

# Exploration of the Pathogenesis of Hp-associated Chronic Atrophic Gastritis in Association with the Theory of Latent Damp-heat

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**Abstract:** *The incidence of Helicobacter pylori infection in China is relatively high, and Helicobacter pylori can mediate the development of normal gastric mucosa to chronic atrophic gastritis, while chronic atrophic gastritis can develop into precancerous changes such as intestinal metaplasia over a long period of time, ultimately leading to gastric cancer. The nature of Helicobacter pylori is similar to that of the latent damp-heat of Traditional Chinese Medicine (TCM). Therefore, this paper discusses the occurrence and development mechanism of chronic atrophic gastritis associated with Helicobacter pylori, and introduces in detail the pathogenesis of chronic atrophic gastritis caused by the theory of latent damp-heat in Chinese medicine, discusses the relationship between H. pylori, chronic atrophic gastritis and latent damp-heat and provides a new treatment for chronic atrophic gastritis based on the theory of "latent damp-heat". It also discusses the relationship between Helicobacter pylori and latent damp-heat, and provides a new treatment idea for chronic atrophic gastritis from the theory of "latent damp-heat".*

**Keywords:** Chronic atrophic gastritis, Helicobacter pylori, Latent damp-heat, Micro-ZhengJia.

## 1. Introduction

Chronic atrophic gastritis (CAG) is a type of chronic gastritis, which is characterized by repeated damage to the epithelium of the gastric mucosa, leading to a decrease in the number of intrinsic gastric glands, and the global prevalence of CAG is 23.9% in the general population [1]. The causes of CAG include Helicobacter pylori (HP) infection, Non-Steroidal Antiinflammatory Drugs (NSAIDs) use, autoimmunity, and age, HP infection is considered to be the main cause of gastric glandular atrophy [2]. HP is a helical gram-negative bacterium, which colonizes the gastrointestinal mucosa of nearly half of the world's population [3]. Hp destroys the intrinsic glands of the stomach by releasing virulence factors and triggering an inflammatory response, leading to decreased secretion of pepsin and gastric acid in the gastric body. In this paper, the pathogenesis of Hp-associated chronic atrophic gastritis is described, and the occurrence and development of Hp-associated chronic atrophic gastritis are discussed based on the theory of latent damp-heat in traditional Chinese medicine (TCM), and discusses the potential correlation between the two.

## 2. Mechanism of Chronic Atrophic Gastritis Induced by HP

### 2.1 Neutralizing the Gastric Acid Environment

Human gastric juice consists of hydrochloric acid (HCL), lipase and pepsin, and gastric acid maintains the pH of the gastric juice below 4, which effectively inhibits the colonization of the stomach by invasive microorganisms. However, Hp has developed an acid domestication mechanism that promotes periplasmic pH regulation in the harsh acidic environment of the stomach by regulating urease activity. The urea channel in the inner membrane of Hp opens completely at pH 5.0, allowing rapid entry of urea into the

bacterium [4]. The urease of Hp breaks down urea into carbon dioxide and ammonia, and ammonia combines with water to produce ammonium hydroxide very quickly. Ammonium hydroxide neutralizes the gastric acid in the vicinity of the HP, and the local microenvironment around the HP becomes more acidic. The local microenvironment around HP becomes nearly neutral [5], and Hp can therefore safely pass through the gastric juice and reach the gastric mucosa.

### 2.2 Movement and Colonization

The motility of H. pylori depends on the flagellum, and the flagellar filament composed of two flagellin proteins (FlaA and FlaB) is an important structure for Hp motility [6]. Relevant studies have shown [7] that the motility of H. pylori decreased by 30-40% when the FlaB gene was disrupted, and the FlaA and FlaB double mutants were completely immotile. This result suggests that both flagellin proteins contribute to motility. Interaction of bacterial adhesins with gastric epithelial cell receptors protects Hp from gastric motility and gastric emptying. Blood group antigen-binding adhesion (BabA) and salivary acid-binding adhesion (SabA) are two well-studied adhesins, both of which are outer membrane proteins, with BabA being the major adhesin, assisting HP colonization by binding Oligosaccharide molecule (Lewis B, Leb) and other related antigens [8]. SabA recognizes and binds to sialoglycan, primarily by binding to Lewis X(Lex) antigen on membrane glycolipids [9]. The efficient motility and colonization mechanism of Hp allows the bacterium to pass through the mucus layer and colonize the gastric mucosa, and colonization is a prerequisite for the subsequent inflammatory response induced by Hp.

### 2.3 Toxin Release

The most important factor that Hp causes epithelial inflammation and destroys the inherent glands of the stomach

is virulence factor, which repeatedly damages the gastric epithelial cells, eventually causing irreversible atrophy of the gastric epithelium. Long-term injury may even lead to intestinal metaplasia and gastric mucosa with dysplasia. *H. pylori* causes damage to host tissues by releasing several virulence factors, including cytotoxin-associated gene A (CagA) and vacuolar cytotoxin A (VacA), etc. The CagA gene is contained in the cag Pathogenicity Island (cagPAI), which also possesses the coding sequence for the type-IV secretion System (T4SS), which is similar to a molecular syringe for injecting bacterial macromolecules such as CagA into host cells. T4SS is similar to a molecular injector that injects the bacterial macromolecule CagA into the cytoplasm of host cells, where CagA activates NF- $\kappa$ B and induces the secretion of interleukin 8 (IL-8) by gastric epithelial cells, which plays a central role in Hp-induced gastric mucosal damage and ultimately leads to the morphologic changes of the gastric epithelial cells [10]. VacA is another proteotoxin secreted by HP, and the c-terminal domain of VacA contains receptor binding sites that bind to cellular associated proteins through the c-terminal region [11]. The c-terminal structural domain of VacA contains a receptor binding site, which contacts the cell surface by binding to cell-associated protein receptors. The p33 and p55 subunits of VacA are first introduced into the mitochondria, and then inserted into the inner mitochondrial membrane and form anion-selective channels, which facilitate the transport of chloride ions and lead to an increase in the luminal concentration of chloride ions. Eventually, membrane-permeable weak bases diffuse into these endocytosed compartments, leading to osmotic Swelling and vacuolization, and the structural integrity of the mitochondria, cytoplasmic and endosomal membranes is thus disrupted, leading to cellular collapse [12].

## 2.4 Immune Escape

Hp evades the innate immune response through various mechanisms, such as evading recognition by toll-like receptors (TLRs) and interfering with recognition by rig-like receptors (RLRs), etc. TLRs are expressed on the surface of plasma membranes or endosomes in the nucleus, recognizing different *H. pylori* PAMPs, such as lipopolysaccharides (LPSs), flagellin, and bacterial nucleic acids. By regulating the expression and structure of surface molecules such as LPS or flagellin, Hp successfully evades recognition by TLRs [13].

Bacterial phagocytosis is a central defense mechanism of the host to eliminate invading bacteria. Following *H. pylori* infection, different phagocytic cells such as neutrophils, lymphocytes, and monocytes are recruited to the gastric mucosa. The ability of Hp to successfully inhibit its uptake by phagocytes is dependent on different virulence genes such as virB7 and virB11, as well as on the core components of the type IV secretion system (T4SS). An additional strategy used by Hp to evade phagocytosis relates to the intrinsic cholesterol  $\alpha$ -glycosylation. Therefore, bacteria lacking cholesterol-glycosyltransferase are more likely to be phagocytosed by macrophages [14]. A distinctive feature of Hp infection is that effector T-cell responses are mostly impaired during infection, resulting in hyporesponsive or incompetent T cells. The *H. pylori* virulence factors that interfere with T-cell responses are VacA, Y-glutamyl transpeptidase (GGT), and arginase. VacA is a key factor in

Hp-mediated suppression of T-cells. VacA inhibits antigen presentation to T-cells, blocks T-cell proliferation, and down-regulates Th1 function by interacting with the calcineurin signaling pathway [14].

## 3. The theory of "Latent Damp-heat"

### 3.1 The Concept of Hidden Pathogen and Its Origin

The Chinese Terms in Traditional Chinese Medicine and Pharmacy defines hidden pathogen as a disease that is sensed but does not develop immediately, and is hidden in the body [15]. The Dictionary of Traditional Chinese Medicine (DTCM) suggests that "hidden pathogen refers to the disease that hides in the body and does not immediately develop." [16] It highlights the biggest characteristic of hidden pathogen, that is the hiding of pathogenic qi. The concept of hidden pathogen first originated in the Huangdi Neijing, "hidden pathogen" concept was first formally put forward in the Wenyi Lun, "there is a different qi between heaven and earth, hiding in the Mo-Yuan, issued for the Wenyi." Hidden pathogen is the evil of Wenyi that is hidden in the Mo-Yuan. With the development of the doctrine of hidden pathogen, people have more understanding of hidden pathogen, and the type of hidden pathogen has been constantly innovated. Wang's Medical Deposit said: "Hidden various disease factors include the six exogenous pathogens, various Yu, retention of food, blood stasis, phlegm-damp, accumulation of qi, xu shui, worm accumulation. "This further broadens the scope of hidden pathogen, in addition to the six exogenous pathogens, phlegm-damp, blood stasis, worm accumulation can be hidden in the human body. Modern medical doctors continue to summarize the experience of the previous generation and gained a better understanding of the hidden pathogen. With the help of modern medical examination methods, pathogenic microorganisms, tumors, stones and other pathological products or metabolites are also included in the category of latent pathogens, so that latent pathogens have a new development.

### 3.2 The Theory of "Latent Damp-heat" in the Spleen and Stomach

Spleen for the Taiyin wet earth, like dry and evil wet, and the stomach is Yangming dry earth, like wet and evil dry," Taiyin wet earth, get the sun began to transport; Yangming dry earth, get the yin maintain moderate." If Yin and Yang are peaceful, then dry and wet, spleen and stomach each perform their duties, Qi will rise and fall smoothly. The Systematized Identification of Warm (Pathogen) Diseases said "Spleen master wet earth quality, is easy to be invaded by dampness, therefore, it is easy to get dampness syndrome in the middle jiao." The spleen is easy to be disturbed by dampness, dampness can be born from within, can also be brought in by the external evil (Hp, etc.). Dampness is Yin evil, dampness evil trapped spleen can be seen in the head and body heavy, sticky stools, greasy Tongue coating and other heavy turbid and sticky like. The stomach preferring moisture to dryness, heat evil disturbs the stomach, consumes qi and damages Yin to produce dryness, and heat evil can also be born by the dampness of the long-held. The stomach likes moistening and hates dryness, heat evil disturbs the stomach, consumes qi and damages Yin to produce dryness, heat evil can also be

produced by dampness evil. Taiping Huimin HeJi Ju Fang said "The spleen and stomach are affected by dampness, and produce heat evil." The heat is yang, heat evil disturbing the stomach is seen in the epigastrium burning, stools hot and dry difficult to dissolve, yellow Tongue coating and other inflammation of the heat of the ascension. The combination of dampness and heat, like oil into the flour, is cemented and difficult to resolve. As Damp and Heat Theory said "When heat gets wet, it will become more hot, and when wet gets hot, it will be more serious." The combination of these two evil spirits produced latent damp-heat [17]. The evil of dampness-heat is difficult to solve, so Yin and Yang lose balance, resulting in the qi of the spleen does not rise, the qi of stomach does not fall, and the qi movement loses its balance. The above reasons lead to the spleen and stomach can not play its function normally, and the function of transporting water and food is reduced. Clinically visible epigastric and abdominal distension and pain, loss of appetite, acid reflux, heartburn, eructation, yellow tongue coating, and other symptoms.

### 3.3 The Etiology and Consequence of Latent Damp-heat in the Spleen and Stomach—Micro-ZhengJia

The name of "ZhengJia" was first mentioned in Synopsis of Prescriptions of the Golden Chamber, It says, "Malaria, whose course is recorded in a month, should be cured on the fifteenth day of the month if it starts on the first day of the month; If not, it should be healed by the end of the month; If it doesn't heal for a month, what's the explanation? Teacher said: This is evil forces formed ZhengJia, called malarial mother." Chronic malaria cannot be cured, malaria is recurrent, finally the malarial evil remains hidden in the body for a long time and forms ZhengJia. Treatise on the Pathogenesis and Manifestations of All Diseases said "All the disease of mass agglomeration, hard and immovable is Zheng; What can be pushed is Jia. Jia means false lump, which is not a fixed mass, that can be pushed." The Zheng has the characteristics of hard and immovable, pain in a fixed place, while the Jia has the characteristics of irregular aggregation and dispersion, pain in an irregular place. Prof. GaoJinliang [18] suggested that the precancerous lesion of gastric cancer is micro-ZhengJia, which is the product of qi stagnation and blood stasis. Referring to the Medical Records as a Guide to Clinical Work" The formation of the Jia is the accumulation of qi, and the Zheng is the retention of blood stasis. The process from the invisible to the visible is the progression of the lump. "The initial stage of the micro-ZhengJia caused by "latent damp-heat" is characterized by the stagnation of qi, and in the long term, the veins and channels become stagnant, and the zhengJia will be formed. Latent damp-heat hidden in the middle Jiao, like smoke gradually smoked, like water gradually accumulated. Latent damp-heat difficult to remove from the human body, disease can not be cured, and eventually develop into a more serious toxic evil. Latent damp-heat toxicity with the characteristics of damp and heat. Dampness is a kind of Yin evil, mainly viscous in nature, which obstructs the function of the spleen and stomach to transport body fluid, resulting in obstructed movement of body fluid. Phlegm and fluid remain stagnant in the body, and qi is affected and unable to move forward. The above stagnant material factors make up the jia. The time of disease occurrence is too long, resulting in stagnation of qi, and the

blood driven by qi is also stagnant in the veins. In addition, heat is a Yang evil, which consumes qi and damages body fluid. With the depletion of qi and the reduction of body fluid, blood becomes more and more viscous, and eventually blood stasis is formed [19]. Blood stasis is a key factor in the formation of micro-ZhengJia. As mentioned in A Treatise on Blood Troubles "Blood stasis in the meridians and zang-fu organs, resulting in zhengjia." Therefore, heat evil, phlegm and dampness, stagnant qi and blood stasis coagulate together, forming abdominal micro-ZhengJia.

## 4. The Association between HP-related Chronic Atrophic Gastritis and the Theory of "Latent Damp-heat"

### 4.1 Association of Hp-associated CAG with Latent Damp-heat

Hp infection is closely associated with the occurrence of CAG, the risk of CAG can be increased by 4 times due to Hp infection [20]. HP is an external evil that enters through the mouth, According to the characteristics and clinical manifestations of HP-related gastritis similar to "dampness-heat syndrome", Chinese medicine considers Hp as damp-heat pathogenic agent [21]. Hp enters the human body from the outside and interferes with the normal function of the spleen and stomach, causing the spleen to be troubled by dampness and the stomach to be damaged by dryness. As a result, the Yin and Yang of the middle jiao are out of balance, and the microenvironment in the stomach is changed. The humid and hot stomach environment provides a "medium" suitable for the growth and reproduction of Hp [22]. From the viewpoint of modern medicine, HP is a kind of spiral Gram-negative bacteria, can regulate the urease activity, neutralize the gastric acid around the bacteria, make the local microenvironment nearly neutral, so as to provide a good environment for its own colonization. Hp, as a damp-heat pathogenic pathogen, reaches the spleen and stomach through the digestive tract and hides in the spleen and stomach, which is related to its characteristics of heavy turbidity and viscosity. Modern medical research has found that Hp binds to the receptors on the surface of the gastric mucosa through BabA, SabA and other bacterial adhesins, so that Hp is firmly planted in the gastric mucosa to avoid being affected by gastric peristalsis and gastric emptying. In addition to the characteristics of dampness, the key to Hp's ability to ambush in the middle Jiao is the strength of the body's healthy Qi and pathogen. "The healthy Qi in the body is sufficient, even if the evil spirit enters the body can not be accepted." (from Huangdi Neijing). This means that as long as there is enough healthy Qi in the human body, the evil spirit entering from the outside cannot overcome it, and the evil spirit cannot remain in the human body. After Hp enters the human body, it causes an inflammatory response, which deplets the healthy Qi in the spleen and stomach and decreases the ability of the spleen and stomach to protect itself. healthy Qi cannot resist pathogen, and pathogen will remain in the human body and continue to destroy the spleen and stomach [23]. In modern medicine, Hp can evade immunity by interfering with immune cell receptor recognition, hindering cell phagocytosis, inhibiting T-cell proliferation and other mechanisms, so that it can hide itself in the immune response. This reflects the process of Hp as a disease pathogen competing with the healthy Qi in the spleen

and stomach.

Latent damp-heat remained in the middle jiao for a long time, and eventually developed into a toxic evil. The pathogenic ability of toxic evil is strong, which can not only affect the function of spleen and stomach transport, but also damage the blood network of the spleen and stomach, resulting in no way to provide blood to the gastric mucosa, so the glands atrophy, and the mucosa on the surface of the stomach becomes thin [24]. In Chinese medicine, bleeding is when the blood is too hot, causing the blood to boil like boiling water, and the blood leaves the vessel and spills out. In modern medical research, the main factors of Hp-induced inflammatory response are virulence factors, including CagA and VacA, etc. CagA activates NF-κB and induces gastric epithelial cells to secrete IL-8, which is the key to Hp-induced inflammatory response. VacA leads to cell swelling and vacuolation, cell structure destruction, loss of repair ability of repeatedly damaged gastric epithelial cells, and eventually irreversible atrophy. The destructive effect of virulence factors on gastric mucosa cells is highly similar to the pathogenic characteristics of dampness-heat virulence. As the Danxi's experiential Therapy said, "If there is dampness and heat in the middle-jiao, it will cause pain for a long time, which is a strong performance of hot qi."

#### 4.2 Association of Hp-associated CAGs with Micro-zhengjia in the Intestine

In modern medicine, CAG with intestinal epithelial hyperplasia and heterogeneous hyperplasia is often referred to as gastric precancerous lesions [25], and Prof. Gao Jinliang suggested that gastric precancerous lesions are the micro-zhengjia in the abdomen produced by stagnation of qi and blood stasis. The material basis for the formation of micro-zhengjia in the abdomen is phlegm and blood stasis. As a dampness and heat latent evil, Hp hid in the middle jiao for a long time, obstructing the transport of body fluid, resulting in the formation of phlegm and fluid, which led to the blockage of qi, affecting the movement of qi and blood in the meridians, and the stagnation of qi and blood, gathering and forming a lump. At this time, mucosal particles or nodules on the surface of the atrophy gastric mucosa could be seen under the gastroscopy [26]. The nature of heat evil is to damage qi and Yin. Heat evil burns the qi and Yin fluid in the body, which reduces the blood in the blood vessels, so blood stasis is formed in the blood vessels. Relevant studies [27] showed that the aggregation and deformation ability of erythrocytes in the blood of patients with CAG was lower than that of normal people, which made the blood of patients with CAG show a high viscosity, and the degree of atrophy of the mucous membrane and the abnormalities of blood rheology were positively correlated. In the beginning, it is an easy jia to treat. If it develops and forms a micro-zhengjia, it becomes an evil entity that is rigid and cannot be moved, making it difficult to treat. If the evil develops further, the micro-zhengjia develops into cancer, and the cancer will travel along the meridians and spread and metastasize [28]. Epidemiological findings [29] showed that the annual incidence rate of gastric cancer was 0.1% within 5 years after the diagnosis of CAG.

#### 5. Summary

CAG, as a kind of chronic gastritis, has the characteristic of long course of illness, modern medicine found that Hp is a common cause of CAG, Hp invasion after the neutralization of gastric acid, movement and colonization, immune escape and a series of mechanisms to "ambush" on the Surface of gastric mucous membrane, and these mechanisms are exactly the same as the Chinese medicine theory of "latent damp-heat". Dampness-heat evil makes the spleen and stomach dry and wet, Yin and Yang are out of balance, the stable state of the stomach is broken, evil invade the stomach mucosa, and because of the pathogenic characteristics of heavy turbidity and viscosity of dampness-evil, it is easy to "hide" in the stomach mucosa, and latent evil for a long time in the middle jiao, consuming healthy Qi, healthy Qi cannot overcome evil, and the conflict between healthy Qi and evil changes from hyperactivity to peace, Hp is "hidden" in the stomach. The further aggravation of evil is an important mechanism for the occurrence of CAG. If evil stays for a long time, toxic evil will form, which will damage the blood network and affect the generation of Qi and blood, so that the stomach network will be lost and the gastric glands will atrophy. Modern medical research has found that the release of virulence factor is an important cause of gastric mucosal atrophy, it can be seen that the dampness-heat poisonous evil and virulence factor is similar. The pathogenic result of "latent damp-heat"—micro-zhengjia, is an innovative definition of precancerous gastric lesions in Chinese medicine. The pathologic histological examination shows that atrophied gastric mucosa develops Pathologic examination showed that the atrophied gastric mucosa had pathological changes such as intestinal metaplasia and heterogeneous hyperplasia. It can be seen that there is a great correlation between Hp and latent damp-heat. Chinese medicine has unique advantages in the treatment of Hp-related CAG, and exploring the potential association between Hp-related chronic atrophic gastritis and the theory of latent damp-heat can provide reference for clinical treatment and research, and explore the advantages of Chinese medicine in the treatment of Hp-positive CAG. However, at present, there are fewer theories about the association between damp-heat and Hp-associated chronic atrophic gastritis, which need to be studied in depth in order to provide more guidance for the prevention and treatment of Hp-positive CAG in TCM in the future.

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