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Peptic ulcers: causes, prevention, perforation and treatment

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ABSTRACT

Peptic ulcer disease (PUD) is a sore on the lining of stomach or duodenum. In some cases, a peptic ulcer may develop just above stomach in esophagus, i.e. esophageal ulcer. Peptic ulcer has always been the most common etiology underlying upper gastrointestinal perforation, while gastric perforation represents 10-15% of all peptic ulcers. Alternation in balance between aggressive and protective factors at the luminal surface of the epithelial cells, leads to development of peptic ulcer. Aggressive factors include *Helicobacter pylori*, hydrochloric acid, pepsins, nonsteroidal anti-inflammatory drugs (NSAIDs), bile acids, ischemia, hypoxia, smoking and alcohol. On the other hands, bicarbonate, mucus layer, mucosal blood flow, prostaglandins (PGs) and growth factors are the most known defensive factors. The shared symptoms include a dull or burning pain in middle or upper stomach between meals or at night, bloating, heartburn, nausea and vomiting are among the most common symptom of peptic ulcer. Some other symptoms in severe cases are dark or black stool (due to bleeding), vomiting blood, weight loss and pain in the mid to upper abdomen. An ulcer may or may not have all or some of the symptoms. In general, ulcers are best diagnosed by instrumental procedures depending on the case and the available facilities in the centre. The most reliable tests include, I) sophagogastroduodenoscopy (EGD), a thin tube with a camera inserted through the mouth into GIT. A biopsy is also taken during an EGD to be examined for *H. pylori*, II), X-ray for the upper GIT taken after drinking a thick barium salt, III) blood test to check if there is anemia and IV) detection of blood in the stool. Perforation is the major complication of PUD and the perforated peptic ulcer needs the use of surgical intervention. About 80% of the indications for peptic ulcer surgery are related to perforate peptic ulcers. Most cases are treated by simple suture of the perforated intestinal wall. In most cases, the best treatment is surgical or laparoscopic suture closure of the perforated ulcer. Natural products have found a special place in the treatment plans for peptic ulcer disease. They exhibit their antiulcerogenic activities by various mechanisms either prophylactic or therapeutic or both. The prophylactic products have considerable antioxidant and anti-inflammatory activities. On the other hand, therapeutic agents possess antisecretory or healing effects. The anti-*H.pylori* activity of some plant extracts, however, may explain their antiulcerogenic activity.

Keywords: Peptic ulcer, perforation, gastrointestinal tract, gastroprotective

INTRODUCTION

Ulcers in the gastrointestinal tract (GIT) are commonly divided into two types according to their location, i.e. being ulcerative colitis (lower) and peptic ulcer (upper).

Ulcerative colitis (UC) is an inflammatory bowel disease primarily affecting the colonic mucosa. In its most limited form it may be restricted to the distal rectum, while in its most extended form, the entire colon could be involved.[1] UC can occur in both sexes and in any age group but most often begins in people between 15 and 30 years of age. The exact causes of UC are still not clear but different factors have been postulated as possible etiologic agents. They are genetic factors, infective agents, immunological basis, smoking, medications and pathological factors.[2]

Peptic ulcer disease (PUD), known as a sore on the lining of stomach or duodenum, affects a considerable number of people worldwide. In some cases, a peptic ulcer may develop just above stomach in esophagus, i.e. esophageal ulcer.

Peptic ulcer has always been the most common etiology underlying upper gastrointestinal perforation[3], while gastric perforation represents 10-15% of all peptic ulcers.[4]

Alternation in balance between aggressive and protective factors at the luminal surface of the epithelial cells, leads to development of peptic ulcer. Aggressive factors include *Helicobacter pylori*, hydrochloric acid, pepsins, nonsteroidal anti-inflammatory drugs (NSAIDs), bile acids, ischemia, hypoxia, smoking and alcohol. On the other hands, bicarbonate, mucus layer, mucosal blood flow, prostaglandins (PGs) and growth factors are the most known defensive factors.[5]

Although in many cases peptic ulcers heal in the absence of special treatment, their warning signs should not be ignored. When the ulcer is not properly treated serious health problems may occur, including bleeding, perforation (a hole through the wall of the stomach) and gastric outlet obstruction from swelling or scarring that blocks the passageway from stomach to the small intestine

Taking NSAIDs can lead to an ulcer without any warning. The risk is especially concerning for the elderly and for those with a prior history of having peptic ulcer disease.

It has been reported that the incidence of PUD have fallen globally since the beginning of 21st century.[6] Many advances have taken place in both diagnosis and management of peptic ulcer disease, including improvements in endoscopic diagnostic and therapeutic facilities, the increased use of proton pump inhibitors and *Helicobacter pylori* eradication therapies. In spite of all these, peptic ulcer perforation rate has remained unchanged and, therefore, is a major health challenge

CAUSES

A number of factors contribute to the prevalence of peptic ulcer and increasing the risk. The most important causes are classified into the following categories.

- Long-term use of nonsteroidal anti-inflammatory drugs (NSAIDs) including aspirin and ibuprofen.
- *Helicobacter pylori (H. pylori)*infection
- A family history of ulcers
- History of other diseases such as liver, kidney, or lung disease
- Regular alcohol intake
- 50 years old or older
- Stress
- Some rare cancerous and noncancerous tumors in the stomach, duodenum, or pancreas known as Zollinger-Ellison syndrome (ZES)

As there are some evidences that H. pylori could be transmitted either from person to person or through food and water, the first step to avoid peptic ulcer is preventing infection by improving personal hygiene and eating well cooked foods.

NSAIDs are a class of analgesic medicines including acetyl salicylic acid and ibuprofen. It is a well-known fact that long-term use of NSAIDs can cause peptic ulcer disease. Development NSAID-induced peptic ulcer is the result of regular use of NSAIDs. It is best to avoid taking medicines that are prescribed by physician with meals and avoid drinking alcohol when taking medicines.

Stress may worsen the signs and symptoms of a peptic ulcer. Smoking interferes with the protective lining of the stomach and increases the secretion of stomach acid leading to higher risk of peptic ulcer. Different foods do not cause or prevent peptic ulcers, but drinking alcohol does make ulcers worse. Excessive use of alcohol can irritate and erode the mucous lining in stomach and intestines, causing inflammation and bleeding.

SYMPTOMS

Small ulcers may not cause any symptoms, while some big ulcers can cause serious bleeding. However, some symptoms are common and general for both small and big ulcers.[7] The shared symptoms include a dull or burning pain in middle or upper stomach between meals or at night, bloating, heartburn, nausea and vomiting are among the most common symptom of peptic ulcer. Some other symptoms in severe cases are dark or black stool (due to bleeding), vomiting blood, weight loss and pain in the mid to upper abdomen. An ulcer may or may not have all or some of the symptoms.

DIAGNOSIS

The diagnosis of PUD caused by *H. pylori* infection is either through invasive or non-invasive methods including endoscopy with biopsy, a urease breath test and detection of antibodies in salivary fluid, serum and urine. The diagnosis of *H. pylori* infection, should then be confirmed using two tests, one is based on the outcomes of biopsied tissue, either resulting in a culture, or urease test. A proton-pump inhibitor and two antibiotics for a period of 14 days, are recommended as the medical treatment. This gives rise to clearance of about 90% of the

bacteria and prevents the development of resistant strains.[8]

In general, ulcers are best diagnosed by instrumental procedures depending on the case and the available facilities in the center. The most reliable tests include, I) sophagogastroduodenoscopy (EGD), a thin tube with a camera inserted through the mouth into GIT. A biopsy is also taken during an EGD to be examined for *H. pylori*, II), X-ray for the upper GIT taken after drinking a thick barium salt, III) blood test to check if there is anemia and IV) detection of blood in the stool.

PREVALENCE

Despite the development in life style and personal care, the prevalence of *H. pylori* infection is still quite high in the developing world. However, its prevalence has declined considerably in the western world. The bacterial infection can be transmitted from person-to-person, and children most commonly acquire infection from mothers. Most published studies demonstrate household crowding, sharing a bed with children, and sharing plates, spoons, or tasting food before feeding a child are related to infection in children.[9]

Hemorrhagic peptic ulcer could be considered as one of the highest incidences for emergency in many hospitals.[10] Although the number of hemorrhagic peptic ulcer cases is decreased worldwide, the overall incidence in elderly patients has remained quite high.[11, 12] Significantly higher incidences of hemorrhagic peptic ulcers in elderly patients than in younger patients have been reported in Norway.[12] It is worth indicating that according to literature, elderly patients are defined as individuals 80 years or older in previous studies.

Bleeding of peptic ulcers is mainly due to *H pylori* infection and high intake of drugs. However, the role of each factor may change based on the prevalence of *H pylori* and use of NSAIDs. For example, in a prospective survey on 204 patients with peptic ulcer bleeding, it has been demonstrated that the use of NSAIDs, aspirin, and clopidogrel are the most important cause of peptic ulcer bleeding in southern Taiwan.[13]

PERFORATION

About 7- 10 in 100,000 cases of gastro-duodenal peptic ulcer are perforated over time.[14] Perforation is the major complication of PUD and the perforated peptic ulcer needs the use of surgical intervention. About 80% of the indications for peptic ulcer surgery are related to perforate peptic ulcers.[15] The role of non-operative management, laparoscopic versus open laparotomy approach and the type of procedure to be used in emergency situations are still under debate.[16] Alternative to surgery include placement of drains or maintenance of naso-gastric decompression which are only mentioned in the literature without indication of some scientific evidences.

The widespread clinical use of H_2 receptor antagonists and proton-pump inhibitors, have resulted in a marked reduction of surgery, especially in the case of uncomplicated peptic ulcer. Common complications associated with perforation of peptic ulcer, however, are remained problem for a long period.[17, 18] About 70 years ago, the first report on nonoperative management of PPU was published. It was performed on a series of 28 patients and indicated the mortality rate of 14%, as compared to direct simple closure with omental patch (approximately 20%).[3] However, the mortality of PPU treated by the nonoperative approach has significantly reduced since then.[4, 19]

PPU is among complicated surgical emergencies and appropriate early management is essential for reducing subsequent problems such as gastrectomy. While the risk of cancer is almost zero for duodenal ulcers, about 6–15% of perforated gastric ulcers (PGU) will have a malignant aetiology.[19, 21] Although the figure seems small, it is important in decision making for treatment to patch or resect.

A research conducted in Royal Infirmary of Edinburgh during 2007-2011, has concluded that almost all perforated gastric ulcers could effectively be managed by laparotomy and omental patch repair.[21] However, initial biopsy and follow-up endoscopy with repeat biopsy was recommended as an essential task to avoid missing an underlying malignancy.

However, it is emphasized that urgent repair of perforation has remained the standard approach for PPU in most cases.[22]

The incidence of perforated PUD depends on geographical area, socio-demographic and possibly some environmental factors.[23] It has been reported that in developing countries, younger male patients suffer from perforated PUD, in contrast to developed countries were the patients with perforated PUD are mainly the elderly.[24, 25] Heavy smoking and alcohol among the young male people in developing countries could be one of the factors causing the higher incidence of PUD. While in the more

developed countries the drug ingestion is mostly among older people.[26] It is also noted that in the developing countries, the patients with perforated PUD present late to definitive management centres.[27] Many patients first sought medical assistance from traditional healers and unauthorized medical personnel prevalent in developing countries.[27]

For children suffering from PPU, the use of an open surgery is preferred as a surgical management.[28] On the other hand, treatment of children with complicated peptic ulcer disease, the use of laparoscopy is both effective and safe.[29]

Prescribing an antacid procedure for a stable patient at the time of initial surgery in the case of an adult patient with perforated peptic ulcer is in debate. However, the role of acid lowering medications in children has not been studied extensively. It has been reported that from 29 pediatric patients with complicated PUD, 5 have been managed with an antacid procedure at initial operation.[30] In a successful rare case of PPU diagnosed in an Asian nine-year-old, based on a literature review, it was decided to treat the perforation with primary repair and omental buttress [31].

PREVENTATION

Some important precautions are recommended by specialist in order to reduce the risk of developing ulcer. Some precautions are recommended to prevent the disease such as quieting smoke, avoiding alcohol drink, reducing intake of aspirin and/or NSAIDs. In many cases, taking NSAIDs can cause ulcer without any warning. The risk is especially concerning for the elderly and for those with a prior history of having peptic ulcer disease. Although the peptic ulcer is rare in children and young adults, especially in well-developed societies, they may rarely be at risk by NSAIDs *Helicobacter pylori* induced ulcers. Some cases have been reported even in western medical reports for developed countries [31]. In fact, acute surgical abdomen in infants and children are relatively few. The diagnosis of possible etiologies needs, therefore, very specialist attention and various diagnostic tests to be examined. However, literature reports about peptic ulcers in children, especially in western countries, is rare and goes back to decades ago.[32,33,34] Change of diet and reducing the wrong eating habits such as fast food and various salty and fried snacks are best recommended precautions for children to reduce the risk of peptic ulcer in modern societies. Considering the advanced world and its related busy minds, the risk of peptic ulcer could highly be reduced by lowering the oxidative stress, especially in aged population. A more relaxed and quite life and taking natural antioxidants are always helpful to prevent ulcers. For example, it has been reported that oral use of ethanol extracts from bark of *Combretum leprosum* Mart. & Eiche (Combretaceae) could have a gastroprotective and anti-ulcerogenic effect due to inhibition of the gastric acid secretion and increase of some mucosal defensive factors.[35]

Turmeric (*Curcuma longa* Linnaeus, Zingiberaceae) is one of the main spices broadly used in Asian foods, its most important constituent, curcumin, has a considerable inhibitory effect on *H. pylori* growth. Its anti *H. pylori* effect is tested both *in vitro* and *in vivo*.[36] Its use in cooked foods could, therefore, effectively prevent *H. pylori* induced peptic ulcer.

TREATMENT OF PEPTIC ULCER DISEASE

It is reasonable that hospital volume could affect outcomes of various endoscopic treatments.[37,39,39] Hospitals with large case volumes may have more experienced endoscopists who resulting in fewer complications and shorter length of hospital stay (LOS). It has been demonstrated that a higher hospital volume leads to a significantly shorter LOS, i.e. lower medical costs of hospitalization. However, the mortality was not altered when the volumes of cases in various hospital were compared.[40]

Synthetic drugs

A severity score method has been purposed to assess quantitatively the PPU. This could help monitoring the evolution of a patient's condition after admission, especially when nonoperative management is the initial action for a patient.[22] However, it should always be remembered that the test does not fully replace the clinical approach, but may supplement individual clinical judgment. It is suggested that the proposed model should be more validated using a larger population for being applicable finally to any PPU case.

It has been reported that about 72% of PPU can be successfully treated by nonoperative models with morbidity and mortality similar to the immediate surgical treatment.[4] However, the indication of nonoperative management for PPU has not been well established. The decision making for therapy is correlated to four parameters: age ≥70 years, fluid

collection detected by ultrasound, contrast extravasation detected by gastroduodenal imaging, and acute physiology and chronic health evaluation II (APACHE) II ≥8. The score obtained by combining these parameters could be an accurate measure for prediction the need for surgery.[4]

The severity of peritonitis should be considered when deciding the treatment approach, because secondary peritonitis is more life threatening for PPU patients than peptic ulcer itself.

The water-soluble contrast imaging is important in determining if the perforation is fully closed. When the contrast agent continues to spillover it is suggested that perforation is not well closed leading to continued leakage of gastrointestinal contents. On the other hand, positive results for the two radiological examinations reflect that peritoneal contamination is severe and aggravating. In addition, age and APACHE II score, which reflect the general condition of patients, are also the important parameters suggesting surgical therapy.[4]

Several clinical strategies are performed for treatment of ulcers, including a change in lifestyle, using specialist recommended synthetic or, in some cases, natural medicines and surgery. The specialist is the best person to find out the most suitable treatment for each individual depending on the cause, symptoms and severity of the peptic ulcer. A number of pharmacological agents have proven to be effective in the management of the acid peptic disorders. These groups include:

- Antacids, control the pH by neutralization the excess acid, such as aluminum hydroxide and magnesium trisilicate.
- Acid suppressive agents, control acid secretion and include proton pump H^+/K^+ ATPase inhibitors which reduce acid levels and increase the healing chance for the ulcer. Some examples are omeprazole (Perilosec), lanzoprazole (Dexilant), esmoprazole (Nexium), lanzoprazole (Prevacid), pantaprazole (Protonix), rabeprazole (Aciphex) and omeprazole/sodium bicarbonate (Zegerid),
- Histamine H_2 receptor antagonists, react as antagonist of histamine receptors such as cimetidine and ranitidine.
- Anticholinergic agents, such as pirenzepine,
- Cytoprotective agents (sucralfate and prostaglandin analogs misoprostol),
- Antimicrobials for eradication of *H. pylori* (amoxicillin, clarithromycin)

There are also specific treatments using a combination of various mechanisms, for example, triple therapy consists of a treatment plan for one week. A proton pump inhibitor such as omeprazole and the antibiotics clarithromycin and amoxicillin are prescribed together for a week.[41,42]

The most common and accepted treatment of peptic ulcers depends on using a number of synthetic drugs that reduce the rate of stomach acid secretion (antiacids), protect the mucous tissues that line the stomach and upper portion of the small intestine (demulcents) or to eliminate *Helicobacter pylori* (*H. pylori*).

A considerable number of ulcers are well treated using inhibitors of proton pump (PPIs). On the other hand, the NSAIDs induced peptic ulcer could be best treated if taking those medicines is stopped.

In the case of ulcer caused by H. pylori infection, special antibiotics are prescribed. The multiple mixture choice of antibiotics are recommended to be taken for one to two weeks together with a PPI. Bismuth is also part of some treatment regimens. If the ulcer is bleeding, it can be best treated using an endoscopic treatment.

Combination therapy using two or more specific synthetic drugs or prescription of a synthetic medicine administrated with a natural pharmacological plant part has received special attention recently and the efficacy of each medication is improved.[43,44]

However, inhibition of acid secretion is always the first common and most important strategy in treatment plan for a peptic ulcer. During the recent three decades public and scientific understanding from the physiology of gastric acid secretion and its effects on peptic ulcer disease has improved considerably. The design of a possible therapeutic plan to inhibit acid secretion is the main goal of physicians following this understanding.[14] During 1970s, histamine-2 receptors (H-2R) the proton pump, that regulates the secretion of gastric acid, were discovered. This important improvement in the field of internal medicine led to the development of H-2R antagonists during the same decade and the design of proton pump inhibitors (PPIs) in the following 1980s. More recent scientific discoveries have confirmed the importance of and the role played by *H.pylori* infection in pathogenesis of peptic ulcer disease. PPI's have been found well effective to suppress gastric acid secretion. It has been reported that PPIs are considerably more effective than H-2RAs

for decreasing morbidity and mortality during non-surgical management of perforated peptic ulcer.[15]

Natural products

In most cases, relapses and adverse reactions is observed following synthetic antiulcer therapy. Therefore, finding and examining a safe medication for management of ulcers with minimum side effects is the serious concern of researchers in pharmacetutical and natural products industries. On the other hand, a considerable number of medicinal plants and their secondary metabolites with anti-ulcer potential have been reported in the scientific literature.

However, some new anti-ulcer agents from natural sources have been introduced during the last 30 years. It is believed that many medicinal plants, herbs and spices, vegetables and fruits are potential sources for control of various diseases including gastric ulcer and ulcerative colitis. A number of medicinal plants and their secondary metabolites with potential anti-ulcer activities have been reported in scientific literature.[46] According to the traditional experiences and modern investigations by different scientists, treatment with natural products could result in promising results and perhaps fewer side effects.

Different parts of medicinal plants are traditionally used in various forms, i.e, freshly obtained plant parts, frozen or dried, extracts using different solvents and essential oils. The most acceptable and commonly prescribed medicinal form of natural sources is solvent extracted plant part. A number of polar and less polar solvents have been used to extract secondary metabolites from plants. The most widely used solvents, however, are, methanol, ethanol, diethyl ether, chloroform, ethyl acetate, n-butanol and water.[46] Although the choice of solvent is determinant in the active constituents, in preparations for medicinal purposes their toxic side effects should be considered carefully. A very scientific knowledge of the biochemical to extracted, its medical benefits is recommended for these preparations.

It has been confirmed that ethanol extract of turmeric (*Curcuma longa* Linnaeus, Zingiberaceae) when administrated orally produced significant anti-ulcerogenic activity in rats. The effect was related to increase gastric wall mucus leading to restoration of the non-protein sulfhydryl (NP-SH) content in the glandular stomachs of the rats.[47]

It is well documented that green tea extract (*Camellia sinensis* L.) can effectively treat ulcerative colitis.[48] Drinking green tea at a daily dose can also reduce body weight and act control diarrhea. It is purposed that it can inhibit the disruption of the colonic architecture, reduction of myeloperoxidase (MPO).

Most apple species have been traditionally used for their gastrointestinal effect and their role in digestion, which is now known to be due to the presence of cartenoids. For example, seven carotenoids have been identified in the peel extract of *Malus domestica* Borkh. Rosaceae (Golden delicious apple). These secondary metabolites have shown to exhibit a potent anti-*H. pylori* activity.[49]

The aqueous extract of *Enantia chlorantha* Oliv. (Annonaceae) stem bark possesses both *in vitro* and *in vivo* activities against *H. pylori*.[50]

Ginger is a common spice used in traditionally in many foods deserts and drinks, especially in Asian countries. It has been shown that aqueous extract of ginger roots possess strong anti-ulcer properties. This property is related to augmentation of mucin secretion and decreased cell shedding rather than offensive acid and pepsin secretion.[51]

The gastroprotective effect of methanolic extract of *Terminalia arjuna* (TA) has been reported on diclofenac sodium induced gastric ulcer of rats with effective dose of 400 mg/kg body weight.[52] The results showed a considerable reduction in lesion index of ulcer induced animals treated with TA compared to ulcerated rats not treated using TA. They also reported a significant increase in pH, NP-SH, GSH and a number of enzymic antioxidants. On the other hand, a significant decrease in volume of gastric juice, free and total acidity, pepsin concentration, acid output, LPO levels and MPO activities in TA treated rats was observed as compared to non-treated animals. It was, therefore, concluded that the free radical scavenging activity of *T. arjuna* makes it a suitable gastroprotective agent.[52]

Hymenaea stigonocarpa Mart. ex Hayne (MHs) is a medicinal plant found in the Brazilian savannah. Its anti-ulcer effect has been investigated in experimental rodent models.[53] It has been found that MHs could display a considerable gastroprotective effect on experimental gastric and duodenal ulcers. It is suggested that these effects are related to the presence of condensed tannins and flavenoids in the plant extracts.

The ethyl acetate extract of *Saussurea lappa* C.B. Clarke (Asteraceae) has shown to exhibit antiulcerogenic properties. It also possesses strong activity against peptic ulcer through a cytoprotective effect.[54]

The ethanol extracts of *Encholirium spectabile* Mart. (Bromeliaceae) aerial parts has a considerable protection effect on gastric mucosa against ulceration.[55]

The ethanolic extract of coconut seed (*Cocus nucifera* L., Arecaceae) when used orally could treat peptic ulcer as compared to control subjects.[56]

Oral administration of *Erythrina indica* L. (Febaceae) extract has shown to possess significant antiulcer properties in rats with peptic ulcer induced by indomethacin. The observed effect is partly due to the presence of polyphenolic compounds in methanolic leaf extracts.[57]

The extracts of some medicinal plants have antibacterial activity which could be effective on peptic ulcers induced by *H. pylori*. Antibacterial and antioxidant activity of medicinal plants can be examined *in vitro*. The *in vitro* assay of essential oil obtained from *Apium nodiflorum* L. (Apiaceae) has shown strong antibacterial activity against *H. pylori*, resulting in minimum inhibitory concentration (MIC) value of 12.5 µg/ml.[58]

The oral administrated of an ethanol extract from *Combretum leprosum* Mart. has shown to have gastroprotective and anti-ulcerogenic effects. It is suggested that the extract could inhibit secretion of gastric acid and increase factors that provide defensive activity of mucosal system.[35]

The wound healing mechanisms of *Rhizophora mangle* L. extract is based on the formation of a thick coating of plant extract which adheres macroscopically to the gastric mucosa. It then forms a physical barrier the same as the topical wounds.[59]

While aloe vera, ginger and honey are best active against both peptic ulcer and ulcerative colitis, licorice, turmeric, Al-Hagnah (*Desmostachia bipinnata*), Catinga de Bode (*Ageratum conyzoides*), Chamomile and ginger have been found to be considerably effective in the treatment of peptic ulcer through their cytoprotective effect in addition to their anti *H. pylori* effect.[60]

Psychological Intervention

It has been noted recently that the psychological conditions play a key role in the development of PUD and recovery from it. The PUD patients usually suffer from emotional disorders including depression and anxiety. Some of the patients suffering from PUD have experienced emotional disorders such as anxiety and depression. Therefore, the exclusive drug therapy may not be well effective and could result in recurrent.

It is known that behavior cognitive therapy is a reliable method leading to improvement of the patient's reality cognition, anxiety, depression and discontent emotions. Psychological intervention can eliminate the irrational way of thinking, as well as the mental and behavior disorders. On the other hand, it is a universally accepted fact that a highly stressful life may lead to acute peptic ulcer.[43]

The efficacy of psychological intervention against ulcer has been studied on 96 PUD patients using a mental intervention together with drug therapy.[61] In the mentioned research, the patients were divided into two groups, trial and control. To the control group the medical advice and Tagamet (800 mg daily) for 6 weeks. The trial group also received the same drug therapy together with the psychological interventions. Their results indicated that healing rate of trial group was significantly higher than control.

Last and not least, it should always be considered that many factors may lead to important and, sometimes dangerous, side effects. The possibility of adverse drug resistances (ADRs) to occur is also of prime importance when designing a treatment plan or a drug regim. A number of factors are associated with ARD occurrence, some of which are patient related, drug related or socially related. Age, race, alcohol intake, smoking, kidney and liver problems, drug dose and frequency, gender, pregnancy, breast feeding, and many other factors may contribute.

SUMMARY

Based on literature review performed in this study, the following conclusions are made. Peptic ulcer disease secondary to *H. pylori* infection is important to be diagnosed due to the high reported incidence of recurrence.

Perforated gastro-duodenal ulcer is normally managed from conservative non-operative therapy to radical surgical treatment (gastrectomy). Most cases are treated by simple suture of the perforated intestinal wall. In most cases, the best treatment is surgical or laparoscopic suture closure of the perforated ulcer. The first step should be treatment of *H.pylori* infection regardless of chosen

intervention. Perforated gastric cancer can be treated urgently by simple suture closure, followed by a second-stage carcinologic gastrectomy without compromising survival. Perforation from peptic ulcer disease is adequately treated with primary closure, omental buttress, and medical management of the underlying etiology.

The incidence of perforated peptic ulcer in children has been decreasing in industrialized, well developed countries. Laparoscopy is a safe and effective tool in the surgical management of complicated peptic ulcer disease in children.

Anxiety and depression can postpone gastric digestion and emptying process. The overloaded gastrointestinal function could make the base for prevalence of peptic ulcer. They also aggravate the somatic symptoms of the ulcer leading to the negative emotions reversely in a vicious circle. Therefore, a psychological intervention amending the circle is an important step for ulcer therapy. In sum, psychological intervention combined treatment is suggested to be considered with higher emphasis in the future medical care.

Natural products have found a special place in the treatment plans for peptic ulcer disease. They exhibit their antiulcerogenic activities by various mechanisms either prophylactic or therapeutic or both. The prophylactic products have considerable antioxidant and anti-inflammatory activities. On the other hand, therapeutic agents possess antisecretory or healing effects. The anti-*H.pylori* activity of some plant extracts, however, may explain their antiulcerogenic activity.

Consumption of a healthy diet composed of fruit pulp and various vegetables could give rise to duodenal healing effects. The observed effects by natural plant extracts may be due to their antioxidant effect and the presence of condensed polyphenols and flavonoids present in their various parts.

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