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ORIGINAL ARTICLE

Global Estimate of Clarithromycin Resistance in Clinical Isolates of *Helicobacter pylori*: a Systematic Review and Meta-Analysis

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SUMMARY

Background: **A high resistance rate to clarithromycin usually leads to failure to eradicate *Helicobacter pylori*. The aim of the present study was to review recent data on *H. pylori* resistance towards clarithromycin in clinical studies worldwide.**

Methods: **PubMed/Medline, Web of Science, and Embase were used for a systematic review from 1 January 2011 to 13 April 2021 to retrieve the clinical trial studies. Data were analyzed according to publication year, age, geographic area, and minimum inhibitory concentration (MIC). Statistical analysis was done by STATA version 14.0 (College Station, Texas).**

Results: **From a total of 4,304 articles, 89 articles related to clinical studies were selected for analysis. The overall *H. pylori* clarithromycin resistance rate was 34.95%. Based on continents, the highest and lowest pooled estimate of the bacterial resistance rates were observed in Asia (35.97%) and North America (7.02%), respectively. The highest and the lowest pooled estimate of *H. pylori* resistance rate to clarithromycin based on country were obtained in Australia (93.4%) and USA (7%), respectively.**

Conclusions: ***H. pylori*** **resistance to clarithromycin in most parts of the world is more than 15%, so it is recommended that each country, after estimating the rate of resistance to clarithromycin, determine the treatment/eradication pattern for *H. pylori* infection.**

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Supplementary Data

Table S1. Characteristics of studies included in the meta-analysis.

First author (year)	Country	Enrollment time	Type of study	Number of patients	Mean age	Number of HP positive	Number of Clar-resistant isolates	Results of MIC (µg/mL)	Clinical Signs
Cosme et al. [1] (2018)	Spain	2013 - 2017	RCT	3,170	NR	3,170	582	> 0.5mg/L	NR
Tay et al. [2] (2012)	Australia	2007 - 2011	RCT	310	53	306	288	≥ 1 µg/mL	NR
Ong et al. [3] (2019)	Korea	2016 - 2018	RCT	125	NR	88	17	> 1mg/L	NR
Liou et al. [4] (2010)	Taiwan	2007 - 2009	RCT	432	48.9	324	39	> 1mg/L	NR
Iwanczak et al. [5] (2014)	Poland	2002 - 2003	RCT	6,565	NR	423	76	> 1 mg/L	DUs = 15 (3.55%) MALT = 1 (0.23%) dysplasia = 3 (0.71%)
Okimoto et al. [6] (2016)	Japan	2012 - 2013	RCT	219	57.4	210	85	> 1 mg/L	DUs = 52 (24.76%) GU = 37 (17.62%)
Liou et al. [7] (2011)	Taiwan	2009 - 2010	Clinical Trial	142	53.7	52	33	≥ 1 µg/mL	PU = 83 (58.45%)
Hsu et al. [8] (2018)	Taiwan	2015 - 2017	RCT	352	54.1	217	30	> 1 mg/L	PU = 152 (43.18%)
Nguyen et al. [9] (2012)	Sweden	2005 - 2006	RCT	222	NR	222	113	> 1 mg/L	NR
Kong et al. [10] (2020)	China	2016 - 2019	RCT	364	47.4	364	210	≥ 1 µg/mL	PU = 65 (17.86%)
Kwon et al. [11] (2019)	Korea	2016 - 2017	Clinical Trial	50	64.7	31	5	> 1 mg/L	PU = 8 (16%) Gastritis = 17 (54.84%)
Chotivitayatarakorn et al. [12] (2017)	Thailand	2015 - 2016	RCT	108	54.2	108	4	NR	NR
Liou et al. [13] (2018)	Australia	2012 - 2017	RCT	451	54.5	411	381	≥ 1 µg/mL	DUs = 48 (11.68%) GU = 58 (14.11%)
Tursi et al. [14] (2012)	Italy	NR	Clinical Trial	119	48.3	73	53	NA	DUs = 8 (10.96%) GU = 5 (6.85%)
Huang et al. [15] (2018)	Taiwan	2015 - 2017	Clinical Trial	70	58.5	39	31	≥ 1 µg/mL	PU = 31 (44.29%) DUs = 8 (20.51%) GU = 25 (64.1%) Gastritis = 27 (69.23%)
Liou et al. [16] (2013)	Taiwan	2009 - 2012	Clinical Trial	135	53.3	96	83	≥ 1 µg/mL	PU = 71 (52.59%)
Pichon et al. [17] (2020)	France	2015 - 2018	Clinical Trial	1,086	51.4	154	28	> 0.5 µg/mL	NR

Table S1. Characteristics of studies included in the meta-analysis (continued).

First author (year)	Country	Enrollment time	Type of study	Number of patients	Mean age	Number of HP positive	Number of Clar-resistant isolates	Results of MIC (µg/mL)	Clinical Signs
Fiorini et al. [18] (2013)	Italy	2010 - 2012	Clinical Trial	254	52.5	236	64	> 0.5 mg/L	PU = 31 (12.2%)
Georgopoulos et al. [19] (2013)	Greece	2010 - 2012	Clinical Trial	510	NR	80	25	> 1 mg/L	NR
Hsu et al. [20] (2014)	Taiwan	NR	RCT	307	54.9	129	17	> 1 mg/L	DU = 57 (44.19%) GU = 106 (82.17%) Gastritis = 66 (51.16%)
Kudo et al. [21] (2012)	Japan	NR	RCT	52	53.8	52	45	≥ 1 µg/mL	GU = 30 (57.69%)
Nishizawa et al. [22] (2015)	Japan	2012 - 2014	RCT	124	60.8	47	17	1 mg/mL	NR
Martos et al. [23] (2014)	Spain	2011 - 2012	Clinical Trial	109	48.5	55	5	≥ 1 µg/mL	PU = 24 (22.02%) dysplasia = 67 (121.82%)
Loffeld et al. [24] (2013)	Netherlands	2004 - 2011	Clinical Trial	925	NR	746	146	> 0.5 µg/mL	DUs = 70 (9.38%) GC = 6 (0.8%) Gastritis = 326 (43.7%)
Long et al. [25] (2018)	China	2016 - 2017	RCT	66	50	66	16	> 2 mg/L	Peptic ulcer = 10 (15.15%) dysplasia = 106 (160.61%)
Zhang et a. [26] (2015)	China	2014	RCT	215	44.3	200	53	NR	Peptic ulcer = 49 (22.79%) dysplasia = 166 (83%)
Tsay et al. [27] (2017)	Taiwan	2013 - 2015	RCT	330	53.9	72	12	> 1 mg/L	Peptic ulcer = 172 (52.12%) Gastritis = 158 (219.44%)
Scaletsky et al. [28] (2011)	Brazil	2003 - 2004	Clinical Trial	217	10.8	45	12	> 1 mg/L	NR
Biernat et al. [29] (2012)	Poland	2008 - 2011	Clinical Trial	178	NR	50	12	> 1 mg/L	DUs = 7 (14%) Gastritis = 114 (228%)
Cosme et al. [30] (2016)	Spain	2012 - 2013	Clinical Trial	240	50	122	18	NR	NR
Caliskan et al. [31] (2015)	Turkey	2012 - 2013	RCT	98	46	98	36	≥ 0.5 µg/mL	NR
Quek et al. [32] (2016)	Vietnam	2015 - 2016	RCT	193	NR	193	165	> 0.5 µg/mL	NR

Table S1. Characteristics of studies included in the meta-analysis (continued).

First author (year)	Country	Enrollment time	Type of study	Number of patients	Mean age	Number of HP positive	Number of Clar-resistant isolates	Results of MIC (µg/mL)	Clinical Signs
Hong et al. [33] (2016)	China	2014	RCT	399	40.2	374	52	NR	NR
Chuah et al. [34] (2016)	Taiwan	2013 - 2015	RCT	164	55.9	48	41	≥ 1 µg/mL	PU = 25 (15.24%) DUs = 37 (77.08%) GU = 52 (108.33%) Gastritis = 66 (137.5%)
Hsu et al. [35] (2015)	Taiwan	2012 - 2015	RCT	440	53	184	19	> 1 mg/L	DUs = 47 (25.54%) GU = 104 (56.52%) Gastritis = 232 (126.09%)
Kuo et al. [36] (2016)	Taiwan	2013 - 2015	Clinical Trial	268	NR	84	37	> 1 mg/L	NR
Bang et al. [37] (2020)	Korea	2018 - 2019	RCT	233	53.5	180	57	> 1 mg/L	PU = 146 (62.66%) GC = 13 (7.22%) Gastritis = 13 (7.22%)
Tai et al. [38] (2019)	Taiwan	NR	RCT	229	54.8	89	13	≥ 1 µg/mL	PU = 26 (11.35%) DUs = 34 (38.2%) GU = 78 (87.64%)
Song et al. [39] (2020)	China	2017 - 2018	RCT	760	41.3	650	218	> 0.5 µg/mL	PU = 85 (11.18%) dysplasia = 675 (103.85%)
Zhou et al. [40] (2014)	China	2008 - 2010	RCT	280	43.4	280	112	> 1 mg/L	NR
Lee et al. [41] (2014)	Korea	2010 - 2013	RCT	332	54.8	36	4	> 1 mg/L	PU = 71 (21.39%) dysplasia = 181 (502.78%) GC = 80 (222.22%)
Wu et al. [42] (2019)	Taiwan	NR	RCT	177	55.5	67	9	> 1 mg/L	DUs = 33 (49.25%) GU = 30 (44.78%) Gastritis = 102 (152.24%)
Mori et al. [43] (2019)	Japan	2014 - 2015	Clinical Trial	55	48.9	38	31	> 8 mg/L	NR
Wang et al. [44] (2016)	China	NR	Clinical Trial	323	40	42	10	> 1 mg/L	NR

Table S1. Characteristics of studies included in the meta-analysis (continued).

First author (year)	Country	Enrollment time	Type of study	Number of patients	Mean age	Number of HP positive	Number of Clar-resistant isolates	Results of MIC (µg/mL)	Clinical Signs
Ji et al. [45] (2016)	China	2009 - 2014	RCT	29,034	48.18	9,687	1,720	≥ 1 µg/mL	NR
Ang et al. [46] (2015)	Singapore	2011 - 2014	RCT	462	48.6	106	19	≥ 1 mg/ml	NR
Chung et al. [47] (2012)	Korea	2010 - 2011	RCT	159	49.6	93	17	> 1.0 µg/Ml	NR
Xie et al. [48] (2018)	China	2013 - 2014	RCT	431	40.22	288	53	> 1.0 µg/Ml	NR
Auesomwang et al. [49] (2018)	Thailand	2013 - 2014	RCT	120	49.6	90	9	> 1 mg/L	NR
Yang et al. [50] (2017)	Taiwan	NR	RCT	797	NR	73	8	NR	NR
Zhou et al. [51] (2015)	China	2013 - 2014	RCT	1,050	43.83	1,050	464	> 1.0 µg/Ml	NR
Luo et al. [52] (2020)	China	2018 - 2019	Clinical Trial	112	47.1	112	85	> 0.5 mg/L	NR
Yu et al. [53] (2019)	China	2018	RCT	200	47.9	200	188	> 0.5mg/L	NR
Ji et al. [54] (2020)	China	2019	RCT	420	47.58	164	109	> 1 µg/mL	NR
Yang et al. [55] (2020)	China	2017 - 2018	RCT	133	NR	101	89	> 0.5mg/L	NR
Furuta et al. [56] (2013)	Japan	2009 - 2013	Clinical Trial	180	56.2	110	101	≥ 1 µg/mL	NR
Suzuki et al. [57] (2020)	Japan	2018 - 2019	RCT	335	61.25	335	82	≥ 1 µg/mL	NR
Tai et al. [58] (2015)	Taiwan	2012 - 2014	RCT	200	NR	68	2	≥ 1 µg/mL	NR
Liou et al. [59] (2013)	Taiwan	2009 - 2011	RCT	900	53.26	552	55	≥ 1 mg/L	NR
Bontems et al. [60] (2011)	France	2007 - 2009	Clinical Trial	165	10.4	165	27	≥ 1.0 µg/mL	NR
Schwarzer et al. [61] (2015)	Sweden	2009 - 2011	Clinical Trial	232	11.2	209	30	≥ 1.0 µg/mL	NR
Liou et al. [62] (2015)	Taiwan	2012 - 2014	RCT	1,300	49.25	812	81	≥ 1 mg/L	NR
Kang et al. [63] (2021)	Korea	2008 - 2019	RCT	257	58.3	257	63	≥ 1.0 µg/mL	NR
Tsay et al. [64] (2014)	Taiwan	2009 - 2010	RCT	122	51.6	95	10	> 1 µg/mL	NR
Fiorini et al. [65] (2017)	Italy	2016	Clinical Trial	116	49	80	64	> 0.5 mg/L	NR
Georgopoulos et al. [66] (2016)	Greece	2012 - 2015	Clinical Trial	353	52.15	303	84	> 0.5 mg/L	NR
Tepeš et al. [67] (2016)	Slovenia	2011 - 2014	RCT	356	48.4	356	36	> 0.5 mg/l	NR
Chen et al. [68] (2019)	China	2017 - 2018	RCT	491	44.25	382	134	> 1 µg/mL	NR
Song et al. [69] (2016)	China	2013 - 2015	Clinical Trial	230	42.9	230	110	> 0.5 mg/L	NR
Fiorini et al. (2018)	Italy	2016 - 2017	Clinical Trial	495	51.95	378	126	> 0.5 mg/L	NR
Alsohaibani et al. [70] (2015)	Saudi Arabia	2011 - 2014	RCT	232	46.94	85	17	≥ 1 µg/mL	NR
Auttajaroon et al. [71] (2019)	Thailand	2017	RCT	100	54	69	9	NR	NR

Table S1. Characteristics of studies included in the meta-analysis (continued).

First author (year)	Country	Enrollment time	Type of study	Number of patients	Mean age	Number of HP positive	Number of Clar-resistant isolates	Results of MIC (μg/mL)	Clinical Signs
Infante et al. [72] (2012)	Spain	2010 - 2011	RCT	239	53	89	18	> 1 mg/L	NR
Xie et al. [73] (2018)	China	2013 - 2014	RCT	384	41.55	205	70	≥ 1.0mg/L	NR
Dong et al. [74] (2015)	China	2014 - 2014	Clinical Trial	297	NR	45	18	≥ 1 μg/mL	NR
Murakami et al. [75] (2013)	Japan	2009 - 2011	RCT	204	60.3	110	95	≥ 1 μg/mL	NR
Hsu et al. [76] (2011)	USA	2008 - 2010	Clinical Trial	117	54.3	57	4	≥ 1 μg/mL	NR
Pih et al. [77] (2020)	Korea	2018 - 2020	Clinical Trial	66	58	66	11	≥ 1 μg/mL	NR
Song et al. [78] (2016)	China	2013 - 2015	Clinical Trial	132	44.4	72	40	> 0.5mg/L	NR
Liou et al. [79] (2016)	Taiwan	2012 - 2015	RCT	600	54.55	187	112	≥ 1 mg/L	NR
Huang et al. [80] (2012)	China	2008 - 2010	RCT	169	52.56	79	9	NR	NR
Pan et al. [81] (2019)	China	2014	RCT	NR	48.97	467	134	≥ 1 μg/mL	NR
Byambajav et al. [82] (2019)	France	2013 - 2017	RCT	270	37.6	131	49	> 0.25 mg/L	NR
Hsiang et al. [83] (2013)	New Zealand	2012	Clinical Trial	592	60.6	73	12	NR	NR
Chen et al. [84] (2015)	Taiwan	2013 - 2014	RCT	175	53.35	124	19	> 1μg/mL	NR
Song et al. [85] (2016)	China	2014 - 2015	Clinical Trial	200	44.8	147	66	≥ 1 mg/L	NR
Georgopoulos et al. [86] (2017)	Greece	2015 - 2016	RCT	155	50.5	135	35	> 1μg/mL	NR
Yu et al. [87] (2019)	China	2018	RCT	160	47.65	145	46	> 0.5 mg/L	NR
Yang et al. [88] (2015)	Taiwan	2010 - 2013	RCT	618	53.45	617	211	> 1 mg/L	NR

RCT - randomized controlled trial, NR - not report, PU - peptic ulcer, DUs - duodenal ulcers, GU - gastric ulcer, GC: gastric cancer.

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