Review

The ecology of *Campylobacter jejuni* in avian and human hosts and in the environment

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Campylobacter jejuni, and its close relative *C. coli*, are highly successful bacteria colonizing the intestinal mucosa of a wide range of avian and animal hosts, including humans. In general, this colonization is either as a commensal, as in birds, or is an asymptomatic transient infection, as in livestock and in humans in endemic regions. However, in susceptible human populations, infection causes acute bacterial enteritis. The ecology of the organism for each outcome of colonization is considered, and evidence suggests that disease symptoms reflect the unfortunate consequences of the expression of bacterial factors associated with adaptation to the host gut environment. Susceptibility to disease appears to be associated with lack of acquired immunity. Although campylobacters do not grow outside the host, they can remain viable for long periods in water, foods, etc. Under such conditions, the organisms adapt to numerous hostile environmental stresses. Although such stressed organisms may be viable, the infectivity of surviving bacteria becomes severely compromised over time. Thus, the comparison of *Campylobacter* ecology in different environments suggests that increasing trends in human campylobacteriosis represent an unfortunate consequence of: decreasing human immunity because of reduced exposure to stress-compromised organisms; intensive farming practices creating monocultures of some strains; and improved processing and retail practices increasing the viability of campylobacters in food reaching the consumer.

Int J Infect Dis 2002; 6: 3S16–3S21

INTRODUCTION

Campylobacter jejuni, and its close relative *C. coli*, are Gram-negative, thermophilic, microaerophilic bacteria that can colonize the intestinal mucosa of many host species and are ubiquitous in the environment. Veterinary interest in these organisms is primarily a consequence of their role as common foodborne pathogens causing acute human enteritis. In this review, the physiologic characteristics of these organisms enabling growth, survival and interaction with the various habitats from which they can be recovered will be discussed. For the purposes of this review, *C. jejuni* and *C. coli* are considered to have similar, if not identical, physiologic properties, and so will be referred to generically as campylobacters or *C. jejuni*. In order to provide the reader with the most comprehensive literature, where possible recent reviews have been cited rather than original manuscripts.

CAMPYLOBACTER INFECTION IN AVIANS

Campylobacters can colonize the intestinal mucosa of most warm-blooded host species.[1,2] However, *C. jejuni* appears to have evolved to preferentially colonize the avian gut. Most information has been obtained from colonization in the broiler chicken, which can be considered the model for avian colonization. Worldwide, a high proportion of broiler flocks are colonized with campylobacters. In countries with national survey data of poultry flocks, up to 95% of flocks can be *Campylobacter*-positive.[3]

Colonization in birds is age-related.[4,5] Infection is undetectable in newly hatched chicks, and is usually detectable only when the birds are 2–3 weeks of age. This lag phase occurs even in organically reared chickens, and may be a general feature of colonization in birds.[3] Spread of infection from individual to individual is extremely rapid, and virtually all birds (flock sizes can be up to 30 000 birds) become positive within 3 days. This rapid transmission is a reflection of a low infective dose and a colonization potential enhanced by in vivo passage.[6] Overall, *Campylobacter* infection in flocks can be viewed as an acute outbreak. Colonization, once it occurs, reaches extremely high levels; about 10^7 colony-forming units (CFUs) per gram of cecal contents[7] or higher. Nevertheless, colonized birds are invariably asymptomatic. Moreover, colonization is persistent, suggesting that any immune response is ineffective in the elimination of infection, at least under these circumstances, although older birds, e.g. layers, may have reduced colonization with time. In summary, *C. jejuni* acts like a commensal in birds, so this situation has large benefits for the bacterium and no detrimental effects on the host.

CAMPYLOBACTER INFECTION IN MAMMALS

Campylobacters can colonize most mammals.[1] However, as a consequence of their causal relationship with intestinal infectious disease, most is known about

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campylobacteriosis in humans. It is now increasingly clear that there are at least two outcomes of infection in humans, depending on whether the population under investigation is disease susceptible or not.

Disease-susceptible populations

In many countries, campylobacters are considered the most common cause of human acute bacterial enteritis, with approximately 1% of susceptible populations developing *Campylobacter*-associated disease per annum.[8] Susceptible populations are primarily located in industrialized countries, such as those in northern Europe and North America.[9] In such populations, exposure is considered to be infrequent. Additional susceptible populations include young children (under 2 years of age) in the non-industrialized countries.[10] In these populations, asymptomatic carriage of campylobacters is extremely rare,[11] but infected individuals generally present with a self-limiting acute watery or bloody diarrhea lasting for 5–7 days. Excretion during this period may be high, but this high level of excretion is generally short-lived. Disease can be severe, with up to 10% of individuals requiring hospitalization.[12] Individuals who become ill show a rapid and effective immune response, which appears to be responsible for the termination of disease and colonization.[13] This response may provide temporary protection from further challenge. No other adult animal populations appear to be as susceptible to disease as humans.[1] Thus, in disease-susceptible human populations, *C. jejuni* acts as a pathogen. This outcome of colonization is detrimental to the host and not very beneficial for the organism, as it reduces the efficacy of bacterial growth.

Colonization in non-disease-susceptible populations

Campylobacters can also be recovered from the feces of many asymptomatic adult humans throughout the non-industrialized world, where the infection is considered to be endemic.[10] Unfortunately, there is very little available information about such infections. Interestingly, the same outcome of colonization prevails in most animals, i.e. age-acquired asymptomatic colonization. It would appear that most of these infections result from transient passage of campylobacters through the gut, with perhaps temporary colonization and limited growth, but without symptoms of disease. The reasons for this are unclear. One explanation is that repeated exposure to campylobacters in the environment, particularly during infancy, generates a protective immune response in potential hosts. This protection is effective against disease, but not necessarily against colonization.[13] Certainly, studies in naturally infected animals (unpublished data) and in humans in the underdeveloped world[14] suggest that multiple *Campylobacter* strains, and even species, can be present, suggesting that there is constant exposure from multiple sources. In such infected animals and humans, excretion is intermittent, low-level, and short-lived, although it may be enhanced when immune competence is compromised. In some animals, e.g. dogs, fecal carriage is increased during stressful periods such as parturition[15] or rehousing. Seasonal variations in sheep and cattle may also reflect similar stresses.[16,17] In endemically exposed populations of animals and humans, campylobacters are transient. Such colonization causes little trouble to the host, once their disease-susceptible period is over, and although it is not very productive for the organism, it does allow periods of genetic exchange, and therefore enables genetic diversity to occur.

THE PHYSIOLOGY, MECHANISMS AND OUTCOMES OF HOST COLONIZATION

Under natural conditions, *Campylobacter* growth is only achieved within a suitable host environment. The prerequisites of growth are to locate a suitable host habitat, to take possession, to maintain station, if necessary in the face of competition or host defenses, to acquire nutrients, and to avoid or respond to hostile changes in habitat conditions. All of these events are mediated by bacterial factors. Some of these factors may induce effects with pathologic consequences for the host.

Most of the information available on *Campylobacter* colonization mechanisms has been derived from oral challenge models in chickens. As far as can be ascertained, colonization in mammals involves similar bacterial factors, although the extent and consequences of infection can be quite different. Experimentally pathogen-free chickens up to 6 weeks of age can be readily and reproducibly colonized with doses as low as 10 CFU of wild-type *Campylobacter* strains.[6] The characteristics of this colonization closely mimic natural infection in broiler flocks, with the apparent exception of the lag phase. However, experimental challenge of young birds, removed from commercial flocks to the laboratory during the lag phase, can be less reliable (Cawthraw et al, unpublished data), and this resistance may be associated with maternal antibodies and/or competitive gut flora.

Initially, organisms are found throughout the avian gut, but, within a short period, colonization is largely confined to the cecum and lower small intestine (LaRagione et al, unpublished data). Within 5 days of challenge, the level of colonizing organisms in chickens reaches a plateau, which is extremely high: up to 10^{10} CFU per gram of cecal contents.[6] Once colonization is established, it is chronic, although levels may fall after 9 weeks or so. Intermittent colonization of the ileum, jejunum and duodenum may occur, and occasionally organisms can be recovered from the spleen and liver, indicating that extraintestinal infection can occur. The site of bacterial growth is the mucus overlying the intestinal epithelial cells, and the bacteria maintain their station in the mucous flow by means of their rapid and characteristic motility, mediated by two bipolar flagella.

In vivo, there is little, or no, evidence of attachment to underlying intestinal epithelial cells. However, attachment in vitro has been reported.[18] The flagella may be involved in this, but the role of fimbriae cannot be excluded. However, there has been some debate recently about the presence of such organelles, and there is little evidence from the genome sequence for structural fimbrial genes.[19]

The molecular basis of colonization is now being elucidated by comparison of the colonization potentials of defined mutants with those of parent wild-type strains in chick models.[1] Among the bacterial factors considered to be important for colonization are, to date, gene products with roles in motility, attachment, protection from oxidative stress, and temperature-dependent regulation. Changes in protein and antigen profiles[20] of bacteria during colonization indicate that growth in the host gut environment involves the upregulation of some genes. This is consistent with the known enhanced colonization potential of laboratory-attenuated strains with in vivo passage.[6]

Some nutrients essential for *Campylobacter* growth may be poorly available or unavailable to the bacteria within the gut lumen. However, these nutrients, such as iron, may be available from host tissues. Bacteria can develop strategies, such as toxin production or invasion, to access such host materials by damaging the integrity of the host intestinal mucosa. Such strategies inevitably have pathogenic consequences for the host. During campylobacteriosis, enteric disease suggests that bacterial toxin expression and/or epithelial cell invasion are potential consequences of colonization.

Invasion

A minor population of organisms colonizing the gut appears to be able to traverse the intestinal epithelium and cause systemic infection.[18] This is reflected in the occurrence of bacteremic phases of infection and the occasional recovery from spleen and liver, even in the commensally infected hosts. These organisms may proceed to cause septicemia, but *C. jejuni* is serum sensitive,[21] so this is an infrequent event. Nevertheless, some individuals present with extraintestinal infections consistent with an invasive organism. Extraintestinal infections may occur as a consequence of translocation between, or invasion through, intestinal epithelial cells. Both can occur and are detectable in in vitro models.[18] These models clearly show that most strains are poorly invasive, but that some strains are highly invasive or even hyperinvasive. The level of invasiveness is independent of the strain source, and is inconsistently related to disease presentation. Thus, there is no clear indication at present of the role of invasiveness in disease. However, it is possible that invasive organisms can localize in niches that are protected from immune responses, within the hosts, thus enabling persistence of infection. Nevertheless, the presence of extraintestinal organisms induces a rapid and substantial circulating immune response, which may contribute to the self-limitation of disease.[13] Until the molecular basis of the invasiveness is identified, the role of this bacterial property in disease and or colonization will remain unclear.

Toxins

All the clinical evidence also suggests that campylobacters express a toxigenic factor during disease-associated host colonization.[22] Although many toxin activities have been described, genome sequencing only identified one gene locus (*cdt*) with homologies to known toxins.[19] The cytolethal distending toxin (CDT) affects epithelial cell morphology, causing distension and eventual cell death in in vitro models.[23] CDT expression varies between strains. This variation appears to be independent of source, and some isolates are CDT negative. This negativity is a consequence of both deletions and polymorphisms within the *cdtB* genes.[24] CDT-negative strains have been isolated from both diarrheic feces and blood, suggesting that CDT is not essential for the clinical symptoms of enteritis or bacteremia. The role of CDT in disease is therefore debatable. However, preliminary data indicate that CDT is expressed in humans during colonization and that it is highly immunogenic.

Host immune responses

To establish colonization and maintain growth, the bacterium must be able to overcome host innate and acquired immunity. Little is known about innate immunity to campylobacters, although preliminary work suggests that host genetic background, at least in chickens, can have an effect on susceptibility to colonization (Barrow, personal communication). Colonized birds,[25] humans post-disease and endemically exposed humans[26] all have detectable anti-*Campylobacter* circulating and mucosal antibodies. In all hosts, these antibodies are acquired rapidly post-challenge, and are directed against multiple antigens. Evidence suggests that initial immune responses may be, at least in part, protective against subsequent challenge.[27] In humans, but not in chickens, these early responses can terminate colonization. Repeated exposure appears to lead to full protection from disease, but not necessarily the transient form of colonization, at least in humans and most animals. This suggests that campylobacters may have some partly effective mechanisms of bacterial avoidance of host immune responses, and that host–pathogen interaction can vary between hosts.

Host-specific expression of bacterial colonization factors

It seems likely that the mammalian and avian intestinal environments are very different. One obvious difference is temperature: 43°C for avians, and 37°C for humans. Such host habitat differences require that campylo-

bacters adapt to the different environments in order to maximize their opportunity for growth. Bacterial mechanisms for adaptation involve the up- or down-regulation of some genes. Human- versus bird-specific expression of bacterial factors is extremely difficult to investigate, but a recent fortuitous isolation of a chicken *C. jejuni* strain, which caused illness in a research worker during a poultry abattoir visit, is enabling such comparisons to be made (Toszeghy et al, unpublished data). Preliminary studies with these matching strains have demonstrated the expression of chicken-specific colonization factors. Such factors may explain the differences in colonization outcome between avian and human hosts.

ECOLOGY OF CAMPYLOBACTERS OUTSIDE THE HOST ENVIRONMENT

For most campylobacters, growth in a host environment is only temporary. Thus the challenges of host-to-host transmission must be faced frequently. Once campylobacters are excreted from the host gut, or spilled during food processing, they encounter multiple hostile environmental factors. Such factors would include extremes of temperature, changes in osmolarity, atmospheric oxygen concentrations, and nutrient deprivation. Survival of such stresses is a prerequisite for reaching another host and further growth. Hostile environmental conditions result in a number of physiologic, morphologic and biochemical responses by campylobacters. All these events should be viewed as reversible to a variable extent, but if the stress continues, or is additive, then the stressed organism will progress inevitably towards bacterial death. In campylobacters, the most obvious response to stress is a change from a spiral form to a coccal form.[28] Development of coccal morphology is concomitant with a loss of culturability, but these two properties are independent. Similarly, culturability is lost before viability, as detected by the metabolism of tetrazolium salts. None of these properties may reflect the changes in infectivity of the organism following stress.[29]

During meat processing, campylobacters are exposed to many environmental stresses. Some strains appear able to survive these stresses better than others. Following through processing those strain types that were present in the live birds makes it clear that some strains do not survive processing well, while others are excellent survivors.[30] The reasons for such differences are unclear. The *Campylobacter* genome sequence has indicated the presence of a few known stress-regulatory systems.[19] Understanding the molecular basis of survival may be an important component in controlling the risk presented by campylobacters in the food chain.

CONCLUSION

In summary, campylobacters have become remarkably successful bacteria by evolving to colonize many hosts and by adapting to survive in environmental conditions where growth cannot occur. The outcome of colonization is host dependent. In birds, the organism acts as a commensal, while in susceptible humans, it acts as a pathogen; in most immune humans and animals, it acts as a transient. Thus disease, when it occurs, is an unfortunate outcome of colonization, and is thought to be related to host immune competence. Endemic exposure to low doses of multiple strain types appears to lead to, in susceptible hosts, immune protection from disease but not necessarily from colonization. This immune protection may be enhanced by the presence in the environment of strains with reduced virulence properties, such as impaired toxin expression or invasiveness, or organisms that have been environmentally stressed, such that infectivity is compromised. Given these observations, it is possible that decreased exposure of humans in industrialized countries to campylobacters may lead to increased disease as a consequence of decreased immunity. This effect could be compounded by the introduction of intensive broiler farm practices, which create monocultures of some, potentially pathogenic, strains. The improved processing and retail practices, by reducing the time taken between animal slaughter and consumer purchase, may also contribute to an increased risk by inadvertently maintaining the viability of these campylobacters. Thus, future assessments of the risk to human health resulting from *Campylobacter* contamination of the food chain should include the consideration of variation in host immunity and bacterial pathogenicity and survival.

ACKNOWLEDGEMENTS

I acknowledge the support of the Department of Environment, Food and Rural Affairs, UK, and the Food Standards Agency, UK, for ongoing *Campylobacter* studies. I would like to take this opportunity to thank all the members of the VLA Campylobacter Research Team for their continued support and contributions to these studies and for sharing their ideas.

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PANEL DISCUSSION

Question: *Your data suggest that transovarian passage of* Campylobacter *is not a problem. The newborn chicks don't seem to carry it from their mother.*

D. Newell: That is correct. Although we have reported the recovery of *Campylobacter* from oviducts in laying hens, we have no evidence of vertical transmission. All our evidence suggests that horizontal transmission from the environment is the source of poultry flock infections. I consider there to be no point in pursuing vertical transmission while horizontal transmission appears to be the major problem. Once this problem has been solved, then the role of vertical transmission can be determined.

Question: *Given this interesting genotypic change associated with environmental stress, would you comment on the methods of assessing clonality in the existing human studies, indicating whether or not this is a valid technique for trying to assess sources of infection?*

D. Newell: Genomic instability is covered by Trudy Wassenaar's presentation. Currently, at least in the UK, human *Campylobacter* strains are typed by a combination of serotyping and phage typing, largely for the purpose of detecting outbreaks. Similarity among strains is then confirmed by pulsed-field gel electrophoresis. Because outbreaks are usually short-term, the problems of genetic instability are minimal, and outbreak-related strains can be identified. We have similar experiences with poultry house outbreaks, which are also short-term.

However, genetic instability, especially in association with environmental stress, becomes far more important as a cause of strain diversity over time and distance. For this reason, neither phenotyping nor genotyping methods can be effectively used to identify sources of human *Campylobacter* infection.

C. Hofacre: I have always had problems in differentiating between invasion and translocation. What is the difference? Is it possible that what we see as invasion is only a momentary view of bacteria migrating into the cell, and that others have already translocated?

D. Newell: Our in vitro models suggest that *Campylobacter* can both invade and translocate. Transmission electron micrographs indicate that organisms enter and reside in the host cell as well as passing between host cells. At present, we do not know what the importance of each of these properties is in terms of disease.

R. Carnevale: If *Campylobacter* were being dispersed on an environmental surface such as a kitchen, what would you speculate would be the number of days for which the organism would remain viable and infectious?

D. Newell: Tom Humphrey has focused much of his work on bacterial survival in the kitchen environment, and has certainly been able to recover *Campylobacter*. He gives chickens to people to cook, and then obtains swabs from various kitchen surfaces, for *Campylobacter*; certainly, the organism can be recovered up to several days later. Tom's team has recovered campylobacters from all over the kitchen, including the kitchen cloth. Cross-contamination in the kitchen is considered a major factor in the transmission of infection from poultry meat.

C. Thornsberry: You suggested that the infective dose for disease for *Campylobacter* is high. Can you quantify this?

D. Newell: The infective dose for humans is very difficult to judge, and is largely dependent on the immune status of the individual. In the human volunteer study reported by Black et al, although infection rates increased with dose, there was no dose relationship with illness. Even doses as high as 10^9 CFU did not always cause illness. Nevertheless, illness has been reported with doses as low as 500 organisms. The infectivity is also dependent on the strain and the environmental stresses to which that strain was exposed.

E. Gonder: Do you see any difference in the pattern of *Campylobacter* populations in a broiler house between a flock that is on a build-up litter and a flock placed in a house that has been cleaned and disinfected?

D. Newell: In the UK and the rest of Europe, we use an all-in, all-out process for poultry production. This means that all litter is taken out when the flock is removed, with total house disinfection and cleansing. The only comparison I can personally make is between organically and intensively farmed broilers. Organically farmed birds are generally left in the same fields as previous flocks, and are surrounded by a *Campylobacter*-contaminated environment. In the UK, intensively farmed birds are in contained environments with restricted environmental exposure. We find that in organic flocks there are multiple strains present in the birds, whereas in intensively reared broilers there tends to be a limited number (mostly only one or two) of strains detectable. We interpret this as indicating that the organic birds are exposed to multiple strains, while the intensively reared birds have a limited exposure. The published evidence suggests that in those farms reusing litter for subsequent intensively reared flocks multiple strains are recovered from the birds.