Medication Adherence Pattern and Factors affecting Adherence in *Helicobacter Pylori* Eradication Therapy

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ABSTRACT

Background

Helicobacter pylori (H. pylori) infection is the most common chronic bacterial infection worldwide affecting approximately half of the world's population. A number of screening tests as well as complex multi-drug therapies are available for the detection and treatment of H. pylori infection. However, the optimum eradication rates of *H. pylori* infection can only be achieved if adherence to drug therapy is higher. Therefore, it is of utmost importance to determine the factors leading to poor adherence to obtain successful treatment outcomes.

Objective

To determine the medication adherence pattern in patients with *H. pylori* infection and assess the factors associated with non-adherence to the prescribed drug therapy.

Method

Patients meeting the inclusion criteria who were confirmed as *H. pylori* positive by rapid urease test (histopathology) and/ or stool antigen test and those under *H. pylori* eradication therapy were considered. Informed consent was taken from the patients or from the patient party in incapacitated patients. They were then interviewed using structured questionnaire. Statistical analysis was done using SPSS version 20 and a p-value < 0.05 was considered as statistically significant.

Result

Among the 70 participants included in this study, 57.10% (n=40) of them were males. The mean (±SD) age of the patients was 42.36 years (±17.93). Higher number (85.70% (n=60)) of the patients were adherent to the recommended medication. Forgetfulness was the reason for missing dose in a majority (80% (n=8)) of the non-adherent patients. A highly significant association (p<0.05) was observed between adherence and absence of symptomatic relief. However, there was no statistically significant association (p>0.05) between patients' adherence to gender, age, literacy, and the prescribed treatment regimen.

Conclusion

Majority of the patients with *H. pylori* infection were adherent to medication. Forgetfulness was the major reason for missing dose in the non-adherent patients.

KEY WORDS

Adherence, Helicobacter pylori, H. pylori eradication therapy

INTRODUCTION

Helicobacter pylori (H. pylori) is apparently the most common chronic bacterial infection present in humans, affecting almost half of the world's population.[1] The infection is acquired from environmental sources but in most cases it is either by fecal-oral or oral-oral route. The pharmacological treatments for the infection includes Standard triple drug therapy and Sequential therapy.[2]

In today's context, although treatment regimen are available to ameliorate signs and symptoms of the infection, failing eradication rates with the regimen still remains a challenging problem.[3,4] Antibiotics resistance to *H. pylori* remains a key factor for treatment failure along with other factors like duration of treatment, new drug combination and most importantly, adherence to medication.[3-5] The determinants of adherence have been categorized as: treatment-related, condition-related, patient-related, health-care team and system related and social and economic factors.[6,7] These factors are major barriers in eradicating *H. pylori* infection and achieving successful treatment outcomes.[3] Every point of contact between the patient and the medical service provides an opportunity to improve adherence to medication.[8]

To date, data about the patient adherence pattern to triple and sequential therapy in eradication of *H. pylori* in Nepal is not available. As Nepal is one of the developing countries where prevalence of *H. pylori* is very high, there is a need to explore the ways to improve patient's adherence for better clinical outcomes. Therefore, we attempted to find out the adherence pattern of patients to *H. pylori* eradication therapy and various factors associated with it.

METHODS

The study was initiated after obtaining ethical clearance from Institutional Review Committee, Kathmandu University School of Medical Sciences (IRC approval no. 28/15). A cross-sectional study was conducted in the Department of Gastroenterology, Dhulikhel hospital, Dhulikhel, Kavre. A total number of 70 patients were included in the study.

Our study was carried out in the patients with H. pylori infection confirmed by endoscopic biopsy and H. pylori stool antigen test. Only those patients with 18 years or above in whom standard triple drug therapy or sequential therapy have been initiated were included in the study. However, those patients who did not give consent to participate were excluded from the study. (Fig. 1.)

The objectives of the study were made explicit to the patients who met the inclusion criteria and confidentiality of the data was assured to them. After taking informed consent from the patients, they were interviewed using structured questionnaire. Information about patient's age, sex, literacy, occupation, smoking and alcohol
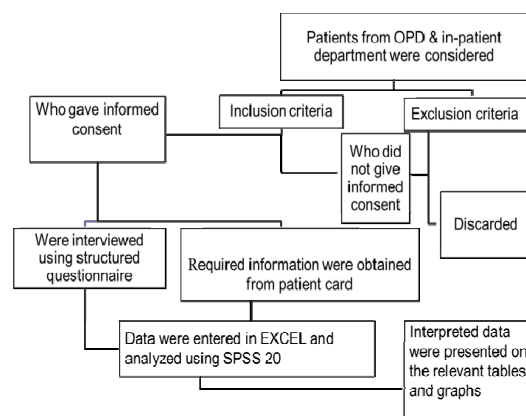

Figure 1. Flow chart showing stepwise procedure of data collection and analysis.

consumption history, personal hygiene were recorded using questionnaire. Regarding the adherence pattern and factors associated with it, information related with dose missed, reason for missing dose, treatment complexity including adverse effects, satisfaction from doctor's information, perception about disease, medication costs etc. were gathered. Furthermore, information regarding use of concomitant drugs or other concomitant diseases and laboratory investigations were recorded from patients' OPD card.

All the gathered information was entered in datasheet using EXCEL (2010). Entered data was then analyzed and tabulated using statistical package for social sciences (SPSS) version 20. All the quantitative variables were expressed in terms of percentage and mean±standard deviation (SD). On the other hand, all the qualitative variables were analyzed using Pearson's chi square test and Fischer exact test. P-value< 0.05 was considered statistically significant.

RESULTS

Among the 70 patients studied, 57.10% (n=40) of them were males and 42.9% (n=30) were females. Their mean (±SD) age was 42.36 years (±17.93) and a majority (64.30% (n=45)) of them were between 30 to 60 years of age. Most (71.40% (n=50)) of the respondents were literate. The standard triple drug therapy was prescribed to 57.10% (n=40) of the total patients whereas the sequential drug therapy was administered to 42.90% (n=30) on a random basis. The details of the prescribed drug therapy are shown in table 1.

Regarding adherence pattern, a majority (85.70% (n=60)) of the patients under our study were adherent to the prescribed drug therapy as shown in figure 2.

Among 14.30% (n=10) of the non-adherent patients, 80% (n=8) of them missed the prescribed dose due to forgetfulness; 10% (n=1) of them due to carelessness and the other 10% (n=1) due to adverse effects as shown in table 2.

Table 1. Treatment regimen details of 70 patients.

| Drug therapy	No. of Patients (%)
Standard triple drug therapy	40 (57.10)
Esomeprazole 20 mg + Clarithromycin 500 mg + Amoxycillin 1000 mg twice daily for 14 days	19 (47.50)
Pantoprazole 40 mg + Clarithromycin 500 mg + Amoxycillin 1000 mg twice daily for 14 days	6 (15)
Lansoprazole 30 mg + Clarithromycin 500 mg + Amoxycillin 1000 mg twice daily for 14 days	15 (37.50)
Sequential drug therapy	30 (42.90)
Esomeprazole 20 mg + Amoxycillin 1000 mg twice daily for 5 days followed by	19 (63.33)
Esomeprazole 20 mg + Clarithromycin 500 mg + Tinidazole 500 mg twice daily for 5 days	
Pantoprazole 40 mg + Amoxycillin 1000 mg twice daily for 5 days followed by	3 (10)
Pantoprazole 40 mg + Clarithromycin 500 mg + Tinidazole 500 mg twice daily for 5 days	
Lansoprazole 30 mg + Amoxycillin 1000mg twice daily for 5 days followed by	8 (26.67)
Lansoprazole 30 mg + Clarithromycin 500 mg + Tinidazole 500 mg twice daily for 5 days	
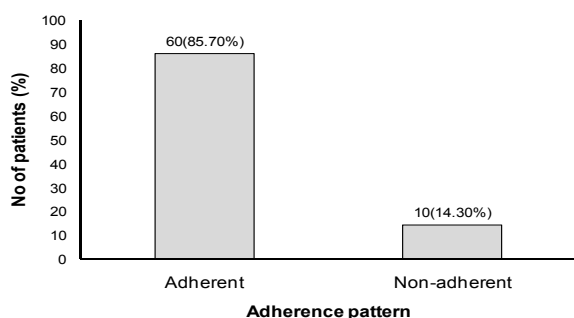
Figure 2. Bar diagram showing adherence pattern among 70 patients.

Higher number (65% (n=35)) of the patients who were adherent belonged to the age group of 30-60 years. Additionally, 56.67% (n=34) of the adherent patients were males and 43.33% (n=26) of them were females. A majority of the adherent patients (71.67% (n=43)) were literate and most of the patients who were non-adherent (80% (n=8)) reported of adverse effects. The most common adverse effects reported by 71.40% (n = 50) of the respondents included gastrointestinal discomfort (nausea, vomiting, diarrhea and constipation), metallic taste, anorexia, and dizziness. Only 1.40% (n=1) of the respondents reported tenesmus and burning pain in abdomen and 2.90% (n=2) reported increased appetite, as shown in figure 3. However, there was no statistically significant association (p>0.05) between patients' adherence with age, gender, literacy and adverse effects (Table 3).

Further, our study revealed that 100% (n=60) of the patients were adherent to medication despite of absence of symptomatic relief (absence or reduction of symptoms

Table 2. Adherence pattern among 70 patients.

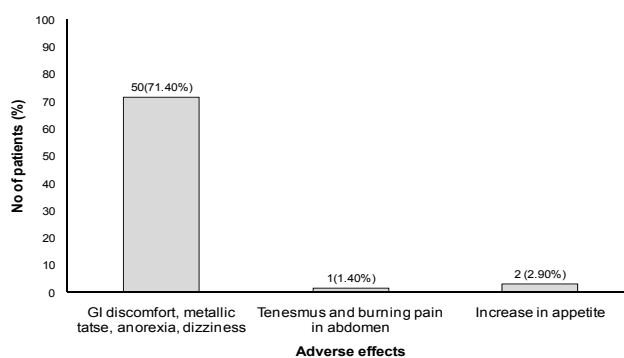| Characteristics	No. of Patients (%)
Patients who missed dose	10 (14.30)
Missing frequency (n = 10)	
Sometimes	10 (14.30)
Often	0 (0)
Always	0 (0)
Reason for missing dose (n=10)	
Forgetfulness	8 (80)
Carelessness	1 (10)
Adverse effects	1 (10)

Figure 3. Bar diagram showing adverse effects among 70 patients.

of the illness) from the medication while 80% (n=8) of the non-adherent patients did not have symptomatic relief. A highly significant association (p<0.05) was observed between adherence and absence of symptomatic relief (Table 3). Nevertheless, there was no significant association between adherence to medication and patient's knowledge about medication; patient's perception about the disease; treatment complexity; follow up of the patients; follow the instructions given by doctor; special attention from doctor; information about the prescribed medication and medication costs (Table 3).

DISCUSSION

Adherence to drug therapy is the foremost factor for the elimination of *H. pylori* infection.[9] It is, therefore, important to understand the determinants of poor adherence which is a must to obtain successful treatment outcomes.[10]

The present study showed higher *H. pylori* infection in males than in females. In consistence with the finding of our study, several studies conducted in Nepal and in other countries reported that *H. pylori* infection was more common in males compared to females.[11-14] Similarly, in a study by Makaju et al. at Dhulikhel Hospital among 224 *H. pylori* patients, a majority of them were males.[13] The lower number of females with *H. pylori* infection might be due to the indiscriminate use of antibiotics for many other illnesses. This explanation is in consistent with a study in which women were reported of consuming 17% more antibiotics than men.[14] On contrary to the findings of the

Table 3. Adherence pattern among 70 patients.

Characteristics	No. of patients (%)	Adherent[£] (n=60) No. (%)	Non-adher-ent[ˆ] (n=10) No. (%)	p-value
Age (years)				
<30	15 (21.40)	13 (21.67)	2(20)	
30-60	45 (64.30)	39 (65)	6(60)	0.866
>60	10 (14.30)	8 (13.33)	2(20)	
Gender				
Male	40 (57.10)	34 (56.67)	6(60)	
Female	30 (42.90)	26 (43.33)	4(40)	0.843
Literacy				
Literate	50 (71.40)	43 (71.67)	7(70)	
Illiterate	20 (28.60)	17 (28.33)	3(30)	0.914
Adverse effects				
Yes	53 (75.71)	45 (75)	8(80)	
No	17 (24.29)	15 (25)	2(20)	0.728
Symptomatic relief				
Yes	2 (2.86)	0 (0)	2(20)	
No	68 (97.14)	60 (100)	8(80)	0.005
Knowledge about medication				
Yes	62 (88.57)	54 (90)	8(80)	
No	8 (11.43)	6 (10)	2(20)	0.391
Patient's perception about disease				
Curable	64 (91.43)	56 (93.33)	8(80)	
Incurable	1 (1.43)	1 (1.67)	0(0)	
Can only be managed symp-tomatically	5 (7.14)	3 (5)	2(20)	0.292
Treatment Complexity				
Yes	10 (14.29)	8 (13.33)	2(20)	
No	60 (85.71)	52 (86.67)	8(80)	0.592
Follow up				
Yes	60 (85.71)	52 (86.67)	8(80)	
No	10 (14.29)	8 (13.33)	2(20)	0.592
Follow instructions				
Yes	68 (97.14)	59 (98.33)	9(90)	
No	2 (2.86)	1 (1.67)	1(10)	0.222
Special attention				
Yes	55 (78.57)	47 (78.33)	8(80)	
No	15 (21.43)	13 (21.67)	2(20)	0.905
Information about prescribed medication				
Yes	54 (77.14)	46 (76.67)	8(80)	
No	16 (22.86)	14 (23.33)	2(20)	0.814
Medication costs				
Affordable	39 (55.71)	35 (58.33)	4(40)	
Not-Affordable	31 (44.29)	25 (41.67)	6(60)	0.281

[£]Patients who had never missed dose
[ˆ]Patients who had missed dose

study, another research by Yangchun et al. found higher rate of infection in females than in males suggesting the role of hormones in their dominance.[15]

Our study found that a majority of the individuals belonged to the age group 30-60 years followed by individuals belonging to 30 years or below. The lowest number of elderly individuals with *H. pylori* infection based on our study is suggestive of decrease in infection with age.[12] The decreasing rate of *H. pylori* infection in old age was probably due to the development of an unfavorable gastric environment with age as suggested by another study.[12] Additionally, our study showed that a majority of the patients acquired persistent infection throughout adulthood. This finding corresponds with a number of other studies in which almost 30-50% of infection was found to occur in early childhood which increased to 90% by the time individuals reached adulthood.[16-18]

A high level of adherence, in most medical therapies, is inevitable to obtain successful treatment outcomes with medication.[19] Studies have, therefore, consistently reported poor adherence to medication as a major determinant of treatment success, and often, poor adherence is not well recognized.[19] As a consequence, our major research focus was to understand the determinants of poor adherence.[9,10,19] Our study showed that a majority of the patients were adherent to medication. Our finding is in accordance with a study done by Mohammad et al. in which a majority of the patients with *H. pylori* infection reported good adherence.[20] Higher adherence rate has been found among those patients with acute conditions such as *H. pylori* infection compared to those with other chronic diseases such as hypertension, type II diabetes mellitus, ischemic heart disease, bronchial asthma, Chronic Obstructive Pulmonary Disease (COPD) etc.[21-25] Most importantly, the treatment regimen for *H. pylori* is also confined to 2 weeks duration which might have helped the patients to adhere to the regimen.[21] In addition, higher adherence among the patients with *H. pylori* infection in the present study might be due to the fact that a majority of them were literate. It might have helped them understand the instructions to take the prescribed medication. The health literacy of the patient might have enabled him/her to understand basic health information and services needed to make appropriate health decisions as suggested by Kocurek.[26]

Non-adherence to medication was found among less than a quarter of patients. In our study, among the non-adherent patients, a majority of them had missed dose due to forgetfulness. Carelessness and the onset of adverse effects were other additional reasons for missing the dose as reported by a very few number of non-adherent patients. In consistent to the findings of the current study, another study by Lefebvre et al. found forgetfulness and onset of adverse effects such as nausea, stomach pain and bad taste of pills as the barriers to *H. pylori* treatment

leading to poor adherence.[19] Additionally, forgetfulness was reported as one of the major reasons for missing dose not just in acute conditions like *H. pylori* infection but in different chronic diseases such as those in type II diabetes mellitus and COPD.[22,23]

A previous study has found that patients who were more likely to be non-adherent were below 65 years of age and had fewer comorbidities.[27] On the other hand, several other studies found that non-adherence to medication was higher during later years of life (60-70 years) and in children compared to adults.[22,26,28] On contrary to the findings from previous studies, in our study, a similar proportion of adherent and non-adherent individuals fell under the same age group of 30 to 60 years though the association was not statistically significant. This might be due to the fact that a majority of the individuals under our study belonged to the age group of 30-60 years. Further, a high literacy rate among the patients under our study and higher number of patients with knowledge about medication might have led to higher adherence in that age group. Moreover, the patients under the age group of 30 to 60 years are a working population, who due to their busy schedule and work load might have missed the dose leading to non-adherence.

Our results showed that higher number of males compared to females were adherent to medication. Similarly, another study by Lefebvre et al. on patients with *H. pylori* infection found higher adherence rate in males compared to females.[19] The lesser number of females being adherent might be due to the fact that they are frequently the primary care giver to their family members and they spend less time and energy taking care of themselves.[29] However, no significant association was found between gender and adherence to medication. This finding is in consistence with a study by Shrestha et al. on patients with COPD where no relationship was found between gender and adherence to therapy.[22]

In our study, among many, one of the factors reported as barriers to adherence was treatment related factors such as a treatment complexity, duration of treatment (10-14 days), pill burden (6-12 pills per day on the standard triple drug therapy), and adverse effects of medication. It should be noted that a majority of the patients under our study missed doses due to the occurrences of adverse effects. Similar findings were reported in a study by Shrestha et al. in which experiences of adverse effects affected adherence to medication in patients with COPD.[22] Non-adherence to medication due to the occurrences of adverse effects has been encountered in patients with type II diabetes mellitus hypertension and in HIV-positive patients as well.[23-25,30] Among the patients in whom adverse effects of medicine were seen, a majority of them reported of gastrointestinal discomfort (nausea, vomiting, diarrhea and constipation) along with metallic taste, anorexia, and dizziness. Our results are in accordance with another study that reported of gastrointestinal disorders with abnormal taste in a majority of the *H. pylori* patients.[20] These adverse effects are, however, bothersome and the patient is more likely to tolerate those mild effects if s/he is clear about the goal of the therapy.[9]

In this study, more than half of the patients were prescribed with the standard triple drug therapy and the rest with the sequential therapy on a random basis. Those therapies comprising two or more medications per day might add burden to the patients leading to poor adherence as suggested by another study.[9] For example, in chronic diseases such as type II diabetes mellitus and hypertension, a large number of pills is to be taken daily creating potential for confusions and omissions of the dose leading to non-adherence as suggested by O'Connor et al.[9] Additionally, pill burden of more than 10 pills per day among HIV positive patients with other comorbidities led to non-adherence to medication as suggested by Monroe et al.[30] However, no significant association was found between the type of regimen (standard or sequential therapy) and adherence to medication in our study. A similar finding was also reported by another study where various eradication regimens for *H. pylori* did not influence patient's adherence to medication.[9] It might be due to the fact that the occurrence of adverse effects was consistently similar for the triple or sequential regimen and that *H. pylori* eradication regimen may not be an important factor in the patients' adherence to the treatment regimens as suggested by Mohammad et al.[20]

One should take into account that adherence is simultaneously affected by multiple factors. Besides treatment related factors, symptomatic relief (absence or reduction of symptoms of the illness) from medication contribute significantly to non-adherence to medication.[31] In addition, rate of progression of disease, and severity of the disease greatly influence medication adherence.[9,19,32] However, our findings suggest that a significantly higher number of the patients were adherent to medication despite of having no reduction of symptoms of the illness. The possible explanation might be that *H. pylori* infection is an acute condition requiring only 10 or 14 days of drug therapy and higher adherence rates have been found among the patients with acute conditions compared to those with chronic diseases.[21] In addition, a study has shown that consistent adherence to medication among the patients with chronic diseases decreased dramatically after the first six months of therapy.[33] So, as the therapy for *H. pylori* doesn't require lifelong treatment, medication adherence rate might have been higher in the patients included in this study despite of not having symptomatic relief.

Patient's perception about the nature and severity of their illness influences adherence to therapy.[26] Our study revealed that a majority of the patients perceived the disease as curable which might have helped them adhere better to the prescribed medication. In addition, most of the patients under the study reported that the

drug regimen was not troublesome to follow. This might have helped them to believe in the effectiveness of the treatment and achieve higher adherence to medication. However, a fewer number of the patients in our study were non-adherent mainly due to the occurrences of adverse effects. Those patients might have had the fear of adverse effects or had concerns regarding the dependency on drugs due to which they did not adhere to the therapy properly.[26] Additionally, lack of beliefs about the effectiveness of the treatment and patient's denial of the illness and the need to take medicines are likely to influence the adherence to medication. Further, health care providers are believed to greatly influence patient's perception about the disease and medication that will in turn affect their adherence to medication.[26] In the present study, it was found that a majority of the patients came for follow up and followed the instructions given by doctors. So, the motivation and attitude of the physician is of utmost importance to encourage the patient to adhere to treatment and attain successful eradication of *H. pylori* infection as emphasized by a previous study.[9] Similarly, another study has found that patients lack the skills or knowledge necessary to complete the medication regimen.[34]

It has been proposed that one of the realistic methods of ensuring adherence to medication is the proper communication on one-on-one basis between the patient and the physician that fills the gaps between them.[9] Similarly, the good adherence of the patients under our study might be because of the opportunity they got to communicate with their health care providers properly. Our study found that most of the patients got both special attention and information about the prescribed regimen from the medical personnel. This has probably improved patient's attitude towards treatment and enhanced their knowledge about prescribed medicines leading to higher adherence. Similarly, another study found that educating the individual patient on their illness by the physician greatly influenced the adherence.[9] The health care providers can help educate the patients about the usefulness of proper medication on time which indeed helps in achieving greater adherence to medication. Furthermore, previous studies have found that patients tend to adhere more to the prescribed medication upon the physician's visit commonly known as 'white-coat adherence.[20,26] Similarly, patients receiving proper counseling on medications either in written or oral form were more likely to adhere to treatment.[20] In our study as well, the major source of motivation for higher adherence to medication might be due to proper medication counseling to the patients from the health care providers. Several studies have shown that patients tend to skip doses, reduce doses, or do not get prescriptions filled because they cannot afford to pay for medications.[12,26] Further, another study has reported that many patients who decided to skip doses or stop taking medicines as a result of cost, did not tell their prescriber which might be due to embarrassment, or taking it as a less important topic or

lack of trust and time during clinical visit.[26] In agreement to previous studies, the present study has shown that most of the non-adherent patients could not afford the prescribed medicines. Although, unaffordability of medicines might have led to non-adherence to medication, no significant association was found in the present study. This disparity might be due to the limited sample size of this study and the fact that it is a mono-centered study which reinforces the need for further multi-centered study.

The current study may be further limited by a lack of "gold standard" method of measuring adherence despite availability of multiple approaches to measuring adherence. Another limitation was the use of open-ended questionnaires for the study which might have missed important questions relevant to the study though it was unlikely. Further, the recall bias of the patients regarding doses missed, and the occurrences of adverse effects are likely to overestimate adherence. In addition to it, possible chances of false claims by the patients though rarely expected might have in one way or the other affected the overall outcomes of the study.

Despite the limitations, we believe that we were able to identify the real scenario of *H. pylori* infection in Nepal and address the factors that have led to the suboptimal adherence to medication. The findings of our study might contribute to achieving higher adherence by directing efforts to mitigating the factors leading to non-adherence. However, our study may not have covered the entire population. Hence, further studies and investigations are warranted.

CONCLUSION

Adherence to medication is the foremost factor in *H. pylori* eradication. Due to the widespread problem of adherence, a large number of patients do not get maximum benefit of medical treatment resulting in poor health outcomes, lower quality of life and increased health care costs. The present study has provided an insight into the problem of non-adherence in the treatment of *H. pylori* infection in Nepal. Hence, initiatives must be taken and strategies made in order to improve adherence to medication and help in complete eradication of *H. pylori* infection. Thus, improving adherence to medication will not only help bring a sustainable change on the health status of the people but also lower the health care costs. Therefore, investigating the reasons behind the non-adherence to medication and making interventions to support the patients from modifying the complex treatment regimen to simple, improving their attitude towards treatment and enhancing their knowledge about medication may help achieve the goal of successful treatment.

REFERENCES

1. Tomb FJ, White O, Kerlavage AR, Clayton AR, Sutton GG, Fleischmann DR et al. The complete genome sequence of the gastric pathogen *Helicobacter pylori. Nature.* 1997; 388: 539–47.

2. Mendall MA, Transmission of *Helicobacter pylori. Seminars in Gastrointestinal Disease.* 1997; 8:113-23.

3. Chey WD, Wong BCY. American College of Gastroenterology guideline for the Management of *Helicobacter pylori* infection. *Am J Gastroenterol*. 2007; 102: 1808-25.

4. Megraud FH. *pylori antibiotic* resistance: prevalence, importance, and advances in testing. *Gut.* 2004; 53: 1374-84.

5. Aronson K Jeffrey. Compliance, concordance, adherence. *Br Clin Pharmacol.* April 2007; 63(4):383-4.

6. Lefebvre M, Hsiu-Ju C, Morse A. Adherence and barriers to *H. pylori* treatment in Arctic Canada. *Int J Circumpolar Health.* 2013; 72: 22791.

7. Howden CW, Blume SW, de LG. Practice patterns for managing *Helicobacter pylori* infection and upper gastrointestinal symptoms. Am J Manag Care. 2007; 13: 37-44.

8. Niv, Y, Abuksis, G. Survey of the opinions, knowledge and practices of surgeons and internists Therapeutic Advances in Gastroenterology regarding *Helicobacter pylori* test-and-treat policy. *J ClinGastroenterol.* 2003;36:139-43.

9. O'Connor A, John P, Taneike I. Improving Compliance with *Helicobacter pylori* Eradication Therapy: When and How? *Ther Adv Gastroenterol.* 2009;2(5):273–9.

10. Di Matteo MR, Giordani PJ, Lepper HS. Patient adherence and medical treatment outcomes: a meta-analysis. *Med Care.* 2002; 40: 794–811.

11. Shrestha R, Koirala K, K.C. SR, Hada BK. *Helicobacter pylori* infection among patients with upper gastrointestinal symptoms: Prevalence and relation to Endoscopy Diagnosis and Histopathology. *J Family Med Prim Care.* 2014;3(2):154-8.

12. Murray LJ, McCrum EE, Evans AE, Bamford KB. Epidemiology of *Helicobacter pylori* infection among 4742 randomly selected subjects from Northern Ireland. *Int J Epidemiol.* 1997; 26: 880-7.

13. Makaju RK, Tamang MD, Sharma Y, Sharma N, Koju R, Ashraf M. Prevalence of *Helicobacter pylori* in Dhulikhel Hospital, Kathmandu University Teaching Hospital: aretrospective histopathologic study. *Kathmandu Univ Med J* 2005;3:355-9.

14. Naja F, Kreiger N, Sullivan T. *Helicobacter pylori* infection in Ontario: Prevalence and risk factors. *Can J Gastroenterol.* 2007Aug;21(8): 501–6.

15. Yangchun Zhu, Xiaoying Zhou, Junbei Wu, Jing Su, and Guoxin Zhang. Risk Factors and Prevalence of *Helicobacter pylori* Infection in Persistent High Incidence Area of Gastric Carcinoma in Yangzhong City. *Gastroenterology Research and Practice.* 2014, Article ID 481365, 10 pages.

16. Bardhan KP. Epidemiological features of *Helicobacter pylori* infection in developing countries. *Clin Infect Dis.* 1997; 25:973-8.

17. Cheng H, Hu F, Zhang L, Yang G, Ma J, Hu J. Prevalence of *Helicobacter pylori* infection and identification of risk factors in rural and urban Beijing, China. *Helicobacter.* 2009;14:128–33.

18. Frenck RW, Clemens J. *Helicobacter* in the developing world. *Microbes Infect.* 2003; 5: 705–13.

19. Lefebvre M, Hsiu-Ju C, Morse A. Adherence and barriers to *H. pylori* treatment in Arctic Canada. *Int J Circumpolar Health.* 2013; 72: 22791.

20. Abbasinazari M, Sahraee Z, Mirahmadi M. The Patients' Adherence and Adverse Drug Reactions (ADRs) which are Caused by Helicobacter pylori Eradication Regimens. *Journal of Clinical and Diagnostic Research.* 2013;7(3): 462-6.

21. DiMatteo MR. Variations in patients' adherence to medical recommendations: a quantitative review of 50 years of research. *Med Care.* 2004; 42:200-9.

22. Shrestha R, Pant A, Shakya Shrestha S, Shrestha B, Gurung RB, Karmacharya BM. A Cross-Sectional Study of Medication Adherence Pattern and Factors Affecting the Adherence in Chronic Obstructive Pulmonary Disease. *KUMJ.* 2015;13: 64-70.

23. Shrestha SS, Shakya R, Karmacharya BM, Thapa P. Medication Adherence to Oral Hypoglycemic Agents Among Type II Diabetic Patients and Their Clinical Outcomes with Special Reference to Fasting Blood Glucose and Glycosylated Hemoglobin Levels. *KUMJ.* 2013;11:226-32.

24. NurSufiza Ahmad, AzuanaRamli, Farida Islahudin, Thomas Paraidathathu. Medication adherence in patients with type 2 diabetes mellitus treated at primary health clinics in Malaysia. *Patient Preference and Adherence.* 2013; 7: 525-30.

25. NurSufiza Ahmad, AzuanaRamli, Farida Islahudin, Thomas Paraidathathu Medication adherence among hypertensive patients of primary health clinics in Malaysia. *Patient Preference and Adherence.* 2012;6: 613–22.

26. Kocurek B. Promoting Medication Adherence in Older Adults and the Rest of Us. Diabetes Spectrum. 2009; 22: 80-84.

27. Jo PM: Effect of medication nonadherence on hospitalization and mortality among patients with diabetes mellitus. *Arch Intern Med.* 2006; 166: 1836–41.

28. Haruma K, Kamada T, Kawaguchi H, Okamoto S, Yoshihara M. Effect of age and *Helicobacter pylori* infection on gastric acid secretion, *J Gastroenterol Hepatol.* 2000; 15(3): 277-83.

29. Sharon J. Rolnick, Pamala A. Pawloski, Brita D. Hedblom, Stephen E. Asche, Richard J. Bruzek. Patient Characteristics Associated with Medication Adherence. *CM & R.* 2013; 11: 54-65.

30. Anne K Monroe, Tashi L Rowe, Richard D Moore, Geetanjali Chander. Medication adherence in HIV-positive patients with diabetes or hypertension: a focus group study. *BMC Health Services Research.* 2013;13: 488.

31. Levy RL, Feld AD. Increasing Patient Adherence to Gastroenterology Treatment and Prevention Regimens. *Am J Gastroenterol.* 1999; 94: 1733-41.

32. Ho PM, Bryson CL, Rumsfeld JS. Medication Adherence. It's Importance in Cardiovascular Outcomes. *Circulation.* 2009; 119: 3028-35.

33. Patterson T, Straten E, Jimenez S. The prevalence of *Helicobacter pylori* antibody in different age groups in Central Texas. *Clin Lab Sci.* 2012; 25(2):102-6.

34. Osterberg L, Blaschke T. Adherence to medication. *N Engl J Med.*