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ORIGINAL ARTICLE

Frequency Study of *Helicobacter pylori* in Algeria

Hassina Guetarni[1,2]*, Zeyneb Driouch[1], Sarah Rabahi[1]

[1]Faculty of Natural Sciences, University Bounaama Djilali of Khemis Miliana, Ain Defla, Algeria.
[2]Laboratory of Natural Substances Valorization, University Bounaama Djilali of Khemis Miliana, Ain Defla, Algeria.

ABSTRACT

Background: Third world countries are exposed to several diseases. Countries including Algeria are at a rise on facing peptic ulcer disease as common, and several factors favor the appearance of this pathology, especially the bacterium *Helicobacter pylori* in the first place.

Objectives: The aim of this work was to detect *Helicobacter pylori* in many patients affected by this bacteria by analyzing different techniques and methods used by Algerian hospitals and laboratories.

Methodology: The screening of the frequency of gastric ulcer and its prevalence in Algeria was determined by a retrospective study spread over a period of four years, in which many factors were studied. The use of endoscopy, urease test as well as anatomy, cytology, and pathological conditions were added to explore this disease.

Results: From eight patients, only seven are affected by *Helicobacter pylori* which showed the presence of a very active urease in the endoscopy room. Different pathologies caused by *Helicobacter pylori* were found after Hematoxylin Eosin and Slow Giemsa staining of histological sections including 77.54% chronic gastritis, 13.36% mild gastritis, and 8.55% upper ulcers.

Conclusion: The presence of *Helicobacter pylori* was determined by using the rapid urease test either by anatomy, pathology, and cytology procedures where several gastritis were found. The ANOVA test revealed that the risk factors for pathologies be presented by 8.55% gastric ulcer, 13.36% mild gastritis, and 77.54% chronic gastritis.

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Algeria, Epidemiology, Frequency, Gastric ulcer, Helicobacter pylori, Infection.	*kmhg2009@yahoo.fr*	*Received: August 15, 2021* *Accepted: June 14, 2022*

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INTRODUCTION

Gastric ulcer is a universal condition, its prevalence is estimated at 10% of the adult population worldwide[1]. It occurs from mucosal lesions[2]. The pathophysiology of the disease involves an imbalance between stressors and mucosal barrier resistance as well as the infection acquired during childhood if located in the mucus lining the gastric mucosa[3].

In 1982, J. Robin Warren and Barry J. Marshall identified a bacterium that colonized the gastric mucosa and called it *Helicobacter* pylori[4]. This bacterium is found 90% in the antral gastric mucosa, and in 70% of gastric ulcers. Living in a community is the most important risk factor for transmission of the bacterium. The infection is gradually transmitted in small endemic foci[5].

Whatever its location, the gastric ulcer evolves towards chronicity, by successive outbreaks, as long as *H. pylori* has not been eradicated. Complications of the ulcer are frequent, in particular digestive bleeding (haematemesis,

melena) spontaneous or after taking aspirin. These hemorrhages can be serious and life-threatening for the patients[6].

Helicobacter pylori infection mainly affects developing countries such as Algeria. For this, our work consists in determining screening methods for ulcer disease caused by *Helicobacter pylori* in patients suffering from ulcer.

MATERIALS AND METHODS

Place of Work

This work was carried out after taking gastric biopsies at the following services:

- Dr Djebeili Mustapha in Chlef
- Dr EL-Aarbi Bouaamrane from Khemis Miliana in Ain Defla
- The functional exploration department headed by the gastroenterologist Dr. Ammi Naima from Kolea in Tipaza
- Anatomy and pathological cytology laboratory of the Fares Yahia hospital from Kolea in Tipaza
- Maccour Hammou hospital in Ain Defla
- Mohamed Boudiaf hospital in Médéa

The epidemiological study was carried out at the level of the anatomo-pathological cytology department of the Fares Yahia of Kolea hospital in Tipaza.

Collection of Gastric Biopsies

From 60 patients, a biopsy fragment is placed in Urea-Indole broth to detect the presence of urease and a fragment in 4% formalin for examination of anatomy and pathological cytology[7-9].

Pathological Anatomy and Cytology Examination of Gastric Biopsies (PCA)

The fragment fixed in 4% formalin is used for examination of anatomy and pathological cytology[7, 9].

Epidemiological Study

A retrospective study was carried out from December 2016 until February 2017. It involved eight patients with the same symptoms, followed by a gastroenterologist, and from January 1, 2014 to December 31, 2016 was carried out on 187 patients with different gastric pathologies followed in the pathological anatomy-cytology department of EPH Elkolea, Tipaza: Fares yahia.

ANOVA-SPSS or one-way analysis of variance is used to determine if there are statistically significant differences between the means of two or more independent groups: frequency, age, gender, physical signs, associated pathologies, gastric pathologies linked to *Helicobacter pylori* and type of sample.

RESULTS

Gastric biopsies are taken by upper gastrointestinal endoscopy from patients with the same symptoms: chronic abdominal pain, epigastralgia, vomiting, heartburn, abdominal bloating, headache, dyspepsia, and weight loss.

Rapid Urease Test

The presence of urease was determined by color change of the Urea-Indole medium from orange to pink after less than one hour in only seven patients. This indicates the degradation of urea by urease produced abundantly by *Helicobacter pylori*. The absence of color change in the Urea-Indole medium cannot be interpreted as an absence of infection. It must be completed by the anatomopathological examination.

Pathology Examination

Hematoxylin Eosin Staining

Patient 1: 66 years old, gastric fibroscopy revealed a pale aspect of the mucosa, a deep rounded lesion covered with a yellowish false membrane. Figure **1** shows an upper ulcer expressed by a total absence of epithelium, crypts and glands, also the presence of cracks in the mucosa. Polynuclear neutrophils are also found, *H. pylori* flagella and epithelial buds cause regeneration.

Patient 2: 23-years-old, the endoscopic appearance showed the presence of redness on the gastric wall. Despite a negative urease result, HE staining showed detachment of the epithelium expressed by mild gastritis (Fig. **2**).

Patient 3: 53-years-old man is on ulcerogenic treatment. The endoscopic appearance shows a clear mucous lake of ordinary abundance, and an abnormality of the superficial mucosa. Three antral and fundal fragments were made: the first fragment is placed in indole urea which gives a positive response after 20 minutes (Fig. **3**). Under an optic microscope after staining of the histological sections, we observed a slightly detached epithelium, sub-epithelial congestion with the presence of an inflammatory infiltrate

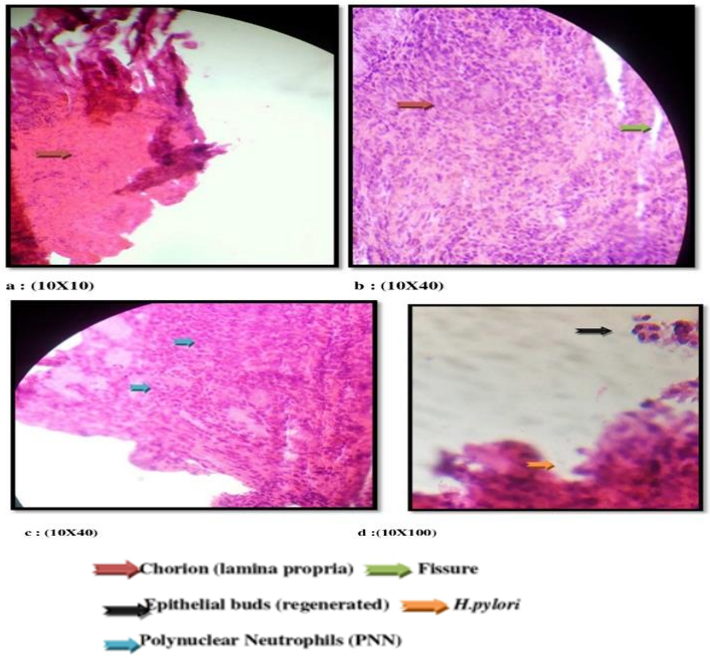

Figure 1. Microscopic observation of upper ulcer, epithelial buds regenerated on the fissured mucosa (HE).

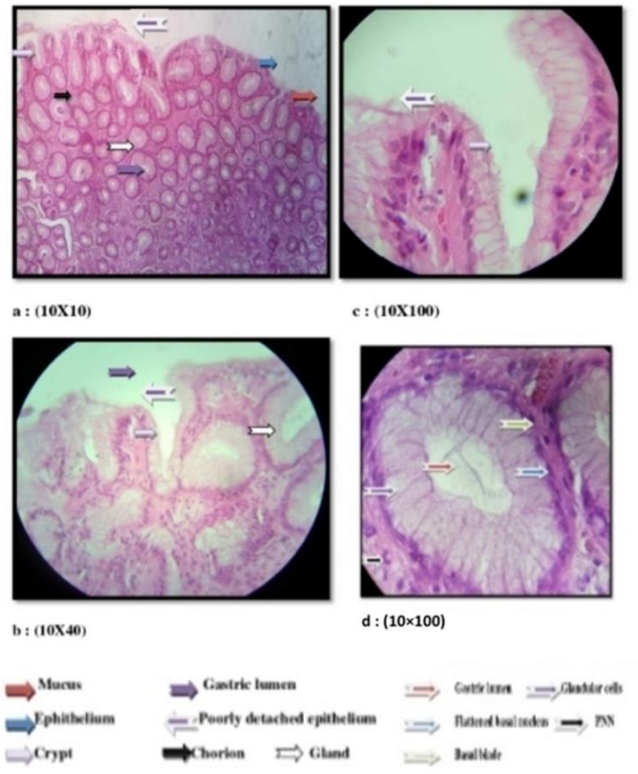

Figure 2. (a-c) Mild non-atropic activity, the presence of mucus glands and epithelial cells (HE); (d) Microscopic observation of a gastric gland after staining at HE.

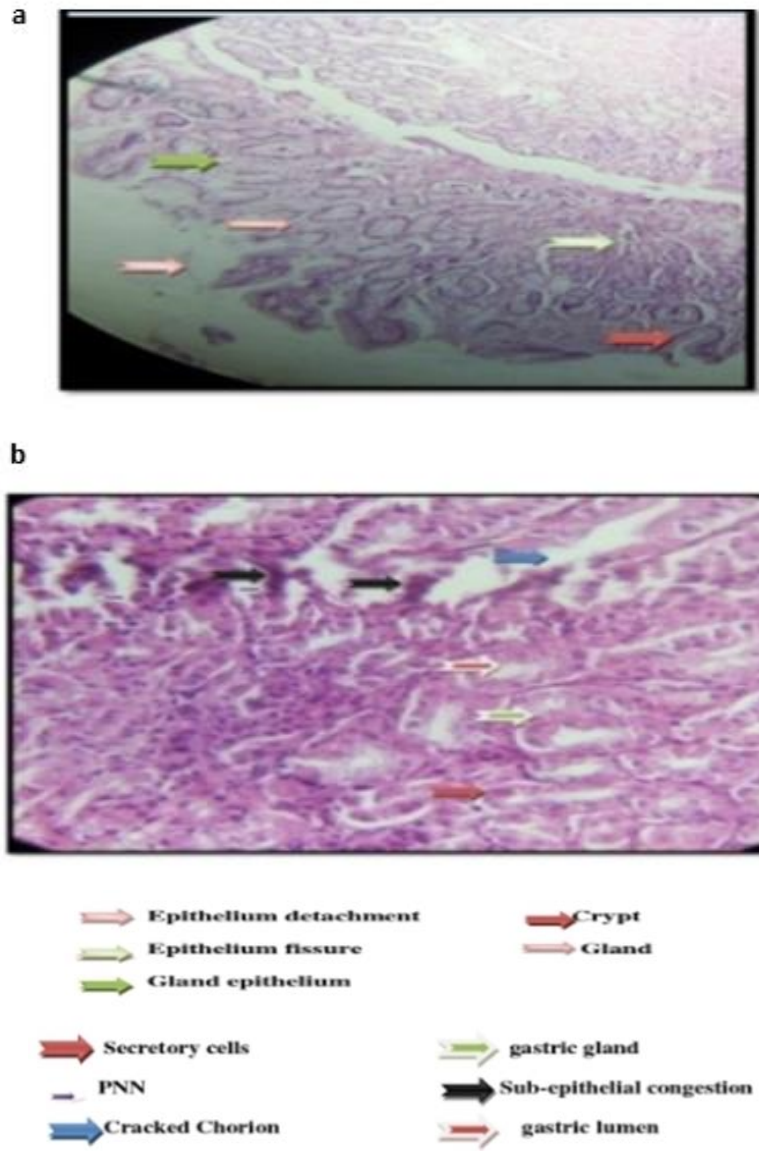

Figure 3. (a) Observation of an epithelial detachment (HE: 100); (b) moderate chronic inflammatory gastritis with subepithelial congestion of fundal tissue (HE: 400).

(lymphocytes, polymorphonuclear neutrophils and plasma cells).

Patient 4: 83-year-old woman, upper gastrointestinal endoscopy showed this patient to have antral erythematous gastritis. Three antral biopsies were taken, the fragment put in the indole urea shows a positive result. In this histological section, we observe an inflammation which still persists. The epithelium can detach with an inflammatory infiltrate (PNN), the mucosal glands are slightly atrophic in the presence of *H. pylori* (an active chronic gastritis slightly atrophic) (Fig. **4**).

Patient 5: 58-year-old woman: erythematous antral gastritis has been observed after upper gastrointestinal endoscopy. Three antral biopsies were taken, one fragment showing the presence of urease. Microscopic examination of the histological section prepared and stained with HE shows the presence of an ulcer associated with gastritis (Fig. **5**). The inflammation is highly developed expressed by a disappearance of the epithelium, crypts and glands. The chorion is fissured and full of an inflammatory infiltrate, indicating a gastric ulcer related to the presence of *H. pylori.*

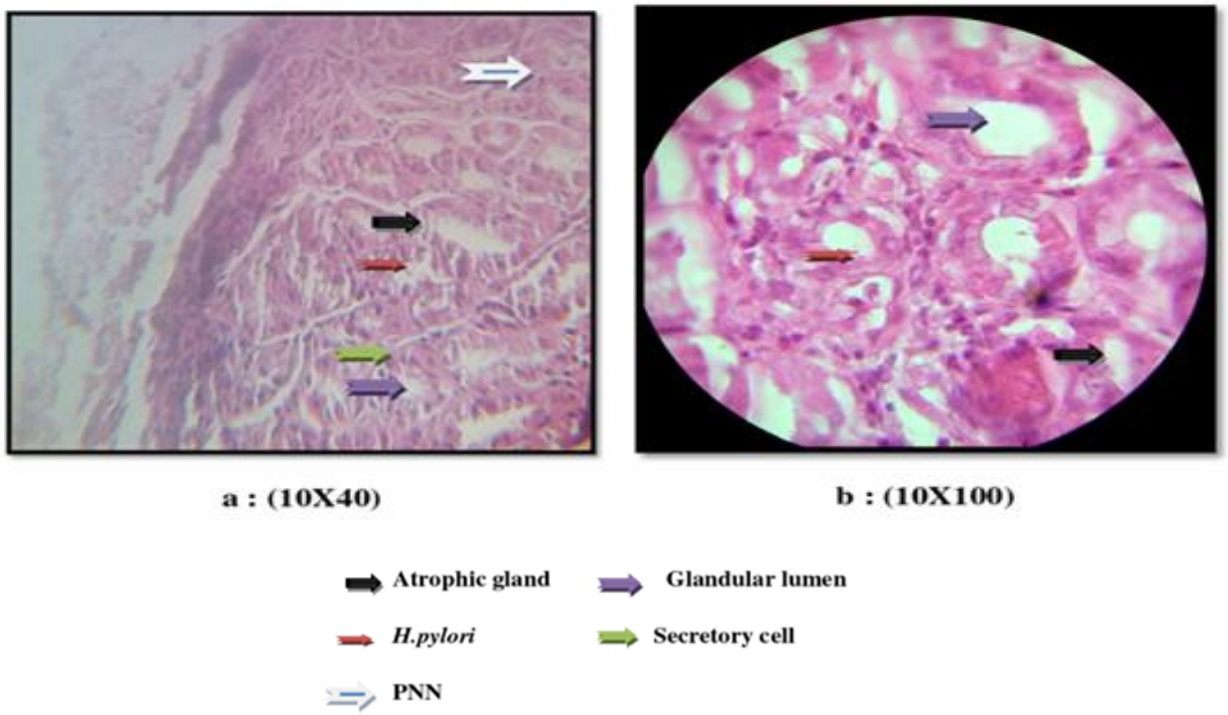

Figure 4. (a-b) Slightly atrophic active chronic gastritis (the presence of polynuclear neutrophils-HE).

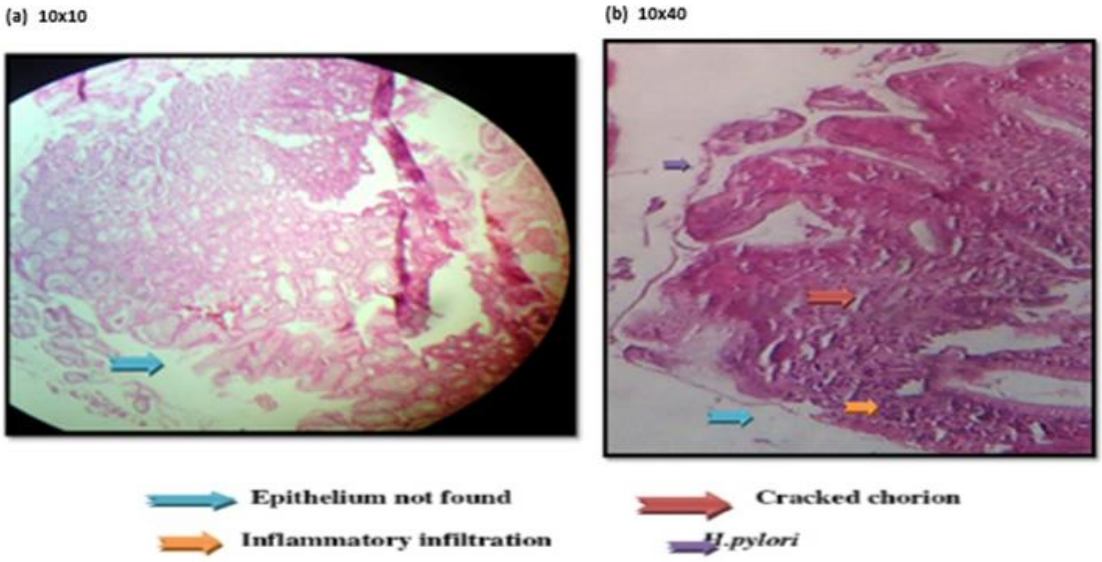

Figure 5. Gastric ulcer (HE).

Patient 6: 18-year-old: young man has antral erythematous gastritis. Three antral biopsies were removed by upper gastrointestinal endoscopy (fragment gave a positive result with urea indole medium) (Fig. **6**). The gastric tissue has transformed into intestinal tissue, so the disappearance of glands and the presence of PNN. Inflammation is caused by *Helicobacter pylori* which colonizes the glandular lumen.

Slow Giemsa Coloring:

Slow Giemsa staining makes it possible to demonstrate the presence of microorganisms in all types of tissues. It can in particular be used to detect the presence of *Helicobacter pylori* in the diagnosis of gastric ulcers or chronic gastritis.

It consists of coloring:

- *Helicobacter pylori* in blue;
- Chromatin, a nucleolus in shades blue;
- Plasma cells: cytoplasm in intense blue;
- Eosinophilic granulations in pink;
- Granulations of mast cells in intense purple.

Patient 7: Under an optical microscope, the cell nuclei are stained blue / purple and the cytoplasm in blue to pink. *H. pylori* colonizes the glandular lumen and is stained blue / purple. Lymphocyte nuclei appear in dark blue and the cytoplasm in light blue (Fig. **7**).

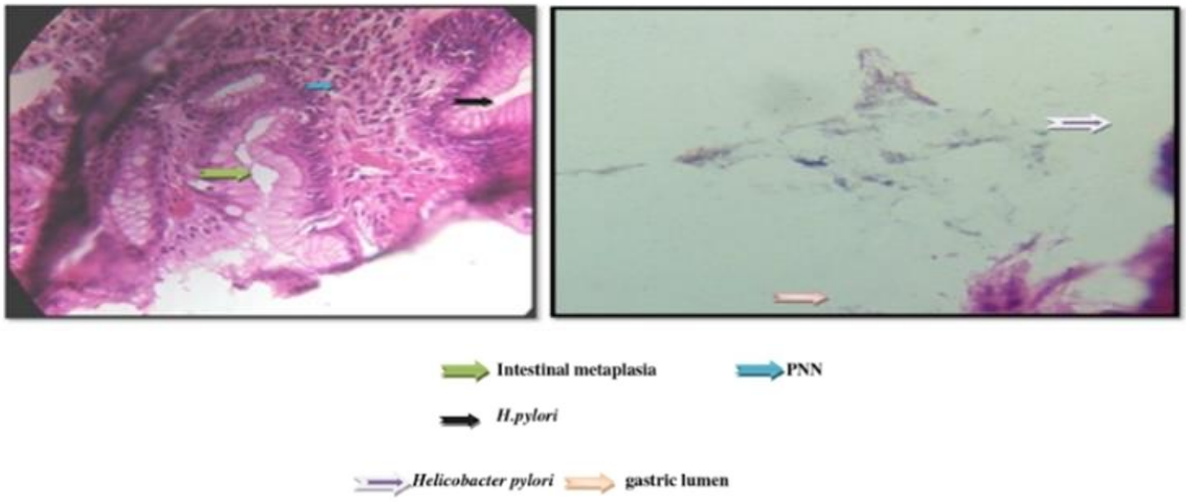

Figure 6. Significant active atrophic gastritis and intestinal metaplasia (HE: 400).

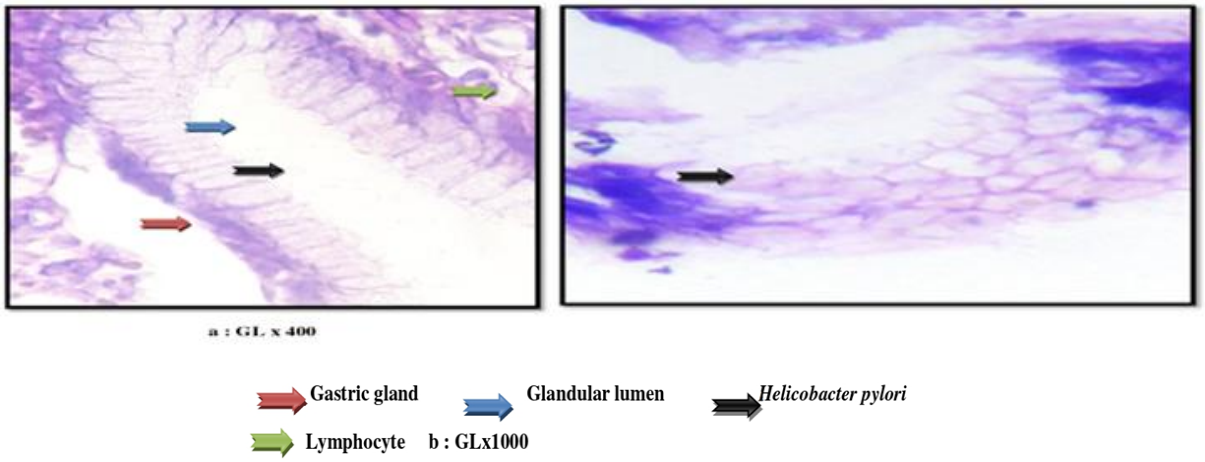

Figure 7. Microscopic observation of chronic *H. pylori* gastritis after Giemsa long staining.

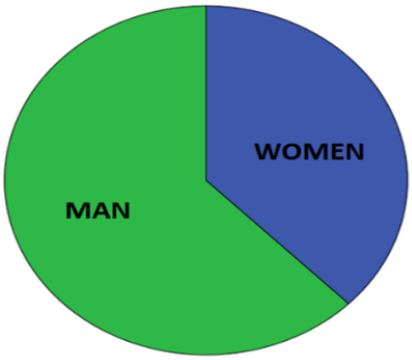

Figure 8. Distribution of patients by sex.

Epidemiological Study

In our study, 62.5% of patients are male and 37.5% are female. This may be due to disease-promoting factors in men than in women (Fig. **8**). All of the patients have chronic abdominal pain, anxiety, stress, and a severe medical condition. Out of this, 50% of cases take ulcerogenic drugs, of which 62.5% of the cases studied have family conflicts, ulcer in relatives and were tobacco users (Fig. **9**, **10**).

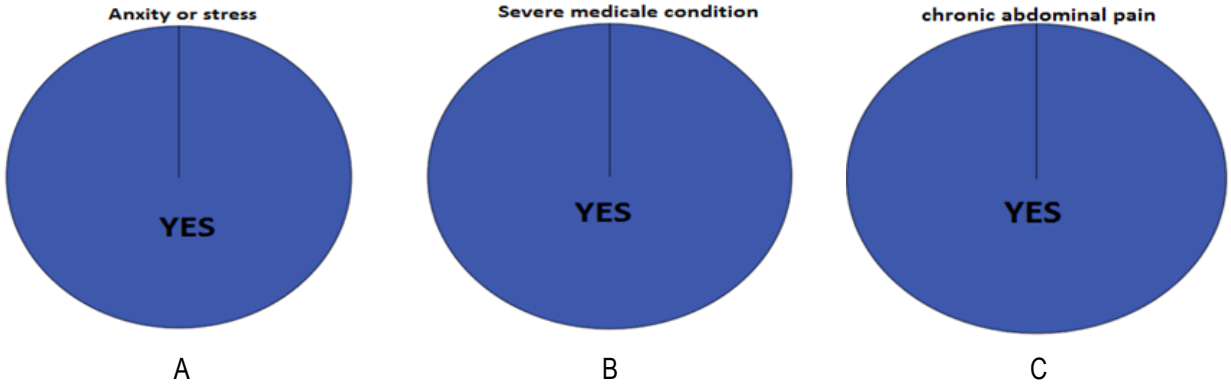

Figure 9. Distribution of patients according to A: Anxiety, B: severe medical condition, C: chronic abdominal pain.

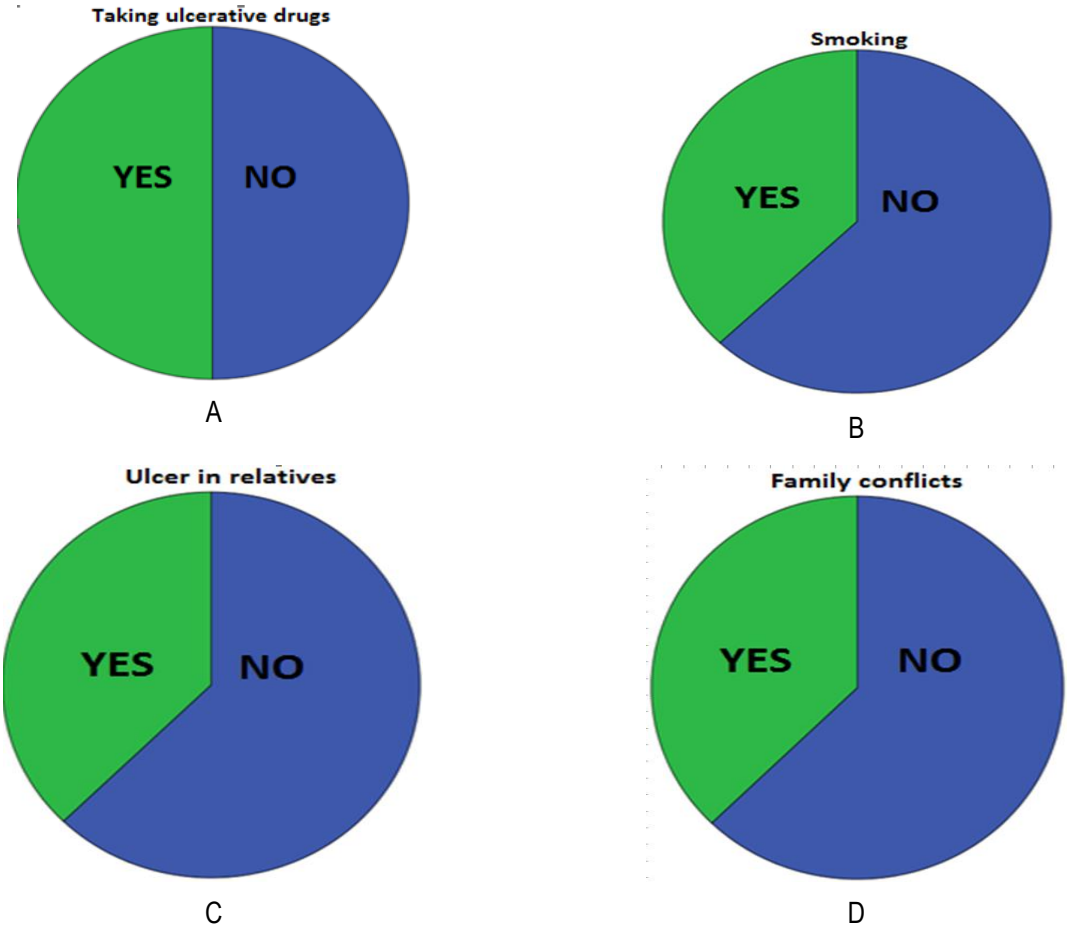

Figure 10. Breakdown of patients by history: A: taking ulcerogenic drugs, B: smoking, C: ulcer in relatives, D: family conflicts.

The ANOVA test was initiated in our study in order to analyze and enhance the data collected over 3 years.

Frequency

From January 2014 until December 2016, we collected a total of 187 patients for different gastric pathologies. The distribution of our patients over the three years has shown that the annual recruitment of patients with the various pathologies in the department varies from year to year. The highest frequency was noted in 2016 by 99 cases and the lowest in 2014 by 30 cases.

Age

This disease is observed from young to adulthood. In 2016, we have registered 54 patients in the age group 36-75 years. From these results, we observe that there is not a significant difference between the youth and adult categories where p> 0.05 (Table **1**).

Gender

During the three years, we found that 54.54% of patients were male. There is not a statistically significant difference between our results with p <0.05. This can be expressed by the probability of exposure of both sexes to this disease (Table **2**).

Physical Signs

An average of 58.37% was recorded with the physical signs of our patients including 100% of patients with physical signs of the disease. A statistically significant difference was found in this study (p <0.05) (Table **3**).

Table 1. Distribution of Patients by Age in the Anatomy-Pathology Department (p >0.05).

Age / Année	0 – 17 Years	≥ 18 – 35 Years	≥ 36 -75 Years	Total
2014	00	11	19	30
2015	00	25	33	58
2016	00	45	54	99
Total	00	81	106	187

Table 2. Distribution of Patients by Sex in the Pathology Department (p <0.05).

Sex/ Year	Male	Feminine	Total
2014	18	12	30
2015	32	26	58
2016	52	47	99
Total	102	85	187

Table 3. Distribution of Patients According to Physical Signs (p <0.05).

Physical Signs	No Signs (Pain on palpation of the epigastrium)	Presence of Sign	Total
2014	00	30	30
2015	00	58	58
2016	00	99	99
Total	00	187	187

Table 4. Distribution of Patients According to Associated Pathologies (p <0.05).

Associated Pathologies	Hiatal Hernia	Liver Cirrhosis	Other	No Association	Total
2014	00	00	01	29	30
2015	01	00	01	56	58
2016	00	00	01	98	99
Total	01	00	03	183	187

Table 5. Annual Frequency of the Various Gastric Pathologies Associated with *H pylori*.

Year	Acute Gastritis	Chronic Gastritis	Gastric Ulcer	Total
2014	06	21	03	30
2015	08	44	05	58
2016	11	80	08	99
Total	25	145	16	187

Table 6. Distribution of Patients by Type of Sample (p <0.05).

Type Of Sample	Antral	Fundic	Total
2014	29	01	30
2015	57	01	58
2016	97	02	99
Total	183	04	187

Associated Pathologies

In this part of the study, 97.86% of patients did not have an association with other diseases and 1.60% have other associated diseases for which a statistically significant difference was found between patients with associated conditions and patients without association (p <0.05) (Table **4**).

Gastric Pathologies Linked to HP

Only 8.55% of patients with Hp-related gastric ulcer were observed, 13.36% of patients with mild gastritis and 77.54% with chronic gastritis. After statistical analysis, we found that there is not a significant difference between patients with acute gastritis and gastric ulcer with p >0.05, but there is a statistically significant difference with p <0.05 between chronic gastritis and gastric ulcer (Table **5**).

Type of Sample

Our results show that 97.86% of patients undergo an antral biopsy sample and 2.13% having undergone a fundal biopsy sample. Statistical analysis indicates that there is a statistically significant difference between our results (p <0.05) (Table **6**).

DISCUSSION

In our study, we carried out rapid tests and macroscopic examinations and microscopic to assess the existence of *Helicobacter pylori* infection in Algerian patients. They are done from samples of gastric biopsies after an upper digestive endoscopy performed by gastroenterologists. The usual method is to introduce a flexible probe with a camera and a light into the patient's mouth, the degree of the lesion can be observed by endoscopy.

According to Belloul[10], gastric ulcer is defined as a loss of substance reaching deep. It is predominant in males and rare in young people under 40 with a peak around the age of 55 to 60. This ulcer is multifactorial (*H.pylori*, NSAID), and is expressed by normal HCl secretion and weak mucus.

The rapid urease test performed in the urea-indole endoscopy room, we gave a positive result at patients expressed by the change in the color from orange to pink.

The purplish red color reflects an alkalinization of the medium following the hydrolysis of urea and the formation of ammonium carbonate. If there is no alkalinization of the medium this can be explained by the negativity of the test. About 10,000 bacteria are needed on a sample to have a positive result[11].

The rapid urease test is based on the abundant production of urease by *H. pylori,* a biopsy where these bacteria are present will increase the pH and cause the color change to less than an hour[12]. *Helicobacter pylori* is a Gram-negative microaerophilic spiral bacterium, colonizing the gastric mucosa of half of humans with a mainly oral-oral mode of human-to-human transmission. Its significant genetic diversity, resulting from recombination which make it possible to follow human migrations, is involved in the physiopathology of gastric infection and its orientation towards associated pathologies linked to infectious chronic gastritis. The diversity of digestive expression is probably due to the presence of cagA and vacA virulence factors[13]. *Helicobacter pylori* produces nickel-containing urease which degrades urea to give ammonia and CO_2. The Ure gene cluster, consisting of seven genes, encodes the two structural subunits UreA and UreB and five accessory proteins: UreI, UreE, UreF, UreG and UreH. Accessory proteins are required for the insertion of nickel ions into the apoenzyme. The native protein consists of six copies each of UreA and UreB; two nickel ions are coordinated in each active UreB site. Urease is found in the cytosol, but can also localize to the surface and elicit a strong immunoglobulin response. Urease aids in host colonization by neutralizing stomach acid[14]. Using the pathological and cytological examination we were able to detect cases of chronic gastritis in four patients, gastric ulcers in two patients, acute gastritis in one patient and intestinal metaplasia in another[15]. Anatomopathology is the most used diagnostic method, it consists of a microscopic examination of gastric biopsy samples. However, the detection of the bacteria depends on the bacterial density and type of biopsy[16].

With the help of anatomo-pathological and cytological examination, we were able to detect cases of chronic gastritis in four patients, gastric ulcers in two patients, acute gastritis in one patient and intestinal metaplasia in another. Pathology is the most widely used diagnostic method, it consists of an examination microscopic gastric biopsy samples. The presence of *Helicobacter pylori* was determined in Algerian patients with ulcer disease (n = 100)[15]. Histological sections were prepared from gastric biopsies taken from patients by upper gastrointestinal endoscopy. The tissues are stained with Hematoxylin-Eosin and Giemsa Lent. The anatomo-pathological and cytological analysis jointly allow the detection of gastritis and the search for complications, such as atrophy, metaplasia, lymphoma or cancer[15].

However, detection of the bacteria depends on bacterial density and type of biopsy[16]. Acute gastritis is inflammation or swelling of the lining of the stomach[17]. Histological lesions are limited to the superficial layers of the wall, their diagnosis is the exclusive domain of endoscopy and histology after biopsy[18]. In gastritis we find different gradations according to the Sydney classification system 1990[19]:

- The presence of polynuclear neutrophils signifies gastritis activity;
- Glandular atrophy and intestinal metaplasia.

Indeed, *Helicobacter pylori* induces a multitude of histological lesions which can either stabilize or evolve slowly according to the chronic gastritis-atrophy sequence, gastric-intestinal metaplasia[20]. Infection acquired in childhood, usually before the age of ten, persists in most people for life without treatment. It constantly leads to chronic gastritis[21]. *H. pylori* can grow on human mucosa, it survives on acidic pH by secreting pH buffering substances in its immediate environment, reducing or weakening the mucus layer of the stomach[22].

Helicobacter pylori infection is the most common bacterial infection in the world. Persistent infection of the gastric mucosa leads to processes inflammatory and may remain silent for decades or progress causing more severe diseases. As soon as the *H. pylori* bacteria colonize the stomach, the epithelial cells and their innate immune receptors recognize the bacteria. This process attachment can be facilitated by the action of adhesins (BabA) expressed by bacteria, which promote the action of other virulence factors (CagA and VacA). Shortly after, the host's innate and adaptive immune systems are activated, resulting in recruitment a wide variety of cells and inflammatory mediators. As long as the CagA-positive contributes to the inflammatory response, as this virulence

factor causes an increase[14] the production of certain cytokines such as IL-1a and IL-8 and the activation of NF-kB[23-25].

Cag A is the most well-studied virulence factor of *H. pylori*. When injected into host cells, CagA can act directly in an unphosphorylated state to influence tight cell junction, cell polarity, cell proliferation and differentiation, cell diffusion, induction of inflammatory response and possibly cell lengthening. In addition, upon entry into the eukaryotic cell, CagA localizes in the plasma membrane where it can be phosphorylated either by kinases of the Abl kinase family or by Src[26].

The virulence factor VacA induces a pro-inflammatory response and multiple cellular activities that facilitate chronic colonization of the gastric mucosa by bacteria[25]. VacA is created from selective anion channels in membranes of those vesicles which have the characteristics of late endosomes and early lysosomes. A current model for vacuolation suggests that these anion-selective channels facilitate the transport of chloride ions, resulting in increased intra-lumenal chloride concentrations. Which gives osmotic swelling and vacuolation. VacA to integrate stably into the inner-mitochondrial membrane. VacA located in the mitochondria where its effects may be responsible for triggering the apoptotic cascade. Typically, during apoptosis, cytochrome C is released from the mitochondrial intermembrane space in the cytoplasm which ultimately results in the death of the cell[27].

H. pylori promotes gastric atrophy, resulting in loss of wall cells. *Helicobacter pylori* infection decreases acid production in patients with gastric ulcer[28]. The adhesion of *Helicobacter pylori* to gastric epithelial cells, which are protected by a gel of mucous layers, mainly composed of MUC5AC and MUC6. In addition to this protective role, constitute preferential binding sites of many pathogens. The main players in the process of adhesion of *H. pylori* to gastric epithelial cells, which contribute decisively to the high prevalence and chronicity of *H. pylori* infection. BabA adhesin recognizes both H-type 1 and Lewis b blood group antigens expressed on the normal gastric mucosa of secretory agents, which contributes to the initial stages of infection[29, 30]

Metaplasia is transformation of a differentiated tissue into another of a different character, and which results in the constitution of a normal tissue in itself, but abnormal by its location[31].

A retrospective study was initiated in our work on patients who have undergone upper gastrointestinal endoscopy. Gastric ulcer is rare before the age of 15 and after 60 years. The maximum frequency is between 25 and 65 years. These findings confirm well-known facts which make ulcer a disease of the adult subject. Men have a greater susceptibility to developing ulcerative disease than women. The gastric ulcer is classically expressed by painful attacks abdominal. Some forms will immediately express themselves by signs of complication like digestive bleeding. Knowledge of the epidemiological profile of ulcer patients appears to us as a necessity, because it will make it possible to identify the target populations who should benefit from an endoscopic exploration if there is any doubt. Stress, anxiety, alcohol or tobacco are considered to be aggravating factors[32].

According to Ibara *et al*.[33] in the distribution by sex, the predominance of the disease is represented by 56.59% of men, 43.41% of women and 16% of smokers. Stress in the same job is encountered in almost 25% of patients.

CONCLUSION

In our work *Helicobacter pylori* was determined after sampling gastric biopsies in the endoscopy room using the rapid urease test. This germ was present in seven out of eight cases.

The pathology test is done at the pathology laboratory level. We found several gradations and types of gastritis (gastritis mild, chronic gastritis and gastric ulcer), the main factor responsible for this pathology is infection with *Helicobacter pylori*.

Statistical study using the ANOVA test revealed relationships between risk factors and associated pathologies. Thus, risk factors for pathologies have been found to be presented by 8.55% gastric ulcer, 13.36% mild gastritis and 77.54% chronic gastritis.

- The results obtained in our work are encouraging and they deserve to be followed by other studies and techniques in the future, such as:

- Determining the frequency of ulcer disease in other developing countries;
- Search for other techniques and methods to explore this disease; *Helicobacter pylori* bacterium culture trial in Algeria;
- Characterize this pathogen at the molecular level using techniques such as real-time PCR;
- Sequencing of *Helicobacter pylori* isolated from gastric biopsies taken from Algerian patients;
- Analyze the molecules and proteins secreted by this bacteria; Search for a vaccination to fight ulcer disease caused by *H. pylori*.

ETHICAL APROVAL

Ethical approval for the study was obtained from Khemis Miliana University, Algeria.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

FUNDING SOURCE

None.

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LIST OF ABBREVIATIONS

cagA	cytotoxin-associated gene A
EPH	Public Hospital Establishments
H.pylori	*Helicobacter pylori*
HE	Hematoxylin Eosin
H-type 1	human blood group antigen H (O) type 1
IL	Interleukin
MUC5AC	Mucin 5, Subtypes A and C
MUC6	Mucon 6
NF-kB	Nuclear factor kappa light chain enhancer of activated B cells
NSAID	Non-Steroidal Anti-Inflammatory Drug
PCA	Pathological and Cytological Anatomy
PCR	Polymerase chain reaction
pH	Hydrogen potential
PNN	Polynuclear neutrophils
SPSS	Statistical Package for the Social Sciences
Src	Sarcoma
URE	Urea
vacA	Vacuolating cytotoxin A

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