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Eradication of *Helicobacter pylori* with Standard Triple Therapy and its Clinical Implications

By

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This is to certify that the dissertation prepared by Endalew Gebeyehu Belete, entitled "**Eradication of *Helicobactor pylori* with Standard Triple Therapy and its Clinical Implications"** and submitted in fulfillment of the requirements for the Degree of Doctor of Philosophy in Pharmacology complies with the regulations of the university and meets the accepted standards with respect to originality and quality.

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ABSTRACT

Eradication of *H. pylori* with standard triple therapy and its clinical implications

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Background: *Helicobacter pylori* eradication based on standard triple therapy (STT) has been accepted to curb risks associated with *H. pylori* infection, commonly chronic gastritis and peptic ulcer disease. However, rate of eradication of *H. pylori* with triple therapy has been claimed to be below the recommended level due to several factors such as adverse drug effects (ADEs) and its determinants. ADEs during triple therapy may initiate poor medication adherence, which in turn reduces rate of eradication and associated patient outcomes. Evaluation of symptom resolution after *H. pylori* eradication therapy is the most common clinical practice in Ethiopia. As a result, studies that aimed at assessment of the rate of *H. pylori* eradication with STT, incidence of ADEs, status of symptom resolution after therapy and predictors for each of these consequences can have paramount importance in improving eradication therapy based on triple therapy regimen.

Methods: STT based on a proton pump inhibitor, amoxicillin and clarithromycin was given to consented *H. pylori* positive adult outpatients in this facility based follow up study from May 2016 to April 2018 at Bahir Dar city in Ethiopia. Pre-developed structured questionnaire as used to collect anthropometric, sociodemographic and clinical data before and after eradication therapy. Eradication was confirmed with *H. pylori* monoclonal stool antigen test conducted after the end of 4–6 weeks of standard triple therapy. Data was analyzed by using descriptive statistics, chi-square test, bivariate and backward LR multivariate logistic regression. Significance was considered when p-value is less than 0.05 at 95%CI.

Results: A total of 421 patients who completed follow up were involved in this study. The overall *H. pylori* eradication rate was 90.02% (379/421). Self-reported ADE was the only factor associated with *H. pylori* eradication rate with adjusted odds ratio of 2.92 (95%CI; 1.52-5.59, p < 0.001). Nearly a quarter (26.1%) of the patients reported ADEs and of all the reported ADEs, more than 85% were revealed as gastrointestinal symptoms, including gastrointestinal discomfort (39.1%), nausea (13.6%), diarrhea (12.9%), constipation (12.7%), and anorexia (10%). Predictors of self-reported ADEs were failure of eradication therapy (AOR: 12.64; 95% CI [3.29 - 48.53], p=0.001), body mass index above 25 (AOR: 2.82; 95%CI [1.26 - 6.31], p = 0.011), pain feeling during long interval between meals (AOR: 2.18; 95%CI [1.20 - 3.98], p = 0.011), failure to achieve complete symptom resolution (AOR: 5-19; 95%CI [1.46 - 18.50], p =0.011) and duration of acid-pepsin disorder more than 3weeks (AOR: 3.67; 95%CI [1.62 - 8.29], p = 0.002). Patients who achieved complete symptom resolution were 84.3%, which was lower than the overall *H. pylori* eradication rate of 90.02%. Positive predictive value and negative predictive value of complete symptom resolution after *H. pylori* eradication therapy was 98.9% (351/355) and 57.6%(38/66), respectively. Being non-user of traditional homemade supplements prepared from Fenugreek and/or Flaxseed (AOR: 2.14 95%CI [1.25 - 3.65], p = 0.005) was the only factor associated with complete symptom resolution.

Conclusions: Modification or replacement of the STT observed in different healthcare institutions are not evidence-based since eradication of *H. pylori* with STT is still within the recommended level for clinical practice. Self-reported ADEs manifested with gastrointestinal symptoms are common during STT. Self-reported ADEs affect *H. pylori* eradication therapy. Body mass index, time duration of acid-pepsin disorder, pain feeling period in a day, eradication status and symptom resolution are determinants of self-reported ADEs. Success of *H. pylori* eradication is predictable

with complete symptom resolution. Use of traditional food supplements prepared from Fenugreek and/or Flaxseed during eradication therapy affects status of symptom resolution.

Key words: *H. pylori* eradication rate, Adverse drug effects, Predictive values, Complete symptom resolution, Associated factors

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1 List of Original Articles

This dissertation is primarily based on the following published articles.

Paper 1: Gebeyehu E, Nigatu D, Engidawork E (2019) *Helicobacter pylori* eradication rate of standard triple therapy and factors affecting eradication rate at Bahir Dar city administration, Northwest Ethiopia: A prospective follow up study. PLoS ONE 14(6): e0217645. https://doi.org/10.1371/journal.pone.0217645

Paper 2: Gebeyehu E, Nigatu D, Engidawork E (2019) Self-reported adverse drug effects and associated factors among *H. pylori* infected patients on standard triple therapy: Prospective follow up study. PLoS ONE 14(11): e0225585. https://doi.org/10.1371/journal.pone.0225585

Paper 3: Gebeyehu E, Nigatu D, Engidawork E (2021) Complete symptom resolution as predictor of *Helicobacter pylori* eradication and factors affecting symptom resolution: Prospective follow up study. PLoS ONE 16(2): e0246624. https://doi.org/10.1371/journal.pone.0246624

2 List of Acronyms/Abbreviations

ADEs: Adverse Drug Effect(s)

AOR: Adjusted odds ratio

BE: Barrett's Esophagus

COR: Crude odds ratio

CagA: Cytotoxin associated gene A

CT: Concomitant Therapy

EAC: Esophageal Adenocarcinoma

FD: Functional Dyspepsia

GC: Gastric Cancer

GERD: Gastroesophageal Reflux Disease

MALT-lymphoma: Mucosa-Associated Lymphoid Tissue (MALT) lymphoma

PPI: Proton Pump Inhibitor

TNF-α: Tumor Necrosis Factor-α

ST: Sequential Therapy

STT: Standard Triple Therapy

WHO: World Health Organization

VacA: Vacuolating cytotoxin A

3 List of Tables

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1. Introduction

1.1 Historical Overview of *Helicobacter pylori*

Helicobacter pylori was discovered in 1984 by Barry Marshall and Robin Warren who demonstrated its role in gastritis and peptic ulcer formation (Marshall, Armstrong, McGechie, & Glancy, 1985; Marshall & Warren, 1984), for which they were awarded the Nobel Prize for medicine in 2005 (Mignon, 2005). Although *H. pylori* was long-lived with mankind globally, it was overlooked for so many years. Genomic studies of hundreds of isolates reveal that all human strains of *H. pylori* had a common ancestor more than 60,000 years ago (Falush et al., 2003). Thus, *H. pylori* has colonized humans ever since they walked out of Africa. Evidence for colonization long before this comes from the lion strain of *H. pylori*, which had a common ancestor to the human strain 200,000 years ago (Eppinger et al., 2006). Some authors proposed that *H. pylori* had benefited human migration through producing folic acid to people with borderline nutrition and poor access to fresh vegetables, and dampening the immune system hyperactivity making allergic responses less troublesome (Y. Chen & Blaser, 2008).

1.2 General microbiological characteristics

H. pylori is a spiral-shaped or curved rod, corkscrew-like bacterium with a few micrometers long and actively motile. Organisms of *H. pylori* can also be found in a horseshoe- like U-form and a round, or coccoid, form in older cultures. *H. pylori* has 4–6 unipolar sheathed flagella, which are of importance for bacterial motility (Owen, 1998). It is a fastidious and microaerophilic Gram-negative bacterium characterized by a curved rod morphology and positive reactions for catalase, oxidase, and urease (Robinson, Letley, & Kaneko, 2017).

In the stomach, most of the *H. pylori* organisms are found in an extracellular location in the gastric mucus and a few organisms are found adhered to the mucosa. Electron micrograph pictures

revealed an intracellular location of the bacterium, and the uptake of *H. pylori* into human epithelial cells has been shown by time-lapse photography (Noach, Rolf, & Tytgat, 1994). Extensive strain variation in *H. pylori* has been demonstrated at both the genomic and the protein level, and the inter-strain variation is higher than in any other bacterium studied so far (Enroth & Engstrand, 2001; Takeuchi, Morimoto, & Sugiura, 2014).

1.3 Epidemiology

Although a continuous decrease in *H. pylori* prevalence was reported from many counties of the world, the infection persists in more than half of the world's population yet (Figure 1) (Leja, Grinberga-Derica, Bilgilier, & Steininger, 2019; Zamani & Ebrahimtabar, 2018). According to systematic review and meta-analysis reports, the prevalence of *H. pylori* infection shows large variations among regions, as Africa had the highest pooled prevalence of *H. pylori* infection (70.1%), whereas Oceania had the lowest prevalence (24.4%) (Hooi et al., 2017). In north European and North American populations, about one-third of adults are still infected, whereas in south and east Europe, South America, and Asia, the prevalence of *H. pylori* is often higher than 50% (Eusebi, Zagari, & Bazzoli, 2014). The prevalence of *H pylori* infection also varies among individual countries, rates as low as 15.8% and as high as 87.7% are reported in Switzerland and Nigeria, respectively (Agréus et al., 2016; Hooi et al., 2017). In Ethiopia, the overall pooled prevalence of *H. pylori* infection was 52.2% with regional variations that range from 71% in Somalia to 39.9% in Oromia (Melese, Genet, Zeleke, & Andualem, 2019). The observed differences between countries appear to be due to economic and social conditions. *H. pylori* infection can be a benchmark for the socioeconomic and health status of a country (Zamani & Ebrahimtabar, 2018).

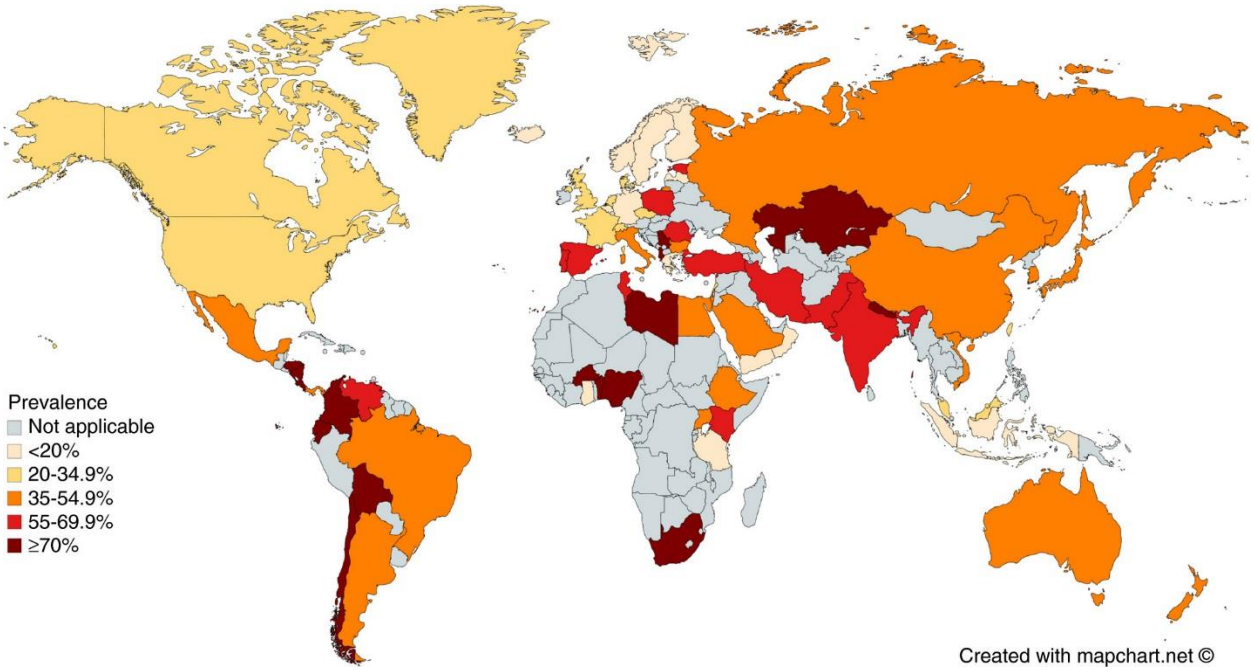

Fig 1: Worldwide prevalence of *Helicobacter pylori* infection (Zamani & Ebrahimtabar, 2018)

1.3.1 *Source and Route of infection*

Infection occurs when *H. pylori* is swallowed. Although the route of transmission is unclear, person-to-person transmission, especially within the same family appears to be prevalent, but environmental contamination is also possible (Eusebi et al., 2014; Kayali et al., 2018). Person-to-person transmission within families appears to be dominant in developed areas specially mother to child (Lindkvist et al., 1996; Mamishi et al., 2016). However, transmission pathway appears to be more complex in rural developing areas, where transmission by contaminated food, water, or via intensive contact between infants and non-parental caretakers may have a greater influence than within-family transmission (Vale & Vítor, 2010). Infection is highest in countries where sewage is not well contained or not adequately treated, however, the bacterium has also been retrieved from vomitus and dental plaques. Person to person transmission is most likely via fecal-oral or oral-oral routes (Mladenova & Durazzo, 2018). *H. pylori* recurrence after successful

eradication can still occur, but seems to be an infrequent event (Eusebi et al., 2014; Kayali et al., 2018). The reinfection rate will increase if there are family members affected (Kayali et al., 2018).

1.3.2 *Risk factors for infection*

Risk factors to *H. pylori* infection include poor social and economic development (overcrowding and lack of adequate facilities with which to boil water or thoroughly cook food), poor hygienic practices, absence of hygienic drinking water, unsanitary prepared food, insects, and consumption of contaminated products which allow the organism to travel easily from person to person (N. Kim, 2005; Leja et al., 2019; Vale & Vítor, 2010). Low socioeconomic conditions in childhood are confirmed to be the most important risk factors for *H. pylori* infection (Eusebi et al., 2014).

Significantly higher prevalence has been reported among age and education level but not among sexes in China (W. Wang et al., 2019). Age is commonly considered as the main risk factor which results in increased prevalence during lifetime although cross-sectional studies does not necessarily give an accurate picture (Gościniak, Poniewierka, & Iwańczak, 2005; Lim et al., 2013; Veldhuyzen van Zanten, Pollak, Best, Bezanson, & Marrie, 1994). *H. pylori* infection occurs mainly during childhood, especially under the age of 5 years, and prevalence in the adulthood depends on infection in the childhood (N. Kim, 2005).

Although there is no conclusive result, several host genetic factors including tumor necrosis factor (TNF)-α are thought to affect susceptibility to *H. pylori* infection-related diseases. A meta-analysis demonstrated that TNF-α -308G>A and -1031 T>C polymorphisms could be protective factors against *H. pylori* infection, and -863C>A a risk factor, especially in Asian populations (X. Sun et al., 2016). The dose-response analysis demonstrated that inverse relationship between alcohol intake and *H. pylori* infection was consistent, regardless of sex, age, geographic areas, detection methods or beverage types (Brenner et al., 1999; Liu et al., 2016).

1.4 Pathophysiology of *H. pylori* infection

Alterations of the stomach mucosa in response to different adverse effects result in various morphological and clinical symptoms. Gastric mucosa alterations can have diverse viewpoints, whereby identical toxic effects may cause different mucosal changes and different toxic agents may produce similar mucosal appearance (Mihály, Micsik, Juhász, Herszényi, & Tulassay, 2014). The initial phases of *H. pylori* infection are believed to elicit an acute inflammatory response often referred to as acute gastritis (Smith & Genta, 2000). *H. pylori* could uniquely persist for decades in the harsh stomach environment, where it damages the gastric mucosa and changes the pattern of gastric hormone release, thereby affecting gastric physiology. By utilizing various virulence factors, *H. pylori* targets different cellular proteins to modulate the host inflammatory response and initiate multiple "hits" on the gastric mucosa, resulting in chronic gastritis and peptic ulceration(F. Wang, Meng, Wang, & Qiao, 2014).

Pathogenic markers in *H. pylori* and host genetics are both of importance for disease outcome. Genotypic or phenotypic markers of *H. pylori* strains may be used to discriminate patients who should undergo eradication therapy from those who might not benefit from it (Enroth & Engstrand, 2001). The pathogen possesses various mechanisms that improve its capacity of mobility, adherence and manipulation of the gastric microenvironment, making possible colonization of an organ with a highly acidic lumen. In addition, *H. pylori* presents a large variety of virulence factors that improve its pathogenicity, of which cytotoxin associated antigen A, vacuolating cytotoxin, duodenal ulcer promoting gene A protein, outer inflammatory protein and gamma-glutamyl transpeptidase can be cited as examples. The host immune system, mainly by means of a Th1-polarized response, also plays a crucial role in the infection course (de Brito et al., 2019).

Common histological findings in ulcerative diseases associated with *H. pylori* are usually chronic active gastritis and chronic follicular gastritis (Shrestha, Koirala, Raj, & Batajoo, 2014). Acute infection results in hypochlorhydria, whereas chronic infection results in either hypo- or hyperchlorhydria, depending on the anatomic site of infection. Most patients chronically infected with *H. pylori* manifest pangastritis with reduced acid secretion due to bacterial virulence factors, inflammatory cytokines, and various degrees of gastric atrophy (Saaed et al., 2021; Walecka-Kapica, Knopik-Dabrowicz, Klupińska, & Chojnacki, 2008). Only ~10% of chronically infected patients, mainly the young, manifest an antral predominant gastritis with increased acid secretion due to a decrease in somatostatin and increase in gastrin secretion; these patients are predisposed to develop peptic ulcer disease. *H. pylori*-induced changes in acid secretion, in particular hypochlorhydria, may allow ingested microorganisms to survive transit through the stomach and colonize the distal intestine and colon. Such perturbation of gut microbiota, i.e. dysbiosis, may influence human health and disease (Smolka & Schubert, 2017).

1.5 *Helicobacter pylori*-Associated Diseases

H. pylori infection is usually acquired during childhood. Infected people usually remain asymptomatic but about 30% of individuals (Kayali et al., 2018) may contribute to the development of diverse gastric and extragastric diseases (Graham, 2015). Upper gastrointestinal diseases: gastritis, peptic ulcer, mucosa-associated lymphoid tissue (MALT) lymphoma, and gastric adenocarcinoma and its precursors are among the common ones manifested in mild to severe forms (Burkitt & Duckworth, 2017).

The principal cause of chronic gastritis, peptic ulcer disease and gastric cancer (GC) is proven to be *H. pylori* infection (Suerbaum & Michetti, 2002). According to the Kyoto global consensus report (Q. Chen & Lu, 2016; Sugano et al., 2015), *H. pylori* gastritis was defined entirely as an

infectious disease and H. pylori-associated dyspepsia as a new category of organic dyspepsia apart from functional dyspepsia. *H. pylori* remains the main etiopathogenetic factor in complicated and uncomplicated peptic ulcer disease (Jonaitis & Pellicano, 2018). Peptic ulcer disease is still one of the most common upper gastrointestinal diseases in the world and more than 90% of the cases are due to *H. pylori* infection (Ballesteros-Amozurrutia, 2000; Yeo & Yang, 2016). Among peptic ulcer patients, prevalence of duodenal ulcer and gastric ulcer associated with *H. pylori* infection was reported to be 90% and 70%, respectively (Kuipers, Thijs, & Festen, 1995).

The strong epidemiological association of *H. pylori* infection and gastric adenocarcinomas provided the basis for the classification of *H. pylori* as a definite human carcinogen by a World Health Organization panel in 1994 (Forman et al., 1991; Huang, Sridhar, Chen, & Hunt, 1998; Nomura et al., 1991). Among the long-term consequences of *H. pylori* infection is gastric malignancies, particularly GC and MALT-lymphoma (F. Wang et al., 2014). MALT lymphoma is a low-grade B-cell marginal zone lymphoma and *H. pylori* has been detected in more than 75% of the patients with MALT-lymphoma (Diaconu, Predescu, Moldoveanu, Pop, & Fierbințeanu-Braticevici, 2017). Meta-analysis studies suggested that eradication of *H. pylori* infection reduces incidence of GC. The benefits of eradication vary with baseline GC incidence, but apply to all levels of baseline risk (Y. C. Lee et al., 2016; Pormohammad et al., 2019). *H. pylori* infection is necessary but not sufficient for the development of gastric adenocarcinoma. There are several mechanisms by which *H. pylori* contributes to the development of GC. Gastric adenocarcinoma is one of the many cancers associated with inflammation, which is induced by *H. pylori* infection, yet the bacteria also cause genetic and epigenetic changes that lead to genetic instability in gastric epithelial cells (Graham, 2015). However, following new diagnostic methodologies such as

species-specific PCR, many other non-*H. pylori* bacteria have been identified which are suggested to have a significant role in the development of GC (J. Li & Perez Perez, 2018).

Approximately, 1% of chronically infected patients are predisposed to develop gastric adenocarcinoma, however, evidence from population studies reported protective role of the infection in gastroesophageal reflux disease (GERD), Barrett's esophagus (BE), and esophageal adenocarcinoma (EAC). This evidence was suggested to be supported by the fact that provoking of GERD in predisposed individuals increases the incidence of refractory GERD, BE, and EAC following eradication of *H. pylori* (Kandulski & Malfertheiner, 2014; Smolka & Schubert, 2017). Especially, infection with CagA-positive strains appears to protect the distal esophagus by causing fundic gland atrophy and impaired gastric acid secretion. Gastric atrophy is the most widely accepted mechanism by which the distal esophagus is protected from abnormal acid exposure in patients with *H. pylori* infection (Kandulski & Malfertheiner, 2014). A meta-analysis study on 84717 BE cases and 390749 controls reported that *H. pylori* infection was associated with reduced risk of BE regardless of geographical location (Erőss et al., 2018).

It has been suggested that infection with *H. pylori* can be involved in various extra-digestive manifestations including neurological, dermatological, hematologic, ocular, cardiovascular (ischemic heart disease, stroke, primary Raynaud phenomena, primary headache), metabolic, halitosis, allergic (responsible for respiratory disorders such as chronic obstructive pulmonary disease, bronchiectasis, pulmonary tuberculosis, bronchial asthma and autoimmune thrombocyte-penia), and hepatobiliary diseases (Dou et al., 2016; Gravina et al., 2018; Prelipcean et al., 2007). The type and severity of these diseases depends on several factors including characteristics of the colonizing strain, the host immune response, and environmental factors such as smoking, a high-salt diet, and the presence of other concurrent infections (Amieva & Peek, 2016). According to

Maastricht V/Florence consensus report, (Malfertheiner, Megraud, O'Morain, & Gisbert, 2017), *H. pylori* infection is linked with unexplained iron deficiency anemia, idiopathic thrombocytopenic purpura, and vitamin B12 deficiency. This report has recommended *H. pylori* eradication for immune thrombocytopenic purpura and iron deficiency anemia disorders after *H. pylori* diagnosis.

1.6 Symptoms of *H. pylori* infection

The clinical features of *H. pylori* range from asymptomatic gastritis to gastrointestinal malignancy (Kayali et al., 2018). Acute *H. pylori* infection usually is not detected clinically, but persistence of the organism causes *H. pylori* chronic gastritis, which is usually asymptomatic but may manifest as epigastric pain, epigastric burning, heartburn, nausea, vomiting, anorexia, early satiety or weight loss (Boixeda et al., 1995). Symptoms may occur with the development of complications of chronic *H pylori* gastritis, which include peptic ulcers, gastric adenocarcinoma, and MALT-lymphoma. *H. pylori*-originated dyspeptic symptoms are currently classified as non-functional, organic disorders. Commonly reported upper gastrointestinal non-functional symptoms include; globus sensation, odynophagia, chest discomfort, heartburn, dysphagia, or vomiting, however, symptoms that appear to be related to functional dyspepsia has been reported in *H. pylori* positive patients (Suzuki, 2017). Even if small fraction of infected individuals develops ulcers, the symptoms which include burping, nausea, and burning or aching in the stomach are usually subtle and can be confused with other diseases. According to reports, small fraction of infected people experiences noticeable symptoms, and for that reason diagnosis of the infection is quite low when compared to the number of people who are actually infected. In addition, *H. pylori* infection is not associated with a hallmark set of outward symptoms to establish the relationship between *H. pylori* infection and ulcers (Boixeda et al., 1995).

A causal relationship between *H. pylori* infection and functional dyspepsia (FD) is well established in a subset of infected patients. In the Kyoto and Maastricht/Florence consensus reports (Koletzko, Macke, Schulz, & Malfertheiner, 2019) H. pylori-associated dyspepsia is defined as an independent entity distinct from FD. *H. pylori* eradication is therefore the most cost-effective approach for infected patients with dyspeptic symptoms and superior to other medical therapies, such as PPIs. The therapeutic gain of *H. pylori* eradication for symptom relief compared to other therapeutic options is significant.

1.7 Diagnosis of *H. pylori* infection

Accurate diagnosis of *H. pylori* infection is mandatory for effective management of many gastroduodenal diseases, and the sensitivity and specificity of an adequate test should exceed 90% in clinical practice (Lopes, Vale, & Oleastro, 2014). Diagnostic testing is recommended for both before and after eradication therapy. Currently, various diagnostic methods are available and commonly divided into invasive and non-invasive methods. Invasive tests are performed via endoscopic biopsy specimens and these tests include histology, culture, rapid urease test and molecular methods. Non-invasive methods include urea breath test, stool antigen test, serology, and molecular methods. As indicated in Table 1, the choice of a method should take into account the clinical condition, accessibility, advantage, disadvantage and cost-effectiveness (Huh & Kim, 2018; Lopes et al., 2014; Sánchez Delgado et al., 2018).

Table 1: Overview of *H. pylori* diagnostic methods

Test	Characteristics	Advantages	Limitations
UBT[1]	Sens: >95% Spec: >95%	• High sensitivity and specificity • Cheap, simple, safe, widely available • Useful to confirm *H. pylori* eradication • No sampling errors	• No data about antibiotic resistance • Special equipment required • False negative results in the case of PPI and antibiotics

SAT[1]	Sens: >95% Spec: >95%	• High sensitivity and specificity • Cheap, simple, safe • Practically useful for children • No need to skilled staffs	• No data about antibiotic resistance • Patient reluctance • False negative results in the case of PPI and antibiotics • Variation in sensitivity and specificity over the different clinical circumstances
Serology[1]	Sens: >95% Spec: 60-90%	• Cheap, simple, safe • Not affected by gastroduodenal bleeding • No false negative result in the case of PPI and antibiotics • Identifies virulence factors	• No data about antibiotic resistance • Failure in distinguish between active and past infection • Not useful to confirm H. pylori eradication
RUT[2]	Sens: 90% Spec: >95%	• High sensitivity and specificity • Cheap, simple, rapid • Practically useful in a clinical setting	• No data about antibiotic resistance • Sampling errors • False negative results in the case of PPI, antibiotics and gastroduodenal bleeding
Direct Detection[2]	Sens: 60-90% Spec: >95%	• Gold standard for direct H. pylori identification with immunofluorescence antibodies • Secondary diagnostic information • Cheap, simple	• No data about antibiotic resistance • Sampling errors • High inter-observer variability • Time-consuming
Culture[2]	Sens: 50-90% Spec: 100%	• Antibiotics sensitivity profiling • The most specific method	• Limited availability, technically challenging • Time-consuming, expensive method • False negative results in the case of PPI, antibiotics and gastroduodenal bleeding
Molecular method[2]	Sens: >95% Spec: >95%	• Antibiotics sensitivity profiling • High sensitivity and specificity • Useful to detect the mutations and virulence factors • Quick and accurate result	• Expensive • Limited availability • Risk of contamination
• UBT: urea breath test; PPI: proton pump inhibitor; SAT: stool antigen test; RUT: rapid urease test; 1Non- invasive tests; Sens: Sensitivity; Spec: Specificity; 2Invasive tests. Source (Huh & Kim, 2018)			

Non-invasive tests are more easily available, better tolerated and more affordable. However, in the presence of alarming signs or symptoms, an endoscopy and a gastric biopsy should be performed in order to reach a diagnosis (Lopes et al., 2014; Sánchez Delgado et al., 2018). A joint guideline on dyspepsia of the American College of Gastroenterology (ACG) and the Canadian Association of Gastroenterology (CAG) recommended a non-invasive test of *H. pylori* for patients <60 years of age (Moayyedi et al., 2017). None of these methods can be considered as a single gold standard in clinical practice (Y. K. Wang et al., 2015), although some recommend bacterial culture from gastric biopsy (Lopes et al., 2014). On the other hand, the Maastricht V/Florence consensus report recommended UBT as the best non-invasive test followed by monoclonal SAT to undertake the test-and-treat strategy but the consensus suggested the use of serological tests only after validation (Malfertheiner et al., 2017). The diagnostic accuracy of the different tests is affected by medications such as proton pump inhibitors (PPIs), bismuth and antibiotics (Gisbert & Pajares, 2004; Sánchez Delgado et al., 2018). Urea breath test and stool antigen test are the most widely used non-invasive tests (Y. K. Wang et al., 2015). Stool antigen test seems to be a cost-effective method (Gisbert & Pajares, 2004).

Detection of *H. pylori* antigen in stools with ELISA monoclonal antibodies is a non-invasive efficient test for the diagnosis of infection in children. However, the available one-step and polyclonal SAT tests are still unreliable (X. Zhou, Su, Xu, & Zhang, 2014). In Ethiopia, the SD BIOLINE *H. pylori* rapid stool antigen test assessment study reported a sensitivity, specificity, positive and negative predictive values of 95.6%, 92.5%, 86.7%, and 97.6%, respectively (Negash, Kassu, Amare, Yismaw, & Moges, 2018).

1.8 Eradication of *H. pylori* infection

All patients with a positive test of *H. pylori* infection should receive eradication therapy and the selected treatment regimen should provide an eradication rate of 90%. Treatment options for the eradication of *H. pylori* continue to evolve and many guidelines are published on *H. pylori* treatment as shown in Table 2 (Sasaki, 2016). However, most are in agreement with the most recent iteration of the Maastricht treatment guidelines. Although alternative therapies, including phytomedicines and probiotics, have been used to improve eradication, current treatment still relies on a combination of antimicrobial agents, such as amoxicillin, clarithromycin, metronidazole, and levofloxacin, and antisecretory agents, such as PPIs (Yang, Lu, & Lin, 2014).Triple therapy is still the most frequently used treatment, especially in areas of low clarithromycin resistance. Its best results are achieved when taken for a minimum of 10 days and with high-dose acid suppression. Quadruple therapy is gaining popularity particularly in areas with increasing resistance to standard triple therapy. Whether three antibiotics or bismuth and two antibiotics are used, excellent eradication rates are achieved, albeit with increased side effects. Levofloxacin as a second-line therapy is widely used; however, bismuth, when available, is an increasingly successful option. Sequential therapy is challenging in terms of compliance and is no longer recommended. This past year witnessed a notable increase in the number of studies based on antimicrobial susceptibility testing and tailored eradication therapy, reflecting the role of culture-guided treatment, which may well represent the future of *H. pylori* treatment and prevent the inappropriate use of antibiotics (O'Morain, Dore, O'Connor, Gisbert, & O'Morain, 2018).

Table 2: Guidelines and their recommended *H. pylori* eradication therapies

Region	First-line therapy	Second-line (salvage) therapy
USA (2007)	Clarithromycin-containing triple therapy for 14 days	Bismuth-containing quadruple therapy for 7–10 days
	Bismuth-containing quadruple therapy for 10–14 days	Levofloxacin-containing triple therapy for 10 days
	Sequential therapy for 10 days	
European Union (2012)	**In areas of <20 % clarithromycin resistance:**	
	Clarithromycin-containing triple therapy for 10–14 days	Bismuth-containing quadruple therapy for 10–14 days
	Bismuth-containing quadruple therapy for 10–14 days	Levofloxacin-containing triple therapy for 10 days
	In areas of >20 % clarithromycin resistance:	
	Sequential therapy for 10 days	Levofloxacin-containing therapy for 10 days
	Bismuth-containing quadruple therapy for 10–14 days	
	Non-bismuth quadruple therapy for 3–10 days	
Japan (2010)	Clarithromycin-containing triple therapy for 7 days	Metronidazole-containing triple therapy for 7 days
Korea (2014)	Clarithromycin-containing triple therapy for 10–14 days	Bismuth-containing quadruple therapy for 7–14 days
	Bismuth-containing quadruple therapy for 7–14 days	Regimen including $\geq$2 other antibiotics
China (2013)	Bismuth-containing quadruple therapy for 10–14 days	Bismuth-containing quadruple therapy for 10–14 days
Australia	Triple therapy 7 days	
	Bismuth-based quadruple therapy for 14 days	
Source (Sasaki, 2016)		

A growing number of meta-analysis and systematic reviews have been published comparing the effectiveness of different treatment regimens for *H. pylori* infection as shown in Table 3, but have not reached a consistent conclusion (Bang & Baik, 2014). Local surveillance networks are required to select appropriate eradication regimens for each region (Savoldi, Carrara, Graham, Conti, & Tacconelli, 2018). To reach the aim of a 90% eradication rate with initial therapy, antibiotics should be tailored according to susceptibility testing. Therapy should be administered for 14 days, emphasizing strict adherence. Success of therapy should be monitored after 4 to 8 weeks by reliable

noninvasive tests. Therefore, the test and treat strategy has been recommended (Jones et al., 2017). Given the varied antibiotic resistant rate across regions, the appropriateness of pooling results together in meta-analysis should be carefully considered and the recommendation of the choice of antibiotics should be localized (Xin et al., 2016).

Table 3: Treatment regimens for *Helicobacter pylori* eradication

Treatment	Regimens	Duration
Standard triple therapy	PPI (standard dose) + amoxicillin (1g) + clarithromycin (500mg) twice daily PPI (standard dose) + metronidazole (500mg) + clarithromycin (500mg) twice daily	7-14d
Bismuth containing quadruple therapy	PPI (standard dose) twice daily + bismuth (standard dose) + metronidazole (500mg) + tetracycline (500mg) four times daily	10-14d
Sequential therapy	PPI (standard dose) + amoxicillin (1g) twice daily for 5d, followed by PPI (standard dose) + metronidazole (500mg) + clarithromycin (500mg) twice daily for 5d	10d
Concomitant therapy (Non-bismuth quadruple therapy)	PPI (standard dose) + amoxicillin (1g) + metronidazole (500mg) + clarithromycin (500mg) twice daily	10d
Hybrid therapy	PPI (standard dose) + amoxicillin (1g) twice daily for 7d, followed by PPI (standard dose) + amoxicillin (1g) + metronidazole (500mg) + clarithromycin (500mg) twice daily for 7d	14d
Levofloxacin-based triple therapy	PPI (standard dose) + amoxicillin (1g) + levofloxacin (500mg) twice daily	10d
Rifabutin-based triple therapy	PPI (standard dose) + amoxicillin (1g) + rifabutin (150mg) twice daily	7-14d
Furazolidone-based quadruple Therapy	Lansoprazole (30 mg) + tripotassium dicitratobismuthate (240mg) + tetracycline (1g) + furazolidone (200mg) twice daily	7d
Novel quadruple therapy	PARC; rabeprazole (20mg, thrice daily for 10d) + amoxicillin (1000mg, thrice daily for 10d) + rifabutin (150mg starting from day 6, twice daily for 5d) + ciprofloxacin (500mg, starting from day 6, twice daily for 5d) PBRC (allergic to amoxicillin); rabeprazole (20mg, thrice daily for 10d) + bismuth subcitrate (240mg, 4 times daily for 10d) + rifabutin (150mg, twice daily for 10d) + ciprofloxacin (500mg, twice daily for 10d)	10d

High dose dual therapy	Lansoprazole (30mg) + amoxicillin (750mg) thrice daily	14d
PPI: Proton Pump Inhibitor; PARC: Proton pump inhibitor, Amoxicillin, Rifabutin and Ciprofloxacin; PBRC: Proton pump inhibitor, Bismuth subcitrate, Rifabutin and Ciprofloxacin; Source (Bang & Baik, 2014)		

1.9 Factors influencing eradication

At present, *H. pylori* eradication therapy for symptomatic patients is universally recognized. A number of prospective cohort studies suggest that *H. pylori* eradication is beneficial to patients by preventing the progression of gastric diseases (Take et al., 2015; You et al., 2006). With the widespread application of eradication therapy, eradication rates have continued to decline steadily over the last decade. However, how to successfully eradicate *H. pylori* is still a concern worldwide. *H. pylori* eradication is affected by a number of variables.(D. Wang, Li, & Gong, 2017). There are a number of factors underlying the successful treatment of *H. pylori* infections, including nature of the bacterium itself, intragastric environment where the bacterium resides, regimens used to eradicate the bacterium, and behavior and reactions of the host. In addition, success depends on patient factors such as age, sex, body mass index, smoking status, drug compliance, CYP2C19 genotype, intragastric acidity, and bacterial antibiotic susceptibility, which is the most common factor for treatment success (J. Y. Lee et al., 2014).

Supplementation of probiotics with different strains of lactobacillus in the eradication of *H. pylori* has been reported to improve the eradication rate and reduced side effects when added to the eradication therapy but their comparative efficacy and effect on compliance was insignificant (McFarland, Huang, Wang, & Malfertheiner, 2016; Shi et al., 2019; F. Wang et al., 2017; Zhang, Qian, Qin, He, & Zhou, 2015). Similarly, a meta-analysis study reported that addition of antioxidants (vitamin, N-acetylcysteine, curcumin, cranberry) to amoxicillin-clarithromycin-based therapy could improve the eradication rate, and vitamin supplementation might be effective at a high dosage. However, antioxidant supplements have no impact on improving side effects (Yang-

Ou, Hu, Zhu, & Lu, 2018). Evidence from these observational studies suggests that moderate alcohol intake is associated with a reduction in *H. pylori* infection of 22% and may facilitate elimination of *H. pylori* (Brenner et al., 1999; Kuepper-Nybelen, Thefeld, Rothenbacher, & Brenner, 2005; Liu et al., 2016). Data generated following both standard triple and sequential therapies suggested that eradication rate in non-ulcer dyspepsia tends to be lower than in peptic ulcer patients (Zullo, De Francesco, Hassan, Morini, & Vaira, 2007).

Related to the pathogen, *H. pylori*, resistance has been reported to be another important factor influencing eradication therapy worldwide. In addition to host factors, bacteria themselves are also widely believed to play a crucial role, and more research is being conducted on bacterial mutation, biofilm formation, efflux pumps as well as other factors. Certain virulence factors secreted by *H. pylori*, which are helpful in bacterial colonization, induction of inflammation, immune evasion and cancer promotion, may also affect outcomes of *H. pylori* eradication (Uotani, Miftahussurur, & Yamaoka, 2015). The two most important *H. pylori* virulence factors are vacuolating cytotoxin A (VacA) and cytotoxin-associated gene A (CagA). VacA gene-encoded vacuolating toxins has been reported to induce apoptosis, inhibit T-cell activity and avoid clearance by host immunity(I. J. Kim & Blanke, 2012). Of the two allelic variations of VagA gene, s1/s2 and m1/m2, higher eradication has been reported in patients infected with VagA-s1 and VagA-m1 strains (D. Wang et al., 2017). However, there is inconsistencies in the relationship between cagA and *H. pylori* eradication, where cure rates in patients infected with cagA-positive strains and cagA-negative ones has been observed to range from no effect to opposite influences (D. Wang et al., 2017). According to reports, in most WHO regions, antibiotic resistance is increasing with considerable heterogeneity among countries. Local surveillance networks are required to select appropriate eradication regimens for each region (Savoldi et al., 2018).

1.10 Rationale for the study

There are several regimens of *H. pylori* eradication therapy that are recommended by different guidelines and scholars, but some of these regimens could be better than others based on the selection criteria. These differences could result in the application of regimens with lower eradication rate while leaving the better ones aside. In Ethiopia, although *H. pylori* eradication therapy is included in the national treatment guideline, there is no uniformity in undertaking eradication therapy among health care institutions and physicians even working in the same healthcare institution. This variability was not based on research findings in the country rather it could have been linked with the use of guidelines and recommendations of other countries. The use of different regimens in eradication therapy could bring about different eradication rates. When the eradication rate is below the recommended level, it affect patient's life experience from different perspectives. In addition, there is no periodic updating of existing guidelines based on findings at national and global level. A national guideline based on local research findings is expected to reduce the drawbacks of using uninvestigated different regimens in a country.

Moreover, the different factors reported to affecting *H. pylori* eradication rate were not assessed in Ethiopia. A 10-day or 14-day STT regimen is commonly used to eradicate *H. pylori* in the study area. The relationships between H. pylori eradication status, and patients' sociodemographic and clinical characteristics are still a subject of controversy (Cho DK, 2010; Suzuki T, 2006; Yoon JH, 2012) and need further investigation. As it is true in other pharmacotherapies, the status of *H. pylori* eradication therapy is affected by many factors, among the common ones being ADEs. Although most ADEs during *H. pylori* eradication therapy have been described as well tolerated, they are associated with poor adherence of patients to medications leading to eradication failure (Kwok, Lam, Katelaris, & Leong, 2008; Paul, Adimoolam, Quereshi, & Eva, 2017; Shakya

Shrestha et al., 2016). Risk factors which might increase the occurrence of ADEs include; gender, extremes of age, disease state, larger doses of the drugs, multiple drugs, past history of ADEs or allergy, genetics, and other sociodemographic and medical profiles of patients (Abbasinazari, Sahraee, & Mirahmadi, 2013; Alomar, 2014; Graham et al., 1992).

Furthermore, people with complaint of acid pepsin disorder usually observed to use some food items either alone or in combination with the triple therapy in the study area. Traditionally used food supplements are commonly prepared as mucilage of Flaxseed or Linseed (*Linum Usitatissimmum*) and Fenugreek (*Trigonella foenum-graecum*), which are known as Telba and Abish, respectively, in the local Amharic language. Although, the protective or healing effect of these supplements in gastritis and peptic ulcer has been supported in nutritional and animal studies (Bernacchia, Preti, & Vinci, 2014; Ganorkar & Jain, 2013; Ghosal et al., 2016; Goyal A, 2014), their effect on eradication rate of *H. pylori* is not studied yet.

One of the common clinical practices in assessment and evaluation of patients after *H. pylori* eradication therapy is to check for resolution of symptoms (Williams, O'Kelly, Kelly, & Feely, 2001). Accordingly, complete symptom resolution has been reported to serve as a marker in assessing patients for *H pylori* status following eradication therapy (McColl et al., 1998). The clinical importance of this practice has been described to be more valuable in developing countries where testing of *H. pylori* after eradication therapy is infeasible due to several reasons mainly patients' economic status. Taking into consideration of all the gaps and problems stated above, this research was initiated to bridge the gaps.

2. Objectives

2.1 General Objective:

To investigate eradication of *H. pylori* with standard triple therapy and assessment of its clinical implications

2.2 Specific objectives:

1. To assess eradication rate of *H. pylori* with STT
2. To identify factors affecting eradication of *H. pylori* with STT
3. To assess adverse drug effects during eradication *H. pylori* with STT
4. To identify factors associated with the occurrence of adverse drug effects
5. To predict eradication success with complete symptom resolution following STT
6. To identify factors affecting complete symptom resolution following STT

3. Materials and Methods

3.1 Study design and area

This facility based prospective follow up was conducted at Bahir Dar city in two healthcare institutions, Adinas General Hospital and Kidanemihret Higher Adinas General Hospital and Kidanemihret Higher Clinic from May 2016 to April 2018. The two healthcare institutions were selected among others because they were using stool antigen test to diagnose *H. pylori*, which is recommended for clinical diagnosis of *H. pylori* before and after eradication therapy. These healthcare institutions are organized based on the services they deliver into different medical units, laboratory, pharmacy, and administration. The medical units include internal medicine, surgery, gynecology & obstetrics, pathology, radiology, and dermatology, staffed with various health professionals. Bahir Dar is the seat of Amhara Regional State, and 565 kilometers away from Addis Ababa, the national capital of Ethiopia.

3.2 Sampling and Sample size calculation

All *H. pylori* positive adult outpatients naive to eradication therapy were taken as the study population and convenience sampling was employed to include all available patients who fulfill inclusion criteria and willing to take part in the study till an estimated number was achieved. The minimum sample size was determined using the formula (Thabane, 2004) and assumptions below:

$$n = \frac{\left(Z_{\alpha/2} + Z_{\beta}\right)^2 Po(1 - Po)}{(Po - Pa)^2}$$

Where,

- n: Minimum sample size
- Po: the minimum recommended eradication rate of a therapy to be tested 90% (Po =90%)

- Pa: Anticipated eradication rate of the population was at least 5% below the minimum recommended (Pa = 85%)
- $Z_{\alpha/2}$ = 1.96, the value of the standard variate at 95% confidence level at 5% significance level
- Z_{β} =1.28 for a 90% power of the test

$$n = [(1.96 + 1.28)^2\ 0.9\ (1\text{-}0.9)]/(0.9\text{-}0.85)^2 = 378$$

There was an estimated drop out during follow up around 15%, making the sample size 378+57 = 435.

3.3 Patients and their follow up

Patients with acid pepsin disorder and positive for *H. pylori* stool antigen test while attending outpatient clinic with age $\geq$18 years, agreed to provide written consent, keen to note and report events related to their eradication therapy, and able to come back to the clinic after 4 - 6 weeks of completion STT to check their *H. pylori* status were included. Patients excluded from the study were age <18 years, referred from other facilities, seriously sick, previous eradication therapy, and unable to listen or speak the local language (Amharic). PPI-based STT with a regimen of omeprazole 20mg or pantoprazole 40mg, clarithromycin 500mg and amoxicillin 1000mg each twice/day either for 10 or 14 days was given to all patients involved in the study.

To maintain the actual clinical practice of healthcare institutions in *H. pylori* eradication therapy, there were no any interferences or interventions made during the process of therapy. Patients were informed to note potential ADEs during the treatment and to pay attention for symptoms they were feeling before and after eradication therapy. At the end of the first phase of data collection, patients were reminded to come back to their respective healthcare institutions for completion of data collection including *H. pylori* status after eradication therapy. Both assessment of complete

symptom resolution and stool antigen testing after eradication therapy were conducted at the final follow up date after 4 - 6 weeks of end of eradication therapy.

3.4 Data collection instruments

Data were collected using a pre-developed structured questionnaire (Annex-1a and 1b) from the literature, comprising of two parts so as data could be collected in both the recruitment and the follow up periods. Weight with standard digital balance and height in meter were measured at the first encounter of data collection. Weight after eradication therapy was measured at the second encounter with the weight balance previously used to measure. Anthropometric, sociodemographic and clinical data was collected during the first encounter of patients at the clinics. On the second encounter, success or failure of *H. pylori* eradication therapy was determine by taking stool sample from each patient. Besides data repeatedly measured, other data such as ADEs, regimen completion, symptom resolution, and use of homemade Flaxseed or Fenugreek as nutritional supplement was collected at the end of the follow up period at their second encounter to check for eradication of *H. pylori* infection. The occurrence of ADEs was evaluated by means of a specific questionnaire filled out during the second encounter before undertaking stool antigen test. ADEs were classified as present and absent to reduce variabilities of patients' response on the intensity of the effects. Self-reported ADEs were measured indirectly through assessment of the responses of patients to a question "what adverse effects you felt during the course of your therapy?". Those who listed one or more ADEs were entered as "Yes" and those without a list as "No".

Measuring the presence of gastrointestinal symptoms through questionnaire has been reported to have good reproducibility (Bovenschen et al., 2006; Garratt et al., 1996). Patient's responses to a question "what you feel/perceive after therapy in reference to your initial illness?", was used to assess resolution of symptom after therapy. Possible responses to this question were structured as

"I feel no symptom at all", "I feel improvement but not complete", and "I feel no improvement at all or worsening". Assessment of resolution of symptoms as predictor of the status of *H. pylori* infection was based on clinical practice and consideration of evidences that reported symptom resolution as a potential indicator of success of eradication therapy (McColl et al., 1998). The approach to assess regimen completion was done indirectly through asking their level of confidence in taking the three medications with possible responses of "with no doubt', "mostly", and "partially".

3.5 Stool antigen test

As recommended in (Shimoyama, 2013), the primary diagnosis of *H. pylori* infection as well as its eradication after 4–6weeks of therapy was confirmed with stool antigen test conducted according to the Manufacturer's descriptions (*SD BIOLINE H. pylori Ag, Standard Diagnostics, Inc. Korea*). The result window of test kit consists of 2 pre-coated lines, "T" (Test Line) and "C" (Control Line). Both the Test Line and the Control Line in result window are not visible before applying any sample. The "T"" window coated with monoclonal anti-*H. pylori* will form a line after the addition of stool specimen (if there is *H. pylori* antigen). The Control window is used for procedural control and a line should always appear if the test procedure is performed correctly and the test reagents are working. Procedurally, with sterile swab about 50mg stool was inserted into a specimen tube containing assay diluents to dissolve the sample. Next, 1 ml of sample diluents was added in a clean test tube. After waiting for 5–10 min, the upper layer was used for the test. Three drops (about 80µl) were put into the sample wells of the test device. Test results were interpreted within 10–15 min. No interpretation was performed after 15 min. A colour band will appear on the result window (control/"C" band and/or test/"T" band). The presence of two colour bands ("T" band and "C" band) within the result window indicates a positive result while, the

presence of only one band ("C" band) within the result window indicates a negative result. When the purple colour band was not visible within the result window (of the "C" window) after performing the test, the result was considered invalid and the specimen were re-tested using a new test kit.

H. pylori stool antigen test utilizes antibody-based techniques which can be polyclonal or monoclonal body. Test kits consisting of polyclonal antibody preparations are less preferred due to associated limitations (Shimoyama, 2013). Commonly reported limitations of stool antigen test include watery stool, temperature, time interval between sample collection and measurement, and use of antisecretory drugs and antibiotics before sample collection. Monoclonal antibody preparation was used in the present study to minimal limitations (Elitsur, Lawrence, & Hill, 2004). Stool antigen test results were recorded on daily bases with predeveloped format (Annex 2).

3.6 Data quality assurance

To ensure the quality of data, a standardized questionnaire was adapted from previous literatures and translated to the local language (Amharic). Two diploma nurses for questionnaire based data collection and two diploma laboratory experts stool antigens test were recruited among employees of the selected clinics to conduct their work under follow up and supervision of one bachler degree pharmacist who was not member of selected clinics. Contractual agreement was made between the principal investigator and recruited health professionals. Training was given to data collectors and the supervisor for two days on data collection instrument, how to present predeveloped questionnaire, and how to record responses and laboratory results. Pre-test was done on 5% of the sample size in another healthcare institution in the study area to ensure whether the predeveloped questionnaire was able to capture what it was intended to capture or not. Accordingly some questions were modified. Besides managing data collection in provision of clarification on the

questionnaire, the supervisor was informed to check data collectors for dressing of their gown and avoid provision of any opinion or advice about the service provision during data collection. To maintain the data quality, filled questionnaires were checked by the supervisor for completeness and inconsistencies and provided debriefing and feedback on daily bases. Similar stool antigen test kits were used to reduce stool antigen test variability to conduct laboratory test before and after eradication therapy.

3.7 Data analysis

Data analysis was made after entered on SPSS statistical package version 23.0. Patients' responses on symptom resolution status; "I feel no symptom at all", "I feel improvement but not complete", and "I feel no improvement at all or worsening" were categorized into complete symptom resolution (feel no symptoms at all) and no complete symptom resolution (all other responses). Descriptive statistics was used to describe percentages, means and standard deviations. Both positive and negative predictive values were calculated according to descriptions given elsewhere (Trevethan, 2017). Bivariate and multivariable logistic regressions were used to identify factors associated with eradication, self-reported ADEs and symptom resolution statuses after *H. pylori* eradication therapy with STT. Bivariate logistic regression analysis was done for all independent variable that fulfill goodness of fit with chi-square test, then all independent variables were analyzed for multivariable logistic regression. Multicollinearity was checked among independent factor using variance inflation factor. Backward LR stepwise logistic regression model was used to run multivariable logistic regression to control confounding effect. Significance was considered when p-value is less than 0.05 at 95%CI.

3.8 Operational definitions

Complete symptom resolution: absence of any symptom related to acid pepsin disorder complaints in *H. pylori* infected patients after 4-6 weeks of eradication therapy in reference to their feelings of illness during healthcare seeking.

No complete symptom resolution: Presence of symptom(s) related to acid pepsin disorder complaints in *H. pylori* infected patients after 4-6 weeks of eradication therapy in reference to their feelings of illness during healthcare seeking expressed in terms of partial improvement, or no change, or worsening of symptoms.

3.9 Ethical consideration

This study was officially approved with a Reference No: BCS/171/16 (Annex 3) by Institutional Review Board at College of Medicine and Health Sciences, Bahir Dar University. Selected healthcare institutions allowed the study after provision of ethical approval letter received from the Board. *H. pylori* eradication therapy was given according to the National General Hospital Guideline with drugs accepted by Food, Medicine, Healthcare Administration and Control Authority (FMHACA) of Ethiopia. All patients fulfilling inclusion criteria were informed about the objectives, benefits and associated challenges of the study as well as their full right to withdraw from the study at any time in point without jeopardizing their healthcare service. Written consent was obtained thereafter from patients willing to participate in the study (Annex 4). Privacy and confidentiality were kept through restricting data access and anonymity.

4. Results

A total of 421 patients completed their follow up study out of 526 consented volunteers. The rate of drop out was 20% which represents 105 patients who left the study group most of them (103) due to failure of finalizing their follow up and the other 2 were excluded during data entry because of incomplete data (Figure 2).

4.1 Anthropometric characteristics of patients

As shown in Table 4, the mean height (±SD) of the patients was 1.64 (± 0.07) meter. The mean body weight (±SD) of patients before and after eradication therapy was 56.72 (±10.19) and 56.79 (±10.18) kg, respectively. The mean body mass index (±SD) of the patients before and after eradication therapy was 20.92 (±3.26) and 20.96 (±3.31), respectively. There was no significant difference in the means of body weight and body mass index before and after eradication therapy.

Table 4: Anthropometric characteristics of patients on *Helicobacter pylori* eradication therapy at Bahir Dar city Administration, May 2016 to April 2018 (n = 421).

Variable	Mean	Std. deviation	Minimum	Maximum
Height	1.64	0.07	1.45	1.90
Weight (kg) before therapy	56.72	10.19	37	93
Weight (kg) after therapy	56. 79	10.18	37	90
BMI* before therapy	20.92	3.26	13.84	31.63
BMI* after therapy	20.96	3.31	13.75	32.05

BMI*: body mass index

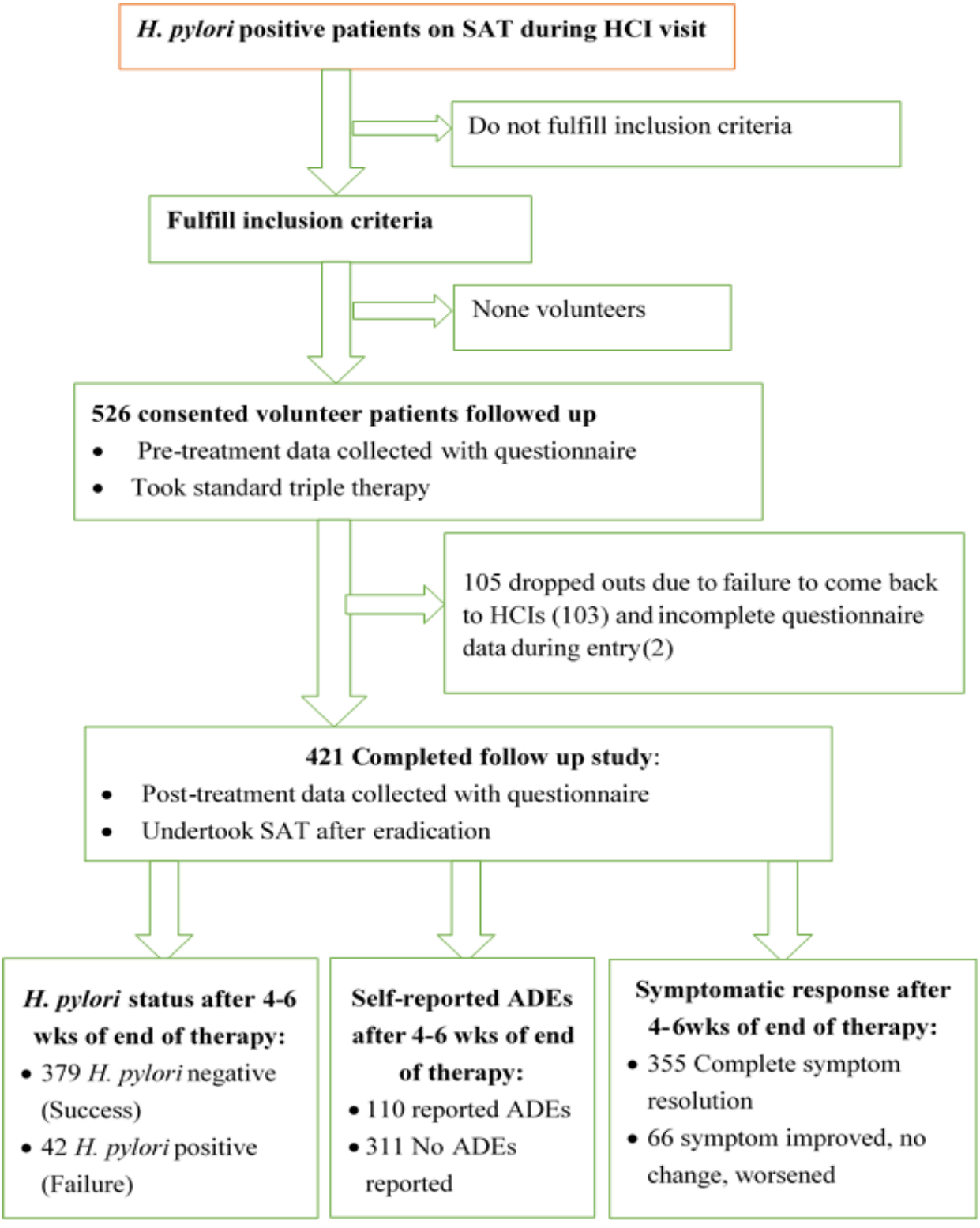

Fig 2: Flow char of the study

4.2 Sociodemographic and medical profile of patients

As shown in Table 5, the ratio of females to males was nearly 2:1. The mean age (±SD) of the patients was 30.63 (± 10.74) years. Nearly, 90% of patients' age was ≤45 years. Close to two-third (63.4%) of the patients were married and more than half (58.2%) of the patients' educational status was below college level. Area of residence for majority (79.8%) of the patients was urban. Occupation wise, 37.8% of the patients were employees of public and private institutions with regular monthly paid salary. Nearly two third (64.8%) of the patients' body mass index was within the normal range. However 22.6% of the patient's body mass index was under weight.

Table 5. Summary of sociodemographic and medical profile of patients on STT at Bahir Dar city from May 2016 to April 2018. (n = 421)

Variable	Variable categories	Frequency (%)
Sex	Female	276(65.6)
	Male	145(34.4)
Age in years	18-24	125(29.7)
	25-34	172(40.9)
	35-44	75(17.8)
	≥45	49(11.6)
Body mass index	≤18.50	95(22.6)
	18.51-25.0	273(64.8)
	>25.0	53(12.6)
Residence	Urban	336(79.8)
	Rural	85(20.2)
Zonal address	Bahir Dar city	169(40.1)
	West Gojjam	96(22.8)
	South Gondar	62(14.7)
	Awi zone	52(12.4)
	Others zones*	42(10.0)
Marital status	Single	145(34.5)
	Married	267(63.4)
	Divorced/Widowed	9(2.1)
Educational status	≤Secondary school	245(58.2)
	College and above	176(41.8)
Occupation	Employed	159(37.8)
	Non-employed**	262(62.2)
Pain feeling period in the day	After meal	217(51.5)
	Persistent in the day	122(29.0)
	Long interval b/n meals	82(19.5)

Time duration of the disorder	≤ 3weeks	67(16.0)
	>3weeks	354(84.0)
Presence of other disease(s)	Yes	108(25.7)
	No	313(74.3)
Self-reported alcohol intake	Yes	237(56.3)
	No	184(43.7)
Type of PPI# used	Omeprazole	113(26.8)
	Pantoprazole	308(73.2)
Duration of therapy	10 days	279(66.3)
	14 days	142(33.7)
Use of Fenugreek or Flaxseed	Yes	135(32.1)
	No	286(67.9)
Regimen completion	Yes	409(97.1)
	No	12(2.9)
Eradication status	Success	379(90.0)
	Failure	42(10.0)
Self-reported ADE(s)	Yes	110(26.1)
	No	311(73.9)
Complete symptom resolution	Yes	355(84.3)
	No	66(15.7)

*Others include: East Gojjam, North Gondar, and Metekel; ** housewives, merchants, farmers, students, and daily laborers; PPI: Proton Pump Inhibitor; ADE(s): Adverse Drug Effect(s)

Summary of patients' response on their first encounter showed that majority (84.0%) of them had been experiencing symptoms of acid-pepsin disorder for more than 3weeks. According to patients' response more than half (51.5%) felt pain after meal whereas 29% reported persistent pain feeling throughout a day. Although it was difficult to quantify the amount, 56.3% of the patients had history of alcohol intake at the time of their first encounter. Presence of other chronic diseases was reported nearly by a quarter (25.7%) of the patients. Nearly two-third (66.3%) of patients received STT for 10-days whereas, the remaining one-third (33.7%) for 14-days. Two PPIs, pantoprazole and omeprazole, were used and the former comprised nearly three-fourth (73.2%) of STT regimens. The use of homemade food supplements prepared from Fenugreek or Flaxseed during eradication therapy was reported in 32.1% of patients. According to patients' response, around 97% had completed their drug regimens.

4.3 *H. pylori* eradication rate of STT

As shown in Table 6, the overall success of *H. pylori* eradication with STT was 90.0% (379/421). Eradication rate among female and male sex was 90.2% (249/279) and 89.6% (130/145), respectively. The eradication rate of *H. pylori* among patients who received 10-days and 14-days regimens was 89.2% (249/279) and 91.5% (130/142), respectively. Similarly, eradication rate of *H. pylori* among patients who received pantoprazole and omeprazole based standard triple therapy was 90.6% (279/308) and 88.5% (100/113) respectively. Eradication among patients who reported recent occurrence (≤3weeks) of the disorder and longer than 3weeks was 92.5% (62/67) and 89.5% (317/354), respectively. Eradication rate of *H. pylori* among patients who reported use of Flaxseed and/or Fenugreek was 86.7% (117/135), whereas in the others with no use, it was 91.6% (262/286). *H. pylori* eradication among patients who reported occurrence of ADE(s) during therapy was 81.8% (90/110) and it was 92.9% (289/311) in those who had not reported adverse effect. Self-reported ADE(s) was significantly associated with eradication status after therapy on chi-square test (p= 0.002).

Table 6: Proportion of *H. pylori* eradication with STT and its test for association at Bahir Dar city from May 2016 to April 2018. (n = 421)

Variable	SAT after HPET*		ER(%)	X^2 test (p-value)
	N or S	P or F		
Sex:				
Male	130	15	89.7	<0.001 (0.991)
Female	249	27	90.2	
Age:				
18-24	111	14	88.8	
25-34	156	16	90.7	0.333 (0.954)
35-44	68	7	90.7	
>45	44	5	89.8	
Body mass index:				
≤18.50	89	6	93.7	
18.51-25.0	243	30	89.0	1.84 (0.399)
>25.0	47	6	88.7	
Living area:				
Bahir Dar city	153	16	90.5	0.014 (0.905)

Out of Bahir Dar	226	26	89.7	
Educational status:				
≤Secondary school	220	25	89.8	<0.001 (0.985)
College and above	159	17	90.3	
Occupation:				
Employee	144	15	90.6	0.015 (0.903)
Non-employee	235	27	89.7	
Time duration of the disorder:				
≤ 3weeks	62	5	92.5	0.277 (0.599)
>3weeks	317	37	89.5	
Pain feeling period in the day:				
After meal	197	21	90.4	
Long interval b/n meals	74	7	91.4	0.494 (0.781)
Persistent in the day	108	14	88.5	
Presence of other disease(s):				
Yes	95	13	88.0	0.413 (0.520)
No	284	29	90.7	
Self-reported alcohol intake:				
Yes	214	23	90.3	0.002 (0.962)
No	165	19	89.7	
Type of PPI[#] used:				
Omeprazole	100	13	88.5	0203 (0.653)
Pantoprazole	279	29	90.6	
Duration of therapy:				
10 days	249	30	89.2	0.329 (0.567)
14 days	130	12	91.5	
Use of Fenugreek or Flaxseed:				
Yes	117	18	86.7	1.97 (0.160)
No	262	24	91.6	
Adverse drug effects:				
Yes	90	20	81.8	10.02 (0.002)
No	289	22	92.9	
Total	279	42	90.0	

#PPI: proton pump inhibitor

4.4 Factors associated with *H. pylori* eradication rate

As shown in Table 7, on both bivariate and multivariate logistic regression analysis, self-reported ADE was the only factor associated with *H. pylori* eradication rate with similar crude and adjusted odds ratio of 2.92 (95%CI; 1.52-5.59) p <0.001. Eradication of *H. pylori* among patients with no self-reported adverse drug effects was 2.92 times more likely to be successful than those who had reported occurrence of adverse drug effect(s) during therapy. There was no association between

H. pylori eradication rate and other variables sex, durations therapy (10 vs 14-days), type of PPI in regimen (omeprazole vs pantoprazole), and users and non-users of Flaxseed/Fenugreek during therapy.

Table 7: Crude and adjusted odds ratios of *H. pylori* eradication with STT at Bahir Dar city from May 2016 to April 2018 (n = 421).

Variable	SAT after STT		COR (CI = 95%)	AOR (CI = 95%)
	N or S	P or F		
Sex:				
Male	130	15	1.0	
Female	249	27	1.06 (0.55-2.07)	
Age:				
18-24	111	14	1.0	
25-34	156	16	1.23 (0.58-2.62)	
35-44	68	7	1.22 (0.47-3.19)	
>45	44	5	1.11 (0.38-3.27)	
BMI:				
≤18.50	89	6	1.89 (0.58–6.19)	
18.51-25.0	243	30	1.03 (0.41-2.62)	
>25.0	47	6	1.0	
Living area:				
Bahir Dar city	153	16	1.1 (0.57-2.12)	
Out of Bahir Dar	226	26	1.0	
Educational status:				
≤Secondary school	220	25	1.0	
College and above	159	17	1.06 (0.55-2.03)	
Occupation:				
Employee	144	15	1.10 (0.57-2.14)	
Non-employee	235	27	1.0	
Time duration of the disorder:				
≤ 3weeks	62	5	1.45 (0.55-3.83)	
>3weeks	317	37	1.0	
Pain feeling period in the day:				
After meal	197	21	1.22 (0.59-2.49)	
Long interval b/n meals	74	7	1.37 (0.53-3.56)	
Persistent in the day	108	14	1.0	
Presence of other disease(s):				
Yes	95	13	0.75 (0.37-1.49)	
No	284	29	1.0	
Self-reported alcohol intake:				
Yes	214	23	1.07 (0.56-2.03)	
No	165	19	1.0	
Type of PPI used:				
Omeprazole	100	13	1.0	

Pantoprazole	279	29	1.25 (0.62-2.50)	
Duration of therapy:				
10 days	249	30	1.0	
14 days	130	12	1.30 (0.65-2.63)	
Use of Fenugreek or Flaxseed:				
Yes	117	18	1.0	
No	262	24	1.68 (0.88-3.21)	
Adverse drug effects:				
Yes	90	20	1.0	
No	289	22	2.92 (1.52-5.59)[a]	2.92(1.52-5.59)[a]
SAT: Stool Antigen Test; STT: Standard Triple Therapy; N(S): Negative (Success); P(F): Positive (Failure); COR: Crude odds ratio; AOR: Adjusted odds ratio; PPI: proton pump inhibitor; BMI: Body Mass Index; [a]p value = 0.001				

4.5 Adverse drug effects reported during eradication therapy

Frequencies and percentage of studied variables and their association with in the occurrence of self-reported ADE(s) during eradication therapy is summarized in Table 8. The overall self-reported ADE was 26.1% (110/421). The rate of self-reported ADE(s) between or among different patient groups were; female and male sexes (29.0% vs 20.7%), body mass index of ≤18.50, 18.51-25.0, and >25.0 (24.2%, 24.2% and 39.6%), omeprazole and pantoprazole based regimens (23.9% vs 26.9%), 10-days and 14-days duration of therapy (28.3% vs 21.8%), within 3week and more than 3week duration of disorder (13.4% vs 28.5%), period of pain feeling in a day (before meal, persistent and long interval between meals: 21.1%, 28.7%, 35.8%), presence and absence of other chronic diseases (23.1% vs 27.2%), with and without history of alcohol intake (21.9% vs 31.5%), users and non-users of flaxseed/fenugreek (25.9% vs 26.2%), achievement and failure of complete symptom resolution (26.6% vs 28.8%), and, success and failure of eradication (23.7% vs 47.6%). Self-reported ADE(s) was significantly association with duration of acid pepsin disorder (p = 0.015), period of pain feeling in a day (p = 0.027) and eradication status after therapy (p = 0.002).

Table 8: Proportions of self-reported ADE(s) and its test of association for studied variables at Bahir Dar city from May 2016 to April 2018. (n = 421).

Variables	ADEs		ADEs (%)	X^2 test (P-value)
	Yes (110)	No (311)		
Sex:				
Female	80	196	29.0	2.97 (0.085)
Male	30	115	20.7	
Age in years:				
18-24	33	92	26.4	
25-34	40	132	23.4	1.69 (0.639)
35-44	23	52	30.7	
≥45	14	35	28.6	
Body mass index:				
≤18.50	23	72	24.2	
18.51-25.0	66	207	24.2	5.72 (0.057)
>25.0	21	32	39.6	
Residence:				
Urban	95	241	17.6	3.44 (0.064)
Rural	15	170	28.3	
Living area:				
Bahir Dar city	45	124	26.7	0.006 (0.938)
Out of Bahir Dar	65	187	25.8	
Educational status:				
≤Secondary school	65	180	26.5	0.012 (0.913)
College and above	45	131	25.6	
Occupation:				
Employee	46	113	28.9	0.819 (0.365)
Non-employee	64	198	24.4	
Time duration of the disorder:				
≤ 3weeks	9	58	13.4	
>3weeks	101	253	28.5	5.89 (0.015)[2]
Pain feeling period in the day:				
After meal	46	172	21.1	
Persistent in the day	35	87	28.7	7.197 (0.027)
Long interval b/n meals	29	52	35.8	
Presence of other disease(s):				
Yes	25	83	23.1	0.447 (0.490)
No	85	228	27.2	
Self-reported alcohol intake:				
Yes	52	185	21.9	4.442 (0.305)
No	58	126	31.5	
Type of PPI[#] used:				
Omeprazole	27	86	23.9	0.257 (0.612)

Pantoprazole	83	225	26.9	
Regimen durations:				
10day	79	200	28.3	1.728 (0.189)
14day	31	111	21.8	
Use of Flaxseed or Fenugreek				
Yes	35	100	25.9	<0.001 (1.00)
No	75	211	26.2	
Self-reported regimen completion				
Yes	100	297	25.2	2.387 (0.122)
No	10	14	41.7	
Complete symptom resolution:				
Yes	91	264	25.6	0.147 (0.702)
No	19	47	28.8	
Success of eradication therapy:				
Yes	90	289	23.7	9.961 (0.002)
No	20	22	47.6	

ADE: Adverse drug effect; PPI: proton pump inhibitor

4.6 Factors associated with adverse drug effects

Bivariate and multivariate logistic regression analysis to identify predictors of self-reported ADE is shown in Table 9. Variables significantly associated with self-reported ADEs on bivariate logistic regression analysis were: residence in urban area (COR: 1.84 95%CI (1.00 – 3.37), more than 3weeks time course of disease (COR: 2.57 95%CI (1.23 – 5.39), pain feeling during long interval between meals (COR: 2.08 95%CI (1.19 – 3.65), being free from alcohol intake (COR: 1.64 95%CI (1.06 – 2.54), and failure of *H. pylori* eradication therapy (COR: 2.92 95%CI (1.52 – 5.59). As indicated in Table 9, variables significantly affecting self-reported ADEs on multivariable binary logistic regression analysis are described below. Patients with body mass index more than 25 were 2.82 (AOR: 2.82; 95%CI (1.26 – 6.31), p = 0.011) times more likely in reporting ADEs compared to patients with body mass index less than 18.5 who were actually underweight. Patients who had been living with acid-pepsin disorder for more than 3weeks were 3.67 (AOR: 3.67; 95%CI (1.62 - 8.29), p = 0.002) times more likely to report ADEs compared with patients having a duration of up to 3weeks. Patients experienced pain during long interval between meals were 2.18 (AOR: 2.18;

95%CI (1.20 – 3.98), p = 0.011) times more likely to report ADEs compared to patients who felt pain after meal. Patients with no complete symptom resolution were 5.19(AOR: 5.19; 95%CI (1.46-18.50), p =0.011) times more likely to report ADEs compared to those who reported complete symptom resolution after eradication therapy. Compared to patients whose *H. pylori* therapy was successful (with negative stool antigen test after therapy), patients whose *H. pylori* eradication therapy was unsuccessful (positive stool antigen test after therapy) were 12.64 (AOR: 12.64; 95% CI (3.29 – 48.53), p<0.001) times more likely to report ADEs.

Table 9: Crude and adjusted odds ratios of self-reported ADEs during STT at Bahir Dar city from May 2016 to April 2018. (n = 421).

Variables	ADEs		Crude odds ratio	Adjusted odds ratio*
	Yes (110)	No (311)		
Sex:				
Female	80	196	1.57(0.97 – 2.52)	
Male	30	115	1.00	
Age in years:				
18-24	33	92	1.0	
25-34	40	132	0.84(0.50-1.44)	
35-44	23	52	1.23(0.66-2.32)	
≥45	14	35	1.11(0.53-2.34)	
Body mass index:				
≤18.50	23	72	1.00	
18.51-25.0	66	207	1.00(0.56 – 1.72)	
>25.0	21	32	2.05(0.99 – 4.24)	2.82(1.26 – 6.31)[1]
Residence:				
Urban	95	241	1.84(1.00 – 3.37)	
Rural	15	170	1.00	
Living area:				
Bahir Dar city	45	124	1.04(0.67-1.62)	
Out of Bahir Dar	65	187	1.0	
Educational status:				
≤Secondary school	65	180	1.05(0.68-1.63)	
College and above	45	131	1.0	
Occupation:				
Employee	46	113	1.26(0.81 – 1.96)	
Non-employee	64	198	1.00	

Time duration of the disorder:				
≤ 3weeks	9	58	1.00	
>3weeks	101	253	2.57(1.23 – 5.39)	3.67(1.62 – 8.29)[2]
Presence of other disease(s):				
Yes	25	83	0.81(0.48 – 1.35)	
No	85	228	1.00	
Self-reported alcohol intake:				
Yes	52	185	1.00	
No	58	126	1.64(1.06 – 2.54)	
Pain feeling period in the day:				
After meal	46	172	1.00	
Persistent in the day	35	87	1.36(0.90 – 2.48)	
Long interval b/n meals	29	52	2.08(1.19 – 3.65)	2.18(1.20 – 3.98)[3]
Regimen durations:				
10day	79	200	1.00	
14day	31	111	0.71(0.44 – 1.14)	
Type of PPI[#] used:				
Omeprazole	27	86	1.0	
Pantoprazole	83	225	1.17(0.71-1.94)	
Use of Flaxseed or Fenugreek				
Yes	35	100	1.00	
No	75	211	1.02(0.64 – 1.62)	
Self-reported regimen completion				
Yes	100	297	1.00	
No	10	14	2.12(0.91- 4.93)	
Complete symptom resolution:				
Yes	91	264	1.00	
No	19	47	1.17(0.65 - 2.10)	5.19(1.46 -18.50)[4]
Success of eradication therapy:				
Yes	90	289	1.00	
No	20	22	2.92(1.52 – 5.59)	12.6(3.29- 48.53)[5]

*P values: [1]= 0.011; [2]= 0.002; [3]= 0.011; [4]= 0.011; [5]=<0.001; #PPI: proton pump inhibitor

As presented in Table 10, more than 85% of self-reported ADE was manifested as gastrointestinal type which includes gastrointestinal discomfort (39.1%), nausea (13.6%), diarrhea (12.9%), constipation (12.7%), and anorexia (10%).

Table 10: Summary of self-reported ADEs among patients on STT at Bahir Dar city from May 2016 to April 2018. (n = 421)

Self-reported adverse drug effect(s) (ADEs)	Relative Frequency and percentage of self-reported ADEs (n =110)	Overall percentage of self-reported ADEs (N= 421)
GI discomfort	43(39.1)	10.2
Nausea	15(13.6)	3.6
Headache and drowsiness	15(13.6)	3.6
Constipation	14(12.7)	3.3
Diarrhea	12(10.9)	2.8
Anorexia	11(10.0)	2.6
Over all	**110(100)**	**26.1**

4.7 Complete symptom resolution in predicting *H. pylori* eradication

As shown in Table 11, the overall success rate of *H. pylori* eradication therapy was 90.0% (279/421), whereas the percentage of patients who achieved complete symptom resolution following eradication therapy was 84.3% (355/421). Percentage of patients who achieved complete symptom resolution (84.3%) after eradication therapy was lower than *H. pylori* eradication rate (90.0%). Thus, complete symptom resolution was achieved in most patients whose eradication therapy was successful. However, successful eradication of *H. pylori* could not certainly bring complete symptom resolution. Similarly, failure of eradication does not assure persistence of symptoms. Positive predictive value and negative predictive value of complete symptom resolution after *H. pylori* eradication therapy was 98.9% (351/355) and 57.6%(38/66), respectively. Therefore, if stool antigen test is considered as a reference standard after eradication therapy, almost 99% of patients who reported complete symptom resolution are expected to be free from *H. pylori* infection in reality. Thus, complete symptom resolution was found to be a powerful predictor of success of *H. pylori* eradication after therapy. In the same way, based on

negative predictive value (57.6%) obtained in the present study, patients who reported persistence of symptoms (no complete symptom resolution) could actually be *H. pylori* positive after eradication therapy. On the other hand, the other 42.4% of patients who reported no complete symptom resolution may be symptom free from *H. pylori* infection. As a result, persistence of symptoms acid pepsin disorder after eradication therapy was a weak predictor of failure of eradication therapy.

Table 11: *H. pylori* stool antigen test status and complete symptom resolution after STT based eradication therapy at Bahir Dar city from May 2016 to April 2018. (n = 421).

		H. pylori stool antigen test after therapy		
		Success (Negative)	Failure (Positive)	PPV and NPV
CSR status	Yes	351	4	351/355 (98.9)
	No	28	38	38/66 (57.6)
	Total	379	42	421

CSR: complete symptom resolution; PPV: positive predictive value; NPV: negative predictive value

4.8 Factors associated with complete symptom resolution

Binary and multivariate binary logistic regression analysis is shown in Table 12. On bivariate logistic regression analysis, pain feeling on long interval between meals (COR: 2.35 95%CI (1.00-5.51)), and being non-user of traditional homemade supplements prepared either from Fenugreek and/or Flaxseed (COR: 2.14 95%CI (1.25 - 3.65) were determinants of complete symptom resolution after *H. pylori* eradiation therapy. However, on multivariate binary logistic regression analysis only being non-user of Fenugreek and/or Flaxseed was found to be significant determinant factors of complete symptom resolution. Compared to those patients who used traditional homemade supplements prepared from Flaxseed or Fenugreek during *H. pylori* eradication therapy, non-users were 2.14 (AOR: 2.14 95%CI (1.25 - 3.65), p = 0.005) times more likely to attain complete symptom resolution.

Table 12: Frequencies of complete symptom resolution after eradication therapy with STT, and its crude and adjusted odds ratios with respect to complete symptom resolution at Bahir Dar city from May 2016 to April 2018. (n = 421).

Variable and their Categories	SRC		Crud odds ratio (95% CI)	Adjusted odds ratio
	Yes (n=355)	No (n=66)		
Sex:				
Male	121	24	1.0	
Female	234	42	1.1(0.64-1.91)	
Age in years:				
18-24	105	20	1.18(0.50-2.81)	
25-34	148	24	1.39(0.60-3.22)	
35-44	62	13	1.07(0.42-2.74)	
>45	40	9	1.00	
Body mass index:				
≤18.50	83	12	2.02(0.84-4.89)	
18.51-25.0	231	42	1.61(0.78-3.31)	
≥25.01	41	12	1.00	
Residence:				
Rural	74	11	1.32(0.66-2.64)	
Urban	281	55	1.00	
Living area address:				
Within Bahir Dar city	45	124	1.21(0.70-2.08)	
Out of Bahir Dar	65	187	1.0	
Educational status:				
Secondary school and below	207	38	1.03(0.61-1.75)	
College and above	148	28	1.00	
Occupation:				
Employee	137	22	1.26(0.72-2.19)	
Non-employee	218	44	1.00	
Pain feeling period in the day:				
After meal	184	33	1.44(0.81-2.57)	
Long interval b/n meals	74	8	2.35(1.00-5.51)	
Persistent in the day	97	25	1.00	
Time duration of the disorder:				
≤ 3weeks	59	8	1.44(0.66-3.18)	
>3weeks	296	58	1.00	
Presence of other disease(s):				
Yes	88	20	0.76(0.42-1.35)	
No	267	46	1.00	
Self-reported alcohol intake:				
Yes	195	42	0.70(0.42-1.35)	
No	160	24	1.00	

Type of PPI used:				
Omeprazole	95	18	1.00	
Pantoprazole	260	48	1.03(0.57-1.85)	
Duration of therapy:				
10 days	232	47	1.00	
14 days	123	19	1.31(0.74-2.33)	
Use of Fenugreek or Flaxseed:				
Yes	104	31	1.00	
No	215	35	2.14(1.25-3.65)	2.14(1.25-3.65)[1]
Self-reported ADEs:				
Yes	91	19	0.85(0.48-1.53)	
No	264	47	1.00	

PPI: proton pump inhibitor; SRC: Symptom Resolved Completely; ADEs: adverse drug effects; P-values: [1]= 0.005

5 Discussion

5.1 Helicobacter pylori eradication

H. pylori eradication rate achieved with STT was 90.02%. Although, studies from different geographical regions of the world have shown a decrease in the success of STT, eradication rate in the present study (90.02%) is in line with the minimum recommended *H. pylori* eradication rate (90%) stated in guidelines indicating that use of STT is acceptable at least in the study area. There are no similar studies in Ethiopia, particularly in the present study area to compare with previously reported eradication rates. Studies performed in different geographic areas of the globe had reported varied *H. pylori* eradication rates. For example, rates comparable (85-94%) (Fock KM, 2000) as well as lower (61-77%) (Ramas, Donday, McNicholl, & Gisbert, 2017) have been reported. Most guidelines and consensus conferences worldwide recommend STT comprising of a PPI, clarithromycin, and amoxicillin or metronidazole to become the universal regimen for eradication therapy of *H. pylori* (Wang B, 2014). An eradication rate of over 90% has been regarded as an optimal eradication cut-off therapy for per-protocol analysis (L. H. Graham DY, Yamaoka Y, 2007). Based on per-protocol analysis, the effectiveness of eradication therapy

regimens of *H. pylori* infection have been stratified into excellent (>95%), good (91% - 95%), borderline (85% - 89%), and unacceptable (<85%) (L. Y. Graham DY, Wu MS, 2014). In view of this categorization, the present eradication rate lies between good and borderline, indicating that STT is within recommended level of effectiveness in the study area.

Several factors have been reported to affect effectiveness of *H. pylori* eradication therapy, the most commonest being adherence to therapy and resistance of *H. pylori* to antibiotics. In susceptible areas, optimum eradication rate of *H. pylori* infection can be achieved if adherence to drug therapy is maintained higher. Accordingly, factors leading to poor adherence has been repeatedly reported to have paramount importance in determining successful *H. pylori* eradication outcomes (Hsu PI, 2005; Shakya Shrestha et al., 2016). Therefore, reported eradication rate differences including this study could be associated with extent of adherence of patients to prescribed medications and/or local susceptibility pattern of *H. pylori* in the study areas. After considering such variabilities across regions, a meta-analysis study has recommended the choice of antibiotics for eradication to follow local susceptibility pattern (Xin Y et al., 2016). Better eradication rate in the present study could be associated with: i) low rate (6%) of resistance to amoxicillin and complete susceptibility for clarithromycin (Asrat D, 2004), ii) higher dose of therapy in relation to lower mean body weight of the patients; iii) longer duration of therapy, 10 – 14 days compared to 7 days therapy.

In the present study, among the variables assessed for their possible effect on eradication, only self-reported ADE was found to affect *H. pylori* eradication rate significantly. Eradication rate among patients who did not experience ADEs during therapy was higher than those who experienced one or more ADEs, as there is a better adherence among the former group of patients than the latter.

The use of potent acid secretion inhibitors, higher doses of antibiotics, and increasing duration of triple therapy have been suggested to improve the efficacy of most *H. pylori* eradication regimens (Abdullahi et al., 2008; Pai MP, 2007). However, in this study, there was no significant difference in the eradication rate of 10-days and 14-days duration of triple therapy. Meta-analysis in Turkey reported that the duration of treatment and the PPI used had no effect (Sezgin, Aydın, Özdemir, & Kanık, 2019). Likewise, there was no significant difference in eradication rate among patient who received omeprazole and pantoprazole based STT, which confirms comparable effectiveness and possibility of alternative use of the two drugs that belong in the same class of acid secretion inhibitors.

Similar to previous report (Gisbert JP, 1996), in the present study, age and sex were not significantly associated with eradication therapy. Patients' mean age 30.63 year in this study is comparable with previously reported 28.8 mean age (Mekonnen Z, 2017) in the same area, but studies done in other countries reported higher mean age ranging from 40 - 53 years (Kabakambira JD, 2018; Liu RP, 2018; Queiroz et al., 2002; Singh N, 2008). Percentage of female patients (65.6%) in the present study is comparable to prevalence of *H. pylori* infection reported for females in studies done in Ethiopia (Dargaze Kibru, 2014; Dobo, 2020) as well as in other countries (62-65%) (Kabakambira JD, 2018; Silva et al., 2001). However, lower (28.6%) (Queiroz et al., 2002) and higher (75%) (Alebie G, 2016; Liu RP, 2018) prevalence in females has also been reported. These variations indicates association of sociodemographic features of countries with prevalence *H. pylori* infection as reported previously (Zamani & Ebrahimtabar, 2018).

In the present study, *H. pylori* eradication rate was not affected with history of alcohol intake before therapy which is consistent with other studies (Queiroz et al., 2002). The effect of alcohol intake on *H. pylori* eradication has been reported to vary from significant effect to no effect at all.

These could be due to differences in defining reported alcohol use and/or cultural differences of alcohol use in the study populations. Although, nearly one-third (32.1%) of patients reported use of traditional food supplements prepared from Flaxseed and/or Fenugreek during therapy in the present study, there was no significant difference in the eradication rate. There are similar reports on absence of effect of diet on *H. pylori* eradication rate (Singh N, 2008), on the other hand, addition of fermented milk is reported to increase eradication (Guo Y, 2016). There is inconsistent report about effect of other chronic diseases on *H. pylori* eradication therapy as reported for diabetes mellitus (Kayar et al., 2015), chronic liver disease and liver cirrhosis (Cheng-En T, 2016), chronic kidney disease (Liang et al., 2017), hypertension (Wan et al., 2018) and chronic lung disease (Xiaoying Zhou, Wu, & Zhang, 2013). In contrast, self-reported chronic diseases in this study have no association with eradication rate which could be due to limitations of determining actual presence and/or extent of the diseases.

5.2 Self-reported adverse drug effects

Different reasons have been suggested for the challenges that made *H. pylori* eradication therapy difficult. Assessment of factors associated with patients and pathogen have been studied to improve treatment outcome. With this view, evaluation of self-reported ADEs that occur during STT and associated risk factors can have paramount importance to reduce its impact. Occurrence of ADEs during *H. pylori* eradication therapy has been reported to be affected by many factors (Jaka, Mueller, Kasang, & Mshana, 2019). Understanding the different effects of the factors can improve the choice of most appropriate medications and provision of the best advice to achieve a better treatment outcome (Ksiądzyna, Szandruk, & Szeląg, 2012; Shakya Shrestha et al., 2016).

In the present study, nearly a quarter (26.13%) of patients reported experiencing of one or more symptoms of ADEs. Even though the percentage of reported ADEs was significant, all the reported

ADEs were mild. Gastrointestinal symptoms including; gastrointestinal discomfort, nausea, vomiting, diarrhea and constipation were the most common manifestations of ADEs. Previous studies have also reported the commonness of gastrointestinal symptoms during eradication therapy (M. Lee et al., 1999; Shakya Shrestha et al., 2016; Y. Q. Zhou et al., 2012). However, reported percentage of ADEs show variability where some are found; comparable (26%) (Arkkila et al., 2005), lower (10% -18%) (Y. I. Chen & Fallone, 2015; Hori, Takagawa, Hida, & Nakamura, 2017; Silva et al., 2001; W. H. Sun et al., 2005) and higher (36%-76%) (H. J. Lee et al., 2015; Masjedizadeh, Zaeemzadeh, Mard, & Vanani, 2015; Queiroz et al., 2002; Ramas et al., 2017) than reported in this study. Different factors including duration of triple therapy, socio-demographic and cultural differences, duration and severity of the disease, pharmacogenetics, and drug combinations and possible interactions could be sources of these variations.

In the present study, self-reported ADEs were significantly affected by body mass index above 25, pain feeling during long interval between meals, failure to achieve complete symptom resolution, failure of eradication therapy, and duration of acid-pepsin disorder more than 3weeks. Patients with body mass index higher than 25 could feel abdominal discomfort more easily (Granstrom & Backman, 1985) since most ADEs during STT are manifested as abdominal discomfort. In addition, slow gastric emptying has been reported in obese people (Maddox, Horowitz, Wishart, & Collins, 1989) which could contribute for increased ADEs expressed as gastrointestinal upset reported during STT. Furthermore, higher ADEs in obese patients could also be associate with slow elimination of drugs specially clarithromycin which has high tissue concentrations as reported previously (Fish, Gotfried, Danziger, & Rodvold, 1994; Honeybourne, Kees, Andrews, Baldwin, & Wise, 1994). Although, it was not identified in this study, negative impact of higher body mass index on *H. pylori* eradication therapy has been reported (Abdullahi et al., 2008), which

might be linked with ADEs that reduce drug intake. In addition, higher *H. pylori* infection rate has been reported (Hamrah et al., 2018; Kouitcheu Mabeku, Noundjeu Ngamga, & Leundji, 2018) in obese people. The need of further studies have been suggested to understanding of effect of body mass index on *H. pylori* infection and its eradication therapy (Pai & Bearden, 2007).

Compared to patients who felt pain of acid-pepsin disorder after meal, those patients who felt pain during long interval between meals (starvation) were more likely to report ADEs of medications. This could be due to reporting of sensation of hunger as ADEs in patients who felt pain during long interval between meals and/or under reporting of ADEs due to missed interpretation of symptoms of ADEs to the meal they have had. All of these missed interpretations and reporting are suggested to be linked with overlap of symptoms of upper abdominal discomfort due to starvation, meal intake and ADEs (Bytzer & Talley, 2001). It has been reported that food intake relief pain symptoms of duodenal ulcer and induces symptoms of gastric ulcer (Me, M, Perez, & Rodrigo, 2015). Similarly, patients on acid-pepsin disorder associated with chronic *H. pylori* infection (symptoms stayed for more than 3weeks) were more likely to report ADEs compared with those who stayed less than 3 weeks. It has been reported that recently appeared ulcer is more active than ulcer stayed longer periods. Thus, lower rate of reporting ADEs in patients with active ulcer may be due to the effect of relative tolerance which could lead to ignoring the mild ADEs compared with more severe pain of the active ulcer itself and/or over reporting of ADEs that could be felt relatively more than the less active chronic ulcer. Lower adherence rate has been reported among patients with chronic diseases compared to those with acute conditions (DiMatteo, 2004), which supports the present study. Parallel to this, another study conducted on eradication of *H. pylori* has reported better rate of eradication in patients with active ulcer than in patients with inactive ulcers (Spiller, 1999). Patients who were unable to achieve complete symptom resolution

of their initial acid-pepsin disorder complaint after therapy reported occurrence of more ADEs compared to those who achieved complete symptom resolution. Most ADEs occur at the beginning of therapy (Ellingrod & Perry, 1994; X. X. Li et al., 2019). Following this fact, patients who experienced ADEs at the beginning of eradication therapy could refrain taking the medications, which could in turn negatively affect eradication rate and achievement of complete symptoms resolution. Failure of *H. pylori* eradication therapy was one of the significant factors affecting self-reported ADEs during STT. This finding may indicate that patients who reported ADEs during therapy could be more likely to miss more doses of medications and thus at higher risk of failure of *H. pylori* eradication therapy.

Other variables which significantly affect self-reported ADEs only on bivariate logistic regression were urban residence and no self-reported alcohol intake. Patients living in urban areas were more likely to report ADEs during *H. pylori* eradication therapy than those living in rural areas. Although evidence is lacking about the effect of residence on *H. pylori* eradication therapy, some controversial reports exist in other therapies (Joshi, Shah, Mistry, & Gor, 2015; Kadhim, 2015; Sousa et al., 2018). The differences could be related to easy access of information in urban patients than rural counter-parts which could create a better awareness that help them pay attention for ADEs. Compared to patients who reported alcohol intake prior to eradication therapy, those who reported no alcohol intake were more likely to report ADEs. Fast elimination of drugs in patients taking alcohol has been reported because of its documented inducer effect (Onder et al., 2002; Sellers & Holloway, 1978).

Because of the inconsistent reports on different factors, it might be important to discuss some other variables that were not significant in the present study. There was a tendency of weak association between female sex and self-reported ADEs in this study. Although, significant difference in the

rate of ADEs among males and females has not been reported in patients on STT, more ADEs in females has been reviewed in many other therapies possibly due to lower body weight and organ size, more body fat, different gastric motility and lower glomerular filtration rate or more attentiveness to recall and report physical illness or symptom perceptions (Graham et al., 1992; Rademaker, 2001; Yu et al., 2016). In line with the present study, studies done elsewhere (Abbasinazari et al., 2013; Y. I. Chen & Fallone, 2015; Fennerty et al., 1998), nonresistance of significant difference in self-reported ADEs between 10days and 14days regimens of STT. In the present study, self-reported regimen completion has no significant effect on ADEs and the rate of completion (94.3%) was comparable with (95.7%) (S. Y. Kim et al., 2008) and a bit lower than (99.8%) (Liang et al., 2017).

5.3 Complete symptom resolution

Assessment of *H. pylori* infected patients after eradication therapy is a common clinical practice effected through checking symptom resolution. All patients who received eradication therapy may not require laboratory testing for *H. pylori* as long as symptomatic assessment can provide evidence about *H. pylori* status (Chey & Wong, 2007). However, when failure of eradication therapy is suspected on clinical assessment, *H. pylori* eradication guidelines recommend retesting after eradication therapy in 4–6 weeks (Atkinson & Braden, 2016; El-Serag et al., 2018; Fendrick, Chey, Margaret, Palaniappan, & Fennerty, 1999). In the present study, positive predictive value (99%) and negative predictive value (58%) were determined to assess the relationship between complete symptom resolution and *H. pylori* eradication status after eradication therapy. Accordingly, complete symptom resolution was found as a powerful predictor of successful eradication, whereas failure of eradication therapy was weakly predicted by persistence of symptoms after therapy. A similar study conducted in United Kingdom has reported positive

predictive value and negative predictive value of 98% and 25%, respectively (McColl et al., 1998). *H. pylori* has been associated with both organic dyspepsia such as peptic ulcer disease and functional dyspepsia (Moayyedi, 2012; Perri et al., 2003). Although the benefit of eradication of *H. pylori* associated with peptic ulcer disease is well accepted, its role in functional dyspepsia has been an area of controversies (Du et al., 2016; Kang, Park, & Shin, 2019; S. E. Kim et al., 2018; Perri et al., 2003; Suzuki, Nishizawa, & Hibi, 2011). Studies showed that successful eradication of *H. pylori* could not necessarily bring about complete symptom resolution and similarly persistence of symptoms does not assure failure of eradication (Fendrick et al., 1999). As reasoned out elsewhere, pain was similarly common in *H. pylori*-positive and *H. pylori*-negative patients. *H. pylori* cannot be summarily accepted as the cause of dyspeptic symptoms even when infection is confirmed (Parsonnet, Blaser, Perez-Perez, Hargrett-Bean, & Tauxe, 1992).

In this study, percentage of successful eradication (90.02%) was higher than percentage of complete symptom resolution (84.3%). A comparable (83.3%) and higher (91%) percentages of complete symptom resolution has been reported by (Pilotto et al., 1999) and (Fennerty et al., 1998), respectively. On the other hand, a study involving 87 peptic ulcer patients has reported a very low percentage of complete symptom resolution (38%) (Fendrick et al., 1999). All dyspepsia symptoms do not originate from *H. pylori* infection as described in a review based on the novel Rome IV definition and Maastricht V/Florence consensus, suggesting that individuals who do not achieve relief from dyspepsia symptoms after *H. pylori* eradication are diagnosed as functional dyspepsia (Suzuki, 2017). In support of this suggestion, after successful *H. pylori* eradication in Asian patients only 30% symptomatic relief has been reported, whereas the remaining 70% were stated to be *H. pylori*-unrelated (Gwee et al., 2009; Kang et al., 2019). Among non-ulcer dyspepsia patients who became *H. pylori* negative after eradication therapy, only 73% symptomatic

improvement has been reported (Laheij, Jansen, van de Lisdonk, Severens, & Verbeek, 1996). Parallel to above mentioned variations, the effect of *H. pylori* eradication on symptomatic improvement among patients with functional dyspepsia entertained controversial reports (Ahmed Khan, 2017; Bazzoli et al., 2002; Jodaki et al., 2016; Mazzoleni et al., 2011; Rokkas, 2012; Suzuki et al., 2011) which might be associated with variations in maintaining the minimum recommended six months period to assess symptom resolution after eradication therapy. Thus, regardless of *H. pylori* negative test status, symptoms could persistent in patients with functional dyspepsia and the same condition could have occurred in the present study where presence of functional and non-functional dyspepsia were not differentiated.

The only factors that affect complete symptom resolution in the present study was the traditional use of homemade preparations of Fenugreek and/or Flaxseed. The effect of use of Fenugreek and/or Flaxseed during acid-pepsin disorder on complete symptom resolution showed results that seems paradoxical to the traditional use of these items. Compared to patients who used Fenugreek and/or Flaxseed, non-users were more significantly able to achieve complete symptom resolution. One possible reason for this condition could be attributed to the use of traditional remedies after feeling of more severe symptoms of dyspepsia and/or after longer period of tolerance of pain symptoms, where severe and/or chronic symptoms have been reported to affect wound healing (Gururatsakul, Holloway, Talley, & Holtmann, 2010; Hetzel et al., 1988). In addition, as reported elsewhere (Basch et al., 2007; Cardoso Carraro, Dantas, Espeschit, Martino, & Ribeiro, 2012; Ghosh, Chandra, & Chatterjee, 2015; Priy et al., 2017; Yadav & Baquer, 2014), the gastrointestinal side effects of the supplements like diarrhea, bloating, and alteration of microflora could mask suggested mucosal protection benefits of the supplements. Moreover, patients may consider the use of traditional supplements as substitutes of medication given for eradication and refrain/fail to

adhere therapy which could negatively affect symptom improvement. On binary logistic regression, period of pain feeling in a day was also found to affect complete symptom resolution significantly. Patients who felt pain during long interval between meals were able to achieve complete symptom resolution compared to patients who felt pain persistently throughout the day.

6. Limitations of the study

Patients selection bias could be there, if healthcare seeking behaviour in private and public facilities exist among *H. pylori* infected poppulation in the catchment area, since our study was done only in private facilities. Because endoscopic examination was not employed to assess patients inviolved in this study, it was not possible to differentiate the type and extent of injury asociated with *H.pylori* infection, and include data on functional and non-functional dyspepsia. These could limit identification of patient groups that could better benefited from *H. pylori* eradication therapy as there are controversies epecially on functional and non-functional dyspepsia. Besides, all patients with gastrointestinal complaints might not be due to *H. pylori* infection because some *H. pylori* infected patients are asymptomatic. Therefore, there could be a rare possibility of being *H. pylori* positive with manifestations of gastrointestinal symptoms, which might be attributed to other disorders. Moreover, self-reported ADEs and symptom resolution might be affected by patients' recall bias and subjectivity of feeling adverse effects and symptoms due to awareness and cultural differences.

7. Conclusions

Modification or replacement of the STT observed in different healthcare institutions are not evidence-based since eradication of *H. pylori* with STT is still within the recommended level for clinical practice. Self-reported ADEs manifested with gastrointestinal symptoms are common during STT. Self-reported ADEs affect *H. pylori* eradication therapy. Body mass index, time duration of acid-pepsin disorder, pain feeling period in a day, eradication status and symptom resolution are determinants of self-reported ADEs. Success of *H. pylori* eradication is predictable with complete symptom resolution. Use of traditional food supplements prepared from Fenugreek and/or Flaxseed during eradication therapy affects symptom resolution negatively.

8. Recommendations

- STT shall be used in *H. pylori* eradication in and around Bahir Dar area.
- To improve eradication rate emphasis should be given to ADEs of medications during STT.
- Patient counseling on ADEs should take into consideration of patients' body mass index, duration of acid-pepsin disorder, period of pain feeling in the day, and symptom resolution status.
- Assessment of complete symptom resolution can be used to predict success of *H. pylori* eradication and for feasibility reasons *H. pylori* testing after eradication therapy should be done only in patients with no complete symptom resolution.
- The traditional practices such as using Fenugreek and/or Flaxseed should be assessed in patients with no complete symptom resolution.

9. Suggestions for future work

- Before shifting into alternatives of *H. pylori* eradication regimens, evaluation of regimens on use should be conducted at the national level using strong evidence generating approaches and designs such as systematic and meta-analyses, and controlled clinical trials.
- Studies targeted to establish local and national *H. pylori* susceptibility pattern and molecular epidemiology needs to be done to guide future eradication therapy.
- To extract benefits and avoid risks associated with the traditional practices such as use Fenugreek and/or Flaxseed during acid pepsin disorder needs to be investigated with controlled clinical studies them.

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Annexes

Annex 1a

Predeveloped structured questionnaire (English version)

Part I. Sociodemographic data of *H. pylori* positive patients on first encounter

Sr. No	Questions	Response
100	Patient Card No: _____	Code given_____
101	Sex	□ Male □ Female
102	Age	_____in years
103	Weight	_____Kg
104	Height	_____Meter
105	Address	Region_____ Zone_____ Woreda_____ Kebele_____ Phone No:_____
106	Residence	□ Rural □ Urban
107	Marital status	□ Single □ Married □ Divorced □ Widowed □ Separated
108	Religion	□ Orthodox □ Protestant □ Muslim □ others, specify _____
109	What is your occupation?	□ House wife □ Gov't Employee □ Private Employee □ Merchant □ Daily laborer □ 7. Others, specify_____
110	Your educational status is?	□ Unable to read and write □ Read and write □ Primary education(1-8Th grade) □ Secondary education (9-12th grade) □ College and above

111	Ethnicity	□ Amhara □ Tigrie □ Agew □ Oromo □ Guragie □ Others
112	Average monthly family income	in birr _____

Part II: Response of *H. pylori* positive patients about the disease on first encounter

Sr. No	Questions	Possible responses
201	Have you ever diagnosed with H pylori infection before this?	□ Yes (old) □ No (New)
202	Have you taken triple therapy previously	□ Yes □ No
203	When your current health problem started?	□ Since this week □ Since last two weeks □ Since a month □ Since three months □ Since six months □ Since a year □ Since two years □ Before three years
204	Have you taken medications in the last two weeks?	□ Yes (can you list_____) □ No
205	When you feel discomfort/pain	□ After meal □ Before meal □ Persistently or Always □ At night
206	Which alcoholic drink(s) you had taken before you came for medical care? (more than one response)	□ Traditional alcoholic drinks (Tella, Arekie, Teji) □ Bears □ Woin □ Wuski □ Others, specify _____
207	Do you have history of other chronic illnesses? (more than one response is possible)	□ Liver disease □ Kidney disease □ Diabetes

		□ Hypertension □ Asthma □ Oher_____
208	Do you smoke?	□ Yes □ No

Part III: Response of *H. pylori* positive patients on second encounter

Sr. No	Questions	Possible responses
300	Can you give me your appointment card?	Card No: _____
301	Could you stand on the balance here?	Patient weight:_____
302	How much confident are you on your medication administration	□ Surely complete (100)% □ Mostly (80%) □ Partially □ Somewhat impossible
303	What are the major adverse drug effect(s) you encounter during therapy	_____ _____ _____ _____ _____
304	Have you used homemade remedies of Fenugreek or Flaxseed during therapy	□ Yes □ No
305	What modern medication other than the three drugs you took for the illness before you came here?	_____ _____ _____
306	What you are feeling now about health problem treated recently?	□ I am feeling nothing □ Improved but still feeling □ Not improved at all

Annex 1b

ቀድሞ የተደራጀ መጠይቅ (የአማረኛ ቅጅ)

ክፍል አንድ. የጨጓራ ባክቴሪ መኖሩ የታወቀላቸው የጥናቱ ተሳታፊዎች የኢኮኖሚያዊ እና ማህበረዊ መጠይቆች

ተ.ቁ	ጥያቄ	መልስ
100	ካርድ ቁጥር: _____	የተሰጠው ልዩ መለያ፡ _____
101	ፆታ፡	☐ ወንድ ☐ ሴት
102	እድሜ	_____በአመት
103	ክብደት	_____በኪሎ ግራም
104	ቁመት	_____በሜትር
105	አድራሻ	ክልል_____ ዞን_____ ወረዳ_____ ቀበሌ_____ ስልክ ቁጥር:_____
106	የመኖሪያ ቦታ	☐ ገጠር ☐ ከተማ
107	የገቢቻ ሁኔታ	☐ ያላገባ ☐ ያገባ ☐ የተፋታ ☐ በሞት የተለያዩ ☐ በቦታ የተለያዩ
108	የሚከተሉት ሀይማኖት	☐ ኦርቶዶክስ ተዋህዶ ☐ ፕሮቴስታንት ☐ እስልምና ☐ ሌላ ይጠቀስ _____
109	ስራ	☐ የቤት እመቤት ☐ የመንግስት ተቀጣሪ ☐ የግል ተቀጣሪ ☐ ነጋዴ ☐ የጉልበት ሰራተኛ ☐ ሌላ ይጠቀስ፡_____
110	የትምህርት ደረጃ	☐ ያልተማረ ☐ ማንበብ እና መጻፍ የሚችል ☐ አንደኛ ደረጃ (1-8ኛ ክፍል) ☐ ሁለተኛ ደረጃ (9-12ኛ ክፍል) ☐ ከፍተኛ ደረጃ እና በላይ

111	ብሄር	☐ አማራ ☐ ትግሬ ☐ አገው ☐ ኦሮሞ ☐ ጉራጌ ☐ ሌላ የገለጥ፡----------–
112	ወርሀዊ ገቢ	በብር _____

ክፍል ሁለት፡ የጨጓራ ባክቴሪ መኖሩ የታወቀላቸው የጥናቱ ተሳታፊዎች ስለህመማቸው የቀረበ መጠይቆች

ተ.ቁ	ጥያቄ	መልስ
201	ካሁን በፊት የጨጓራ ባክቴሪያ ስለመያዝህ በምርመራ አረጋግጠህ ታውቃለህ(ሽ)?	☐ አዎ (ተገኝቶብኛል) ☐ የለም (መጀመሪያዬ ነው)
202	ካሁን በፊት የጨጓራ ባክቴሪያ የሚያጠፋ ህፍምና ወስደሀል(ሻል)?	☐ አዎ ☐ የለም
203	አሁን እያመመህ(ሽ) ያለው ህመም መቼ ጀመረህ(ሽ)?	☐ ከሳምንት ወዲህ ☐ ሁለት ሳምናት ሆኖአል ☐ አንድ ወር ሁኖአል ☐ ሶስት ወር ☐ ስድስት ወር ☐ አንድ አመት ☐ ሁለት አመት ☐ ከሁለት አመት በላይ
204	ባለፉት ሁለት ሳምንታት የወሰድኸው(ሸው) መደሀኒት አለ?	☐ አዎ (ምን_____) ☐ የለም
205	የህመም ስሜቱ ሚሰማህ(ሽ) መቼ ነው?	☐ ከምግብ በኋላ ☐ ከምግብ በፊት ☐ ቀኑን በሙሉ ☐ ለሊት
206	ከአመት ወዲህ የጠጣሀቸውን(ሸውን) አልኮል መጠጦች ብታሳውቀኝ(ቂኝ)? (ከአንድ በላይ መልስ ይቻላል)	☐ እቤት ሚዘጋጁትን (ጠላ፤ አረቄ፤ ጠጂ) ☐ ቢራ ☐ ወይን ☐ ውስኪ ☐ ሌላ ይጠቀስ _____
207	አሁን ከምትታከመው ሌላ ምን ህመም አለብህ(ሽ)? (ከአንድ በላይ መልስ ይቻላል)	☐ የጉበት ህመም ☐ የኩላሊት ህመም ☐ የስኳር ህመም ☐ የደም ግፊት

		☐ አስም ☐ ሌላ ይጠቀስ_____
208	ታጨሳለህ(ሽ)?	☐ አዎ ☐ የለም

ክፍል ሶስት፡ የጨጓራ ባክቴሪ መኖሩ የታውቆ ክህምና ጨርሰው ለተመለሱ የጥናቱ ተሳታፊዎች የቀረበ መጠይቅ

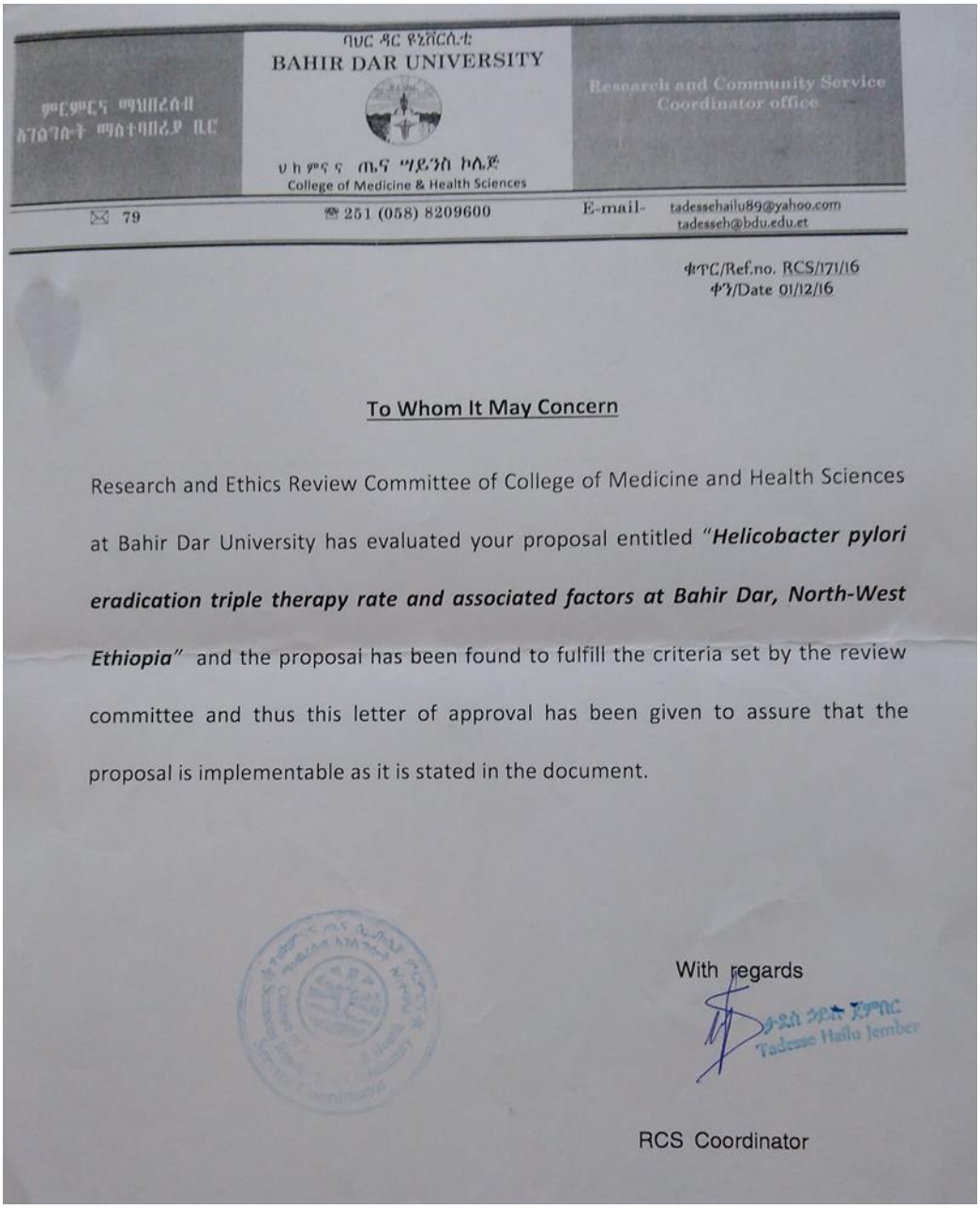
ተ.ቁ	**ጥያቄ**	**መልስ**
300	የቀጠሮ ካርድህን(ሽን) ልትሰጠኝ(ጭኝ) ትችላለህ(ሽ)?	ትክክለኛነቱን እና ጊዜውን ማረጋገጥ:
301	እባክህ ከክብደት መለኪያው ቁም?	ክብደት በኪሎ ግራም:_____
302	ለህክምና የተሰጡህን መድሀኒቶች ለመውስድህ ምን ያህል እርግጠኛ ነህ?	☐ መቶ በመቶ ☐ በብዛት (≥ 80%) ☐ በከፊል ☐ በትንሹ
303	መድሀኒቶችን ስትወስድ ያጋጠሙህ(ሽ) የጎንዮሽ ጉዳቶች ምን ምን ነበሩ?	_____ _____ _____ _____ _____
304	ለጨጓራ ህመሙ ባህላዊ ህክምና በተልባ ወይም በአብሽ ታደርግ(ጊ) ነበር?	☐ አዎ ☐ የለም
305	ከተሰጠህ(ሽ) መድሀኒት በተጨማሪ ምን ሌላ መድሀኒት ወስደሃል(ሻል)?	_____ _____
306	ስለጨጓራ ህመምህ ከህክምናው በኋላ ምን ይስማሀል?	☐ ሙሉ በሙሉ ተሽሎኛል (ምንም አይሰማኝም ☐ ቢሻለኝም የህመም ስሜቱ አለ ☐ ምንም አልተሻለኝም ☐ ብሶብኛል

Annex 2

H. pylori stool antigen test (SAT) data collection sample form

S. No	Date of 1st test	Name	Card No	SAT test before Rx	Regimen of triple therapy (10 days or 14 days)	Date of 2nd test	SAT test after Rx
1.							
2.							
3.							
4.							
5.							
6.							
7.							
8.							
9.							
10.							
11.							
12.							
13.							
14.							
15.							
16.							
17.							
18.							
19.							
20.							

Annex 3



ባህር ዳር ዩኒቨርሲቲ
BAHIR DAR UNIVERSITY

ምርምርና ማህበረሰብ አገልግሎት ማስተባበሪያ ቢሮ

Research and Community Service Coordinator office

የህክምና ጤና ሳይንስ ኮሌጅ
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ቁ.ጥ.ር/Ref.no. RCS/171/16
ቀን/Date 01/12/16

To Whom It May Concern

Research and Ethics Review Committee of College of Medicine and Health Sciences at Bahir Dar University has evaluated your proposal entitled "***Helicobacter pylori eradication triple therapy rate and associated factors at Bahir Dar, North-West Ethiopia***" and the proposai has been found to fulfill the criteria set by the review committee and thus this letter of approval has been given to assure that the proposal is implementable as it is stated in the document.

With regards

ታደሰ ኃይሉ እምበር
Tadesse Hailu Jember

RCS Coordinator

Annex 4

Written Consent

My name is Endalew Gebeyehu. I am the principal investigator of a research entitled "*H. pylori* eradication rate of standard triple therapy and factors affecting its eradication rate at Bahir Dar city administration, Northwest Ethiopia: A prospective follow up study". I am an academic staff at department of Pharmacology, College of Medicine and Health Sciences, Bahir Dar University and PhD candidate at department of Pharmacology and Clinical Practice, School of Pharmacy, Addis Ababa University.

This study has obtained ethical approval from Research Ethics Committee of College of Medicine and Health Sciences, Bahir Dar University. Your participation in this study is based on your voluntariness. If you agree to participate what is expected from you is your presence on appointment and deliver relevant information to data collector healthcare professionals related to *H. pylori* eradication therapy. Undergoing *H. pylori* eradication therapy does not necessarily mean that you are free of the infection after therapy. Assessing extent of eradication and the factors affecting eradication through findings obtained in this research obtained could have paramount importance in improving *H. pylori* eradication therapy. We assure you that the confidentiality and privacy of the information collected will be kept through recording data anonymously and restricting data access.

I appreciate your participation in this study. Thank you!!

Name and signature of participant patients_____.

Name and signature of principal investigator_____.