Metronidazole-resistant *Helicobacter pylori* strains among Saudi patients with dyspepsia

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**ABSTRACT**

**Objectives:** To determine how common are metronidazole-resistant (MTZ-R) *Helicobacter pylori* (*H. pylori*) strains in Saudi patients. **Design:** A prospective study in patients with dyspepsia attending for gastroscopy at Asir Central Hospital, Abha, Saudi Arabia. **Methods:** Each biopsy specimen was inoculated on a Skirrow's selective medium and incubated at 37 °C under a microaerophilic atmosphere for 3 to 7 days. Suspected colonies were tested further for identification and susceptibility testing. **Results:** A total of 40 different *H. pylori* strains were studied. Of the 40 strains isolated, 16 (40.0%) were MTZ-R. Females showed a higher, though not significant, rate of MTZ-R (47%) than males (33%) (p=0.37). Furthermore, patients with MTZ-R strains showed lower median age (35 years), compared to those with susceptible ones (45 years). However, the difference was not significant (t=1.89, p=0.07). Moreover, MTZ-R was not significantly affected by the type of endoscopic diagnosis (duodenal ulcer (30%) and gastritis (50%), p=0.20). **Conclusions:** Since MTZ-R *H. pylori* strains are frequent (40%), it is recommended to test MTZ susceptibility if possible before treatment, to guide the selection of appropriate therapy and to avoid eradication failure, in particular patients with a history of *H. pylori* treatment failure. Metronidazole resistance was not affected by age, sex or diagnosis.

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**Keywords:** *Helicobacter pylori*, metronidazole-resistant, dyspepsia, Saudi Arabia.

*Helicobacter pylori* (*H. pylori*) is the most common cause of chronic superficial gastritis in humans and has been strongly linked to most patients with duodenal and gastric ulcers. It is also strongly associated with the intestinal type gastric adenocarcinoma. Because eradication of *H. pylori* has been shown to resolve gastritis and cure peptic ulcers and may also decrease the mortality from gastric cancer, more attention has turned towards antimicrobial therapy. The current practice has been the use of bismuth-based triple therapies which achieves a higher eradication rate and prevents the rapid emergence of resistance when monotherapy is used. The recommended standard triple therapy includes metronidazole plus bismuth compound and tetracycline or amoxicillin. Such triple therapy is highly effective against the *Helicobacter pylori* susceptible organisms but is largely ineffective when metronidazole resistance occurs. Furthermore, as most triple therapies contain metronidazole as an active component, metronidazole resistance will significantly decrease the rate of *H. pylori* eradication and subsequently ulcer healing. This prospective study was undertaken to assess the rate of metronidazole resistance to *H. pylori* organisms in Saudi patients as only one study has been reported from Saudi Arabia.

**Material and methods** Among patients referred to the GI Unit for UGI gastroscopy, 40 consecutive patients with dyspeptic symptoms were prospectively evaluated and had endoscopic biopsies of the antral gastric mucosa within 5 cm of the pylorus. Samples were sent for bacteriological examination of *H. pylori*. None of the patients received metronidazole or any other antimicrobials in the last six months. Biopsies were transported in either sterile swabs with transport media (transube sterile, ref MW 170 mfg. in UK) or in sterile vials containing sterile normal saline. Upon receipt, each biopsy specimen was directly inoculated on the surface of a

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### Table 1 - Distribution of 40 H. pylori strains according to their susceptibility to Metronidazole by age, sex and diagnosis

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>MTZ-R* (N=16) 40%</th>
<th>MTZ-S* (N=24) 60%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age in years (Median ± SD)</td>
<td>35</td>
<td>45</td>
</tr>
<tr>
<td>M-W test = 261 (n=16, n=24)</td>
<td>p=0.06 (2-tail)</td>
<td></td>
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<tr>
<td>Sex:</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>7 (33%)</td>
<td>14 (67%)</td>
</tr>
<tr>
<td>Female</td>
<td>9 (47%)</td>
<td>10 (53%)</td>
</tr>
<tr>
<td>Chi-square = 0.82, DF = 1, p=0.37</td>
<td></td>
<td></td>
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<tr>
<td>Diagnosis:</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Duodenal ulcer</td>
<td>6 (30%)</td>
<td>14 (70%)</td>
</tr>
<tr>
<td>Gastritis</td>
<td>10 (50%)</td>
<td>10 (50%)</td>
</tr>
<tr>
<td>Chi-square = 1.67, DF = 1, p=0.20</td>
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</tbody>
</table>

MTZ-R = Metronidazole-resistant
MTZ-S = Metronidazole-susceptible

Differences in prevalence of MTZ-R *H. pylori* strains among different ages, sexes and underlying diagnosis.

**Results** Metronidazole susceptibility testing in the *H. pylori* strains isolated according to age and sex are shown on the Table. All *H. pylori* isolates were susceptible to amoxicillin and tetracycline. It is evident that MTZ-R *H. pylori* strains were more prevalent among younger patients, though the difference did not achieve statistical significance. Likewise, no significant difference was found when the data were analyzed according to sex and underlying diagnosis.

**Discussion** The present study showed that of 40 different *H. pylori* strains isolated from 40 different patients, 16 (40%) were metronidazole-resistant (MTZ-R). This rate was lower than the 84%, 65% and 66% reported from Zaire, Brazil and recently from western Saudi Arabia, respectively. However, it was higher than the 27% and 30% reported from Belgium Nova Scotia and Canada, respectively. The reasons for this variation are not clear. However, in developing countries, frequent misuse of the drug for parasitic infections, abnormal pharmacokinetics, poor formulation and inadequate treatment duration are possible explanations for the higher organism's resistance. Female patients showed a higher (47%), though not significant, rate of MTZ-R than males (33%), in contrast to the reports from Africa. On the other hand, MTZ-R was not significantly affected by either gender or endoscopic diagnosis although MTZ-R *H. pylori* were more frequent among young patients.

A precise mechanism of metronidazole resistance in *H. pylori* is unclear. Metronidazole, having a systemic activity, accepts electrons from a reduced electron transfer protein, thereby the drug is reduced via its nitro group. Resistant strains have lost the ability to achieve a sufficiently low redox potential for the necessary reduction of metronidazole. A mutation in the nitroreductase of the organism is thought to be responsible for the resistance. For practical reasons and since *H. pylori* eradication rate has been shown to decrease dramatically if there is resistance to metronidazole, this problem can be overcome by the addition of bismuth to antihelicobacter regimes as well as finding a better substitute for metronidazole according to the local sensitivity pattern of *H. pylori*.

**Conclusion** We conclude that MTZ-R *H. pylori* strains constitute 40% to 60% in the Saudi population making sensitivity tests for *H. pylori* an important step towards the selection of the most appropriate therapeutic agents against *H. pylori*.  

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