The Blessings and Curses of Intestinal Inflammation

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The intestinal immune system has to strike a delicate balance between initiating inflammatory responses against invading bacterial pathogens and avoiding their induction against microbiota colonizing the lumen. Adequate inflammatory responses against bacterial invasion result in the luminal secretion of antimicrobial peptides, as well as the release of cytokines in tissue that recruit and activate phagocytes. However, pathogens have evolved to utilize these environmental changes in the inflamed intestine to promote colonization. This review focuses on the costs and benefits of intestinal inflammation and the fine interplay between the host, its microbiota, and enteric pathogens.

Introduction
The healthy intestine is permanently populated with a diverse microbial community, termed the microbiota, which is composed of over 300 different species of prokaryotic and eukaryotic microorganisms. The microbiota provide benefit to the host by supplying nutrients and offering some protection against colonization by pathogens. This complex bacterial community reaches densities of $10^{10}$–$10^{11}$ organisms per gram of luminal content in the large intestine. One challenge to the intestinal immune system is to avoid an excessive immune response against this large luminal microbial community, while at the same time maintaining the ability to trigger an appropriate inflammatory response against the introduction of microbes into tissue, which may occur after an injury to the epithelium or a crossing of the epithelial barrier by invasive pathogens. This task is accomplished by several sentinel functions that enable the host to detect a compromised barrier and immediately initiate an appropriate inflammatory response. The rapid induction of innate defenses is designed to limit microbial dissemination and either clear the infection or control it until the host can mount specific adaptive immune responses. However, acute intestinal inflammation can also harm the host, because it is associated with diarrhea and changes in the intestinal environment that can be exploited by pathogens. Here, we review recent advances in microbial pathogenesis and innate immunity that provide new insights into the costs and benefits of acute intestinal inflammation.

Sentinel Functions for Surveillance of Microbial Translocation from the Gut
The innate immune system senses microbial translocation into tissue by detecting conserved microbe-specific molecular patterns using three major pattern recognition systems: Toll-like receptors (TLRs), nucleotide-binding and oligomerization domain (Nod)-like receptors (NLRs), and complement (Figure 1). TLRs are located on the host cell surface or in a vesicular compartment and function as a “bar code reader” that distinguishes bacterial patterns from those associated with viral agents. For example, the presence of viral nucleic acids is detected through TLR3, TLR7, and TLR8, while TLR1, TLR2, TLR4, TLR5, and TLR6 recognize products that are unique to bacteria (reviewed in Iwasaki and Medzhitov [2004]). To distinguish between luminal bacteria and those present in intestinal tissue, expression of TLRs is compartmentalized in intestinal epithelial cells. For example, TLR5, which recognizes bacterial flagellin, is expressed at the basolateral surface of human intestinal epithelial cells (Gewirtz et al., 2001), while TLR4, which recognizes the lipid A moiety of lipopolysaccharide (LPS) from Gram-negative bacteria, is found in vesicular structures in the cytoplasm of these cells (Hornef et al., 2002). This functional compartmentalization of TLRs enables the epithelium to serve as a sentinel for microbial translocation from the intestinal lumen. A second line of sentinel cells is formed by myofibroblasts, myeloid-derived antigen-presenting cells localized in the basement membrane directly beneath the intestinal epithelium where they monitor bacterial invasion by expressing TLR4 (Walton et al., 2009). As bacteria penetrate deeper into tissue, they encounter phagocytes, such as macrophages and dendritic cells. The majority of resident intestinal macrophages in humans lack expression of TLR4 and its coreceptor, CD14, under normal conditions. These macrophages are refractory to inflammatory cytokine production, but they display potent phagocytic activity to remove microbes (reviewed in Weber et al. [2009]). In contrast, resident intestinal dendritic cells respond to stimulation with TLR ligands and are important sources of cytokine production during infection.

The second family of pattern recognition systems, termed NLRs, is located in the host cell cytosol. Some NLRs function in detecting the presence of viral nucleic acids in the cytoplasm. However, the majority of enteric bacterial agents are extracellular or remain within a vesicular compartment and thus do not come into direct contact with NLRs (although there are few notable exceptions, such as Listeria monocytogenes and Shigella spp., which can reside in the cytosol). Nonetheless, NLRs function as an important sensory system for bacterial “patterns of pathogenesis,” detecting for instance the presence of virulence factors, such as toxins, type III secretion systems (T3SS), or type IV secretion systems (T4SS) produced by pathogens that do not enter the cytoplasm (reviewed in Vance et al. [2009]). For example, the invasive enteric pathogen Salmonella enterica serotype Typhimurium (S. Typhimurium) deploys a T3SS to inject proteins into the host cell cytosol, which induces
actin rearrangement and membrane ruffling, resulting in bacterial invasion of the intestinal epithelium (reviewed in Zhou and Galán [2001]). The operation of this T3SS is accompanied, perhaps inadvertently, by translocation of flagellin, the structural component of flagella, into the cytosol of macrophages (Sun et al., 2007), which is detected as a “pattern of pathogenesis” by a NLR termed NLRC4, formerly known as Ipaf, an acronym for interleukin (IL)-1β-converting enzyme (ICE) protease-activating factor (Franchi et al., 2006; Miao et al., 2006). In turn, Ipaf activates caspase-1, resulting in pyroptotic cell death, which is accompanied by proteolytic activation of IL-1β and IL-18 (Bergsbaken et al., 2009). Caspase-1 can also become activated during S. Typhimurium infection by a T3SS-dependent injection of SopE, a protein involved in host cell invasion, into the host cell cytosol (Müller et al., 2009). Helicobacter pylori, a noninvasive pathogen residing in the gastric lumen in close association with the epithelium, uses a T4SS to inject the CagA protein into host cells to manipulate their physiology. A byproduct of operating the T4SS is the delivery of cell wall fragments (muramyl dipeptides) into the host cell cytoplasm, a process sensed by the Nod1 protein (Viala et al., 2004). Nod1 and Nod2, a second intracellular sensor of bacterial cell wall fragments (Girardin et al., 2003), are expressed in the intestinal epithelium and may enable these sentinels to detect lumenal pathogens that manipulate host cell physiology using secretion systems.

The third pattern recognition system, complement, is a humoral component of the host innate immune surveillance. After crossing the epithelial lining, bacteria become exposed to complement component 3 (C3), which can distinguish bacterial surfaces from those of host cells or viruses. This pattern recognition event represents the first step in the alternative pathway of complement activation. Although rarely discussed in this context, bacterial pattern recognition through C3 may act in concert with bacterium-specific TLRs to distinguish the “bar code” of bacteria from that of other groups of microbes. C3b, one of the cleavage products of C3 generated during complement activation, contains a reactive thioester group, which forms esters with hydroxyl groups of bacterial surface carbohydrates,

### Figure 1. Host Factors Involved in Orchestrating Exudative Intestinal Inflammation during the Early (Innate) Phase of a Bacterial Infection

Detection of bacteria by innate immune sensors (complement, TLRs, and NLRs) results in an initiating response (C3a, C5a, IL-23, IL-1β, and IL-18) that helps to amplify inflammatory signals in tissue by nonspecifically stimulating immune cells (macrophages, mast cells, T cells) to release inflammatory mediators (histamine, CXC chemokines, TNF-α, IL-17, IL-22, and IFN-γ), which promote neutrophil recruitment, acutely increased vascular permeability, and the formation of tissue exudates.
such as LPS of Gram-negative bacteria or teichoic acid of Gram-positive bacteria. In the absence of specific antibodies, opsonization of bacteria by C3b is required for efficient phagocytosis by neutrophils, macrophages, and dendritic cells, which proceeds through complement receptor 3 (CR3, also known as CD11b/CD18 or Mac1) and CR4 (also known as CD11c/CD18). Activation of the alternative pathway leads to the deposition of complement components C5b, C6, C7, C8, and C9 on the bacterial surface where these proteins assemble into a bactericidal terminal membrane attack complex. Importantly, complement activation generates the soluble fragments C3a and C5a, known as the anaphylatoxins, which are potent inducers of inflammatory responses (reviewed in Haas and van Strijp [2007]).

The Orchestration of Exudative Inflammation

It is clear from the above examples that pattern recognition enables the host to detect a breach in the mucosal barrier, to distinguish bacteria from other microbes (using TLRs and complement), and in some cases, to assess the pathogenic potential of a bacterium (using NLRs). This information is integrated to mount an inflammatory reaction that is appropriate to the threat. For example, the host reacts to an acute viral infection with inflammatory infiltrates that are dominated by macrophages, dendritic cells, and/or lymphocytes. In contrast, the appropriate response to a bacterial infection is characterized by acutely increased vascular permeability, infiltrates that are dominated by neutrophils, and the formation of tissue exudates (reviewed in Tsolis et al. [2008]). The latter pathological changes in tissue are commonly referred to as exudative inflammation.

The development of exudative inflammation is in part orchestrated by cytokines. The detection of bacteria by TLRs and NLRs results in an initiating cytokine response that is limited in scope, but includes the release of mediators, which in turn help to amplify responses in tissue (Figure 1). One mediator initiating the amplification of cytokine responses in tissue is IL-23, which can be released by dendritic cells (van Beelen et al., 2007) or CD14+ intestinal macrophages (Kamada et al., 2008). Production of IL-23 in these cells is dependent on NF-κB and can result from stimulation of bacterium-specific TLRs (Siegemund et al., 2007) or the intracellular bacterial sensor Nod2 (van Beelen et al., 2007). IL-23 amplifies cytokine responses by stimulating antigen-experienced T helper (Th)17 cells, γδ T cells, and natural killer (NK) T cells to produce IL-17 and IL-22 (Godinez et al., 2009; Goto et al., 2009; Rachitskaya et al., 2008). This cytokine release during the initial stages of inflammation proceeds through an antigen-independent mechanism (Guo et al., 2009), resulting in a marked increase in IL-17 and IL-22 expression in the ileal mucosa of naive animals within 2–5 hr after infection with S. Typhimurium (Raffatellu et al., 2007, 2008). A second mechanism amplifying cytokine responses in tissue is initiated by a subset of NLRs that activate caspase-1. While transcription of the genes encoding IL-1β and IL-18 is NF-κB dependent and can be induced by stimulating bacterium-specific TLRs, these cytokines are produced as inactive proforms that need to be cleaved by caspase-1 to become biologically active. IL-18 can amplify responses by stimulating antigen-experienced CD8+ T cells and Th1 cells to rapidly secrete interferon (IFN)-γ early during bacterial infection by an antigen-independent mechanism (Guo et al., 2009; Srinivasan et al., 2007). Similarly, IL-1β induces the release of IL-17 from Th17 cells by a T cell receptor-independent mechanism, thereby amplifying early effector responses (Guo et al., 2009; Lee et al., 2010). The resulting increase in cytokine production becomes apparent during infection with invasive enteric pathogens, such as S. Typhimurium, where the products of the above amplification mechanisms, IL-17, IL-22, and IFN-γ, are among the most prominently induced cytokines in intestinal tissue during the early phases of inflammation (Godinez et al., 2008; Raffatellu et al., 2008).

Activation of the alternative complement pathway by bacterial surface carbohydrates stimulates exudative inflammation through the generation of anaphylatoxins, the most potent of which is C5a (reviewed in Guo and Ward [2005]). C5a stimulates basophils and mast cells to release tumor necrosis factor (TNF)-α and histamine (Figure 1). Histamine contributes to inflammation by promoting vasodilation. Furthermore, C5a, C3a, and histamine are mediators of endothelial contraction, thereby contributing to the increased vascular permeability and the formation of tissue exudates characteristic of exudative inflammation. C5a is a potent neutrophil chemoattractant and can therefore contribute directly to recruiting these cells. C5a can also synergize with LPS in stimulating human leukocytes to release IL-8, a member of the CXC chemokine family, a group of neutrophil chemoattractants. Additional mechanisms contributing to neutrophil recruitment are mediated by IL-17, IL-1β, and TNF-α, cytokines that stimulate epithelial cells to release CXC chemokines (Cromwell et al., 1992; Raffatellu et al., 2008). Thus, complement (through C5a), NLRs (through caspase-1-mediated IL-1β production), and TLRs (through IL-17) cooperate in generating exudative inflammatory infiltrates dominated by neutrophils.

Inducible Mucosal Barrier Functions and the Consequences of Their Failure

The benefit of exudative inflammation resides in the orchestration of three major antibacterial response arms that contribute to barrier functions against microbial dissemination (Figure 2). Each arm is designed to control bacteria residing in a different host niche. One arm of the response is orchestrated by IFN-γ and is directed against intracellular bacteria. IFN-γ-mediated activation checks bacterial replication in macrophages, a preferred target of intracellular pathogens. Neutrophil recruitment represents a second arm and is directed against extracellular bacteria in tissue. Once opsonized by C3b, extracellular bacteria become efficiently phagocytosed and killed by neutrophils. A third arm has been discovered more recently and is directed against luminal bacteria. This part of the response is orchestrated by IL-22, which stimulates a lumenal release of antimicrobials by epithelial cells (Raffatellu et al., 2009; Zheng et al., 2008). The antimicrobial mechanisms induced in the intestinal epithelium during inflammation include the release of proteins mediating iron and zinc deprivation (lipocalin-2 and calprotectin, respectively), a bactericidal C-type lectin (regenerating islet-derived 3 gamma [RegIIIγ]), antimicrobial peptides (defensins), nitric oxide produced by inducible nitric oxide synthase (iNOS), oxygen radicals produced by dual oxidase 2 (Duox2), and increased mucus production (Meijas-Luque et al., 2010; Raffatellu et al., 2009; Zheng et al., 2008). These antimicrobial mechanisms are likely aimed at clearing luminal bacteria.
from the vicinity of the epithelium (Brandl et al., 2007, 2008; Zheng et al., 2008).

The advantages conferred by the antibacterial barrier functions orchestrated during exudative inflammation are illustrated by clinical manifestations associated with their inactivation. For example, patients with mutations in genes that encode components of the IFN-γ axis exhibit increased susceptibility to disseminated infections with nontyphoidal Salmonella serotypes, suggesting that an inhibition of bacterial replication in macrophages contributes to mucosal barrier functions (Lammas et al., 2002; MacLennan et al., 2004).

Neutrophils form a second important barrier against systemic bacterial dissemination. This defense is not only effective against classical extracellular bacteria, but also against the extracellular stages of some facultative intracellular pathogens that may be present during their transition between host cells. For example, the facultative intracellular pathogen S. Typhimurium causes a localized gastroenteritis in immunocompetent individuals, while neutropenic patients develop a life threatening bacteremia (Noriega et al., 1994; Tumbarello et al., 1995). A second condition predisposing to the development of S. Typhimurium bacteremia is an advanced HIV infection (reviewed in Gordon [2008]). IL-17 deficiency has recently been identified as the immune defect responsible for this clinical observation (Raffatellu et al., 2008). In addition to impairing neutrophil recruitment, Th17 depletion also reduces IL-17 production in the bone marrow, which in turn prevents production of granulocyte-colony stimulating factor (G-CSF), a cytokine required for granulopoiesis (Ye et al., 2001). This results in reduced microbicidal activity of neutrophils from patients with advanced HIV disease (Coffey et al., 1998; George et al., 1998). S. Typhimurium bacteremia is also associated with other conditions resulting in a reduced microbicidal activity of neutrophils (Humbert et al., 1990; Tauber et al., 1983), including chronic granulomatous disease (Winkelstein et al., 2000) and sickle cell anemia (Okuonghae et al., 1993).

The importance of neutrophils in checking bacterial dissemination is further highlighted by the fact that major virulence factors of enteric pathogens associated with systemic infections in immunocompetent individuals are designed to outmaneuver this barrier function. For instance, unlike commensal Escherichia coli or E. coli isolates associated with localized enteric infections, E. coli isolates associated with newborn meningitis (NMEC) express a capsular polysaccharide (CPS), termed the K1 antigen. Expression of the K1 antigen lowers C3b fixation on the bacterial surface, thereby reducing opsonophagocytosis by neutrophils (Horwitz and Silverstein, 1980). S. enterica serotype Typhi (S. Typhi), which causes a severe systemic infection termed typhoid fever, expresses a CPS termed the Vi antigen. The Vi antigen is absent from closely related pathogens, such as S. Typhimurium, which cause a localized enteric infection in immunocompetent individuals. Expression of the Vi antigen correlates with reduced C3b fixation and reduced opsonophagocytosis of clinical S. Typhi isolates (Looney and Steigbigel, 1986). Similarly, the food-borne pathogen Brucella abortus disseminates to internal organs and synthesizes a linear O-antigen, which prevents C3b fixation (Barquero-Calvo et al., 2007). In conclusion, evasion of opsonophagocytosis by neutrophils is a shared virulence strategy of pathogens, including NMEC, S. Typhi, and B. abortus, which are able to cross the mucosal barrier of the gastrointestinal tract and disseminate to internal organs. In contrast, C3b is efficiently deposited on the surfaces of closely related organisms, such as commensal E. coli, E. coli isolates associated with enteric infections, or S. Typhimurium, thereby rendering them unable to overcome a neutrophil barrier and disseminate to internal organs in immunocompetent individuals.

Finally, antimicrobial mechanisms induced in the intestinal epithelium during inflammation constitute a third barrier function, which is directed against translocation of luminal bacteria. For example, infection with HIV is associated with increased translocation of gut microbiota (Brenchley et al., 2006). Studies in rhesus macaques infected with simian immunodeficiency virus (SIV) show that increased microbial translocation from the gut is associated with reduced IL-17 and IL-22 production in the intestinal mucosa resulting from a depletion of Th17 cells (Raffatellu et al., 2008). Depletion of CD4+ T cells, which includes the...
Th17 subset, also increases translocation of gut microbiota in a mouse model (Gautreaux et al., 1994), which supports the idea that cytokines produced by these cells are important for maintaining mucosal barrier functions. Translocation of gut microbiota is furthermore a contributing factor in the pathogenesis of inflammatory bowel disease (IBD), a condition in which the host develops an excessive inflammatory reaction against intestinal microbial communities by unknown mechanisms. For instance, preventing the induction of barrier functions by inactivation of TLR4 increases microbial translocation, thereby exacerbating intestinal inflammation in models of IBD (Fukata et al., 2006). Conversely, cytokines that enhance barrier functions against microbiota translocation, including IL-23 and IL-22, confer protection against IBD (Duerr et al., 2006; Zenewicz et al., 2005). This finding suggests that neutrophils are largely responsible for the collateral tissue damage accompanying exudative inflammation, thereby contributing to intestinal fluid accumulation and diarrhea. Diarrhea and the resulting dehydration can become life threatening, which illustrates that the protection against bacterial translocation and dissemination conferred by exudative inflammation can come at a high cost and needs to be tightly controlled to limit the damage inflicted on the host.

A second potential drawback of exudative inflammation is less obvious and has been revealed only recently. The luminal pathogen Citrobacter rodentium triggers intestinal inflammation in mice by deploying a T3SS for intimate attachment to epithelial cells, resulting in a disruption of tight junctions (Guttmann et al., 2006). This inflammatory response is associated with changes in the gut microbiota, including an increased abundance of bacteria belonging to the phylum Proteobacteria, specifically members of the family Enterobacteriaceae (Lupp et al., 2007). Similarly, exudative inflammation caused by invasive enteric pathogens, such as Campylobacter jejuni and S. Typhimurium, is accompanied by an increased abundance of Enterobacteriaceae (Lupp et al., 2007; Stecher et al., 2007). Changes in the gut microbiota have also been observed in IBD patients, in whom chronic intestinal inflammation is accompanied by a significant increase in Enterobacteriaceae and a reduced biodiversity of bacteria belonging to the phylum Firmicutes (reviewed in Marteau, 2009). Importantly, intestinal inflammation induced by pathogens belonging to the Proteobacteria, including C. rodentium, Campylobacter jejuni, and S. Typhimurium, results in their overgrowth in the intestinal lumen of mice (Lupp et al., 2007; Stecher et al., 2007). In the case of S. Typhimurium, the resulting increase in its luminal abundance enhances transmission of the pathogen to a susceptible host, thereby placing virulence factors important for triggering inflammation under a positive selection (Lawley et al., 2008; Wickham et al., 2007). The ability of S. Typhimurium to trigger exudative inflammation depends on two T3SSs, which mediate invasion of the intestinal epithelium and subsequent survival within macrophages, respectively (Tsolis et al., 1999). Mutational inactivation of these two virulence factors renders S. Typhimurium unable to benefit from exudative inflammation by outgrowing the gut microbiota and increasing its transmission success (Lawley et al., 2008; Stecher et al., 2007).

Pathogens triggering intestinal inflammation take advantage of at least two environmental changes that accompany this host response (Figure 3). The first notable alteration of the intestinal environment occurring during inflammation is the removal of luminal contents by the flushing action of diarrhea. The remaining microbes in this niche rely predominantly on nutrients found in the mucus layer for supporting their growth (Kriván et al., 1992; McCormick et al., 1988). The mechanisms by which pathogens can take advantage of this situation are still poorly understood, but initial studies suggest that the ability to colonize the mucus layer plays an important role in their ability to outgrow the microbiota. For example, S. Typhimurium uses motility and chemotaxis toward mucus carbohydrates to colonize this niche, and both properties are essential for benefiting from inflammation by outgrowing the intestinal microbiota in mice. Importantly, growth in mucus only provides an advantage during inflammation, because S. Typhimurium mutants unable to elicit this host response (due to an inactivation of both T3SSs) can no longer use motility and chemotaxis to outcompete other gut microbes (Stecher et al., 2008).

A second important change in the gut environment encountered during acute exudative inflammation is the epithelial release of antimicrobials into the lumen. Antimicrobials can influence the microbiota composition, as segmented filamentous bacteria (SFB), which are members of the phylum Firmicutes, are lost from the gut microbial community in mice expressing a human a-defensin gene (DEFAS) in Paneth cells of the small intestine (Salzman et al., 2010). Recent evidence suggests that pathogens triggering inflammation possess virulence mechanisms that render them resistant against antimicrobials, and this property enhances their competitiveness in the lumen of the inflamed gut. For instance, one of the antimicrobials released into the intestinal lumen of Rhesus macaques during inflammation is lipocalin-2 (Raffatellu et al., 2009), which prevents bacterial iron uptake by binding and inactivating enterobactin, a low-molecular-weight compound (siderophore) released by many enteric bacteria to chelate iron and internalize the resulting complex through specialized outer membrane receptors (Figure 3). S. Typhimurium synthesizes and releases a glycosylated derivative of enterobactin, termed salmochelin (Hartke et al., 2003), which is no longer bound by lipocalin-2, thereby rendering...
the pathogen resistant against this antimicrobial protein (Fischbach et al., 2006). Utilization of salmochelin enhances the ability of S. Typhimurium to grow in the lumen of the inflamed intestine, while no benefit is apparent in the absence of intestinal inflammation or in lipocalin-2-deficient mice (Raffatellu et al., 2009). Thus, resistance against antimicrobials released into the intestinal lumen can enable pathogens to exploit inflammatory responses during their competition with the microbiota. As a result, the environmental changes encountered in the inflamed gut favor the overgrowth of pathogens, thereby enhancing their transmission by the fecal/oral route.

Concluding Remarks
Recent years have seen a rapid advance in our understanding of how inflammatory responses help to restrict the translocation of gut microbiota and prevent the dissemination of bacterial pathogens. Some of the barrier functions induced during inflammation, such as the responses against luminal bacteria orchestrated by the IL-23/IL-22 axis, are just beginning to be explored, and a more detailed knowledge of these pathways promises to provide new insights into mechanisms contributing to increased microbial translocation in HIV-infected individuals and IBD patients. It has long been appreciated that intestinal inflammation also comes at a price, since it is associated with collateral tissue damage and diarrhea. However, the fact that pathogens have learned to exploit this host response during their competition with the intestinal microbiota is an important emerging concept, which remains incompletely understood. Further analysis of the mechanisms by which pathogens trigger inflammation to take advantage of the resulting changes in the intestinal environment is expected to provide important insights into why some bacteria evolved to cause gastrointestinal disease.

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REFERENCES

Figure 3. Differences in the Lumenal Environment of the Normal and the Inflamed Gut
Pathogens triggering intestinal inflammation do not inhabit the same niche as the intestinal microbiota. The microbiota inhabits the normal intestine, an environment rich in nutrients derived from ingesta. Pathogens use their virulence factors to induce drastic changes in the intestinal environment, including removal of intestinal contents and the epithelial release of antimicrobials such as lipocalin-2. Lipocalin-2 prevents microbial iron acquisition by sequestering the siderophore enterobactin. By specializing on growth in the mucus layer and producing siderophores that confer lipocalin-2 resistance (e.g., salmochelin), pathogens can exploit inflammation during their competition with the microbiota. As a result, the environmental changes encountered in the inflamed gut favor the overgrowth of pathogens, thereby enhancing their transmission by the fecal/oral route.
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