Human Campylobacteriosis—A Serious Infectious Threat in a One Health Perspective

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Abstract Zoonotic Campylobacter species—mainly C. jejuni and C. coli—are major causes of food-borne bacterial infectious gastroenteritis worldwide. Symptoms of intestinal campylobacteriosis include abdominal pain, diarrhea and fever. The clinical course of enteritis is generally self-limiting, but some infected individuals develop severe post-infectious sequelae including autoimmune disorders affecting...
the nervous system, the joints and the intestinal tract. Moreover, in immunocompromised individuals, systemic spread of the pathogens may trigger diseases of the circulatory system and septicemia. The socioeconomic costs associated with *Campylobacter* infections have been calculated to several billion dollars annually. Poultry meat products represent major sources of human infections. Thus, a “One World—One Health” approach with collective efforts of public health authorities, veterinarians, clinicians, researchers and politicians is required to reduce the burden of campylobacteriosis. Innovative intervention regimes for the prevention of *Campylobacter* contaminations along the food chain include improvements of information distribution to strengthen hygiene measures for agricultural remediation. Given that elimination of *Campylobacter* from the food production chains is not feasible, novel intervention strategies fortify both the reduction of pathogen contamination in food production and the treatment of the associated diseases in humans. This review summarizes some current trends in the combat of *Campylobacter* infections including the combination of public health and veterinary preventive approaches with consumer education. The “One World—One Health” perspective is completed by clinical aspects and molecular concepts of human campylobacteriosis offering innovative treatment options supported by novel murine infection models that are based on the essential role of innate immune activation by bacterial endotoxins.

1 Introduction

Food-borne microbial infections of the human gastrointestinal tract and resulting diseases are associated with very high degrees of morbidity and mortality in the world’s population. According to the World Health Organization (WHO 2020), unsafe food products cause 600 million cases of food-borne diseases and 420,000 deaths annually, especially in children and elderly people. The WHO calculated that about 33 million years of healthy lives are lost through eating unsafe food worldwide every year, and this number is likely an underestimation (WHO 2020). Over the past two decades, *Campylobacter jejuni* has been recognized as the leading source of bacterial gastroenteritis around the globe (Wassenaar and Blaser 1999; Young et al. 2007; Altekruse 2008; Dasti et al. 2010; Burnham and Hendrixson 2018). Gut disease outcomes vary from mild, non-inflammatory, self-limiting diarrhea to severe, inflammatory, bloody diarrhea associated with severe abdominal pain, which can last for a few weeks. However, *C. jejuni*-infection is also associated with more severe neurological sequelae in some patients, such as the Guillain-Barré syndrome (GBS) and the Miller Fisher syndrome (MFS) (Talukder et al. 2011; Wakerley et al. 2014). Statistical evaluations indicate that *Campylobacter* infections are responsible for considerable costs of medication and health service. In the USA alone, it was estimated that *Campylobacter* illnesses in humans cost a burden of up to $6.2 billion annually (Forsythe 2000). In fact, in numerous studies from the USA and other developed nations, *Campylobacter* was reported to cause diarrheal disease 2–7 times more frequently than pathogenic *Salmonella, Escherichia* or *Shigella* species (Acheson and
In some countries, the fraction of reported *Campylobacter* cases has increased over the years. For example, the Robert Koch Institute’s Annual Statistical Reports indicate that the incidence of reported *Campylobacter* cases in Germany constituted 45 and 77% of all reported intestinal bacterial infections in 2006 and 2019, respectively (Fig. 1). However, it was estimated that the actual numbers of campylobacteriosis cases in Germany and other countries are likely to be much larger and could exceed more than four times the published statistics (EFSA 2011; Stingl et al. 2012).

*C. jejuni* is a member of the ε-proteobacterial subphylum of Gram-negative bacteria. These bacteria have a relatively small circular chromosome of 1.59–1.77 million base pairs, with an average guanosine and cytosine (GC) content of about 30.3–30.6%. The high gene density of about 94–94.3% establishes it as one of the most compact bacterial genomes sequenced so far (Parkhill et al. 2000; Fouts et al. 2005; Hofreuter et al. 2006). *C. jejuni* is quite fastidious in vitro, and bacterial growth under laboratory conditions requires nutrient-rich media, yet it is well-adapted to temperatures of 40–42 °C and microaerobic conditions (Stingl et al. 2012). The catabolic capabilities of *C. jejuni* are highly restricted because several genes required for carbohydrate utilization are missing or incomplete. In this respect, the organism differs from *Salmonella enterica* serovar Typhimurium and other bacterial gut pathogens (Hofreuter 2014). Regardless of these metabolic limitations, *C. jejuni* can effectively colonize the intestines of numerous animal hosts as a commensal. In fact, *C. jejuni* can inhabit the intestinal tract of a broad variety of wild birds and agriculturally relevant poultry, cattle and pigs (Oyarzabal and Backert 2012). Consequently, the handling and consumption of contaminated poultry and other meat products, raw milk and water have been established as the most frequent sources of *C. jejuni* infection in humans (Pielsticker et al. 2012). Upon oral uptake, *C. jejuni* colonizes the distal ileum and colon of the human host. *C. jejuni* is tremendously
successful in competing with the human intestinal microbiota (Masanta et al. 2013). An infectious dose of a few hundred bacteria is sufficient to result in intestinal colonization and can lead to campylobacteriosis. Despite the economic importance and clear clinical manifestations of this disease, the molecular mechanisms underlying the pathogenesis of \textit{C. jejuni} infections are still poorly understood. Even though human campylobacteriosis is of global importance, studies to gain insights into \textit{C. jejuni} pathogenesis have long been hampered by the absence of suitable experimental in vivo models (Newell 2001).

2 The One Health Concept: General Theory and Practical Approaches

The concept of “One Health” is based on the idea to achieve better public health outcome globally using the design and implementation of official programs as well as scientific research by multiple disciplines that need to work together. No single discipline or sector in our society possesses sufficient knowledge, skills and resources to preclude the emergence or re-occurrence of (zoonotic) diseases in the globalized world of today. Originally, this notion was stemming from the “One Medicine” concept, which demanded for an alliance between veterinary and human medicine in response to certain diseases (Schwabe 1984). This was adapted in 2004 to the “One World—One Health” concept, as conceived by the Wildlife Conservation Society (One World One Health 2020b). This initiative for the first time enunciated an interdisciplinary projection for the prevention and spread of important diseases, while at the same time maintaining the integrity of natural ecosystems. In this regard, the Wildlife Conservation Society defined 12 specific principles or practical approaches, termed the so-called Manhattan principles (Table 1), summarizing important milestones in this concept (One World One Health 2020a). Further global efforts for the establishment of official “One Health” strategies were performed by the WHO, United Nations, and various other globally operating institutions, as summarized in previous review articles (Zinsstag et al. 2011; Bardosh 2016).

Globally, we are now facing an era where the human population and degree of industrialization steadily increase, with negative effects on land use, wildlife ecology and the global climate. In addition, geopolitical conflicts can destabilize societies, and global climate changes may trigger or worsen negative developments in almost all ecosystems, while industrialization is generally associated with substantial environmental pollution, impairment of overall biodiversity by disappearance or loss of species as well as migration of millions of people due to war, social instability and natural catastrophes. These rapid global effects are ultimately associated with the emergence and re-emergence of countless infectious and non-infectious diseases (WHO 2020). Previous and very recent outbreaks of diseases caused by zoonotic viruses including Ebola fever, Zika fever, West Nile fever, MERS, avian influenza and Covid-19 clearly illustrate how animal microbes and human health are intimately
Table 1  Manhattan principles by the “wildlife conservation society” list the following 12 recommendations*

|   | Recommendation |
|---|----------------|
| 1 | Recognize the essential link between human, domestic animal and wildlife health and the threat disease poses to people, their food supplies and economies, and the biodiversity essential to maintaining the healthy environments and functioning ecosystems we all require |
| 2 | Recognize that decisions regarding land and water use have real implications for health. Alterations in the resilience of ecosystems and shifts in patterns of disease emergence and spread manifest themselves when we fail to recognize this relationship |
| 3 | Include wildlife health science as an essential component of global disease prevention, surveillance, monitoring, control and mitigation |
| 4 | Recognize that human health programs can greatly contribute to conservation efforts |
| 5 | Devise adaptive, holistic and forward-looking approaches to the prevention, surveillance, monitoring, control and mitigation of emerging and resurging diseases that take the complex interconnections among species into full account |
| 6 | Seek opportunities to fully integrate biodiversity conservation perspectives and human needs (including those related to domestic animal health) when developing solutions to infectious disease threats |
| 7 | Reduce the demand for and better regulate the international live wildlife and bushmeat trade not only to protect wildlife populations, but to lessen the risks of disease movement, cross-species transmission and the development of novel pathogen-host relationships. The costs of this worldwide trade in terms of impacts on public health, agriculture and conservation are enormous, and the global community must address this trade as the real threat it is to global socioeconomic security |
| 8 | Restrict the mass culling of free-ranging wildlife species for disease control to situations where there is a multidisciplinary, international scientific consensus that a wildlife population poses an urgent, significant threat to human health, food security or wildlife health more broadly |
| 9 | Increase investment in the global human and animal health infrastructure commensurate with the serious nature of emerging and resurging disease threats to people, domestic animals and wildlife. Enhanced capacity for global human and animal health surveillance and for clear, timely information-sharing (that takes language barriers into account) can only help improve coordination of responses among governmental and nongovernmental agencies, public and animal health institutions, vaccine/pharmaceutical manufacturers and other stakeholders |
| 10 | Form collaborative relationships among governments, local people and the private and public (i.e., non-profit) sectors to meet the challenges of global health and biodiversity conservation |
| 11 | Provide adequate resources and support for global wildlife health surveillance networks that exchange disease information with the public health and agricultural animal health communities as part of early warning systems for the emergence and resurgence of disease threats |
| 12 | Invest in educating and raising awareness among the world’s people and in influencing the policy process to increase recognition that we must better understand the relationships between health and ecosystem integrity to succeed in improving prospects for a healthier planet |

*Source https://oneworldonehealth.wcs.org/About-Us/Mission/The-Manhattan-Principles.aspx
coupled. In fact, it has been calculated that approximately 60% of all emerging infectious diseases are of zoonotic origin in nature and the majority of those (about 72%) originate from wildlife (Jones et al. 2008). Therefore, a broader knowledge about health and disease of humans, domestic animals and wildlife is urgently required. For this purpose, the “One Health” approach is particularly important in achieving better control of zoonotic infectious diseases, reducing the spread of antibiotic resistances and food safety issues (Destoumieux-Garzón et al. 2018). The last decades have also seen a significant increase in the occurrence of infectious microbes including *Campylobacter* species and many other zoonotic pathogens (Gölz et al. 2014; Iannino et al. 2019). Local animal husbandry practices, combined with international trade and traffic, have raised the risk of emergence and spread of specific pathogens, some of which can potentially cause pandemics, as the recent outbreak with SARS-CoV-2 has demonstrated. This scenario emphasizes the importance of human and animal ecosystems in the appearance and proliferation of some pathogens associated with snowballing globalization of certain health risks. Therefore, the “One Health” initiative created an important global strategic effort highlighting the need for a joint approach, which requires interdisciplinary cooperation and integrates cross-disciplinary expertise to ensure sustainable health of global flora and fauna in all ecosystems as well as mankind.

3 Human Campylobacteriosis—From Clinical Investigations to Novel Treatment Options Using Innovative Murine Models of Infection

3.1 Human Campylobacteriosis—Basic Characteristics

The fact that *Campylobacter* species that are pathogenic to humans, mainly *C. jejuni* and *C. coli*, form part of the commensal intestinal microbiota of wild and domestic animals is the basis for the transfer of respective bacterial infections to humans, which predominantly occurs by ingestion of contaminated meat products, raw milk and water. Pathogen transmission from wild birds and pets is still under debate, and actual data indicate that these additional *Campylobacter* reservoirs might be responsible for an accountable number of disease cases (Smith et al. 2020). Source attribution studies have proven that the highest risk for human *Campylobacter* infection is associated with consumption of contaminated meat from chicken and other poultry (Cody et al. 2019; Kaakoush et al. 2015). The virtual absence of clinical signs in these animals provides the basis for formation, continuous propagation and tolerance of the large pathogen reservoirs in the poultry breeding industry worldwide. This constitutes a major key in understanding the epidemiology of human campylobacteriosis given that clinical manifestations in poultry would interfere with industrial meat production procedures leading to eradication of *Campylobacter* pathogens by veterinary therapeutic interventions. However, this is not the case: Actual measures to
reduce human infections are rather focused on the minimization of *Campylobacter* contamination in the meat production chains (see Chapters “Management Strategies for Prevention of *Campylobacter* Infections Through the Poultry Food Chain: A European Perspective”, “Emission Sources of *Campylobacter* from Agricultural Farms, Impact on Environmental Contamination and Intervention Strategies” and “Phage Biocontrol of *Campylobacter*: A One Health Approach” in this book). Since human *C. coli* infections are far less frequently responsible for campylobacteriosis cases (about 1–5%), the following considerations and discussions will be focusing on *C. jejuni* as the major pathogen causing human campylobacteriosis worldwide.

In contrast to birds, humans become severely infected by ingestion of *C. jejuni* at very low doses. Around 500 live bacteria are sufficient to effectively colonize the intestinal lumen, enter the mucus layer by motility and invade the epithelial layers to establish inflammation by activation of the innate immune system (Fig. 2). The use of proton pump inhibitors has been shown to substantially increase the risk for *C. jejuni* infection indicating that the acidic environment of the human stomach

![Fig. 2 Pathogenesis and modulation of *Campylobacter jejuni* infection.](image)

Both host and dietary factors such as interleukin-10 (IL-10), single IgG IL-1 related receptor (SIGIRR) and zinc, respectively, suppress innate immune responses induced by *C. jejuni* lipooligosaccharide (LOS). As a result, the reduced inflammation levels lead to amelioration of campylobacteriosis symptoms and reduce the risk for the onset of post-infectious sequelae including RA or GBS. **Source** Mousavi et al. 2020 (adapted)
represents an effective physiological barrier directed against the pathogen (Hafiz et al. 2018). Depending on both, the immune status of the human host and the virulence factor repertoires of the infecting pathogenic strains, infected patients display a highly variable intestinal disease complex after a mean incubation period of 1–5 days (as reviewed by Skirrow 1977; Price et al. 1979; Walker et al. 1986; Blaser 1997; Awofisayo-Okuyelu et al. 2017; Facciolà et al. 2017). While some patients exhibit rather mild symptoms, others suffer from watery diarrhea or from severe campylobacteriosis characterized by purulent, bloody diarrhea, abdominal cramps and fever (Walker et al. 1986; Blaser 1997; Kist and Bereswill 2001; Janssen et al. 2008). In some instances, affected patients are even at risk for severe post-infectious autoimmune diseases such as GBS, MFS or reactive arthritis (RA) weeks or months after the initial infectious gastrointestinal manifestation (Allos 1997; Kist and Bereswill 2001; Mortensen et al. 2009). Moreover, C. jejuni infection is considered a potential trigger for irritable bowel syndrome (IBS), celiac disease and even inflammatory bowel diseases (IBD) which may persist lifelong (reviewed by Kaakoush et al. 2015; Keithlin et al. 2014). It is noteworthy that in immune-compromised patients spread of C. jejuni may cause extra-intestinal systemic manifestations affecting even the brain (Kaakoush et al. 2015).

However, in otherwise healthy individuals, C. jejuni-induced disease is usually self-limiting and lasts for several days up to two weeks. Even though antimicrobial treatment may reduce the duration of campylobacteriosis by 1–2 days (Ternhag et al. 2007), antibiotic application is not appropriate in general to mitigate the symptoms. One major reason is that the worldwide C. jejuni strain repertoire displays increasing resistance rates to macrolides and fluoroquinolones that represent first-line and second-line options for the treatment of particularly severe systemic disease manifestations, respectively (Lübbert 2016). Furthermore, the antibiotic concentrations can only insufficiently be controlled in C. jejuni-induced disease, particularly in the scenario of severe diarrhea with absorptive malfunctions of the inflamed mucosa. This resulted in the recommendation that antibiotic compounds should generally not be used for the treatment of campylobacteriosis with few exceptions, particularly for severely affected patients presenting with immunosuppressive comorbidities. In consequence, infected individuals do not receive causal medical treatment and rather need to sustain disease with symptomatic measures including rehydration and substitution of electrolytes to assure sufficient sodium absorption. While improvements in anti-pathogenic treatment options of campylobacteriosis are rather disappointing, the diagnostic repertoire for C. jejuni infection has continuously and successfully been improved, for instance by development of novel strategies in order to detect viable but not culturable (VBNC) C. jejuni bacteria (see also Chapter “Molecular Mechanisms of Campylobacter Biofilm Formation and Quorum Sensing” of this book). The search for novel alternative drugs to combat campylobacteriosis in recent preclinical studies applying novel murine infection and inflammation models revealed promising results, which await further approval and validation in clinical studies (see Chapter “Murine Models for the Investigation of Colonization Resistance and Innate Immune Responses in Campylobacter Jejuni Infections” of this book).


3.2 Burden of Disease

Intestinal *C. jejuni* infections and the above-mentioned post-infectious complications have been progressively rising during the last two decades worldwide (Lackner et al. 2019; Kaakoush et al. 2015). Calculated rates for the year 1997 in high-income countries were in the range of 4–5 incidents per 100,000 inhabitants. Valid global data from all reporting nations revealed that in the year 2015 incidences increased to 14–15 per 100,000 humans with a much higher estimated number of unknown cases—calculated to be in minimum 5 times higher. Thus, *Campylobacter* infections cause a high socioeconomic burden (Kaakoush et al. 2015). The increase in human campylobacteriosis cases worldwide is well in line with the rise in consumption of raw milk and other animal products including *C. jejuni* contaminated chicken and other poultry meat in high-income countries (Cody et al. 2019). Actual data from low-middle income countries show the same trend (Thomas et al. 2020) but are often too scarce to draw scientifically validated conclusions regarding worldwide incidence and prevalence rates (Kaakoush et al. 2015). By taking all these facts into account, we can summarize that campylobacteriosis is a serious inflammatory intestinal disease affecting the global human population. Mortality rate statistics indicate that newborn infants, children and immunosuppressed individuals including the elderly are at particular risk for developing severe systemic complications. Detailed data on the epidemiology of *C. jejuni* infections are summarized by Romdhane and Merle (Chapter “The Data Behind Risk Analysis of Campylobacter Jejuni and Campylobacter Coli Infections” in this book).

In recent years, more calculations on the costs of *Campylobacter* infections and the burden of *Campylobacter*-associated diseases were published. Annual costs for the USA were estimated to range from 1.2 to 4 billion $ (Eberle and Kiess 2012; Batz et al. 2014). The cost of food-borne campylobacteriosis to public health systems and to loss of individual health and productivity in the EU is estimated to be around €2.4 billion per year (EFSA 2014), with an underlying mean cost per case estimate of €267 (Pitter et al. 2018). In this context, measures of disease burden by calculating disability-adjusted life years (DALY), quality-adjusted life years (QALY), years of potential life lost (YPLL), for instance, are becoming increasingly important parameters to set priorities in health care or to assess and shape risk-based food safety policies (Fig. 3). In a recent systematic review, Lackner and colleagues analyzed studies published between 1996 and 2016 from 27 countries, with the majority of the studies focusing on Europe (Lackner et al. 2019). After adjusting study-specific DALY to 100,000 people, large differences were observed between countries, ranging from 0.4 DALY per 100,000 people in France (Van Lier and Havelaar 2007) to 109 DALY per 100,000 in Poland (Mangen et al. 2016). Differences in DALY between and even among countries were largely attributed by Lackner and co-workers to the different incidences applied in the calculations (Lackner et al. 2019). When focusing exclusively on food-borne burden of disease for *Campylobacter*, calculations ranged from 0.5 DALY per 100,000 people in Greece (Gkogka et al. 2011) to 21.2 DALY per 100,000 in New Zealand (Lake et al. 2010). In the global context, disease burden
Fig. 3  **Burden of disease measures.** Schematic presentation of the calculation of the DALY. *Source* Public Health England (2015) (adapted)

of *Campylobacter* was generated and compared to other food-borne or diarrheal diseases (Kirk et al. 2015). The authors estimated that overall, *Campylobacter* caused 3.7 million DALY (2.9–5.3; 95% UI) in 2010 (out of estimated 78.7 million DALYs for all 22 diseases included in the study), corresponding to 31 DALY per 100,000 people (22–46; 95% UI). The ratio of DALY between the age groups <5–≥5 was 1.87 (1.26–2.92) compared to 0.76 for all food-borne diseases included.

Large differences were observed between regions for DALY per 100,000 people [African Region: 70 (41–112; 95% UI), Region of the Americas: 13 (8–18), Eastern Mediterranean Region: 90 (56–130) European Region: 9 (6–13), South-East Asian Region: 33 (9–83), Western Pacific Region: 10 (4–17)]. A discounted, QALY-based EU estimate resulted in 15.23 QALY loss per 1000 human *Campylobacter* cases (Pitter et al. 2018). Within that, gastroenteritis accounted for 9.96 QALY loss in 1000 human cases, *Campylobacter*-related RA accounted for 2.33 QALY loss per 1000 gastroenteritis cases, and a discounted health burden of 2.94 QALY loss due to GBS in 1000 human *Campylobacter* gastroenteritis cases. For the USA, Batz and co-workers estimated 16 QALY lost per 1000 campylobacteriosis cases, summing up to 13,256 QALY losses annually in the USA (Batz et al. 2014). Taken together, severe symptoms of campylobacteriosis lead to a significant limitation of infected individuals and cause a high socioeconomic burden worldwide.
When it comes to questioning the molecular basis of *C. jejuni*-induced intestinal pathogenesis in human patients, it is noteworthy that the bacterial virulence and pathogenicity factors mediating campylobacteriosis have been investigated to date. However, our knowledge regarding the inflammatory immune responses in the human host is still limited mainly because convenient murine infection models have not been available for a long time (see below). It is known for decades that the onset of *C. jejuni*-induced disease depends on the translocation of the highly motile pathogens from the gut lumen to the epithelial cell layer as well as on epithelial adherence and subsequent active invasion of the subepithelial tissues including the lamina propria (Backert et al. 2013 and Chapter “*Campylobacter* Virulence Factors and Molecular Host–Pathogen Interactions” in this book). Thus, essential roles of *C. jejuni* flagella, adhesins and invasins as essential pathogenicity factors in the onset, progression and clinical outcome of campylobacteriosis have been determined at the molecular level and were independently confirmed by results from a multitude of in vitro as well as in vivo studies (Cróinín and Backert 2012; Backert and Hofreuter 2013). While these bacterial factors serve as valid targets for novel treatment strategies, the inflammatory syndrome induced by *C. jejuni* in the human host is much less studied and awaits further investigation.

During the last decades of research, a substantial change in basic paradigms of immunopathogenic concepts of *C. jejuni*-induced enteritis was necessary to identify bacterial molecules that are essential for the induction of intestinal inflammation during human campylobacteriosis (reviewed by Phongsisay 2016). While many scientists still follow the concept that the disease is mainly caused by a bacterial exotoxin, *Campylobacter* research was initially focused on the intensive search for a potent Cholera-like toxin (CLT), which was thought to be common to all *C. jejuni* strains (reviewed by Walker et al. 1986). This line of investigations was not successful but has led to the identification of the cytolethal distending toxin (CDT), which contributes to the virulence of *C. jejuni* but is not produced by all pathogenic strains (Facciòla et al. 2017; Pickett and Whitehouse 1999; Bang et al. 2001). In conclusion, exotoxins like CDT and CLT are not essential for the onset and progression of campylobacteriosis but may aggravate the disease when they are produced by the infecting *C. jejuni* strain(s).

Today, we follow a second concept assuming that intestinal inflammation and the post-infectious autoimmune diseases triggered by campylobacteriosis in humans are mainly caused by an intense massive innate immune response to bacterial endotoxins derived from the motile, adhesive and invasive *C. jejuni* that had translocated to the subepithelial compartment. This “endotoxin concept” was formulated very early based on results from studies of histopathological changes during intestinal campylobacteriosis in *C. jejuni*-infected humans including healthy volunteers and hospitalized patients (Black et al. 1988; Blaser et al. 1979; Price et al. 1979). In the absence of a potent exotoxin common to all *C. jejuni* strains, the accumulation
of neutrophils and macrophages histologically observed at intestinal sites of hyper-
acute inflammation support the integrative view that C. jejuni endotoxins including
lipooligosaccharides (LOS) trigger the pathogenesis of campylobacteriosis mainly
via activation of the innate immune system (Fig. 2). In this regard, campylobacteriosis
is very similar to the onset of massive innate immune activation by the LOS of Neis-
seria species such as Neisseria meningitidis and N. gonorrhoeae, primarily affecting
other body compartments (Black et al. 1988; Moran et al. 1996). The revival of this
second concept of C. jejuni-mediated gastroenteritis paved the way for the identifica-
tion of bacterial agents essentially involved in intestinal inflammation during campy-
lobacteriosis. A breakthrough in the understanding of molecular immunopathogen-
esis of human campylobacteriosis was based on the observation that both intestinal
inflammation and the development of post-infectious sequelae are significantly asso-
ciated with the production of sialylated LOS variants A, B and C by the infecting C.
jejuni strains (Mortensen et al. 2009). The major role of this prominent endotoxin in
pathogenesis was further confirmed recently by detailed analysis of intestinal barrier
damage and LOS-mediated inflammatory signaling pathways in intestinal biopsies
taken from C. jejuni-infected patients (Bücker et al. 2018). The corresponding results
demonstrated that diarrhea in human campylobacteriosis results from sodium malab-
sorption induced by invading C. jejuni via a LOS-mediated cytokine storm initiated
by the activated innate immune cells. Analyses of global gene expression revealed
that the pathogenic LOS is the master regulator of this inflammatory scenario, which
leads not only to the inhibition of sodium channels, but also to the breakdown of
intestinal epithelial barrier functions, to apoptosis, and to tissue destruction (Bücker
et al. 2018; reviewed by Chapters “Campylobacter Virulence Factors and Molecular
Host–Pathogen Interactions” and “Diarrheal Mechanisms and the Role of Intestinal
Barrier Dysfunction in Campylobacter Infections” in this book). Thus, the hetero-
genality of campylobacteriosis symptoms seen in humans results, in part, from the
scattered distribution, modular composition and variability of C. jejuni surface LOS
which is due to the tremendous genetic variability of the pathogen (reviewed in
Chapter “Population Biology and Comparative Genomics of Campylobacter Species
of this book).

The roles of bacterial LOS and the innate immune system in the induction of
enteritis supported the investigation of molecular mechanisms underlying campy-
lobacteriosis (Mortensen et al. 2009). Besides their roles in human infection, LOS and
other carbohydrate endotoxins of C. jejuni maintain the bacterial anatomic structures
and protect the pathogens against environmental stress—by biofilm formation, for
instance (reviewed by Chapter “Molecular Mechanisms of Campylobacter Biofilm
Formation and Quorum Sensing” in this book). C. jejuni LOS is a surface glycolipid
consisting of an oligosaccharide moiety and a lipid A core. Binding to its receptor,
Toll-like receptor 4 (TLR4), is essential for the activation of innate immune cells
(reviewed by Phongsisay 2016). Variations in LOS structures affect the inflamma-
tory potency of C. jejuni and explain the variability seen in human disease outcome.
Sialylation of the oligosaccharide moiety enhances bacterial invasion, binding to
TLR4 and cytokine production by immune cells. Moreover, since some sialylated
oligosaccharide chains in *C. jejuni* LOS are structurally related to human gangliosides, infection with respective pathogenic bacterial strains induces production of anti-ganglioside antibodies which in line with macrophage activation cause axonal destruction leading to GBS. In conclusion, although the O-antigen characteristic of bacterial lipopolysaccharide (LPS) is not present in LOS of the majority of *C. jejuni* strains (Karlyshev et al. 2005; Naito et al. 2010), the lipid A moiety of this truncated LPS molecule per se is a highly potent TLR4 agonist, and the sialylated LOS triggers severe forms of campylobacteriosis and post-infectious sequelae including GBS (Fig. 2). Thus, the functional parts of the LOS molecule provide the molecular basis for a better understanding of both, the diverse intestinal disease manifestations and the development of post-infectious sequelae in humans.

Our knowledge regarding *C. jejuni*-induced intestinal pathogenesis was further augmented by detailed investigation of the intestinal histopathology during campylobacteriosis in infected human patients. It has been known for decades that the intestinal histopathological features of campylobacteriosis are characterized by large ulcerative epithelial tissue destruction that is mostly driven by neutrophilic granulocytes and macrophages accumulating in high numbers in and under the epithelium at intestinal sites of *C. jejuni* entry (Price et al. 1979; Kaakoush et al. 2015; Backert et al. 2017). In response to LOS derived from invading *C. jejuni* bacteria, these innate immune cells produce toxic oxygen radicals including nitric oxide, peroxynitrate and superoxide in line with pro-inflammatory mediators, which in sum cause massive epithelial apoptosis mounting in ulcerative tissue destruction and bloody diarrhea (Walker et al. 1986; Kaakoush et al. 2015). Macrophage derived TNF-α, IL-6 and IL-8 as well as IL-1β, IL-12 and IL-23 from dendritic cells act as initiators and promoters of inflammatory responses. Activated T-cells produce IFN-γ, IL-17, IL-22 and anti-inflammatory cytokines IL-4 and IL-10 dampening the immune responses and thereby supporting self-limitation of disease (reviewed by Al-Banna et al. 2018). This inflammatory scenario was confirmed independently by artificial *C. jejuni* infection of ex vivo biopsies (Edwards et al. 2010). The resistance of *C. jejuni* to killing by phagocytosis and its ability to reside within phagocytes for up to 7 days is a very important—but often overlooked—feature of the pathogen (Kiehlbauch et al. 1985). Given that resistance to phagocytosis is an important feature of *C. jejuni* that developed during interactions with amoebae, the study of *C. jejuni* survival in those organisms is of great and stimulating importance for *Campylobacter* research (Vieira et al. 2015). While the bacterial factors mediating intracellular survival in phagosomes await further investigation, resistance to phagocytosis explains (i) the inability of macrophages and granulocytes to clear initial *C. jejuni* infection and (ii) the active transfer of live pathogens by migrating macrophages to mesenteric lymph nodes (Price et al. 1979; Walker et al. 1986; Kaakoush et al. 2015). In light of the major role of LOS in initiation of the inflammatory responses and the pronounced resistance of mice to LOS (see below), it is of note that human monocytes ingest *C. jejuni* more rapidly and vigorously than murine macrophages (Kiehlbauch et al. 1985). In conclusion, the results obtained from analyses of *C. jejuni*-induced intestinal immunopathology in human patients support the integrative view that the massive activation of the innate immune system via TLR4 signaling induced by *C. jejuni* LOS
is responsible for both, the initial symptom complex of intestinal campylobacteriosis (Mortensen et al. 2009; Bücker et al. 2018) as well as the severe post-infectious sequelae such as GBS or RA (Kaakoush et al. 2015). Taken together, our knowledge on innate immune activation by C. jejuni endotoxins is a prerequisite for the treatment of human campylobacteriosis, which also supports the prophylaxis of post-infectious sequelae (reviewed by Mousavi et al. 2020 and by Chapter “Murine Models for the Investigation of Colonization Resistance and Innate Immune Responses in Campylobacter Jejuni Infections” in this book).

3.4 Novel Murine Models of C. jejuni Infection Offering Detailed Investigations and Treatment Strategies for Campylobacteriosis and Associated Long-Term Sequelae

The development of novel treatment options for human campylobacteriosis depends on the availability of robust and standardized animal models, which display both the symptoms and the molecular pathogenesis induced by Campylobacter infections in humans. Most recently, the major role of C. jejuni LOS in the induction and progress of campylobacteriosis was further confirmed by research groups working independently from each other on the establishment of novel animal models for the investigation of C. jejuni-host interactions. The development of highly convenient murine infection models for campylobacteriosis was a great challenge since conventional mice only respond very weakly to bacterial LPS/LOS and further display a pronounced intestinal colonization resistance against C. jejuni mediated by the murine gut microbiota. Notably, due to their low TLR4 responses, the LOS resistance of mice is approximately 10,000 fold higher (Warren et al. 2010; Munford 2010) as compared to humans (Taveira da Silva et al. 1993). Hence, detailed investigation of the LOS-driven inflammatory responses in humans was severely hampered for long time periods by the lack of appropriate murine infection models. In conclusion, the recent progress in the development of novel murine models of C. jejuni infection is based on the modification of both the microbiota composition as well as the LOS responses of mice (reviewed by Mousavi et al. 2020, and by Chapter “Murine Models for the Investigation of Colonization Resistance and Innate Immune Responses in Campylobacter Jejuni Infections” in this book). These murine models of C. jejuni infection were developed on the basis of the ground breaking investigations by Linda Mansfield (Mansfield et al. 2007), Christian Jobin (Lippert et al. 2009), Bruce Vallance (Stahl et al. 2014) and Richard Guerrant (Giallourou et al. 2018), who demonstrated that genetically modified mice with a reduced intestinal microbiota, sensitized to LOS by genetic manipulation or by dietary modifications inducing zinc depletion can be effectively infected by C. jejuni and display key symptoms of human campylobacteriosis (Poly and Guerry 2008; Heimesaat and Bereswill 2015; Stahl et al. 2017; Mousavi et al. 2020). Thus, the major role of C. jejuni LOS in the
induction of campylobacteriosis was impressively confirmed by independent studies focused on manipulation of the murine immune system via IL-10 deficiency (Mansfield et al. 2007), single IgG IL-1 related receptor (SIGIRR) deficiency (Stahl et al. 2014, 2017) and zinc depletion (Giallourou et al. 2018), all of which resulted in abolished murine LOS resistance as a consequence of increased activation of the murine TLR4 signaling pathways (Munford, 2010; Warren et al., 2010). It is well documented that IL-10 (Emoto et al. 2003; Robertson et al. 2006, 2007), SIGIRR signaling pathways and zinc (Snyder and Walker 1976; Ohata et al. 2010; Chen et al. 2012) effectively suppress LPS/LOS-mediated inflammatory responses in mice. Moreover, oral zinc supplementation constitutes a valid measure to protect children in low and middle income countries from bacterial diarrhea including campylobacteriosis (Lazzerini and Wanzira 2016).

Taken together, the novel murine infection models represent a major breakthrough in campylobacteriosis research since the immunopathology in the murine intestines characterized by apoptosis, granulocyte and macrophage recruitment, production of pro-inflammatory cytokines such as IFN, TNF, IL-6, IL-8 as well as the activation of T and B cells is very similar to the immune and histopathological responses seen in C. jejuni-infected humans (Price et al. 1979; Bücker et al. 2018). Given that i) we confirmed these findings in our own investigations (Bereswill et al. 2011; Haag et al. 2012b; Masanta et al. 2013; Heimesaat and Bereswill 2015), ii) all these different animal models have in common that mice presenting with clinical signs of campylobacteriosis are sensitized to LOS by completely independent manipulations, and iii) TLR4-deficient mutants of these LOS-sensitized mice showed significantly less intestinal inflammatory responses (Haag et al. 2012b; Stahl et al. 2014, 2017), these novel insights provide final proof that C. jejuni LOS plays a key role in C. jejuni-induced inflammatory diarrhea in humans and other vertebrate hosts (reviewed by Chapter “Murine Models for the Investigation of Colonization Resistance and Innate Immune Responses in Campylobacter Jejuni Infections” in this book). These highly innovative murine infection models have generated substantial progress in the understanding of the molecular mechanisms underlying pathogen-host interactions during campylobacteriosis, and their standardization paves the way for the development of novel treatment strategies focused on (i) neutralization of LOS and pro-inflammatory oxygen radicals, (ii) strengthening intestinal epithelial barrier function, (iii) inactivation of the barrier-breaking C. jejuni-related factors including motility, tissue destruction by proteases and other invasins, as well as (iv) vaccination. While some murine models of infection could be developed to the preclinical level for validation of most of these novel intervention strategies (Stahl et al. 2017; Masanta et al. 2013; Heimesaat and Bereswill 2015), development of a potent vaccine is still most challenging given the role of sialylated LOS in the induction of post-infectious sequelae such as GBS, MFS or RA (reviewed by Chapter “Murine Models for the Investigation of Colonization Resistance and Innate Immune Responses in Campylobacter Jejuni Infections” in this book). In particular, the secondary abiotic IL-10-deficient mouse model of campylobacteriosis has been proven to be highly useful for the analysis of C. jejuni infection, mainly because disease induction in this infection model depends on motility and invasive properties of the pathogen (Schmidt et al.
It is of note here that commensal *Escherichia coli*, which lack any invasive or other pathogenic properties, do not induce any immunopathology upon peroral challenge of secondary abiotic IL-10-deficient mice (Haag et al. 2012b). Recently, the secondary abiotic IL-10-deficient murine model was standardized and could be further developed to the preclinical level for pharmaceutical analysis of alternative drugs, including curcumin, resveratrol, carvacrol, ascorbate and vitamin D, which effectively suppressed inflammation in course of campylobacteriosis (reviewed by Chapter “Murine Models for the Investigation of Colonization Resistance and Innate Immune Responses in *Campylobacter Jejuni* Infections” in this book). There is good evidence that the dampening of the innate immune responses in the onset of intestinal campylobacteriosis by those interventions might reduce the risk for the development of post-infectious sequelae.

Given the central and general role of IL-10 in maintaining gut homeostasis by suppression of inflammatory responses (Neumann et al. 2019; Iyer and Cheng 2012), it is also of great impact that conventional infant mice, which do not raise a sufficient IL-10 response in their intestines, become effectively colonized by *C. jejuni* and display the typical course of self-limiting campylobacteriosis seen in humans (Haag et al. 2012a). Moreover, those mice cleared the intestinal disease and developed immune cell infiltrates at extra-intestinal sites including the liver, the kidneys and the lungs. These features highlight conventional infant mice as useful model to study systemic manifestations of campylobacteriosis including the onset of post-infectious sequelae including RA or GBS. The numbers of patients developing severe post-infectious autoimmune diseases following intestinal campylobacteriosis including RA (1–13%), GBS (0.001%), IBD such as ulcerative colitis and Crohn’s disease, IBS or celiac disease are increasing to non-tolerable levels worldwide (Keithlin et al. 2014; Kaakoush et al. 2015; Facciolà et al. 2017). Particularly, immunocompromised patients are at risk to develop extra-intestinal complications of initial intestinal campylobacteriosis entailing a multitude of disease manifestations ranging from meningitis, brain abscesses and cardiovascular complications to bacteremia and septicemia. The appearance of these secondary diseases induced by initial intestinal *C. jejuni* infection underlines the socioeconomic and individual burden of *C. jejuni*-induced inflammatory enteritis in humans. This scenario is basic to the insight that we are in urgent need for the development of novel treatment options which dampen the acute inflammation caused by the initial intestinal LOS response of the innate immune system, in order to prevent severe autoimmune reactions and extra-intestinal spread of *C. jejuni* (Keithlin et al. 2014). Valid data on the pathogenesis of GBS indicate that *C. jejuni* infection with strains producing sialylated LOS induces the production of antibodies specific for similar structured molecules decorating the myelin surface of axons in the nervous system, which leads to immune complex-mediated destruction of nervous tissues and subsequently results in GBS (Goodfellow and Willison 2016). Furthermore, similar immune-mediated post-infectious mechanisms are proposed for RA. Most recently, the innovative development of a *C. jejuni*-induced murine GBS model will allow not only for the study of molecular mechanisms underlying the GBS-inducing capacity of *C. jejuni*, but also enforces measures for prophylaxis and treatment of GBS in the near future (Brooks et al. 2017, 2019). However, the future
developments will reveal whether murine models of infection may add to prevention and treatment in this regard as well.

4 Concluding Remarks

The above-outlined substantial scientific progress in understanding the molecular interactions underlying \textit{C. jejuni} pathogenesis supports the principal view that bacterial LOS plays a major role in molecular immunopathogenesis of acute campylobacteriosis and its post-infectious sequelae. Thus, the initial intestinal inflammatory symptom complex induced by motile, adhesive and invasive \textit{C. jejuni} in the intestinal epithelium is mainly driven by activation of the innate immune system and aggravated by bacterial exotoxins—in case these are produced by the infecting strain. This basic concept is strongly supported by the fact that the post-infectious sequelae are autoimmune diseases caused by the adaptive immune system which is initially primed by the hyper-activation of the innate immune system in response to the endotoxin LOS of the invading bacteria (Fig. 2). Therefore, the revival of the old concept of \textit{C. jejuni}-induced inflammatory diarrhea (Moran et al. 1996; Blaser 1997) in line with the application of novel murine infection models will pave the way for preclinical evaluation of innovative prophylactic and treatment strategies to combat human campylobacteriosis in the near future. Actual therapeutic interventions for improvement of clinical symptoms during campylobacteriosis target bacterial LOS signaling pathways including anti-inflammatory approaches to dampen inflammation and tissue destruction alongside with the inactivation of bacterial pathogenicity and virulence factors such as motility, adhesins and invasins, respectively (reviewed by Chapter “Murine Models for the Investigation of Colonization Resistance and Innate Immune Responses in \textit{Campylobacter Jejuni} Infections” in this book). Given that exclusive targeting of pathogenic structures is always accompanied by the risk of resistance development, it seems recommendable to combat both \textit{C. jejuni} factors in line with immune responses by combined application of synergistically acting molecules.

Finally, closing the circle between asymptomatic colonization in poultry and acute disease in infected humans, the pronounced LPS/LOS tolerance of birds including chickens which is 100-fold higher as compared to mice and even 1,000,000-fold higher (Adler and DaMassa 1979) as compared to humans (da Silva et al. 1993) might provide the basis for the understanding why chickens and other poultry do not develop intestinal inflammation upon \textit{C. jejuni} colonization and are therefore a major source for human infection (Young et al. 2007). Thus, all the novel discoveries in the active and dynamic field of campylobacteriosis research support the optimistic view that novel murine models in combination with clinical studies enable us to develop novel drugs for prophylaxis and treatment of human campylobacteriosis, which will in turn prevent or lower the risk for post-infectious sequelae in the near future.
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