Isolation and eradication of a clinical isolate of Helicobacter pylori resistant to five antimicrobials in Germany

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Sir,

Colonization/infection with Helicobacter pylori is contracted during childhood, persists lifelong and causes chronic gastritis, which may be complicated by peptic ulcer disease, gastric cancer or mucosa-associated lymphoid tissue (MALT) lymphoma.1 Failed H. pylori eradication therapy or antimicrobial therapy due to unrelated infections are the main risk factors for the development of resistance.2 In Germany, primary resistance amounts to 29% for metronidazole, 6% for clarithromycin, 15% for fluoroquinolones, 4% for double resistance (clarithromycin and metronidazole) and 1% for triple resistance (clarithromycin, metronidazole and fluoroquinolones) (E. Glocker, M. Kist and N. Wüppenhorst, unpublished data). After the first eradication therapy, resistance rates rise to 50% for metronidazole, 58% for clarithromycin, 30% for double resistance and 8% for triple resistance. Resistance to rifampicin/rifabutin (1.4%) and tetracycline is rare; amoxicillin resistance has not been described in Germany, so far.2–4 H. pylori resistant to three or more antimicrobials (multiresistant) have been described before, e.g. in Germany and Bulgaria.5,6

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

H. pylori was identified twice from a middle-aged male patient with functional dyspepsia. Gastroendosonography 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.1 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 [13C]urea 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.7 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 [13C]urea breath test. Re-gastroendoscopy 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/rifabutin 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 (rrnAB) was found in both isolates, which was shown to be associated with resistance or reduced susceptibility to tetracycline.7 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 \( H. pylori \) 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 \( H. pylori \) 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 \( H. pylori \) infections and underlines the need for ongoing studies to keep antibiotic resistance under surveillance.

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The use of daptomycin in continuous renal replacement therapy

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Sir, Daptomycin is licensed in the USA and Europe for the treatment of complicated skin and soft tissue infections caused by Gram-positive organisms, at a dose of 4 mg/kg once daily, and right-sided endocarditis with associated bacteremia, at a dose of 6 mg/kg once daily.\(^1\) Daptomycin has 92% plasma protein binding in vitro, a volume of distribution of 0.097 L/kg and a plasma elimination half-life of \( \sim 9 \) h and is primarily excreted unchanged by the kidneys. Patients with a creatinine clearance \(< 30\) mL/min exhibit AUC values twice those of patients with normal renal function. Daptomycin is removed by haemodialysis (HD); \( \sim 15\% \) of an administered dose is eliminated in a 4 h HD session. Therefore, in patients with reduced renal function, including those receiving HD, the recommended daily dose interval is 48 h.\(^2\) To our knowledge there is little published about the use of daptomycin in patients who undergo continuous renal replacement therapy (CRRT), and in only one case were plasma concentrations recorded.\(^3\)

A person in their thirties, who was previously well, was admitted to our Emergency Department following a motorcycle accident, having suffered extensive trauma. The patient was transferred to the intensive care unit following surgery and empirical antibiotic therapy of amoxicillin/clavulanic acid and clindamycin was commenced. On the fourth day of recovery the patient developed septic shock and acute renal failure. Blood cultures and wound swabs from the left leg were collected and CRRT was started. We used a LYNDRA dialysis system (Belico, Italy). The programme we used was continuous venous–venous haemofiltration (CVVH) 24 h/day, using a high-filtration polysulphone membrane (HFT 22, surface area 2.2 m\(^2\), Belico) with a blood flow of 150 mL/min and a dialyser flow of 3000 mL/h (50% pre and 50% post).

Antibiotic therapy was changed to a combination of glycopeptide plus piperacillin/tazobactam. On the seventh day, blood cultures and wound swabs grew methicillin-resistant \( S. aureus \) (MRSA). An antimicrobial susceptibility test was carried out using the VITEK-2 system (bioMérieux, Marcy l’Étoile, France). MRSA was susceptible to rifampicin, co-trimoxazole, linezolid, tigecycline and...