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# PEPTIC ULCER DISEASE: AN OVERVIEW OF RECENT ADVANCEMENTS

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## ABSTRACT

Peptic ulcer disease is one of the most prevalent gastrointestinal disorders that affect millions of people per year. The pathophysiology of peptic ulcer has centered on an imbalance between aggressive and protective factors in the stomach. Ulcer healing is a cumulative effect of several physiological and constitutive processes that occurs in tandem. A high degree of coordination and regulation during complex sequence of ulcer healing is carried out by different factors. Among them prostaglandins and growth factors have received much attention in recent years. Prostaglandin gets synthesized in the mucosal cells by cyclooxygenase (COX) enzyme. Therefore, induction of COX-2 expression leading to higher level of prostaglandin appears to be an important contributing factor in drug mediated ulcer healing apart from the respective mechanisms of different drugs.

**Key words:** Peptic ulcer, Healing, prostaglandins and Cyclooxygenase

## INTRODUCTION

For more than a century, peptic ulcer disease (PUD) has been a major health problem throughout the world as it affects millions of people each year. It is characterized by symptoms of burning epigastric pain, vomiting and gastrointestinal hemorrhage. Clinically, it is defined as disruption of gastroduodenal mucosal integrity of stomach or duodenum leading to a local defect of excavation due to active inflammation. The major forms of peptic ulcer include gastric and duodenal ulcer[1].

Epidemiologically, peptic ulcer represents a global disorder because of its wide spread occurrence with high morbidity, mortality and economic loss. Approximately 10% of adults suffer annually from peptic ulcer disease and 5,00,000 new cases along with 4,00,000 cases of recurrence are reported each year. An estimated 15,000 deaths per year occur as a consequence of complicated PUD[1]. The financial impact of this common disorder has been substantial, with an estimated burden on direct and indirect health care costs of ~ $10 billion per year in the United States[1].

Such a high global incidence rate, simpler to severe pathophysiological effects and uniform occurrence across all ages, races and ethnicity, makes peptic ulcer an important target that continues to arrest the attention of both clinicians and researchers; hence there is a need for major therapeutic strategy. Important advances have occurred in last two decades that have improved our understanding for this disease as well as our approach towards its treatment.

### Pathophysiology of gastric ulcers

The pathophysiology of peptic ulcer has centered on an imbalance between aggressive and protective factors in the stomach[2]. Major breakthrough occurred when different factors that lead to integrity and disruption of gastric mucosa were unveiled.

Gastric mucosal integrity is maintained through a balance between aggressive and defensive factors (Fig. 1). The former include acid, pepsin, *Helicobacter pylori (H pylori)*, nonsteroidal anti-inflammatory drugs (NSAIDs), smoking, alcohol, ischemia and corticosteroid use whereas

later include mucus, bicarbonate, blood flow, prostaglandins and growth factors. Among these aggressive factors, acid and pepsin confers the contributory role in ulcerogenesis[3].

The ability of gastric mucosa to resist injury by endogenous secretions (acid and pepsin) and by ingested irritants (alcohol and NSAIDs) is attributed to a number of factors, which are collectively termed as mucosal defence[4]. These lines of defense act finally for ulcer healing process that cause the repair and reconstruction of mucosal architecture through growth and redevelopment of gastric glands, growth of new blood vessels (angiogenesis) and re-innervation of the mucosa by extrinsic and intrinsic nerves[5].

**Ulcer healing**

Ulcer healing, a genetically programmed repair process, is an active and complicated array of different mechanisms that involves filling of mucosal defect with proliferating and migrating epithelial cells and connective component so as to reconstruct the mucosal architecture[6]. Ulcer healing is considered to be a spontaneous process, where either the precipitating cause of ulceration gets removed or there occurs a readjustment of the gastric milieu to a state that favours healing. Healing requires angiogenesis in the granulation tissue at the base of the ulcer, together with replication of epithelial cells at the ulcer margins and subsequent re-establishment of glandular architecture[7].

Ulcer healing is a cumulative effect of several physiological and constitutive processes that occurs in tandem and requires a high level of co-ordination and regulation. There occurs a two-tier strategy that forms the basis of both normal as well as drug mediated ulcer healing. First involves decrease of acid concentration in the lumen of the stomach while second one involves strengthening of mucosal defense system and tissue repair mechanism.

**Role of Prostaglandins in ulcer healing**

A high degree of coordination and regulation during complex sequence of ulcer healing is carried out by different factors. Among them prostaglandins (PGs) and growth factors have received much attention in recent years[8,9]. The gastric mucosa contains abundant level of PGs mainly $PGE_2$ and $PGI_2$, which provide their effect by stimulating mucosal bicarbonate and mucus secretion, increasing blood flow, preventing the disruption of mucosal barrier, accelerating cell proliferation, stimulating cellular ionic transport processes, retarding cAMP production, promoting formation of surface phospholipids, maintaining gastric mucosal sulfhydryl compounds, stabilizing cellular lysosomes and cell membrane[1,10-13].

However, these PGs exhibit a dual character in their functioning because along with being a strong ulcer healing agent, PGs are also a well known mediators in different features of inflammation- pain (dolor), swelling (tumor), erythema (rubor), warmth (calor) and loss of function (function laesa). This duality of PGs in their functioning is well established when on one side inhibition of their synthesis by aspirin and NSAIDs causes anti-inflammatory, analgesic and antipyretic effect while on the other hand it produces the side effects of gastric ulceration, bleeding and renal dysfunction. The therapeutic and adverse side effects of these agents are due to the inhibition of prostanoid synthesis.

**Cyclo-oxygenase Enzymes (COX)**

The duality of PGs as a mediator of physiologic and pathologic function was clarified when two different isoforms of Cyclooxygenase enzyme (COX) were identified. COX is the key enzyme responsible for the synthesis of PGs via arachidonic acid, exist in two isoforms- COX-1 and COX-2. According to the classical COX hypothesis, COX-1 considered to be a classical COX enzyme and is constitutively expressed; while COX-2 is expressed as an inducible enzyme in most cells[14]. Nevertheless, there is also a constitutive expression of COX-2 in the kidney, brain, and female reproductive system[15]. PGs, which are products of COX-1, exert different physiological or "housekeeping" effects while the products of COX-2 are essentially involved in inflammation[16]. The molecular identification of two isoforms of COX have led to the development of selective COX-2 inhibitors as new NSAIDs drugs that are devoid of gastric toxicity[17]. Selective COX-2 inhibitors such as celecoxib and rofecoxib are endowed with significantly improved gastric tolerability associated

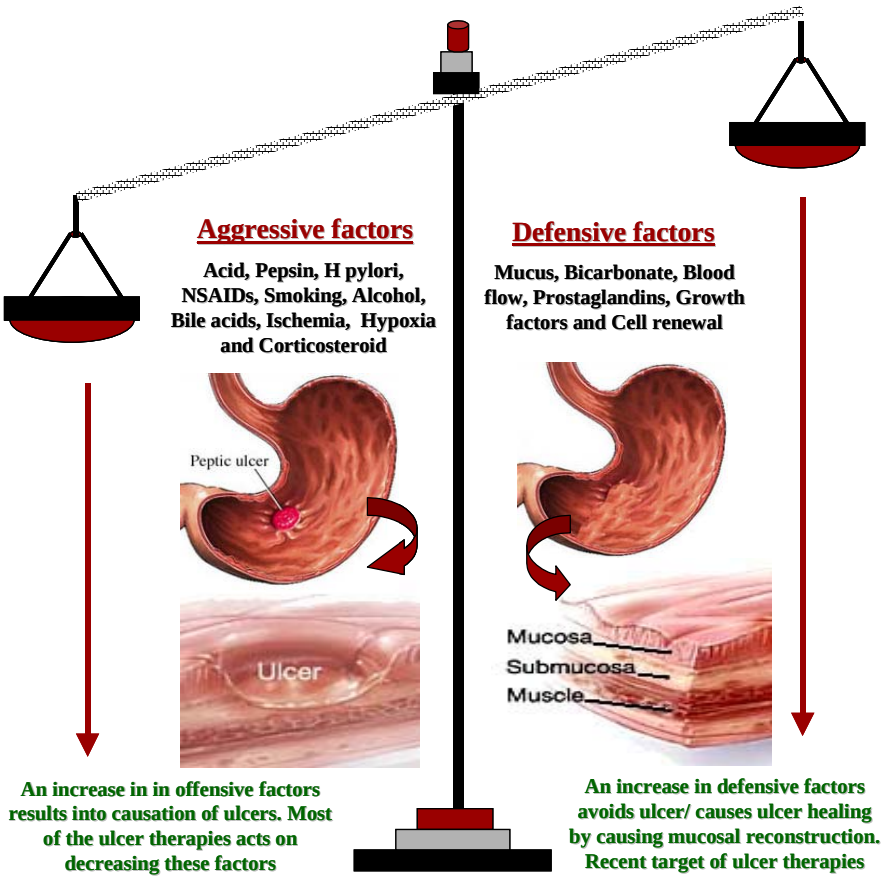


**Fig. - 1: Different offensive and defensive factors whose imbalance results into causation of ulcer while the normal balance results into mucosal reconstruction**

with a therapeutic efficacy comparable to traditional NSAIDs[18].

However, recent advances reveal that the classical COX hypothesis is oversimplistic. There emerges a broad consensus on the fact that COX-2 plays more complex and wider biological role than mere involvement in inflammation and pain[19]. Important among them are healing process in various gastrointestinal pathologies[20] and some regulatory effect in renal system[21]. Further, Gilory *et al.* (1999)[22] has shown that COX-2 produces PGs that exerts anti-inflammatory action while Brzozowski *et al.* (2001)[23] have highlighted their role in gastric ulcer healing.

These observation brought a change in the classical COX hypothesis and have strengthen the view that COX inhibition is not associated with gastric damage in normal mucosa, but it can be detrimental when gastric mucosal defense is impaired. Further support to this hypothesis was provided by Mizuno *et al.* (1997)[24] who have demonstrated that COX-2 is strongly expressed at the margin of healing ulcers in mice and Brzozowski *et al.* (2001) and Dharmani *et al.,* (2005)[23,25] that have reported that administration of selective COX-2 inhibitors delay healing of gastric ulcers. All these findings mark a shift in our understanding of ulcer healing mechanisms. COX-2 enzyme and PG synthesis starts appearing to be an important target for the treatment modalities of gastric ulcers and continues to arrest the attention of researchers.

In regard to the latest developments in the field of gastric ulcer therapy and emergence of COX-2 as a potent drug target that can not only triggers angiogenesis via enhanced production of PGE2

but also lead to faster ulcer healing, our group has actively participated in deducing the exact role of COX-2 in mucosal reconstruction[25]. When we have compared the existing drug treatment modalities like Omeprazole, Misoprostol and a COX-2 inhibiting NSAID, Celecoxib, we found that OMZ is the most potent ulcer-healing drug[26-28]. Furthermore when we tried to deduce about the possible factors that promote mucosal reconstruction and re-synthesis at ulcer healing, it was clearly established that COX-2 and its product PGE2 are pivotal. The expression analysis of COX-2 gene both at the level RNA as well as protein revealed that elevation in ulcer healing and COX-2 expression runs in parallel signifying that induction of COX-2 expression leading to higher level of prostaglandin is an important contributing factor in drug mediated ulcer healing apart from the respective mechanisms of different drugs[25].

**Current therapeutic strategies**

Anti-ulcer drugs mainly focuser on decreasing the acid secretion and/or strengthening the mucosal defence system. The treatment goals for peptic ulcers are to relieve symptoms, promote ulcer healing and prevent ulcer recurrence and complications. There are so many classes of drugs currently used to combat acid-peptic disorders. The current treatment strategies of gastric ulcer include following categories of drugs each of which act through a different mechanism. **1) *Acid neutralizing/ inhibitory drugs*** This category of drugs includes: (a) ***$H_2$ receptor antagonists*** (cimetidine, ranitidine and famotidine) (b) ***Proton pump inhibitors*** (omeprazole, lansoprazole and raberoprazole) (c) ***Antacid*** **2) *Cytoprotective agents*** (sucralfate) **3) *Prostaglandin analog*** (misoprostol) **4) *Miscellaneous drugs*** (anticholinnergic drugs and rabempimide)

**1. Acid neutralizing/inhibitory drugs**

This class of drugs mainly acts through potent inhibition of acid secretion or neutralization. This mainly includes $H_2$ receptor antagonists, proton pump inhibitor and antacids

**a) $H_2$ receptor antagonists**: The description of selective $H_2$ receptor was the landmark in the history of pharmacology and set the stage for the modern approach of the treatment of acid-peptic diseases. Four different $H_2$ receptor antagonists are available (cimetidine, ranitidine, famotidine and nizatidine). All the four drugs are available in dosage form for oral administration, intravenous and intramuscular preparation.

$H_2$ receptor antagonists inhibit acid production by reversibly competing with histamine for binding to $H_2$ receptors on the basolateral membranes of parietal cells. The most prominent effects of these drugs are on the basal acid secretion. Significant inhibition is reported in stimulated acid production (feeding, gastrin, hypoglycemia or vagal stimulation). These agents are thus particularly effective in suppressing nocturnal acid secretion.

The acid inhibitory effect obtained with high doses of $H_2$ receptor antagonists is built up rapidly but has the tendency to fade. The term tolerance has been applied to characterize this phenomenon. The reason for tolerance effect of $H_2$ antagonists is still not entirely understood. Another disadvantage of ranitidine therapy is that it is associated with marked rebound hypersecretion of acid[29].

**b) Proton pump inhibitors**: The most effective suppressors of gastric acid secretion undoubtedly are the gastric $H^+K^+$ATPase/proton pump inhibitors (PPIs). They are the most effective drugs used in anti-ulcer therapy and have found worldwide popularity over the past decade[3]. Currently, there are several different PPIs available for the clinical use: Omeprazole, lansoprazole, raberoprazole and pantoprazole. They are á-pyridylmethylsulfinyl benzimidazole with different substitutions on the pyridines or the benzimidazole groups.

These agents are “prodrugs” requiring activation in an acid environment. They are supplied to body in the form of enteric-coated capsules or tablets that pass through the stomach intact and are absorbed in the proximal small bowel. Once absorbed, all PPIs have a relatively short plasma half life (about one to two hours). Their duration of action is much longer because of their unique mechanism of action. These agents enter the parietal cells from the blood and because of their weak basic nature, accumulate in the acidic secretory canaliculi of the parietal cell, where they are activated by a proton-catalysed process that results in the formation of a thiophilic sulfonamide or sulfenic acid. This activated form reacts by covalent binding from the extracellular domain of

$H^+K^+$ATPase. Binding of cysteine 813, in particular, is essential for inhibition of acid production, which is irreversible for that pump molecule[30].

PPIs are mainly used principally to promote healing of gastric and duodenal ulcers and also in treatment of acid related conditions such as ulcers, GERD, NSAIDs induced gastropathy and ZE syndrome. PPIs are also used in combination with antibiotics for eradication of *H pylori.*

**c) Antacids**: Antacids are used usually for symptomatic relief from pain now-a-days however in the past antacids were the only drugs available to treat peptic ulcers.

Antacids that are weak bases react with the HCl of the stomach and produces salt and water. This raises the pH of the gastric content, which inactivates pepsin. Alkalinization of gastric contents increases gastric motility, through the action of gastrin. The most commonly used agents are mixture of aluminum hydroxide and magnesium hydroxide. Combination of aluminum and magnesium hydroxide provide a relatively fast and sustained neutralizing capacity.

**2. Cytoprotective agents**

Cytoprotective/ cell protective agents help in protection of the lining of stomach. Sucralfate and misoprostol are the two important cytoprotective agents. These agents are second line medication and are not first choice for treating ulcers. Sucralfate, a basic aluminum salt of sulfated sucrose act by forming a physical barrier to attack by acid, bile salts and pepsin across the mucosa. It doesn't work by inhibiting acid but forms a protective layer over a gastric ulcer to shield it against acid so that healing can occur. It also binds to the site of active ulceration. Sucralfate may act by several mechanisms, as they may bind with growth factors, enhance PG synthesis, stimulate mucus and bicarbonate secretion and enhance mucosal defenses and repair.

Misoprostol, a synthetic PG analog, is another cytoprotective agent, which is clinically widely used drug against NSAID induced gastric ulcer. Misoprostol moderately blocks acid release into the stomach and helps in maintaining the integrity of the stomach. Its therapeutic effects are mediated through enhancement of mucosal defenses and repair. PG analogs enhances mucus bicarbonate secretion, stimulate mucosal blood flow and decreases mucosal cell turnover.

**3. *H. pylori* therapy**

*H pylori* is associated with majority of gastric as well duodenal ulcers. Eradication of *H pylori* leads to a better treatment for peptic ulcer. *H pylori* related peptic ulcers are treated with drugs that kill the bacteria, reduces stomach acid, and protect the stomach lining. Eradication of *H pylori* includes double, triple and quadruple therapies or combination products (which consist of multiple drugs combined into one package). Antibiotics are used to kill the bacteria, while those two types of acid-suppressing drugs are mainly used: $H_2$ blockers and PPI. The most effective therapy for *H pylori* is the three-drug regimens, since cure rates are typically higher with these therapies (83.3%)[31]. Two-drug regimens tend to have a lower cure rate and four-drug regimens, while very effective, are more complicated to take. Therefore, a three-drug regimen or possibly a combination product is recommended as the most effective means of treating ulcers caused by *H pylori*.

**4. Miscellaneous drugs**

Certain other drugs such as anticholinnergic drugs are also use to reduce the acid secretion. They can reduce the basal acid production by 40-50%. Rebamipide, an amino acid analog of 2 (1H)-quinolinone, is a novel mucosal protective and ulcer healing drug developed in Japan[32] Carbenoxolone, a component of licorice root and a derivative of glycrrhizic acid, has been also used as an anti-ulcer agent in Europe.

**Conclusion**

Studies along with establishing the role of COX-2 enzyme in the process of both natural and drug mediated ulcer healing, will also be helpful in providing necessary information for the development of better ulcer therapeutic modalities that strengthens the defensive mucosal system and targets mainly the repair and reconstruction of mucosal architecture in addition of inducing a fall in the levels of offensive factors.

Induction of COX-2 protein expression that controls the reparative mechanism through angiogenesis and adaptive cytoprotection along with elevation in the synthesis of prostaglandin

seems to be the certain candidates for the ulcer healing modalities. Endogenous prostaglandins ($PGE_2$), having modulating roles on COX-2 expression is an additional aspect. Drugs that can lead to an elevation in the expression level of COX-2 remains more successful in ulcer healing while its inhibition produces a downward effect.

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