Peptic disease in elderly patients

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N Khaghan, PR Holt. Peptic disease in elderly patients. Can J Gastroenterol 2000;14(11):922-928. The increase in life expectancy demands that more attention be given to gastrointestinal problems, such as peptic ulcer disease, in elderly people. This review summarizes many of the physiological changes that have a role in peptic ulcer disease in elderly patients. How *Helicobacter pylori* infection modifies the course of peptic disease is also reviewed. The clinical presentation of peptic diseases often differs in elderly people, and atypical symptoms are common. Accurate diagnosis requires aggressive endoscopic evaluation. Treatment regimens using H₂ receptor antagonists, proton pump inhibitors and regimens to eradicate *H pylori* may also need to be altered in elderly patients.

Key Words: Elderly people; *Helicobacter pylori*; Peptic ulcer

L'ulcère gastro-duodénal chez les patients âgés

RÉSUMÉ : L'augmentation de l'espérance de vie exige qu'une attention plus grande soit portée aux troubles gastro-intestinaux, par exemple l'ulcère gastro-duodénal, chez les personnes âgées. Le présent article donne un résumé d'un bon nombre de changements physiologiques qui jouent un rôle dans l'ulcère gastro-duodénal chez les patients âgés. On y traite aussi de l'incidence des infections à *Helicobacter pylori* sur l'évolution de la maladie. Le tableau clinique diffère souvent chez les personnes âgées, et les symptômes atypiques ne sont pas rares. La pose d'un diagnostic précis requiert une évaluation endoscopique minutieuse. Il est également parfois nécessaire de modifier les traitements composés d'antagonistes des récepteurs H₂ ou d'inhibiteurs de la pompe à protons et les traitements visant à éradiquer *H. pylori* chez les patients âgés.

PATHOPHYSIOLOGY

Recent advances in public health and medical care technologies have prolonged the average life span throughout the world. However, this prolonged life span has been accompanied by a higher incidence of chronic diseases in elderly people. Gastrointestinal diseases play a significant role in such chronic illness. As part of this problem, peptic ulcer disease has become a major cause of morbidity and mortality in elderly patients.

In 1991, McCarthy (1) estimated that 25% of all admissions to hospitals and 20% of all deaths in the United States were due to gastrointestinal disease. Of the deaths from gastrointestinal disease, one-fifth were due to peptic disease of the stomach and duodenum. Many authors in the Western world over the past two decades have clearly shown that the first diagnosis of peptic ulcer disease and admissions to hospital for complications of peptic ulcer disease occur almost entirely in individuals over the age of 65 years (2-4). Thus, peptic ulcer disease is a disease of elderly men and women, and no longer mainly a disease of young men, as was the case in the 1940s and 1950s.

A wide range of physiological changes are thought to be associated with the process of aging, including changes in the organs of the gastrointestinal tract. In previous reviews, such effects as decreases in motility, and in gastric, pancreatic, biliary or intestinal secretions, and changes in absorptive capacity have been described. More careful analyses of the physiological effects of aging that excluded the influence of disease resulted in a major reconsideration of what can be attributed to physiological changes as a part of the process of aging.

Table 1 summarizes the major issues surrounding peptic diseases in elderly patients. The following are important: the role of *Helicobacter pylori* infection in altering the control of gastric acid secretion and in determining the incidence and course of peptic disease in older patients; crucial differences in the clinical picture of older patients with peptic disease; the issue of whether the evaluation and the diagnostic approaches that are usually used in younger patients should differ when considering peptic disease in elderly patients; and

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TABLE 1
Major issues concerning elderly patients with peptic disease

Changes in gastric acid and pepsin secretion
Changes related to esophageal or gastric motility
The role of <i>Helicobacter pylori</i> infection
Difference in clinical practice
Whether evaluation and diagnostic approaches should differ
Whether treatment should differ

whether treatment options should be altered because a patient is over the age of 65 years (Table 2).

Until recently, it was generally believed that gastric acid secretion declined with advancing age. For example, Baron (5) described a decrease in basal secretion and peak acid output after histamine stimulation with increasing age. This study, however, used 30 years as the age to divide a small number of young and older subjects. More recent studies from the United States and elsewhere reported that basal and stimulated gastric hydrogen ion secretions did not fall if patients with atrophic gastritis and *H pylori* infection were excluded (6-8). Most of these studies did not include sufficient numbers of volunteers older than 65 years of age. A more comprehensive prospective study that included 22 subjects older than 65 years of age found no significant effect of age on gastric acid secretion after adjusting for the influence of atrophic gastritis and smoking (9). Serum gastrin levels were similar at all age groups but became elevated in the presence of atrophic gastritis. However, pepsin output was significantly depressed in older subjects in this study. A study in rats up to 24 months of age demonstrated a reduction in basal and gastrin-stimulated acid output, and lower serum and antral gastrin concentrations in older animals (10). A recent study in Sprague-Dawley rats between the ages of seven and 90 weeks suggested that gastrin receptor mRNA was markedly higher in 65- and 90-week-old rats than in younger animals (11). The causes and consequences of these changes are unclear.

Further data showing that acid secretion is maintained in old age came from a study using a noninvasive quininium resin method, which distinguishes acid secretion above and below pH 3.5. In this study, basal secretion was found to be below 3.5 in nearly 90% of 248 elderly volunteers (12). Subjects with consistent hyposecretion usually showed serological evidence of atrophic gastritis. In young and elderly Japanese volunteers, gastric acid secretion was studied both in the 1970s and in the 1990s, showing greater acid secretion in the young and elderly individuals over these two decades in both *H pylori*-positive and -negative subjects (13). This study suggested that elderly Japanese people had lower basal and maximal acid secretion than younger individuals.

It is well recognized that defense mechanisms play a major role in limiting the initiation, progress and healing of peptic ulcers. Gastric and duodenal bicarbonate secretion is an important factor that helps to limit the amount of luminal acid that traverses the mucin layer covering the mucosa. Limited

TABLE 2
Physiological changes with age

Aggressive factors
Gastric hydrogen ion secretion
Defense mechanisms
Bicarbonate secretion
Mucin production
Prostaglandin concentration
Blood flow
Adaptation to injury

studies in rodents (14,15) and in humans (16) have suggested that bicarbonate secretion may be lower in older animals and humans than in young animals and humans. The effect of injury on such bicarbonate secretion has not been studied. The secretion of mucopolysaccharides provides an important barrier to acid-induced injury of the stomach. There have been relatively few studies of changes in mucin secretion as a function of age (17), nor has there been any systematic evaluation of changes in hydrogen ion transfer through the mucin layer. Furthermore, studies by Dial and Lichtenberger (18) indicating the importance of the hydrophobic properties of the gastric mucosa in protecting gastric epithelial cells have not focused on changes that might occur during the aging process.

Cryer et al (19,20) evaluated changes in prostaglandin (PG) concentrations in the gastroduodenal mucosa of animals and humans, as well as the PG responses of the mucosa to injury. These results have been confirmed by others (21). These studies have pointed to lower concentrations of PGE₂ and PGF_α in the fundus and antrum of the stomach as well as in the duodenum of elderly subjects (aged 56 to 81 years). Furthermore, studies of the effect of stimulants that injure the mucosa upon PG production also suggest that the response is impaired as a function of age (22). Recent findings that very small doses of acetylsalicylic acid (ASA) reduce PG concentrations of the stomach dramatically raise the question of whether some of the previous results of PG concentration may have been due to subjects taking intermittent salicylates (23). All of these data imply that these individuals have a relatively deficient defense mechanism associated with PG secretion.

Changes in blood flow have also been demonstrated to occur as a function of age. Arteriosclerotic vascular changes are almost universally present in elderly people, but their impact on gastrointestinal mucosal blood flow has not been demonstrated to be important. On the other hand, limited studies have suggested that mucosal blood flow may be lower in older animals than in their younger counterparts (24,25). One group of investigators who studied this problem using taurocholate to increase back diffusion of acid concluded that increased injury in older rats was due to impaired blood supply to the stomach because of a defect in capsaicin-sensitive sensory neurons (26).

An important way to understand changes in physiology as

a function of age is to examine the coordinated effect of injury to the stomach. Such studies can examine the initial extent of injury that is caused by a uniform or standard injurious agent, the subsequent overall healing rate of such injuries or some of the individual steps during the healing process, such as restitution of injured surface or proliferation of epithelial cells. Studies in organs other than those in the gastrointestinal tract have demonstrated defects in the rate of repair of experimental injuries.

Several studies have not shown an increase in ulcer size after application of injurious agents in older rodents compared with younger rodents (27,28). Gastric ulceration induced by acetic acid applied either to the serosa or to the mucosa showed no consistent differences in ulcer size or in ulcer healing in Sprague-Dawley rats aged two to three months, 11 to 12 months or 23 to 24 months (29). In this study, even the administration of indomethacin failed to alter the healing rate of older animals any more than in the younger animals (29). Similarly, Tsukimi and Okabe (28) showed no changes in the healing of gastric ulcers in older rats.

Hypertonic saline application to the stomach was shown to induce more gastric damage in aging rats than in young rats (30). However, studies of acute ASA-induced gastric injury have found conflicting results in animals (31,32). Investigators using cold restraint-induced stress ulcerations also have reported variable results (33,34). Differing injurious agents may have variable effects in different strains of animals.

Because of these differences, it is pertinent to examine some of the individual steps that are associated with prevention of gastric ulceration or accompany effective healing of such ulcers once produced. Epithelial repair after superficial injury is called restitution, a process that takes place immediately after injury and involves cell migration over the injured area. Several peptides are involved, including epidermal growth factor, acidic and basic fibroblast growth factor, cytokines and trefoil peptides. No studies have specifically focused on this process in the gastric mucosa of aging animals.

Majumdar et al (35) performed a series of studies to characterize differences in gastric proliferation and responses to injury in Fisher 344 rats studied between the ages of four and 24 months. This group described an increase in mucosal proliferation in the older animals accompanied by a rise in mucosal membrane tyrosine kinase activity (35) and in other phosphotyrosine proteins (36), including pp60 c-src (37). Basal levels of the mRNA for epidermal growth factor receptor (EGFR) and of EGFR-ligand transforming growth factor- α were higher in the gastric mucosa of older rats (38). The delay in epithelial restitution that occurs after 2 M sodium chloride-induced gastric injury was accompanied by impairment in the response of EGFR in aging rats compared with that in their younger counterparts (38,39). Delayed proliferation was also associated with reduced tyrosine kinase activity (40).

A reduced proliferative response following injury in older animals has been confirmed by several other investigators

(30,41), in contrast with observations showing a high rate of cell proliferation in aging rats under basal conditions (28,42,43).

Although it is generally believed that esophageal transit and gastric emptying are affected by age, the data do not support this prejudice. The majority of studies that have suggested that motor function is deranged have included individuals with diseases that alter esophageal and gastric motility such as diabetes and neuromuscular disorders. Tertiary contraction of the esophagus is much more common in elderly persons than in young persons, yet this represents a radiological entity without physiological consequences (44). Gastroesophageal reflux occurs more commonly (45). Furthermore, achlorhydria, when it is present due to atrophic gastritis, is well known to be associated with delayed gastric emptying of solids. However, there is some suggestion that the emptying of liquids may be slightly slower because of greater relaxation of the body of the stomach. This function is known to be controlled by the vagus nerve (46). It should also be remembered that many elderly individuals take medications that are associated with anticholinergic actions, which may affect the emptying of both the esophagus and the stomach.

CLINICAL MANIFESTATIONS

Clinical manifestations of peptic disease differ between elderly and young patients. The classical symptoms of peptic disease may be absent, atypical and often nonspecific in elderly patients (47). Older patients often suffer from other serious medical conditions such as diabetes, as well as from disabilities such as the neurological sequelae from cerebrovascular accidents, which may alter or diminish the symptoms of peptic diseases (47). Even physical signs such as abdominal guarding and rebound can be less prominent in elderly patients because of such coexisting disease, previous surgery or current drugs, including anti-inflammatory medications or corticosteroids. A dramatic example of differences in the clinical picture in elderly patients is seen with acute gastroduodenal perforation, in which the signs of chemical peritonitis resulting from the action of gastric contents may be absent when the patient is hypochlorhydric (48).

The initial symptoms of elderly patients with duodenal or gastric ulcers are often vague and nonspecific (49). Patients present more frequently with anorexia, weight loss, dyspepsia or complications of ulcers such as bleeding, perforation or anemia (Table 3). Abdominal pain occurs less frequently in older patients with peptic ulcers than in younger control subjects (50), and may be absent in as many as one-third of elderly patients who present with bleeding ulcers and in more than half of patients using nonsteroidal anti-inflammatory drugs (NSAIDs) (50).

Gastrointestinal bleeding is a common first manifestation of peptic ulcer disease in the older patient. As a result, these patients may come to medical attention because of systemic manifestation of subacute or chronic blood loss such as shortness of breath, chest pain or loss of consciousness. Thirty-five per cent to 45% of all cases of active upper gas-

TABLE 3
Age-related differences in peptic ulcer presentation

Elderly patients	Younger patients
Anorexia	Abdominal Pain
Weight loss	Dyspepsia
Gastrointestinal bleeding	Gastrointestinal bleeding
Dyspepsia	Anemia
Perforation	
Anemia	

gastrointestinal hemorrhage occur in patients older than 60 years of age; half of these cases are caused by peptic ulcer disease (51). Other causes of upper gastrointestinal hemorrhage in elderly patients are shown in Table 4. Bleeding from any cause in an elderly patient, however, may be aggravated by the concomitant use of anticoagulant drugs (such as coumadin or heparin) or antiplatelet agents (such as ticlopidine, and ASA and other NSAIDs).

Peptic ulcer disease: Gastric ulcer disease is considered principally a disease of advanced age because it is found more commonly in elderly than in young patients. Gastric ulcers in older patients tend to be large and occur with greater propensity higher in the stomach (50). The majority of non-NSAID-associated gastric ulcers in such patients are found high on the lesser curve; therefore, special attention should be paid to examination of the fundus during endoscopy. Many previous studies have suggested specific factors that may be very important in the development of gastric ulcers in elderly patients, including the use of ASA and other NSAIDs, the rising prevalence of gastritis due to *H pylori* infection with advanced age and the high prevalence of smoking (52).

Giant gastric ulcers, defined as ulcers larger than 2.5 cm in diameter, also occur more frequently in elderly patients. The peak incidence occurs from 60 to 70 years of age in men and from 70 to 80 years of age in women. These ulcers usually are benign but often mimic the clinical features of gastric cancer. About one-half of giant gastric ulcers present clinically as an acute or chronic bleed. In one study, the mortality rate from bleeding of giant gastric ulcers was as high as 37% (53), suggesting that early surgical intervention may be warranted. On the other hand, the perforation rate in these patients has been quoted to be as low as 5% (53).

Gastroesophageal reflux: Gastroesophageal reflux is more common than peptic ulcer disease in both elderly and younger patients. The increased incidence of gastroesophageal reflux disease (GERD) in older patients may be due to the decrease in amplitude of esophageal peristalsis and delayed acid clearance from the esophagus, the increased incidence of sliding type hiatus hernia and the reduction in salivary bicarbonate response to esophageal acid exposure (54). Many medications may also decrease the lower esophageal sphincter pressure and thus make elderly patients more prone to GERD. When heartburn and acid regurgitation are predomi-

TABLE 4
Causes of upper gastrointestinal bleeding in elderly patients

Gastric ulcer	Esophageal or gastric varices
Duodenal ulcer	Mallory-Weiss tear
Pyloric channel ulcer	Gastric carcinoma
Gastritis	Aorta-enteric fistula
Esophagitis	Mycotic aneurysm
Duodenitis	Dieulafoy lesion

TABLE 5
Methods of testing for *Helicobacter pylori*

Histology of biopsy samples
Culture of biopsy tissue or gastric contents
CLO testing
Urea breath testing
Serology for of immunoglobulin A and G antibodies to <i>H pylori</i>

nant symptoms, they can be regarded as highly specific indicators of reflux, but when they are present together with other dyspeptic symptoms, reflux cannot be diagnosed reliably (55). Retrosternal pain occurs much less commonly in elderly than in young patients. Vomiting and anorexia are encountered more often in elderly patients with reflux than in young patients with reflux, and are more frequently described than heartburn (56). GERD is more difficult to diagnose in elderly patients because of increased pain tolerance and the increased gastric pH that may accompany atrophic gastritis. Symptoms may be attributed to other underlying diseases such as coronary artery disease (57). Because symptoms are frequently so atypical, more intensive investigation in elderly individuals is often required to obtain a specific diagnosis.

***H pylori*:** It has long been recognized that there is an association among *H pylori*, gastritis and peptic ulcer disease. Antibodies to *H pylori* infection are found in over 50% of people in developed countries who are older than 60 years of age (58). In one study, the prevalence was found to approach 90% in patients over the age of 60 years (59). In elderly patients, *H pylori* infection is usually the cause of gastritis. The most important cause of *H pylori*-negative gastritis appears to be overt or covert NSAID ingestion (60).

Several methods are available to detect the presence of *H pylori* infection, including urease testing of antral biopsy samples (CLO test), culture of gastric biopsy tissue or gastric contents, by ¹³carbon or ¹⁴carbon urea breath testing, or by the presence of serological markers of immunoglobulin (Ig) A and IgG antibodies (Table 5). With the CLO test, pieces of gastric biopsy tissue are placed into a solution containing urea with the formation of ammonium hydroxide, which, in the presence of a pH indicator, turns the sample red. It is important to recognize that our laboratory has found this test to be relatively insensitive in elderly patients (61). The urea breath test for the detection of urease activity involves oral

administration of 13 carbon- or 14 carbon-labelled urea, which is converted by bacterial urease to 13 carbon dioxide or 14 carbon dioxide, is absorbed and is then eliminated in the breath, where the labelled carbon dioxide can be detected and measured. Chronic *H pylori* infection elicits local and systemic immunological responses, leading to the production of IgA and IgG antibodies. Testing of serum IgG level only is preferred because this antibody is a more accurate reflection of current infection status (62). Detection of IgG antibodies is not influenced by the patchy distribution of the organism in the stomach, which may occur in elderly patients.

EVALUATION

Initial tests for patients with peptic symptoms include esophagogastroduodenoscopy and upper gastroduodenal barium study. Endoscopy has been shown to be more accurate than barium studies in the diagnosis of peptic diseases in elderly patients, just as in young patients. Endoscopy is well tolerated and safe, even in very old patients (63). Caution is warranted during sedation in elderly patients, as in younger patients with cardiovascular or pulmonary diseases, and monitoring of oxygen saturation is mandatory. In elderly patients, barium studies can be used to evaluate some upper gastrointestinal complaints if endoscopy is contraindicated because of medical conditions that make sedation dangerous, such as a recent myocardial infarction.

At all ages, the advantages of endoscopy include the ability to take mucosal biopsies for the diagnosis of *H pylori*, and to determine the pathology of gastric ulcers and the ability to visualize directly esophagitis and duodenitis. Most patients prefer endoscopy to barium radiology (64), especially elderly patients who are frail and have difficulty moving around.

Evaluation of elderly patients with gastrointestinal bleeding should include tests for altered coagulation, aspiration of stomach contents and a diagnostic test such as esophagogastroduodenoscopy. A lesion can be confirmed as the source of bleeding by endoscopic examination if there is active bleeding or stigmata of recent bleeding, such as a visible vessel or a clot in the ulcer. Identification of the source of bleeding can provide prognostic information and determine the course of therapy. The prognosis also is determined by transfusion requirements and the presence of concurrent illnesses.

TREATMENT

Early recognition and precise diagnosis are crucial to provide effective treatment of elderly patients with peptic ulcer disease. The failure to diagnose peptic disease rapidly complicates timely therapy. Patients of all ages with peptic ulcer disease should be advised to stop smoking, eliminate alcoholic beverages on an empty stomach and eat regular meals.

If *H pylori* is diagnosed, this infection should be treated in all patients with a peptic ulcer. If *H pylori* is not eradicated by the initial treatment regimen, patients need to be retreated one to two months later because eradication of *H pylori* has been shown to reduce the rate of peptic ulcer relapse markedly. The most common reason for *H pylori* treatment failure

is noncompliance, which occurs frequently in the elderly population. Therefore, the simpler the regimen and the shorter the length of treatment the better the results. The newer regimens that include omeprazole, amoxycillin, and metronidazole or clarithromycin for 10 days are as effective as and better tolerated than earlier triple therapy regimens that included colloidal bismuth and required two to three weeks of treatment.

If the patient has no evidence of *H pylori* infection and is consuming NSAIDs, it is important for the patient to either stop taking the NSAID completely or switch to lower doses of the NSAID. This approach is often difficult in elderly patients with chronic arthritis. NSAIDs induce peptic ulceration predominately because of inhibition of gastroduodenal PG synthesis so that patients may alternatively be treated with a new class of anti-inflammatory drugs that inhibit the cyclo-oxygenase (COX) 2 pathway and have little effect on gastric PG concentrations.

Mortality from upper gastrointestinal bleeding has remained unchanged, despite the widespread diagnostic and therapeutic use of endoscopy and improved methods of resuscitation. The main reason is that most upper gastrointestinal bleeds occur in elderly patients and that more than 80% to 90% of the mortality occurs in this age group. A major reason for the frequency of bleeding episodes in elderly patients is the widespread use of NSAIDs for the treatment of arthritis. Therefore, it is hoped that newer anti-arthritis medications such as the COX2 inhibitors that cause less gastric or duodenal ulceration might lower the prevalence of gastrointestinal bleeding. If the NSAIDs need to be continued in older patients who have demonstrated evidence of peptic disease, then cotreatment with high dose H_2 receptor antagonists or proton pump inhibitors (PPIs) is mandatory.

The present mainstays of treatment for peptic ulcer disease are the H_2 receptor antagonists, PPIs, anti-*H pylori* treatment or cytoprotective agents such as sucralfate. Histamine receptor-blocking agents are still the most widely used agents for the treatment of peptic disease in elderly patients. These drugs work by direct suppression of gastric acid secretion – mainly nocturnal acid secretion. H_2 receptor antagonists have an extremely low side effect profile, and several preparations can be administered only once or twice daily. Dosage adjustment is needed only in patients with renal or hepatic disease even in older patients. There have been no proven difference in the adverse reaction profiles of different H_2 receptor antagonists in elderly patients. In particular, cimetidine causes no more confusion, depression, memory impairment or hallucinations than other H_2 receptor antagonists. A meta-analysis of adverse reactions to cimetidine totalling over 600 patients showed no significant differences in side effects between patients treated with cimetidine or controls (65).

PPIs inhibit the gastric epithelial hydrogen/potassium ATPase pump, and are also very effective for short term therapy of peptic acid diseases. No side effects specifically applicable to elderly patients from the use of these drugs have been reported. Drug interactions with omeprazole include

prolonged action of warfarin and phenytoin half-life (66). Secretary studies have shown that nocturnal acid secretion is more completely abolished with PPIs than with the H₂ receptor antagonists.

Cytoprotective agents such as sucralfate are mostly effective against ulcers caused by stress or topical agents. They are believed to improve the mucosal barrier by stimulating mucosal PG synthesis. Sucralfate is difficult to administer in elderly patients because the drug needs to be taken four times daily, because of the large size of the pills and because of the side effect of constipation. Because of its aluminum content, elderly patients with renal failure should not use sucralfate for long term maintenance.

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SUMMARY

This review describes some of the physiological changes in the gastrointestinal tract of elderly patients and some of the peptic diseases encountered in this population. The diagnosis of peptic diseases and treatment require a careful and systematic approach by physicians. Because the clinical presentation of peptic diseases is usually obscure in elderly patients, prompt investigation is warranted in most cases. H₂ receptor antagonists, PPIs and regimens to eradicate *H pylori* have a high success rate in the treatment of documented organic disease. Given the increase in life expectancy in our population, much consideration needs to be given to gastrointestinal problems in elderly patients in the next decade.

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