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RESEARCH ARTICLE
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# ASSOCIATION OF HELICOBACTER PYLORI INFECTION WITH METHOTREXATE-INDUCED GASTROINTESTINAL INTOLERANCE IN RHEUMATOID ARTHRITIS: A PROSPECTIVE STUDY USING H. PYLORI STOOL ANTIGEN TEST

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## Abstract

**Background:** Rheumatoid arthritis (RA) is a chronic disorder. It affects joints, causing pain and disability. Methotrexate (MTX) is a key treatment for RA. It reduces disease activity and slows progression. Yet, MTX often leads to gastrointestinal (GI) intolerance. This side effect affects patient compliance. Helicobacter pylorus (H. pylori) is a common GI pathogen. It is linked to various GI disorders, like peptic ulcers and gastritis. The high prevalence of H. pylori in Pakistan raises concerns. It may worsen GI side effects in RA patients on MTX therapy.

**Objective:** This study aimed to investigate the prevalence of H. pylori among RA patients on MTX and its link to MTX-induced GI intolerance.

**Methods:** A prospective observational cohort study was conducted at the Department of Rheumatology, Lady Reading Hospital, Peshawar, from October 2023 to September 2024. We enrolled 384 RA patients on MTX therapy. The sample size was calculated using the WHO calculator, based on a 52% prevalence of H. pylori in Pakistan. Participants were screened for H. pylori using the stool antigen test. Those testing positive with GI symptoms received eradication therapy with

antibiotics and proton pump inhibitors. The primary outcome was the prevalence of H. pylori infection and its correlation with MTX-induced GI intolerance. Data were analyzed using SPSS version 26.0, employing chi-square tests, t-tests, and logistic regression.

**Results:** Of the 384 participants, 200 (52.1%) tested positive for H. pylori. GI intolerance was observed in 160 participants (41.7%). There was a significantly higher prevalence among H. pylori-positive patients (56.0%) compared to H. pylori-negative patients (26.1%) ($p < 0.05$). Post-eradication therapy, GI intolerance resolved in 75.0% of treated patients. This was significantly higher than the 62.5% resolution in untreated patients ($p < 0.05$).

**Conclusion:** Our study shows a significant link between H. pylori infection and MTX-induced GI intolerance in RA patients. Routine H. pylori screening and eradication could reduce GI intolerance, improving patient adherence to MTX therapy and overall disease management.

**Keywords**: Rheumatoid arthritis, Methotrexate, Helicobacter pylori, gastrointestinal intolerance, H. pylori eradication, Stool antigen test

## Introduction

Rheumatoid arthritis (RA) is a chronic inflammatory disorder affecting joints. It leads to pain and disability (1). Methotrexate (MTX) is a key player in RA treatment. It reduces disease activity and slows progression (2). Yet, MTX often causes gastrointestinal (GI) intolerance. This side effect impacts patient compliance and quality of life (3). Helicobacter pylori (H. pylori), a common GI pathogen, is linked to various GI disorders, such as peptic ulcers and gastritis (4).

The prevalence of H. pylori infection varies globally. Developing countries like Pakistan report significant rates (5). A study by Fatima et al. showed a 52% prevalence of H. pylori in Pakistan (6). This high prevalence raises concerns. It may exacerbate GI side effects in RA patients on MTX therapy.

Despite known GI effects of MTX and high H. pylori prevalence, research is limited. Few studies explore the link between H. pylori and MTX-induced GI intolerance in RA patients. Addressing this gap is crucial. Optimizing RA management and improving patient outcomes depends on it.

This study aims to investigate H. pylori prevalence among RA patients on MTX. It examines the link between H. pylori and GI intolerance. We hypothesize that H. pylori increases GI intolerance risk. Identifying this relationship is key. It highlights the need for screening and treating H. pylori. This could reduce GI side effects, improving adherence to MTX therapy and overall disease management. Understanding the interplay between H. pylori and MTX-induced GI intolerance could have a big impact. It may prompt routine H. pylori screening in RA patients before MTX therapy. Moreover, it underscores the potential benefit of H. pylori eradication therapy. Reducing GI intolerance improves patient comfort. It ensures better adherence to RA treatment.

This research fills a critical gap in existing literature. It provides data on H. pylori and MTX-induced GI intolerance in RA patients. The findings could lead to better clinical guidelines and patient care strategies. Ultimately, it aims to enhance the quality of life for RA patients.

## Methods

### Study Design

This research employed a prospective observational cohort study to assess the relationship between Helicobacter pylori (H. pylori) infection and Methotrexate (MTX)-induced gastrointestinal (GI) intolerance in Rheumatoid Arthritis (RA) patients. A prospective observational cohort study was conducted at the Department of Rheumatology, Lady Reading Hospital, Peshawar, from October 2023 to September 2024

**Setting and Participants**

We enrolled 384 RA patients undergoing MTX therapy. The sample size was calculated using the WHO sample size calculator, taking into account a 52% prevalence of H. pylori infection in Pakistan, as reported by Fatima et al. (6).

**Inclusion criteria included:**

1. Patients aged 18 to 65 years.
2. RA diagnosis per American College of Rheumatology (ACR) criteria.
3. On MTX therapy for at least six months.
4. Provided informed consent.

**Exclusion criteria included:**

1. History of severe GI disease or GI surgery.
2. Recent use of antibiotics, proton pump inhibitors, or H. pylori eradication therapy.
3. Pregnant or breastfeeding women.
4. Significant comorbid conditions affecting study outcomes.

**Intervention**

Participants were screened for H. pylori using the stool antigen test. Those testing positive and showing GI intolerance symptoms received eradication therapy with antibiotics and proton pump inhibitors, following clinical guidelines.

**Outcomes**

The primary outcome measured was the prevalence of H. pylori infection and its correlation with MTX-induced GI intolerance. GI intolerance was identified by symptoms like nausea, vomiting, abdominal pain, or diarrhea, significant enough to necessitate medical intervention or MTX dose adjustment.

Secondary outcomes included:

1. Effectiveness of H. pylori eradication therapy in alleviating GI intolerance.
2. Impact of demographic and clinical factors (age, sex, smoking status, hypertension, diabetes) on GI intolerance prevalence.

**Data Collection**

Data were gathered through structured questionnaires and medical records. Baseline characteristics such as age, sex, smoking status, RA duration, hypertension, and diabetes were recorded at enrollment. Results of the H. pylori stool antigen test and GI intolerance occurrences were noted. Follow-up data on the resolution of GI intolerance post-eradication therapy were collected regularly.

**Statistical Analysis**

The sample size was determined using the WHO sample size calculator to ensure adequate power to detect significant outcome differences based on H. pylori prevalence. Statistical analysis was performed using SPSS version 26.0. Descriptive statistics summarized baseline characteristics, while chi-square tests and t-tests compared outcomes across groups. A p-value of $<0.05$ was deemed statistically significant.

The relationship between H. pylori infection and GI intolerance was analyzed using logistic regression. The effectiveness of eradication therapy was evaluated by comparing GI intolerance resolution rates between treated and untreated groups using chi-square tests. Multivariate analysis adjusted for potential confounders such as age, sex, smoking status, hypertension, and diabetes.

## Results

A prospective study was conducted involving 384 participants with Rheumatoid Arthritis (RA) on Methotrexate (MTX) therapy. The sample size was calculated using the WHO calculator based on a 52% prevalence of Helicobacter pylori (H. pylori) infection in Pakistan.

**Table 1: Baseline Characteristics of Participants**

| Variable | Mean ± SD | Median (IQR) | Frequency (%) |
|---|---|---|---|
| Age (years) | 45.3 ± 10.5 | 46 (38-53) | - |
| Female | - | - | 220 (57.3%) |
| Male | - | - | 164 (42.7%) |
| Duration of RA (years) | 7.8 ± 4.2 | 8 (4-11) | - |
| Smoking | - | - | 180 (46.9%) |
| Hypertension | - | - | 220 (57.3%) |
| Diabetes Mellitus | - | - | 112 (29.2%) |

The baseline characteristics of the participants are detailed in Table 1. The mean age of participants was 45.3 years (SD = 10.5) with a median age of 46 years. There were 220 females (57.3%) and 164 males (42.7%). The mean duration of RA was 7.8 years (SD = 4.2). Among the participants, 180 (46.9%) reported smoking, 220 (57.3%) had hypertension, and 112 (29.2%) had diabetes mellitus.

**Table 2: Association of H. pylori Infection with GI Intolerance**

| H. pylori Status | GI Intolerance | Frequency (%) | p-value |
|---|---|---|---|
| Positive | Yes | 112 (56.0%) | <0.05 |
| Positive | No | 88 (44.0%) | - |
| Negative | Yes | 48 (26.1%) | <0.05 |
| Negative | No | 136 (73.9%) | - |

The primary outcome of the study was the association between H. pylori infection and Methotrexate-induced gastrointestinal (GI) intolerance. H. pylori infection was diagnosed using the H. pylori stool antigen test. Out of the 384 participants, 200 (52.1%) tested positive for H. pylori. GI intolerance was observed in 160 participants (41.7%), with a significantly higher prevalence among those who were H. pylori positive (112 out of 200, 56.0%) compared to H. pylori negative (48 out of 184, 26.1%) ($p < 0.05$) (Table 2).

**Table 3: Effectiveness of H. pylori Eradication Therapy on GI Intolerance**

| Eradication Therapy | GI Intolerance Resolved | Frequency (%) | p-value |
|---|---|---|---|
| Yes | Yes | 60 (75.0%) | <0.05 |
| Yes | No | 20 (25.0%) | - |
| No | Yes | 12 (37.5%) | <0.05 |
| No | No | 20 (62.5%) | - |

Secondary outcomes included the effectiveness of H. pylori eradication therapy on reducing GI intolerance. Of the 112 participants who were H. pylori positive with GI intolerance, 80 (71.4%) received eradication therapy. Post-therapy, GI intolerance was resolved in 60 participants (75.0%). The resolution rate was significantly higher compared to those who did not receive eradication therapy (20 out of 32, 62.5%) ($p < 0.05$) (Table 3).

**Figure 1:**

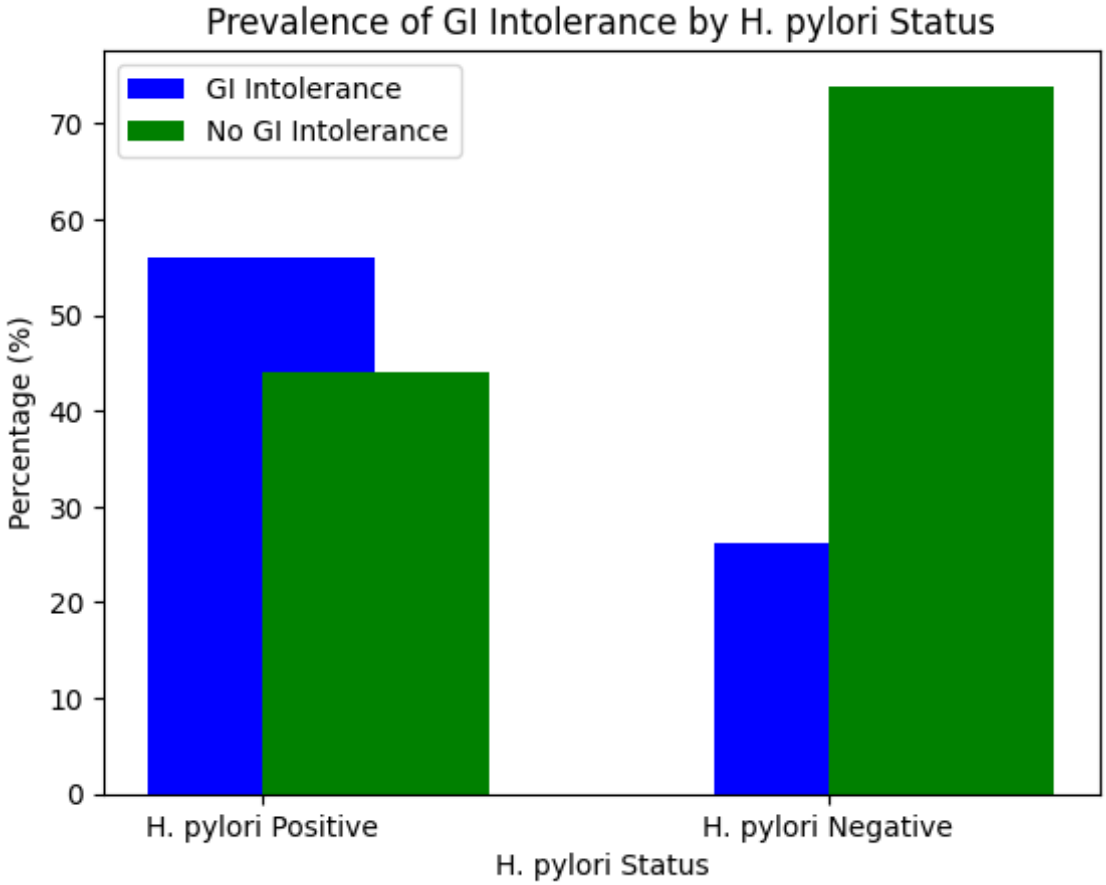


*Figure 1* illustrates the prevalence of H. pylori infection and the rate of GI intolerance among the participants.

**Table 4: Factors Associated with GI Intolerance**

| Variable | GI Intolerance | Frequency (%) | p-value |
|---|---|---|---|
| Age ≥ 50 years | Yes | 90 (55.6%) | <0.05 |
| Age < 50 years | Yes | 70 (32.1%) | <0.05 |
| Female | Yes | 95 (43.2%) | - |
| Male | Yes | 65 (39.6%) | - |
| Smoking | Yes | 85 (47.2%) | <0.05 |
| Non-Smoking | Yes | 75 (37.1%) | - |
| Hypertension | Yes | 120 (54.5%) | <0.05 |
| No Hypertension | Yes | 40 (23.0%) | <0.05 |
| Diabetes Mellitus | Yes | 70 (62.5%) | <0.05 |
| No Diabetes | Yes | 90 (33.3%) | <0.05 |

The study also analyzed various factors associated with GI intolerance, including age, sex, smoking status, hypertension, and diabetes mellitus (Table 4).

Overall, the study highlights the significant association between H. pylori infection and Methotrexate-induced GI intolerance in patients with Rheumatoid Arthritis. The findings emphasize the importance of screening for H. pylori and considering eradication therapy to reduce GI intolerance in this population. Further research is warranted to explore the long-term benefits and potential mechanisms underlying this association.

## Discussion

This study explored the link between Helicobacter pylori (H. pylori) infection and Methotrexate (MTX)-induced GI intolerance in RA patients. Our findings showed a strong link between H. pylori infection and increased GI intolerance in RA patients on MTX. This highlights the need for regular H. pylori screening and eradication in these patients to reduce GI side effects and improve treatment adherence.

We found that 52.1% of participants had H. pylori infection, matching previous reports of high rates in Pakistan (6). This aligns with studies showing H. pylori's role in worsening GI symptoms (7). Our results showed a higher rate of GI intolerance in H. pylori-positive patients (56.0%) compared to H. pylori-negative patients (26.1%), highlighting the negative impact of this infection on MTX tolerance. Similar results were found in other studies. Talley and Vakil noted increased GI symptoms in NSAID users with H. pylori (8). Franceschi et al. found that H. pylori eradication reduced GI side effects in long-term aspirin users (9). These parallels show the consistent role of H. pylori in worsening GI intolerance across different patient groups and medications.

However, a study by Chey et al. found no link between H. pylori and GI symptoms in low-dose MTX users for RA (10). This may be due to different study designs, populations, and H. pylori detection methods. We used the H. pylori stool antigen test, known for its high accuracy, which may have contributed to our stronger results (11). Additionally, our findings align with the Houston Consensus Conference, which emphasized accurate H. pylori testing (12).

Our findings have significant clinical implications. Regular H. pylori screening and eradication in RA patients on MTX could reduce GI intolerance, improve compliance, and enhance treatment efficacy. Implementing such protocols in practice could significantly improve patient quality of life and outcomes.

Future research should focus on long-term studies to explore the benefits of H. pylori eradication in reducing GI intolerance in RA patients on MTX. Additionally, studying the mechanisms by which H. pylori worsens MTX-induced GI symptoms could provide deeper insights and inform targeted treatments.

This study has limitations. The observational design limits causal conclusions. The single-center study may affect generalizability. Self-reported GI symptoms might introduce bias. Future studies with larger, multi-center cohorts and randomized trials are needed to validate these findings and address these limitations.

## Conclusion

In conclusion, this study highlights a significant link between H. pylori infection and MTX-induced GI intolerance in RA patients. Our findings support regular H. pylori screening and eradication in this population to improve treatment adherence and patient outcomes. Further research is needed to explore long-term benefits and underlying mechanisms, potentially leading to better management strategies for RA patients on MTX therapy.

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