A role for *Campylobacter jejuni*-induced enteritis in inflammatory bowel disease?

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Running title: A role for *Campylobacter* in IBD?
The inflammatory bowel diseases (IBD), Crohn’s disease and ulcerative colitis, are T cell-mediated diseases that are characterized by chronic, relapsing inflammation of the intestinal tract. The pathogenesis of IBD involves the complex interaction between the intestinal microflora, host genetic and immune factors, and environmental stimuli. Epidemiological analyses have implicated acute bacterial enteritis as one of the factors that may incite or exacerbate IBD in susceptible individuals. In this review, we examine how interactions between the common enteric pathogen *Campylobacter jejuni*, the host intestinal epithelium, and resident intestinal microflora may contribute to the pathogenesis of IBD. Recent experimental evidence indicates that *C. jejuni* may permit the translocation of normal, non-invasive, microflora via novel processes that implicate epithelial lipid rafts. This breach in intestinal barrier function may in turn prime the intestine for chronic inflammatory responses in susceptible individuals. Insights into the interactions between enteric pathogens, the host epithelia, and intestinal microflora will improve our understanding of disease processes that may initiate and/or exacerbate intestinal inflammation in IBD patients, and provide impetus for the development of new therapeutic approaches for the treatment of IBD.

Key words: *Campylobacter*, Crohn’s disease, intestinal, epithelial, inflammation, IBD
More than 1 in 1000 people in developed countries are affected by the inflammatory bowel diseases (IBD), Crohn’s disease (CD) and ulcerative colitis (UC) (22, 109). These diseases are characterized by chronic, relapsing inflammation of the intestinal tract, and the presence of activated T lymphocytes. In CD, these activated T cells are primarily of the Th1 and Th17 subsets (35, 96, 111), whereas Th2 and NK T cells predominate in UC (36, 47). IBD causes life-time morbidity and, in Canada alone, accounts for a financial burden exceeding $1.8 billion per year in economic costs (including >$700 million in direct medical costs) (22). At present there is no cure, and therapeutics are primarily aimed at suppressing inflammatory responses. Treatment with anti-TNFα antibodies has met with some success, however, its therapeutic limitations and elevated cost, and the side-effects of other conventional immunosuppressive drugs, underscore the need for novel therapeutic strategies (22).

As is the case for many chronic diseases, the pathogenesis of IBD involves the cumulative interaction of many variables; these include host immunity and genetic susceptibility, the intestinal microflora, and environmental factors (8, 66, 74, 131). The complexity of these interactions is consistent with the heterogeneous clinical manifestations of IBD, and the non-universal efficacy of currently available therapeutics. This underscores the tremendous challenges faced by clinicians and researchers in identifying the causes of IBD. Notwithstanding its multifactorial origin, accumulating evidence consistently implicates intestinal microorganisms across the global distribution of IBD.
The Role of Intestinal Microorganisms in IBD

An ever increasing number of studies indicate that chronic inflammation in IBD is driven by inappropriate and excessive mucosal immune responses towards the intestinal microflora, but the mechanisms involved remain obscure. Early reports had indicated that typical IBD may develop in a small number of people following an episode of acute dysentery (98, 127). In IBD model systems, animals develop less severe disease when raised in germ-free conditions (93, 107). Inflammation occurs more frequently in regions of the intestine that are colonized by the highest density of bacteria, and diversion of the fecal stream (27, 106) or treatment with antibiotics (63, 110, 114) may attenuate inflammation in some patients with IBD. These patients also exhibit exaggerated immune responses to their own intestinal bacterial antigens, indicating a loss of immunological tolerance towards the intestinal microflora (28, 68, 91). In addition, the association of Crohn’s disease with polymorphism of the NOD2/CARD15 gene, which acts as an intracellular sensor of bacteria-derived muramyl dipeptide (a component of Gram-positive and Gram-negative bacterial cells walls), as well as the more recently recognized role of IL23/TH17, further support that derangements of the delicate equilibrium between microbial flora and host immunity are at the core of the etiopathogenesis of IBD (25, 46). While it is generally accepted that intestinal bacteria (i.e., including normal resident or “commensal” bacteria which are comprised of taxa that can be beneficial or detrimental to varying degrees, and/or bonafide pathogens) play a role in the pathogenesis of IBD, the
specific mechanisms by which these bacteria may cause intestinal inflammation remain obscure.

At least three non-exclusive hypotheses have been proposed for the involvement of luminal bacteria in IBD; namely these include (1) the dysbiosis hypothesis; (2) the persistent infection hypothesis; and (3) the luminal antigen translocation hypothesis (Table 1).

The dysbiosis hypothesis suggests that an imbalance between "beneficial" versus "detrimental" resident intestinal bacterial species may incite chronic inflammatory responses. Endogenous microbial communities seem to differ between healthy subjects and IBD patients (32). Evidence also indicates that the biodiversity of fecal microorganisms in CD patients is globally diminished (72, 90), and in particular, there is a marked decrease in the prevalence of butyrate-producing Firmicutes, which exhibit anti-inflammatory activity within the intestine (119). The intestinal microflora of CD patients also has a higher prominence of potentially detrimental bacteria such as *Bacteroides vulgatus* (41, 104, 124), which have been shown to induce intestinal inflammation in animal models of IBD (88, 101, 102).

The persistent infection hypothesis suggests that IBD may arise as a result of persistent infection with enteric pathogens. *Mycobacterium avium* subspecies *paratuberculosis* is one of the pathogens that has been most commonly implicated in the etiopathogenesis of IBD (4). This intracellular pathogen causes chronic granulomatous colitis in cattle (i.e., Johne’s disease) that bears similar pathohistological characteristics to that of CD in humans (14). However, a direct etiological role for *Mycobacterium avium paratuberculosis* in IBD remains controversial (66). *Clostridium difficile* (21, 33, 80,
(57, 108) have also been cited as putative IBD-causing pathogens. Here again, no direct cause-to-effect relationship has yet been established between these enteric microbes and development of IBD. Studies also have implicated *Escherichia coli*, particularly adherent and invasive *E. coli* strains, which are able to invade epithelial cells and replicate within macrophages, in IBD patients, as well as in murine models of colitis, via mechanisms that remain obscure (9, 24, 75, 112). High prevalence of *E. coli* belonging to the B2+D phylogenetic group was recently reported in patients with IBD (61). Currently, supporting data for the dysbioisis and persistent pathogen hypotheses have yet to conclusively demonstrate whether the microorganisms involved are causative in nature, or whether their occurrence in IBD patients is coincidental because the disease state allows these bacteria to readily colonize the intestine. One argument possibly weighing against these hypotheses is that immunosuppressive agents (which would be expected to favor the pathogen and exacerbate disease) are often used successfully to treat IBD.

The luminal antigen translocation hypothesis suggests that defects in the intestinal barrier function and/or impaired mucosal clearance facilitates increased translocation of luminal antigens, including resident intestinal bacteria, across the intestinal barrier where they prime mucosal immune responses that may lead to the loss of immunologic tolerance towards the luminal antigens (115). In susceptible hosts, failure to down regulate these inflammatory responses promotes chronic inflammation, as the host is unable to eliminate the luminal microflora. In some experimental studies, it has been observed that epithelial barrier dysfunction may precede the onset of inflammation in IBD (69, 87, 103). Moreover, mice which express epithelial cell-specific dominant
negative E-cadherin, a pivotal element of the adherens junction, spontaneously develop histological features typical of IBD at 3 months of age (48). While these studies suggest that a loss of epithelial barrier integrity can induce inflammation in susceptible hosts, the mechanisms implicated have yet to be fully elucidated (3, 20, 65). Moreover, evidence unequivocally supporting an initiating role for loss of intestinal barrier function in IBD is still lacking.

Many of the inflammatory mediators implicated in IBD, such as TNF-α, are up-regulated in response to activation of the transcriptional regulator, NF-κB (77, 125). Consistent with a prominent role for microorganisms in the pathogenesis of IBD, several bacterial products, including lipopolysaccharide (LPS), peptidoglycan, and flagellin, are potent activators of the NF-κB pathway through their activation of microbial-associated molecular pattern recognition receptors, such as Toll-like receptors (TLRs) and NOD2 (77, 125). Altered expression of these receptors may play a fundamental role in IBD pathogenesis by affecting microbial recognition and subsequent activation of NF-κB-mediated inflammation. Polymorphic mutation of the bacterial LPS receptor, TLR4, is associated with CD and UC (31), and increased TLR4 expression has been observed in the intestinal epithelium of many IBD patients (13). It has also been recently reported that peripheral blood monocytes from IBD patients exhibit increased TLR2 expression, and this is correlated with a marked increase of TLR2-mediated TNF-α production (12). Furthermore, defects in the NOD2 / CARD15 gene significantly increase susceptibility to CD (50, 85, 25). It is thought that polymorphic mutations in NOD2, which are commonly observed in CD patients, may result in the loss or gain of NOD2 function, and could lead to either a lack of bacterial detection and elimination, or hyperactivation of immune
responses upon detection (29, 70, 84, 92, 129). In both cases, this may result in excessive inflammatory responses against bacterial residents of the intestinal tract. Thus, intestinal inflammation in IBD patients may result from deregulated bacterial recognition in combination with increased bacterial translocation, or higher mucosal densities of certain bacterial taxa.

**IBD Following Acute Pathogen-Induced Enteritis**

Consistent with a pathogenic consequence from disruptions in the homeostatic balance between microbial flora and host intestine, acute microbial infections may directly be responsible for relapse in IBD (130). As this aspect of IBD seems to be conserved across the global distribution of the disease, the possible pathogenic role for ubiquitous microbial products in IBD needs to be investigated.

Early reports indicated that IBD develops in a small number of people following an episode of acute bacterial enteritis (45, 57, 80, 83, 121, 130). Similar processes of post-infectious intestinal inflammation, and symptoms of irritable bowel syndrome, have also been reported after various enteric viral infections (39, 59, 60), or after parasitic infection with *Entamoeba histolytica* (15, 98, 100) or the globally distributed Protozoan enteropathogen *Giardia duodenalis* (11, 23). Table 2 summarizes specific bacterial, parasitic, and viral pathogens that have been implicated in IBD, and the proposed mechanisms by which they may contribute to IBD pathogenesis.

Among the pathogens recently implicated in IBD pathogenesis are *Campylobacter* and *Salmonella* (38), which are the two most common causes of human bacterial enteritis.
A more recent study using cohorts of over 13,000 infected and 26,000 control patients even more convincingly established a role for *Campylobacter* or *Salmonella* acute gastroenteritis in the development and relapse of IBD (44). Results from another study also indicate that upon *Salmonella* infection, early transepithelial bacterial sampling and migration of dendritic cells into the gut lumen may represent early mechanisms whereby acute enteritis by common pathogens may contribute to the development of symptoms in IBD (2). Together, and consistent with a recent editorial article in Gastroenterology (58), these observations demonstrate that research is needed to better understand how, in susceptible patients, acute infection with common and ubiquitous microorganisms such as *Campylobacter spp.* or *Salmonella spp.* may represent a pivotal event that sets the IBD process of inappropriate intestinal immune response in motion. Human infections with these pathogens are typically self-limiting and as such, the host generally eliminates the offending pathogen from the intestine. However, these infectious agents, while not acting as the etiologic chronic inflammatory stimulus in IBD, appear to initiate and/or exacerbate inflammation in patients with the IBD genetic background. In the following paragraphs, this review examines mechanisms whereby the common enteric pathogen, *Campylobacter jejuni*, disrupts intestinal epithelial structure and function, thereby permitting the translocation of luminal material, including resident intestinal bacteria, into the sub-epithelial compartment. This in turn may prime the intestine for subsequent chronic inflammatory responses in susceptible hosts. A better understanding of these processes will help identify novel therapeutic targets in IBD.
Campylobacter jejuni and Inflammatory Disorders of the Bowel

C. jejuni is the most prevalent causes of human bacterial enteritis in North America (99). Chickens (43) and livestock animals such as cattle (52-54) and pigs (89) serve as reservoirs for C. jejuni, which may be transmitted to humans via contaminated food or water (34, 62). Infected humans exhibit a range of symptoms varying from mild to severe diarrhea, and histological examination of affected intestinal tissues commonly reveals infiltration of neutrophils into the lamina propria (128).

While distinct from IBD, Irritable Bowel Syndrome (IBS) is another poorly understood chronic disorder of the intestine that was recently linked to post-infectious events. Indeed, campylobacteriosis has been recognized as one of the most common risk factors for post-infectious IBS. In May 2000, the municipal water supply of Walkerton, Ontario (Canada) was contaminated with livestock waste containing E. coli O157:H7 and Campylobacter species. Subsequent waterborne infections caused acute enteritis in more than 2300 people, of whom more that 36% subsequently developed post-infectious IBS (compared to 10% of subjects without gastroenteritis) (73). As mentioned previously, a small number of people may also develop IBD following an episode of acute campylobacteriosis (38, 44). The mechanisms by which this pathogen incites inflammatory disorders in the bowel remain obscure; however, there is a purported link between post-infectious IBS and IBD that is centered on the loss of intestinal epithelial barrier function and failure to downregulate inflammation following intestinal epithelial injury (120).
Enteric pathogens can damage the epithelium and disrupt intestinal barrier function via a number of pathological mechanisms that include inducing host cell death, targeting epithelial tight and adherens junctions, and causing inflammation-mediated damage (86). With respect to \textit{C. jejuni}, cellular damage appears to be largely due to cytotoxic effects and/or host-cell invasion (105, 128). According to genome sequence analysis, the only known toxin produced by \textit{C. jejuni} is cytolethal distending toxin (CDT), a DNase-like toxin produced by several species of bacteria. This toxin causes cell cycle arrest (132) and ultimately apoptotic death of lymphocytes and monocytes (49), and non-apoptotic death of endothelial cells (7). Recent evidence indicates that \textit{C. jejuni} causes non-apoptotic death (i.e., oncosis) of human intestinal epithelial cells, in a CDT-independent manner (55).

Invasion of the mucosa appears to be one of the primary mechanisms through which \textit{C. jejuni} causes intestinal injury. The invasive ability of \textit{C. jejuni} is strain- and host cell-type-dependent (55, 133), and invasion is associated with non-apoptotic death of human colonic epithelial cells (6, 55). In many cases, cell death (as a result of microbial or inflammatory stimulation, or exposure to drugs) may result in a loss of intestinal barrier function (1, 17, 18, 42, 122). Some studies have shown that invasion of epithelia by certain strains of \textit{C. jejuni} is associated with increased epithelial permeability (6, 64, 133). However, it has yet to be conclusively determined whether barrier dysfunction is a consequence of epithelial damage associated with increased cell death, or is due to the
targeting of the epithelial tight junctions, as has been recently observed for this pathogen (16, 64, 67).

Campylobacter jejuni Promotes Intestinal Translocation of Commensal Bacteria:
Potential Implications for IBD

Two recent studies have demonstrated that *C. jejuni*-mediated disruption of the intestinal epithelial structure and function results in the translocation of non-invasive bacteria across the epithelium. These two studies utilized different *C. jejuni* strains to assess *C. jejuni*-mediated translocation of non-invasive *E. coli*. Consistent with the ability of *C. jejuni* to interact with epithelial cells in a strain-dependent fashion, two distinct mechanisms of bacterial translocation were observed. Namely, *C. jejuni* RM1221 induced translocation of non-invasive bacteria across the epithelium via a paracellular pathway (64), whereas *C. jejuni* 81-176 induced bacterial translocation through a transcellular mechanism (56).

In the first study, *C. jejuni* RM1221, a strain isolated from chickens, caused increased epithelial permeability, disruption of the tight junctional protein, claudin-4, and translocation of non-invasive *E. coli, in vivo* as well as *in vitro* (64) (Fig. 1A). This is in agreement with other recent studies demonstrating that *C. jejuni* targets the tight junctions to subvert the epithelial barrier (16, 67). In such a manner, *C. jejuni* while facilitating its own dissemination by disrupting tight junctional integrity, may inadvertently ‘open the gate’ for resident intestinal bacteria to translocate across the intestinal epithelial barrier via a paracellular route. *C. jejuni* RM1221-mediated *E. coli*
translocation was prevented by epidermal growth factor (EGF) (64), a gastrointestinal peptide that is well known for its broad mitogenic bioactivities and its ability to promote epithelial differentiation (5, 94, 95). EGF also up-regulates the key tight junctional proteins claudin-4 and zonula occludens-1, and restores tight junctional integrity (10, 117). Thus it is plausible that EGF treatment prevented *C. jejuni*-mediated *E. coli* translocation by regulating paracellular permeability.

While tight junctions serve to restrict paracellular translocation of luminal bacteria, they also maintain cellular polarity by confining the distribution of membrane proteins between the apical and basolateral cell membranes (116). Cellular polarity plays a central role in allowing the host to discriminate between pathogens and commensal bacteria. For example, TLR5, a pattern recognition receptor for bacterial flagellin, is generally localized to the basolateral side of enterocytes, so that only bacteria that translocate across the epithelium (i.e., primarily pathogens) are detected (40). More research is needed to clearly determine whether disruption of epithelial tight junctions by enteric pathogens, such as *C. jejuni*, may promote relocation of pathogen recognition receptors to the apical surface and thereby permit luminal material, including commensal bacteria and/or their products, to activate the receptors. Indeed, enteric pathogens that disrupt tight junctions such as enteropathogenic *E. coli* and *Yersinia pseudotuberculosis* also utilize this mechanism to relocate basolateral bacterial adhesion receptors to the apical membrane in order to facilitate their own epithelial adhesion and invasion (76, 79).

Another study demonstrating that translocation of non-invasive bacteria is increased in *C. jejuni*-infected human intestinal epithelia, used the well-characterized human clinical *C. jejuni* isolate 81-176 (56). In this study, *C. jejuni* induced rapid translocation
of non-invasive *E. coli* across human colonic epithelial monolayers via a transcellular pathway. Indeed, *E. coli* translocation occurred across an intact barrier in the absence of increased paracellular permeability, and evidence indicated that this involved a novel lipid raft-dependent endocytic mechanism (56). Although invasive pathogens can ‘shuttle’ other, non-invasive, bacteria into epithelial cells (39), *C. jejuni* invasion was not required, as an invasion-defective mutant of *C. jejuni* 81-176, and other non-invasive clinical isolates of *C. jejuni* and *C. fetus* also induced *E. coli* translocation. Figure 1 summarizes hypothetical pathways through which acute *C. jejuni* enteritis may contribute to the development and/or exacerbation of symptoms in IBD.

Other studies have observed that commensal bacteria are internalized and translocate across the intestinal epithelium via a transcellular route during periods of inflammatory and metabolic stress (19, 81). *C. jejuni*-infected epithelial cells also exhibit swollen mitochondria, loss of mitochondrial transmembrane potential, and ATP depletion, all indicative of metabolic stress (26, 37, 51, 55, 82). Consistent with a role for cellular stress in IBD, it has also been observed that enterocytes of IBD patients display elevated transcellular antigen transport (97, 113, 118), and occasionally contain intracellular bacteria (124). This evidence suggests that *C. jejuni* may play a role in the pathogenesis of IBD by promoting the internalization and translocation of commensal bacteria, at least in part, via stress-related pathways that have yet to be identified.

Normally, recognition of internalized commensal bacteria by cytosolic receptors such as NOD2 would lead to appropriate effector immune responses and effective elimination of the bacteria (71, 126). Future research will assess whether, in intestinal epithelial cells containing a loss-of-function NOD2 protein, such as might occur in people that carry
certain NOD2 polymorphisms, defective elimination of intracellular bacteria may allow
for increased proliferation which in turn would provide a powerful antigenic stimulus that
would promote activation of commensal-specific T cells (Fig. 1D). It also remains to be
established whether detection of intracellular bacteria in epithelial cells containing a gain-
of-function NOD2 protein would result in excessive NF-κB activation and inflammation.

*C. jejuni* itself acts as a strong inflammatory stimulus (78), as do host cells ruptured
during *C. jejuni*-induced non-apoptotic cell death. Studies need to determine whether this
combination may, in adjuvant fashion, create a co-stimulatory milieu that is conducive to
T cell activation and subsequent inflammation.

**Conclusion**

IBD is a multifaceted disease in which intestinal microflora, host genetics and immunity,
and environmental factors all play significant roles in pathogenesis. Prominent among
these factors is the multitude of bacterial species that comprise the intestinal microflora,
and which act as the antigenic stimulus for T cell activation and effector responses. Some
studies implicate the involvement of an “unbalanced” microflora (dysbiosis), or specific
pathogens such as adherent-invasive *E. coli*. However at present, no single species of
pathogenic, or detrimental, intestinal bacteria has been identified as “The” etiologic
antigenic stimulus in IBD. Rather, immune responses may be targeted toward members
of the normal resident intestinal microflora. Regardless of the nature of the microbial
stimulus, IBD is a T cell-mediated disease, and therefore a mechanism must exist by
which these intestinal antigens can interact with the mucosal immune system and activate T cells and perpetuate effector responses. Increased translocation of bacteria across the epithelium may occur as a result of a primary barrier defect, which remains controversial, or be the consequence of epithelial damage due to microbes or inflammatory injury. Enteric pathogens can damage the epithelial barrier by directly targeting tight and adherens junctions, or by causing cellular destruction. Evidence suggests that *C. jejuni* disrupts intestinal epithelial structure and function, and thereby permits the translocation of luminal material, including resident intestinal bacteria, into the sub-epithelial compartment. This in turn may prime the intestine for subsequent inflammation in susceptible hosts. Recent findings indicate the *C. jejuni* causes translocation of non-invasive *E. coli* via two distinct mechanisms: one that involves the disruption of epithelial tight junctions and increased paracellular trafficking of bacteria (64), and the other that involves increased transcellular trafficking via epithelial lipid rafts (56). While these studies suggest hypothetical mechanisms by which *C. jejuni* may contribute to the pathogenesis of IBD, many unanswered questions remain. Regardless, an ever-increasing body of evidence based on large human cohort studies indicates that acute *C. jejuni* gastroenteritis promotes the development and/or exacerbation of symptoms in patients with IBD. Improving our understanding of epithelial responses to *C. jejuni*, may shed new light on the mechanisms responsible for the initiation and/or relapse of intestinal inflammation in IBD patients. In turn, uncovering the mechanisms whereby these responses may disrupt microbial-host intestinal homeostasis will help identify novel therapeutic targets in IBD.
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Figure 1. Under normal conditions, infection by a pathogen results in protective mucosal inflammatory events that resolve upon microbial clearance. This figure illustrates hypothetical mechanisms of *C. jejuni*-mediated intestinal epithelial barrier disruption that may contribute to the development and/or exacerbation of symptoms in patients with IBD. Adding to these processes, it has yet to be shown whether acute *C. jejuni* gastroenteritis is able to modify the endogenous gut flora, possibly contributing to a chronic pro-inflammatory milieu.

(A) *C. jejuni* RM1221 disrupts epithelial tight junctions and increases paracellular permeability, allowing non-invasive “commensal” microorganisms, including *E. coli*, to translocate across the intestinal epithelium (64). In the context of an aberrant genetic background, these may in turn induce an immune response that overrides tolerance, in turn promoting inflammation instead of resolving it.

(B) Another hypothesis is that disruptions of epithelial tight junctions may lead to loss of cellular polarity and relocation of various basolateral receptors to the apical surface. This may predispose the intestine to heightened intestinal inflammation in susceptible patients, as increased interaction of resident intestinal bacteria with microbial recognition receptors, such as TLRs, incites NF-κB-mediated inflammation. In addition, interaction of bacteria with adhesion receptors may further facilitate mucosal colonization.

(C) At least some strains of *C. jejuni* (for example 81-176), may induce internalization and translocation of non-invasive *E. coli* via a transcellular mechanism using lipid rafts (i.e., without affecting paracellular permeability) (56). Moreover, epithelial cells
ruptured as a result of *C. jejuni*-mediated non-apoptotic cell death may create a co-
stimulatory milieu that is conducive to T cell activation (55).

(D) Internalized commensal bacteria may in turn interact with cytosolic NOD2 receptors.

In genetically predisposed individuals, defective NOD2 activation may lead to either
a lack of bacterial detection and elimination, or hyperactivation of the NF-κB
pathway upon detection. In both cases, an excessive inflammatory response would
occur against resident intestinal bacteria.
Table 1: Summary of hypotheses through which intestinal bacteria may be implicated in IBD pathogenesis.

- **The dysbiosis hypothesis**
  Proposes that an imbalance between "beneficial" versus "detrimental" resident intestinal bacterial species may incite chronic inflammatory responses (41, 72, 90, 104, 119, 124).

- **The persistent infection hypothesis**
  Proposes that IBD may arise as a result of persistent infection with enteric pathogens (4, 9, 21, 24, 33, 57, 80, 108, 112, 130).

- **The luminal antigen translocation hypothesis**
  Proposes that defects in the intestinal barrier function and/or impaired mucosal clearance facilitates increased translocation of luminal antigens, including resident intestinal bacteria, across the intestinal barrier where they may prime mucosal immune responses that lead to loss of immunologic tolerance towards the luminal antigens (3, 20, 69, 87, 103, 115).
**Table 2.** Summary of specific bacterial, parasitic, and viral pathogens that have been implicated in the development of IBD, and the proposed mechanisms by which they may contribute to IBD pathogenesis.

<table>
<thead>
<tr>
<th>Pathogen</th>
<th>Proposed mechanism(s) of IBD pathogenesis</th>
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<tbody>
<tr>
<td><em>Campylobacter</em> (38, 44, 83)</td>
<td>Increased translocation of intestinal microflora due to loss of intestinal epithelial barrier function as a result of tight junctional disruption (64) or increased lipid raft-mediated transcytosis (56) (i.e., consistent with 'the luminal antigen translocation hypothesis')</td>
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<tr>
<td><em>Salmonella</em> (38, 44)</td>
<td>Unknown</td>
</tr>
<tr>
<td><em>Mycobacterium avium</em> subspecies <em>paratuberculosis</em> (4); <em>Clostridium difficile</em> (21, 33, 80, 130); <em>Yersinia enterocolitica</em> (57, 108); adherent and invasive <em>Eschericia coli</em> (9, 24, 112)</td>
<td>Chronic inflammation due to persistent pathogenic infection (i.e., consistent with the 'persistent infection hypothesis')</td>
</tr>
<tr>
<td><em>Giardia duodenalis</em> (11, 23)</td>
<td>Loss of intestinal epithelial barrier function as a result of <em>Giardia</em>-induced enterocyte apoptosis (17) (i.e., consistent with 'the luminal antigen translocation hypothesis')</td>
</tr>
<tr>
<td><em>Entamoeba histolytica</em> (15, 98, 100)</td>
<td>Depletion of colonic mucus (15) (i.e., consistent with 'the luminal antigen translocation hypothesis')</td>
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<tr>
<td>Rotavirus, Norwalk virus, adenovirus (39); Rubella virus, Epstein-Barr virus, and adenovirus (59); Norovirus (60)</td>
<td>Unknown</td>
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