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Review

Exploring the Contribution of *Campylobacter jejuni* to Post-Infectious Irritable Bowel Syndrome: A Literature Review

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Abstract: This comprehensive review investigates the specific impact of the foodborne pathogen *Campylobacter jejuni* (*C. jejuni*) on gastrointestinal health, focusing on its connection to post-infectious irritable bowel syndrome (PI-IBS). This review examines the pathogen's pathophysiology, clinical implications and epidemiological trends using recent research and data to highlight its prevalence and association with PI-IBS. A detailed literature analysis synthesizes current research to illuminate *Campylobacter*'s long-lasting effects on gut microbiota and intestinal function. It provides a detailed analysis of the literature to shed light on *C. jejuni*'s long-term impact on gut microbiota and intestinal function. The findings suggest the need for multifaceted prevention and treatment approaches considering individual, microbial and epidemiological factors, thus contributing to a more nuanced understanding of PI-IBS following *C. jejuni* infection.

Keywords: *Campylobacter jejuni*; post-infectious irritable bowel syndrome (PI-IBS); gastrointestinal microbiota; immunity; enteric infection; inflammation; diarrhea

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1. Introduction

Campylobacter jejuni, a leading bacterial foodborne pathogen behind global gastroenteritis episodes, significantly triggers both intestinal and systemic aftereffects [1–3]. These include the onset of Guillain–Barré syndrome (GBS), reactive arthritis and complications in pre-existing conditions, including irritable bowel syndrome (IBS), inflammatory bowel disease (IBD) as well as post-infectious irritable bowel syndrome (PI-IBS) [2] through mechanisms that are still obscure [4]. With its considerable influence on public health, *C. jejuni* has become the subject of extensive research, particularly concerning its role in gastrointestinal wellness. Emerging insights propose that the root of IBS following infection may be linked to compromised intestinal barrier integrity. Clinical research indicates that ≈30% of individuals with a recent history of confirmed bacterial gastroenteritis exhibit symptoms akin to IBS, a condition referred to as PI-IBS [5]. Symptoms of PI-IBS can endure for 8–10 years after an episode of enterocolitis, with the main symptoms reported as abdominal pain and cramps, weight loss and bloody diarrheic stools [6,7]. The association between *C. jejuni* infection and the subsequent onset of PI-IBS remains a critical area of investigation. PI-IBS is recognized by enduring gastrointestinal symptoms that persist following the resolution of acute bacterial gastroenteritis [3]. This disorder poses significant clinical challenges, given its intricate pathophysiology and the lack of clear diagnostic indicators. Remarkably, nearly 10% of individuals from a recent cohort of 669 individuals who

experienced travelers' diarrhea were prone to developing persistent symptoms that were consistent with PI-IBS [8]. The molecular configuration of *C. jejuni*'s lipooligosaccharide (LOS) is pivotal in determining the infection's progression. Isolates capable of synthesizing sialylated ganglioside mimics within LOS (classified as A, B or C) exhibit enhanced invasive capabilities and a raised ability to translate epithelial cell monolayers [9]. These specific isolates are more commonly linked to severe outcomes, such as bloody diarrhea, and are associated with prolonged symptomatology. Furthermore, subsequent findings have highlighted mucosal anomalies in the colons of patients diagnosed with PI-IBS [5]. Microscopic colitis is another condition that shares symptom similarities with PI-IBS, but the two have distinct differences [10]. Typically, microscopic colitis is diagnosed in individuals over 50, whereas PI-IBS more commonly affects younger people. Furthermore, patients with microscopic colitis experience chronic watery diarrhea without abdominal pain, in contrast to PI-IBS, in which abdominal pain is a prevalent symptom alongside bowel irregularities [10].

This pathogen presents a paradoxical nature, serving as a harmless commensal within the chicken gut yet triggering a range of illnesses upon human infection. Numerous environmental sources significantly elevate the risk of human *Campylobacter* infections, with most outbreaks linked to the consumption of undercooked poultry meats and their products—encompassing meats from laying hens, turkeys, ostriches, ducks and broilers [11–13]. It has been estimated that poultry meats and products are responsible for approximately 60–80% of global campylobacteriosis cases, underscoring their critical role in transmitting this disease [11]. Within the United States, a population-based study showcased a significantly elevated risk of developing PI-IBS among individuals with sporadic cases of *Campylobacter* infection [14]. In PI-IBS patients, predominant *C. jejuni* isolates belonged to the ST-21 clonal complex, a well-documented lineage in acute human infections, including those leading to liver infections and extraintestinal dissemination [9]. Contrarily, strains from the ST-22 clonal complex were disproportionately represented among those contributing to PI-IBS onset and confirmed in patients with GBS [15], whereas the ST42 clonal complex presented a minimal risk association. Given the absence of specific treatment protocols for PI-IBS, typically symptoms are addressed based on the subtype of IBS present [16]. Although certain treatment approaches like mesalamine, corticosteroids and glutamine have been explored directly in the context of PI-IBS, the prevailing guidelines for management are derived from general strategies employed in treating IBS [10]. This approach emphasizes the need for symptom-based treatment plans, highlighting the gap in targeted therapies for PI-IBS.

IBS affects 10–20% of the population, with around 10% of individuals developing PI-IBS following a *C. jejuni* infection [1,17]. Delineating the specific pathomechanisms underlying PI-IBS is challenging, especially due to the combinations of its various forms [1,17]. In 2019, due to the absence of sensitive and specific markers for diagnosis, the Rome Foundation Working Group introduced symptomatic diagnostic criteria for PI-IBS, leveraging the Rome IV guidelines [7]. They characterized PI-IBS as an intricate and multifactorial condition underpinned by various potential mechanisms, including altered visceral motility, increased visceral sensitivity, microbiome variations, changes in intestinal permeability, immune system dysregulation, chronic low-grade inflammation, enteroendocrine pathway alterations, affected neuromuscular function, post-infectious dyspepsia and genetic factors [18,19].

Persistent inflammation underpins many IBS symptoms, with mucosal inflammation affecting the enteric nervous system's function [20]. This initiates a series of reactions within the mucosa and submucosa, including the activation of visceral hypersensitivity, disrupted motor functions and a reduction in phase III inter-digestive waves, all contributing to the development of small intestinal bacterial overgrowth [20]. The reported incidence of PI-IBS stands at ≈20% under the Rome III criteria, whereas the Rome IV criteria suggest a slightly lower incidence rate of between 10% and 12.8% [18]. Based on the predominant bowel pattern, as measured by the Bristol stool scale, PI-IBS classifications

were proposed, including most common mixed (IBS-M), diarrhea-dominant (IBS-D) and constipation-dominant (IBS-C) [1,7,17]. Beyond the three primary clinical forms, additional research has identified three distinct variants of IBS: pain-predominant IBS (P-IBS), PI-IBS and post-diverticulitis (IBS-PD). Any other gastrointestinal symptoms fitting the IBS profile are classified as unclassified (IBS-U) under the ROME III diagnostic criteria [21]. A bowel pattern qualifies as predominant if it accounts for ≥25% of bowel movements and is categorized as hard/lumpy (indicative of IBS-C), loose/watery (suggestive of IBS-D) or a combination of both (referred to as IBS-M) [7]. Patients with PI-IBS are more inclined to exhibit a diarrhea-predominant pattern compared to those with sporadic IBS. Identifying the specific PI-IBS subtype associated with each patient is critical in guiding disease management and therapeutic interventions. The impact of chronic gastrointestinal symptoms following an infection may surpass the scope of what the Rome criteria define [10]. Recently, Berumen et al., 2021 highlighted that, beyond a 21% prevalence of PI-IBS post-*Campylobacter* enteritis, an additional 9% of individuals experienced new-onset abdominal pain and bowel irregularities yet did not fulfill the Rome criteria for IBS diagnosis [14]. Furthermore, GI infections not only prompt the onset of new IBS cases but can also alter the phenotype of preexisting IBS conditions. Notably, about half of the individuals with IBS-C transitioned to either IBS-M or IBS-D following an episode of *Campylobacter* enteritis [14]. In a cohort study, researchers found that IBS developed in 301 out of 1418 patients with culture-confirmed *Campylobacter* infections [14]. This finding is significant because it relies on culture-confirmed cases, offering a more accurate representation of the prevalence of PPI-IBS following a *Campylobacter* infection. Remarkably, the study also re-affirmed that infection with *Campylobacter* can lead to a shift in the existing subtype of IBS, with approximately 50% of patients experiencing a change from constipation-predominant IBS-C to either IBS-M or IBS-D, which emphasizes the profound impact that such infections can have on the clinical presentation and symptomatology of IBS in affected individuals [14].

The intricate relationship between gastrointestinal infections and the subsequent development of PI-IBS remains a subject of significant clinical and scientific interest. Among the pathogens implicated in PI-IBS, *C. jejuni* is the leader due to its prevalent association with acute gastroenteritis (AGE) and its distinctive mechanisms affecting the human gastrointestinal tract. The consequences of a *C. jejuni* infection span from direct disruption of the gut barrier to profound alterations in the host's immune system, gut microbiota, nervous system functionality and even psychological well-being. Understanding these mechanisms in detail catalyzes the specific pathogenic strategies employed by *C. jejuni* and reveals the complex response mounted by the human host in the face of such infections. Given the multifaceted nature of PI-IBS development post-*Campylobacter* infection, it is necessary to delve deeper into each contributing factor and its interconnections. Therefore, this review aims to comprehensively examine the multifaceted pathophysiological mechanisms underlying the development of PI-IBS following *C. jejuni* infection. Specifically, it focuses on the disruption of gut barrier function, immune system activation, alterations in gut microbiota composition, neural dysfunction and the impact of psychological factors. By exploring these interconnected pathways, this analysis seeks to clarify the complex interplay between microbial infection and host responses that contribute to the onset of PI-IBS to help identify potential therapeutic targets and strategies for preventing and managing the condition.

2. Key Factors in the Emergence of PI-IBS

In the intricate landscape of gastrointestinal disorders, the emergence of PI-IBS presents a compelling case study of the dynamic interplay between infectious agents and host physiological responses. This review delves into the key factors in transitioning from a transient *C. jejuni* infection to the enduring perturbations characteristic of PI-IBS. Infectious enteritis (IE) is a well-recognized factor that increases the risk of developing IBS, specifically a subset known as PI-IBS. The incidence of PI-IBS associated with *Campylobacter* infections exceeds 20% [4]. The severity of *Campylobacter* enterocolitis is known to influence the risk of developing PI-IBS, with factors such as bloody stools, hospitalization, and

the duration of acute illness being correlated with higher risk [5]. However, the specific *Campylobacter* lineages and underlying genetic factors contributing to PI-IBS remain poorly understood [6]. Factors predisposing individuals to PI-IBS encompass genetic predispositions (*TLR-9*, *IL-6* and *CDH1* genes), psychosocial elements (including stress, fatigue, anxiety and depression), diet, smoking, pathogenic infections (predominantly with *Campylobacter*) and its severity, stool frequency with diarrhea, antibiotic exposure, a younger age and females being more susceptible [4,7,22]. The utilization of antacids may escalate the severity of gastroenteritis by lowering stomach acid levels, which serve as a critical defense mechanism against ingested pathogens [23]. This reduction in stomach acidity could heighten the risk of developing PI-IBS by facilitating the survival and subsequent colonization of infectious agents in the gastrointestinal tract [23]. Recent clinical studies have found that individuals with *Campylobacter* infections exhibit significantly elevated rates of anxiety, depression and smoking compared to those without such infections [4]. The likelihood of developing PI-IBS following a bacterial gastroenteritis event, for instance, with *Campylobacter*, varies widely from 4% to 46%, influenced by the diagnostic criteria for IBS, the specific pathogen involved and the length of the observational period [4]. Within the United States, PI-IBS is estimated to represent nearly 70% of *Campylobacter*'s total impact on human health, quantified in terms of Disability Adjusted Life Years (DALY) [4].

Recently, Iacob et al. showed that patients with AGE (acute gastroenteritis) had a significantly higher risk of developing PI-IBS than those with upper respiratory tract infections (URTI) [22]. The relative risk for PI-IBS after AGE was 4.16, with female patients at a higher risk (79%) than males (18%). *C. jejuni* infection had the highest risk for PI-IBS. These findings underscore the increased risk of PI-IBS following AGE, especially in females with specific pathogens like *C. jejuni* [22]. Similarly, individuals with a history of anxiety and depression exhibit delayed recovery from PI-IBS over a follow-up period ranging from six to eight years [24]. The mechanism through which psychological factors heighten the risk of developing PI-IBS is not fully understood. Notably, it is becoming increasingly evident that interactions between the microbiota–gut–brain axis can profoundly influence the intestinal immune system, affecting the immune response to pathogens [24]. Chronic psychological stress compromises the immune system, altering cytokine secretion patterns and increasing infection susceptibility. Moreover, prolonged stress disrupts the balance between T helper-1 and T helper-2 (Th1/Th2) cells, accumulating myeloid-derived suppressor cells within the peripheral blood and bone marrow, leading to immunosuppression [24].

In a previous comprehensive study of a cohort exposed to contaminated drinking water (NoV, *Campylobacter* spp. and *G. lamblia*), researchers prospectively evaluated the risk of developing PI-IBS, focusing on psychological factors and immune responses during the acute phase and one-year post-outbreak [24]. The findings revealed that infectious gastroenteritis and psychological factors, specifically anxiety and somatization (but not depression), were linked to a heightened risk of PI-IBS development. Additionally, individuals who progressed to PI-IBS exhibited a reduced count of $CD4^+$ $CD8^-$ $IL2^+$ T cells and Th1 cells, alongside an increase in Th2 cells at the time of infection, suggesting that a dominant Th2 immune response to the infectious agent may predispose individuals to PI-IBS. These insights underscore the influence of psychological factors, particularly anxiety and somatization, on the risk of PI-IBS, potentially by predisposing individuals to infectious gastroenteritis and favoring a Th2-skewed immune response at the infection's onset [24]. Further analysis of the role of immune activation in PI-IBS, including in-depth phenotyping of peripheral blood mononuclear cells alongside the quantification of plasma cytokine levels, revealed a higher count of $CD4^-$ $CD19^+$ B cells in patients with PI-IBS compared to those without the condition [24].

3. Host–Pathogen Interactions in *Campylobacter* Infections: Understanding the Link to PI-IBS

Exploring the nuanced interactions between the host and pathogen is essential for unraveling the complexities of *C. jejuni* infections and their progression to PI-IBS. Since

Campylobacter was first recognized as a pathogenic culprit, its species, which is responsible for infections in both animals and humans, have been classified through phylogenetic analyses, with the startling disclosure that human disease can be initiated by ingesting as few as 500–800 of these highly pathogenic bacteria, and cases have been documented where even 100 cells or fewer prompted infections, emphasizing the organism's formidable infectivity and the critical need for rigorous food safety and hygiene measures to thwart *Campylobacter*-induced illnesses [11]. A significant adverse outcome following infection with *C. jejuni* is the onset of irritable bowel syndrome (IBS), initially identified by Spiller and associates in 2000, which is linked to intensified activation of enteroendocrine cells (EC) [1]. The recognition of irritable bowel syndrome (IBS) following acute infectious enteritis has been extensively documented across numerous studies [17,19]. However, it was not until 1962 that the notion of PI-IBS was formally introduced into the scientific literature [17,19]. This foundational concept was first brought to light by Chaudhary and Truelove in 1962, marking a pivotal moment in understanding PI-IBS. In 2009, PI-IBS was outlined as the acute emergence of IBS symptoms in patients who had not previously been diagnosed with IBS, occurring directly after an acute episode characterized by at least two symptoms among fever, vomiting, diarrhea or a confirmed bacterial infection through stool culture analysis [25]. Since this initial recognition, a wealth of epidemiological evidence has emerged, elucidating the link between PI-IBS and a diverse array of pathogens, encompassing bacteria, protozoa and viruses. Research has identified several key pathogens responsible for PI-IBS, including *Shigella* spp., pathogenic *E. coli*, *Salmonella* spp., *Clostridium* spp., *C. jejuni*, *Giardia duodenalis*, *Trichinella britovi*, rotavirus and norovirus, as well as instances where multiple pathogens act in an ensemble to trigger the condition [7,14,17,19,25]. For instance, *C. jejuni* infection leads to significant mucosal damage, including ulcerations, in contrast to viral infections, which typically cause more transient inflammation without leading to ulcerations [24]. Exposure to live *C. jejuni* or its secretory–excretory products can activate dormant virulence genes in otherwise non-invasive strains of *E. coli* [2]. Such genetic activations could directly initiate pro-inflammatory signaling within the intestinal epithelium. A compelling genomic investigation differentiated *C. jejuni* isolates from patients who developed PI-IBS from non-PI-IBS, revealing significant genetic variations contributing to disease susceptibility [9]. Variants in genes related to bacterial stress response (Cj0145_phoX), adhesion (Cj0628_CapA) and essential metabolic pathways for biotin (*Cj0308*_bioD), purine (*Cj0514*_purQ) and isoprenoid synthesis (*Cj0894c*_ispH) were notably linked to the development of PI-IBS. In vitro assays showed that isolates associated with PI-IBS exhibited higher levels of adhesion and invasion and increased secretion of the pro-inflammatory cytokines IL-8 and TNFα in colonocytes compared to strains from non-PI-IBS patients [9]. For the 22 genomic markers, a risk score was devised for predicting PI-IBS onset, prominently including markers from *Cj1631c*, identified as a putative heme oxidase gene associated with bacterial virulence. These findings spotlight the significance of specific *Campylobacter* genotypes in enhancing virulence and elevating PI-IBS risk, offering deeper insights into the intricate interactions between the host and pathogen in this condition [9].

The interaction of *C. jejuni* with intestinal cells damages the differentiated cells located at the tips of the villi and halts the cell cycle in the proliferating cells within the crypts [26]. This disruption leads to villous atrophy, culminating in the hallmark presentation of bloody diarrhea associated with the infection. In vivo studies have speculated on the impact of *Campylobacter* cytolethal distending toxin (*CdtB*) and potential mechanisms such as small intestinal bacterial overgrowth and the depletion of interstitial cells of Cajal (ICCs) [27,28]. The cytotoxic effects of *CdtB*, which reduce ICCs and alter the gut microbiome, may explain the short-term pathophysiology of PI-IBS. ICCs play a crucial role in regulating gastrointestinal motility by generating and propagating electrical slow waves, and they facilitate communication between the autonomic nervous system and smooth muscle cells (Table 1) [27].

Table 1. Diagnostic criteria for PI-IBS based on Rome IV.

1.	Recurrent abdominal pain, on average at least 1 d/wk in the last 3 mo, with symptom onset at least 6 mo before diagnosis, associated with 2 or more of the following: • Defecation • Change in stool frequency • Change in stool form (appearance)
2.	Should not meet IBS criteria before the onset of acute illness
3.	Symptoms appear either immediately after resolution of acute infectious gastroenteritis or within 30 d of resolution of acute symptoms
4.	Infectious gastroenteritis characterized by one of the following: • Positive stool culture in a symptomatic individual (preferred) • At least 2 of the following acute symptoms (when stool culture not available): • Fever • Vomiting • Diarrhea

Numerous studies have highlighted that a combination of factors, including the depletion of interstitial cells of ICCs, changes in the metabolism of enterochromaffin cells (notably in the secretion of serotonin [5-HT] and peptide YY) and an increase in activated mast cells, are implicated in abnormalities in intestinal neuro perception as well as disruptions in absorption, secretion and motility [17]. Upon mechanical or chemical activation of enterochromaffin cells, serotonin engages with receptors on various cell types, including afferent nerve fibers and enterocytes [29]. This interaction stimulates motility and the secretion of bicarbonate and chloride, as well as modulating pain perception [29]. Moreover, serotonin is implicated in promoting mucosal inflammation, as it interacts with serotonin receptors on a diverse array of leukocytes, highlighting its multifaceted role in gastrointestinal function and immune response. People diagnosed with PI-IBS display increased levels of postprandial serotonin following meals compared to healthy subjects and patients with IBS-C [30]. Additionally, a reduced serotonin turnover rate has been noted in the rectal mucosa of patients with both PI-IBS and IBS-C, evidenced by a low ratio of 5-hydroxyindoleacetic acid to 5-hydroxytryptamine (5-HT), suggesting a deficiency in serotonin recycling [27,30]. The synthesis of serotonin (5-HT) is regulated by the host and gut commensals, particularly those within the spore-forming *Clostridiales* order of the *Firmicutes* phylum [27].

4. *Campylobacter jejuni*-Induced Disruptions: Intestinal Permeability, Immune Dysregulation and the Pathogenesis of PI-IBS

This section delves into the specific disruptions induced by *C. jejuni*, including increased intestinal permeability, immune system dysregulation and their consequential roles in the pathogenesis of PI-IBS. Upon attachment and invasion into human intestinal epithelial cells (IECs), *C. jejuni* manipulates the host's cytoskeletal regulation to optimize its invasive capabilities [31]. After successfully invading, *C. jejuni* is found within cytoplasmic compartments termed *Campylobacter*-containing vacuoles (CCVs) [31]. Pathogens' virulence factors can compromise the epithelial barrier and enhance intestinal permeability by activating myosin light-chain kinase, which facilitates the degradation of tight junction (TJ) proteins, disrupts actin functionality and triggers apoptosis in intestinal epithelial cells (IECs). Epithelial barrier integrity is maintained by cell-to-cell adhesion, largely governed by TJ. In the Walkerton cohort, genetic variations in the E-cadherin gene (*CDH1*) were linked to an increased risk of PI-IBS [32].

Several in vivo and in vitro studies have further revealed that disruptions in the barrier and subsequent bacterial translocation are associated with the degradation of occludin and claudin-4, reductions in zonula occludens proteins and elevated expression of myosin light-chain kinase (MLCK), which is known to mediate barrier dysfunction [10,33]. In-

testinal damage significantly compromises gut integrity, enabling both transcellular and paracellular internalization of *Campylobacter* and its progression toward underlying connective tissues [34]. This damage facilitates the movement of *Campylobacter* and triggers the translocation of luminal pathogenic bacteria, including *Salmonella*, *E. coli* [9] and *Clostridium*, into internal organ compartments [34]. The resultant breach in the intestinal barrier thus serves as a conduit for these pathogens, potentially leading to systemic infections and amplifying the inflammatory response within the gut environment. *HtrA* plays a pivotal role in safeguarding *C. jejuni* against the accumulation of denatured or improperly folded proteins in the periplasm under stress conditions [35]. Upon secretion into the extracellular space during infection, *HtrA* directly interacts with host cell surface proteins, which have been shown to exert proteolytic activity. The initial identified target of *HtrA* was the adherens junction protein and tumor suppressor, occludin, claudin-8 and E-cadherin, which *HtrA* cleaves into various fragments [36]. Additionally, a more recently identified target of *HtrA* is the tight junction protein occludin [35]. The cleavage of these key structural proteins by *HtrA* results in the transient disruption of cell-to-cell junctions within the epithelium, facilitating the transmigration of *C. jejuni* across epithelial barriers by moving between adjacent cells [35].

PI-IBS patients characterized by high fecal proteolytic activity demonstrate enhanced in vivo and ex vivo distal gut permeability, which appears to be directly proportional to the level of fecal proteolytic activity [10]. A distinct group of PI-IBS patients exhibited significantly enhanced in vivo intestinal permeability, as indicated by the lactulose–mannitol excretion ratio [27]. Longitudinal studies following bacterial gastroenteritis have demonstrated that, although increased intestinal permeability generally decreases over time, it persists in those who develop PI-IBS [27]. Some clinical studies have shown that 5 out of 10 patients with *Campylobacter*-induced PI-IBS have increased intestinal permeability [10]. Furthermore, some PI-IBS patients exhibit elevated proteinase activity along with increased intestinal permeability. Specifically, elevation in serine proteinase activity may be responsible for the heightened intestinal permeability observed in a subset of PI-IBS patients [37]. These data suggest one or more mechanisms by which *Campylobacter* infection may induce abnormal gut physiology and function, potentially explaining the symptoms frequently reported in patients with IBS-D. Additionally, robust case-control studies have shown that *Campylobacter* and other enteric infections are associated with the development of PI-IBS [4,38,39], supporting the plausibility that *Campylobacter* is a causative factor in PI-IBS. However, contrasting findings from a larger study on the Walkerton water outbreak indicated that only 16% of PI-IBS patients exhibited increased permeability [32]. This sustained increase in intestinal permeability is a precursor to low-grade immune activation. Although a baseline level of physiological inflammation is normal, research in individuals with IBS and PI-IBS has identified ongoing low-grade intestinal immune activation. Alterations in the innate immune system, particularly in mast cells and macrophages within the intestinal mucosa of PI-IBS patients, have been noted. Specifically, the increase in immune cells, including mast cells, macrophages, monocytes, T lymphocytes and intraepithelial lymphocytes, has been recorded for up to five years, tracking infection [10]. Starting from day 11 of human post-infection, B lymphocytes significantly increase the production of circulating antibodies, predominantly targeting the flagellin of *C. jejuni* as their epitope [40]. These antibodies remain detectable in circulation for up to one year following the initial infection [40]. Furthermore, colonic supernatants from PI-IBS patients hold the capacity to activate mast cells, which are recognized as key mediators of visceral hypersensitivity in IBS [10]. For instance, PI-IBS patients show a decrease in resident CD68 and calprotectin-positive macrophages compared to healthy controls [27]. Furthermore, an increase in mast cells closely associated with nerve fibers in the terminal ileum mucosa has been observed in PI-IBS patients, with studies suggesting a link between this close nerve–mast cell interaction and symptoms such as abdominal bloating and pain [27]. Substantial evidence indicates intestinal mucosa damage constitutes a major reaction to PI-IBS. Such damage is as a precursor to establishing a low-grade inflammatory state [27,41]. The increase in

permeability indicates a compromise in the normal gut barrier function, facilitating the entry of bacterial products into the lamina propria [30]. A heightened gut permeability function could further contribute to immune dysregulation and nerve hypersensitivity. The damage to nerves and subsequent nerve remodeling has the potential to influence both motility and secretion, underscoring the complex interplay of factors contributing to the pathophysiology of PI-IBS [30]. Vulnerability to infection has been associated with the composition of the microbiota. This sequence of events allows antigens to penetrate the mucosa from the lumen, initiating immune stress and producing inflammatory cytokines, furthering the cycle of inflammation and symptomatology associated with PI-IBS. A current multivariate analysis revealed an association between PI-IBS and elevated C-reactive protein (CRP) levels [18]. This finding has led to speculation that high CRP levels might play a role in developing PI-IBS by indicating more severe inflammation and potentially signaling the presence of mucosal damage. Moreover, alterations in the levels of various cytokines, such as IL-2, IL-6 and iIL-10, along with transforming growth factor beta (TGF-β), and changes in the expression of toll-like receptors (TLRs) 2, 4, 7, 8 and 9, have been reported as specific markers of a post-infectious condition [21]. The activation of cellular NF-κB signaling pathways, similar to the response elicited by other relatively benign bacteria, can be initiated by interacting pathogen-associated molecular patterns (PAMPs) with cellular TLR [36]. This mechanism may reflect a broader, more generalized tissue immune response to infection, indicating a commonality in the host's defense strategy against a diverse array of microbial pathogens.

Immunohistochemical analyses of mucosal samples from PI-IBS patients have revealed the antigen-induced secretion of interleukins IL-4, IL-8, IL-1β and IL-22 by epithelial cells [1,30]. Despite IL-4 typically being regarded as anti-inflammatory, it has been hypothesized that, in the context of PI-IBS, IL-4 may facilitate antigen endocytosis, leading to prolonged immune activation [17]. A recent examination differentiated between two main types of γδ T cells: Vδ1 γδ T cells, primarily located in local mucosal tissue, and Vδ2 γδ T cells, which are predominant in peripheral blood [42]. Interestingly, in patients with PI-IBS, Vδ1 γδ T cells, rather than Vδ2 γδ T cells, were found to be dominant in both peripheral blood and colonic tissues. Additionally, these Vδ1 γδ T cells displayed an enhanced capacity for proliferation, activation and production of IL-17 following IL-23 stimulation in PI-IBS patients [42]. These findings indicate that Vδ1 γδ T cells are the primary γδ T cell subtype in both peripheral and intestinal tissues of PI-IBS patients and are significant producers of IL-17, suggesting their potential as novel therapeutic targets for managing PI-IBS.

Further investigations have identified increased concentrations of IFN-γ, IL-10 and TNF-α alongside decreased levels of IL-10 and IL-13 in the mucosa of individuals with PI-IBS, highlighting an imbalance between anti-inflammatory and pro-inflammatory mediators [17]. This disequilibrium may exacerbate TJ dysfunction and epithelial permeability, perpetuating a harmful cycle. Others have identified a greater prevalence of $CD8^+$ T cells and resident macrophages in the intestinal mucosa of PI-IBS patients with a history of *Shigella* infection than in those with non-IBS infection [43]. This persistent elevation in CD8+ T cells and macrophages, primed for activation by specific antigens, is believed to contribute to the ongoing gut inflammation and distress state. In a PI-IBS murine model induced by *Trichinella spiralis*, investigators noted that dendritic cells within the lamina propria displayed heightened expression of co-stimulatory molecules and an augmented capacity to stimulate and attach to $CD4^+$ T cells, a phenomenon closely linked with sustained visceral hypersensitivity [44].

Individuals diagnosed with PI-IBS exhibit distinct gastrointestinal changes when compared to those with sporadic IBS [41]. One earlier comparative analysis showed two distinct differences between cases of PI-IBS following *Campylobacter* infection and those attributed to other pathogens like *Salmonella* and *Shigella* [45]. The most significant change was a 3.71-fold increase in IgG antibodies targeting vinculin, a human cell adhesion protein, among individuals previously infected with *Campylobacter* spp. This correlation between anti-vinculin antibodies and post-*Campylobacter* IBS is particularly compelling. Previous

research has linked the internalization of *C. jejuni* with vinculin, and emerging data suggest that anti-vinculin antibodies could act as a biomarker for IBS [45]. Consistency in the relationship between *Campylobacter* infections and the presence of anti-vinculin antibodies has been observed across different studies, including an evaluation of military personnel conducted in 2015 [28]. This study detected elevated levels of anti-vinculin antibodies in individuals who developed PI-IBS following a *Campylobacter* infection. Similarly, an earlier study reported increased anti-*CdtB* and anti-vinculin antibodies in patients with PI-IBS [28].

Likewise, PI-IBS cases of post-*Shigella* gastroenteritis exhibited a heightened count of mast cells in the terminal ileum. These cells emit mediators like histamine, IL-1β, IL-6 and TNF-α, which have the potential to activate or sensitize visceral nociceptors, thereby contributing to the abdominal discomfort and pain characteristic of PI-IBS [7]. Notably, an excessive release of IL-8, triggered by the body's recognition of pathogen-associated LOS, marks the pathogenesis of *Campylobacter* infections [46].

Additional mediators that could play a role include tumor necrosis factor-alpha (TNF-α) and interferon-gamma (interferon-γ) [47]. Typically, inflammation is linked to activating cyclooxygenase-2 (COX-2) enzymes and the subsequent increase in prostaglandins, which sensitizes visceral afferents, stimulating secretion and promoting intestinal motility [47]. In cases of PI-IBS via *C. jejuni* infection, the uptake of macromolecules through endocytosis increases, resulting in low-grade inflammation characterized by the release of pro-inflammatory cytokines [1]. Enhanced macromolecule permeability was evidenced by a temperature-dependent augmentation in horseradish peroxidase (HRP) absorption within the PI-IBS group. This phenomenon indicates the activation of the transcytotic pathway in colonic mucosa functional assessments of PI-IBS patients, shown by increased HRP transport at 37 °C but not at 12 °C causing the immune activation [48]. Such macromolecule uptake signifies the translocation of antigens from the intestinal lumen to the mucosa, presenting significant pathological implications for mucosal balance when this process is prompted [1]. Subsequent exposures to *C. jejuni* have been shown to induce elevated levels of ileal β-defensin 2, IL-8, TLR-4 and β-defensin 6, persisting long after the initial infection has resolved [28]. This persistent inflammatory response suggests that low-grade inflammation may play an integral role in pathogenesis. Peters and colleagues demonstrated in vitro that *Campylobacter* strains linked to PI-IBS exhibit significantly higher levels of invasion and attachment to T84 cells than strains not associated with PI-IBS [9]. This suggests that individuals with higher exposure to particular *Campylobacter* strains might be at an increased risk of developing PI-IBS, indicating the presence of a biological gradient where the extent of exposure to pathogenic strains correlates with the likelihood of PI-IBS development.

Notably, inflammation and mucosal damage are significant markers in patients who have experienced prior infections, such as with *C. jejuni*. This observation is supported by a study which revealed a heightened presence of macrophages and T lymphocytes in consecutive intestinal biopsies [41]. In the context of IBS, it is posited that infection by *C. jejuni* may precipitate the generation of autoantibodies, for instance, against vinculin [1]. As a PI-IBS rat model demonstrated, these autoantibodies can directly impact intestinal functions, leading to symptoms such as diarrhea resulting from destabilized TJs [1]. An additional pathway in PI-IBS could involve the discharge of histamine from mast cells situated in close proximity to nerve endings [1]. In PI-IBS subjects, there have been reports of activated mast cells around nerve fibers in the ileum [10]. These mast cells release tryptase, which can stimulate neuronal excitation by cleaving the protease-activated receptor-2 (PAR-2) correlated with heightened permeability and increased visceral sensitivity. Notably, neuronal activation in the submucosa was significantly elevated in PI-IBS patients compared to healthy individuals, persisting even two years after the resolution of the initial infectious event [10]. The emission of histamine or prostaglandin E2 (PGE-2), coupled with a low-grade pro-inflammatory response, might contribute to visceral hypersensitivity and disruptions in intestinal barrier integrity, such as leaky gut syndrome. These mediators may also be responsible for hyperalgesia, a critical IBS symptom that warrants further

investigation within the realm of PI-IBS research. Furthermore, elevated IL-1 expression in rectal specimens of PI-IBS patients underscores the pathophysiological significance of inflammation in developing PI-IBS [41]. The augmented presence of immune cells and intensified cytokine signaling are pivotal in the pathophysiological underpinnings of PI-IBS. Research has identified an upsurge in IL-1β mRNA expression within rectal tissue biopsies following acute infectious gastroenteritis (AGE) [7,24]. Specifically, individuals who experienced *Campylobacter* enteritis displayed an increase in enterochromaffin cells, intraepithelial lymphocytes and intestinal permeability, persisting for up to a year post-infection [7]. Disruption of the epithelial barrier often coincides with accentuated hypersensitivity in IBS, exacerbating abdominal pain symptoms within this condition [48] Prior clinical examination has demonstrated that patients with IBS-D and PI-IBS exhibit heightened permeability in the small intestine to 339 Da ^{51}-Cr-ethylenediaminetetraacetic acid (EDTA), in contrast to control subjects, which links the acute barrier disruption resulting from infection and the persistence of this barrier defect, aligning with the leaky gut concept, to the emergence of IBS symptoms [48].

Previous authors identified a notable increase in the frequency of activated/memory CD45^{+} þ T cells, alongside a decline in the frequency of B cells within the colonic lamina propria [27]. Moreover, they observed that the frequencies of lymphocytes from the epithelial lining and the lamina propria were inversely correlated with mucosal microbial diversity [27]. This insight indicates a possible dynamic interaction between the gut microbiota and immune system activation in PI-IBS, highlighting the complex interplay between microbial populations and the host's immune response in the pathology of this condition. Furthermore, others have discovered that increased *Bacteroides* and *Escherichia* within the gut microbiota of poultry slaughterhouse workers heightened their vulnerability to pathogenic bacteria [17,49]. This observation suggests that either primary or secondary disruptions in the intestinal microbiome play significant roles in the genesis of PI-IBS, emphasizing the complex interplay between host immune responses and microbial populations in its development. Understanding the pathogens responsible for acute gastroenteritis and identifying the risk factors for developing PI-IBS hold critical clinical significance, given the absence of a definitive cure for IBS, emphasizing the importance of risk factor knowledge for PI-IBS prevention.

5. *C. jejuni*'s Role in Shaping Microbiota and Contributing to PI-IBS

Our understanding of the human gut microbiome's influence on health and well-being is rapidly expanding. Such microbial communities are crucial in adaptive host metabolism, physiology, nutrition and immune function [50]. The diverse population of gut resident microbes, comprising bacteria, fungi, protozoa, viruses and their metabolic by-products, inhabit both the surface and interior of the host [51]. These gut microbes play crucial roles in food digestion, fermentation and providing energy to the intestinal tract [52]. Metabolic components, including short-chain fatty acids, bile acids, vitamins and amino acids, are generated throughout physiological processes. The microbes, alongside their metabolites, significantly contribute to maintaining gastrointestinal immune homeostasis and influencing resistance to pathogen invasion [53]. Conversely, disturbances in the gut microbiota, known as dysbiosis, have been associated with various pathological and systemic diseases. Although the precise definition of dysbiosis remains controversial, it is clear that disruptions to the gut microbiota can have significant negative consequences [54,55]. The epithelial lining within the human digestive tract serves as a formidable barrier, defending the host from the invasion of microorganisms, including the resident microbiota [56]. Numerous gastrointestinal microbial pathogens, such as *Campylobacter*, invade cells and compromise the integrity of the epithelial barrier. This invasive behavior is succeeded by transcellular or paracellular migration through the epithelial layer. A recent investigation revealed that patients with PI-IBS exhibit specific patterns of dysbiosis, distinguishing their microbial profiles from those typically observed in individuals with IBS [27]. Using qPCR assays to analyze microbiota changes in patients with PI-IBS and those with IBS-D

revealed comparable microbial compositions between these groups [57]. This similarity in microbiota findings hints at a potentially analogous pathophysiological mechanism underlying both conditions, suggesting that disturbances in gut microbiota associated with PI-IBS might also play a critical role in developing and manifesting IBS-D symptoms [57]. Long alterations in the small bowel microbiota can occur following a *C. jejuni* infection, including a reduction in the levels of *Methanobrevibacter smithii*, the predominant archaeal methanogen in humans [58]. This decrease in the *M. smithii* population is a biomarker for gastrointestinal (GI) diseases such as IBS. Notably, the load of *M. smithii* is typically higher in healthy adults than in those suffering from chronic gastrointestinal conditions [58]. A recent analysis uncovered a connection between specific microbial markers in PI-IBS and the host's amino acids. Hydrogen sulfide, a by-product of the interaction between digestive microbiota and protein metabolism, is a detrimental compound [21]. This gas can damage the intestinal epithelium by acting as a signaling molecule and leads to the formation of tetrathionate, which can facilitate the growth and proliferation of *Salmonella*, including other pathogens [21,33].

Changes in the intestinal bacterial microbiota are linked with several chronic gastrointestinal disorders, encompassing PI-IBS, idiopathic chronic diarrhea and microscopic colitis in humans, underscoring the critical role of gut microbiome composition in the pathogenesis and symptomatology of these conditions [29]. The gut microbiome demonstrates a robust resilience to various external stressors, including gastrointestinal infections, exposure to antibiotics, xenobiotics and shifts in diet. For instance, *Bacteroidetes*, *Firmicutes* and *Actinobacteria* typically represent the predominant microbial taxa within the gut [10]. Nonetheless, during infectious enteritis and its sequelae, as seen in PI-IBS, there is a notable perturbation in the core microbiome composition. Specifically, individuals with PI-IBS exhibited a 12-fold increase in the abundance of Bacteroidetes and a substantial decrease of 35 fold in *Firmicutes* and *Clostridiales* compared to healthy subjects, highlighting the significant microbial shifts associated with PI-IBS development [10,59].

The effects of the intestinal microbiota on human health and disease is well recognized, and though research in the last decade has not pinpointed a direct cause-and-effect relationship with a singular pathogen, numerous studies have indicated that individuals with IBD or IBS tend to have a lower presence of protective, anti-inflammatory bacteria alongside a higher prevalence of aggressive, pro-inflammatory bacteria [2]. Notably, levels of *Faecalibacterium prausnitzii*, belonging to the *Firmicutes* phylum, considered a probiotic bacterium and known for its anti-inflammatory properties, have been found to be diminished in cases of IBD [2,60]. On the other hand, Proteobacteria, especially the abundance of *E. coli*, are notably higher in patients with Crohn's disease, illustrating the significant but complex role of gut microbiota composition in developing and exacerbating these conditions [2]. In PI-IBS, there is a noted increase in the *Firmicutes*–*Bacteroides* ratio alongside a reduction in microbial diversity [30]. Such shifts can significantly alter the luminal environment through changes in the composition of bile acids, bile salts and proteases, leading to bile acid malabsorption in PI-IBS patients, a known trigger for diarrhea [10]. Proteases play a crucial role in mediating intestinal barrier dysfunction and visceral hypersensitivity, which are strongly linked to IBS. Elevated levels of fecal proteolytic activity were correlated with increased symptom severity and reduced microbial diversity in patients with *C. jejuni*-induced PI-IBS [10]. Commensal microbes can synthesize β-glucuronidases, inhibiting the host's proteolytic activity and consequently protecting the intestinal epithelium [61]. This observation has led to the hypothesis that a reduction in microbial β-glucuronidase enzymatic activity could play a role in developing IBS.

Additionally, enhanced density of enteroendocrine cells and a subsequent increased release of serotonin may impact intestinal motility. For up to a year following the initial *Campylobacter* infection, individuals who develop PI-IBS can exhibit an acute rise in the number of enteroendocrine cells and T lymphocytes, along with increased gut permeability [58]. The cytotoxic impact of *CdtB*, produced by *C. jejuni*, can reduce the number of ICCs and induce alterations in the gut microbiome, explaining the pathophysiology of PI-IBS in the

initial stages following infection [28]. However, the enduring nature of PI-IBS symptoms, persisting for as long as eight years post-infection for some patients, remains challenging to elucidate solely based on these mechanisms. Additionally, the phenomenon where some individuals experience a symptom-free interval between the initial *Campylobacter* infection and the subsequent development of IBS symptoms adds another layer of complexity. This suggests that additional factors, including immune system modulation, genetic predisposition or further changes in the gut microbiota over time, might contribute to prolonged and delayed symptomatology in some cases of post-*Campylobacter* post-sequelae [28].

In an intriguing study with experimental PI-IBS rats, the administration of *Lactobacillus rhamnosus* GG supernatant increased the expression of serotonin reuptake transporter (SERT) messenger RNA and protein within the colon [62]. Through probiotic intervention, microbial modulation can rectify the serotonergic imbalance observed in PI-IBS. Recent clinical research has uncovered that patients with constipation-predominant IBS-C exhibit a correlation between fecal concentrations of *Lactobacillus* and *Bifidobacterium* and levels of interleukin IL-10, an anti-inflammatory cytokine [63]. Conversely, in patients with diarrhea-predominant IBS-D, there appears to be a connection between the presence of both Gram-positive and Gram-negative bacteria and the levels of C-X-C motif chemokine ligand 11, a chemokine involved in inflammatory responses.

Tkach and colleagues recently compared the efficacy of fecal microbiota transplantation (FMT) against traditional pharmacotherapy in patients with PI-IBS, and FMT demonstrated notable effectiveness, safety and tolerability [16]. PI-IBS, often triggered by infections leading to gut microbiota disturbances, is typically managed initially with non-absorbable antibiotics, like rifaximin-α, or probiotics to amend the microbiota imbalance [16]. However, this research highlighted the superior outcomes of a single FMT session, benefiting over 60% of PI-IBS patients—a success rate aligning with a standard 4-week pharmacotherapy regimen. The study also revealed a significant presence of potentially pathogenic bacteria such as *Staphylococci*, *Streptococci* and various strains of *E. coli*, *Klebsiella* spp., *Proteus* spp. and *Enterobacter* spp. in PI-IBS patients' feces. Notably, both treatment groups exhibited a marked reduction in intestinal dysbiosis frequency and severity one month post-treatment, with the FMT group showing significantly better outcomes. Furthermore, FMT led to a favorable shift in the gut microbiome composition, notably increasing *Firmicutes* and *Bacteroidetes* levels, which normalized solely in FMT-treated patients. This group also saw normalization in Actinobacteria levels and other conditionally pathogenic flora, unlike the standard care group, which only demonstrated a tendency toward such changes. The exceptional microbiological efficiency of FMT in PI-IBS patients might be attributed to the altered metabolic activity of the gut microbiota stimulated by the high concentration of regulatory molecules and metabolites in the donor feces. This metabolic shift notably boosts the levels of *Firmicutes* and *Bacteroidetes* and the production of short-chain fatty acids, especially butyrate, contributing to therapeutic benefits [16]. Otherwise, a decrease in anaerobic metabolites, notably short-chain fatty acids and secondary bile acids, increases the colonic lumen's pH [64]. This shift in pH can compromise colonization resistance, a mechanism that helps to prevent the overgrowth of harmful microbes in the gut. Consequently, this altered environment may facilitate the proliferation of pathogens and members of the *Proteobacteria* phylum, including facultative anaerobes like *Enterobacteriaceae* [64].

Specifically, in poultry abattoir workers, who are at a higher risk of infection with *Campylobacter*, an elevation in bacteria from the *Bacteroidetes* phylum (i.e., *Bacteroides* and *Prevotella*) was noted—a characteristic similarly observed in PI-IBS patients but not in those with IBS, who typically show an increased ratio of *Firmicutes* to *Bacteroidetes* [10,27,65]. On the other hand, travelers who develop infectious diarrhea exhibit low levels of *Bacteroidetes*, hinting at a potential protective role of this phylum. Interestingly, the likelihood of developing PI-IBS following traveler's diarrhea is two times lower than after other forms of gastroenteritis, suggesting differential impacts of microbial composition on the risk and nature of gastrointestinal infections [27]. Furthermore, previous authors have noted the

depletion of the *Subdoligranulum variable* in PI-IBS, a butyrate-producing bacterium, which has been shown to induce the production of interleukin IL-1β, a proinflammatory cytokine, in biopsy samples from PI-IBS patients but not in samples from healthy individuals [27,66]. Conclusively, this highlights a unique response of the host's immune system to a normally symbiotic microbe under pathological conditions, suggesting a nuanced and dual-natured interaction with the microbiota.

6. Diarrhea to Disorder: Tracing the Path from *Campylobacter jejuni* Infection to PI-IBS

PI-IBS manifests as a disturbance in the normal functioning of the gastrointestinal system, marked by abdominal discomfort, bloating and altered defecation patterns, such as diarrhea and constipation [2]. This section traces the trajectory from the initial onset of diarrhea following *C. jejuni* infection to establishing PI-IBS, exploring the critical transitions that convert an acute gastrointestinal disturbance from the clinical findings. On the other hand, IBD, which includes conditions like Crohn's disease and ulcerative colitis, is distinguished by pronounced inflammation within the digestive tract [2]. This inflammation stems from a complex interplay of genetic predispositions, immune system responses and environmental factors, among which microbial communities play an important but not fully elucidated role. Notably, although IBS and IBD are separate gastrointestinal entities, there exists an intriguing overlap where a subset of individuals with IBD in clinical remission report symptoms characteristic of IBS. Furthermore, in both conditions, episodes following infections have been observed to precipitate disease flare-ups, underscoring a potential common pathway in their pathogenesis linked to post-infectious activation [2]. The association between IBS, microscopic colitis and hyperplasia of enterochromaffin cells is well documented, pinpointing the release of serotonin from these cells as a key factor disrupting normal intestinal movements and altered serotonin pathways, causing increased sensitivity, altered motility, inflammation and enhanced permeability of the gut, characteristic of PI-IBS [1,29]. The inflammatory condition is reportedly marked by a heightened presence of T-lymphocytes and mast cells, an upsurge in pro-inflammatory cytokine expression and the latter situated near enteric nerve fibers within the gastrointestinal mucosa of affected individuals [67]. The observation indicates that exposure to pathogenic entities disrupting intestinal barrier integrity and altering neuromuscular functionality initiates persistent inflammation, thereby perpetuating the symptoms associated with irritable bowel syndrome. Mucosal inflammation observed in IBS patients frequently correlates with a prior episode of infectious gastroenteritis caused by bacteria, parasites or viruses, leading to what is known as PI-IBS [68]. This connection is reinforced by evidence from various studies, including a meta-analysis highlighting a roughly seven-fold increase in the risk of developing PI-IBS [20,69].

In the context of acute campylobacteriosis, the primary mechanisms causing diarrhea include sodium malabsorption and a compromised epithelial ion barrier, leading to a condition known as leak-flux diarrhea [70,71]. The findings explained that diarrhea associated with human campylobacteriosis stems from sodium malabsorption triggered by the invasion of *C. jejuni*. This process is propelled by a cytokine storm mediated by LOS, initiated by the activated cells of the innate immune system [70]. Comprehensive gene expression analyses have identified that pathogenic LOS is the principal regulator of this inflammatory cascade. This regulation leads to the inhibition of sodium channels and precipitates a series of detrimental outcomes, including the compromise of intestinal epithelial barrier integrity, the induction of apoptosis and extensive tissue destruction [70].

Additionally, transporters are involved in the absorption of Na^+ and Cl^-, such as the epithelial sodium channel (ENaC), sodium-hydrogen antiporter 3 (NHE3) and down-regulation in adenoma (DRA), due to their susceptibility to modulation by pro-inflammatory cytokines, a phenomenon also observed in cases of campylobacteriosis [1]. This insight supports the plausible hypothesis that active ion transport mechanisms may undergo up- or down-regulation during and following infectious enteritis caused by *C. jejuni*, perpetuated by low-grade mucosal inflammation, which emerges as a secondary

consequence of this disruption in the epithelial barrier in PI-IBS. The primary symptom of loose stools in PI-IBS patients suggests a reduction in the duration of contact between ingesta and the absorptive surface area, potentially occurring alongside visceral hypersensitivity due to the hyperactivity of intrinsic primary afferent neurons [1]. Damage to the epithelium's cellular and paracellular components can initiate a cascade of alterations in the immune and neuromuscular systems [9]. These changes can subsequently affect gut motility and sensory perception, potentially playing a role in the onset of PI-IBS [9]. Alterations in TJ proteins leading to increased permeability could account for loose stools in PI-IBS patients, irrespective of any change in contact time. It is significant to mention that these observations represent the inaugural set of paracellular ion permeability measurements in the context of PI-IBS. Beyond the role of active ion secretion, diarrhea observed in IBS-D may also arise from a malabsorptive mechanism [48]. The ENaC is the primary sodium absorption system in the distal colon and rectum. Prior research has shown that ENaC-dependent sodium absorption is notably diminished in cases of lymphocytic colitis, contributing to diarrhea [48]. This dysfunction of ENaC points to a significant pathomechanism within the large intestine, illustrating its involvement in conditions such as ulcerative colitis and campylobacteriosis, where impaired sodium absorption plays a pivotal role in the manifestation of diarrheal symptoms [48]. Functional and expression analyses of the sigmoid colon have identified claudins (1–5 and 8), occludin and tricellulin as crucial constituents of TJ that dictate the epithelial barrier's function in the colon [48]. Recent studies have highlighted that, among these, only claudin-1, along with epithelial resistance, tended toward a reduction in IBS-D, whereas the expression levels of other strand-forming claudins remained unchanged [48].

Furthermore, the invasion of luminal bacterial antigens like LOS into the mucosal layer has been identified as a significant trigger for mucosal inflammation [1,7]. This inflammation compromises the integrity of the intestinal barrier by stimulating cytokine release, which deregulates tight junctions and fosters epithelial leaks [1,17]. Consequently, it creates a deleterious cycle, where the interplay between microbial infection and host responses exacerbates intestinal dysfunction, illustrating the possible complex pathogenesis of PI-IBS. Although the O-antigen typically associated with bacterial lipopolysaccharide (LPS) is absent in the LOS of most *C. jejuni* strains, the lipid A component of this truncated LPS molecule alone functions as a highly effective TLR-4 agonist [72]. Furthermore, sialylated forms of LOS are implicated in triggering severe manifestations of campylobacteriosis and its post-infectious complications, including GBS and PI-IBS. Therefore, the distinct components of the LOS molecule lay a foundational understanding of the varied presentations of intestinal diseases and the emergence of post-infectious sequelae in human hosts [72].

The prevailing understanding of the pathophysiological mechanisms behind PI-IBS posits that exposure to pathogenic organisms precipitates alterations in the gut microbiome [7]. PI-IBS is characterized by elevated levels of neutrophils and mast cells within the colonic mucosa, indicative of an altered immunity. Recent studies have identified that deacetylase, encoded by *C. jejuni* and akin to bacterial sirtuin (*SliP*), plays a pivotal role in activating human neutrophils during infection. This sirtuin is secreted into neutrophils, where it binds to and deacetylates the host's histones, thereby fostering neutrophil activation and the generation of neutrophil extracellular traps (NETs). These NETs have been observed to concentrate within abscess formations in colonic crypts, suggesting a targeted immune response by neutrophils to *C. jejuni* within the intestinal environment [73]. These processes are instrumental in driving the inflammation and pathology observed in campylobacteriosis. Interestingly, *SliP*'s translocation into neutrophils is facilitated by the bacterium's flagella, suggesting a sophisticated mechanism of host interaction [73]. Upon secretion, *SliP*'s association with neutrophil histones leads to diminished acetylation, directly influencing the host's epigenetic landscape. Despite the mutant strain's efficient gastrointestinal tract colonization, *SliP*'s presence is important for inducing inflammation and intestinal pathology [73], which highlights histone deacetylation by *SliP* as a novel

pathway through which *C. jejuni* elicits inflammatory responses and contributes to tissue damage during infection.

7. Mechanistic and Molecular Concepts and Their Significant Role in Disease Manifestation

Given the extensive range of virulence mechanisms, this review primarily concentrates on those factors most closely associated with the development of PI-IBS, highlighting the multifaceted nature of *Campylobacter*'s pathogenic mechanisms and its significant role in disease manifestation. Remarkably, *C. jejuni* possesses a more constrained repertoire of virulence determinants in comparison to other gastrointestinal pathogens. Contrary to the extensive arsenal of "molecular weapons" found in pathogens such as *E. coli*, *Salmonella*, *Yersinia* or *Listeria* spp., which include a variety of toxins, numerous secretion systems and effector molecules, *C. jejuni*'s weaponry of disease-promoting factors is notably modest [74]. Key virulence attributes identified in *C. jejuni* encompass capsular polysaccharides, the *CmeABC* efflux pump, cytolethal distending toxin (CDT), LOS, high-temperature requirement A (*HtrA*) protease, *CadF* adhesin and Type III and Type VI secretion systems (T3SS and T6SS), alongside mechanisms contributing to antimicrobial resistance [74,75]. In exploring the molecular underpinnings of *C. jejuni*-induced intestinal pathogenesis in humans, it is significant to recognize that extensive investigations have been conducted into the bacterial virulence and pathogenicity factors associated with campylobacteriosis but not PI-IBS. *Campylobacter* spp. possesses a complex array of virulence factors that enhance its pathogenicity. These include invasive capabilities, defense mechanisms against oxidative stress, toxin production and iron acquisition, strengthening its ability to cause disease [11]. The bacterium's capacity to enter a viable but non-culturable state, along with its proficiency in adherence and colonization, further amplifies its pathogenic potential. Moreover, the secretion of specific protein sets, translocating across host cellular barriers, and flagella-mediated motility are critical components of *Campylobacter*'s virulence arsenal, facilitating its establishment and propagation within host organisms [11].

Earlier human trials by Croft and colleagues that aimed to determine the response of bacterial pathogens to the human host identified a few genetic mechanisms pivotal for initiating infection and sustaining colonization in humans [76]. According to clinical human infection, 11 genes were correlated with acute or persistent human infections. These genes encoded functions critical for host cell invasion, bile sensing, flagella modification and other processes that could serve as potential therapeutic targets. The study pinpointed the *cipA* gene as having the most substantial link with recurrent, enduring infections. Notably, the *chuA* and *chuD* genes, responsible for haemin uptake, and *cfrA*, a gene for ferric-enterobactin uptake, were all expressed over 100-fold higher in vivo. Despite *C. jejuni*'s inability to synthesize siderophores, the *cfrA* protein facilitates the uptake of a broad spectrum of siderophores produced by other microorganisms [76]. Interestingly, *cfrA*, unlike *chuA*, is essential for chicken colonization, suggesting a significant role for microbiome-derived siderophores and *cfrA* in *C. jejuni*'s infection process in humans. Additionally, elements of the sap antimicrobial peptide resistance efflux pump, crucial for chicken colonization, displayed unique upregulation during human infections, highlighting the complex interplay between bacterial virulence factors and host-specific colonization strategies [76].

C. jejuni secretes a highly pro-inflammatory molecule, ADP-heptose, and associated heptose phosphates into its surrounding environment [77]. This molecule orchestrates a pro-inflammatory cascade mediated by NF-κB, encompassing the upregulation of genes such as CXCL8, CXCL2, TNF alpha-induced protein-2 (TNFAIP-2) and human prostaglandin-endoperoxide synthase-2 (PTGS-2) [77]. Interestingly, this inflammatory response necessitates an operational alpha kinase-1 (ALPK-1) receptor while it proceeds independently of the TLR and NOD-like receptor (NLR) signaling pathways. Furthermore, the intracellular peptidoglycan receptors NOD-1 and NOD-2, along with the NLRP-3 inflammasome, detect the intrusion of *C. jejuni* and initiate innate immune responses [77]. The discovery of

ADP-heptose as a powerful and novel pro-inflammatory agent marks the unveiling of a previously unidentified virulence factor of *C. jejuni*, which may play a significant role in developing enteritis. These findings designate ADP-heptose and its related heptose phosphates as possible important virulence determinants in *C. jejuni*, playing a crucial role in the bacterium's pathogenicity during human infections. Consequently, these compounds are recognized as significant virulence factors, contributing to acute human enteric infections by activating the ALPK1-NF-κB pro-inflammatory pathway [77].

Novel advancements in electron and confocal immunofluorescence microscopy have unveiled insightful details regarding the *HtrA*-dependent disruption of the intestinal epithelium by *C. jejuni* [78]. Investigations have demonstrated that *C. jejuni* bacteria expressing HtrA can induce substantial damage to cellular junctions, a phenomenon not replicated by either soluble purified *HtrA* or *HtrA*-containing outer-membrane vesicles (OMVs), even at concentrations significantly exceeding physiological levels [78]. The research further revealed that only those bacterial cells engaged in active protein biosynthesis can effectively cleave junctional proteins. This process precedes the paracellular transmigration of *C. jejuni* across the epithelial barrier. These disclosures highlight the compulsory role of *HtrA* in the pathogenic mechanisms employed by *C. jejuni* and provide a deeper understanding of its virulence strategies [78].

The frequency of strains possessing genes responsible for the sialylation of LOS among patients suffering from human enteric diseases appears to fluctuate between 50% and 60% [79]. Autoimmune responses in campylobacteriosis are triggered by antibodies targeting LOS from the *Campylobacter* cell wall, which cross-react with specific sugar moieties on host cell targets [80]. Moreover, particular sialylated LOS structures influence the intensity of acute campylobacteriosis and the likelihood of developing post-infectious sequelae [80]. The LOS of *C. jejuni* functions as an endotoxin, engaging the innate immune system via the activation of TLR-4 and subsequent signaling cascades, including pathways regulated by the mammalian target of rapamycin (mTOR). This interaction prompts apoptotic mechanisms within the intestinal epithelia following *C. jejuni* adhesion and invasion. Inflammation in this context is predominantly driven by cytokines such as interleukin-6 (IL-6), IFN-γ and TNF-α, outlining the complex interplay between bacterial factors and the host's immune response in the pathology of campylobacteriosis [80].

The activity of sialyltransferases (cstII) significantly contributes to the pathogenicity of *Campylobacter* by endowing its LOS with a protective shield that aids in the disruption of epithelial cells, an action reminiscent of human ganglioside-induced diarrhea [11]. The gene *wlaN* plays a crucial role in the synthesis of LPS. The *spoT* gene is pivotal for stringent response regulation, and the catalase *KatA* gene is essential for converting H_2O_2 into H_2O and O_2, offering protection against oxidative stress [11]. The genes *cj0012c* and *cj1371* also encode proteins that safeguard against reactive oxygen species. The Peb4 chaperone has emerged as another vital virulence mechanism in *Campylobacter*, facilitating the export of proteins to the outer membrane. Moreover, a suite of virulence genes, including cosR, *cj1556*, *spoT*, *ppk1*, *csrA*, *nuoK* and *cprS*, along with genes responsible for cell surface modifications (i.e., *waaF*, *pgp1* and *peb-4*), play significant roles in stress responses and cell surface modifications, respectively. These virulence-associated genes are implicated in the orchestration of different human infections, underscoring their critical roles in the bacterium's ability to cause enteric disease [11].

Conclusively bridging the gap from the asymptomatic colonization of poultry and acute disease manifestation in infected humans (involving the significant tolerance of birds, including chickens) to LPS as well as LOS has emerged as a critical factor. This tolerance is remarkably higher in birds, being one hundred times greater than that in mice and up to a million times higher than that in humans [71,72]. This disparity in LPS/LOS sensitivity may elucidate why chickens and other poultry harbor *C. jejuni* without succumbing to intestinal inflammation, serving as a primary reservoir for human infections [71,72]. Understanding this differential response to LPS/LOS between species sheds light on the epidemiological

dynamics of *C. jejuni* transmission and offers insights into the mechanisms underlying host specificity and pathogenicity.

8. Conclusions

The current review highlights emerging evidence indicating that *Campylobacter* infection can lead to PI-IBS through various mechanisms, including autoimmunity, low-grade inflammation, gastrointestinal motility changes and gut microbiome disruptions. These findings suggest a multifaceted pathophysiological process whereby the body's immune response to infection and alterations in the gut's normal function and microbial composition contribute to developing and persisting PI-IBS symptoms. In conclusion, this review comprehensively illustrates the significant role of *C. jejuni* in gastrointestinal health, particularly in developing PI-IBS. Highlighting the pathogen's escalating global incidence, its profound impact on gut microbiota and the resultant clinical challenges, this review emphasizes the need for improved epidemiological surveillance, targeted clinical strategies and a deeper understanding of pathogen–host dynamics.

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