We describe the isolation and successful eradication of H. pylori showing resistance to clarithromycin, metronidazole, fluoroquinolones and rifampicin/ritafurbin, and reduced susceptibility to tetracycline.

H. pylori was identified twice from a middle-aged male patient with functional dyspepsia. Gastroduodenoscopy revealed a moderate antral gastritis; peptic ulcer disease and any other pathologies were ruled out. Relevant co-morbidities were asthma bronchiale and obstructive sleep apnoea. The patient received two courses of standard first-line H. pylori treatment, consisting of a proton pump inhibitor (PPI; standard dose twice daily), amoxicillin (1 g twice daily) and clarithromycin (250 mg twice daily) for 7 days (French triple), followed by one course of PPI (standard dose twice daily), clarithromycin (500 mg twice daily) and metronidazole (400 mg twice daily) for 7 days (Italian triple), and, afterwards, a rescue therapy with PPI (standard dose twice daily), amoxicillin (1 g twice daily) and rifabutin (150 mg twice daily) for 10 days. Following each eradication therapy, the patient reported significant but transient improvement of symptoms. However, H. pylori was still present, as proven by histopathology, rapid urease test and ¹³Curea breath test. Due to several respiratory tract infections, the patient had been treated in the past with moxifloxacin, clindamycin and azithromycin. There was no information about treatment with tetracycline during the last 12 months. Gastric tissue samples (antrum and corpus) were sent to the Institute of Medical Microbiology and Hygiene (Freiburg, Germany) for microbiological examination. Grown bacteria were identified as H. pylori and antimicrobial susceptibility testing (Etest®) was performed as described previously. The following breakpoints were used: metronidazole, 8 mg/L; clarithromycin, 1 mg/L; levofloxacin, 1 mg/L; amoxicillin, 2 mg/L; tetracycline, 1 mg/L; and rifampicin, 4 mg/L.

The strain showed resistance to metronidazole (MIC ≥ 256 mg/L), clarithromycin (MIC 16 mg/L), levofloxacin (MIC ≥ 32 mg/L) and rifampicin (MIC ≥ 32 mg/L), but was susceptible to amoxicillin (MIC 0.047 mg/L); the MIC of tetracycline was slightly higher than usually observed (0.75 mg/L). Based on these results, the patient received PPI (40 mg of omeprazole three times daily) and amoxicillin (1 g three times daily) for 14 days, which resulted in clinical improvement. Six months later, the patient presented again with dyspepsia and a positive ¹³Curea breath test. Re-gastroduodenoscopy followed by susceptibility testing of H. pylori revealed susceptibility to amoxicillin (MIC 0.032 mg/L), but resistance to metronidazole (MIC ≥ 256 mg/L), clarithromycin (MIC 24 mg/L), levofloxacin (MIC ≥ 32 mg/L) and rifampicin (MIC ≥ 32 mg/L) and tetracycline (MIC 1.5 mg/L). Genotyping resistance-associated genes showed mutations in the 23S rRNA (A2147G) and gyrA (D91G) genes, confirming phenotypic resistance to clarithromycin and levofloxacin. Phenotypic resistance to rifampicin/ritafurbin was confirmed by detection of a D530V mutation in the rpoB gene in the strain isolated first and a D530N mutation in the latter strain. A possible explanation for these apparently inconsistent findings may be a mixed infection with different strains or clones. A single base pair A926G mutation in the 16S rRNA genes (rrnA/B) was found in both isolates, which was shown to be associated with resistance or reduced susceptibility to tetracycline. Whether this point mutation leads to treatment failures or...
whether it may be overcome by higher doses or longer therapies remains to be established.

Eventually, we recommended a prolonged therapy including PPI (40 mg of omeprazole three times daily) and amoxicillin (1 g three times daily) for 4 weeks, which turned out to be successful, as shown by negative $^{13}$C urea breath test, rapid urease test, histopathology, culture and molecular genetic testing 6 weeks after therapy.

Multiresistant clinical \textit{H. pylori} isolates exist in Germany and will probably be increasingly detected in the future. To avoid treatment failures, to minimize the risk of the development of antimicrobial resistance and to reduce costs, we recommend susceptibility testing after the first unsuccessful empirical \textit{H. pylori} eradication therapy. In patients who have already received multiple antibiotic treatments due to unrelated bacterial infections, susceptibility testing prior to the first eradication attempt may be considered. The presented case demonstrates the risk of upcoming difficult-to-treat \textit{H. pylori} infections and underlines the need for ongoing studies to keep antibiotic resistance under surveillance.

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