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Campylobacter jejuni and associated immune mechanisms: short-term effects and long-term implications for infants in low-income countries

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Abstract

Purpose of review—*Campylobacter jejuni* is recognized as one of the most common causes of food-borne gastrointestinal illness worldwide, resulting in a self-limiting dysentery in developed countries. However, it is increasingly gaining attention due to its association with postinfectious complications such as Guillain–Barré Syndrome and recently recognized importance in early childhood diarrhea in developing countries. We hypothesize that the inflammation mediated by *C. jejuni* infection causes environmental enteric dysfunction, and with contribution from diet and the host, microbiome may be responsible for growth faltering in children and developmental disability.

Recent findings—Diet plays a major role in the impact of *C. jejuni* infection, both by availability of micronutrients for the bacteria and host as well as shaping the microbiome that affords resistance. Early childhood repeated exposure to the bacterium results in inflammation that affords long-term immunity but, in the short term, can lead to malabsorption, oral vaccine failure, cognitive delay and increased under-5 mortality.

Summary—As interest in *C. jejuni* increases, our understanding of its virulence mechanisms has improved. However, much work remains to be done to fully understand the implications of immune-mediated inflammation and its potential role in diseases such as environmental enteric dysfunction.

Keywords

Campylobacter jejuni; environmental enteric dysfunction; inflammation; malnutrition; microbiota

INTRODUCTION

Campylobacter jejuni is recognized as one of the most common causes of food-borne gastrointestinal illness worldwide [1]. It is a gram-negative, curved or spiral-shaped organism with a bipolar flagellum. *C. jejuni* requires a microaerophilic environment for growth and replicates slowly, making diagnosis by culture challenging. Although more than

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There are no conflicts of interest.

10 different species of *Campylobacter* exist, some of which are known to be commensal organisms in human oral flora, *C. jejuni* is most commonly associated with human disease. *C. jejuni* is a commensal organism in most birds, and infection in humans is frequentlyassociated with exposure to undercooked or poorly handled poultry or contaminated water sources. However, it can also be a commensal organism in ruminants and is sometimes isolated from unpasteurized milk.

The resulting illness is characterized by fever, abdominal cramping and bloody diarrhea, making it difficult to clinically distinguish from dysentery due to shigellosis, salmonellosis or amebiasis and is typically self-limiting in immunocompetent patients. The incubation period from infection to symptom onset is up to 72 h, with infections classically resolving within 1 week [2]. Rates of *C. jejuni* infection are difficult to assess: for the United States, estimates are around 2 million cases each year [3]; worldwide, incidence of *C. jejuni* appears to vary by location, with the highest prevalence prior to 2 years of age observed in Bangladesh [4■■]. Currently, the case fatality rate is estimated to be as high as 9% [1]. Culture remains the gold standard for diagnosis of *C. jejuni*, although use of PCR may now replace this.

C. jejuni is distinct from other causes of dysentery in its association with postinfectious complications such as Guillain–Barré syndrome, reactive arthritis and postinfectious irritable bowel syndrome. We hypothesize that a previously un-recognized postinfectious complication is environmental enteric dysfunction (EED). *C. jejuni* is increasingly gaining attention due to the socioeconomic impact of this bacteria, both in the short and long term.

In the following review, we will examine the immune system's response to *C. jejuni* infection, the impact of nutrition and host microbiome on infection and the impact of the subsequent inflammation and its potential role in EED (Table 1).

Dependency upon the microbiota

To date, our understanding of the pathogenic mechanisms utilized by *C. jejuni* has been limited by the difficulty in establishing a functional animal model. Several advances have been made with regard to murine models, including the use of either germ-free or gnotobiotic mice or those with specific immunologic mutations, including knockout of the single IgG IL-1-related receptor that normally functions to downregulate MyD88 innate immune signaling [12■]. There are different hypotheses regarding the specific barriers to *C. jejuni* in wild-type mice, one of which is that colonization resistance is afforded by the murine microbiota. This hypothesis has been investigated in several studies demonstrating resistance to *C. jejuni* following the establishment of 'adult' gut flora [5,15,16]. In fact, O'Loughlin *et al.* showed that mice treated with a single antibiotic, ampicillin, were more susceptible to colonization with *C. jejuni*. Analysis of the microbiome of the antibiotic-treated mice revealed decreased levels of microbial diversity and specifically of *Enterococcus faecalis* [18■■]. *E. faecalis* inhibited the growth of *C. jejuni in vitro* and when gavaged into ampicillin-treated mice restored resistance to colonization by *C. jejuni.* Thus, it appears that the microbiota is integral to *C. jejuni* resistance in the mouse model, with even minor alterations in gut flora allowing for establishment of infection [18■■]. Infant mice

were susceptible to *C. jejuni* infection and gut inflammation [16], suggesting that the early microbiota may not afford the same protection as those found in 'adult' flora [25].

Bacterial virulence factors

Our understanding of how *C. jejuni* infection causes disease remains limited. Full-genome sequencing of several *C. jejuni* strains has helped to shed light on variations in virulence between campylobacters and how this may alter the interactions with and symptoms displayed by the host. Specifically, *C. jejuni* has demonstrated the ability to synthesize various heat shock proteins when exposed to temperatures outside of the preferred 37–42 °C range or utilize varying amino acids based on host nutrient availability [26]. Although host colonization factors were, to a large extent, conserved between strains, loci for lipooligosaccharide and polysaccharide synthesis were more diverse [27].

Pathogenesis of campylobacteriosis begins with adherence, and from murine models it is evident that the bacteria must invade cells to elicit a host response [28]. The bacteria begin invading cells in the distal small bowel, then spreading to the colon. Damage localizes at the tips of intestinal villi as opposed to within the crypts [28]. Following cellular invasion, *C. jejuni* upregulates toxin and protein production and avoids lysosomal fusion to the vacuole containing the bacterium. This likely contributes to evasion of the host immune system [28–30]. Although bacterial virulence factors allow for the survival of the bacteria within host cells, the resultant immune response is likely responsible for the clinical manifestations of infection [13,26,28]. For example, campylobacter production of cytolethal distending toxin both promotes an inflammatory response via IL-8 as well as assists in evasion of the immune system via arrest of the cell cycle [31]. At the same time, Toll-like receptors on intestinal epithelial cells as well as gut dendritic cells are activated. This initiates both the innate and adaptive immune pathways, allowing for the recruitment of inflammatory cells that are likely responsible for the resultant diarrhea, as well as the ultimate clearance of the organism [6–8,25,32–35]. *C. jejuni*'s interaction with gut cells leads to the damage of differentiated cells at villous tips and the arrest of the cell cycle in proliferating cells of the crypts, causing villous atrophy, resulting in the characteristic bloody diarrhea [3,28].

Campylobacter jejuni and environmental enteric dysfunction

Following the immune response, what are the downstream effects of infection and how do they play into the outcomes of *C. jejuni*? Our hypothesis is that repeated exposure to *C. jejuni* heavily contributes to subclinical inflammation and EED. Although the concept of malabsorption and its direct correlation to poor outcomes in developing countries is not novel, the development of a well delineated and directly measurable entity denoted EED is increasing in popularity over the last decade.

Although the specific definition varies, in general, EED is a condition resulting from the interaction between malnutrition and enteric infection, leading to villous blunting, malabsorption and chronic inflammation in the small bowel, the outcome of which is poor absorption and growth stunting. EED typically is clinically silent, that is not manifesting as overt diarrhea [36■,37]. As a clinically asymptomatic disease, intervention to prevent or treat the consequences of EED is problematic. More important than growth stunting alone

has been the association of EED with vaccine failure, increased susceptibility to infections, decreased cognitive function and increased rates of death in children less than 5 years of age [37,38]. Further research is required to fully delineate a time course for the development of EED, which would provide clinicians a more precise target for intervention and/ or prevention.

Campylobacter jejuni and the impact of malnutrition

Where nutrition is concerned, the question becomes whether EED is a self-perpetuating cycle. If malnutrition leads to villous blunting and thus poor absorption, does the resultant malabsorption then foster further malnutrition, or is there a limit to the dysfunction one can accrue? Recently, Liu *et al.* [39] demonstrated that even short-term protein malnutrition can lead to decreased weight gain, increased pathogen burdens and stifled epithelial cell proliferation in a murine model of *Cryptosporidium parvum* infection. Although *C. parvum* and *C. jejuni* infections differ greatly in their pathogenesis and rates of occurrence per location, the conclusion of this study is that diet plays a major role in the body's ability to initiate repair mechanisms even after abbreviated periods of protein malnutrition.

Further, earlier and more frequent pathogen exposures, such as those that may be encountered in settings of heavy population density and poorer sanitation practices, may have heightened impacts and insurmountable deficits in the setting of persistent protein malnutrition. Indeed, Hossain *et al.* [40] demonstrated that higher intestinal permeability, as measured by lactulose/mannitol uptake in children, correlated with decreased weight for age as well as higher rates of enteropathy for children who were already considered to be underweight. In addition, younger age and specific micro-nutrient deficiencies also correlated with enteropathy. Although it has been demonstrated that for adults, particularly travelers to developing nations, villous blunting and malabsorption may develop in a picture similar to EED, these effects seem to be reversible once the traveler is removed from the offending environment [38]. However, malnutrition in children is heavily associated with early mortality, particularly for children under the age of 5 years [21■,36■].

Taken together, these studies demonstrate that malnutrition-induced intestinal damage begins early in life and specifically targets the processes by which the body would correct damage inflicted by diarrheal pathogens. This results in furthering the blunting and malabsorption seen with dietary deficiency. Moreover, if the negative effects begin early in life and result in increased rates of infection, vaccine failure, cognitive deficits and death, the window for intervention is exceedingly narrow and represents a major challenge for both clinicians and families in the fight against childhood diarrheal diseases [36■]. Interestingly, Naylor *et al.* [41■] demonstrated that greater maternal height, an indicator of good maternal health, was associated with protection against growth stunting in the infant, indicating that good maternal nutritional status may help protect against the deleterious effects of nearly ubiquitous enteric pathogens and their associated damage.

C. jejuni's role in malnutrition remains difficult to tease out, if only because both campylobacteriosis and malnutrition are common. When one observes an association of campylobacter with malnutrition, it can be difficult to discern if this is causal or merely a consequence of overlap between two common illnesses. For example, Amour *et al.*, via

analysis of children enrolled in the MAL-ED study, found that a third or more of children were malnourished and that most children tested positive for *C. jejuni* by 1 year of age. In addition, higher burdens of *C. jejuni* in stool correlated with lower length-for-age scores and higher levels of systemic inflammation, with exclusive breast-feeding, among other factors, being protective [4■■]. Given such high rates of exposure to *C. jejuni* for children in developing countries, the known correlation between *C. jejuni*, the child microbiome and long-term systemic inflammation, and the presence of ongoing subclinical inflammation in EED, urgent research is needed to truly elucidate causality and potential interventions to prevent massive morbidity and mortality.

C. jejuni infections in developing countries are frequently asymptomatic, whereas this is rare for developed nations, suggesting that frequent and early exposure to the bacteria allows for the development of immunity [3]. Bereswill *et al.* reinforced the notion that location-specific diets affect immunity via a murine model, in which mice fed with a 'westernized diet' showed greater susceptibility to colonization with and systemic spread of *C. jejuni* as compared with wild-type mice on conventional mouse chow [42]. This was hypothesized to be partially related to the composition of the microbiota developed by Westernized diets as compared with other diets, in that the amount of *Escherichia coli* was higher [25]. It is well established that diet alone can play a major role in the composition of the microbiome. The microbiota in turn has an impact on susceptibility to pathogens, potentially through alterations in the availability of micronutrients based on which host microbes are processing or, specifically for *C. jejuni*, by allowing penetration of commensal organisms into previously inaccessible locations via leaky junctions created during its own invasion of host cells [25,43]. Further demonstrations that alteration of the microbiome could affect pathogen susceptibility were experiments with mice on low fat/low protein diets, which resulted not only in worsened villous blunting following gavage with specific commensal organisms, but additionally prolonged colonization with *Salmonella typhimurium* [44].

Campylobacter jejuni and innate trained immunity

Innate and acquired immune responses may protect from diarrhea due to campylobacteriosis. However, does this immunity come at a cost of inducing EED? As previously mentioned, other research has indicated that *C. jejuni* infections not only were linked with reduced growth curves but also with increased systemic inflammation [4■■]. Indeed, Heimesaat *et al.* [45] demonstrated that mice challenged immediately postweaning were easily infected with *C. jejuni* and were still colonized at low levels weeks later. Moreover, elevated levels of inflammatory cells were noted in lung, liver, kidney and heart as compared with control mice [45]. Persistent inflammation is of note as the potential exists for the inflammatory response from one infection to promote a heightened inflammation to a second. This hypothesis has previously been studied by Burgess *et al.*, who demonstrated that induction of inflammation and protection against *Entamoeba histolytica* infection conferred by prior exposure to segmented filamentous bacteria (SFB), a clostridia-related species that is considered to be a commensal organism in mice [46,47]. The protection was attributed to an epigenetic upregulation of the cytokines IL-23 and IL-17A produced by bone marrow dendritic cells after an SFB infection. In fact, protection could be conferred following transplantation of bone marrow dendritic cells from an SFB-infected to a naïve

mouse [46]. This illustrates the concept of ‘innate trained immunity’, or the notion that innate immune cells can develop memory type functions, taking on the role of adaptive immunity and confer protection to repeated insults at later time points [48].

In a setting of high population density and poor sanitation, innate trained immunity may represent a beneficial outcome of recurring exposures to multiple pathogenic organisms over time. In the previously discussed experiments, protection was conferred via heightened immune response. Although this could hold true for the increased inflammation seen following *C. jejuni* infections, making the response beneficial and account for the immunity seen in the adult population in developing countries, the concern is that these heightened levels of inflammatory cells may, in fact, lead to heightened responses to repeated insults and that this is a cause of EED.

Concluding remarks

Although our understanding of *C. jejuni* and its associated virulence mechanisms has vastly improved over the last few years, there is still much work to be done to fully understand this bacteria’s role in diseases such as EED. With improvements in testing efforts, it is increasingly being identified in diarrheal stools, allowing *C. jejuni* to garner added attention and research interest. As a result, we have seen that various virulence factors are expressed by *C. jejuni* under different conditions, which partially explains the different phenotypes of infection, but the full interplay between host response, nutrient availability and the stress response of the bacteria still remain unclear. It is evident that nutrition plays a role in the process of *C. jejuni* and inflammation and that the greatest insult is likely early protein malnutrition followed by repeated inflammatory insults both from *C. jejuni* as well as other pathogenic bacteria encountered from poorly sanitized water sources. The question still remains, however, as to whether intervening on clean water, sanitation or nutrition alone will be enough to surmount the negative impact of diarrheal diseases or if multifaceted efforts prior to birth will be required to make a notable impact against EED. As we increase our understanding of the role that innate trained immunity and diet play in this process, we come closer to accurately defining and diagnosing EED, thus providing distinct points for and methods of intervention.

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KEY POINTS

- *C. jejuni* invasion into host cells triggers both innate and adaptive immune responses, assisting with clearance of the organism but resulting in long-lasting inflammation that can have both positive and negative outcomes for the host.
- Although *C. jejuni* is known to result in a self-limiting dysentery in developed countries, we hypothesize that early, repeated exposures to the bacteria in developing countries may result in subclinical inflammation and environmental enteric dysfunction.
- Alterations in the host microbiota influence *C. jejuni*'s ability to colonize as well as affect the clinical manifestations of disease.
- Malnutrition alters the host microbiome as well as reduces the host's ability to repair damage caused by *C. jejuni* infection, resulting in a self-perpetuating cycle that can lead to oral vaccine failure, growth faltering, cognitive delay and early childhood mortality.
- Innate trained immunity may be the mechanism through which *C. jejuni* leads to the aforementioned complications.

Table 1

Advances in our understanding of Campylobacter jejuni

Inflammatory pathways
Innate immunity leads to persistent inflammation; adaptive immunity is required to clear infection [5]
C. jejuni infection leads to Th1 polarization [6]
C. jejuni activates MyD88 via TLR2 leading to induction of IL-6 [7]
TLR4-MyD88 and TLR4-TRIF activate dendritic cells in *C. jejuni* infection [8]
Innate and T-cell immunity lead to release of IFN-g, IL-17A and IL-22 to promote protection against *C. jejuni* [9]
C. jejuni infection disrupts TLR9 signaling, abrogating protection to DSS-induced colitis [10]
TLR2 is protective while TLR4 leads to inflammation [11]
SIGIRR-deficient mice represent a murine model of *C. jejuni* enterocolitis [12■]
Bacterial virulence factors
C. jejuni survives within vacuoles and produces CDT leading to cell death [13]
Alterations in *C. jejuni* virulence factors allow for different tissue colonization [14]
Role of microbiota
Limited defined enteric flora allows for persistent colonization with *C. jejuni* [5]
Reconstitution of mice with ‘murine flora’ vs ‘human flora’ confers protection to *C. jejuni* [15]
‘Westernized diet’ vs ‘conventional diet’ leads to heightened susceptibility to *C. jejuni* [15]
’Week old mice are easily colonized by *C. jejuni* [16]
Elevated *E. coli* levels allow for colonization and infection with *C. jejuni* [17]
Treatment with ampicillin leads to decreased *E. faecalis*, which allows for *C. jejuni* colonization [18■■]
Implications of *Campylobacter* in disease
Elevated inflammation makes infant mice more susceptible to *C. jejuni* [16]
Malnutrition increases risk for *C. jejuni* infection and infection is associated with growth stunting and decreased weight gain [19]
Early intestinal infections and malnutrition predispose to cognitive deficits and growth stunting [20]
Campylobacter is one of the most frequently identified pathogens in the first 2 years of life among 8 sites in the MAL-ED studies and is most commonly associated with bloody diarrhea [20]
High *C. jejuni* burden is associated with lower length-for-age scores [4■■]
Heightened systemic inflammation is correlated with higher mortality for children with acute severe malnutrition; *C. jejuni* was one of the most frequently identified pathogens [21■]
Postinfectious complications
C. jejuni infection in rats leads to SIBO, and those developing SIBO were more likely to have stool changes (P-IBS) [22]
A significant number of *C. jejuni* infections lead to postinfectious sequelae [23]
Advances in diagnostics
PCR is highly sensitive and can determine pathogen burden for *Campylobacter* [24]

CDT, cytolethal distending toxin; P-IBS, postinfectious irritable bowel syndrome; SIBO, small intestinal bacterial overgrowth; SIGIRR, single IgG IL-1-related receptor.