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# Introductory Chapter: Complications of Gastroduodenal Ulcers

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## 1. Introduction

In the past decades, after the widespread therapeutic use of antisecretive drugs (cimetidine, ranitidine, and proton pump inhibitors), the incidence of peptic ulcer disease showed a real and significant decrease. The treatment of the *Helicobacter pylori* infections contributed to these results, demonstrated by the reduced prevalence of these infections [1]. However, the expected reduction in ulcer disease complications did not clearly occur [2, 3]. It is possible to hypothesize a role in the widespread use, also as self-medication, of drugs with gastric injurious side effect such as acetylsalicylic acid (ASA) or nonsteroidal anti-inflammatory drugs (NSAIDs) and besides a role of inaccurate therapy for *H. pylori* infection [4]. Some research studies have shown the role of independent risk factors and a synergic action performed by the use of NSAIDs and the presence of *H. pylori* infection on the evolution of gastroduodenal mucosal impairment/ulceration, ulcer bleeding, and perforation [5]. There are also other significant risk factors of gastroduodenal ulcer occurrence and their complications, such as alcohol consumption, nicotine use, stress life conditions, immunosuppressor therapies, gastric acid hypersecretion states with hypergastrinemia, hyperhistaminemia, etc. [6–8]. In the gastroduodenal site, the mucosal transitional zones are the areas of major risk of development of peptic ulcer because of being exposed to damaging effects of pepsin, gastric acid secretion, bile, and pancreatic juice. The gastric ulcers are usually located along the lesser curvature, in continuousness with the fundus, site of the gastric acid production by the parietal cells. The duodenal ulcers habitually occur in the duodenal bulb and in the prepyloric area.

## 2. Pathophysiology of peptic ulcer and *H. pylori* infection

The pathophysiology of the gastric ulcers is characterized by the reduction of acid secretion, chronic gastritis, duodenogastric reflux of bile and pancreatic juice; on the other hand, in the duodenal ulcers there are elevation of gastric acid secretion, increase of parietal cell mass, and duodenal acid/pepsin charge. The identification of *H. pylori* infection as leading cause of peptic ulcer has completely changed the knowledge of the disease. Briefly we can believe that in the general population, the prevalence of the *H. pylori* infection as cause of peptic ulcer is very high, over 90% of patients with duodenal ulcer and 75% circa of patients with gastric ulcer. Furthermore, the *H. pylori* can be found in the gastroduodenal tract without disease. Usually the *H. pylori* is present in the patients with chronic gastritis

that can develop in atrophic gastritis. The treatment therapies of *H. pylori* infection have been currently performed in the last decades and have shown effective, high recovery rate in peptic ulcer disease [9]. The usual way of the diagnosis is by endoscopic examination, and the medical therapy is currently effective. The complications of peptic ulcers, as bleeding, perforation, outflow obstruction usually require the endoscopic or radiological interventions or in some cases surgical procedures. The *H. pylori* causes damage, injury within the gastroduodenal mucosa followed by inflammatory response with mucosal ulceration. The *H. pylori*, in the gastric lumen, develops defense mechanism with production of urease enzyme, conversion of urea into ammonia and carbon dioxide, gastric acid tamponade, decreasing adverse gastric acidity. The alkalinization of the gastric setting causes decrease of somatostatin production, reduction of gastrin secretion, restriction. In summary, the disruption of secretory balance of gastrin is followed by parietal cell hyperplasia and rise of gastrinemia and gastric acidity [10]. The non-steroidal anti-inflammatory drugs (NSAIDs) and acetylsalicylic acid (ASA) accomplish peptic ulcers by local and systemic actions. These drugs, as acid, develop on gastroduodenal mucosal cells, cytotoxic action, and damage cell proliferation. The systemic action of NSAIDs develops by prevention of gastric prostaglandin output and its protective action versus mucosal damage of acidity by increase of mucus and bicarbonate production and increment of mucosal blood perfusion [11].

## 2.1 Briefly clinical appearance of uncomplicated peptic ulcer

Most evident symptom is the epigastric pain. This symptom can show a characteristic temporal cadency: the pain becomes worse in gastric ulcer after eating, but, on the contrary, it decreases over a period of time in duodenal ulcer after taking some meal. This traditional symptomatological distinction between gastric and duodenal ulcer is no longer the evident clinical data. Often the epigastric pain can be radiated to the back and linked to dyspepsia with the symptoms such as nausea, gastroduodenal reflux, heartburn, belching, etc. The diagnostic program for uncomplicated peptic ulcer encompasses gastroduodenal endoscopy as first step. In the gastric ulcer it is necessary to complete the examination with biopsy of the lesion for the risk of malignancy; endoscopy will be repeated, also with biopsy if it needs, to check for healing after the therapy. In the duodenal ulcer biopsies and further endoscopies are less required. In the diagnosed or suspected peptic ulcer, the test for *H. pylori* is routinely performed as mucosal biopsy for histological and microbiological control or with urease test [12].

## 3. Complications of peptic ulcer

The more frequent complication of peptic ulcer disease (PUD) is the bleeding (hemorrhage), followed by perforation and obstruction [13]. Some differences in the frequency among various complications can be found in the geographic distribution, due to amount of NSAIDs and ASA use, diffusion of *H. pylori* infection, lifestyles of the community. In fact the risk factors for complication occurrence in PUD, as hemorrhage or perforation, are the therapeutic use of NSAIDs or ASA, often as incorrect automedication, and untreated *H. pylori* infection.

### 3.1 Risk factors for peptic ulcer complications

In most cases peptic ulcer hemorrhage is connected with the use of NSAIDs and ASA. The risk degree is dose-dependent: the therapeutic employment of high

dose is a greater risk factor for bleeding, compared with the use of medium or low dose of drugs [14]. The bleeding risk by NSAIDs is also drug-specific, for example, higher for Ketoralac and certainly higher for the synchronous use of aspirin and NSAIDs. Moreover these drugs play a real, concrete role in the occurrence of peptic ulcer perforation [15]. Likewise the presence of *H. pylori* infection is associated with the event of peptic ulcer complications as hemorrhage, but its role and mode of action are debatable in the development of the complication [16]. There are some hypotheses, sometimes conflicting, on the *H. pylori* actions: it was reported that the eradication of *H. pylori* infection reduces the bleeding complication; possible independent action or synergic interaction on peptic ulcer hemorrhage has been described; finally protective effect of *H. pylori* in the occurrence of hemorrhage was also communicated [17]. In some studies there is evidence of the absence of association between *H. pylori* infection and ulcer perforation [18]. Other risk factors for the development of the gastroduodenal ulcer complications, in particular bleeding, are the age over 60 years, associated use of corticosteroid and anticoagulants with NSAIDs, the presence of major comorbidities [19]. We could hypothesize a major incidence of peptic ulcer complications as bleeding or perforation in the patients with long history of ulcer disease without correct treatment, but there are not the studies comparing the incidence of complications before and after the worldwide introduction in the therapy of proton pump inhibitors and the eradication of *H. pylori* infection [16]. The pathological features of the peptic ulcer are an important factor that can modify the risk of complications: chronic ulcers, the penetrating character, and the great size of the lesions. The penetration into the gastroduodenal wall up to serosa, with sclerotic tissue, and erosive action on the blood vessels (sometimes of great size as gastroduodenal artery) are the pathological characteristics of bleeding and perforated peptic ulcers. All the complications of peptic ulcers require the preliminary therapeutic management: suspend ingestion of food, drinks, drugs; start the fluid resuscitation, immediate suspension, if previously foreseen in therapy, of ASA, NSAIDs, and also anticoagulant if possible, administer acid suppressive therapy with intravenous proton pump inhibitor (PPI), treatment of *H. pylori* infection, if certainly present [20]. The treatment of *H. pylori* infection actually decreases recurrent ulcers and the incidence of the complications. Consequently the therapeutic procedures for the eradication of the *H. pylori* infection (PPI, antibiotics per os, because the efficacy of antibiotics e.v. has not certainly demonstrated) have a fundamental role in the prevention of the complications and recurrences of the peptic ulcer disease [21].

### 3.2 Bleeding

The occurrence of hemorrhage complication is clearly higher than perforation. The evaluation of annual incidence of bleeding shows a large range of variation from 36 to 44%, followed by perforation with the range from 6 to 14% [22]. Bleeding complications can develop with various degrees of severity. Peptic ulcers cause almost half of all cases of upper gastrointestinal hemorrhage. The more serious events of bleeding usually are due to chronic duodenal ulcers; however, both gastric and duodenal ulcers have the overlappable trend to bleed. Gastroduodenal bleeding from peptic ulcer is a well-known clinical occurrence, in some cases with high morbidity. The reason of major severity of this complication in the duodenal ulcer is connected to anatomical condition: the ulcer situated on the posterior wall of duodenal bulb penetrates and exposes the gastroduodenal artery, which can be eroded followed usually by copious hemorrhage. In the other sites of the duodenal bulb, as anterior wall, there are no major blood vessels. The peptic ulcers in the second portion of duodenum, so-called postbulbar ulcers, are less usual than bulbar



ulcers; however, bleeding complication is frequent also in this site. The clinical manifestation of bleeding is characterized by the amount and speed of hemorrhage. The massive and sudden bleeding appears with hematemesis, followed by melena, can cause hypovolemic condition and, in some cases, hypovolemic shock. Blood loss that develops less rapidly manifests with melena, also accompanied in some cases by hemodynamic alterations. In other cases continuous and moderate blood loss induces chronic anemia. Clinical data achieve the evaluation of the severity of hemorrhage and the general conditions, as hemodynamic stability, hypovolemic status, etc. The knowledge of these findings is central for the starting of urgent resuscitation therapy. However, the diagnosis must be completed by endoscopy to define the pathological features of bleeding ulcer, essential notion to perform the correct therapeutic approach: medical, endoscopic, surgical therapy. In the context of hemorrhagic complication, the control of possible active blood losses is necessary by checking stably the nasogastric tube, the stool, and the value of hematocrit and hemoglobin level. After the bleeding has stopped, rebleeding is possible, also within a short period of time. The urgent and current therapeutic approach in the patients with bleeding peptic ulcer includes fluid resuscitation, intravenous proton pump inhibitor (PPI) therapy, blood transfusions in some cases if necessary, therapeutic endoscopic procedures, if required. Usually this approach stops bleeding and cures the ulcer. However, the evolution of the bleeding complication is not favorable in the minority of patients, and the therapeutic resolution demands the surgical procedures. There are some clinical conditions that require surgery: patient with hypovolemic status and hemodynamic alteration not responding to powerful fluid resuscitation therapy; recurrent bleeding after early interruption, in most cases after unsuccessful further endoscopic treatment; finally in the patients with moderate, small, but continuous hemorrhage that needs prolonged fluid infusion and repeated blood transfusion.

### **3.3 Perforation**

The global frequency of perforation in the evolution of peptic ulcer disease ranges between 2 and 10%. However, the sites of lesion, in the gastroduodenal tract, show different occurrence chance of the complication. The major frequency of perforation is in duodenal ulcer, reaching 60%; in the antral and gastric body site, the ulcer perforation develops by 20% [23, 24]. This clinical event is spontaneous. The free perforation in the peritoneal cavity causes upper abdominal pain; typically this pain is sudden, that is, the patient recalls precisely its onset and associates it with what he was doing. The first step of the peritoneal flogosis is a chemical peritonitis due to the gastric and biliopancreatic secretions. However, the reaction of peritoneal serous mitigates the gastroduodenal irritants with the light exudate, and the abdominal pain can ameliorate for a short frame time. This first phase is followed quickly by the return of the severe epigastric and then diffuse abdominal pain. The patient appears very suffering and reduces the movements of the abdominal wall with short breaths and bending off the thighs upward. The objective abdominal examination shows hypomobility of the wall, usually its board-like rigidity; with percussion tympanic sound instead of the normal dullness over the liver, because of the air leaking from the stomach; on auscultation, peristaltic sound is weak or absent. There are also atypical or less typical clinical presentations of peptic ulcer perforations. A small duodenal perforation with a small amount of gastroduodenal secretion flowing out along the right parietocolic douche can simulate acute appendicitis. Anyway in some patients the clinical appearance of perforation can be less pronounced with little symptomatological evidence and possible diagnostic pitfall. Finally, the so-called covered or sealed perforation is possible, due to the closure

by the omentum or by the liver, or also the posterior, retroperitoneal perforation (epiploon retrocavity); these start with discrete clinical symptoms. However, the septic focus is active and usually develops in circumscribed peritonitis, as sub-hepatic or subdiaphragmatic abscess and also in generalized peritonitis [25, 26]. Within the laboratory findings, there is evidence of leukocytosis, with mild level in the early phases, after some hours more elevated. In the imaging studies, plain X-rays, with patient upright, of the lower chest and the abdomen reveal in most cases (plus than 80%) free subdiaphragmatic air. The clinical and this imaging data allow the diagnosis of ulcer perforation [27]. If the free intrabdominal air cannot be detected, the imaging study may be completed by US and CT. Both these exams can demonstrate also little amount of free air or fluid; the small fluid collection can be detected in the pelvic space. In particular there is evidence of the possible findings of little leaks through perforated ulcer by CT with oral contrast [27]. The early management of perforated peptic ulcer encloses fluid infusion, intravenous proton pump inhibitor, antibiotics with wide antimicrobial activity, and positioning of the nasogastric tube. The central therapeutic role in the peptic ulcer perforation is played by surgery, usually by mini-invasive approach, following one of several procedures of surgical ulcer closure [23, 24, 28]. The altered conditions in the patients with every free perforation are indication to urgent surgery. In the patients with little leaks through perforated ulcer or spontaneous closing of perforation, localized intraperitoneal inflammatory disease and well stable clinical conditions can be performed by nonoperative treatment by nasogastric tube, PPI, and antibiotics. However, the conservative management should allow a quick amelioration, that is, within 24 hours; but any delay in the improvement or also small deterioration of clinical condition requires urgent surgical procedure [29, 30].

### 3.4 Pyloric obstruction

The stenosis is the less frequent complication of the peptic ulcer, based on the evolution of the disease due to inflammation, edema, muscular spasm, followed by repair process with scarring. The detected frequency ranges between 5 and 8%. In detail, the development of this complication comprises various factors, some functional, other pathological. The functional factors are spasm, pyloric dysmotility, decrease of gastric motility, due to peptic ulcer disease; the pathological factors are inflammation, edema, fibrosis, and finally, scarring and stenosis. The first phase of dysfunction with edema and inflammation causes the reversible gastric obstruction, the following phase of fibrosis and scarring induces the irreversible obstruction [23]. The majority of patients who complain symptoms of gastric outlet obstruction have an history of peptic ulcer disease. The clinical appearance is characterized by anorexia, nausea, early satiety, epigastric pain, vomiting. This long untreated clinical condition is followed by weight loss and deterioration of general condition. A typical symptom is the decreased efficacy of antiacid drugs. This is the clue for the indication of altered acid gastric secretion condition: pyloric obstruction conducts to stasis with increase in the gastric pH, following rise of gastrin issue and overflow of acid secretion. Usually the diagnosis of stenosis and exclusion of malignancy are achieved by endoscopy, endobiopsy, and imaging exams, such as conventional radiography and CT scan. The initial medical management is based on re-establishment of hydroelectrolytic balance and gastric decompression by nasogastric tube for 48–72 hours. In some cases these procedures allow the resumption of oral diet and recovery of nutritional status. There are some studies that report the positive role of the treatment of *H. pylori* infection on the resolution of the outlet obstruction [31]. Also the NSAIDs use has been detected to cause gastropyloric obstruction and the favorable role of drug's suspension on the resolution of complication [32]. The

operative treatment of gastric obstruction includes endoscopic procedures such as balloon dilation and surgical treatment as highly selective vagotomy with pyloroplasty, truncal vagotomy with gastrojejunostomy, or antrectomy.

#### **4. Conclusions**

Peptic ulcer complications are still remarkable medical problem. Although the current medical therapy of peptic ulcer, as PPI drugs, control of *H. pylori* infection, the decrease of the disease frequency was not followed by reduction of complications. Bleeding, perforation, and gastric-pyloric obstruction are evident. Proper treatment for bleeding encloses urgent medical approach and frequently therapeutic endoscopic procedures, usually followed by favorable evolution of complication. The failure of these therapies requires the surgery. For the perforation the central therapeutic role is usually played by surgical procedures; the opportunities for conservative therapy are limited. Gastric-pyloric obstruction can be treated with endoscopic approach and balloon dilation; in case of failure, the surgery is necessary.

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