Do we eradicate *Helicobacter pylori* in hospitalized patients with peptic ulcer disease?

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BACKGROUND: *Helicobacter pylori* infection is the most common chronic infection in humans. It is a major contributor to the cause of duodenal and gastric ulcers worldwide. Its eradication has been shown to reduce rates of *H pylori*-related ulcers as well as other complications such as gastric cancer.

OBJECTIVE: To determine the rate of appropriate treatment in patients following a diagnosis of *H pylori* infection on biopsy during esophagoduodenoscopy for upper gastrointestinal bleeding over a four-year period at a tertiary centre in Vancouver, British Columbia. Also evaluated was the rate of eradication confirmation using the urea breath test.

METHODS: A retrospective review of 1501 inpatients who underwent esophagoduodenoscopy for upper gastrointestinal bleeding (January 2006 to December 2010) was undertaken. Patients who were biopsy stain positive for *H pylori* were selected for drug review either via a provincial database (PharmaNet) or via records from patients' family practitioners. Data were also obtained via two provincial laboratories that perform the urea breath test to determine the rates of confirmation of eradication.

RESULTS: Ninety-eight patients had biopsy-proven *H pylori*. The mean (± SD) age was 56.13±17.9 years and 65 were male. Data were not available for 22 patients; the treatment rate was 52.6% (40 of 76). Of those treated, 12 patients underwent a post-treatment urea breath test for eradication confirmation.

CONCLUSION: There was substantial discrepancy between the number of diagnosed *H pylori* infections and the rate of treatment as well as confirmation of eradication. Numerous approaches could be taken to improve treatment and eradication confirmation.

Key Words: Helicobacter pylori; *Peptic ulcer disease; Upper GI bleeding*

Éradique-t-on l'*Helicobacter pylori* chez les patients hospitalisés en raison d'un ulcère gastroduodénal?

HISTORIQUE : L'infection par l'*Helicobacter pylori* est l'infection chronique la plus courante chez les humains. Elle contribue énormément aux ulcères duodénaux et gastriques de par le monde. Il est démontré que son éradication réduit le taux d'ulcères liés à l'*H pylori*, de même que d'autres complications, telles que le cancer gastrique.

OBJECTIF : Déterminer le taux de traitement pertinent des patients après une biopsie diagnostique d'infection par l'*H pylori* dans le cadre d'une œsophagoduodénoscopie afin de traiter des saignements des voies digestives supérieures sur une période de quatre ans dans un centre de soins tertiaires de Vancouver, en Colombie-Britannique. Évaluer également le taux de confirmations d'éradication à l'aide du test respiratoire à l'urée.

MÉTHODOLOGIE : Les chercheurs ont entrepris une étude rétrospective de 1 501 patients hospitalisés qui ont subi une œsophagoduodénoscopie pour soigner des saignements des voies digestives supérieures entre janvier 2006 et décembre 2010. Les patients dont la biopsie était positive à l'*H pylori* ont été sélectionnés pour subir une évaluation des médicaments par l'entremise d'une base de données provinciale (PharmaNet) ou du dossier des patients créé par leur médecin de famille. Ils ont également obtenu des données par l'entremise de deux laboratoires provinciaux qui exécutent des tests respiratoires à l'urée pour déterminer le taux de confirmations d'éradication.

RÉSULTATS : Quatre-vingt-dix-huit patients présentaient un *H pylori* démontré par biopsie. Ils avaient un âge moyen (± ÉT) de 56,13±17,9 ans, et 65 étaient de sexe masculin. On ne possédait pas de données au sujet de 22 patients, tandis que le taux de traitement s'élevait à 52,6 % (40 sur 76). Parmi les patients traités, 12 ont subi un test respiratoire à l'urée après le traitement pour confirmer l'éradication.

CONCLUSION : On a constaté un écart substantiel entre le nombre d'infections par l'*H pylori* diagnostiquées et le taux de traitement, de même que les confirmations d'éradication. On pourrait adopter de multiples approches pour améliorer le traitement et confirmer l'éradication.

Helicobacter pylori is the most prevalent chronic infection worldwide, with serological evidence of infection in up to 10% of patients 18 to 30 years of age and up to 50% of patients older than 60 years of age in the United States (1). In developing countries, up to 80% of the population is infected with *H pylori* (2). Typically acquired in the first few years of life, *H pylori* infection usually persists indefinitely unless treated (3).

The WHO classifies *H pylori* as a carcinogen owing to its association with several gastric malignancies (4). Infection also increases the risk of gastric mucosa-associated lymphoid tissue lymphomas, and evidence suggests that clearing the *H pylori* infection can cause regression of lymphoma in 70% to 80% of cases (5,6).

H pylori represents a major cause of nonsteroidal anti-inflammatory drug-related peptic ulcer disease (PUD), accounting for 90% to 100% of duodenal ulcers and 60% of gastric ulcers (7). Upper gastrointestinal (GI) bleeding caused by PUD from untreated *H pylori* infection can vary from mild asymptomatic anemia to life-threatening acute hemorrhage necessitating hospital admission and endoscopic evaluation. Expenditures attributable to *H pylori*-related PUD have been estimated to be $5.65 billion in the United States (8).

Effective therapies exist for the treatment of *H pylori* using a standard combination of antibiotics and a proton pump inhibitor (PPI) under the recommendations of the American College of Gastroenterology (9). As per these guidelines, triple therapy consists of a PPI, clarithromycin, and amoxicillin or metronidazole for 10 to 14 days. The acceptable alternative is quadruple therapy consisting of a PPI or H_2-receptor antagonist, bismuth, metronidazole and tetracycline for 10 to 14 days.

A meta-analysis has shown a remission rate at 12 months of 97% for gastric ulcer and 98% for duodenal ulcer following successful eradication of *H pylori* infection (10). Further rationale for eradication is evident from studies demonstrating mucosal healing (11) as well as decreased incidence of recurrent GI bleeding in patients in whom *H pylori* is treated (12,13). In particular, eradication has been believed to be most critical in individuals with an established history of bleeding PUD because of a high risk of rebleeding in patients in whom *H pylori* is not eradicated.

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Because of potential morbidities in infected individuals and the availability of safe, effective therapy, treatment is recommended in all patients with documented *H pylori* infection. However, despite readily available medical therapy, many factors that may prevent treatment of patients following their diagnosis of *H pylori* infection exist. There are a lack of data examining the rates of treatment for *H pylori*-positive inpatients presenting with upper GI bleeding.

In the present study, our objectives were to determine the rate of appropriate eradication therapy in hospitalized patients who presented with upper GI bleeding and were found to have biopsy-proven *H pylori* infection on esophagoduodenoscopy (EGD) over a four-year period. We also sought to evaluate the rate of eradication confirmation using the urea breath test after completion of eradication therapy for *H pylori*.

METHODS

A retrospective chart review of patients requiring hospital admission and inpatient EGD for acute upper GI bleeding from January 1, 2006 to December 31, 2010 at St Paul's Hospital, a tertiary referral centre located in Vancouver, British Columbia, was performed.

Patients who underwent a mucosal biopsy (gastric or duodenal), performed at the time of EGD, and stained positive for *H pylori* were selected for the assessment of appropriate drug therapy (triple or quadruple therapy, American College of Gastroenterology [9]). This was evaluated by interrogating a provincial pharmacy database (PharmaNet), which documents all filled prescriptions of patients in British Columbia. Records from patients' family physicians were also assessed when PharmaNet data were unavailable.

The eradication confirmation data were collected from two provincial laboratories in British Columbia (LifeLabs Medical Laboratory Services and BC Biomedical Laboratories) that provide outpatient urea breath testing. The rate of urea breath testing was determined from the data. The analysis evaluated the rate of appropriate treatment in patients with biopsy-proven *H pylori* infection and the rate of eradication confirmation. The present study was approved by the Providence Health Care Research Ethics Board as a quality assurance study.

RESULTS

A total of 1501 patients were admitted to St Paul's Hospital requiring inpatient EGD for evaluation of upper GI bleeding in the four-year period from January 1, 2006 to December 31, 2010 (Figure 1).

Of these patients, 98 (6.5%) had positive *H pylori* staining on mucosal biopsy performed at the time of EGD. The mean (± SD) age of these patients was 56.13±17.9 years (range 17 to 90 years); 65 (66%) were male.

Twenty-two of the 98 (22%) patients were lost to further data collection for reasons including unavailable records (n=9) and unavailable primary physician (n=13).

Of the remaining 76 patients, 40 (52.6%) were treated with standard triple therapy as documented in PharmaNet or primary physician's records. Records from the two laboratories revealed that 30% (n=12) of those treated underwent an eradication confirmation urea breath test.

DISCUSSION

Despite the fact that *H pylori* infection is a readily curable cause of PUD, which can be life threatening and costly, it remains inappropriately treated. Our study suggests that there is substantial discrepancy between the number of diagnosed *H pylori* infections and the rate of treatment and documentation of its eradication. In our study, which involved a population of inpatients who presented with acute upper GI bleeding, it is even more prudent that they be treated with the appropriate medical therapy because they represent a high-risk population for rebleeding.

A recent study performed in Toronto (Ontario) (14) examined the rates of treatment for both outpatients and inpatients undergoing EGD for various indications. The investigators found that 90% of all patients were treated appropriately; however, subgroup analysis revealed that inpatients were significantly less likely to receive appropriate therapy (71%). In addition, they found that 68% of patients

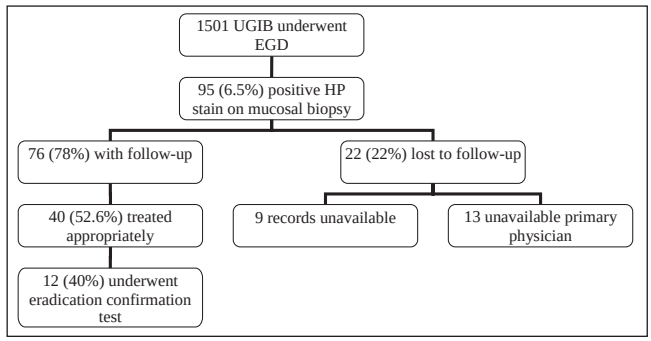

Figure 1) *Flow diagram of treatment and eradication rates. EGD Esophagoduodenoscopy; HP* Helicobacter pylori; *UGIB Upper gastrointestinal bleeding*

received eradication confirmation. In 1999, another study conducted in five states in the United States demonstrated that the screening rate for *H pylori* was 54% in patients receiving EGD and those testing positive were treated 70% of the time (15). Similarly, an older study from California (USA) (16) found that only 47% of diagnosed patients were treated. In contrast to those studies, our investigation only included inpatients with acute GI bleeding; however, the treatment rates were comparable in some instances.

The goal of therapy is eradication of *H pylori* organisms from the host, which can be demonstrated by a negative urea breath test following therapy. Because of emerging antibiotic resistance in *H pylori* strains (17), persistence of infection may occur despite treatment using standard therapy. Eradication rates for triple therapy have been estimated to range from 70% to 85% due to increasing clarithromycin resistance (9). Therefore, eradication confirmation is useful to assess the adequacy of therapy as well as consideration for further second-line management. Although all of the patients who underwent post-treatment testing were successfully treated (12 of 12), our study shows an underutilization of the urea breath test post treatment. Implementation of treatment protocols to include urea breath test post-therapy may increase rates of testing and ensure eradication.

Failure to treat is likely due to multiple factors, particularly in the inpatient setting where an individual patient may be under the care of multiple physicians. Owing to the technicalities of histological preparations, there exists an inherent delay in which a diagnosis can be made from a biopsy sample. From the experience at our centre, many patients will experience an acute GI bleeding episode, have it resolved and be discharged from the hospital while final biopsy results remain pending. In those instances, therapy may not be initiated if the biopsy results are not subsequently communicated to the patient's primary physician. In fact, previous studies (18,19) have illustrated how this 'missed' test result represents a substantial problem for inpatients, with a systematic review demonstrating lack of follow-up in up to 61.6% of in-hospital test results (18). Other possible factors that contribute to low treatment rates may lie in incomplete dictation of clinical notes that do not indicate a possible diagnosis of *H pylori*, failure of the laboratory to forward pathology results or lack of physician follow-up for the patient.

For the inpatient population at medical centres across Canada, current electronic medical record systems can be programmed to flag new results, including pathology. This would improve treatment rates by alerting the physician in charge of the patient's care to take an appropriate course of action. If that capability is available, we recommend that such protocol be implemented.

Particularly pertaining to the inner-city patient population at our institution, people with difficult access to health care due to psychosocial risk factors would benefit from a multidisciplinary diagnostic and treatment approach with assistance from social worker and community nurses to implement treatment once diagnosis is confirmed. Ways to implement this include a social work visit at the time of endoscopy for high-risk patients and, perhaps, the consideration of

empirical treatment if endoscopy finding and clinical history are suggestive of *H pylori* infection. However, empirical treatment with antibiotics and PPI carries a small risk of causing *Clostridium difficile*-associated colitis, even in regimens containing oral metronidazole (20,21); therefore, we do not recommend this as primary approach unless follow-up is not possible.

Possible remedies to improve treatment rates in the outpatient setting include supplying patients at the time of endoscopy with necessary postdated prescriptions and specific instructions to follow up with the physician's office in a predetermined length of time. The office would then be able to instruct patient to fill the prescription or not, depending on the biopsy result. The postdated prescription would prevent patients from inadvertently taking the medications if not medically indicated.

Novel approaches to enhancing treatment rates for the general public include use of advances in technology, such as smartphone applications, that can automatically generate notifications for patients to securely access their medical information. Similarly, text messages could be generated automatically to prompt patients to contact the physician's office for further instruction on the availability of biopsy results.

Although not performed at our centre, rapid urease testing could enable prompt diagnosis of *H pylori* in the endoscopy suite with comparable specificity as histology in the setting of upper GI bleeding (95% CI 0.90 to 0.96) (22). This would eliminate any delay in communication so that the patients can receive appropriate treatment before leaving the hospital. Despite the higher cost, this approach may be more desirable in patients who are less likely to follow up with their primary physician after hospitalization.

Limitations of the present study were confined to the experiences of a single centre; however, similar findings of low treatment rates and confirmation testing were also reported in other studies (14-16).

In summary, *H pylori* infections that are diagnosed at the time of acute GI bleeding are not effectively being treated, as our study suggests. Those who are treated do not receive confirmation of eradication in the face of increasing failure rates with usual therapy. Improvement in this area is urgently required to ensure proper delivery of therapy for an otherwise treatable condition that has serious adverse health outcomes and significant economic cost.

KEY MESSAGES

- Despite advances in *H pylori* detection and therapy, treatment of patients with acute GI bleeding in hospital appears to be inappropriately low.
- Steps to enhance therapy for *H pylori* in hospitalized patients with upper GI bleeding need to implemented.
- Outpatient follow-up to ensure appropriate treatment for these patients needs to be instituted to ensure eradication of *H pylori*.

REFERENCES

1. Pounder R, Ng D. The prevalence of *Helicobacter pylori* infection in different countries. Aliment Pharmacol Ther 1995;(9 Suppl 2):33.
2. Malaty H. Epidemiology of *Helicobacter pylori* infection. Best Pract Res Clin Gastroenterol 2007;21:205-14.
3. Suerbaum S, Michetti P. *Helicobacter pylori* infection. N Engl J Med 2002;347:1175-86.
4. International Agency for Research on Cancer. Infection with *Helicobacter pylori*. In: IARC monographs on the evaluation of carcinogenic risks to humans. Vol. 61 Schistosomes, liver flukes and *Helicobacter pylori*. Lyon, France: International Agency for Research on Cancer, 1994: 177-240
5. Bayerdorffer E, Neubauer A, Rudolph B, et al. Regression of primary gastric lymphoma of mucosa-associated lymphoid tissue type after cure of *Helicobacter pylori* infection. Lancet 1995;345:1591-4.
6. Paronnet J, Hansen S, Rodriguez L, et al. *Helicobacter pylori* infection and gastric lymphoma. N Engl J Med 1994;330:1267-71.
7. Kuipers E, Thijs J, Festen H. The prevalence of *Helicobacter pylori* in peptic ulcer disease. Aliment Pharmacol Ther 1995;(9 Suppl 2):59-69.
8. Sonnenberg A, Everhart J. Health impact of peptic ulcer in the United States. Am J Gastroenterol 1997;92:614-20.
9. Chey W, Wong B. American College of Gastroenterology guideline on the management of *Helicobacter pylori* infection. Am J Gastroenterol 2007;102:1808-25.
10. Leodolter A, Kulig M, Brasch H, et al. A meta-analysis comparing eradication, healing and relapse rates in patients with *Helicobacter pylori*-associated gastric or duodenal ulcer. Aliment Pharmacol Ther 2001;15:1949-58.
11. Rauws EA, Tytat GNJ. Cure of duodenal ulcer associated with eradication of *Helicobacter pylori*. Lancet 1990;335:1233-5.
12. Japstersen D, Koerner T, Schorr W, et al. *Helicobacter pylori* eradication reduces the rate of rebleeding in ulcer hemorrhage. Gastrointest Endosc1995;41:5-7.
13. Graham DY, Hepps KS, Ramirez FC, et al. Treatment of *Helicobacter pylori* reduces the rate of rebleeding in peptic ulcer disease. Scan J Gastroenterol 1993;28:939-42.
14. Yogeswaran K, Chen G, Cohen L, et al. How well is *Helicobacter pylori* treated in usual practice? Can J Gastroenterol 2011;25:543-6.
15. Hood HM, Wark C, Burgess PA, et al. Screening for *Helicobacter pylori* and nonsteroidal anti-inflammatory drug use in Medicare patients hospitalized with peptic ulcer disease. Arch Intern Med 1999;159:149-54.
16. Roll J, Weng A, Newman J. Diagnosis and treatment of *Helicobacter pylori* infection among California Medicare patients. Arch Intern Med 1997;157:994-8.
17. Megraud F. *H pylori* antibiotic resistance: Prevalence, importance, and advances in testing. Gut 2004;53:1374-84.
18. Callen J, Georgiou A, Li J, Westbrook JL. The safety implications of missed test results for hospitalized patients: A systematic review. BMJ Qual Saf 2011;20:194-9.
19. Roy CL, Poon EG, Karson AS, et al. Improving patient care. Patient safety concerns arising from test results that return after discharge. Ann Intern Med 2005;143:121-8.
20. Archimandritis A, Souyioultzis S, Katsorida M, Tzivras M. *Clostridium difficile* colitis associated with a 'triple' regimen, containing clarithromycin and metronidazole, to eradicate *Helicobacter pylori*. J Intern Med 1998;243:251-3.
21 Yearsley KA, Gilby LJ, Ramadas AV, Kubiak EM, Fone DL, Allison MC. Proton pump inhibitor therapy is a risk factor for *Clostridium difficile*-associated diarrhea. Aliment Pharmacol Ther 2006;24:613-9.
22. Gisbert JP, Abraira V. Accuracy of *Helicobacter pylori* diagnostic tests in patients with bleeding peptic ulcer: A systematic review and meta-analysis. Am J Gastroenterol 2006;101:848-63.