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Full Length Research Paper

Prevalence and Emergence of Drug Resistance in *Helicobacter pylori*: Review

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ABSTRACT

Helicobacter pylori is spiral shaped Gram negative bacterium, colonizes the stomach and can persist for a lifetime if not completely eradicated. Infection caused by this bacterium is the most common in the world and it is much widespread in developing countries. Prevalence of *Helicobacter pylori* antibiotic resistance is increasing. It is the main factor displeasing efficacy of current treatment regimens. The epidemiology of Helicobacter pylori resistance to antibiotics is poorly documented in developing countries with many reasons. Therefore, this review aims to assess the prevalence and drug resistance pattern of *Helicobacter pylori*. Different literature was searched with different electronic databases and reviewed systematically to get tangible findings. This review tries to include recent articles across the world by giving more emphasis for Africa performed on prevalence and drug resistance patterns of *Helicobacter pylori*. According to this review there is a need to embark on more studies to draw attention to the clinical and epidemiological significance of this pathogens.

Keywords: Prevalence, drug resistance, *helicobacter pylori*

INTRODUCTION

Helicobacter pylorus is a small, spiral, gram-negative bacillus that appears to inhabit the mucous layer overlying the gastric epithelial cells in humans (Tadesse et al., 2013). *Helicobacter pylori* infection is usually acquired during the early years of life and persists for several years (Altyar et al., 2015). Many literature indicates the prevalence of *Helicobacter pylori* infection has been reported to increase with many risk factors (Cherian et al., 2008). The exact routes of infection by *Helicobacter pylori* are still not identified. However a few researcher suggests faecal-oral or oral–oral routes and is associated with close contact (interfamilial) and poor sanitation (Etukudo et al., 2012). According to previous sero-epidemiologic studies, about 50% and nearly 90% of adults in the developed and developing countries respectively were seropositive (Tadege et al., 2005). The public health impact of *Helicobacter pylori* infection merits attention. In order to intend preventive strategies, the elucidation of the mode of spread of this potentially fatal pathogen is crucial (Ndip et al., 2004). Worldwide *Helicobacter pylori* antibiotic resistance towards different antibiotics is increasing. The prevalence of resistance also shows variation across different geographic areas, and associated with the consumption of antibiotics (Francesco et al., 2010).

METHODS

The literatures were searched in different electronic data base like Pub Med and Google scholars based on the key words like *Helicobacter pylori* infection, prevalence and drug resistance. Studies published on different reputable journals and emphasizing for objective of this study were reviewed systematically. Articles written in English language and having full length forms were only included. Articles published before 1997 were excluded.

RESULTS AND DISCUSSION

Prevalence of *Helicobacter pylori* Infection

Helicobacter pylorus is found in half the population of the world. Its prevalence is highly uneven in relation to geography, ethnicity, age, and socioeconomic factors high in developing countries and lower in the developed world. In general, there has been a

decreasing trend in the prevalence of *Helicobacter pylori* in many parts of the world in recent years. On the other hand, the impact of this bacterium is still well known in less developed regions (Hastings et al., 2014). *Helicobacter pylori* is an important cause of acute and chronic gastritis, peptic ulcers, gastric adenocarcinoma, and mucosa-associated lymphoid tissue lymphoma (Zhannat et al., 2014). The overall prevalence is different across different geographic area and population, this may be due to socioeconomic differences between populations (Yvonne et al., 2001). *Helicobacter pylori* is acquired during childhood or at any age, but the incidence is higher in children. The prevalence of *Helicobacter pylori* in childhood (<10 years) was reported 80% in developing countries (Secka et al., 2014). The infection rate among children has reached to 50-60% in Bangladesh, 48% in Ethiopia and 50% in Egypt. *Helicobacter pylori* infection is prevalent in Iran, and the estimated prevalence of *Helicobacter pylori* infection is reported 65% (Najafi et al., 2014).

Helicobacter pylori is extensive in Africa. As reviewed in (Cherian et al., 2008) Infection rates for adults are 85% in Nigeria, 82.8% in Senegal, and 77.5% in Zaire. In Nigeria 82% of those infected acquire the bacterium by age 10; in South Africa 80% by age 10; and in Zaire 66% by age 9. And also the epidemiology of African refugee children resettled in Australia are 34 % Sudanese, 29% Burundian, 12% Liberian, 11% Congolese 12% Eritreans, and 4% from other countries (Cherian et al., 2008).

At present there are only few studies addressing the likelihood of *Helicobacter pylori* infection in Ethiopian patients (Tdege et al., 2005). But a few studies reveal the prevalence of *Helicobacter pylori* infection in different patients, for instance, in dyspeptic patients in Northwest Ethiopia is 88.9% in male, 82,8% in female, 81.8% at age(<20 years),82.3% at age (20-29), 81.0% at age (30-39), 84.4% at age (40-49), 100% at age (50-79), 85.8% in rural population and 85.2% in urban population. From the total subjects blood group O was the most common blood group (43.3%) in the patients followed by blood groups B (28.4%), A (22.3%) and AB (6.0%) (Moges et al., 2006). However, the frequency of *Helicobacter pylori* in dyspeptic (63%) and non-dyspeptic patients (49%) using Enzyme Immuno Assay and in dyspeptic patients (70%), and non-dyspeptic patients (54%) using immunoblot, in the blood group O (43%) followed by A (23.5%), B (22.5%) and AB (11%) (Tadege et al., 2005). The study in South Ethiopia shows, endoscopic findings and *Helicobacter pylori* status of 834 consecutive gastroscopy patients, 22% normal, 9% oesophagitis and oesophageal carcinoma, 31%gastritis, 7% pyloric ulcer, 6% pyloric cancer, 16% doudnal ulcer, 13% pyloric stenosis (Henriksen et al., 1999). The prevalence of *Helicobacter pylori* infection in TB patients in Jimma, Southwest Ethiopia is 26.3% at age (18-34), 26.3% at age (35-44), 47.4% at age (>45), in general prevalence of *H. pylori* infection in TB positive patients and healthy controls was 19 (35.2%) and 11(20.4%) respectively. In this study, *Helicobacter pylori* among TB patients were higher compared with the data for healthy controls from the same area. This suggests that the two infections are interconnected; means that the variability of *Helicobacter pylori* infection in the two groups is significantly different (Kebede et al., 2015).

Emergence of drug resistance *Helicobacter pylori*

If possible, the infectious disease treatment should have be chosen based on culture and susceptibility testing using biological material. This is not always practicable in *Helicobacter pylori* infected patients because it requires an invasive procedure in certain patients. For a higher chance of eradicating the infection during the first attempt, an experimental first line therapy should be chosen based on the pattern of local antimicrobial resistance (Federico et al., 2014). Multiple therapeutic regimens have been demonstrated to effectively cure patients of *Helicobacter pylori* infection. Metronidazole or clarithromycin must be included to obtain eradication rates exceeding 90%. The highly effective regimen includes metronidazole, omeprazole, and clarithromycin and may be administered for 7 to 14 days, yielding greater than 90% eradication. No single agent has been shown to be effective for curing infection in the majority of patients, because of the increasing problem of antimicrobial resistance, regimens with either tetracycline or amoxicillin and metronidazole represent cost effective options in developing countries (Versalovic et al., 2003). There has been a significant decrease in the success rate of empirical triple therapy to treat *Helicobacter pylori* infection, mostly due to a rapid increase in the prevalence of antibiotic resistant strains. Antibiotic resistance is a constantly evolving process and there are significant regional variations in *Helicobacter pylori* antibiotic resistance rates. As such, local surveillance of antibiotic resistance is warranted to guide clinicians in their therapeutic choice. Standard culture based antimicrobial susceptibility testing and molecular methods provide key opportunities to modify *Helicobacter pylori* treatment based on the detection of antibiotic resistant strains, thus enhance eradication rates and decrease *Helicobacter pylori* associated disease (Smith et al., 2014). Different publication revealed that antibiotics are the basis of treatment for *Helicobacter pylori*, usually highly sensitive to certain antibiotics, particularly Amoxicillin and to antibiotics in the macrolide class, like Clarithromycin. Either class of antibiotics serves successfully as a second antibiotic in a three-drug regimen. Other antibiotics that are

sometimes used include Tetracycline, Metronidazole and Ciprofloxacin. However, prevalence of *Helicobacter pylori* antibiotic resistance is increasing worldwide, and is the main factor affecting the effectiveness of current therapeutic regimens (Weerasekara et al., 2014). *Helicobacter pylori* resistance to antibiotics is uneven worldwide, being lower in developed countries and higher in developing Countries, and also in Ethiopia (Henriksen et al., 1999), due to widespread and indiscriminate use of antibiotics (Egan et al., 2007). The main antibiotic resistance mechanisms for *Helicobacter pylori* is point mutations on the chromosome of bacteria that leads to changes in each drug's site of action and acquisition of foreign genes carried on mobile genetic elements can also play a role (Weerasekara et al., 2014), in addition to frequent use of antimicrobials (selection pressure), so that the resistant bacteria resist and survive the harsh environment and followed by spread of the resistance genes and transferred by mobile genetic elements among bacterial population (Khademi et al., 2015). Several studies have been performed that signifies the *Helicobacter pylori* prevalence of resistance to antibiotics. However, several of them have limitations, in representativeness and number of the tested strains (Megraud et al., 2004). As indicated in all patients with active or recurrent peptic ulceration that, combined therapy including two of the following antibiotics amoxicillin, tetracycline, metronidazole or clarithromycin, plus a proton pump inhibitor, bismuth salt or ranitidine bismuth citrate is the therapy most commonly used to eradicate *Helicobacter pylori* (Aiman et al., 2008). However, the most successful eradication therapy includes combination treatment regimen in which the number, the frequency and the duration of medications and therapy should be considered (Khademi et al., 2015).

Metronidazole resistance: Metronidazole is the compound used to treat *Helicobacter pylori* infection and its effect is concentration dependent. The metronidazole resistance rate varies significantly in different geographical areas, being 92.4% in Africa, 44.1% in America, 37.1% in Asia, and 17.0% in Europe (Yang et al., 2014). Due to the common use of metronidazole to treat parasitic infections the prevalence of metronidazole resistance is much higher in developing countries than in developed countries (Frenck et al., 2003). For example as high as 80-90% in developing countries, as reported in Africa (Burkina Faso, Zaire). The cause of this resistance may also be linked to treatment of genital infections, especially trichomonasis and, hence, strains isolated from women are more likely to be resistant than strains isolated from men. Another Possible reason may be the use of such compounds to diagnose dental infections (Megraud et al., 1998). According to the previous review (Francesco et al., 2010) the overall resistance of metronidazole is 28.1%, and revealed that, in Africa 92.4%, America 44.1%, Asia 37.1%, to 17.0%. The lowest metronidazole resistance in Europe was observed in Sweden 14.4%; and The Netherlands 14.4%, the highest being detected in Denmark 28.3%, In Asia, metronidazole resistance rate was high in Korea 49.6% and low in Japan 14.7%.

Resistance of *Helicobacter pylori* to metronidazole, isolates in Dakar, Senegal, from 2007-2009 shows 85% (Seck et al., 2013). The in vitro metronidazole resistance of 19 Ethiopian strains of *Helicobacter pylori* is high as compared to 19 Norwegian strains according to Henriksen (Henriksen et al., 1999), which are 18 strains in Ethiopia is resistant, but only 3 strains in Norway. Metronidazole resistance in South Africa also very high 95.5% (Tanih et al., 2010). Generally, resistance of metronidazole was commonly encountering a finding of clinical significance that calls for continuous surveillance of antibiograms to guide empiric treatment.

Clarithromycin resistance: Eradication of *Helicobacter pylori* infection is important because of its high prevalence and implications in other diseases (Yang et al., 2014). The eradication of *Helicobacter pylori* not only improves peptic ulcer healing but also prevents its recurrence and reduces the risk of developing gastric cancer. However, the prevalence of antibiotic resistance in *Helicobacter pylori* is increasing worldwide and does a growing public health problem need more attention. Especially, resistance to clarithromycin is the most important factor causing treatment failure and is responsible for the decline of the *Helicobacter pylori* eradication rate (Binh et al., 2013). Combinations of anti-secretory agents and antimicrobial agents have been proposed as first line or second line therapy for its treatment. Nonetheless, treatment outcome depends on many factors, including intragastric acidity and resistance to antimicrobial agents. Resistance is, 13.4% in Africa, 21.0% in Asia, 11.1% in Europe and 29.3% in United States (Yang et al., 2014). In which, the highest resistance was reported in Spain 49.2%, and lowest in Sweden 1.5%, and The Netherlands 0.8%, In Asian countries, also a high clarithromycin resistance rate was detected in Japan 40.7%, while the lowest value was found in Malaysia 2.1%. Resistance rate in USA by regions is 15% in Northeast, 14% in south, 4% in West, 11% in Midwest and the total resistant is 45% (Duck et al., 2004). Primary and combined resistance in paediatric *Helicobacter pylori* isolates from 2000-2001 in Bulgarian children is 12.4% for clarithromycin and 4.5% combined with Metronidazole (Boyonava et al., 2002). Among Brazilian localities, *Helicobacter pylori* clarithromycin resistance presents high prevalence, varying from 7-16% in adults and 27% in children (Suzuki et al., 2013). For that reason, considering the

clinical importance of primary *Helicobacter pylori* resistance to clarithromycin, its prevalence should be considered before choosing eradication regimens.

Amoxicillin resistance: Amoxicillin is one of the first line antibiotics used for eradication of *Helicobacter pylori* and its resistance is not common worldwide. The mechanisms of resistance to amoxicillin are known for their complexity, which explains the large variations in its prevalence worldwide. Amoxicillin, cross the outer cell membrane of *Helicobacter pylori* through porin channels and diffuse to the bacterial cytoplasm. Once inside the cell, amoxicillin binds to penicillin binding proteins (PBPs) inhibiting their transpeptidase activity and, thereby, impairing the synthesis of the peptidoglycan wall. In general, bacterial resistance to amoxicillin is due to mutational modification in or around the penicillin-binding motifs of PBPs (Vale et al., 2011). According to previous review (Francesco et al., 2010), amoxicillin resistance was detected in Europe, available data from two studies enrolling 599 patients found a prevalence rate <1%. In contrast, conflicting data were reported in African and Asia, where amoxicillin resistance was absent in Senegal, while 85.6% in Cameroon, ranging from 0% in Japan, 8.8%, in Korea and 36.1% in Taiwan; although another study performed in Taiwan found prevalence as low as 0.9% and 2.2% in Alaska. Primary resistance of *Helicobacter pylori* isolates from Bulgarian children is 0% (Boyonava et al., 2002), 0% in Spain Madrid (Agudo et al., 2009), very small in Western central Colombia (Alvarez et al., 2009), but 7.2% in Hamadan Iran from gastric biopsies (Majlesi et al., 2013). Amoxicillin resistance of *Helicobacter pylori* among Kenyans is 0% (Kimang et al., 2010).

Tetracycline resistance: While currently not used widely, tetracycline are a component of the bismuth based triple therapy regimen which was recommended in1990 to treat *Helicobacter pylori* infection. Their site of action is the ribosome. It is thought that *Helicobacter pylori* do not acquire resistance to tetracycline (Aiman et al., 2008). Although the resistance rate of clarithromycin and metronidazole has been increased, resistance of tetracycline and amoxicillin was not observed (Debets et al., 1999). Tetracycline resistance rate of *Helicobacter pylori* did not significantly different across different geographic area. For example, in Europe 2.1%, Asia 2.4%; and America 2.7%, but higher in Africa 43.9%. In fact, the resistance was absent in 352 patients from Alaska, 0.3% in Sweden 0.2% in Taiwan and 0% in Spain (Lopez et al., 1997). In contrast, higher in Korea 8.8%, Chile 26.8% and Cameroon, 43.9% (Francesco et al., 2010).

Levofloxacin resistance: The use of levofloxacin for *Helicobacter pylori* eradication is increasing worldwide because of its role in save therapy regimens following the failure of other treatments (Francesco et al., 2011). Levofloxacin is bactericidal antibiotics in the quinolone class; its mechanism of action is blocking of bacterial DNA replication by binding the enzyme DNA gyrase, coded for by genes gyrA and gyrB. *Helicobacter pylori* resistance to these antibiotics is developed by mutations in gyrA QRDR (quinolone resistance-determining region) (Fernandez et al., 2009). *Helicobacter pylori* resistant to levofloxacin are 2.29% in America, 8.9% Europe, 8.39% in Asia (Wu et al., 2012). *Helicobacter pylori* also show resistant to rifamputin and multidrug (Chey et al., 2007).

Multidrug resistant *Helicobacter pylori*: *Helicobacter pylori* emerge as two or more drug resistant bacteria. For example (Clarithromycin + metronidazole) resistant is observed 4.9% in Bulgaria (Boyanova et al., 2009) 5.2% in Hong Kong (Hung et al., 2009), 2.2% in Ireland (Hooton et al., 2006), 3.5% in Italy (Zullo et al., 2007), 6.6% in Japan (Kato, 2009), 0.6 % in seweden (Storskrubb et al., 2006). (Clarithromycin + levofloxacin) resistant is observed 3.5% in Hong Kong (Hooton et al., 2006), 1.6% in Italy. (Metronidazole + levofloxacin) resistant is 4.9% in Italy (Zullo et al., 2007). (Clarithromycin +metronidazole + rifamputin) resistant is 0.9% in Germany (Wueppenhorst et al., 2009). (Clarithromycin +metronidazole +levofloxacin) resistant is 15% in Alaska (Ndip et al., 2008), 13.4% in Germany, 0.8% in Italy (Zullo et al., 2007). (Clarithromycin + levofloxacin + rifampicin) shows 0.08% resistant in Germany (Wueppnhorst et al., 2009). However, (Clarithromycin + metronidazolr +levofloxacin + rifampicin) shows 4.9% resistance in Bulgaria (Boyanova et al., 2009) and 0.7% resistance in Germany (Wueppenhorst et al., 2009). However, no clear documented data that show multidrug resistant *Helicobacter pylori* in Africa. Due to drug resistance the treatment of *Helicobacter pylori* infection continues to evolve. Triple therapy has been modified in that it is now recommended to use double-dose (80 mg) proton-pump inhibitor (PPI), quadruple dose (2 g) amoxicillin, and clarithromycin (1 g) for at least 10 days, and preferably 14 days (Neil et al., 2018). This might be a challenge in developing country in many aspects.

CONCLUSION

Although *Helicobacter pylori* presents an incredible challenge as a significant cause of gastric related morbidities, a shortage of knowledge on its prevalence, epidemiology and antimicrobial chemotherapy exist in worldwide and in Ethiopia. There is need therefore to embark on more studies to draw attention to the clinical and epidemiological significance of this pathogen. Worldwide *Helicobacter pylori* antibiotic resistance towards different antibiotics is increasing. The amount of data I have reported in this review reveals that the knowledge about *Helicobacter pylori* antibiotic resistance is a topic with a speedily and

regularly increasing. These data emphasize the need of a steady surveillance of *Helicobacter pylori* antibiotic resistance, so as to tailoring therapy is feasible for clinical practice.

REFERENCES

1. Agudo S, Alarcon T, Cibrelus L, Urruzuno P, Martinez MJ, Brea ML (2009). High percentage of clarithromycin and metronidazole resistance in Helicobacter pylori clinical isolates obtained from Spanish children. Revista Espanola Quimioterapia. 22:88-92.

2. Aiman M, Momenah, Atif H, Asghar (2008). Prevalence and antibiotic resistance among helicobacter pylori clinical isolates from main hospitals in the western region of Saudi Arabia. Pakistan Journal of Medical Sciences. 24:100-103.

3. Altyar IE, Abdalla AM, Abdalwahab SS, Abdalwahab SS (2015). The Seroprevalence of Helicobacter pylori Infection in Tripoli (Libya). Nature and Science. 13:81-86.

4. Alvarez A, Moncayo JI, Santacruz JJ, Santacoloma M, Corredor LF, Reinosa E (2009). Antimicrobial Susceptibility and Mutations Involved in ClarithromycinResistance in Helicobacter pylori Isolates from Patients in theWestern Central Region of Colombia. Antimicrobial agents and chemotherapy. 53:4022-4024.

5. Binh TT, Suzuki R, Shiota S, Kwon DH, Yamaoka Y (2013). Complete genome sequences of Helicobacter pylori clarithromycin-resistant strains. Genome Announc. 1:912-913.

6. Boyonava L, Koumanava R, Gergova G, Popava M, Mitov I, Kovacheva Y, Berjian S, Katsarov N, Nikolav R, Krastev Z (2002). Prevalence of resistant Helicobacter pylori isolates in Bulgarian children. Journal of medical microbiology. 51:786-790.

7. Boyanova L, Ilieva J, Gergova G, Spassova Z, Nikolov R, Davidkov L, Evstatiev L, Kamburov V, Katsarov N, Mitov I (2009). Evaluation of clinical and socio-demographic risk factors for antibacterial resistance of Helicobacter pylori in Bulgaria. Journal of medical Microbiology. 58: 94-100.

8. Cherian S, Forbes D, Sanfilippo F, Cook A, Burgner D (2008). The epidemiology of Helicobacter pylori infection in African refugee children resettled in Australia. The Medical Journal of Australia. 189:438-441.

9. Chey WD, Wong BCY (2007). American College of gastroenterology guideline on the management of Helicobacter pylori infection. American journal of gastroenterology. 102:1808-1825.

10. De Francesco V, Giorgio F, Hassan C, Manes G, Vannella L, Panella C, Ierardi E, Zullo A (2010). Worldwide H. pylori Antibiotic Resistance: a Systematic Review. Journal of Gastrointestinal Liver Diseases. 19: 409-414.

11. De Francesco V, Zullo A, Hassan C, Giorgio F, Rosania R, Ierardi E (2011). Mechanisms of Helicobacter pylori antibiotic resistance: An updated appraisal. World Journal of Gastrointestinal Pathophysiology. 2:35-41.

12. Debets Ossenkopp YJ, Herscheld AJ, Pot RGJ, Kuipres EJ, Kusters JG, Vandenbroucke Grauls CMJE (1999). Prevalence of Helicobacter resistance to metronidazole, clarithromycin, amoxicillin, tetracycline and trovafloxacin in Netherlands. Journal of antimicrobial chemotherapy. 43:511-515.

13. Duck WM, Sobel J, Pruckler JM, Song Q, Swerdlow D, Friedman C, Sulka A, Swaminathan B, Taylor T, Hoekstra M, Griffin P, Smoot D (2004). Antimicrobial Resistance Incidenceand Risk Factors amongHelicobacter pylori–InfectedPersons, United States Emerging Infectious Diseases. 10:1250-1265.

14. Egan BJ, Katicic M, Connor HJO, Morain CAO (2007). Treatment of Helicobacter pylori. Blackwell Publishing Ltd, Helicobacter 12(Suppl.1):31-37.

15. Etukudo OM, Ikpeme EE, Ekanem EU (2012). Seroepidemiology of Helicobacter pylori infection among children seen in a tertiary hospital in Uyo, southern Nigeria. Pan African Medical Journal. 12:1937-8688.

16. Fernandez MC, Romero JV (2009). Infection with Helicobacter pylori Prevalence, research and impact of antibiotic resistance. Revista Espanola de Enfermedades digestivas. 101:743-756.

17. Federico A, Gravina AG, Miranda A, Loguercio C, Romano M (2014). Eradication of Helicobacter pylori infection: Which regimenfirst? World Journal of Gastroenterology. 20: 665-672.

18. Frenck RW, Clemens J (2003). Helicobacter in the developing world. Microbes Infection. 5: 705-713.

19. Hastings EV, Yasui Y, Hanington P, Goodman KJ, CAN Help Working Group (2014). Community-driven research on environmental sources of H. pylori infection in arctic Canada, Gut Microbes. 5:5606-5061.

20. Henriksen TH, Nysaeter G, Kebede TM, Berstad A, Setegn D, Brorson B, Kebede T, Berstad A (1999). Peptic ulcer disease in South Ethiopia is strongly associated with Helicobacter pylori. Transactions of the royal society of tropical medicine and hygiene. 93: 171-173.

21. Hung KH, Sheu BS, Chang WL, Wu HM, Liu CC, Wu JJ (2009). Prevalence of primary fluoroquinolone resistance among clinical isolates of Helicobacter pylori at a University Hospital in Southern Taiwan. Helicobacter. 14:61-65

22. Hooton C, Dempsey C, Keohane J, O'Mahony S, Crosbie O, Lucey B (2006). Helicobacter pylori: prevalence of antimicrobial resistance in clinical

isolates. Brazilian Journal of Biomedical Sciences. 63:113-116.

23. Kato S (2009). Helicobacter pylori eradication therapy in children. Nippon Rinsho. 67:2311-2316.

24. Kebede W, Mathewos B, Abebe GH (2015). Pylori Prevalence and Its Effect on CD4+ Lymphocyte Count in Active Pulmonary Tuberculosis Patients at Hospitals in Jimma, Southwest Ethiopia. International Journal of Immunology. 3: 7-13.

25. Khademi F, Poursina F, Hosseini E, Akbari M, Ghasemian Safaei H (2015). Helicobacter pylori in Iran: A systematic review on the antibiotic resistance. Iran Journal of Basic Medical Sciences. 18:2-7.

26. Kimang'a DN, Revathi G, Kariuki S, Sayed S, Devani S (2010). Helicobacter pylori: Prevalence and antibiotic susceptibility among Kenyans. South African Medical Journals. 100: 53-57.

27. López-Brea M, Domingo D, Sanchez I Teresa Alarcon T (1997). Evolution of resistance to metronidazole and clarithromycin in Helicobacter pylori clinical isolates from Spain Journal of Antimicrobial Chemotherapy. 40:279-281.

28. Majlesi A, Khorasani MS, Khalilian AR, Aslani MM, Jaefari M, Mohammad Yousef Alikhani MU (2009). Antibiotic Susceptibility of Helicobacter pylori Clinical Isolates in Hamadan, West of Iran. International Journal of Entric Pathogenesis. 1:23-29.

29. Megraud F (1998). Antibiotic resistance in Helicobacter pylori infection. British Medical Bulletin. 54: 207.

30. Megraud F (2004). H pylori antibiotic resistance: prevalence, importance, and advances in test. Gut. 53:1374–1384.

31. Moges F, Kassu A, Mengistu G, Adugna S, Andualem B, Nishikawa T, Ota F (2006). Seroprevalence of Helicobacter pylori in dyspeptic patients and its relationship with HIV infection, ABO blood groups and life style in a university hospital, Northwest Ethiopia. World Journal of Gastroenterology. 12:1957-1961.

32. Najafi M, Seighali F (2014). Eradication of Helicobacter pylori with triple therapy regimen (Omeprazole, Clarithromycin and Amoxicillin) in children for seven days (A Pilot Study). J Pediatr Rev. 2:72-77

33. Ndip RN, Malange Takang AE, Ojongokpoko JE (2008). Helicobacter pylori isolates recovered from gastric biopsies of patients with gastro-duodenal pathologies in Cameroon: current status of antibiogram. Tropical Medicine for Internal Health. 13:848-854.

34. Neil R. O'Morain, Maria P. Dore, Anthony J. P. O'Connor, Javier P. Gisbert, Colm A. O'Morain (2018) . Treatment of Helicobacter pylori infection in 2018. Helicobacter. 23(Suppl. 1):e12519.

35. Ndip RN, Malange AE, Akoachere JFT, MacKay WG,Titanji VPK, Weaver LT (2004). Helicobacter pylori antigens in the faeces of asymptomatic children in the Buea and Limbe health districts of Cameroon: apilot study. Tropical Medicine and International Healt. 9: 36-44.

36. Secka O, Moodley Y, Antonio M, Berg DE, Tapgun M (2014). Population Genetic Analyses of Helicobacter pylori isolates from Gambian Adults and Children. 9:456-458.

37. Seck A, Burucoa C, Dia D, Mbengue M, Onambele M, Raymond J, Breurec (2003). Primary antibiotic resistance and associated mechanisms in Helicobacter pylori isolates from Senegalese patients. Annals of Clinical Microbiology and Antimicrobials. 123: 452-459.

38. Smith SM, O'Morain C, McNamara D (2014). Antimicrobial susceptibility testing for Helicobacter pylori in times of increasing antibiotic resistance. World Journal of Gastroenterology. 20: 9912-9921.

39. Storskrubb T, Aro P, Ronkainen J, (2006). Antimicrobial susceptibility of Helicobacter pylori strains in a random adult Swedish population. Helicobacter. 11: 224-230.

40. Tadesse E, Gebru Mulugeta G, Shimelis T (2013). Evaluation of SD BIOLINE rapid antibody test for diagnosis of Helicobacter pylori. 41,55:62-66.

41. Tadege T, Mengist Y, Desta K, Asrat D (2005). Seroprevalence of Helicobacter pylori Infection in and its Relationship with ABO Blood Groups. Ethiopian Journal of Health Development. 19:55-59.

42. Vale FF, Rosa MR, Oleastro M (2011). Helicobacter pylori resistance to antibiotics. Science against microbial pathogens: communicating current research and technological advances A.

43. Versalovic J (2003). Helicobacter pylori: Pathology and Diagnostic Strategies. Am J Clin Pathol. 119:403-412.

44. Weerasekara D, Dissanayake DMBT, Athukorala GIDDAD, Weerasekera MM, Fernando SSN (2014). Antibiotic resistance in Helicobacter pylori: Recent insights. Sri Lankan Journal of Infectious Diseases. 4:2-8.

45. Wu W, Yang Y, Sun G (2012). Recent Insights into Antibiotic Resistance in Helicobacter pylori Eradication. Hindawi Publishing Corporation Gastroenterology Research and Practice.

46. Wueppenhorst N, Stueger HP, Kist M, Glocker E (2009). Identification and molecular characterization of triple- and quadruple-resistant Helicobacter pylori clinical isolates in Germany. Journal of Antimicrobial Chemotherapy. 63: 648-653.

47. Yvonne THP, van Duynhoven, Rob de Jonge (2001). Transmission of Helicobacter pylori: a rolefor food? Bulletin of the World Health Organization. 79: 455-460.

48. Yang JC, Lu CW, Lin CJ (2014). Treatment of Helicobacter pylori infection: Current status and future concepts. World Journal of Gastroenterology. 20: 5283-5293.

49. Zhannat z. Nurgalieva, Hoda M, malaty, David Y, Graham, Almuchambetova R, Machmudova A, Kapsultanova D, Michael S Osato, Blaine F, Hollinger B, Abai zhangabylov (2014). Helicobacter pylori infection in Kazakhstan: effect of water source and household hygiene. 67:201-206.

50. Zullo A, Perna F, Hassan C (2007). Primary antibiotic resistance in Helicobacter pylori strains isolated in northern and central Italy. Aliment Pharmacology Therapeutics. 25: 1429-1434.