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MINIREVIEW

Urease-Positive Thermophilic *Campylobacter* Species

Motoo Matsuda[1]* and John E. Moore[2]

Laboratory of Molecular Biology, School of Environmental Health Sciences, Azabu University, Sagamihara 229-8501, Japan,[1] *and Northern Ireland Public Health Laboratory, Department of Bacteriology, Belfast City Hospital, Belfast BT9 7AD, Northern Ireland, United Kingdom*[2]

FIRST DESCRIPTION OF *CAMPYLOBACTER LARI*

When in 1980 Skirrow and Benjamin examined the cultural characteristics of 1,220 *Campylobacter* isolates from a variety of sources, they described 42 new thermophilic *Campylobacter* isolates that were nalidixic acid (NAL) resistant and salt tolerant, referred to as NAL-resistant thermophilic *Campylobacter* (NARTC) (29). The first isolation of NARTC organisms was made from the feces of a symptomless 6-year-old boy in 1976; however, most strains (number of isolates, 26) were isolated from wild birds, in particular seagulls (*Larus argentatus* and *Larus ridibundus*). Of the other 15 isolates, 1 isolate was from the feces of a child, 6 were from dogs, 1 was from a healthy rhesus monkey, 2 were from cats, 2 were from poultry, 1 was from a bird, and 2 were from water (3, 29). The NARTC group was described on the basis of a comparison with 12 reference strains, representing various species of *Campylobacter*, in terms of their cell morphology, 28 physiological and biochemical characteristics, NAL resistance, trimethylamine *N*-oxide hydrochloride tolerance, and DNA-DNA hybridization (3). In relation to the designation of *C. lari*, Benjamin et al. (3) first proposed the name *Campylobacter laridis* for the new species; however, the name was later revised to *C. lari* (34).

FIRST ISOLATION OF UPTC

In England in 1985, five years after the original description of *C. lari* organisms, Bolton et al. (5) identified the first 10 isolates of urease-positive thermophilic *Campylobacter* (UPTC) organisms from the natural environment, namely, river water, seawater, mussels, and cockles (5), although the investigators were unable to isolate this organism from any warm-blooded animal or human specimens. These UPTC strains were gram negative and amphitrichate, oxidase, catalase, and nitrate positive; they grew at 37 and 42°C but not at 28°C; they were hippurate and hydrogen sulfide negative; and they were susceptible to NAL but resistant to cephalothin and grew in the presence of 1.5% (wt/vol) NaCl. This was the first demonstration of the occurrence of UPTC organisms. Further work suggested that these UPTC organisms belonged to *C. lari*, possibly as a biovar, based on the numerical analysis of high-resolution sodium dodecyl sulfate-polyacrylamide gel electrophoresis (PAGE) of proteins combined with computerized analysis of the profiles (24).

Following the description of UPTC organisms in the environment, the descriptions of these organisms isolated from humans were published in 1988 and in 1990, when UPTC isolates were obtained from patients in France (4, 14). Two isolates were found in 1986 in the feces of a 50-year-old man and a 60-year-old woman with diarrheal disease; subsequently, one isolate was obtained from the appendix of a 10-year-old boy with appendictis in 1987, and one was obtained from the urine of a 54-year-old male patient with a urinary tract infection in 1989 (4, 14). However, whether UPTC is associated with gastrointestinal or other human disease still remains unclear. Mégraud et al. (14) characterized UPTC as a variant of *C. lari* on the basis of a hybridization dot blot assay of the whole genomic DNA. To date, these isolates are the only four clinical isolates of the UPTC group that have been identified in humans throughout the world; hence this taxon does not appear to be a frequent human pathogen. Although in the early 1990s thermophilic campylobacters began to be isolated from the feces of humans with gastrointestinal disease, no UPTC organisms have been isolated from the tens of thousands of such specimens at the Northern Ireland Public Health Laboratory, Belfast City Hospital, Northern Ireland.

NATURAL RESERVIORS OF UPTC ORGANISMS

Wilson and Moore (36) demonstrated that 42% of the shellfish grown in Northern Ireland coastal waters were positive for thermophilic *Campylobacter* spp. which were isolated from 380 shellfish samples of bivalve molluscs (cockles, mussels, scallops, and oysters), where the percentages of distribution of *Campylobacter* spp. among these isolates were as follows: *C. jejuni*, 2%; *C. coli*, 8%; urease-negative *C. lari*, 24%; *Campylobacter* spp., 9%; UPTC, 57% (number of isolates, 91). Since the majority of the isolates (57%) belonged to the UPTC group, the results indicated that the urease test should be included in the characterization of campylobacters from marine environments and fecal specimens. This was the second description of UPTC organisms isolated from the natural environment following the first report by Bolton et al. (5).

During the 6-month period from September 1993 to February 1994, Endtz et al. (6) examined Dutch shellfish for the presence of *Campylobacter* spp. The sampling regime was extensive, whereby 59 batches of mussels were examined (where 1 batch was composed of 100 individual mussels), and the study

* Corresponding author. Mailing address: Laboratory of Molecular Biology, School of Environmental Health Sciences, Azabu University, Fuchinobe 1-17-71, Sagamihara 229-8501, Japan. Phone: 81 42 769 1942. Fax: 81 42 754 7661. E-mail: matsuda@azabu-u.ac.jp.

also included 41 batches of oysters (10 to 12 oysters per batch) harvested from marine waters of the Oostershelde estuary in the province of Zeeland, The Netherlands. This study was performed in order to gain insight into the epidemiology of *C. lari* infection in The Netherlands due to the consumption of raw mussels and oysters. *Campylobacter* spp. were detected in 41 out of 59 batches of mussels (69%) and in 11 out of 41 batches of oysters (27%). When the investigators further characterized 39 *Campylobacter* spp. by using additional phenotypic tests, including numerical analysis of electrophoretic protein patterns and genotyping by random amplification of polymorphic DNA, 37 of the 39 isolates were identified as *C. lari*, and 14 of the 37 isolates of *C. lari* were urease positive, i.e., UPTC. Among the 14 UPTC isolates, 1 isolate was resistant to NAL. In this report, Endtz et al. (6) demonstrated by using PAGE analysis of whole-cell proteins and DNA analysis that *C. lari* was phenotypically and genotypically diverse and that UPTC isolates should be considered as a new biovar within the *C. lari* species.

In Japan, the first finding of two UPTC isolates, CF89-12 and CF89-14, in freshwater from two different rivers in Okayama prefecture and their phenotypic and genotypic characterization were demonstrated (10). Pulsed-field gel electrophoresis (PFGE) analysis after separate digestion with ApaI, SalI, and SmaI of the genomic DNA and conventional fixed-field agarose gel electrophoresis suggested that both genomes of the isolates were approximately 1,862 kb in size. In relation to these two Japanese isolates of UPTC, surprisingly, shorter flagellin (*flaA*)-like sequences than those of *C. jejuni* and *C. coli*, containing internal termination codons (TAG), incomplete genes, or pseudogenes of flagellin, were demonstrated (26). Cloning and sequencing of the 16S ribosomal DNA (rDNA) and 16S-23S rDNA internal spacer region from these two Japanese UPTC isolates have also been reported (15).

Fresh fecal samples were obtained from wild birds, including oystercatchers, gulls, lapwings, geese, bar-tailed godwits, and corvids (crows), from two sites including an urban waste tip in Lancaster, England, and the intertidal zone of Morecambe Bay in England. From these samples *C. jejuni*, *C. coli*, *C. lari*, and a large proportion of UPTC organisms were identified (7); this was the first report of UPTC being isolated from a warm-blooded animal host.

In Northern Ireland, Moore et al. (8, 17) investigated the prevalence of thermophilic *Campylobacter* spp. in 205 fresh fecal specimens collected from members of the gull family (*Larus* spp.) from three costal locations, Newcastle, Portavogie, and Kilkeel, and detected *Campylobacter* spp. in 28 (13.7%) (17). Of these campylobacters, 21 of 28 isolates obtained belonged to the UPTC taxon (75%), followed by 5 belonging to *C. lari* (17.9%) and 2 belonging to *C. jejuni* (7.1%). Consequently, they suggested that seagulls are an important warm-blooded host of this bacterial taxon in Northern Ireland.

Obiri-Danso and Jones examined the distribution of thermophilic campylobacters in two freshwater bathing sites on the River Lune in northwestern England between 1996 and 1997. Of 236 *Campylobacter* isolates, the majority were identified as *C. jejuni*, followed by *C. coli*, UPTC (6 to 10%), and *C. lari* (4 to 9%) (19). Moreover, of the 82 *Campylobacter* isolates obtained from mallard feces, 90% were *C. jejuni*, 7% were *C. coli*, and 3% were UPTC. After examining the effects of UVB radiation and temperature on the survival of natural populations and pure cultures of *C. jejuni*, *C. coli*, *C. lari*, and UPTC organisms in surface water, Obiri-Danso et al. (20) suggested that *C. lari* and UPTC from birds predominate in the bathing waters in Morecambe Bay, as they are better able to survive.

In 1998, two UPTC isolates, designated YC98-1 and YC98-2, were identified by biochemical characterization after isolation from the intestinal contents of crows (*Corvus levaillantii*) around Yokohama City, Japan (12). The biochemical characteristics of these isolates were identical to those of UPTC isolates described previously. PFGE, performed after separate digestion with ApaI, SalI, and SmaI of the genomic DNA from the two isolates, indicated that the respective PFGE profiles were distinctly different and distinguishable from each other. More recently, when Waldenstrom et al. (35) analyzed the presence of different *Campylobacter* species in two species of wild birds, the Redshank (*Tringa totanus*) and the Barnacle goose (*Branta leucopsis*), that coexist on grazed coastal meadows in southern Sweden, they recovered 72 UPTC isolates from 123 Redshank specimens but none from the 116 goose samples examined. In this study, the species identification of isolates was carried out by employing amplified fragment length polymorphism (AFLP) profiling as well as 16S rRNA gene sequence analysis and extensive phenotypic characterization as required.

Almost all UPTC organisms have been isolated from the natural environment, including river water, seawater and shellfish, as well as from wild birds, but no organisms have been isolated from any other domestic or wild animals. Thus, the natural environment including wild birds appears to be an important reservoir of these organisms.

CARRIAGE OF PLASMIDS IN UPTC ORGANISMS

In relation to the plasmids associated with UPTC organisms, only one description has appeared to date. When a screening investigation was carried out for the presence of plasmid DNA in 47 UPTC isolates from Europe and Asia (38 isolates from Northern Ireland, 5 from England, 2 from France, and 2 from Japan), the presence of plasmid DNA was observed in 12 isolates, a frequency of approximately 26% (11). Seven of these 12 UPTC isolates were from Northern Ireland, and 5 were from England. No plasmid DNA was observed in the isolates from France and Japan. Though 3 of the 12 isolates had two plasmid DNA fragments of approximately 2.0 to 3.0 kb in length, the other 9 isolates each had only one plasmid of approximately 2.4 to 5.2 kb in length. Other species within the genus have also been shown to harbor plasmids, including the cryptic plasmid tentatively encoding transmembrane proteins in *C. jejuni* (9).

STRAIN AND PHYLOGENETIC ANALYSIS OF UPTC ORGANISMS

Although the taxonomy of the thermophilic campylobacters has recently been reviewed, the position of the UPTC organisms remains dynamic (16). Following the two original descriptions characterizing UPTC as a biovar (24) and as a variant (14) of *C. lari* in 1988, Vandamme et al. (32) in 1991 described the phylogenetic position of a representative UPTC isolate (*C.*

lari CCUG 18267) within *C. lari* by means of DNA-rRNA hybridization. With respect to strain discrimination within the UPTC taxon, Owen et al. (25) applied molecular typing to thermotolerant species of *Campylobacter* by using biotin-labeled cDNA probes of 16S-23S rRNA from *C. jejuni* NCTC11168, eight isolates of *C. lari* including the type strain (NCTC11352), and three isolates of UPTC (NCTC11937, NCTC11845, and NCTC11928) isolated from river water; the relative discrimination achieved with the different endonucleases was PstI > PvuII > HaeIII and HindIII. HaeIII ribopatterns were generally the easiest to interpret, although two isolates were nontypeable. Consequently, the three UPTC isolates were differentiated into three ribotypes based on the four restriction enzymes employed. When Alderton et al. (1) analyzed 16S rDNA sequences between *C. lari* 12947^T and UPTC CCUG 18267, the sequence similarity of the two isolates was 99.2%.

On and Harrington studied the taxonomy and epidemiological relationships among *Campylobacter* species including UPTC strains by numerical analysis of AFLP profiles and identified a high level of genetic diversity in *C. lari*, particularly among UPTC isolates (22). Their description was the first report that showed a substantive difference at the DNA level between NARTC and UPTC biovars. However, the taxonomic positions of these biovars warranted closer scrutiny. On et al. (23) examined 29 *C. lari* isolates obtained from humans, shellfish, and subantarctic and production animals as well as from the environment by extensive phenotypic characterization, whole-cell protein profiling, AFLP analysis, 16S rDNA sequencing, and DNA-DNA hybridization. Based on their findings, they proposed the subspecies epithets *C. lari* subsp. *lari* for classical strains, *C. lari* subsp. *ureasum* for the UPTC strains, and *C. lari* subsp. *subantarcticus* for the subantarctic animal isolates.

When multilocus enzyme electrophoresis (MLEE) analysis is used, variations in the alleles of the housekeeping genes encoding enzymes can be detected by estimating variations in the net electrophoretic changes of the polypeptides. Thirty-one UPTC isolates, including three reference strains (NCTC12892, NCTC12895, and NCTC12896), and three *C. lari* isolates, which were isolated from several countries and sources, were compared genotypically by using MLEE (13). MLEE typing revealed the presence of 23 different electrophoretic types (ETs) among the 31 UPTC isolates, and 14 isolates shared six ET profiles. Three different ETs were identified for the three *C. lari* isolates examined, and no ETs were shared by UPTC and *C. lari* isolates. Quantitative analyses were subsequently performed by using allelic variation data, and the results demonstrated that the mean genetic diversity was 0.655. In conclusion, MLEE demonstrated that the UPTC isolates examined are genetically hypervariable and form a cluster separate from the *C. lari* cluster.

Moore et al. (18) characterized UPTC organisms isolated from shellfish by using five phenotyping schemes, including two biotyping schemes, Penner passive hemogglutination serotyping, phage typing, and antibiogram typing, and two genotyping schemes including flagellin typing and MLEE; their results showed that the biotyping and MLEE methods were the most successful at discriminating UPTC organisms at the subspecies level, whereas serotyping, phage typing, antibiogram typing, and flagellin typing were unsuccessful subtyping methods. Therefore, the investigators recommended that biotyping and MLEE be considered for use in characterizing UPTC organisms in epidemiological studies.

PATHOGENESIS AND VIRULENCE FACTOR(S) OF UPTC

To date, it appears that UPTC organisms are not significant gastrointestinal pathogens for humans, as the reports of their isolation from fecal specimens from symptomatic patients, even of healthy individuals, are rare. Nor have the organisms been associated with any episode of bacteremia or other human infection. Regardless, they have established themselves as part of the natural microflora of gulls (*Larus* spp.), although it is not clear if such colonization is asymptomatic or subclinical. Hence, it is important to be able to describe the mechanism of their colonization of this particular host and the reasons why they do not appear to colonize the gastrointestinal tract of humans or any other warm-blooded animal.

In relation to the pathogenesis of UPTC, Sekizuka et al. (26) described short *flaA*-like sequences containing internal termination codons (TAG), incomplete genes, or pseudogenes of *flaA* in two Japanese UPTC isolates. When our laboratory examined the flagellin and flagella of these two Japanese isolates by sodium dodecyl sulfate-PAGE, following biochemical purification and electron microscopy, no flagellin or flagella were detected (T. Sekizuka, personal communication). Furthermore, 11 UPTC isolates from the natural environment, i.e., seawater and shellfish, in Northern Ireland carried the shorter *flaA* gene without any internal termination codons and a flagellin component of a smaller molecular size than the flagellin components of *C. lari*, *C. jejuni*, and *C. coli* (T. Gondo, personal communication).

CHARACTERIZATION OF UREASE FROM UPTC ORGANISMS

UPTC organisms, unlike their close phylogenetic neighbors *C. lari*, *C. jejuni*, and *C. coli*, phenotypically produce urease, and it is this feature that allows one to differentiate these from the other thermophilic *Campylobacter* organisms. An additional urease-positive taxon of *Campylobacter* was recently described for catalase-negative, urease-positive *Campylobacter*, namely, *Campylobacter sputorum* biovar paraureolyticus (21, 33). However, no phenotypic or genotypic characteristics of urease from either of these *Campylobacter* taxa have yet been described.

Recent studies have suggested that the quality of the diet of seagulls may vary owing to the availability of material that is easily scavenged (31), which has a physiological influence on blood and plasma composition. Alonso-Alvarez and Ferrer have suggested that there is a moderate physiological adaptation to long periods of fasting, whereby undernourished gulls use tissue protein directly as an energy source in the diet, thereby conserving fat stores for periods of more extreme starvation (2). The increased use of proteins in energy production would lead to elevated levels of urea from oxidative deamination of amino acids to keto acids, which are able to enter the Krebs cycle for energy production. Urea may then be utilized by the UPTC organisms as an energy source through a

membrane-bound ATPase, similar to the F_0F_1 proton-translocating ATPase, whereby generation of a transmembrane electrochemical potential would provide the electromotive force for protons to enter the cell via an F_0F_1 proton-translocating ATPase to generate ATP, which has been shown to be an energy-yielding mechanism in *Ureaplasma urealyticum* through the hydrolysis of urea (30). Such catabolism of urea would increase the ammonia concentration in the bird's gut, thereby curtailing the biosynthesis of mucin and facilitating the colonization of the UPTC organisms at the mucosal surface, as has been suggested for *Helicobacter pylori* in humans (27). Furthermore, it has been recently suggested by Sidebotham et al. that by raising the pH above 8, through ammonia production from urea, this process may be a protective mechanism for *H. pylori* to prevent overpopulation (28).

CONCLUSIONS

Since the first isolation of UPTC in 1985, approximately 200 UPTC isolates obtained from the natural environment, including wild birds in Europe and Asia, have been detected and reported. Although four clinical isolates of UPTC were obtained from humans in France in the period from 1986 to 1989, the possible association of UPTC with human disease still remains unclear. Recently, three subspecies taxa have been proposed, one of which, *C. lari* subsp. *ureasum*, would be for the UPTC organisms. Further studies are thus required to help define the potential role, if any, these organisms have in medicine for humans, as well as the mechanism of colonizing the guts of birds, particularly *Larus* spp.

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