SMGroup

Helicobacter Pylori Infection in Peptic Ulcer Diseases

Márcia Aparecida Sperança[1*] and Rodrigo Buzinaro Suzuki[1,2]

[1]Universidade Federal do ABC, Centro de Ciências Naturais e Humanas, Brazil

[2]Department of Genotyping, Hemocenter, Marilia Medical School, Brazil

***Corresponding author:** Márcia Aparecida Sperança, Universidade Federal do ABC - Center for Natural and Human Sciences, Rua Arcturus, 03 - Jardim Antares, Bloco Delta, Sala 226, Laboratórios 105/107, CEP 09606-070 São Bernardo do Campo - São Paulo – Brazil, Tel: 55.11.2320 6253/6187; Email: marcia.speranca@ufabc.edu.br

Published Date: November 15, 2015

ABSTRACT

Management and treatment of peptic ulcer disease, caused by different physiological alterations according to its gastric localization and etiology, have changed dramatically since the discovery of *Helicobacter pylori. H. pylori*, a Gram-negative microaerophylic bacterium, are associated with a broad spectrum of digestive tract diseases such as chronic gastritis, gastric and duodenal ulcers and gastric cancer and lymphoproliferative disorders. *H. pylori* infection prevalence and clinical outcome varies according to bacterial virulence factors and host and environmental characteristics such as age, ethnic group, genera, geography and socioeconomic conditions. Peptic ulcer disease associated to *H. pylori* is a result of a chronic infection progress, and knowledge of specific pre-ulcers alterations caused by *H. pylori* can help in its prevention and management. The interplay of gastritis phenotype related to the bacterium colonization and resulting acid secretion induction and/or impairment are key determinants in ulcer disease outcomes. In this chapter, virulence factors of *H. pylori* associated to peptic ulcer disease will be discussed considering its regional characteristics.

GENERAL ASPECTS OF HELICOBACTER PYLORI

In 1979, Robin Warren, an Australian pathologist, performing histological exams of gastric biopsies, often observed curved microorganisms in inflammatory cells infiltrated tissue. These

Copyright © Sperança MA.This book chapter is open access distributed under the Creative Commons Attribution 4.0 International License, which allows users to download, copy and build upon published articles even for commercial purposes, as long as the author and publisher are properly credited.

organisms were not present inside the gastric mucosa, but in the mucus covering the tissue [1]. Warren found that similar structures found in the gastric mucosa were described in the late nineteenth century by European pathologists, but at that time the isolation of that bacterium was not possible and this fact remained forgotten for generations of physicians and pathologists [2].

Interested in these remarks, Barry Marshall and Robin Warren tried to isolate bacteria organisms from gastric biopsies samples. Based on the curve morphology and on Gram-negative staining characteristics, the investigators used the isolation methodology employed for *Campylobacter* species, corresponding to inoculation of the biopsy sample into selective media and cultivation in microaerophilic conditions. In 1982 Warren and Marshall isolated for the first time, the bacterium *Helicobacter pylori*, and initiated a new era in gastric microbiology [1,3].

H. pylori gastric contamination is the most common of all human infections, occurring in similar rates in men and women [4]. The most accepted hypothesis about the mode of transmission of this bacterium is directly from person to person through oral-oral and fecal-oral rotes [2]. *H. pylori* has also been found in saliva, dental plaque and feces, indicating that oral and fecal cavities are possibly involved in the bacterium transmission [5,6]. In addition, its presence in the gastric juice indicates the possibility of oral-oral transmission [7].

Prevalence of *H. pylori* infection varies widely by geographic area, host age, race and is closely related to socioeconomic and sanitary conditions [8-10]. A small proportion of people infected by *H. pylori* develop digestive tract clinical conditions such as chronic gastritis, gastric and duodenal ulcers and gastric cancer and lymphoproliferative disorders [11]. Symptoms resulting from gastric disease arise in adulthood, though the acquisition of *H. pylori* occurs in childhood [12]. In some individuals, presence of bacteria in the gastric mucosa induces chronic inflammation and thus, profoundly affects gastric physiology, causing chronic gastritis which can evolve to more severe gastric diseases as peptic ulcer [13], gastric cancer and lymphoma. Treatment of *H. pylori* infection results in ulcer healing and in reduction of the risk for gastric cancer and lymphoma, confirming its role in the etiology of these diseases [14-16].

HELICOBACTER PYLORI AND PEPTIC ULCER DISEASE

The risk of an adult infected by *H. pylori* to develop peptic ulcer disease is four times higher than in an *H. pylori* negative individual [17]. Management and treatment of peptic ulcer disease, caused by different physiological alterations according to its gastric localization and etiology, has changed dramatically since the discovery of *H. pylori* [18]. Previous treatment with dietary modifications, antacids, gastric acid suppression with H2-receptor antagonists and proton pump inhibitors, were changed to antibiotic therapy for eradication of *H. pylori* infection. Moreover, the eradication of *H. pylori* infection cure both gastric and duodenal ulcers, and the cure rates are similar, suggesting that *H. pylori* is the key factor in peptic ulcer diseases independent of the ulcer site [19].

Copyright © Sperança MA.This book chapter is open access distributed under the Creative Commons Attribution 4.0 International License, which allows users to download, copy and build upon published articles even for commercial purposes, as long as the author and publisher are properly credited.

Since peptic ulcer disease associated to *H. pylori* is a result of a chronic infection progress, knowledge of specific pre-ulcers alterations caused by H. pylori can help in its prevention and management. Therefore, the role of *H. pylori* in the etiology and evolution of chronic gastritis to peptic ulcer disease has been largely investigated. The interplay of gastritis phenotype and acid secretion are key determinants in ulcer disease outcomes. *H. pylori* colonized gastric mucosa undergoes alteration in acid secretion as a result of gastric hormone release and disruption of neural pathways. Corpus-predominant gastritis and corpus atrophy are accompanied by hypochlorhydria and carry the highest risk for gastric ulcer and cancer, whereas antrum-predominant gastritis with little involvement of the corpus fundic mucosa is associated with hyperchlorhydria and predisposes to duodenal ulcer disease [20,21].

H. pylori colonization differential pattern in the gastro-duodenal tract are associated to host and bacterium genetic factors whose interaction results in specific physiological alterations leading to gastric and/or duodenal ulcers [22]. As the bacterium resides in the mucosa and do not entry gastric cells, it was adapted to produce and elicit molecules involved in survival in a high acid environment, to adhere in gastric mucous and to escape from host immune mechanisms [23].

The acid gastric environment is microbicidal and the only bacterium adapted to survive in gastric location is *H. pylori*, which present several molecular mechanisms against acid milieu. During host co-evolution a selected molecular mechanism to locally change the acid surroundings correspond to a urea sensitive detection system [24] associated to urease enzymes responsible to convert urea into ammonia and bicarbonate [25]. Also, motility and chemotaxis systems were selected in order to avoid gastric acid juice and to enable adherence to gastric mucosa, respectively [26]. All these biological molecular strategies to survive in gastric environment and to persist in the mucosa, involve the production of virulence factors by *H. pylori*, such as the urease enzyme complex [27], a modified Lipopolysaccharide **(LPS)** [28]; Blood Group Antigen-Binding Adhesion molecules **(BabA)** [29], Outer Membrane Inflammatory Adhesion Proteins **(OipA)** [30], Cytotoxin-Associated Gene A **(CagA)** [31], Vacuolating Cytotoxin **(VacA)** [32,33], Duodenal Ulcer Promoting Gene **(DupA)** [34] and factor induced by epithelium contact **(IceA)** [35].

H. PYLORI VIRULENCE FACTORS ASSOCIATED TO PEPTIC ULCER DISEASE

H. pylori virulence factors are associated to genomic regions with high plasticity and diversity, being present, absent, up-regulated or differentially expressed during bacteria growth and gastric colonization persistence [36]. The plastic *H. pylori* genome present strong phylogeographic structure attained during co-evolution process in human [37], resulting in different bacteria strains with specific virulence factors and disease outcome according to geographic and population distribution [38].

The urease molecular complex and *vacA* gene are ubiquitous in *H. pylori* strains corresponding to bacteria essential virulence factors. Ammonia and bicarbonate produced by *H. pylori* urease enzyme complex can directly cause damage to gastric mucosa or indirectly by toxic compounds derived from ammonia chemical processing. Also, the urease enzyme is a strong antigen, produced in high concentration, increasing tissue injure by local inflammatory response [39].

Copyright © Sperança MA.This book chapter is open access distributed under the Creative Commons Attribution 4.0 International License, which allows users to download, copy and build upon published articles even for commercial purposes, as long as the author and publisher are properly credited.

The *H. pylori* vacA gene, correspond to an anion channel-forming cytotoxin [40] implicated in the formation of intracellular vacuoles in epithelial cell lines [41-43]. There are three principal polymorphic regions in *vacA* gene identified as Signal **(s)**, Intermediate **(i)** and Middle **(m)**, presenting two main types (type 1 and type 2) each [4,44]. Transport of the toxin to the bacteria membrane depends on the s type allele; s1, subdivided into s1a, s1b and s1c, are responsible for the transport of the toxin to the bacteria membrane, and the s2 allele is defective [4, 45]. The toxin present cell tropism for a broader range of cells when the allele is m1 [46] than is m2 type [32, 47]. The i region is intermediate between the s and m, [48] which i1 type associated to a stronger vacuolating activity than the i2 type [49]. The more severe forms of *H. pylori* related disease present association of the s1, i1, and m1 types [50]. Populations from Western countries showed association of vacA s1 or m1 with increased risk of peptic ulcer diseases [4, 51]. In Asia, where there is a high predominance of s1 alelle, the vacA m region mosaicism shows a variation within East region population [52], with m1 strains being more prevalent in regions where there is a higher prevalence of gastric cancer, suggesting that m1 strains of *H. pylori* are more pathogenic. In a Brazilian population, strains harboring the vacA m1 genotype were more frequently associated with the development of duodenal ulcer disease when compared to gastric ulcer [53].

Some strains of *H. pylori* harbor a type IV secretion system, derived from a transposable element, where virulence factors, such as CagA, are encoded [54]. The complete system is responsible to introduce the CagA toxin into the host epithelial cell [55]. CagA protein presents a phosphorylation polymorphic repeated motif in its C-terminus, the EPIYA (composed of five amino acids Glu-Pro-Ile-Tyr-Ala), where the tyrosine residue is phosphorylated by SFK family kinases [56], triggering modifications in cell signaling pathways, cytoskeleton rearrangement, and abnormal cell proliferation [57]. There are four distinct EPIYA motifs, named EPIYA-A to EPIYA-D, distinguished by the number of motifs and flanking sequences, resulting in different amount of phosphorylation sites [58]. In Western and in Southeast Asian countries, cagA-positive patients are at a higher risk to develop peptic ulcer disease [59,60].

Adhesion molecules as OipA and BabA are also involved in the pathophysiology of peptic ulcer disease. The adhesin BabA adhere to ABO/Lewis B blood group antigens located in the gastric human mucosa, inducing expression of several inflammatory cytokines. There are two genes encoding BabA, *babA1* and *babA2* genes, differing by deletion of 10 bases in the signal sequence of *babA1*, which is inactive [61]. Presence of BabA encoded by *babA2* gene is associated to increased risk of peptic ulcer disease [62], being enhanced by the presence of cagA [63].

OipA adhesion molecule is expressed by occurrence of CT dinucleotide repeats slipped strand mispairing in some *H. pylori* strains [30]. Studies using mutants of *oipA* gene revealed its effect on the signaling host cell pathways through tyrosine phosphorylation and actin cytoskeleton inducing alterations [64]. OipA protein is associated to increased mucosal inflammation by induction of Interleukin 8 **(IL-8)** and to duodenal ulcer disease [65].

Persistence of *H. pylori* infection is also associated to the modified LPS which mimics human Lewis blood group antigens and present a very low pyrogenic activity when compared to LPS from others enteric bacteria [66,67]. Genes associated to the biosynthetic pathways for production

Copyright © Sperança MA.This book chapter is open access distributed under the Creative Commons Attribution 4.0 International License, which allows users to download, copy and build upon published articles even for commercial purposes, as long as the author and publisher are properly credited.

of *H. pylori* LPS present bacteria population specificity and thus, could produce different gastric disease phenotypes [68,69].

Expression of *H. pylori* DupA virulence factor occur in approximately half of the bacteria strains worldwide, and is associated to increase the risk of duodenal ulcer disease by a mechanism involving neutrophil infiltration and protection against physiological alterations associated to corpus gastritis, including inhibition of atrophy by hypochloridria related to the development of gastric ulcer [70,71]. Disease outcome produced by presence of DupA is independent from host population regional characteristics [72-74].

The IceA coding gene has two allelic forms *iceA1* and *iceA2* [75], and expression of *iceA1* is related to induction of acute antral inflammation by increasing expression of IL-8, being a marker for peptic ulcer disease in different populations [59,76,77].

HOST RISK FACTORS ASSOCIATED TO H. PYLORI AND PEPTIC ULCER DISEASE

H. pylori disease outcome are strongly related to bacterial virulence factors and human host behavior and genetic background. Above, the virulence factors involved in bacterium pathogenesis was discussed. In this section, host specificities associated to *H. pylori* infection and peptic ulcer disease will be point out. Regional studies are very important to know specificities which can be used to prevent and to manage gastric diseases caused by *H. pylori*.

A number of studies have shown the participation of non- *H. pylori* risk factors such as smoking, alcohol intake and Nonsteroidal Antiinflammatory Drug **(NSAID)** use in the etiology of peptic ulcer disease [78,79]. Some of these factors are also associated to an increased risk of peptic ulcer disease related to *H. pylori* as NSAID intake [80].

Aging is another important factor associated to peptic ulcer disease related to *H. pylori*, since development of severe gastric diseases depends on chronic and persistence of the bacterium colonization during a long time. Several cells and regulatory hormones and genes from immunological human system are involved in *H. pylori* persistent chronic infection. Thus, genetic human variants of immunological molecular features can be associated to increased risk for peptic ulcer disease. Description of these factors is out of the scope of this chapter and was recently reviewed [81].

Considering the plasticity and genetic diversity of *H. pylori* worldwide, bacterium and human co-evolution specificities, and host genomic variation, regional *H. pylori* and human population's investigation have to be carried out in order to improve treatment and prevention of severe gastric diseases as peptic ulcer.

References

1. Warren JR, BJ Marshall. Unidentified curved bacilli on gastric epithelium in active chronic gastritis. Lancet. 1983: 1: 1273-1275.
2. Dunn BE, Cohen H, Blaser MJ. Helicobacter pylori. Clin Microbiol Rev. 1997; 10: 720-741.
3. Jones DM, Lessells AM, Eldridge J. Campylobacter like organisms on the gastric mucosa: culture, histological, and serological studies. J Clin Pathol. 1984; 37: 1002-1006.
4. Atherton JC, Cao P, Peek RM Jr, Tummuru MK, Blaser MJ, et al. Mosaicism in vacuolating cytotoxin alleles of Helicobacter pylori. Association of specific vacA types with cytotoxin production and peptic ulceration. J Biol Chem. 1995; 270: 17771-17777.

Copyright © Sperança MA.This book chapter is open access distributed under the Creative Commons Attribution 4.0 International License, which allows users to download, copy and build upon published articles even for commercial purposes, as long as the author and publisher are properly credited.

5. Momtaz H, Souod N, Dabiri H, Sarshar M. Study of Helicobacter pylori genotype status in saliva, dental plaques, stool and gastric biopsy samples. World J Gastroenterol. 2012; 18: 2105-2111.

6. Assumpção MB, Martins LC, Melo Barbosa HP, Barile KA, de Almeida SS. Helicobacter pylori in dental plaque and stomach of patients from Northern Brazil. World J Gastroenterol. 2010; 16: 3033-3039.

7. Mendall MA, Northfield TC. Transmission of Helicobacter pylori infection. Gut. 1995; 37: 1-3.

8. Brown LM. Helicobacter pylori: epidemiology and routes of transmission. Epidemiol Rev. 2000; 22: 283-297.

9. Graham DY, Malaty HM, Evans DG, Evans DJ Jr, Klein PD, et al. Epidemiology of Helicobacter pylori in an asymptomatic population in the United States. Effect of age, race, and socioeconomic status. Gastroenterology. 1991; 100: 1495-1501.

10. Duque X, Vilchis J, Mera R, Trejo-Valdivia B, Goodman KJ, et al. Natural History of Helicobacter pylori Infection in Mexican Schoolchildren: Incidence and Spontaneous Clearance. J Pediatr Gastroenterol Nutr. 2012; 55: 209-216.

11. Mégraud F. [Helicobacter pylori infection: Review and practice]. Presse Med. 2010; 39: 815-822.

12. Ernst PB, Gold BD. Helicobacter pylori in childhood: new insights into the immunopathogenesis of gastric disease and implications for managing infection in children. J Pediatr Gastroenterol Nutr. 1999; 28: 462-473.

13. Pattison CP, Combs MJ, Marshall BJ. Helicobacter pylori and peptic ulcer disease: evolution to revolution to resolution. AJR Am J Roentgenol. 1997; 168: 1415-1420.

14. Sugiyama T, Sakaki N, Kozawa H, Sato R, Fujioka T. Sensitivity of biopsy site in evaluating regression of gastric atrophy after Helicobacter pylori eradication treatment. Aliment Pharmacol Ther. 2002; 16 Suppl 2: 187-190.

15. Wilhelmsen I, Berstad A. Quality of life and relapse of duodenal ulcer before and after eradication of Helicobacter pylori. Scand J Gastroenterol. 1994; 29: 874-879.

16. Na HS, Hong SJ, Yoon HJ, Maeng JH, Ko BM. [Eradication rate of first-line and second-line therapy for Helicobacter pylori infection, and reinfection rate after successful eradication]. Korean J Gastroenterol. 2007; 50: 170-175.

17. Kuipers EJ, Thijs JC, Festen HP. The prevalence of Helicobacter pylori in peptic ulcer disease. Aliment Pharmacol Ther. 1995; 9 Suppl 2: 59-69.

18. Smoot DT, Go MF, Cryer B. Peptic ulcer disease. Prim Care. 2001; 28: 487-503.

19. Leodolter A, Kulig M, Brasch H, Meyer-Sabellek W, Willich SN, 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: 1949-1958.

20. Malfertheiner P. The intriguing relationship of Helicobacter pylori infection and acid secretion in peptic ulcer disease and gastric cancer. Dig Dis. 2011; 29: 459-464.

21. Suerbaum S, Michetti P. Helicobacter pylori infection. N Engl J Med. 2002; 347: 1175-1186.

22. Datta De D, S Roychoudhury. To be or not to be: The host genetic factor and beyond in Helicobacter pylori mediated gastro-duodenal diseases. World J Gastroenterol. 2015. 21: 2883-2895.

23. Blaser MJ, Atherton JC. Helicobacter pylori persistence: biology and disease. J Clin Invest. 2004; 113: 321-333.

24. Huang JY, Sweeney EG, Sigal M, Zhang HC, Remington SJ. Chemodetection and Destruction of Host Urea Allows Helicobacter pylori to Locate the Epithelium. Cell Host Microbe. 2015; 18: 147-156.

25. Schoep TD, Fulurija A, Good F, Lu W, Himbeck RP. Surface properties of Helicobacter pylori urease complex are essential for persistence. PLoS One. 2010; 5: e15042.

26. Nina R Salama, Mara L Hartung, Anne Müller. Life in the human stomach: persistence strategies of the bacterial pathogen Helicobacter pylori. Nat Rev Microbiol. 2013; 11: 385-399.

27. Dunn BE, Campbell GP, Perez-Perez GI, Blaser MJ. Purification and characterization of urease from Helicobacter pylori. J Biol Chem. 1990; 265: 9464-9469.

28. Wang G, Rasko DA, Sherburne R, Taylor DE. Molecular genetic basis for the variable expression of Lewis Y antigen in Helicobacter pylori: analysis of the alpha (1,2) fucosyltransferase gene. Mol Microbiol. 1999; 31: 1265-1274.

29. Bäckström A, Lundberg C, Kersulyte D, Berg DE, Borén T. Metastability of Helicobacter pylori bab adhesin genes and dynamics in Lewis b antigen binding. Proc Natl Acad Sci U S A. 2004; 101: 16923-16928.

30. Yamaoka Y, Kwon DH, Graham DY. A M(r) 34,000 proinflammatory outer membrane protein (oipA) of Helicobacter pylori. Proc Natl Acad Sci U S A. 2000; 97: 7533-7538.

31. Wang HP, YL Zhu, W Shao. Role of Helicobacter pylori virulence factor cytotoxin-associated gene A in gastric mucosa-associated lymphoid tissue lymphoma. World J Gastroenterol. 2013; 19: 8219-8226.

Copyright © Sperança MA.This book chapter is open access distributed under the Creative Commons Attribution 4.0 International License, which allows users to download, copy and build upon published articles even for commercial purposes, as long as the author and publisher are properly credited.

32. Pagliaccia C,de Bernard M, Lupetti P, Ji X, Burroni D. The m2 form of the Helicobacter pylori cytotoxin has cell type-specific vacuolating activity. Proc Natl Acad Sci U S A. 1998; 95: 10212-10217.

33. Murakita H, Hirai M, Ito S, Azuma T, Kato T, et al. Vacuolating cytotoxin production by Helicobacter pylori isolates from peptic ulcer, atrophic gastritis and gastric carcinoma patients. Eur J Gastroenterol Hepatol. 1994; 6: 29-31.

34. Douraghi M,Mohammadi M, Oghalaie A, Abdirad A, Mohagheghi MA. dupA as a risk determinant in Helicobacter pylori infection. J Med Microbiol. 2008; 57: 554-562.

35. Peek RM Jr,Thompson SA, Donahue JP, Tham KT, Atherton JC. Adherence to gastric epithelial cells induces expression of a Helicobacter pylori gene, iceA, that is associated with clinical outcome. Proc Assoc Am Physicians. 1998; 110: 531-544.

36. Baldwin DN,Shepherd B, Kraemer P, Hall MK, Sycuro LK. Identification of Helicobacter pylori genes that contribute to stomach colonization. Infect Immun. 2007; 75: 1005-1016.

37. Linz B,Balloux F, Moodley Y, Manica A, Liu H. An African origin for the intimate association between humans and Helicobacter pylori. Nature. 2007; 445: 915-918.

38. Shiota S,Suzuki R,Matsuo Y,Miftahussurur M,Tran TT1. Helicobacter pylori from gastric cancer and duodenal ulcer show same phylogeographic origin in the Andean region in Colombia. PLoS One. 2014; 9: e105392.

39. Stingl K,Uhlemann EM, Schmid R, Altendorf K, Bakker EP. Energetics of Helicobacter pylori and its implications for the mechanism of urease-dependent acid tolerance at pH 1. J Bacteriol. 2002; 184: 3053-3060.

40. McClain MS, P Cao, TL Cover. Amino-terminal hydrophobic region of Helicobacter pylori vacuolating cytotoxin (VacA) mediates transmembrane protein dimerization. Infect Immun. 2001. 69: 1181-1184.

41. Telford JL,Ghiara P, Dell'Orco M, Comanducci M, Burroni D. Gene structure of the Helicobacter pylori cytotoxin and evidence of its key role in gastric disease. J Exp Med. 1994; 179: 1653-1658.

42. Cover TL. The vacuolating cytotoxin of Helicobacter pylori. Mol Microbiol. 1996; 20: 241-246.

43. Cover TL, SA Halter, MJ Blaser. Characterization of HeLa cell vacuoles induced by Helicobacter pylori broth culture supernatant. Hum Pathol. 1992; 23: 1004-1010.

44. Rhead JL, Letley DP, Mohammadi M, Hussein N, Mohagheghi MA, et al., A new Helicobacter pylori vacuolating cytotoxin determinant, the intermediate region, is associated with gastric cancer. Gastroenterology. 2007; 133: 926-936.

45. van Doorn LJ, Henskens Y, Nouhan N, Verschuuren A, Vreede R. The efficacy of laboratory diagnosis of Helicobacter pylori infections in gastric biopsy specimens is related to bacterial density and vacA, cagA, and iceA genotypes. J Clin Microbiol. 2000; 38: 13-17.

46. Ji X, Fernandez T, Burroni D, Pagliaccia C, Atherton JC. Cell specificity of Helicobacter pylori cytotoxin is determined by a short region in the polymorphic midregion. Infect Immun. 2000; 68: 3754-3757.

47. Amieva MR, El-Omar EM. Host-bacterial interactions in Helicobacter pylori infection. Gastroenterology. 2008; 134: 306-323.

48. Levi S, Beardshall K, Swift I, Foulkes W, Playford R. Antral Helicobacter pylori, hypergastrinaemia, and duodenal ulcers: effect of eradicating the organism. BMJ. 1989; 299: 1504-1505.

49. Sugiyama T, Nishikawa K, Komatsu Y, Ishizuka J, Mizushima T. Attributable risk of H. pylori in peptic ulcer disease: does declining prevalence of infection in general population explain increasing frequency of non-H. pylori ulcers? Dig Dis Sci. 2001; 46: 307-310.

50. Jang S, Jones KR, Olsen CH, Joo YM, Yoo YJ. Epidemiological link between gastric disease and polymorphisms in VacA and CagA. J Clin Microbiol. 2010; 48: 559-567.

51. Sugimoto M, Zali MR, Yamaoka Y. The association of vacA genotypes and Helicobacter pylori-related gastroduodenal diseases in the Middle East. Eur J Clin Microbiol Infect Dis. 2009; 28: 1227-1236.

52. Yamaoka Y, Reddy R, Graham DY. Helicobacter pylori virulence factor genotypes in children in the United States: clues about genotype and outcome relationships. J Clin Microbiol. 2010; 48: 2550-2551.

53. Suzuki RB, Cola RF, Cola LT, Ferrari CG, Ellinger F. Different risk factors influence peptic ulcer disease development in a Brazilian population. World J Gastroenterol. 2012; 18: 5404-5411.

54. Censini S, Lange C, Xiang Z, Crabtree JE, Ghiara P. cag, a pathogenicity island of Helicobacter pylori, encodes type I-specific and disease-associated virulence factors. Proc Natl Acad Sci U S A. 1996; 93: 14648-14653.

55. Odenbreit S, Püls J, Sedlmaier B, Gerland E, Fischer W. Translocation of Helicobacter pylori CagA into gastric epithelial cells by type IV secretion. Science. 2000; 287: 1497-1500.

56. Yasui K, Niwa N, Takemura H, Opthof T, Muto T. Pathophysiological significance of T-type Ca2+ channels: expression of T-type Ca2+ channels in fetal and diseased heart. J Pharmacol Sci. 2005; 99: 205-210.

Copyright © Sperança MA.This book chapter is open access distributed under the Creative Commons Attribution 4.0 International License, which allows users to download, copy and build upon published articles even for commercial purposes, as long as the author and publisher are properly credited.

57. Tsutsumi R, Higashi H, Higuchi M, Okada M, Hatakeyama M. Attenuation of Helicobacter pylori CagA x SHP-2 signaling by interaction between CagA and C-terminal Src kinase. J Biol Chem. 2003; 278: 3664-3670.

58. Stein M, Rappuoli R, Covacci A. Tyrosine phosphorylation of the Helicobacter pylori CagA antigen after cag-driven host cell translocation. Proc Natl Acad Sci U S A. 2000; 97: 1263-1268.

59. van Doorn LJ, Figueiredo C, Sanna R, Plaisier A, Schneeberger P. Clinical relevance of the cagA, vacA, and iceA status of Helicobacter pylori. Gastroenterology. 1998; 115: 58-66.

60. Sahara S, Sugimoto M, Vilaichone RK, Mahachai V, Miyajima H. Role of Helicobacter pylori cagA EPIYA motif and vacA genotypes for the development of gastrointestinal diseases in Southeast Asian countries: a meta-analysis. BMC Infect Dis. 2012; 12: 223.

61. Yamaoka Y. Roles of Helicobacter pylori BabA in gastroduodenal pathogenesis. World J Gastroenterol. 2008; 14: 4265-4272.

62. Fujimoto S, Olaniyi Ojo O, Arnqvist A, Wu JY, Odenbreit S. Helicobacter pylori BabA expression, gastric mucosal injury, and clinical outcome. Clin Gastroenterol Hepatol. 2007; 5: 49-58.

63. Ishijima N, Suzuki M, Ashida H, Ichikawa Y, Kanegae Y. BabA-mediated adherence is a potentiator of the Helicobacter pylori type IV secretion system activity. J Biol Chem. 2011; 286: 25256-25264.

64. Tabassam FH, DY Graham, Y Yamaoka. OipA plays a role in Helicobacter pylori-induced focal adhesion kinase activation and cytoskeletal re-organization. Cell Microbiol. 2008; 10: 1008-1020.

65. Liu J, He C, Chen M, Wang Z, Xing C. Association of presence/absence and on/off patterns of Helicobacter pylori oipA gene with peptic ulcer disease and gastric cancer risks: a meta-analysis. BMC Infect Dis. 2013; 13: 555.

66. Yokota S, Ohnishi T, Muroi M, Tanamoto K, Fujii N. Highly-purified Helicobacter pylori LPS preparations induce weak inflammatory reactions and utilize Toll-like receptor 2 complex but not Toll-like receptor 4 complex. FEMS Immunol Med Microbiol. 2007; 51: 140-148.

67. Nilsson C, Skoglund A, Moran AP, Annuk H, Engstrand L. An enzymatic ruler modulates Lewis antigen glycosylation of Helicobacter pylori LPS during persistent infection. Proc Natl Acad Sci U S A. 2006; 103: 2863-2868.

68. Salaün L, Saunders NJ. Population-associated differences between the phase variable LPS biosynthetic genes of Helicobacter pylori. BMC Microbiol. 2006; 6: 79.

69. Moran AP. The role of lipopolysaccharide in Helicobacter pylori pathogenesis. Aliment Pharmacol Ther. 1996; 10: 39-50.

70. Hussein NR. The association of dupA and Helicobacter pylori-related gastroduodenal diseases. Eur J Clin Microbiol Infect Dis. 2010; 29: 817-821.

71. Wang MY, Chen C, Shao C, Wang SB, Wang AC. Intact long-type DupA protein in Helicobacter pylori is an ATPase involved in multifunctional biological activities. Microb Pathog. 2015; 81: 53-59.

72. Talebi Bezmin Abadi A. The Helicobacter pylori dupA: A Novel Biomarker for Digestive Diseases. Front Med (Lausanne). 2014; 1: 13.

73. Queiroz DM, Rocha GA, Rocha AM, Moura SB, Saraiva IE. dupA polymorphisms and risk of Helicobacter pylori-associated diseases. Int J Med Microbiol. 2011; 301: 225-228.

74. Jung SW, Sugimoto M, Shiota S, Graham DY, Yamaoka Y. The intact dupA cluster is a more reliable Helicobacter pylori virulence marker than dupA alone. Infect Immun. 2012; 80: 381-387.

75. Figueiredo C, Quint WG, Sanna R, Sablon E, Donahue JP. Genetic organization and heterogeneity of the iceA locus of Helicobacter pylori. Gene. 2000; 246: 59-68.

76. Linpisarn S, Suwan W, Lertprasertsuk N, Koosirirat C, Steger HF. Helicobacter pylori cagA, vacA and iceA genotypes in northern Thai patients with gastric disease. Southeast Asian J Trop Med Public Health. 2007; 38: 356-362.

77. Kidd M, Peek RM, Lastovica AJ, Israel DA, Kummer AF. Analysis of iceA genotypes in South African Helicobacter pylori strains and relationship to clinically significant disease. Gut. 2001; 49: 629-635.

78. Rosenstock S, Jørgensen T, Bonnevie O, Andersen L. Risk factors for peptic ulcer disease: a population based prospective cohort study comprising 2416 Danish adults. Gut. 2003; 52: 186-193.

79. Rosenstock SJ, Jørgensen T. Prevalence and incidence of peptic ulcer disease in a Danish County--a prospective cohort study. Gut. 1995; 36: 819-824.

80. al-Assi MT, Genta RM, Karttunen TJ, Graham DY. Ulcer site and complications: relation to Helicobacter pylori infection and NSAID use. Endoscopy. 1996; 28: 229-233.

81. Miftahussurur M, Yamaoka Y. Helicobacter pylori virulence genes and host genetic polymorphisms as risk factors for peptic ulcer disease. Expert Rev Gastroenterol Hepatol. 2015.

Copyright © Sperança MA.This book chapter is open access distributed under the Creative Commons Attribution 4.0 International License, which allows users to download, copy and build upon published articles even for commercial purposes, as long as the author and publisher are properly credited.