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Articles

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ResiNet – a nationwide German sentinel study for surveillance and analysis of antimicrobial resistance in *Helicobacter pylori*

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About 30% of the German population (20 to 30 million people) are currently infected with *Helicobacter pylori*. In about four to six million of these people, the infection will lead to complications such as peptic ulcers (20%), gastric cancer (<1%), or very rarely to MALT (mucosa associated lymphoid tissue) lymphoma. *H. pylori* associated diseases like peptic ulcers or MALT-lymphoma can be healed by an antimicrobial eradication therapy as recommended by the Maastricht Consensus 2000 (1). However, increasing resistance to commonly used antibiotics like clarithromycin or metronidazole are compromising the eradication of *H. pylori* and causing therapy failures. Knowledge of the current resistance status of *H. pylori* therefore would be helpful for designing an optimally adapted therapy and preparing therapeutic recommendations.

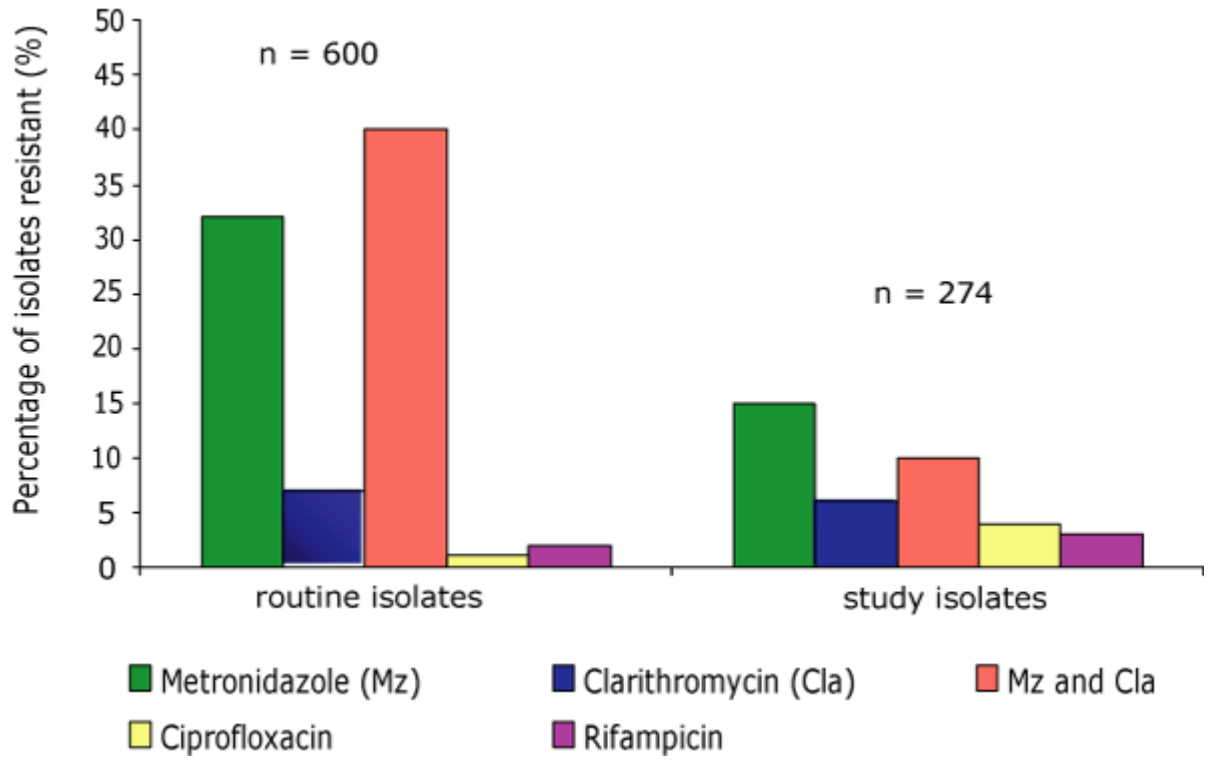
The largest German study of *H. pylori* so far, investigated the resistance patterns of 554 clinical routine isolates (2). About 70% of the examined strains were resistant to metronidazole, and 50% to clarithromycin. The majority of the isolates exhibited resistances against both antibiotics.
One of the major tasks of the German National Reference Centre for *Helicobacter pylori*, set up in 2000, was to perform a nationwide sentinel study called 'ResiNet'. The aim of the study is to establish a reliable database from which information on the development and risk factors of antimicrobial resistance in *H. pylori* in Germany can be obtained, and evidence based recommendations for H. pylori eradication therapy drawn up.

The database aims to analyse the prevalence of resistance against antibiotics such as amoxicillin, clarithromycin, metronidazole, quinolones, tetracyclines and rifamycin, stratified for:
- age and gender
- ethnic groups
- underlying clinical conditions like gastritis or peptic ulcers
- prior antimicrobial treatment
- different geographical areas
- time-dependent trends

Before starting ResiNet, one hundred questionnaires were sent to microbiological laboratories in Germany to get information about the current status of *H. pylori* diagnostics. In addition, 5200 questionnaires were sent to German gastroenterologists to evaluate their current strategies of diagnostics and eradication regimes. In both investigations, interest in cooperation with ResiNet was evaluated. Data analysis revealed that microbiological investigation of gastric biopsies does not play an important role in the primary diagnosis of *H. pylori* infection and therefore, as a rule, patients are treated following the Maastricht guidelines without prior susceptibility testing. Interestingly, a tendency was apparent to change therapy after detecting a possible resistance. However (cases of treatment failure included), gastroenterologists did not initiate susceptibility testing, mainly due to inaccessibility of a competent microbiological laboratory that was familiar with the appropriate techniques.

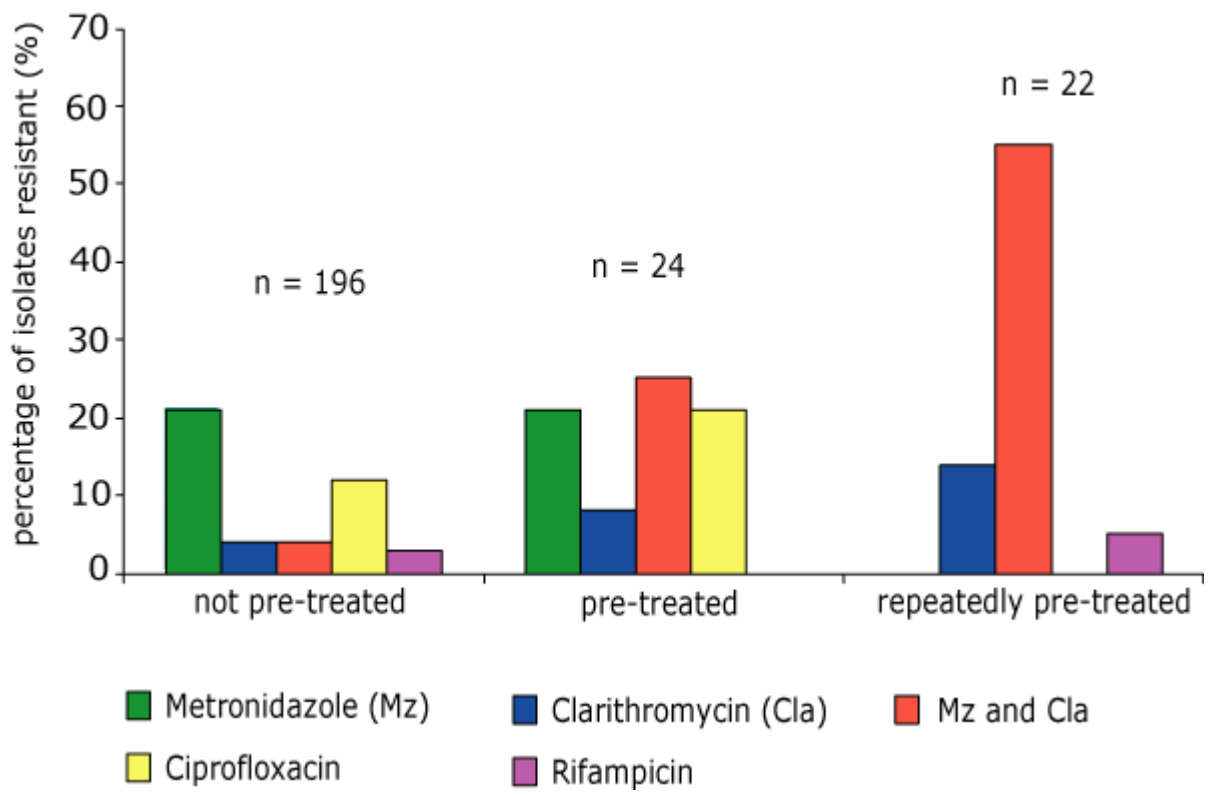
After these preceding investigations, ResiNet started in June 2001 as a pilot project with two cooperating laboratories, increasing to 16 laboratories currently participating in the study. The prospective study design focussed on collecting data as minimally biased and representative as possible. During the study weeks, two groups of gastroenterological sentinel practices, each closely collaborating with their respective microbiological study centres, consecutively enrolled patients who were admitted for gastroduodenoscopy, gave their informed consent, and whose gastric biopsy Helicobacter urease test result was positive within the first 60 minutes. Each gastroenterologist enrolled three to five patients over the age of 18 years every week for six weeks, equally distributed over a 12 month period. Patients were unselected in respect of any treatment failure in the past, or any other clinical or socioeconomic characteristics. Clinical and epidemiological data were prospectively collected. All microbiological study centres applied standardised operating procedures provided by the National Reference Centre, and used identical lots of culture media during identical study weeks. One desirable secondary outcome of ResiNet is the achievement of nationwide standardised and quality controlled culture and resistance testing procedures for *H. pylori*.
The data shown is from a total of 274 patients up to September 2003. Complete clinical and epidemiological data including preceding treatment regimes as well as resistance data of the respective isolates were available for analysis.

Figure 1. Prevalence of *H. pylori* resistance according to source



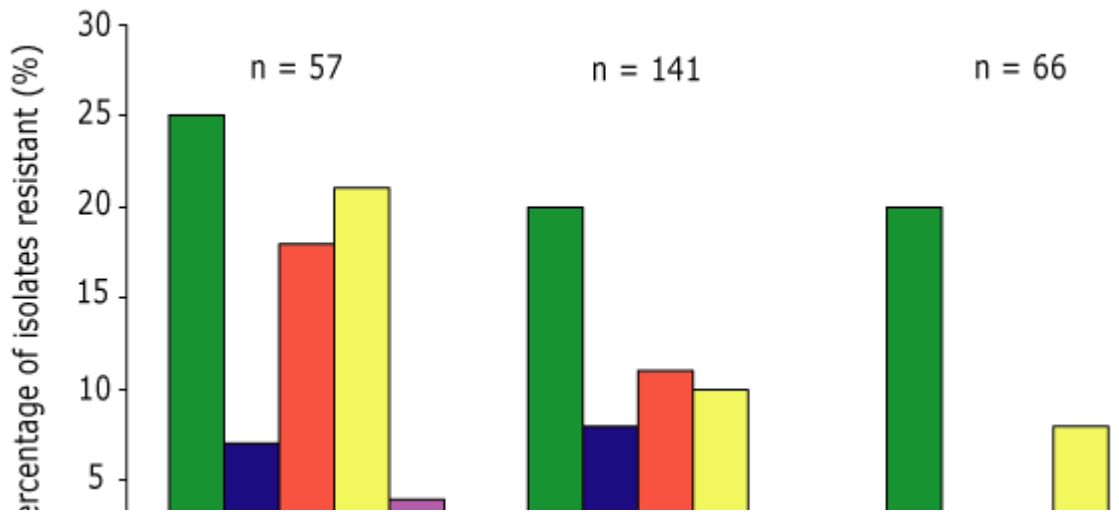
Resistance data obtained from *H. pylori* isolates from gastric biopsies sent routinely for microbiological investigation differ significantly from those systematically collected from study patients (Figure 1). Differences are obvious at the first glance for the frequencies of single resistances to metronidazole (32% vs. 15%) and especially for isolates being doubly resistant to metronidazole and clarithromycin (40% vs. 10%), clearly indicating that data from routine investigations are not representative and often heavily biased by selection of patients investigated. Out of a total of 274 study patients, 196 had not been pre-treated for *H. pylori* infection, 24 reported one pre-treatment, and 22 had had repeated treatments previously. Pre-treatment data were missing from 32 patients. The still preliminary data clearly show that pre-treatment and especially repeated pre-treatment were associated with a remarkable increase of single resistances to clarithromycin and especially with double resistances to metronidazole and clarithromycin. (Fig. 2)

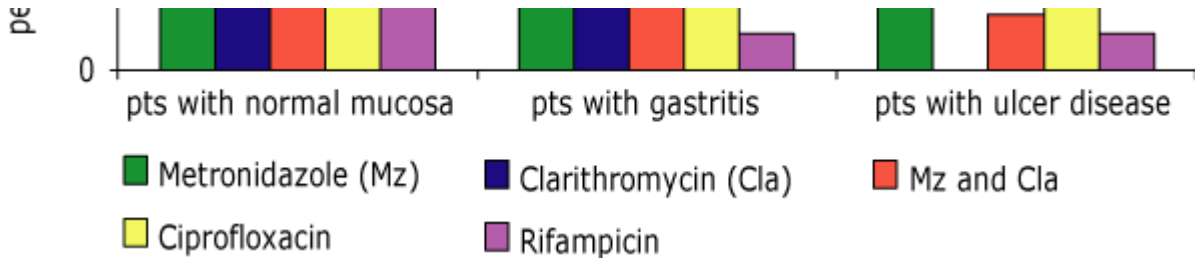
Figure 2. Prevalence of H. pylori resistance according to frequency of pre-treatment



Endoscopical findings of study patients were peptic ulcer disease (25%), gastritis or other pathological changes (53%), and normal gastric mucosa (22%). Interestingly enough, more sensitive strains were isolated from patients with peptic ulcer disease, whereas individuals with normal gastric mucosa harboured resistant strains most frequently. Patients with gastritis ranged between both groups. (figure 3)

Figure 3. Prevalence of H. pylori resistance according to type of underlying disease





In conclusion, these data provide evidence that systematic and prospective data are essential for representative resistance surveillance studies. Data from routinely investigated biopsies are clearly not sufficient. Furthermore it is obvious that repeated empirical treatment regimes are especially associated with the post-treatment presence of strains exhibiting double resistance to metronidazole and clarithromycin.

Present data support the following recommendations if eradication treatment is indicated:

- patients without previous antimicrobial therapy may be empirically treated
  empiric treatment of all patients, regardless of their
- medical history is associated with an increase of double resistant isolates
  it appears wise to undertake a microbiological investigation of gastric biopsies in all patients
- previously treated with antimicrobials and to test the H. pylori isolates for resistance so that a specific and appropriate therapy may be adopted

References:

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