Review - Treatment of Helicobacter pylori Infection 2020

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Anthony O'Connor[1], Takahisa Furuta [2] , Javier P. Gisbert[3] and Colm O'Morain[1]

1. Department of Gastroenterology, Tallaght University Hospital/Trinity College Dublin, Ireland.
2. The Center for Clinical Research, Hamamatsu University School of Medicine, Hamamatsu, Japan.
3. Gastroenterology Unit, Hospital Universitario de La Princesa, Instituto de Investigación Sanitaria Princesa (IIS-IP), Universidad Autónoma de Madrid (UAM), Centro de Investigación Biomédica en Red de Enfermedades Hepáticas y Digestivas (CIBEREHD), Madrid, Spain.

Correspondence: Dr. Anthony O'Connor
Department of Gastroenterology
Tallaght University Hospital
Belgard Road, Tallaght
Dublin, Ireland D24NR0A
Email: jpoconno@tcd.ie
Telephone: +353 858798996
Facsimile: +353 14143851

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Abstract

This review summarizes important studies regarding *Helicobacter pylori* therapy published from April 2019 to April 2020. The main themes that emerge involve studies assessing antibiotic resistance and there is also growing momentum behind the utility of vonoprazan as an alternative to proton pump inhibitor (PPI) therapy and also bismuth-based regimens as a first-line regimen. Antibiotic resistance is rising wherever it is being assessed and clarithromycin resistance in particular has reached a point where it may no longer be a viable therapy without previous testing in many regions of the world. The evidence for the efficacy of a bismuth-based quadruple therapy as a first-line therapy is now very clearly established, and there is substantial evidence that it is the best performing first-line therapy. The utility of vonoprazan as an alternative to PPI therapy, especially in resistant and difficult-to-treat groups, has also been considered in great detail this year, and it may offer an opportunity in the near future to reduce the problem of antibiotic resistance.

Key words: triple therapy, bismuth, vonoprazan, dual therapy, sequential therapy, hybrid therapy, antibiotic resistance.

Introduction

The past year has been another busy period for research publications on the treatment of *Helicobacter pylori*. This review summarizes important studies regarding *H. pylori* therapy published from April 2019 to April 2020. The epicenter of studies has continued to shift from Europe to Asia and now Africa also. The main themes that emerge involve studies assessing antibiotic resistance and there is also growing momentum behind the utility of vonoprazan as an alternative to proton pump inhibitor (PPI) therapy and also bismuth-based regimens as a first-line regimen. Data regarding specific regimens are explored in greater detail below. Certain aspects regarding the safety of treatments for *H. pylori* infection such as the potential increase in resistance to bacteria other than *H. pylori* and the impact of eradication therapy on the gut microbiota are outside the scope of this review.

Dual therapy

It has been proposed that giving longer courses of less complex dual therapies, *e.g.* PPI and amoxicillin four times a day, can also improve compliance and eradication rates. One study on a 14-day high-dose dual therapy in a region of high antibiotic resistance prevalence in China showed that it was both effective and safe for first-line treatment with an eradication rate of 92.5% and a low adverse event rate of 7.5% [1]. The addition of bismuth was not helpful in this study other than for smokers. A similar study also from China reported 88% eradication with 21% adverse events [2]. In Turkey, the eradication rate for a 14-day dual therapy was 91% with no adverse events [3].

Triple therapy

Triple therapy (TT) remains the standard of care in the published international guidelines of the European Helicobacter and Microbiota Study Group (EHMSG) in areas of low clarithromycin resistance [4]. Two studies from the Americas looked at the outcomes and both showed poor eradication rates albeit with divergent results for TT with clarithromycin compared to levofloxacin [5,6]. In the US, 78% of patients receiving clarithromycin-based TT achieved eradication, compared

to 49% with levofloxacin-based TT [5]. On the other hand, in Argentina 75% of patients were cured with clarithromycin TT but 93% achieved eradication with levofloxacin TT [6]. Interestingly, a Japanese study, where eradication rates with clarithromycin TT were evaluated over time during the period 2013-2018, showed that treatment success improved markedly over that time period, coinciding with the use of the potassium competitive acid blocker (P-CAB), vonoprazan, becoming the preferred means of acid inhibition over PPI [7]. This will be explored in more detail later in this review.

Increasing treatment duration has been proposed as a means of improving eradication rates with TT but this was not borne out in a Korean trial comparing 7- with 14-day regimens which reported similar poor success rates of 64% and 66%, respectively [8]. A meta-analysis of 45 studies from Turkey was in agreement with just 60% achieving eradication with both 7- and 14-day regimens [9]. In Indonesia, however, a 14-day TT regimen was significantly more effective than a 10 day TT (87% vs 68%) [10]. Two meta-analyses addressed the question of whether TT with clarithromycin or metronidazole was more effective [11,12]. Both concluded that the regimens were equally, poorly efficacious with a trend in more recent years in favour of metronidazole TT since it is more effective following the rise in clarithromycin resistance . A study of 7,896 subjects from Israel examined the different PPIs used for eradication therapy and found esomeprazole to be associated with a greater proportion of successful eradication than other PPIs (85 vs. 77%) [13]. Data from Tanzania suggested that antibiotic resistance and poor adherence are the two factors most closely associated with TT failure [14]. Again in Africa, in Ethiopia, a study showed that developing an adverse drug reaction on TT reduced the chances of eradication, most likely via an inhibiting effect on adherence to therapy [15]. The presence of type 2 diabetes was shown in another study to also be associated with TT failure with 74% eradication in the diabetes mellitus group compared to 85% in the non-diabetic group [16].

Hybrid, sequential and concomitant non-bismuth therapies

Original research on concomitant, sequential, and hybrid therapies has been sparse this year. In Egypt, one study showed very high eradication rates of: 90% with 10-day sequential therapy, 97% with 14-day sequential therapy, and 63% for standard 7-day TT [17]. Elsewhere, in Myanmar, 10-day sequential therapy was compared to 14-day concomitant therapy and found to be equally efficacious (82% vs 79% eradication) with lower costs [18]). Again with a view to foresee cost control, safety and adherence, a study from one Italian group who pioneered sequential therapy showed 10-day regimens to be of equal efficacy to 14-day regimens (87% vs 90% eradication) [19]. Data from Korea collated over the course of the last decade suggested a much lower eradication rate of 70% although it is notable that this rate did not decline in spite of rising antibiotic resistance rates [20]. A non-bismuth concomitant quadruple therapy (QT) where three antibiotics are given at once for 10 days was used in Greece and found to have an 87% eradication rate, which did not improve when treatment was extended to 14 days [21]. The reverse hybrid therapy (PPI plus amoxicillin for 14 days, with clarithromycin plus metronidazole added for the initial 7 days) is considered to be a means of combining the benefits of the sequential and concomitant regimens. A trial from Taiwan this year compared this to concomitant therapy and reported comparable eradication rates (95% *vs* 93%) with a lower frequency of adverse events [22]. Ten-day concomitant therapy performs well on cost-effectiveness analysis with esomeprazole, as characterised by the lowest cost-effectiveness analysis ratio (CEAR) (179€), followed by the same regimen using pantoprazole (183€) compared to a hybrid regimen which, although equivalent in eradication rate, had a slightly higher CEAR (187€). In contrast, the sequential regimen was not considered cost-effective (CEAR: 216€) [23].

Antibiotic resistance

An unprecedented number of studies last year reported on the important topic of antimicrobial resistance of *H. pylori* strains [24-60]. These are outlined in Table 1. A great degree of divergence

was observed in antibiotic resistance rates throughout the world with an unacceptably high level of clarithromycin resistance however, being a recurring theme, with only 8 of 33 studies reporting a resistance rate less than the 15% threshold at which the Maastricht guidelines recommend clarithromycin-based TT to be abandoned [4]. A meta-analysis of 27 studies, including 4,825 patients treated with both clarithromycin- and metronidazole-containing regimens illustrated the clinical importance of monitoring resistance rates, noting low overall eradication rates for both regimens, 75% for clarithromycin and 72% for metronidazole [11]. In areas with low metronidazole and high clarithromycin resistance rates, metronidazole had a significantly higher eradication rate (92% vs. 71%) while even in areas with high metronidazole and low clarithromycin resistance rates, the eradication rate with clarithromycin-based TT was only 73%. Together these data call into question the continuing viability of clarithromycin as a mainstay of *H. pylori* eradication treatment without previous testing.

Personalised treatment

A series of articles published in the journal *Helicobacter* this year addressed the question of personalised or tailored treatment, which had hitherto been considered in a second-line context but is now gaining interest as a first-line intervention. A meta-analysis looked at 2,890 patients submitted to endoscopy and *H. pylori* culture, reporting cure rates using the antibiotic to which susceptibility was detected, with 72% in patients harbouring clarithromycin-susceptible strains, 93% in patients harbouring metronidazole-susceptible strains, and 84% in patients harbouring a levofloxacin-susceptible strain [61]. In Korea, a study used personalised treatment, after testing with dual priming oligonucleotide (DPO) polymerase chain reaction (PCR) and asking for a previous antibiotic exposure in order to predict resistance. The tailored first-line treatment based on antibiotic susceptibility, reported an eradication rate of 92% [51]. Another first-line study also conducted in Korea involved administration of either a 7-day clarithromycin-containing TT, a 7-day moxifloxacin-containing TT, or a 7- or 14-day bismuth quadruple therapy (BQT) based on the MIC of

the various antibiotics and reported 93% eradication with common adverse events such as epigastric pain, nausea, and vomiting occurring less commonly than with empirical therapies [52]. A multicentre study of 467 *H. pylori*-positive patients assigned to receive tailored therapy vs. empirical therapy, revealed eradication rates for tailored TT, traditional bismuth-containing QT, and tailored bismuth-containing QT of 67%, 64%, and 86%, respectively [53]. Beyond susceptibility-guided treatment, another means of personalising treatment is based on the CYP2C19 status. Genetic differences in the activity of the enzyme CYP2C19 (the homozygous EM, heterozygous EM (HetEM), and poor metabolizer) dictate how effective PPI will be. A group in Colombia found cure rates to improve from 84% to 92% in a group consisting mainly of rapid metabolisers when omeprazole doses were chosen based on the CYP2C19 polymorphism, which may be useful particularly in populations with a broad spread of CYP2C19 polymorphisms [62].

Bismuth-based therapy

Bismuth-based therapies were looked at in great detail this year both as primary and second-line therapies. Most of the studies examined bismuth as part of a BQT regime with a PPI, a tetracycline-class antibiotic and another antibiotic. One study of 118 patients treated with a BQT regimen containing amoxicillin and doxycycline reported 90% eradication with 97% adherence to therapy [63]. A retrospective analysis of American patients suggested a 14-day regimen with bismuth and tetracycline to be the most effective first-line eradication treatment in that country, with an 87% eradication rate [64]. A three-in-one single capsule formulation containing bismuth subcitrate, metronidazole and tetracycline (Pylera®) may be used with PPI for *H. pylori* eradication purposes, and a Spanish study of 200 patients using this treatment achieved cure in 91% of patients with 96% adherence [65]. A systematic review and meta-analysis on Pylera® concluded that a 10-day treatment achieved an effective eradication rate of approximately 90% both in first- and second-line therapy, regardless of the type and dose of the PPI, in patients with clarithromycin- or metronidazole-resistant strains, and in those previously treated with clarithromycin [66]. It has been

proposed that H_2-receptor antagonists induce less bismuth absorption and, as a consequence, less systemic toxicity than PPIs. With this in mind, a pilot randomised clinical trial was conducted looking at eradication rates for patients receiving ranitidine rather than a PPI alongside Pylera® and found similar eradication rates (91%) compared to 94% in those receiving PPI although intolerance levels were the same in this small pilot cohort [67].

Two studies compared such therapies with standard concomitant QTs and found comparable results between the two regimes. A study from Spain compared a 10-day BQT with a 14-day standard QT arm, and found a slightly superior eradication for the bismuth group, 88% *vs* 86% [68]. A Korean cohort where both arms received a 14-day therapy reported 88% eradication in the bismuth group and 79% in the QT group [69]. Two trials compared BQT to susceptibility-guided treatment and revealed very high levels of eradication in both arms in both trials, ie a study of 150 patients in Korea reporting 96% eradication for patients both with a tailored treatment and a BQT, and a separate group in China reported 97% for both regimens [70,71]. A study in China looking at minocycline in combination with amoxicillin vs metronidazole found the best cure rates for amoxicillin with 86% eradication in a 14-day BQT compared to 77% when metronidazole was used and 72% when amoxicillin and clarithromycin were used in BQT without minocycline [72]. The duration of therapy has obvious implications in matters like cost of and adherence to therapy, and a study in Turkey showed that BQT could be shortened from 14 to 10 days without weakening the success rate [73]. Another factor influencing adherence is whether or not the tablets can be taken once daily, and in the ONCE trial in Thailand, a once-daily treatment regimen containing levofloxacin, modified-release clarithromycin, bismuth and PPI reported 94% eradication when used for 14 days compared to 84% for a 7-day therapy [50].

A novel and very interesting use of bismuth has been as an adjunct to standard TT. A large, high-quality study from the European Registry on *H. pylori* Management (Hp-EuReg) on 1,141 patients receiving this regimen showed cure in 93% of the patients, with 36% reporting adverse events,

three-quarters of which were mild and self-limiting [74,75]. A smaller Chinese study on 216 patients compared standard TT with and without bismuth and reported similar eradication rates, 98% for the group with bismuth and 95% without [76].

Bismuth remains a useful second-line option and a study in Korea looking at 15 years of data for the drug in treatment failures suggests an overall eradication rate of 79% with no significant changes over the period in question (2003 to 2018) and adverse events in 57% of patients [77]. Another Korean study showed even better results with 93% of second-line patients using bismuth-based therapy with twice daily dosing being equally efficacious as four times daily dosing [78]. In China, a study on BQT used as a rescue therapy comparing amoxicillin plus berberine vs. tetracycline plus furazolidone found similar eradication rates (76% vs 77%) with a significantly lower rate of adverse events in the amoxicillin and berberine group [79]. The European Registry on *H. pylori* Management (Hp-EuReg) reported on penicillin-allergic patients and found excellent eradication rates for bismuth as both first-line (91%), second-line (78%) and third-line (75%) therapies in this cohort [80]. A Chinese study also on penicillin-allergic patients reported 87% eradication for bismuth-based therapy with tetracycline and metronidazole [81]. The antibiotic furazolidone, to which resistance remains uncommon, may also be used as part of a QT with a Chinese group reporting 10-day and 14-day regimens achieving eradication rates of 94% and 98% respectively, with adverse drug reactions seen in 8.2% [82].

Vonoprazan

Vonoprazan is the first clinically available P-CAB [83]. Vonoprazan can attain more potent gastric acid inhibition in comparison to PPIs [84, 85]. The pH $\geq$4 and $\geq$5 holding-time ratios achieved by vonoprazan (20 mg twice daily on day 7 of the treatment) were 100% and 99%, respectively [82]. Moreover, vonoprazan can attain pH 7 in the stomach within approximately 3 hours of the initial dosing of 20 mg [85]. Therefore, vonoprazan can create the ideal pH condition in the stomach for eradication of *H. pylori* from day 1 of the eradication therapy. Since 2015, when vonoprazan was

used clinically in Japan, the eradication therapy has dramatically changed. The current most popular standard regimen for *H. pylori* eradication in Japan is the triple regimen with vonoprazan (20 mg b.i.d.), amoxicillin (750 mg b.i.d.) and clarithromycin (200 mg or 400 mg b.i.d.) for 7 days, while regimens used outside of Japan have been changed from the TT to non-bismuth quadruple therapies or BQTs [86,87].

As the first-line therapy, Ashida *et al.* reported that the eradication rate attained by a triple regimen with vonoprazan (20 mg), amoxicillin (750 mg), and clarithromycin (200-400 mg) twice daily for 7 days was 91% (427/468) [88]. Kusunoki *et al.* reported an eradication rate of 92% (384/415) with the same vonoprazan-containing regimen, while eradication rates attained by the PPI-containing regimens were 85% (57/67) when esomeprazole was used, 85% (384/454) when lansoprazole was used, and 82% (341/415) when rabeprazole was used [89]. Saito *et al.* compared vonoprazan and esomeprazole as first-line therapies and reported that the vonoprazan-based regimen attained higher eradication rates than the esomeprazole-based regimen [90]. Takara *et al.* also reported the superiority of vonoprazan as first-line therapy in comparison to PPIs [91]. Lyu *et al.* performed a systematic search and reported that the efficacy of vonoprazan-based TT was superior to that of PPI-based TT for first-line *H. pylori* eradication [92]. Ierardi *et al.* summarised three prospective studies comparing vonoprazan and PPI as first-line therapies and confirmed that vonoprazan was better than conventional PPIs for *H. pylori* treatment in every case [93]. Deguchi *et al.* demonstrated that a change of acid inhibitor from PPI to vonoprazan increased the eradication rates of *H. pylori* in Japan based on the analysis of a nationwide claims database including >1.6 million patients [94]. In summary, it can be concluded that vonoprazan is superior to PPI as first-line therapy with amoxicillin and clarithromycin. Finally, Shinmura *et al.* reported that the eradication rates by the vonoprazan-based regimens could be further improved when antimicrobial agents were selected based on susceptibility testing [95].

Concerning second-line therapy, Ashida *et al.* reported that the eradication rate attained by the triple regimen including vonoprazan (20 mg), amoxicillin (750 mg)(, and metronidazole (250 mg) twice daily for 7 days was 95% (42/44) [88]. However, Saito *et al.* demonstrated that there was no significant difference between vonoprazan and esomeprazole in the second-line eradication rate [90]. Sue *et al.* compared a vonoprazan-based third-line therapy consisting of vonoprazan (20 mg), amoxicillin (750 mg), and sitafloxacin (100 mg) b.i.d. for 7 days with a PPI-based third-line therapy and found that the vonoprazan therapy was superior [96]. In summary, it can be concluded that vonoprazan is equal or superior to PPIs in second- and third-line therapies.

Dual therapy with PPI and amoxicillin has been recently proposed to improve eradication rates. In this dual therapy, amoxicillin and PPI are prescribed three (t.i.d.) or four (q.i.d.) times daily for at least two weeks [97-102]. However, b.i.d. dosing of vonoprazan (20 mg) could attain the potent acid inhibition from day 1 as noted above [93,94]. Furuta *et al.* reported that dual therapy with vonoprazan (20 mg) b.i.d. and amoxicillin (500 mg) t.i.d. for 1 week attained a 93% eradication rate, which was not inferior to the TT with vonoprazan (20 mg), amoxicillin (750 mg) and clarithromycin (200 mg) b.i.d. for 1 week [103]. Suzuki *et al.* showed that dual therapy with vonoprazan (20 mg) and amoxicillin (750 mg) b.i.d. for 7 days attained almost the same eradication rate as vonoprazan (20 mg), amoxicillin (750 mg), and clarithromycin (200 mg) b.i.d. for 7 days [104]. Therefore, when vonoprazan is used as the acid inhibitor, dual therapy with amoxicillin can be one of the standard therapies in Japan.

There are clinically important merits for dual therapy with vonoprazan and amoxicillin, especially because it allows to avoid clarithromycin. First, because clarithromycin is a well-known inhibitor of p-glycoprotein (p-Gp) and cytochrome P450 3A4 (CYP3A4), the interaction between clarithromycin and substrates of P-Gp and CYP3A4 is of concern [105,106]. Furthermore, clarithromycin increases plasma levels of the substrates of CYP3A4 and MDR1, such as statins, cyclosporine, warfarin and triazolam [107-110]. Clarithromycin is also known to increase the risk of elongation of the QT

interval [111], which constitutes a risk of sudden death by arrhythmia [112]. Thirdly, macrolide antibiotics are known to stimulate the intestinal peristalsis, which may lead to diarrhoea during the eradication treatment [113]. Although these adverse events are relatively infrequent, the avoidance of clarithromycin might contribute to their reduction.

As noted above, the potent acid inhibition attained by vonoprazan improves the eradication rates of *H. pylori* infection in comparison with PPIs. However, current data about vonoprazan has come only from Eastern Asia. Therefore, its strong power needs to be confirmed outside this geographic area in Western countries and should be related to the different local antibiotic resistance rates [93]. Usefulness of vonoprazan in other regimens should also be tested.

Reinfection

A large-scale multicentre, prospective open cohort observational study in China reported an annual reinfection rate after successful eradication treatment of 1.5% per person-year and this reinfection was independently associated with several risk factors, namely membership of a minority group, a lower level of education, a family history of gastric cancer, and residence in Western or Central China [114].

Probiotics and other adjuncts

In *H. pylori* eradication regimens, probiotics are proposed to decrease side effects, improve compliance and thereby increase eradication rates. A network meta-analysis of 40 studies with 8,924 patients performed this year showed a higher eradication rate and lower incidence of total side effects in the probiotic group compared to controls. Further analysis showed that prolonged use of probiotics before, throughout and after treatment improved eradication rates and that probiotics combined with BQT was the best combination [115]. Lactobacilli were shown in that meta-analysis to be the best choice of probiotic strains and two studies this year even investigated *Lactobacillus reuteri* along with PPI as an alternative to antibiotics for *H. pylori* eradication. One trial in Romania, conducted on 23 patients with functional dyspepsia, reported an eradication rate of 65% [116].

However, in a group in Italy, cure was only achieved in 3 out of 24 patients (12%) [117]. Aside from Lactobacilli, two other studies this year showed small beneficial adjuvant effects for a two-bacterial-strain formula, containing *Bifidobacterium animalis lactis* BB12 and *Enterococcus faecium* L3, and another for *Saccharomyces boulardii* [118,119].

Conclusion

There have been many studies pertaining to *H. pylori* eradication treatment in the published literature over the last 12 months, often with diverse results, although several broad themes have emerged. Bismuth-based therapies continue to show a clear advantage for first-line therapy. In addition, there is a crisis in rising antibiotic resistance rates. Clarithromycin resistance rates in almost all regions have now passed the point where clarithromycin-based TT cannot be considered without previous testing and it is time for global clinical practice to reflect this. Vonoprazan is a very promising emerging option for several reasons including the fact that it may offer the opportunity to improve the resistance problem and should be trialled in more regions in the coming years.

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Table 1. *Helicobacter pylori* resistance to antibiotics in the studies published during the last year worldwide

Author	**N**	**Region**	**AMO %**	**CLA %**	**MET %**	**QUINOLONE %**	**TET %**	**RIF %**	**FUR %**
Europe									
Saracino [24]	739	Italy	-	37.8	33.6	(LVX) 25.6	-	-	-
Palmitessa [25]	92	Italy	-	37.7	26.2	(LVX) 16.4	-	-	-
Fernández-Reyes [26]	99	Spain	0	12.1	24.2	(LVX) 13.1	0	-	-
Morilla [27]	1604	Spain	-	19	40	(LVX) 17	-		
Bluemel [28]	1851	Germany	-	11.3	-	(LVX) 13.4	2.5	-	-
Dumitru [29]	90	Romania	-	20	-	30	-	-	-
Gemilyan [30]	55	Armenia	-	3.6	79.4	-	-	-	-
Korona-Glowniak [31]	35	Poland	-	14.3	31.4	(LVX) 11.4	-	25.7	-
Asia									
Hashemi [32]	157	Iran	14.6	24.2	43.9	(CIP) 21.7	20.4	-	-
Kageyama [33]	208	Japan	13	48	49	-	-	-	-
Eed [34]	200	Saudi Arabia	-	39.9	-	8.4	-	-	-
Lee [35]	580	Korea	9.5	17.8	29.5	(LVX) 37 (CIP) 37	0	-	-

Tuan [36]	55	Cambodia	9.1	25.5	96.4	(LVX) 67.3	0	-	-
Haddadi [37]	128	Iran	35.5	7.2	70.1	-	8.2	-	-
Hamidi [38]	80	Iran	30	22	68	(LVX) 28	16	50	-
Shoosanglertwijit [39]	1894	Thailand	0	10.7	14.2	(CIP) 21.43 (LVX) 0	0	-	-
Gao [40]	111	China	5.5	42.1	-	41.7	12.9	-	-
Rezaei [41]	73	Iran	-	23	45	-	-	-	-
Mujtaba [42]	40	Pakistan	11.1	22.2	33.3	(CIP) 55.5	-	-	-
Seo [43]	431	Korea	-	21.3	-	-	-	-	-
Liu [44]	804	China	1.2	19.0	78.4	(LVX) 23.3	2.3	1.7	-
Farzi [45]	68	Iran	30.9	33.8	82.4	(LVX) 27.9	4.4	-	-
Hanafiah [46]	59	Malaysia	-	35.6	59.3	(LVX) 25.4	-	-	-
Wang [47]	100	China	9.0	31.0	78.0	(LVX) 56.0	15.0	-	-
Chang [48]	203	Korea	-	17.4	-	-	-	-	-
Shetty [49]	113	India	7.1	20.4	81.4	(LVX) 54.9	5.3	-	-
Auttajaroon [50]	100	Thailand	-	13	62.8	26.0	-	-	-
Kwon [51]	31	Korea	-	16.1	6.5	-	-	-	-
Lee [52]	69	Korea	6.7	31.0	41.8	(MOX) 39.2	-	-	-

Pan [53]	467	China	-	26.1	96.8	(LVX) 28.7	-	-	-
Africa									
Mabeku [54]	140	Cameroon	97.1	13.6	97.9	-	2.9	-	-
North, Central and South America									
Miftahussurur [55]	63	Dominican Republic	1.6	3.1	82.8	(LVX) 35.9 (SIT) 0	0	0	0
Ortiz [56]	189	Honduras	10.7	11.2	67.9	(LVX) 20.9	-	-	-
Arévalo-Jaimes [57]	126	Colombia	-	38.1	-	-	-	-	-
Arenas [58]	69	Chile	-	26	-	-	-	-	-
Parra-Sepúlveda [59]	1435	Chile	4.2	29.2	37.5	(LVX) 20.8	1.4	-	-
Oporto [60]	44	Chile	11.3	40.9	81.8	(LVX) 43.1	13.6	-	-

* Meta-analysis AMO = amoxicillin, CLA = clarithromycin, MET = metronidazole, TET = tetracycline, RIF = rifabutin, FUR = furazolidone, LVX = levofloxacin, CIP = ciprofloxacin, MOX = moxifloxacin, SIT = sitafloxacin