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PEPTIC ULCER DISEASE-DIAGNOSIS AND TREATMENT

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Abstract:

Introduction: *The acid peptic injury in the gastrointestinal tract is called peptic ulcer, it results from a rupture in the mucosa to the submucosa. Generally, most of the peptic ulcers locate in the stomach or in the duodenum in its proximal part, however, the may also locate in Meckel's diverticulum or in the oesophagus. In this review, we mean by the "peptic ulcer" term the ones in the stomach or duodenum.*

Aim of work: *In this review, we will discuss the recent strategies to diagnose and treat peptic ulcer disease.*

Methodology: *We did a systematic search for most recent evidence regarding the peptic ulcer disease diagnosis and treatment in the emergency department using PubMed search engine (http://www.ncbi.nlm.nih.gov/) and Google Scholar search engine (https://scholar.google.com). We only included full articles.*

Conclusions: *The quickly decreasing incidence and prevalence of infections with Helicobacter pylori along with the widespread increase of the use of strong anti-secretory agents can mean that peptic ulcers have become significantly less important concerns than they were twenty years ago. Management has become more difficult than before due to the increasing development of antibiotics resistance globally and the widespread increase in the administration of anti-thrombotic agents among the elderly.*

Key words: *Peptic Ulcer disease, diagnosis, management.*

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INTRODUCTION:

The acid peptic injury in the gastrointestinal tract is called peptic ulcer, it results from a rupture in the mucosa to the submucosa. Generally, most of the peptic ulcers locate in the stomach or in the duodenum in its proximal part, however, the may also locate in Meckel's diverticulum or in the oesophagus. In this review, we mean by the "peptic ulcer" term the ones in the stomach or duodenum [1].

Previously, it was thought that the hypersecretory acidic environment, stress ,or dietary factors are the main causes of the peptic ulcer diseases, but, after Helicobacter pylori infection had been discovered, this perception have changed, currently , the main causes of peptic ulcer are the increasing use of nonsteroidal anti-inflammatory drugs (NSAIDs), and Helicobacter pylori infection.

In this paper, we will review the recent strategies to diagnose and treat peptic ulcer disease.

METHODOLOGY:

We did a systematic search for most recent evidence regarding the peptic ulcer disease diagnosis and treatment in the emergency department using PubMed search engine (http://www.ncbi.nlm.nih.gov/) and Google Scholar search engine (https://scholar.google.com). We only included full articles.

The terms used in the search were: peptic ulcer disease, diagnosis, management

Epidemiology:

It has been estimated that the prevalence of peptic ulcer disease in general population during lifetime is about 5−10%, and incidence 0•1–0•3% per year. But, more recent studies have shown a sharp decreasing trends in the numbers of prevalence, incidence, hospital admissions, and mortality associated with the disease in the past 20–30 years especially in high-income countries [2,3]. This may be because of the new therapies, or they might be due to a cohort trend that cannot be fully explained by known causes (eg, H pylori infection and NSAID treatment).

In countries of Europe that have different systems for health-care along with significant disparities in the socioeconomic status of residents, between the years 1921 and 2004, the mortality associated with gastric ulcers was higher than the mortality associated with duodenal ulcers. In South America, Central America, and Asia, a decrease in the mortality associated gastric ulcers and a duodenal ulcer has been detected.

In Asia, a gradual decrease in the incidence of peptic ulcer disease has been observed among different racial groups, including Chinese, Malay, and Indian populations, for the last twenty years. This decrease comes in parallel with a decline in H pylori-associated peptic ulcer disease [4].

Although the increase in the use of NSAIDs cannot explain recent trends in mortality related to ulcers reported by some studies, other studies have, in fact, recorded decreasing admissions into hospitals due to complicated peptic ulcer disease in the twenty-first century.The decline in complicated peptic ulcer disease may be correlated with the increasing prevalence of the use of anti-secretory medications globally and the more rational use of NSAIDs than previously [5].

Pathogenic mechanisms and risk factors:

Helicobacter pylori infections and the use of NSAIDs are considered to be the most important predisposing factors for the development of both duodenal and gastric ulcers.[6] However, it is worth mentioning that not all individuals infected with H pylori infection or use NSAIDs will definitely develop peptic ulcers, which suggests that susceptibility of individuals to bacterial virulence and drug toxicity is important to start mucosal injury.

The presence on an interaction between the pathogenic organism and host-related factors determines the prognosis of H pylori infections. The ability of bacterial strains to secrete several proteins is thought to be related to their virulence and to the response of the host immunity. The bacterial organism is known to produce urease which creates an alkaline media, to make the environment appropriate for its survival within the stomach and under the mucosal barrier. It also secretes adhesins like blood group antigen adhesin or outer inflammatory protein adhesin, which enhances the bacterial attachment to the gastric epithelium [7].

Almost all strains of H pylori bacteria include the vacA gene, which is responsible for encoding a vacuolating cytotoxin. The mechanism in which the VacA protein participates to the pathophysiology of the condition is not well-understood. Alterations of the structure of the vacA gene may be associated with functional implications. The interactions of the host along with the mucosal inflammatory response to an infection with H pylori can both be determined, partially, using genetic testing to predict the prognosis of peptic ulcer and other acid-related conditions [7].

NSAIDs and aspirin are considered to be crucial predisposing factors for the development of peptic ulcers and related complications. Compared with individuals who do not routinely use them, users of NSAIDs have a significantly higher risk of developing complicated peptic ulcer [8].

The concomitant use of NSAIDs with SSRIs, aldosterone antagonists, corticosteroids, or anticoagulants dramatically elevates the risk of developing an upper GI bleeding [9]. The mechanisms in which smoking and poor socioeconomic status affect the risk of developing peptic ulcers are not well-understood [10]. Multiple studies have found an associated between the use of aspirin an elevated incidence of peptic ulcers in patients who have some specific genetic polymorphisms. However, the clinical significance of these findings remains to be unclear and need further assessments [11].

Many individuals who routinely use NSAIDs also have an H pylori infection. The presence of an interaction between both factors in the development of peptic ulcers remains to be an area od debate. Randomized trials have demonstrated that achieving complete eradication of H pylori is important for individuals who start using NSAIDs but not beneficial in individuals who chronically use NSAIDs. A previous meta-analysis 13 of multiple studies concluded that uncomplicated peptic ulcers were more likely in individuals with positive H pylori tests than individuals with negative H pylori tests. The explanation of these results was that both infection with H pylori and NSAIDs use can independently elevate the incidence of developing peptic ulcers, and that the disease was generally not common among individuals without H pylori infection who do not routinely use NSAIDs [12].

H pylori-negative, and NSAIDs-negative peptic ulcers can be found in at least twenty percent cases. the presence of serious comorbidities can also increase the incidence of developing the disease. For example, just following the Great East Japan Earthquake in the year 2011, an unexpected elevation in the incidence of H pylori-negative bleeding multiple peptic ulcers was observed [13]. Residence in a shelter for refugees was also associated with a strong increase in the risk of developing bleeding peptic ulcers [14].

A Danish study 46 found that the presence of psychological stress was significantly correlated with increased incidence of peptic ulcers, partially by affecting health risk behaviors. The real incidence and prevalence of idiopathic peptic ulcers that are not associated with NSAIDs and H pylori infections are not well known [15].

Pathophysiology:

The exact mechanisms in which H pylori causes the development of multiple types of injuries in the mucosa of the gastroduodenal tract is not well understood. Inflammation associated with the infection can lead to either hypochlorhydria or hyperchlorhydria. This will determine the type of the ulcer that will be formed. These consequences could be mediated indirectly with cytokines that will block the secretions of parietal cells,49 or directly by the products of H pylori [16].

The development of pangastritis is correlated with the development hyposecretion and is associated to forming gastric ulcers. On the other hand, ten to fifteen percent of individuals with positive H pylori have gastritis that is antral predominant and associated with the presence of duodenal ulcers. The inhibition of somatostatin along with the resulting secretion of gastrin elevates the secretion of histamine from the enterochromaffin-like cells, causing an elevation in the secretion of acid from parietal and gastric chief cells. Therefore, the important role of these interactions between gastrin and somatostatin during these steps seems to be clear.

On the contrary, achieving complete eradication of H pylori bacteria will be followed by a significant elevation in the expression of somatostatin and an associated reduction in the expression of gastrin in patients who have duodenal ulcers.

NSAIDs can cause significant injuries to the mucosa of the gastroduodenal tract by both systemic mechanisms and local mechanisms, of which, the most important mechanism is the systemic blocking of expressed cyclooxygenase 1-derived prostaglandins. Decreased mucosal prostaglandin concentrations is correlated with lower bicarbonate and mucus secretion, blocking of the proliferation of cells, and reduced blood flow to the mucosa, which are crucial to maintain the integrity of the mucosa. The COX theory is evidenced by studies that showed that the co-administration of prostaglandins exogenously decreased mucosal injury [17]. However, this theory does not totally explain the whole spectrum of mucosal injury. Individuals using NSAIDs routinely may have a significant reduction in prostaglandins concentrations without necessarily developing gastric ulcers [18].

NSAIDs start injury of the mucosa within cells by disrupting the mucosal phospholipids or the cellular membranes. The decreased integrity of mucosa can be followed by reactions in tissues that are amplified by the presence of luminal contents like acids, food, pepsin, bile, and/or H pylori [19]. Therefore, prostaglandins inhibition, vascular injuries, and topical changes are the most important predisposing factors in the pathophysiology of NSAIDs-related gastric and duodenal ulcers. The use of aspirin (even in low doses) could also lead to mucosal injuries among individuals by causing both topical mechanisms and systemic mechanisms, although the direct evidence of these systemic effect is not solid. Once the injury has been caused, prostaglandins are likely to have an essential role in repair of mucosa, since NSAIDs have been demonstrated to cause delayed healing of ulcers.

The pathophysiological mechanisms that lead to the occurrence of idiopathic peptic ulcers are not clearly understood. A disturbed balance between the mucosal defensive mechanisms and the aggressive factors, like the presence of gastric acid hypersecretion, is thought to be present. However, most studies on gastric secretion were performed in the pre-H pylori era, and we now understand that most of these alterations were resulting from the impact of H pylori infection. Other potential pathogenetic mechanisms include ischemia, drugs use, metabolic abnormalities, viral infections, radiotherapy, histamine, basophilia, and eosinophilic infiltration [20].

Clinical presentation and diagnosis:
Clinical manifestations of peptic ulcers have a very low predictive value due to being non-specific. Patients who have duodenal ulcers classically always feel hungry and/or have nocturnal pain in the abdomen. On the other hand, patients who have gastric ulcers have postprandial pain in the abdomen, vomiting, nausea, and loss of weight. Patients who have untreated peptic ulcers will classically have relapsing symptoms due to the spontaneous healing and relapse of the condition while the causing factor (H pylori infection or NSAIDs use) is still present. Older patients who have peptic ulcers are usually asymptomatic or only show mild clinical manifestations.

The development of perforation, hemorrhage, or obstruction of the gastric outlet are the most common manifestations of complicated peptic ulcers. Hemorrhage, which presents with melena or haematemesis, can start suddenly without the presence of any warning manifestations in about fifty percent of cases. The rates of admissions to hospitals due to hemorrhage from a complicated peptic ulcer have decreased gradually globally, but the case fatality rate is still stable at five to ten percent. 8,9 Perforation of peptic ulcers classically manifests with a sudden severe pain in the upper abdomen. Based on the age of the patient and the presence of comorbidities, mortality rates can be up to twenty percent.

Endoscopy is considered to be the best diagnostic test used to confirm the presence of peptic ulcers. Apart from excluding the presence of cancers, the detection of H pylori infections with biopsy or a rapid urease test is crucial to the determine the management and treatment plans. As H pylori is the main cause of most cases of peptic ulcers, a test-and-treat protocol with a non-invasive test (like urea breath test) to rule out the presence of an infection has been recommended in individuals younger than fifty years who have dyspepsia and no alarming signs, and in geographical areas where gastric carcinoma is no prevalent and H pylori infection prevalence is higher than twenty percent.[21] In older individuals, performing an upper GI endoscopy is preferred initially to confirm or rule out the presence of the disease.

Management:
Achieving proper prevention of recurrence is the main long-term target that decreases associated morbidity and mortality rates. Increasing evidence have been suggesting that complete eradication of H pylori bacterial organism is alone enough to cure associated ulcers and decrease relapse rates and later bleedings without the need of maintenance therapy. However, proper eradication of H pylori bacterial organism is considered to be a huge challenge in most areas of the world due to the increasing prevalence and incidence of antimicrobials resistance. The gold first-choice therapies that are usually used consist of a proton-pump inhibitor and two antimicrobial agents, such as clarithromycin and amoxicillin or metronidazole given for seven to fourteen days (this is known as PPI-based triple therapy) [22].

However, due to the elevating incidence rates of antimicrobial resistance, the efficacy of the PPI-based triple therapy in achieving complete H pylori eradication has decreased from more than ninety percent (during the last twenty years) to less than seventy percent currently in many areas around the world [23]. Therefore, ideal therapy must be planned

according to the results of antibiotics sensitivity tests. However, these tests are not always readily available, so the first-line therapies, in these cases, must be determined according to local endemic organisms. In general, if sensitivity testing is not available, PPI-based triple therapy regimens containing clarithromycin must not be used in areas where the local resistance against clarithromycin resistance higher than fifteen percent [24]. In countries where low resistance against clarithromycin is recorded or when the patient has been confirmed to have an infection that is sensitive to clarithromycin, both PPI-clarithromycin-amoxicillin or PPI-clarithromycin-metronidazole regimens can be used. eradication rates can be improved using of higher doses of PPI (double the conventional dose) and by administration of drugs for longer durations.

Currently, the recommended empiric first-line treatment is either a bismuth-containing quadruple protocol for fourteen days or a non-bismuth-based quadruple protocol for fourteen days; these two protocols have been found to achieve eradication in more than ninety percent of cases [25].

Another protocol of quadruple treatment is the sequential therapy that include a five-day dual treatment with PPI and amoxicillin followed then by a five-day triple therapy with a PPI, clarithromycin, and either tinidazole or metronidazole. The overall eradication rates of sequential therapy is higher than that of seven-day and ten-day triple therapy protocols but not better than the eradication rates achieved by fourteen-day triple therapy, bismuth-based therapy, and non-bismuth-based treatment, and therefore, this treatment is not routinely recommended.

When a rescue treatment is needed, levofloxacin-containing triple treatment can achieve eradication in more than eighty percent of cases [26]. However, the presence of resistance against quinolones among H pylori organisms decreases the efficacy of levofloxacin-containing therapies. A bismuth-containing quadruple protocol can be an effective second-choice for treatment after the failure of standard triple protocols, with eradication achieved in more than ninety percent of cases. The use of this regimen is usually recommended following the failure of other non-bismuth-containing quadruple protocols.

There has been an increasing interest in probiotics use as adjuvant therapies to improve eradication of H pylori infections and decrease the rates of side effects associated with antimicrobials use. However, further studies are still required. A randomized phase three trial that studied the efficacy of an oral recombinant vaccine against H pylori included more than four thousand children in China who had no history of an H pylori infection. The authors of the study found the efficacy of the vaccine to be about seventy percent within the next three years following admininstration [27].

The use of treatment with an antisecretory pharmacological agent is usually recommended as a strategy to prevent peptic ulcers in patients who are at risk of developing NSAID-associated peptic ulcers. In a previous randomized controlled trial, an H_2 receptor blocker was found to be beneficial for the prevention of developing ulcers in individuals with average aspirin use. Whether the use of PPI is associated with more efficacy than H_2 blockers for aspirin users is still not known, with any solid evidence present on this issue to provide a conclusion. In a previous randomized trial, investigators concluded that pantoprazole was superior to famotidine for the prevention of developing upper GI hemorrhage and attacks of severe dyspepsia. On the contrary, a randomized trial that was conducted in multiple centers concluded that among high-risk users of aspirin, the recurrence rates of hemorrhage were the same among both groups of PPI and standard-dose H_2 blockers. PPIs are obviously beneficial for the prevention of ulcer-related hemorrhage in aspirin users. However, famotidine is still considered a convenient alternative to be used in patients with low compliance to PPIs. Among individuals who routinely use NSAIDs, several recommendations are available to prevent and decrease the occurrence of gastroduodenal ulcers and associated complications. These recommendations include protocols for the use of co-therapy of NSAIDs with a PPI, an H_2 blocker, or misoprostol [28].

In addition to their negative effects on the gastric mucosa, NSAIDs and aspirin have been found to be associated with lower GI hemorrhages with which acid suppression does not have beneficial effects. Two large randomized studies where investigators used looked for both upper and lower GI events as outcomes, concluded that that celecoxib was associated with higher efficacy than other NSAIDs. The benefits of celecoxib over other NSAIDs could be attributable to the significant decrease in secondary anemia that develops due to bleeding in the small bowels.

Most patients with peptic ulcers cure following six to eight weeks of treatment. If ulcers fail to cure, compliance of the patient to the drug must be assessed. Blood investigations and a carefully obtained medical history will usually show some use of NSAIDs, which is usually overlooked in refractory ulcers cases. increasing the doses of PPI dose to double the dose for other six to eight weeks can be beneficial, despite the absence of reliable evidence that proves the benefits of this strategy in these patients. Serological blood investigations can be used to diagnose false-negative infections with H pylori. After the exclusion of NSAIDs surreptitious use, or false-negative infections with H pylori, less common etiologies of peptic ulcer must be assessed, examples of these etiologies include cancers, viral infections (like cytomegalovirus), inflammatory bowel diseases, upper abdominal radiotherapy, vasculitis, cocaine abuse, and Zollinger- Ellison syndrome. With the decreasing incidence and prevalence of infections with H pylori, idiopathic cases of ulcers are being recognized more frequently, and these patients are usually at higher risk of recurrence, hemorrhagic complications, and mortality [29].

The worldwide decrease of the prevalence and incidence of peptic ulcers over the last one hundred years has happened most obviously during the last twenty years. These declining trends may be associated with the cohort effect that happened prior to the introduction of strong anti-secretory drugs and H pylori therapy. The parallel reduction in the frequency of infections with H pylori that resulted from improving socioeconomic status has had an essential role. In addition, the widespread increase of PPIs use has likely to have an effect on the rapid reduction of peptic ulcers prevalence. On the other hand, PPIs overuse, which is predicted to be inappropriately used in about half the cases, could have led to an unexpected new adverse event that is now being slowly increasing.

CONCLUSIONS:

The quickly decreasing incidence and prevalence of infections with Helicobacter pylori along with the widespread increase of the use of strong anti-secretory agents can mean that peptic ulcers have become significantly less important concerns than they were twenty years ago. However, management has become more difficult than before due to the increasing development of antibiotics resistance globally and the widespread increase in the administration of anti-thrombotic agents among the elderly. Peptic ulcers which are not associated with infections with H pylori or the NSAIDs use are currently becoming a significant diagnostic and therapeutic concern. This paper aims at providing a balanced discussion of the most recent advances in the pathophysiological mechanisms of peptic ulcers development, guidelines on treatments of H pylori infection, approaches to treat complicated peptic ulcers, and the unmet needs in terms of our knowledge and management of this increasingly challenging condition.

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