National Essential Medicine List Medication Review Process
Adult Hospital Level
Component: Emergencies and injuries

Date: 26 November 2015

Medication name: Azithromycin

Indication: *H. pylori* eradication

Question: What is the comparative efficacy of azithromycin compared to clarithromycin in the treatment of *H.Pylori* infection?

Background:
Helicobacter pylorus (H. pylori) has been implicated in the development of gastro-duodenal disease, including gastritis, peptic ulcer, gastric adenocarcinoma and lymphoma.
Current clinical practice within the Gastro-intestinal unit at Groote Schuur Hospital is based on the findings from the Maastricht IV consensus report 2010. In the 4th Maastricht consensus conference 44 experts from 24 countries took part and examined key clinical aspects regarding diagnostics and therapeutics related to gastro-duodenal disease. Recommendations were provided based on current evidence and plausibility to guide health practioners. For confirmed H.Pylori infection triple therapy is used with a minimum 10 day course of Clarithromycin 500mg twice daily, single doses of Amoxicillin 1g and Omeprazole 20mg orally.

Given the financial budget constraints within a resource limited South African context we are constantly striving to provide the most appropriate and cost effective medical treatment. Azithromycin offers the potential of a less costly and yet effective alternative to clarithromycin.

Azithromycin, a new generation macrolide, has properties that make it a promising compound in regimens for H pylori eradication. Following a single oral dose, azithromycin accumulates in the human gastric mucosa, redistributes from mucosal tissue to the mucus layer, and from the mucus to gastric juice. There, it reaches gastric tissue concentrations that persist above the minimal concentration for 90% inhibition (MIC90) for H pylori over a 5-d period. Exposing the micro-organism to consistent amounts of the drug.

Indications for Azithromycin:
Azithromycin is bacteriostatic at low concentrations and bactericidal at high concentrations.
Indicated for use in *H. pylori* eradication.

Search strategy
The following terms, “azithromycin” and “*H. Pylori* eradication” were used.
Pubmed and google were searched.

Summary of Evidence Reviewed

Efficacy and Safety

- Dong J, Yu XF, Zou J. Azithromycin-containing versus standard triple therapy for Helicobacter pylori eradication: a meta-analysis. World J Gastroenterol. 2009 Dec 28;15(48):6102-10[i].
- Sarkeshikian SS, Iranikhah A, Ghadir MR. Azithromycin based triple therapy versus standard clarithromycin based triple therapy in eradication of Helicobacter pylori infection in Iran: a randomized controlled clinical trial. Turk J Gastroenterol. 2013;24(1):10-4[ii].

Cost and Affordability

Contract circular prices: HP02-2015 AI[iii].

Cost Per unit:

	Unit cost
Azithromycin	**500 mg tablet**
Cost in ZAR	**3.34**
Azithromycin	**250 mg tablet**
Cost in ZAR	**2.43**
Clarithromycin	**500 mg tablet**
Cost in ZAR	**3.42**

A. Dong J, Yu XF, Zou J. Azithromycin-containing versus standard triple therapy for Helicobacter pylori eradication: a meta-analysis. World J Gastroenterol. 2009 Dec 28;15(48):6102-10.

Dong et al's 2009 meta-analysis of 14 randomized controlled trials conducted between 1945 and 2009, comparing azithromycin with clarithromycin in triple therapy regimens. Not all included studies used the same triple-therapy treatment regimen. In addition, the dose and duration of azithromycin therapy differed between studies.

The overall point estimate for the outcome was not statistically significant with an odds ratio of 1.17 (95% CI 0.64-2.14; P= 0.61).

Eradication rates and side effects were analysed, both by intention-to-treat and per-protocol analysis. Across all studies there was 81% heterogeneity. Four of the fourteen studies reported superior eradication rates with azithromycin use, and the remaining ten showed no significant difference in *H pylori* eradication. In 2 of the 4 studies (Lu et al and Laine et al) azithromycin dose of 500mg daily for 7 days was used. The remaining 2 studies (Zhao et al and Ivashkin et al) used a higher azithromycin dose of 1g daily for 3 days. Of the 10 studies that showed no difference 1 study done by Laurent et al favoured the clarithromycin arm , a contributing factor to this outcome could be that azithromycin was used in lower doses and shorter duration.

	Eradication rate	
	ITT-Analysis	**PP-Analysis**
Azithromycin regimen	**72.01%** (95%CI 58.09 to85.93%)	**75.81%** (95%CI 72.44 to79.18)
Clarithromycin regimen	**69.78%** (95%CI 66.47 to73.09%)	**72.44%** (95%CI 69.05 to75.83)
Odds ratio	**1.17** (95% 0.64 to2.14)	**1.22** (95%CI 0.61 to2.43)

The results indicate that there is no statistically significant difference between the two groups. In 4 studies which showed higher eradication rates, drug doses were either higher or duration was longer than the remanding 10 studies. A study done by Laurent et al used much lower azthromycin doses

for a shorter duration and favoured the clarithromycin arm. This implies that the dosing and duration could affect the eradication of *H.pylori* when compared with standard first line therapy.

Adverse effects

Data for the occurrence of adverse effects were collected from 10 RCTs as 4 studies failed to report on adverse effects. The total number of adverse effects with azithromycin differed significantly from clarithromycin regimen:

	Total % Adverse effects
Azithromycin regimen	**15.8%** (95% CI 12.50 to19.12%)
Clarithromycin regimen	**25.20%** (95% CI 21.44 to28.96%)
Odds ratio	**0.58** (95% CI 0.41 to 0.82)
P-value	0.002

These results are in favour of the Azithromycin regimen having fewer adverse effects as compared to clarithromycin group.

Comment

The findings in this meta-analysis show that when comparing an Azithromycin based regimen to a Clarithromycin based triple therapy the outcomes are similar. Eradication rates are similar as compared to the control group. The final point estimate on the forest plot shows no statistically significant difference between the 2 comparison groups.

Review of 10 studies reporting common adverse effects, showed a statistically significant reduction in reported effects.

In the meta-analysis 4 trials favoured the azithromycin arm; all were of good quality In terms of study design. These studies used either a higher dose of 1g daily or longer treatment course of 7 days. The remaining 10 studies either used a lower dose or shorter duration of treatment. Based on these findings we appreciate that efficacy is affected by both dosage of drug and duration of treatment.

B. Sarkeshikian SS, Iranikhah A, Ghadir MR. Azithromycin based triple therapy versus standard clarithromycin based triple therapy in eradication of Helicobacter pylori infection in Iran: a randomized controlled clinical trial. Turk J Gastroenterol. 2013;24(1):10-4.

This was a prospective, open label; randomized controlled trial carried out between 2007-2009, 236 participants who presented with dyspepsia. All participants received upper gastrointestinal endoscopy and underwent rapid urease testing to confirm Helicobacter pylori infection. They were then randomized to a treatment arm, which consisted of 10 days of clarithromycin, amoxicillin, and omeprazole, (CAO) or 10 days of azithromycin, amoxicillin, and omeprazole (AAO). Urease breath test was performed in patients 6 weeks after end of treatment to assess eradication. All side effects were recorded. Seventy six participants completed the clarithromycin based triple therapy and 89 participants the azithromycin based therapy. Per protocol, eradication rate was 83% with clarithromycin and 75% in the azithromycin group with a p-value of 0.158. Adverse effects were comparable within the two groups.

The outcome from this study suggest that azithromycin based triple therapy can be as effective as clarithromycin combination. The azithromycin based regimen could be considered as an alternative choice for Helicobacter pylori eradication, in areas where health resources are limited.

Group 1 (CAO)	**Group 2 (AAO)**
Clarithromycin 500mg 12 hourly for 10 days	Azithromycin 250mg 12 hourly for 4 days
	Azithromycin 250mg daily for 6 days
Omeprazole 20mg 12 hourly	Omeprazole 20mg 12 hourly
Amoxicillin 1g 12 hourly	Amoxicillin 1g 12 hourly

Total participants enrolled:	n=236
Number of participants loss to follow up:	n=71/236
Participants analysed by Per protocol:	n=165 Group 1: n= 76 Group 2: n= 89

Results

No confidence intervals available

	Eradication rate by Per protocol analysis
Azithromycin regimen	75%
Clarithromycin regimen	83%
P-value	0.158

Percentage Adverse effects

CAO Group 1. n=17/76	22.3%
AAO Group 2. n=31/89	16.8%

Comment

The outcome from this study show that there is no significant difference with a p-value of 0.158, calculated using a per protocol analysis. The report of adverse effects between the 2 groups were similar with no apparent statistical significance.

In this study the regimen of clarithromycin used was in keeping with the Maastricht IV consensus and thus high eradication rates can be expected. Compared to the experimental group there was no statistically significant difference.

An important limitation to this study could be the loss of 71 participants who were not included in the analysis since they failed to complete the trial. And no reasons were mentioned as to why they dropped out.

Summary/Recommendations:

	Unit cost	Regimen options		
Azithromycin	500mg tablet	500mg dly x 7d	1g dly x 3d	250mg 12 hourly x 4d/ 250mg dly 6d
Cost in ZAR	3.34	23.38	20.04	19.44/14.58
Clarithromycin	500mg tablet	500mg 12 hourly x 7d	500mg 12 hourly x 10d	500mg 12 hourly x 14d
Cost in ZAR	3.42	47.88	68.40	95.76

The outcomes presented by Dong *et al* showed no significant difference between the 2 treatment groups. We need to be cognisant of the fact that the dose of clarithromycin used in many of the trials within the meta-analysis was 500mg twice daily for only 7 days.

The recommendation from the 2012 Maastricht IV Consensus Report[iv] is to extend the duration of PPI-clarithromycin-containing triple therapies from 7 to 10-14 days to improve eradication by 5%. This recommendation is based on 4 meta-analyses showing similar results: an eradication improvement of 4% with 10-day treatment, and 5-6% with 14-day treatment.

From the meta analysis using a high dose or longer duration of azithromycin has shown no significant difference when compared to a 7 day clarithromycin course. Efficacy is maintained, adverse effects are less and a significant cost benefit can be appreciated when using azithromycin. In the trial done by Saied et al has also showed no difference when using azithromycin in lower doses of 250mg but for a longer duration of 10 days compared to the clarithromycin regimen recommended by the Maastricht IV consensus. Therefore based on these findings use of azithromycin within resource limited settings could be of benefit

Importantly to note that even though azithromycin is the more cost effective option based on the findings from the meta-analysis done by Dong et al; suggestions from the Maastricht IV consensus advocate at least 10 days of clarithromycin treatment to have eradication rates of 80%. If we were to prolong the duration of azithromycin longer than 7 days we do not know if this would affect the efficacy at all, azithromycin has a long half-life of up to 27 days. This would translate into increased cost.

References:

[i] Dong J, Yu XF, Zou J. Azithromycin-containing versus standard triple therapy for Helicobacter pylori eradication: a meta-analysis. World J Gastroenterol. 2009 Dec 28;15(48):6102-10.

[ii] Sarkeshikian SS, Iranikhah A, Ghadir MR. Azithromycin based triple therapy versus standard clarithromycin based triple therapy in eradication of Helicobacter pylori infection in Iran: a randomized controlled clinical trial. Turk J Gastroenterol. 2013;24(1):10-4.

[iii] Contract circular: HP02-2015 AI. http://www.health.gov.za/

[iv] Malfertheiner P, Megraud F, O'Morain CA, Atherton J, Axon AT, Bazzoli F, Gensini GF, Gisbert JP, Graham DY, Rokkas T, El-Omar EM, Kuipers EJ; European Helicobacter Study Group. Management of Helicobacter pylori infection—the Maastricht IV/ Florence Consensus Report. Gut. 2012 May;61(5):646-64.