health
Department:
Health
REPUBLIC OF SOUTH AFRICA

South African

National Essential Medicine List
Hospital Level Medication Review Process
Component: Alimentary

MEDICINE MOTIVATION:

1. Executive Summary

Date: 4 June 2020
Medicine (INN): Clarithromycin + Amoxicillin + Proton pump inhibitor
Medicine (ATC): J01FA09 + J01CA04 + A02BC
Indication (ICD10 code): K25.0-7/K25.9/K26.0-7/K26.9/K27.0-7/K27.9 + (B96.8)
Patient population: Patients diagnosed with *Helicobacter pylori* infection
Prevalence of condition: In developing countries about 80% of adults are infected with Helicobacter pylori.
Level of Care: Secondary level of care
Prescriber Level: Medical officer, doctor
Current standard of Care: Proton pump inhibitor + Metronidazole + Amoxicillin; if penicillin allergy present or resistance substitute with azithromycin
Efficacy estimates: (preferably NNT): Not possible to calculate from available evidence.
Motivator/reviewer name(s): Gillian Watermeyer, Renier Coetzee
PTC affiliation: Western Cape Provincial Pharmacy and Therapeutics Committee

2. Name of author(s)/motivator(s)

Gillian Watermeyer, Renier Coetzee

3. Author affiliation and conflict of interest details

Primary reviewer:

- Gillian Watermeyer: Division of Gastroenterology, Department of Medicine, Groote Schuur Hospital and University of Cape Town; co-opted expert supporting the Adult Hospital Level Committee (2017-2020); Conflicts declared include: Sponsorship for travel, Honoraria for speaking at meetings, and Member of advisory boards for various pharmaceutical companies (Abbvie, Takeda, Adcock Ingram, Janssen).

Secondary reviewer:

- Renier Coetzee: School of Pharmacy, University of the Western Cape, Cape Town, South Africa; Adult Hospital Level Committee (2017-2020); no applicable conflict of interest to declare.

4. Background

Helicobacter pylori infection is one of the most prevalent gastro intestinal infections worldwide (Malfertheiner et al, 2002).[1] In developed countries, the prevalence is about 20% to 50%, while in developing countries about 80% of adults are infected (Everhart et al., 2000).[2]

The treatment of gastric ulcer disease should aim to eradicate the infection and decrease acid production. This causes a decrease in peptic ulcer recurrence and then a decrease in complications like bleeding, perforation and malignancy development.

Current standard of care: The current standard treatment guidelines (2019) recommend triple therapy for the management of patients diagnosed with peptic ulcer disease associated with *H. pylori* infection. The first-line treatment consists of a proton pump inhibitor (PPI), amoxicillin and metronidazole.

Proton pump inhibitors (PPIs)
PPI, e.g.:
Lansoprazole, oral, 30 mg 12 hourly for 7 days.
AND
H. PYLORI ERADICATION
Amoxicillin, oral, 1 g 12 hourly for 7 days.
OR
For severe penicillin allergy:
Azithromycin, oral, 500 mg daily for 3 days.

AND
Metronidazole, oral, 400 mg 12 hourly for 7 days.
Failure of *H. pylori* eradication: Discuss with specialist.

SAGE motivation: The South African Gastroenterology Society (SAGES) submitted a recommendation for the review of the treatment of *H. pylori* infection. Numerous trials utilizing azithromycin-based regimens with different methods, drug combinations and treatment durations have demonstrated conflicting results. As an infectious disease, the ultimate aim of *H.pylori* eradication should be 100%, given the association with adverse gastrointestinal and non-gastrointestinal pathology. It is therefore requested to review the current standard of care against international standard of care regimens; the former is based on heterogeneous data and lack of local drug efficacy studies.

Previous NEMLC recommendation: A meta-analysis by Dong et al (2009), was cited as the evidence during the previous review of the Alimentary Chapter.[3] For the purpose of this review the meta-analysis was appraised. In the meta-analysis, 14 randomised trials (n=1431 patients) that compared azithromycin-containing triple-therapy regimen with standard triple-therapy regimens for first-line treatment of H. pylori infection showed that azithromycin-containing triple-therapy regimens could be equally effective in eradication of H. pylori compared with standard first- line triple-therapy regimens (72.01% vs. 69.78% for patients with or without azithromycin; OR= 1.17; 95% CI: 0.64-2.14). The occurrence of side effects was 15.81% and 25.20% (OR = 0.58; 95% CI: 0.41-0.82) for treatment with or without azithromycin, respectively. Furthermore, for the azithromycin-containing group there were fewer reports of associated diarrhoea, nausea and taste disturbance.

The duration of concomitant antibiotic treatment was mostly seven days (range seven to 14 days), although the duration of azithromycin treatment ranged from three to seven days. The azithromycin dose was generally 500mg/day (range 250mg to 1g/day). The most commonly used proton-pump inhibitor was omeprazole, then lanzoprazole, esomeprazole and pantoprazole. The most commonly used antibiotic was amoxicillin, then metronidazole, clarithromycin, levofloxacin and tinidazole.

Methodological quality was assessed using the Jadad score based on randomisation, double-blinding and information on withdrawals/ drop-outs, with a score from 1 to 5 points. Trials were assessed to be of low to moderate quality, using Jadad score.

Authors reported that the funnel plot had a slightly asymmetrical distribution, but the Egger's regression test suggested no significant asymmetry of the funnel plot (P = 0.84), suggesting that publication bias was low. There was no significant difference between the pooled *Helicobacter pylori* eradication rates with azithromycin (72.01%, 95% CI 58.09 to 85.93) and without azithromycin (69.78%, 95% CI 66.47 to 73.09), with an odds ratio of 1.17 (95% CI 0.64 to 2.14; 14 RCTs; I^2=81%), with significant heterogeneity, using an intention-to-treat analysis.

The findings of the meta-analysis need to be cautiously interpreted considering the following limitations. Many of the individual studies in the meta-analysis are small (likely underpowered to detect meaningful differences if any) and methodology quality is low to moderate. Generalisability is also restricted as no studies involved southern African/African

patients. Heterogeneity was also high (81%). The authors did not report how many reviewers performed the validity assessment.

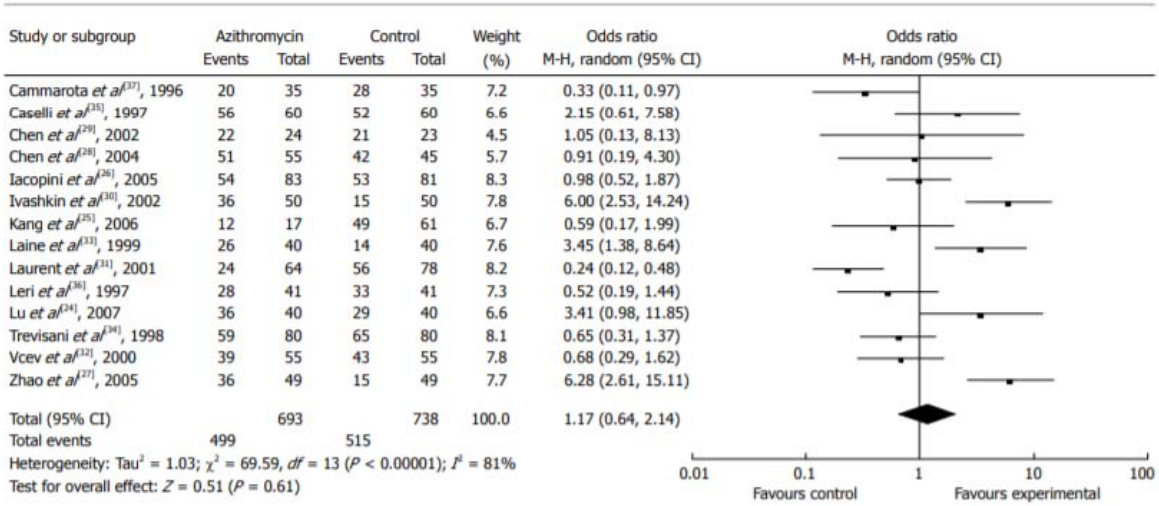


Figure 2 Effect of azithromycin-containing triple therapy *versus* standard triple therapy on eradication rates by intention-to-treat analysis.

The European Helicobacter and Microbiota Study Group and Consensus panel (2017) recommends a proton pump inhibitor (PPI)-clarithromycin-based triple therapy with PPI, clarithromycin, and amoxicillin (or metronidazole where its resistance rate is low) as the first-line eradication therapy only when clarithromycin resistance is below 15%. If clarithromycin resistance exceeds 15%, bismuth quadruple therapy (bismuth, PPI, tetracycline, and metronidazole) or non-bismuth quadruple therapy (PPI, amoxicillin, clarithromycin, and metronidazole; also known as concomitant therapy) may be offered for 10–14 days as an alternative to first-line triple therapy.[4]

5. Objective

To review the current evidence for Triple therapy (TT) as first line treatment of adult patients diagnosed with *Helicobacter pylori* infection

Research Question: Is the alternative regimen of proton pump inhibitor+amoxicillin+clarithromycin (PAC) comparable/superior to current standard of care in South Africa for the eradication of *H pylori* infection in adults in terms of effectiveness and safety?

PICOT criteria:

Population	*Helicobacter pylori* positive adult patients
Intervention	Clarithromycin containing Triple therapy: Proton pump inhibitor + amoxicillin + clarithromycin (PAC) or any pharmacological regimen (as primary eradication therapy)
Comparison	Standard of care: Proton pump Inhibitor + amoxicillin + metronidazole (PAM) Penicillin allergy: PPI + metronidazole + azithromycin.
Outcomes	Eradication of *Helicobacter pylori* infection, adverse events
Time	10-14 days
Study designs	Systematic reviews with meta-analysis published between 2010 and 2020. (Observational data excluded).

6. Methods

a. Data sources:

PubMed, and Cochrane Central Register of Controlled Trials

Date of search: 20 May 2020

b. Search strategy:

- PubMed: "triple" AND "*Helicobacter pylori*"[Mesh]
  Filters: meta-analysis, age greater than 18, date of publication in the past 10 years.

- Cochrane Central Register of Controlled Trials - amoxicillin AND clarithromycin AND triple AND helicobacter pylori

A total of 79 publications were identified of which 11 studies were deemed appropriate to address the research question.

Publications were excluded if any of the following were also present:

- Published in a languages other than English
- PAC and PAM pooled together for efficacy

7. Evidence synthesis

i. Li et al. (2020)[5]

Type of study	n	Population	Comparators	Primary out come	Effect size	Comment
Systematic review and meta-analysis	18 RCTs 3264 patients	*H pylori* infected adults 1st line therapy	PAM vs. PAC	Successful *H pylori* eradication	**Eradication rates (ITT):** 71% in PAC group 75.2% in PAM groups RR =0.96, p=0.38 **Eradication rates (PP):** 79.6% in PAC group vs.80.1% in PAM group (RR=1.02, p=0.65)	Both regimens are effective as 1st line therapy The choice should be guided by local resistance patterns.

Comment:

PAM is effective in clarithromycin-resistant cases (70.4% versus 48.2%, RR = 0.65, p = 0.002). PAC showed efficacy in metronidazole-resistant cases (87.3% versus 58.6%, RR = 1.43, p = 0.0006).

PAM treated patients had significantly higher risk of headache and nausea.

ii. Murata et al (2020)[6]

Type of study	n	Population	Comparators	Primary out come	Effect size
Systematic review and meta-analysis	4825 patients 27 studies	H pylori infected adults 1st line therapy	PAM vs. PAC	Successful *H pylori* eradication	Overall eradication rates between PAC and PAM were similar (74.8% and 72.5%, RR: 1.13, 95% CI: 0.91–1.39, P = 0.27) in the intention-to-treat analysis

Comment:

The authors divided RCTs into four groups based on resistance to clarithromycin (<15% or≥15%) and metronidazole (<15% or≥15%). In areas with low metronidazole- and high clarithromycin-resistance rates, PAM (PPI + amoxicillin + metronidazole) had a significantly higher eradication rate than PAC (92.5% vs. 70.8%,RR: 0.29, 95% CI: 0.13–0.68). In areas with high metronidazole- and low clarithromycin-resistance rates, the eradication rate with PAC was only 72.9%.

Study weaknesses: varying doses and durations of therapy.

iii. Yeo et al (2017)[7]

Study type	n	Population	Comparators	Primary out come	Effect size
Systematic review and meta-analysis	32 852 117 trials	H pylori infected adults 1st line therapy	17 major regimens for H. pylori eradication	Successful *H pylori* eradication	Using PAC for a duration of 7 day as the reference 10- day PAC and 14-day PAC yielded superior eradication rates: OR 1.32 (95% CI 1.04-1.69) and OR 1.72 (95% CI 1.37-2.17). In contrast 7-day PAM was inferior to 7- day PAC with an OR of 0.82 (95% CI 0.56-1.19). 10-day PAM yielded an OR 1.29 (95% CI 0.56-3.01) when compared to 7 day PAC.

Comment:

Compared with 7-day clarithromycin-based triple therapy, sequential therapy (ST) for 14 days had the highest effectiveness (OR=3.74, 95% CI 2.37 to 5.96). ST for 14 days (OR=6.53, 95% CI 3.23 to 13.63) and hybrid therapy for 10 days or more (OR=2.85, 95% CI 1.58 to5.37) represented the most effective regimen in areas with high and low clarithromycin resistance, respectively.

iv. Nyssen et al (2016)[8]

Study type	n	Population	Comparators	Primary out come	Effect size
Systematic review and meta-analysis	44 RCTs 12,284 patients	H pylori infected adults 1st line therapy	PAC triple therapy vs. sequential therapy (SEQ)	Successful *H pylori* eradication	Overall analysis showed that SEQ was significantly more effective than PAC T (82% vs. 75%) in the intention-to-treat analysis; RD 0.09, 95% confidence interval (CI) 0.06 to 0.11; P < 0.001.

Comment:

Results were highly heterogeneous (I^2 = 75%), and 20 studies did not demonstrate differences between therapies.
Subgroup analyses showed that SEQ and STT therapies were equivalent when STT lasted for 14 days.

v. Chen et al (2018)[9]

Study type	n	Population	Comparators	Primary outcome	Effect size
Systematic review and meta-analysis	6632 23 RCTs	H pylori infected adults 1st line therapy	Triple therapy (PAC) vs. Concomitant therapy	Successful *H pylori* eradication	Concomitant therapy of any duration was superior to triple therapy (RR: 1.15; 95% CI 1.09–1.21; p< 0.001). 7-day concomitant therapy was superior to 7-day triple therapy (RR: 1.16; 95% CI: 1.12–1.21; p< 0.001) 5- or 7-, or 10- or 14-day concomitant therapy was superior to 10-day triple therapy (RR: 1.15; 95% CI: 1.08–1.23; p< 0.001). However, 5- or 10-day concomitant therapy was not superior to 14-day triple therapy (RR: 1.02; 95% CI: 0.89–1.16; p= 0.796).

Comment:

Concomitant therapy was defined as a PPI plus amoxicillin, clarithromycin, and metronidazole or tinidazole given twice a day for 5–14 days. Triple therapy was defined as a PPI plus amoxicillin and clarithromycin given twice a day for 5–14 day. Concomitant therapy was more effective than triple therapy in clarithromycin-resistant strains, but not in clarithromycin-susceptible strains. The frequency of adverse effects was significantly higher in concomitant therapy than triple therapy (RR: 1.19; 95% CI: 1.06–1.34; P= 0.004).
Weaknesses: significant heterogeneity (I2= 74.0%, p< 0.001), varying doses combined.

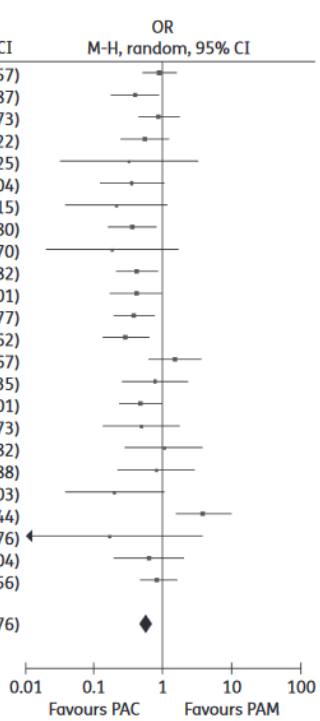
vi. Piug et al (2016)[10]

Study type	n	Population	Comparators	Primary outcome	Effect size
Systematic review and meta-analysis	22 RCTs 3821 patients included	H pylori infected adults - 1st line therapy	Triple therapy (PAM) vs. other therapies	Successful *H pylori* eradication	PAM versus clarithromycin-including triple therapies showed a significant difference in favour of PAC(70% versus 77.1%; OR0.70, 95% CI0.56–0.88) and PPI, metronidazole and clarithromycin (PMC) therapy (66.4% versus 77.7%; OR0.55, 95% CI 0.39–0.76) Sensitivity analyses showed a similar efficacy of PAM versus PAC when drugs were administered for 14 days (80% versus 84%; OR 0.70, 95% CI 0.44–1.12).

(b) PP

Study or subgroup	PAM Events	PAM Total	PAC Events	PAC Total	Weight	OR M-H, random, 95% CI
Auriemma (97)	123	156	124	154	6.9%	0.90 (0.52, 1.57)
Bhatia (104)	22	52	35	54	5.3%	0.40 (0.18, 0.87)
Filipec (a) (118)	90	113	92	113	6.2%	0.89 (0.46, 1.73)
Filipec (b) (118)	93	112	98	109	5.2%	0.55 (0.25, 1.22)
Filipec (c) (118)	54	57	55	56	1.2%	0.33 (0.03, 3.25)
Harris (127)	38	50	53	59	3.8%	0.36 (0.12, 1.04)
Huang (132)	21	27	33	35	2.0%	0.21 (0.04, 1.15)
Koivisto (137)	83	106	100	110	5.2%	0.36 (0.16, 0.80)
Labenz (142)	28	33	30	31	1.3%	0.19 (0.02, 1.70)
Lind (3)	93	114	191	209	6.0%	0.42 (0.21, 0.82)
Loghmari (147)	19	39	32	46	4.7%	0.42 (0.17, 1.01)
Malfertheiner (148)	100	132	113	127	6.0%	0.39 (0.20, 0.77)
Misiewicz (153)	83	113	103	114	5.5%	0.30 (0.14, 0.62)
Miyaji (154)	60	70	59	74	4.8%	1.53 (0.63, 3.67)
Namiot (156)	31	40	31	38	3.6%	0.78 (0.26, 2.35)
Namiot (157)	52	78	65	81	5.7%	0.49 (0.24, 1.01)
Pieramico (159)	49	57	50	54	3.0%	0.49 (0.14, 1.73)
Pilotto (160)	30	35	34	40	3.0%	1.06 (0.29, 3.82)
Pilotto (162)	40	46	41	46	3.0%	0.81 (0.23, 2.88)
Sancar (168)	5	10	20	24	2.1%	0.20 (0.04, 1.03)
Savarino (169)	62	70	46	69	4.7%	3.88 (1.59, 9.44)
Stack (172)	15	17	18	18	0.7%	0.17 (0.01, 3.76)
Sun (20)	37	44	50	56	3.4%	0.63 (0.20, 2.04)
Uygun (177)	77	121	53	79	6.6%	0.86 (0.47, 1.56)
Total (95% CI)		1692		1796	100.0%	0.59 (0.45, 0.76)
Total events	1305		1526			

Heterogeneity: $\tau^2=0.18$; $\chi^2=43.14$, df=23 ($P=0.007$); $I^2=47\%$
Test for overall effect: $Z=3.95$ ($P<0.0001$)



vii. Liou et al (2016)[11]

Study type	n	Population	Comparators	Primary outcome	Effect size
Systematic review and meta-analysis	13 RCTs including 2749 patients in the sequential therapy group and 2424 patients in the 14-day triple therapy group	H pylori infected adults 1st line therapy	Sequential therapy vs. 14 day PAC	Successful *H pylori* eradication	Overall, sequential therapy for 10 or 14 days was not significantly superior to14-day triple therapy [RR 1.04, 95% CI 0.99–1.08, P=0.145]. However, there was significant heterogeneity (I2=57.6%, P=0.005). In the subgroup analysis of four trials 14-day sequential therapy was significantly more effective than 14-day triple therapy (RR: 1.09, 95% CI: 1.04–1.16, P=0.002), and there was no significant heterogeneity (I2=0%, P=0.624) in this comparison. Sequential therapy given for 10 days was not superior to 14-day triple therapy (RR: 1.03, 95% CI: 0.98–1.09, P=0.207).

Comments:

Sequential therapy was defined as a PPI plus amoxicillin given for the first 5–7 days, followed by a PPI plus nitroimidazole derivatives and clarithromycin for the next 5–7 days (all given twice daily). There was no significant difference in the risk of adverse effects.

Weaknesses: combined different doses.

viii. Xiao et al (2014)[12]

Study type	n	Population	Comparators	Primary outcome	Effect size
Systematic review and meta-analysis	9 RCTs 1275 patients	H pylori infected adults 1st line therapy	Levofloxacin-based triple therapy vs. clarithromycin based TT	Successful *H pylori* eradication	Eradication rate in the levofloxacin-based therapy group was higher than that in the standard triple therapy group regardless of treatment duration (80.2% vs. 77.4%, RR = 1.03, 95% CI = 0.94–1.13).

Comments:

There was no significant difference between two groups in the incidence of overall adverse events or in the occurrence of discontinuing therapy due to side effects.
Weaknesses: The included articles are limited to China, Korea, Spain, and Italy which may limit the generalizability of these results to other countries and populations.

ix. Kim et al (2013)[13]

Study type	n	Population	Comparators	Primary outcome	Effect size
Systematic review and meta-analysis	6 RCTs 1759 patients	H pylori infected adults 1st line therapy	Sequential therapy vs. PAC	Successful *H pylori* eradication	Pooled estimates of the ITT and PP eradication rate were 79.4% (95% CI, 76.3% to 82.2%) and 86.4% (95% CI, 83.5% to 88.8%), respectively, for the ST group, and 68.2% (95% CI, 62.1% to 73.8%) and 78.9% (95% CI, 68.9% to 81.7%), respectively, for the TT group.

Comments:

The sequential therapy consisted of a PPI and amoxicillin for the first 5 days followed by a PPI and two other antibiotics for the following 5 days. The authors did not find a significant difference in the rate of adverse events between the ST and TT groups.
Weaknesses: Data limited to Korea. Most of the studies included scored 3 on the Jadad scale and there were no studies with high quality scores (4 or 5). No reference to blinding in all the trials. Moderate degree of heterogeneity.

x. Yoon et al (2013)[14]

Study type	n	Population	Comparators	Primary outcome	Effect size
Systematic review and meta-analysis	17 RCTs 3419 patients	H pylori infected adults 1st line therapy	Sequential therapy (SQT) vs. PAC	Successful *H pylori* eradication	The eradication rate was 81.8% (95% CI: 78.9−84.6) for SQT and 74.3% (95% CI: 69.6−78.8) for PAC. The pooled RR was 1.10 (95% CI: 1.04−1.16, *P* = 0.0005)

Comments:

There were no significant differences between SQT and STT in the risk of side effects (the pooled RR: 0.98, 95% CI: 0.87−1.10, *P* = 0.73).
Weaknesses: Asian subjects only. Significant Heterogeneity.

xi. Venerito et al (2013)[15]

Study type	n	Population	Comparators	Primary outcome	Effect size
Systematic review and meta-analysis	12 RCTs 2753 patients	H pylori infected adults 1st line therapy	Bismuth quadruple therapy (BQT) vs. PAC	Successful *H pylori* eradication	BQT achieved eradication in 77.6% of patients, whereas PAC) achieved an eradication rate of 68.9% [risk difference (RD) = 0.06, 95% CI: –0.01/0.13].

Comments:

In the subgroup analysis for treatment duration, the 10-day BQT was more effective than the 7-day PAC (RD = 0.25, 95% CI: 0.18/0.32), whereas no differences were observed between PAC and BQT given for 7 or 10 days. Compliance and side effect rates were similar for both therapies.

8. Quality of evidence

The 11 meta-analysis have similar strengths and weaknesses.

- **Strengths**
  - Large numbers of RCTs included allowing sub-group analyses
  - The exclusion of observational studies

- **Weaknesses**
  - No South African data
  - Most of the studies included had low quality scores
  - No reference to blinding in all the trials
  - Moderate degree of heterogeneity

9. Duration of H pylori eradication

Increasing the duration of PPI-based triple therapy increases *H. pylori* eradication rates. For PAC, prolonging treatment duration from 7 to 10 or from 10 to 14 days is associated with a significantly higher eradication rate. The conclusion of this Cochrane review states that the optimal duration of therapy for PAC and PAM is at least 14 days.[16]

10. Antibiotic susceptibility data for *Helicobacter pylori*

Local susceptibility data are limited, and susceptibility data is not routinely collected by the National Health Laboratory Services.

Eastern Cape region –*Tanih et al (2010)*[17]

Two hundred *H. pylori* strains obtained from gastric biopsies of patients presenting with gastric-related morbidities attending a tertiary hospital in the Eastern Cape were evaluated for their susceptibility to seven antibiotics (metronidazole, clarithromycin, tetracycline, amoxicillin, gentamicin, ciprofloxacin and erythromycin).

Marked susceptibility was observed for ciprofloxacin (100%) and amoxicillin (97.5%), and good activity for clarithromycin (80%) and gentamicin (72.5%). However, marked resistance (95.5%) was observed for metronidazole.

Table I. Antibiotic sensitivity results of *H. pylori* strains isolated from gastric biopsy specimens

Antibiotics	Antrum No sus (%)	Corpus No sus (%)	Antrum No res (%)	Corpus No res (%)	Overall Sus (%)	Overall Res (%)	MIC µg/ml
Clarithromycin	87 (82.07)	73 (77.65)	19 (17.92)	21 (22.34)	160 (80)	40 (20)	0.125 - 1.0
Tetracycline	69 (66.34)	66 (68.75)	35 (33.65)	30 (31.25)	135 (67.5)	65 (32.5)	1.25 - 2.0
Amoxicillin	103 (98.09)	92 (96.84)	2 (1.90)	3 (3.15)	195 (97.5)	5 (2.5)	2.5 - 5.0
Metronidazole	6 (5.94)	3 (3.03)	95 (94.05)	96 (96.96)	9 (4.5)	191 (95.5)	>10
Gentamicin	84 (75.67)	61 (68.53)	27 (24.32)	28 (31.46)	145 (72.5)	55 (27.5)	5 - 8.0
Erythromycin	69 (64.48)	42 (45.16)	38 (35.51)	51 (54.83)	111 (55.5)	89 (44.5)	2.5 - 5.0
Ciprofloxacin	107 (100)	93 (100)	00 (0)	00 (0)	200 (100)	00 (0)	0.0625 - 1.0

Res = resistance; Sus = susceptibility. Zone diameter breakpoints for clarithromycin testing were <14 mm resistance (R) and ≥14 susceptible (S); for tetracycline and amoxicillin <16 mm (R) and ≥16 (S); for metronidazole testing <10 mm (R) and ≥10 (S); for ciprofloxacin <17 mm resistance (R) and ≥17 mm susceptible (S); for gentamicin <15 mm resistance (R) and ≥15 susceptible (S); and for erythromycin testing <19 mm resistance (R) and ≥20 susceptible (S).[1,13]

Western Cape region

Dr Dion Levin (personal communication). Of 48 patients with PCR confirmed H pylori at Groote Schuur Hospital no cases were found to have clarithromycin resistance (email communication submitted). Susceptibility to amoxicillin and metronidazole was not performed.

Gauteng region - *Hoosien et al (2018)*[18]

A recent study only published in abstract form showed that 13.6% of H pylori strains in a cohort of patients at Chris Hani

Baragwanath Academic Hospital were clarithromycin resistant.

11. Clinical practice Guidelines

ACG Clinical Guideline: Treatment of Helicobacter pylori Infection (2017)[19]

Most of the treatment regimens, including concomitant therapy, hybrid therapy, and levofloxacin-containing regimens, have been found to be most effective in international trials. It is impossible to make confident, evidence-based recommendations regarding the relative efficacy of these regimens. As concomitant, sequential and hybrid therapies are generally composed of the same four drugs, and the available data suggest that they provide similar efficacy and tolerability, practical issues such as simplicity of the regimen take on greater importance.

Using this logic, concomitant therapy seems the best choice of the clarithromycin quadruple therapies for both first-line and salvage therapy. Of the levofloxacin treatment regimens, the levofloxacin sequential therapy offers the most robust first-line efficacy data based upon available international trials.

Table: Recommended first-line therapy for H. pylori infection

Regimen	Drugs (doses)	Dosing frequency	Duration (days)	FDA approval
Clarithromycin triple	PPI (standard or double dose)	BID	14	Yes[a]
	Clarithromycin (500 mg)			
	Amoxicillin (1 grm) or Metronidazole (500 mg TID)			
Bismuth quadruple	PPI (standard dose)	BID	10–14	No[b]
	Bismuth subcitrate (120–300 mg) or subsalicylate (300 mg)	QID		
	Tetracycline (500 mg)	QID		
	Metronidazole (250–500 mg)	QID (250)		
		TID to QID (500)		
Concomitant	PPI (standard dose)	BID	10–14	No
	Clarithromycin (500 mg)			
	Amoxicillin (1 grm)			
	Nitroimidazole (500 mg)[c]			
Sequential	PPI (standard dose)+Amoxicillin (1 grm)	BID	5–7	No
	PPI, Clarithromycin (500 mg)+Nitroimidazole (500 mg)[c]	BID	5–7	
Hybrid	PPI (standard dose)+Amox (1 grm)	BID	7	No
	PPI, Amox, Clarithromycin (500 mg), Nitroimidazole (500 mg)[c]	BID	7	
Levofloxacin triple	PPI (standard dose)	BID	10–14	No
	Levofloxacin (500 mg)	QD		
	Amox (1 grm)	BID		
Levofloxacin sequential	PPI (standard or double dose)+Amox (1 grm)	BID	5–7	No
	PPI, Amox, Levofloxacin (500 mg QD), Nitroimidazole (500 mg)[c]	BID	5–7	
LOAD	Levofloxacin (250 mg)	QD	7–10	No
	PPI (double dose)	QD		
	Nitazoxanide (500 mg)	BID		
	Doxycycline (100 mg)	QD		

BID, twice daily; FDA, Food and Drug Administration; PPI, proton pump inhibitor; TID, three times daily; QD, once daily; QID, four times daily.

[a]Several PPI, clarithromycin, and amoxicillin combinations have achieved FDA approval. PPI, clarithromycin and metronidazole is not an FDA-approved treatment regimen.

[b]PPI, bismuth, tetracycline, and metronidazole prescribed separately is not an FDA-approved treatment regimen. However, Pylera, a combination product containing bismuth subcitrate, tetracycline, and metronidazole combined with a PPI for 10 days is an FDA-approved treatment regimen.

[c]Metronidazole or tinidazole.

AGREE assessment:

The above guideline were assessed using the AGREE appraisal method. Three reviewers independently reviewed the guideline. Reviewers concluded that the guideline was well-written, requiring context specific adaptions for

implementation. Sensitivity data needs careful interpretation as local resistance patterns may differ to that of North America. Overall Quality was rated as 5.7 out of 7.

12. Interpretation of the evidence and comments

Both PAM and PAC are appropriate 1st line strategies to eradicate *H pylori* in adults; efficacy and safety appear broadly similar. Local antibiotic susceptibility data is not readily available and is not routinely collected.

The duration of therapy for H pylori eradication should be 14 days at full doses. Increasing duration of therapy to 14 days significantly improves eradication rates of PAC and PAM regimens. Recommendations for duration of proton pump inhibitor should further be determined by the presence of an ulcer.

EVIDENCE TO DECISION FRAMEWORK

	JUDGEMENT	SUPPORTING EVIDENCE & ADDITIONAL CONSIDERATIONS
QUALITY OF EVIDENCE	**What is the overall confidence in the evidence of effectiveness?** Confident: [X] Not confident: [ ] Uncertain: [ ]	Evidence suggests that both azithromycin and clarithromycin are effective for eradication of *Helicobacter pylori.* For azithromycin, available evidence is of low to moderate quality; whilst funding by pharmaceutical industry for clarithromycin trials is noted. There may be a macrolide class effect, though local resistance patterns should further guide therapy.
BENEFITS & HARMS	**Do the desirable effects outweigh the undesirable effects?** Benefits outweigh harms: [X] Harms outweigh benefits: [ ] Benefits = harms or Uncertain: [ ]	
THERAPEUTIC INTERCHANGE	Therapeutic alternatives available: Yes: [X] No: [ ] *List the members of the group:* Azithromycin and clarithromycin.	*Rationale for therapeutic alternatives included:* Available evidence suggests that azithromycin and clarithromycin are efficacious. *References:* Dong et al, 2019[3]; Li et al, 2020.[5] *Rationale for exclusion from the group:* n/a *References:* n/a
VALUES & PREFERENCES / ACCEPTABILITY	**Is there important uncertainty or variability about how much people value the options?** Minor: [ ] Major: [ ] Uncertain: [X] **Is the option acceptable to key stakeholders?** Yes: [ ] No: [ ] Uncertain: [X]	Values varies across the stakeholder groups. - Gastroenterologists – values varies across the country. - Patients – adherence would be better with daily dosing and shorter duration of azithromycin.
RESOURCE USE	**How large are the resource requirements?** More intensive: [X] Less intensive: [ ] Uncertain: [ ]	Price of medicines/ month: **Medicine** / **Cost (ZAR)** Azithromycin, oral, 500mg daily x 10days: R 59.21* Azithromycin, oral, 500mg daily x 3days: R 17.76* Clarithromycin, oral, 500 mg 12 hrly x 14days: R 85.01** *Contract circular HP02-2019AI (weighted average prices) ** SEP database (average price of 7 cheapest listed products) - https://mpr.code4sa.org/ [Accessed 04/06/200] **Additional resources:** n/a
EQUITY	**Would there be an impact on health inequity?** Yes: [ ] No: [X] Uncertain: [ ]	
FEASIBILITY	**Is the implementation of this recommendation feasible?** Yes: [X] No: [ ] Uncertain: [ ]	Dependant on accessibility of medicines.

Type of recommendation	We recommend against the option and for the alternative	We suggest not to use the option or to use the alternative	We suggest using either the option or the alternative	We suggest using the option	We recommend the option
	X	☐	☐	☐	☐

Recommendation:

Based on this evidence review, the Adult Hospital Level Committee reccomends that azithromycin be retained as part of the recommended triple therapy for eradicationof *Helicobacter pylori*. However, clarithromycin could be considered as a therapeutic alternative where there are supply constraints with azithromycin.

Duration of therapy for clarithromycin (as part of triple therapy) should be extended for 14 days, whilst azithromycin could be extended to 10 days (as the elimination half-life is 68 to 72 hours).

Of note is that an increase in resistance of metronidazole would limit the therapeutic efficacy of triple therapy in penicillin-allergic pateients – more local antibiotic susceptibility data is required.

Empiric therapy should not be instituted without diagnostics and treatment failure should be guided by sensitivity and culture.

Rationale: Available evidence suggests that azithromycin is comparable to clarithromycin in terms of efficacy; though evidence is of low to moderate quality. Increasing duration of therapy to 14 days has been shown to improve eradication rates of proton pump inhibitor + amoxicillin + clarithromycin (PAC) and proton pump inhibitor + amoxicillin + metronidazole (PAM) regimens. However, local sensitivity patterns is required to guide combination triple therapy for *Helicobacter pylori* eradication.

Level of Evidence: II Moderate quality meta-analyses, Antibiotic susceptibility studies, Expert opinion

NB: PLEASE SEE BELOW FOR FINAL NEMLC RECOMMENDATION.

Review indicator: Price and antimicrobial susceptibility data

Evidence of efficacy	Evidence of harm	Price reduction
X		X

VEN status: n/a

Vital	Essential	Necessary

Monitoring and evaluation considerations: Resistance patterns

Research priorities: Resistance patterns

NEMLC MEETING OF 11 JUNE 2020:

NEMLC DISCUSSION:

Azithromycin: Despite the biological elimination half-life of 68 to 72 hours, tissue concentrations were reported to be as long as 14 days. Thus, the NEMLC recommended that the duration of therapy of azithromycin be retained at 3 days, and not be extended to 10 days.

- *Sampson et al.*[1] evaluated whole blood and intracellular concentrations (peripheral blood mononuclear cells and polymorphonuclear cells) for 21 days after a single dose of azithromycin (250 mg to 1000 mg). Concentrations in cells were measured as two orders of magnitude higher intracellularly than in blood and declines very slowly over 21 days.

[1] Sampson MR, Dumitrescu TP, Brouwer KL, Schmith VD. Population pharmacokinetics of azithromycin in whole blood, peripheral blood mononuclear cells, and polymorphonuclear cells in healthy adults. CPT Pharmacometrics Syst Pharmacol. 2014;3(3):e103. https://pubmed.ncbi.nlm.nih.gov/24599342/

- *Amsden et al.*[2], similarly, showed similar intracellular concentrations over 10 days after administration of an azithromycin dose of 1500 mg as a single dose or over 3 days to healthy volunteers. Mean cellular concentrations at 10 days was 18 and 17 mg/L for granulocytes (PMNs) and 27 and 21 mg/L for monocyte/lymphocyte (M/Ls) for the respective doses. In contrast the corresponding serum concentrations for both dosage regimens was <0.05 mg/L.
- *Minimum inhibitory concentrations (MIC):* MIC for azithromycin for *H.pylori* eradication is lacking (noting that azithromycin is concentrated in cellular tissues). EUCAST only provides MICs for clarithromycin. Expert opinion recommends that MIC of 1 mg/L for azithromycin is adequate. Both studies (Sampson et al and Amsden et al) showed that at 21 days, cellular concentrations was generally higher than 1 mg/L.

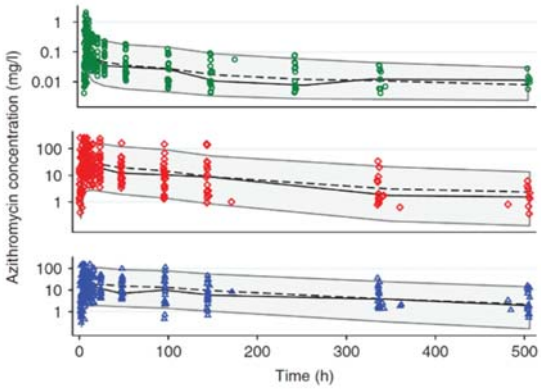


Figure 5 Visual predictive checks. Markers, observed data; shaded area, 90% prediction interval; solid lines, median of observed data; dashed lines, median of simulated data; green circles, whole blood; red diamonds, peripheral blood mononuclear cells; blue triangles, polymorphonuclear cells.

Sourced from Sampson et al (2014)

Duration of therapy of other antibiotics: Cochrane review by Yuan et al (2013)[3] states that the optimal duration of therapy for PAC and PAM is at least 14 days.

Metronidazole: More substantial antimicrobial susceptibility data is needed to inform whether metronidazole should be included in the regimen to for H.pylori eradication or not.

NEMLC RECOMMENDATIONS: NEMLC recommended that the duration of therapy for azithromycin be retained as 3 days. For other antibiotics, amoxicillin and metronidazole, duration of therapy to be extended for 14 days for the eradication of *H.pylori.* Clarithromycin was cost-prohibitive and could be considered as a therapeutic alternative where there are supply constraints with azithromycin. And, more substantial local antimicrobial susceptibility studies were required to confirm metronidazole resistance in our local setting.
Rationale: Despite an elimination half-life of 68 to 72 hours, azithromycin tissue concentrations have been shown to be adequate (>1 mg/L) 21 days after administration of a single dose of 1.5 g or 3 day course of 500 mg per day. For other antibiotics (amoxicillin and metronidazole), 14-day duration of therapy is recommended as a Cochrane review showed that *H. pylori* eradication rates for 14-days PPI triple therapy was significantly higher than for 7 days (*H. pylori* persistence, regardless of regimen and dose: RR 0.66 (95% CI 0.6 to 0.74), NNT 11 (95% CI 9 to 14).
Level of Evidence: I Metaanalysis and systematic review, Pharmacokinetic studies

[2] Amsden GW, Gray CL. Serum and WBC pharmacokinetics of 1500 mg of azithromycin when given either as a single dose or over a 3 day period in healthy volunteers. J Antimicrob Chemother. 2001;47(1):61-66. https://pubmed.ncbi.nlm.nih.gov/11152432/

[3] Yuan Y, Ford AC, Khan KJ, et al. Optimum duration of regimens for Helicobacter pylori eradication. Cochrane Database Syst Rev. 2013;(12):CD008337. https://pubmed.ncbi.nlm.nih.gov/24338763/

References

[1] Malfertheiner P, Megraud F. European Helicobacter Pylori Study Group (EHPSG). Current concepts in the management of Helicobacter pylori infection-the Maastricht 2-2000 Consensus Report. Aliment Pharmacol Ther. 2002;16:167–180. https://pubmed.ncbi.nlm.nih.gov/11860399/
[2] Everhart JE, Kruszon-Moran D. Seroprevalence and ethnic differences in Helicobacter pylori infection among adults in the United States. J Infect Dis. 2000;181:1359–1363. https://pubmed.ncbi.nlm.nih.gov/10762567/
[3] Dong J, Yu XF, Zou J. Azithromycin-containing versus standard triple therapy for Helicobacter pylori eradication: a meta-analysis. World J Gastroenterol 2009; 15(48): 6102-6110. https://pubmed.ncbi.nlm.nih.gov/20027685/
[4] Malfertheiner P, Megraud F, O'Morain CA on behalf of the European Helicobacter and Microbiota Study Group and Consensus panel, et al. Management of Helicobacter pylori infection—the Maastricht V/Florence Consensus Report. Gut 2017;66:6-30. https://gut.bmj.com/content/gutjnl/66/1/6.full.pdf
[5] Li B, Lan X, Wang L, et al. Proton-pump inhibitor and amoxicillin-based triple therapy containing clarithromycin versus metronidazole for Helicobacter pylori: A meta-analysis. Microb Pathog. 2020;142(October 2019). https://pubmed.ncbi.nlm.nih.gov/32074497/
[6] Murata M, Sugimoto M, Mizuno H, Kanno T, Satoh K. Clarithromycin Versus Metronidazole in First-Line Helicobacter Pylori Triple Eradication Therapy Based on Resistance to Antimicrobial Agents: Meta-Analysis. J Clin Med. 2020;9(2):543. https://pubmed.ncbi.nlm.nih.gov/32079208/
[7] Yeo YH, Shiu SI, Ho HJ, et al. First-line Helicobacter pylori eradication therapies in countries with high and low clarithromycin resistance: A systematic review and network meta-analysis. Gut. 2018;67(1):20-27. https://pubmed.ncbi.nlm.nih.gov/27670375/
[8] Nyssen OP, McNicholl AG, Megraud F, et al. Sequential versus standard triple first-line therapy for Helicobacter pylori eradication. Cochrane Database Syst Rev. 2016;(6):CD009034. https://pubmed.ncbi.nlm.nih.gov/27351542/
[9] Chen MJ, Chen CC, Chen YN, et al. Systematic Review with Meta-Analysis: Concomitant Therapy vs. Triple Therapy for the First-Line Treatment of Helicobacter pylori Infection. Am J Gastroenterol. 2018;113(10):1444-1457. https://pubmed.ncbi.nlm.nih.gov/30171216/
[10] Puig I, Baylina M, Sánchez-Delgado J, et al. Systematic review and meta-analysis: Triple therapy combining a proton-pump inhibitor, amoxicillin and metronidazole for Helicobacter pylori first-line treatment. J Antimicrob Chemother. 2016;71(10):2740-2753. https://pubmed.ncbi.nlm.nih.gov/27342548/
[11] Liou JM, Chen CC, Lee YC, et al. Systematic review with meta-analysis: 10- or 14-day sequential therapy vs. 14-day triple therapy in the first line treatment of Helicobacter pylori infection. Aliment Pharmacol Ther. 2016;43(4):470-481. https://pubmed.ncbi.nlm.nih.gov/26669729/
[12] Xiao SP, Gu M, Zhang GX. Is levofloxacin-based triple therapy an alternative for first-line eradication of Helicobacter pylori? A systematic review and meta-analysis. Scand J Gastroenterol. 2014;49(5):528-538. https://pubmed.ncbi.nlm.nih.gov/24611790/
[13] Kim JS, Ji JS, Choi H, Kim JH. Sequential therapy or triple therapy for Helicobacter pylori infection in Asians: Systematic review and meta-analysis. Clin Res Hepatol Gastroenterol. 2014;38(1):118-125. https://pubmed.ncbi.nlm.nih.gov/24238722/
[14] Yoon H, Lee DH, Kim N, et al. Meta-analysis: Is sequential therapy superior to standard triple therapy for helicobacter pylori infection in asian adults? J Gastroenterol Hepatol. 2013;28(12):1801-1809. https://pubmed.ncbi.nlm.nih.gov/24118110/
[15] Venerito M, Krieger T, Ecker T, Leandro G, Malfertheiner P. Meta-analysis of bismuth quadruple therapy versus clarithromycin triple therapy for empiric primary treatment of helicobacter pylori infection. Digestion. 2013;88(1):33-45. https://pubmed.ncbi.nlm.nih.gov/23880479/
[16] Yuan Y, Ford AC, Khan KJ, et al. Optimum duration of regimens for Helicobacter pylori eradication. Cochrane Database Syst Rev. 2013;(12):CD008337. https://pubmed.ncbi.nlm.nih.gov/24338763/
[17] Tanih NF, Okeleye BI, Naidoo N, et al. Marked susceptibility of South African Helicobacter pylori strains to ciprofloxacin and amoxicillin: clinical implications. S Afr Med J. 2010;100(1):49–52. https://pubmed.ncbi.nlm.nih.gov/20429489/
[18] Hoosien E, Kassianides C, Ally R. Difference in the prevalence of clarithromycin- resistant Helicobacter Pylori strains in public and private hospital settings in Johannesburg. SAMJ August 2018:59. https://journals.co.za/content/journal/10520/EJC-100f71edae
[19] Chey WD, Leontiadis GI, Howden CW, Moss SF. ACG Clinical Guideline: Treatment of Helicobacter pylori Infection [published correction appears in Am J Gastroenterol. 2018 Jul;113(7):1102]. Am J Gastroenterol. 2017;112(2):212–239. https://pubmed.ncbi.nlm.nih.gov/28071659/