Gastric Cancer Due to Chronic *H. pylori* Infection

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Helicobacter pylori is an established cause of many gastrointestinal pathologies including peptic ulcer disease, gastritis, and gastric cancer. It is an entity that affects the global population, and its true nature has only been known since the 1980s. Although there is much known about *H. pylori* including its pathophysiology, detection, and eradication, resistance to therapy models is common. This is problematic because untreated or inadequately treated *H. pylori* increases morbidity and mortality related to gastric cancer and peptic ulcer disease among others. In order to improve the treatment and reduce resistance, there is significant ongoing research identifying new detection and eradication methods for *H. pylori*.

Keywords: Helicobacter pylori ; carcinogenesis ; gastric cancer

1. Introduction

Helicobacter pylori is a bacterium that is commonly found amongst the generally healthy population. However, it has also been found in patients with gastric pathologies such as chronic gastritis, peptic ulcer disease (PUD), and gastric cancer. It was first reported by Bottcher and Letulle in 1875 when they observed the bacteria present on the margins of peptic ulcers [1]. However, the true nature of the bacterium was not discovered until the 1980s by B.J. Marshall when he isolated and cultured samples from peptic ulcer disease and identified and described causation between PUD pathology and *H. pylori* [2]. Since that time, many gastrointestinal diseases have been paired to the existence of *H. pylori* in the gastric environment: gastric and duodenal ulcers in 1 to 10% of infected patients, gastric carcinoma in 0.1 to 0.3%, and gastric mucosa associated lymphoid tissue (MALT) lymphoma in less than 0.01% [3]. *H. pylori* is thought to be introduced to the gastric environment during the early years of life and persist indefinitely unless treated. Although present from a young age, it can remain silent and undiagnosed until gastric pathology manifests due to chronic inflammation of the underlying gastric mucosa. *H. pylori* possesses many virulence factors that allow it to survive the toxic and harsh environment of the stomach and change the surrounding environment such that it promotes carcinogenesis ultimately leading to gastric cancer. Once diagnosed with gastric cancer, the prognosis is poor due to discovery at an advanced age and advanced disease state [4]. Importantly, eradication of *H. pylori* can prevent gastric cancer from forming. It is imperative that researchers understand current treatment models as well as novel therapeutic agents targeted for *H. pylori* eradication.

2. Pathophysiology/Pathogenesis

H. pylori is recognized as a grade 1 carcinogen by the International Agency for Research on Cancer [5]. *H. pylori* has been linked to the development of chronic active gastritis and atrophic gastritis which can lead, albeit over time, to cancer through a sequence of cellular events. There have been two randomized controlled trials with the development of gastric cancer as the primary outcome: Wong et al. and Fukase et al. [6][7]. Both studies were performed amongst Far East populations at an increased risk for *H. pylori* infection [8]. Wong et al. followed 1630 *H. pylori* positive patients for 7 years. The group of patients with no eradication measures taken had 11/813 (1.4%) develop gastric carcinoma compared to 7/817 (0.9%) patients that received eradication therapy developing gastric carcinoma [6]. Fukase et al., similarly, enrolled 544 patients located in Japan with a 3-year follow-up. 9/272 (3.3%) patients that received *H. pylori* eradication therapy developed gastric cancer and 24/272 (8.8%) patients that did not receive therapeutic intervention developed gastric cancer [7]. Both studies highlight the clear association between *H. pylori* infection and the development of gastric adenocarcinoma. For this to take place, *H. pylori* must be present for a prolonged period to create an environment conducive for itself and eventually, carcinogenesis. *H. pylori* possesses many virulence factors and properties that allow it to survive in the harsh gastric environment in addition to causing chronic inflammation and eventual carcinogenesis.

H. pylori pathogenesis and sequential outcomes are accomplished by a combination of virulence factors that are dependent on both host and environmental factors. Pathogenesis first requires *H. pylori* entry into the stomach after which colonization and infection result in disease outcomes. First, *H. pylori* must survive the acidity of the stomach, move toward the gastric epithelium via flagella, and attach to host cells using adhesins. Receptor interaction then allows bacteria to

cause damage to tissues by toxin release [9]. The most favorable conditions for *H. pylori* are 37 °C, pH of 4.0 to 6.0, microaerophilic conditions, and adequate water and nutrients [2]. Once *H. pylori* enters the stomach, it can alkalize its surrounding environment by using the innate enzyme urease, encoded by the urease gene cluster to neutralize hydrochloric acid [9]. Once the surrounding environment is a viable pH, the bacteria move towards the host gastric epithelium using flagella-mediated motility. The favored location for *H. pylori* is in the first part of the duodenum within the super-epithelial mucus layer gastric pits. It is not detected in the subepithelial space of the stomach or in the epithelium of the gastric glands [2]. Once it arrives at the appropriate layer of host epithelium, *H. pylori* uses specific adhesins to attach to host cell receptors allowing for colonization and persistent infection. After *H. pylori* is established within the correct position, it will release virulence factors such as cytotoxin-associated gene A (CagA) and vacuolating cytotoxin A (VacA). With the release of these virulence factors, tissue damage occurs, and the body responds by secreting chemokines that initiates an immune response furthering inflammation [9].

Shown using mouse models, after CagA translocates into host epithelial cells, it enhances mitotic activity of gastric epithelial cells contributing to malignancy if left unchecked [9]. Several studies indicate that *H. pylori* strains with CagA are directly associated with acute gastritis, gastric ulcer, and gastric cancer development [10][11]. Unlike CagA, which has one main virulence process, VacA possesses many. After internalization, VacA creates large pores in the cytoplasmic membrane, allowing for further bacterial urease effect on the gastric epithelial cell [9]. Eventually, VacA enters the epithelial cell mitochondria targeting pro-apoptotic factors promoting increased epithelial cell-turnover. Additionally, VacA can control host immune T-lymphocytes by reducing their activation and decreasing the host's inflammatory response allowing for *H. pylori*'s continued survival [9]. Combining the innate survival techniques and toxin producing abilities that *H. pylori* possesses, continued infection and inflammatory process will eventually allow for carcinogenesis to take place.

3. Diagnostic Methods in Practice

To appropriately diagnose *H. pylori*, there are several tests clinically available. These tests can be classified into two groups: invasive testing and non-invasive testing. Invasive testing requires endoscopic evaluation for tissue sampling allowing for histology, rapid urease test, culture, and molecular methods. Non-invasive testing includes urea breath test, stool-antigen testing, and serological testing.

Invasive testing has the benefit of providing direct visual evidence of infection such as gastritis or ulceration, but these are nonspecific in most cases. It can also diagnose advanced pathology such as cancer. After obtaining a biopsy via endoscopy, the specimen can be used for direct detection of *H. pylori* infection. However, the diagnostic accuracy of this method depends on the biopsy site, size, number of biopsies, staining methods used, use of proton pump inhibitors (PPIs), recent use of antibiotics, and experience of pathologists [12]. To counteract some of these modifiable risks, it is recommended that two weeks prior to histologic testing, all PPIs and antibiotics be stopped. Samples should be obtained from standardized sites: the antrum and corpus of the stomach, with two biopsies taken from each section to minimize sample error and increase the odds of accurate diagnosing. An additional test that can be used after biopsy is the rapid urease test (RUT). After a sample is obtained and prepared, a urea antigen agent is added to measure the activity of the *H. pylori* urease enzyme by converting to ammonia and leading to an increase in the sample pH and a color change on pH monitor paper. Use of H2-receptor antagonists, PPIs, antibiotics, bismuth compounds, and the presence of blood reduce the accuracy of RUT. However, this method is inexpensive, easy to perform, specific, provides results in a timely manner, and widely available [13].

Tissue culture is another method that can be used for *H. pylori* testing. Culturing for *H. pylori* is time-consuming and expensive for laboratories and there are many factors that may interfere with accurate results: poor quality of specimens, delayed transport, exposure to aerobic environment during transport and preparation, and inappropriate mediums required for growth [14]. However, culturing is extremely useful because it can also help determine antibiotic sensitivity for strains. Lastly, polymerase chain reaction (PCR) can be used for the diagnosis of *H. pylori*. PCR amplifies *H. pylori* genetic material from saliva, stool, and gastric juice samples making it favorable because it requires fewer bacteria in samples, faster results, and no need for special processing supplies or transportation like that of culturing [15]. PCR will also detect mutations in *H. pylori* that may indicate antibiotic resistance allowing for more appropriate treatment regimens to be used.

4. Treatment Regimens in Practice

Current treatment modalities for successful eradication of diagnosed *H. pylori* rely on antimicrobial agents and antisecretory agents. Antimicrobial agents used for *H. pylori* treatment include but are not limited to clarithromycin, levofloxacin, metronidazole, tetracycline, rifabutin, and bismuth-containing compounds [16]. Used synergistically to achieve

antibiotic bactericidal effect, antisecretory medications like H2-receptor antagonists and PPIs are also used. PPIs are mostly preferred used because they are most effective in increasing the gastric pH when compared to that of H2-receptor antagonists. PPIs have also been shown to impose antimicrobial activity against *H. pylori* [17].

To best combat *H. pylori* infection, many combination therapies using antibiotics and antisecretory agents have been studied. The Maastricht I Consensus Report recommends that treatment regimens used should achieve an eradication rate of at least 80% and propose a standardized report card to be used to evaluate the outcome of new therapeutic regimens for *H. pylori* infection [18]. Furthermore, specific guidelines are put forth for regions and populations depending on *H. pylori* infection rate, prevalence specific to a particular area, and resistance patterns. Despite the different studied treatment regimens and region-tailored treatments, guidelines for first line and rescue therapies are generally similar. Traditionally, the standard first-line therapy contains a PPI and two antibiotics, usually clarithromycin and amoxicillin. Metronidazole can substitute amoxicillin if there is a penicillin allergy. The recommended therapeutic duration of standard therapy is 10 to 14 days in the United States and 7 days in Europe and Asia. If first line therapy were to fail and no proof of eradication was obtained, bismuth-containing quadruple therapy or levofloxacin based triple therapy are recommended as a rescue therapies [16]. However, new data has emerged illustrating changes in *H. pylori* antibiotic susceptibility. A meta-analysis of studies comparing clarithromycin triple therapy and bismuth quadruple therapies performed from around the world suggest that these two treatments are similar in efficacy, compliance, and tolerability [19]. Furthermore, a recent meta-analysis including 12 random controlled trials and 2753 patients showed eradication rates of 77.6% with bismuth quadruple therapy compared to 68.9% eradication rate with clarithromycin triple therapy with ten days of bismuth quadruple therapy found to be more effective than 7 days of clarithromycin therapy [20]. The most recent meta-analysis of *H. pylori* eradication treatments is continuing to show that 10 to 14 days of bismuth quadruple therapy is superior to 7 days of clarithromycin triple therapy with an 85% compared to 73% eradication rate, respectively [21]. Based on these data, it can be proposed that a 10-to-14-day course of bismuth quadruple therapy is recommended over clarithromycin triple therapy.

The importance of *H. pylori* eradication is illustrated by Choi et al. in which a randomized control trial of 1838 individuals with diagnosed *H. pylori* and confirmed first-degree relatives with gastric cancer were analyzed after eradication treatment. This group was randomly assigned to receive eradication therapy or placebo and followed for 9.2 years. Over this time, 10 participants in the treatment group and 23 participants in the placebo group developed gastric cancer. Interestingly, of the 10 participants in the treatment group in whom gastric cancer developed, 5 had persistent *H. pylori* infection [22].

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