Intra-abdominal infection with *Campylobacter curvus*: case report and review of the literature

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**Abstract**

**Background.** *Campylobacter curvus* is a Gram-negative bacteria associated with periodontal disease in humans. Cases of extra-oral manifestations of infection are rare with only six reported cases of extra-oral infection including this report that have been identified in the current literature. Molecular methods are generally used to identify *C. curvus* while optimal antibiotic choice and duration to treat extra-oral infections for this pathogen is unknown.

**Case presentation.** A 63-year-old male with a background history of alcoholic pancreatitis presented with fever and malaise who was found to have radiological intra-abdominal collections. Drainage of these collections identified *C. curvus* via matrix-assisted laser desorption/ionisation time of flight (MALDI-TOF) mass spectrometry with high probability and identification further confirmed by whole-genome sequencing. Antibiotic susceptibility testing to erythromycin and ciprofloxacin of *C. curvus* was performed using E-test diffusion methods along with investigation for the presence of resistance genes. The patient was treated with intravenous piperacillin-tazobactam followed by ciprofloxacin for 4 weeks total with good clinical recovery.

**Conclusions.** Extra-oral manifestations with the pathogen *C. curvus* are rare with few cases described in the literature. There is minimal data on susceptibility patterns, optimal antibiotic treatment and duration. Treatment of extraintestinal *C. curvus* infections in humans should encompass both adequate source control and antibiotic therapy.

**BACKGROUND**

The *Campylobacter* genus comprises a large group of over 30 bacterial species with its more familiar members *Campylobacter jejuni* and *Campylobacter coli* implicated mainly in gastrointestinal disease [1]. Extra-intestinal infection with *Campylobacter* spp. including bacteremia, urinary tract infections and extraluminal collections are also known to occur with lesser-known members in the genus such as *Campylobacter curvus* emerging as pathogens causing infections in humans [2]. Originally identified as *Wolinella curva* in 1984 from human oral samples, *C. curvus* is a motile curved Gram-negative bacillus [3–5]. Following immunotypic and genetic analyses, *W. curva* was revised to *C. curvus* given homology to other *Campylobacter* species [6]. Notable for its association in periodontal disease and sporadic infectious diarrhoea, extra-oral infections with *C. curvus* are rare [7]. A review of the literature demonstrates only five case reports of extra-oral infection to date [8–11]. We describe here a case of *C. curvus* intra-abdominal infection including the methodology for identification and management as well as a comparison to the cases identified in the literature for management of extra-oral infections with this species.

**CASE REPORT**

A 63-year-old male presented with 4 weeks of malaise and fever in the setting of a prior pancreatic pseudocyst co-infection with *Enterococcus faecalis*, *Klebsiella pneumoniae* and mixed coagulase negative staphylococci, on a background of alcoholic pancreatitis. This infected pseudocyst had been
drained followed by 6 weeks of intravenous piperacillin-tazobactam and a further 2 weeks of oral ciprofloxacin with amoxicillin-clavulanate. Treatment was completed 5 months prior with complete clinical recovery, marked radiological reduction in the collections and resolution of inflammatory markers. His medical history was also notable for hypertension and alcoholic cardiomyopathy.

Examination at representation to hospital demonstrated right basal crackles in the lungs and a non-tender abdomen. Investigations demonstrated an elevated white cell count of 16.33×10⁹ per litre with a predominant neutrophilia and a C-reactive protein of 156 mg l⁻¹ (normal limits: 0–8 mg l⁻¹). Other abnormalities included sodium, potassium and creatinine levels of 123 mmol l⁻¹, 5.3 mmol l⁻¹, and 201 μmol l⁻¹ respectively. Liver function tests remained normal with a normal lipase level of 36 U l⁻¹. A computed tomography (CT) scan of his abdomen showed interval progression of pre-existing retroperitoneal and intraperitoneal collections with the largest collection measuring 129×58 mm (Fig. 1).

Ceftriaxone and metronidazole were commenced empirically, and CT-guided drains were inserted into the largest two collections. Sixty millilitres of purulent specimen was aspirated. Although there were no immediate complications, the patient later developed hypotension secondary to the underlying cardiomyopathy and transferred to the intensive care unit. Antimicrobial therapy was changed to piperacillin-tazobactam. Following haemodynamic stabilisation, he returned to the surgical ward 48 h later. A repeat CT scan showed near resolution of the two main collections.

Gram-stain of aspirated material demonstrated numerous polymorphic leukocytes and Gram-negative bacilli under high powered field microscopy (Fig. 2). After 2 days of incubation, tiny white non-haemolytic colonies were cultured on horse blood agar under anaerobic conditions at 37 degrees Celsius (Fig. 3). The organism was oxidase-positive, catalase-negative, H₂S non-producing, urease-negative, and motile. Using matrix-assisted laser desorption/ionisation time of flight (MALDI-TOF) mass spectrometry (Bruker; Preston, Victoria), the isolate was identified as *C. curvus* with a score of 2.143.

Genomic DNA was extracted from the cultured colonies and amplicon libraries prepared using Nextera XT Library Preparation kit. Sequencing was performed on a NextSeq 500

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**Fig. 1.** Axial view of a computed tomography scan of the abdomen at presentation demonstrating one of the large intra-abdominal collections measuring 129×58 mm.

**Fig. 2.** Gram-stain demonstrating small Gram-negative bacilli (red arrow) in the presence of polymorphonuclear cells (blue arrow) on high power field microscopy.

**Fig. 3.** Growth of tiny white colonies after 48 h on horse blood agar under anaerobic conditions at 37 degrees Celsius with section magnified.
Table 1. Summary of biochemical properties of C. curvus

| Catalase | Urease | Nitrite reduction | $H_2$ requirement for growth | $H_2$S production | Indole acetate hydrolysis | Hippurate | Oxidase | Motility |
|----------|--------|-------------------|-----------------------------|-------------------|--------------------------|----------|---------|---------|
| +/-      | +      | +                 | +                          | +                 | -                        | -        | +       | +       |

References: [26–28].

 platform with a NextSeq Mid-Output (2×150 bp) kit (Illumina Inc., CA, USA). Raw FASTQ files were used to construct draft genomes using showll (v1.0.9), and genome annotation was performed using prokka (v1.14.6) [12]. Pangenome analysis was performed using roary (v3.13.0) with 90% minimum percentage identity for BLASTP. Whole-genome sequencing supported speciation of C. curvus. Abricate (v1.0.1) was used to detect antibiotic resistance genes from the genomic sequence, however, no antimicrobial resistance genes could be detected from the draft genome.

Antibiotic testing using E-test diffusion methods showed a ciprofloxacin and erythromycin minimum inhibitory concentration (MIC) of 0.19 µg ml$^{-1}$ and 16 µg ml$^{-1}$ respectively. The patient completed 10 days of intravenous piperacillin-tazobactam followed by oral ciprofloxacin for a further 3 weeks. At the time of antibiotic cessation, the patient had near radiological resolution of the drained collections and normalisation of his inflammatory markers. He remained clinically stable 2 months post-antibiotic cessation following hospital discharge.

**DISCUSSION**

Campylobacter spp. are a group of bacteria with its most familiar members C. jejuni and C. coli known to cause primarily gastrointestinal infection in humans [13]. Lesser-known species in the genus such as C. curvus are emerging as potential pathogens causing human disease. C. curvus is a non-fermenting, oxidase positive, microaerophilic Gram-negative bacillus that produces pinpoint colonies on blood agar when cultured under microaerophilic conditions [7]. Further biochemical characteristics of C. curvus are shown in Table 1. Isolation of C. curvus in human samples outside the oral cavity is rare and its relationship to human pathology is poorly understood [3]. Found as commensal bacteria in the human mouth, notably periodontal pockets of diseased gums, a causal role for these organisms in periodontal disease has not been clearly established [14].

Humans are known hosts to C. curvus with rates of carriage presumed low. One study of human faecal specimens investigating presumed gastroenteritis identified C. curvus in only one of 320 samples [15]. In a similar microbiome study, C. curvus DNA from intestinal biopsies was found in only 1.4 and 4.6% of patients with ulcerative colitis and healthy controls respectively [16]. C. curvus as a cause of infectious diarrhoea is rare with C. curvus isolated in only 0.0004–0.05% of children with infectious gastroenteritis [3, 17]. This was similar to another study of infectious diarrhoea whereby C. curvus was isolated in only 15 patients over a 4 year period [7].

Extra-oral infection with C. curvus is rare. A search of the literature using the PubMed and EMBASE library databases for articles on C. curvus that have been published to date was conducted. Search terms included ‘Campylobacter curvus’ OR ‘Wolinella curva’. Twenty-three and sixty-three results based on these terms were found in the PubMed and Embase databases respectively with only five case reports of extra-oral infection, comprising two cases of liver abscesses, two cases of pulmonary infection and a case of chorioamnionitis (Table 2) [8–11].

In four cases, C. curvus was isolated on bacterial media when cultured under anaerobic conditions. All five cases prior to this report required molecular detection methods for identification of C. curvus with 16S rRNA sequencing the main method used. Three cases with infected collections were polymicrobial and in the case of C. curvus-associated chorioamnionitis, Haemophilus parainfluenza was also detected via molecular methods. In contrast to predominantly monomicrobial infections with C. foetus, C. curvus appears to exhibit co-habitation with other bacteria leading to polymicrobial infection similar to C. showae [13, 18]. Whilst C. curvus was the only pathogen isolated in this patient’s collection, this may be attributable to pre-treatment with antibiotics or selective pressures from previous therapy.

Whilst prior studies relied on molecular techniques to identify C. curvus, the isolate from this study was identified using MALDI-TOF MS with a high probability score. MALDI-TOF MS correctly identifies up to 91 and 83% of all non-jejuni/coli Campylobacter strains and C. curvus isolates respectively [19]. The isolate demonstrated identification of C. curvus with a score of 2.143 suggesting a high probability match. Whole-genome sequencing was used to confirm speciation and based on the genomic context from pan-genomes against other Campylobacter spp., the isolate appeared most related to C. curvus (Fig. 4).

Susceptibility testing and antibiotic MIC reports for C. curvus strains are limited due to the rarity of the infection. Reported MICs in the literature are variable but include: bacitracin >128 µg ml$^{-1}$, ceftriaxone >32 µg ml$^{-1}$, cefuroxime >256 µg ml$^{-1}$, chloramphenicol 2–4 µg ml$^{-1}$, ciprofloxacin 0.047 µg ml$^{-1}$, clindamycin 0.5–1 µg ml$^{-1}$, erythromycin 2 µg ml$^{-1}$, gentamicin 2 µg ml$^{-1}$, metronidazole 0.38–2 µg ml$^{-1}$, and penicillin 32 µg ml$^{-1}$ [4, 8]. Susceptibility to β-lactams in Campylobacter spp are variable with minimal data in particular to piperacillin-tazobactam [20]. One study examining C. coli/C. jejuni found low resistance to amoxicillin but high resistance to piperacillin thought secondary to poor penetration due to the bulky side chain in the latter [21].
Table 2. Summary of clinical characteristics, risk factors, diagnostics and management of patients with extraoral infections due to Campylobacter curvus

| Case | Patient's sex and age | Diagnosis | Risk factors | Identification technique | Time to isolation (duration) | Associated organisms | Intervention | Antibiotic therapy | Outcome | Ref |
|------|-----------------------|-----------|--------------|--------------------------|-----------------------------|------------------------|--------------|-------------------|---------|-----|
| 1    | 52M                   | Liver abscess | Diverticulitis | 16S RNA gene sequencing   | 3 days                      | unknown                | Radiological drainage | Ceftriaxone + Metronidazole | Survived | [8] |
| 2    | 68F                   | Liver abscess | Ovarian cancer | 16S RNA gene sequencing   | unknown                     | unknown                | Radiological drainage | Piperacillin + Tazobactam | Survived | [9] |
| 3    | 59M                   | Lung abscess | Lung cancer   | 16S RNA gene sequencing   | 2 days                      | unknown                | Lung resection | Amoxicillin + Gentamicin + Metronidazole | Survived | [10] |
| 4    | 65F                   | Emphysema   | Bronchiectasis | 16S RNA gene sequencing   | unknown                     | unknown                | Chest drainage       | Ceftriaxone + Metronidazole | Survived | [11] |
| 5    | 29F                   | Chorioamnionitis | Pregnancy | Molecular diagnostics (not specified) | 2 days                      | unknown                | Delivery | Piperacillin + Tazobactam | Both survived | This case |
| 6    | 64M                   | Intra-abdominal collection | Chronic pancreatitis | MALDI-TOF, whole genome sequencing | 2 days                      | unknown                | Radiological drainage | Piperacillin + Tazobactam | Survived | This case |

Limited data exists for C. curvus susceptibility to erythromycin but this isolate appeared consistent to other non-C. jejuni/coli species that show erythromycin resistance. This is potentially due to limited data on C. jejuni, C. coli and C. gracilis. 

E-test diffusion testing of the isolate demonstrated an MIC of 0.19 µg ml⁻¹ for ciprofloxacin and 16 µg ml⁻¹ for erythromycin. Although interpretation for these MIC values is not available for non-jejuni/coli Campylobacter spp due to limited data on C. curvus, we interpreted the isolate to be ciprofloxacin susceptible and erythromycin resistant by extrapolating EUCAST breakpoints for C. jejuni/C. coli species [22]. No gene could be detected in the draft genome that would confer antimicrobial resistance. Nevertheless, the draft genome harboured several sets of virulence genes encoding components of the bacterial flagellar system (fliG, fliN, fliM, fliS, fliW, fliE, fliF, fliQ, fliR, flaA, flaB, flaG, flaC, and flaG), flagellin A (flaA), and a secreted flagellin C (flaC). Notably, resistance via upregulation of motility and down regulation of metabolism following treatment with erythromycin has been found in C. jejuni [23].

The optimal duration of treatment following source control is uncertain, ranging between 2 days to 6 weeks. Given the propensity for C. curvus to form biofilms and its persistence in inhospitable environments, a prolonged treatment course may be prudent to ensure clearance of infection. The patient was treated with 3 weeks of ciprofloxacin following drainage [25].

**CONCLUSION**

Extraoral manifestations of C. curvus are rare with infections predominantly due to polymicrobial collections. Identification of C. curvus is classically reliant on molecular techniques due to its fastidious nature but the MALDI-TOF MS may be adequate in identifying most C. curvus isolates. Management
of extraoral infections require good surgical debridement or removal of the infection with a prolonged treatment course of antibiotics.

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Author contributions
T.P.C.K. is the main author of this article. T.P.C.K. and G.D.L. were responsible for clinical treatment of the patient. T.M. is the clinical scientist who isolated the organism and assisted with the biochemical and susceptibility testing. L.E.X.L. is the senior medical scientist who conducted whole genome sequence and assisted in writing the genomic analysis.

Conflicts of interest
The authors declare that there are no conflicts of interest.

Ethical statement
Written informed consent was obtained for the aforementioned case.

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