CONCEPTS AND CONTROVERSIES IN DISORDERS OF UPPER GASTROINTESTINAL TRACT

Nwokediuko SC, Ijoma U, Obienu O and Anigbo G

Gastroenterology Unit, Department of Medicine, University of Nigeria Teaching Hospital Ituku/Ozalla, Enugu State, Nigeria.

Corresponding Author: Prof. Sylvester C. Nwokediuko, Gastroenterology Unit, Department of Medicine, University of Nigeria Teaching Hospital, Ituku/Ozalla, PMB 01129, Enugu, Enugu State, Nigeria. *E-Mail:* sylvester.nwokediuko@unn.edu.ng, scnwokediuko@yahoo.com; *Phone:* +2348033218181

ABSTRACT

The upper gastrointestinal tract is one part of the digestive system where tremendous innovations and advancements in knowledge have been recorded in the last several decades. The discovery of Helicobacter pylori by Warren and Marshal in 1983 and the introduction of Rome process for the classification, diagnosis and management of functional gastrointestinal disorders in 1990 set the stage for a plethora of research efforts which have culminated in improvements in the understanding of diseases of upper gastrointestinal tract.

However, there are still wide knowledge gaps and unresolved issues which should attract the attention of researchers. Some of these unresolved issues are highlighted in this review.

Till date, the term "dyspepsia" remains confusing to medical practitioners and physicians, including gastroenterologists. A consensus on the definition has been elusive. Some researchers hold the view that the term should encompass all symptoms emanating from the upper gastrointestinal tract, including symptoms of gastroesophageal reflux disease. Others (including proponents of Rome criteria) maintain that gastroesophageal reflux disease should be separated from dyspepsia. The recent discovery that functional dyspepsia and gastroesophageal reflux disease share a common pathophysiologic mechanism (impaired fundal accommodation) further confounds the argument.

Similarly, functional dyspepsia and gastroparesis are two entities that have more similarities in symptomatology, pathophysiology and response to treatment than differences. Idiopathic gastroparesis has all the signatures of conditions included as functional gastrointestinal disorders in the Rome criteria. Further revisions of Rome criteria are expected to address this.

One curious aspect of Rome IV is the inclusion of reflux hypersensitivity in functional gastrointestinal disorders. This entity is clearly part of gastroesophageal reflux disease. This calls for a new definition for GERD. Belching is grouped under gastroduodenal disorders rather than esophageal disorders for unclear reasons. This seeming misclassification needs to be revisited.

Gastroesophageal reflux disease and eosinophilic esophagitis (EoE) are two conditions that are also more similar than different, especially the variant of EoE that responds to proton pump inhibitors (PPIs). Finally, the geographic enigma in gastric cancer in relation to Helicobacter pylori remains unresolved, despite the plethora of explanations that have been advanced. By highlighting these unresolved issues, future researchers are expected to remain consistent and focused in the search for answers.

INTRODUCTION

The upper gastrointestinal tract (UGIT) consists of the bucal cavity, pharynx, esophagus, stomach and duodenum. For gastroenterologists and for purposes of endoscopy, the UGIT includes the esophagus, stomach and duodenum. There have been numerous remarkable innovations and technological advancements in disorders of UGIT in the last several decades. Of the novelties recorded, the discovery of Helicobacter pylori (HP) and the introduction of Rome process in functional gastrointestinal disorders (FGIDs) have had an overarching influence in shaping clinical management strategies and research efforts in this area of gastroenterology.

Helicobacter pylori is one of the most prevalent bacterial infections in the globe, affecting approximately 50% of the world population[1]. Warren and Marshall were the first to describe this organism in gastric biopsies in 1983[2]. This Gram-negative bacillus infects the human gastric mucosa and produces chronic gastritis, peptic ulcer disease, distal gastric adenocarcinoma and mucosa-associated lymphoid tissue (MALT) lymphoma[3]. Helicobacter pylori may also be associated with extra-gastrointestinal disorders such as immune thrombocytopenic purpura, refractory iron deficiency anemia and vitamin B12 deficiency[1,4,5].

The Rome process is an international effort to help in the diagnosis and treatment of FGIDs by creating scientific data. Since 1989 when the first set of criteria was developed, there have been 4 other revisions (Rome I, II, III and IV). The Rome foundation has sought to maintain a strong knowledge base. The latest version (Rome IV) was launched in May 2016 and it includes a new definition for FGIDs, diagnostic criteria, inclusion of new entities, and major changes in criteria for diagnosis of existing disorders[6]. The FGIDs, currently called "disorders of gut-brain interaction", are classified by symptoms related to any combination of disturbance of motility, visceral hypersensitivity, altered mucosal and immune function, altered gut microbiota and altered central nervous system processing.

These and other advancements in knowledge have thrown up several controversies and unresolved issues. This review aims at bringing some of these contentious issues to the front burner not just for purposes of stimulating more research but to keep researchers focused in the search for explanations.

An electronic literature search was conducted in turn on selected disorders of upper gastrointestinal tract using PubMed, Google scholar, and Scopus. The disorders were Dyspepsia, GERD, Gastroparesis, Belching, Eosinophilic esophagitis, Helicobacter pylori and Gastric cancer. The search words used in each case were Controversies, Unresolved issues, plus the specific disorder. From the articles retrieved in the first round of search, additional references were manually identified from the cited references.

Confusion in Nomenclature

Dyspepsia remains a confusing term. Classifications that preceded Rome III diagnostic criteria included heartburn and regurgitation as part of dyspepsia but the Rome III diagnostic criteria[7] restricted dyspepsia to disorders thought to originate from the gastroduodenal region. Heartburn and regurgitation, which are typical symptoms of gastroesophageal reflux disease (GERD) were excluded from dyspepsia. Subsequently, it was argued that excluding heartburn in functional dyspepsia (FD) studies was misguided as new data indicated that heartburn and regurgitation occurred frequently in FD even after GERD had been objectively excluded[8]. These led to the concept that heartburn and dyspepsia are really part of one disease complex. In real life scenarios, patients from communities who present to primary care physicians complain of multiple upper gastrointestinal symptoms, making symptom-based diagnoses difficult[9]. Up to 20% of patients with FD may also have GERD if pH-metry is used[10,11].

Evidence that FD and GERD are part of the same disease spectrum in a major subset is accumulating. The normal fundal relaxation that follows a meal is lost in a subset of patients (up to 40%) with FD. This is termed fundal dysaccomodation[12]. Functional dyspepsia patients have a higher frequency of occurrence of GERD symptoms than expected by chance[8]. Recent research findings indicate that transient lower esophageal sphincter relaxation (TLESR), which is the underlying mechanism of GERD, has a close link with gastric accommodation. Individuals with gastric accommodation dysfunction will experience more heartburn and this explains the relationship between GERD and FD[12]. The long held view that GERD is an organic disorder of UGIT as distinct from typical FGIDs like FD is thus challenged. This lends credence

to the subtle attempt in Rome IV to deemphasize the terms, organic and functional and to promote a model in which disease phenotype would be determined by the relative influence of motility, visceral hypersensitivity, altered mucosal and immune function, altered gut microbiota and altered central nervous system processing (Table1).

Table 1

Determinants of phenotypic presentation of gastrointestinal disease (Rome IV model)

Motility disturbance
Visceral hypersensitivity
Altered mucosal and immune function
Altered gut microbiota
Altered central nervous system processing.

This paradigm change, when fully implemented is likely to herald a new dawn in the classification of diseases of gastrointestinal tract (GIT).

Functional Dyspepsia and Gastroparesis

Functional dyspepsia and gastroparesis are two sensorimotor disorders of upper gastrointestinal tract. Both conditions present with epigastric pain or discomfort, easy satiety, postprandial fullness and pressure, nausea, vomiting and weight loss[13-15]. In a major subset of patients with FD the underlying mechanism is impairment of fundal accommodation while gastroparesis is caused by impaired gastric emptying. Unfortunately, these pathophysiologic events do not produce specific symptoms that are useful in the clinical differentiation of the two conditions. Furthermore, studies in both idiopathic and diabetic gastroparesis have identiûed other mechanisms, including visceral hypersensitivity and impaired gastric accommodation (typical pathophysiologic mechanisms in FD) as stronger determinants of the symptom pattern and severity[16,17]. Patients with FD who have abnormal fundal accommodation commonly complain of early satiety, epigastric pain and discomfort, postprandial fullness and nausea. However FD patients without impaired fundal accommodation may also present with similar symptoms[18,19]. Similarly, patients with gastroparesis (defined as delayed gastric emptying of solid food meal in the absence of mechanical obstruction) present with epigastric pain, postprandial fullness, nausea and vomiting. Furthermore, up to 30% of FD patients have delayed gastric emptying[14,20]. Therefore, neither history nor pathophysiologic mechanisms can satisfactorily separate the two entities (table 2).

Table 2: Overlap of symptoms, pathophysiology and therapeutic options in FD and Gastroparesis

FEATURE	FD	GASTROPARESIS
Symptoms		
Epigastric pain/discomfort	+++	+++
Easy satiety	++	++
Postprandial fullness	++	++
Nausea	+	++
Vomiting	+	+++
Weight loss	+	+
Pathophysiology		
Impaired fundal accommodation	++	+
Impaired gastric emptying	++	+++
Visceral hypersensitivity	++	+
Treatment		
Nutritional support	+	+++
Prokinetics	++ (especially in PDS)	+++
PPI	+	?
TCA	+ (especially in EPS)	+

FD: Functional dyspepsia *PDS: Postprandial distress syndrome* *PPI: Proton pump inhibitor*
TCA: Tricyclic antidepressant *EPS: Epigastric pain syndrome*

A questionnaire was developed to enable effective clinical differentiation but the objectives have remained unachieved because of the high degree of overlap[21]. Six of the 9 questions on the Gastroparesis Cardinal Symptom Index record common symptoms of FD. In an attempt to break up disorders of gastric sensorimotor function into specific entities along pathophysiologic lines, there is a tendency to lose the uniqueness of the broad category.

Whereas FD is the prototype FGID, and gastroparesis has remained an organic entity, it is highly probable that future revisions of Rome criteria might include gastroparesis in the FGID in keeping with the proposal to deemphasize the terms, organic and functional.

Inclusion of Hypersensitive Esophagus (Reflux Hypersensitivity) in FGIDs

One of the changes that were made in Rome III to develop Rome IV is the addition of an entity with known etiology. The reflux hypersensitive syndrome[22] (now part of esophageal disorders in Rome IV) encompasses patients who have normal acid levels (on pH-metry) but are sensitive to the physiological reflux and so develop heartburn. These patients used to be grouped under GERD and by definition, they actually have GERD. Gastroesophageal reflux disease as defined by the Montreal consensus group[23] is "a condition which develops when the reflux of stomach contents causes troublesome symptoms and/or complications". The removal of reflux hypersensitivity from GERD clearly calls for a new definition for GERD to avoid confusion in nomenclature.

Reflux Esophagitis, Non Erosive Reflux Disease (NERD), Reflux Hypersensitivity and Functional Heartburn

The pathophysiological relationship between non erosive reflux disease (NERD) and reflux esophagitis remains unresolved[24]. The thinking that NERD and reflux esophagitis are components of a continuous pathological spectrum has been challenged by studies that demonstrated differences in pathophysiology, epidemiology and response to therapy[25,26]. Mechanistic natural history studies have yielded inconsistent results[27-29] but in general, there is a suggestion that lack of progression of NERD to reflux esophagitis is more common than progression. Based on these, Fass and Ofman[30] proposed that patients with GERD exhibit 3 different phenotypes: NERD, reflux esophagitis and Barrett's esophagus and that most NERD and reflux esophagitis patients remain within their respective GERD phenotype throughout their life time. This new paradigm proposes that the genetic make-up of individuals exposed to similar environmental factors may ultimately determine the specific GERD phenotype[26,30].

The most recent attempt at elucidating the mechanisms at play in erosive esophagitis and NERD is provided in Rome IV criteria for the diagnosis of FGID[22]. The definition of GERD is more restrictive as reflux hypersensitivity now leans more towards the functional realm than true GERD. This schema proposes that reflux esophagitis, NERD, and functional heartburn are components of a disease spectrum allowing for overlaps[22]. The main determinants of phenotypic presentation here are esophageal hypersensitivity and acid exposure. Symptoms in erosive esophagitis are dominated by abnormal acid exposure whereas symptoms in functional heartburn are dominated by hypersensitivity. Symptoms in NERD and reflux hypersensitivity are related to a combination of both acid exposure and hypersensitivity[22].

In Rome II, reflux hypersensitivity (hypersensitive esophagus) was part of functional heartburn, but was removed from that group in Rome III. At the same time it became part of GERD as Rome III and Montreal consensus definition of GERD were published the same year (2006). In Rome IV, reflux hypersensitivity is back to FGID (esophageal disorders). The "ding-dong" that has characterized the exercise is a strong testimony to the seeming poor understanding of the mechanisms and unresolved nature of the issues. Furthermore, the role of weakly acid reflux in generating symptoms and esophagitis remains to be elucidated.

GERD and Eosinophilic Esophagitis

Eosinophils are a type of white blood cells that have coarse granules within their cytoplasm. They play an important role in the body's response to allergic reactions, asthma and parasitic infections. Sometimes, eosinophils cause inflammation in certain organs and result in symptoms.

Eosinophilic esophagitis (EoE) is a chronic, immune mediated disorder defined by symptoms of esophageal dysfunction, eosinophilic inflammation

localized to the esophagus, and exclusion of other recognized causes of esophageal eosinophilia[31,32]. Diagnosis requires symptoms of esophageal dysfunction, 15 or more eosinophils per high power field on microscopic examination of esophageal biopsy after 8 weeks of high dose proton pump inhibitor (PPI), and the absence of alternative causes of eosinophilia[31-33].

Symptoms of GERD and EoE are similar. Some efforts have been made at highlighting the differences between the 2 entities[34], but esophageal eosinophilia is common to both conditions, though GERD usually produces less florid infiltration of the esophagus by eosinophils that are concentrated in the distal esophagus[35]. Surprisingly, up to 40% of patients with EoE respond to PPI, with the result that there is a third variant called PPI-responsive eosophageal eosinophilia (PPI-REE)[36]. Efforts at explaining this strange occurrence have thrown up several postulations, with varying levels of evidence. The postulations include:

1. ***Eosinophilia is a marker of GERD***
   Mild eosinophilia is a marker of GERD[37,38], however, a study has indicated that it is distinctly uncommon to have dense esophageal eosinophilia in patients with GERD[39].
2. ***GERD and EoE can co-exist but are unrelated***
   The basis for this hypothesis is the high prevalence of GERD in the general population and the expectation that chance alone can account for a high prevalence of GERD in patients with EoE[40].
3. ***EoE contributes to or causes GERD***
   It is postulated that products of eosinophils such as vasoactive intestinal peptide (VIP) and platelet activating factor may induce lower esophageal sphincter (LES) relaxation and give rise to GERD[41,42].
4. ***GERD contributes to or causes EoE***
   Dilatation of intercellular spaces of esophageal squamous epithelium occurs in GERD[43,44]. This can lead to increased permeability, leading to penetration by antigens in food leading to EoE.

The mechanism of response to PPI in PPI-REE remains unresolved. The postulations are that the response to PPI may be through an acid-dependent mechanism[45,46] or through an acid-independent, anti-inflammatory pathway[47-49]. In summary, despite all the research efforts to elucidate the differences between EoE and GERD, there is a very high degree of overlap between them and numerous questions remain unanswered.

Belching

Belching (eructation) can be defined as the audible oral expulsion of a gas bolus from the upper GIT. In most individuals, belching occurs as a physiological event and is not perceived as a symptom of disease. However, belching becomes a medical problem and reason for consultation if it is excessive, such that the patient or those around him complain. It may lead to social problems and a decreased quality of life[50].

Belching can occur from one of two mechanisms: gastric belch, which is the result of a vagally mediated reflex that leads to relaxation of LES and venting of gastric air; and supra-gastric belch, which is largely a behavioral peculiarity. In supra-gastric belch, pharyngeal air is sucked or injected into the esophagus, after which it is immediately expelled before it reaches the stomach. Patients who belch excessively invariably exhibit an increased incidence of supra-gastric, not gastric belches.

Traditionally anatomic regions are used to categorize the FGIDs in adults. In Rome III and Rome IV diagnostic criteria[6,7], belching is included in gastroduodenal disorders despite the fact that the symptom is more esophageal than gastric. Gastric belch actually resembles GERD as the underlying event is relaxation of LES[51-53]. The only difference is that in the former the refluxate is wholly or predominantly gas while in the latter it is liquid. If reflux hypersensitivity (which used to be part of GERD in Rome III) is grouped under esophageal disorders, what prevents gastric belch from being categorized as an esophageal disorder? More curious is the fact that the predominant form of belch is supra-gastric belch. The pathophysiologic events that lead to supra-gastric belch do not involve the stomach. The air sucked or injected from the pharynx is expelled from the esophagus immediately it gets there. The air neither originates from the stomach nor reaches it[54].

Similarly, the rumination syndrome (characterized by regurgitation) is more esophageal than gastroduodenal as the pathophysiologic mechanism resembles that of GERD. In GERD, reflux hypersensitivity and rumination syndrome, the

retrograde flow of gastric content is usually effortless, as distinct from vomiting. Nausea and vomiting disorders are appropriately included in gastroduodenal disorders. Appropriate grouping of various disorders would reduce confusion in the classification and management of the FGIDs, a domain that is already bedeviled by numerous controversies and unresolved issues.

Geographical Enigmas of *Helicobacter pylori* (HP) and Gastric Cancer

The discovery of HP by Warren and Marshall[2] opened the floodgate of research into the relationship between the organism and various gastroduodenal diseases. Helicobacter pylori causes acute and chronic gastritis, duodenal ulcer, gastric ulcer, and distal gastric adenocarcinoma[55,56]. Helicobacter pylori has been classified as a group 1 carcinogen[57], same category as tobacco and asbestos. Globally, HP is the strongest known risk factor for gastric cancer[58,59].

However, Holocombe[60] in 1992 observed the incongruence between HP prevalence and gastric cancer in Africa. In Africa, the prevalence of HP infection is high but the incidence of gastric cancer is low. This was described as the African enigma. Similar enigmas have been described in China, Colombia, Costa Rica, India and Malaysia[61]. The prevalence of HP in a population is clearly not the only determinant of gastric cancer risk. The major factors that have been advanced to explain this geographical enigma include:

1. Oncogenic potential of HP

Strain-specific properties of HP associated with gastric cancer have been described. These include:

(a.) *The cag pathogenicity island (PAI):* The presence of a chromosomal region called cag PAI is one of the striking variations among HP strains from unrelated persons. The cag PAI encodes an antigenic effector protein called cagA into host cells through a type IV secretion system (T4SS)-mediated process[62,63]. The T4SS is also required for HP-induced upregulation of proinflammatory cytokine secretion by gastric epithelial cells[64]. There is ample evidence to show that the risk of stomach cancer or precancerous lesions is higher in persons infected with cagA-positive HP strains than in persons infected with cagA-negative strains[65,66]. Furthermore, strains producing high levels of cagA are linked to an increased risk of premalignant lesions compared to strains producing lower levels of cagA[67,68].

(b.) *Vacuolating toxin:* A protein called VacA is secreted by HP through an autotransporter or type V secretion pathway[69,70]. Most VacA-induced cellular alterations result from the ability of the organism to form pores in cell membranes[71,72]. Strains containing vacA alleles classified as s1,i1 or m1 (which encode the more active forms of vacA) are associated with a high risk of stomach cancer or precancerous lesions (such as intestinal metaplasia) than strains classified as s2, i2 or m2[71,73,74].

Other virulence factors that have been described in HP are outer membrane proteins (OMP) and duodenal ulcer promoting gene (DUPA). Associations of specific OMPs or dupA with gastric cancer are not as striking as those of cagPAI and vacA. There may also be interactions by multiple strain-specific features with the result that the risk of gastric cancer is highest in individuals infected with strains harboring multiple constituents and lowest among strains harboring few or none of the constituents[75,76]. In all, there is a spectrum of strains, ranging from those that carry a very low risk to those that are associated with high risk of gastric cancer.

2. Th2 type response to HP

Cytokines are the chemical messengers of the immune system. They are either pro-inflammatory or anti-inflammatory. Anti-inflammatory cytokine es tend to promote allergic responses and are associated with high IgE levels.

T lymphocytes expressing CD4, also known as helper T cells are the most prolific cytokine producers. They can be subdivided into Th1 and Th2 and the cytokines they produce are known as Th1-type and Th2-type cytokines. Th1-type cytokines, being pro-inflammatory, are

responsible for killing intracellular parasites. They also perpetuate autoimmune responses. Typical Th1 cytokines include interferon gamma, tumor necrosis factor alpha (TNF-á), and IL-2â. If pro-inflammatory cytokines are excessively elaborated in the course of an immune reaction, the result is uncontrolled tissue damage. To counteract this, the Th2 cytokines which are anti-inflammatory come into action. Typical Th2-type cytokines include Interleukin 4, 5 and 13 which are associated with promotion of IgE and eosinophilic responses in atopy. Interleukin-10 also has anti-inflammatory response. In normal situations, humans produce a well-balanced Th1 and Th2 response suited to the immune challenge.

In experimental animals, a Th2 type response has been induced by co-infection of mice with HP and nematodes[77] with resultant protection against gastric atrophy (which is a premalignant lesion). Similarly, the specific IgG subclass response to HP in sub-Saharan Africa is predominantly IgG1, which suggests a Th2 response[78]. This modulation is thought to be related to intestinal parasites. Colombian researchers also demonstrated high levels of IgE in the serum and predominance of eosinophilic infiltration in the gastric mucosa of populations at low risk of gastric cancer compared to those at high risk[79]. This particular explanation sounds plausible in Africa where intestinal parasitosis is rife.

3. Role of diet

Dietary components can modulate HP pathogenicity by mechanisms that range from simple anti-oxidant to complex anti-carcinogenic activities. Dietary habits may be an important determinant of the outcome of HP infection. High salt diet and a diet low in fruits and fresh vegetables have been associated with increased gastric cancer risks[80,81]. In India, the compound Curcumin, which has anti-inflammatory properties is found in spices and has been linked to a low risk of gastric cancer[82,83].The mechanisms by which diet influences gastric cancer risk remain to be fully elucidated but is believed to contribute to the geographic enigma of this malignant disease.

4. Host genetic susceptibility

Expression of inflammatory cytokines is the hallmark of immune response to microbial infections. Polymorphisms in genes of these cytokines may affect outcomes in HP infection. Polymorphisms in gene cluster of IL-1 (a pro-inflammatory cytokine with potent acid suppressive effect) have been associated with gastric cancer risk[84,85]. Ethnicity may also play a crucial role, for example, the Japanese population has much lower acid secretion as compared to western population[86].

5. Gastric microbiota

Analogous to the influence of colonic microbiota on human health and disease[87], the gastric microbiota may influence gastric immunobiology and possibly gastric disease. Results from animal and human studies indicate that gastric colonization by bacteria that normally colonize the lower GIT could affect the outcome of HP infection and the risk of gastric cancer[88-91]. Helicobacter pylori is closely associated with gastric cancer, but the role of other intragastric flora in facilitating or inhibiting the effect of HP in gastric cancer development remains unknown.

6. Co-evolution of HP and human host

Co-evolution of HP and human hosts over a long time determines the development of commensal or symbiotic relationship. This was demonstrated in a study in Colombia which revealed that individuals of African descent had relatively benign gastric pathology with little evidence of progression to malignancy[92]. Co-evolution of HP and humans over a long time explains the low incidence of disease in these populations. Mismatch between the geographic origin of HP strains and the geographic ancestry of human hosts has been associated with more severe gastric pathology and development of precancerous gastric lesions[92], and this further supports the hypothesis. In other words, disruption in co-evolved bacterial-human relationships may contribute to elevated gastric cancer risk.

Helicobacter pylori and GERD

The controversy that trails the relationship between HP and GERD has continued to rage[93-95]. Although all infected individuals develop histologic gastritis, only a small proportion develop significant clinical disease. About 10-20% of HP-positive patients have a lifetime risk of developing peptic ulcer while only 1-2% run the risk of developing distal gastric cancer[96,97]. The outcome of infection is influenced by a variety of host, bacterial and environmental factors. The acute phase of gastritis is usually not clinically apparent, but in specific experimentally monitored situations[98-102] it may be associated with transient dyspeptic symptoms such as nausea, fullness, and vomiting which are largely non-specific. During acute infections the proximal and distal stomach are usually equally affected (pangastritis), which is often associated with hypochlorrhydria. The hypochlorrhydria tends to resolve within months, but persistent infection may occur in individuals who are genetically predisposed as shown by studies on monozygotic twins[99,102]. For individuals who progress to chronic gastritis, the distribution of gastritis is determined by the level of acid secretion. This results from the interplay between the effect of acid on the growth of bacteria and the resultant effect of mucosal inflammation on acid secretion.

The eventual outcome of HP infection is determined by this interaction. In individuals in whom acid secretion remains intact, the organism tends to colonize the antrum where few acid-producing cells are present. This results in gastritis that is antrum-predominant. Conversely, in individuals in whom acid secretion has been impaired, the distribution of the organism is more diffuse, involving both the antrum and body, and organisms in the body are in closer contact with the mucosa giving rise to a corpus-predominant pangastritis[103]. Corpus gastritis from HP often leads to hypochlorrhydria and eradication therapy leads to an increase in acid secretion[104,105]. Furthermore, in corpus-predominant HP-induced gastritis, the acid-suppressive effect of PPIs is augmented by the hypochlorrhydria that is inherent in the pathology[106]. It has been shown that HP-positive patients with GERD respond faster to PPI treatment[107] but the significance of this observation in the routine care of patients remains to be determined. Currently, no guideline recommends the determination of HP status before treatment decisions are made in GERD. However, it is common knowledge that subjects who exhibit pro-inflammatory genotypes have a higher risk of corpus-predominant pangastritis, predisposing them to atrophic gastritis, intestinal metaplasia and gastric cancer[84].

Epidemiologic studies clearly support the suggestion of a protective role of HP against GERD, Barrett's esophagus and esophageal adenocarcinoma[108-110]. However one meta-analysis showed no association between HP eradication and development of new cases of GERD in patients with dyspepsia[110], but a recent randomized controlled study in Asia reported an increased prevalence of reflux esophagitis following HP eradication[111]. The period of follow-up was different in the two studies and that may explain the discrepancy. More prospective studies are needed to throw more light on the relationship. The best that can be said of this association is that epidemiological studies show a negative association between the prevalence of HP and the severity of GERD and incidence of esophageal adenocarcinoma, but the effect of HP status on symptom severity, symptom recurrence and treatment efficacy in GERD is as yet unsettled. Eradication of HP does not exacerbate pre-existing GERD or affect treatment efficacy[112,113]. Since long term PPI may be associated with an increased risk of gastric premalignant lesions such as atrophic gastritis, HP eradication in GERD patients is justifiable [114,115].

In conclusion, the UGIT has been the epicenter of research in the last several decades. Numerous discoveries and improvements in knowledge have been recorded, but several issues remain unresolved. The Rome process has specifically impacted positively in the understanding and management of FGID, but several issues remain controversial and are expected to be subjects of research in the near future.

REFERENCES

1. Malfertheiner P, Megraud F, O'Morain CA, Atherton J, Axon ATR, Bazzoli F, *et al.* Management of Helicobacter pylori infection–the Maastricht IV/Florence consensus report. Gut 2012; 61: 646–664.
2. Marshall BJ and Warren JR. Unidentiûed curved bacilli in the stomach of patients

with gastritis and peptic ulceration. Lancet 1984; 1: 1311–1315.
3. Vakil N and Megraud F. Eradication therapy for Helicobacter pylori. Gastroenterology 2007; 133: 985–1001.
4. Banic' M, Franceschi F, Babic Z and Gasbarrini A. Extragastric manifestations of Helicobacter pylori infection. Helicobacter 2012; 17(Suppl. 1): 49–55.
5. Chen B-F, Xu X, Deng Y, Ma SC, Tang LQ, Zhang SB *et al.* Relationship between Helicobacter pylori infection and serum interleukin18 in patients with carotid atherosclerosis. Helicobacter 2013; 18: 124–128.
6. Drossman DA. Functional gastrointestinal disorders: history, pathophysiology, clinical features, and Rome IV. Gastroenterology 2016; 150: 1262-1279.
7. Drossman DA. The functional gastrointestinal disorders and the Rome III process. Gastroenterology 2006; 130: 1377-1390.
8. Vakil NH, Halling K, Ohlsson L and Wernersson B. Symptom overlap between postprandial distress and epigastric pain syndrome of Rome III dyspepsia classification. Am J Gastroenterol 2013; 108: 767-774.
9. Veldhuyzen van Zanten S, Armstrong D, Barkun A, Junghard O, White RJ and Wiklund IK. Symptom overlap in patients with UGI complaints in the Canadian confirmatory acid suppression test (CAST) study: further psychometric validation of the reflux disease questionnaire. Aliment Pharmacol Ther 2007; 25: 1087-1097.
10. Tack J, Caenepeel P, Arts J, Leek J, Sifrim D and Janssens J. Prevalence of acid reflux in functional dyspepsia and its association with symptom profile. Gut 2005; 54: 1370-1376.
11. Xiao YL, Peng S, Tao J, Wang A, Lin J, Hu P *et al.* Prevalence and symptom pattern of pathologic esophageal acid reflux in patients with functional dyspepsia based on the Rome III criteria. Am J Gastroenterol 2010; 105: 2626-2631.
12. Pauwels A, Altan E and Tack J. The gastric accommodation response to meal intake determines the occurrence of transient lower esophageal sphincter relaxations and reflux events in patients with gastroesophageal reflux disease. Neurogastroenterol Motil 2014; 26: 581-588.
13. Tack J, Talley NJ, Camilleri M, Holtmann G, Hu P, Malagelada JR *et al*. Functional gastroduodenal disorders. Gastroenterology 2006; 130: 1466–1479.
14. Parkman HP, Hasler WL and Fisher RS. American Gastroenterological Association technical review on the diagnosis and treatment of gastroparesis. Gastroenterology 2004; 127: 1592–1622.
15. Delgado-Aros S, Camilleri M, Cremonini F, Ferber I, Stephens D and Burton DD. Contributions of gastric volumes and gastric emptying to meal size and postmeal symptoms in functional dyspepsia. Gastroenterology 2004; 127: 1685–1694.
16. Karamanolis G, Caenepeel P, Arts J and Tack J. Determinants of symptom pattern in idiopathic severely delayed gastric emptying: gastric emptying rate or proximal stomach dysfunction? Gut 2007;56: 29–36.
17. Kumar A, Attaluri A, Hashmi S, Schulze KS and Rao SS. Visceral hypersensitivity and impaired accommodation in refractory diabetic gastroparesis. Neurogastroenterol Motil 2008; 20: 635–642.
18. Karamanolis G, Caenepeel P, Arts J and Tack J. Association of the predominant symptom with clinical characteristics and pathophysiological mechanisms in functional dyspepsia. Gastroenterology 2006; 130: 296-303.
19. Van Lelyveld N, Schipper M and Samsom M. Lack of relationship between chronic upper abdominal symptoms and gastric function in functional dyspepsia. Dig Dis Sci 2008; 53: 1223-1230.
20. Abell TL, Bernstein RK, Cutts T, Farrugia G, Forster J, Hasler WL *et al.* Treatment of gastroparesis: a multidisciplinary clinical

review. Neurogastroenterol Motil 2006; 18: 263-283.

21. Cassilly DW, Wang YR, Friedenberg FK, Nelson DB, Maurer AH and Parkman HP. Symptoms of gastroparesis cardinal symptom index in symptomatic patients referred for gastric emptying scintigraphy. Digestion 2008; 78:141-151.
22. Aziz Q, Fass R, Gyawali CP, Miwa H, Pandolfino JE and Zerbib F. Esophageal disorders, FGID: Diagnostic groups. Gastroenterology 2016; 150: 1368-1379.
23. Vakil N, van Zanten SV, Kahrilas P, Dent J and Jones R. Global Consensus Group. The Montreal definition and classification of gastroesophageal reflux disease: a global evidence-based consensus. Am J Gastroenterol 2006; 101: 1900-1920.
24. Quigley EM. Gastroesophageal reflux disease spectrum or continuum? QJM 1997; 90: 75-78.
25. Fass R. Erosive esophagitis and non-erosive reflux disease (NERD): comparison of epidemiologic, physiologic and therapeutic characteristics. J Clin Gastroenterol 2007; 41: 131-137.
26. Fass R. Non-erosive reflux disease (NERD)- a spectrum of disease or special entities? Z Gastroenterol 2007; 45: 1156-1163.
27. Labenz J, Nocon M, Lind T, Leodolter A, Jaspersen D, Meyer-Sabellek W *et al.* Prospective follow-up data from the ProGERD study suggest that GERD is not a categorical disease. Am J Gastroenterol 2006; 101: 2457-2462.
28. Sontag SJ, Sonnenberg A, Schnell TG, Leya J and Metz A. The long-term natural history of gastroesophageal reflux disease. J Clin Gastroenterol 2006; 40: 398-404.
29. Bardhan KD, Royston C and Nayyar AK. Reflux rising! An essay on witnessing a disease in evolution. Dig Liver Dis 2006; 38: 163-168.
30. Fass R and Ofman J. Gastroesophageal reflux disease-should we adopt a new conceptual framework? Am J Gastroenterol 2002; 97: 1901-1909.
31. Dellon E, Gonsalves N, Hirano I, Furuta G, Liacouras C and Katzka D. ACG clinical guideline: evidenced based approach to the diagnosis and management of esophageal eosinophilia and eosinophilic esophagitis (EoE). Am. J. Gastroenterol 2013; 108: 679–692.
32. Liacouras C, Furuta G, Hirano I, Atkins D, Attwood SE, Bonis PA *et al.* Eosinophilic esophagitis: updated consensus recommendations for children and adults. J. Allergy Clin. Immunol. 2011; 128: 3–20.
33. Spechler, S. J., Genta, R. M. and Souza, R. F. Thoughts on the complex relationship between gastroesophageal reflux disease and eosinophilic esophagitis. Am. J. Gastroenterol 2007; 102: 1301–1306.
34. Kia L and Hirano I. Distinguishing GERD from eosinophilic oesophagitis: concepts and con troversies. Nat Rev Gastroenterol Hepatol doi:10.1038/nrgastro.2015.75
35. Odze RD. Pathology of eosinophilic esophagitis: what the clinician needs to know. Am J Gastroenterol 2009; 104: 485–490.
36. Brown, L. F., Goldman, H. and Antonioli, D. A. Intraepithelial eosinophils in endoscopic biopsies of adults with reflux esophagitis. Am J Surg Pathol 1984; 8: 899–905.
37. Ma J, Altomare A, Guarino M, Cicala M, Rieder F, Fiocchi C, *et al.* HCl-induced and ATP-dependent upregulation of TRPV1 receptor expression and cytokine production by human esophageal epithelial cells. Am J Physiol Gastrointest Liver Physiol 2012; 303: G635–G645.
38. Souza R,Huo X, Mittal V, Schuler CM, Carmack SW, Zhang HY, Zhang X, *et al.* Gastroesophageal reflux might cause esophagitis through a cytokine-mediated mechanism rather than caustic acid injury. Gastroenterology 2009; 137: 1776–1784.
39. Attwood, S. E., Smyrk, T. C., Demeester, T. R. and Jones, JB. Esophageal eosinophilia with dysphagia. A distinct clinicopathologic syndrome. Dig Dis Sci1993; 38: 109–116.

40. Shaheen, N and Provenzale, D. The epidemiology of gastroesophageal reflux disease. Am J Med Sci 2003; 326: 264–273.
41. Cheng L, Harnett KM, Cao W, Liu F, Behar J, Fiocchi C *et al*. Hydrogen peroxide reduces lower esophageal sphincter tone in human esophagitis. Gastroenterology 2005; 129: 1675–1685.
42. Farre, R., Auli, M., Lecea, B., Martinez, E. and Clave, P. Pharmacologic characterization of intrinsic mechanisms controlling tone and relaxation of porcine lower esophageal sphincter. J Pharmacol Exp Ther 2006; 316: 1238–1248.
43. Calabrese C, Fabbri, Bortolotti M and Febo GD. Dilated intercellular spaces as a marker of oesophageal damage: comparative results in gastro-oesophageal reflux disease with or without bile reflux. Aliment Pharmacol Ther 2003;18: 525–532.
44. Ravelli A M, Villanacci V, Ruzzenenti N, Grigolato P, Tobanelli P, Klersy C *et al*. Dilated intercellular spaces: a major morphological feature of esophagitis. J Pediatr Gastroenterol Nutr 2006; 42: 510–515.
45. Tobey N A, Hosseini SS, Argote CM, Dobrucali AM, Awayda MS and Orlando RC. Dilated intercellular spaces and shunt permeability in nonerosive acid-damaged esophageal epithelium. Am J Gastroenterol 2004; 99: 13–22.
46. van Rhijn B D, Weijenborg PW, Verheij J, van den Weerman MA, Verseijden C,van den Wijngaard RM *et al*. Proton pump inhibitors partially restore mucosal integrity in patients with proton pump inhibitor-responsive esophageal eosinophilia but not eosinophilic esophagitis. Clin Gastroenterol Hepatol 2014; 12: 1815–1823.e2.
47. Lapenna D, de Gioia S, Ciofani G, Festi D and Cuccurullo F. Antioxidant properties of omeprazole. FEBS Lett. 1996; 382: 189–192.
48. Kedika, R. R., Souza, R. F and Spechler, S. J. Potential anti-inflammatory effects of proton pump inhibitors: a review and discussion of the clinical implications. Dig Dis Sci 2009; 54: 2312–2317.
49. Cheng E, Souza RF and Spechler SJ. Eosinophilic esophagitis: interactions with gastroesophageal reflux disease. Gastroenterol Clin North Am 2014; 43: 243–256.
50. Bredenoord AJ and Smout AJ. Impaired health-related quality of life in 2010; 22: 1420–1423
51. Wyman JB, Dent J, Heddle R, Dodds WJ, Toouli J and Downton J. Control of belching by the lower oesophageal sphincter. Gut 1990; 31: 639–646.
52. Dent J, Holloway RH, Toouli J and Dodds WJ. Mechanisms of lower oesophageal sphincter incompetence in patients with symptomatic gastrooesophageal reflux. Gut 1988; 29:1020 –1028.
53. Kessing BF, Conchillo JM, Bredenoord AJ, Conchillo JM, Bredenoord AJ, Smout AJ and Masclee AA. Review article: the clinical relevance of transient lower oesophageal sphincter relaxations in gastro-oesophageal reflux disease. Aliment Pharmacol Ther 2011; 33:650 –661.
54. Bredenoord AJ, Weusten BLAM, Sifrim D, Timmer R and Smout AJ. Aerophagia, gastric, and supragastric belching: a study using intraluminal electrical impedance monitoring. Gut 2004; 53: 1561 –1565.
55. Marshall BJ and Windsor HM. The relation of Helicobacter pylori to gastric adenocarcinoma and lymphoma: pathophysiology, epidemiology, screening, clinical presentation, treatment, and prevention. Med Clin North Am 2005; 89(2): 313–344.
56. Kusters JG, van Vliet AHM and Kuipers EJ. Pathogenesis of Helicobacter pylori infection. Clin Microbiol Rev 2006; 19(3):449–490.
57. International Agency for Research on Cancer. IARC monographs on the evaluation of the carcinogenic risks to humans. Schistosomes, liver flukes and Helicobacter pylori. Lyon: International Agency for Research on Cancer, 1994; 61: 177.
58. de Martel C, Forman D and Plummer M. 2013. Gastric cancer: epidemiology and risk

factors. Gastroenterol Clin North Am 2013; 42 : 219–240.
59. IARC Working Group on the Evaluation of Carcinogenic Risks to Humans. 2012. Biological agents. Volume 100 B. A review of human carcinogens. IARC Monogr Eval Carcinog Risks Hum 100: 1–441.
60. Holcombe C. Helicobacter pylori: the African enigma. Gut. 1992; 33: 429–431.
61. Ghoshal UC, Chaturvedi R and Correa P. The enigma of Helicobacter pylori infection and gastric cancer. Indian J Gastroenterol 2010; 29(3): 95–100.
62. Tegtmeyer N, Wessler S and Backert S. Role of the cag-pathogenicity island encoded typeIV secretion system in Helicobacter pylori pathogenesis. FEBS J 2011; 278:1190–1202.
63. Hatakeyama M. *Helicobacter pylori* CagA and gastric cancer: a paradigm for hit-and-run carcinogenesis. Cell Host Microbe 2014;15: 306–316.
64. Odenbreit S, Püls J, Sedlmaier B, Gerland E, Fischer Wand Haas R. Translocation of Helicobacter pylori CagA into gastric epithelial cells by type IV secretion. Science 2000; 287:1497–1500.
65. Blaser MJ, Perez-Perez GI, Kleanthous H, Cover TL, Peek RM, Chyou PH *et al.* Infection with Helicobacter pylori strains possessing cagA is associated with an increased risk of developing adenocarcinoma of the stomach. Cancer Res 1995; 55: 2111–2115.
66. Plummer M, van Doorn LJ, Franceschi S, Kleter B, Canzian F, Vivas J *et al.* Helicobacter pylori cytotoxin-associated genotype and gastric precancerous lesions. J Natl Cancer Inst 2007; 99:1328–1334.
67. Loh JT, Shaffer CL, Piazuelo MB, Bravo LE, McClain MS, Correa P *et al.* Analysis of cagA in Helicobacter pylori strains from Colombian populations with contrasting gastric cancer risk reveals a biomarker for disease severity. Cancer Epidemiol Biomarkers Prev 2011; 20: 2237–2249.
68. Ferreira RM, Pinto-Ribeiro I, Wen X, Marcos-Pinto R, Dinis-Ribeiro M, Carneiro F *et al.* 23 September 2015. Helicobacter pylori cagA promoter region sequences inûuence CagA expression and interleukin 8 secretion. J Infect Dis. http://dx.doi.org/10.1093/infdis/jiv467.
69. Boquet P and Ricci V. Intoxication strategy of Helicobacter pylori VacA toxin. Trends Microbiol 2012; 20: 165–174.
70. Kim IJ and Blanke SR. Remodeling the host environment: modulation of the gastric epithelium by the Helicobacter pylori vacuolating toxin (VacA). Front Cell Infect Microbiol 2012; 2: 3
71. Rhead JL, Letley DP, Mohammadi M, Hussein N, Mohagheghi MA, Eshagh Hosseini M *et al.* A new Helicobacter pylori vacuolating cytotoxin determinant, the intermediate region, is associated with gastric cancer. Gastroenterology 2007; 133: 926–936.
72. Gangwer KA, Shaffer CL, Suerbaum S, Lacy DB, Cover TL and Bordenstein SR. Molecular evolution of the Helicobacter pylori vacuolating toxin gene vacA. J Bacteriol 2010; 192: 6126–6135.
73. Basso D, Zambon CF, Letley DP, Stranges A, Marchet A, Rhead JL *et al.* Clinical relevance of Helicobacter pylori cagA and vacA gene polymorphisms. Gastroenterology 2008; 135: 91–99.
74. Winter JA, Letley DP, Cook KW, Rhead JL, Zaitoun AA, Ingram RJ *et al.* A role for the vacuolating cytotoxin, VacA, in colonization and Helicobacter pylori-induced metaplasia in the stomach. J Infect Dis 2014; 210: 954–963.
75. Gerhard M, Lehn N, Neumayer N, Borén T, Rad R, Schepp W *et al.* Clinical relevance of the Helicobacter pylori gene for blood-group antigen-binding adhesin. Proc Natl Acad SciUSA 1999; 96:12778–12783.
76. Figueiredo C, Machado JC, Pharoah P, Seruca R, Sousa S, Carvalho R *et al.* Helicobacter pylori and interleukin 1 genotyping: an opportunity to identify high-risk individuals for gastric carcinoma. J Natl Cancer Inst 2002; 94:1680–1687.
77. Fox JG, Beck P, Dangler CA, Beck P, Dangler CA, Whary MT *et al.* Concurrent enteric helminth infection modulates

inflammation and gastric immune responses and reduces helicobacter-induced gastric atrophy. Nat Med. 2000; 6: 536–542.78. Segal I, Ally R, Mitchell H. Helicobacter pylori–an African perspective. QJM. 2001; 94: 561–565.

79. Whary MT, Sundina N, Bravo LE, Correa P, Quinones F, Caro F *et al.* Intestinal helminthiasis in Colombian children promotes a Th2 response to Helicobacter pylori: possible implications for gastric carcinogenesis. Cancer Epidemiol Biomarkers Prev. 2005; 14: 1464–1469.
80. de Martel C, Forman D, Plummer M. Gastric cancer: epidemiology and risk factors. Gastroenterol Clin North Am 2013; 42: 219–240.
81. Cover TL, Peek RM, Jr. Diet, microbial virulence, and Helicobacter pylori-induced gastric cancer. Gut Microbes 2013; 4: 482–493.
82. Bengmark S. Curcumin, an atoxic antioxidant and natural NFkappaB, cyclooxygenase-2, lipooxygenase, and inducible nitric oxide synthase inhibitor: a shield against acute and chronic diseases. JPEN J Parenter Enteral Nutr. 2006; 30: 45–51.
83. Foryst-Ludwig A, Neumann M, Schneider-Brachert W, Naumann M. Curcumin blocks NF-kappa B and the motogenic response in Helicobacter pylori-infected epithelial cells. Biochem Biophys Res Commun. 2004; 316: 1065–1072.
84. El-Omar EM, Carrington M, Chow WH, McColl KE, Bream JH, Young HA *et al.* Interleukin-1 polymorphisms associated with increased risk of gastric cancer. Nature 2000; 404: 398-402.
85. Camargo MC, Mera R, Correa P, Peek RM, Fontham ET, Goodman KJ *et al.* Interleukin-1beta and interleukin-1 receptor antagonist gene polymorphisms and gastric cancer: a meta-analysis. Cancer Epidemiol Biomarkers Prev 2006; 15: 1674-1687.
86. Kinoshita Y, Kawanami C, Kishi K, Nakata H, Seino Y and Chiba T. Helicobacter pylori independent chronological change in gastric acid secretion in the Japanese. Gut 1997; 41: 452-458.
87. Knight ZA, Tan K, Birsoy K, Schmidt S, Garrison JL, Wysocki RW *et al.* Molecular profiling of activated neurons by phosphorylated ribosome capture. Cell. 2012; 151: 1126–1137.
88. Walker MM and Talley NJ. Bacteria and pathogenesis of disease in the upper gastrointestinal tract: Beyond the era of Helicobacter pylori. Aliment Pharmacol Ther 2014; 39: 767–779.
89. Aviles-Jimenez F, Vazquez-Jimenez F, MedranoGuzman R, Mantilla A(3) and Torres J. Stomach microbiota composition varies between patients with non-atrophic gastritis and patients with intestinal type of gastric cancer. Sci Rep 2014; 4: 4202.
90. Sheh A and Fox JG. The role of the gastrointestinal microbiome in Helicobacter pylori pathogenesis. Gut Microbe 2013; 4: 505–531.
91. Martin M and Solnick JV. The gastric microbial community, Helicobacter pylori colonization, and disease. Gut Microbe 2014; 5: 345–350.
92. Kodaman N, Pazos A, Schneider BG, Piazuelo MB, Mera R, Sobota RS *et al.* Human and Helicobacter pylori coevolution shapes the risk of gastric disease. Proc Natl Acad Sci 2014; USA111:1455–1460.
93. Hussein NR, Napaki SM and Atherton JC. A study of Helicobacter pylori-associated gastritis patterns in Iraq and their association with strain virulence. Saudi J Gastroenterol 2009; 15: 125-127
94. Vakil N, Talley NJ, Stolte M, Sundin M, Junghard o and Bolling-Sternevald E. Patterns of gastritis and the effect of eradicating Helicobacter pylori on gastro-oesophageal reflux disease in western patients with non-ulcer dyspepsia. Aliment Pharmacol Ther 2006; 24: 55-63
95. Grande M, Cadeddu F, Villa M, Attinà GM, Muzi MG, Nigro C *et al.* Helicobacter pylori and gastroesophageal reflux disease. World J Surg Oncol 2008; 6:74.
96. Ernst PB and Gold BD. The disease spectrum of Helicobacter pylori: the immunopathogenesis of gastroduodenal

ulcer and gastric cancer. Annu Rev Microbiol 2000; 54: 615–640.

97. Kuipers, EJ. Review article: exploring the link between Helicobacter pylori and gastric cancer. Aliment Pharmacol Ther 1999; 13: 3–12.
98. Kuipers EJ, Pena AS, van Kamp G, Uyterlinde AM, Pals G, Pels NF *et al.* Seroconversion for Helicobacter pylori. Lancet 1993; 342:328–331.
99. Malaty HM, Engstrand L, Pedersen NL and Graham DY. Helicobacter pylori infection: genetic and environmental inûuences. A study of twins. Ann Intern Med 1994; 120: 982–986.
100. Morris A and Nicholson G. Ingestion of Campylobacter pyloridis causes gastritis and raised fasting gastric pH. Am J Gastroenterol 1987; 82: 192– 199.
101. Sobala GM, Crabtree JE, Dixon MF, Schorah CJ, Taylor JD, Rathbone BJ *et al.* Acute Helicobacter pylori infection: clinical features, local and systemic immune response, gastric mucosal histology, and gastric juice ascorbic acid concentrations. Gut 1991; 32: 1415–1418.
102. Kuipers EJ, Uyterlinde AM, Pena AS, Hazenberg HJ, Bloemena E, Lindeman J *et al.* Increase of Helicobacter pylori-associated corpus gastritis during acid suppressive therapy: implications for long-term safety. Am J Gastroenterol 1995; 90: 1401–1406.
103. El-Omar EM, Oien K, El-Nujumi A, Gillen D, Wirz A, Dahill S *et al.* Helicobacter pylori infection and chronic acid hyposecretion. Gastroenterology 1997; 113: 15–24.
104. Ruiz B, Correa P, Fontham ETH and Ramakrishnan T. Antral atrophy, Helicobacter pylori colonization, and gastric pH. Am J Clin Pathol 1996; 105: 96–101.
105. Verdu´ E, Armstrong D, Fraser R, Viani F, Idstro¨m JP, Cederberg C *et al.* Effect of H. pylori status on intragastric pH during treatment with omeprazole. Gut 1995; 36: 539–543.
106. Holtmann G, Cain C and Malfertheiner P. Gastric *Helicobacter pylori* infection accelerates healing of reûux esophagitis during treatment with the proton pump inhibitor pantoprazole. Gastroenterology 1999; 117:11–16.
107. Ronkainen J and Agreus L. Epidemiology of reflux symptoms and GORD. Best Practice and Research Clinical Gastroenterology 2013; 27: 325-337.
108. Fischbach LA, Nordenstedt H, Kramer JR, Gandhi S, Dick-Onuoha S, Lewis A *et al.* The association between Barrett's esophagus and Helicobacter pylori infection: a meta-analysis. Helicobacter 2012; 17: 163-175.
109. Zhuo X, Zhang Y, Wang Y, Zhuo W, Zhu Y and Zhang X. Helicobacter pylori infection and esophageal cancer risk: association studies via evidence-based meta-analysis. Clinical Oncology 2008; 20: 757-762.
110. Yaghoobi M, Farrokyar F, Yuan Y and Hunt RH. Is there an increased risk of GERD after Helicobacter pylori eradication? A meta-analysis. Am J Gastroenterol 2010; 105: 1007-1013.
111. Lee YC, Cheri TH, Chiu HM, Shun CT, Chiang H, Liu TY *et al.* The benefit of mass eradication of Helicobacter pylori infection: a community-based study of gastric cancer prevention. Gut 2013; 62: 676-682.
112. Zagari RM, Romano M, Ojetti V, Stockbrugger R, Gullini S, Annibale B *et al.* Guidelines for management of *Helicobacter pylori* infection in Italy. The III Working Group Consensus Report 2015. Digestive and Liver Disease 2015; 47: 903-912.
113. Malfertheiner P, Megraud F, O'Morain CA, Atherton J, Axon ATR, Bazzoli F *et al.* Management of *Helicobacter pylori* infection-the Maastricht IV/Florence Consensus Report. Gut 2012; 61: 646-664.
114. Moayyedi P, Wason C, Peacock R, Walan A, Bardhan K, Axon ATR *et al.* Changing patterns of Helicobacter pylori gastritis in long-standing acid suppression. Helicobacter 2000; 5: 206-214.
115. Fox JG and Kuipers EJ. Long-term proton pump inhibitor administration, Helicobacter pylori and gastric cancer: lessons from the gerbil. Gut 2011; 60: 567-568.