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☐ Case Report ☐

In vivo Pefloxacin-resistant *Campylobacter fetus* Responsible for Gastro-intestinal Infection and Bacteremia Associated with Arthritis of the Hip

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The authors report a case of Campylobacter fetus subsp. fetus gastro-intestinal infection and bacteremia with poly-arthritis, mainly of the hip, in a French patient simultaneously suffering from cirrhosis of the liver. The outcome was enventually favorable, however only after a trial of ineffective pefloxacin-gentamicin therapy. The authors suggest: (i) gentamicin should not be given alone in C. fetus subsp. fetus infections, and (ii) pefloxacin should not be given if antibiotic sensitivities data are not available. The inconclusive reliability of disk diffusion tests for C. fetus subsp. fetus should be recognized.

Key-Words: Pefloxacin, *Campylobacter fetus* subsp. *fetus*, Hip

Although *Campylobacter* is known to be a major cause of gastro-intestinal infections in humans, *C. fetus* subsp. *fetus* is rarely isolated from human feces; it has seldom been reported to be responsible for extraintestinal infections in patients with predisposing conditions (Han *et al.* 1992; Penner *et al.* 1991). We have recently observed a case of *C. fetus* subsp. *fetus* gastro-intestinal infection and bacteremia with poly-arthritis, mainly of the hip, in a French patient simultaneously suffering from cirrhosis of the liver. The outcome was enventually favorable, however only after a trial of ineffective pefloxacin-gentamicin therapy. Due to the limited knowledge of *in vitro* susceptibility of the organism, (Goossens *et al.* 1989; Kwon *et al.* 1994) and even still less clinical data available, we thought that this case of *in vivo* pefloxacin-resistant *C. fetus* infection was worth being reported.

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CASE REPORT

A 58-year-old French man with a history of heavy drinking and cirrhosis of the liver, arrived complaining of a pain in his right hip joint. It had started ten-days prior, and prevented him from walking without a cane. There was no history of recent trauma to his right hip. His temperature was 38℃. His peripheral leukocyte count was 15,000/μL (75% neutrophils). The serum level of CRP was 100 mg/L. One day after his admission to the hospital, he developed diarrhea, a fever (39.5℃) and widespread pain in the joints of his knees, his wrists and his ankles. Tomodensitometry of the hip revealed a right-sided liquid effusion.

Blood cultures (VITAL^R, BioMérieux, France) proved positive in less than 72 hours and microscopic examination revealed spiral-shaped

Gram-negative bacilli of various length and darting motility; these were highly suggestive of *Campylobacter*.

After 24 hours, the isolate was identified as *C. fetus* subsp. *fetus* by the presence of tiny pin-point colonies only on agars incubated under microaerophilic conditions positive for catalase, for oxidase and for nitrate reductase; and furthermore, by the presence of an inhibition zone around the cephalothin disk and not around the nalidixic acid disk, as well as by the reaction pattern in the API Campy^{R} identification system (bioMérieux). The same organism was isolated from stool culture after 72 hours of incubation on a Campylosel agar (bioMérieux) at 37℃, but could not be found on a Campylosel agar incubated at 42℃.

A disk diffusion test was performed on a Mueller-Hinton blood agar (bioMérieux) incubated under microaerophilic conditions (Genera-bag^{R}, bioMérieux); *Staphylococcus aureus* ATCC 25923 was tested under the same conditions as a control (Courvalin *et al.* 1985). Rough estimates of the MICs, determined by the disk diffusion test according to the recommendations by the French Society for Microbiology (Acar *et al.* 1994; Courvalin *et al.* 1985), were amoxycillin : 0.30 μg/mL (no difference when clavulanic acid was added to amoxycillin), cefotaxime : 1 μg/mL, imipenem : 0.75 μg/mL, gentamicin : 0.25 μg/mL, pefloxacin : 1 μg/mL, ofloxacin and ciprofloxacin : 0.25 μg/mL, erythromycin : 0.10 μg/mL, and tetracycline : 0.05 μg/mL.

The patient was placed on intravenous pefloxacin-gentamicin (400 mg~80 mg twice a day). After ten days of antibiotic treatment, the hip pain and fever had only slightly decreased, and the serum level of CRP had not significantly decreased; consequently, the pefloxacin-gentamicin therapy was replaced by amoxycillin-gentamicin (3 g~80 mg twice a day) (Goossens *et al.* 1989).

The bactericidal activities at peak and valley serum concentrations were determined before, and 48 hours after the initiation of the new treatment. Results were attained using an appropriate bacterial inoculum in exponential growth phase prepared from a VITAL^{R} broth (Mérieux) (Courvalin *et al.* 1985). Bactericidal activities of sera (less than 0.01% of the culture viable at 36 h) were more satisfactory with the amoxycillin-gentamicin therapy, 1/32 ~1/2 (peak~valley serum dilutions), than with the pefloxacin-gentamicin therapy (1/8~1/2).

Time-kill experiments were performed with the same inoculum, using a simplified dilution method in a Mueller-Hinton broth (Courvalin *et al.* 1985), with final antibiotic concentrations at 12.5 μg/mL of amoxycillin, 5 μg/mL-2.5 μg/mL of amoxycillin-clavulanic acid, 3.75 μg/mL of cefotaxime, 5 μg/mL of imipenem, 7.5 μg/mL of gentamicin, 2.5 μg/mL of pefloxacin or ofloxacin, 3.75 μg/mL of erythomycin, and 3.75 μg/mL of tetracycline. The following combinations were tested: amoxycillin-gentamicin, amoxycillin-clavulanic acid-gentamicin, cefotaxime-gentamicin, imipenem-gentamicin, pefloxacin-gentamicin, ofloxacin-gentamicin, erythomycin-gentamicin, tetracycline-gentamicin. All agents and combinations tested were bactericidal even when tested alone, except for cefotaxime and pefloxacin.

Three weeks after initiating the antibiotic therapy, the patient was able to walk without a cane. Amoxycillin only was administered for another three more weeks. Six months after ending the antibiotic therapy, the patient was walking without any pain. His peripheral leukocyte count and serum level of CRP became within the normal range. Tomodensitometry of the hip also became normal.

DISCUSSION

Very few reports of *Campylobacter* infections of the joints have appeared in English and French literature, and *C. fetus* subsp. *fetus* has accounted for most of the cases (Han *et al.* 1992; Penner *et al.* 1991). Most patients with joint infections caused by *C. fetus* subsp. *fetus* had severe underlying diseases including an immunocompromised state, cirrhosis of the liver (like our patient), malignancy or diabetes. So far, all but one (Han *et al.* 1992) of the published cases of arthritis of the hip, due to *C. fetus* subsp. *fetus*, have occurred after total hip arthroplasty. Comparison with the case re-

port of Han *et al.* (1992) suggests that the more favorable outcome in our patient might be explained by the absence of previous trauma of the hip in conjunction with the rapid diagnosis and immediate initiation of antibiotic therapy.

Isolation of *C. fetus* is quite difficult, since it requires enriched media and microaerophilic conditions, as well as the fact that primary isolation from clinical specimens generally takes more than 72 hours (Tenover *et al.* 1988); therefore in this case, the usefulness of the VITAL^R blood culture system might be emphasized. Since not all cases of acute diarrhoeas are explored bacteriologically, and likewise since the isolation of *Campylobacter* from stool specimens is rather fastidious, particularly in the case of *C. fetus*, their frequency as a cause for intestinal infection might be underestimated (Tenover *et al.* 1988; Penner *et al.* 1991).

Antibiotic susceptibility tests are not yet standardized, and the MICs determined by disk diffusion tests are only a rough estimate (Courvalin *et al.* 1985; Kwon *et al.* 1994). However, the results of our disk diffusion tests are in general agreement with our time kill experiments, and these are both in general agreement with the results obtained by Goossens *et al.* (1989) and by Kwon *et al.* (1994). Kwon *et al.* (1994) have already suggested the inconclusive reliability of disk diffusion tests for *C. fetus* subsp. *fetus*.

The best antibiotic therapy for systemic *Campylobacter* infections is not clearly established; nevertheless combinations of gentamicin with a β-lactam (mainly amoxycillin and imipenem) or with a new quinolone (mainly ofloxacin and ciprofloxacin) have been recommended (Goossens *et al.* 1989; Kwon *et al.* 1994; Van der Auwera *et al.* 1985). It has also been suggested that new quinolones might be a therapeutic alternative to β-lactam and erythromycin for *C. fetus* and *C. jejuni* infections, respectively (Goossens *et al.* 1989; Van der Auwera *et al.* 1985).

Although there are reports of *C. fetus* subsp. *fetus* and *C. jejuni* isolates, resistant to new quinolones (Gootz *et al.* 1991; Meier *et al.* 1993), to our knowledge, the activity of pefloxacin against *C. fetus* subsp. *fetus* has not yet been compared to the activities of other new quinolones such as ofloxacin, and ciprofloxacin. Since the pefloxacin-gentamicin therapy was not clinically effective; moreover, since this isolate of *C. fetus* subsp. *fetus* appeared to be less susceptible to pefloxacin than to ofloxacin, to ciprofloxacin, to imipenem, to gentamicin, to erythromycin, to tetracycline (*in vitro*) and to amoxycillin (both *in vivo* and *in vitro*), we suggest that gentamicin should not be given alone for *C. fetus* subsp. *fetus* infections, and that pefloxacin should not be given if antibiotic sensitivities data are not available.

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