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Highly Rifampin-Resistant *Listeria monocytogenes* Isolated from a Patient with Prosthetic Bone Infection

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1 **Highly rifampicin-resistant *Listeria monocytogenes***
2 **isolated from a patient with prosthetic bone infection**

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16 Listeriosis is a rare but severe foodborne infection due to *Listeria monocytogenes* (*Lm*).
17 *Lm* is naturally susceptible to a wide range of antibiotics, including penicillins,
18 aminoglycosides, tetracyclines, macrolides, co-trimoxazole, linezolid, moxifloxacin,
19 glycopeptides and rifampicin but not to cephalosporins (1-3). *Lm* resistance to antimicrobials
20 is rare; it was estimated around 1.3% from 4,668 clinical isolates tested in the National
21 Reference Centre for *Listeria* (NRCL) (3), involving mostly fluoroquinolones, but not
22 rifampicin (1, 3-5).

23 We report here the characterization of a *Lm* human clinical isolate (CLIP 2009/01237)
24 highly resistant to rifampicin. A 68-year-old male had protracted intra-medullar femoral nail
25 infection. His history included radiotherapy for femoral plasmocytoma with subsequent
26 fractures. He presented with pain and instability, and was afebrile. A purulent collection was
27 evidenced and the prosthetic device removed, albeit incompletely. Pus cultures remained
28 sterile and he was discharged without treatment. He was readmitted four weeks later with
29 fever and pus flow emitted from the operative site. As pneumonia was suspected, he received
30 ceftriaxone and ciprofloxacin for 48 hours. A collection in the femoral region formed, and
31 surgical debridement was performed. Pus grew *Lm*. As for most sporadic cases of listeriosis,
32 the contamination source was not identified. Amoxicillin 6g/d was prescribed.

33 *Lm* identification was confirmed using the API *Listeria* system (bioMérieux, Marcy
34 l'Etoile, France) and the strain typed as belonging to genoserogroup IVb (6). Susceptibility to
35 antibiotics was determined by disk diffusion according to the European Committee on
36 Antimicrobial Susceptibility Testing (EUCAST) guidelines (3, 7-8). The strain was resistant
37 to high-levels of rifampicin but otherwise susceptible. The MIC of rifampicin was $> 32 \mu\text{g/ml}$,
38 as determined by Etest (bioMérieux).

39 Resistance to rifampicin is mostly mediated by mutations in *rpoB*, which encodes the
40 β -subunit of the RNA polymerase, and mutations in *rpoB* have been associated with

41 resistance to rifampicin (9-11). The *rpoB* gene (3,555 bp) of this rifampicin-resistant isolate
42 was amplified and sequenced. Comparisons with *rpoB* of susceptible strain (12) identified
43 missense mutation S488L in a conserved domain previously shown to be associated with
44 rifampicin resistance (“resistance locus”) in both *E. coli* and *Lm* mutants obtained *in vitro*
45 (13). A similar substitution (S531L) has been reported in the central region of the β -subunit of
46 the RNA polymerase of rifampicin-resistant *M. tuberculosis* (11). Another non-synonymous
47 mutation was detected at codon 1178 (A1178T).

48 To our knowledge, S488L and A1178T substitutions have not been described in *Lm*
49 (14). This strain was the only one displaying high resistance to rifampicin among the 5,114
50 human isolates tested in the NRCL since 1994. A single isolate from another patient with a
51 borderline rifampicin MIC (4 μ g/ml) did not exhibit any mutation in the *rpoB* resistance locus
52 (our unpublished data).

53 According to the information we have, this patient was not exposed to rifampicin,
54 arguing for a mechanism reminiscent to spontaneously arising *M. tuberculosis* resistance to
55 rifampicin in infections with large inoculum (11). Mutations in *rpoB* reported here could also
56 be the consequence of the previous ciprofloxacin-exposure, which has been shown to promote
57 mutations associated with rifampicin-resistance in *Staphylococcus aureus* (15). To our
58 knowledge, we provide here the first report of a highly rifampicin-resistant *Lm* human clinical
59 isolate.

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