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Review Article

Eradication of *Helicobacter Pylori* in Iran: A Review

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ABSTRACT

Helicobacter pylori (*H. pylori*) infection is one of the most common bacterial infections, affecting almost half of the world's population. It is associated with peptic ulcer disease, gastric adenocarcinoma, and lymphoma. In Iran, the prevalence of *H. pylori* infection has been reported to be between 36% and 90% in different geographic regions.

Several studies have assessed the efficacy of different therapeutic options for first-line and second-line *H. pylori* eradication in Iran; however, the results are conflicting. Therefore, we conducted a review to evaluate different studies in order to select the best options and to provide recommendations for *H. pylori* eradication in Iran. Accordingly, we searched through PubMed to obtain relevant randomized clinical trials published in English language up to June 2017.

According to our study, among first-line eradication regimens, bismuth-based furazolidone- or clarithromycin-containing quadruple therapies, hybrid regimen, and concomitant therapy seem to be appropriate options. Also, 10- or 14-day clarithromycin-containing triple therapy can be used if local *H. pylori* resistance to clarithromycin is known to be less than 15%.

For second-line *H. pylori* eradication, bismuth-based quadruple therapies and 14-day levofloxacin-based triple therapy can be used, provided that antibiotics other than those used in the first-line regimen are used. Third-line *H. pylori* eradication regimens have not been addressed in Iranian studies. However, most guidelines recommend treatment according to the results of culture and susceptibility testing.

Although we limited our investigation to *H. pylori* eradication regimens in Iran, the results are transferrable to any region as long as the patterns of antibiotic resistance are the same.

KEYWORDS:
Helicobacter pylori, Eradication, Iran

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INTRODUCTION

Helicobacter pylori (*H. pylori*) infection is among the most common bacterial infections, affecting almost half of the world's population.[1] It is associated with peptic ulcer disease, gastric adenocarcinoma, and lymphoma.

In Iran, the prevalence of *H. pylori* infection has been reported to be at least 36% in Kurdistan and as high as 90% in Ardabil.[2,3] Therefore, it is essential to introduce an effective *H. pylori* eradication regimen in this country. On the other hand, although *H. pylori* infection is very prevalent in Iran, it is not cost-effective to treat every person infected by the bacterium. According to Maastricht V Consensus Report, the indications for *H. pylori* eradication include: peptic ulcer disease (regardless of activeness and complications), mucous-associated lymphoid

Table 1: **Resistance pattern of *H. pylori* to different antibiotics during the previous years in different parts of Iran**

City	Year	Number	Method	Amox.	Met.	Tetra.	Cla.	Other	MDR
Tehran[5]	1997 - 2000	70	DDM	1.4	33	0	1.4		
Hamadan[6]	2001 - 4	135	DDM	3.7	36.3	0.7	3.7		
Tehran[7]	2005	120	DDM	1.6	57.5	0	16.7		
Tehran[8]	2005 - 08	160	DDM	7.3	55.6	38.1	7.3	Fur: 4.5	
Mashhad[9]	2008	124	DDM	9.8	64.6	0	17.1		
Tehran[10]	2010	42	DDM	2.4	40.5	4.8	14.3	Cip: 2.4	
Sari[11]	2011	197	DDM	23.9	65.5	37	45	Fur: 61	Dual Met + Cla: 22.6
Sari[12]	2012		DDM	10	78	9.3	34	Levo: 5.3 Moxi: 4.6	
Tabriz[13]	2012	112	DDM	28	76.8	18.6	14.3	Cip: 33 Rif: 28.6	
Tehran[14]	2013	153	-	7.2	63.8	-	26.5		
Ilam[15]	2013	50	DDM	6	44	6	16	Azith: 4	
North of Iran[16]	2015	20	DDM	5	57	27	24	Fur: 38 Azith: 19	
Kashan[17]	2015	95	E test				33.7		
Isfahan[18]	2013	78	DDM/E	6	55		15		
Mashhad[9]	2013	124	DDM	9.8	64	0	17		
Tehran[19]	2015	111	-	15	51		32	Cip: 30 Rif: 14	Dual Met + Cla: 22.6
Systematic review[20]	2015	21 Studies	-	16	61	12	22	Cip: 21 Levo: 5 Fur: 21	
Shiraz[21]	2016	100	E test				20		
Sari[22]	2016	30	DDM	10	63.3	6.6	16.6	Levo: 3.3	

Amox: Amoxicillin, Met: Metronidazole, Tetra: Tetracycline, Cla: Clarithromycin, Fur: Furazolidone, Cip: Ciprofloxacin, Levo: Levofloxacin, Azith: Azithromycin, Moxi: Moxifloxacin, Rif: Rifampin, MDR: Multi-drug resistance, DDM: disk diffusion method

tissue lymphoma (MALT), long term non-steroidal anti-inflammatory drug (NSAID) therapy in patients with a history of peptic ulcer disease (PUD), patients receiving long term proton pump inhibitors (PPIs), unexplained iron deficiency anemia, idiopathic thrombocytopenic purpura, gastric cancer prevention in special situations (including first degree relatives or previous history of gastric neoplasia), gastric atrophy, chronic gastritis with dyspepsia, chronic gastritis with mucosal atrophy/erosions, and if requested by individual patient.[4]

In order to treat *H. pylori* infection, antibiotic resistance is the most important issue. During the previous 20 years, resistance of *H. pylori* to antibiotics has increased in different parts of Iran (table 1). This is mainly due to common use of antibiotics in this country. Therefore, the most ideal option is to treat according to the results of culture and susceptibility tests. However, culture is not easily available.

In this article we have reviewed the efficacy of different first-line and second-line *H. pylori* eradication therapies in Iran.

Data Collection Method:

The present narrative review includes randomized controlled trials related to *H. pylori* eradication in Iran. In order to find the relevant papers, we searched through PubMed website for studies published in English language up to June 2017 with the following key words: ("*Helicobacter pylori*" or "*H. pylori*"), and (Iran), and ("eradication" or "therapy" or "treatment"). Two gastroenterologists selected relevant studies after reviewing their abstracts. Since the number of second-line *H. pylori* eradication regimens were very few, non-randomized clinical trials were also included for the assessments of second-line therapies.

Table 2: The efficacy of standard triple therapy with different durations of administration

Year	City	Therapy	Treatment duration (days)	Number of patients.	Underlying disease	Eradication assessment method.	Duration from therapy (week)	Per-protocol eradication rate
2003	Ardabi[24]	OAC	7	45	Gastritis	UBT	8	42
2006	Tehran[25]	OAC	7	120	*H. pylori* (+)	UBT	6	91.8
2012	Kerman[26]	OPC	7	34	*H. pylori* (+)	?	?	73
2010	Rasht[27]	OAC	10	107	NUD	Stool Antigen	8	90.7
2010	Tehran[28]	OAC	10	104	PUD	UBT	8	90.4
2013	Ghom[29]	OAC	10	76	*H. pylori* (+)	UBT	6	83
2013	Ahvaz[30]	OAC LAC EAC	10	98 97 98	*H. pylori* (+)	UBT	6	91.9 80.4 91.8
2015	Ahvaz[31]	OAC	10	100	*H. pylori* (+)	UBT	8	93.9
2007	Kermashah[32]	OAC (C: half dose) OAC	14 14	53 53	*H. pylori* (+)	UBT	6	88 89
2009	Yazd[35]	OAC	14	53	*H. pylori* (+)	UBT	4 - 6	70
2013	Shiraz[34]	OAC OPC	14	110 110	PUD	UBT	6	90.8 87
2014	Tehran[33]	OAC	14	39	GU	Biopsy	8	82.9
2015	Tehran[36]	OAC OAC	14 14 (A:28)	33 33	*H. pylori* (+)	Stool Antigen	4	63.6 90.9

O: Omeprazole, L: Lansoprazole, P: Pantoprazole, E: Esomeprazole, Amox: Amoxicillin, Cla: Clarithromycin, GU: Gastric ulcer, PUD: Peptic ulcer disease, NUD: Non-ulcer dyspepsia, UBT: Urea breath test

Data including the kind of therapy, number of patients, indications for treatment, intention to treat, and per-protocol *H. pylori* eradication rates were recorded in data gathering forms.

First-line *H. pylori* Eradication Regimens:

The ideal first-line *H. pylori* therapy is the regimen with more than 90% per-protocol eradication rate. However, according to Toronto Consensus Report, achieving > 85% eradication rate can also be considered appropriate.[23]

Clarithromycin-Containing Triple Therapy:

Clarithromycin-containing triple therapy consisted of clarithromycin plus a proton pump inhibitor (PPI), and amoxicillin or metronidazole is considered as the standard triple therapy. According to Maastricht V and Toronto Consensus Reports, standard triple therapy is suitable only in countries with less than 15% *H. pylori* resistance to clarithromycin.[4,23]

In Iran, 14 studies have evaluated the efficacy of clarithromycin-containing triple therapy, but the durations of regimens were different. Three studies evaluated 7-day therapy and only one could achieve ideal eradication rate.[24-26] Also, five studies assessed 10-day triple therapy. Four of these studies reported > 90% *H. pylori* eradication rate.[27-31] Furthermore, five other studies evaluated the efficacy of 14-day standard therapy, of them three showed appropriate eradication of *H. pylori*,[32-36] (table 2).

Accordingly, although *H. pylori* resistance to clarithromycin is increasing in our country, 10-day and 14-day standard triple therapies still seem to be appropriate options for first-line *H. pylori* eradication in Iran. In fact, the effects of antibiotics in vivo are not the same as those observed in vitro. Furthermore, low gastric pH may facilitate antibiotic activity. Most antibiotics have the most activity at neutral pH; however, clarithromycin especially has the most activity at higher pH (around 8). Thus, clarithromycin is the only antibiotic that benefits from a high pH caused by PPI.[37]

Table 3: The efficacy of furazolidone-containing triple therapy with different durations of administration

Year	City	Therapy	Treatment duration (days)	Number of patients.	Underlying disease	Eradication assessment method.	Duration from therapy (week)	Per-protocol eradication rate
2003	Ardabi[24]	OFT OFT (T: 200 BID F: 500 BID)	4 7	41 42	Gastritis	UBT	8	20.6 29.4
2014	Sari[39]	OAF (F: 200 BID) OAF (F: 200 TDS)	10 10	105 105	PUD	UBT	8	81 89
2015	Ahvaz[30]	OCipF (F: 100 BID)	10	100	*H. pylori* (+)	UBT	8	62
2015	Sari[38]	OAF (F: 200 TDS)	10	116	PUD	UBT	8	90.5
2003	Yazd[42]	OAF (F: 200 BID) OAF (F: 50 BID)	14	63 61	DU	Biopsy	6	88.9 67.9
2004	Sari[40]	OAF (F: 200 BID)	14	50	DU	UBT	12	54
2011	Ghom[41]	OAF (F: 200 BID)	14	43	PUD	UBT	12	61

O: Omeprazole, Amox: Amoxicillin, Tetra: Tetracycline, Fur: Furazolidone, DU: Duodenal ulcer, PUD: Peptic ulcer disease, NUD: Non-ulcer dyspepsia, UBT: Urea breath test, BID: twice daily, TDS: three times daily

Furazolidone-Containing Triple Therapy:

Furazolidone is an alternative to metronidazole in areas with high *H. pylori* resistance to metronidazole. Seven studies have evaluated furazolidone-containing triple therapies in Iran (including a PPI + amoxicillin + furazolidone). One of the earliest studies had compared the efficacy of 4-day versus 7-day furazolidone-based triple therapy. But both regimens showed very low per-protocol *H. pylori* eradication rates (20% vs. 29%, respectively).[24] During the previous 3 years, three other studies evaluated the efficacy of 10-day furazolidone-based triple therapies. Among these studies, those with higher doses of furazolidone (200 mg three times a day vs. 200 mg twice a day or daily) could achieve optimal eradication rates.[30,38,39]

Furthermore, three other studies assessed the efficacy of 14-day furazolidone-based triple therapies, but only one study could achieve appropriate eradication rate.[40-42] Administration of low doses of furazolidone seems to be the main reason for failure of the mentioned regimens (table 3).

Although regimens with higher doses of furazolidone could achieve acceptable eradication rates, adverse reactions to the treatment increased with higher doses of the drug. Therefore, this regimen cannot be suggested as a suitable option.

Bismuth-Metronidazole Quadruple Therapy:

Up to now, 12 studies have evaluated the efficacy of 10-day and 14-day bismuth plus metronidazole-containing quadruple therapies in Iran.[25,27,28,33,43,49] However, only three of these studies could achieve acceptable *H. pylori* eradication rates (table 4).

According to Maastricht V Consensus Report, in countries with low or even high dual resistance to clarithromycin and metronidazole, bismuth-containing quadruple therapies can be used as suitable first-line options.[4] However, the results of Iranian studies are not concordant with this recommendation. Searching through the mentioned studies shows that administration of sub-optimal doses of bismuth or metronidazole is probably the main reason for failure of this regimen in Iranian studies. On the other hand, *H. pylori* resistance to metronidazole has increased from 33% to 76.8% during the previous 10 years in Iran.[5,13,22] This may also have contributed to the failure of this regimen in the country.

Table 4: The efficacy of bismuth and metronidazole-containing quadruple therapy for *H. pylori* eradication

Year	City	Therapy	Treatment duration (days)	Number of patients.	Underlying disease	Eradication assessment method.	Duration from therapy (week)	Per-protocol eradication rate
2006	Tehran[25]	OABM (M: 500 BID) OSBM (M: 500 BID)	10	120	*H. pylori* (+)	UBT	6	85.8 92.8
2000	Tehran[46]	RABM	14	53	DU	UBT	4	52
2001	Tehran[49]	RTBM	14	73	DU	UBT	8	73
2006	Semnan[47]	OABM (M: 500 BID)	14	63	*H. pylori* (+)	UBT	4	75.7
2007	Tehran[45]	OABM (M: 500 BID)	14	107	PUD	UBT	8	83.1
2009	Tehran[44]	OABM (M: 500 BID)	14	30	*H. pylori* (+)	UBT	8	69
2010	Rasht[27]	OABM (M: 500 BID)	14	107	NUD	Stool Antigen	8	85.7
2012	Tehran[48]	OABM (M: 500 BID)	14	27	*H. pylori* (+)	UBT	4	67.8
2013	Tehran[33]	OABM (M: 500 BID)	14	110	PUD	UBT	6	56
2013	Bandar Abas[43]	OABM (A: 500 TID) (M: 250 TID)	14	100	*H. pylori* (+)	UBT	4	82.3
2015	Ahvaz[30]	OABM (M: 500 BID) OTBM (T: 500 BID)	14	100 100	*H. pylori* (+)	UBT	8	77.7 84.4

O: Omeprazole, Amox: Amoxicillin, B: Bismuth subcitrate, Tetra: Tetracycline, M: Metronidazole, S: Ampi-Sulbactam, DU: Duodenal ulcer, PUD: peptic ulcer disease, NUD: non-ulcer dyspepsia, UBT: urease breath test BID: twice daily, TDS: three times daily

Bismuth-Furazolidone Quadruple Therapies:

Furazolidone has been used in combination with bismuth in several studies in Iran. The first study was conducted in 2007 by Daghaghzadeh and colleagues. They evaluated the efficacy of 7-day bismuth-furazolidone quadruple therapy on 87 patients and reported 84.8% per-protocol eradication rate.[50] Further studies evaluated the efficacy of the same regimen with longer duration of therapy. Two studies assessed the efficacy of 10-day bismuth plus furazolidone-containing quadruple therapy, which both reported acceptable eradication rates.[28,38] Also, nine other studies evaluated the efficacy of 14-day therapy, of them six studies reported ideal eradication rates.[30,40,41,45,46,50-52] However, they were mostly accompanied by severe side effects of the treatment (table 5).

Bismuth-Clarithromycin Quadruple Therapy:

Bismuth plus clarithromycin quadruple therapy has also been used in 10-day or 14-day regimens. The only study that assessed the efficacy of 10-day regimen reported sub-optimal *H. pylori* eradication rate,[53] but two out of three 14-day regimens could achieve ideal eradication rates.[49,51,54] However, in one of these two studies, 13% of the patients reported severe adverse effects of the therapy[51] (table 5).

Sequential Therapy:

Sequential therapy is a novel *H. pylori* eradication regimen, which contains a PPI plus amoxicillin during the first half of therapy and the PPI + clarithromycin + metronidazole or tinidazole just during the second half. Three studies have evaluated the efficacy of sequential therapies in Iran,[27,55,56] but only one study reported acceptable *H. pylori* eradication rate,[56] (table 6). On the other hand, 6% of the patients in the latter study reported severe adverse effects of the drugs. These results are in concordance

Table 5: The efficacy of Bismuth plus Furazolidone- or Clarithromycin-containing quadruple therapies for *H. pylori* eradication

Year	City	Therapy	Treatment duration (days)	Number of patients.	Underlying disease	Eradication assessment method.	Duration from therapy (week)	Per-protocol eradication rate
2007	Isfahan[50]	OABF	7	78	*H. pylori* (+)	UBT	4	84.8
2010	Tehran[28]	OABM-F OABC-F	10 (M: 5, F: 5, C: 5)	103 103	PUD	UBT	8	91.3 88.7
2015	Sari[38]	OABF OABM-F	10 (M: 5, F: 5)	120 120	PUD	UBT	8	86.6 82.5
2000	Tehran[46]	RABF	14	53	DU	UBT	4	82
2001	Tehran[51]	OABF	14	63	DU	UBT	12	90
2004	Sari[40]	OABF (F: 100 BID) OABF (F: 200 BID)	14 14	50 50	DU	UBT	12	72 92
2007	Isfahan[50]	OABF	14	78	*H. pylori* (+)	UBT	4	82.6
2007	Tehran[45]	OABF OABF-M	14 (F: 7, M: 7)	104 103	PUD	UBT	8	95.2 95.3
2009	Shiraz[34]	OABF	14	69	*H. pylori* (+)	UBT	4-6	56
2011	Ghom[41]	OABF	14	43	*H. pylori* (+)	UBT	12	85.3
2012	Sari[40]	OABF	14 (F: 7)	80	PUD	UBT	12	90.2
2012	Sari[56]	OABF	14 (F: 7)	124	PUD	UBT	8	88.7
2015	Tehran[53]	OABC	10	60	*H. pylori* (+)	UBT	8	65.2
2001	Tehran[49]	OBCT (C: 250 BID)	14	73	DU	UBT	8	88
2001	Tehran[51]	OABC	14	55	DU	UBT	12	90
2013	Isfahan[54]	OABC OABC + probiotic	14	90	PUD	UBT	4	82.1 84.4

O: Omeprazole, R: Ranitidine, Amox: Amoxicillin, B: Bismuth subcitrate, Tetra: Tetracycline, M: Metronidazole, C: Clarithromycin, F: Furazolidone, DU: Duodenal ulcer, PUD: Peptic ulcer disease, UBT: Urea breath test, BID: twice daily

Table 6: The efficacy of non-bismuth quadruple therapies for *H. pylori* eradication

Year	City	Therapy	Treatment duration (days)	Number of patients.	Underlying disease	Eradication assessment method.	Duration from therapy (week)	Per-protocol eradication rate
2010	Rasht[56]	Sequential	14	107	NUD	Stool Antigen	8	81
2012	Sari[35]	Sequential	14	137	PUD	UBT	8	89.1
2013	Sari[55]	Sequential	14	199	PUD	UBT	8	79.9
2013	Sari[58]	Hybrid	14	197	PUD	UBT	8	92.9
2015	Sari[59]	Hybrid	10 14	124 126	PUD	UBT	8	83.8 92.8
2016	Sari[59]	Hybrid	14	100	PUD	UBT	8	89.3
2016	Sari[59]	Concomitant	10	100	PUD	UBT	8	85.9

PUD: Peptic ulcer disease, NUD: Non-ulcer dyspepsia, UBT: Urea breath test

with the results of a meta-analysis by Gatta and co-workers who included 5666 patients to receive sequential therapy. The overall per-protocol *H. pylori* eradication rate by the mentioned meta-analysis was 84.3%, which was not ideal for first-line *H. pylori* eradication.[57]

Hybrid Therapy:

Hybrid therapy is another novel *H. pylori* eradication regimen consisted of a PPI + amoxicillin during the first half of the treatment and concurrent administration of PPI + amoxicillin + clarithromycin + metronidazole during the second half of the treatment.

Up to now, only three studies have evaluated the effects of hybrid regimen for eradication of *H. pylori* in Iran and all have achieved acceptable eradication rates,[55,58,59] (table 6). Also, data from most other countries have shown ideal *H. pylori* eradication rates by hybrid regimen.[60] The success of this regimen seems to be related to concurrent administration of three antibiotics in the second half of treatment course.

Concomitant Therapy:

Another type of non-bismuth quadruple regimen is the concomitant therapy. It includes concurrent administration of a PPI + amoxicillin + clarithromycin + metronidazole during the entire treatment protocol.

Up to now, only one study has evaluated the efficacy of concomitant therapy in Iran. In 2016, Alhooei and colleagues evaluated the efficacy of 10-day concomitant therapy on 126 patients with peptic ulcer disease. They reported 85.9% per-protocol eradication rate, which is almost suitable.[59]

Also, studies from other countries have mostly shown ideal *H. pylori* eradication by concomitant therapy.[61-63] According to Maastricht V Consensus Report, concomitant therapy is the most effective non-bismuth quadruple therapy and can be used if the prevalence of dual resistant strains to clarithromycin and metronidazole is less than 15%. Furthermore, the recommended duration of concomitant therapy is 14 days, unless shorter durations of therapies are proven to be effective locally.[4] Accordingly, further studies with longer duration of treatment by concomitant regimen may achieve higher eradication rates in Iran.

Quinolone-Containing Regimens:

Up to now, only three studies have evaluated the efficacy of fluoroquinolone-containing regimens for *H. pylori* eradication; however, all of them reported sub-optimal eradication rates. In 2010, Aminian and co-workers assessed the effects of a 14-day triple therapy in which ciprofloxacin had been administered just during the first 7 days. They reported 70% per-protocol eradication rate.[27] Another study was conducted by Karbasi and colleagues in 2013. They divided 60 patients with *H. pylori* into two groups to receive pantoprazole-bismuth-ciprofloxacin with or without N-acetyl cysteine. Per-protocol eradication rates were 60.7% and 70%, respectively.[64] Also, in 2015, Masoodi and others evaluated the effects of 10-day bismuth-based gemifloxacin-containing quadruple therapy. They reported 72.7% per-protocol eradication rate.[53]

In Iran, the rates of *H. pylori* resistance to fluoroquinolones, especially to ciprofloxacin has increased dramatically during the previous 5 years; playing an important role in the failure of this regimen.[10,19]

Azithromycin-Containing Therapy:

During the previous years, four studies have evaluated the efficacy of azithromycin-containing regimens for *H. pylori* eradication, but none of these regimens could achieve acceptable eradication rates.[29,35,44,47] In 2006, Mousavi and colleagues assessed the efficacy of bismuth-based azithromycin-containing regimen in Semnan.[47] Also, in 2009, a subsequent study evaluated the efficacy of the same regimen in Tehran. The *H. pylori* eradication rates were 78% and 68%, respectively.[44] On the other hand, two recent studies evaluated the effects of azithromycin-containing triple therapy. The per-protocol eradication rates were 75% and 77%, respectively.[29,35] Accordingly, azithromycin-containing therapies do not seem to be ideal options for first-line *H. pylori* eradication in Iran.

Treatment Failure:

As we have previously described,[65] failure of *H. pylori* treatment depends on multiple factors related to both the bacterium and the host. In fact, the effects of antibiotics in vivo are not the same as those observed in vitro, because antibiotics must diffuse to the gastric mucosal layer where the bacteria reside. Moreover, low gastric pH may compromise antibiotic

Table 7: The efficacy of second line therapies for *H. pylori* eradication

Year	City	First Regimen	Second Regimen	Number of Patients	Per-protocol Eradication Rate
2001	Tehran[73]	OABM	OTBF	80	90
2003	Tehran[74]	OABM	OABF	90	78.7
2010	Isfahan[75]	OABM	OABC OAzBOf	110 110	74.7 86.7
2012	Sari[37]	Sequential	OABF (F: 7days)	36	82.9
2015	Rasht[52]	OABM	OBTMOf OABCT	104 104	86.7 76
2016	Sari[77]	OABM OABF	OABC OABC	32 31	87 82.7
2016	Sari[79]	Non-bismuth clarithromycin-containing	PAL	61	91.8

O: Omeprazole, Amox: Amoxicillin, B: Bismuth subcitrate, Tetra: Tetracycline, M: Metronidazole, C: Clarithromycin, F: Furazolidone, Of: Ofloxacin, Az: Azithromycin

activity. Most antibiotics have the greatest activity at neutral pH; nevertheless, clarithromycin has especially the greatest activity at higher pH (around 8) and metronidazole has the greatest activity at lower pH (around 6). Thus, clarithromycin is the only antibiotic that benefits from a high pH caused by PPI.[37] Furthermore, sometimes *H. pylori* transforms into coccoid shape, which keeps it from the effects of antibiotics.[66] Also, some strains, including Cag A-negative strains and those carrying Vac As2m2 allele, show resistance to antibiotics.[67] However, the most important factor influencing response to treatment is primary resistance to antibiotics, which is increasing all over the world due to extensive use of antibiotics.[68]

Among host factors, compliance to treatment plays an important role. Patients may not completely adhere to treatment due to adverse effects or combination of multiple drugs in multiple daily doses. Besides, the patient's underlying disease also affects the *H. pylori* eradication rate. Some studies have shown that patients with non-ulcer dyspepsia have lower eradication rates compared with those with PUD.[67,69]

Since low gastric pH lowers the effects of antibiotics, PPIs are administered to increase gastric pH. Most PPIs are metabolized by cytochrome P450 in the liver. Therefore, patients with extensive metabolizing do not attain sufficient PPI levels to achieve optimal pH level for antibiotic effects.[70]

Smoking is also another factor influencing the response to treatment.[71] It reduces gastric mucosal blood flow and increases gastric acid secretion; therefore lowering antibiotics activity.

All the mentioned factors should be kept in mind in patients with treatment failure.

Second-Line Treatment Regimens:

The ideal second-line *H. pylori* eradication therapy is the regimen that can achieve > 80% per-protocol eradication rate.[72] Few studies have addressed second-line therapies in Iran (table 7).

- In 2001, Sotoudehmanesh and colleagues evaluated the effects of 14-day OTBF (O: omeprazole, T: tetracycline, B: bismuth, F: furazolidone) on 80 patients who had previously failed treatment with 2 weeks of omeprazole + amoxicillin + bismuth + metronidazole (OABM) therapy. The per-protocol eradication rate was 90%.[73]
- In 2003, Ebrahimi-Daryani and co-workers conducted a study to evaluate the effects of 14-day bismuth- and furazolidone containing quadruple therapy on 90 patients who had failed treatment with metronidazole-based quadruple therapy. The per-protocol *H. pylori* eradication rate was 78.7%.[74]
- In 2010, 220 patients who had failed treatment with OABM were randomized to receive either OABC (C: clarithromycin) or OBAzOf (Az: azithromycin, Of: ofloxacin). Per-protocol eradication rates were 74.7% and 86.7%, respectively.[75]

Table 8: **Recommended treatment regimens for *Helicobacter pylori* eradication in Iran**

First-line therapeutic options:
- 10- or 14-day clarithromycin-containing triple therapy*
• PPI twice daily + amoxicillin 1g BD + clarithromycin 500 mg BD
- 10-day bismuth-based furazolidone-containing quadruple therapy
• PPI BD + amoxicillin 1g BD + bismuth 240 mg BD + furazolidone 200 mg BD
• PPI BD + amoxicillin 1g BD + bismuth 240 mg BD for 10 days; metronidazole 500 mg BD just over the first 5 days and furazolidone 200 mg BD over the second 5 days
- 14-day bismuth-based clarithromycin-containing quadruple therapy
• PPI twice daily + amoxicillin 1g BD + bismuth 240 mg BD + clarithromycin 500 mg BD
- 14-day hybrid therapy:
• PPI BD and amoxicillin 1 g BD for 14 days and clarithromycin 500 mg BD + tinidazole 500 mg BD just over the last 7 days
- 10-day concomitant regimen:
• PPI twice daily + amoxicillin 1 g BD + clarithromycin 500 mg BD+ metronidazole 500 mg BD for 10 days
Second-line therapeutic options:**
- 14-day bismuth-based quadruple therapies
• PPI BD + amoxicillin 1 g BD + bismuth 240 mg BD + furazolidone 200 mg BD#
• PPI BD + amoxicillin 1 g BD + bismuth 240 mg BD + clarithromycin 500 mg BD
• PPI BD + tetracycline 500 mg BD + bismuth 240 mg BD + furazolidone 200mg BD
- 14-day levofloxacin-based triple therapy
• PPI BD + amoxicillin 1 g BD + levofloxacin 500 mg BD
Third-line therapeutic options:
- The optimal regimen must be chosen according to the pattern of antibiotic susceptibility of *H. pylori* &

BD: Twice a day;
* In case of known *H. pylori* clarithromycin resistance < 15%.
** If antibiotics other than those used in the first-line regimen are used.
# Furazolidone can be used only during the first 7 days.
& Rifabutin-containing triple therapy may also be a suitable option.

- In 2012, Fakheri and colleagues investigated the efficacy of a modified bismuth- and furazolidone-containing 14-day quadruple therapy after failure with classic sequential therapy. The regimen contained furazolidone only during the first 7 days. They achieved 82.9 % per-protocol eradication rate.[52]
- In 2015, Mansour Ghanaei and others investigated the effects of two different 7-day quintuple therapies on 208 patients who had failed previous therapy with OABM regimen. The patients were randomly given OBTMOf or OABCTi (Ti: tinidazole). The per-protocol eradication rates were 86.7% and 76%, respectively.[76]
- In 2016, Fakheri and colleagues assessed the efficacy of 14-day bismuth- and clarithromycin-containing quadruple therapy on two groups of patients who had failed previous therapy with OABF or OABM regimens. The eradication rates were 82.7% and 87%, respectively.[77]
- Also, in 2017, Fakheri and co-workers evaluated the efficacy of 14-day levofloxacin-based triple therapy. They achieved 91.8% per-protocol eradication rate. Of note, the frequency of severe adverse effects was very low (3.2%).[78]

According to Maastricht V Consensus Report, either a bismuth quadruple therapy or a fluoroquinolone-containing triple or quadruple therapy are recommended after failure of standard triple therapy or even after failure of a non-bismuth quadruple regimen.[4] The results of studies performed in Iran are in concordance with the statements of the Maastricht V Consensus Report.

Third-Line Treatment Regimens:

In Iran, no study has dealt with patients who have failed second-line *H. pylori* eradication regimens. According to Maastricht V Consensus Report, after failure of second-line treatment, regimens should be chosen according to the results of culture and susceptibility testing or molecular determination of genotype resistance.[4] However, if culture is not available, fluoroquinolone-containing regimen is

recommended after failure of a second-line treatment with bismuth-containing quadruple therapy. However, in countries with a known high fluoroquinolones resistance, or in case of failure with second-line fluoroquinolone-containing therapies, a combination of bismuth with different antibiotics or a rifabutin-containing rescue therapy should be considered.[4]

Limitations:

The present narrative review has some limitations, including the unavailability of data about the results of *H. pylori* culture in each study, heterogeneity of studies in the number of patients, doses of antibiotics, duration of therapies, kinds of PPIs, and the underlying peptic disorders. These could lead to discrepancies in eradication rates, because higher doses and longer duration of therapy can increase the success rates and the underlying peptic disorder would influence the rate of *H. pylori* eradication. Furthermore, our study was restricted to English reports.

In conclusion, according to our study, among first-line eradication options, bismuth-based furazolidone- or clarithromycin-containing quadruple therapies, hybrid regimen, and concomitant therapy seem to be appropriate options. Also, 10- or 14-day clarithromycin-containing triple therapy can be used if local *H. pylori* resistance to clarithromycin is known to be less than 15% (table 8).

For second-line *H. pylori* eradication, bismuth-based quadruple therapies and 14-day levofloxacin-based triple therapy seem to be suitable options, provided that antibiotics other than those had been used in the first-line regimen. Third-line *H. pylori* eradication regimens have not been addressed in Iranian studies. However, most guidelines recommend treatment according to the results of culture and susceptibility testing (table 8).

Although we limited our investigation to *H. pylori* eradication regimens in Iran, the results are transferrable to any region as long as the patterns of antibiotic resistance are the same.

ETHICAL APPROVAL

There is nothing to be declared.

CONFLICT OF INTEREST

The author declares no conflict of interest related to this work.

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