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Review

Eradication of *Helicobacter pylori*: Past, present and future

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ABSTRACT

Helicobacter pylori is the major cause of chronic gastritis and peptic ulcers. Since the classification as a group 1 carcinogenic by International Agency for Research on Cancer, the importance of the complete *H. pylori* eradication has obtained a novel meaning. Hence, several studies have been made in order to deepen the knowledge in therapy strategies. However, the current therapy presents unsatisfactory eradication rates due to the lack of therapeutic compliance, antibiotic resistance, the degradation of antibiotics at gastric pH and their insufficient residence time in the stomach. Novel approaches have been made in order to overcome these limitations. The purpose of this review is to provide an overview about the current therapy and its limitations, while highlighting the possibility of using micro- and nanotechnology to develop gastric drug delivery systems, overcoming these difficulties in the future.

Contents

Abbreviations: AA, acrylic acid; AGS cells, human gastric adenocarcinoma cell line; AHA, acetohydroxamic acid; AS OND, antisense oligonucleotides; AuChi, chitosan-modified gold nanoparticles; BPO, benzoyl peroxide; Ch, cholesterol; Con A, conconavalin A lectin; CTB, cholera toxin B subunit; DPPC, 1,2-dipalmitoyl-sn-glycero-3-phosphocoline; E170, epikuron 170; GME, *Garcinia mangostana extract*; GNP, gliadin nanoparticles; *H. pylori*, *Helicobacter pylori*; HEM, hydroxyethyl methacrylate; HPMC, hydroxy propyl methyl cellulose; LLA, linolenic acid; MPs, microparticles; NIPASM, *N*-isopropylacrylamide; NPs, nanoparticles; PE, phosphatidylethanolamine; RBC, ranitidine bismuth citrate; SA, stearylamine; SPs, small particles; TEGDMA, triethyleneglycol dimethacrylate; UEA 1, Ulex Europaeus agglutinin I lectin; *γ*-PGA, poly-*γ*-glutamic acid.

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1. Introduction

Helicobacter pylori (*H. pylori*) is a gram-negative bacterium, usually in a spiral-shaped form, that can be converted in coccoid cells under a hostile environment [1,2]. These bacteria present several structural and morphological characteristics that favor their penetration within the mucosa and consequently the colonization of the gastric antrum and the human duodenal mucosa [2,3]. Their major virulence factors lie on four to six flagella enhancers of their mobility, urease production, phospholipase secretion, cytotoxin production and their ability to adhere to the target cells [1–3]. These virulence factors enable their mobility through the gastric mucus and the colonization of the surface between the mucus gel layer and the epithelial cells [3,4]. Adhesins are responsible for the adherence to carbohydrates of the mucosa and to epithelial cells, namely through the adhesion to polysaccharides, laminins and Lewis b antigen among others, playing an important role in the pathogenesis of the bacteria [3–6].

Currently, the worldwide population infected is around 50%, being even higher in developing countries [7]. Prevalence rates of *H. pylori* infection varies according to race/ethnicity, socioeconomic conditions and age, being highest with aging [7]. Commonly, their colonization is asymptomatic, resulting only in histological signs of chronic gastritis [8,9]. However, approximately 20% of the infected population evolves into a clinical condition, commonly chronic gastritis and peptic ulcer [8,9]. This incomprehensive and complex *H. pylori*–human relationship, where only a portion of the infected people manifests a disease, have led to a controversy about the seriousness of *H. pylori* infection [8]. Nevertheless, the risk resulting from an unsuccessful eradication is higher in the cases of clinical manifestation, since persistent infections may lead to gastric cancer, such as gastric mucosa-associated lymphoma tissue and adenocarcinomas [7,8,10]. In fact, bacteria eradication in patients with low-grade lymphomas often results in the remission of the cancer [7]. According to these facts, the International Agency for Research on Cancer (IARC), subordinated to the World Health Organization (WHO), declared *H. pylori* as a human carcinogenic (group 1) [7]. Although without a clear explanation, other extradigestive conditions, namely idiopathic thrombocytopenic purpura, iron deficiency anemia, ischemic heart disease, stroke, Parkinson's disease and Alzheimer's disease have been recently related to the presence of *H. pylori* [11].

The importance of the therapy in clinical manifestation of *H. pylori* is unquestionable. However, despite all the endeavors, the current therapy presents many limitations which have led to the failure of *H. pylori* eradication. This review provides an overview about the traversed pathway until the current therapy and its limitation. Furthermore, a summary of all the reports with micro- and nanoparticles applied to gastric delivery through active or passive targeting to the bacteria or through mucoadhesiveness to the gastric mucosa will also be discussed.

2. Treatment of *H. pylori* infection

2.1. Overview of the discovery of H. pylori

The discovery of *H. pylori* resulted from a slow and gradual progression (Fig. 1). The first report about gastric ulceration was written in 1586 by an Italian physician named Marcello Donati [1,12,13]. During several years, the pathogenesis of this disease was exclusively associated to stress and dietary factors, being treated by resorting to bed rest and special diet [1]. In the second half of 18th century, the use of bismuth compounds, namely bismuth subnitrate, to treat gastric ulcers became very popular as a result of the work of Gorham and Kussmaul [13,14]. Actually, bismuth compounds have antibacterial properties that were unknown at that time [13,14].

In 1875, Bottcher and Letulle noticed the existence of bacteria in ulcer margins and suggested their relation to gastric disease [14]. However, the presence of spiral organisms in human gastric washings was reported by W. Jaworski, a Poland professor, only in 1889 [15]. He also theorized that the bacteria may be related to the development of gastric ulcers [1]. Nevertheless, his research work was poorly publicized since it was written in Polish [15]. The first recognized report appeared only in the latter half of the 19th century, when Bizzozero observed the

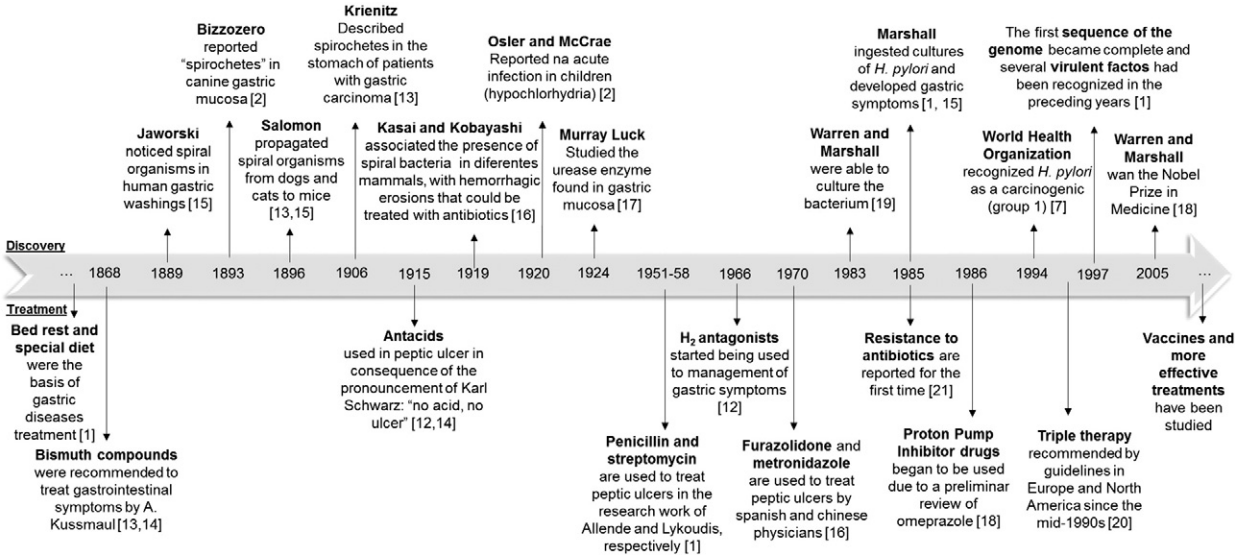

Fig. 1. Timeline of the *H. pylori* discovery and the progress of the therapy against the bacterium.