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The Relationship between the Sydney Classification and the First-Line Treatment Efficacy in *Helicobacter*-Associated Gastritis

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Highlights of the Study

- Severity of chronic inflammation, where bacterial density is the highest, was found as the most effective criteria for eradication.
- The presence of intestinal metaplasia (IM) and atrophy requires only an absolute treatment.
- The presence of IM is not a decisive criterion for the success of the standard triple therapy.

Keywords
Eradication · Gastritis · *Helicobacter pylori* · Intestinal metaplasia · Sydney classification

Abstract

Objective: *Helicobacter pylori* is responsible for a wide spectrum of diseases. Due to ease of use and access, the standard triple therapy is being used as first-line eradication in many areas. Intestinal metaplasia (IM) is a precancerous lesion that requires eradication therapy. Our aim is to investigate the effect of IM on the standard triple therapy success in *H. pylori*-positive patients. ***Subjects and Methods:*** The patients who were referred to Düzce University Hospital and Avrasya Hospital Gastroenterohepatology clinic between January 2014 and December 2016 and diagnosed with *H. pylori*-positive gastritis and underwent first-line eradication were evaluated retrospectively. Biopsy specimens were evaluated according to the updated Sydney system. All patients diagnosed with *H. pylori* started treatment with pantoprazole 40 mg b.i.d., amoxicillin 1 g b.i.d. and clarithromycin 500 mg b.i.d. for 14 days. ***Results:*** The mean age of 181 patients included in the study was 55.5 ± 7.8. The success rate of *H. pylori* eradication was found to be low in severe chronic inflammation ($p = 0.001$). The success rate was found to be high among patients with no neutrophil activity ($p = 0.009$). As the intensity of IM increased, density of *H. pylori* was found to be decreased ($p = 0.019$). There was no correlation between glandular atrophy, IM, and *H. pylori* eradication success rate ($p = 0.390$ and $p = 0.812$). ***Conclusion:*** The severity of chronic inflammation is the most effective Sydney criteria for success of eradication, while the presence on IM does not have any effect.

Introduction

Helicobacter pylori infection, which affects 50% of the world's population, causes chronic and nonatrophic gastritis which then leads to atrophic gastritis and intestinal metaplasia (IM) [1]. Since the presence of IM and atrophy

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Table 1. The parameters and scale values used in histopathological staging of biopsy preparations according to Sydney classification

Feature	Definition	Degree			
		0 (none)	1 (mild)	2 (moderate)	3 (severe)
Chronic inflammation	Density of the lymphocytes and plasma cells in the lamina propria	2–5 lymphocyte, plasma and macrophage	5–10 cells ×40	11–20 cells ×40	>21 cells ×40
Neutrophil infiltration	Neutrophilic infiltrates of the lamina propria or surface epithelium	None	<1/3 of surface infiltrated	1/3–2/3 of surface infiltrated	>2/3 of surface infiltrated
Glandular atrophy	Loss of specialized glands	None	Mild	Moderate	Severe
Intestinal metaplasia	Intestinal metaplasia of the epithelium	None	<1/3 of mucosa involved	1/3–2/3 of mucosa involved	>2/3 of mucosa involved
H. pylori	Density of *H. pylori* overlying epithelium	None	1–3 organism	A layer of bacterium	Cluster of bacterium

represents long-term infection and increases the risk of progression to gastric cancer, it is important to determine if the existence of IM makes infection eradication more difficult. Even though there are multiple treatment regimens, the standard triple therapy is still the first choice in many countries [2]. Increasing antibiotic resistance may cause the standard triple therapy to look inadequate, especially in patients with IM. Thus, we aimed to find the relationship between the density of IM and the standard triple therapy (pantoprazole 40 mg b.i.d., amoxicillin 1 g b.i.d. and clarithromycin 500 mg b.i.d.) success in *H. pylori* gastritis cases evaluated based on the Sydney classification. We also aimed to evaluate the effect of chronic inflammation, glandular atrophy, and neutrophil activity on the success of *H. pylori* eradication therapy. Our purpose is to guide clinicians in terms of treatment choice. We plan to contribute to the literature by evaluating the criteria that clinicians should consider when choosing *H. pylori* therapy.

Materials and Methods

The patients who were referred to Düzce University Hospital and Avrasya Hospital Gastroenterohepatology clinics with dyspepsia between January 2014 and December 2016 were enrolled in this retrospective study. ICD codes recorded in the hospital records were used for scanning. The medical records of the patients with diagnosis of dyspepsia and gastritis were investigated, and the ones diagnosed with *H. pylori* gastritis according to the Sydney classification system were selected. Exclusion criteria were: age <18 years old, history of gastric and intestinal surgery, current pregnancy or breast-feeding, history of drug allergies, history of PPI, H_2 receptor antagonist, bismuth and antibiotic use in the last 4 weeks, and severe psychiatric and neurological disorders that can cause noncompliance.

The following information was obtained from patient files and pathology reports: age and sex of the patient, the site of endoscopic gastric biopsy and histopathological evaluations. Esophagogastroduodenoscopy was performed after 8 h of fasting. Two biopsy specimens were taken from the antrum and corpus of the stomach for pathological evaluation. Sections of paraffin blocks of biopsy materials were stained with Giemsa stain, and routine histopathological evaluations were made by light microscopy. The parameters of the Sydney classification system used for pathological diagnosis are shown in Table 1.

All patients with *H. pylori*-positive gastritis were treated with pantoprazole 40 mg b.i.d., amoxicillin 1 g b.i.d., and clarithromycin 500 mg b.i.d. for 14 days. Fifteen days after the treatment ended, 90 patients underwent esophagogastroduodenoscopy, and control biopsies were taken from the antrum and the corpus. The cases whose histopathological evaluation concluded as *H. pylori* negative were accepted as successful eradication. The other 91 patients' eradication success was evaluated with immunochromatographic test. Monoclonal antibodies were used to detect *H. pylori* antigen in stool. Absence of fecal antigen was accepted as successful eradication.

Statistical Analyses

The Statistical Package for Social Sciences (SPSS) program was used for statistical analysis. After the data of the patients were entered into the SPSS (version 18) program, continuous variables were expressed as mean ± SD and categorical variables as percentage. The relationship between categorical features was evaluated with Pearson's χ^2 analysis. A 95% CI was used during all analyses performed in the SPSS program. $p < 0.05$ was considered as statistically significant in all tests.

Results

One hundred and eighty-one patients were included in the study. The mean age of the patients was 55.5 ± 7.8, and 52% were female. The relationship between chronic inflammation, neutrophil activity, glandular atrophy, sever-

Table 2. Comparison of the severity of chronic inflammation with *H. pylori* density and success of *H. pylori* eradication therapy

	Chronic inflammation[a] (n = 181)			p value
	mild (n = 16)	moderate (n = 113)	severe (n = 52)	
H. pylori[b], n (%)				
Mild	10 (62.5)	55 (48.7)	11 (21.2)	0.002
Moderate	2 (12.5)	40 (35.4)	24 (46.2)	
Severe	4 (25.0)	18 (15.9)	17 (32.7)	
Treatment[c], n (%)				
Unsuccessful	2 (12.5)	17 (15.0)	22 (42.3)	0.001
Successful	14 (87.5)	96 (85.0)	30 (57.7)	

Data are presented as n (%). [a] Shows the intensity of lymphocytes and plasma cells in lamina propria according to the Sydney system. [b] Refers to the density of *H. pylori* in gastric mucosa. [c] Shows the success of *H. pylori* eradication therapy.

Table 3. Comparison of *H. pylori* density and *H. pylori* eradication therapy success with the degree of neutrophil infiltration activity severity

	Activity[a] (n = 181)				p value
	none (n = 62)	mild (n = 62)	moderate (n = 50)	severe (n = 14)	
H. pylori[b], n (%)					
Mild	40 (72.7)	30 (48.4)	4 (8.0)	2 (14.3)	0.001
Moderate	10 (18.2)	22 (35.5)	27 (54.0)	7 (50.0)	
Severe	5 (9.1)	10 (16.1)	19 (38.0)	5 (35.7)	
Treatment[c], n (%)					
Unsuccessful	5 (9.1)	14 (22.6)	16 (32.0)	6 (42.9)	0.009
Successful	50 (90.9)	48 (77.4)	34 (68.0)	8 (57.1)	

Data are presented as n (%). [a] Indicates the degree of neutrophil infiltration to lamina propria or surface epithelium according to the Sydney system. [b] Refers to the density of *H. pylori* in gastric mucosa. [c] Shows the success of *H. pylori* eradication therapy.

Table 4. Comparison of *H. pylori* density and *H. pylori* eradication treatment success with the severity of corpus and antrum atrophy

	Atrophy[a] (n = 181)				p value
	none (n = 83)	mild (n = 14)	moderate (n = 57)	severe (n = 27)	
H. pylori[b], n (%)					
Mild	29 (34.9)	2 (14.3)	30 (52.6)	15 (55.6)	0.041
Moderate	33 (39.8)	8 (57.1)	15 (26.3)	10 (37.0)	
Severe	21 (25.3)	4 (28.6)	12 (21.1)	2 (7.4)	
Treatment[c], n (%)					
Unsuccessful	21 (25.3)	5 (35.7)	11 (19.3)	4 (14.8)	0.390
Successful	62 (74.7)	9 (64.3)	46 (80.7)	23 (85.2)	

Data are presented as n (%). [a] Indicates the degree of loss in the antrum and corpus glands according to the Sydney system. [b] Refers to the density of *H. pylori* in gastric mucosa. [c] Shows the success of *H. pylori* eradication therapy.

ity of IM, *H. pylori* density, and the success of *H. pylori* eradication therapy were evaluated. The relationship between chronic inflammation and *H. pylori* is shown in Table 2. As the severity of *H. pylori* increased, an increase in the severity of chronic inflammation (p = 0.002) was observed. In patients with severe chronic inflammation, the success rate of *H. pylori* eradication therapy was found to be low (p = 0.001; p values are used as a trend in all tables).

As the severity of *H. pylori* increased, the severity of neutrophil infiltration activity also increased (p = 0.001; Table 3). Treatment success rate was found to be significantly higher in patients without neutrophil infiltration activity (p = 0.009). It was similar among the patients with mild, moderate, and severe neutrophil infiltration activity (p = 0.420). In our study, a decrease in *H. pylori* density was observed as the severity of atrophy in the antrum and corpus increased (p = 0.041). However, there was no relationship between atrophy severity and *H. pylori* eradication success rate (p = 0.390; Table 4).

In terms of IM severity, there was no correlation between the severity of IM and *H. pylori* eradication success (p = 0.812). Nevertheless, as the severity of IM increased, a decrease in the density of *H. pylori* was revealed (p = 0.019; Table 5).

Discussion

H. pylori requires eradication therapy in patients with peptic ulcer, dyspepsia, gastric MALT lymphoma, atrophic gastritis, iron deficiency anemia, chronic idiopathic thrombocytopenic purpura, vitamin B_{12} deficiency, his-

Table 5. Comparison of the *H. pylori* density and *H. pylori* eradication treatment success with the severity of intestinal metaplasia

	Intestinal metaplasia[a] (n = 181)				p value
	none (n = 78)	mild (n = 15)	moderate (n = 59)	severe (n = 29)	
H. pylori[b], n (%)					
Mild	22 (28.2)	7 (46.7)	32 (54.2)	15 (51.7)	0.019
Moderate	32 (41.0)	7 (46.7)	16 (27.1)	11 (37.9)	
Severe	24 (30.8)	1 (6.7)	11 (18.6)	3 (10.3)	
Treatment[c], n (%)					
Unsuccessful	20 (25.6)	3 (20.0)	13 (22.0)	5 (17.2)	0.812
Successful	58 (74.4)	12 (80.0)	46 (78.0)	24 (82.8)	

Data are presented as n (%). [a] Expresses the presence of IM in mucosa epithelium according to the Sydney system. [b] Refers to the density of *H. pylori* in gastric mucosa. [c] Shows the success of *H. pylori* eradication therapy.

tory of early gastric cancer resection, and first-degree relatives who have gastric cancer [3]. The Sydney system used in the classification of chronic gastritis provides information about *H. pylori* density, activity, chronic inflammation, atrophy, and IM. As the risk of developing gastric cancer in individuals infected with *H. pylori* is proportional to the severity of inflammation and atrophy, the Sydney classification is of clinical importance as well as pathological [4]. Herein, we aimed to see whether the severity of Sydney criteria, especially IM, was effective in the success of first-line *H. pylori* eradication therapy.

The density of *H. pylori* was found to be significantly higher in patients with severe chronic inflammation (p = 0.002). Eradication therapy success was decreased in the presence of high bacterial density (p = 0.001). Similarly, there was a significant decrease in the severity of *H. pylori* in patients without neutrophil infiltration, while the treatment success was significantly higher (p = 0.001). When a person is infected with *H. pylori*, cytotoxic agents secreted from the gastric mucosa start the inflammatory response [5]. Chronic inflammation, as *H. pylori* severity increases, leads to an increase in neutrophil activity. In conclusion, there is a positive correlation between *H. pylori* density, chronic inflammation, and neutrophil activity. The success of *H. pylori* eradication therapy is closely related to bacterial density. In patients with increased bacterial density, the success of the standard triple eradication therapy is expected to be low. In a study done by Jakic-Razumovic et al. [6] comparing the Sydney criteria before and after eradication therapy, the success of treatment was found to be lower in patients with severe chronic inflammation compared to cases with mild inflammation. However, in the same study, there was no significant change in neutrophil activity before and after treatment, and there was no relationship between bacterial load and neutrophil activity. In our study, increased bacterial load was found in cases with high neutrophil activity, which resulted in decrease in eradication success. The study of Suzuki et al. [7] also supports our study. The eradication success rate was 56.8% in the patient group consisting of 37 patients, whereas due to high neutrophil activity and bacterial density, *H. pylori* was not eradicated in 16 subjects.

When we evaluated the relationship between glandular atrophy, IM, and *H. pylori* eradication therapy success, atrophy and IM did not show a significant effect. *H. pylori* density was found to be decreased significantly in cases where atrophy and IM severity was increased (p = 0.041 and p = 0.019). Neutrophils and macrophages that cause chronic inflammation form free oxygen radicals and damage the surrounding tissue DNA [8]. When they cause DNA mutation in gastric isthmus stem cells, they either cause atrophy or IM [9]. Glandular atrophy is the loss of antrum and corpus glands. Long-term infection causes recurrent mucosal damage, which leads to the replacement of the glandular layer with fibrous tissue. The increase in its severity and prevalence of atrophy increases the risk of gastric cancer [10]. Two mechanisms have been proposed as the cause of decreased severity of *H. pylori* in areas with atrophy. First, *H. pylori* may be colonized only in the gastric epithelium [11]. Therefore, it cannot live on an atrophic or a metaplasic ground. Second, the bacteria can survive in a narrow pH range but cannot in the hypochlorhydric gastric environment [5]. In many studies, the effects of *H. pylori* eradication on atrophy and IM were investigated since they are precancerous. However, there are a limited number of studies investigating the impact of atrophy and IM on eradica-

tion therapy [11, 12]. Kalkan et al. [11] found, in their study of 200 patients, that treatment success was lower in patients with atrophy and IM, but due to the lack of studies on this subject, they could not explain the cause. Kamada et al. [12] could not find any significant effect of the severity of glandular atrophy in the antrum on the success of *H. pylori* eradication therapy. Our study also supports Kamada et al. [12]. Although the severity of atrophy increased, there was no significant change in treatment success. The treatment success rate was 82% even in patients with moderate to severe atrophy. This result suggests that *H. pylori* density is more effective than the presence of atrophy in treatment success.

Our study showed that the increase in IM severity, similar to glandular atrophy, did not have a significant effect on the success of *H. pylori* eradication therapy. Chen et al. [13] investigated the effect of IM on the treatment of gastric ulcer caused by *H. pylori* and found that the rate of healing was higher in IM-positive cases. They found that the presence of IM did not significantly affect the treatment success (81.6% in the IM group, 85.3% in the group without IM) and that it was not a predictor of the treatment failure. In contrast, Vázquez Romero et al. [14] compared the relationship between IM presence and the first-line therapy in their study and found the success rates to be 61.2 and 72.7% in IM-positive and -negative individuals, respectively. According to their statistically significant ($p = 0.036$) results, they suggested that the presence of IM might be a factor which decreases the success rate of the standard triple therapy. However, they emphasized that this may be due to the restrictive factors of the study, such as low number of patients and irregular follow-up. In our study, we demonstrated that the presence of IM alone had no effect on the treatment success, but it could have an effect on the density of *H. pylori*.

Due to the change in the environmental structure caused by IgA secretion and to the decreased acidity of metaplastic areas, bacteria cannot survive in these areas [15]. In general, although IM is considered as a sequela of inflammation and as part of the progressive process, some researchers believe that it may develop due to exogenous or dietary factors independent of *H. pylori* [16]. In their study, Konakci et al. [16] found that the presence of *H. pylori* was low (1.8%) in patients with IM, and they attributed this to the fact that the detection of IM areas was limited only to the biopsy area studied by the pathologist, that is, pathologist's subjective evaluation. In another study done on 358 patients evaluating gastric mucosal changes in *H. pylori* gastritis, there was no significant relationship found between IM and bacterial density [17]. Olmez et al. [18], in their study on subtypes of gastric IM, showed that there was no significant relationship between IM and *H. pylori*, although they found 38.6% of *H. pylori* positivity in the complete- and the incomplete-type IM. In contrast to these studies, we found a significant relationship between the intensity of IM and *H. pylori*. The presence of low bacterial density in metaplastic areas enables a stable success rate even under severe metaplasia. Moreover, metaplasia subtypes are also valuable since they affect the bacterial density by providing a suitable habitat for the bacteria [19].

Another mechanism underlying the treatment success in severe IM is probably related to IM subtypes. It was reported in the Maastricht Consensus Report that the evaluation of 2 biopsies from the antrum and the corpus using the Sydney classification system showed maximum benefit in determining gastric inflammatory changes [20]. However, the Sydney classification system evaluates only the presence and intensity of IM. In a study examining gastric IM and its subtypes, IM subtyping was not found to be significant in risk assessment and it did not provide information on the prognosis [21]. In addition, in another study investigating the benefit of subtyping, the risk of progression to gastric cancer was found to be 4–11 times higher in cases with incomplete (type I) IM [19]. The necessity of initiating eradication therapy regardless of the subtypes and the need for advanced techniques in their placement results in the absence of subtyping in routine examinations. Since this is a retrospective study, the cases were examined according to the Sydney criteria, so subtyping was not done. As the studies in the literature indicate, *H. pylori* is not found in type I IM [22]. Steadman et al. [23] reported that the gastric antral biopsy results of 3 patients showed *H. pylori* in metaplastic areas. They described the presence as the transport of bacteria to metaplastic areas through the mucus and did not accept the possibility of the bacteria attaching to metaplastic areas [23]. In Genta et al. [24] study on 378 patients, only in 32 patients was *H. pylori* found closely associated with IM. They attributed this relationship to different types of IM. Based on these studies, the fact that bacteria were not found in metaplastic areas suggests that the patients included in our study were type I IM, since studies have shown that *H. pylori* can only hold on type II IM [25].

One of the most important factors determining the success of the treatment is the density of *H. pylori* in the gastric epithelium. As in our study, many studies have shown that eradication treatment success is high in cases where bacterial density is mild [26, 27]. Onal et al. [27]

also investigated the effect of *H. pylori* density on eradication therapy and used the standard triple therapy for this purpose. In their study, they found that the treatment success rate was lower in patients who had a high density of bacteria. Although the eradication success with the standard triple therapy seems to have lost its effectiveness in the 2000s due to the increased clarithromycin resistance, it is still preferred in the first-line treatment because of its ease of use and reliability [20]. In our study, due to patients' compliance to treatment, we used the standard triple therapy and achieved a high treatment success rate (77%). We have shown that the most valuable Sydney criterion for predicting failure in the treatment is an increase in the severity of chronic inflammation and neutrophil activity associated with an increase in the density of *H. pylori*.

One of the limitations of our study is its retrospective design, which is the reason why eradication tests are performed 2 weeks after the completion of *H. pylori* therapy. It could also have been better to perform the same tests in 181 patients to evaluate eradication success. Another limitation is the absence of subtyping. It could have given better information about the relationship between IM, pathogenesis of *H. pylori*, and eradication.

Conclusion

Since the presence of IM and atrophy is an important risk factor for progression to gastric cancer, it is important to determine if infection eradication is more difficult with IM presence. As the presence of IM suggests long-term infection, the standard triple therapy used in primary care may be inadequate in eradication. In this study, we aimed to determine the effect of these parameters on the success of the first-line treatment. We observed that the severity of chronic inflammation, where the bacterial density is the highest, was the most effective Sydney criterion for eradication success.

Statement of Ethics

This retrospective study was approved by the Ethical Review Board of Düzce University (No.: 2016/105).

Disclosure Statement

There is no conflict of interest.

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