Journal of Global Antimicrobial Resistance 18 (2019) 177–178

Contents lists available at ScienceDirect

Journal of Global Antimicrobial Resistance

journal homepage: www.elsevier.com/locate/jgar

Letter to the Editor

Invasive meningococcal disease due to ciprofloxacin-resistant *Neisseria meningitidis* Sequence Type 7926: the first case in Italy, likely imported

Sir,

Ciprofloxacin is commonly recommended for chemoprophylaxis of close contacts of cases of invasive meningococcal disease (IMD) [1]. Although only sporadic cases of IMD due to ciprofloxacin-resistant *Neisseria meningitidis* have been reported to date, it remains an important public-health concern worldwide [2]. Ciprofloxacin resistance is mainly due to point mutations in the quinolone resistance-determining region (QRDR) of the *gyrA* gene, encoding subunit A of DNA gyrase [3].

In Italy, antimicrobial susceptibility testing of *N. meningitidis* is routinely performed for isolates responsible for IMD within the National Surveillance System [4]. Here we describe a case of IMD due to a serogroup B ciprofloxacin-resistant *N. meningitidis* isolate belonging to sequence type 7926 (ST-7926) in Italy, likely imported.

On 1 July 2018, an adult Russian citizen who had previously travelled to Georgia before his arrival in Italy was admitted to the emergency department of Rimini Hospital (Rimini, Italy) due to fever, oliguria, asthenia and dyspnoea. The main parameters on blood testing were as follows: leukocytes, 22×10^9/L; platelets, 126×10^9/L; prothrombin time, 1.34 s; creatinine, 3.46 mg/dL; and C-reactive protein, 186 mg/L. The patient was treated empirically with piperacillin/tazobactam (4.5 g as a first dose then 2.25 g four times a day) due to suspected sepsis originating in the urinary tract. After 7 h he was transferred to the intensive care unit where, due to neurological impairment, cerebral spinal fluid (CSF) was collected and analysed, with the following results: leukocytes, 3000/μL; glucose, 5 mg/dL; and protein, 5.68 g/L.

N. meningitidis of serogroup B was identified by real-time PCR of the CSF sample, and a bacterial strain was cultured from blood. Antimicrobial susceptibility testing was performed by Etest (bioMérieux, Oxoid Ltd. Solna, Sweden) and the results were interpreted according to European Committee on Antimicrobial Susceptibility Testing (EUCAST) breakpoints (http://www.eucast.org/fileadmin/src/media/PDFs/EUCAST_files/Breakpoint_tables/v_8.1_Breakpoint_Tables.pdf). The isolate was resistant to ciprofloxacin [minimum inhibitory concentration (MIC) =0.25 mg/L] and was intermediate to penicillin G showing an MIC of 0.125 mg/L (penicillin-intermediate breakpoints, 0.064 mg/L > MIC ≤ 0.25 mg/L). The meningococcal isolate was susceptible to cefotaxime (MIC = 0.012 mg/L), chloramphenicol (MIC = 0.75 mg/L), meropenem (MIC = 0.032 mg/L), minocycline (MIC = 0.032 mg/L) and rifampicin (MIC = 0.023 mg/L).

The patient was successfully treated with ceftriaxone (2 g twice daily) and was discharged after 12 days without sequelae. The patient's close contacts, who had previously received ciprofloxacin (500 mg orally, single dose) in the first round of prophylaxis, were recalled for treatment with rifampicin (600 mg every 12 h for 2 days).

The meningococcal isolate was sent to the National Reference Laboratory for IMD of the Istituto Superiore di Sanità (Rome, Italy) as co-ordinator of the IMD National Surveillance System. Bacterial DNA was extracted from an overnight culture using a QIAamp® Mini Kit (QIAGEN, Hilden, Germany) according to the manufacturer's instructions. Whole-genome sequencing was performed using MiSeq Illumina technology. The PubMLST database (http://pubmlst.org/neisseria/) was used to define the multilocus sequence typing (MLST), the variable regions (VRs) of PorA and FetA protein antigens, and the QRDRs.

The isolate was serogroup B, PorA VR1 of family 17, PorA VR2 of family 16-4 (P1.17,16-4), FetA VR of family 3-9 (F3-9), ST-7626 (genotypic formula: B:P1.17,16-4:F3-9:ST-7926). ST-7626 belongs to a not yet assigned (UNK) clonal complex (cc), and reported for the first time in Italy. A new *gyrA* allele (*gyrA-212*) harbouring the T91I amino acid substitution associated with resistance to fluoroquinolones as well as a new *penA* allele (*penA-787*) showing two amino acid substitutions (F504L and A510V) among the five responsible for a penicillin-intermediate phenotype were also identified. The *penA-787* allele was previously reported in an invasive meningococcal serogroup W strain isolated in Russia in 2017 (as reported on the website https://pubmlst.org/; last accessed 28 June 2019). No mutations were present in the *parC*, *parE* and *mtrR* genes.

The four-component meningococcal group B (4CMenB) vaccine antigenic variants were: factor H binding protein (fHbp) 1.37; Neisserial Heparin Binding Antigen (NHBA) 180; and PorA VR2 16-4. A deletion in the *Neisseria* adhesin A (*nadA*) coding gene was also found.

In summary, an imported case of IMD due to a ciprofloxacin-resistant *N. meningitidis* isolate belonging to ST7926 was reported for the first time in Italy. Molecular analysis of target genes associated with antimicrobial resistance confirmed the mutation in the *gyrA* gene responsible for the ciprofloxacin-resistant phenotype.

Two IMD cases have been reported in the country owing to ciprofloxacin-resistant meningococci: the first, in 2009, was an imported strain of serogroup A, ST-4789 (cc5); the second, in 2010, was serogroup C, ST11 (cc11) isolated from a sporadic IMD case [4,5].

Overall, antimicrobial resistance in *N. meningitidis* is still rare in Italy [4]. Therefore, ciprofloxacin remains a first-line drug for chemoprophylaxis of close contacts of IMD cases given the very small number of resistant strains. Antimicrobial susceptibility and

https://doi.org/10.1016/j.jgar.2019.07.010

genome analysis of invasive meningococcal strains is required for the possible introduction of new resistant strains.

Funding

This research did not receive any specific grant from funding agencies in the public, commercial or not-for-profit sectors. Data were collected within the IMD National Surveillance System, DPCM 3/3/2017 [GU n.109 del 12/5/2017].

Competing interests

None declared.

Ethical approval

Not required.

Acknowledgments

The authors thank Florigio Lista, Silvia Fillo, Andrea Ciammaruconi and Antonella Fortunato (Molecular Biology Section, Army Medical and Veterinary Research Center, Rome, Italy). This publication made use of the Neisseria MLST website (http://pubmlst.org/neisseria/), developed by Keith Jolley and sited at the University of Oxford (Oxford, UK). Development of this site has been funded by the Wellcome Trust and the European Union.

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Received 7 May 2019

Available online 17 July 2019