Peptic Ulcer: Chapter Closed?

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Abstract

The incidence of peptic ulcer disease (PUD) peaked in the late 19th century while transiting into the 20th century. With entry in the new millennium a significant decrease of PUD has occurred. However, demographic changes with an increasing elderly population associated with multiple comorbidities and polypharmacy became responsible for a persistent high rate of peptic ulcer complications. The acid driven concept of PUD has directed the development of surgical procedures and drugs with an increasing potency in acid suppression. High speed of symptom resolution and rapid ulcer healing was obtained with the introduction of proton pump inhibitors, but cure of PUD has failed. The arrival of *Helicobacter pylori* has revolutionized the history of PUD which has become a curable disease by successful cure of the infection. However, new challenges have emerged with an increase of treatment failures due to increasing antibiotic resistance of *H. pylori*. The changing pattern in the prevalence of etiologies other than *H. pylori* demands for accurate identification of the ulcerogenic cause in the individual patient to allow for proper selection of therapy. Management of peptic ulcer bleeding remains a critical clinical challenge. The chapter of PUD is reduced in size and has become more heterogeneous – but is not closed!

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Gastric and duodenal peptic ulcer disease (PUD) has been the plague of the 19th and early 20th century. The incidence of PUD peaked at the time of industrial revolution due to crowding and poor sanitation but presented with significant geographical variations in magnitude and temporal relationship [1]. In the second part of the 20th century, PUD decreased. The decline has primarily been attributed to duodenal ulcers, whereas gastric ulcers remained fairly stable [2]. However, the estimate was that still 1 out of 10 subjects would suffer of PUD during their life time toward the end of the last century [3]. A main clinical characteristic of PUD has always been the chronicity and the trend of cyclical recurrence with peaks during autumn and winter months, reason for frequent severe complications. In spite of the overall decrease of PUD and complications, the mortality rate of peptic ulcer-related complications, bleeding and perforation, has not significantly changed and remains of great concern [4].

Therapy: From Billroth via H₂-Receptor Antagonists to Proton Pump Inhibitor

In 1881, Theodor Billroth performed the first gastric resection in a patient with gastric cancer, and with this operation, he opened the era of resective gastric surgery also for PUD. The variants of Billroth I and II subtotal gastric resection became the predilected treatment of PUD for many decades. The concept of Schwartz “no acid-no ulcer”

Fig. 1. Modern ERA of PUD management. PPI, proton pump inhibitor; PUD, peptic ulcer disease; NSAID, nonsteroidal anti-inflammatory drug.

eventually directed surgery to less demolitive interventions with the introduction of several variations of truncal-, proximal- and highly selective vagotomy aiming at the reduction of gastric acid secretion. The competing medical field focused its efforts on the development of drugs to neutralize or inhibit the gastric acid production [5].

The first drugs used extensively were antacids and a significant list of publications addressed their therapeutic benefit [6]. Due to the regular phenomenon of acid rebound after intake of antacids frequent dosing and large amounts of the neutralizing agent were a necessary requirement. Antacid intake was associated with considerable side effects.

The breakthrough with medical therapy in the management of PUD arrived with the introduction of powerful acid suppressants. The era of H2 receptor antagonists started with cimetidine in the mid-seventies, and some years later, ranitidine became the bestseller of this class of drugs [7]. H2-receptor antagonists became the first to challenge the therapeutic dominance of surgery [8] and reduced the need for surgical vagotomies. The rapid and high healing rate of peptic ulcers with H2-receptor antagonists and the introduction of the novel strategy of maintenance therapy with their long-term intake to prevent ulcer relapses took on successfully [7]. There has, however, remained an Achilles veel with the prolonged use of H2-receptor antagonists because of their loss in acid inhibiting potency over time due to the phenomenon of tachyphylaxis and thus resulting in the insufficient control of ulcer relapses and complications. H2-receptor antagonists did not change the natural history of PUD.

A higher level of gastric acid suppressive potency was reached with the introduction of proton pump inhibitors (PPIs). Omeprazole came first in 1989 and was followed by lansoprazole, pantoprazole, rabeprazole with several further pharmaceutical modifications and galenic formula-

tions (i.e., esomeprazole, dexlansoprazole). The clinical experience with PPI in healing and prevention of peptic ulcer made them advance to the state of art in medical therapy of PUD. Rapid relief of symptoms, rapid healing of the ulcerated lesion, absence of loss in the pharmacological action on long-term use, and the absence of relevant side effects [9–11].

The high performance of acid suppressants, PPIs in primis, overruled all other antiulcerogenic principles, which still deserve to be mentioned as they have played an important role in ulcer therapy during a restricted time period. They included anticholinergic/antimuscarinic drugs (pirenzepine), inhibitors of pepsin (pepstatin), mucosa protectives (sucralfate, misoprostol, bismut salts), gastrin antagonists (proglumide), neuroleptics, and prokinetics. Misoprostol, in some countries, has maintained a modest role for its cytoprotective effect and effective prevention of drug induced peptic ulcerations.

Despite the enormous progress and therapeutic benefit with PPIs in management of PUD they have not completely changed the natural course of the disease as they do not remove the cause. Whenever PPIs are discontinued the ulcers relapse.

The break through arrived with the discovery of *Helicobacter pylori* and the introduction of eradication therapies (Fig. 1).

***H. pylori* Turns Up: Shift of Paradigm and Cure of PUD**

Before the discovery of *H. pylori* many factors were considered of relevance in the pathogenesis of PUD, based on various strengths of evidence.

They included (a) strong evidence for cigarette smoking, drugs (i.e., aspirin), (b) moderate evidence for ge-

netic factors, and (c) lack or equivocal evidence for diet, caffeine, alcohol and psychological stress [2]. None of the epidemiological candidate factors provided sufficient mechanistic plausibility and clinical evidence of causality in PUD. The gastrolesive function of aspirin was recognized as possible cause of a specific drug-related ulceration but is not to be considered within the context of PUD characterized by frequent ulcer relapses. Therefore, the acid-driven pathogenetic concept remained the unifying hypothesis in PUD and as such called for gastric acid suppressant therapy. Potent acid suppression provided rapid healing of peptic mucosal lesions but failed to provide definitive cure of PUD.

The discovery of *Campylobacter pylori* [12] revolutionized the traditional concepts in PUD.

The bacterium renamed *H. pylori* in 1989 after revision of the taxonomic classification changed the natural history of PUD and cure of the disease became a reality through eradication of *H. pylori*. PUD was in complete control with millions of people cured and Marshall et al. [13] were awarded with the Nobel Prize for their discovery.

Chapter Closed?

The chapter on the pathogenesis of PUD had to be rewritten. The long lasting concept of the “acid-mucosal resistance imbalance” although not removed had to be subordinated to the primary pathogenetic role of *H. pylori* infection. *H. pylori*-positive peptic ulcer moved from a primarily acid driven to an infectious disease, and antibiotic therapy has become the standard of care. Successful *H. pylori* eradication therapy guaranteed healing of peptic lesions, prevention of recurrence, and complications. Thus complete cure of PUD could be obtained by the elimination of *H. pylori* [14].

However, the chapter on PUD could not get closed for 2 reasons, one being related to problems inherent to *H. pylori* therapy and the second to the changing pattern in prevalence of ulcer etiologies other than *H. pylori*.

H. pylori Resistance to Antibiotics and Treatment Failure

The treatment of *H. pylori*-induced PUD based on the combination of PPI and 2 antibiotics has initially been highly effective.

The worldwide rise in *H. pylori* resistance to the most effective antibiotics (clarithromycin, metronida-

zole, levofloxacin) used in standard treatment regimen and the absence of novel antibiotic substances poses a serious risk for the successful management of the infection [15, 16]. New therapeutic strategies and treatment modifications including rescue regimens to overcome bacterial resistance may not fully compensate for the increasing rate of treatment failures [17]. Currently, there is promise and high expectation with the introduction of more potent acid suppressants (Pcabs) to render acid-sensitive antibiotics with no *H. pylori* resistance, such as amoxicillin, more effective [18]. A vaccine for primary prevention and therapy is not available but remains auspicious.

Changing Pattern in Peptic Ulcer Prevalence

The significant decrease of *H. pylori*-positive PUD – concerns the duodenal ulcer in particular – in many regions of the world [19] is related to the decreasing prevalence of *H. pylori* infection.

However, other reasons contribute to the declining prevalence of *H. pylori*-induced ulcers and are to be carefully considered. Patients with dyspeptic symptoms tested positive for *H. pylori* by a noninvasive method (serology, urea breath test, fecal antigen test) receive eradication treatment without the objective endoscopic prove of the presence or absence of a peptic ulcer. The same is likely to occur as consequence of repeated PPI intake for dyspeptic symptoms without *H. pylori* testing or because of a false-negative *H. pylori* test in patients with peptic ulcer on PPI on endoscopy [20].

Peptic ulcers are still there and the prevalence of endoscopically detected peptic ulcers in a recent meta-analysis from 3 population-based studies ranged from 4.5% in European countries to 17% in China [21].

In the etiology of PUD because of the aforementioned reasons, the predominance has shifted from *H. pylori* to nonsteroidal anti-inflammatory drugs (NSAID), aspirin, and other gastrolesive substances. The simultaneous presence of *H. pylori* infection in patients treated with drugs harmful to the gastric and duodenal mucosa increased their ulcerogenic potential and the risk for peptic ulcer bleeding [22]. The demographic evolution and an increased elderly population with comorbidities are the reasons for multiple drug intake that harms the stomach. NSAIDs and aspirin are often combined with the use of antithrombotic agents and lead to ulcer complications. Management of peptic ulcer bleeding is a frequent and serious challenge [23].

Table 1. Etiological classification of peptic ulcers [1]

- *Helicobacter pylori* infection
- Drug (i.e., NSAIDs, ASS, SSRI)
- *H. pylori* and NSAIDs positive
- *H. pylori* and NSAIDs negative*
- Acid hypersecretory state (i.e., Zollinger-Ellison syndrome)
- Anastomosis ulcer after subtotal gastric resection
- Tumors (i.e., cancer, lymphoma)

* Requires search for other specific causes.

NSAID, nonsteroidal antiinflammatory drug; ASS, Acetylsalicylic acid; SSRI, Serotonin reuptake inhibitor.

Table 2. Etiological classification of peptic ulcers [2]

Rare specific causes

- Crohn's disease
- Eosinophilic gastroenteritis
- Systemic mastocytosis
- Radiation damage
- Viral infections (e.g., cytomegalovirus or herpes simplex infection, in immunocompromised patients)
- Colonisation of stomach with *H. heilmannii*
- Severe systemic disease
- Cameron ulcer (gastric ulcer where a hiatal hernia passes through the diaphragmatic hiatus)

New kids on the block

- Depression
- Idiopathic ulcer

Several new and specific etiological signatures of peptic ulcers although with a rather low impact concerning their prevalence are of clinical relevance. It is essential requirement for every clinician to qualify the etiology of PUD, as it will lead to the appropriate therapy (Table 1, 2). The definition of idiopathic PUD in the absence of *H. pylori* infection and NSAIDs is still in search for further clarifications.

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Conclusion

The chapter of PUD had to be rewritten by the discovery of *H. pylori*. Cure of PUD has become reality by successful *H. pylori* eradication. Reconciliation of acid targeting principles with antibiotics has changed and saved the lives of millions of people.

PUD has decreased significantly but has not disappeared. The chapter on PUD is not closed. Etiologies are diverse and heterogeneous and demand for selective therapies for controlling PUD and reduce complications. Peptic ulcer complications remain a serious therapeutic challenge.

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