

ETIOPATHOGENESIS OF PEPTIC ULCER: back to the past?

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ABSTRACT - Objective - To review some aspects of the etiopathogenesis of peptic ulcerous disease especially on the basis of studies on its correlation with *Helicobacter pylori* (*H. pylori*). **Methods** - A search was made in the data bases MEDLINE, LILACS and PubMed, and in Brazilian and foreign books, referring to the incidence and prevalence of infection by *H. pylori* and of peptic ulcerous disease in various populations of different countries. **Results** - It was observed that the prevalence of *H. pylori* infection is similar in individuals with peptic ulcerous disease and the general population. There are differences between countries with respect to the prevalence of infection and of gastric or duodenal peptic ulcers. In many countries the prevalence of infection by *H. pylori* shows stability while the prevalence of peptic ulcerous disease is declining. The prevalence of peptic ulcerous disease without *H. pylori* infection varies between 20% and 56% in occidental countries. **Discussion** - The observations might be suggestive of *H. pylori* being only one more factor to be summed together with other aggressive components in the genesis of peptic ulcerous disease. We would therewith be returning to the classic concept that peptic gastric and duodenal ulcers have multifactorial etiology and would result from imbalance between aggressive and defensive factors. The focus of studies should be enriched with the identification of the defensive factors and of other aggressive factors besides the well known *H. pylori* and non-steroidal anti-inflammatory drugs, since these two aggressors do not exhaust the full causal spectrum.

HEADINGS - Peptic ulcer. Stomach Ulcer. Duodenal ulcer. *Helicobacter* infections.

INTRODUCTION

Peptic ulcers are sites of loss of continuity of part of the wall of organs of the gastrointestinal tract exposed to the gastric chloridopeptic secretion. The organs affected are more frequently the stomach and the duodenum. Under some conditions it is also possible to observe peptic lesions in the esophagus and jejunum among other less common sites⁽⁴⁰⁾. Lesions are chronic and single in the majority of cases but can be multiple in about 5% to 20% of cases, simultaneously affecting the stomach and the duodenum or even other segments, as occurs in the Zollinger and Ellison Syndrome^(13, 40).

The etiology of the peptic ulcerous disease (PUD), gastric or duodenal, is becoming one of the most intriguing problems of gastroenterology. Up to some time before the last two decades of the past century it was considered a disease of multifactorial origin. It was assumed that it would be installed in constitutionally predisposed individuals, in consequence of disequilibrium between the action of aggressive and defensive factors upon the gastroduodenal mucosa. Duodenal ulcer would develop

from the predominance of aggressive factors while gastric ulcer would result mainly from the failure of defensive factors⁽⁵⁷⁾.

Some authors even hypothesized that they would be different diseases. Duodenal ulcer is usually diagnosed in younger age, typically with higher acid secretion and affecting mainly males. Gastric ulcer occurs more frequently in older patients, acid secretion is near-normal or reduced and the sex-ratio is not skewed⁽⁵⁷⁾.

In Brazil, epidemiological surveys revealed that duodenal peptic ulcers are more prevalent than the gastric in a 3:1 proportion, besides being more prevalent in males^(13, 53). In the UK, the incidence of peptic ulcer was 12% higher in men than in women⁽⁹⁾, although the prevalence of infection by *Helicobacter pylori* (*H. pylori*) is not associated with sex^(50, 58, 64).

After Marshall and Warren⁽⁴³⁾ presented studies on the correlation between gastritis and peptic ulcer, and on the pathogenic action of *H. pylori* plus the fast evolution of knowledge on the theme, this association became established and is universally accepted. In 1994, the US National Institutes of Health recognized that *H. pylori* was directly involved

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in peptic ulcer pathogenesis⁽¹⁸⁾. On the bases of the facts that the majority of peptic ulcers were associated with the presence of *H. pylori* and that eradication of the bacteria lead to significant reduction of reinstallation of the ulcers, the microorganism became considered a decisive etiologic factor in the genesis of PUD, besides the non-steroidal anti-inflammatory drugs (NSAID)⁽¹²⁾. Recurrence of the disease is higher in patients infected by the bacterium (13.4% per year), relative to the patients submitted to therapy for eradication of *H. pylori* (2.5% per year)⁽⁴⁵⁾. Since then, PUD became considered either an infectious⁽²⁶⁾ or an iatrogenic (NSAID-induced) disease; it would be a rare disease in the absence of these two factors. It became valid to affirm that in peptic ulcer the treatment of *H. pylori* means the cure of the disease⁽¹⁷⁾. More recently, to the classic aphorism “No acid no ulcer”⁽⁵⁶⁾ the *dictum* “No *Helicobacter pylori* no ulcer” was associated^(10, 29).

This work discusses the etiopathogenesis of PUD based on a review of medical bibliography on the correlation and association between PUD and *H. pylori*.

METHODS

A search was made on the databases MEDLINE, LILACS and PubMed using the following keywords: “Peptic ulcerous disease or PUD”, “*Helicobacter pylori*-negative” or “*H. pylori*-negative” or “*Hp*-negative” and “peptic ulcerous disease” or “peptic gastric ulcer” or “GUP” or “peptic duodenal ulcer” or “DUP”, as well as on Brazilian and foreign books on the theme. Searches were restricted to publications in English, Portuguese or Spanish.

The searches, including the supplementations, yielded 56 original or review articles and 8 books. Some studies were discarded due to the inclusion of patients under 18 years of age, of patients in use of any NSAID (including aspirin) or with concomitant diseases that could lead to lower prevalence of infection by *H. pylori* (such as atrophic gastritis, malignant ulcerous disease, cirrhosis with portal hypertension and hepatic insufficiency), as well as those bearing diseases that could cause gastric or duodenal ulcers (Crohn disease, cytomegalovirus infection, stress-related ulcer, Behcet disease). In the studies involving peptic ulcer patients, infection by *H. pylori* was diagnosed by direct demonstration of the bacteria in biopsy specimens⁽¹⁹⁾ combined with another diagnostic test, usually the Rapid Urease Test. The only exceptions to this rule were the epidemiologic studies of the infection that employed other tests (e.g., urease test on biopsies, ¹³C-urea breath test, seroprevalence of antibodies, culture and stool antigen test). Patients were classified as having *H. pylori*-negative ulcer if no test was positive and at least two tests were negative; an exception was a Brazilian study of PUD⁽⁴²⁾, included due to the scarcity of studies in the country.

RESULTS

Infection by *H. pylori* is detected worldwide. Incidence and prevalence of the infection vary according to age of individuals and to socioeconomic conditions of each region. There is no reported difference between sexes^(50, 58). Studies in different countries reveal prevalence of infection between 11% and 69% in the general population⁽⁷⁾ and between 8.9% and 72.8% in children, respectively in developed and developing countries⁽⁴²⁾. Along recent years a reduction of the infection rates was observed, most evident in occidental industrialized countries and in some oriental emergent economies^(5, 6, 7). Various studies indicate that the incidence and prevalence of colonization by *H. pylori* have declined progressively with industrialization in different countries^(4, 34). While the prevalence of infection is higher in underdeveloped and developing countries, there is also a reduction of the infection in them, attributed to the eradication therapy and to the improvement of sanitary conditions observed in the last two decades⁽⁷⁾.

Brazilian studies on the prevalence of infection by *H. pylori* were conducted in limited population samples of some states. It was found high, from 59.5% in Rio de Janeiro (RJ) to 96% in São Luis (MA)⁽³⁵⁾. High prevalence was also reported in a low income community of Fortaleza (CE): 73.3% in the age range from 11 to 20 years and above 87% at 60 years of age or more⁽⁵²⁾. In the city of São Paulo, prevalence of infection was below 65.6% in the population of high income⁽⁵⁰⁾; among blood donors the infection was of 66.5% of 746 males and of 63.2% in 247 females⁽⁶⁴⁾. An overall decline in prevalence of *H. pylori* was noted in both high and low socioeconomic status countries⁽⁷⁾.

The duodenum is the major location of peptic ulcers in the western population; the gastric location is more frequent in oriental countries, particularly Japan⁽⁴⁶⁾. The relevance of *H. pylori* for the genesis of the mucosal ulceration is well supported by the identification of the bacterium in 90%-95% of duodenal ulcer patients and 60%-80% of patients with gastric ulcer, as compared to 25%-30% in symptomatic controls⁽⁴⁶⁾. In developing countries, all studies up to now are consistent in detecting the bacterium in over 90% of bearers of peptic ulcers⁽¹⁷⁾. Otherwise, the decline in the incidence of PUD cannot be explained by population or demographic changes⁽⁹⁾ while the increase in the frequency of non-*H. pylori* ulcers cannot be explained solely by the declining rates of infection⁽²³⁾. In Brazil, the prevalence of duodenal ulcer decreased from 8.6% in 1996 to 3.3% in 2005⁽⁵⁴⁾.

The review of Blaser⁽⁵⁾ showed that the rate of PUD, especially at the duodenum, was increasing in the USA and in Europe during the last decade, while there was evidence that the rate of *H. pylori* colonization was declining for a long time. Another review of Sung et al.⁽⁶¹⁾ encompassing various countries reported reduction of both the rates of

PUD and of the proportion of ulcerous patients infected by the bacterium, especially in occidental countries. A variety of studies referring to diverse world regions have been pointing to an increase throughout recent time of the prevalence of *H. pylori*-negative duodenal ulcer or idiopathic peptic ulcer^(8, 16, 29, 31-33, 37, 38, 47, 51, 55, 59, 63) (Table 1). A meta-analysis of seven double blind, randomized trials in North America found that 20% of patients with *H. pylori*-associated ulcers had ulcer recurrence within 6 months despite successful *H. pylori* eradication and no reported NSAID use⁽³⁷⁻³⁹⁾.

No role could be proposed for the smoking habit on the basis of two studies, either on non-*H. pylori* and non-NSAID duodenal ulcers or on *H. pylori*-associated ulcers^(49, 63).

In developed countries there was wide variation in the rates of DUP and of infection by *H. pylori*. In Scotland the prevalence of infection was 65%, and 95% of the ulcers were associated with infection⁽⁴⁵⁾. Results from the USA suggest that the proportion of *H. pylori*-negative ulcer, while varying somewhat, appears to be rising⁽⁶⁰⁾; the prevalence of infection in some regions may be of only 30%, and about 20% of the PUD patients are not infected⁽⁴⁵⁾. Quan and Talley⁽⁴⁹⁾ systematically reviewed the prevalence of unexplained ulceration in the period between 1995 and 2001, finding that a relevant proportion of PUD patients were not infected by *H. pylori*. Other studies in the USA showed that 20% to 50% of the peptic ulcers were not related to *H. pylori* infection or to the use of NSAID^(14, 15, 23, 25). In studies published along the last

ten years, totaling 16,080 patients, the average prevalence of *H. pylori* infection in duodenal peptic ulcer was of 81%; the rate declined to 77% when only the last five years of the sample were considered⁽²⁵⁾. In New York, among non-users of NSAID, only 61% of peptic ulcer patients presented the *H. pylori* infection (conversely, 39% of PUD patients were *H. pylori*-negative); among 2,900 patients bearers of duodenal ulcer, 27% did not report usage of NSAID and were *H. pylori*-negative⁽¹⁴⁾.

In the USA the hospitalization rate due to PUD experienced an average reduction of 21% between 1998 and 2005, more pronounced among women with gastric ulcer. Among hospitalized individuals, 47% did not present *H. pylori* infection. Higher rates of *H. pylori*-negative PUD patients were found at ages equal or above 65 years (54%) and among white skin color (56%)⁽²²⁾.

The incidence of not further complicated PUD in the UK decreased to little more than half between the years 1997 and 2005, the reduction of duodenal ulcer being greater than that of gastric ulcer. The number of confirmed *H. pylori*-negative cases increased from 5% to 12% from the first to the last year in the study⁽⁹⁾.

In Japan and Hong Kong, the rates of PUD not associated with usage of NSAID or with *H. pylori* infection were of only 1.3% and 4.1%, respectively^(15, 30). Both of these studies highlighted that the proportions of idiopathic PUD were increasing. In Korea, the prevalence of *H. pylori* infec-

TABLE 1. Prevalence of *Helicobacter pylori*-negative peptic ulcer among non-NSAID users

Reference (Country)	Year of publication	Method of <i>H. pylori</i> detection	Number of patients	Ulcer type	% non-NSAID <i>H. pylori</i> -negative
McCull et al. ⁽⁴⁴⁾ (Scotland)	1993	Histology and CLO test	12	DU	50
Graham et al. ⁽²⁶⁾ (USA)	1995	Histology and CLO test	139	DU	33
Bakkevold ⁽³⁾ (Norway)	1995 - 1996	Histology and CLO test	62 25	DU GU	18 12
Lanza et al. ⁽³⁸⁾ (USA)	1996	Histology and CLO test	183	DU	30
Peterson et al. ⁽⁴⁷⁾ (USA)	1996	Histology and CLO test	128	DU	27
Sprung et al. ⁽⁶⁰⁾ (USA)	1997	Histology and CLO test	59	DU	52
Kemppainen et al. ⁽⁵²⁾ (Finland)	1997	Histology and CLO test	125	PUD	30
Jyotheeswaran et al. ⁽³¹⁾ (USA)	1998	Histology and CLO test	160 145	DU GU	39 39
Laine et al. ⁽³⁷⁾ (USA)	1998	Histology and CLO test	619	DU	20
Schubert et al. ⁽⁵⁵⁾ (USA)	1999	Histology and CLO test	41 43	DU GU	39 47
Ciocola et al. ⁽¹⁶⁾ (USA)	1999	Histology and CLO test	2394	DU	27
Xia et al. ⁽⁶³⁾ (Australia)	1999	Histology and CLO test	14 33	DU GU	43 58
Bytzer et al. ⁽⁸⁾ (Denmark)	2001	Histology and CLO test	276	DU	19
Bakkevold ⁽³⁾ (Norway)	2007 - 2008	Histology and CLO test	47 28	DU GU	43 57
Feinstein et al. ⁽²²⁾ (USA)	2010	Histology and CLO test	770 548	DU GU	50 40
Marques et al. ⁽⁴²⁾ (Brazil)	2011	CLO test	391 103	DU GU	36 43

NSAID: non-steroidal anti-inflammatory drug; CLO: rapid urease test; DU: duodenal ulcer; GU: gastric ulcer; PUD: peptic ulcer disease, location unspecified

tion in association with gastric ulcer was increasing in more recent years, whereas *H. pylori* infection in duodenal ulcer was decreasing⁽³⁰⁾.

The prevalence of PUD has not been adequately evaluated in Brazil, while the prevalence of *H. pylori* infection is high. A report on patients in the southern states revealed low prevalence of duodenal peptic ulcer⁽⁵⁴⁾. Marques et al.⁽⁴²⁾ studied 1478 consecutive higher digestive organ endoscopic examinations realized in a tertiary care hospital in the city of São Paulo, finding peptic ulcers in 494 (33.4%). Infection with *H. pylori* was diagnosed in 252 (64%) patients with duodenal ulcer, 59 (57%) of bearers of gastric ulcer and 143 (53%) patients with normal endoscopy. The rates of *H. pylori*-negative patients were moderately high, 36% of the duodenal and 43% of the gastric ulcerous.

DISCUSSION

It seems significant that, more recently, there has been an accumulation of medical studies coming from different regions indicating that an appreciable proportion of gastric and duodenal peptic ulcers is not related to *H. pylori* infection or to the use of NSAID. An appraisal of the data compiled above indicates that about 20% to 56% of PUD did not find a defined etiology, being included in the idiopathic PUD category.

The review of Blaser⁽⁵⁾ showed that the rate of PUD, especially of duodenal localization, started an increasing trend in the USA and Europe, while there was evidence that the rate of *H. pylori* colonization was starting to fall. In industrialized countries, after a peak in the early decades of the last century, the incidence of PUD and the prevalence *H. pylori* colonization started a declining trend. It has been questioned why the occurrence of PUD is increasing at the same time when the prevalence of *H. pylori* infection declines⁽⁶⁾.

It has been observed that the prevalence of PUD did not change in concomitance with the regimes of *H. pylori* eradication in the countries with low prevalence of the infection⁽⁶⁾. The increase in the rate of eradication of the bacterium in the USA did not result in reduction of the rates of hospital admissions related to complications from PUD⁽⁴¹⁾.

Varied argumentation has been presented attempting to justify the occurrence of PUD in the absence of *H. pylori* infection but we consider that the great majority, if not the totality of the justifications do not resist criticisms.

Patients without present evidence of colonization by *H. pylori* would have had a previous infection responsible for permanent alterations in the gastro-duodenal mucosa that facilitated development of the PUD⁽⁴⁵⁾.

It remains controversial whether gastric mucosal atrophy and duodenal metaplasia are reversible or not after eradication of the infection⁽⁶²⁾. Furthermore, such possible mucosal alterations are difficult to confirm in consequence of not being possible, in the majority of cases, to obtain data on the previous conditions with respect to the presence of *H. pylori* in the population included in the studies^(20, 62). Anatomopathological studies on peptic ulcers refer signs of inflammation in the regions surrounding the ulcer but not signs of

mucosal atrophy⁽⁶²⁾. About 30% of patients with idiopathic ulcers show histological characteristics suggestive of previous infection, indicating that eradication of the infection does not protect against recurrence of the peptic ulcer⁽¹⁵⁾. About 20% or more of the cured of *H. pylori* infection may develop subsequent *H. pylori*-negative ulcer⁽³⁶⁾.

Elevation of gastric pH in consequence of the utilization of some antibiotics, high doses of H₂ antagonists or of proton pump inhibitors would strongly reduce urease activity, therewith leading to false-negative results with respect to *H. pylori* infection through the urease or respiratory tests^(1, 28, 36). Furthermore, these medications reduce bacterial density in the organ⁽²⁷⁾.

Gastric alkalization and the use of some antibiotics could be causes of false-negative urease or respiratory tests. Otherwise, these queries might not apply to the studies reviewed here, which were all based on histologic search for the bacteria in biopsy materials.

The rise in the number of idiopathic peptic ulcers has been attributed to diagnostic errors. Gisbert et al.⁽²⁴⁾ observed that the rate of diagnostic sensitivity from biopsies with urease test and histological examination was of 83% in analyses of samples from corpus and antrum concomitantly, decreasing to 78% with material collected from only one of the regions. In order to be sure of the absence of the infectious cause of the peptic ulcer, it is also recommended that samples should be examined from both antrum and corpus, and utilizing two different tests, with negative results for both⁽⁶²⁾. A lower bacterial density in the antrum can lead to false-negative urea respiratory tests^(1, 20, 28, 36).

It is general to endoscopic procedures that samples be taken from both antrum, where the majority of the ulcers reside, and corpus, where bacterial populations are higher. It is also general knowledge of specialists that in biopsies of areas immediately adjacent to peptic ulcers the finding of bacteria is not highly probable, the results being negative even in cases with intense colonization density. If these facts are assumed well known to endoscopists it should be wise to accept that the biopsies are good representatives of reality, being also improbable that the pathologists would have recently lost the ability to identify the bacteria. Examination of the biopsy fragments through the usual Giemsa staining allows demonstration of the bacteria in 80% to 97% of cases⁽²¹⁾.

The diagnosis of infection by *H. pylori* is impaired in cases of peptic ulcers with acute complications (bleeding, obstruction, perforation)^(11, 24).

Studies compiled in this review did not include patients with obstruction or perforation installed upon PUD. In all patients with acute bleeding, the search for *H. pylori* was conducted in gastric biopsies obtained after the bleeding was controlled, with repetition of the procedure whenever necessary. It is also not likely that false-negative results would occur repetitively, especially after the complication is circumvented. In such circumstances, Bakkevold⁽³⁾ repeated the gastric biopsy and found that, when the bacteria are present, both histopathological and rapid urease tests were positive for diagnosis of the infection.

Gastric biopsies might not reveal the presence of bacteria in cases where the colonization and the ulcerous disease are restricted to the duodenum⁽⁴⁸⁾.

The study of Pietroiusti et al.⁽⁴⁸⁾ refers to 608 PUD patients of which 6,9% (42 patients) did not present gastric infection. Among the latter, *H. pylori* was not detected in the duodenum in 24 (57%), whereas 18 patients had a positive duodenal culture for *Helicobacter* that is 2.9% from the total sample. The authors informed that duodenal colonization by species of *Helicobacter* other than *H. pylori* cannot be excluded since the *cagA*-negative genotype was higher in patients with isolated duodenal colonization, when compared with patients presenting the usual pattern of colonization. While there are no explanations for the exclusive duodenal location, its prevalence is so scanty that would not justify the rise of *H. pylori*-negative PUD.

The finding of *H. pylori*-negative cases could derive from the extensive use of antibiotics starting from the last decades of the past century. Such usage could contribute in a short term basis to negative results in bacterial detection tests^(21, 24, 61).

This possibility might be relevant but with some pondering. The large majority of antibiotics do not affect specifically *H. pylori*. In case a temporary eradication is obtained, clinical symptoms should also disappear from the temporary cure of the disease and consequently the patients would not have the need for looking after medical assistance and would not be submitted to the endoscopic examination. Even when this examination is conducted at least the scar of the lesion should be observed.

CONCLUSION

The prevalence of *H. pylori* infection is similar in individuals with PUD and in the general population. Since the incidence and prevalence of the infection by the bacteria is

similar in males and females, other factors should be advocated to explain the reasons for the higher prevalence of duodenal PUD in males and for the finding in some countries, including Brazil, of the 3:1 ratio of prevalence between duodenal and gastric ulcers. There are differences between countries with respect to the prevalence of infection and of gastric and duodenal peptic ulcers. In various countries, the prevalence of infection is stable while that of PUD is decreasing. Occurrence of *H. pylori*-negative PUD is being detected in significant proportions and these are higher than would be expected according to the etiologic conception of being an infectious disease.

These considerations might be taken in support of the conception that *H. pylori* would be only one more of the strong aggressive factors known to cause peptic ulcers, aside with the NSAID. Under this panorama, we would be turning back to the concept that peptic gastric and duodenal ulcers have a multifactorial etiology and result, as it was assumed in the past, from disequilibrium between aggressive and defensive factors acting in the mucosa. A consequence of the recognition of this conception would be the reinforcement of the focus on the search for the possible other factors.

At present there is little doubt that eradication of *H. pylori* is mandatory to ensure successful treatment of gastric and duodenal ulceration⁽⁴⁶⁾. The 1994 National Institutes of Health Consensus Conference concluded that ulcer disease was an infectious disease that could be cured by bacterial eradication⁽²⁾. However, the more recent reports suggesting that a considerable proportion of peptic ulcer may be non-infectious in origin would indicate a change in the management strategies since non-infectious ulcer cannot be cured with antibiotics. A call for concern would spring from the report of Bytzer et al.⁽⁸⁾ indicating that *H. pylori*-negative duodenal ulcers were associated with a poorer prognosis mainly because of a higher rate of ulcer and symptom relapse.

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RESUMO - Objetivo - Revisar a etiopatogenia da doença ulcerosa péptica com base em revisão de estudos sobre a correlação entre *Helicobacter pylori* (*H. pylori*) e doença ulcerosa péptica. **Métodos** - Foi realizada busca nas bases de dados MEDLINE, LILACS e PubMed, e em livros brasileiros e estrangeiros referentes à incidência e prevalência de infecção pelo *H. pylori* e de doença ulcerosa péptica em várias populações de diferentes países.

Resultados - Observamos que a prevalência da infecção pelo *H. pylori* é semelhante em indivíduos com doença ulcerosa péptica e a população geral; que existem diferenças entre países no que tange as prevalências de infecção e a de úlceras péptica gástrica e duodenal e que, em muitos países, a prevalência de infecção pelo *H. pylori* se mantém estável, enquanto a prevalência de doença ulcerosa péptica está em queda. A prevalência de doença ulcerosa péptica na ausência de infecção pelo *H. pylori* varia de 20% a 56% nos países ocidentais. **Discussão** - As observações sugerem que o *H. pylori* constituiria somente mais um fator a ser somado ao rol dos agressores na gênese da doença ulcerosa péptica. Assim, estaríamos retornando ao conceito de que as úlceras pépticas, gástrica e duodenal, têm etiologia multifatorial e decorreriam, como era admitido no passado, do desequilíbrio entre fatores agressivos e defensivos da mucosa. O foco dos estudos deveria ser redirecionado à identificação dos fatores defensivos e de outros fatores agressivos além dos bem conhecidos *H. pylori* e medicamentos anti-inflamatórios não-esteróides, desde que esses dois agentes não cobrem todo o espectro de causas.

DESCRIPTORES - Úlcera péptica. Úlcera gástrica. Úlcera duodenal. Infecções por *Helicobacter*.

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