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JSM Gastroenterology and Hepatology

Review Article

Regional Antibiotic Resistance of *Helicobacter pylori*

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Submitted: 05 October 2016

Accepted: 24 November 2016

Published: 28 November 2016

Keywords

- *Helicobacter pylori*
- Regional resistance
- Metronidazole
- Clarithromycin
- Levofloxacin

Abstract

Antibiotic resistance is considered the cause of unsuccessful eradication of *Helicobactor pylori (H. pylori)* infections. Awareness of regional resistance rates of *H. pylori* isolates can improve not only empiric antibiotic therapy but also lead to the development of second line treatment and rescue regimens. At present, the most common treatment is empiric eradication. Global regional regimen therapies should be based upon regional in vitro antibiotic resistance rates. This approach is crucial in successfully treating the individual patient. However, in regions where antibiotic susceptibility testing is unavailable, epidemiological data for secondary *H. pylori* resistance are essential for the judicious use of antibiotics following several treatment failures. Primary *H. pylori* resistance to clarithromycin is less prevalent worldwide than *H. pylori* resistance to metronidazole. Secondary resistance that develops *in vivo* in previously susceptible organisms has been documented in cases of therapeutic failures. All antibiotics used to treat *H. pylori* are widely used to treat other bacterial infections. Pretreatment exposure of *H. pylori* to inadequate levels of these drugs as well as the use of inadequate regional antibiotics is associated with secondary resistance. Herein, we review regional resistance rates of *H. pylori* isolates to clarithromycin, metronidazole and levofloxacin, the main antimicrobial agents used for eradication of *H. pylori*.

ABBREVIATIONS

H. pylori: Helicobacter pylori; CLA: Clarithromycin; MET: Metronidazole; LEV: levofloxacin; PPI: proton pump inhibitor; AMP: Amoxicillin; TET: Tetracycline

INTRODUCTION

Peptic ulcers and gastritis are caused by *Helicobacter pylori (H. pylori*) infections. *H. pylori* have also been associated with gastric adenocarcinoma, mucosa-associated lymphoid tissue lymphoma, chronic immune thrombocytopenic purpura in adults and iron deficiency anemia [1]. Person-to-person transmission by oral-oral, fecal-oral or gastro-oral exposure is most likely the route of transmission [2]. Antibiotic resistance is considered the cause of unsuccessful eradication of *H. pylori* infections. Other causes are attributed to inappropriate treatment, resistant strains and poor adherence to treatment protocols.

Consensus reports have recommended a proton pump inhibitor (PPI) and two antibiotics, either amoxicillin (AMP), metronidazole (MET) or clarithromycin (CLA) for 7-14 days as primary treatment showed a cure rate of 80% to 90% [3-5]. The resistance rates of *H. pylori* isolates to MET and CLA are much higher in treated than untreated patients [6]. Second-line regimens include triple or quadruple therapy with PPI, bismuth salts, tetracycline (TET) and/ or MET for 14 days. Levofloxacin (LEV) is recommended as a rescue therapy in adults [7]. TET is not approved for use in children under 8 years of age [8] and treatment with LEV is not recommended before age 18 [9].

The most common causes of treatment failure are poor compliance, resistance to antibiotics and re-infection [5]. Secondary resistance (resistance developed *in vivo* in previously susceptible organisms) has been documented in cases of therapeutic failures. The combined effect of spontaneous mutation and recombination during infection could be responsible for the emergence of antimicrobial resistance. Resistance to CLA is associated with mutations of the 23S rRNA gene. Resistance to MET is mostly mediated by mutations of the oxygen-insensitive NADPH nitroreductase (rdxA) gene [10].

H. pylori is acquired in childhood. In recent years, several studies have reported antibiotic resistance to *H. pylori* in children and adolescents. *H. pylori* resistance differs between countries and regions. In a recent multinational European study, primary resistance to CLA and MET was 20% and 23%, respectively [11]. Kalach et al. [12], reported that the prevalence of CLA resistance (~23%) remained stable during a 10-year period in French children, whereas MET resistance significantly decreased from 43.3% to 32% during the last 5 years of the study.

In the USA, *H. pylori* resistance rates to AMP, CLA and MET were 4%, 41% and 45%, respectively [13]. In vitro resistance to CLA was found associated with failure of first-line therapy [14,15]. The in vitro effect of resistance to MET is indeterminate; however, the increasing antibiotic resistance to *H. pylori,* has prompted researchers to issue international consensus statements recommending regional surveillance of *H. pylori* resistance [3,4,16].

CLARITHROMYCIN

CLA is the primary antibiotic used in eradicating *H. pylori,* which is why resistance to CLA is associated with treatment failure. The reported success in eradicating *H. pylori* using triple therapy (including CLA) in patients with isolated resistance to *H. pylori* was found to be <70% [17-19]. Taking this into account, the most recent Maastricht recommendations suggest that susceptibility testing be performed prior to initiation of eradication treatment in regions with high CLA resistance rates [3].

In developed countries, *H. pylori* resistance to macrolides is high, seemingly due to the frequent prescribing of newer antibiotics (CLA and azithromycin) in treating upper respiratory infections, acute otitis media and community-acquired pneumonia [11]. In a recent large European multicenter study [20], the reported resistance to CLA was 17.5%. In comparison, secondary resistance after one eradication treatment failure with CLA increased to 63.2% and after 2 eradication treatments increased to 75.4% (tertiary resistance) [21].

In most regions where CLR susceptibility has been studied, resistance rose over time. In Bulgaria, CLR resistance rose from 10% in 1996-1999 to 19% in 2003-2004 [22] and in Belgium from 6% in 1990 to 56% in 2009 [23]. The Japanese National Surveillance Study examined 3707 *H. pylori* isolates from 2002 to 2005 and reported that CLA resistance rates increased from 18.9% to 27.7% during this 3-year period [24]. In the USA, a dramatic increase in CLA resistance was reported. The prevalence of CLA resistance increased from 6.1% in 1993 to 12.9% in 2002 [25-27]. The military veterans' population in the USA exhibited an overall 17.8% CLA resistance rate between 2009 and 2013 [28]. In the USA, the rate of CLA resistance in a pediatric population was reported to be as high as 50% [29].

METRONIDAZOLE

MET, in order to eradicate this bacterium, has been widely used in combination therapies such as MET-based triple therapy, concomitant therapy and bismuth-containing quadruple therapy [30-32]. Studies have shown that treatment success depends on several factors, such as smoking status and patient compliance, nevertheless, antibiotic resistance has been found to be the major cause of failure [33-34]. MET resistance has significantly increased in Europe, the USA, Asia and Africa. The overall European resistance rate is 17%, less than 40% in all other countries and distinctly higher in both Asia and the USA. Previously published studies have demonstrated that primary MET resistance remains stable in European countries [35]. According to current guidelines reported by Malfertheiner et al, MET should be the preferred antibiotic for first-line therapy in Europe [30] however, not in Asian patients.

An Italian study found that primary MET resistance was present in 22.9% and in 50% of Italian and immigrant patients, respectively, suggesting that foreign patients should probably be treated with different first-line therapies [36]. A higher prevalence of resistance to MET has been reported in developing countries (50%-80%) such as Mexico (76.3%) [37] and lower rates of resistance in Japan (9-12%) [38]. MET resistance rates in the USA were recently reported at 21.5% [28].

H. pylori resistance to MET ranges from 20% to 40% in Europe and the USA, yet, only a 14.9% resistance rate was reported in northern Italy [39]. One possible explanation is the different rates of prior use of MET in various countries. In developing countries, MET resistance rates are high, perhaps owing to the greater use of the drug for treating parasitic infections [40,41]. In Alaskan native populations, women have higher rates of MET resistance than men. Prior use of MET, used to treat gynecological infections, was found associated with increased MET resistance [42-43], and yet, compared to CLA resistance can be surmounted by regimens containing bismuth [3] (Table 1).

LEVOFLOXACIN

LEV is a fluoroquinolone antibacterial agent with a broad spectrum of activity against gram-positive and gram-negative bacteria. Due to these properties, LEV is largely prescribed in treating respiratory system and genitourinary tract infections, thus, *H. pylori* resistance to LEV is contingent on the use of this antibiotic in clinical practice. The probability of *H. pylori* resistance to LEV increases in persons >45 years of age [44] with a history of quinolone intake ten years prior to an eradication attempt with LEV-based therapy [45]. LEV resistance is highly variable among various geographical regions depending upon how frequent quinolones are used in clinical practice [3].

Several reports raise concerns over the recent rapid increase in *H. pylori* resistance to quinolones and its efficacy in second-line regimens [46,47]. Prevalence of LEV-resistant *H. pylori* strains is growing, with a steady annual increase during the past few years [48] ranging from 18% up to >30% in Europe and Asia [49,50]. Eradication rates of 57% have recently been reported in South Korea [51] where a high resistance to LEV has been estimated [52].

Two recent studies [53,54] reported high eradication rates of *H. pylori* infection using LEV-based triple therapy. However, the increasing resistance to LEV, which is recommended in many second-line therapies, is of major concern [3]. Given the rapid mutation rate of fluoroquinolones [55,56], there is apprehension of a rapid emergence of resistance to LEV while on therapy. In eastern European countries, the rate was similar (3.9%) [48]. In the USA, the reported LEV resistance rate was reported at 31.9% [28]. A Portuguese study reported a high resistance rate of 20.9% in strains isolated from 110 adult patients [57]. In the Netherlands, a rate of 4.7% resistance was reported with trovafloxacin, a drug not yet introduced to the Dutch market. In regions with low secondary resistance, LEV is an attractive treatment option for patients after two failed eradication attempts.

CONCLUSION

The fact that most *H. pylori* infected patients are still being

Table 1: Resistance values for antimicrobial agents in different countries.

Country (by continent)	Year	Pts	AMO	CLA	MET	TET	LEV	RIF	Multi Drug	Reference
Asia										
South Korea	1994-2012	3181	19.2	35.9	15.2		18.3			6
South Korea							42.9	28.6		52
Japan	2002-2005	3,707	31.2-38.2	18.9-27.7	3.3-5.3					24
Japan	1996-1999	388		12.9	12.4				2.3	38
Europe										
All over Europe	1999-2002	1233	0.6	24	25				6.9	11
France	1994-2005	377	0	22.8	36.7				7.9	12
Italy	2010	162	2.1-11.7	17.3-55.8	30.4-41.1		8.8-10.8	2.1-5.8		18
Italy	2004-2006	255		16.9	29.4		19.1			36
Italy	2000	167	0	1.8	14.9					39
Italy	2000	100							8-10	53
Italy		34	11.8				16.7			
18 European countries	2008-2009	2204		17.5	34.9		14.1			20
Germany	2005-2012	436	0	7.5-75.4	32.7-80.1	<5	11.7-36.4	<5 -6.2		21
Bulgaria	1996-2004	1205	0.8-1.5	12.5-12.6	15.0-25.6	3.4-5.2			4.3-4.9	22
Bulgaria	2012-2013	50	2	22.0	34	2.0-2.1	18	12	12	49
Belgium	1990-2009	10801	0	16.9-23.7	23.4-30.6	<0.01	13-38.6 (Cipro)		4.7-18.5	23
Ireland	2008-2009	85				0	11.7	0		44
France	1996-1999	60					3.3 (Cipro)			46
10 Eastern European countries	1996-2000	2340	0.9	9.5	37.9	1.9	3.9 (Cipro)		6.1	47
Portugal	1990-1999	473	0	19.0	30.6	0	9.6 (Cipro)		8.6-11.4	57
The Netherlands	1997-1998	231	0	1.7	21.2	0	4.7 (Trova-floxacin)			
Middle East										
Israel	1999-2002	265		15	31.4				26.6-37.4	16
Egypt	2002-2003	48	2 (AMP)	4	100		1 (Cipro)			40
Iran	1997-2000	70	58	75	71-81	68	65 (Cipro)			41
Iran	2015	111	15.3 (AMP)	32.4	61.3		30.6		22.6-34.5	50
America										
USA (Detroit)	1999	31	4.4	41	45.4	0				13
USA (Texas)	1993-1999	6632	<1	10.6-12	21.6-39	<1				27
USA (Texas)	2009-2013	656		16.4	20.3	24.2	31.3			28
USA (Texas)	2010-2012	38		50						29
USA (Alaska)	1998-2002	125		30	66					42
USA (Alaska)	1999-2003	964	2	31	44	0				43
USA (Alaska)	1998-2002	125					8.8			45
Mexico	1995-1997	195	18	24	80				30	37

Abbreviations: Pts:Patients; CLA: Clarithromycin; MET: Metronidazole; LEV: levofloxacin; AMP: Amoxicillin; TET: Tetracycline; Rif : Rifabutin

empirically treated increases the importance of regional susceptibility data. The awareness that many naïve patients exhibit antibiotic resistance, stresses the need for regional guided treatment regimens. Worldwide, empiric eradication regimen therapies should be based upon regional in vitro antibiotic resistance rates. This approach is essential in successfully treating the individual patient. The awareness of regional antimicrobial resistance is very crucial in reducing the universal frustrating first and second line therapy and rescue treatment.

ACKNOWLEDGEMENTS

The authors thank Mrs. Phyllis Curchack Kornspan for her editorial advice.

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Cite this article

Shmuely H, Domniz N, Yahav J (2016) Regional Antibiotic Resistance of Helicobacter pylori. JSM Gastroenterol Hepatol 4(5): 1074.