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ORIGINAL ARTICLE

Biochemical, Histopathological, and Ophthalmologic Associations with Antibiotic Resistance in *Helicobacter pylori* Related Gastritis in Pediatric Surgical Patients

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ABSTRACT

Background: *Helicobacter pylori* infection is a major cause of chronic gastritis in children, and increasing antibiotic resistance poses a significant challenge to successful eradication. Persistent infection may lead not only to severe gastric mucosal inflammation but also to systemic biochemical disturbances and extra-gastric manifestations, including ocular surface involvement. Data integrating histopathological severity, biochemical alterations, ophthalmologic findings, and antibiotic resistance in pediatric surgical patients are limited.

Objective: To evaluate the association of biochemical parameters, histopathological severity, and ophthalmologic findings with antibiotic resistance in *H. pylori*–related gastritis among pediatric surgical patients.

Methods: This cross-sectional study was conducted at Nishtar Medical University, Multan, and Sahara Medical College, Narowal, from June 2022 to March 2023. A total of 100 pediatric patients (5–16 years) with histologically confirmed *H. pylori* gastritis were included. Gastric biopsies were assessed using the Updated Sydney System. Antibiotic resistance to clarithromycin and metronidazole was determined using biopsy-based methods. Biochemical markers including hemoglobin, serum ferritin, C-reactive protein, and albumin were measured. All patients underwent ophthalmologic evaluation focusing on ocular surface parameters.

Results: Antibiotic resistance was observed in 72% of patients, with metronidazole resistance being most common. Resistant infections were significantly associated with higher histopathological severity scores, increased neutrophilic activity, and greater *H. pylori* density ($p<0.001$). Biochemically, resistant cases showed lower hemoglobin and ferritin levels and higher CRP concentrations ($p<0.05$). Ophthalmologic abnormalities, including reduced tear break-up time and increased meibomian gland dysfunction, were significantly more frequent in resistant infections.

Conclusion: Antibiotic-resistant *H. pylori* gastritis in pediatric surgical patients is linked to more severe gastric inflammation, systemic inflammatory and iron-deficiency changes, and increased ocular surface dysfunction. These findings emphasize the need for susceptibility-guided therapy and a multidisciplinary approach to improve clinical outcomes in affected children.

Keywords: *Helicobacter pylori*, pediatric gastritis, antibiotic resistance, histopathology, biochemical markers, ophthalmologic findings.

INTRODUCTION

Helicobacter pylori (*H. pylori*) infection remains one of the most prevalent chronic bacterial infections worldwide and is a well-established cause of chronic active gastritis, peptic ulcer disease, and gastric mucosa-associated lymphoid tissue disorders[1]. In pediatric populations, *H. pylori*–related gastritis is particularly important because infection is often acquired early in life and may persist for years if untreated, leading to prolonged mucosal inflammation, nutritional consequences, and recurrent gastrointestinal symptoms. Children presenting to pediatric surgical units frequently undergo endoscopic evaluation for persistent epigastric pain, vomiting, anemia, or suspected peptic pathology, making this group clinically relevant for studying the disease burden and biological behavior of *H. pylori* infection[2,3].

Histopathological examination of gastric biopsies remains the cornerstone for diagnosing and grading *H. pylori*–associated gastritis[4]. The Updated Sydney System provides a standardized framework for evaluating key pathological features, including chronic inflammation, neutrophilic activity, bacterial density, atrophy, and intestinal metaplasia. The severity of these histological parameters reflects the intensity and chronicity of infection and has been linked to clinical symptoms, risk of complications, and response to eradication therapy. In children, understanding histopathological severity is particularly important because early inflammatory changes may be reversible if timely and effective treatment is instituted[5,6].

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A growing global concern in the management of *H. pylori* infection is the rapid rise in antibiotic resistance, especially to commonly used agents such as clarithromycin and metronidazole. Antibiotic resistance significantly reduces eradication success rates and contributes to persistent infection, repeated treatment failures, and prolonged mucosal inflammation[7]. Pediatric populations are especially vulnerable because inappropriate or repeated empirical antibiotic exposure may select resistant strains early in life. Consequently, resistant *H. pylori* infections may represent a more aggressive biological phenotype characterized by higher bacterial load, greater histopathological damage, and enhanced systemic inflammatory responses[8].

Beyond localized gastric pathology, *H. pylori* infection has been increasingly recognized as a systemic inflammatory condition with extra-gastric manifestations. Chronic infection can influence iron metabolism, inflammatory cytokine production, and oxidative stress pathways, resulting in biochemical abnormalities such as iron-deficiency anemia, hypoalbuminemia, and elevated inflammatory markers. In children, these biochemical disturbances may contribute to growth impairment, fatigue, and poor surgical outcomes, highlighting the importance of a comprehensive biological assessment rather than a purely gastrointestinal focus[9,10].

In recent years, attention has also been directed toward possible ophthalmologic associations of *H. pylori* infection. Immune-mediated mechanisms, molecular mimicry, and systemic inflammation have been proposed to link *H. pylori* with ocular surface disorders, including dry eye disease, tear film instability, and meibomian gland dysfunction[11]. While such associations have been explored mainly in adults, pediatric data remain scarce, and the

relationship between ocular findings, histopathological severity of gastritis, and antibiotic resistance has not been adequately investigated[12].

Given these gaps, an integrated evaluation encompassing histopathological severity, biochemical markers of systemic inflammation and nutritional status, and ophthalmologic findings may provide a more complete understanding of *H. pylori* infection in children[13]. This is particularly relevant in pediatric surgical patients, who often represent more complex or symptomatic cases and in whom treatment failure due to antibiotic resistance can have broader clinical implications. Therefore, this study was designed to explore the biochemical, histopathological, and ophthalmologic associations of antibiotic-resistant *H. pylori*–related gastritis in pediatric surgical patients, with the aim of identifying markers that may help predict disease severity and guide more targeted, susceptibility-based management strategies[14].

MATERIALS AND METHODS

This hospital-based cross-sectional observational study was conducted at Nishtar Medical University, Multan, Pakistan, and Sahara Medical College, Narowal, Pakistan, two tertiary-care teaching institutions that routinely manage pediatric surgical patients requiring gastrointestinal evaluation. The study was carried out over a period of ten months, from June 2022 to March 2023. A total sample size of 100 pediatric patients was included using non-probability consecutive sampling.

The study population comprised children aged 5 to 16 years who were referred to pediatric surgery units and subsequently underwent upper gastrointestinal endoscopy as part of diagnostic work-up for persistent upper gastrointestinal symptoms. These symptoms included chronic epigastric pain, dyspepsia, recurrent vomiting, unexplained anemia, or clinical suspicion of peptic pathology. Only patients with histologically confirmed *Helicobacter pylori*–associated gastritis were enrolled. Written informed consent was obtained from parents or legal guardians prior to inclusion in the study.

Patients were excluded if they had received prior *H. pylori* eradication therapy, had taken antibiotics, proton pump inhibitors, or bismuth compounds within four weeks before endoscopy, or had known chronic systemic inflammatory diseases, autoimmune disorders, or pre-existing ocular diseases under treatment. Patients with incomplete clinical, laboratory, or histopathological records were also excluded from analysis.

Upper gastrointestinal endoscopy was performed according to standard pediatric protocols. Multiple gastric biopsy specimens were obtained from both the antrum and corpus of the stomach in each patient. One set of biopsy samples was used for histopathological examination, while additional specimens were utilized for *H. pylori* detection and antibiotic resistance assessment.

All biopsy specimens were fixed in 10% buffered formalin and processed routinely. Histological evaluation was performed using hematoxylin and eosin staining, with modified Giemsa staining applied when necessary to improve visualization of *H. pylori*. Histopathological grading was carried out according to the Updated Sydney System, assessing the degree of chronic inflammation, neutrophilic activity, bacterial density, gastric atrophy, and intestinal metaplasia. Each parameter was graded on a scale of 0 to 3, and a composite histopathological severity score was calculated by combining chronic inflammation, activity, and bacterial density scores.

Assessment of antibiotic resistance was performed using gastric biopsy–based methods. Clarithromycin resistance was identified through molecular detection of macrolide resistance–associated mutations in gastric tissue samples where laboratory facilities were available. Metronidazole resistance was determined using validated institutional protocols based on phenotypic or molecular approaches. Based on these findings, *H. pylori* strains were categorized as antibiotic-sensitive, clarithromycin-resistant, metronidazole-resistant, or dual-resistant.

For biochemical analysis, venous blood samples were collected under aseptic conditions from all enrolled patients. Laboratory investigations included measurement of hemoglobin concentration, serum ferritin levels, C-reactive protein, and serum albumin. These parameters were selected to evaluate anemia, iron status, nutritional state, and systemic inflammatory response associated with *H. pylori* infection.

A structured ophthalmologic evaluation was conducted for all patients within one week of endoscopic examination by experienced ophthalmologists. The assessment included documentation of ocular surface–related symptoms, tear break-up time measurement, Schirmer I test for tear production, and clinical grading of meibomian gland dysfunction. All examinations were performed following standard pediatric ophthalmology guidelines.

Demographic characteristics, clinical data, endoscopic findings, histopathological scores, biochemical results, antibiotic resistance profiles, and ophthalmologic findings were recorded on a predesigned proforma. Data were entered and analyzed using SPSS software version 26. Quantitative variables were expressed as mean ± standard deviation or median with interquartile range, while qualitative variables were presented as frequencies and percentages. Comparisons between antibiotic-sensitive and antibiotic-resistant groups were performed using appropriate statistical tests, including independent t-test, Mann–Whitney U test, and Chi-square test. A p-value of less than 0.05 was considered statistically significant.

Ethical approval for the study was obtained from the Institutional Review Boards of both participating institutions. The study was conducted in accordance with the principles of the Declaration of Helsinki, and confidentiality of patient data was strictly maintained throughout the research process.

RESULTS

A total of 100 pediatric surgical patients with histologically confirmed *Helicobacter pylori*–associated gastritis were included in the final analysis. The mean age of the study population was 10.7 ± 3.2 years (range 5–16 years). Male patients constituted 56% (n=56), while 44% (n=44) were females. The most common presenting complaints were chronic epigastric pain and dyspepsia, followed by recurrent vomiting and unexplained anemia. Endoscopic findings predominantly showed antral erythema and nodularity, with a smaller proportion demonstrating pangastritis or erosive changes.

Baseline demographic and clinical characteristics: The demographic distribution and clinical presentation of the study population are summarized in Table 1. No statistically significant difference was observed between male and female patients regarding age or presenting symptoms.

Table 1. Baseline demographic and clinical characteristics of pediatric patients (n=100)

Variable	Value
Age (years), mean ± SD	10.7 ± 3.2
Male, n (%)	56 (56.0)
Female, n (%)	44 (44.0)
Epigastric pain/dyspepsia, n (%)	62 (62.0)
Recurrent vomiting, n (%)	21 (21.0)
Unexplained anemia, n (%)	17 (17.0)
Antral gastritis on endoscopy, n (%)	58 (58.0)
Pangastritis, n (%)	27 (27.0)
Erosions/ulceration, n (%)	15 (15.0)

Antibiotic resistance patterns: Analysis of antibiotic susceptibility revealed a high frequency of resistance among *H. pylori* isolates. Clarithromycin resistance was observed in 36% (n=36) of cases, while metronidazole resistance was detected in 60% (n=60). Dual resistance to both antibiotics was identified in 24% (n=24) of patients. Only 28% (n=28) of isolates were sensitive to both antibiotics. These resistance patterns are detailed in Table 2.

Histopathological findings and association with resistance: Histopathological evaluation using the Updated Sydney System showed variable severity of gastric mucosal involvement. Patients

with antibiotic-resistant *H. pylori* demonstrated significantly higher grades of chronic inflammation, neutrophilic activity, and bacterial density compared to antibiotic-sensitive cases. The composite histopathological severity score was markedly elevated in resistant infections ($p < 0.001$). Atrophy and intestinal metaplasia were uncommon and showed no significant association with resistance status. These findings are presented in Table 3.

Table 2. Antibiotic resistance patterns in *H. pylori*–positive pediatric patients (n=100)

Resistance pattern	n (%)
Sensitive to both antibiotics	28 (28.0)
Clarithromycin resistant only	12 (12.0)
Metronidazole resistant only	36 (36.0)
Dual resistant (CLA + MTZ)	24 (24.0)

Table 3. Histopathological severity according to antibiotic susceptibility

Parameter (0–3)	Sensitive (n=28) Mean ± SD	Resistant (n=72) Mean ± SD	p-value
Chronic inflammation	1.6 ± 0.6	2.3 ± 0.7	<0.001
Neutrophilic activity	1.2 ± 0.7	2.1 ± 0.6	<0.001
H. pylori density	1.4 ± 0.6	2.2 ± 0.5	<0.001
Atrophy	0.2 ± 0.4	0.3 ± 0.5	0.38
Intestinal metaplasia	0.1 ± 0.2	0.1 ± 0.3	0.91
Severity score (0–9)	4.2 ± 1.5	6.6 ± 1.4	<0.001

Biochemical parameters and resistance status: Biochemical analysis revealed that children with antibiotic-resistant *H. pylori* infection had significantly lower hemoglobin and serum ferritin levels, indicating a higher prevalence of iron deficiency. In addition, serum CRP levels were significantly elevated in resistant cases, reflecting a heightened systemic inflammatory response. Serum albumin levels were also modestly but significantly lower in resistant infections. These biochemical differences are summarized in Table 4.

Table 4. Comparison of biochemical parameters between antibiotic-sensitive and resistant groups

Parameter	Sensitive (n=28)	Resistant (n=72)	p-value
Hemoglobin (g/dL)	12.2 ± 1.1	11.1 ± 1.3	0.001
Serum ferritin (ng/mL), median (IQR)	30 (20–44)	16 (9–27)	0.002
CRP (mg/L), median (IQR)	2.4 (1.1–4.6)	6.2 (3.4–10.1)	<0.001
Serum albumin (g/dL)	4.2 ± 0.4	4.0 ± 0.5	0.02

Ophthalmologic findings and correlation with resistance: Ophthalmologic assessment demonstrated a significantly higher frequency of ocular surface abnormalities in children with antibiotic-resistant *H. pylori* infection. Reduced tear break-up time (<10 seconds) and moderate-to-severe meibomian gland dysfunction were more common in resistant cases. Symptom scores were also significantly higher in this group, suggesting greater ocular surface discomfort. These findings are detailed in Table 5.

Table 5. Ophthalmologic findings in relation to antibiotic resistance

Ophthalmologic parameter	Sensitive (n=28)	Resistant (n=72)	p-value
Ocular symptom score (0–12)	2.1 ± 1.4	5.3 ± 2.2	<0.001
TBUT (seconds)	11.6 ± 3.1	8.4 ± 2.8	<0.001
TBUT <10 seconds, n (%)	8 (28.6)	47 (65.3)	0.001
Schirmer I (mm/5 min)	14.1 ± 5.0	11.0 ± 4.7	0.01
Moderate–severe MGD, n (%)	5 (17.9)	34 (47.2)	0.004

Overall, the results demonstrate that antibiotic-resistant *H. pylori* infection in pediatric surgical patients is consistently associated with greater histopathological severity, more pronounced systemic inflammatory and iron-deficiency biochemical abnormalities, and a higher burden of ocular surface dysfunction, as shown across Tables 2–5.

DISCUSSION

This study provides an integrated evaluation of biochemical, histopathological, and ophthalmologic associations of antibiotic-resistant *Helicobacter pylori* gastritis in pediatric surgical patients, an area that has received limited attention in pediatric literature, particularly from South Asian clinical settings[15]. By combining gastric histology with systemic biochemical markers and ocular surface assessment, the findings offer a multidimensional understanding of disease severity in children with resistant *H. pylori* infection[16].

One of the most important observations of this study is the high prevalence of antibiotic resistance, particularly to metronidazole and clarithromycin. The resistance rates observed in our cohort are consistent with regional and international pediatric data reporting rising resistance to first-line eradication therapies[17]. Such resistance is clinically significant because it compromises eradication success, prolongs infection, and increases the likelihood of recurrent symptoms and repeated antibiotic exposure. In pediatric surgical patients, who often represent a more symptomatic subset, these resistance patterns highlight the limitations of empirical therapy and strongly support susceptibility-guided treatment strategies[18].

Histopathological analysis revealed that antibiotic-resistant *H. pylori* infections were associated with significantly higher grades of chronic inflammation, neutrophilic activity, and bacterial density. These findings suggest that resistant strains may persist longer within the gastric mucosa, leading to sustained immune activation and greater tissue injury[19]. The significantly higher composite histopathological severity scores in resistant cases reinforce the concept that antibiotic resistance is not merely a microbiological phenomenon but is closely linked to disease aggressiveness at the tissue level. The relative rarity of gastric atrophy and intestinal metaplasia in our pediatric cohort aligns with existing knowledge that such pre-neoplastic changes are uncommon in children and typically evolve after long-standing infection[20].

From a biochemical perspective, children with resistant *H. pylori* infection demonstrated lower hemoglobin and serum ferritin levels, indicating a stronger association with iron-deficiency anemia. This supports the hypothesis that persistent gastric inflammation impairs iron absorption through altered gastric acidity, mucosal damage, and inflammatory cytokine–mediated iron sequestration[7]. Additionally, significantly elevated CRP levels in resistant cases reflect a heightened systemic inflammatory response. These biochemical disturbances are particularly relevant in pediatric populations, where iron deficiency and chronic inflammation can negatively affect growth, cognitive development, and surgical recovery[9,11].

A novel and clinically intriguing finding of this study is the significant association between antibiotic-resistant *H. pylori* infection and ocular surface abnormalities. Children with resistant infection showed shorter tear break-up time, higher ocular symptom scores, and a greater prevalence of moderate-to-severe meibomian gland dysfunction[12]. These findings support emerging evidence that *H. pylori* infection may exert extra-gastric effects through immune-mediated mechanisms, molecular mimicry, and systemic inflammation. Persistent infection, especially in the presence of antibiotic resistance, may amplify these pathways, resulting in tear film instability and ocular surface inflammation even in pediatric patients. This expands the current understanding of *H. pylori* as a multisystem inflammatory condition rather than a purely gastrointestinal pathogen[16,18].

The integration of ophthalmologic findings with histopathological and biochemical data strengthens the biological plausibility of a “high-inflammatory phenotype” associated with antibiotic-resistant *H. Pylori* [5]. Resistant cases in our study consistently demonstrated greater gastric inflammation, higher systemic inflammatory markers, and more frequent ocular surface dysfunction. This clustering of findings suggests that ocular symptoms may serve as a subtle clinical marker of persistent or severe infection in children, particularly in those with poor response to standard eradication therapy[12].

Clinically, these results have important implications. In pediatric surgical practice, children presenting with refractory dyspeptic symptoms, iron-deficiency anemia, or unexplained ocular discomfort may warrant a lower threshold for invasive diagnostic evaluation and resistance testing. Incorporating susceptibility-guided therapy may improve eradication rates, reduce repeated antibiotic exposure, and potentially mitigate both gastrointestinal and extra-gastric inflammatory consequences[14]. Furthermore, collaboration between pediatric surgeons, gastroenterologists, and ophthalmologists may enhance holistic patient care in complex cases[15].

Despite its strengths, this study has certain limitations. The cross-sectional design limits causal inference between antibiotic resistance and systemic or ocular manifestations[4]. Molecular resistance testing was not available for all antibiotics in every case, and the study did not assess post-eradication resolution of biochemical or ophthalmologic abnormalities. Additionally, the findings are derived from two centers and may not be fully generalizable to all pediatric populations[6].

In conclusion, the present study demonstrates that antibiotic-resistant *H. pylori*–associated gastritis in pediatric surgical patients is linked to increased histopathological severity, pronounced systemic inflammation, iron deficiency, and significant ocular surface involvement. These findings underscore the importance of resistance-aware diagnostic strategies and support a multidisciplinary approach to the management of pediatric *H. pylori* infection, particularly in children with persistent or severe disease[11,19].

CONCLUSION

Antibiotic-resistant *Helicobacter pylori* infection in pediatric surgical patients is associated with more severe gastric histopathological inflammation, heightened systemic inflammatory response, iron-deficiency–related biochemical abnormalities, and increased ocular surface dysfunction. These findings highlight the clinical importance of susceptibility-guided therapy and support a multidisciplinary approach for early identification and effective management of resistant *H. pylori* gastritis in children.

Conflict of Interest: The authors declare that there is no conflict of interest related to this study.

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Data Availability: The datasets generated and analyzed during the current study are available from the corresponding author upon reasonable request.

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