THE PREVELANCE OF HELICOBACTER PYLORI AMONG PATIENTS WITH CHRONIC IDOPATHIC URTICARIA

Sheema Mohsin Mustafa and Ahmed Bolad
Al Neelain University, Faculty of Medicine, Department of Microbiology and Unit of Immunology, Al Neelain Medical Research Centre

INTRODUCTION: Helicobacter pylori (H. pylori) is Gram negative, spiral flagellated bacteria that infect approximately 50 percent or more of the world population (Goodman et al., 2001). It is one of the most common chronic bacterial infections that affect humans at any age, women are affected just as often as men (Brown, 2000). Approximately two third of world population is infected with H. pylori, initial infection typically occurs during childhood after oral ingestion and the bacterium persists for life in the host unless treated (Everhart, 2000).

The prevalence of H. pylori is 30% in the developed countries, as opposed to >80% in most developing countries (Atherton et al., 2005). In Sudan, evidence about the prevalence of H. pylori infection is very patchy and there is only one study which showed high prevalence (80%) of H. pylori infection among patients with symptoms of gastritis, 56% with duodenal ulcer, while 60% with duodenitis and 16% in symptomless individuals (Elbagir et al., 2001). The prevalence of infection rises with age and correlates positively with low socioeconomic status during childhood (Malaty et al., 1994). Several risk factors including gender, age and lifestyle e.g. smoking, play a role in the variation of disease prevalence (Baik et al., 2012).

H. pylori is the main causative agent of gastrointestinal diseases including chronic gastritis, peptic ulcer associated disorders, gastric and duodenal carcinomas leading to morbidity and mortality in humans (Black et al., 2004). Apart from its well-demonstrated role in gastroduodenal diseases, some have suggested a potential role of H. pylori infection in several extra-intestinal pathologies including haematological, cardiovascular,
neurological, metabolic, autoimmune, and dermatological diseases. However, more systematic studies are required to clarify the proposed association between *Helicobacter pylori* and skin diseases.

Some studies have found an etiopathogenetic link between *H. pylori* infection and chronic idiopathic urticaria (CIU) and possible skin improvement after its eradication (Chi. *et al.*, 2013).

**Chronic idiopathic urticaria (CIU):** Urticaria is a mucocutaneous disease characterized by erythematous, edematous and pruritic lesions of the dermis and/or hypodermis, resulting from the degranulation of mast cells and basophils and the release of inflammatory mediators, mainly histamine.

It affects from 15 to 25% of the population at some stage of life, and is classified as acute (lesions lasting less than six weeks) or chronic, when the lesions last for more than six weeks, either daily or on most days of the week (Kanani *et al.*, 2011).

Chronic idiopathic urticaria (CIU) accounts for 1% of the cases of urticaria (Castillo *et al.*, 2011) especially among women in the third and fourth decades of life (Ferrer 2009).

Several etiologic factors for CU have been described, including chronic infections and parasitic infestations. The infection by *H. pylori* has been the subject of investigation as a possible etiologic factor for CIU in the last few years (Wedi *et al.*, 2009) and several pathophysiologic mechanisms have been suggested to explain the association between CIU and *H. pylori*.

First an IgE mediated immune response to bacterial infections, since the patients with higher IgE levels on diagnosis show a more significant improvement of the symptoms of CIU in response to treatment institution (Castillo *et al.*, 2012).

Second, the release of auto-antibodies induced by the immunogenic bacterial cell wall (Kanani *et al.*, 2011), whose molecules are similar to the thyroid antiperoxidase antibodies (Kilic *et al.*, 2010).

Finally, the presence of *H. pylori* in the gastric mucosa stimulates the activated eosinophils to release cytotoxic proteins, which are involved in the pathophysiology of urticaria and interfere with the production of pro-inflammatory cytokines and with the
expression of epitopes of adhesion to the endothelial cells, which triggers a systemic immune response (Castillo et al., 2012). Also, substances produced by the *Helicobacter pylori*, such as urease, protease, phospholipase and cytokines, can trigger the complement response (Wedi et al., 2009).

However, as it has been shown that persistent infection caused by *H. pylori* could be a potential trigger for chronic urticaria, the infection by this organism in these patients should be identified and eradicated, as this is one of the most successful therapeutic approaches.

**Literature review:**

*Helicobacter pylori* was first isolated by Warren and Marshall (Warren et al., 1983) in 1982 it was linked with chronic antral gastritis and peptic ulceration, at first they named the bacterium as *Campylobacter pyloridis*, later on it was renamed as *Helicobacter pylori* (Warren et al. 1984).

The genus Helicobacter belongs to the subdivision of the Proteobacteria, order Campylobacterales, family Helicobacter-aceae. The genus Helicobacter consists of over 20 recognized species (Fox, 2002). Members of the genus Helicobacter are all microaerophilic organisms and in most cases are catalase and oxidase positive, and many but not all species are also ureases positive.

Helicobacter species can be subdivided into two major lineages, the gastric Helicobacter species and the enterohepatic (nongastric) Helicobacter species. Both groups demonstrate a high level of organ specificity, such that gastric helicobacters in general are unable to colonize the intestine or liver, and vice-versa.

**Microbiology**

**The Genome:-**

The size of the two Sequenced *H. pylori* genomes is approximately 1.7 Mbp, with a G+C content of 35% to 40%. The *H. pylori* strain 26695 genome includes 1,587 genes, whereas the genome of strain J99 includes only 1,491 genes (Boneca et al., 2003). Both genomes contain two copies of the 16S, 23S, and 5S rRNA genes. Many strains carry one or more cryptic plasmids, which do not seem to carry antibiotic resistance genes or
virulence genes, some of these plasmids form the basis of *H. pylori* (Heuermann *et al.*, 1995-1998).

*H. pylori* is genetically heterogeneous, suggesting a lack of clonality (Kansau *et al.*, 1996). The genetic heterogeneity is possibly an adaptation of *H. pylori* to the gastric conditions of its host, as well as to the distinct patterns of the host-mediated immune response to *H. pylori* infection (Kuipers *et al.*, 2000). Diversity is also seen at the nucleotide level via several mechanisms, including transcriptional and translational phase variation and mutation (Falush *et al.*, 2001).

**Morphology:**

*H. pylori* is a gram-negative bacterium, measuring 2 to 4 Mm in length and 0.5 to 1 Mm in width. Although usually spiral-shaped, the bacterium can appear as a rod, while coccoid shapes appear after prolonged in vitro culture or antibiotic treatment (Kusters *et al.*, 1996). The organism has 2 to 6 unipolar, sheathed flagella which often carry a distinctive bulb at the end. The flagella confer motility and allow rapid movement in viscous solutions such as the mucus layer overlying the gastric epithelial cells (O’Toole *et al.*, 2000).

The overall composition of the cell envelope of *H. pylori* is similar to that of other gram-negative bacteria. It consists of an inner (cytoplasmic) membrane, periplasm with peptidoglycan, and an outer membrane. The outer membrane consists of phospholipids and LPS. The *H. pylori* outer membrane phospholipid moiety contains cholesterol glucosides (Tannaes *et al.*, 2005), which is very rare in bacteria.

The exact mechanisms whereby *H. pylori* is acquired are largely unknown. *H. pylori* has a narrow host range and are found almost exclusively in humans and some nonhuman primates.

*H. pylori* has on rare occasions been isolated from pet animals; thus, the presence of pets may be a risk factor for *H. pylori* infection (Brown *et al.*, 2001) but a conclusive evidence for zoonotic transmission of *H. pylori* is not yet available.

Initial infection typically occurs during childhood after oral ingestion and the bacterium persists for the life of the host unless treated (Everhart JE 2000). An oral-oral route of transmission is supported by studies demonstrating increased transmission in
chronic care facilities and in institutionalized individuals (Lambert et al., 1995). However, some researchers believe that *H. pylori* may also spread by a fecal-oral route, food prepared under less ideal conditions or exposed to contaminated water or soil, inadequate sanitation practices, low social class, and crowded or high-density living conditions seem to be related to a higher prevalence of *H. pylori* infection.

Iatrogenic transmission of *H. pylori* following endoscopy is the only proven mode. Waterborne transmission, probably due to fecal contamination or contaminated well water, may be an important source of infection, especially in parts of the world in which untreated water is common [Brown, 2000].

**Pathogenesis of *H. Pylori* Infection**

**Gastric colonization:**

The stomach is protected by a mucosal barrier that prevents gastric secretions and other destructive agents from injuring the epithelial and deeper layers of the stomach wall (Radosz-Komoniewska et al., 2005). The integrity of the mucosal layer is maintained by tight cellular junctions and the presence of a protective mucus layer. Prostaglandin is derived from the cell membrane lipids and serves as a chemical messenger that protects the stomach lining by improving blood flow, increasing bicarbonate secretion, and enhancing mucus production (Porth, 2002).

This pathogen has adapted to having a complete life in the human stomach (Scott et al., 2007). However, evolution of *H. pylori* with humans over years has effectively refined the interactions that occur between bacterial and host factors, transmission between hosts, survival during acidic stress within hosts, and avoidance of immune response (Blaser, 1997; Scott et al., 2007).

*H. pylori* have evolved several mechanisms to evade primary host defences such as acidity and peristalsis in order to establish persistent infection within the stomach. The pathogen elaborates a number of enzymes of which urease is one of the most important (Peek, 2005). Two major subunits of this enzyme have been identified (*ureA* and *ureB*). This accessory protein catalyses the cleaving of urea into ammonia and hydrogen carbonate thereby achieving a local neutralization of the acid pH in the cytoplasm and on the periplasm (Suarez et al., 2006). Thus, the pathogen can successfully survive in the gastric
lumen (pH 1 - 2) for a short time before it penetrates into the bicarbonate-buffered mucus layer of the gastric mucosa, its real habitat (Benanti et al., 2009). The mucus layer has a pH gradient reaching from the epithelial cell surface (pH 7) to the lumen (pH 2), and the pathogen reacts chemotactically to this gradient (Haas, 2002).

Motility within the gastric mucosal is aided by five or six polar flagella, motility is required for persistent infection, a component of the flagellar secretion apparatus, which regulates flagellar biosynthesis, and regulates urease activity (Peek, 2005).

Other very important virulence factors are adhesins, an essential step in the colonization by *H. pylori* and its selective tissue tropism leading to the establishment of intimate interactions with the epithelial surface. These interactions are largely mediated via outer membrane Proteins (OMPs) that serve as adhesins. The *H. pylori* genome has more than 30 genes which encode OMPs that are divided into Hop (*Helicobacter* outer membrane proteins). The Hop group of proteins contains *H. pylori* adhesion molecules such as BabA, SabA, AlpA/B, HopZ and OipA (Backert *et al.*, 2011).

The BabA protein probably represents the best-characterized *H. pylori* adhesion protein. There are two distinct babA alleles, *babA1* and *babA2*. The BabA2 outer membrane protein, which is encoded by the *bab* (blood group antigen binding) genes (Maeda *et al.*, 2007). The BabA2 protein can bind fucosylated polysaccharides, which are blood antigens known as Lewis blood antigens (Leb) (Sheu *et al.*, 2003).

Binding of *H. pylori* to Leb on the epithelial surfaces via BabA enhances the type 4 secretion system (T4SS)’s, ability to exert the pathogenicity of *H. pylori* that includes triggering production of proinflammatory cytokines (Ishijima *et al.*, 2011), a well-established response of the epithelium to the infection. These antigens have been found both on the surface of the mucous membrane and in *H. pylori* lipopolysaccharide.

**Lipopolysaccharides (LPS):** The majority of *H. pylori* strains express LPS that contains fucosylated oligosaccharide antigens that are structurally and immunologically closely related to human blood group antigens. These bacterial antigens (Lewis antigens) display marked antigenic variation and are thought to contribute to immune evasion. Initially thought to mediate cell adhesion, current data indicate that Lewis antigens seem to have only a limited role in adhesion (Mahdavi *et al.*, 2003) and colonization.
The finding that Lewis antigen expression enhances bacterial internalization by epithelial cells (Lozniewski et al. 2003) suggests that Lewis antigen expression potentially affects the innate immune response.

*H. pylori* LPS stimulates NF-κB and IL-8 production in both epithelial cells and immune cells in a CagA-independent manner (Lepper et al., 2004), but the NF-κB activation observed in epithelial cells upon stimulation with *H. pylori* is not mediated by LPS. *H. pylori* LPS is unlikely to represent a major factor in the immune activation by *H. pylori*. It is unclear whether the ability to mimic a wide range of host blood group antigens through phase variation of the Lewis antigenic determinants carried by the LPS either promotes gastric autoimmunity or even further attenuates the immune-stimulatory effects of LPS. (Amedei et al, 2003)

Among the virulence factors expressed by *H. pylori*, in addition to the adhesins described above, there are bacterial products that are translocated into host epithelial cells *via* a type 4 secretion system (T4SS) encoded within the *cag* pathogenicity island (*cag*PAI) as well as factors that are secreted by *H. pylori* and exert their effects independently of the intact bacteria interacting with the epithelium. Cag PAI consists of a cluster of 31 genes, most of which code for a T4SS. The T4SS is in essence a needle-like structure that penetrates the epithelial cell membrane and translocates *H. pylori* products into epithelial cells. One of the products injected is the effector protein CagA which is encoded at one end of *cag* PAI and does not seem to have a homologues in other bacterial species (Odenbreit S et al., 2000).

CagA is perhaps the most virulent factor associated with *H. pylori* and its presence in an infecting strain is regarded as a risk factor for peptic ulcer disease and gastric cancer. CagA co-localizes with tight junction proteins, causing decreased cell-cell adhesion and loss of cell polarity (Amieva et al., 2003). CagA positive strains are often associated with increased IL-8 production, however; *H. pylori* induces IL-8 secretion through multiple mechanisms, some of which are CagA independent (Fischer et al., 2009).

Another important factor is (VacA) Vacuolating toxin A, which was named for its ability to induce numerous large vacuoles in host cells. Unlike CagA, VacA forms an autotransporter structure to secrete itself without the need for host cell contact (Sewald et al., 2008). It inserts into mitochondrial membranes, causing mitochondrial dysfunction and
subsequent apoptotic death of the cell (Palframan et al., 2012). VacA disrupts the barrier function of epithelial cells, allowing leakage of crucial nutrients such as iron, nickel, and amino acids. This likely improves *H. pylori* growth (Papini E et al., 1998).

*In vitro*, VacA inhibits antigen presentation and T cell activation, but it is not clear whether these activities occur *in vivo* (Amieva et al., 2008). In spite of the dramatic effects of VacA on epithelial cells, it is unclear whether VacA plays a causative role in these diseases. More likely, VacA facilitates nutrient acquisition, improving the ability of *H. pylori* to colonize the gastric epithelium (Yamaoka et al., 2005).

**Classic *H. pylori*-associated diseases**

**Gastritis:**

Gastritis refers to inflammation of the gastric mucosa and is classified as acute or chronic gastritis. Acute gastritis refers to the transient inflammation of the gastric mucosa (Kuipers et al., 1995). It is most commonly associated with local irritants such as bacterial endotoxins, caffeine, alcohol, and aspirin (Furuta et al., 2009). Depending on the severity of the disorder, the mucosal response may vary from moderate oedema and hyperaemia to haemorrhagic erosion of the gastric mucosa (Porth, 2002). Clinical manifestations of acute gastritis include heartburn, transient gastric distress, which may lead to vomiting and, in more severe situations, bleeding and hematemesis. Acute gastritis is usually a self-limiting disorder; complete regeneration and healing usually occur within several days (Porth, 2002).

Chronic gastritis is characterized by the absence of grossly visible erosions and the presence of chronic inflammatory changes leading eventually to atrophy of the glandular epithelium of the stomach (Kuipers et al., 1995). The changes may become dysplastic and possibly transform into carcinoma, *H. pylori* and a number of factors such as chronic alcohol abuse, cigarette smoking, and chronic use of non-steroid anti-inflammatory drugs (NSAIDs) may contribute to the development of the disease (Furuta et al., 2009).

There are four major types of chronic gastritis: *H. pylori* gastritis, autoimmune gastritis, multifocal atrophic gastritis and chemical gastritis (Ernst et al., 2006).
**Peptic ulcer disease:**

Forms of peptic ulcer are duodenal and gastric ulcers (van Doorn et al., 1999). It has been documented that virtually all persons with duodenal ulcer and 70% of those with gastric ulcer have H. pylori infection. Duodenal ulcers occur five times more commonly than gastric ulcers; it occurs at any age and frequently is seen in early adulthood. Gastric ulcers tend to affect older age groups, with a peak incidence between 55 and 70 years of age. Both types of ulcers affect men three to four times more frequently than women (Porth, 2002).

Clinical manifestations of peptic ulcer include discomfort and pain. The pain, which is burning, gnawing, or cramp like, is usually rhythmic and frequently occurs when the stomach is empty - between meals and at 1 or 2 O’clock in the morning. The pain is usually located over a small area near the midline of the epigastrium near the xiphoid, and may radiate to below the costal margins, to the back, or, rarely, to the right shoulder (Furuta et al., 2009).

The pains tends to recur at intervals of weeks or months, during an exacerbation, it occurs daily for a period of several weeks and then remits until the next recurrence. Characteristically, the pain is relieved by food or antacids (Porth, 2002). Complications of peptic ulcers include haemorrhage, obstruction, and perforation.

**Gastric carcinoma:**

*H. pylori* is an accepted cause of gastric adenocarcinoma and MALT lymphoma (official name: extranodal marginal zone B cell lymphoma of mucosa-associated lymphoid tissue). Gastric adenocarcinoma is classified into intestinal subtype and diffuse subtype. Intestinal type adenocarcinoma is more common and has been well studied. The sequence of pathological changes leading to intestinal type cancer starts with gastritis, followed by gastric atrophy (loss of glandular structure) and progression to intestinal metaplasia, dysplasia, and finally carcinoma(Kim et al., 2011).

Among factors that increase the risk of gastric cancer is genetic predisposition, carcinogenic factors in diet (e.g., *N*-nitroso compounds and benzopyrene found in smoked and preserved foods), autoimmune gastritis, and gastric adenomas or polyps (Furuta et al., 2009).
Stomach cancers are either ‘intestinal’, arising from areas of intestinal metaplasia with histological features reminiscent of intestinal epithelium, or ‘diffuse’, arising from normal gastric mucosa (Palmer et al., 2002). Between 50 and 60% of gastric cancers occur in the pyloric region or adjacent to the antrum (Furuta et al. 2008). Unfortunately, stomach cancers often are asymptomatic until late in their course. Symptoms, when they do occur, are usually vague and include indigestion, anorexia, weight loss, vague epigastric pain, vomiting and abdominal masses (Porth, 2002).

**Immunological response to *H. pylori* infection:**

*H. Pylori* induce a host immune response, but the persistence of the infection suggests that the response is not effective in eliminating the infection. Furthermore, multiple lines of evidence suggest that the immune response contributes to the pathogenesis associated with the infection.

**The Innate Response to *H. pylori*:**

The innate immune system plays a key role in the initiation and the subsequent progression of the *H. pylori* associated pathogenesis. Gastric epithelial cells (GECs) are primary target for *H. pylori* infection, and actively contribute to the innate immune responses via signaling through pattern recognition receptors, such as Toll-like receptors (TLRs). The gastric epithelial cells express TLR2, TLR4, TLR5, and TLR9 that interact respectively with lipoproteins, LPS, flagellin, and Cp G motifs (Ishihara S et al., 2004).

Although LPS is the classical bacterial ligand for TLR4, *H. pylori*-derived LPS reported to signal through TLR-2 and have low binding affinity for the TLR4. One study showed that *H. pylori* enzymes, LpxE and LpxF, desphosphorylate the lipid A of its’ LPS, leading to a decrease in recognition by TLR-4 (Cullen et al., 2011).

Lipopolysaccharide (LPS) is a glycolipid found on the outer membrane of gram negative bacteria (Cullen et al., 2011), it has three distinct units: lipid A, which is responsible for the toxic effect, a core polysaccharide of five sugars linked through ketodeoxyoctulonate to lipid A, and the O-antigen, an outer polysaccharide consisting of up to 25 repeating units of three to five sugars (Levinson, 2011).

*H. pylori* expresses O-antigens with great diversity; the bacterium has Lewis antigens, which are made of carbohydrates, that resemble human blood group antigens.
the bacterium is able to evade TLR’s because the normally detectable O-antigen is recognized as a “self” molecule by this type of receptors. It also modifies the lipid A, this leads to an inability of cationic antimicrobial peptides (CAMP’s) to bind to typically negatively charged structures like lipid A (Cullen et al., 2011).

This reduced binding of LPS to its receptors results in decreased activation of monocyte-macrophages, preventing their contribution to innate immune response. Interestingly, *H. pylori* LPS has also been shown to possess anti-phagocytic properties *in vitro* (Grebowska et al., 2008).

Flagellin is the protein component of bacterial flagella needed for motility and colonization (Brooks et al., 2013). *H. pylori* rely on five or six polar flagellae made of two separate subunits, FlaA and FlaB, to enable movement within the gastric mucus and to counteract peristalsis (Gewirtz et al., 2004). TLR5 is a PRR that recognizes flagellin. However, studies showed that *H. pylori* flagellin was not recognized by TLR5, and thus failed to induce nuclear factor (NF)-κB activation (Andersen et al., 2005).

*H. pylori* DNA is intracellularly recognized by dendritic cells (DC) through endosomal TLR9, which produces a net anti-inflammatory effect, rather than a pro-inflammatory effect (Otani et al., 2012). DC also recognizes *H. pylori* RNA through endosomally localized TLR8 in which a cytoplasmic nucleic acid sensor RIG-I of the RIG-like helicase receptor family (RLRs) concurrently takes part (Geijtenbeek et al., 2003).

Upon PAMP recognition, TLRs trigger cell signaling pathways resulting in:

1. The activation of the transcription factors nuclear factor-κB (NF-κB), activating protein-1 (AP-1) and interferon regulatory factors (IRFs).
2. Expression of inflammatory cytokines, antimicrobial peptides and type I interferon (IFN).
3. The subsequent recruitment of neutrophils, activation of macrophages and dendritic cells and the induction of IFN-stimulated genes (Yokota et al., 2007). *H. pylori* has been shown to induce secretion of inflammatory cytokines (IL-1b, IL-6, IL-8) from peripheral blood mononuclear cells and IL-8 from purified human monocytes and monocyte-derived macrophages (Mandell et al., 2004).

**Adaptive immunity response**
A) Cellular response:

Adaptive immune responses towards *H. pylori* infection have also been identified. *H. pylori* causes continuous gastric inflammation in virtually all infected people. This inflammatory response initially consists of neutrophils, followed by lymphocytes (T- and B-cells), plasma cells and macrophages, along with varying degrees of epithelial cell degeneration and injury (Goodwin *et al.*, 1986).

Chronic active gastritis is associated with an increased CD4/CD8 T-cell ratio within the gastric mucosa and accumulation of CD4+ T-helper lymphocytes in the lamina propria of the gastric mucosa. *H. pylori* infection results in a Th1-predominant host immune response in the gastric mucosa and induction of IFN-γ (interferon-γ) and IFN-γ-related genes. A Th1-predominant immune response is associated with elevated levels of the pro-inflammatory cytokines IL-12, IL-18 and TNF-α (Tummala *et al.*, 2004). The severity of gastritis associated with *H. pylori* infection was correlated with mucosa expression of the TNF-α and IFN-γ (Lehmann *et al.*, 2002).

B) Humoral immune response:

*H. pylori* induce a strong specific systemic and local antibody response and infected individual had antibodies against whole bacteria or part of it (Nessa *et al.*, 2001) and increase in plasma cells in gastric mucosa which produce IgA (Mattsson A *et al.*, 1998). Other important antibody was IgG that binds to *H. pylori* and enhances phagocytosis (Tosi *et al.*, 1990). These antibodies lead to complement activation by either classical or alternative pathways (Berstad *et al.*, 2001). The role of the secretory IgA is important in neutralizing urease and VacA as well as inhibiting adherence of *H. pylori* to gastric mucosa (Cover *et al.*, 1996). Despite this vigorous immune response, *H. pylori* is not eradicated unless an infected individual is treated with a combination of antibiotics, and lifelong chronic infection usually develops.

Some studies have suggested a link between idiopathic chronic urticaria and *H. pylori* infection. Several authors demonstrated that *H. pylori* eradication was associated with a remission of urticaria symptoms (Abdou *et al.*, 2009). However; remission or improvement in urticarial symptoms after *HP* eradication does not necessarily indicate a causal relationship between *H.pylori* and CIU, since triple therapy might eradicate other misdiagnosed subclinical infections as well (Campanati *et al.*, 2013).
One of the suggested pathogenic mechanisms is an increase in gastric vascular permeability during infection resulting in increased exposure of the host to alimentary allergens. The other one is immunological stimulation by chronic infection leading to, through mediator release, a non-specific increase in sensitivity of the cutaneous vasculature to vasopermeability enhancing agents. Another hypothesis is that infection with H. pylori may induce production of pathogenetic antibodies, possibly, by molecular mimicry (Hernando-Harder et al., 2009). Helicobacter pylori infection might be a source of circulating immune complexes and these immune complexes may trigger urticaria (Ben Mahmoud et al., 2011).

Chronic infection with H. pylori normally causes production of specific antibodies. For instance, IgG and IgA antibodies to H. Pylori-associated lipoprotein were found to play a role in the pathogenesis of CIU (Bakos et al., 2003). When IgA-, IgG-, and IgE-mediated immune responses against H. pylori antigens were analyzed, some bacterial immune responsive proteins were identified in cases of CIU (Mini et al., 2005).

Some speculate that H. pylori infection might trigger the production of IgE antibodies by cross reaction between H.pylori and gastric parietal cells or by causing inflammation in the gastrointestinal tract which might facilitate the absorption of antigens. Once this occurs, the production of IgE antibodies responsible for the urticarial symptoms might continue even after the eradication of H. pylori (Hizal et al., 2000).

Several inflammatory mediators released during the immune response to H. pylori infection, such as IL-1, TNF-α, may play a role in the pathogenesis of urticaria lesions, at least in producing a non-specific increase in sensitivity of the cutaneous vasculature to vasopermeability-enhancing agents (Campli et al., 1998).

The infection process development impairs the barrier function of the alimentary tract mucosa, thus impairing food processing. This creates conditions for allergic food particles to enter bloodstream, which is facilitated by inflammatory lesions of the intestinal tract (Karel’skaia et al., 2005).

H. pylori may also upregulate the cytotoxic eosinophilic cationic protein secreted by activated eosinophils, which contributes to the etiopathogenesis of chronic urticaria (Ojetti et al., 2001).
**H. pylori diagnosis:**

Serological tests that detect anti-*H. pylori* IgG antibodies: are non-invasive, less expensive, not influenced by sampling error, and less likely to be confounded by suppression of *H. pylori* infection by colloidal bismuth, proton pump inhibitors, or antibiotics (Dunn et al., 1997). Serological tests are widely used (Suerbaum et al., 2002) but they cannot differentiate a current infection from a past exposure (Vaira et al., 2002). Performance of serological tests depends on the antigen preparation used, and as *H. pylori* strains differ among geographic locations, local validation of the test is necessary (Makristathis et al., 2004). A commercial serum ICT (ACCURATE) rapid card test can also be used for detection of anti-*H. pylori*.

**Stool antigen tests by immunochromatography (S-ICT):** These are non-invasive diagnostic methods that are regarded as global tests (Hirschl et al., 2005). Previous studies have reported wide variations in the sensitivity and specificity of the stool antigen tests, which is likely due to variations in the clonality of the antibodies, differing prevalence of *H. pylori* infection before and after eradication treatment, and differing definitions of standard methods. On the other hand, the sensitivity and specificity of the S-ICT by rapid immunoassay, range 52.5–95.0% and 55.5–96.0%, respectively (Shimoyama et al., 2001). The S-ICT is non-invasive, cost effective, and requires less than 15 min to perform. Therefore, it is convenient for patients and can be easily performed even in small laboratories and primary outpatient clinics.

**Treatment of H. Pylori:**

The ideal therapeutic regimen for *H. pylori* infection should achieve an eradication rate of $\geq 80\%$. Treatment may depend on the patient, treatment indication, local antibiotic-resistance profile, and whether the patient was treated previously for *H. pylori* infection.

**A) FIRST-LINE THERAPY:**

**Triple therapy:**

Comprising two antibiotics, amoxicillin and clarithromycin, and a proton pump inhibitor (PPI) for 1 or 2 wk, was recommended as the initial treatment of choice at several
consensus conferences (Chey et al., 2007]. Eradication rates with triple therapy ranges between 70% and 85% (Fujioka et al., 2012).

B) Quadruple therapy:

Triple therapy regimens are becoming less effective, therefore, alternative therapies are needed. Quadruple therapy containing PPI, bismuth, metronidazole and tetracycline given for 10-14 days, is a good alternative for first line treatment of H. pylori infection (Malfertheiner et al., 2012]. Success rates range between 75% and 90%.

C) Sequential therapy:

The sequential regimen is a simple dual therapy including a PPI plus 1 g amoxicillin (both twice daily) given for the first 5 days, followed by triple therapy including a PPI, 500 mg clarithromycin, and a mitronidazole antimicrobial (all twice daily) for the remaining 5 days. Its initial reported success rate was > 90% (Scaccianoce et al., 2006].

D) SECOND-LINE THERAPIES

In patients who were treated for H. pylori infection, and did not achieve eradication, second-line therapy is required, that is if triple therapy fails, either a bismuth-containing quadruple therapy or levofloxacin-containing triple therapy can be used as second line therapy (Malfertheiner et al., 2012).

Levofloxacin-containing therapy can be used as second line therapy in case of triple-therapy failure (Gisbert et al., 2013) or as second-line therapy in case of failure of bismuth-containing quadruple therapy in areas of high clarithromycin resistance. Levofloxacin-containing therapy consists of PPI, levofloxacin and amoxicillin and is used for 10 days.

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