chuah et al.[22]	E-test		>1	>8	>1	>4	
2003	Furuta et al.[25]	Agar	>0.5	>1				
2011	Furuta et al.[24]	Molecular		>1	≥16			
2002	Georgopoulos et al.[26]	Agar		>2	>8		>4	
1999	Gomollon et al.[27]	E-test	>8	>2	>32			
2011	Hori et al.[28]	Agar		≥1	≥8			
2003	Isomoto et al.[29]	E-test		>2	>8			
2009	Kuo et al.[18]	E-test	>0.5		>8	>1	>4	
2012	Kudo et al.[39]	Agar	≥0.5	≥1	≥8			
2013	Kuo et al.[19]	E-test	>0.5		>8	>1	>4	
2014	Liang et al.[21]	E-test		>1	>8		>4	
2011	Liou et al.[30]	E-test	≥0.5	≥1	≥8	>1		
2005	Matsumoto et al.[31]	E-test	>8	>1	>8	>1		
2003	Murakami et al.[33]	E-test	>0.5	>1		>16		
2006	Murakami et al.[34]	E-test	>0.5	>1		>16		
2006	Murakami et al.[35]	E-test		>1		>16		
2008	Murakami et al.[32]	E-test	>0.5	>1		>16		
2007	Nishizawa et al.[36]	Agar	>0.5	>1		>8		
2004	Shimoyama et al.[37]	Agar	>0.5	>1		>16		
2007	Shirai et al.[38]	Agar	≥0.5	>1		≥8		
2014	Tai et al.[43]	E-test	>0.5				>1	>4
2005	Togawa et al.[40]	Agar						
2009	Ueki et al.[41]	Agar	≥0.5	≥1		≥8		
2003	Watanabe et al.[42]	E-test		≥1				
2002	Wong et al.[44]	E-test						
2003	Wong et al.[45]	E-test	>2	>2		>8		
2006	Wu et al.[47]	E-test		>1		>8		>4
2011	Wu et al.[46]	E-test	>0.5			>8		>4

AMO: amoxicillin; CLAR: clarithromycin; LEV: levofloxacin; MET: metronidazole; MIC: minimum inhibitory concentration; RIFAB: rifabutin.

Resistance rates to antibiotics used in first-line

In total, 2787 patients were analysed in our review; of these, resistance was determined before the second treatment in 1764 (63.3%). Additional details on the method for determining resistance and the minimum inhibitory concentration (MIC) are shown in Table 1.

We analysed the prevalence of secondary resistance to the different antibiotics:

(a) Amoxicillin: 1729 patients were analysed. Only 10 (0.36%) developed secondary resistance.
(b) Clarithromycin: 1747 cultures were obtained for resistance, 1026 (58.72%) of which showed resistance.
(c) Metronidazole: of 68 patients assessed, 61 (89.7%) had secondary resistance to the drug.
(d) Lastly, of 35 patients who received the combination clarithromycin and metronidazole as first-line treatment, 18 (40.9%) were resistant to both antibiotics (Table 2).

Resistance rates to antibiotics not used in first-line

In our review we also analysed the prevalence for other antibiotics not used in first-line treatment: 4.9% resistance to quinolones and 0.05% to tetracyclines. Of the patients who did not receive metronidazole (2719), 405 (14.9%) were resistant.

Discussion

The WHO (World Health Organisation) has classified *H. pylori* as high-priority on its priority pathogens list, as an infection with a high degree of resistance to antibiotics and as representing a public health problem.[48] In line with other published studies,[49–52] the results of our review show a high prevalence of secondary resistance to clarithromycin (>50%). The secondary resistance rates to metronidazole are even higher (89.7%). In contrast, secondary resistance to amoxicillin is rare. One interesting fact is that 40.9% have dual resistance to metronidazole and clarithromycin after treatment failure. These figures are in line with data

Table 2 Articles included in the review. First-line treatments received and prevalence of secondary resistance.

Author	Year	Country	First-line	*n*	*n* R	*n* R AMO (%)	*n* R CLAR (%)	*n* R MET (%)	*n* R MET and CLAR (%)	*n* R QUIN (%)	*n* R TET (%)
Borody et al.[17]	2006	Australia	PPIAC	52	52	0	11 (21.1)	8 (15.3)	28 (53.8)		
Chi et al.[20]	2003	Taiwan	PPIAC	100	74		35 (47.2)	44 (59.4)	13 (17.5)		
Chuah et al.[22]	2012	Taiwan	PPIAC	128	32	0				9 (28.1)	0
Chuah et al.[23]	2012	Taiwan	PPIAC	101	34	0		9 (26.4)		11 (32.3)	0
Furuta et al.[25]	2003	Japan	PPIAC	17	17	0	12 (70.5)				
Furuta et al.[24]	2011	Japan	PPIAC	74	59		49 (83)	12 (20.3)			
Georgopoulos et al.[26]	2002	Greece	PPIAC	95	67		18 (26.8)	19 (28.3)	10 (14.9)		
Gomollon et al.[27]	1999	Spain	PPIAC	21	19	0	3 (15.7)	3 (15.7)	3 (15.7)		
Hori et al.[28]	2011	Japan	PPIAC	82	12		11 (91.6)	0			
Isomoto et al.[29]	2003	Japan	PPIAC	123	72		45 (62.5)	20 (27.7)			
Kudo et al.[39]	2012	Japan	PPIAC	52	47	0	45 (95.7)	2 (4.2)			
Kuo et al.[18]	2009	Taiwan	PPIAC	166	99	6 (6)		56 (56.5)		21 (21)	0
Kuo et al.[19]	2013	Taiwan	PPIAC	150	46	2 (4.3)	21 (45.6)	27 (58.6)		13 (28.2)	0
Liang et al.[21]	2014	Taiwan	PPIAC	61	17	0	6 (35.2)	3 (17.6)		4 (23.5)	0
Liou et al.[30]	2011	Taiwan	PPIAC	142	52	1 (1.9)	33 (63.4)	8 (15.3)		8 (15.3)	
Matsumoto et al.[31]	2005	Japan	PPIAC	60	35	0	21 (60)	3 (8.5)		5 (14.28)	
Murakami et al.[33]	2003	Japan	PPIAC	92	90	0	56 (62.2)	22 (24.4)			
Murakami et al.[34]	2006	Japan	PPIAC	61	57	0	48 (84.21)	3 (5.2)			
Murakami et al.[35]	2006	Japan	PPIAC	88	88			21 (23.8)			
Murakami et al.[32]	2008	Japan	PPIAC	169	162	0	128 (79)	14 (8.6)			
Nishizawa et al.[36]	2007	Japan	PPIAC	107	107	0	96 (89.7)	4 (3.7)			
Shimoyama et al.[37]	2004	Japan	PPIAC	70	62	0	52 (83.8)	0			
Shirai et al.[38]	2007	Japan	PPIAC	132	86	0	74 (86)	5 (5.8)			
Tai et al.[43]	2014	Taiwan	PPIAC	158	44	1 (2.2)				14 (31.8)	
Togawa et al.[40]	2005	Japan	PPIAC	23	23		12 (52.1)				
Ueki et al.[41]	2009	Japan	PPIAC	104	95	0	85 (89.4)	5 (5.2)			
Watanabe et al.[42]	2003	Taiwan	PPIAC	33	27		12 (44.4)			1 (3.7)	
Wong et al.[44]	2002	China	PPICM	26	22		15 (91.6)	5 (22.7)	9 (40.9)		
Wong et al.[44]	2002	China	PPIAC	11	10		6 (60)	4 (40)	4 (40)		
Wong et al.[44]	2002	China	RANCM	7	4		3 (75)	2 (50)	2 (50)		
Wong et al.[44]	2002	China	PPIAM	1	1		0	0	0		
Wong et al.[45]	2003	China	PPIAC	34	28	0	21 (75)	9 (32.1)	8 (28.5)		
Wong et al.[45]	2003	China	PPIAM	23	16		3 (18.7)	16 (100)	3 (18.7)		
Wong et al.[45]	2003	China	PPICM	11	9		7 (77.7)	8 (88.8)	7 (77.7)		
Wu et al.[47]	2006	Taiwan	PPIAC	93	44		30 (68.1)	22 (50)			0
Wu et al.[46]	2011	Taiwan	PPIAC	120	55	0		29 (52.7)			1 (1.8)

AMO: amoxicillin; CLAR: clarithromycin; MET: metronidazole; PPIAC: proton-pump inhibitor, amoxicillin and clarithromycin; PPIAM: proton-pump inhibitor, amoxicillin and metronidazole; PPICM: proton-pump inhibitor, clarithromycin and metronidazole; QUIN: quinolones; R: resistant; RANCM: ranitidine, clarithromycin and metronidazole; TET: tetracyclines.

from previous studies in which secondary resistance ranged from 46.9% to 83.3% for clarithromycin, 16.7% to 43.8% for metronidazole and 16.7% to 50% for quinolones.[53]

We also analysed the prevalence of resistance to other antibiotics that were not administered as first-line. Interestingly, resistance rates to quinolones were low (4.9%) and to tetracycline, almost non-existent (0.05%). In the case of quinolones, the low resistance rate may reflect both a selection of strains sensitive to the antibiotic and a low underlying prevalence. In the case of metronidazole, the ''baseline'' rate of resistance was 14.9%, much lower than the 89% found after treatment failure.

To our knowledge, this is the first study to systematically assess secondary resistance rates to antibiotics. One of the limitations of our study was the conspicuous lack of data available in Western countries. Moreover, the small number of studies detected does not allow any subgroup analysis.

Our study confirms that it is advisable to avoid the re-administration of clarithromycin after a first failure of eradication therapy. The data on metronidazole, however, are less conclusive. Although different studies and reviews show that treatment with metronidazole at high doses and for 10 days or more may reverse resistance in vitro,[54] a recent multicentre observational study shows that repetition of the antibiotic is associated with very low cure rates in the context of failure of a previous metronidazole treatment.[55]

Of the articles included in our systematic review, a third did not have adequate allocation sequence concealment and blinding of the investigators (Fig. 2). There is therefore a greater risk of bias and the results of the systematic review, as well as the quality of the results, could be affected. It should also be noted that most of the included studies were conducted in Asian populations, and only three in Mediterranean populations, meaning that they are less applicable in clinical practice in our area.

In conclusion, our study suggests that secondary resistance after an initial treatment with metronidazole and clarithromycin is very high. In contrast, resistance to amoxicillin is extremely rare, even after treatment failure.

Conflicts of interest

The authors declare that they have no conflicts of interest.

Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.gastre.2018.11.021.

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