Editorial

Helicobacter pylori Infection and Hematologic Disorders: what do We Really Know?

The first description of H. pylori eradication reversing long-standing IDA was in 1997 [8] and since then several trials have reported that eradication of the microorganism could really resolve IDA [9-12], an important public health problem especially in developing countries. Despite of it, these studies present some limitations and their results were not corroborated with others, in which it was not found an important association between H. pylori eradication in the treatment of IDA [13,14].

Nevertheless, a meta-analysis of observational epidemiologic studies revealed an increased risk of IDA in H. pylori infected patients [15], and randomized controlled trials suggested that H. pylori eradication could improve iron absorption [16,17]. Two other meta-analysis of randomized control trials have supported this association [18,19]. In one of them it was demonstrated how the effect of H. pylori is more evident in patients with moderate to severe anemia compared with those with mild anemia [18]. In the other one it was suggested that H. pylori eradication therapy combined with iron administration seems to be more effective than iron administration alone for the treatment of IDA [19].

Considering these evidences, H. pylori is suggested to cause IDA by several mechanisms, including iron loss due to active hemorrhage secondary to gastritis, peptic ulcer disease or gastric cancer [20]; reduced iron absorption caused by pan gastritis [21]; and iron utilization for protein synthesis by the bacterium for colonization in the host environment [22]. In addition, H. pylori strains possessing virulence factors CagA and VacA have also been reported to participate in iron acquisition and colonization without damaging host tissue, being responsible for chronicity [23].

As we can conclude, H. pylori infection has been well studied in relation to IDA and some of the most important Consensus (Maastricht IV Consensus and Second Asia-Pacific Consensus) [24,25], on H. pylori as well as the British Society of Gastroenterology [26] have decided on their guidelines that testing and eradication of this bacterium have to be done in individuals with recurrent and unexplained IDA. Recently, the Guidelines for the management of H. pylori infection in Italy (The III Working Group Consensus Report 2015) considered that in patients with IDA H. pylori infection should be sought and treated [27]. Nevertheless, it would be important that larger sample randomized controlled trials were done in order to clarify the relationship between H. pylori infection and the small proportion of the contaminated subjects that develop such condition.

As regards to ITP, it is an autoimmune hematological condition in which destruction of the platelets is mediated by anti-platelet auto-
antibodies in reticuloendothelial system [28]. The possible association between this disease and *H. pylori* infection was first described in 1998 [29] and since then several studies have been demonstrating that there is a consistent role in determining ITP played by this infection [30,31], especially in patients with mild thrombocytopenia [31].

In addition, important studies have demonstrated significant improvement in the platelet count after *H. pylori* eradication in individuals with chronic ITP [32,33] as well as favorable platelet response in the patients in whom *H. pylori* was successfully eradicated [34,35]. Other important observation is that the absolute number of plasma cytokid dendritic cells, which is generally reduced in patients with ITP, is also reduced in patients with ITP and concomitant *H. pylori* infection; but it was observed that this number increased in those individuals after *H. pylori* eradication, one important aspect if we consider the possible relationship between the infection and ITP development [36]. In contrast, one study suggested that the administration of macrolides in individuals with ITP may increase the platelet count independently from *H. pylori* infection, through an immunomodulatory effect intrinsic to the drug [37]. Another study reported a poor response to *H. pylori* eradication therapy in patients with chronic ITP in Western countries [38] and it was also reported that *H. pylori* eradication had no effect on the platelet count in individuals with ITP in Italy [39].

Concerning the pathogenic mechanisms, some hypothesis have been proposed to explain the possible association of *H. pylori* infection and ITP. The most plausible of them is the molecular mimicry [40], which is defined as similar structures shared by molecules from dissimilar genes or by their protein products [41]. For instance, it has been postulated that *H. pylori* surface antigen, such as CagA, evokes host systemic immune response that produces auto-antibodies with cross-react with host platelets [40,42]. Other researchers suggested that genetic influences could also be involved in the development of ITP in individuals infected with *H. pylori*. It was demonstrated that differences in HLA class II allele patterns between patients with ITP with or without *H. pylori* infection have been described and the presence of HLA-DRB1*03 pattern was associated with an increased probability of increase in platelet number in response to *H. pylori* infection [43].

Regarding to these findings and based on the significant positive platelet increase in patients with ITP in whose *H. pylori* was effectively done, it was also recommended by important Consensus, such as IV Maastricht Consensus and the Second Asia-Pacific Consensus Guidelines, that patients with ITP have to be submitted to *H. pylori* eradication therapy [24,25]. Despite of it, as well as in IDA, larger randomized controlled trials with long-term follow-up are still required before a firm conclusion can be drawn.

In conclusion, *H. pylori* infection has been associated with several extra digestive disorders and among them important emphasis has been attributed to IDA and ITP. If we consider strong scientific criteria, in these two conditions *H. pylori* infection can be really classified as a relevant factor of morbidity, aspect which has been demonstrated by several studies, especially meta-analysis. In 2005, the European Helicobacter Study Group, in the Third Maastricht Consensus Conference [44], defined for the first time eradication of *H. pylori* in patients with extra intestinal diseases – IDA and ITP – based on the reversal of IDA and significant positive platelet increase in patients with ITP. Thereafter, we have been seeing several gradual changes in the recommendations for diagnosis and treatment of *H. pylori* infection, including the indication of the microorganism eradication in some gastrointestinal disorders. Future studies will surely point more extra digestive diseases possibly associated to *H. pylori* infection, highlighting our understanding about this ancient microorganism that has co-evolved with humans for over 60,000 years.

References
