Helicobacter pylori Testing as a Screening Mechanism for Peptic Ulcer Disease

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Abstract— *Helicobacter pylori* testing is not a suitable screening mechanism for peptic ulcer disease (PUD). A literature review was conducted to find studies that either showed association between *H. pylori* infection and PUD or proved the efficacy of the screening mechanisms for *H. pylori*. This was done to assess the possibility of using the *H. pylori* testing as a screening mechanism for PUD. Only publications written in English and available as "free full text" were utilized in the analysis. Search terms were pubmed MESH terms *H. pylori* and peptic ulcer disease. An association between *H. pylori* infection and an increased risk of developing PUD was found. However, the development of PUD was found to be a result of many other factors as well, most notably: Non-steroidal anti-inflammatory drug (NSAID) use and smoking status. Furthermore, infections with *H. pylori* only rarely lead to development of PUD as many cases of *H. pylori* remain unproblematic and often asymptomatic. Ability of the various tests for *H. pylori* to detect an infection was assessed and extrapolated to show sensitivities and specificities of the various tests if they were used in PUD screening. Although there is a small but statistically significant association between *H. pylori* infection and PUD, using any of the currently available *H. pylori* tests as a screening mechanism for PUD is not reliable due to a low specificity and sensitivity.

Index Terms— *H. pylori*, peptic ulcer disease, screening, C-Urea Breath test, ELISA serology, stool antigens, preventative medicine.

1 Introduction

PEPTIC Ulcer Disease (PUD) is a disorder in which the integrity of the mucosal lining of the esophagus, stomach, or duodenum is compromised. Worldwide, the annual incidence and prevalence rates for PUD are 0.10-0.19% and 0.03-0.17% respectively (Sung J. et al). [18]. There are two main causes of PUD; *H. pylori* infection, and the use of NSAIDs. A detailed patient history can be enough to rule out NSAID use as a probable cause but checking for *H. pylori* requires special testing. *H. pylori* can be confirmed noninvasively through diagnositic identification of *H. pylori* antibodies in the serum, antigen testing of the stool, or performing a Carbon Isotope-Urease Breath test. Currently, the more invasive upper esophagogastroduodenal endoscopy with gastric biopsy and culture is considered to be the reference method for diagnosis of *H. pylori*. The "gold standard" diagnostic test for PUD is endoscopy. Oral contrast radiography may be preformed in patients who are not able to undergo an endoscopic procedure.

There has been a growing need in the medical community for a reliable screening mechanism for the detection of PUD. The more minimally invasive tests for *H. Pylori* screening are herein assessed for their suitability to this puepose.

The knowledge of a know association between PUD and H. pylori promoted a number of stuies derermining the prevelance of *H. pylori* concomitant with PUD. In a study of 1000 dyspeptic patients, the frequency of *H. pylori* infection among those with endoscopic diagnosis of gastritis, duodenal ulcer, gastric ulcer, and normal mucosa was 70.1% (398/568), 86.2% (150/174), 71.9% (64/89), and 33.5% (54/161), respectively (Reza, M. et al). [8].

80% of peptic ulcers are believed to be associated with *H. pylori* but not all of those patients with a *H. pylori* infection will develop an ulcer. Nearly half of the world's population is infected with *H. pylori* (Sung, J. et al). [18]. However, infection with *H. pylori* does not always result in PUD. Recent literature shows that only 0.1-0.2% of *H. pylori* infections annually will go on to produce an ulcer and only 2-5% of the infected population have an ulcer (Parsonnet, J.). [13].

The ability to use a screening mechanism for H. pylori in order to accurately diagnose PUD would be significant, largerly because of the non-invasive nature of available H. pylori testing when compaired to the invasive diagnostic testing currently used for PUD, such as endoscopy. This would save the patient and physician valuable time and resources as well as allow the patient to avoid the hazards of more invasive procedures.

2 Methods

2.1 Publication Search Criteria

The research literature was found using the Pubmed database. The terms used to find literature included peptic ulcer disease (MESH), *Helicobacter pylori* (MESH), screening for *H. pylori* (MESH). The search criteria used were: articles published between 1995-present, cohort studies, case studies, randomized control trials, and case-control trials. All articles used were written in the English language. A total of 65 articles were considered.

Once a list of articles had been created, abstracts of the literature were assessed to decipher whether the article would be pertinent to the research topic in question. Google Scholar, Pubmed, and Hutchinson Hospital library were used to access full-text versions of the pertinent articles. Only "free full-text" copies of articles were used and if an article was not available for free it was not included in this research.

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2.2 Selected Publications

A total of 41 research articles were included in this analysis. They were analyzed for the efficacy of *H. pylori* screening mechanisms as well as correlation between *H. pylori* infection and diagnosis of PUD. Percent of missed cases that would result, as a consequence of using each screening mechanism for *H. pylori*, were tallied and interpretation of the findings will be presented in the results section.

TABLE 1:
Summary of Study Designs Reviewed

Study Design	Number of Studies
Randomized Controlled Trials	0
Non-Randomized Controlled Trials	4
Observational Studies with Controls	11
Observational Studies without Controls	3

3 Results

The first question to be answered was if *H. pylori* infection has an association with PUD. The results were tallied and summarized in Table 2.

TABLE 2:
Risk of Developing PUD Increases with H. pylori Infection

H. pylori Infection is Associated with Increased PUD.	
	Number of Studies
Studies Rejecting the Hypothesis	1
Studies Supporting the Hypothesis	11

An overwhelming majority of the studies suggested that there was indeed an increased risk of PUD when *H. pylori* infection was identified. Of the 12 papers reviewed 11 of them suggested association between infection and PUD [1,3-5,7,9-15]. The remaining paper found that a high number of ulcers can occur independently of *H. pylori* infection and that *H. pylori* infection may be acquired after the development of an ulcer (Hobsley, M. et al). [20]. For the purpose of answering this question, the studies used were not categorized based on their assessment of other variables that may contribute to PUD such as smoking, NSAID use, duration of dyspepsia, or alcohol use. Although not used as a criterion for *H. pylori* association with PUD, many of the studies did note other significant risk factors for PUD development. Mentioning of the two other leading risk factors within the used papers were tallied. They are shown in Table 3 only for the sake of completion, as they are not the topic of this paper.

TABLE 3:
Other Risk Factors for PUD

Other Risk Factors for Developing PUD.		
	NSAID use	Smoking
Number of Studies Confirming Risk Factor	7	4
Number of Studies Opposing Risk Factor	0	0

The next topic to be addressed was that infection with *H. pylori* does not always result in disease. In fact, many of the papers reviewed showed that the vast majority of *H. pylori* cases do not progress to PUD and that many cases identified were completely asymptomatic. Table 4 shows the number of studies for and against *H. pylori* infection progressing to PUD.

TABLE 4:
H. pylori Infection Progression to PUD

Hypothesis: H. pylori Infection does not Always to PUD.	
	Number of Studies
Studies Rejecting the Hypothesis	0
Studies Supporting the Hypothesis	8

For this portion of analysis, the number of *H. pylori* positive cases, PUD confirmed cases and their concomitance were tallied. If less than fifty percent of the *H. pylori* positive cases had PUD for that particular study the null hypothesis was rejected. If greater than fifty percent of the *H. pylori* cases showed PUD then the null hypothesis was accepted. All of the 8 papers that analyzed *H. pylori* infection and PUD found that less than fifty percent of *H. pylori* cases had PUD [2,5,6,12,14-17].

The next area of concern is how sensitive and specific each screening method is in the detection of *H. pylori* and the degree to which that correlates with cases of PUD. Table 5 shows the sensitivity and specificity of each method to detect *H. pylori* as provided by the United States Center for Disease Control (CDC).

TABLE 5:
Sensitivity and Specificity of H. pylori Screening Methods

Screening Method	Sensitivity	Specificity
Histology	88-95%	90-95%
Culture	80-90%	95-100%
C-Urea Breath Test	90-95%	90-95%
Serology (ELISA)	80-95%	80-95%

Using the sensitivities of the various *H. pylori* screening methods from Table 5 along with the findings from the study conducted by Reza M. et al. [8] that nearly 80% of patients with peptic ulcers are infected with *H. pylori*, each test's sensitivity to detect PUD was then calculated. To do this, the sensitivity for each test in Table 5 was calculated using 1000 patients in order to determine the number of cases of H. pylori that would be missed per thousand patients. Knowing that

only 80% PUD is infected with *H. pylori*, the number of positive cases was then multiplied by 0.80 (80%) to give a maximum possible sensitivity of the test for PUD. Table 6 shows the calculated sensitivities for each test in the detection of PUD.

TABLE 6:
Sensitivities of H. pylori Screening Methods for PUD

Screening Method	Sensitivity for PUD	False Negative per 100 cases
Histology	70-76%	24-30
Culture	64-72%	28-36
C-Urea Breath Test	72-76%	24-28
Serology (ELISA)	64-76%	24-36

After the sensitivity to detect PUD for each screening method was calculated, the specificity for each screening was calculated as well. By taking the various screening specificities from Table 5 along with the data from the study done by Parsonet J. et al. [13] that only up to 5% of *H. pylori* infected individuals have an ulcer, the specificity of each screening mechanism for PUD was calculated. By taking the sensitivity of each test for *H. pylori* to detect the infection (Table 5), and assuming only 5 out of 100 cases would have an ulcer, (Parsonet, J.) [13] a false positive rate was generated along with a new specificity for the test to detect PUD. Results are summarized in Table 7.

TABLE 7:
Specificities of H. pylori Screening Methods for PUD

Screening Method	Specificity for PUD	False Positives per 100 H. pylori Cases
Histology	5.3-5.6%	85-90
Culture	5.5-5.0%	90-95
C-Urea Breath Test	5.3-5.6%	85-90
Serology (ELISA)	5.3-6.3%	75-90

While their ability to detect an *H. pylori* infection is sufficient, the specificity and to a lesser extent the sensitivity, for all of the screening methods were substantially lower when calculated for PUD. This is attributed mainly to the fact that not all *H. pylori* infections result in PUD and that not all PUD patients have an infection with *H. pylori*. Further analysis of the results can be found in the discussion that follows.

4 Discussion

The method used to prove or disprove association between *H. pylori* and PUD was to analyze the studies that looked at potential risk factors for PUD and tally the findings rejecting or supporting association. As shown in Table 2, nearly all of the studies confirmed an association between *H. pylori* infection and a higher risk of developing PUD [1,3-5,7,9-15]. Of the more notable papers supporting an increased risk, Parsonett, J. et al [13] suggests that the relative risk of developping an ulcer increases from 3.3 to 6.3. The problem with this portion of the analysis was finding studies that looked at *H. pylori* infection specifically. These studies were selected because they considered *H. pylori* infection as an independent risk factor. This was done in an attempt to minimize an assumption of association due to other risk factors such as NSAID use, age, smoking status, gender, socioeconomic statue, ect. A problem with analyzing the studies in this way is that other risk factors that play a significant role in development of PUD are overlooked. Many of the studies did note the importance of other factors in the development of PUD [1-5,7,9,13,14,16]. As demonstrated in Table 3, smoking and NSAID use were found to be two major risk factors along with *H. pylori* infection. The published study (Hbosley, M. et al.) [20] that did not support this hypothesis argued that H. pylori infection may in fact be secondary to duodenal ulceration and not a prerequisite. The argument was based upon their data that found a 78% incidence in *H. pylori* infection in patients with a history of chronic ulceration, and only 41% in those with only a short history of ulceration (Hobsley, M. et al). [20]. One weakness that must be pointed out is that, in the studies used to address the hypothesis in this paper, chronicity of the ulceration was not used as a selection criterion. A potential consequence of this would be that if a study only used chronic PUD patients there may be a higher incidence of *H. pylori* than if a study used only subjects with a short history of ulceration. In the manner that the results were tallied this would more likely lead to a conclusion of an increased risk than if only short-term ulceration subjects were used. Overall, the literature suggests that there is an increase of risk of developing PUD in the prescence of an *H. pylori* infection. This supports the hypothesis that there is an association between *H. pylori* infection and an increased risk for developing PUD.

It was shown that there is an increased risk of developing PUD from an *H. pylori* infection but not 100% of *H. pylori* patients will go on to develop PUD. Studies were then selected to test the hypothesis that *H. pylori* infection does not usually result in PUD. The method used to quantify this was to review studies of patients who had an *H. pylori* infection and tally the percent that went on to develop PUD. The difficulty in this area of review was finding studies that had a countable number of *H. pylori* positive cases that correlated to a specific number of PUD cases. Eight of the papers suggested that less than 50% of cases of *H. pylori* went on to develop PUD [2,5,6,12,14,15,16,17]. Through reviewing the papers it was found that nearly half of the world's population (50%) is infected with *H. pylori* (Parsonett, J. et al). [13]. In order to accept the hypothesis that *H. pylori* does not usually go on to produce PUD, a prevalence rate for PUD of <0.25 must be observed. A study conducted by Sung J. et al [18] which evaluated the global incidence and prevalence of PUD found that the prevalence rate of PUD is only 0.03-0.17%. This supports the hypothesis that *H. pylori* infection does not normally progress to PUD.

Proper sampling and sampling bias becomes a potential problem in validating this assumption. Papers were not ex-

cluded based upon geographic, socioeconomic, gender, or age parameters used in the sample. Incidence and prevalence of *H. pylori* infection vary greatly amongst different populations. Literature shows that the highest number of infection with *H. Pylori* would be found in a population that is male, over forty, in an unindustrialized country and of low socioeconomic status (Malaty, H. et al). [1]. PUD also varies amongst different populations in a similar manner (Pounder, R. et al). [7]. This means that if only male subjects over 40 from low socioeconomic status in unindustrialized countries were used, there would be a disproportionately high prevalence of *H. pylori*.

As stated earlier, it was found that *H. pylori* infection does not usually progress to PUD, providing one explanation for the large differences in prevalence between the two conditions. Another reason for the large difference is that many cases of *H. pylori* remain asymptomatic and do not require consult, whereas nearly all PUD cases present with at least some symptoms, causing the patient to seek medical attention. This is demonstrated by a study conducted by Graham, D (1991) [1] that examined 490 asymptomatic volunteers and found that 253 of the subjects (52%) tested positive for *H. pylori*.

The last hypothesis to be examined is that *H. pylori* testing is not a reliable screening mechanism for PUD. To prove this hypothesis a number of steps were taken.

Firstly, the efficacy of the tests to detect an *H. pylori* infection must be taken into consideration. For this portion of the hypothesis figures on sensitivity and specificity were taken directly from the CDC and are displayed in Table 5. According to their figures, the C-Urea Breath test was found to be the most sensitive in the detection of *H. pylori* while culture was found to be the most specific. Values from the CDC were used due to the credibility of the institution and their lack of bias. Once the sensitivity and specificity of each test in detecting *H. pylori* was know, the values when using the same test for PUD must be extrapolated.

Critical inexplapolating this data was determining the number of patients with PUD are actually infected with *H. pylori.* All of the literature consulted provided varying percent of *H. pylori* positive PUD cases ranging anywhere from 30-80%. The large variation is most likely do to the variation between the studies in their selection of subjects. Differences in factors such as smoking status, alcohol consumption, socioeconomic status, diet, ect that would affect the prevalence of *H. pylori* in the sample and thus the amount of PUD patients with a positive *H. pylori* test [1,3-7,9]. The figure, 80% of PUD patients, was chosen because it was one of the highest found through review of the literature (Reza, M. et al). [8]. This would give the *H. pylori* tests the greatest chance to produce an acceptable level of sensitivity. It is important to note that choosing a lower percentage would drastically decrease the sensitivity and, to a lesser extent, the specificity of the tests for detecting PUD. It was found that the C-Urea Breath test was the most sensitive *H. pylori* test in detecting PUD (Table 6). Not surprisingly, as it had the highest sensitivity for detecting *H. pylori*. Even with the highest sensitivity, it still missed an unacceptable number, 24% to 28%, of PUD positive cases. The gold standard for detecting PUD is endoscopy. While the sensitivity varies depending on the experience and skill of the endoscopist it is generally above 90% (Soll, A.) With a sensitivity of 90% only 10% of cases would be missed. The number of missed cases when using the lowest sensitivity *H. pylori* screening method would generate nearly three to three and a half times as many missed cases. Even with the most sensitive *H. pylori* test, the C-Urea Breath test, nearly two and a half to three times as many PUD positive cases would not be detected. The sheer lack of sensitivity alone supports the hypothesis that a *H. pylori* test is not a reliable screening method for PUD but for the sake of completeness the specificity of each test was taken into consideration. This was done to approach the issue from a different angle. While the sensitivity is looking at the reliability of the tests based on how many missed cases there would be, the specificity would look at how many of the tests that came back positive would actually have PUD. In theory, a test could still be useful if the specificity were high enough.

When addressing the specificity, the biggest question to address was how many *H. pylori* infected individuals would go on to develop PUD. It was found that 2%-5% of patients who are *H. pylori* positive would go on to develop an ulcer at some point in their lifetime with an annual incidence rate of 0.1% and 0.2% (Parsonett, J. et al). [13]. If extrapolated to the world's population, that would be 6,000,000 new cases of PUD attributed to *H. pylori* annually and nearly 120,000,000 would suffer from the disease at some point in their lifetime. (Parsonett, J. et al). [13]. Demonstrating that if a cheap and reliable *H. pylori* test could prove to be specific enough to outweigh its lack of sensitivity then it could have a significant impact on world health. The value 5% was chosen because it would give the *H. pylori* tests the best chance at producing a specificity significant enough to outweigh the lack of sensitivity.

As shown in Table 7, the specificities for each of the *H. pylori* tests to detect PUD were far too low to be clinically useful. This was to be expected because the tests for *H. pylori* are simply not designed to detect PUD. In order for any of the screening tests to have a chance at having specificity high enough there would need to be a much higher incidence of PUD from a *H. pylori* infection. For example, if 70% of *H. pylori* cases went on to produce PUD then specificities would be expected to fall in the in the range of 70%-85%. This would be much better than the 5.0%-6.3% seen using the 5% figure. If there were a higher incidence of PUD from *H. pylori* then it would also be expected to see higher than 80% *H. pylori* positive cases in PUD, which would also help to improve the sensitivity of the screening tests. However, this is simply not the case.

As demonstrated in Table 6 and Table 7, when applying the screening test for *H. pylori* to PUD it was found that serology was the most sensitive and specific overall although it too failed to produce a sensitivity or specificity significant enough to merit use in practice. Two of the studies in particular examined the possibilities of serology for *H. pylori* specifically in detecting PUD. In one study conducted by Quatero, A. et al [25], a whole blood serology test for *H. pylori* infection was used to assess its effectiveness in detecting PUD. What they found was that in 836 patients with dyspepsia, 171 had symptoms that merited endoscopy. Out of the 171 patients, 32 had PUD that was confirmed via endoscope. Of those 32 confirmed PUD cases, only 12 (32%) had a positive serology test (Quatero, A. et al). [25]. In a similar study conducted by Xia,

H. et al [26], two hundred and fifty-two patients who were referred for endoscopy were selected. 106 (42%) of the patients were *H. pylori* positive and 48 (19%) had PUD. When using serology alone in detecting PUD they found a specificity and sensitivity of 60% and 52% respectively. Both studies agreed that serology was a poor PUD test despite its excellent performance in detecting *H. pylori* (Xia, A. et al) [26] due to a lack of sensitivity and specificity. The literature reviewed as well as the figures shown in Table 6 and Table 7 support the hypothesis that a *H. pylori* test is not a reliable screening mechanism for PUD.

5 Conclusion

At first glance the idea of using a test for *H. pylori* as a screening mechanism for PUD seemed like a viable idea. However, after performing an indepth annalysis of available publications on the topic it was easy to see that too many variables are at play for this to be a reliable detection method for PUD. The first of these issues is that although there is an association between *H. pylori* infection and an increased risk for PUD only a small proportion of those infected with *H. pylori* go on to develop into an ulcer. Secondly, not all peptic ulcers are infected with *H. pylori*, so a screening that uses detection of the bacteria would miss these cases. And thirdly, when applying the *H. pylori* test as PUD screening the test would generate too little specificity and unreliable sensitivity to act as a viable test.

After review of the literature it was found that although there is an increased risk of developing PUD when there is a *H. pylori* infection, the hypothesis that a *H. pylori* test can be used as a reliable screening mechanism for PUD could not be accepted. This was attributed to the fact that not all *H. pylori* cases progress to PUD. Although the *H. pylori* tests are highly sensitive and specific at detecting *H. pylori* infection, they could not be used clinically as reliable screening tools for PUD due to low sensitivities and specificities.

6 Recommendations

Future research should include case-control studies that examine the various screening mechanism for *H. pylori* as well as take into account additional risk factors such as smoking, NSAID uses, age, and dyspeptic symptoms when predicting PUD status. One area of future research that may hold more promise as a screening mechanism for PUD would be serology. A study examining blood profiles for a more accurate (than *H. pylori* screening) marker for PUD may prove to be very helpful in finding a new diagnostic tool for detecting PUD. A prospective cohort study that follows *H. pylori* positive individuals would also be helpful in confirming the positive correlation between *H. pylori* infection and increased risk of PUD. However, the ethical dilemma of leaving confirmed *H. pylori* positive cases untreated would hamper such a study due to a fear of further and more serious disease that could have been prevented by *H.pylori* eradication.

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