

# Meningitis and Endocarditis Caused by *Campylobacter fetus* after Raw-Liver Ingestion

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**We report *Campylobacter fetus* meningitis associated with endocarditis in a 75-year-old diabetic man after he consumed raw liver. *C. fetus* was isolated from blood samples and cerebrospinal fluid. Cure was obtained with combined intravenous imipenem-gentamicin for 4 weeks; no relapse occurred after 6 months of follow-up.**

## CASE REPORT

On 21 August 2010, a 75-year-old man consulted at a French Emergency Department for fever and chills lasting 7 days that had begun after 2 weeks (29 July to 11 August) in Lebanon, where he had eaten raw sheep liver on 5 August. Thirty-six hours postprandial, he developed choleric diarrhea and recovered spontaneously within 24 h. His type 2 diabetes was treated with oral antidiabetic drugs, and 2 adenomatous sigmoid polyps had been resected the preceding year. His physical examination was normal. The initial laboratory results were a white blood cell (WBC) count of 11,500/ $\mu$ l, a C-reactive protein (CRP) level of 10 mg/liter, and a normal blood smear. The patient remained afebrile throughout hospitalization in our Infectious Diseases Department and was discharged 2 days later with a diagnosis of viral gastroenteritis. On 28 August, the department requested his return because blood cultures grew *Campylobacter*-like Gram-negative bacilli (BacT/Alert; bioMérieux, Lyon, France). He had a high fever associated with poor general condition and altered consciousness but no headache or neck stiffness. Cardiac auscultation detected a moderate aortic regurgitation murmur. Laboratory tests showed a CRP level of 91 mg/liter and a WBC count of 13,000/ $\mu$ l. His cerebrospinal fluid (CSF) was clear, with 40 red cells/ $\mu$ l and polynuclear pleocytosis (65% of 1,430 WBC/ $\mu$ l). The CSF protein and glucose levels were, respectively, 1.14 g/liter and 1.23 g/liter (glycemia, 2.68 g/liter). CSF and all 3 blood-sample cultures grew *Campylobacter fetus*, which was first identified with a negative hippurate test and by its susceptibility pattern (nalidixic acid resistance and cefalotin susceptibility) (1) and later confirmed by a mass spectrometry (Microflex, Bruker Daltonik GmbH, Bremen, Germany) score of 2.2 and 16S rRNA gene sequencing, using previously described BigDye Terminator chemistry on an Applied Biosystems genetic analyzer (2). GenBank database searches showed the amplified sequences to be 100% identical to the 16S rRNA gene sequence of the reference *C. fetus* subsp. *fetus* strain.

Antimicrobial susceptibility testing by the agar disk diffusion method (Bio-Rad, Marnes-la-Coquette, France) and Etest (bioMérieux, Marcy l'Etoile, France) showed resistance to cefotaxime (MIC, 8 mg/liter), rifampin (MIC, >32 mg/liter), and nalidixic acid (MIC unavailable) and susceptibility to amoxicillin (MIC, 1.5 mg/liter), imipenem (MIC, 0.064 mg/liter), and ciprofloxacin (MIC, 0.38 mg/liter), as well as amoxicillin-clavulanic

acid, cefalotin, erythromycin, gentamicin, and chloramphenicol (MICs unavailable).

Transesophageal echocardiography visualized a 4-mm, mobile, hypoechoic image on the aortic valve suggestive of a cardiac vegetation, without regurgitation. A complete imaging workup, including spinal cord and brain magnetic resonance imaging, detected no other septic site. Gastroscopy and colonoscopy found antral gastritis but no colorectal abnormality. HIV serology was negative, and plasma protein electrophoresis was normal. No clinical or biological signs of alcoholism were found.

Intravenous imipenem (50 mg/kg/day), given for 4 weeks, combined with gentamicin (5 mg/kg/day) for 5 days, obtained clinical and biological improvements, and no other blood culture was positive. Control echocardiography 3 weeks later found no vegetation. Moreover, clinical and biological follow-up at 6 months confirmed his full sustained recovery.

*Campylobacter* infections are cattle-transmitted cosmopolitan zoonoses. A MEDLINE search using “meningitis” and “*Campylobacter fetus*” as keywords (MeSH) identified 20 cases of *C. fetus* meningitis published in English, French, or German, which are described in Table 1. The median age for all patients was 50 years.

The *C. fetus* contamination route was rarely identified. Our patient ate raw sheep liver that could have become infected from the sheep gut via bacteremia or could have been directly soiled during butchering/preparation, because sheep intestinal flora can include *C. fetus*. His diarrhea after that meal could attest to enteric invasion, before the bacteremic phase. Unfortunately, stool cultures to identify *C. fetus* were not done in Lebanon. Some *C. fetus* infection case reports have described indirect transmission: through raw milk (3), insufficiently cooked chicken, beef, or sheep meat or liver (4), or khat chewing (5). Several cases of inoculation

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TABLE 1 Clinical and bacteriological features, CSF characteristics, treatments, and outcomes of *C. fetus* meningitis cases reported in the literature<sup>a</sup>

Case no. (reference)	Sex/age (yr)	Underlying condition(s)	Clinical course	Bacteriology	CSF result(s)	Echocardiography	Treatment	Outcome
1 (15)	M/47	Chronic alcoholism	Fever, neck stiffness, diarrhea	<i>C. fetus</i> ( <i>Vibrio fetus</i> ) in CSF and BC	2,128 WBC/ $\mu$ l; 80% N; P, 1.52 g/liter; G, 0.24 g/liter	No	PEN, TET	Cured
2 (16)	M/55	Chronic lymphocytic leukemia	Fever, neck stiffness, distal paresthesia, arthralgia	<i>C. fetus</i> subsp. <i>fetus</i> in CSF and BC	240 N/ $\mu$ l	No	PEN, TET	Cured
3 (17)	F/48	Rheumatic fever	Fever, pericarditis, neck stiffness, hemiparesis	<i>C. fetus</i> ( <i>Vibrio fetus</i> ) in BC	1,399 WBC/ $\mu$ l; 89% N	No	PEN, CHL	Cured
4 (18)	M/50	Diabetes mellitus	Fever, headache, diarrhea	<i>C. fetus</i> subsp. <i>fetus</i> in CSF	3,436 WBC/ $\mu$ l; 58% N; P, 0.96 g/liter; G, 0.20 g/liter	No	PEN, AMP, CHL	Cured
5 (19)	F/69	Diabetes mellitus, idiopathic thrombocytopenic purpura	Fever, confusion	<i>C. fetus</i> subsp. <i>fetus</i> in CSF and BC	1,230 WBC/ $\mu$ l; 92% N	No	PEN, CHL, SEZ	Died
6 (20)	M/40	None	Fever, neck stiffness, diarrhea	<i>C. fetus</i> subsp. <i>fetus</i> in CSF	8,464 WBC/ $\mu$ l; 66% L; P, 1.2 g/liter; G, 0.50 g/liter	No	AMP, PEN, STR, ERY	Cured
7 (21)	M/50	None	Fever, headache, convulsions, hemiparesis, abdominal pain	<i>C. fetus</i> subsp. <i>fetus</i> in CSF and BC	36 WBC/ $\mu$ l; 100% L; P, 0.73 g/liter; G, 0.70 g/liter	No	AMP, CHL	Cured
8 (22)	M/68	Metastatic adenocarcinoma of the rectum	Fever, diarrhea, malaise	<i>C. fetus</i> subsp. <i>fetus</i> in CSF	Meningitis	No	ERY	Died (other cause?)
9 (22)	M/65	Alcoholic cirrhosis	Fever, convulsion, malaise	<i>C. fetus</i> subsp. <i>fetus</i> in CSF	Meningitis	NR	CFZ, GEN, ERY, AMP	Relapse then cured
10 (23)	M/38	Chronic alcoholism	Fever, neck stiffness	<i>C. fetus</i> subsp. <i>fetus</i> in CSF	2,040 WBC/ $\mu$ l; 84% N; P, 1 g/liter; G, 0.48 g/liter	No	AMX	Cured
11 (24)	M/47	Kidney transplant recipient	Fever, headache	<i>C. fetus</i> subsp. <i>fetus</i> in CSF and BC	48 WBC/ $\mu$ l; 70% N; 30% L; P, 0.8 g/liter; G, 1.04 g/liter	No	CHL	Cured
12 (25)	F/39	Chronic alcoholism, epilepsy	Fever, neck stiffness, hemiparesis	<i>C. fetus</i> subsp. <i>fetus</i> in CSF	1,800 N/ $\mu$ l; P, 1.31 g/liter; G, 0.05 g/liter	No	SAM	Cured
13 (25)	M/36	Chronic alcoholism	Fever, confusion	<i>C. fetus</i> subsp. <i>fetus</i> in BC	154 N/ $\mu$ l; P, 0.95 g/liter; G, 0.22 g/liter	No	AMP	Cured
14 (26)	M/55	Alcoholic hepatitis, diabetes mellitus	Fever, neck stiffness	<i>C. fetus</i> in CSF	400 WBC/ $\mu$ l; 75% L; 23% N; P, 0.83 g/liter; G, 1.06 g/liter (ratio, 0.3)	No	AMP, MOX	Cured
15 (27)	M/83	Chronic alcoholism	Fever, confusion	<i>C. fetus</i> subsp. <i>fetus</i> in CSF and BC	577 WBC/ $\mu$ l; 96% N; P, 0.6 g/liter; G, 0.91 g/liter	No	AMC, RIF, NET, CIP, CRO	Died (other cause)
16 (11)	M/47	Chronic alcoholism	Fever, neck stiffness, cellulitis	<i>C. fetus</i> subsp. <i>fetus</i> in BC	300 WBC/ $\mu$ l; majority of N; P, 0.85 g/liter; G, 0.57 g/liter (ratio, 0.4)	Yes, no IE	CTX, VAN	Cured
17 (28)	M/71	Diabetes mellitus	Fever, neck stiffness, confusion	<i>C. fetus</i> subsp. <i>fetus</i> in CSF and BC	11,100 WBC/ $\mu$ l; 98% N; P, 5.08 g/liter; G, 0.95 g/liter (ratio, 0.2)	No	IPM for 4 wk	Cured
18 (29)	M/51	Head injury	Fever, convulsion	NR	Meningitis	NR	NR	Cured
19 (30)	M/40	Crohn's disease treated with infliximab	Fever, headache	<i>C. fetus</i> in CSF, BC, and SC	344 WBC/ $\mu$ l; majority of N; P, 0.33 g/liter; G, 0.68 g/liter	No	ERY	Cured
20 (5)	M/28	Epilepsy, khat chewing	Fever, diarrhea, neck stiffness	<i>C. fetus</i> in BC	170 WBC/ $\mu$ l; normal P and G	Yes, no IE	CRO, CIP, AZM	Cured
21 (this report)	M/75	Diabetes mellitus	Fever, diarrhea, confusion	<i>C. fetus</i> in CSF and BC	1,430 WBC/ $\mu$ l; 65% N; P, 1.14 g/liter; G, 2.68 g/liter (ratio, 0.5)	TTE and TEE, aortic endocarditis	IPM for 4 wk + GEN for 1st 5 days	Cured

<sup>a</sup> Abbreviations: M, male; F, female; BC, blood culture; SC, stool culture; CSF, cerebrospinal fluid; WBC, white blood cells; N, neutrophils; L, lymphocytes; P, CSF protein level; G, CSF glucose level; ratio = G:glycemia; IE, infectious endocarditis; NR, not reported; AMX, amoxicillin; AMC, amoxicillin-clavulanic acid; AMP, ampicillin; SAM, ampicillin-sulbactam; AZM, azithromycin; CFZ, cefazolin; CTX, ceftriaxone; CRO, ceftriaxone; CHL, chloramphenicol; CIP, ciprofloxacin; ERY, erythromycin; GEN, gentamicin; IPM, imipenem; MOX, moxalactam; NET, netilmicin; PEN, penicillin; RIF, rifampin; SEZ, sulfadiazine; STR, streptomycin; TET, tetracycline; VAN, vancomycin; TTE, transthoracic echocardiography; TEE, transesophageal echocardiography.

via a peritoneal dialysis catheter (6) or in slaughterhouse workers (7) have been published.

Known risk factors for *C. fetus* infection in adults are aging, male sex (76%), implanted medical devices and/or immunocompromised state (diabetes mellitus, cancer, steroid therapy, HIV infection, and liver diseases, including cirrhosis and alcohol abuse) (8, 9), but 26% of the patients had no underlying condition (8). Among the 21 *C. fetus* meningitis cases, 8 (38%) patients suffered from alcoholism and 5 (24%) had diabetes mellitus. Other underlying diseases were chronic lymphocytic leukemia, cirrhosis, cancer, kidney transplantation, and infliximab-treated Crohn's disease. Our elderly patient was in good general condition, and his diabetes was controlled without any complications.

Clinical manifestations of *C. fetus* meningitis can be discrete, although neurological abnormalities and fever were noted, respectively, in 95% and 100% of published cases. Only 9 (43%) patients had neck stiffness, and 4 (19%) had encephalitis symptoms (hemiparesis or paresthesia). Four (19%) patients had fever associated with mental confusion, without any sign of meningeal irritation. Headaches were the only neurological manifestation for 4 (19%) patients. Finally, 2 (10%) patients convulsed. Thus, CSF should be obtained from every patient with *C. fetus* bacteremia when neurological signs appear, even an isolated headache.

More commonly described than meningitis, *C. fetus* endocarditis mainly occurs on preexistent valvulopathy and preferentially affects the aortic valve (10). To our knowledge, no reported *C. fetus* infection manifested as meningitis and endocarditis, but endocarditis was excluded by echocardiography for only 2 previous meningitis cases (5, 11). These two infectious loci are probably secondary to bacteremia. Although our patient had a clinically moderate aortic regurgitation murmur, echocardiography visualized a vegetation without valvulopathy. *C. fetus* endocarditis might be diagnosed more frequently if echocardiography were to become systematic for *C. fetus* meningitis patients, even those without a heart murmur.

To date, no controlled study has examined *C. fetus* infection treatment. According to the 2009 data of the French National Referral Center for *Campylobacter* and *Helicobacter*, nearly 20% of *C. fetus* strains are resistant to ciprofloxacin and doxycycline, and 10% are resistant to erythromycin (12). Fluoroquinolone use was significantly associated with higher mortality of patients with *C. fetus* bacteremia (8). No resistance to amoxicillin-clavulanic acid or gentamicin has been identified in France (12). Cefotaxime activity is poorer than that of other  $\beta$ -lactams (13), as for our patient. Intravenous imipenem-aminoglycoside for 4 weeks remains the recommended treatment for severe infections (8, 13). Imipenem resistance was reported only once (14). Our patient is the second case of *C. fetus* meningitis treated with intravenous imipenem; both had favorable outcomes after 4 weeks. Prolonged monitoring is necessary because of potential relapses. Among 111 *C. fetus* subsp. *fetus* strains isolated in Quebec from 1983 to 2000, all were susceptible to ampicillin, gentamicin, meropenem, and imipenem, with respective MIC<sub>90</sub>s of 4, 1, 0.12, and  $\leq 0.06$  mg/liter (13). Because of its good meningeal compartment diffusion compared to imipenem, meropenem might be another effective agent against *C. fetus* meningitis, but its use has never been reported.

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