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Review

Campylobacter concisus

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Abstract

Campylobacter concisus has been described as the etiological agent of periodontal disease, inflammatory bowel diseases, and enterocolitis. It is also detected in healthy individuals. There are differences between strains in healthy individuals and affected ones by production of two exototoxins. In this mini review authors discuss major facts about cultivation, isolation, virulence and immune response to *C. concisus*.

Key words: Campylobacter concisus; periodontitis; diarrhea.

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Introduction

At this very moment, there are only 161 papers in the Pub.Med.gov database. The first description of *Campylobacter concisus* occurred in 1981 by Tanner *et al*. who described these bacteria isolated from the oral cavity of patients with periodontal lesions [1]. *C. concisus* is spiral -shaped with a single polar flagellum, a slow-growing, fastidious organism with the optimal growth temperature of 37 °C, on media enrichment with blood, preferring horse blood. Biochemically, it is urease and catalase negative, and oxidase positive [2]. *C. concisus* is susceptible to ciprofloxacin and macrolides, but resistance to ciprofloxacin has been described in 5% of the strains [3]. *C. concisus* is not only associated with periodontitis, it can be found in the oral cavity of healthy persons [4-6]. There are only three studies on its isolation not only from the digestive tract but from two patients with underlying carcinoma: one had polymicrobial brain abscess [7], in one case of bacteremia was described with *C. concisus* gastroenteritis [8], and in one immunocompromised patient with pulmonary disease [9].

Although initial studies focused upon the presence and role of *C. concisus* in periodontal disease, over the last 30 years it has been investigated in intestinal disease, including enteritis and more recently inflammatory bowel diseases (IBD). It was an established opinion that the human's oral cavity is the only reservoir but findings linked the strains from poultry and ruminants [10]. For the first time it was isolated from feces in 1987. The first reports of its possible role in gastrointestinal disease in children with diarrhea came from Sweden [11]. There was a large study at the Red Cross Children's Hospital in South Africa over almost two decades in which it was found that *C. concisus* accounted for 25.02% of *Campylobacters*, being the second most prevalent species after *C. jejuni* (32.57%). The disadvantage of this study was the lack of a control group [12,13]. In Denmark, there were several representative studies in which *C. concisus* was found with a high prevalence in diarrheic stool samples in adults and children. In a healthy population, isolation of *C. concisus* was described by Engberg *et al.* There was variability between the *C. concisus* isolates, but without clear phenotypic or genotypic differences between strains from patients with diarrhoea and isolates from healthy carriers [14]. Their presence in the stool of healthy children was described in a study from Belgium [15]. In a large study conducted in Denmark, the incidence of *C. concisus* was almost as high as in *Campylobacter jejuni* [16]. The clinical manifestations of enteric *C. concisus* infection include prolonged diarrhea with a milder course compared to *C. jejuni/coli* [17].

The first liaison between *C. concisus* and inflammatory bowel disease (IBD) came from the analysis of *Campylobacter* species in biopsy specimens from children with Crohn's disease (CD) [18,19]. Man

et al. described similar results comparing fecal isolates from patients with CD and from healthy controls [20]. In addition, similar results were obtained for the patients with ulcerous colitis (UC) [21]. Mukhopadhya and colleagues in Scotland also detected *C. concisus* more often in biopsy specimens from adults with UC compared to controls ($p = 0.0019$) [22]. It is established that the reservoir for *C. concisus* is oral cavity [23].

A substantial number of reports on the pathogenic influence of *C. concisus* on many diseases of the gastrointestinal system, including gastroesophageal reflux disease, Barrett's esophagus has appeared lately [24]. The results showed that microorganism influences expression of carcinogenesis biomarker and cytokines in cell line models and possibility promotes oesophageal adenocarcinoma [25].

Isolation and identification

Isolation and identification methodology have been evolved since it was first described. At the very beginning for isolation, only the filtration method was used, and for identifying a "Cape Town protocol" and biochemical testing as well as testing of conditions for cultivation (The Cape Town protocol, 1998) [26]. Lee *et al*. determined that *C. concisus* isolates grew in anaerobic conditions without the presence of H_2, formate, or fumarate, and in microaerobic conditions in the presence of H_2 growth is better [27]. Nowadays, for isolation selective and non-selective media has been in use in combination with filtration technique, and for identification, PCR, RT-PCR, Maldi TOF are applicable. The most often used primers target for *C. concisus*, are genes for 16S rDNA, 23S rDNA, or chaperonin-60 (cpn60) [28].

Strains typing

The introduction of MALDI-TOF MS (Matrixassisted laser desorption/ionization time-of-flight mass spectrometry) has enabled rapid identification and at the same time typing of isolates [29].

MLST analysis of fecal and oral *C. concisus* isolates divided the strains into two major groups, and based on several other research papers results, it was also proposed the grouping into two genomospecies (GS1 and GS2) with different pathogenicity potential. *C. concisus* Genomospecies 2 is better adapted to the human gastrointestinal tract as compared with *C. concisus* Genomospecies 1 [30].

The most explorative method for genetic typing is whole- genome sequencing. Kaakoush *et al*. first compare the genomes of *C. concisus*, analyzing one reference strain and the strain UNSWCD [31,32]. Chung *et al*. sequenced 27 oral *C. concisus* strains from IBD patients and healthy controls and contributed to the investigations of strain pathogenicity by describing two genomic islands (CON_PiiA and CON_piiB) that contained proteins homologous to a type IV secretion system, and some effector proteins [33]. The sequence and analyze the genome of a *C. concisus* from a biopsy of a child with Crohn's disease (UNSWCD) has been the second such genome for this species. This genome is smaller than the 2.1 Mb *C. concisus* reference BAA-1457, 138 genes from UNSWCD and 281 from BAA-1457 were unique when compared against the other. This provided evidence of expression for 217 proteins previously defined as 'hypothetical' in *Campylobacter*. Substantial functional differences were observed between the UNSWCD and the reference strain, revealed differences in membrane proteins, response to stimulus, molecular transport, and electron carriers. Many of the observed differences are consistent with UNSWCD having adapted to greater surface interaction with host cells, as opposed to BAA-1457 which may prefer a free-living environment [34].

Antimicrobials susceptibility testing

There are few reports on antimicrobials susceptibility of *C. concisus*. One of them is coming from Belgium. The authors concluded that strains are sensitive to macrolides as well as other applied antimicrobials. Resistance occurred in a low percentage. Sensitivity testing was performed using CLSI criteria, on sheep blood agar in microaerobic conditions [3].

Pathogenicity

C. concisus can survive at wide variations in pH [35] and remains active in acidic environments. which may enable passage or probably persistence in gaster [37]. The contact with the gut epithelial cells is possible through the action of polar flagellum [19]. *C. concisus* can invade host cells [38] and that potential is increased in the presence of the inflammatory cytokines, TNF-α and IFN-γ [20]. These bacteria can produce biofilm [37], and induce apoptosis with epithelial barrier dysfunction by oral and fecal *C. concisus* strains because of apoptotic leaks with moderate TJ changes, demonstrating a leak-flux mechanism that parallels the clinical manifestation of diarrhea [38]. It is established that strains isolated from chronic intestinal diseases were 500-fold more invasive than isolates from acute gastroenteritis cases and healthy controls. The putative virulence factor from the plasmid is exotoxin9/DnaI,

associated with increased survival in epithelial cells. Exotoxin9/DnaI levels were significantly higher in fecal samples from CD patients compared to healthy controls**.** One of the key elements involved in barrier damage is Zot (Zonula occludens toxin), a toxin that disrupts intercellular tight junctions (TJ) [39]. One group proposed that a primary barrier function defect caused by *C. concisus* Zot is a mechanism by which zot-positive *C. concisus* strains may trigger the onset and relapse of IBD [40]. Mahendran *et al*. described the association between polymorphisms in the zot gene and association to clinical disease [41]. Kaakoush *et al*. have proposed differentiation of pathogenic *C. concisus* isolates into two groups: adherent and invasive *C. concisus* (AICC), and adherent and toxinogenic *C. concisus* (AToCC) [42]. Gemmel *et al*. have found that type IV and VI secretion systems genes, known to be important for pathogenicity in the Campylobacter genus, were present in the genomes assemblies, with 82% containing Type VI secretion system genes [43]. Their findings described *C. concisus* strains as genetically diverse, with the variability in bacterial secretion system content which may play the role in their virulence potential. It is determined that genes related to cell wall/membrane biogenesis were more common in oral isolates, whereas genes involved in cell transport, metabolism, and secretory pathways were more prevalent in enteric isolates [44].

C. concisus and diseases

Gingivitis and Periodontitis

Gingivitis is a common bacterial disease that affects 90% of the population, while periodontitis is not so often, but is a very serious condition that affects the supporting tissues of the tooth. As periodontitis progresses, a loss of attachment between the gingivae and the teeth may lead to the formation of a periodontal pocket, which then allows extensive colonization by anaerobic bacteria causing further inflammation of the mucosa. There are several theories proposed about the role of bacteria in the etiology of periodontitis. However, studies have not revealed a clear association between *C. concisus* and gingivitis and periodontitis, its role in human oral inflammatory diseases remains unclear, as well as for other bacteria in the human oral cavity [45].

Diarrheal syndrome of bacterial etiology

Nowadays, the genus *Campylobacter* is the most often associated with enterocolitis. *C. jejuni* and *C. coli* are the most often isolated microorganisms in these patients. Would *C. concisus* join the number of isolated thermotolerant campylobacters? According to many authors, probably it is a newly recognized pathogen with a history of association with a human host**.**

Inflammatory bowel disease (IBD)

IBD is comprised of Crohn's disease (CD) and Ulcerative colitis (UC) (ICD-10: K50-K51). They are characterized by an excessive immune response to an unknown microbial trigger, in genetically susceptible hosts [46,47]. In the etiology of UC and CD, which are believed to be closely related, an exact pathogenic mechanism was not exactly described. The presence of *C. concisus* in the saliva of healthy individuals and patients with inflammatory bowel disease (IBD) was examined. *C. concisus* was detected in 97% of the healthy individuals and 100% of the patients with IBD tested. The *C. concisus* culture positivity rate in younger children was significantly lower than that in the other age groups [48]. Liu *et al*. [45] using genomic analysis of oral *C. concisus* strains identified a potential bacterial molecular marker associated with active Crohn's disease. In humans, one of the most widely studied genes is NOD2, which was the first to be associated with CD. NOD2 is a protein with a key function in immunoregulation. On a cellular level, bacterial interaction with gut mucosa cells may rely on the mucosa composition, barrier defects, and the local host-mediated inflammatory response.

Immune response to *C. concisus*

Limited information is available on immunity in *C. concisus* infection. *C. concisus* has the capability to activate the innate immune system and to stimulate neutrophil cells to increased adherence molecule expression and oxidative burst response. These two characteristics are both crucial for acute inflammation. The opsonic activity of heat-treated serum from patients was not increased compared to heat treated control serum suggesting a weak systemic IgG response to infection [49]. Chen *et al*., have found that *C. concisus* upregulated IL-18 and IL-1β in oral epithelial cells supported a role of *C. concisus* in oral inflammatory diseases, and probably in cancerogenesis [50]. Kirk *et al*., have found that faecal isolates of *C. concisus* were sensitive to the bactericidal effects of the serum, which may explain why these bacteria were not implicated in bacteremia [51]. It was detected that *C. concisus*-positive patients had increased IgG antibodies. Patients with high IgG levels more often reported headache, and they had a trend toward more mucus in stools, whereas IgG levels were unrelated to age, duration of diarrhea, number of stools per day, and weight loss [52]. Heat-

killed *C. concisus*, mediate high immunostimulatory activity. *C. concisus*, exhibited robust TLR4 stimulatory activity [53].

Mass spectrometric analyses of the lipid of *C. concisus* revealed a novel moiety with two or three phosphoryl substituents. Molecular and fragment ion analysis indicated that the oligosaccharide portion of the LOS had only a single phosphate and hallmarks of the *C. jejuni* LOS. *C. concisus* LOS and live bacteria induced less TNF-α secretion in human monocytes than did *C. jejuni*. Furthermore, the *C. concisus* bacteria were less virulent than *C. jejuni.* According to the authors, all of those findings support the significance of the LOS as a determinant in the relative pathogenicity of *C. concisus* [54].

Kaakoush *et al*. described a comprehensive global profile of innate immune responses to *C. concisus* infection in differentiated THP-1 macrophages infected with an adherent and invasive strain of *C. concisus*. They observed inflammasome assembly in *C. concisus*-infected macrophages. Global profiling of the transcriptome they investigated, revealed the significant regulation of a total of 8,343 transcripts upon infection with *C. concisus*, which included the activation of key inflammatory pathways involving CREB1, NF-β, STAT, and interferon regulatory factor signaling, micro mRNAs, and 333 noncoding RNAs which were significantly regulated upon infection, including MIR221. That molecule has been associated with colorectal carcinogenesis [55]. However, the immune system is complex, and a lot of investigations are needed to answer all the questions related to innate and adaptive immune response.

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