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***Helicobacter pylori* infection and other bacteria in pancreatic cancer and autoimmune pancreatitis**

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Abstract

Helicobacter pylori (*H. pylori*) is an infectious agent influencing as much as 50% of the world's population. It is the causative agent for several diseases, most especially gastric and duodenal peptic ulcer, gastric adenocarcinoma and mucosa-associated lymphoid tissue lymphoma of the stomach. A number of other,

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extragastric manifestations also are associated with *H. pylori* infection. These include neurological disorders, such as Alzheimer's disease, demyelinating multiple sclerosis and Parkinson's disease. There is also evidence for a relationship between *H. pylori* infection and such dermatological diseases as psoriasis and rosacea as well as a connection with infection and open-angle glaucoma. Generally little is known about the relationship between *H. pylori* infection and diseases of the pancreas. Most evidence about *H. pylori* and its potential role in the development of pancreatic diseases concerns pancreatic adenocarcinoma and autoimmune forms of chronic pancreatitis. There is data (albeit not fully consistent) indicating modestly increased pancreatic cancer risk in *H. pylori*-positive patients. The pathogenetic mechanism of this increase is not yet fully elucidated, but several theories have been proposed. Reduction of antral D-cells in *H. pylori*-positive patients causes a suppression of somatostatin secretion that, in turn, stimulates increased secretin secretion. That stimulates pancreatic growth and thus increases the risk of carcinogenesis. Alternatively, *H. pylori*, as a part of microbiome dysbiosis and the so-called oncobio, is proven to be associated with pancreatic adenocarcinoma development *via* the promotion of cellular proliferation. The role of *H. pylori* in the inflammation characteristic of autoimmune pancreatitis seems to be explained by a mechanism of molecular mimicry among several proteins (mostly enzymes) of *H. pylori* and pancreatic tissue. Patients with autoimmune pancreatitis often show positivity for antibodies against *H. pylori* proteins. *H. pylori*, as a part of microbiome dysbiosis, also is viewed as a potential trigger of autoimmune inflammation of the pancreas. It is precisely these relationships (and associated equivocal conclusions) that constitute a center of attention among pancreatologists, immunologists and pathologists. In order to obtain clear and valid results, more studies on sufficiently large cohorts of patients are needed. The topic is itself sufficiently significant to draw the interest of clinicians and inspire further systematic research. Next-generation sequencing could play an important role in investigating the microbiome as a potential diagnostic and prognostic biomarker for pancreatic cancer.

Key Words: *Helicobacter pylori*; Pancreatic cancer; Autoimmune pancreatitis; Carcinogenesis; Microbiome; Molecular mimicry

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Core Tip: *Helicobacter pylori* is the causative agent for several gastrointestinal diseases and a number of extragastric manifestations. The role of *Helicobacter pylori* in the inflammation characteristic of autoimmune pancreatitis seems to be explained by a mechanism of molecular mimicry between several proteins (mostly enzymes) of *Helicobacter pylori* and pancreatic tissue. The topic is itself sufficiently significant to draw the interest of clinicians and inspire further systematic research. Next-generation sequencing could play an important role in investigating the microbiome as a potential diagnostic and prognostic biomarker for pancreatic cancer.

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INTRODUCTION

Helicobacter pylori (*H. pylori*) is a bacterium colonizing gastric mucosa and has been a center of researchers' attention for more than three decades. The bacterium has been identified in biological samples even several tens of thousands of years old. For example, it was discovered in the body of a mummified man approximately 50-years-

old at death and found in a frozen Alpine glacier between Italy and Austria. This mummy, named the “Iceman,” is estimated to have lived 5000–6000 years ago. Researchers searching for the presence of *H. pylori* infection found a bacterial strain from Asia, thereby helping to prove that several thousands of years ago people migrated from Asia to Europe[1,2].

H. pylori has been confirmed as the cause of chronic active gastritis, which may progress into peptic ulcer or even gastric carcinoma. The infection is often associated with extragastric manifestations such as hypochromic anemia or immune thrombocytopenia[3,4]. There are, however, a number of other neurological, cardiovascular, metabolic, allergic and hepatobiliary diseases, including diseases of the eye, that are associated with the presence of *H. pylori* infection[5]. There are two forms of *H. pylori* gastric colonization. One of these manifests as body predominant infection (or pangastritis) with hypoacidity and atrophic gastritis. These patients are predisposed to gastric ulcers and gastric adenocarcinoma. The second form of colonization is associated with predominantly antral gastritis, leading to increased gastrin production, probably *via* local impairment of somatostatin release and reduction of antral D-cells. This results in hypersecretion of acid and, thereby, predisposition to prepyloric and duodenal ulcer. Moreover, it is specifically this second form of colonization of the antral gastric mucosa by *H. pylori* that has been identified as a potential risk factor for the development of pancreatic carcinoma. In addition, *H. pylori*-positive antral gastritis is described as a primarily infectious disease[6-9].

The *H. pylori* bacterium is associated with several virulence factors (Table 1)[6-11].

The global prevalence of *H. pylori* infection remains high. An especially strong prevalence is reported in Japan and China, where it reaches 60%-90%, but similar prevalence data has been recorded in Russia and certain countries in Eastern Europe. In Western and Central Europe, the reported prevalence ranges between 30% and 40% [12]. This begs the question whether such a frequently observed bacterium, which is of course connected mainly to diseases of the stomach and duodenum, could also play a part in the pathogenesis of other diseases beyond the gastroduodenal ones.

H. PYLORI AND OTHER BACTERIA IN PANCREATIC CARCINOMA

Cancer and cardio-cerebrovascular diseases are major causes of mortality worldwide [13,14]. Pancreatic cancer is one of the most lethal malignancies, its incidence is rising, and its prognosis is extremely poor[15,16]. Pancreatic cancer continues to have the lowest 5-year relative survival rate among solid tumors (at 7%-9%) and is projected to become the second leading cause of cancer-related death by 2030 in western countries [17].

There is general agreement that any role *H. pylori* plays in inducing pancreatic carcinoma is based on pathophysiological changes. Currently, there are two hypotheses[18,19]: (1) Patients with *H. pylori* infection have a reduced number of antral D-cells, which causes a suppression of somatostatin secretion and that in turn stimulates increased secretion of secretin and pancreatic bicarbonate. In a mouse model, secretin stimulates pancreatic growth and DNA synthesis in the cells of pancreatic ducts, and this may induce proliferation of epithelial cells; and (2) *H. pylori* growth in the gastric corpus mucosa leads to atrophic gastritis and hypoacidity causing bacterial overgrowth and increased production of bacterially catalyzed N-nitrosamines and transportation of these endogenous carcinogens to the host pancreas *via* the bloodstream. Proliferation mediated through carcinogens such as N-nitrosamines leads to the development of pancreatic carcinoma.

Clinical observations have shown it is crucial to identify the concrete virulence factor possessed by the bacterium. Risk of pancreatic carcinoma has been shown to be associated with *H. pylori* strains that are negative for cytotoxin-associated gene A (CagA)[20-22]. These findings are universally accepted, even though there have been some smaller studies that did not quite so unequivocally confirm these results. A study published in 2012 reported only insignificantly increased risk of pancreatic carcinoma in persons with CagA-positive *H. pylori* and only slightly decreased risk of pancreatic carcinoma development in persons with CagA-positive *H. pylori*[23].

A meta-analysis from Liu *et al*[24] showed no evidence for higher pancreatic cancer risk in patients with atrophic gastritis and confirmed just a slight association for higher risk with CagA-negative *H. pylori* strains. By contrast, in a case-control study, Huang *et al*[25] showed that atrophic gastritis in *H. pylori*-negative patients might bring increased risk of pancreatic cancer.

Table 1 *Helicobacter pylori* virulence factors–peptic ulcer disease and gastric carcinoma

Virulence factor	Classification	Disease association
CagA	Cytotoxin-associated gene A	Peptic gastric/duodenal ulcer
DupA	Duodenal ulcer promoting gene	Duodenal peptic ulcer
VacA	Vacuolating cytotoxin A	Peptic gastric ulcer, premalignant disease progression
OipA	Outer inflammatory protein A	Peptic ulcer disease, gastric cancer

Gastric acid secretion is what regulates the function of pancreatic duct cells and their production of bicarbonate and the watery portion of pancreatic juices. This mechanism may influence the state and function of pancreatic duct epithelial cells and lead to pancreatic duct cell dysplasia, the final result of which may be the development of pancreatic carcinomas. Eradication of *H. pylori* in patients with peptic duodenal ulcers leads to a decrease in gastric hyperacidity and even to restoration of normal gastric secretion[26]. Similarly, in patients with atrophic gastritis, eradication of the bacteria leads to improvement or even normalization of hypo- or anacidity[27].

Nilsson *et al*[28] reported finding *H. pylori* present in pancreatic tissue of patients with pancreatic adenocarcinomas, pancreatic neuroendocrine tumors, multiple endocrine neoplasia type 1 and chronic pancreatitis. *H. pylori* DNA was detected in 75% of patients with pancreatic adenocarcinomas, and *H. pylori* infection was present in 57% of patients with neuroendocrine tumors, 38% of patients with multiple endocrine neoplasia type 1 and surprisingly 60% of patients with chronic pancreatitis. The samples obtained from other benign pancreatic diseases were all negative. In gastroduodenal biopsies, the positivity of *H. pylori* was detected in 33% of cases, but surprisingly 60% of the samples tested positive for the presence of *Helicobacter bilis*. *H. pylori* DNA was not detected in any of the tissue samples from the gallbladder and common bile duct. Those authors conclude that *H. pylori* is often present in pancreatic carcinoma tissues, and it is highly probable that the infection plays a part not only in the development and progression of pancreatic carcinoma but also of chronic pancreatitis.

Despite the rather ambiguous clinical results for the association between *H. pylori* infection and pancreatic carcinomas as well as the unclear pathogenetic mechanism for the induction of pancreatic carcinomas, most of the published meta-analytical studies do support the conclusion that the bacterium plays a role in inducing pancreatic carcinomas[19,20,29-31]. A recent Japanese study evaluated the risk of pancreatic carcinoma along with concurrent *H. pylori* infection and atrophic gastritis on a large cohort of more than 20000 patients. Although in a normal Japanese population no statistically significant relationship was observed between pancreatic carcinoma and atrophic gastritis, in a subset of *H. pylori*-positive smokers with atrophic gastritis there was a significant risk for the induction of pancreatic carcinomas[32].

It is clear that the role of the microbiome is becoming one of the crucial research areas regarding risk of pancreatic carcinoma[33]. There can be no doubt that pancreatic adenocarcinoma is often associated with microbiome dysbiosis and the oncobio[34, 35]. Oncobiosis alters the immune system because the oncobio[34, 35]. Oncobiosis alters the immune system because the oncobio[34, 35]. Oncobiosis alters the immune system because the oncobio[34, 35].

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Although *H. pylori* colonization is associated with pancreatic cancer[38], as mentioned, so too are oral flora. *Porphyromonas gingivalis* and *Capnocytophaga gingivalis*, in particular, play an important role in pancreatic cancer development[39-41]. The availability of next-generation sequencing has contributed to improving our understanding of the orointestinal microbiome and shown that this has potential to become a noninvasive diagnostic and prognostic biomarker for pancreatic cancer[42].

Even though bacteria are found in pancreatic tumor tissues, the mechanism of their colonization remains unknown[43]. A study from Japan showed the detection rate for *Fusobacterium* species in pancreatic cancer tissue to be 8.8%[44].

A meta-analysis published in 2012[45] and another study[46] confirmed the hypothesis that general and abdominal fatness is associated with an increased risk of pancreatic cancer. Moreover, it has been shown that alterations in the bacterial composition, also known as dysbiosis, contribute to various gastrointestinal and metabolic disorders such as obesity and diabetes[42,47]. Smoking or dietary sources

could also play roles and could enhance pathophysiological actions related to carcinogenic effect in the pancreas of N-nitrosamines associated with *H. pylori*[18]. The possible roles of bacteria, including *H. pylori*, and other factors in pancreatic cancer development are illustrated in **Figure 1** (prepared in accordance with Li *et al*[43] and created in collaboration with the Service Center for E-Learning at Masaryk University, Faculty of Informatics).

H. PYLORI AND AUTOIMMUNE PANCREATITIS

Autoimmune pancreatitis (AIP) type-1 belongs to the group of immunoglobulin G4 (IgG4)-related diseases. The characteristic signs of this disease group are chronic inflammatory reaction, pronounced fibrotization of tissues and presence of mononuclear inflammatory infiltrate with plasma cells positive for IgG4[48]. IgG4 is an immunoglobulin that is among the least represented across the immunoglobulin spectrum, making up less than 5% of that spectrum overall[49]. A current hypothesis explaining the mechanism of the disease is based on the effect of molecular mimicry between a pathogen, most commonly *H. pylori*, and an antigen, most commonly carbonic anhydrase II, serine protease inhibitor Kazal type 1 or lactoferrin[50].

In 2005, Guarneri *et al*[51] described a significant resemblance between human carbonic anhydrase II and *H. pylori* alfa-carbonic anhydrase, an enzyme vital for the bacteria's survival in the severely acidic environment of the stomach. Human carbonic anhydrase II is produced by the pancreatic duct epithelial cells. As such, *H. pylori* may therefore directly influence the process of AIP development, given that it carries a protein very similar to carbonic anhydrase II. In 2009, Frulloni *et al*[52] described *H. pylori* plasminogen-binding protein (PBP). Patients with AIP show positivity for antibodies against this protein in up to 95% of cases. PBP was not detected in patients with chronic alcohol-induced pancreatitis or in patients with intraductal papillary mucinous neoplasia. *H. pylori* PBP is molecularly very similar to the enzyme ubiquitin-protein ligase E3 component n-recogin 2. This enzyme is substantially produced by pancreatic acinar cells and therefore, hypothetically, may represent another mechanism through which *H. pylori* infection induces the development of AIP. The potential mechanism by which *H. pylori* might contribute to AIP is presented in **Figure 2** (edited in accordance with Chmiela and Gonciarz[53] and Kountouras *et al* [54] and created in collaboration with the Service Center for E-Learning at Masaryk University, Faculty of Informatics).

Dore *et al*[55] found that the levels of pancreatic enzymes in patients with chronic pancreatitis and concurrent positivity of *H. pylori* infection can be influenced by eradication of the bacteria[55]. Detection of *H. pylori* in the pancreatic tissue of patients with chronic pancreatitis is a significant finding, and it poses a question as to the role of the bacteria in the development of chronic pancreatitis[28].

Similar to the question about the relationship between *H. pylori* and pancreatic carcinoma, just as equivocal are the conclusions and opinions as to the role of *H. pylori* infection in the development of AIP. When evaluating the influence of *H. pylori* infection but also the presence of IgG4, cytokine and PBP, one prospective English study found no differences among a group of patients with AIP, a group of patients with IgG4-associated diseases and healthy controls[56]. The results of that study, therefore, do not support the presumption that *H. pylori* plasminogen plays a role in AIP.

In 2018, Backhus *et al*[48] published a paper summarizing new pathways in the pathogenesis of IgG4-related diseases[48]. One mechanism may be the transformation from beta cells to plasma cells and activation of eosinophilic granulocytes associated with the secretion of proinflammatory cytokines. As a result of this process, elevated IgE levels and eosinophilia are detected in some individuals with IgG4-related disease [57]. IgG4-expressing plasmablasts appear to play a key role in the pathogenesis of IgG4-related disease. Plasmablasts that express CD19, CD20-CD27+ and CD38++ are most likely the precursors of tissue antibodies produced by plasma cells[58]. It would be valuable to determine the role of intestinal dysbiosis, which may be a mediator of the experimental autoimmune form of pancreatitis through the activation of plasmacytoid dendritic cells[59]. Innate immune responses against intestinal microflora are probably involved in the development of experimental AIP. Intestinal dysbiosis increases sensitivity to experimental AIP *via* the activation of plasmacytoid dendritic cells that mediate chronic fibroinflammatory responses.

Contrary data also have been found regarding AIP as a potential risk factor for pancreatic cancer. A multicentric study from the Mayo Clinic including a total of 1064

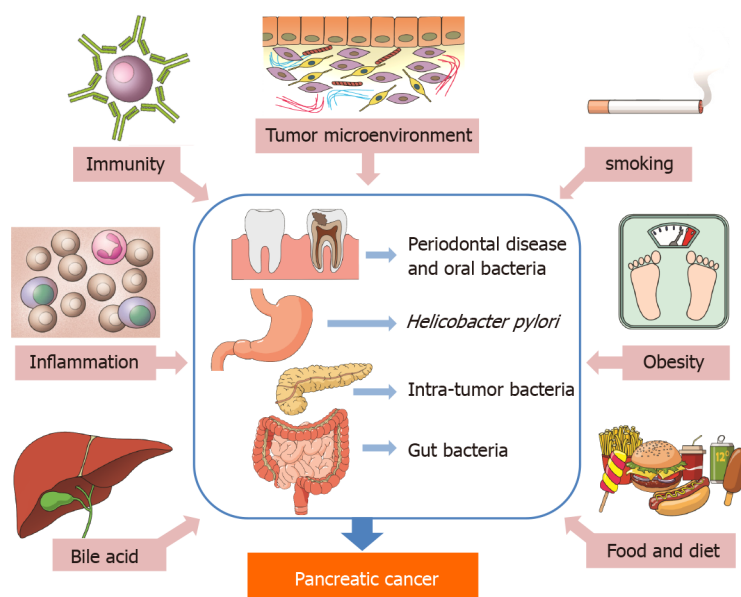


Figure 1 The possible roles of bacteria, including *Helicobacter pylori*, and other factors in pancreatic cancer development.

patients with AIP did not show a significant increased risk of malignancies[60]. Other studies, however, suggest that AIP slightly increases the risk of pancreatic cancer. Macinga *et al*[61] assessed the occurrence of AIP in pancreatic masses resected for focal pancreatic enlargement. In 295 pancreatic resections, AIP was diagnosed in 15 patients (5.1%). Within this group of patients with AIP, pancreatic adenocarcinoma was diagnosed in 6 cases (40%). Moreover, Ikeura *et al*[62] showed a trend towards greater pancreatic cancer development in patients with AIP (4.8%) against patients with other chronic pancreatitis (2.4%).

CONCLUSION

H. pylori infection is an important etiological factor for diseases of the stomach and duodenum. Its role in the induction of peptic gastroduodenal ulcer disease, gastritis (especially antral), carcinomas and mucosa-associated lymphoid tissue lymphoma of the stomach has already been sufficiently described. Its role in pancreatic carcinogenesis or in the induction of AIP remains unclear. However, there are a number of research findings and conclusions tending to confirm and others to deny its effect and involvement. Nonetheless, it can be stated in summary that *H. pylori* infection is one of many factors within a complex that plays a role in the development of both of these diseases.

Oral bacteria, gut bacteria, *H. pylori* and intratumor bacteria must contribute to the etiology and pathogenesis of pancreatic cancer. Four mechanisms are important for this process: (1) bacteria stimulate chronic inflammation (with inflammatory mediators facilitating cell proliferation, mutagenesis, oncogene activation and angiogenesis); (2) bacteria may influence the pathogenesis of cancer by activating NF-kappa B and inhibiting cellular apoptosis; (3) bacteria can produce some substances that act in a carcinogenic manner; and (4) bacteria may overgrow, bacterial dysbiosis may occur, and oncobiome interactions may arise.

The oncobiome and bacterial metabolites (short-chain fatty acids, secondary bile acids, polyamines and indole derivatives) are important factors in the induction of pancreatic cancer. Next-generation sequencing could play an important role in investigating the microbiome as a potential future, noninvasive diagnostic and prognostic biomarker for pancreatic cancer.

Recently, evidence has suggested a positive association between bacteria and pancreatic cancer. Activation of related immune inflammation and increased nitrosamine exposure could be the most important mechanisms. Bacterial stimulation of chronic inflammation and the oncobiome could be related to autoimmune mechanisms.

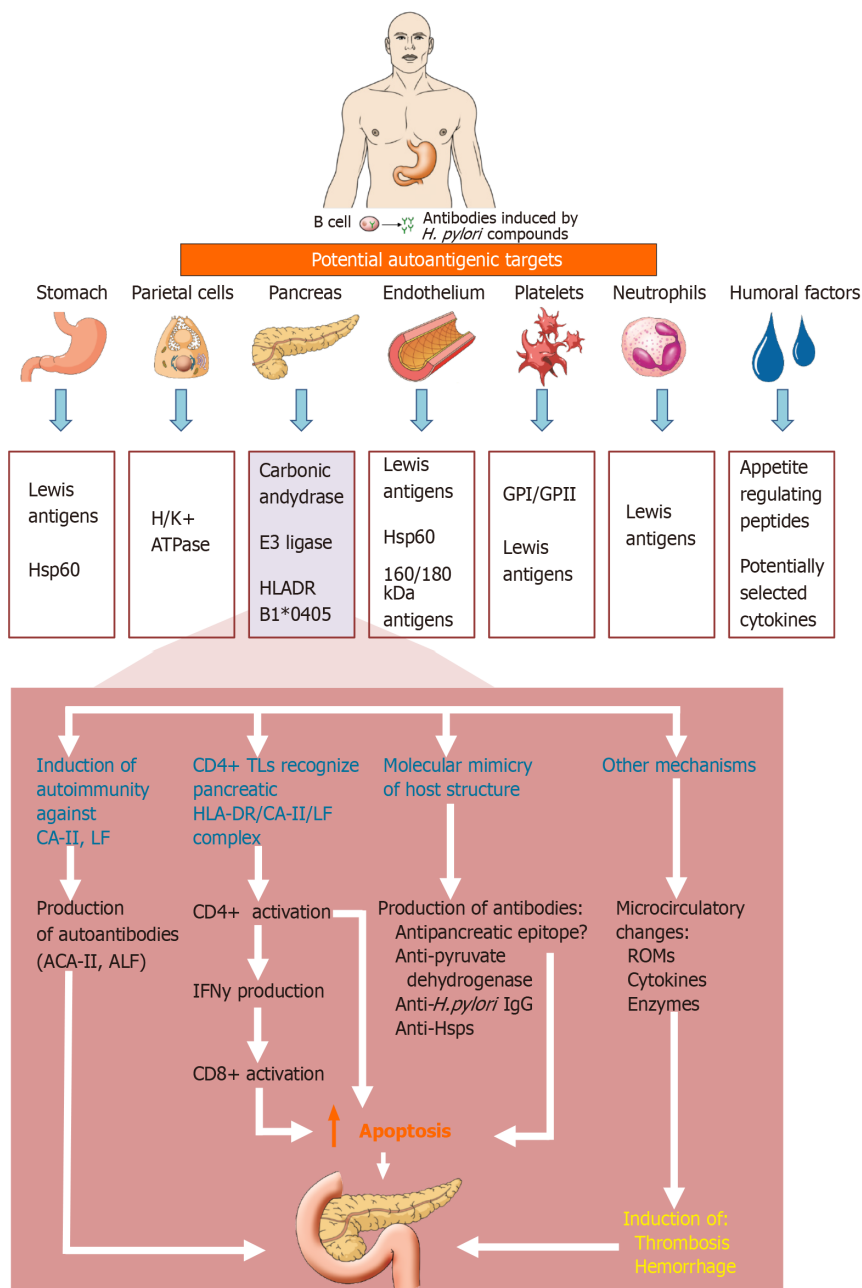


Figure 2 The potential mechanism by which *Helicobacter pylori* might contribute to autoimmune pancreatitis. *H. pylori*: *Helicobacter pylori*; GP: Glycoproteins; Hsp: Heat shock protein; H+/K+ ATPase: H+/K+-adenosine triphosphatase; HLA-DR: Human leukocyte class II DR antigens; CA-II: Carbonic anhydrase type II antigens; ACA-II: Anticarbonic anhydrase II antibody; LF: Lactoferrin; ALF: Antilactoferrin antibody; TLs: T lymphocytes; IFN- γ : Interferon- γ ; anti-Hsps: Antibodies against heat shock proteins; ROMs: Reactive oxygen metabolites.

In the case of AIP, the role of *H. pylori* seems to be explained by inflammation stimulation *via* mechanisms of molecular mimicry between several proteins (mostly enzymes) of *H. pylori* and pancreatic tissue. Patients with AIP often show positivity for antibodies against *H. pylori* proteins. Being a part of microbiome dysbiosis, *H. pylori* is also being considered as a potential trigger of autoimmune inflammation of the pancreas. Moreover, according to some sources, AIP slightly increases the risk of pancreatic cancer and is regarded as a potential risk factor.

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