# THE FACTORS RELATED TO H. PYLORI INFECTION RESISTANCE AFTER ERADICATION OR ITS RECURRENCE IN SULAIMANI CITY

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### Abstract

*Helicobacter pylori (H. pylori) infection can lead to peptic ulcers, chronic gastritis, lymphoma and gastric cancer. This study aimed to assess the factors related to H. pylori resistance after eradication and its recurrence after 6 months. 574 patients tested for H. pylori and those who positive has been assessed for recurrence after 6 months or resistance to treatment and factors related to recurrence in correlation with demographic data. 51% of men and 49% of women were still testing positive for H. pylori after receiving treatment. The majority of patients who tested positive again for H. pylori were taking clarithromycin-based triple therapy, with only a small percentage being treated with levofloxacin, rate of resistance and recurrence were 23.54% and 8.7%, respectively. Most common symptoms after recurrence were epigastric pain and nausea (62.96%) and dyspepsia (55.55%). The highest rate of recurrence is related to $O^+$ blood group, which is 47.82%. Recurrence rate after H. pylori eradication by standard therapy (clarithromycin triple treatment) or levofloxacin-based therapy is 8.7%. Poor sanitation, low income, and treatments regimens are independent risk factors for recurrence of H. pylori. Reducing the frequency of eating outdoors and treating family members may reduce H. pylori infection recurrence.*

*Keywords: H. Pylori Infection, Triple Therapy, Resistance and Recurrence After Eradication*

## 1. INTRODUCTION

*Helicobacter pylori* is a pathogenic bacteria in human gastric mucosa, was isolated for the first time by Marshall and Warren in 1982 (Hooi et al., 2017). *H. pylori* infection can lead to chronic gastritis, gastric ulcer, duodenal ulcer, mucosa-associated lymphoid tissue (MALT), and even gastric cancer (Jafar et al., 2023; O'Connor et al., 2020). The presence of genetic elements, such as ABO blood type and Lewis blood type, can impact the onset of an infection (Guevara & Cogdill, 2020). Drinking water contains this particular bacterium, and unsanitary behavior makes it easier for fecal-oral transmission to occur (Ahmad & Abdulkareem, 2024; Zou et al., 2020).

*H. pylori* are transmitted via contaminated food or water. The bacteria can be contracted by individuals through consumption of inadequately washed or undercooked food, or by ingesting contaminated water (Bauer & Meyer, 2011; Stefano et al., 2018). Exposure to domestic animals play also a role in transmission (Kotilea et al., 2019). One

more way the virus can spread is through physical contact with the bodily fluids, such as feces, vomit, or saliva, of someone who is infected (Wei et al., 2021).

Diagnosing *H. pylori* infection can be achieved through invasive techniques such as endoscopic biopsy, as well as non-invasive methods like blood or urine tests, urea breath tests, serological tests, and stool samples. Urea breath and stool antigen tests detect current active infection whereas urine and serological tests indicate previous *H. pylori* infection but not recent active infection (Al-Moslih, 2012).

Many studies have been conducted on the success rates of treating *H. pylori* through various therapies such as triple therapy (with clarithromycin), quadruple therapy, and levofloxacin-based therapy, achieving response rates of 84.4%, 89.4%, and 97.4% respectively (O. M. Mohammed et al., 2020). This study aims to assess the factors leading to *H. pylori* resistance after eradication or its recurrence after a period of 6 months.

## 2. RESEARCH METHODS

A descriptive cross-sectional study was conducted to assess the factors leading to *H. pylori* resistance or recurrence after eradication in patients infected with *H. pylori* after a period of 6 months or beyond this period. A total of 574 individuals were assessed to determine eligibility for participation in this research project. The cases were selected randomly from subjects attending KCGH center in Sulaimani Teaching Hospital between January 2021 and February 2022. Patient's information was taken by direct interview in GIT Center Sulaimani teaching hospital, depending on a standard questionnaire that included demographic data and clinical conditions.

Out of 574 patients, 100 participants were recruited for the study after fulfilling inclusion criteria. Patients aged more than 17 years, both genders and those who were able to give consent were included in this study whereas those who were uncooperative or refused to participate, unable to give consent, and patients with communication difficulties were excluded.

A full history was taken, full clinical examination was done and investigations were sent for *H. pylori* infection status. A test using urea breath or stool antigen was conducted to verify the success of the eradication treatment and for monitoring in the future. Patients included were those aged above 15 years, both sexes, patient tested positive for *H. pylori* infection and eradicated and followed up for more than 6 months after treatment between January 2021 to February 2022 and patients who had been treated for *H. pylori* in the past and experienced symptoms returned to the medical center and tested positive for the bacteria once more. Whereas pregnant patients and those who tested positive for *H. pylori* infection but didn't come back for follow up or cured were excluded.

Informed consent was taken from each participant prior to collecting data, information kept anonymous, approvals were granted from The Council of Arab Board of Health Specializations in Iraq, department of health, Kurdistan center for Gastroenterology, and Internal Medicine Teaching Hospital.

Data entry was done by Excel (Microsoft, 2016) and statistical analyses were performed with Statistical Package for Social Sciences (SPSS Inc., Chicago, IL, USA) version 26 for windows. Data were expressed by percentages, means and standard deviations. In order to determine significance, differences were deemed important if the P value was less than 0.05. Results were visualized using pie charts and tables. The chi square test was employed to analyze categorical variables within the study groups.

## 3. RESULTS AND DISCUSSION
### 3.1. Results

In this case, 51% of the patients who tested positive for *H. pylori* after treatment were men, while 49% were women. The data from Figure 1 indicates that there is no notable correlation between gender and H. pylori reinfection, with a P-value greater than 0.05.
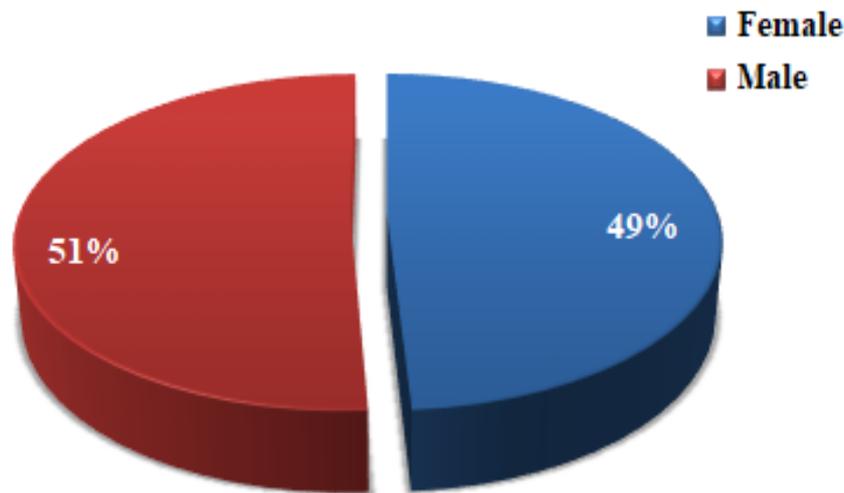


**Figure 1. Percentage of patients with *H. pylori* by gender**

The highest rate of positivity is in the age range of 26-30 years, which is equivalent to 17% and has an average age of 38.05 years and standard deviation (SD) of 16.2. Since it is P>0.05, there is no clear connection between age groups and the frequency of positive bacterial reinfection, according to Figure 2, this positivity was shown in different age groups.
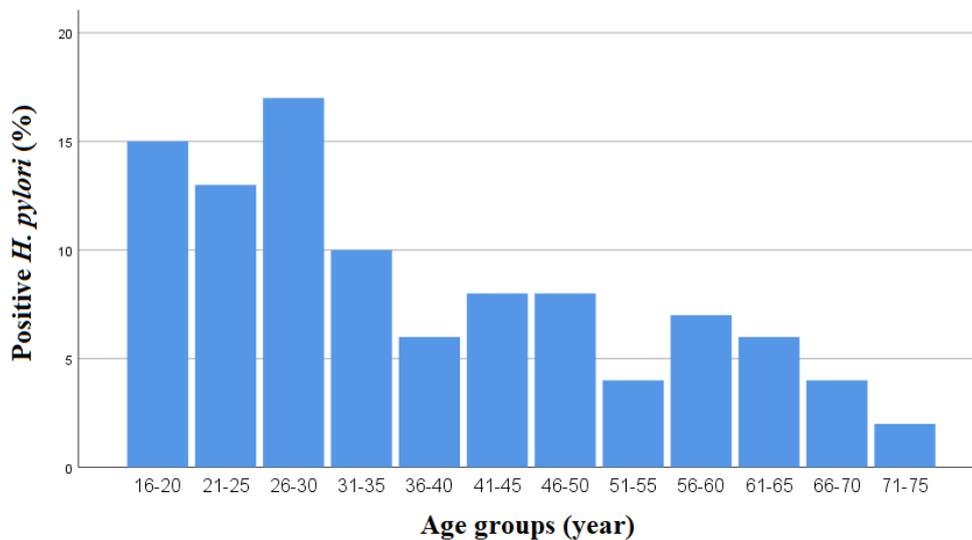
**Figure 2. Percentage of positive *H. pylori* reinfection in different age groups**

Table 1 demonstrates that about 18.4 % of patients were in the middle socioeconomic group, 25.4% of patients were in the poor socioeconomic group and 56.1 % of patients were in good socioeconomic group. Seventy percent of individuals in need of medical care come from large families with more than 5 members, while the remaining 30% reside in smaller households with less than 5 members. Seventy six percent of people have no history of contact with people with *H. pylori*. In this research, most of the people with positive *H. pylori* were workers, students and housewives, 30%, 26% and 21%, respectively.

**Table 1. Respondent Demographic**

| Variables | | Mean ± SD | No (%) |
|---|---|---|---|
| **Age (year)** | | 38.05 ± 16.2 | No. (%) |
| **Gender** | | | |
| | Male | | 51 (51) |
| | Female | | 49 (49) |
| **Socioeconomic status** | | | |
| | Poor | | 27 (27) |
| | Middle | | 18 (18) |
| | Good | | 55 (55) |
| **number of family members** | | | |
| | < 5 | | 30 (30) |
| | 5 ≤ | | 70 (70) |
| **Smoker** | | | 37 (37) |
| **Alcohol intake** | | | 2 (2) |
| **History of contact with people having *H. Pylori*** | | | 24 (24) |
| **Type of water** | | | |
| | System water(filtered) | | 66 (66) |

| | | |
|---|---|---|
| | No-filter system(well) | 34 (34) |
| **Duration of recurrence, (month)** | | 8.85 ± 14.62 |
| **Type of food consumed** | | |
| | Restaurant | 26 (26) |
| | Home-made | 49 (49) |
| | Both | 25 (25) |
| **Occupation** | | |
| | Worker | 30 (30) |
| | Student | 26 (26) |
| | Housewife | 21 (21) |
| | Teacher | 3 (3) |
| | Engineer | 1 (1) |
| | Health worker | 3 (3) |
| | Not working | 12 (12) |
| | Employee | 2 (2) |
| | Retired | 2 (2) |

574 people were examined, of which 264 had *H. pylori*-negative infection and 310 had *H. pylori*-positive infection. 310 patients with *H. pylori* infection were treated, of which 73 patients had resistance and 27 patients had recurrence. The remaining 210 patients cured or didn't come back for follow-up. As a result, 100 patients were enrolled in the study, of which 93 patients were on clarithromycin based triple therapy and 7 patients were on Levo-based therapy.

Table 2 visualizes that recurrence and resistance infections have certain clinical symptoms. Resistance cases included 82.19% of epigastric pain and nausea symptoms, 24.65% of GERD symptom, and 31.5% of dyspepsia symptom, and only 2.73% of them were asymptomatic. Among the recurrence, 62.96% of epigastric pain and nausea symptoms, 25.92% of GERD symptom, 55.55% of dyspepsia symptom, and only 3.7% of them were asymptomatic. Significant relationship was observed between symptoms and recurrence or resistance ($P<0.05$).

**Table 2. Main Clinical Symptoms of Resistance and Recurrence**

| Symptoms | Resistance [No (%)] | Recurrence [No (%)] |
|---|---|---|
| Epigastric pain and nausea | 60 (82.19) | 17 (62.96) |
| GERD | 18 (24.65) | 7 (25.92) |
| Dyspepsia | 23 (31.5) | 15 (55.55) |
| Asymptomatic | 2 (2.73) | 1 (3.7) |
| **Symptoms** | **Resistance [No (%)]** | **Recurrence [No (%)]** |
| Epigastric pain and nausea | 60 (82.19) | 17 (62.96) |
| GERD | 18 (24.65) | 7 (25.92) |
| Dyspepsia | 23 (31.5) | 15 (55.55) |
| Asymptomatic | 2 (2.73) | 1 (3.7) |

OGD findings are shown in Table 3. In both cases of resistance and recurrence, most individuals had no OGD findings. No significant relationship was observed between OGD findings and resistance or recurrence cases (P>0.05).

**Table 3. Endoscopic Findings of Patients**

|  | Findings | Persistent [No (%)] | Relapse [No (%)] |
|---|---|---|---|
| OGD | No | 50 (68.49) | 13 (48.14) |
|  | PU (deudenal and gastric) | 12 (16.43) | 10 (37) |
|  | Gastritis (antral, fundal) | 12 (16.43) | 4 (14.81) |
|  | Gastric lymphoma | 1 (1.36) | 0 (0) |
|  | MALTOMA | 0 (0) | 0 (0) |
|  | GC | 0 (0) | 0 (0) |

The relationship between socio-demographic status and resistance or recurrence is given in Table 4. The percentage of female in resistant (52.05%) and the percentage of men in recurrence (59.25%) are higher. Both resistance (47.88%) and recurrence (77.77%) have good socioeconomic status. In both cases of resistance (60%) and recurrence (88%), most of the patients used system water as a source of drinking with a (p <0.005).

**Table 4. Relationship Between Socio-Demographic and Resistance or Recurrence**

| Variables | Resistance [No. (%)] | Recurrence [No. (%)] |
|---|---|---|
| **Gender** | | |
| Male | 35 (47.94) | 16 (59.25) |
| Female | 38 (52.05) | 11 (40.74) |
| **Socioeconomic status** | | |
| Poor | 22 (30.13) | 5 (18.51) |
| Middle | 17 (23.28) | 1 (3.7) |
| Good | 34 (46.57) | 21 (77.77) |
| **Number of Family Members** | | |
| < 5 | 17 (23.28) | 13 (48.14) |
| 5 ≤ | 56 (76.71) | 14 (51.85) |
| **Smoker** | 27 (36.98) | 10 (37.07) |
| **History of contact with people having *H. pylori*** | 17 (23.29) | 7 (25.92) |
| **Type of water** | | |
| System water | 42 (57.53) | 24 (88) |
| No-filter system | 31 (42.46) | 3 (11.11) |
| **Type of food consumed** | | |
| Restaurant | 20 (27.39) | 6 (22.22) |
| Home-made | 36 (49.31) | 13 (48.14) |
| Both | 17 (23.29) | 8 (29.63) |
| **Occupation** | | |
| Student | 19 (26.02) | 7 (25.95) |
| Worker | 21 (28.76) | 9 (33.33) |

| Variables | Resistance [No. (%)] | Recurrence [No. (%)] |
|---|---|---|
| Housewife | 16 (21.91) | 5 (18.51) |
| Not working | 9 (12.32) | 3 (11.11) |
| Employee | 0 (0) | 2 (7.4) |
| Health worker | 3 (4.11) | 0 (0) |
| Teacher | 2 (2.74) | 1 (3.7) |
| Engineer | 1 (1.37) | 0 (0) |
| Retired | 2 (2.74) | 0 (0) |

In the study of blood groups ABO/Rh among patients infected with H. pylori, the highest rate of resistance and recurrence is related to O+ blood group, which is equal to 53.62% and 47.82%, respectively. Because P value is equal to 0.05, it means that there is a significant relationship between blood group type and resistance or recurrence. Details are shown in Table 5.

**Table 5. Relation Between Blood Groups, Resistance and Relapse Cases**

| Blood groups | Resistance [No. (%)] | Recurrence [No. (%)] | p-value |
|---|---|---|---|
| $B^+$ | 8 (11.59) | 1 (4.34) | 0.04 |
| $O^+$ | 37 (53.62) | 11 (47.82) | 0.001 |
| $A^+$ | 15 (21.74) | 3 (13.04) | 0.02 |
| $AB^+$ | 8 (11.59) | 5 (21.74) | 0.09 |
| $A^-$ | 0 (0) | 2 (8.69) | 0.1 |
| $B^-$ | 0 (0) | 1 (4.34) | 0.06 |
| $AB^-$ | 1 (1.44) | 0 (0) | 0.2 |

## 3.2. Discussion

*H. pylori* infection is a very common bacterial infections that affect around about 50% of human (Torres et al., 2005). Among patients who were resistance or recurrent for *H. pylori*, 93% were on triple therapy (clarithromycin based) and 7% were on levofloxacin-based treatment, it means still triple therapy (clarithromycin, PPI, amoxicillin or metronidazole) were the most common type of regimen used for the treated patients with resistance or recurrence, rate of resistance and recurrence were 23.54% and 8.7%, respectively. Drug resistance and the quality of drug used and patient compliance to drug may be one of the causes of resistance or recurrence *H. pylori* in our locality this is supported by another local study done by Mohammed O. Mohammed et al which show the response rate of 84.4% to triple clarithromycin based therapy, nearly 26 % was resistance in that study (O. M. Mohammed et al., 2020).

The main reason of *H. pylori* eradication regimes failure is drug resistance. There are several theoretical reasons for the failure of the eradication regime. Briefly, the drug should be at a higher concentration in the tissue where the bacteria are located compared to the minimum bactericidal concentration (MBC) for a sufficient amount of time to eradicate them. The environment where *H. pylori* reside is distinct due to its acidity. Anti-bacterial should have the capability to diffuse into mucosa of stomach, because such drugs are taken orally typically, so systemic route is the main access to gastric mucosa.

The misuse of drugs, elevated pH levels that render the drug inactive, high bacterial counts, and drug resistance are all contributing factors to drugs failing to reach concentrations higher than the minimum bactericidal concentration (MBC) for *H. pylori*. There is no such study that considers these potential mechanisms of failure effectively, but resistance to clarithromycin seems to be the most important incidence.

According to twenty studies from 1999-2003 (1975 patients), and with clarithromycin based regimen, the eradication rate of *H. pylori* was 87.8% for clarithromycin-susceptible strains versus 18.3% for clarithromycin-resistant strains (Mégraud, 2004).

Resistance to various antibacterial agents is becoming more common, even among drugs previously thought to be effective against *H. pylori*. Tetracycline, amoxicillin, and rifabutin have all been reported as experiencing resistance, although the impact on treatment outcomes remains uncertain due to the infrequency of these resistance patterns (Hooi et al., 2017).

In developed countries, *H. pylori* infection prevalence varies from 20%-40% with a recurrence rate of 1%-2% after successful eradication and an annual incidence of 2%-6% (Salih, 2009). However, the prevalence in developing countries varies from 70%-90% with a relapse rate of 10%-70% after successful eradication treatment. It is more prevalent in developing countries mainly due to overcrowding, low socioeconomic conditions, contaminated food and water, lack of patient care and costs expensive treatment of eradication treatment courses (Hooi et al., 2017; Salih, 2009).

In the present study, a recurrence rate of 8.7% in patients after 24 months of eradication treatment was reported. This is comparable to the results of Morgan et al. who reported a one-year recurrence rate of 8.7 to 18.1 % (Morgan et al., 2013).

The research demonstrates a strong correlation between blood types and the likelihood of resistance and recurrence following treatment for *H. pylori* infection. Highest rate of resistance and recurrence eradication is related to $O^+$ blood group, which is equal to 53.62% and 47.82%, respectively, and the lowest levels of resistance and recurrence eradication were related to blood groups $A^-$, $B^-$ and AB (Kanbay et al., 2005). A similar finding obtained from M. Salih et al (Jaff, 2011). Individuals with blood type O may have a higher likelihood of contracting an H. pylori infection, possibly because of a higher prevalence of secretor status among them (Jaff, 2010). This view is supported by Alkout et al. that who demonstrated that H antigen represents a significant receptor in the gastric and duodenal mucosal cells to which *H. pylori* adheres (Alkout et al., 2000), which also promotes *H. pylori* colonization (Heneghan et al., 1998). People with blood type O show higher inflammatory responses to *H. pylori* with higher levels of lymphocytic infiltration into the gastrointestinal mucosa (Alkout et al., 2000; Heneghan et al., 1998) lower levels of von Willebrand' factor (Franchini et al., 2007)and higher frequency than secretor status (Franchini et al., 2007; Heneghan et al., 1998); all this together increased sensitivity to peptic ulceration.

In this research, it was found that the rate of H. pylori reinfection is similar for both males and females, with no significant relationship between gender and H. pylori reinfection based on statistical analysis ($P > 0.05$) (Alazmi et al., 2010; Asrat et al., 2004; Petrović et al., 2011). A study in Cameroon showed that the prevalence of this bacterium was about 52.27% and contrary to the results of the present study, the percentage of bacterial infection increases with age (Ndip et al., 2004). In Brazil, a different research found that around 63.4% of the population had this bacterial infection, and much like the current study, the likelihood of being infected did not go up with age (Abasiyanik et al., 2004) and there was no significant relationship between age and *H. pylori* infection ($P > 0.05$).

Regarding the acquisition of infection, the results of this study show that *H. pylori* infections increase to a peak in adulthood at 29 years with an average age of 38 years. These present research observations were consistent with the findings of other reports, for example a study done by Malaty HM et al shows that by the age of 18-23 the prevalence of *H. pylori* is 24.5% (Malaty et al., 2002).

In earlier research, the authors hypothesized that smoking could contribute to the recent rise in *H. pylori* infection among individuals aged 15 and above (Wu, 2003). However, in the present study, there is no statistically significant relationship between *H. pylori* reinfection and smokers ($P < 0.05$).

The disease prevalence, role of socioeconomic status and occupation in epidemiology of infection are unclear. However, most of the people with *H. pylori* infection were workers with moderate socio-economic status (Murray et al., 1997), although there was no significant relationship between *H. pylori* infection with socio-economic status and occupation of people ($P > 0.05$).

The rate of resistance in people who use systemic water (filtered) is almost equal to that in people who use non-systemic water and the rate of recurrence is higher in our study in people who use systemic water than in those who use non-systemic water (well water) ($P < 0.05$).

In the present study, it was observed that most people with resistance have specific clinical symptoms including epigastric pain and dyspepsia and most people with recurrence after eradication have clinical symptoms such as epigastric pain, dyspepsia and GERD. There was a significant relationship between resistance and recurrence with clinical symptoms ($P < 0.05$), In previous study done in Sulaimani by Mohammed MO et al, the most common clinical symptoms of patients was epigastric pain which was about 65.3%, which the findings of our study were in line with this study (O. M. Mohammed et al., 2020).

The Endoscopic finding in our study shows that most of the cases with resistance and recurrence had no OGD (68.49% in resistance and 48.4% in recurrence cases), the most common OGD finding in our study was peptic ulcer and gastritis (antral and fundal), the same finding was found in a study done by Mohammed Omer et al in which most of the cases in that study had normal OGD finding followed by gastropathy, duodenal ulcer, gastric ulcer (M. O. Mohammed et al., 2017).

However, present study does have some limitations; it was conducted in a specific geographic area, which may limit the generalizability of the findings to other populations with different demographic characteristics or healthcare systems. Also, this research may be subject to selection bias, as patients were recruited from a single healthcare center, and those who did not return for follow-up were excluded from the analysis. Another significant limitation is the recall bias; meaning that patients may not recall all symptoms or might even overestimates reporting their symptoms which indeed have huge impact on the findings. Moreover, longer-term follow-up could provide more insights into the durability of treatment outcomes and the true recurrence rate. Finally, the absence of a control group makes it challenging to compare the effectiveness of different treatment regimens directly and assess the impact of potential confounding variables.

## 4. CONCLUSION

This study concluded that among patients who were again positive for H. pylori, 93% were on triple (clarithromycin based) therapy and 7% were on levofloxacin-based treatment, rate of resistance and recurrence was 23.54% and 8.7%, respectively.

Moreover, individuals who are O+ are more prone to H. pylori infection and its symptomatic complications in digestive system than other ABO blood groups. Furthermore, most people with resistance or recurrence after eradication have specific clinical symptoms, including epigastric pain, dyspepsia and GERD. Also, there is a significant relationship between resistance and recurrence with clinical symptoms.

As most of the resistance or recurrent cases were on triple (clarithromycin-based) therapy and some of them were on levofloxacin-based therapy, so we suggest a wide study depending more on alternatives as quadruple or rifabutin-based regimens and compare with the other treatment to find the most effective treatment in our locality.

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