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Beyond *Campylobacter jejuni*: Understanding *Campylobacter coli* infections in a systemic model of disease

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In this issue of *Virulence*, the authors of the article entitled "Virulence genes and cytokine profile in systemic murine *Campylobacter coli* infection" utilized a mouse model in order to explore the pathogenic mechanisms and cytokine responses involved in *Campylobacter coli* (*C. coli*) systemic infections.[1] The clinical isolate *C. coli* 26536 was first analyzed for the presence of known virulence genes by polymerase chain reaction, and then these genes were sequenced before and after *C. coli* 26536 infection of Balb/c mice to ensure that these genes were stable. *C. coli* 26536 were found to persist in the liver and the spleen of the Balb/c mice for at least 8 days, with greater persistence in the liver. The observed cytokine profiles in the plasma and liver of infected mice were clearly different, demonstrating differences between the systemic and local inflammatory responses. This study is the first to focus on clarifying some of the mechanisms involved in the pathogenesis of systemic. *C. coli* infections that can occur in immunocompromised individuals.

Campylobacter continues to cause the greatest number of confirmed foodborne bacterial infections in developed countries, and the incidence of infections caused by *Campylobacter* has increased from 2008 to 2012.[2,3] *Campylobacter* are gram negative, curved, microaerophilic bacteria that can be transmitted to humans through consumption or handling of contaminated poultry, which are the reservoir for most human campylobacteriosis cases.[2] Infection with *Campylobacter* usually results in gastroenteritis, including watery or bloody diarrhea, cramps, and fever, depending on the virulence of the bacterial strain and host susceptibility.[4] *Campylobacter* infections can also result in extra-intestinal manifestations including, but not limited to bacteremia, Guillain-Barre syndrome, reactive arthritis, sepsis, or meningitis in immunocompromised individuals.[4] According to the Centers for Disease Control and Prevention, the most commonly identified causes of campylobacteriosis are *C. jejuni* and *C. coli*.[3] The most common causes of bacteremia are *C. jejuni, C. coli*, and *C. fetus*, however other emerging *Campylobacter* spp. have also been identified as causes of both gastrointestinal and extra-intestinal diseases.[4,5]

As most studies involving *Campylobacter* pathogenesis have focused on *C. jejuni*, there is little known about the pathogenic mechanisms of less prevalent *Campylobacter* spp, such as *C. coli*. It has been reported that *C. coli* are able to invade the human intestinal epithelial cell lines T84 and Caco-2, as well as transcytose a polarized T84 monolayer, suggesting that they can cross the gut epithelium to cause systemic disease in susceptible individuals.[6–9] Klancnik et al. have begun to try to understand the mechanisms by which *C. coli* affect the host during a systemic infection, which is not common, but can result in a 10–15% mortality rate in immunocompromised individuals.[10,11]

Ongoing research continues to add to our knowledge base of *Campylobacter*, and different strains can be categorized based on the presence or absence of specific genes, allowing us to determine how these pathogens might cause illnesses and how we can prevent them from causing disease. Since *Campylobacter* are genetically diverse, it is important to confirm the presence of known virulence factors in different strains as they are introduced to various experimental conditions. Klancnik et al. demonstrated that *C. coli* 26536 stably expressed the known virulence factors *cadF, virB11, cdtB*, and *ceuE*, whether they were detected after being grown from −80°C frozen stocks or isolated from livers of intravenously infected mice. In addition to confirming which virulence genes were present in *C. coli* 26536, the authors took advantage of a mouse model of systemic infection to observe the spread and persistence of this clinical isolate in the liver and spleen. *C. coli* 26536 CFU in the liver peaked on day 1 post-infection, and gradually decreased over 8 days, which is similar to what the authors reported previously in mice infected with *C. jejuni*.[12] In contrast, bacterial numbers in the spleen gradually increased from day 1 to day 8 post infection, but not to the levels present in the liver. The authors mention a possible role for macrophages in acting as a reservoir for *Campylobacter* survival. Although the authors report that hematoxylin/eosin staining in the liver and spleen reveals inflammatory infiltrate,

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it would be interesting to see a study that focuses on the role of macrophages in this mouse model of systemic *Campylobacter* infection, including macrophage phagocytosis, activation, and survival.

Analysis of cytokine profiles can be very informative when trying to determine how the host and pathogen are interacting, especially when they can be correlated with bacterial persistence and clearance. While examining cytokine production in the plasma and liver of infected mice compared to controls, Klancvik et al. found differing cytokine profiles. In the plasma of infected mice, only IL-12 and IFN-γ levels were significantly greater than controls on days 8 and 3, respectively. In the liver, TNF-α was significantly induced on day 1 and subsequently continued to decrease on days 3 and 8. At the same time, significant levels of IL-10 were produced in the liver on day 1 and increased thru day 8. After TNF-α induction on day 1, bacterial numbers in the liver began to decrease over time as the levels of IL-10 increased, even though IL-10 is an anti-inflammatory cytokine. In similar experiments with *C. jejuni*, Klancvik et al. also observed significant TNF-α production in the livers of infected mice, with the gradual decrease over 8 days, but unlike the results in the current article, IL-10 levels decreased and IFN-γ increased over time.[12] The authors attribute the early and increasing IL-10 phenomenon to the healing process involved in the resolution of *C. coli* infections, which may be necessary due to the persistent nature of this particular strain. As the current data provide a glimpse of the complex interactions between a susceptible host and *C. coli*, additional experiments studying a more extensive cytokine profile could help in understanding the dynamic mechanisms involved in *C. coli* infections. Clearly, the genetic diversity of *Campylobacter* spp. can affect the host response in different ways, and there is much more to explore in terms of the different responses generated by the different species.

Finally, this article begins to address some important areas that are affecting the population with regard to foodborne disease, and further substantiates the need to continue these efforts. The first area this article addresses is the potential impact of other *Campylobacter* spp, besides *C. jejuni*, on public health, and the fact that their incidence in illnesses may be severely underreported and understood. If these other *Campylobacter* spp. are not detected or identified as a cause for gastrointestinal illnesses or extra-intestinal illnesses, and their interactions with the host are not understood, their emergence could have a greater impact on public health in the future in a manner similar to the way non-O157 Shiga toxin-producing *Escherichia coli* have emerged a significant cause of foodborne illness. The second issue that this article addresses is the greater susceptibility to foodborne disease in developed countries of a significant proportion of the population as compared to the general population. This susceptibility is attributable to immunodeficiency, be it age, immunosuppressive treatments, genetic disorders, pregnancy, or other immunosuppressing conditions.[13] In these populations, the dose of a particular foodborne pathogen necessary to cause disease is reduced and the severity of disease is increased. While some research is being conducted to investigate these susceptible populations, more research is needed in order to understand the great number of immune deficiencies in different world populations and its impact on the development of guidance for the microbiological safety of foods.

Disclosure of Potential Conflicts of Interest

The author declares no conflict of interest.

Disclosure

The findings and conclusions presented in this editorial are those of the author and do not necessarily represent the views, opinions or policies of the US Food and Drug Administration.

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